Nanojars: Versatile Platform for Pyrazole Synthesis and Chemistry, and Selective Extraction of Anions

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NANOJARS: VERSATILE PLATFORM FOR PYRAZOLE SYNTHESIS AND CHEMISTRY, AND SELECTIVE EXTRACTION OF ANIONS

by

Basil Mohammed Ahmed

A dissertation submitted to the Graduate College in partial fulfillment of the requirements for the degree of Doctor of Philosophy Chemistry Western Michigan University June 2018

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NANOJARS: VERSATILE PLATFORM FOR PYRAZOLE SYNTHESIS AND CHEMISTRY, AND SELECTIVE EXTRACTION OF ANIONS

Basil Mohammed Ahmed, Ph.D.
Western Michigan University, 2018

This work is centered around nanojars, a family of nano-sized anion-incarcerating agents. It addresses various aspects of nanojar chemistry, such as synthesis strategies (including green methodologies) for pyrazole ligands needed for the preparation of nanojars, characterization and study of the mechanism of assembly of nanojars, and selective extraction of anions from water using nanojars.

Nanojars are neutral, supramolecular coordination complexes of the general formula \([\text{anion} \subset \{\text{Cu}(\mu\text{-OH})(\mu\text{-pz})\}_n]\), formed by the reaction of \(\text{Cu}^{2+}\), \(\text{HO}^-\) and pyrazolate ions \((\text{C}_3\text{H}_2\text{N}_2^-\text{, pz}^-)\) in the presence of oxoanions with large hydration energy (e.g. \(\text{CO}_3^{2-}\), \(\text{SO}_4^{2-}\), \(\text{PO}_4^{3-}\), \(\text{HPO}_4^{2-}\)). Nanojars are comprised of \(n = 26–36\) repeating units of the formula \([\text{Cu(OH)(pz)}]\), which are arranged in stacks of three or four. The stacking of metallamacrocycles creates a hydrophilic central cavity occupied by the incarcerated anion, surrounded by a hydrophobic periphery, which provides solubility in numerous organic solvents. Nanojars are robust under neutral to extremely alkaline \((\text{pH} > 14)\) conditions and bind certain anions with high strength. Under acidic conditions, however, nanojars reversibly break down and release the anion. Consequently, nanojars are excellent candidates for anion extraction agents.
The main objectives of this work are: (1) Synthesize and characterize various pyrazole ligands, including tethered multi-pyrazole ligand. In particular, pyrazoles with aliphatic and oligo(ethylene glycol) chains are targeted, which are expected to further expand the solubility of nanojars, in aliphatic solvents (such as ISOPAR\textsuperscript{TM}, suitable for industrial scale extractions) and water, respectively. (2) Prepare and characterize nanojars using the synthesized pyrazole ligands. Characterization techniques include NMR and UV–vis spectroscopy, mass spectrometry, X-ray crystallography and thermogravimetric analysis. (3) Study the mechanism of formation of nanojars, using pH titration, UV–vis spectroscopy and mass spectrometry. (4) Study the extraction of sulfate (SO\textsubscript{4}\textsuperscript{2–}) and carbonate (CO\textsubscript{3}\textsuperscript{2–}) ions from aqueous media by nanojars, and develop a method for selective extraction of these anions.

Besides the anticipated outcomes based on the objectives described above, a number of unforeseen, yet fundamentally significant results for the broader field of chemistry are also presented. Unexpected results during the organic synthesis work inspired computational studies, which resulted in demystification of misunderstood theoretical concepts related to the reactivity of pyrazole derivatives. Thus, the “adjacent lone pair effect”, and the drastic deprotonation reactivity difference between 3- and 5-alkylpyrazole isomers, as well as between five- and six-membered aromatic molecules, was elucidated. The unusual and contrasting reactivity of amino- and hydroxypyrazole derivatives toward aldehydes and ketones under either neutral or acidic conditions was also studied, providing not only an understanding of the mechanism of the reactions, but also a variety of novel bis- and non-scorpionate tris(pyrazolyl)methane ligands. Furthermore, the selective C-4 deuteration of pyrazole substrates by D\textsubscript{2}O was studied, and a convenient procedure for large-scale deuteration was developed.
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LIST OF ABBREVIATIONS

1D  One-dimensional
2D  Two-dimensional
3D  Three-dimensional
3-EtpzH  3-Ethylpyrazole
3-MepzH  3-Methylpyrazole
3-nPrpzH  3-n-Propylpyrazole
3-nBupzH  3-n-Butylpyrazole
3-nOctpzH  3-n-Octylpyrazole
4-BrpzH  4-Bromopyrazole
4-(CH₃OCH₂CH₂O)pzH  4-(2-Methoxyethoxy)pyrazole
4-(CH₃(OCH₂CH₂)₂O)pzH  4-(2-(2-Methoxyethoxy)ethoxy)pyrazole
4-(CH₃(OCH₂CH₂)₃O)pzH  4-(2-(2-(2-Methoxyethoxy)ethoxy)ethoxy)pyrazole
4-ClpzH  4-Chloropyrazole
4-CF₃pzH  4-Trifluoromethylpyrazole
4-FpzH  4-Fluoropyrazole
4-(HOCH₂CH₂CH₂)pzH  4-(3-hydroxypropyl)pyrazole
4-IpzH  4-Iodopyrazole
4-MepzH  4-Methylpyrazole
4-nBupzH  4-n-Butylpyrazole
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<td>4-OctpzH</td>
<td>4-n-Octylpyrazole</td>
</tr>
<tr>
<td>4-PhpzH</td>
<td>4-Phenylpyrazole</td>
</tr>
<tr>
<td>ALP</td>
<td>Adjacent Lone Pair</td>
</tr>
<tr>
<td>Ar</td>
<td>Aromatic group</td>
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<tr>
<td>Bn</td>
<td>Benzyl</td>
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<tr>
<td>Bu4N+</td>
<td>Tetrabutlammonium</td>
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<td>CS</td>
<td>Cyanostar</td>
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<tr>
<td>d</td>
<td>Doublet</td>
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<td>(D_{\text{calc}})</td>
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<td>DCM</td>
<td>Dichloromethane</td>
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<td>DFT</td>
<td>Density functional theory</td>
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<td>DHP</td>
<td>3,4-dihydro-2(H)-pyran</td>
</tr>
<tr>
<td>DMAS</td>
<td>(N,N)-dimethylaminosulfonyl</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMF-DMA</td>
<td>(N,N)-Dimethylformamide dimethylacetal</td>
</tr>
<tr>
<td>DMSO-(d_6)</td>
<td>Deuterated dimethylsulfoxide</td>
</tr>
<tr>
<td>DSS</td>
<td>Sodium 2,2-dimethyl-2-silapentane-5-sulfonate</td>
</tr>
<tr>
<td>EDD</td>
<td>Electron density difference</td>
</tr>
<tr>
<td>ESI-MS</td>
<td>Electrospray ionization mass spectrometry</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>ESI-TOF</td>
<td>Electrospray ionization time-of-flight</td>
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<tr>
<td>EtOH</td>
<td>Ethanol</td>
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<td>Fudan materials</td>
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<tr>
<td>FW</td>
<td>Formula weight</td>
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<tr>
<td>GOF</td>
<td>Goodness of fit</td>
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<tr>
<td>H$_2$PyC</td>
<td>1$H$-pyrazole-4-carboxylic acid</td>
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<td>H-bonding</td>
<td>Hydrogen bonding</td>
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<tr>
<td>Hdmpz</td>
<td>3,5-dimethylpyrazole</td>
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<tr>
<td>HDMS</td>
<td>High definition mass spectrometry</td>
</tr>
<tr>
<td>HF</td>
<td>Hartree–Fock method</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest occupied molecular orbital</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>$^3$Pr</td>
<td>Isopropyl</td>
</tr>
<tr>
<td>ITC</td>
<td>Isothermal titration calorimetry</td>
</tr>
<tr>
<td>$J$</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>C18-crown-6</td>
<td>18-crown-6 ether</td>
</tr>
<tr>
<td>$K_a$</td>
<td>Acidity constant</td>
</tr>
<tr>
<td>kJ mol$^{-1}$</td>
<td>Kilojoule per mole</td>
</tr>
<tr>
<td>kV</td>
<td>Kilovolts</td>
</tr>
<tr>
<td>L</td>
<td>Ligand (when it comes with chemical formula)</td>
</tr>
<tr>
<td>L</td>
<td>Liter (when it comes with solutions)</td>
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<td>LC–MS</td>
<td>Liquid chromatography–mass spectrometry</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
<tr>
<td>M</td>
<td>Molar</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>Megahertz</td>
</tr>
<tr>
<td>MOFs</td>
<td>Metal–organic frameworks</td>
</tr>
<tr>
<td>MOM</td>
<td>Methoxymethyl</td>
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<tr>
<td>MP2</td>
<td>Møller–Plesset perturbation theory (second level)</td>
</tr>
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<td>m/z</td>
<td>Mass/charge</td>
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<tr>
<td>n-BuLi</td>
<td>n-Butyl lithium</td>
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<td>NMR</td>
<td>Nuclear magnetic resonance</td>
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<td>OEG.</td>
<td>Oligo(ethylene glycole)</td>
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<td>OH</td>
<td>Hydroxy group</td>
</tr>
<tr>
<td>p-C₆H₄F</td>
<td>para-Fluorophenyl</td>
</tr>
<tr>
<td>pH</td>
<td>Potential of hydrogen</td>
</tr>
<tr>
<td>PhCOO⁻</td>
<td>Benzoate anion</td>
</tr>
<tr>
<td>pKₐ</td>
<td>The negative logarithm of acidity constant</td>
</tr>
<tr>
<td>PO₄³⁻</td>
<td>Phosphate anion</td>
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<td>ppm</td>
<td>Parts per million</td>
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<tr>
<td>PPN⁺</td>
<td>Bis(triphenylphosphine)immonium cation</td>
</tr>
<tr>
<td>PTFE</td>
<td>Polytetrafluoroethylene</td>
</tr>
<tr>
<td>pz</td>
<td>Pyrazolate</td>
</tr>
<tr>
<td>pzH</td>
<td>Pyrazole</td>
</tr>
<tr>
<td>pzCH₂CH₂pz</td>
<td>1,2-bis(1H-pyrazolyl-3-yl)ethane</td>
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<td>q</td>
<td>Quadruplet</td>
</tr>
<tr>
<td>ReO₄⁻</td>
<td>Perrhenate anion</td>
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<tr>
<td>Rf</td>
<td>Retention factor</td>
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<td>rflns.</td>
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<td>RSC</td>
<td>Royal Society of Chemistry</td>
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</tr>
<tr>
<td>SBUs</td>
<td>Secondary building units</td>
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<td>'Bu</td>
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<td>Trifluoroacetic acid</td>
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<td>THF</td>
<td>Tetrahydrofuran</td>
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<td>THP</td>
<td>Tetrahydropyran-2-yl</td>
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<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
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<td>tren</td>
<td>Tris(2-aminoethyl)amine</td>
</tr>
<tr>
<td>TTU</td>
<td>Tren-tris-urea</td>
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<td>UV–vis</td>
<td>Ultraviolet–visible</td>
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<td>V</td>
<td>Volt</td>
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<td>VB</td>
<td>Valence bond</td>
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<td>VT</td>
<td>Variable-temperature</td>
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<td>w₁/₂</td>
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<td>WO₄²⁻</td>
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<tr>
<td>ΔXE</td>
<td>Electrons nondelocalization effect</td>
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<td>δ</td>
<td>Chemical shift</td>
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<td>Molar extinction coefficient</td>
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<tr>
<td>λ</td>
<td>Wavelength at maximum absorbance</td>
</tr>
<tr>
<td>φ</td>
<td>Bond angle</td>
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CHAPTER 1

INTRODUCTION

1.1 Anion binding and extraction

Anion binding and removal from water by synthetic receptors is one of the most extensively researched topics in the field of supramolecular chemistry, because of the important roles that anions play in various environmental, biological and chemical processes. Among these anions are sulfate and phosphate, which are known to interfere with the disposal of aqueous nuclear waste by vitrification, and they can cause eutrophication originating from the continuous discharge of fertilizers. In addition, arsenate, chromate and selenate are known for their toxicity and carcinogenicity.

The removal of anions from water is usually achieved by liquid–liquid extraction, as well as by other techniques such as solid–phase extraction and selective crystallization. The extraction processes depend mainly on the binding strength of the anions with water, which is sorted in the Hofmeister series depending on the hydration energies of the anions (Figure 1.1). Removal of the anions with large hydration energy from water is very challenging because of their high affinity for water. For instance, carbonate and sulfate, which have very large hydration energies ($\Delta G_{h}^{\circ} = -1315 \text{ kJ mol}^{-1}$, $-1090 \text{ kJ mol}^{-1}$, respectively), are much harder to remove from water compared to anions with smaller hydration energies, such as nitrate and perchlorate ($\Delta G_{h}^{\circ} = -306 \text{ kJ mol}^{-1}$, $-214 \text{ kJ mol}^{-1}$, respectively).

Figure 1.1: Hofmeister series.
In addition, selective recognition and extraction of these anions from mixtures is a very challenging problem, due to their similar properties, such as size and charge. For instance, phosphate and arsenate anions have the same charge, very similar size and acidity constant. Therefore, the design of novel chemical systems, capable of efficient and selective extraction of anions from solutions, is gaining increasing attention in recent years. The most effective and practical way to bind and extract hydrophilic anions from water is by encapsulating and isolating them completely from the surrounding environment by using cage-like extracting agents. In order to complete the separation process, the extracting agent needs to be able to transfer the anions from water into a different, immiscible phase to collect them easily. A brief review of the major classes of currently known anion receptors is present below.

1.1.1 Tripodal anion receptors

Tripodal anion receptors represent a class of acyclic anion binding agents which consist of three conformationally flexible arms where the ligating groups are attached to coordinate the guest anion. Tripodal anion receptors show relatively high selectivity toward tetrahedral oxoanions, originating from the shape complimentary between the flexible arms and the tetrahedral oxoanions. With their hydrogen-bonding functionalized arms, tripodal receptors have been shown to coordinate with the guest anions by formation of capsules or pseudo-capsules assemblies. The formed molecular capsules are able to isolate the encapsulated anion from the solution. To encapsulate multi-charged oxoanions and hydrated anions, higher coordination number is required; therefore, dimeric capsules are created by two tripodal molecules with the guest anion. Tris(2-aminoethyl)amine based tris(urea/thiourea) ligand (TTU) (Figure 1.2) are well-known types of tripodal anion receptors, which were reported for the first time in 1995.

![Figure 1.2: Chemical structure of tripodal urea/thiourea anion receptor (TTU) (X = O, S).](image)
Selective binding for anions is achieved by using specific substituents for the receptor. Bachas and co-workers have studied the effect of scaffold rigidity and cavity size on selectivity of the receptors to construct ion-selective electrodes, by using tris(urea) receptor of \(N\)-butyl-4-oxo-4\(H\)-chromene-2-carboxamide substituted group based on either a tren scaffold (see Figure 1.2) or a cis-1,3,5-tris(aminomethyl)cyclohexane scaffold (Figure 1.3).\(^{19}\)

![Figure 1.3: Chemical structure of tripodal urea receptor cis-1,3,5-tris(aminomethyl)cyclohexane.](image)

The electrodes based on the ionophore that incorporates the flexible tren scaffold show high affinity toward hydrophilic anions, with an improved selectivity for sulfate. In contrast, the ionophore with the rigid cis-1,3,5-tris(aminomethyl)cyclohexane scaffold exhibits a more affinity toward hydrophobic anions.

Das and co-workers have demonstrated selective binding for sulfate over dihydrogen phosphate, acetate, nitrate and perchlorate by using a tren-based receptor with 4-nitrophenyl functionalities.\(^{20}\) Replacing urea with thiourea by the same group led to preferential binding toward phosphate by two independent dimeric capsule assemblies, as indicated by \(^1\)H NMR titration, compared to other anions such as carbonate, sulfate and fluoride. The higher selectivity toward phosphate is related to the aromatic \(\pi\)--\(\pi\) stacking and aryl C–H…N interactions between the receptor side arms.\(^{17}\)

Yang, Wu and co-workers studied the host-guest binding behavior by cyclic voltammetry, using tren-based receptor with 2-ferrocenyl functionalities, and by fluorescence spectroscopy, using tris(urea) receptor with 3-quinoline functionalities.\(^{21}\) The studies were performed using sulfate and fluoride anions. In addition, they compared the binding strength between the former and the later ligand with sulfate anion using \(^1\)H NMR, and they indicated higher affinity of the later receptor to sulfate than the former one. Furthermore, both of these receptors bind sulfate.
significantly stronger than fluoride. This result points to a better complementarity of the receptor with tetrahedral anions such as sulfate, than the spherical anions such as fluoride.

Efficient and selective extraction of sulfate anions from water was achieved by the same group by developing a tripodal hexaurea receptor (Figure 1.4), even in the presence of excess nitrate and chloride anions.\(^{22}\)

![Figure 1.4: Chemical structure of the tripodal hexaurea receptor (a), X-ray structure of the receptor with the fully encapsulated sulfate anion via hydrogen bonding (b). Figure b is reproduced from reference 12 with permission from The Royal Society of Chemistry.](image)

Complementarity, chelate effect and hydrophobicity of the receptor led to overcome the large hydration energy of the sulfate anions.\(^{22}\) All six urea groups in the receptor are involved in hydrogen bonding with the sulfate anion to form a total of twelve hydrogen bonds, allowing full encapsulation of the anion inside the receptor in the tetrahedral cavity.

A tren based tris(urea) receptor functionalized with pentafluorophenyl has been prepared by Ghosh and his co-workers, who studied its binding in solution with various anions and showed that the receptor favors anions with large hydration energies (\(\text{H}_2\text{PO}_4^- > \text{SO}_4^{2-} > \text{CO}_3^{2-} > \text{CH}_3\text{COO}^- > \text{F}^- > \text{Cl}^- >> \text{Br}^-\)), with high selectivity observed for dihydrogen phosphate.\(^{12}\) On the other hand, this receptor showed higher binding for phosphate and sulfate anions compared to the same receptor where phenyl is the substituted group.\(^{23}\) Higher selectivity toward sulfate over other
anions such as dihydrogen phosphate, acetate, chloride, bromide, iodide, nitrate and perchlorate was achieved by using the same functional group, pentafluorophenyl-substituted tris(urea) receptor based on the more rigid cyanuric acid platform (Figure 1.5), in the solid state, solution and gas phase.\(^{24}\)

![Figure 1.5: Chemical structure of a cyanuric acid based pentafluorophenyl urea receptor.](image)

Gale and his co-workers investigated the anion binding affinities of a series of fluorinated phenyl tren based tris(urea) and tris(thiourea) receptors (see Figure 1.2) \((X = O \text{ or } S; \ R = \text{Ph, } p-C_6H_4F, \ C_6F_5, \ p-C_6H_4(CF_3), \ 3,5\text{-bis}(CF_3)C_6H_3)\) with different anions in solution such as chloride, sulfate, dihydrogen phosphate, hydrogen carbonate and nitrate, by using \(^1\)H NMR titration.\(^{25}\) The study revealed that the receptors bind anions according to the trend \(\text{SO}_4^{2-} > \text{H}_2\text{PO}_4^- > \text{Cl}^- > \text{HCO}_3^- >> \text{NO}_3^-\), which shows high selectivity toward sulfate and only limited binding with nitrate anion. It’s also observed that the more acidic thiourea-based receptors showed lower binding constants than those of the equivalent urea-based receptors, and the stability constants decrease with increasing electron-withdrawing ability of the substituents.

2-Aminothiazolium-containing tripodal receptors based on a benzene platform show a strong affinity towards sulfate when a phenyl group is present at the 4-position of the thiazoline ring, and affinity toward acetate in the absence of the phenyl group (Figure 1.6).\(^{26}\) The phenyl group on the thiazoline ring has played an important role in the formation of a cone conformation
upon sulfate binding through mutual aromatic static interaction. The isothermal titration calorimetry (ITC) method was used to investigate the affinities of these receptors toward anions.

Figure 1.6: Chemical structures of 2-aminothiazoline based receptors.

Hossain et al. have recently reported the synthesis of $p$-phenylene-bridged hexafUNCTIONal tripodal receptor consisting of two differently functionalized clefts, a urea-based inner cleft and a thiourea-based outer cleft (Figure 1.7). Experimental studies ($^1$H NMR titration and 2D NOESY) and theoretical calculations (high-level DFT) demonstrated that the receptor can effectively bind sulfate anions in a two-step binding process. The 1:2 stoichiometric complex formed is stabilized through complementary hydrogen-bonding interactions. The enhanced H-bonding ability as well as the structural complementarity of the thiourea functionalities lead to stronger interactions with the anion than in the case of the urea analogue. Therefore, the first sulfate anion binds preferentially at the thiourea-based outer cleft, followed by the second sulfate anion, which binds at the urea-based inner cleft. This binding propagation was further supported by DFT calculations, illustrating that the thiourea-bound complex is energetically more favorable than the urea-bound complex.

Figure 1.7: Chemical structure of $p$-phenylene-bridged hexafUNCTIONal mixed urea/thiourea tripodal receptor.
The calculated binding constants gathered from the titration of the ligand with other anions such as hydrogen sulfate, hydrogen phosphate, perchlorate and nitrate revealed the overall binding trend $\text{SO}_4^{2-} > \text{HSO}_4^- > \text{H}_2\text{PO}_4^- > \text{ClO}_4^- \ or \ \text{NO}_3^-$.

In general, it is clear that the urea receptors prefer to bind the tetrahedral sulfate anion selectively,$^{12}$ compared to a tren based tripodal amide receptor (Figure 1.8), which showed selectivity toward hydrogen sulfate over chloride, bromide, nitrate and phosphate.$^{28}$

![Figure 1.8: Chemical structure of a tren based amide receptor.](image)

1.1.2 Cyclic anion receptors

A variety of synthetic receptors have been developed to tackle the challenging task of achieving high affinity and selectivity for anions in aqueous media. Cyclic receptors, in which the binding units are arranged around the closed rings have played a key role. Considering their preorganized structure and thermodynamic stability (chelate, macrocycle and macrobicycle effect), cyclic receptors offer advantages over acyclic receptors in binding anions.$^{29}$ All cyclic receptors described in this section are functionalized with amine, amide, pyrrole and indole anion-binding groups.

Sessler and co-workers prepared cyclo[8]pyrroles (Figure 1.9) by the oxidative self-coupling of bipyroles in the presence of $\text{H}_2\text{SO}_4$, which have been used for liquid-liquid extraction of sulfate anions from aqueous solution along with Aliquat 336N as a phase-transfer catalyst.$^{30}$ An isotopic exchange experiment with sodium sulfate spiked with a radioactive $\text{SO}_4^{2-}$ tracer has shown that the receptor ($R = \text{C}_{11}\text{H}_{23}$) has very high exchange constant, which means that the more hydrophilic sulfate anion can be usefully extracted into an organic layer from a much higher concentration of lipophilic anions, such as nitrate.$^{31}$
Moyer, Sessler and co-workers have explored the effect of the substituents in macrocycles on the liquid–liquid anion exchange of sulfate, using two classes of neutral macrocyclic receptors in chloroform solution containing Aliquat 336N as phase-transfer catalyst (Figure 1.10).³²

![Chemical structure of sulfate complex of cyclo[8]pyrrole.](image1)

1. $R = C_{11}H_{23}$
2. $R = C_2H_5$

The study revealed that the substituents have a strong influence on the ability of the receptor to enhance sulfate extraction. For instance, the dansyl substituents on the tetramide macrocycles appear effective, whereas in the case of calix[4]pyrroles, the fluorine substituents


1. $n = 1$
2. $n = 2$
3. $R^1 = H$, $R^2 = CH_3$
4. $R^1 = H$, $R^2 = $ dansyl
5. $R^1 = t$-butyl, $R^2 = CH_3$
apparently weaken the extraction ability of the receptor, contrary to the expectation that the electron-withdrawing groups should enhance anion binding by strengthening the hydrogen bonds. Higher concentration of the fluorinated calix[5]pyrrole receptor is required to push the sulfate distribution ratio to technologically useful values.

Later, the same group has shown that the use of a methyltrialkylammonium (alkyl = C₆–C₁₀) cation allows simple, unfunctionallized calix[4]pyrrole to work as a selective sulfate anion extractant. The enhancement in the selectivity for sulfate extraction is attributed to the concurrent binding of the sulfate anion and the methyltrialkylammonium cation to the cone-conformation of the calix[4]pyrrole, rendering the host an ion-pair receptor.

Based on the calix[4]pyrrole receptor, Sessler and co-workers have designed and synthesized receptor derivatives with higher affinity to anions (Figure 1.11). The observed higher affinity originates from the additional two acidic hydrogen-bonding donors provided by the bipyrrrole units, as well as to the anion encapsulation.

The calix[4]pyrrole-based anion receptors were found to extract the sulfate anion as methylalkyl ammonium salts from water into organic media with higher efficiency than the parent calix[4]pyrrole.
Sessler and co-workers have recently reported a receptor derivative based on the calix[4]pyrrole motif; bis-calix[4]pyrroles are capable of binding two oxoanions (1:2 ratio), specifically $\text{H}_2\text{PO}_4^-$, $\text{H}_2\text{PO}_7^{3-}$ and $\text{SO}_4^{2-}$ (Figure 1.12).\textsuperscript{35}
Anion-templated synthesis of macrocycles with geometry complimentary to the guest anion is an alternative strategy for anion binding. Beer and co-workers have shown for the first time the templating role of sulfate anion in the high yield synthesis of a [2]catenane (Scheme 1.1). The synthesized catenane did not form in the presence of other anions such as chloride, fluoride and acetate. The higher selectivity towards sulfate is attributed to the electrostatic attraction and complementarity between the orthogonal arrangement of four amide groups from two units of the receptor, and the tetrahedral geometry of the sulfate anion.
Mani and co-workers reported a class of large macrocycles containing $N,N$-di(pyrrolylmethyl)-$N$-methylamine moieties (Scheme 1.2).\textsuperscript{38} The observed anion binding of the two receptors is different regardless of their similar pyrrolic and amine NH donors. This difference was attributed to the degree of flexibility provided by the linkers (ethylene vs phenylene). $^1$H NMR titration experiments revealed that the receptor with a phenylene spacer binds anions in 1:2 ratio (Scheme 1.2), whereas the other receptor binds the anion in 1:1 ratio. Furthermore, the $^1$H NMR titration experiments showed different affinities for anions, and the relative order was $\text{SO}_4^{2-} > \text{F}^- > \text{Cl}^- > \text{Br}^- > \text{PhCOO}^-$ for both receptors.
Flood and co-workers reported that the cyanostar (CS) macrocycle (Figure 1.13) can stabilize a dimer of hydrogen sulfate anions in a sandwich-like arrangement by twenty CH⋯⋯O hydrogen bonds (ten hydrogen bonds provided by each macrocycle). Crystal structure characterization revealed that the S–O⋯⋯O–S distance between the dimeric hydrogen sulfates inside the cavity of the receptor is ~ 2.51 Å, which is shorter than that in the free hydrogen sulfate dimer (2.62 Å). In addition to the crystallographically confirmed structure with two layers of the cyanostar hosting a dimer of the hydrogen sulfate (Figure 1.13), ESI-MS analysis revealed the presence of three stacked cyanostar macrocycles hosting a dimer of hydrogen sulfate anions. The presence of the complex equivalents 2:2 and 3:2 (host:guest) in solutions is also confirmed by NMR spectroscopic methods.

Figure 1.13: Chemical structure of cyanostar (a), top view crystal structure of the complex (Bu₄N)₂(CS)₂(HSO₄)₂ (b), side view crystal structure of the complex (Bu₄N)₂(CS)₂(HSO₄)₂ (c). Figures b and c are reprinted from reference 39. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.
In addition to the two-dimensional macromonocyclic receptors, three-dimensional macrobicyclic receptors have also been prepared in order to achieve high selectivity and binding affinity toward anions in aqueous solutions. Nelson and co-workers, Bowman-James and co-workers, Ghosh and co-workers have structurally characterized the encapsulation of sulfate in the cavity of protonated macrobicyclic receptors with different spacers (furan, m-xylyl, 2,6-dicarbonopyridyl and p-xylyl, respectively) in aqueous solvent (Figure 1.14). The study of the crystal structures of sulfate complexes of these receptors revealed that the anion is encapsulated inside the cavity by eight, five and eight NH⋯O hydrogen bonds in the case of furan, m-xylyl and 2,6-dicarbonopyridyl spacers, respectively, whereas four NH⋯O and six CH⋯O hydrogen bonds are present in the case of the receptor with p-xylyl spacer.

![Figure 1.14: Chemical structure of macrobicyclic receptors with furan spacer (a), m-xylyl spacer (b), 2,6-dicarbonopyridyl spacer (c), p-xylyl spacer (d).](image)

Later, Bowman-James and co-workers reported the design and synthesis of a tricyclic anion receptor, which consists of two tetraamide monocycles attached together by two ethylene chains (Figure 1.15). Structural and binding studies indicated that this receptor is selective for linear anions such as FHF⁻ and N₃⁻. The four bridging amines are protonated in the presence of excess H₂SO₄. The protonated receptor exists as a complex with two sulfate anions and two water molecules inside the cage. Crystallographic study of the complex showed that each sulfate is bound by four NH⋯O hydrogen bonds with the amide groups and by one OH⋯O H-bond with a water molecule.
1.1.3 Metal-based anion receptors

Metal ions play an important role in anion recognition processes in two ways: (1) they can work as the active site for anion binding by attractive electrostatic interactions, (2) they can be used to orient the hydrogen bond donor substituents to a rigid arrangement favoring selective anion binding. The complex receptors are normally designed so that the hydrogen bond donor groups (e.g. amine, amide etc.) are covalently linked to the metal ions to form a coordination complex that provides a suitable orientation of the hydrogen bond donors for binding anions. The coordination geometry of the metal ions (tetrahedral, square planar or octahedral), in addition to the nature and length of the spacer connecting ligand and hydrogen bond donors normally dictate the shape and size of the anion binding site within the receptor.\(^{12}\)

Loeb and co-workers have demonstrated a remarkable selectivity for sulfate anion by a platinum(II) complex (Figure 1.16).\(^{44}\) The square-planar coordination geometry preference Pt(II) and the free rotation around the Pt(II)–N bonds in the complex give the possibility of three options (up and down) with respect to the butyl urea substituents: all up (cone conformation) three up/one down and two up/two down. The crystal structure of the complex showed that the receptor adopted
the cone conformation with all eight N–H groups oriented toward the cavity, which provide complete encapsulation of the sulfate anion. 1H NMR titration experiments of the complex [Pt(ligand)4](BF4)2 with different anions such as chloride, bromide, iodide, dihydrogenephosphate, sulfate, triflate, perrhenate and nitrate, showed a preferential binding toward sulfate and dihydrogenephosphate.

![Chemical structure of the urea-functionalized iso-quinoline ligand (a) and crystal structure of the tetrakis Pt(II) complex of the ligand with sulfate anion (b).](image)

Figure 1.16: Chemical structure of the urea-functionalized iso-quinoline ligand (a) and crystal structure of the tetrakis Pt(II) complex of the ligand with sulfate anion (b). Figure b reprinted with permission from reference 44. Copyright 2004 American Chemical Society.

Beer and co-workers have demonstrated the selective binding of sulfate by tetra-imidazolium zinc metalloporphyrin anion receptor (Figure 1.17).45 UV–vis spectroscopic studies indicated that the receptor is capable of strongly complexing sulfate in competitive water-DMSO solvent mixture. The strong anion binding is attributed to a combination of electrostatic attraction with Zn(II) and hydrogen bonding with the imidazolium methine groups.
Encapsulation of sulfate in a molecular capsule by six urea groups was achieved by the coordination of six mono-pyridylurea ligands around an octahedral Cu(II) center, which resulted in the formation of two $C_3$-symmetric clefts at the two ends of the molecule (Figure 1.18). X-ray structure showed that two molecules aligned along the $C_3$-axis to create a cavity that encapsulates the sulfate anion inside its center. Inside the formed capsule, all six urea groups are involved in strong hydrogen bonding with the encapsulated sulfate anion.
Custelcean, Hay and co-workers have used computer-aided design based on a monourea ligand coordination with NiSO₄ or ZnSO₄.⁴⁷ They successfully obtained a series of hexakis-urea functionalized M₄L₆ tetrahedral cages with an anion coordinated in the cavity by twelve hydrogen bonds, provided from six urea groups arranged along each edge of the tetrahedral cage. The obtained cage cavities with six urea anion-binding sites have high selective encapsulation capability for tetrahedral o xoanions such as SO₄²⁻, SeO₄²⁻, CrO₄²⁻, MoO₄²⁻, WO₄²⁻, and PO₄³⁻, over anions of different shapes and charges such as F⁻, Cl⁻, Br⁻, I⁻, NO₃⁻, BF₄⁻, ClO₄⁻, ReO₄⁻, PF₆, CH₃CO₂⁻, CH₃SO₃⁻, CF₃SO₃⁻, CO₃²⁻, SO₃²⁻, and SeO₃²⁻ (Figure 1.19).
1.1.4 Other types of anion receptors

Eventual application of supramolecular chemistry in anion binding requires continued development of new molecular receptors to achieve the required efficiency and selectivity toward the targeted anion in the desired media. This goal has led researchers to explore other hydrogen bond donor and acceptor groups such as carbazole, indole, pyrrole-sulfonamides and indolecarbazoles, as anion receptors.

Davis, Beer and co-workers have shown by $^1$H NMR titration that two indolocarbazoles assemble around a sulfate anion in a 2:1 receptor:anion stoichiometry (Figure 1.20).\textsuperscript{48} X-ray structure confirmed the stoichiometry of the complex in the solid state. This assembly process around the sulfate anion allowed the formation of a pseudo-rotaxane, when a hybrid crown ether-isophthalamide macrocycle was combined with a 1:1 mixture of sulfate and the indolocarbazole ligand (Figure 1.20). This work demonstrated the important role that indolocarbazole may play in anion assembly processes.
Figure 1.20: The structure and hydrogen bonding of 2:1 indolocarbazole-sulfate complex (a), and sulfate-templated pseudo-rotaxane (b).

Schubert and co-workers have used triazolinium-based mono- and bis-tridentate receptors for selective binding of sulfate (Figure 1.21). Furthermore, they have demonstrated that the controlled degree of methylation can help in the formation of mono- or bis-tridentate complexes. The anion binding behavior of the receptors shown in (Figure 1.21a and b) toward sulfate, were estimated by $^1$H NMR spectroscopy in CD$_3$CN/CD$_3$OD (4:1 v/v); Job’s plots show that the receptors bind to sulfate in 1:1 and 1:2 stoichiometries, respectively.

Figure 1.21: Chemical structure of triazolinium based mono-tridentate receptor (a), bis-tridentate receptor (b), triazolinium based mono-tridentate receptor complex with SO$_4^{2-}$ in 1:1 stoichiometry (c), and triazolinium based di-tridentate receptor complex with SO$_4^{2-}$ in 2:1 stoichiometry (d).
Huggins and co-workers have used molecular receptors based on pyrrole-sulfonamides for binding anions (Figure 1.22). Anion binding studies of the receptors have been conducted with different anions by $^1$H NMR titration experiments, indicating that receptors 6 and 7 (Figure 1.22) bind to hydrogen sulfate stronger than to other anions such as chloride, bromide, nitrate and benzoate. Receptors 8 and 9 (Figure 1.22) bind hydrogen sulfate weaker than receptors 6 and 7.

![Figure 1.22](image)

Figure 1.22: Chemical structure of pyrrole-sulfonamide based receptors (a, b), and chemical structure showing the hydrogen bonding of receptor 2 with the encapsulated hydrogen sulfate (c).

The computational study they have conducted showed that HSO$_4^-$ is bound to the receptor (7, Figure 1.22) by five hydrogen bonds (two from the pyrrolic NH and two from sulfonamide NH), and the fifth hydrogen bond was donated from the hydrogen sulfate to the carbonyl group of the ester moiety. The latter hydrogen bond is attributed to be responsible for the observed selectivity of the receptors (6 and 7 see Figure 1.22) toward hydrogen sulfate.

1.2 Copper(II) pyrazolate chemistry

Multinuclear copper(II) complexes are continuously attracting attention due to their interesting magnetic properties and potential catalytic activity, their relevance to the active centers of a number of metalloproteins, their application in the synthesis of metal-organic frameworks (MOFs), and their applications in the anion encapsulation area. The pyrazolate anion (C$_3$H$_3$N$_2^-$) can coordinate to copper through both N-atoms, and form copper pyrazolate complexes ranging from di-, tri-, tetra-, penta-, hexa- to polynuclear structures, including 1D chains as well as 2D and 3D networks. Copper (II) pyrazolate complexes are prepared by the direct reaction of pyrazole with Cu(I) or Cu(II) ions in the presence of bases, by oxidizing...
Cu(I) pyrazolate complexes, by solvothermal reactions of copper salts with pyrazole, or by self-assembly reactions from presynthesized copper pyrazolate complexes. 

Monica, Moret and co-workers have prepared an octanuclear copper(II) pyrazolate complex \([\text{Cu(II)}_8(\text{dmpz})_8(\text{OH})_8]\) (Hdmpz = 3,5-dimethylpyrazole), by the reaction of \([\text{Cu(I)}(\text{dmpz})]_n\) with \(O_2\) in a wet solvent at atmospheric pressure and room temperature. The obtained octanuclear copper(II) complex consists of a cyclic planar system of copper(II) centers connected by hydroxide and 3,5-dimethylpyrazolate units to form a toroidal shaped molecule. The authors demonstrated the catalytic activity of the complex by the oxidation of organic substrates such as triphenylphosphine, aromatic primary amines, dibenzylamine, and carbon monoxide to form triphenylphosphine oxide, azobenzenes, \(N\)-benzyldienebenzylamine and carbon dioxide, respectively (Scheme 1.3). Each mole of the complex reacted with triphenylphosphine to give 4 moles of the triphenylphosphine oxide, suggesting that the octanuclear complex transformed in solution to tautomeric species of the general formula \([\text{Cu}_8(\text{dmpz})_8(\text{O})_{x}(\text{OH})_{8-2x}(\text{H}_2\text{O})_x]\) (\(x = 1 – 4\)), which might behave as the catalytically active species.

Scheme 1.3: Oxidation reactions catalyzed by an octanuclear Cu(II) complex.

Monari, Pandolfo, Pettinari, Pombeiro and co-workers have reported the formation of a trinuclear triangular copper complex \([\text{Cu}_3(\mu_3-\text{OH})(\mu-\text{pz})_3(\text{EtCOO})_2(\text{H}_2\text{O})]\)·\(\text{H}_2\text{O}\) (Figure 1.23a), by the addition of pyrazole to a water solution of \(\text{Cu(ETCOO)}_2\cdot\text{H}_2\text{O}\), and leaving the resulting solution to crystallize at 12 °C. A different compound \([\text{Cu}_3(\mu_3-\text{OH})(\mu-\text{pz})_3(\text{EtCOO})_2(\text{H}_2\text{O})]\) (Figure 1.23b), is produced when the reaction and crystallization are carried out at 18–22 °C. The presence of the lattice water molecule in the former compound leads to the formation of a very different assembly than in the latter compound. Propionate ions in both complexes are involved in intra- and intermolecular hydrogen bonding to generate complex supramolecular 2D MOFs. The obtained compounds reveal remarkable activity and selectivity as catalysts or catalyst precursors.
for liquid biphasic (MeCN/H₂O) peroxidative oxidation of cyclohexane and cyclopentane to the corresponding alcohols and ketones.

Figure 1.23: Chemical structure of [Cu₃(µ₃-OH)(µ-pz)₃(EtCOO)₂(H₂O)]·H₂O (a), and [Cu₃(µ₃-OH)(µ-pz)₃(EtCOO)₂(H₂O)] (b).

Due to the biological activity of the redox-active trinuclear copper clusters as the active centers of several copper proteins such as ascorbate oxidase, laccase, and ceruloplasmin, much effort has been made to synthesize, characterize and study the properties of trinuclear copper clusters.

Raptis and co-workers made significant progress in the synthesis, characterization and study of the structural, magnetic, electrochemical, and spectroscopic properties of trinuclear copper(II) pyrazolate complexes. The complexes prepared, including (PPN)[Cu₃(µ₃-OH)(µ-pz)₃Cl₃], (PPN)₂[Cu₃(µ₃-O)(µ-pz)₃Cl₃], (PPN/Bu₄N)₂[Cu₃(µ₃-Cl)₂(µ-pz)₃Cl₃] and (Et₃NH)[Cu₃(µ₃-OH)(µ-pz)₃Cl₃(pzH)] (Scheme 1.4) have been characterized crystallographically and showed for the first time, planar Cu(II)(µ₃-O) and the Cu(II)(µ₃-Cl)₂ motifs. Measurements of the magnetic susceptibility revealed that the three copper centers of (PPN)₂[Cu₃(µ₃-O)(µ-pz)₃Cl₃] show strong antiferromagnetic coupling with Jₐₕₐₜ = –500 cm⁻¹.

Scheme 1.4: Structure and transformation of the trinuclear Cu(II) complexes.
In another study, the same group have shown the effect of copper-substitution on the structure and nuclearity of Cu(II) pyrazolates. In this study, they showed that the replacement of the terminal chloride ligands of $[\text{Cu}_3(\mu_3-X)(\mu-pz)_3\text{Cl}_3]^{n-}$ ($X = O, \text{OH}; n = 1, 2$) or $[\text{Cu}_3(\mu_3-\text{Cl})(\mu-pz)_3\text{Cl}_3]^{2-}$ complexes for cyanate, acetate or bromide ligands maintains the integrity of the triangular species and $\text{PPN}[\text{Cu}_3(\mu_3-\text{OH})(\mu-pz)_3(\text{NCO})_3]$, $\text{PPN}[\text{Cu}_3(\mu_3-\text{OH})(\mu-pz)_3(\text{O}_2\text{CCH}_3)_3(\text{H}_2\text{O})]\cdot\text{H}_2\text{O}$, $\text{Bu}_4\text{N}[\text{Cu}_3(\mu_3-\text{OH})(\mu-pz)_3(\text{O}_2\text{CCH}_3)_3] \cdot 3\text{H}_2\text{O}$ and $(\text{Bu}_4\text{N})_2[\text{Cu}_3(\mu_3-\text{Br})(\mu-pz)_3\text{Br}_3]$ were obtained and characterized spectroscopically and crystallographically. In contrast, replacement of chloride with benzoate ligands resulted in tetranuclear and hexanuclear complexes $(\text{Bu}_4\text{N})_2[\text{Cu}_4(\mu_3-\text{OH})_2(\mu-4-X-pz)_2(\mu-\text{O}_2\text{CPh})_2(\mu-\text{O}_2\text{CPh})_4]$ ($X = \text{H, Cl, Br, NO}_2$) and $(\text{Bu}_4\text{N})_2[\text{Cu}_6(\mu_3-\text{OH})_3(\mu-4-\text{NO}_2-pz)_6(\mu-\text{O}_2\text{CPh})_3(\mu-\text{O}_2\text{CPh})_2(\text{H}_2\text{O})]\cdot(\text{CH}_2\text{Cl}_2)_{0.5}$. Removing all chloride ions in the absence of appropriate ligands leads to higher nuclearity metallacycles $[\text{Cu}(\mu-\text{OH})(\mu-pz)]_n$ ($n = 6, 8, 9, 12, 14$) (Scheme 1.5).

Scheme 1.5: Transformation of $[\text{Cu}_3(\mu_3-X)(\mu-pz)_3\text{Cl}_3]^{n-}$ to $[\text{Cu}_3(\mu_3-\text{OH})(\mu-pz)_3(\text{NCO})_3]^{-}$, $[\text{Cu}_3(\mu_3-\text{OH})(\mu-pz)_3(\text{O}_2\text{CCH}_3)_3(\text{H}_2\text{O})]^{-}$, $[\text{Cu}_4(\mu_3-\text{OH})_2(\mu-4-X-pz)_2(\mu-\text{O}_2\text{CPh})_2(\mu-\text{O}_2\text{CPh})_4]^{2-}$, $[\text{Cu}_6(\mu_3-\text{OH})(\mu-4-\text{NO}_2-pz)_6(\mu-\text{O}_2\text{CPh})_3(\mu-\text{O}_2\text{CPh})_2(\text{H}_2\text{O})]^{2-}$ and $[\text{Cu}(\mu-\text{OH})(\mu-pz)]_n$ upon replacement of chloride ligand with cyanate, acetate, benzoate, and without an appropriate ligand, respectively.
Trinuclear copper(II) pyrazolates have been applied as secondary building units (SBUs) to obtain multicomponent metal-organic frameworks (MOFs),\(^{53,54,55,56,57}\) in which different metal ions are organized into specific SBUs through one-pot synthesis.\(^{70}\)

Li and co-workers synthesized multicomponent MOFs by combining 4-pyrazolecarboxylic acid (H\(_2\)PyC) as the only organic ligand, with Zn(II) and Cu(II) ions (Figure 1.24).\(^{57}\) The obtained MOF (FDM-3; FDM = Fudan materials) has three geometrically and compositionally different SBUs: triangular, octahedral and square pyramidal. These SBUs are arranged in a cubic symmetry to form four different polyhedral cages (Figure 1.24).\(^{56}\) The metals in these SBUs have switchable redox states (Cu\(^{I}/Cu^{II}\)) while maintaining the SBUs geometry, as monitored by X-ray diffraction and X-ray photoelectron spectroscopy. Furthermore, the interchangeability of Cu(I) and Cu(II) in these MOFs was studied by their catalytic performances in the decomposition process of H\(_2\)O\(_2\).

In the anion-encapsulation field, Raptis, Mezei and co-workers have used copper(II) pyrazolate motifs to prepare neutral anion-incarcerating agents that consist of three or four stacked metallamacrocycles of the general formula \([\text{cis-Cu}^{II}(\mu_{3}-\text{OH})(\mu_{3}-\text{pz})]_n\) (n = 6, 8, 9, 12 and 14) (Figure 1.25).\(^{58}\) X-ray crystallographic study of the obtained compounds, (PPN)[Cl\(_n\)\(\{\text{Cu}^{II}(\mu_{3}-\text{OH})(\mu_{3}-\text{pz})\}\]_n (PPN) and (PPN)[Cl\(_n\)\(\{\text{Zn}^{II}(\mu_{3}-\text{OH})(\mu_{3}-\text{pz})\}\]_n, revealed the formation of neutral, polynuclear anion-incarcerating architectures.
OH)(µ-pz)\}_{6+12\}_{2}$ 10, (Bu4N)[Cl⊂{[Cu(µ-OH)(µ-pz)\}_{6+12\}_{2}}\, 11, (Bu4N)\, _{2}[CO3⊂{Cu(µ-OH)(µ-pz)\}_{6+12+9}]}\, 12 and (PPN)\, _{2}[SO4⊂{Cu(µ-OH)(µ-pz)\}_{8+14+9}]}\, 13 (Figure 1.26) showed encapsulated anions inside the cavity of the supramolecular host. The supramolecular host-guest architectures 10 and 13 were obtained serendipitously in an attempt to remove chlorides from the complex (PPN)[Cu3(µ3-O)(µ-pz)3Cl3] in a wet solvent. The transformation process of the triangular trinuclear complex into the polymeric cis-rings occurs through ring-opening, oligomerization and ring-closing of the Cu–pz backbone. A similar procedure using (Bu4N)[Cu3(µ3-O)(µ-pz)3Cl3] yielded 12, whereas 11 was prepared by the reaction of Cu(OH)$_2$ and pyrazole in the presence of Bu4NCl.

Figure 1.25: Metallamacroyclic rings [{cis-CuII(µ-OH)(µ-pz)}$_n$] (n = 6, 8, 9, 12 and 14)
The metallamacrocycles consist of distorted square-planar CuII-centers connected by µ-pyrazolate groupsthat provide hydrophobicity at the outer-surface of the rings, whereas µ-OH groups pointing to the center of the rings provide hydrophilicity for the cavity.

![Figure 1.26: Ball and stick diagram of the assemblies](image)

The pyrazolate and hydroxyl groups of the larger rings are either both in-plane with CuII-centers or out-of-pane; in the former case, the in-plane pyrazolates point their trans-OH groups (in-plane) to the center of the rings, while out-of-plane pyrazolates alternate in up and down orientation relative to the mean plane of the copper centers and pointing their respective trans-OH groups to the opposite sides. The larger rings act as hosts (O donors) for the smaller rings, which in turn adopt a conical shape where the hydroxyl groups are oriented toward the center and the pyrazolates are oriented in the opposite direction. Therefore, the hydroxyl groups and pyrazolates are appropriately oriented to provide better interaction between the larger (12–14 membered) and smaller (6–9 membered) rings via Cu····O interactions and H-bonding. In the case of 10 and 11, two [[Cu(µ-OH)(µ-pz)]_{6+12}] units sandwich a chloride anion by twelve H-bonds, six from each [[Cu(µ-OH)(µ-pz)]_{6+12}] unit, specifically from the 6 membered ring hydroxyl groups. The aggregate is further supported by an additional 12 H-bonds between the two 12-membered rings on each side of the sandwich (Scheme 1.6).
Scheme 1.6: Schematic diagram showing the assembly of \([\text{Cl} \subset ([\text{Cu}(\mu-\text{OH})(\mu-pz)]_{6+12})_2] \) in 10 and 11. Reprinted from reference 58. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

In the case of 12, the carbonate ion is encapsulated between the \([([\text{Cu}(\mu-\text{OH})(\mu-pz)]_{6+12}) \) unit and a 9-membered ring, in which all the carbonate oxygens are in H-bonding distance to all of the hydroxyl groups of the 9- and 6-membered rings. Additional H-bonding and \(\text{Cu} \cdots \text{O} \) interactions between rings provide robustness to the structure. The same pattern was observed in the case of 13, in which the rings are connected to each other by H-bonding and \(\text{Cu} \cdots \text{O} \) interactions and hold the sulfate ion by H-bonding from the 8- and 9-membered rings.

Later, Mezei and co-workers (our group) have prepared the anion-encapsulating agents “nanojars” directly from their original components by reacting \(\text{CuSO}_4\), pyrazole and KOH in 1:1:2 ratio, in the presence of \((\text{Bu}_4\text{N})_2\text{SO}_4\) to form \((\text{Bu}_4\text{N})_2\{\text{SO}_4 \subset ([\text{Cu}(\mu-\text{OH})(\mu-pz)]_{6+12+10})\) and \((\text{Bu}_4\text{N})_2\{\text{SO}_4 \subset ([\text{Cu}(\mu-\text{OH})(\mu-pz)]_{8+14+9})\) nanojars, which have been demonstrated crystallographically. The obtained nanojars revealed unprecedented binding strength toward sulfate anion. The binding strength was tested by the vigorous stirring of a DCM solution of nanojars with saturated aqueous \(\text{Ba(OH)}_2\) solution. After two weeks of stirring, no precipitation of \(\text{BaSO}_4\) was observed and the electronic spectrum of the blue nanojars solution remained unchanged. Furthermore, they have demonstrated the selectivity toward sulfate over nitrate and perchlorate even in the presence of large excess of nitrate and perchlorate in the reaction mixture.

In another study, one or two phosphate or arsenate ions were incarcerated within nanojars, capped nanojars and nanohelicages. The phosphate- and arsenate-incarcerating nanojars were obtained by the reaction of \(\text{Cu(OH)}_2\) with pyrazole, \(\text{Bu}_4\text{NOH}\) and \(\text{H}_3\text{PO}_4\) or \(\text{Na}_2\text{HAsO}_4\), respectively. Isolation of individual nanojars \((\text{Bu}_4\text{N})_2\{\text{HXO}_4^{2-} \subset ([\text{Cu}^{II}(\mu-\text{OH})(\mu-pz)]_{3+1})\) \((X = \text{P or} \)
As), capped nanojar \((\text{Bu}_4\text{N})[\text{PO}_4^{3-}\{\text{Cu}^{II}_{30}(\mu-\text{OH})_{27}(\mu-\text{OCH}_3)(\mu-\text{pz})_{30}(\text{CH}_3\text{OH})_2}\}]\) 15, and helicages \((\text{Bu}_4\text{N})_2[(\text{XO}_4^{3-})_2\{\text{Cu}^{II}_{15}(\mu-\text{OH})_2(\mu-\text{OH})_6(\mu-\text{pz})_{18}\}]\) (16, \(X=\text{P}\); 17, \(X=\text{As}\)) (Figure 1.27), were attained by the selective dissolution and crystallization of the reaction products from solvents of different polarities.

![Figure 1.27: Schematic assembly of the capped nanojar 15 from the Cu_{6+12+9} nanojar and a cyclic trinuclear unit (a), crystal structure of 15 (red: Cu_9 ring; violet: Cu_{12} ring; light-blue: Cu_6 ring; dark grey: trinuclear ring; light grey: methanol) (b), schematic assembly of helicage 16 from two cyclic and three linear trinuclear units (only two are shown for clarity) (c), and crystal structure of 16 and 17 (only the left-handed M, L/L enantiomers are shown) (d and e, respectively). Reproduced from reference 72 with permission from The Royal Society of Chemistry.](image)

The nanojars \((\text{Bu}_4\text{N})_2[\text{HPO}_4^{2-}\{\text{Cu}^{II}(\mu-\text{OH})(\mu-\text{pz})\}]_{31}\) and \((\text{Bu}_4\text{N})_2[\text{HAsO}_4^{2-}\{\text{Cu}^{II}(\mu-\text{OH})(\mu-\text{pz})\}]_{31}\) were obtained by diffusion of hexane vapors into toluene extracts of the product mixtures. The HXO_4^{2-} ions are incarcerated within the formed nanojars, which are comprised of
an 8+14+9-membered \([\text{Cu(OH)}(\text{pz})]_n\) ring combination \((n = 8, 9, 14)\), with pseudo-mirror symmetry. In both nanojars, the X–OH bonds point toward the 9-membered ring, while the other three O-atoms point toward the 8-membered ring. The \(\text{HXO}_4^{2–}\) anions are bound by a total of thirteen hydrogen bonds: four hydrogen bonds between each O-atoms of \(\text{HXO}_4^{2–}\) and the OH groups of the 9-membered ring, and one hydrogen bond between the X–OH and the OH groups of the 8-membered ring. The hydrogen atom of the \(\text{HXO}_4^{2–}\) anion is not involved in the hydrogen bonding, as no hydrogen bond acceptor is available within hydrogen bonding distance from the X–OH.

In addition, the capped nanojar, \((\text{Bu}_4\text{N})[\text{PO}_4^{3–}\subset\{\text{Cu}^{II}_{30}(\mu\text{-OH})_{27}(\mu_3\text{-OCH}_3)(\mu\text{-pz})_{30}(\text{CH}_3\text{OH})_2]\})\) was obtained when the solvent system used for crystal growing was changed to more polar methanol/\(n\)-butyl acetate. The fully deprotonated \(\text{PO}_4^{3–}\) ion was incarcerated within \(\text{Cu}_{6+12+9}\) nanojar with pseudo-three-fold symmetry, similar to the carbonate-nanojars found earlier,58 albeit with some modifications. The presence of an additional \(\text{Cu}_3(\mu_3\text{-OCH}_3)(\mu\text{-pz})_3\) trinuclear unit capping the 9-membered ring, which is found rotated at 180º relative to the 6+12 ring-combination found in \((\text{Bu}_4\text{N})_2[\text{CO}_3^{2–}\subset\{\text{Cu}(\mu\text{-OH})(\mu\text{-pz})\}_{27}]\) is the most significant difference. As the \(\text{Cu}_3(\mu_3\text{-OCH}_3)(\mu\text{-pz})_3\) trinuclear unit binds, three OH groups of the 9-membered ring are bent away from the 12-membered ring, creating two pockets that are occupied by two methanol solvent molecules. Within the nanojar, the incarcerated \(\text{PO}_4^{3–}\) ion is bound by a total of twelve hydrogen bonds: three hydrogen bonds from the 6-membered ring and nine from the 9-membered ring, as well as by weak Cu–O bonds (average 2.37(1) Å) formed between one of the four O-atoms of \(\text{PO}_4^{3–}\) and the three Cu-atoms of the trinuclear unit.

Furthermore, the unprecedented helicage structures, \((\text{Bu}_4\text{N})_2[(\text{PO}_4^{3–})_2\subset\{\text{Cu}^{II}_{15}(\mu_3\text{-OH})_2(\mu\text{-OH})_6(\mu\text{-pz})_{18}\}]\) and \((\text{Bu}_4\text{N})_2[(\text{AsO}_4^{3–})_2\subset\{\text{Cu}^{II}_{15}(\mu_3\text{-OH})_2(\mu\text{-OH})_6(\mu\text{-pz})_{18}\}]\) were obtained by the vapor diffusion of hexane to a bromobenzene/nitrobenzene (1:1) solution of the phosphate or arsenate containing products, respectively. These structures, comprised of three linear trinuclear \(\text{Cu}_3(\mu_3\text{-OH})(\mu\text{-pz})_4\) units bridging two cyclic trinuclear \(\text{Cu}_3(\mu_3\text{-OH})(\mu\text{-pz})_3\) units, incarcerate two unusually closely spaced, head-to-head \(\text{PO}_4^{3–}\) or \(\text{AsO}_4^{3–}\) ions. These anions are bound by three relatively short hydrogen bonds (average 2.672(8) Å in \(\text{16}\), 2.68(2) Å in \(\text{17}\)) and by three typical Cu–O bonds (average 1.945(5) Å in \(\text{16}\), 1.95(2) Å in \(\text{17}\)) to the linear trinuclear units, and by three weak Cu–O bonds to the cyclic trinuclear units (average 2.274(7) Å in \(\text{16}\), 2.25(2) Å in \(\text{17}\)). As a
result of binding PO$_4^{3-}$ or AsO$_4^{3-}$ ions, the pyrazolate moieties immediately coordinated to the Cu$_3$(μ$_3$-OH)(μ-$pz$)$_3$ units are tilted either in a clockwise ($\Delta$) or a counter-clockwise ($\Lambda$) fashion. When the two essentially parallel, cyclic trinuclear fragments are joined together, a twisted arrangement of the three bridging linear trinuclear units results, and nanoscale chirality appears. Within the racemic crystals of 16 and 17, the two axially chiral, $p$ ($\Delta\Lambda$) and M ($\Lambda\Lambda$) enantiomers are found segregated in alternating layers.

1.3 Synthesis methods of pyrazole derivatives

During the past few decades, pyrazole derivatives have attracted considerable attention, due to their diverse pharmaceutical applications$^{73}$ and agricultural use.$^{74}$ Pyrazole derivatives are commonly prepared by the two mostly applied pyrazole synthesis methods of Knorr$^{75}$ and Pechmann$^{76}$. In Knorr pyrazole synthesis, a $\beta$-ketoaldehyde or the corresponding acetal/ketal, prepared from ethyl or methyl formate and a ketone, is condensed with hydrazine to produce pyrazole derivatives (Scheme 1.7a).$^{73b,77}$ The Pechmann pyrazole synthesis consists of the 1,3-dipolar cycloaddition of diazomethane to alkynes (Scheme 1.7b).$^{78,79}$ 3-Diazoalkenes spontaneously undergo intramolecular 1,3-dipolar cycloaddition to yield 3(5)-alkylpyrazoles (Scheme 1.7c).$^{80}$ In addition, there are other common methods of synthesis of 3(5)-alkylpyrazoles, such as the conversion of a ketone to a $\beta$-(dimethylamino)vinyl ketone using $N,N$-dimethylformamide dimethyl acetal (Scheme 1.7d),$^{79}$ or by using acetylene (or its bis-trimethylsilyl derivative) and an acyl chloride to obtain a $\beta$-chlorovinyl ketone (Scheme 1.7e),$^{81}$ followed in both cases by reaction with hydrazine to afford 3(5)-alkylpyrazoles. 3(5)-Alkylpyrazoles can be obtained from aldehydes via $\alpha,\beta$-unsaturated tosylhydrazones (Scheme 1.7f).$^{82}$ 3(5)-Alkylpyrazoles can also be prepared via the reaction of hydrazine with iodo$^{83}$ or methoxyenynes$^{84}$ (Scheme 1.7g). Furthermore, oxidation of 2-pyrazolines, produced by the reaction of enones or enals with hydrazine,$^{79,85}$ afford the corresponding pyrazoles (Scheme 1.7h).$^{79,86}$
1.4 Objectives and goals

The long-term goal of this project is to develop selective anion-binding and extraction agents, capable of recognizing individual anions and of transferring them from aqueous media to an immiscible organic solvent (preferably long-chain aliphatic solvents). The short-term goal is to achieve selectivity among anions with comparable hydration energies, such as sulfate ($\text{SO}_4^{2-}$, $\Delta G_h^\circ = -1064 \text{ kJ/mol}$) and carbonate ($\text{CO}_3^{2-}$, $\Delta G_h^\circ = -1324 \text{ kJ/mol}$) and to extract one of these anions selectively in the presence of a large excess of the other anion, using nanojars as anion binding and extraction agents.

Scheme 1.7: Current procedures of synthesis of 3(5)-alkylpyrazoles.
The specific objectives are:

1) Synthesize and characterize various pyrazole ligands, including tethered multi-pyrazole ligands (with two, three and four connected pyrazole units). In particular, pyrazoles with aliphatic and oligo(ethylene glycol) chains are targeted, which are expected to further expand the solubility of nanojars, in aliphatic solvents (such as ISOPARTM, suitable for industrial scale extractions) and water, respectively.

2) Prepare and characterize nanojars using the synthesized pyrazole ligands. Characterization techniques include NMR and UV–vis spectroscopy, mass spectrometry, X-ray crystallography and thermogravimetric analysis.

3) Study the mechanism of formation of nanojars, using pH titration, UV–vis spectroscopy and mass spectrometry.

4) Study the extraction of sulfate (SO$_4^{2-}$) and carbonate (CO$_3^{2-}$) ions from aqueous media by nanojars, and develop a method for selective extraction of these anions.
CHAPTER 2

EXPERIMENTAL

2.1 General procedures and instrumentation

2.1.1 General procedures

Molecular sieves (3 Å) were dried by heating to 260 °C under a high vacuum for 12 hours. THF was dried using sodium and benzophenone and distilled under N₂ atmosphere. Ethanol was dried over 3 Å molecular sieves for 5 days and stored under N₂ atmosphere. Na₂CO₃ was dried at 250 °C for 7 days and was left to cool down in a vacuum desiccator over fresh Drierite. Ethyl acetate was dried over 3 Å molecular sieves for 5 days. All other reagents and solvents are commercially available and were used as received. Thin layer chromatography (TLC) was performed on Sigma–Aldrich silica gel plates and viewed under UV light (256 nm and/or 354 nm wavelengths) or an iodine bath. Column chromatography was performed using flash silica gel from Dynamic Adsorbents and VWR.

1-aminopyrazole, pyrazole-3(5)-carbaldehyde, pyrazole-4-carbaldehyde, 4-hydroxy-pyrazole, 3-hydroxy-pyrazole, 4-fluoropyrazole, 4-chloropyrazole, 4-bromopyrazole, 4-iodopyrazole, 4-nitropyrazole, 4-formylpyrazole, 3-formylpyrazole, pyrazole-4-sulfonic acid, 3,5-diethylpyrazole, 3,5-di-tert-butylpyrazole, 3,5-bis(trifluoromethyl)pyrazole, 3,5-diphenylpyrazole, 4-phenylpyrazole, 4-n-butylpyrazole, and 4-(3-hydroxypropyl)pyrazole were prepared according to published procedures.

Nanojars of the general formula [anion⊂{Cu(OH)(R-pz)}ₙ]²⁻, where anion = CO₃²⁻ or SO₄²⁻, R stands for various pyrazole (pz) substituents and n = 26 – 34, were prepared by Dr. Gellert Mezei. All of the X-ray crystallographic characterizations and studies were done by Dr. Gellert Mezei. Computational chemistry studies were done by Dr. Yirong Mo, Liangyu Guan, and Dr. Joel Karty, and by Dr. Yirong Mo and Huaiyu Zhang.
2.1.2 General instrumentation

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Jeol JNM-ECP400 instrument operating at 400 MHz at temperatures varying from –60 to +150 °C using deuterated solvents. Vacuum was measured with a McLeod gauge connected to a Schlenk line. Melting points were determined on a MEL-TEMP II (Laboratory Devices, USA) apparatus. UV–vis spectra were obtained on a Shimadzu UV-1650PC spectrophotometer. Mass spectra were recorded using a Waters Model Synapse G1 HDMS instrument using LC–MS grade solvents. X-ray diffraction data were collected on a Bruker SMART APEX II diffractometer using graphite-monochromated Mo-Kα ($\lambda = 0.71073$ Å) radiation at 100 K. pH was measured with a Mettler Toledo S20 SevenEasy pH-meter, calibrated with pH 4.01, 7.00, and 10.01 standard buffer solutions. Thermogravimetric analysis was performed on a TA Instrument Model Q500 analyzer.

2.2 Synthesis

2.2.1 Synthesis of starting materials and ligands

2.2.1.1 Synthesis of 3(5)-alkylpyrazoles

The synthetic procedures of 3(5)-alkylpyrazoles (Table 2.1) were originally published in *RSC Adv*. 2015, 5, 24081–24093, and are reproduced by permission of The Royal Society of Chemistry. [http://pubs.rsc.org/en/content/articlelanding/2015/ra/c5ra00837a#!divAbstract](http://pubs.rsc.org/en/content/articlelanding/2015/ra/c5ra00837a#!divAbstract).

2.2.1.1.1 Synthesis of 1-(tetrahydropyran-2-yl)pyrazole

A heavy-wall glass pressure flask was charged with pyrazole (50.0 g, 73.4 mmol) and 3,4-dihydro-2H-pyran (68.2 g, 81.1 mmol). The mixture was homogenized and then heated to 125 °C for 24 hours in an oven. After cooling to room temperature, the product was subjected to vacuum to remove traces of excess DHP. Pure THP-protected pyrazole (as indicated by $^1$H and $^{13}$C NMR) is obtained in quantitative yield (111 g) (Scheme 2.1). The product can be distilled at 64–65 °C (0.08 mmHg), if further purification is desired. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.60 (d, 1H, $^3$J = 2.2 Hz, 5-H-pz), 7.55 (s, 1H, 3-H-pz), 6.29 (m, 1H, 4-H-pz), 5.38 (dd, 1H, $^3$J = 9.9 Hz, $^3$J = 2.6 Hz, CH–THP), 4.02–4.07 (m, 1H, CH$_2$O–THP), 3.65–3.73 (m, 1H, CH$_2$O–THP), 1.97–2.19 (m, 3H, CH$_2$–THP), 1.55–1.76 (m, 3H, CH$_2$–THP) ppm. $^1$H NMR (400 MHz, DMSO- d$_6$): δ 7.86 (d, 1H, $^3$J = 2.2 Hz, 5-H-pz), 7.48 (s, 1H, 3-H-pz), 6.30 (s, 1H, 4-H-pz), 5.39 (dd, 1H, $^3$J = 9.9 Hz, $^3$J = 2.6 Hz, CH–THP), 3.88–3.95 (m, 1H, CH$_2$O–THP), 3.57–3.67 (m, 1H, CH$_2$O–THP), 2.03–2.14
(m, 1H, CH$_2$–THP), 1.85–1.97 (m, 2H, CH$_2$–THP), 1.58–1.72 (m, 1H, CH$_2$–THP), 1.48–1.58 (m, 2H, CH$_2$–THP) ppm. $^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$): δ 139.7, 127.6, 106.1, 87.6, 67.9, 30.6, 25.0, 22.6 ppm.

![Scheme 2.1: Green protection of pyrazole (DHP = 3,4-dihydo-2H-pyran).](image)

2.2.1.1.2 General procedure for the preparation of 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles

Method A: 1-(tetrahydropyran-2-yl)pyrazole (5.000 g, 32.85 mmol) is dissolved in anhydrous THF (50 mL) in a Schlenk flask under a dry N$_2$ atmosphere. The solution is chilled to −78 °C by stirring for 15 minutes in a dry-ice/isopropanol bath. nBuLi (1.6 M in hexane, 21 mL, 32.85 mmol) is added dropwise from an N$_2$-purged syringe. Stirring at −78 °C is continued for another 30 minutes, then the 1-iodo- or 1-bromoalkane (36.14 mmol; in the case of 1,6-diiodohexane: 10.95 mmol) is added dropwise over 20 minutes. After stirring at −78 °C for 3 hours, the solution is left to warm up to room temperature and is quenched with water (1 mL). The volatiles are removed on a Rotavap, 80 mL water is added to the residue and it is extracted with ethyl acetate (or diethyl ether) (3 × 80 mL), followed by washing with a 10% aqueous sodium thiosulfate solution (80 mL; only when 1-iodoalkane is used as starting material), brine (80 mL) and drying with anhydrous MgSO$_4$. After removing the volatiles on the Rotavap, the residual oil is heated to ~75 °C (only when alkyl is C$_1$–C$_6$) under high vacuum (~0.15 mmHg) to remove traces of the unreacted 1-(tetrahydropyran-2-yl)pyrazole and excess 1-haloalkane. Pure 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles (by $^1$H and $^{13}$C NMR) are thus obtained (Scheme 2.2). When alkyl is C$_1$–C$_4$, the products can be distilled in vacuum, if needed. When alkyl is C$_5$ and longer, distillation leads to isomerization and/or deprotection. In those cases, purification is accomplished by column chromatography (see example for C$_{16}$ below). 1,6-Bis(1-(tetrahydropyran-2-yl)pyrazol-5-yl)hexane is purified by recrystallization from ethyl acetate/hexane. The products are colorless oils (C$_1$–C$_9$) or colorless crystalline solids (C$_{10}$, C$_{12}$, C$_{16}$, 1,6-bis(1-(tetrahydropyran-2-
yl)pyrazol-5-yl)hexane). For conversion calculations, distinct proton signals in the $^1$H NMR spectrum are used: 3-$H$-pyrazole, 4-$H$-pyrazole or $CH$–THP signals for Method A, and $R$–$CH_2$–$X$ ($R$ = alkyl, $X$ = I or Br) signals for Method B.

Method B: same as method A, except that 1-(tetrahydropyran-2-yl)pyrazole is used in 10% excess instead of the iodoalkane.

Scheme 2.2: Synthesis of 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles ($R$ = primary alkyl group; $X$ = I or Br).

2.2.1.1.2.1 5-Methyl-1-(tetrahydropyran-2-yl)pyrazole

B.p. 71–72 °C (0.08 mmHg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.43 (d, 1H, $^3J = 1.3$ Hz, 3- $H$-pz), 6.03 (d, 1H, $^3J = 1.5$ Hz, 4-$H$-pz), 5.24 (dd, 1H, $^3J = 9.9$ Hz, $^3J = 2.6$ Hz, $CH$–THP), 4.00–4.05 (m, 1H, $CH_2$O–THP), 3.61–3.68 (m, 1H, $CH_2$O–THP), 2.42–2.52 (m, 1H, $CH_2$–THP), 2.34 (s, 3H, $CH_3$), 2.06–2.14 (m, 1H, $CH_2$–THP), 1.92–2.00 (m, 1H, $CH_2$–THP), 1.54–1.77 (m, 3H, $CH_2$–THP) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 139.1, 106.2, 84.5, 67.8, 29.4, 25.1, 22.9, 11.0 ppm. For 3- methyl-1-(tetrahydropyran-2-yl)pyrazole, only the 3-$H$-pz (7.47 ppm, d, 1H, $^3J = 2.2$ Hz) and 4-$H$-pz (6.06 ppm, d, 1H, $^3J = 2.2$ Hz) protons could be clearly distinguished from the corresponding protons of the 5-methyl isomer in the $^1$H NMR spectrum (400 MHz, CDCl$_3$) of the isomer mixture obtained after heating the pure 5-methyl isomer to 125 °C in a pressure tube. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd. for C$_9$H$_{14}$N$_2$NaO 189.1004; found 189.0998.

2.2.1.1.2.2 5-Ethyl-1-(tetrahydropyran-2-yl)pyrazole

B.p. 90–91 °C (0.12 mmHg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.45 (d, 1H, $^3J = 1.5$ Hz, 3- $H$-pz), 6.05 (d, 1H, $^3J = 1.5$ Hz, 4-$H$-pz), 5.24 (dd, 1H, $^3J = 9.9$ Hz, $^3J = 2.6$ Hz, $CH$–THP), 4.00–4.05 (m, 1H, $CH_2$O–THP), 3.60–3.66 (m, 1H, $CH_2$O–THP), 2.62–2.78 (m, 2H, $CH_2$CH$_3$), 2.44–2.54 (m, 1H, $CH_2$–THP), 2.07–2.13 (m, 1H, $CH_2$–THP), 1.91–1.98 (m, 1H, $CH_2$–THP), 1.54–1.77 ppm.
(m, 3H, CH₂–THP), 1.27 (t, 3H, 3J = 7.5 Hz, CH₂CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 145.4, 139.1, 104.3, 84.3, 67.8, 29.5, 25.1, 23.0, 18.6, 12.8 ppm. HRMS (ESI-TOF) m/z: [M + Na]⁺ calcd. for C₁₀H₁₆N₂NaO 203.1160; found 203.1158.

2.2.1.1.2.3 5-n-Propyl-1-(tetrahydropyran-2-yl)pyrazole

B.p. 95–96 °C (0.20 mmHg). ¹H NMR (400 MHz, CDCl₃): δ 7.45 (d, 1H, 3J = 1.8 Hz, 3-H-pz), 6.04 (d, 1H, 3J = 1.6 Hz, 4-H-pz), 5.24 (dd, 1H, 3J = 9.9 Hz, 3J = 2.6 Hz, CH–THP), 4.00–4.06 (m, 1H, CH₂O–THP), 3.60–3.67 (m, 1H, CH₂O–THP), 2.56–2.71 (m, 2H, CH₂CH₂CH₃), 2.44–2.55 (m, 1H, CH₂–THP), 2.07–2.14 (m, 1H, CH₂–THP), 1.90–1.97 (m, 1H, CH₂–THP), 1.54–1.77 (m, 5H, CH₂–THP and CH₂CH₂CH₃), 1.00 (t, 3H, 3J = 7.3 Hz, (CH₂)₂CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 143.8, 139.1, 105.0, 84.2, 67.8, 29.6, 27.3, 25.1, 23.0, 22.0, 14.0 ppm. HRMS (ESI-TOF) m/z: [M + Na]⁺ calcd. for C₁₁H₁₈N₂NaO 217.1317; found 217.1298.

2.2.1.1.2.4 5-n-Butyl-1-(tetrahydropyran-2-yl)pyrazole

B.p. 99–100 °C (0.10 mmHg). ¹H NMR (400 MHz, CDCl₃): δ 7.45 (d, 1H, 3J = 1.4 Hz, 3-H-pz), 6.04 (d, 1H, 3J = 1.8 Hz, 4-H-pz), 5.24 (dd, 1H, 3J = 9.9 Hz, 3J = 2.6 Hz, CH–THP), 4.00–4.06 (m, 1H, CH₂O–THP), 3.60–3.67 (m, 1H, CH₂O–THP), 2.59–2.72 (m, 2H, CH₂(CH₂)₂CH₃), 2.44–2.55 (m, 1H, CH₂–THP), 2.07–2.14 (m, 1H, CH₂–THP), 1.90–1.97 (m, 1H, CH₂–THP), 1.54–1.77 (m, 5H, CH₂–THP and CH₂CH₂CH₂CH₃), 1.41 (m, 2H, (CH₂)₂CH₂CH₃), 0.94 (t, 3H, 3J = 7.3 Hz, (CH₂)₃CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 144.0, 139.1, 104.9, 84.2, 67.8, 30.8, 29.6, 25.1, 25.0, 23.0, 22.5, 13.9 ppm. HRMS (ESI-TOF) m/z: [M + Na]⁺ calcd. for C₁₂H₂₀N₂NaO 231.1473; found 231.1474.

2.2.1.1.2.5 5-n-Pentyl-1-(tetrahydropyran-2-yl)pyrazole

B.p. 104–106 °C (0.10 mmHg) (isomerization occurs). Before distillation (after heating to 75 °C in vacuum, no isomerization): ¹H NMR (400 MHz, CDCl₃): δ 7.45 (d, 1H, 3J = 1.5 Hz, 3-H-pz), 6.04 (d, 1H, 3J = 0.7 Hz, 4-H-pz), 5.24 (dd, 1H, 3J = 9.9 Hz, 3J = 2.6 Hz, CH–THP), 4.00–4.06 (m, 1H, CH₂O–THP), 3.59–3.67 (m, 1H, CH₂O–THP), 2.58–2.72 (m, 2H, CH₂(CH₂)₃CH₃), 2.44–2.55 (m, 1H, CH₂–THP), 2.06–2.14 (m, 1H, CH₂–THP), 1.90–1.97 (m, 1H, CH₂–THP), 1.54–1.78 (m, 5H, CH₂–THP and CH₂CH₂ (CH₂)₂CH₃), 1.31–1.41 (m, 4H, (CH₂)₂(CH₂)₂CH₃), 0.90 (t, 3H, 3J = 6.8 Hz, (CH₂)₄CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 144.1, 139.1, 104.9, 84.2, 67.9, 31.6, 29.6, 28.3, 25.3, 25.1, 23.0, 22.5, 14.1 ppm. For 3-n-pentyl-1-(tetrahydropyran-
2-yl)pyrazole, only the 3-H-pz (7.48 ppm, d, 1H, $^3J = 2.2$ Hz), 4-H-pz (6.08 ppm, d, 1H, $^3J = 2.6$ Hz) and CH–THP (5.30 ppm, dd, 1H, $^3J = 9.9$ Hz, $^3J = 2.6$ Hz) protons could be clearly distinguished from the corresponding protons of the 5-n-pentyl isomer in the $^1$H NMR spectrum (400 MHz, CDCl$_3$) of the isomer mixture obtained after distillation. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd. for C$_{13}$H$_{22}$N$_2$NaO 245.1630; found 245.1637.

2.2.1.1.2.6 5-i-Pentyl-1-(tetrahydropyran-2-yl)pyrazole

B.p. 78–79 °C (~0.005 mmHg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.45 (d, 1H, $^3J = 1.5$ Hz, 3-H-pz), 6.03 (d, 1H, $^3J = 0.7$ Hz, 4-H-pz), 5.24 (dd, 1H, $^3J = 10.2$ Hz, $^3J = 2.6$ Hz, CH–THP), 4.03 (m, 1H, CH$_2$O–THP), 3.63 (m, 1H, CH$_2$O–THP), 2.58–2.72 (m, 2H, CH$_2$CH$_2$CH(CH$_3$)$_2$), 2.50 (m, 1H, CH$_2$–THP), 2.11 (m, 1H, CH$_2$–THP), 1.94 (m, 1H, CH$_2$–THP), 1.47–1.78 (m, 6H, CH$_2$–THP and CH$_2$CH$_2$CH(CH$_3$)$_2$), 0.94 (d, 6H, $^3J = 6.6$ Hz, (CH$_2$)$_2$CH(C$_3$)$_2$) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 144.2, 139.2, 104.8, 84.2, 67.9, 37.7, 29.6, 27.8, 25.1, 23.2, 23.0, 22.5 ppm. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd. for C$_{13}$H$_{22}$N$_2$NaO 245.1609.

2.2.1.1.2.7 5-n-Hexyl-1-(tetrahydropyran-2-yl)pyrazole

B.p. 121–123 °C (0.20 mmHg) (isomerization occurs). Before distillation: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.45 (d, 1H, $^3J = 1.3$ Hz, 3-H-pz), 6.04 (d, 1H, $^3J = 1.5$ Hz, 4-H-pz), 5.24 (dd, 1H, $^3J = 9.9$ Hz, $^3J = 2.6$ Hz, CH–THP), 4.00–4.06 (m, 1H, CH$_2$O–THP), 3.59–3.67 (m, 1H, CH$_2$O–THP), 2.58–2.72 (m, 2H, CH$_2$(CH$_2$)$_2$CH$_3$), 2.44–2.55 (m, 1H, CH$_2$–THP), 2.06–2.14 (m, 1H, CH$_2$–THP), 1.90–1.97 (m, 1H, CH$_2$–THP), 1.54–1.78 (m, 5H, CH$_2$–THP and CH$_2$CH$_2$CH(CH$_3$)$_2$CH$_3$), 1.26–1.42 (m, 6H, (CH$_2$)$_2$(CH$_2$)$_2$CH$_3$), 0.89 (t, 3H, $^3J = 7.2$ Hz, (CH$_2$)$_2$CH$_3$) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 144.1, 139.2, 104.9, 84.2, 67.9, 31.7, 29.6, 29.1, 28.6, 25.3, 25.1, 23.0, 22.7, 14.2 ppm. For the 3-n-hexyl-1-(tetrahydropyran-2-yl)- pyrazole, only the 3-H-pz (7.48 ppm, d, 1H, $^3J = 2.2$ Hz), 4-H-pz (6.08 ppm, d, 1H, $^3J = 2.6$ Hz) protons could be clearly distinguished from the corresponding protons of the 5-n-hexyl isomer in the $^1$H NMR spectrum (400 MHz, CDCl$_3$) of the isomer mixture obtained after distillation. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd. for C$_{14}$H$_{24}$N$_2$NaO 259.1786; found 259.1786.

2.2.1.1.2.8 5-n-Heptyl-1-(tetrahydropyran-2-yl)pyrazole

B.p. 128–130 °C (0.15 mmHg) (isomerization occurs). Before distillation: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.45 (d, 1H, $^3J = 1.5$ Hz, 3-H-pz), 6.04 (d, 1H, $^3J = 1.5$ Hz, 4-H-pz), 5.24 (dd, 1H, $^3J = 2.6$ Hz) and 5-n-heptyl-1-(tetrahydropyran-2-yl)-pyrazole, only the 3-H-pz (7.48 ppm, d, 1H, $^3J = 2.2$ Hz), 4-H-pz (6.08 ppm, d, 1H, $^3J = 2.6$ Hz) protons could be clearly distinguished from the corresponding protons of the 5-n-heptyl isomer in the $^1$H NMR spectrum (400 MHz, CDCl$_3$) of the isomer mixture obtained after distillation. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd. for C$_{14}$H$_{24}$N$_2$NaO 259.1786; found 259.1786.
$^{3}J = 9.9 \text{ Hz, } ^{3}J = 2.6 \text{ Hz, } CH-\text{THP}$, 4.03 (m, 1H, CH$_{2}$O–THP), 3.63 (m, 1H, CH$_{2}$O–THP), 2.58–2.72 (m, 2H, CH$_{2}$(CH$_{2}$)$_{3}$CH$_{3}$), 2.44–2.55 (m, 1H, CH$_{2}$–THP), 2.06–2.14 (m, 1H, CH$_{2}$–THP), 1.90–1.97 (m, 1H, CH$_{2}$–THP), 1.54–1.78 (m, 5H, CH$_{2}$–THP and CH$_{2}$CH$_{2}$(CH$_{2}$)$_{4}$CH$_{3}$), 1.23–1.43 (m, 8H, (CH$_{2}$)$_{2}$(CH$_{2}$)$_{3}$CH$_{3}$), 0.88 (t, 3H, $^{3}J = 6.8 \text{ Hz, (CH$_{2}$)$_{6}$CH$_{3}$}$ ppm. $^{13}$C NMR (101 MHz, CDCl$_{3}$): $\delta$ 144.1, 139.1, 104.9, 84.2, 67.8, 31.8, 29.6, 29.4, 29.1, 28.7, 25.3, 25.1, 23.0, 22.7, 14.2 ppm. HRMS (ESI-TOF) $m/z$: [M + Na]$^{+}$ calcd. for C$_{15}$H$_{26}$N$_{2}$NaO 273.1943; found 273.1924.

2.2.1.1.2.9 5-n-Octyl-1-(tetrahydropyran-2-yl)pyrazole

$^{1}$H NMR (400 MHz, CDCl$_{3}$): δ 7.45 (d, 1H, $^{3}J = 1.8 \text{ Hz, 3-H-pz}$), 6.04 (d, 1H, $^{3}J = 1.7 \text{ Hz, 4-H-pz}$), 5.24 (dd, 1H, $^{3}J = 9.9 \text{ Hz, } ^{3}J = 2.6 \text{ Hz, CH-THP}$), 4.03 (m, 1H, CH$_{2}$O–THP), 3.63 (m, 1H, CH$_{2}$O –THP), 2.65 (m, 2H, CH$_{2}$(CH$_{2}$)$_{6}$CH$_{3}$), 2.50 (m, 1H, CH$_{2}$–THP), 2.11 (m, 1H, CH$_{2}$–THP), 1.93 (m, 1H, CH$_{2}$–THP), 1.54–1.78 (m, 5H, CH$_{2}$–THP and CH$_{2}$CH$_{2}$(CH$_{2}$)$_{4}$CH$_{3}$), 1.23–1.43 (m, 10H, (CH$_{2}$)$_{2}$(CH$_{2}$)$_{6}$CH$_{3}$), 0.87 (t, 3H, $^{3}J = 6.8 \text{ Hz, (CH$_{2}$)$_{7}$CH$_{3}$}$ ppm. $^{13}$C NMR (101 MHz, CDCl$_{3}$): $\delta$ 144.1, 139.2, 104.9, 84.2, 67.9, 31.9, 29.6, 29.4 (two overlapping peaks), 29.3, 28.7, 25.3, 25.1, 23.0, 22.8, 14.2 ppm. HRMS (ESI-TOF) $m/z$: [M + Na]$^{+}$ calcd. for C$_{16}$H$_{28}$N$_{2}$NaO 287.2099; found 287.2084.

2.2.1.1.2.10 5-n-Nonyl-1-(tetrahydropyran-2-yl)pyrazole

$^{1}$H NMR (400 MHz, CDCl$_{3}$): δ 7.45 (d, 1H, $^{3}J = 1.5 \text{ Hz, 3-H-pz}$), 6.04 (d, 1H, $^{3}J = 1.8 \text{ Hz, 4-H-pz}$), 5.24 (dd, 1H, $^{3}J = 9.9 \text{ Hz, } ^{3}J = 2.6 \text{ Hz, CH-THP}$), 4.03 (m, 1H, CH$_{2}$O–THP), 3.63 (m, 1H, CH$_{2}$O –THP), 2.65 (m, 2H, CH$_{2}$(CH$_{2}$)$_{6}$CH$_{3}$), 2.50 (m, 1H, CH$_{2}$–THP), 2.11 (m, 1H, CH$_{2}$–THP), 1.93 (m, 1H, CH$_{2}$–THP), 1.54–1.78 (m, 5H, CH$_{2}$–THP and CH$_{2}$CH$_{2}$(CH$_{2}$)$_{6}$CH$_{3}$), 1.20–1.42 (m, 12H, (CH$_{2}$)$_{2}$(CH$_{2}$)$_{6}$CH$_{3}$), 0.87 (t, 3H, $^{3}J = 6.8 \text{ Hz, (CH$_{2}$)$_{8}$CH$_{3}$}$ ppm. $^{13}$C NMR (101 MHz, CDCl$_{3}$): $\delta$ 144.1, 139.2, 104.9, 84.2, 67.9, 32.0, 29.8, 29.6, 29.47, 29.43, 29.39, 28.7, 25.3, 25.1, 23.0, 22.8, 14.2 ppm. HRMS (ESI-TOF) $m/z$: [M + Na]$^{+}$ calcd. for C$_{17}$H$_{30}$N$_{2}$NaO 301.2256; found 301.2247.

2.2.1.1.2.11 5-n-Decyl-1-(tetrahydropyran-2-yl)pyrazole

$^{1}$H NMR (400 MHz, CDCl$_{3}$): δ 7.45 (d, 1H, $^{3}J = 1.8 \text{ Hz, 3-H-pz}$), 6.04 (d, 1H, $^{3}J = 1.5 \text{ Hz, 4-H-pz}$), 5.24 (dd, 1H, $^{3}J = 9.9 \text{ Hz, } ^{3}J = 2.6 \text{ Hz, CH-THP}$), 4.03 (m, 1H, CH$_{2}$O–THP), 3.63 (m, 1H, CH$_{2}$O –THP), 2.65 (m, 2H, CH$_{2}$(CH$_{2}$)$_{8}$CH$_{3}$), 2.50 (m, 1H, CH$_{2}$–THP), 2.11 (m, 1H, CH$_{2}$–THP), 1.93 (m, 1H, CH$_{2}$–THP), 1.54–1.78 (m, 5H, CH$_{2}$–THP and CH$_{2}$CH$_{2}$(CH$_{2}$)$_{7}$CH$_{3}$), 1.23–1.43
(m, 14H, (CH$_2$)$_2$(CH$_2$)$_7$CH$_3$), 0.87 (t, 3H, $^3$J = 6.8 Hz, (CH$_2$)$_9$CH$_3$) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ 144.1, 139.2, 104.9, 84.2, 67.9, 32.0, 29.68, 29.63, 29.59, 29.47, 29.43 (two overlapping peaks), 28.7, 25.3, 25.1, 23.0, 22.8, 14.2 ppm. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd. for C$_{18}$H$_{32}$N$_2$NaO 315.2412; found 315.2412.

2.2.1.1.2.12 5-n-Dodecyl-1-(tetrahydropyran-2-yl)pyrazole

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.45 (s, 1H, 3-H-pz), 6.04 (s, 1H, 4-H-pz), 5.24 (dd, 1H, $^3$J = 9.9 Hz, $^3$J = 2.6 Hz, CH–THP), 4.03 (m, 1H, CH$_2$O–THP), 3.63 (m, 1H, CH$_2$O–THP), 2.65 (m, 2H, CH$_2$(CH$_2$)$_{10}$CH$_3$), 2.50 (m, 1H, CH$_2$–THP), 2.10 (m, 1H, CH$_2$–THP), 1.93 (m, 1H, CH$_2$–THP), 1.54–1.78 (m, 5H, CH$_2$–THP and CH$_2$CH$_2$(CH$_2$)$_9$CH$_3$), 1.23–1.43 (m, 18H, (CH$_2$)$_9$CH$_3$), 0.87 (t, 3H, $^3$J = 6.6 Hz, (CH$_2$)$_{11}$CH$_3$) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ 144.1, 139.2, 104.9, 84.2, 67.9, 32.0, 29.4–29.8 (nine overlapping peaks), 28.7, 25.3, 25.1, 23.0, 22.8, 14.2 ppm. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd. for C$_{20}$H$_{36}$N$_2$NaO 343.2725; found 343.2724.

2.2.1.1.2.13 5-n-Hexadecyl-1-(tetrahydropyran-2-yl)pyrazole

M.p. 54 °C. Purification of the 5-alkyl isomer was carried out by column chromatography. 15.5 g of crude material was loaded onto 800 g silica gel (Dynamic Adsorbents, 32–63 m; stationary phase width/height: ~9.5 × 26 cm) and was eluted with ~6 L hexane/ethyl acetate (6:1). 3.8 g 1-iodohexadecane was recovered as the first fraction, followed by 1.1 g of a mixture of 1-iodohexadecane and 1-(tetrahydropyran-2-yl)pyrazole, and finally by 9.4 g pure 5-n-hexadecyl-1-(tetrahydropyran-2-yl)- pyrazole. R$_f$ = 0.25 (TLC). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.45 (d, 1H, $^3$J = 0.8 Hz, 3-H-pz), 6.04 (d, 1H, $^3$J = 0.8 Hz, 4-H-pz), 5.24 (dd, 1H, $^3$J = 10.1 Hz, $^3$J = 2.4 Hz, CH–THP), 4.00–4.06 (m, 1H, CH$_2$O–THP), 3.59–3.67 (m, 1H, CH$_2$O–THP), 2.58–2.72 (m, 2H, CH$_2$(CH$_2$)$_{14}$CH$_3$), 2.44–2.55 (m, 1H, CH$_2$–THP), 2.07–2.14 (m, 1H, CH$_2$–THP), 1.90–1.97 (m, 1H, CH$_2$–THP), 1.54–1.78 (m, 5H, CH$_2$–THP and CH$_2$CH$_2$(CH$_2$)$_{13}$CH$_3$), 1.18–1.42 (m, 26H, (CH$_2$)$_2$(CH$_2$)$_{13}$CH$_3$), 0.87 (t, 3H, $^3$J = 6.8 Hz, (CH$_2$)$_{15}$CH$_3$) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ 144.1, 139.1, 104.9, 84.2, 67.9, 32.0, 29.8 (seven overlapping peaks), 29.64, 29.59, 29.47 (two overlapping peaks), 29.43, 28.7, 25.3, 25.1, 23.0, 22.8, 14.2 ppm. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd. for C$_{24}$H$_{46}$N$_2$NaO 399.3351; found 399.3350.
2.2.1.1.14 1,6-Bis(1-(tetrahydropyran-2-yl)pyrazol-5-yl)hexane

M.p. 70–71 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)):\(^\delta\) 7.45 (d, 2H, \(^3\)J = 1.4 Hz, 3-H-pz), 6.03 (d, 2H, \(^3\)J = 1.4 Hz, 4-H-pz), 5.23 (dd, 2H, \(^3\)J = 9.9 Hz, \(^3\)J = 2.6 Hz, CH–THP), 3.99–4.05 (m, 2H, CH\(_2\)O–THP), 3.58–3.66 (m, 2H, CH\(_2\)O–THP), 2.59–2.73 (m, 4H, CH\(_2\)(CH\(_2\))\(_4\)CH\(_2\)), 2.44–2.55 (m, 2H, CH\(_2\)–THP), 2.06–2.14 (m, 2H, CH\(_2\)–THP), 1.90–1.97 (m, 2H, CH\(_2\)–THP), 1.54–1.77 (m, 10H, CH\(_2\)–THP and CH\(_2\)CH\(_2\)(CH\(_2\))\(_2\)CH\(_2\)CH\(_2\)), 1.38–1.47 (m, 4H, (CH\(_2\))\(_2\)(CH\(_2\))\(_2\)(CH\(_2\))\(_2\)) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)):\(^\delta\) 143.8, 139.1, 104.9, 84.2, 67.8, 29.6, 29.1, 28.5, 25.2, 25.1, 23.0 ppm. HRMS (ESI-TOF) \(^m/\zeta\): [M + Na]\(^+\) calcd. for C\(_{22}\)H\(_{34}\)N\(_4\)NaO\(_2\) 409.2579; found 409.2579.

2.2.1.1.3 General procedure for the deprotection of 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles

5-Alkyl-1-(tetrahydropyran-2-yl)pyrazole (20 mmol) is dissolved in ethanol (200 mL) and conc. HCl (10 mL) is added dropwise under stirring. After stirring at room temperature for 8 hours, complete deprotection is indicated by the absence of 5-alkyl-1-(tetrahydropyran-2-yl)pyrazole signals in the \(^1\)H NMR spectrum of the reaction mixture. The volatiles are removed on a Rotavap at 35 °C and the residual aqueous solution is neutralized with NaHCO\(_3\) to pH ~8, followed by extraction with diethyl ether (3 × 100 mL) and drying of the combined organic layers with anhydrous MgSO\(_4\). After removing the solvent and drying under high vacuum, pure 5-alkylpyrazoles (by \(^1\)H and \(^{13}\)C NMR) are obtained (Scheme 2.3), that can be further purified by vacuum distillation or recrystallization (solid products). In the case of 1,6-bis(1-(tetrahydropyran-2-yl)pyrazol-5-yl)hexane, neutralization with NaHCO\(_3\) provides a white precipitate, which is filtered, washed with brine, dried, dissolved in hot nitrobenzene, filtered, and, after removal of the solvent, dried at 100 °C under high vacuum. The products are colorless oils, with the exception of the C\(_{16}\) derivative and 1,6-bis(pyrazol-5-yl)hexane, which are colorless crystalline solids.

\[
\begin{array}{ccc}
\text{N} & \text{N} & \text{R} \\
\text{O} & & \\
\end{array}
\]

\[
\begin{array}{cccc}
\text{R} & \text{N} & \text{N} & \text{R} \\
\text{aq. HCl} & & & 100\% \\
\end{array}
\]

Scheme 2.3: Synthesis of 3(5)-alkylpyrazoles via deprotonation of 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles.
2.2.1.1.3.1 3(5)-Methylpyrazole

B.p. 58–59 ºC (0.16 mmHg). ¹H NMR (400 MHz, CDCl₃): δ 7.48 (d, 1H, ³J = 1.8 Hz, 3-H-pz), 6.07 (s, 1H, ³J = 1.5 Hz, 4-H-pz), 2.34 (s, 3H, CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 143.2, 135.1, 104.5, 12.0 ppm.

2.2.1.1.3.2 3(5)-Ethylpyrazole

B.p. 74–75 ºC (0.70 mmHg). ¹H NMR (400 MHz, CDCl₃): δ 7.50 (s, 1H, 3-H-pz), 6.09 (s, 1H, 4-H-pz), 2.72 (q, 2H, ³J = 7.7 Hz, CH₂CH₃), 1.28 (t, 3H, ³J = 7.7 Hz, CH₂CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 149.4, 135.1, 103.0, 20.1, 13.7 ppm.

2.2.1.1.3.3 3(5)-n-Propylpyrazole

B.p. 72–73 ºC (0.12 mmHg). ¹H NMR (400 MHz, CDCl₃): δ 7.49 (d, 1H, ³J = 2.2 Hz, 3-H-pz), 6.08 (d, 1H, ³J = 1.8 Hz, 4-H-pz), 2.65 (t, 2H, ³J = 7.5 Hz, CH₂CH₂CH₃), 1.68 (m, 2H, CH₂CH₂CH₂CH₃), 0.97 (t, 3H, ³J = 7.3 Hz, (CH₂)₂CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 147.7, 135.2, 103.6, 28.8, 22.8, 13.9 ppm.

2.2.1.1.3.4 3(5)-n-Butylpyrazole

B.p. 84–85 ºC (0.10 mmHg). ¹H NMR (400 MHz, CDCl₃): δ 7.48 (d, 1H, ³J = 1.7 Hz, 3-H-pz), 6.08 (d, 1H, ³J = 1.6 Hz, 4-H-pz), 2.67 (t, 2H, ³J = 7.9 Hz, CH₂(CH₂)₂CH₃), 1.64 (m, 2H, CH₂CH₂CH₂CH₃), 1.38 (m, 2H, (CH₂)₂CH₂CH₃), 0.93 (t, 3H, ³J = 7.5 Hz, (CH₂)₃CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 147.8, 135.2, 103.4, 31.7, 26.5, 22.5, 13.9 ppm.

2.2.1.1.3.5 3(5)-n-Pentylpyrazole

B.p. 98–99 ºC (0.11 mmHg). ¹H NMR (400 MHz, CDCl₃): δ 7.49 (d, 1H, ³J = 1.2 Hz, 3-H-pz), 6.08 (d, 1H, ³J = 2.2 Hz, 4-H-pz), 2.66 (t, 2H, ³J = 7.7 Hz, CH₂(CH₂)₂CH₃), 1.65 (m, 2H, CH₂CH₂(CH₂)₂CH₃), 1.29–1.38 (m, 4H, (CH₂)₂(CH₂)₂CH₃), 0.88 (m, 3H, (CH₂)₃CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 148.2, 135.3, 103.5, 31.6, 29.2, 26.8, 22.5, 14.1 ppm.

2.2.1.1.3.6 3(5)-i-Pentylpyrazole

B.p. 66 ºC (~0.005 mmHg). ¹H NMR (400 MHz, CDCl₃): δ 7.49 (d, 1H, ³J = 1.8 Hz, 3-H-pz), 6.08 (d, 1H, ³J = 1.8 Hz, 4-H-pz), 2.68 (t, 2H, ³J = 7.9 Hz, CH₂CH₂CH(CH₃)₂), 1.52–1.66 (m, 3H, CH₂CH₂CH(CH₃)₂), 0.92 (d, 6H, ³J = 6.6 Hz, (CH₂)₂CH(CH₃)₂) ppm. ¹³C NMR (101 MHz,
CDCl3): δ 148.2, 135.2, 103.4, 38.5, 27.8, 24.7, 22.5 ppm. HRMS (ESI-TOF) m/z: [M − H]− calcd. for C₈H₁₃N₂ 137.1079; found 137.1084.

2.2.1.1.3.7 3(5)-n-Hexylpyrazole

B.p. 126–127 ºC (0.20 mmHg). ¹H NMR (400 MHz, CDCl₃): δ 7.48 (d, 1H, 3 J = 1.5 Hz, 3-H-pz), 6.08 (d, 1H, 3 J = 1.5 Hz, 4-H-pz), 2.66 (t, 2H, 3 J = 7.9 Hz, CH₂(CH₂)₄CH₃), 1.65 (m, 2H, CH₂CH₂(CH₂)₃CH₃), 1.26–1.40 (m, 6H, (CH₂)₂(CH₂)₃CH₃), 0.88 (t, 3H, 3 J = 1.5 7.0 Hz, (CH₂)₅CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 148.1, 135.5, 103.5, 31.7, 29.5, 29.1, 26.8, 22.7, 14.2 ppm.

2.2.1.1.3.8 3(5)-n-Heptylpyrazole

B.p. 112–119 ºC (0.10 mmHg). ¹H NMR (400 MHz, CDCl₃): δ 7.48 (d, 1H, 3 J = 1.8 Hz, 3-H-pz), 6.08 (d, 1H, 3 J = 1.8 Hz, 4-H-pz), 2.66 (t, 2H, 3 J = 7.7 Hz, CH₂(CH₂)₅CH₃), 1.65 (m, 2H, CH₂CH₂(CH₂)₄CH₃), 1.20–1.39 (m, 8H, (CH₂)₃(CH₂)₄CH₃), 0.87 (t, 3H, 3 J = 7.0 Hz, (CH₂)₆CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 148.0, 135.6, 103.4, 31.9, 29.5, 29.4, 26.8, 22.7, 14.2 ppm.

2.2.1.1.3.9 3(5)-n-Octylpyrazole

B.p. 126–128 ºC (0.15 mmHg). ¹H NMR (400 MHz, CDCl₃): δ 7.48 (d, 1H, 3 J = 2.0 Hz, 3-H-pz), 6.08 (d, 1H, 3 J = 2.0 Hz, 4-H-pz), 2.66 (t, 2H, 3 J = 7.7 Hz, CH₂(CH₂)₆CH₃), 1.64 (m, 2H, CH₂CH₂(CH₂)₅CH₃), 1.20–1.40 (m, 10H, CH₂CH₂(CH₂)₅CH₃), 0.87 (t, 3H, 3 J = 7.0 Hz, (CH₂)₇CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 148.0, 135.3, 103.4, 32.0, 29.54, 29.47, 29.43, 29.3, 26.8, 22.8, 14.2 ppm.

2.2.1.1.3.10 3(5)-n-Nonylpyrazole

B.p. 140–142 ºC (0.07 mmHg). ¹H NMR (400 MHz, CDCl₃): δ 7.48 (d, 1H, 3 J = 1.8 Hz, 3-H-pz), 6.08 (d, 1H, 3 J = 1.8 Hz, 4-H-pz), 2.66 (t, 2H, 3 J = 7.9 Hz, CH₂(CH₂)₇CH₃), 1.65 (m, 2H, CH₂CH₂(CH₂)₆CH₃), 1.20–1.40 (m, 12H, CH₂CH₂(CH₂)₆CH₃), 0.87 (t, 3H, 3 J = 7.0 Hz, (CH₂)₈CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 148.1, 135.3, 103.4, 32.0, 29.6, 29.53, 29.50, 29.42, 29.40, 26.8, 22.8, 14.2 ppm.
2.2.1.1.3.11 3(5)-n-Decylpyrazole
B.p. 131 °C (~0.005 mmHg). 1H NMR (400 MHz, CDCl3): δ 7.48 (d, 1H, 3J = 1.8 Hz, 3-H-pz), 6.08 (s, 1H, 3J = 1.8 Hz, 4-H-pz), 2.65 (t, 2H, 3J = 7.7 Hz, CH2(CH2)8CH3), 1.64 (m, 2H, CH2CH2(CH2)7CH3), 1.23–1.37 (m, 14H, (CH2)2(CH2)7CH3), 0.87 (t, 3H, 3J = 6.8 Hz, (CH2)9CH3) ppm. 13C NMR (101 MHz, CDCl3): δ 148.1, 135.4, 103.5, 32.0, 29.69, 29.65, 29.5 (two overlapping peaks), 29.4 (two overlapping peaks), 26.8, 22.8, 14.2 ppm.

2.2.1.1.3.12 3(5)-n-Dodecylpyrazole
1H NMR (400 MHz, CDCl3): δ 7.49 (d, 1H, 3J = 1.8 Hz, 3-H-pz), 6.07 (s, 1H, 3J = 1.5 Hz, 4-H-pz), 2.68 (t, 2H, 3J = 7.9 Hz, CH2(CH2)10CH3), 1.66 (m, 2H, CH2CH2(CH2)9CH3), 1.18–1.38 (m, 18H, (CH2)2(CH2)13CH3), 0.87 (t, 3H, 3J = 6.8 Hz, (CH2)11CH3) ppm. 13C NMR (101 MHz, CDCl3): δ 147.9, 135.2, 103.6, 32.0, 29.7–29.8 (three overlapping peaks), 29.6, 29.4–29.5 (four overlapping peaks), 26.8, 22.8, 14.2 ppm.

2.2.1.1.3.13 3(5)-n-Hexadecylpyrazole
M.p. 46.5–47 °C. 1H NMR (400 MHz, CDCl3): δ 7.48 (s, 1H, 3-H-pz), 6.08 (s, 1H, 4-H-pz), 2.65 (t, 2H, 3J = 7.7 Hz, CH2(CH2)14CH3), 1.64 (m, 2H, CH2CH2(CH2)13CH3), 1.18–1.38 (m, 26H, (CH2)2(CH2)9CH3), 0.87 (t, 3H, 3J = 6.8 Hz, (CH2)15CH3) ppm. 13C NMR (101 MHz, CDCl3): δ 148.0, 135.3, 103.5, 32.0, 29.4–30.0 (twelve overlapping peaks), 26.8, 22.8, 14.2 ppm. HRMS (ESI-TOF) m/z: [M – H]– calcd. for C19H35N2 291.2800; found 291.2780.

2.2.1.1.3.14 1,6-Bis(pyrazol-3(5)-yl)hexane
M.p. 87–88 °C (for the hydrate: m.p. 68–69 °C). 1H NMR (400 MHz, DMSO-d6): δ 7.46 (s, 2H, 3-H-pz), 6.02 (s, 2H, 4-H-pz), 2.55 (t, 4H, 3J = 7.7 Hz, CH2(CH2)4CH2), 1.56 (m, 4H, CH2CH2(CH2)2CH2CH2), 1.30 (m, 4H, (CH2)2(CH2)2(CH2)2) ppm. 13C NMR (101 MHz, DMSO-d6): δ 147.2, 134.8, 103.4, 29.5, 29.0, 26.5 ppm. HRMS (ESI-TOF) m/z: [M – H]– calcd. for C12H17N4 217.1453; found 217.1470.

2.2.1.1.4 One-pot synthesis of 3(5)-alkylpyrazoles
Step 1. Pyrazole (10.000 g, 0.1469 mol) and 3,4-dihydro-2H-pyran (16.75 mL, 15.44 g, 0.1836 mol) are added to a 500 mL round-bottom pressure flask, which is sealed with a PTFE front seal bushing. The pyrazole dissolves completely in the 3,4-dihydro-2H-pyran and provides a
homogeneous solution. The flask is placed in an oven and kept at 125 ºC for 24 hours. After cooling to room temperature, the excess unreacted 3,4-dihydro-2\(H\)-pyran is removed under vacuum.

Step 2. The flask containing pure 1-(tetrahydropyran-2-yl)pyrazole is evacuated and purged with \(\text{N}_2\). Anhydrous THF (300 mL) is added via \(\text{N}_2\) purged syringe, and the solution is chilled to \(-78\) ºC under stirring for 30 minutes. \(n\)BuLi (1.6 M in hexanes, 92 mL, 0.15 mol) is added dropwise over 90 minutes. After stirring for an additional 30 minutes at \(-78\) ºC, 1-haloalkane (Method A: 0.1616 mol; Method B: 0.1335 mol) is added via syringe. The solution is stirred at \(-78\) ºC for 3 hours, then is let to warm up to room temperature overnight. The THF solvent and the excess haloalkane (method A) or excess 1-THP-pyrazole (Method B) are removed under vacuum.

Step 3. Deprotection is accomplished by dissolving the 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles in EtOH (300 mL) and stirring with 37% HCl (50 mL) for 4 hours. The solvent is removed under vacuum at 35 ºC, the residue is neutralized with saturated aqueous NaHCO\(_3\) solution (to pH ~8) and is extracted with diethyl ether (5 \(\times\) 100 mL). The combined organic fractions are washed with brine (100 mL) and dried over anhydrous MgSO\(_4\). If 1-iodoalkane was used in the second step, additional washing with a dilute aqueous sodium thiosulfate solution is employed before drying with MgSO\(_4\), to remove iodine contamination. After filtration and evaporation of the solvent, the product is dried in vacuum (for longer alkyl chains the drying is carried out at 75 ºC, to remove any remaining traces of haloalkane). Pure 3(5)-alkylpyrazoles (by \(^1\)H NMR) are thus obtained, which can be further purified by vacuum distillation. For 3(5)-hexylpyrazole (obtained by Method A from 1-bromohexane), yield: 20.536 g (92%). For 3(5)-decylpyrazole (obtained by method B from 1-bromodecane), yield: 27.675 g (91%).
Table 2.1: Synthesis of 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles and 3(5)-alkylpyrazoles by alkylation of THP-protected pyrazole. Conversion is based on the ratio of integrated \(^1\)H NMR signals of the product and the residual limiting reactant (THP-protected pyrazole for method A; haloalkane for method B) in the crude reaction mixture (\(^a \)mixture of 5-alkyl and 3-alkyl isomers). Reproduced with permission, from reference 111.

![Chemical structure diagram](image)

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\(^a\) Mixture of 5-alkyl and 3-alkyl isomers.
Table 2.1: Continued.

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2.2.1.2 Synthesis of 3,5-dialkylpyrazoles

The synthetic procedures of 3,5-dialkylpyrazoles are reprinted with permission, from *J. Org. Chem.* 2016, 81, 1718–1722.<sup>110</sup> Copyright 2016 American Chemical Society.

2.2.1.2.1 Telescopic synthesis of 3(5)-butyl-5(3)-hexylpyrazole

The following steps are carried out in a 500 mL pressure flask (one pot) (Scheme 2.4). The contents are protected from atmospheric moisture between steps by using an N<sub>2</sub> blanket.

Step 1. Protection of 1H-Pyrazole. THP protection of 1H-pyrazole is accomplished according to our green method previously described (see section 2.2.1.1.1) by heating 1.200 g (17.62 mmol) of 1H-pyrazole and 2.00 mL (1.85 g, 22.0 mmol) of 3,4-dihydro-2H-pyran for 24 h.
at 125 °C. After removal of the slight excess of DHP in vacuum, 2.68 g (100%) of pure 1-(tetrahydropyran-2-yl)pyrazole is obtained.

Step 2. Synthesis of 5-hexyl-1-(tetrahydropyran-2-yl)pyrazole. The flask containing the THP-protected pyrazole is evacuated and purged with N₂, and then anhydrous THF (40 mL) is added via an N₂-purged syringe. The solution is chilled to −78 °C and stirred for 30 min, and then the nBuLi solution (1.6 M in hexanes, 11.0 mL, 17.6 mmol) is added dropwise over 10 min. After the mixture is stirred at −78 °C for 30 min, 1-bromohexane (2.72 mL, 3.20 g, 19.3 mmol) is added, and the solution is stirred at −78 °C for 90 minutes and then allowed to warm to room temperature overnight under stirring. The flask is then connected to a vacuum (0.005 mmHg), and both the excess bromohexane and unreacted 1-THP-pyrazole are removed by gently heating the flask in a water bath at 55 °C. ¹H NMR shows a 96% conversion.

Step 3. Isomerization to 3-hexyl-1-(tetrahydropyran-2-yl)pyrazole. To the 5-hexyl-1-THP-pyrazole obtained from 1-bromohexane is added a solution of I₂ (7.0 mg, 28 µmol) in DHP (2 mL) under an N₂ atmosphere. The flask is closed and set in an oven at 125 °C for 24 h. After the mixture is cooled to room temperature, ¹H NMR of the product shows an isomeric mixture of 85 mol % 3-hexyl-1-THP-pyrazole and 15 mol % 5-hexyl-1-THP-pyrazole. In the absence of I₂, it takes 8 days to reach the 85/15 equilibrium mixture of isomers at 125 °C. If 5-hexyl-1-THP-pyrazole is prepared using 1-iodohexane instead of 1-bromohexane, traces of residual iodine in the product have the same catalytic effect.

Step 4. Synthesis of 5-butyl-3-hexyl-1-(tetrahydropyran-2-yl)pyrazole. The flask containing the mixture described above is evacuated and purged with N₂. Anhydrous THF (70 mL) is added, and the mixture is chilled to −78 °C for 30 min. nBuLi (1.6 M in hexanes, 10.0 mL, 16.0 mmol) is added dropwise over 10 min and stirred for 30 min, and then 1-bromobutane (1.90 mL, 2.42 g, 17.6 mmol) is added. After being stirred for 3 h at −78 °C, the solution is allowed to warm to room temperature overnight under stirring. One milliliter of water is added, and the THF is removed under vacuum. ¹H NMR shows an 89% conversion of 3-hexyl-1-(tetrahydropyran-2-yl)pyrazole to 5-butyl-3-hexyl-1-THP-pyrazole along with traces of unreacted 5-hexyl- and 3-hexyl-1-THP-pyrazole.

Step 5. Deprotection to 3(5)-butyl-5(3)-hexylpyrazole. To the material obtained above are added 200 mL of ethanol and 50 mL of HCl (37% in H₂O). After the mixture is stirred for 8 h (¹H
NMR shows complete deprotection) the solvent is removed under vacuum. Five milliliters of water is added to the residue, and the pH is adjusted to 8 with a saturated NaHCO₃ solution. The mixture is extracted with diethyl ether (3 × 80 mL), and the combined organic layers are dried over MgSO₄ overnight. The solid material is filtered out, and the solvent is removed under vacuum to give crude 3(5)-butyl-5(3)-hexylpyrazole (3.760 g) as dark red-brown oil. ¹H NMR shows a small amount of 3(5)-hexyl-1H-pyrazole impurity. If 1-iodobutane is used instead of 1-bromobutane in the previous step, 3(5)-butyl-5(3)-hexyl-4-iodopyrazole byproduct is also identified by ESI-MS.

Step 6. Purification of 3(5)-butyl-5(3)-hexylpyrazole. The crude material is purified by column chromatography using hexane:ethyl acetate (2:1) as eluent. The main product, 3(5)-butyl-5(3)-hexylpyrazole, is obtained as a yellow oil (1.941 g, 53% overall yield based on 1H-pyrazole) with Rₖ = 45%. If 1-iodobutane is used instead of 1-bromobutane in step 4, the yield of the product drops to 46% (1.671 g), and 0.649 g of 3(5)-butyl-5(3)-hexyl-4-iodopyrazole is also isolated as a byproduct.

Scheme 2.4: Telescoping synthesis of 3,5-dialkylpyrazoles from pyrazole (DHP = 3,4-dihydro-2H-pyran; R = n-hexyl or n-heptyl; R′ = n-butyl), with % conversions (based on ¹H NMR).

2.2.1.2.2 General method of preparation of 3,5-dialkyl-1-(tetrahydropyran-2-yl)pyrazoles

1-THP-pyrazole, 5-alkyl-1-THP-pyrazoles, and 3,5-dialkyl-1-THP-pyrazoles are prepared as described above (steps 1–4). The protected 3,5-dialkylpyrazoles are extracted from the crude residues obtained after quenching with water and removal of the THF (step 4), using 4 mL of water
and three portions of 4 mL of diethyl ether (per millimole of substrate). The combined organic layers are washed with 60 mL of brine and dried over MgSO₄. After evaporation of the solvent, the crude products are purified by column chromatography using dichloromethane:ethyl acetate (4:1) as eluent and are obtained pure (by ¹H NMR, ¹³C NMR, and ESI-MS) as yellow oils ($R_f$ = 87% for 3(5)-R₁-5(3)-R₂pyrazole, where $R_1 = n$-butyl and $R_2 = n$-hexyl or $n$-heptyl).

2.2.1.2.2

5-Butyl-3-hexyl-1-(tetrahydropyran-2-yl)pyrazole

Yield: 1.515 g (61% based on 1H-pyrazole). ¹H NMR (400 MHz, CDCl₃): δ 5.84 (s, 1H, 4-H-pz), 5.14 (dd, 1H, $^3J = 10.4$ Hz, $^3J = 2.4$ Hz, CH-THP), 4.02–4.06 (m, 1H, CH₂O–THP), 3.57–3.63 (m, 1H, CH₂O–THP), 2.53–2.67 (m, 4H, CH₂(CH₂)₄CH₃ and CH₂(CH₂)₂CH₃), 2.41–2.52 (m, 1H, CH₂–THP), 2.05–2.08 (m, 1H, CH₂–THP), 1.84–1.91 (m, 1H, CH₂–THP), 1.50–1.8 (m, 7H, CH₂–THP, CH₂CH₂(CH₂)₃CH₃ and CH₂CH₂CH₂CH₃), 1.20–1.44 (m, 8H, (CH₂)₂(C₄H₉(CH₂)₄CH₃ and (CH₂)₂CH₂CH₃), 0.93 (t, 3H, $^2J = 7.32$ Hz (CH₃)₃CH₃), 0.86 (t, 3H, $^2J = 6.6$ Hz (CH₃)₃CH₃). ¹³C NMR (101 MHz, CDCl₃): δ 153.2, 144.5, 103.6, 84.2, 68.1, 31.8, 30.8, 29.9, 29.8, 29.4, 28.6, 25.10, 25.06, 23.3, 22.7, 22.5, 14.2, 14.0. HRMS (ESI-TOF) $m/z$: [M + Na]⁺ calcd. for C₁₈H₃₂N₂NaO 315.2412; found 315.2415.

2.2.1.2.2.2

5-Butyl-3-heptyl-1-(tetrahydropyran-2-yl)pyrazole

Yield: 3.137 g (62% based on 1H-pyrazole). ¹H NMR (400 MHz, CDCl₃): δ 5.84 (s, 1H, 4-H-pz), 5.14 (dd, 1H, $^3J = 10.4$ Hz, $^3J = 2.4$ Hz, CH-THP), 4.02–4.06 (m, 1H, CH₂O–THP), 3.57–3.63 (m, 1H, CH₂O–THP), 2.53–2.67 (m, 4H, CH₂(CH₂)₄CH₃ and CH₂(CH₂)₂CH₃), 2.41–2.51 (m, 1H, CH₂–THP), 2.05–2.08 (m, 1H, CH₂–THP), 1.85–1.89 (m, 1H, CH₂–THP), 1.51–1.77 (m, 7H, CH₂–THP, CH₂CH₂(CH₂)₄CH₃ and CH₂CH₂CH₂CH₃), 1.21–1.44 (m, 10H, (CH₂)₂(CH₂)₄CH₃ and (CH₂)₂CH₂CH₃), 0.93 (t, 3H, $^2J = 7.6$ Hz (CH₃)₃CH₃), 0.85 (t, 3H, $^2J = 6.8$ Hz, (CH₃)₃CH₃). ¹³C NMR (101 MHz, CDCl₃): δ 153.2, 144.5, 103.6, 84.2, 68.1, 31.9, 30.8, 29.9, 29.8, 29.7, 29.2, 28.6, 25.09, 25.06, 23.3, 22.7, 22.5, 14.2, 14.0. HRMS (ESI-TOF) $m/z$: [M + Na]⁺ calcd. for C₁₉H₃₄N₂NaO 329.2568; found 329.2559.

2.2.1.2.3

Alternative general method of preparation of 3,5-dialkylpyrazoles

3,5-Dialkyl-1-(tetrahydropyran-2-yl)pyrazoles are deprotected as described above (step 5), using 8 mL of ethanol and 2 mL of HCl (37% in H₂O) per mmol of substrate for 8 h. After removal of the solvent, addition of 0.4 mL of H₂O, neutralization and extraction with 3 × 6 mL of diethyl
ether (per millimole of substrate), followed by drying with MgSO$_4$ and removal of the solvent in high vacuum, pure products are obtained (based on $^1$H NMR, $^{13}$C NMR, and ESI-MS).

2.2.1.2.3.1 3(5)-Butyl-5(3)-hexylpyrazole

Yield: 1.061 g (99% based on 3(5)-butyl-5(3)-hexyl-1-THP-pyrazole). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.83 (s, 1H, 4-$^H$-pz), 2.56–2.60 (m, 4H, $CH_2(CH_2)_4CH_3$ and $CH_2(CH_2)_2CH_3$), 1.56–1.65 (m, 4H, $CH_2CH_2(CH_2)_3CH_3$ and $CH_2CH_2CH_2CH_3$), 1.26–1.41 (m, 8H, $(CH_2)_2(CH_2)_3-CH_3$ and $(CH_2)_2CH_2CH_3$), 0.91 (t, 3H, $^2J = 7.60$ Hz, $(CH_2)_3CH_3$, 0.86 (t, 3H, $^2J = 6.8$ Hz, $(CH_2)_3CH_3$). $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 149.5, 102.1, 31.7, 31.6, 29.4, 29.1, 27.2, 26.8, 22.7, 22.5, 14.1, 13.9. HRMS (ESI-TOF) $m/z$: [M + H]$^+$ calcd. for C$_{13}$H$_{25}$N$_2$ 209.2017; found 209.2023.

2.2.1.2.3.2 3(5)-Butyl-5(3)-heptylpyrazole

Yield: 2.133 g (94% based on 3(5)-butyl-5(3)-heptyl-1-THP-pyrazole). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.84 (s, 1H, 4-$^H$-pz), 2.55–2.60 (m, 4H, $CH_2(CH_2)_5CH_3$ and $CH_2(CH_2)_2CH_3$), 1.56–1.65 (m, 4H, $CH_2CH_2(CH_2)_4CH_3$ and $CH_2CH_2CH_2CH_3$), 1.26–1.42 (m, 10H, $(CH_2)_2(CH_2)_4CH_3$ and $(CH_2)_2CH_2CH_3$), 0.91 (t, 3H, $^2J = 7.20$ Hz, $(CH_2)_3CH_3$, 0.86 (t, 3H, $^2J = 6.8$ Hz, $(CH_2)_3CH_3$). $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 149.4, 102.0, 31.9, 31.6, 29.5, 29.4, 29.2, 27.2, 26.9, 22.7, 22.5, 14.2, 13.9. HRMS (ESI-TOF) $m/z$: [M + H]$^+$ calcd. for C$_{14}$H$_{27}$N$_2$ 223.2174; found 223.2197.

2.2.1.2.4 Alternative method of preparation of 3(5)-hexyl-5(3)-methylpyrazole

The synthetic procedure of 3(5)-hexyl-5(3)-methylpyrazole is reprinted with permission, from *Org. Lett.* 2014, 16, 4680–4683.$^{109}$ Copyright 2014 American Chemical Society.

Step 1. 3(5)-methylpyrazole (14.02 g, 0.171 mole), 3,4-dihydro-2$^H$-pyran (31 mL, 0.340 mole) and trifluoroacetic acid (0.08 mL, 0.001 mole) were mixed and refluxed for 6 hrs., followed by addition of NaH (0.323 g, 0.013 mol). The protected pyrazole 26.58 g (94%) as a ~2:1 mixture of 1-THP-3-methylpyrazole and 1-THP-5-methylpyrazole was obtained via distillation under reduced pressure (Scheme 2.5). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.47 (d, 1H, $^3J = 2.2$ Hz), 7.43 (d, 1H, $^3J = 1.5$ Hz), 6.06 (d, 1H, $^3J = 2.2$ Hz), 6.03 (d, 1H, $^3J = 0.7$ Hz), 5.27 (dd, 1H, $^3J = 2.2$, $^3J = 10.2$), 5.25 (dd, 1H, $^3J = 2.6$, $^3J = 9.5$), 4.10–4.03 (1H, m), 4.06–3.99 (1H, m), 3.71–3.63 (1H, m), 3.68–3.60 (1H, m), 2.52–2.41 (1H, m), 2.34 (3H, s), 2.28 (3H, s), 2.17–1.97 (5H, m), 1.74–1.54...
(6H, m) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 149.2, 139.1, 128.4, 106.2, 105.9, 87.5, 84.5, 68.1, 67.8, 30.5, 29.4, 25.1, 25.0, 22.93, 22.89, 13.7, 11.0 ppm.

Step 2. $^n$BuLi (1.6 M in hexane; 19.0 mL, 0.030 mole) was added dropwise to the protected pyrazole (5.000 g, 0.030 mole) in dry THF (50 mL) under an N$_2$ atmosphere at −78 ºC. After stirring for 30 min., 1-iodohexane (5.55 mL, 0.0376 mole) was added dropwise. Stirring was continued at −78 ºC for 3 hrs., and then at room temperature overnight. After quenching with water (1 mL) and removal of the solvent, the residue was dissolved in ethyl acetate (160 mL), washed with water (3 × 80 mL) and brine (3 × 80 mL), and dried with MgSO$_4$. The oily residue obtained after evaporation of the solvent was dissolved in ethanol (200 mL) and was stirred with conc. HCl (20 mL) overnight. After neutralization with NaHCO$_3$ to pH ~8, the EtOH was evaporated and the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over MgSO$_4$, filtered and evaporated. 3(5)-hexyl-5(3)-methylpyrazole as a colorless oil (3.10 g, 93% yield based on 1-THP- 3-methylpyrazole was obtained via vacuum distillation (0.12 mmHg, b.p. 112–119 ºC) (Scheme 2.5); 1-THP-5-methylpyrazole is not reactive and was recovered by distillation, b.p. 70–72 ºC at 0.12 mmHg). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.83 (s, 1H, 4-$H$-pz), 2.58 (t, 2H, $^3J = 7.7$ Hz, $CH_2$), 2.26 (s, 3H, $CH_3$), 1.61 (m, 2H, $CH_2$), 1.38–1.23 (m, 6H, $CH_2$), 0.87 (t, 3H, $^3J = 6.7$ Hz, $CH_2CH_3$) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 149.2, 144.8, 103.1, 31.7, 29.5, 29.1, 27.0, 22.7, 14.2, 12.5 ppm.

![Scheme 2.5: Synthesis of 3(5)-hexyl-5(3)-methylpyrazole (DHP = 3,4-dihydro-2$H$-pyran; TFA = trifluoroacetic acid).](image-url)
2.2.1.3 Synthesis of 4-n-octylpyrazole, OEG-pyrazoles, 4-ethoxypyrazole and 3,5-dimethyl-4-octylpyrazole

The synthetic procedures of 4-n-octylpyrazole, OEG-pyrazoles, 4-ethoxypyrazole and 3,5-dimethyl-4-octylpyrazole were originally published in *Dalton Trans.* 2016, 45, 8327–8339,104 and are reproduced by permission of The Royal Society of Chemistry.

http://pubs.rsc.org/en/content/articlelanding/2016/dt/c6dt00847j#!divAbstract.

2.2.1.3.1 Synthesis of decanal diethyl acetal

Decanal (47.1 mL, 39.1 g, 250 mmol), triethyl orthoformate (41.6 mL, 37.1 g, 250 mmol) and p-toluenesulfonic acid monohydrate (476 mg, 2.50 mmol) are dissolved in 250 mL absolute ethanol. After standing for 1 hour at room temperature, 1H NMR indicates that the reaction is practically complete. The solution is left to stand overnight, then it is poured into 500 mL of saturated sodium bicarbonate solution (~96 g NaHCO₃/L H₂O at 20 °C), and is extracted with ethyl acetate (5 × 100 mL). The combined organic extracts are dried overnight with anhydrous Na₂SO₄, followed by evaporation of the solvent and drying under high vacuum to yield 56.4 g (98%) of decanal diethyl acetal (Scheme 2.6). 1H NMR (400 MHz, CDCl₃): δ 4.46 (t, 1H, 3J = 6Hz), 3.62 (dq, 2H, 3J = 7Hz), 3.47 (dq, 2H, 3J = 7 Hz), 1.58 (m, 2H), 1.25 (m, 14H), 1.19 (t, 6H, (t, 3H, 3J = 7 Hz) ppm. 3 J = 7 Hz), 0.86 (t, 3H, 3J = 7 Hz) ppm.

2.2.1.3.2 General method of preparation for 7-ethoxy-2,5,8-trioxadecane, 10-ethoxy-2,5,8,11-tetraoxatridecane and 13-ethoxy-2,5,8,11,14-pentaoxahexadecane

NaH (60% dispersion in mineral oil, 4.000 g, 100 mmol) is placed in a 250 mL three-neck, round-bottom flask, which is connected to a Schlenk line. A condenser is attached, the third neck is sealed with a rubber septum, and the system is evacuated and purged with nitrogen three times. The mineral oil is washed away from the sodium hydride by rinsing with anhydrous hexane. The hexane (50 mL) is introduced with an N₂-purged syringe, and the mixture is stirred for 3 minutes. After the NaH has settled, the supernatant is removed with a syringe, and the procedure is repeated three more times. The residue is then dried thoroughly by applying high vacuum. Neat bromoacetaldehyde diethyl acetal (100 mL, 131 g, 0.664 mol) is added by syringe under stirring, followed by the dropwise addition of the oligo(ethylene glycol) monomethyl ether, CH₃(OCH₂CH₂)ₙOH (50.00 mmole; n = 1, 3.950 mL, 3.8045 g; n = 2, 5.800 mL, 6.007 g; n = 3, 8.000 mL, 8.210 g). The reaction is exothermic and is accompanied by a color change from light
grey to brown. After heating to 100 °C for 48 hours under stirring, the reaction mixture is left to cool down to room temperature. Water (20 mL) is added to quench the unreacted NaH, and the excess bromoacetaldehyde diethyl acetal is distilled off under high vacuum at ∼30 °C. The dark brown viscous residue is taken up into dichloromethane (200 mL) and is washed with water (40 mL) twice, followed by drying the organic layer with MgSO₄ overnight. After filtration, the solvent is removed under vacuum at ∼30 °C and the product is obtained as red-brown viscous oil in close to quantitative yield (Scheme 2.6). Although the product is of sufficient purity to be used in the next step, vacuum distillation can be employed if further purification is needed.

2.2.1.3.2.1 7-Ethoxy-2,5,8-trioxadecane

Obtained as colorless oil after distillation (b.p. 47–49 °C at 0.005 mmHg). ¹H NMR (400 MHz, CDCl₃): δ 4.63 (t, 1H, 3J = 5 Hz, CH(OCH₂CH₃)₂), 3.65–3.68 (m, 4H, OCH₂CH₃), 3.52–3.59 (m, 6H, OCH₂CH₂ and OCH₂CH), 3.36 (s, 3H, OCH₃), 1.20 (t, 6H, OCH₂CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 101.3, 72.03, 70.9, 70.96, 62.4, 59.1 ppm. HRMS (ESI-TOF) m/z: [M + Na]⁺ calcd. for C₉H₂₀NaO₄ 215.1259; found 215.1254.

2.2.1.3.2.2 10-Ethoxy-2,5,8,11-tetraoxatridecane

Obtained as colorless oil after distillation (b.p. 72–73 °C at 0.005 mmHg). ¹H NMR (400 MHz, CDCl₃): δ 4.67 (t, 1H, CH(OCH₂CH₃)₂), 3.50–3.79 (m, 14H, OCH₂ and OCH₂CH₃), 3.35 (s, 3H, OCH₃), 1.19 (t, 3H, CH₂CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 101.4, 72.0, 71.7, 70.9, 70.7, 70.6, 65.7, 62.5, 59.2, 15.4 ppm. HRMS (ESI-TOF) m/z: [M + Na]⁺ calcd. for C₁₁H₂₄NaO₅ 259.1521; found 259.1514.

2.2.1.3.2.3 13-Ethoxy-2,5,8,11,14-pentaoxahexadecane

Obtained as brown viscous oil. ¹H NMR (400 MHz, CDCl₃): δ 4.62 (t, 1H, 3J = 6 Hz, CH(OCH₂CH₃)₂), 3.62–3.66 (m, 12H, CH₂CH₃ and OCH₂CH₂), 3.51–3.59 (m, 6H, OCH₂CH₂), 3.36 (s, 3H, OCH₃), 1.20 (t, 6H, CH₂CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 101.3, 72.012, 71.967, 70.965, 70.705, 70.667, 70.664, 70.613, 62.4, 59.1 ppm.
2.2.1.3.3 General method of preparation for 3-R-2-octyl-prop-2-enal, 3-R-2-(2-methoxy-ethoxy)-prop-2-enal, 3-R-2-(2-(2-methoxyethoxy)ethoxy)-prop-2-enal and 3-R-2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-prop-2-enal (R = NMe₂ and OEt)

POCl₃ (6.38 ml, 10.5 g, 68.4 mmol) is added to a 100 mL Schlenk-flask equipped with a pressure-equalizing addition funnel, sealed with a rubber septum. The system is evacuated and purged with nitrogen a few times while cooling in an ice bath. DMF (5.86 ml, 5.53 g, 75.7 mmol) is injected into the addition funnel via N₂-purged syringe, and is added dropwise to POCl₃ under stirring. Decanal diethyl acetal (7.26 g, 31.5 mmol) or CH₃(OCH₂CH₂)₂OCH₂CH(OEt)₂ (31.5 mmol; z = 1, 6.05 g; z = 2, 7.43 g; z = 3, 8.82 g) is added via syringe to the colorless crystalline Vilsmeier reagent obtained. The ice bath is replaced with a water bath and the reaction mixture is allowed to warm up to room temperature. The color of the reaction slowly turns yellow. The temperature of the water bath is raised to 70 – 75 °C, causing the color to quickly turn dark orange and then dark red. A vigorous reaction ensues, accompanied by a large increase in pressure (relieved through the Schlenk line’s oil bubbler). The reaction mixture is kept at the same temperature for 2 hours, then the dark brown-red, viscous solution is poured into 50 g crushed ice and is left to stand overnight. Next day, the mixture is extracted with CH₂Cl₂ (2 × 25 mL), followed by Et₂O (25 mL). The aqueous phase is neutralized with solid K₂CO₃ (20 g), which is added in small portions, under stirring, until pH ≈ 8. The orange-red solution is extracted again with CH₂Cl₂ (5 × 25 mL) and Et₂O (2 × 20 mL). The combined organic extracts are dried overnight with anhydrous MgSO₄. After filtration, the solvent is evaporated under vacuum and DMF is distilled off in vacuum on a water bath at 80 °C. The resulting dark red-brown oil consists of a mixture of 3-(dimethylamino)-2-n-octyl-prop-2-enal and 3-ethoxy-2-n-octyl-prop-2-enal in the case of CH₃(CH₂)₈CH(OEt)₂, and OEG-substituted dimethylamino and ethoxy-propenal, as well as smaller amounts of EtO-substituted dimethylamino- and ethoxy-propenal in the case of CH₃(OCH₂CH₂)₂OCH₂CH(OEt)₂ (Scheme 2.6). These mixtures are used without separation in the next step.
2.2.1.3.4 General method of preparation for 4-octylpyrazole, 4-(2-methoxyethoxy)pyrazole, 4-(2-(2-methoxyethoxy)ethoxy)pyrazole and 4-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)pyrazole

The mixtures obtained above are dissolved in methanol (60 mL), hydrazine monohydrate (1.95 ml, 1.98 g, 39.5 mmol) is added and the mixture is refluxed for 2 hours. After cooling to room temperature, the solvent is removed under vacuum. The dark red-brown oil is subjected to purification by vacuum distillation or column chromatography (Scheme 2.6).

Scheme 2.6: Synthesis of 4-octylpyrazole and OEG-pyrazole ligands.

2.2.1.3.4.1 4-Octylpyrazole

Vacuum distillation using a Vigreux column provides pure 4-octylpyrazole as a colorless liquid (b.p. 143 °C at ~0.1 mmHg), which solidifies on cooling. Yield: 4.21 g (75% based on decanal). $^1$H NMR (400 MHz, CDCl$_3$): δ 12.07 (s, br, 1H), 7.40 (s, 2H), 2.49 (t, 2H, $^3$$J$ = 8 Hz), 1.56 (m, 2H), 1.30 (m, 10H), 0.90 (t, 3H, $^3$$J$ = 7 Hz) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ 132.5, 121.2, 32.0, 31.2, 29.6, 29.4, 24.2, 22.8, 14.2 ppm.

2.2.1.3.4.2 4-(2-Methoxyethoxy)pyrazole

Purified by column chromatography on silica gel (300 g) using neat ethyl acetate as eluent ($R_f$ = 0.49). The product (1.52 g) is obtained as an orange oil in 34% overall yield (based on ethylene glycol monomethyl ether). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.29 (s, 2H, 3.5-$H$-pz), 4.01–4.03 (m, 2H, OCH$_2$), 3.67–3.70 (m, 2H, OCH$_2$), 3.42 (s, 3H, OCH$_3$) ppm. $^{13}$C NMR (101 MHz,
CDCl₃): δ 145.5, 121.1, 71.1, 59.2 ppm. HRMS (ESI-TOF) m/z: [M + Na]⁺ calcd. for C₆H₁₀N₂NaO₂ 165.0640; found 165.0643.

2.2.1.3.4.3 4-(2-(2-Methoxyethoxy)ethoxy)pyrazole

Purified by column chromatography on silica gel (300 g) using neat ethyl acetate as eluent (Rₛ = 0.35). The product (1.50 g) is obtained as an orange-red oil in 26% overall yield (based on diethylene glycol monomethyl ether). ¹H NMR (400 MHz, CDCl₃): δ 7.28 (s, 2H, 3,5-H-pz), 4.02 (t, 2H, OCH₂, 3J = 4 Hz), 3.78 (t, 2H, OCH₂, 3J = 4 Hz), 3.68 (t, 2H, OCH₂, 3J = 4 Hz), 3.56 (t, 2H, OCH₂, 3J = 4 Hz), 3.37 (s, 3H, OCH₃) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 145.5, 120.9, 71.9, 71.2, 71.7, 69.9, 59.1 ppm. HRMS (ESI-TOF) m/z: [M + Na]⁺ calcd. for C₈H₁₄N₂NaO₃ 209.0902; found 209.0902.

2.2.1.3.4.4 4-(2-(2-(2-Methoxyethoxy)ethoxy)ethoxy)pyrazole

Purified by column chromatography on silica gel (300 g) using an eluent gradient as follows: 95:5 EtOAc:hexanes first, neat EtOAc second, 95:5 EtOAc:MeOH third, and 90:10 EtOAc:MeOH last. The product (1.44 g) is obtained as an orange-yellow oil in 20% overall yield (based on triethylene glycol monomethyl ether). ¹H NMR (400 MHz, CDCl₃): δ 7.28 (s, 2H, 3(5)-H-pz), 4.00–4.02 (m, 2H, OCH₂), 3.76–3.79 (m, 2H, OCH₂), 3.62–3.71 (m, 6H, CH₂OCH₂CH₂), 3.53–3.55 (m, 2H, OCH₂), 3.36 (s, 3H, OCH₃). ¹³C NMR (100 MHz, CDCl₃): δ 145.5, 121.0, 71.9, 71.3, 70.7, 70.6, 70.5, 69.9, 59.1 ppm. HRMS (ESI-TOF) m/z: [M + Na]⁺ calcd. for C₁₀H₁₈N₂NaO₄ 253.1164; found 253.1173.

2.2.1.3.4.5 4-Ethoxypyrazole

Obtained as a side-product during the column chromatography of the mono-, di- and triethylene glycol methyl ether substituted pyrazoles described above, in 5:8, 5:10 and 5:7 molar ratios, respectively (4-EtOpyrazole:4-OEGpyrazole). ¹H NMR (400 MHz, CDCl₃): δ 7.28 (s, 2H, 3,5-H-pz), 3.94 (q, 2H, 3J = 7 Hz, CH₂CH₃), 1.37 (t, 3H, 3J = 7 Hz, CH₂CH₃). ¹³C NMR NMR (101 MHz, CDCl₃): δ 145.6, 120.8, 67.5, 15.0 ppm. HRMS (ESI-TOF) m/z: [M + Na]⁺ calcd. for C₅H₉N₂O 113.0715; found 113.0695.
2.2.1.3.5 Synthesis of 3,5-dimethyl-4-octylpyrazole

Step 1. Synthesis of 3-(n-octyl)pentane-2,4-dione. A mixture of acetylacetone (30.0 ml, 29.2 g, 0.292 mol) and 1-iodooctane (53.0 ml, 70.5 g, 0.293 mol) is added dropwise to a stirred suspension of anhydrous K\textsubscript{2}CO\textsubscript{3} (50.0 g, 0.362 mol) in 50 mL acetonitrile. The reaction mixture is refluxed overnight with stirring. After cooling to room temperature, the solid is filtered off and washed with acetone. The organic solvents are evaporated on a rotavap, water is added to the residue and it is extracted with diethyl ether. After evaporation of the ether, the residue (60.7 g) is fractionally distilled under vacuum (0.15–0.20 mmHg) using a Vigreux column, and the fraction distilling at 104 °C (43.5 g) is redistilled. The fraction distilling at 117 °C (41.0 g, yield: ~66%) is found to be a mixture of the keto and enol forms of 3-(n-octyl)-pentane-2,4-dione, with a small amount of O-alkylated enol. This mixture is used in the next step without further purification.

Step 2. Hydrazine hydrate (N\textsubscript{2}H\textsubscript{4} 50–60% in H\textsubscript{2}O, 12.414 g) is added dropwise to a solution of 3-(n-octyl)pentane-2,4-dione (38.851 g) in 150 mL EtOH with stirring. The mixture is refluxed for 14 hours and the solvent is evaporated on a rotavap. The residue (38.664 g) is fractionally distilled under vacuum, using a Vigreux column. The fraction distilling at 155–160 °C (32.721 g) is redistilled, yielding 32.125 g (56% based on acetylacetone) of pure 3,5-dimethyl-4-n-octylpyrazole boiling at 160 °C (Scheme 2.7). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): 2.31 (t, 2H, \textsuperscript{3}J = 8 Hz), 2.19 (s, 6H), 1.41 (m, 2H), 1.27 (m, 10H), 0.87 (t, 3H, \textsuperscript{3}J = 7 Hz) ppm. \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): 142.0, 115.8, 32.0, 30.8, 29.6, 29.5, 29.4, 23.1, 22.8, 14.2, 11.0.

Scheme 2.7: Synthesis of 3,5-dimethyl-4-octylpyrazole
2.2.1.4 Synthesis of 1,2-bis(1H-pyrazole-3-yl)ethane

The synthetic procedures of 1,2-bis(1H-pyrazole-3-yl)ethane were originally published in *Chem. Commun.* 2017, 53, 1029–1032, and are reproduced by permission of The Royal Society of Chemistry. http://pubs.rsc.org/en/content/articlelanding/2017/cc/c6cc09197k#!divAbstract.

Method A: Step 1. Synthesis of diethyl 2,4,7,9-tetraoxodecanedione. Sodium metal (small pieces, 11.500 g, 500 mmol) is placed into a 1000 ml three-necked round bottom flask equipped with a stir-bar, condenser and addition funnel, and connected to a Schlenk line. After evacuation and purging with N₂, the flask is placed into an ice bath and anhydrous diethyl ether (500 ml) is added by syringe. A mixture of diethyl oxalate (73.000 g, 500 mmol) and 2,5-hexanedione (28.500 g, 250 mmol) is slowly added under stirring, and the dark brown suspension is further stirred for 2 hours at 0 °C. After warming up to room temperature overnight under an N₂ atmosphere, the reaction mixture is refluxed for 1 hour. The brown suspension is filtered out, washed with diethyl ether, and dried under high vacuum. The solid is then dissolved in deionized water (2 L) and acidified to pH ~ 3 with a 10% aqueous solution of H₂SO₄ (200 mL). A light yellowish-brown precipitate forms, which is filtered out and dried under high vacuum (22.310 g). Recrystallization from hot ethanol affords 14.593 g (19%) of diethyl 2,4,7,9-tetraoxodecanedione, as shiny, brownish plates (Scheme 2.8). NMR in CDCl₃ shows the pure enolic form. ¹H NMR (400 MHz, CDCl₃): δ 6.43 (s, 2H, COC=CHCOH), 4.34 (q, 4H, ³J = 7.2 Hz, CH₃CH₂), 2.91 (s, 4H, COCH₂CH₂CO), 1.36 (t, 6H, ³J = 7.1 Hz, CH₂CH₂) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 202.5, 163.4, 162.0, 102.5, 62.7, 35.3, 14.1 ppm.

Step 2. Synthesis of 1,2-bis(5-carboethoxy-1H-pyrazole-3-yl)ethane. To a hot solution of diethyl 2,4,7,9-tetraoxodecanedione (14.000 g, 44.5 mmol) in 100 ml ethanol is gradually added hydrazine hydrate (5.05 g, 4.90 mL, 100 mmol). A crystalline solid forms, which is filtered out and dried under high vacuum (22.310 g). Recrystallization from hot ethanol affords 14.593 g (19%) of diethyl 2,4,7,9-tetraoxodecanedione, as shiny, brownish plates (Scheme 2.8). NMR in CDCl₃ shows the pure enolic form. ¹H NMR (400 MHz, CDCl₃): δ 6.43 (s, 2H, COC=CHCOH), 4.34 (q, 4H, ³J = 7.2 Hz, CH₃CH₂), 2.91 (s, 4H, COCH₂CH₂CO), 1.36 (t, 6H, ³J = 7.1 Hz, CH₂CH₂) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 202.5, 163.4, 162.0, 102.5, 62.7, 35.3, 14.1 ppm.

Step 3. Synthesis of 1,2-bis(5-carboxy-1H-pyrazole-3-yl)ethane. 1,2-bis(5-carboethoxy-1H-pyrazole-3-yl)ethane (10.000 g, 32.6 mmole) is dissolved in a 10% aqueous NaOH solution
(100 mL) and is boiled for 1 hour. After cooling, a 20% aqueous H$_2$SO$_4$ solution (40 mL) is added gradually, under stirring, to pH~3. The brown precipitate is filtered out, suspended in 37% HCl (250 mL) and boiled for 30 minutes. Filtration and drying in high vacuum affords 6.528 g (80%) of 1,2-bis(5-carboxy-1H-pyrazol-3-yl)ethane as a beige powder (Scheme 2.8). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.48 (s, 2H, pz-H), 2.95 (s, 4H, CH$_2$CH$_2$) ppm. $^{13}$C NMR (101 MHz, DMSO-$d_6$): $\delta$ 163.0, 146.9, 141.1, 106.8, 25.8 ppm.

Step 4. Synthesis of 1,2-bis(1H-pyrazol-3-yl)ethane (LH$_2$). 1,2-bis(5-carboxy-1H-pyrazol-3-yl)ethane (4.66 g, 18.62 mmole) is added to a vial preheated to 330 °C in a sand bath covered with a watch glass. As the material starts melting, a white smoke is evolved which condenses onto the watch glass. After all the material has melted, the vial is taken out of the sand bath and left to cool to room temperature. The white solid condensed onto the watch glass (~ 50 mg) is pure 1,2-bis(1H-pyrazol-3-yl)ethane. The dark brown molten residue is extracted with boiling ethanol under stirring. After filtration, the ethanolic extract is heated and stirred for 2 hours with activated carbon, then filtered and evaporated to give a yellowish-brown oil (1.5 g). Upon trituration with diethyl ether, pure 1,2-bis(1H-pyrazol-3-yl)ethane is obtained as a pale yellow powder (900 mg; overall yield: 32%) (Scheme 2.8). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 12.48 (s, 2H, NH), 7.45 (s, 2H, 5-H-pz), 6.03 (s, 2H, 4-H-pz), 2.88 (s, 4H, CH$_2$CH$_2$) ppm. $^{13}$C NMR (101 MHz, DMSO-$d_6$): $\delta$ 147.1, 134.0, 103.4, 26.9 ppm. HRMS (ESI-TOF) $m/z$: [M+Na]$^+$ calcd. for C$_8$H$_{10}$N$_4$Na$^+$ 185.0803; found 185.0808. Slow evaporation of an EtOH/H$_2$O solution of 1,2-bis(1H-pyrazol-3-yl)ethane produces single-crystals suitable for X-ray diffraction.

Scheme 2.8: Synthesis of 1,2-bis(1H-pyrazol-3-yl)ethane in method A.
Method B: Step 1. Synthesis of (1E, 7E)-1,8-bis(dimethylamino)octa-1,7-diene-3,6-dione.

A solution of 2,5-hexanedione (10.00 g, 0.0876 mol) and dimethylformamide dimethylacetal (81.45 mL, 73.07 g, 0.613 mol) in dimethylformamide (100 mL) is refluxed in a 250 mL round-bottom flask at 115 °C for 24 hours. The color of the solution gradually turns yellow and finally dark red. The excess DMF-DMA and the DMF solvent are distilled out under high-vacuum with heating on a water bath (at ~60 °C). The viscous, dark-red oily residue (20.129 g) is purified by column chromatography on silica gel (1.5 kg) using EtOAc/MeOH gradient elution (first 9:1, then 8:2, 7:3, 2:1 and 1:1). \( R_f \) is 30% with EtOAc:MeOH (2:1) and 7% with EtOAc:MeOH (9:1). (1E, 7E)-1,8-bis(dimethylamino)octa-1,7-diene-3,6-dione is obtained as a brown solid (yield: 4.183 g, 21%) (Scheme 2.9). Further purification can be carried out by recrystallization from an ethyl acetate solution by hexane vapor diffusion, which affords single crystals suitable for X-ray diffraction. \( ^1H \) NMR (400 MHz, CDCl₃): \( \delta \) 7.49 (d, 2H, \( ^3J = 13 \) Hz, \( =CH \)), 5.05 (d, 2H, \( ^3J = 13 \) Hz, \( =CH \)), 2.79–3.00 (m, 12H, N(CH₃)₂), 2.64 (s, 4H, CH₂CH₂) ppm. \( ^{13}C \) NMR (101 MHz, CDCl₃): \( \delta \) 197.2, 152.5, 96.1, 44.8, 37.0, 36.2 ppm. HRMS (ESI-TOF) \( m/z \): [M+Na]+ calcd. for C₁₂H₁₀N₂NaO₂⁺ 247.1422; found 247.1427.

Step 2. Synthesis of 1,2-bis(1H-pyrazole-3-yl)ethane (LH₂).

(1E, 7E)-1,8-bis(dimethylamino)octa-1,7-diene-3,6-dione (1.000 g, 4.45 mmole) is dissolved in ethanol (50 mL) and hydrazine monohydrate (0.54 mL, 0.56 g, 11 mmole) is added. After refluxing for 6 hours, a brown precipitate is filtered out. The dark brown filtrate is stirred with activated carbon for 30 minutes with heating, and then is filtered while hot. The solvent is removed under vacuum and 1,2-bis(1H-pyrazole-3-yl)ethane is obtained as a light yellow solid (yield: 0.656 g, 91%) (Scheme 2.9).

![Scheme 2.9: Synthesis of 1,2-bis(1H-pyrazole-3-yl)ethane in method B.](image-url)
2.2.1.5 Synthesis of \( N,1\)-bis(pyrazol-3(5)-yl) methanimine 18

The synthetic procedures of this section through section 2.2.1.12 are reprinted with permission, from \textit{J. Org. Chem.} \textbf{2017}, 82, 10549–10562.\textsuperscript{112} Copyright 2017 American Chemical Society.

Pyrazole-3(5)-carbaldehyde (2.024 g, 21.06 mmol) was dissolved in anhydrous ethanol (600 mL) by gently warming (\(\sim 50\) °C) under an N\(_2\)-atmosphere. After cooling to room temperature, the solution was added by cannula to a flask containing 3(5)-aminopyrazole (1.750 g, 21.06 mmol) and 3 Å molecular sieves (200 mL). The reaction mixture was allowed to stand at room temperature and was swirled occasionally (stirring is to be avoided as it leads to the breakup of the molecular sieve particles, forming a paste). Periodical monitoring showed that the reaction was complete after 9 days at 25 °C. After most of the solvent was removed under vacuum, the product (white solid) was precipitated by the addition of excess diethyl ether and then was filtered out and quickly rinsed with a small amount of ethanol. Yield: 2.809 g, 17.43 mmol (83%) (Scheme 2.10). M.p. 188–189 °C. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 13.40 (s, br, 1H, NH-pz), 12.78 (s, br, 1H, NH-pz), 8.81 (s, 1H, CH= N), 7.81 (s, br, 1H, CH-pz), 7.67 (s, br, 1H, CH-pz), 6.77 (d, 1H, \(^3\)\(J = 1.6\) Hz, CH-pz), 6.42 (d, 1H, \(^3\)\(J = 1.6\) Hz, CH-pz) ppm. \(^13\)C NMR (101 MHz, DMSO-\(d_6\)): \(\delta\) 158.1, 153.3, 149.2, 132.6, 104.7, 96.1 ppm. HRMS (ESI-TOF) \(m/z\): [M – H]\(^-\) calcd. for C\(_7\)H\(_6\)N\(_5\)^-, 160.0628; found, 160.0642.

Scheme 2.10: Synthesis of \( N,1\)-bis(pyrazol-3(5)-yl) methanimine 18.

2.2.1.6 Synthesis of \( N\)-(4-((1H-pyrazol-3-yl)methylene)-4\(H\)-pyrazol-3-yl)-1-(1H-pyrazol-3-yl) methanimine 19

Pyrazole-3(5)-carbaldehyde (1.057 g, 11.00 mmol) was dissolved in 60 mL ethanol acidified with HCl (37% in H\(_2\)O, 0.90 mL, 11 mmol) with slight heating. 3(5)-Aminopyrazole (0.914 g, 11.0 mmol) was added, and the solution was stirred at room temperature for 12 h, followed by refluxing for 30 min. After cooling, the reaction mixture was stirred overnight with sodium bicarbonate. The solution was filtered, and the solvent was removed under vacuum. The
crude product (2.023 g) was purified by column chromatography on silica gel using 1,2-
dichloroethane/methanol gradient elution (8:1, 6:1, 4:1, 2:1, 1:1, 1:2, 1:4, followed by neat methanol). R_f was 37% with 1,2-dichloroethane/methanol (4:1). The pale yellow solid (425 mg) contained small amounts (1.8%) of pyrazole-3(5)-carbaldehyde. Further purification was achieved by column chromatography on neutral aluminum oxide using ethyl acetate/methanol gradient elution (9:1, 8:1, 6:1, 4:1, 2:1, 1:1, 1:2, followed by neat methanol). R_f was 40% with ethyl acetate/methanol (9:1). Pure compound 19 was isolated as a white solid. Yield: 393 mg, 1.64 mmol (30%), based on pyrazole-3(5)-carbaldehyde (Scheme 2.11). M.p. 142–143 °C. ^1H NMR (400 MHz, ethanol-d_6): δ 8.21 (s, 1H, C_H=N), 7.79 (s, 1H, C_H-pz), 7.53 (s, 1H, CH-pz), 7.36 (s, 1H, CH-pz), 6.98 (s, 1H, CH), 6.82 (s, 1H, CH-pz), 5.70 (s, 1H, CH) ppm. ^1H NMR (400 MHz, DMSO-d_6): δ 12.95 (s, br, 2H, NH-pz), 8.25 (s, 1H, CH=N), 7.81 (s, 1H, CH-pz), 7.59 (s, 1H, CH-pz), 7.50 (s, 1H, CH-pz), 6.99 (s, 1H, CH), 6.86 (s, 1H, CH-pz), 5.73 (s, 1H, CH) ppm. ^13C NMR (101 MHz, DMSO-d_6): δ 151.3, 145.9, 139.5, 138.2, 130.6, 113.8, 109.1, 102.0, 57.0 ppm. HRMS (ESI-TOF) m/z: [M – H]^- calcd. for C_{11}H_{8}N_{7}^-, 238.0846; found, 238.0864.

Scheme 2.11: Synthesis of N-(4-((1H-pyrazol-3-yl)methylene)-4H-pyrazol-3-yl)-1-(1H-pyrazol-3-yl)methanimine 19.

2.2.1.7 Synthesis of N-(pyrazol-1-yl)-1-(pyrazol-3(5)-yl)methanimine 20

1-Aminopyrazole (279 mg, 3.35 mmol) and pyrazole-3(5)-carbaldehyde (161 mg, 1.67 mmol) were dissolved in ethanol (20 mL). Hydrochloric acid (37% in H_2O, 137 µL, 1.67 mmol) was added, and the mixture was refluxed overnight. The solvent was removed under vacuum. The residue was dissolved in chloroform, and the product precipitated by addition of diethyl ether. The white solid was quickly rinsed with a small amount of chloroform to remove any remaining unreacted 1-aminopyrazole and was dried under a high vacuum. Yield: 208 mg, 1.29 mmol (77%) (Scheme 2.12). M.p. 131–132 °C. ^1H NMR (400 MHz, CDCl_3): δ 9.23 (s, 1H, CH=N), 7.70 (d,
1H, $^3J = 1.4$ Hz, 5-$H$-pz), 7.67 (d, 1H, $J = 2.2$ Hz, 5-$H$-pz), 7.55 (s, 1H, 3-$H$-pz), 6.80 (d, 1H, $^3J = 1.8$ Hz, 4-$H$-pz), 6.37 (t, 1H, $^3J = 1.8$ Hz, 4-$H$-pz). $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 144.1, 142.2, 138.0, 133.3, 129.1, 106.5, 106.2. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd. for C$_7$H$_7$N$_5$Na$^+$, 184.0593; found, 184.0569.

Scheme 2.12: Synthesis of N-(pyrazol-1-yl)-1-(pyrazol-3(5)-yl)methanimine 20.

2.2.1.8 General procedure for the preparation of bis- and tris(pyrazolyl)methane ligands

The aldehyde or ketone was dissolved in ethanol (10−150 mL) together with 3(5)-aminopyrazole or 3(5)-hydroxy-1H-pyrazole in a 1:2 molar ratio (of carbonyl/amino groups). The mixture was acidified with 37% HCl (1 mol %), then sonicated for 15 min, and refluxed for 30 min. After most of the ethanol was removed under vacuum, the reaction mixture was poured into excess diethyl ether. The solid product was filtered, rinsed with diethyl ether, and dried under a high vacuum. Pure compounds were obtained from aldehydes, whereas the products derived from ketones were purified by column chromatography (Scheme 2.13). Reaction conversions are shown in (Table 2.2), and isolated yields are provided below.

Scheme 2.13: General procedure for the preparation of bis- and tris(pyrazolyl)methane ligands (exemplified on compound 21).
Table 2.2: Reaction products of various aldehydes and ketones with 3(5)-aminopyrazole and 3(5)-hydroxypyrazole leading to bis- and tris(pyrazolyl)methane ligands, with the corresponding conversions (by $^1$H NMR). Reproduced with permission, from reference 112.

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2.2.1.8.1 Bis(3(5)-aminopyrazol-4-yl)-pyrazol-3(5)-yl-methane 21

White solid, m.p. 205–206 °C. Yield: 84% (426 mg, 1.74 mmol, from 200 mg of pyrazole-3-carbaldehyde). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.48 (s, 1H, 5-$H$-pz), 7.11 (s, 2H, 5-$H$-pz), 6.06 (s, 1H, 4-$H$-pz), 4.98 (s, 1H, $CH$) ppm. $^{13}$C NMR (101 MHz, DMSO-$d_6$): $\delta$ 151.1, 129.8, 107.8, 103.5, 28.5 ppm. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd. for C$_{10}$H$_{12}$N$_8$Na$^+$, 267.1077; found, 267.1077.

2.2.1.8.2 Bis(3(5)-hydroxy)pyrazol-4-yl)-pyrazol-3(5)-yl-methane 22

Yellow solid, m.p. 179 °C. Yield: 63% (1.612 g, 6.55 mmol, from 1.000 g of pyrazole-3-carbaldehyde). $^1$H NMR (400 MHz, D$_2$O): $\delta$ 7.78 (s, 1H, 5-$H$-pz), 7.52 (s, 2H, 5-$H$-pz), 6.29 (s, 1H, 4-$H$-pz), 5.23 (s, 1H, $CH$) ppm. $^{13}$C NMR (101 MHz, D$_2$O): $\delta$ 159.5, 150.5, 133.6, 133.5, 105.4, 27.3 ppm. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd. for C$_{10}$H$_{10}$N$_6$O$_2$Na$^+$, 269.0750; found, 269.0750.

2.2.1.8.3 Bis(3(5)-amino-5(3)-methylpyrazol-4-yl)-pyrazol-3(5)-yl-methane 23

White solid, m.p. 219–220 °C. Yield: 98% (560 mg, 2.06 mmol, from 202 mg of pyrazole-3-carbaldehyde). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.38 (s, br, 4H, $NH_2$), 7.60 (d, 1H, $^3J = 1.8$ Hz, 5-$H$-pz), 5.98 (d, 1H, $^3J = 2.4$ Hz, 5-$H$-pz), 5.25 (s, 1H, $CH$), 1.94 (s, 6H, $CH_3$) ppm. $^{13}$C NMR (101 MHz, DMSO-$d_6$): $\delta$ 150.0, 149.7, 140.8, 131.9, 104.4, 103.7, 27.9, 10.6 ppm. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd. for C$_{12}$H$_{16}$N$_8$Na$^+$, 295.1390; found, 295.1375.

2.2.1.8.4 Bis(3(5)-aminopyrazol-4-yl)-pyrazol-4-yl-methane 24

White solid, m.p. 164–165 °C. Yield: 71% (771 mg, 3.16 mmol, from 428 mg of pyrazole-4-carbaldehyde). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.43 (s, 2H, 5-$H$-pz), 7.36 (s, 2H, 3,5-$H$-pz), 5.15 (s, 1H, $CH$) ppm. $^{13}$C NMR (101 MHz, D$_2$O): $\delta$ 149.8, 133.3, 131.2, 122.2, 109.3, 24.9 ppm. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd. for C$_{10}$H$_{12}$N$_8$Na$^+$, 267.1077; found, 267.1086.

2.2.1.8.5 Bis(3(5)-hydroxy)pyrazol-4-yl)-pyrazol-4-yl-methane 25

Light-yellow solid, m.p. 198 °C. Yield: 84% (313 mg, 1.28 mmol, from 150 mg of pyrazole-4-carbaldehyde). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.30 (s, 4H, 3,5-$H$-pz), 4.90 (s, 1H, $CH$) ppm. $^{13}$C NMR (101 MHz, DMSO-$d_6$): $\delta$ 158.7, 132.3, 129.7, 124.7, 108.7, 24.6 ppm. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd. for C$_{10}$H$_{10}$N$_6$O$_2$Na$^+$, 269.0757; found, 269.0757.
### 2.2.1.8.6 3,5-Bis(bis(3(5)-aminopyrazol-4-yl)methyl)pyrazole \(26\)

White solid, m.p. 162–163 \(^\circ\)C. Yield: 91\% (309 mg, 0.735 mmol, from 100 mg of pyrazole-3,5-dicarbaldehyde). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 7.44 (s, 4H, 4-\(H\)-pz), 5.83 (s, 1H, 4-\(H\)-pz), 5.21 (s, 2H, CH) ppm. \(^1\)C NMR (101 MHz, D\(_2\)O): \(\delta\) 149.7, 147.9, 131.5, 108.7, 102.5, 27.4 ppm. HRMS (ESI-TOF) \(m/z\): \([M + Na]^+ \) calcd. for C\(_{17}\)H\(_{20}\)N\(_{14}\)Na\(^+\), 443.1887; found, 443.1887.

### 2.2.1.8.7 3,5-Bis(bis(3(5)-hydroxypyrazol-4-yl)methyl)pyrazole \(27\)

Light-yellow solid, which decomposes at 220 \(^\circ\)C. Yield: 70\% (177 mg, 0.417 mmol, from 100 mg pyrazole-3,5-dicarbaldehyde). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 7.60 (s, 4H, 4-\(H\)-pz), 5.90 (s, 1H, 4-\(H\)-pz), 5.16 (s, 2H, CH) ppm. \(^1\)C NMR (101 MHz, D\(_2\)O): \(\delta\) 158.1, 132.3, 131.5, 106.2, 102.8, 27.4 ppm. HRMS (ESI-TOF) \(m/z\): \([M + Na]^+ \) calcd. for C\(_{17}\)H\(_{16}\)N\(_{10}\)NaO\(_4\)^+\, 447.1248; found, 447.1225.

### 2.2.1.8.8 Bis(3(5)-aminopyrazol-4-yl)-imidazol-4-yl-methane \(28\)

White solid, m.p. 210–211 \(^\circ\)C. Yield: 98\% (498 mg, 2.04 mmol, from 200 mg of imidazole-4-carbaldehyde). \(^1\)H NMR (400 MHz, D2O): \(\delta\) 8.59 (s, 1H, 2-\(H\)-imidazole), 7.19 (s, 2H, 5-\(H\)-pz), 7.05 (s, 1H, 5-\(H\)-imidazole), 5.19 (s, 1H, CH) ppm. \(^1\)C NMR (101 MHz, D\(_2\)O): \(\delta\) 150.8, 134.7, 134.3, 131.2, 116.6, 105.7, 26.2 ppm. HRMS (ESI-TOF) \(m/z\): \([M + Na]^+ \) calcd. for C\(_{10}\)H\(_{12}\)N\(_{8}\)Na\(^+\), 267.1077; found, 267.1083.

### 2.2.1.8.9 Bis(3(5)-hydroxypyrazol-4-yl)-imidazol-4-yl-methane \(29\)

Yellow solid, m.p. 131–132 \(^\circ\)C. Yield: 94\% (1.169 g, 4.75 mmol, from 500 mg of imidazole-4-carbaldehyde). \(^1\)H NMR (400 MHz, D\(_2\)O): \(\delta\) 7.97 (s, 1H, 2-\(H\)-imidazole), 7.11 (s, 2H, 5-\(H\)-pz), 6.67 (s, 1H, 5-\(H\)-imidazole), 4.83 (s, 1H, CH) ppm. \(^1\)C NMR (101 MHz, D\(_2\)O): \(\delta\) 160.6, 136.9, 134.2, 133.7, 115.8, 104.8, 26.5 ppm. HRMS (ESI-TOF) \(m/z\): \([M + Na]^+ \) calcd. for C\(_{10}\)H\(_{10}\)N\(_{6}\)NaO\(_2\)^+\, 269.0757; found, 269.0757.

### 2.2.1.8.10 Bis(3(5)-aminopyrazol-4-yl)-imidazol-2-yl-methane \(30\)

White solid, m.p. 240–241 \(^\circ\)C. Yield: 99\% (254 mg, 1.04 mmol, from 100 mg of imidazole-2-carbaldehyde). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 7.47 (s, 1H, 4/5-\(H\)-imidazole), 7.46 (s, 1H, 4/5-\(H\)-imidazole), 7.31 (s, 2H, 5-\(H\)-pz), 5.59 (s, 1H, CH) ppm. \(^1\)C NMR (101 MHz, D\(_2\)O): \(\delta\) 150.9, 147.6, 131.5, 119.3, 103.2, 27.9 ppm. HRMS (ESI-TOF) \(m/z\): \([M + Na]^+ \) calcd. for C\(_{10}\)H\(_{12}\)N\(_{8}\)Na\(^+\), 267.1077; found, 267.1087.
2.2.1.8.11 Bis(3(5)-hydroxyazol-4-yl)-imidazol-2-yl-methane 31

Light-yellow solid, m.p. 176 °C. Yield: 75% (478 mg, 1.94 mmol, from 250 mg of imidazole-2-carbaldehyde). 1H NMR (400 MHz, D₂O): $\delta$ 7.32 (s, 2H, 4,5-H-Im), 7.1 (s, 2H, 5-H-pz), 5.2 (s, 1H, CH) ppm. 13C NMR (101 MHz, D₂O): $\delta$ 160.5, 148.3, 133.9, 119.0, 101.4, 27.7 ppm. HRMS (ESI-TOF) m/z: [M + Na]+ calcd. for C₁₀H₁₀N₆NaO₂⁺, 269.0757; found, 269.0773.

2.2.1.8.12 Bis(3(5)-aminopyrazol-4-yl)-phenyl-methane 32

Off-white solid, m.p. 103 °C. Yield: 97% (718 mg, 2.82 mmol, from 310 mg of benzaldehyde). 1H NMR (400 MHz, DMSO-d₆): $\delta$ 7.26–7.25 (m, 4H, 5-H-pz, CH-phenyl), 7.18–7.14 (m, 3H, CH-phenyl), 5.08 (s, 1H, CH) ppm. 13C NMR (101 MHz, DMSO-d₆): $\delta$ 149.9, 145.1, 130.6, 128.7, 128.3, 126.3, 108.9, 34.4 ppm. HRMS (ESI-TOF) m/z: [M + Na]+ calcd. for C₁₃H₁₄N₆Na⁺, 277.1172; found, 277.1180.

2.2.1.8.13 Bis(3(5)-aminopyrazol-4-yl)-4-hydroxyphenyl-methane 33

Off-white solid, m.p. 156–157 °C. Yield: 94% (210 mg, 0.777 mmol, from 101 mg of 4-hydroxybenzaldehyde). 1H NMR (400 MHz, DMSO-d₆): $\delta$ 8.66 (s, br, 5H, NH₂, OH), 7.59 (s, 2H, 5-H-pz), 7.05 (d, 2H, $^3J = 8.6$ Hz, CH-phenyl), 6.68 (d, 2H, $^3J = 8.6$ Hz, CH-phenyl), 5.43 (s, 1H, CH) ppm. 13C NMR (101 MHz, DMSO-d₆): $\delta$ 156.4, 146.0, 133.4, 132.2, 129.2, 115.6, 110.9, 32.4 ppm. HRMS (ESI-TOF) m/z: [M + Na]+ calcd. for C₁₃H₁₄N₆NaO⁺, 293.1121; found, 293.1121.

2.2.1.8.14 Bis(3(5)-aminopyrazol-4-yl)-4-cyanophenyl-methane 34

Pale-yellow solid, m.p. 292–293 °C. Yield: 83% (177 mg, 0.634 mmol, from 102 mg of 4-cyanobenzaldehyde). 1H NMR (400 MHz, DMSO-d₆): $\delta$ 7.77 (d, 2H, $^3J = 8.6$ Hz, CH-phenyl), 7.66 (s, 2H, 5-H-pz), 7.47 (d, 2H, $^3J = 8.6$ Hz, CH-phenyl), 5.71 (s, 1H, CH) ppm. 13C NMR (101 MHz, DMSO-d₆): $\delta$ 149.4, 146.4, 132.9, 132.2, 129.3, 115.6, 110.9, 32.4 ppm. HRMS (ESI-TOF) m/z: [M + Na]+ calcd. for C₁₄H₁₃N₇Na⁺, 302.1124; found, 302.1139.

2.2.1.8.15 Bis(3(5)-aminopyrazol-4-yl)-4-(N,N-diphenylamino)phenylmethane 35

Scarlet-red solid, m.p. 216–217 °C. Yield: 90% (285 mg, 0.676 mmol, from 205 mg of 4-(N,N-diphenylamino)benzaldehyde). 1H NMR (400 MHz, DMSO-d₆): $\delta$ 9.01 (br s, 4H, NH₂), 7.50 (s, 2H, 5-H-pz), 7.26 (t, 4H, $^3J = 7.3$ Hz, CH-phenyl), 7.19 (d, 2H, $^3J = 7.3$ Hz, CH-phenyl), 6.96 (m, 8H, CH-phenyl), 5.30 (s, 1H, CH) ppm. 13C NMR (101 MHz, DMSO-d₆): $\delta$ 147.8, 147.4,
145.8, 138.7, 131.7, 130.0, 129.3, 124.4, 124.0, 123.2, 110.0, 33.0 ppm. HRMS (ESI-TOF) m/z: [M + Na]^+ calcd. for C_{25}H_{23}N_{7}Na^+, 444.1907; found, 444.1891.

2.2.1.8.16  N,N-Bis(bis(3(5)-aminopyrazol-4-yl)methylphenyl)aniline 36

Maroon-red solid, m.p. 225–226 °C. Yield: 48% (132 mg, 0.221 mmol, from 139 mg of bis(4-formylphenyl)phenylamine). A small amount of a brown precipitate was filtered out before the product was precipitated out from the solution with diethyl ether. \( ^1H \) NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) 9.65 (br s, 4H, \( \text{N}H_2 \)), 7.61 (s, 4H, 5-\( H \)-pz), 7.22 (m, 6H, \( CH \)-phenyl), 7.94 (m, 7H, \( CH \)-phenyl), 5.44 (s, 1H, \( CH \)). \( ^13C \) NMR (101 MHz, DMSO-\( d_6 \)): \( \delta \) 147.8, 146.5, 145.9, 138.2, 132.0, 129.9, 129.3, 124.3, 123.5, 122.9, 110.4, 32.7 ppm. HRMS (ESI-TOF) m/z: [M + Na]^+ calcd. for C_{32}H_{31}N_{13}Na^+, 620.2717; found, 620.2727.

2.2.1.8.17  Bis(3(5)-aminopyrazol-4-yl)methane 37

Off-white solid, m.p. 157–158 °C. Yield: 71% (423 mg, 2.37 mmol, from 101 mg of formaldehyde). \( ^1H \) NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) 7.07 (s, 2H, 5-\( H \)-pz), 3.22 (s, 2H, \( CH_2 \)) ppm. \( ^13C \) NMR (101 MHz, DMSO-\( d_6 \)): \( \delta \) 151.7, 129.6, 104.7, 16.5 ppm. HRMS (ESI-TOF) m/z: [M + Na]^+ calcd. for C_{7}H_{10}N_{6}Na^+, 201.0859; found, 201.0842.

2.2.1.8.18  1,1-Bis(3(5)-aminopyrazol-4-yl)decane 38

White solid, m.p. 158–159 °C. Yield: 51% (1.004 g, 3.30 mmol, from 1.011 g of 1-decanal). \( ^1H \) NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) 7.12 (s, 2H, 5-\( H \)-pz), 3.42 (t, 1H, \( J = 7.3 \) Hz, \( CH \)), 1.70 (q, 2H, \( J = 7.0 \) Hz, \( CH_2 \)), 1.21 (s, 14H, \( CH_2 \)), 0.84 (t, 3H, \( J = 7.0 \) Hz, \( CH_3 \)) ppm. \( ^13C \) NMR (101 MHz, DMSO-\( d_6 \)): \( \delta \) 151.2, 128.5, 109.6, 36.3, 31.8, 29.7, 29.6, 29.2, 28.5, 28.0, 22.6, 14.5 ppm. HRMS (ESI-TOF) m/z: [M + Na]^+ calcd. for C_{16}H_{28}N_{6}Na^+, 327.2267; found, 327.2248.

2.2.1.8.19  2,2-Bis(3(5)-aminopyrazol-4-yl)butane 39

Purified by column chromatography on silica gel using CHCl_3/CH_3OH gradient elution (3:1, 2:1, 1:1, 1:2, 1:3, 1:4, followed by neat CH_3OH). R_f was 0.49 with CHCl_3/CH_3OH (3:1) and 0.57 with CHCl_3/CH_3OH (2:1). The pure product was isolated as a light-yellow solid, m.p. 176–177 °C. Yield: 19% (130 mg, 0.590 mmol, from 225 mg of 2-butanone). \( ^1H \) NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) 7.23 (s, 2H, 5-\( H \)-pz), 1.86 (q, 2H, \( J = 7.3 \) Hz, \( CH_2 \)), 1.32 (s, 3H, \( CH_3 \)), 0.66 (t, 3H, \( J = 7.0 \) Hz, \( CH_3 \)) ppm. \( ^13C \) NMR (101 MHz, DMSO-\( d_6 \)): \( \delta \) 150.9, 128.4, 110.7, 33.9, 31.3, 25.0, 9.2 ppm. HRMS (ESI-TOF) m/z: [M + Na]^+ calcd. for C_{10}H_{16}N_{6}Na^+, 243.1328; found, 243.1325.
2.2.1.8.20 2,2-Bis(3(5)-aminopyrazol-4-yl)pentane 40

Purified by column chromatography on silica gel using ClCH₂CH₂Cl/CHCl₃/CH₃OH gradient elution (3:1:1 followed by 2:1:1) and then ClCH₂CH₂Cl/CH₃OH gradient elution (2:1, 1:1, 1:2, 1:4, followed by neat CH₃OH). R_f was 0.27 with ClCH₂CH₂Cl /CHCl₃/CH₃OH (2:1:1). The pure product was isolated as a very light-yellow solid, m.p. 179–180 °C. Yield: 18% (511 mg, 2.18 mmol, from 1.035 g of 2-pentanone). ¹H NMR (400 MHz, DMSO-d₆): δ 11.3 (s, br, NH), 7.22 (s, 2H, 5-H-pz), 3.67 (s, br, NH₂), 1.80 (m, 2H, CH₂), 1.35 (s, 3H, CH₃), 1.08 (m, 2H, CH₂), 0.83 (t, 3H, 3 J = 6.2 Hz, CH₃) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 151.3, 127.9, 111.1, 41.6, 33.7, 25.8, 17.7, 15.1 ppm. HRMS (ESI-TOF) m/z: [M + Na]^+ calcd. for C₁₁H₁₈N₆Na^+, 257.1485; found, 257.1489.

2.2.1.8.21 3,3-Bis(3(5)-aminopyrazol-4-yl)pentane 41

Purified by column chromatography on silica gel using ClCH₂CH₂Cl/CH₃OH gradient elution (4:1, 3:1, 2:1, 1:1). R_f was 0.31 with ClCH₂CH₂Cl/CH₃OH (3:1). The product was rinsed with a minimum amount of ClCH₂CH₂Cl to remove traces of 3-aminopyrazole. The pure product was isolated as a light-yellow solid, m.p. 181–182 °C. Yield: 8% (215 mg, 0.915 mmol, from 997 mg of 3-pentanone). ¹H NMR (400 MHz, DMSO-d₆): δ 7.28 (s, 2H, 5-H-pz), 1.80 (q, 2H, 3 J = 7.3 Hz, CH₂), 0.55 (t, 3H, 3 J = 7.2 Hz, CH₃) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 151.0, 129.1, 109.2, 37.4, 25.7, 8.4 ppm. HRMS (ESI-TOF) m/z: [M + Na]^+ calcd. for C₁₁H₁₈N₆Na^+, 257.1485; found, 257.1490.

2.2.1.8.22 1,1-Bis(3(5)-aminopyrazol-4-yl)cyclopentane 42

Purified by column chromatography on silica gel using CHCl₃/CH₃OH gradient elution (10:1, 8:2, 7:3, 2:1, 1:1, 1:2, 1:4, followed by neat CH₃OH). R_f was 0.25 with CHCl₃/CH₃OH (2:1). The product was further purified by dissolving in 15 mL of ethanol, precipitating with excess diethyl ether, and sonicating the filtered product with water, followed by filtration and drying. The pure product was obtained as a light-gray solid, m.p. 146–147 °C. Yield: 13% (464 mg, 2.00 mg, from 2.497 g of cyclopentanone). ¹H NMR (400 MHz, DMSO-d₆): δ 7.26 (s, 2H, 5-H-pz), 3.80 (s, br, 4H, NH₂), 1.98 (s, 4H, CH₂), 1.58 (s, 4H, CH₂) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 151.1, 127.9, 110.6, 41.3, 37.7, 23.4 ppm. HRMS (ESI-TOF) m/z: [M + Na]^+ calcd. for C₁₁H₁₆N₆Na^+, 255.1328; found, 255.1319.
2.2.1.8.23 1,1-Bis(3(5)-aminopyrazol-4-yl)-1-phenyl-ethane 43

Purified by column chromatography on silica gel using CH₂Cl₂/CH₃OH gradient elution (10:1, 10:1.5, 10:2, 7.5:2.5, 7:3, 2:1, 1:2, 1:4, followed by neat CH₃OH). Rₚ was 0.47 with CH₂Cl₂/CH₃OH (10:1) and 0.18 with CH₂Cl₂/CH₃OH (10:2). The pure product was isolated as a brownish-yellow solid, m.p. 181–182 °C. Yield: 12% (345 mg, 1.29 mmol, from 1.298 g of acetophenone). ¹H NMR (400 MHz, DMSO-d₆): δ 7.18–7.31 (m, 5H, CH-phenyl), 6.97 (s, 2H, 5-H-pz), 1.85 (s, 3H, CH₃) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 150.9, 147.7, 129.8, 128.5, 127.6, 126.4, 111.9, 29.4 ppm. HRMS (ESI-TOF) m/z: [M + Na]⁺ calcd. for C₁₄H₁₆N₆Na⁺, 291.1328; found, 291.1307.

2.2.1.9 General procedure for deamination

To a 25 mL round bottom flask containing the substrate (21, 24, 26, 28, or 30) in H₂O (5–20 mL) was added hypophosphorous acid (50% aqueous solution) in a 1:10 molar ratio (amino group/H₃PO₂). The solution was acidified with 37% HCl (1:4 molar ratio, substrate/HCl) and was cooled to 0 °C in an ice bath. A solution of NaNO₂ (1.5% in H₂O; 1:2.2 molar ratio of amino group/NaNO₂) was added dropwise, under stirring. The resulting mixture was stirred at 0 °C for 15 min and then allowed to warm to room temperature followed by stirring for 30 min at 35 °C. The solution was then allowed to cool to room temperature and was basified with 20% aqueous NaOH to pH ~12. The solvent was removed under vacuum, and the solid residue was sonicated and refluxed with ethyl acetate (3 × 25–60 mL). Pure products were obtained after filtering out the inorganic solids and evaporating the solvent (Scheme 2.14).

Scheme 2.14: Deamination procedure (exemplified on 24) by diazotation followed by reduction with H₃PO₂.
2.2.1.9.1 Bis(pyrazol-4-yl)-pyrazol-3(5)-yl-methane 45

White solid, m.p. 195 °C. Yield: 57% (50 mg, 0.23 mmol, from 100 mg of 21). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.48 (s, 1H, 5-H-pz), 7.40 (s, 4H, 3,5-H-pz), 6.06 (s, 1H, 4-H-pz), 5.30 (s, 1H, CH) ppm. $^{13}$C NMR (101 MHz, DMSO-$d_6$): $\delta$ 137.9, 129.6, 127.7, 124.0, 103.2, 30.9 ppm. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd. for C$_{10}$H$_{10}$N$_6$Na, 237.0859; found, 237.0835.

2.2.1.9.2 Tris(pyrazol-4-yl)methane 46

Purified by sonication and refluxing in ethyl acetate and acetonitrile (3 × 25 mL each). The pure product was obtained as a white solid, m.p. 239–240 °C. Yield: 40% (35 mg, 0.16 mmol, from 100 mg of 24). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 12.58 (s, 3H, NH-pz), 7.36 (s, 6H, 3,5-H-pz), 5.17 (s, 1H, CH) ppm. $^{13}$C NMR (101 MHz, DMSO-$d_6$): $\delta$ 140.2, 129.0, 127.9, 30.1 ppm. HRMS (ESI-TOF) $m/z$: [M − H]$^-$ calcd. for C$_{10}$H$_9$N$_6$-, 213.0894; found, 213.0868.

2.2.1.9.3 3,5-Bis(bis(pyrazol-4-yl)methyl)pyrazole 47

Purified by sonication in dimethyl sulfoxide, followed by column chromatography on silica gel using CHCl$_3$/CH$_3$OH (2:1). The pure product (R$_f$ = 0.66) was isolated as a white solid, m.p. 234–235 °C. Yield: 40% (30 mg, 0.083 mmol, from 103 mg of 26). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 12.58 (s, 4H, NH-pz), 12.21 (s, 1H, NH-pz), 7.44 (s, 4H, 3,5-H-pz), 7.30 (s, 4H, 3,5-H-pz), 5.83 (s, 1H, 4-H-pz), 5.26 (s, 1H, CH), 5.16 (s, 1H, CH) ppm. $^{13}$C NMR (101 MHz, DMSO-$d_6$): $\delta$ 155.7, 147.3, 138.3, 126.8, 124.5, 123.2, 101.5, 32.0, 29.5 ppm. HRMS (ESI-TOF) $m/z$: [M − H]$^-$ calcd. for C$_{17}$H$_{15}$N$_{10}$-, 359.1486; found, 359.1475.

2.2.1.9.4 Imidazol-4-yl-bis(pyrazol-4-yl)methane 48

Yellow solid, m.p. 131–132 °C. Yield: 63% (165 mg, 0.77 mmol, from 300 mg of 28). $^1$H NMR (400 MHz, D$_2$O): $\delta$ 7.59 (s, 1H, 2-H-imidazole), 7.40 (s, 4H, 3,5-H-pz), 6.7 (s, 1H, 5-H-imidazole), 5.27 (s, 1H, CH) ppm. $^{13}$C NMR (101 MHz, D$_2$O): $\delta$ 141.6, 136.2, 133.1, 123.8, 115.6, 29.9 ppm. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd. for C$_{10}$H$_{10}$N$_6$Na, 237.0859; found, 237.0876.

2.2.1.9.5 Imidazol-2-yl-bis(pyrazol-4-yl)methane 49

Yellow solid, m.p. 269–270 °C. Yield: 21% (65 mg, 0.30 mmol, from 300 mg of 30). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 12.64 (s, 2H, NH-pz), 11.68 (s, 1H, NH-imidazole), 7.42 (s, 4H, 3,5-H-pz), 6.96 (s, 1H, 4-H-imidazole), 6.76 (s, 1H, 5-H-imidazole), 5.33 (s, 1H, CH) ppm. $^{13}$C
NMR (101 MHz, DMSO-\textit{d}_6): \delta 150.4, 127.4, 122.6, 116.3, 32.2 ppm. HRMS (ESI-TOF) \textit{m/z}: [M + Na\textsuperscript{+}] calcd. for C\textsubscript{10}H\textsubscript{10}N\textsubscript{6}Na\textsuperscript{+}, 237.0859; found, 237.0860.

2.2.1.10 One-pot, telescoping synthesis of bis(pyrazol-4-yl)-pyrazol-3(5)-yl-methane 45

Pyrazole-3-carbaldehyde (200 mg, 2.082 mmol) and 3(5)-aminopyrazole (346 mg, 4.164 mmol) were dissolved in ethyl alcohol (20 mL). To the solution was added 37% HCl (40 \textmu L), and the mixture was sonicated for 15 min, followed by refluxing for 30 min. Then the solvent was removed under vacuum, and hypophosphorous acid (50% in H\textsubscript{2}O; 2.748 g, 20.82 mmol) and water (10 mL) were added. After the mixture cooled to 0 °C in an ice bath, a solution of NaNO\textsubscript{2} (308 mg, 4.46 mmol) in water (10 mL) was added dropwise, under stirring. The resulting mixture was stirred at 0 °C for 15 min and then at 35 °C for 30 min. After cooling to room temperature, the solution was basified with NaOH (20% in H\textsubscript{2}O) to pH ~ 12. The solvent was removed under vacuum, and the solid residue was sonicated and refluxed with ethyl acetate (3 \times 60 mL). The pure product (pale-yellow solid) was obtained after filtering out the insoluble inorganic solids and evaporating the solvent under a vacuum (376 mg, 1.76 mmol, 85%) (Scheme 2.15).

Scheme 2.15: One-pot, telescoping synthesis of compound 45.

2.2.1.11 Reaction of bis(3(5)-aminopyrazol-4-yl)-pyrazol-3(5)-yl-methane 21 with pyrazole-3(5)-carbaldehyde.

The reactions were carried out similarly to the preparation of 18, using 21 (50.0 mg, 0.204 mmol) and pyrazole-3(5)-carbaldehyde (19.6 mg, 0.204 mmol in the case of the 1:1 reaction, and 39.3 mg, 0.409 mmol in the case of the 1:2 reaction). Both reactions led to an equilibrium mixture after 10 days of sitting in the presence of molecular sieves (3 Å) in ethanol (none of the two went to completion). In the case of the 1:1 reaction, 21, 50, and 51 were identified by \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6), and no pyrazole-3(5)-carbaldehyde was present (see section 3.1.6.1.5). 21: \delta
\begin{align*}
\sim & 7.50, 7.10, 6.06, 4.97 \text{ ppm.} \quad 50: \delta 8.88, 7.82, 7.60, 7.08, 6.792, 6.787, 6.18, 5.31 \text{ ppm.} \quad 51: \delta 8.84, 7.78, 7.58, 7.22, 6.75, 6.16, 5.71 \text{ ppm.}
\end{align*}

In the case of the 1:2 reaction, 50, 51, and pyrazole-3(5)-carbaldehyde were identified by \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6), and no 21 was present. 50: \delta 8.88, 7.75, 7.58, 7.10, 6.79, 6.79, 6.17, 5.35 \text{ ppm.} 51: \delta 8.85, 7.73, 7.56, 7.22, 6.76, 6.14, 5.75 \text{ ppm.} Pyrazole-3(5)-carbaldehyde: \delta 9.92, 7.86, 6.77 \text{ ppm.} If the final solutions were acidified with HCl (37\% in H\textsubscript{2}O, 10 \mu\text{L}), both 50 and 51 broke down leading to 21 and pyrazole-3(5)-carbaldehyde.

2.2.1.12 Attempted reaction of pyrazole-3(5)-carbaldehyde with pyrazole, 3-methylpyrazole and 3-aminopyridazine

Pyrazole-3(5)-carbaldehyde was dissolved in ethanol acidified with HCl (1:1 molar ratio), and pyrazole, 3-methylpyrazole or 3-aminopyridazine, was added (1:2 molar ratio). After 12 h of reflux, \textsuperscript{1}H NMR and ESI-MS indicated the presence of starting materials (the aldehyde was converted to acetal) and the absence of products analogous to 21 in the resulting solutions.

2.2.1.13 Green protection methodology of different functional groups

The general procedure for green protection was originally published in \textit{Green. Chem. 2016}, \textit{18}, 6209–6214, and is reproduced by permission of The Royal Society of Chemistry.

http://pubs.rsc.org/en/content/articlelanding/2016/gc/c6gc02562e#!divAbstract.

General procedure: The substrate to be protected (100 mg) and 3,4-dihydro-2\textit{H}-pyran (1.1–16.0 equivalents) are added to a 4 mL heavy-wall borosilicate glass pressure tube (pressure rating: 150 psi), which is closed with a threaded plug. The contents are homogenized by sonication and the tube is placed in a preheated oven at 125 °C for 24 hours (Scheme 2.16). After cooling to room temperature, the tube is connected to vacuum through a flask cooled with dry ice, in which the excess DHP is recovered. In many cases, the protected product can be employed directly in subsequent synthetic steps in the same flask. If high purity products are desired, the substrate and DHP must be anhydrous (especially if excess DHP is employed). Alternatively, the products can be purified by silica gel chromatography.
Scheme 2.16: Solvent- and catalyst-free, quantitative protection of NH, OH and SH functional groups with a THP group. Reproduced with permission, from reference 113.

2.2.1.13.1 Tetrahydro-2H-pyran-2-yl benzoate

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.08 (dd, 2H, $^3J = 7.0$ Hz, $^3J = 1.4$ Hz, CH-phenyl), 7.56 (t, 1H, $^3J = 7.3$ Hz, CH-phenyl), 7.44 (t, 2H, $^3J = 8.0$ Hz, CH-phenyl), 6.25 (m, 1H, CH-THP), 3.96–4.02 (m, 1H, C$_2$H$_2$O-THP), 3.73–3.77 (m, 1H, C$_2$H$_2$O-THP), 1.53–1.92 (m, 6H, C$_2$-THP) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 165.2, 133.2, 130.4, 129.8, 128.5, 93.2, 63.3, 29.4, 25.1, 18.7 ppm.

2.2.1.13.2 Tetrahydro-2H-pyran-2-yl stearate

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.95 (s, 1H, CH-THP), 3.85–3.91 (m, 1H, CH$_2$O-THP), 3.64–3.68 (m, 1H, CH$_2$O-THP), 2.33 (t, 2H, $^3J = 7.6$ Hz, C(O)CH$_2$), 1.75–1.85 (m, 2H, C(O)CH$_2$CH$_2$), 1.50–1.70 (m, 6H, CH$_2$-THP), 1.21–1.28 (m, 28H, C(O)CH$_2$CH$_2$(CH$_2$)$_{14}$CH$_3$), 0.86 (t, 3H, $^3J = 7.0$ Hz, C(O)CH$_2$CH$_2$(CH$_2$)$_{14}$CH$_3$) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.7, 92.5, 63.4, 34.6, 32.0, 29.7, 29.6, 29.5, 29.4, 29.35, 29.31, 29.21, 25.0, 24.9, 22.7, 18.8, 14.2 ppm. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd. for C$_{23}$H$_{44}$NaO$_3$+ 391.3182; found 391.3176.

2.2.1.13.3 2-(Phenylthio)tetrahydro-2H-pyran

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.48 (d, 2H, $^3J = 7.2$ Hz, CH-phenyl), 7.20–7.30 (m, 3H, CH-phenyl), 5.21 (t, 1H, $^3J = 5.2$ Hz, CH-THP), 4.16–4.20 (m, 1H, CH$_2$O-THP), 3.57–3.60 (m, 1H, CH$_2$O-THP), 2.00–2.05 (m, 1H, CH$_2$-THP), 1.81–1.86 (m, 2H, CH$_2$-THP), 1.62 (m, 3H, CH$_2$-THP) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 135.5, 130.8, 128.8, 126.7, 85.2, 64.5, 31.6, 25.6, 21.7 ppm.
2.2.1.13.4 1(2)-(Tetrahydro-2H-pyran-2-yl)-1(2)H-1,2,3-benzotriazole

$^1$H NMR (400 MHz, CDCl₃): $\delta$ 8.05 (d, 1H, $^3J = 8.4$ Hz, CH-phenyl), 7.87–7.90 (m, 2H, CH-phenyl), 7.73 (d, 1H, $^3J = 8.8$ Hz, CH-phenyl), 7.47 (t, 1H, $^3J = 6.8$ Hz, CH-phenyl), 7.34–7.44 (m, 2H, CH-phenyl), 6.02 (dd, 1H, $^3J = 8.4$ Hz, $^3J = 3.2$ Hz, C-H-THP), 3.90–3.95 (m, 1H, C-H₂O-THP), 3.74–3.82 (m, 1H, C-H₂O-THP), 2.56–2.65 (m, 1H, CH₂-THP), 2.16–2.24 (m, 2H, CH₂-THP), 1.71–1.88 (m, 3H, CH₂-THP) ppm. $^{13}$C NMR (100 MHz, CDCl₃): $\delta$ 146.3, 144.2, 132.5, 127.6, 127.0, 124.4, 119.8, 118.6, 111.2, 90.8, 85.8, 67.6, 67.0, 30.0, 29.4, 24.9, 24.8, 21.7, 21.5 ppm.

2.2.1.13.5 1(2)-(Tetrahydro-2H-pyran-2-yl)-1(2)H-1,2,3-triazole

$^1$H NMR (400 MHz, CDCl₃): $\delta$ 7.69 (s, 1H, 4-H-triazole), 7.62 (s, 1H, 5-H-triazole), 7.58 (s, 2H, 4-H-triazole and 5-H-triazole), 5.62–5.66 (m, 1H, C-H-THP), 3.88–3.94 (m, 1H, C-H₂O-THP), 3.61–3.67 (m, 1H, C-H₂O-THP), 2.28–2.40 (m, 1H, CH₂-THP), 1.92–2.10 (m, 2H, CH₂-THP), 1.53–1.68 (m, 3H, CH₂-THP) ppm.

2.2.1.13.6 4-Nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole

$^1$H NMR (400 MHz, CDCl₃): $\delta$ 8.35 (s, 1H, 5-H-pz), 8.08 (s, 1H, 3-H-pz), 5.39 (dd, 1H, $^3J = 9.2$ Hz, $^3J = 2.6$ Hz, CH-THP), 4.05–4.09 (m, 1H, CH₂O-THP), 3.69–3.75 (m, 1H, CH₂O-THP), 2.11–2.17 (m, 1H, CH₂-THP), 1.64–2.04 (m, 5H, CH₂-THP) ppm. $^{13}$C NMR (100 MHz, CDCl₃): $\delta$ 135.6, 127.1, 88.5, 67.9, 30.7, 24.8, 21.8 ppm. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd. for C₈H₁₁N₃NaO₃$: 220.0692; found 220.0711.

2.2.1.13.7 2-Phenoxytetrahydro-2H-pyran

$^1$H NMR (400 MHz, CDCl₃): $\delta$ 7.27–7.31 (m, 2H, CH-phenyl), 7.06–7.08 (m, 2H, CH-phenyl), 5.44 (t, 1H, $^3J = 3.3$ Hz, CH-THP), 3.91–3.94 (m, 1H, CH₂O-THP), 3.60–3.63 (m, 1H, CH₂O-THP), 1.99–2.03 (m, 1H, CH₂-THP), 1.80–1.90 (m, 2H, CH₂-THP), 1.50–1.78 (m, 3H, CH₂-THP) ppm. $^{13}$C NMR (100 MHz, CDCl₃): 157.1, 129.2, 121.4, 116.4, 96.2, 61.8, 30.4, 25.3, 18.8 ppm.

2.2.1.13.8 1(2)-(Tetrahydro-2H-pyran-2-yl)-1(2)H-1,2,4-triazole

$^1$H NMR (400 MHz, CDCl₃): $\delta$ 8.21 (s, 1H, 5-H-triazole), 8.08 (s, 2H, 3-H-triazole and 5-H-triazole), 7.87 (s, 1H, 3-H-triazole), 5.38 (dd, 1H, $^3J = 8.8$ Hz, $^3J = 4.4$ Hz, CH-THP), 3.95–3.99
2.2.1.13.9 2-(Decylthio)tetrahydro-2H-pyran

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.80–4.83 (m, 1H, C$_H$-THP), 4.04–4.09 (m, 1H, C$_H$O-THP), 3.64–3.71 (m, 1H, C$_H$2O-THP), 2.43–2.70 (m, 2H, SCH$_2$), 1.58–1.69 (m, 3H, CH$_2$-THP) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 94.7, 64.7, 31.9, 31.5, 30.4, 30.0, 29.64, 29.61, 29.40, 29.3, 29.2, 25.7, 22.7, 21.9, 14.2 ppm.

2.2.1.13.10 4-Chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.59 (s, 1H, 5-$H$-pz), 7.46 (s, 1H, 3-$H$-pz), 5.29–5.33 (m, 1H, C$_H$-THP), 3.64–3.71 (m, 1H, C$_H$2O-THP), 2.80–2.89 (m, 3H, CH$_2$-THP) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 137.9, 125.8, 110.7, 88.0, 67.7, 30.3, 24.7, 22.2 ppm. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd. for C$_8$H$_{11}$ClN$_2$NaO$^+$ 209.0452; found 209.0454.

2.2.1.13.11 4-Bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.59 (s, 1H, 5-$H$-pz), 7.46 (s, 1H, 3-$H$-pz), 5.29–5.33 (m, 1H, C$_H$-THP), 3.64–3.71 (m, 1H, C$_H$2O-THP), 2.80–2.89 (m, 3H, CH$_2$-THP) ppm.

2.2.1.13.12 1-(Tetrahydro-2H-pyran-2-yl)-1H-benzimidazole

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.06 (s, 1H, CH-imidazole), 7.77–7.79 (m, 1H, CH-phenyl), 7.50–7.52 (m, 1H, CH-phenyl), 7.26–7.31 (m, 2H, CH-phenyl), 5.48 (dd, 1H, $^3$$J = 9.6$ Hz, $^3$$J = 2.0$ Hz, CH-THP), 4.10–4.12 (m, 1H, CH$_2$O-THP), 3.71–3.77 (m, 1H, CH$_2$O-THP), 2.08–2.21 (m, 3H, CH$_2$-THP), 1.68–1.81 (m, 3H, CH$_2$-THP) ppm.

2.2.1.13.13 3,5-Diphenyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.88 (d, 2H, $^3$$J = 8.4$ Hz, CH-phenyl), 7.58 (d, 2H, $^3$$J = 8.0$ Hz, CH-phenyl), 7.27–7.5 (m, 6H, CH-phenyl), 6.64 (s, 1H, 4-$H$-pz), 5.22 (dd, 1H, $^3$$J = 10.2$ Hz, $^3$$J = 2.2$ Hz, CH-THP), 4.16–4.18 (m, 1H, CH$_2$O-THP), 3.62 (t, 1H, $^3$$J = 11.7$ Hz, CH$_2$O-THP), 2.65–2.74 (m, 1H, CH$_2$-THP), 2.07–2.10 (m, 1H, CH$_2$-THP), 1.54–1.88 (m, 4H, CH$_2$-THP) ppm.
$^{13}$C NMR (100 MHz, CDCl$_3$): δ 151.2, 145.6, 133.5, 130.6, 129.1, 128.8, 127.8, 126.0, 103.9, 84.5, 67.8, 29.8, 24.9, 23.1 ppm. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd. for C$_{20}$H$_{20}$N$_2$NaO$^+$ 327.1467; found 327.1478.

2.2.1.13.14 1(2)-(Tetrahydro-2H-pyran-2-yl)-1(2)H-indazole

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.15 (s, 1H, 5-H-pz), 8.03 (s, 1H, 3-H-pz), 7.71–7.73 (m, 1H, CH-phenyl), 7.58–7.6 (m, 1H, CH-phenyl), 7.37–7.41 (m, 1H, CH-phenyl), 5.72 (dd, 1H, $^3$J = 9.6 Hz, $^3$J = 2.4 Hz, C-H-THP), 4.01–4.05 (m, 1H, C$_2$O-THP), 3.72–3.78 (m, 1H, C$_2$O-THP), 2.54–2.63 (m, 1H, CH$_2$-THP), 2.06–2.18 (m, 2H, CH$_2$-THP), 1.50–1.82 (m, 3H, CH$_2$-THP) ppm.

2.2.1.13.15 1-(Tetrahydro-2H-pyran-2-yl)-1H-pyrazole

$^1$H NMR (400 MHz, CDCl$_3$): 7.57 (d, 1H, $^3$J = 2.4 Hz, 5-H-pz), 7.52 (d, 1H, $^3$J = 1.6 Hz, 3-H-pz), 6.26 (t, 1H, $^3$J = 2 Hz, 4-H-pz), 5.36 (dd, 1H, $^3$J = 9.6 Hz, $^3$J = 2.4 Hz, CH-THP), 4.00–4.04 (m, 1H, C$_2$O-THP), 3.63–3.69 (m, 1H, C$_2$O-THP), 1.97–2.13 (m, 3H, CH$_2$-THP), 1.48–1.69 (m, 3H, CH$_2$-THP) ppm.

2.2.1.13.16 1-(Tetrahydro-2H-pyran-2-yl)-1H-imidazole

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.58 (s, 1H, 2-H-imidazole), 6.96–7.00 (m, 2H, 4-H-imidazole, 5-H-imidazole), 5.12 (dd, 1H, $^3$J = 2.4 Hz, $^3$J = 9.6 Hz, CH-THP), 3.94–3.97 (m, 1H, C$_2$O-THP), 3.54–3.60 (m, 1H, C$_2$O-THP), 1.75–1.93 (m, 3H, CH$_2$-THP), 1.48–1.66 (m, 3H, CH$_2$-THP) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): δ 135.6, 129.1, 117.0, 100.8, 67.9, 31.5, 24.8, 22.5 ppm.

2.2.1.13.17 3(5)-Methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.45 (d, 1H, $^3$J = 2.2 Hz, 5-H-pz), 7.42 (s, 1H, 3-H-pz), 6.05 (d, 1H, $^3$J = 2.2 Hz, 4-H-pz), 6.02 (d, 1H, $^3$J = 0.8 Hz, 4-H-pz), 5.25 (td, 1H, $^3$J = 7.7 Hz, $^3$J = 2.2 Hz, CH-THP) 4.00–4.07 (m, 1H, C$_2$O-THP), 3.63–3.69 (m, 1H, C$_2$O-THP), 2.41–2.50 (m, 1H, CH$_2$-THP), 2.32 (s, 3H, CH$_3$), 2.27 (s, 3H, CH$_3$), 2.05–2.12 (m, 1H, CH$_2$-THP), 1.92–2.03 (m, 2H, CH$_2$-THP), 1.51–1.71 (m, 3H, CH$_2$-THP) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): δ 149.2, 139.1, 139.0, 128.4, 106.2, 105.8, 87.5, 84.4, 68.1, 67.8, 30.5, 29.4, 25.1, 25.0, 22.88, 22.82, 13.7, 10.98 ppm.
2.2.1.13.18 4-Octyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.36 (s, 2H, 3-$H$-pz and 5-$H$-pz), 5.30 (dd, 1H, $^3J = 10.0$ Hz, $^3J = 2.4$ Hz, CH$_2$-THP), 4.02–4.06 (m, 1H, CH$_2$O-THP), 3.63–3.70 (m, 1H, CH$_2$O-THP), 2.42 (t, 2H, $^3J = 11.6$ Hz, CH$_2$(CH$_2$)$_6$CH$_3$), 2.00–2.12 (m, 3H, CH$_2$-THP), 1.49–1.72 (m, 5H, CH$_2$-THP, CH$_2$CH$_2$(CH$_2$)$_5$CH$_3$), 1.24–1.30 (m, 10H, CH$_2$CH$_2$(CH$_2$)$_5$CH$_3$), 0.86 (t, 3H, $^3J = 6.8$ Hz, (CH$_2$)$_7$C$_3$) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 139.5, 125.6, 122.6, 87.6, 67.9, 32.0, 30.9, 30.5, 29.4, 25.1, 24.3, 22.8, 14.2 ppm. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcld. for C$_{16}$H$_{28}$N$_2$NaO$^+$ 287.2093; found 287.2083.

2.2.1.13.19 3,5-Dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.79 (s, 1H, 4-$H$-pz), 5.11 (dd, 1H, $^3J = 10.0$ Hz, $^3J = 2.0$ Hz, CH$_2$-THP), 3.99–4.04 (m, 1H, CH$_2$O-THP), 3.56–3.62 (td, 1H, $^3J = 11.6$ Hz, $^3J = 2.8$ Hz, CH$_2$O-THP), 2.36–2.46 (m, 1H, CH$_2$-THP), 2.24 (s, 3H, CH$_3$), 2.18 (s, 3H, CH$_3$), 2.01–2.05 (m, 1H, CH$_2$-THP), 1.84–1.89 (m, 1H, CH$_2$-THP), 1.49–1.72 (m, 3H, CH$_2$-THP) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 148.4, 139.9, 106.3, 84.4, 68.1, 29.7, 25.1, 23.2, 13.7, 10.9 ppm. HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcld. for C$_{10}$H$_{16}$N$_2$NaO$^+$ 203.1154; found 203.1178.

2.2.1.13.20 N-(tetrahydro-2H-pyran-2-yl)benzamide

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.76–7.81 (m, 2H, CH-phenyl), 7.41–7.53 (m, 3H, CH-phenyl), 6.60 (br, 1H, $^3J = 7.3$ Hz, NH), 5.30 (t, 1H, $^3J = 8.4$ Hz, CH$_2$-THP), 4.01 (d, 1H, $^3J = 11.0$ Hz, CH$_2$O-THP), 3.63–3.69 (m, 1H, CH$_2$O-THP), 1.41–1.95 (m, 6H, CH$_2$-THP) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.8, 131.8, 129.2, 127.2, 127, 78.4, 66.2, 29.9, 22.0 ppm.

2.2.1.13.21 2-Butoxytetrahydro-2H-pyran

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.52 (m, 1H, CH$_2$-THP), 3.80–3.83 (m, 1H, CH$_2$O-THP), 3.65–3.75 (m, 1H, OCH$_2$), 3.45–3.51 (m, 1H, CH$_2$O-THP), 3.33–3.40 (m, 1H, OCH$_2$), 1.48–1.90 (m, 8H, CH$_2$-THP, OCH$_2$CH$_2$), 1.30–1.40 (m, 2H, CH$_2$CH$_2$CH$_3$), 0.88 (t, 3H, $^3J = 7.7$ Hz, CH$_3$) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 98.9, 67.4, 62.3, 31.9, 30.8, 25.6, 19.7, 19.5, 14.0 ppm.
2.2.1.14 Selective, ambient-temperature C-4 deuteration of pyrazole derivatives by D₂O


2.2.1.14.1 General procedure for catalyzed deuteration in an NMR tube at 25 °C

The pyrazole substrate (0.156 mmole) is dissolved in D₂O (99.97 atom % D; 0.5 mL) directly in a freshly opened ampule, to which DCl (37.0 wt. % in D₂O, 99.5 atom % D) or NaOD (39.9 wt. % in D₂O, 99.8 atom % D) is added; the solution is then transferred to an NMR tube. In the case of the experiments ran in an NMR tube equipped with coaxial insert, a 16 mM aqueous solution of sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS sodium salt) in D₂O is used as reference. The first ¹H NMR scan is collected within 2–3 minutes following addition of the substrate to the solvent; additional scans are collected after 1–30 minutes, depending on the rate of the deuteration (Scheme 2.17).

2.2.1.14.2 General procedure for non-catalyzed deuteration in an NMR tube at 70 °C

The pyrazole substrate (0.156 mmol) is added to an NMR tube purged with N₂, to which D₂O (99.96 atom % D, 0.5 mL) is transferred from a freshly opened ampoule (under a blanket of N₂) via an N₂-purged syringe. The clear solution is placed in an oil bath at 70 °C for 48 hours (9 days in the case of 3(5)-aminopyrazole). In the case of 3(5)-amino-5(3)-phenylpyrazole (which is poorly soluble in water), the deuteration is carried out in CD₃OD (99.89 atom % D) at 55 °C. ¹H NMR indicates 99% deuteration of the C-4 position in all cases. The products are isolated in quantitative yield by evaporation of the solvent under high vacuum (Scheme 2.17).

Scheme 2.17: Selective, ambient-temperature C-4 deuteration of pyrazole derivatives. Reproduced with permission, from reference 114.
2.2.1.14.2.1 3(5)-Aminopyrazole-$d_4$ (from 3(5)-aminopyrazole)

Orange-brown oil. $^1$H NMR (400 MHz, D$_2$O): $\delta$ 7.41 (s, 1H, 5-$H$-pz) ppm. $^{13}$C NMR (101 MHz, D$_2$O): $\delta$ 153.9, 132.2, 92.9 ppm. HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd. for C$_3$H$_4$DN$_3$Na$^+$ 107.0438; found 107.0462.

2.2.1.14.2.2 3(5)-Hydroxypyrazole-$d_3$ (from 3(5)-hydroxypyrazole)

Light yellow solid (m.p. 147–148 °C). $^1$H NMR (400 MHz, D$_2$O): $\delta$ 7.43 (s, 1H, 5-$H$-pz) ppm. $^{13}$C NMR (101 MHz, D$_2$O): $\delta$ 163.0, 134.3, 91.0 ppm. HRMS (ESI-TOF) m/z: [M–H]$^-$ calcd. for C$_3$H$_2$DN$_2$O$^-$ 84.0313; found 84.0342.

2.2.1.14.2.3 5-Amino-1-methylpyrazole-$d_3$ (from 5-amino-1-methylpyrazole)

White solid (m.p. 71–72 °C). $^1$H NMR (400 MHz, D$_2$O): $\delta$ 7.25 (s, 1H, 3-$H$-pz), 3.55 (s, 3H, CH$_3$) ppm. $^{13}$C NMR (101 MHz, D$_2$O): $\delta$ 146.3, 139.1, 91.3, 33.6 ppm. HRMS (ESI-TOF) m/z: [M+H]$^+$ calcd. for C$_4$H$_7$DN$_3$+ 99.0775; found 99.0767.

2.2.1.14.2.4 3(5)-Amino-5(3)-methylpyrazole-$d_4$ (from 3(5)-amino-5(3)-methylpyrazole)

Light yellow solid (m.p. 45–46 °C). $^1$H NMR (400 MHz, D$_2$O): $\delta$ 2.10 (s, 3H, CH$_3$) ppm. $^{13}$C NMR (101 MHz, D$_2$O): $\delta$ 154.3, 143.8, 92.2, 10.4 ppm. HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd. for C$_4$H$_6$DN$_3$Na$^+$ 121.0595; found 121.0619.

2.2.1.14.2.5 3(5)-Amino-5(3)-hydroxypyrazole-$d_5$ (from 3(5)-amino-5(3)-hydroxypyrazole)

Light yellow solid (m.p. 207–208 °C). $^{13}$C NMR (101 MHz, D$_2$O): $\delta$ 173.9, 171.7, 160.8, 159.6, 75.6, 36.3 ppm. HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd. for C$_3$H$_4$DN$_3$NaO$^+$ 123.0387; found 123.0410.

2.2.1.14.2.6 3(5)-Amino-5(3)-tert-butylpyrazole-$d_4$ (from 3(5)-Amino-5(3)-tert-butylpyrazole)

Light orange-brown solid (m.p. 76–77 °C). $^1$H NMR (400 MHz, D$_2$O): $\delta$ 1.19 (s, 9H, CH$_3$) ppm. $^{13}$C NMR (101 MHz, D$_2$O): $\delta$ 157.4, 154.2, 89.3, 30.7, 29.2. HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd. for C$_7$H$_{12}$DN$_3$Na$^+$ 163.1064; found 163.1088.
2.2.1.14.2.7 3(5)-Amino-5(3)-trifluoromethylpyrazole-\textit{d}_4 (from 3(5)-amino-5(3)-trifluoromethylpyrazole)

White solid (m.p. 92–93 °C). $^{13}$C NMR (101 MHz, D$_2$O): $\delta$ 148.7, 142.2, 121.1, 88.7 ppm. HRMS (ESI-TOF) \textit{m}/\textit{z}: [M–H]$^-$ calcd. for C$_4$H$_2$DF$_3$N$_3$– 151.0347; found 151.0342.

2.2.1.14.2.8 3(5)-Amino-5(3)-phenylpyrazole-\textit{d}_4 (from 3(5)-Amino-5(3)-phenylpyrazole)

Brown solid (m.p. 122–123 °C). $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 7.61 (dd, 2H, $^3J = 1.1$ Hz, $^2J = 7.5$ Hz, CH-phenyl), 7.37–7.25 (m, 3H, CH-phenyl) ppm. $^{13}$C NMR (101 MHz, CD$_3$OD): $\delta$ 155.4, 147.6, 132.6, 130, 129.2, 126.5, 90.4 ppm. HRMS (ESI-TOF) \textit{m}/\textit{z}: [M+Na]$^+$ calcd. for C$_9$H$_8$DN$_3$Na$^+$ 183.0751; found 183.0730.

2.2.1.14.3 General procedure for large-scale deuteration

The pyrazole substrate (1.564 mmol) is loaded into a Schlenk flask, which is then purged with N$_2$ three times. D$_2$O or CD$_3$OD (99.89 atom % D, 5.0 mL) is added via N$_2$-purged syringe and the solution is acidified with DCl (37.0 wt. % in D$_2$O, 99.5 atom % D; 139 $\mu$L, 1.564 mmol). After standing for 24 hours under an N$_2$ atmosphere, the solution is slightly basified with anhydrous sodium carbonate (87 mg, 0.82 mmol) and the solvent is removed under vacuum. Dry ethyl acetate (25 mL) is added via N$_2$-purged syringe and the suspension is sonicated followed by stirring for 8 hours. After allowing the solid to settle, the clear solution is transferred to an empty Schlenk flask under an N$_2$ atmosphere. Evaporation of the ethyl acetate solvent under high vacuum affords pure C-4 deuterated (97–99 atom % D) pyrazole derivatives in 78–97% yield.

2.3 pH titration and UV–vis monitoring

Stock solutions of Cu(NO$_3$)$_2$/pyrazole (1:1 molar ratio) and NaOH/Na$_2$CO$_3$ are prepared by dissolving in water 9.7862 g of Cu(NO$_3$)$_2$2.5H$_2$O (42.07 mmol) and 2.8644 g (42.07 mmol) of pyrazole, and 4.5377 g of NaOH (113.4 mmol) and 0.2398 g (1.934 mmol) of Na$_2$CO$_3$H$_2$O, respectively, in 1000.0±0.3 mL volumetric flasks. The concentration of NaOH is verified by titration with potassium hydrogen phthalate (0.1122±0.0003 M) and the solution is protected from atmospheric CO$_2$. Samples for pH and UV–vis measurements are prepared in 25.00±0.06 mL volumetric flasks, by using 10.00 mL of a Cu(NO$_3$)$_2$/pyrazole (1:1 molar ratio) stock solution and increasing amounts of the NaOH/Na$_2$CO$_3$ stock solution (up to a Cu:Hpz:NaOH molar ratio of
1:1:3) or HNO₃ (up to a Cu:Hpz:HNO₃ molar ratio of 3:3:18), completed to 25.00 mL with water followed by filtration.

2.4 Mass spectrometric measurements

Mass spectrometric analysis of the organic compounds and nanojars are performed by using an electrospray ionization source. Sample solutions 10⁻⁴–10⁻⁵ M are prepared in CH₃CN for fluorinated compounds and nanojars, except for the nanojars with butyl or longer alkyl chain substituents, in which case a 1:1 (vol.) mixture of CH₃CN/THF is used, otherwise MeOH is used for other organic compounds. Samples are infused by a syringe pump at 5 µL/min and nitrogen is supplied as nebulizing gas at 500 L/h. The electrospray capillary voltage is set to –2.5 or +3.0 kV, respectively, with a desolvation temperature of 110 °C. The sampling and extraction cones are maintained at 40 V (100 V for nanojars with long alkyl chain substituents) and 4.0 V, respectively, at 80 °C.

2.5 Solution preparation for ¹H NMR monitoring

2.5.1 ¹H NMR monitoring of the reaction of pyrazole-3(5)-carbaldehyde and 3(5)-aminopyrazole

The procedures are reprinted with permission, from J. Org. Chem. 2017, 82, 10549–10562.¹¹² Copyright 2017 American Chemical Society.

Pyrazole-3(5)-carbaldehyde (3.2 mg, 0.033 mmol) is dissolved in ethanol-d₆ (0.56 mL) by gently heating in a firmly closed 1-dram vial. In the case of the acid-catalyzed experiments, DCl (35% solution in D₂O; 3.0 µL, 1.2 mg, 0.033 mmol) is added. After letting the solution cool down to room temperature, 3(5)-aminopyrazole is added to obtain a 1:1 (2.7 mg, 0.033 mmol) or 1:2 molar ratio (5.5 mg, 0.066 mmol) of aldehyde:aminopyrazole. The solution is mixed thoroughly and is loaded immediately into an NMR tube. The ¹H NMR monitoring experiment is started 3 minutes after mixing the aldehyde with the aminopyrazole. Room temperature spectra are collected every 5 minutes for 40 minutes, then every 15 minutes up to a total reaction time of 24 hours. The temperature of the instrument is then increased to 55 °C and spectra are collected after 5, 10 and 15 minutes, then every 30 minutes up to 24 hours.
2.5.2 \(^1\)H NMR monitoring of deprotonation of 1-(tetrahydropyran-2-yl)pyrazole

1-(tetrahydropyran-2-yl)pyrazole (57 mg, 0.37 mmol) is dissolved in THF-\(d_8\) (1 g) and is loaded into an NMR tube and purged with N\(_2\) three times and left under N\(_2\) atmosphere. The NMR tube cooled down to –55 °C and substoichiometric amount of \(n\)BuLi (1.6 M in hexanes) added to the 1-(tetrahydropyran-2-yl)pyrazole THF-\(d_8\) solution via N\(_2\) purged syringe. \(^1\)H NMR was done immediately after the addition of \(n\)BuLi, and peaks of both protonated and deprotonated species were observed. Slight excess of \(n\)BuLi (1.6 M in hexanes) added, and variable-temperature \(^1\)H NMR was done (t = 0 is immediately after addition of \(n\)BuLi). Variable-temperature \(^1\)H NMR continued until the material decomposition above ~0 °C, and an off-white precipitate falls out of the solution.
3.1 Organic chemistry results

3.1.1 Solvent- and catalyst-free, quantitative protection of hydroxyl, thiol, carboxylic acid, amide and heterocyclic amino functional groups

The results discussed in this section were originally published in *Green. Chem.* **2016, 18**, 6209–6214, and are reproduced by permission of The Royal Society of Chemistry.

The reaction of neat DHP with various substrates bearing different reactive functional groups, such as hydroxyl, thiol, carboxylic acid, amide and heterocyclic amino groups, proceeds in the absence of a catalyst at 125 °C to produce the THP-protected substrate, often in quantitative yield (Scheme 2.16, Table 3.1). Protection reactions employing DHP are typically carried out in the presence of an acidic catalyst, which activates DHP by protonation.115 We find that while the catalyst-free reaction does not occur at ambient temperature, the acidity of the substrate proton to be replaced by the THP group increases sufficiently at higher temperatures to enable reactivity in the absence of a catalyst. Thus, many substrates are quantitatively protected at 125 °C. The proposed mechanism of the protection reaction, by electrophilic addition of the substrate to DHP, is exemplified with benzimidazole in (Scheme 3.1). The clean protection of benzimidazole by quantitative transformation into 1-(tetrahydropyran-2-yl)benzimidazole is demonstrated in (Figure 3.1). After removing the excess DHP under vacuum, pure protected product is obtained quantitatively. Further synthetic steps can be carried out on this intermediate in the same flask.

The utility of a same-pot protection step in telescoping syntheses had been illustrated with the one-pot synthesis of 3-alkyl- and 3,5-dialkylpyrazoles.111,110

As the first step in the protection mechanism is a proton transfer, substrates with increased acidity are expected to be protected more readily by DHP, whereas less acidic substrates are expected to have reduced reactivity. A series of substrates, with pK<sub>a</sub> values ranging from 4.2 to 27, have been tested (Table 3.1).
Although a direct correlation between substrate acidity and reactivity toward DHP is indeed found, the conversion is affected by several other variables: miscibility of substrate and DHP, amount of DHP employed, nucleophilicity of the atom to be protected, steric hindrance, reaction time and reaction temperature. While the optimization of each variable for every substrate is beyond the scope of this communication, the following guiding principles have been established.

Table 3.1: Protection of different functional groups with DHP (at 125 °C in 24 h). pKₐ values shown in italics represent predicted values, calculated using Advanced Chemistry Development Software v11.02 (© 1994–2016 ACD/Labs). Conversions are based on the ratio of integrated ¹H NMR signals of the THP-protected product and the residual substrate, and are verified by ¹³C NMR spectroscopy. Reproduced with permission, from reference 113.

<table>
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<tr>
<th>Substrate</th>
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<th>Conversion (%)</th>
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Table 3.1: Continued.
Table 3.1: Continued.

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Scheme 3.1: Proposed mechanism of protection with 3,4-dihydro-2H-pyran (exemplified on benzimidazole). Reproduced with permission, from reference 113.

3.1.1.1 Substrate acidity

Increasing acidity of the substrate favors conversion. For instance, pyrazole (pK<sub>a</sub> 14.2) requires 24 hours for complete conversion (at 125 °C with 1.1 equiv. of DHP), while 1,2,3-benzo triazole (pK<sub>a</sub> 8.2) is completely protected in 6 hours. On the other hand, indole (pK<sub>a</sub> 17) and aniline (pK<sub>a</sub> 27) are not protected at all. It is noted that all four substrates mentioned here are miscible with DHP under the given reaction conditions. Consequently, we can predict that this methodology should be suitable for the protection of substrates such as 1,2,3,4-tetrazole (pK<sub>a</sub> 4.9),
phthalimide (pKₐ 8.3), theophylline (pKₐ 8.8), purine (pKₐ 8.9) and 5,7-diazaindazole (pKₐ 9.6), but not carbazole (pKₐ 17.1), isoindole (pKₐ 17.0) or less acidic substrates.

Figure 3.1: $^1$H NMR spectra documenting the quantitative protection of benzimidazole by 3,4-dihydro-2H-pyran to give pure 1-(tetrahydropyran-2-yl) benzimidazole. Reproduced with permission, from reference 113.

3.1.1.2 Miscibility of the substrate with DHP/Amount of DHP employed

The conversion is affected if the substrate does not mix with the protecting agent (DHP). In those cases, the conversion can be increased by using larger amounts of DHP. For example, benzimidazole is more acidic (pKₐ 12.8) than pyrazole (pKₐ 14.2), yet under similar conditions (1.1 equiv., 125 °C, 24 h) the conversion is only 83%. Increasing the amount of DHP to 2 equivalents, however, provides 100% conversion under the same reaction conditions. Similarly, although indazole does not mix with DHP, 100% conversion can be achieved at 125 °C in 24 h
with 3 equiv. of DHP. In the case of 3,5-diphenylpyrazole, 100% conversion can be achieved (at 125 °C at 24 h) if 8 equivalents of DHP are employed.

3.1.1.3 Nucleophilicity of the atom to be protected

Although increasing acidity of the substrate facilitates the protonation of DHP (first step in Scheme 3.1), decreasing nucleophilicity of the anionic intermediate (N\textsuperscript{-}, O\textsuperscript{-} or S\textsuperscript{-}) is unfavorable for the nucleophilic attack on the protonated, electrophilic DHP cation (second step in Scheme 3.1). Owing to the larger electronegativity of the O-atom and the delocalization of the negative charge over three (vs. one) non-bonding electron pairs, O\textsuperscript{-} is a much weaker nucleophile than N\textsuperscript{-}. Thus, despite a larger acidity compared to heterocyclic amines (such as pyrazole or imidazole), only 50% conversion is observed for phenol under the same experimental conditions (1.1 equiv. of DHP, 125 °C, 24 h). The nucleophilicity of carboxylates is further reduced by delocalization of the negative charge over two O-atoms. Carboxylic acids, ca. one million times more acidic than phenol, are only sparingly protected under the experimental conditions mentioned above. Nevertheless, quantitative protection is achieved if DHP is used in excess (Table 3.1). In the case of aromatic substrates, conjugation provides additional stabilization of the anionic intermediate (phenoxide, carboxylate) and leads to even further reduction of nucleophilicity. Alcohols are more easily protected than phenols (despite being ca. one million times less acidic than phenol), due to the superior nucleophilicity of alkoxides compared to phenoxide. Sulfur, due to its low electronegativity, larger size and better polarizability, is an excellent nucleophile; hence, thiophenol is easily protected.

3.1.1.4 Steric hindrance

As expected, steric hindrance does hamper conversion. For example, while pyrazole is completely protected in 24 hours (at 125 °C with 1.1 equiv. of DHP), 3,5-dimethylpyrazole is converted only 50% under the same conditions, and 3,5-ditet-butylpyrazole is not protected at all. These substrates have similar acidities and are all miscible with DHP under the reaction conditions.

3.1.1.5 Reaction time

Longer reaction times do not increase conversion significantly. For example, in the case of 3,5-diphenylpyrazole, extending the reaction time from 24 to 72 hours (at 125 °C with 5.0 equiv. of DHP) leads to a marginal increase in conversion, from 92 to 96%. Similarly, in the case of
benzimidazole, tripling the reaction time (at 125 °C with 1.1 equiv. of DHP) leads to an increase in conversion from 83 to 93%, but completion is not reached.

3.1.1.6 Reaction temperature

Higher temperatures do favor conversion, as the acidity of the substrate increases with temperature. For instance, pyrazole is protected only 92% after 20 hours at 125 °C; however, complete protection is achieved if the temperature is raised to 150 °C. Lower temperatures can also be employed, at the expense of lower conversions. At 100 °C, pyrazole is protected only 68% (after 24 hours with 1.1 equiv. DHP); nevertheless, increasing the amount of DHP to 2.0 equiv. provides 100% conversion under the same conditions. The combined influence of reaction temperature, reaction time and amount of DHP in the case of pyrazole is illustrated in (Table 3.2). Water is also found to react with DHP under the aforementioned conditions, providing an equilibrium mixture of 5-hydroxypentanal and 2-hydroxytetrahydropyran, along with their THP-protected products, 5-(2-tetrahydropyanyloxy)pentanal and 2-(2-tetrahydropyanyloxy)tetrahydropyran.116,117,118,119 The reagents used in this study were not anhydrous; therefore, small amounts of the above-mentioned compounds are observed in those products that are obtained in the presence of DHP in large excess. These side-products are not observed if the reagents are anhydrous, or if DHP is used in close to stoichiometric amounts.

Table 3.2: Protection of pyrazole using varying amounts of DHP, at different temperatures and over varying periods of time. Conversions are based on the ratio of integrated $^1$H NMR signals of THP-protected product and residual pyrazole. Reproduced with permission, from reference 113.

<table>
<thead>
<tr>
<th>DHP (mole equiv)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
</tr>
</thead>
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<tr>
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<td>24</td>
<td>100</td>
</tr>
<tr>
<td>1.1</td>
<td>125</td>
<td>20</td>
<td>92</td>
</tr>
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</tr>
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<td>2.0</td>
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3.1.2 Lithiation/alkylation of THP-pyrazole

The results discussed in this section were originally published in RSC Adv. 2015, 5, 24081–24093,\(^{111}\) and are reproduced by permission of The Royal Society of Chemistry.

Lithiation of THP-protected pyrazole with \(^{n}\)BuLi at \(-78^\circ\text{C}\), followed by the addition of a primary haloalkane, leads to 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles with excellent conversions, as shown by \(^1\)H NMR (Table 2.1). As expected for \(\text{SN}_2\) nucleophilic substitutions in general, this alkylation works best with least hindered, primary alkyl halides. Indeed, close to quantitative conversions (89–99\%) are obtained with 1-iodo- and even with 1-bromoalkanes (except for C\(_{16}\)). Under identical experimental conditions, secondary alkyl and vinyl iodides provide low conversions (cyclohexyl: 16\%; isopropyl: 7\%; \(\text{sec}\)-butyl: <1\%; vinyl: 7\%), and no reaction is observed with \(\text{tert}\)-butyl iodide and iodobenzene. Refluxing the reaction mixture under nitrogen does not provide a significant improvement. Allyl- and benzyl bromides give conversions of 7\% and 36\%, respectively. Isobutyl iodide (1-iodo-2-methylpropane), although a primary alkyl iodide, also provides a poor conversion (7\%), further evidencing that steric crowding around the electrophilic reaction center is a critical limiting factor. Isopentyl iodide (1-iodo-3-methylbutane), in which the branching is one carbon atom further from the reaction center, reacts efficiently, with conversion similar to the \(n\)-butyl and \(n\)-pentyl analogs.

Lithiation/alkylation of THP-pyrazole were performed by two methods:

Method A. Initially, the alkylations were carried out with excess (10 mole \%) iodoalkane, to maximize the conversion of pyrazole to alkylpyrazole. Excellent conversions were obtained indeed (94–100\%, Table 2.1), and the small amounts (less than 6\%) of unreacted 1-(tetrahydropyran-2-yl)pyrazole left behind in the reaction mixture can easily be removed by gentle heating under reduced pressure. The excess 1-iodoalkane (up to C\(_7\)) can also be removed under similar conditions, at temperatures that do not affect the product. The removal of the higher iodoalkanes, however, becomes increasingly more difficult as their boiling point increases, and the higher temperatures needed for the distillation (under reduced pressure) of C\(_8\) and longer iodoalkanes lead to isomerization of the product and even loss of the protecting group. While this is not a problem if the target is the preparation of unprotected 3(5)-alkylpyrazoles, the isolation of pure THP-protected alkylpyrazoles (C\(_8\) and up) has to be performed by column chromatography.
Pure 5-hexadecyl-1-(tetrahydropyran-2-yl)pyrazole is obtained, for example, by elution with hexane/ethyl acetate (6:1) on a silica gel column.

Method B. To simplify the purification of THP-protected alkylpyrazoles (C\textsubscript{8} and up) and eliminate the need for chromatography, we next carried out alkylations with excess (10 mole %) 1-(tetrahydropyran-2-yl)pyrazole, instead of excess iodoalkane. In this case, the iodoalkane is completely consumed during the reaction (except for C\textsubscript{16}), and the excess unreacted 1-(tetrahydropyran-2-yl)pyrazole is readily removed by heating to 55–60 °C under reduced pressure (0.1–0.2 mmHg) (Table 2.1: entries 11, 13, 15, 18, 20, 21).

3.1.3 \textsuperscript{1}H NMR confirmation of deprotonation site in THP-pyrazole

In order to confirm that the deprotonation/lithiation site in THP-pyrazole is the same site of alkylation, we have monitored the deprotonation of 1-(tetrahydropyran-2-yl)pyrazole by \textsuperscript{n}BuLi in an NMR tube under an N\textsubscript{2} atmosphere, using THF-\textit{d}\textsubscript{8} as solvent. The NMR tube containing the 1-(tetrahydropyran-2-yl)pyrazole solution was cooled down to –55 °C and a substoichiometric amount of \textsuperscript{n}BuLi (1.6 M in hexanes) was added. \textsuperscript{1}H NMR spectrum was recorded immediately after the addition of \textsuperscript{n}BuLi, and peaks of both protonated and deprotonated species were observed (Figure 3.2). The spectrum is stable over time (1 hour). Next, a slight excess of \textsuperscript{n}BuLi was added, and variable-temperature \textsuperscript{1}H NMR spectra were recorded (t = 0 is immediately after addition of \textsuperscript{n}BuLi) (Figure 3.3). No shifts are observed as time passes or as the temperature increases; however, decomposition occurs above ~0 °C, and an off-white precipitate falls out of the solution.
Figure 3.2: $^1$H NMR spectrum of 1-(tetrahydropyran-2-yl)pyrazole in THF-$d_8$ at –55 °C, immediately after a substoichiometric amount of $^n$BuLi was added. Peaks of both the protonated (red) and deprotonated (blue) species are observed. Reproduced with permission, from reference 110.

Figure 3.3: Variable-temperature $^1$H NMR spectra of 1-(tetrahydropyran-2-yl)pyrazole in THF-$d_8$, with a slight excess of $^n$BuLi added. Reproduced with permission, from reference 110.
3.1.4 I$_2$-catalyzed thermal isomerization of 5-alkyl- to 3-alkyl-1-THP-pyrazoles

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Isomerization of the unreactive 5-alkyl-1-THP-pyrazole isomer to the reactive 3-alkyl-1-THP-pyrazole isomer, is crucial for the synthesis of 3,5-dialkyl-1-THP-pyrazole by further lithiation/alkylation of monoalkyl-1-THP-pyrazole. Such protective group switching is usually accomplished by an acid-catalyzed, sequential or direct deprotection-reprotection route. Thermal isomerization of 5-alkyl- to 3-alkyl-1-THP-pyrazoles, presented herein, offers a new green alternative, which eliminates the need for solvents, additional reagents and work-up. In addition, presence of a catalytic amount of iodine (I$_2$) greatly reduces the reaction time needed to reach equilibrium. This discovery is rooted in our observation that when 5-hexyl-1-THP-pyrazole is prepared from 1-iodohexane, it undergoes isomerization much faster than when it is prepared from 1-bromohexane, under the same conditions. Indeed, addition of 0.08 mol% I$_2$ to 5-hexyl-1-THP-pyrazole prepared from 1-bromohexane reduces the isomerization time at 125 °C from 8 days to 24 hours, confirming our hypothesis that trace amounts of iodine originating from 1-iodohexane catalyze the isomerization. The mechanism of isomerization is likely similar to the one proposed for the 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) catalyzed SEM group transposition in SEM-protected pyrazoles, as well as the N,N-dimethylaminosulfonyl (DMAS), benzyl (Bn), methoxymethyl (MOM) and SEM protecting group switching in N-protected imidazoles catalyzed by DMAS-Cl, BnBr, MOM-Cl or SEM-Cl, respectively. The protecting agents listed above are alkylating agents which, upon alkylation of the free N2-atom of the N1-protected diazole, induce the elimination of the protecting group and render the N1-atom free. The liberated protecting group alkylates the next substrate and propagates the reaction. In our case (Scheme 3.2), the alkylating agent is presumed to be 2-iodotetrahydropyran, which initially forms from the reaction of 3,4-dihydro-2H-pyran (formed in trace amounts as a result of partial deprotection of the substrate upon heating) with HI (formed from the reaction of I$_2$ with the pyrazole ring, leading to 4-iodopyrazole). Alternatively, I$_2$ can react directly with 3,4-dihydro-2H-pyran to produce 2,3-diiodotetrahydropyran, which can react similarly to 2-iodotetrahydropyran as the initial alkylating agent.
Scheme 3.2: Proposed mechanism of the I$_2$-catalyzed thermal isomerization of 5-alkyl- to 3-alkyl-1-THP-pyrazoles (R = alkyl). Reproduced with permission, from reference 110.

3.1.5 One-pot telescoping synthesis of 3,5-dialkylpyrazoles

Aiming at greener preparative methods, we developed a telescopic synthesis of 3,5-dialkylpyrazoles (53% overall yield based on 1$H$-pyrazole) by combining five synthetic steps into a one-pot method (Scheme 2.4). The solvent- and catalyst-free quantitative step of pyrazole protection and the solvent-free isomerization step of the unreactive 5-alkyl-1-THP-pyrazole to the reactive 3-alkyl-1-THP-pyrazole isomer are both crucial to the value of this method. Our method significantly reduces the consumption of organic solvents and additional reagents and eliminates the use of highly toxic or explosive starting materials and reagents (such as hydrazine, diazomethane, and derivatives, often employed for the synthesis of pyrazole derivatives). Because the one-pot method requires no purification of the intermediates, losses are eliminated, and waste production is greatly diminished.

Improved overall yields of 3,5-dialkylpyrazoles (60% based on 1$H$-pyrazole) are obtained if the THP-protected 3,5-dialkylpyrazoles are purified before deprotection, as column chromatographic
separation on the protected pyrazoles is more efficient than on the deprotected products. Pure 3,5-
dialkylpyrazoles are obtained after deprotection with HCl and removal of the solvent in vacuum.
This new methodology could also be applied to the synthesis of various other 3,5-disubstituted
pyrazoles (e.g., alkyl, halogen, hydroxyl, amino, azido, carbonyl, organo-element substituents),
both symmetrical and unsymmetrical, by employing the appropriate electrophiles.

3.1.6 Reaction of amines with aldehydes and ketones

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2017, 82, 10549–10562. \(^{112}\) Copyright 2017 American Chemical Society.
While it is well-known that the formation of Schiff bases from aromatic aldehydes and aromatic
amines is facilitated under acidic conditions, \(^{126}\) no Schiff base product (\(N,1\)-bis(pyrazol-3(5)-
yl)methanimine, 18 (Scheme 3.3)) is obtained from the reaction of pyrazole-3(5)-carbaldehyde
with 3(5)-aminopyrazole (1:1 molar ratio) in the presence of HCl in refluxing ethanol. Instead, a
complex mixture forms, from which bis(3(5)-aminopyrazol-4-yl)-pyrazol-3(5)-yl-methane 21
(Scheme 3.3) was isolated by crystallization and structurally characterized by single-crystal X-ray
diffraction (see section 3.2.4.4.3). When the same reaction is run at room temperature in the
absence of acid, however, an equilibrium mixture of Schiff base 18 and starting materials is
obtained (Scheme 3.3). In order to get insight into the reaction mechanism and to understand the
different outcomes described above, we monitored the reaction of pyrazole-3(5)-carbaldehyde
with 3(5)-aminopyrazole continuously by \(^1\)H NMR in ethanol-\(d_6\) (in NMR tube) under four
different conditions. Also, we ran the same reactions on a larger scale in ethanol and periodically
analyzed samples withdrawn from the reaction mixture by electrospray ionization mass
spectrometry (ESI-MS in CH\(_3\)OH or CH\(_3\)CN) in addition to \(^1\)H NMR (in DMSO-\(d_6\)).
Complementing the \(^1\)H NMR spectroscopic study, the ESI-MS analysis provides crucial
information about the identities of the reaction intermediates and final products.
Scheme 3.3: Different outcomes of the reaction of pyrazole-3-carbaldehyde with 3(5)-aminopyrazole in the absence or presence of HCl. Reproduced with permission, from reference 112.

3.1.6.1 Reaction monitoring by $^1$H NMR/ESI-MS and mechanistic details

Two observations need to be pointed out about the pyrazole-3(5)-carbaldehyde and 3(5)-aminopyrazole starting materials, before considering their reaction. First, the as-prepared pyrazole-3(5)-carbaldehyde is a dimer in the solid state,\textsuperscript{88,127} whereas in solution it has been reported to exist as either the pure monomer (in pyridine-$d_6$) or together with its dimeric forms (2:1 mixture of monomer and dimers in DMSO-$d_6$) (Scheme 3.4).\textsuperscript{127b}

Scheme 3.4: Monomeric and dimeric forms of pyrazole-3(5)-carbaldehyde. Reproduced with permission, from reference 112.

In our hands, the monomeric form was observed exclusively in both DMSO-$d_6$ (δ 9.93, 7.93, 6.77 ppm) and ethanol-$d_6$ (δ 9.91, 7.68, 6.77 ppm), implying dissociation of the insoluble dimer upon dissolution (heating to ~50 °C is required to speed up dissolution). In the presence of HCl (1:1 molar ratio), the signal of the proton adjacent to the pyrazole N-atom is slightly shifted in DMSO-$d_6$ (δ 9.90, 7.89, 6.77 ppm), whereas in ethanol-$d_6$ all three signals are drastically shifted as the aldehyde is transformed into diethyl acetal (δ 8.30, 6.75, 5.84 ppm), with only small amounts (1–2%) of aldehyde present (Figure 3.4). The formation of the acetal is also documented by ESI-MS, which shows its Na$^+$ adduct at $m/z$ 193.1.
Figure 3.4: DCl-catalyzed reaction of pyrazole-3(5)-carbaldehyde and 3(5)-aminopyrazole (in 1:1 and 1:2 molar ratios) monitored over time by $^1$H NMR in ethanol-$d_6$. Reproduced with permission, from reference 112.

When 3(5)-aminopyrazole is added to the latter solution, the peak in the $^1$H NMR spectrum corresponding to the free aldehyde ($\delta$ 9.90 ppm) is absent. Consequently, we conclude that the reactive form is the monomeric aldehyde and that the equilibrium is continuously driven toward the aldehyde, which is then immediately consumed.

Second, during the acid-catalyzed reactions in ethanol-$d_6$, selective deuteration of 3(5)-aminopyrazole at the C-4 position was observed. Thus, in the reaction with pyrazole-3(5)-carbaldehyde, the signal of the 3(5)-aminopyrazole proton at the C-4 position disappears much more rapidly than the one of the proton at the C-3 position (as seen in Figure 3.4).
The following NMR studies, assisted by ESI-MS measurements, offer important insights into the mechanism of the reaction of 3(5)-aminopyrazole with pyrazole-3(5)-carbaldehyde.

3.1.6.1.1 Aldehyde/amine in 1:1 molar ratio in the absence of acid

The reaction of pyrazole-3(5)-carbaldehyde with 3(5)-aminopyrazole in ethanol-$d_6$ in the absence of an acid catalyst is slow at 25 °C and yields an equilibrium mixture of the Schiff base product 18 and starting materials (Figure 3.5). A maximum conversion of 90% is observed after 24 h. ESI-MS confirms the Schiff base (18 + H+: $m/z$ 162.1; 18 + Na+: $m/z$ 184.1) as the only major species observed besides the starting materials. If the reaction is run in anhydrous ethanol in the presence of molecular sieves (3 Å), the equilibrium reaction is forced to completion by removing the water byproduct from the reaction mixture. Thus, Schiff base 18 is obtained with 100% conversion.

3.1.6.1.2 Aldehyde/amine in 1:2 molar ratio in the absence of acid

The presence of a second equivalent (100% excess) of 3(5)-aminopyrazole forces the Schiff base-forming equilibrium reaction to completion (Figure 3.5). Thus, 100% conversion is obtained after 24 h at 25 °C. The same outcome is obtained when excess pyrazole-3-carbaldehyde is employed (Figure 3.6). The excess 3(5)-aminopyrazole can be separated from the Schiff base product by washing the solid residue (obtained after solvent evaporation) with dichloromethane.
Figure 3.5: Reaction of pyrazole-3(5)-carbaldehyde and 3(5)-aminopyrazole (1:1 and 1:2 molar ratios) monitored over time by $^1$H NMR in ethanol-$d_6$ (in the absence of acid, at 25 °C). Reproduced with permission, from reference 112.
Figure 3.6: Reaction of pyrazole-3(5)-carbaldehyde and 3(5)-aminopyrazole (1.1:1 then 1.5:1 molar ratio) monitored over time by $^1$H NMR in ethanol-$d_6$ (in the absence of acid). 10% excess aldehyde is insufficient for driving the equilibrium reaction to completion; with a 50% excess, the reaction is practically complete. Reproduced with permission, from reference 112.
3.1.6.1.3 Aldehyde:amine in 1:1 molar ratio in the presence of acid
In contrast to the case without an acid catalyst, the reaction of pyrazole-3(5)-carbaldehyde with 3(5)-aminopyrazole in ethanol-$d_6$ in the presence of DCl (1 equiv) at 25 °C yields no Schiff base. Instead, a complex mixture is obtained slowly (Figure 3.4), which contains significant amounts of unreacted starting materials along with compounds 19, 21, 50, 51, and 52 (Scheme 3.5) after 24 h. Subsequent heating of the reaction mixture at 55 °C for 24 h leads to complete consumption of the starting materials; also, 21 becomes more prominent in the final reaction mixture. Identification of compounds 19, 21, 50, 51, and 52 in this complex mixture was facilitated by ESI-MS analysis, which shows them as their H$^+$ and/or Na$^+$ adducts: 19 + H$^+$ ($m/z$ 240.1), 19 + Na$^+$ ($m/z$ 262.1), 21 + H$^+$ ($m/z$ 245.1), 21 + Na$^+$ ($m/z$ 267.1), 50 + H$^+$ ($m/z$ 323.1), 50 + Na$^+$ ($m/z$ 345.1), 51 + H$^+$ ($m/z$ 401.2), 51 + Na$^+$ ($m/z$ 423.2), 52 + H$^+$ ($m/z$ 162.1), 52 + Na$^+$ ($m/z$ 184.1) (Figure 3.7).

3.1.6.1.4 Aldehyde:amine in 1:2 molar ratio in the presence of acid
If pyrazole-3(5)-carbaldehyde and 3(5)-aminopyrazole are reacted in a 1:2 molar ratio in the presence of DCl (1 equiv), the reaction is faster, and almost complete conversion to 21 is observed after 22 h at 25 °C (Figure 3.4); heating the reaction mixture for 3 additional hours at 55 °C leads to 100% conversion. On a large scale, the reaction is complete after 30 min when refluxed in ethanol at 78 °C. Using smaller amounts of DCl (0.01 equiv) or a weak acid (CH$_3$COOH, 1 equiv) as a catalyst leads to the same product, although the reaction proceeds slightly slower.
Scheme 3.5: Contrasted reaction mechanisms of the non-catalyzed (a) and acid-catalyzed (b) reaction of pyrazole-3(5)-carbaldehyde with 3(5)-aminopyrazole. HB represents either water or 3(5)-aminopyrazole. Reproduced with permission, from reference 112.
On the basis of the results presented above, two different reaction mechanisms are proposed, depending on whether acid is absent or present (Scheme 3.5). The final outcome also depends on the relative amounts of pyrazole-3(5)-carbaldehyde and 3(5)-aminopyrazole. In the absence of acid, only Schiff base 18 is obtained in equilibrium with the starting materials. The equilibrium reaction is pushed to completion either by using excess amine or aldehyde reagent or by removing the water byproduct from the reaction mixture. In the presence of acid, a completely different outcome is observed. Although the dehydration of the carbinolamine addition product is acid- catalyzed and would be greatly facilitated under acidic conditions, at the same time the rate of the amine attack is reduced due to protonation. It has been shown that in Schiff base-forming
reactions in general, the rate-determining step at neutral pH is the dehydration of the carbinolamine intermediate, whereas under acidic conditions amine attack becomes the rate-determining step.\textsuperscript{126} In the special case of 3(5)-aminopyrazole, however, a different type of reactivity is promoted under acidic catalysis: The C-4 position becomes highly reactive and leads to the preferential formation of compound 52, which can further react with both the amine and the aldehyde reagents. Thus, two different pathways ensue next, when the aldehyde/amine ratio is 1:1 (or anything less than 1:2). First, the nonequilibrium reaction of 52 with 3(5)-aminopyrazole leads to 21, which is stable to both HCl and NaOH (in equimolar amounts) in refluxing ethanol solution. This irreversible pathway leaves behind unreacted pyrazole-3(5)-carbaldehyde, which can react either with 21 or with 52. Second, the reversible reaction of 52 with pyrazole-3(5)-carbaldehyde leads to Schiff base 19. At the same time, however, 21 can also react with pyrazole-3(5)-carbaldehyde, leading reversibly to Schiff bases 50 and 51. Compound 19 was isolated in pure form from the reaction mixture by column chromatography, along with pure 21; both are characterized by \textsuperscript{1}H and \textsuperscript{13}C NMR spectroscopy (see Appendix A).

3.1.6.1.5 Reaction of bis(3(5)-aminopyrazol-4-yl)-pyrazol-3(5)-yl-methane 21 with 1 or 2 equivalents of pyrazole-3(5)-carbaldehyde

Pure bis(3(5)-aminopyrazol-4-yl)-pyrazol-3(5)-yl-methane 21 was reacted with either 1 or 2 equivalents of pyrazole-3(5)-carbaldehyde in anhydrous ethanol, in the presence of 3 Å molecular sieves (25 °C, 10 days). In the case of the 1:1 reaction, all of the aldehyde is consumed and an approximately equimolar mixture of 21, 50, and 51 is obtained, demonstrating that although the Schiff-base forming reaction between 21 and pyrazole-3(5)-carbaldehyde is complete, the resulting compound 50 disproportionates to 21 and 51 in an equilibrium reaction (Figure 3.8). In contrast, in the case of the 1:2 reaction all of 21 is consumed, and the major product is 51; smaller amounts of the aldehyde and 50 are still present after 10 days. Although 50 and 51 have not been isolated in pure form, their \textsuperscript{1}H NMR signals could be distinguished in both mixtures by tracking their time-dependent relative concentrations (Figure 3.8).
Figure 3.8: Reaction of 21 with pyrazole-3(5)-carbaldehyde (1:1 and 1:2 molar ratio) in ethanol (in the absence of acid) monitored periodically by $^1$H NMR (in DMSO-$d_6$). Reproduced with permission, from reference 112.
When pyrazole-3(5)-carbaldehyde and 3(5)-aminopyrazole are reacted in a 1:2 molar ratio (or higher) in the presence of acid, 100% conversion to 21 is observed, which is easily obtained pure, in high yield, by precipitation from the ethanolic reaction mixture with diethyl ether. In this case, the intermediate 52 preferentially reacts with 3(5)-aminopyrazole to irreversibly form 21, as documented by the absence in the ¹H NMR spectrum of significant signals corresponding to compounds 19, 50, 51, or 52. Even if small amounts of 52 would initially react with pyrazole-3(5)-carbaldehyde to reversibly form 19, the latter compound equilibrates with 52, which in turn is irreversibly and ultimately completely consumed by reacting with the remaining 3(5)-aminopyrazole. Similarly, any amounts of 50 or 51 would eventually be completely consumed, as the whole reaction mixture cleanly converges to 21.

The reaction pathways presented in (Scheme 3.5) were further tested by reacting Schiff bases 18 and 19 with 3(5)-aminopyrazole (in 1:1 and 1:3 molar ratios, respectively) in refluxing ethanol in the presence of HCl. Both reactions lead to the formation of 21, although slower than in the case of the direct reaction of pyrazole-3(5)-carbaldehyde and 3(5)-aminopyrazole in a 1:2 molar ratio. This observation is attributed to the fact that the Schiff bases first need to dissociate into their aldehyde and amine constituents, before those can react via the pathway leading to 21. Similarly, the complex mixture obtained from pyrazole-3(5)-carbaldehyde and 3(5)-aminopyrazole in a 1:1 molar ratio in the presence of acid can be converted to 21 by adding additional 3(5)-aminopyrazole to the reaction mixture.

It has become apparent that the unexpected reactivity of 3(5)-aminopyrazole at its C-4 position with an aldehyde reagent under acidic conditions, leading not to the expected Schiff base 18 but to 21 (as opposed to common amines), originates in the electron-donating ability of the amino group attached to the pyrazole nucleus. Indeed, the reaction of 3(5)-hydroxypyrazole, bearing a different electron-rich moiety, leads to an analogous product bis(3(5)-hydroxypyrazol-4-yl)-pyrazol-3(5)-yl-methane (22) (see Table 2.2). Related products were also reported to result from the reaction of aldehydes with various substituted hydroxypyrazoles. The need for an electron-donating substituent to activate the pyrazole nucleus toward the observed reactivity is further demonstrated by the inability of the parent, unsubstituted pyrazole or 3(5)-methylpyrazole to form a product analogous to 21 and 22 (see section 2.2.1.12). This reactivity is reminiscent of the reaction of formaldehyde with phenol and aniline.
3.1.6.1.6 Reaction of pyrazole-3(5)-carbaldehyde with 1-aminopyrazole

In order to observe the reactivity leading to the tris(pyrazolyl)methane product, the activating amino group must be attached to the C-3(5) position of the pyrazole nucleus. Obviously, if the amino group is at the C-4 position, such reactivity is precluded, and only the Schiff base is expected as product. Under identical conditions as with 3(5)-aminopyrazole (1:2 molar ratio of aldehyde/amine, reflux in ethanol with HCl), pyrazole-3(5)-carbaldehyde reacts with 1-aminopyrazole to yield exclusively the Schiff base \( N-(\text{pyrazol-1-yl})-1-(\text{pyrazol-3(5)-yl})\text{methanimine} \ 20 \) (Scheme 3.6). 3(5)-Amino-5(3)-methylpyrazole produces the expected tris(pyrazolyl)methane product 23 (see section 2.2.1.8.3).

Scheme 3.6: Reactivity difference between 3(5)-aminopyrazole and 1-aminopyrazole. Reproduced with permission, from reference 112.

3.1.6.1.7 Unreactivity of 3-aminopyridazine with pyrazole-3(5)-carbaldehyde

Similar reactivity to 3-aminopyrazole has been observed with a related heterocycle, 2-aminoindole,\textsuperscript{132} but not with 3-aminopyridazine (Scheme 3.7), the six-membered analogue of 3(5)-aminopyrazole (see section 2.2.1.12). These results evoke a similar, drastic deprotonation reactivity difference, between five- and six-membered, methyl-substituted aromatic heterocycles.\textsuperscript{109}
3.1.6.2 Factors affecting the acid-catalyzed reaction of 3(5)-amino- and 3(5)-hydroxypyrazole with aldehydes or ketones

We carried out a comprehensive study of the reaction of 3(5)-aminopyrazole and 3(5)-hydroxypyrazole with a variety of aldehydes and ketones (2:1 molar ratio, in the presence of HCl). Thus, we compared the reactivity of aldehydes vs. ketones, and explored the effect on conversion of aliphatic vs. aromatic substituents (with or without electron withdrawing/donating groups), as well as steric bulk of the substituent. The obtained series of novel tris- and bis(pyrazolyl)methane ligands and the corresponding conversions are shown in Table 2.2.

3.1.6.2.1 Aldehyde vs ketone and the effect of steric bulk

Although both aldehydes and ketones react to produce tris- or bis(pyrazolyl)methane products, the conversion is considerably lower in the case of ketones due to steric hindrance introduced by the second substituent on the carbonyl group. The effect of steric hindrance is clearly evidenced in the pentanone isomer series (Table 2.2): a lower conversion is observed with 3-pentanone (41, 36%) than with 2-pentanone (40, 40%), whereas cyclopentanone offers a higher conversion (42, 45%). The conversion drops drastically in the case of ketones with phenyl substituents: only 15% conversion is observed with acetophenone 43, and no reaction occurs at all with benzophenone 44.
3.1.6.2.2 Aliphatic vs aromatic substituents

Quantitative conversion is observed with all aromatic (non-enolizable) aldehydes, regardless of the substituent (electron-withdrawing CN or electron-donating OH, 32–34). In contrast, lower conversions are obtained in the case of formaldehyde 37 and aliphatic (enolizable) aldehydes even in the absence of steric hindrance 38, due to competing side-reactions (such as aldol condensation in the latter case) (Table 2.2).

3.1.6.3 Deamination of bis(3(5)-aminopyrazol-4-yl)methane derivatives

Deamination\textsuperscript{133} of 21, 24, 26, 28, and 30 was accomplished by conversion to the corresponding diazonium salts followed by reduction with hypophosphorous acid (Scheme 2.14). The reaction was carried out in a one-pot setup, where the diazonium salt is instantaneously reduced upon its formation.\textsuperscript{134} Although quantitative conversions were observed, the yields of pure deaminated products are lower due to difficulties in separating the products from the inorganic salt byproducts, which are soluble in the same solvents as the products (see section 2.2.1.9).

3.1.6.4 One-pot, telescoping synthesis of bis(pyrazol-4-yl)-pyrazol-3(5)-yl-methane

The quantitative conversion of pyrazole-3(5)-carbaldehyde and 3(5)-aminopyrazole (1:2 molar ratio) to 21 in the presence of HCl allows for the telescoping synthesis of bis(pyrazol-4-yl)-pyrazol-3(5)-yl-methane 45, without the need to isolate and purify compound 21 (Scheme 2.15). Thus, the one-pot reaction offers a significantly improved yield of 45 (85% vs. 48%).

3.1.7 Deuteration of pyrazole derivatives at C-4 position by D\textsubscript{2}O

The results discussed in this section are reprinted with permission, from \textit{J. Org. Chem.} 2018, 83, 1649 – 1653.\textsuperscript{114} Copyright 2018 American Chemical Society.

Here we present a preparative and kinetic study of selective C-4 deuteration of the 3(5)-aminopyrazole 53 or 3(5)-hydroxy pyrazole 54 nucleus in D\textsubscript{2}O in the presence or absence of DCl or NaOD (Scheme 3.8), along with derivatives 55–60 (Figure 3.9). H/D exchange of 98–99% was achieved in a single run in the case of substrates 53–59 dissolved in a 1.1% (0.30 M) solution of DCl in D\textsubscript{2}O. Because of its poor solubility in water, 60 was deuterated in CD\textsubscript{3}OD (DCl 1.1%, 0.25 M) instead of D\textsubscript{2}O, which led to 95% H/D exchange for the C-4 position in a single run. The maximum value of product D atom % attainable in one run depends on the isotopic purity of the solvent and the catalyst and the ratio between substrate and deuterated solvent. If desired, higher
D atom % values can be obtained by evaporating the solvent after the first run and repeating the procedure with fresh solvent.

Scheme 3.8: Deuteration of 3(5)-amino/hydroxypyrazole substrates with D$_2$O. Reproduced with permission, from reference 114.

![Scheme 3.8](image)

Figure 3.9: Variously substituted 3(5)-amino/hydroxy-pyrazole substrates used in the deuteration study.

![Figure 3.9](image)

3.1.7.1 Selectivity of deuteration at the pyrazole C-4 position

The selectivity of deuteration at the pyrazole C-4 position (following the fast deuteration of the much more acidic NH groups) was demonstrated by conducting a reaction in an NMR tube
equipped with a coaxial insert containing a solution of sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS sodium salt) in D₂O as reference. Monitoring the ratio of the proton signals of the pyrazole C-3(5) position in 53 and of the reference proves that no deuteration occurs at the C-3(5) position (Figure 3.10). Selective deuteration of the C-4 position is also corroborated by ¹³C NMR spectroscopy, which shows a 1:1:1 triplet signal only for the C-4 pyrazole carbon atom (see Appendix A); the splitting is due to coupling to deuterium (nuclear spin = 1). The deuteration is further confirmed by high-resolution mass spectrometry (see section 2.2.1.14). Consequently, the proton at the pyrazole C-3(5) position can also be used as an internal reference in kinetic experiments, as described in the following section.

Figure 3.10: ¹H NMR monitoring of the selective deuteration of 3(5)-aminopyrazole 53 in D₂O with 100 mol % DCl (1:1 molar ratio relative to the substrate) at 25 °C, using sodium 3-(trimethylsilyl)-1-propanesulfonate in D₂O as reference in a coaxial insert. Reproduced with permission, from reference 114.
3.1.7.2 Study the kinetics of H/D exchange

To study the H/D exchange kinetics, we monitored the progress of the deuteration reaction of 53–60 over time using $^1$H NMR spectroscopy. At varying intervals of time, the fraction of the deuterium-exchanged substrate was determined by integrating the peak corresponding to the exchanging proton (pyrazole C-4 position) against an internal reference proton peak from the substrate (pyrazole C-3(5) position for 53 and 54, CH$_3$ protons for 55, 56 and 58, phenyl protons for 60) or an external reference (CH$_3$ protons of DSS sodium salt in coaxial tube in the case of 59). The reactions were monitored until no further deuteration occurred (Figure 3.10 and Appendix A), and the maximum D atom % obtained was determined. Plotting the natural logarithm of the substrate molar concentration against time produces a straight line in all cases, indicating a first-order reaction with respect to the pyrazole substrate (Figure 3.11). Overall, the deuteration reaction is pseudo-first-order, as the deuterating agent (solvent) is in large excess. The corresponding rate constants and half-lives are collected in Table 3.3. In the case of 3(5)-aminopyrazole 53, an activation energy of 79 kJ/mol is derived from the rate constants obtained at 25 and 70 °C, by using the Arrhenius equation.

Figure 3.11: Plot on a logarithmic scale of the molar concentration of 3(5)-aminopyrazole 53 during deuteration in D$_2$O with 100 mol % DCI at 25 °C, indicating first-order kinetics. Reproduced with permission, from reference 114.
Table 3.3: Kinetic data for the deuteration of substrates 53–59 (0.30 M in D₂O) and 60 (0.25 M in CD₃OD) at 25 °C, along with the maximum D atom% obtained. Notes: a) reaction was not monitored until completion; 90% deuteration was observed after 40 days; b) At 70 °C. c) value could not be determined because complete deuteration was observed before the first NMR scan; d) values are obtained in CD₃OD, as 60 is poorly soluble in D₂O. Reproduced with permission, from reference 114.

<table>
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<th>Substrate</th>
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<th>$D$ (%)</th>
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<tr>
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<td>DCl (100 mol %)</td>
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<td>0.29$^d$</td>
<td>95$^d$</td>
</tr>
</tbody>
</table>

3.1.7.2.1 Factors influencing the rate of the deuteration reaction

Analysis of (Table 3.3) reveals that both the reaction conditions and the substituents of the pyrazole substrate influence the rate of the deuteration reaction.

3.1.7.2.1.1 Influence of temperature and acid/base catalyst

In the absence of a catalyst, the deuteration of 3(5)-aminopyrazole 53 by D₂O at ambient temperature is very slow (half-life: 408 h at 25 °C); at a higher temperature, however, a considerably faster rate is observed (half-life: 6.8 h at 70 °C). Catalysis by DCl (1 mol %) or NaOD (100 mol %) at 25 °C reduces the half-life from 408 to 6.3 h, whereas larger DCl amounts of 10 and 100 mol % lead to a further reduction in half-life to 53 and 51 min, respectively (Figure 3.12). These observations are in favor of the reaction mechanism shown in Scheme 3.9. The fact that an
amount of a strong base (NaOD, 100 mol %) leads to a much smaller rate increase than the same amount of a strong acid (DCl, 100 mol %) indicates that the second step, of proton abstraction from the conjugated acid of the pyrazole substrate (catalyzed by a base), is faster than the first step of formation of the conjugated acid. Therefore, the rate-determining step is the acid-catalyzed D atom transfer from the electrophilic deuteration agent (D₃O⁺ stronger electrophile than D₂O) to the nucleophilic pyrazole substrate.

Figure 3.12: Progress of the deuteration of 3(5)-aminopyrazole 53 in D₂O under different conditions. Reproduced with permission, from reference 114.

Scheme 3.9: Proposed noncatalyzed (a) and acid-catalyzed (b) mechanisms of deuteration (B–D represents D₂O). In the case of the NaOD-catalyzed reaction, B⁻ represents DO⁻. Reproduced with permission, from reference 114.
3.1.7.2.1.2 Influence of the pyrazole substituents

All pyrazole substituents studied, including electron-donating (OH, CH$_3$, t-Bu) and electron-withdrawing (C$_6$H$_5$, CF$_3$) groups, lead to an increased rate of deuteration (Table 3.3, Figure 3.13). Electron-donating groups increase the nucleophilicity of the pyrazole substrate, promoting D atom transfer from the electrophilic deuteration agent, whereas electron-withdrawing groups facilitate proton elimination from the intermediate by increasing its acidity. In the case of CH$_3$ or t-Bu substituents at the pyrazole 3(5)-position, the rate constant increases by a factor of $\sim$3, whereas an N–CH$_3$ substituent on the pyrazole nucleus adjacent to the NH$_2$ group leads to an increase by a factor of $\sim$6. A CF$_3$ substituent at the pyrazole 3(5)-position leads to an even larger increase of the rate constant by a factor of $\sim$12; an OH substituent at the same position increases the rate so drastically that complete deuteration of the C-4 position is observed in less than 3 min (before the first NMR scan is obtained).

Figure 3.13: Progress of the deuteration of differently substituted 3(5)-aminopyrazoles at 25 °C in D$_2$O with 100 mol % DCl. Reproduced with permission, from reference 114.
3.1.7.3 The role of the amino/hydroxy group in the C-4 deuteration of the pyrazole

To demonstrate the role of the NH2 group in the C-4 deuteration of the pyrazole nucleus, we carried out analogous reactions with the parent, nonsubstituted pyrazole, as well as with other electron-donor groups, namely 3(5)-methylpyrazole and 3(5)-hydroxypyrazole. Using 100 mol % DCl in D2O, 3(5)-aminopyrazole is deuterated 99% at the C-4 position after 8 h at 25 °C. Under the same conditions, only 7% and 10% deuteration is observed with the parent pyrazole and 3(5)-methylpyrazole, respectively. In the case of 3(5)-hydroxypyrazole, however, 96% deuteration is obtained after 8 h at 25 °C. We conclude that a strong electron-donor group, such as NH2 or OH, is required to activate the pyrazole nucleus toward facile deuteration of its C-4 position. In addition, other pyrazoles bearing groups such as NHR, NR2 or OR (R = various substituents) are also expected to undergo efficient deuteration.

3.1.7.4 The effect of the amino group position and the ring size on the deuteration reaction

In order to obtain the observed deuteration of the pyrazole nucleus, we demonstrated that the activating amino group must be attached to the C-3(5) position. Under the same experimental conditions that lead to practically complete deuteration of the C-4 position of 3(5)-amino-pyrazole (100 mol % DCl, 25 °C, 8 h), virtually no C-H deuteration is observed in the case of 4-aminopyrazole (61, Figure 3.14) and 1-aminopyrazole 62. It is also interesting to note that no deuteration is observed in the case of 3-aminopyridazine 63, the six-membered analogue of 3(5)-aminopyrazole. This observation is consistent with other results, which show a similar, drastic deprotonation reactivity difference between five- and six-membered, methyl-substituted aromatic heterocycles.109

![Figure 3.14: Different isomers of aminopyrazole 53, 61, and 62 along with 3-aminopyridazine 63 used in the deuteration study. Reproduced with permission, from reference 114.](image)
3.1.8 Reactivity differences of five- vs. six-membered aromatic molecules

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Methyl-substituted, six-membered aromatic molecules are deprotonated to benzylic carbanions, whereas deprotonation of 3(5)-methylpyrazole (NH protected) occurs at an endocyclic CH group (Scheme 3.10).

Scheme 3.10: Deprotonation of 3(5)-methylpyrazole 64 and 3-methylpyridazine 65 (R = Protecting group).

The results of quantum mechanical computations at the MP2/6-311+G(d,p) level in the gas phase concur with the experimental findings, showing that the deprotonated product of 64 (R = H) on C5 of the aromatic ring 64b is more stable than the one deprotonated on the methyl group 64a by 13.1 kcal/mol (enthalpy, equivalent to a pKₐ difference of 9.5). In contrast, 65a is more stable than 65b by 18.9 kcal/mol (pKₐ difference of 13.7). The higher stability of 65a compared to 64a is originating from the much higher conjugation energy in the substituted six-membered rings than in the five-membered rings. On average, the conjugation effect stabilizes the deprotonated product
a by 21 kcal/mol more in the six-membered rings than in the five-membered rings. This is due to the lowering of the LUMO orbitals with the enlargement of the conjugated ring. In terms of VB theory, there are more resonance structures for six-membered rings than five-membered rings, leading to higher resonance energies in the former. Obviously, in both 64b and 65b there is negative hyperconjugation from the in-planar lone pair on the deprotonated carbon (C5 in 64b and C6 in 65b) to adjacent σ anti-bonds in the form of n → σ*. Both the conjugation and hyperconjugation effects can be visualized with the electron density difference (EDD) between ΨD (delocalized ground state of a or b) and ΨL (reference electron-localized resonance state of a or b), as shown in Figure 3.15.

Figure 3.15: Electron density difference (EDD) maps showing the conjugation in a and the hyperconjugation in b for deprotonated 3-methylpyrazole 64 and 3-methylpyridazine 65. The blue and red colors represent loss or gain of electron density, respectively. Reproduced with permission, from reference 109.

It can be seen that the delocalization of the negative charge from the substituted methylene group to the ring is more extensive and significant in 65a (pyridazine) than in 64a (pyrazole), whereas the hyperconjugation effect mainly occurs from the endocyclic carbon (C5 for 64b and C6 for 65b) to the adjacent σ bonds. The reduction of the conjugative stabilization from 65a to
64a (23.1 kcal/mol) is significant, but still not enough to explain the change of the energy difference between the two deprotonated products (32.9 kcal/mol).

After the concept of a hybrid orbital was initially proposed by Pauling,\textsuperscript{135} it has been well understood that hybridization is closely related to bond length, bond strength, and bond angle.\textsuperscript{136} In our case, the hybridization of the carbon atoms in the five-membered rings is different from the one in the six-membered ring. The computational calculations revealed that the deprotonation energy decreases with the reduction of the NCC angle. This can be explained by the enhancement of the s character in the hybrid orbital of the central carbon atom and the subsequent increase of the C–H bond polarity. With a bond angle ($\phi$) of 108° in 64 and 120° in 65, we can predict that rehybridization would favor the deprotonation of 64 at C5 over the deprotonation of 65 at C6 by 9–10 kcal/mol. This correlates well with the observed difference of the nondelocalization effect ($\DeltaXE$) between 64 and 65 (9.2 kcal/mol).

3.1.9 Deprotonation reactivity differences between 3-alkyl- and 5-alkyl-1-THP-pyrazole isomers

The results discussed in this section are reprinted with permission, from *J. Org. Chem.* 2016, 81, 1718–1722.\textsuperscript{110} Copyright 2016 American Chemical Society.

*N*-protected 3-alkylpyrazoles are easily deprotonated by $^n$BuLi at the 5-position of the aromatic ring, while the 5-alkyl isomers are completely unreactive under the same conditions (Scheme 3.11).

![Scheme 3.11: Deprotonation of 3-methyl-1-R-pyrazole 64 and 5-methyl-1-R-pyrazole 66 isomers. R = methyl (computations) or tetrahydropyran-2-yl (synthesis). Reproduced with permission, from reference 110.](image-url)
The computational study revealed that the 1,3-dimethylpyrazole 64 and 1,5-
dimethylpyrazole 66 isomers are essentially isoenergetic at the HF or MP2 theoretical levels. However, their deprotonated products have very different energies: 64b is much more stable than 66a. The conventional explanation is the ALP effect, which suggests that the repulsion between the two lone pairs on the adjacent carbon and nitrogen atoms destabilizes 66a. The calculations based on the pairwise Coulomb interaction show that there is indeed a slight decrease (2.2 kcal/mol) from the repulsion between the two lone pairs in 66a to the repulsion between the single lone pair with the σCN bond in 64b (Figure 3.16). This amount, however, is small and is correlated to the structural change, i.e., the CN bond in these two species.

![Figure 3.16: Adjacent pair–pair Coulomb interactions in 64b and 66a (a.u.). Reproduced with permission, from reference 110.](image)

Further investigation into the electron delocalization effect in these systems. Table 3.4 compiles the major results, where DE(total) is the energy change between a fully delocalized and a fully localized Lewis state (the most stable resonance structure) and DE(π) and DE(σ) refer to the energy change by localizing π- and σ-electrons, respectively. The sum of DE(π) and DE(σ) is very close to DE(total), suggesting negligible coupling between the delocalizations of σ- and π-electrons. It is interesting that there is little change from 64 and 66 to 64b and 66a for the σ-electron delocalization in isomers (64 vs 66 and 64b vs 66a). However, the π-conjugation in 66a is less stabilizing than in 64b by 13 kcal/mol, which accounts for 60% of the energy gap between 64b and 66a. With all electron pairs localized on either two atoms (bonds) or individual atoms (lone pairs), 64b is still more stable than 66a by 8 kcal/mol, which most likely is a consequence of electrostatic interactions: there is an H nucleus and a CH3 group around the negatively charged carbon in 64b but only a single H nucleus in 66a (Figure 3.16). Therefore, we conclude that it is not the repulsion between adjacent lone pairs of electrons (ALP effect) that leads to the drastic
difference between the deprotonation energies of the two isomers, but rather reduced π-resonance (62% or 13 kcal/mol) and attractive electrostatic interactions (38% or 8 kcal/mol).

Table 3.4: Relative energies of 66 vs 64 and 66a vs 64b in addition to their inherent electron delocalization energies (DEs) for σ- and π-electrons (kcal/mol). Reproduced with permission, from reference 110.

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<th>66</th>
<th>64b</th>
<th>66a</th>
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<tr>
<td>DE(π)</td>
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<td>104.26</td>
<td>102.87</td>
<td>88.38</td>
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</table>

3.2 Metal–organic/coordination chemistry

3.2.1 Synthesis and fractionation of nanojars

3.2.1.1 Synthesis and study of the properties of carbonate-nanojars

The results discussed in this section were originally published in *Dalton Trans.* 2016, 45, 8327–8339,104 and are reproduced by permission of The Royal Society of Chemistry.

Nanojars of the general formula \[\text{[CO}_3^{2-}\text{-Cu(OH)(Rpz)}_n\] (pz = pyrazolate anion, R = substituent(s), n = 27–31) are synthesized using a one-pot reaction, by stirring copper(II) nitrate, the pyrazole ligand (or a 1:1 mixture of two different pyrazole ligands) and a base (Cu:Rpz:OH in 1:1:2 molar ratio) in tetrahydrofuran for three days. Various hydroxides, such as MOH (M = Li+, Na+, K+, Rb+, Cs+, Bu4N+, Et4N+) and M(OH)2 (M = Sr2+, Ba2+) can be employed as bases, along with the corresponding carbonates, which provide the incarcerated CO$_3^{2-}$ ion. Alternatively, copper carbonate Cu$_2$CO$_3$(OH)$_2$ can be used both as copper- and carbonate-source, although it provides lower yields than the THF-soluble copper(II) nitrate.

Tetrabutylammonium was initially used as counterion in all cases, as it had been shown to promote crystallization. In the case of highly hydrophobic nanojars based on pyrazoles with butyl or longer alkyl substituents, however, no ESI-MS signals can be detected when the counterion is
Bu₄N⁺. The lack of ionization is attributed to extensive ion-pair formation, due to strong hydrophobic interactions between the long alkyl chains of the nanojars and the large Bu₄N⁺ counterions. Alkali metal counterions (Li⁺, Na⁺, K⁺, Rb⁺, Cs⁺) offer partial remedy for the problem, although in this case the MS signal is weakened by another factor: highly hydrophobic nanojars are insoluble in neat acetonitrile, therefore less polar tetrahydrofuran has to be added to the MS solvent in a 1:1 ratio to achieve solubility, which further suppresses the MS signal. Et₄N⁺ behaves similarly to Bu₄N⁺, although it does induce noteworthy changes in the crystal structure of the nanojar (see Crystallography section). Besides tetraalkylammonium and alkali or alkaline-earth metal cations, [K₃ₐ-18-crown-6]⁺ has also been successfully employed as counterion, which forms in-situ when 18-crown-6 is added to the reaction mixture. The identity of a particular counterion associated with the nanojar is confirmed by ESI-MS(+) (of the metal cations, only Rb⁺ and Cs⁺ have m/z values within the mass spectrometer’s detection window). The size distribution of the different [CO₃²⁻⊂{Cu(OH)(pz)}ₙ] nanojars (n = 27−31) varies slightly with the particular reaction conditions, such as the copper source, counterion and the base. In contrast, a much more pronounced variation is produced by the different substituents on the pyrazole ligands.

3.2.1.1.1 Effect of pyrazole substituents on carbonate-nanojar structure

As seen in Figure 3.17, the pyrazole 4-positions point radially away from the nanojar. Therefore, no steric hindrance is predicted to be caused by substituents in the 4-position. Substitution at the pyrazole 3- and/or 5-positions, however, is expected to be more critical for nanojar formation, due to the all-cis configuration of the pyrazole ligands, which places substituents on the pyrazole units close to the neighboring ligands. The steric hindrance is expected to be most significant for the two smaller side-rings, with pyrazole units pointing to the same side of the ring, while the larger, central ring can relieve the hindrance by orienting the pyrazole units alternately above and below the ring mean-plane (see also sections 3.2.4.4.13 and 3.2.4.4.14).
All experiments discussed below are carried out in tetrahydrofuran as reaction medium, an excellent solvent for all nanojars, but not for the NaNO₃ by-product, which precipitates out of the reaction medium. The product mixtures are analyzed by ESI-MS in acetonitrile solutions, or, in the case of pyrazoles with butyl or longer chains, in a less polar CH₃CN/THF (1:1) mixture. Although the relative intensity of ESI-MS signals is dependent on individual ionization efficiencies, the various [CO₃{Cu(OH)(pz)}ₙ]²⁻ nanojars (n = 27–31) have identical charge and very similar size and shape, and are expected to have similar ionization efficiencies under identical ESI-MS conditions. Therefore, the observed ESI-MS signals should provide reliable information about the relative concentration of different nanojars based on the same ligand in a given solution. Indeed, this has been confirmed for nanojars based on the parent pyrazole ligand, using ¹H NMR spectroscopy. In the case of the mixed-pyrazole nanojars, however, ionization efficiencies drop drastically as the amount of the hydrophobic ligand component within a nanojar of a given size increases.

Formic acid is commonly used as an additive for mobile phases in reversed-phase liquid chromatography separations, as a buffer component, to improve peak shapes, and to promote ionization by producing [M+H]⁺ ions. We find that nanojars are extremely sensitive to even traces of formic acid in the mass spectrometer; consequently, substituted nanojar species [CO₃²⁻{Cuₙ(OH)ₙ(HCOO)ₙ₋ₚ(pz)}ₙ₋ₚ] (y = 1–3) are inevitably found in most spectra (at slightly
lower $m/z$ values than the pure nanojar), unless the instrument is opened up and thoroughly cleaned prior to injection of nanojar samples. In addition, adduct species are also observed occasionally, at larger $m/z$ values than the pure nanojar.

3.2.1.1.1 Substitution of the pyrazole 4-position

Nanojars $[\text{CO}_3\subset\{\text{Cu(OH)(4-Rpz)}\}_n]^2^−$ (n = 27−31) based on pyrazoles substituted in the 4-position with chains of varying lengths (up to 11 atoms) have been successfully prepared (Table 3.5), indicating that linear chains do not interfere with nanojar formation, regardless of their length (Figure 3.17). In addition, nanojars with $R = \text{F, Cl, Br, I, phenyl and CF}_3$ have been observed (Table 3.5 entries 2−5, 14, 15), showing that moderately bulky groups in the immediate vicinity of the pyrazole 4-position are also tolerated. In the case of 4-trifluoromethylpyrazole, a hexanuclear species $[\text{Cu}_6\text{O}_2(4-\text{CF}_3\text{pz})_9]^−$ ($m/z$ 1629) is also formed beside the nanojars. Pyrazoles with potentially coordinating moieties ($R = \text{SO}_3\text{H, COOH, CH}=\text{O, OH}$) in the 4-position do not form nanojars: only insoluble, presumably polymeric products are obtained in those cases. With 4-nitropyrazole (LH), a soluble mixture of mono- to hexanuclear species (as indicated by the Cu-isotope pattern of the ESI-MS signals) is obtained (Figure 3.18). Within this mixture, $[\text{CuL}_2]^−$ ($m/z$ 288), $[\text{Cu}_2\text{L}_4]^−$ ($m/z$ 575), $[\text{NaCu}_3\text{OL}_5(\text{NO}_3)_2]^−$ ($m/z$ 690), $[\text{Cu}_3\text{OL}_5]^−$ ($m/z$ 767), $[\text{Cu}_4\text{O}_2\text{L}_6]^−$ ($m/z$ 959), $[(\text{Bu}_4\text{N})\text{Cu}_3\text{OL}_6]^−$ ($m/z$ 1122) and $[\text{Cu}_6\text{O}_2\text{L}_9]^−$ ($m/z$ 1422) are identified as major components. The structure of related di-, tri-, tetra- and hexanuclear copper(II)-pyrazolate species has been established by X-ray diffraction. Partial reduction of $\text{Cu}^{2+}$ to $\text{Cu}^+$ during ESI-MS is also common.
Table 3.5: [Nanojar]_{2}^{-} species with differently substituted pyrazoles detected by ESI-MS(−). Occasionally, minor amounts of singly-charged [Counterion^{+}(Nanojar_{2}^{-})]^{-} species are also observed (not shown). Reproduced with permission, from reference 104.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pyrazole (LH)</th>
<th>Nanojar [CO_{3}C{Cu(OH)L}<em>{n}]</em>{2}^{-}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HpzH</td>
<td>m/z 2023 (n = 27), 2171 (n = 29), 2244 (n = 30), 2318 (n = 31)</td>
</tr>
<tr>
<td>2</td>
<td>4-FpzH</td>
<td>m/z 2266 (n = 27), 2431 (n = 29), 2514 (n = 30), 2597 (n = 31)</td>
</tr>
<tr>
<td>3</td>
<td>4-ClpzH</td>
<td>m/z 2488 (n = 27), 2670 (n = 29), 2761 (n = 30), 2852 (n = 31)</td>
</tr>
<tr>
<td>4</td>
<td>4-BrpzH</td>
<td>m/z 3088 (n = 27), 3314 (n = 29), 3428 (n = 30), 3541 (n = 31)</td>
</tr>
<tr>
<td>5</td>
<td>4-LpzH</td>
<td>m/z 3723 (n = 27), 3996 (n = 29), 4133 (n = 30), 4270 (n = 31)</td>
</tr>
<tr>
<td>6</td>
<td>4-EtOpzH</td>
<td>m/z 2618 (n = 27), 2809 (n = 29), 3001 (n = 31)</td>
</tr>
<tr>
<td>7</td>
<td>4-MepzH</td>
<td>m/z 2212 (n = 27), 2374 (n = 29), 2455 (n = 30), 2536 (n = 31)</td>
</tr>
<tr>
<td>8</td>
<td>4^-BupzH</td>
<td>m/z 2780 (n = 27), 2984 (n = 29), 3188 (n = 31)</td>
</tr>
<tr>
<td>9</td>
<td>4^-OctpzH</td>
<td>m/z 3538 (n = 27), 3798 (n = 29), 4058 (n = 31)</td>
</tr>
<tr>
<td>10</td>
<td>4-(HOCH_{2}CH_{2}CH_{2})pzH</td>
<td>m/z 2807 (n = 27), 2910 (n = 28), 3013 (n = 29), 3116 (n = 30), 3218 (n = 31)</td>
</tr>
<tr>
<td>11</td>
<td>4-(CH_{3}OCH_{2}CH_{2}O)pzH</td>
<td>m/z 3023 (n = 27), 3245 (n = 29), 3466 (n = 31)</td>
</tr>
<tr>
<td>12</td>
<td>4-(CH_{3}(OCH_{2}CH_{2})_{2})pzH</td>
<td>m/z 3618 (n = 27), 3751 (n = 28), 3883 (n = 29), 4016 (n = 30), 4149 (n = 31)</td>
</tr>
<tr>
<td>13</td>
<td>4-(CH_{3}(OCH_{2}CH_{2})_{3})O pzH</td>
<td>m/z 4212 (n = 27), 4522 (n = 29), 4832 (n = 31)</td>
</tr>
<tr>
<td>14</td>
<td>4-CF_{3}pzH</td>
<td>m/z 2941 (n = 27), 3157 (n = 29), 3372 (n = 31)</td>
</tr>
<tr>
<td>15</td>
<td>4-PhpzH</td>
<td>m/z 3050 (n = 27), 3274 (n = 29), 3386 (n = 30), 3498 (n = 31)</td>
</tr>
<tr>
<td>16</td>
<td>3-MepzH</td>
<td>m/z 2455 (n = 30)</td>
</tr>
<tr>
<td>17</td>
<td>3-EtpzH</td>
<td>m/z 2665 (n = 30)</td>
</tr>
<tr>
<td>18</td>
<td>3^-PrpzH</td>
<td>m/z 2876 (n = 30)</td>
</tr>
<tr>
<td>19</td>
<td>3^-BupzH</td>
<td>m/z 3086 (n = 30)</td>
</tr>
<tr>
<td>20</td>
<td>3^-OctpzH</td>
<td>m/z 3928 (n = 30)</td>
</tr>
<tr>
<td>21</td>
<td>3-CF_{3}pzH/HpzH (1:1)</td>
<td>[CO_{3}C{Cu(OH)<em>{n}(3-CF</em>{3}pz)<em>{y}(pz)</em>{n-y}}]_{2}^{-} (n = 27, 29, 30; y \approx 3−17) m/z 2125−2822</td>
</tr>
</tbody>
</table>
Table 3.5: Continued.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pyrazole (LH)</th>
<th>Nanojar $[\text{CO}<em>3\subseteq{\text{Cu(OH)}<em>n(\text{LH})</em>{y}(\text{pz})</em>{n-y}}]^{2-}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>3-PhpH/HpzH</td>
<td>$[\text{CO}<em>3\subseteq{\text{Cu(OH)}<em>n(3-PhpH)</em>{y}(\text{pz})</em>{n-y}}]^{2-}$</td>
</tr>
<tr>
<td></td>
<td>(1:1)</td>
<td>$(n = 27, 29, y \approx 5 - 19) \text{ m/z 2251–2893}$</td>
</tr>
<tr>
<td>23</td>
<td>3,5-Me2pzH/HpzH</td>
<td>$[\text{CO}<em>3\subseteq{\text{Cu(OH)}<em>n(3,5-Me2pz)</em>{y}(\text{pz})</em>{n-y}}]^{2-}$</td>
</tr>
<tr>
<td></td>
<td>(1:1)</td>
<td>$(n = 27 - 31, y \approx 0 - 14) \text{ m/z 2023–2515}$</td>
</tr>
<tr>
<td>24</td>
<td>3,5-Me2-4-OctpzH/HpzH</td>
<td>$[\text{CO}<em>3\subseteq{\text{Cu(OH)}<em>n(3,5-Me2-4-Octpz)</em>{y}(\text{pz})</em>{n-y}}]^{2-}$</td>
</tr>
<tr>
<td></td>
<td>(1:1)</td>
<td>$(n = 29 - 31, y \approx 11 - 17) \text{ m/z 3015–3366}$</td>
</tr>
<tr>
<td>25</td>
<td>3,5-Et2pzH/HpzH</td>
<td>$[\text{CO}<em>3\subseteq{\text{Cu(OH)}<em>n(3,5-Et2pz)</em>{y}(\text{pz})</em>{n-y}}]^{2-}$</td>
</tr>
<tr>
<td></td>
<td>(1:1)</td>
<td>$(n = 27 - 32, y \approx 0 - 15) \text{ m/z 2023–2813}$</td>
</tr>
<tr>
<td>26</td>
<td>3-\text{Bu}-5-HexpzH/HpzH</td>
<td>$[\text{CO}<em>3\subseteq{\text{Cu(OH)}<em>n(3-\text{Bu}-5-Hexpz)</em>{y}(\text{pz})</em>{n-y}}]^{2-}$</td>
</tr>
<tr>
<td></td>
<td>(1:1)</td>
<td>$(n = 27, 29 - 31, y \approx 0 - 6) \text{ m/z 2023–2665}$</td>
</tr>
<tr>
<td>27</td>
<td>3-Me-5-CF3pzH/HpzH</td>
<td>$[\text{CO}<em>3\subseteq{\text{Cu(OH)}<em>n(3-Me-5-CF3pz)</em>{y}(\text{pz})</em>{n-y}}]^{2-}$</td>
</tr>
<tr>
<td></td>
<td>(1:1)</td>
<td>$(n = 27, 29, 30, y \approx 0 - 11) \text{ m/z 2023–2696}$</td>
</tr>
</tbody>
</table>

Figure 3.18: ESI(–) spectrum of the product mixture obtained from Cu(NO$_3$)$_2$, 4-NO$_2$pz, NaOH, Bu$_4$NOH, and Na$_2$CO$_3$. Reproduced with permission, from reference 104.
3.2.1.1.2 Substitution of the pyrazole 3(5)-position

Alkyl substituents of various lengths (e.g., methyl to n-octyl) are also tolerated at the pyrazole 3(5)-position (Table 3.5). It is likely that the longer alkyl chains turn away from the nanojar after the first CH2-unit connected to the pyrazole nucleus, thus avoiding interference from neighboring pyrazole units of the same Cu₃-ring. In contrast to 4-alkylpyrazoles, the Cu₃ₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐₐ¢}
Figure 3.19: ESI-MS(–) spectrum of [CO$_3$$\subset$[Cu$_n$(OH)$_m$(3-Phpz)$_y$(pz)$_{n-y}$]]$_2^-$ species observed (y:n−y & m/z shown). Reproduced with permission, from reference 104.

Figure 3.20: ESI-MS(–) spectrum of [CO$_3$$\subset$[Cu$_n$(OH)$_m$(3-CF$_3$pz)$_y$(pz)$_{n-y}$]]$_2^-$ species observed (y:n−y & m/z shown). Reproduced with permission, from reference 104.
Figure 3.21: ESI(−) spectrum of the product mixture obtained from Cu(NO₃)₂, 3-NO₂pzH, NaOH, Bu₄NOH, and Na₂CO₃. Reproduced with permission, from reference 104.

### 3.2.1.1.1.3 Simultaneous substitution of the pyrazole 3- and 5-positions

As expected, no nanojars are obtained with 3,5-disubstituted pyrazoles as sole ligands, not even with the smallest methyl substituent. When used in a 1:1 molar mixture with HpzH, however, 3,5-dialkylpyrazoles and 3(5)methyl-5(3)trifluoromethylpyrazole do form mixed nanojars. The ESI-MS(−) spectrum of the nanojars \([\text{CO}_3\subset[Cu_n(\text{OH})_6(3,5-\text{Me}_2pz)_y(pz)_{n-y}]^2^-]\), obtained from a 1:1 molar mixture of 3,5-Me₂pzH and HpzH, and Cu₂CO₃(OH)₂ as copper/carbonate source, shows three major groups of peaks \((n = 27, y \approx 0–9; n = 28, y \approx 6–13; n = 30, y \approx 10–14)\) and small amounts of nanojars with \(n = 29, y \approx 9–14,\) and \(n = 31, y = 10–14\) (Figure 3.22).
When Cu(NO₃)₂ and Na₂CO₃ are used as copper and carbonate sources, respectively, a slightly different distribution is observed, with n = 30 as the major group, small amounts of n = 28, 29, and only traces of n = 27, 31 (Figure 3.23). Different ratios of 3,5-Me₂pzH and HpzH also lead to different distributions: a 2:1 molar mixture leads almost exclusively to n = 30, y ≈ 13–20 (most abundant peak: y = 14), with small amounts of n = 28, y ≈ 12–18, while a 5:1 ratio leads to n = 30, y ≈ 14–20 (most abundant peak: y = 20). Using 3,5-Me₂pzH:HpzH ratios higher than 1:1 favors nanojars with larger value of y, but increasing amounts of low-nuclearity species are also produced at the same time.
A 1:1 molar mixture of 3,5-Me2-4"OctpzH and HpzH also provides nanojars [CO3⊂{Cuₙ(OH)ₙ(3,5-Me₂-4"Octpz)ₙ(pz)ₙ−ₙ}]²⁻, among which the ones with n = 30, y = 10–16 constitute the major group. The ESI-MS(−) of [CO₃⊂{Cuₙ(OH)ₙ(3,5-Et₂pz)ₙ(pz)ₙ−ₙ}]²⁻ shows three major groups, n = 27, y ≈ 0–3; n = 29, y ≈ 0–10; n = 30, y ≈ 9–14, and small amounts of n = 31, y ≈ 0–11 and n = 32, y = 12–15 (Figure 3.24). In the case of [CO₃⊂{Cuₙ(OH)ₙ(3"Bu-5"Hexpz)ₙ(pz)ₙ−ₙ}]²⁻, the major peaks correspond to the parent nanojars (n = 27, 29–31; y = 0), but smaller amounts of substituted species (y = 1–6) are also observed. In the case of a 3(5)-Me-5(3)-CF₃pzH:HpzH (1:1) mixture, the major species is [Cu₃O(pz)₃(3-Me-5-CF₃pz)₂]⁻ (m/z 706), along
With other low-nuclearity species, and small amounts of nanojars are also observed: 
\([\text{CO}_3\{\text{Cu}_n(\text{OH})_m(3-\text{Me}-5-\text{CF}_3\text{pz})_y(\text{pz})_{n-y}\}]^{2-}\) (n = 27, y ≈ 0–2; n = 29, y ≈ 0–2; n = 30, y ≈ 1–11) (Figure 3.25). In the case of pyrazoles with bulkier substituents, such as bis(trifluoromethyl)-, di-‘butyl- and diphenylpyrazole, however, not even mixed nanojars can be obtained. Di-‘butyl- or diphenylpyrazole mixtures with HpzH (1:1) lead to \([\text{CO}_3\{\text{Cu}(\text{OH})_m(\text{pz})_n\}]^{2-}\) (n = 27–31) as the only THF-soluble products.
In the case of 3,5-(CF₃)₂pzH:HpzH (1:1), the main species observed by ESI-MS(−) is the trinuclear 
\([\text{Cu}_3\text{O}(\text{pz})_3\{3,5-(\text{CF}_3)_2\text{pz}\}_2]^-\) (m/z 814), along with its adducts \([\text{Na}_y\text{Cu}_3\text{O}(\text{pz})_3\{3,5-(\text{CF}_3)_2\text{pz}\}_2+y]^-\) (y = 1, m/z 1040; y = 2, m/z 1266; y = 3, m/z 1492; y = 4, m/z 1718; y = 5, m/z 1944) and \([\text{(Bu}_4\text{N})\text{Cu}_3\text{O}(\text{pz})_3\{(3,5-\text{CF}_3)_2\text{pz}\}_3]^-\) (m/z 1260), as well as \([\text{Cu}_3\text{O}(\text{pz})_2\{(3,5-\text{CF}_3)_2\text{pz}\}_3]^-\) (m/z 950), \([\text{Cu}_3\text{OH}(\text{pz})_3\{(3,5-\text{CF}_3)_2\text{pz}\}_3]^-\) (m/z 1018) and its adduct \([\text{Na}_2\text{Cu}_3\text{OH}(\text{pz})_3\{(3,5-\text{CF}_3)_2\text{pz}\}_3]^-\) (m/z 1470). In addition, mononuclear \([\text{Cu}\{(3,5-\text{CF}_3)_2\text{pz}\}_2]^-\) (m/z 470), tetranuclear \([\text{Na}_y\text{Cu}_4\text{O}(\text{pz})_3\{(3,5-\text{CF}_3)_2\text{pz}\}_3+y]^-\) (y = 1, m/z 1307; y = 2, m/z 1533; y = 3, m/z 1759), hexanuclear \([\text{Na}_y\text{Cu}_6\text{O}_2(\text{pz})_6\{(3,5-\text{CF}_3)_2\text{pz}\}_3+y]^-\) (y = 1, m/z 1651; y = 2, m/z 1877; y = 3, m/z 2103) as well as the free ligand and its Na-adducts, \([\text{Na}_y\{(3,5-\text{CF}_3)_2\text{pz}\}_1+y]^-\) (y = 0, m/z 203; y = 1, m/z 429; y = 2, m/z 655), are also observed. Concurrently, the ESI-MS(+) spectrum of the same solution shows, beside the dominant Bu₄N⁺ ion, mostly trinuclear species \([\text{Na}_y\text{Cu}_3\text{O}(\text{pz})_3\{3,5-(\text{CF}_3)_2\text{pz}\}_3+y]^+\) (y = 0,
m/z 408; y = 1, m/z 634; y = 2, m/z 860; y = 3, m/z 1086; y = 4, m/z 1312; y = 5, m/z 1538), and smaller amounts of hexanuclear species [(Bu₄N)ᵧNaₓCu₆O₂(pz)₆{(3,5-CF₃)₂pz}₁₊y+z⁺]⁺ (y = 0, z = 3, m/z 1697; y = 0, z = 4, m/z 1923; y = 0, z = 5, m/z 2149; y = 2, z = 0, m/z 1910; y = 2, z = 1, m/z 2136; y = 2, z = 2, m/z 2362), [Na₃Cu₆O(OH)(pz)₆{(3,5-CF₃)₂pz}₅]⁺ (m/z 1901) and [(Bu₄N)₃Na₂Cu₆O₂(pz)₇{(3,5-CF₃)₂pz}₅]⁺ (m/z 2672). In general, we observe that the larger the substituents at the pyrazole 3/5 positions, the less favorable the formation of the corresponding nanojars becomes, and the more low-nuclearity species are obtained.

3.2.1.1.2 Breakdown of the carbonate-nanojar mixture into Cu₂⁷ and Cu₂⁹ nanojars upon treatment with pyridine and into only Cu₂⁷ upon treatment with ammonia

The results discussed in this section were originally published in *Chem. - Eur. J.* 2016, 22, 5499−5503. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission. Upon dissolution of the (Bu₄N)₂[CO₃{Cu(OH)(pz)}ₙ] (n=27, 29, 30, 31) nanojar mixture in neat pyridine, an immediate diminishing of the abundance of the Cu₃₁ nanojar was observed in the ESI-MS(−) spectra, accompanied by an increase in the abundance of the Cu₂⁹ nanojar. Upon standing, the Cu₃₁ nanojar (as well as the minor Cu₃₀ nanojar) peak completely disappeared. The relative abundances of the Cu₂⁷ and Cu₂⁹ nanojars, compared with the initial abundances, indicate that the Cu₃₁ nanojar has been converted to the Cu₂⁹ nanojar (Figure 3.26).
Figure 3.26: ESI-MS(–) spectrum of (Bu4N)2[CO3⊂{Cu(OH)(pz)}n] nanojars in CH3CN. Top: as-synthesized (n = 27, 29, 30, 31); center: after standing in pyridine solution for 7 days (n = 27, 29); bottom: after standing in THF solution saturated with NH3 for 7 days (n = 27). Reproduced with permission, from reference 105.
The process was monitored continuously by \textsuperscript{1}H NMR (Figure 3.27), which also confirms the gradual conversion of the Cu\textsubscript{31} nanojar to the Cu\textsubscript{8\textsuperscript{+13\textsuperscript{+8}}} nanojar. The bottom spectrum of the overlaying is shortly after dissolution in pyridine-\textit{d}_5, whereas the top spectrum is after 7 days. Peaks at 22.36, 26.47, 27.92 and 30.10 ppm are tentatively attributed to the Cu\textsubscript{30} (Cu\textsubscript{8\textsuperscript{+14\textsuperscript{+8}}}) nanojar, which is present in the original mixture (as shown by ESI-MS), and is a possible intermediate in the Cu\textsubscript{8\textsuperscript{+14\textsuperscript{+9}}} to Cu\textsubscript{8\textsuperscript{+13\textsuperscript{+8}}} nanojar transformation.

An even more dramatic outcome was observed when a THF solution of [CO\textsubscript{3}\{Cu(OH)(pz)\}_n] was saturated with gaseous ammonia at room temperature. Although no significant changes could be noticed by ESI-MS immediately after saturation, the Cu\textsubscript{31}, Cu\textsubscript{30}, and Cu\textsubscript{29} nanojars gradually disappear over time, and only the Cu\textsubscript{27} nanojar was left after a few days (Figure 3.26). NH\textsubscript{3} likely coordinates to the nanojars’ Cu atoms and produces short-lived intermediates (undetectable by ESI-MS and \textsuperscript{1}H NMR techniques) that immediately re-assemble to form the most stable nanojar, [CO\textsubscript{3}\{Cu(OH)(pz)\}\textsubscript{27}]\textsuperscript{2\textsuperscript{-}}. It is important to note that in the absence of pyridine or ammonia, nanojars do not interconvert between different Cu\textsubscript{n} sizes, because the distribution of different Cu\textsubscript{n} nanojars does not change upon dissolution in common solvents. Monodisperse (Bu\textsubscript{4}N)\textsubscript{2}[CO\textsubscript{3}\{Cu(OH)(pz)\}\textsubscript{27}] can thus be obtained by ammonia etching, a process reminiscent of the preparation of monodisperse Au\textsubscript{25} nanorods and nanospheres (ca. 1 nm) by etching polydisperse Au nanoparticles (1–3.5 nm) with thiols.\textsuperscript{142}
Figure 3.27: $^1$H NMR monitoring of the conversion of the (Bu$_4$N)$_2$[CO$_3$⊂{Cu(OH)(pz)}$_n$] ($n = 27$, 29, 30, 31) nanojar mixture to a mixture of Cu$_{27}$- and Cu$_{29}$-nanojars in pyridine-$d_5$. Reproduced with permission, from reference 105.
3.2.1.1.3 Solubilizing nanojars in hydrocarbon solvents and water

The results discussed in this section were originally published in *Dalton Trans.* 2016, 45, 8327–8339,\textsuperscript{104} and are reproduced by permission of The Royal Society of Chemistry.

For liquid–liquid extraction purposes, solubility of the nanojar in long-chain aliphatic solvents is desirable. Characteristics of such solvents (typically C\textsubscript{9}–C\textsubscript{18} alkanes/isoalkanes) include low toxicity, low vapor pressure, low flammability (high flash point), negligible solubility in water, chemical inertness, no odor or color, and low price. Nanojars comprised of the parent pyrazole ligand (HpzH), however, are insoluble in aliphatic solvents.\textsuperscript{71} As illustrated in (Figure 3.17), attachment of aliphatic chains of increasing lengths to the pyrazole 4-position leads to a gradual increase of the solubility of the corresponding nanojar in aliphatic solvents, such that nanojars based on 4-n-octylpyrazole are readily soluble in n-hexadecane (C\textsubscript{16}, longest straight-chain alkane that is liquid at room temperature; mp = 18 °C) and even in heavy mineral oil (C\textsubscript{15}–C\textsubscript{50}). The same is true for the 3-n-octylpyrazole derivative, as well as the heteroleptic nanojars based on mixtures of non-substituted pyrazole and 3,5-dimethyl-4-n-octylpyrazole or 3-n-butyl-5-n-hexylpyrazole.

Although all nanojars prepared so far are soluble in tetrahydrofuran, the solubility of the ones based on 4-halopyrazoles in toluene is drastically reduced compared to the parent nanojar and the alkyl- or ether-substituted ones. Thus, only the 4-fluoro-derivative is sparingly soluble in toluene, while the other halo-derivatives are practically insoluble. It is also noteworthy to mention that the solubility of the parent nanojar (but not of the ones with alkyl chain substituents) in toluene is lower when the counterion is a metal cation, compared to the Bu\textsubscript{4}N\textsuperscript{+}-salt.

Some future applications of nanojars might require solubility in water. Again, nanojars based on the parent non-substituted pyrazole are insoluble in water.\textsuperscript{71} Polar, hydrophilic substituents, such as sulfonate, carboxylate or hydroxyl groups, would be expected to increase the solubility of the corresponding nanojars in water. However, those groups are also good donors (especially in their deprotonated forms), and, in the presence of Cu\textsuperscript{2+}, lead to the formation of polymeric products instead of nanojars.\textsuperscript{143,144,145} To impart solubility in water while maintaining nanojar structure, we prepared novel pyrazole ligands with oligo(ethylene glycol) methyl ether chains attached to the 4-position, 4-CH\textsubscript{3}(OCH\textsubscript{2}CH\textsubscript{2})\textsubscript{Z}OpzH (z = 1–3) (Scheme 2.6). While Na\textsubscript{2}[CO\textsubscript{3}⊂{Cu(OH)(4-CH\textsubscript{3}(OCH\textsubscript{2}CH\textsubscript{2})\textsubscript{Z}Opz)}\textsubscript{n}] (n = 27–31) nanojars are negligibly soluble in
water when \( z = 1 \), the corresponding ones with \( z = 2 \) have noticeable solubility, and become readily soluble when \( z = 3 \).

3.2.1.1.4 Resistance of carbonate-nanojars to high pH

The results discussed in this section and section 3.2.1.1.5 are reprinted with permission, from *Inorg. Chem.* 2016, 55, 7717–7728. Copyright 2016 American Chemical Society. Nanojars \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset\{\text{Cu(OH)}(\text{pz})\}_n]\) are exceptionally stable under alkaline conditions: no changes are observed in the ESI-MS and UV–vis spectra of a solution of nanojars in \( \text{CH}_2\text{Cl}_2 \) after 20 weeks of vigorous stirring with an aqueous 1 M NaOH solution (pH 14). Amazingly, nanojars are resistant even to extreme alkalinities: both a solid sample and a THF solution of the nanojars are recovered unchanged after stirring for 5 weeks with a 10 M NaOH (30%) solution in water.

3.2.1.1.5 Reactivity of carbonate-nanojars at pH < 7

In contrast to neutral or basic pH, nanojars are unstable under acidic pH, and even mildly acidic conditions lead to protonation of their OH\(^-\) (pK\(_a\) of water, 15.7) and the pz\(^-\) (pK\(_a\) of pyrazole, 14.2) moieties (Scheme 3.12). Weak acids, such as hydrated transition metal ions \( M^{2+}(\text{aq}) \) (\( M = \text{Cu}, \text{Pb}, \text{Ni}, \text{Cd}, \text{Mn}; \text{pK}_a \) 7.5, 7.6, 9.9, 10.1 and 10.6, respectively)\(^{146}\) and \( \text{NH}_4^+(\text{aq}) \) ions (pK\(_a\) 9.2) as their nitrate salts in wet THF \( ([M(\text{H}_2\text{O})_n]^{x+} + \text{H}_2\text{O} \rightarrow [M(\text{OH})(\text{H}_2\text{O})_{n-1}]^{(x-1)+} + \text{H}_3\text{O}^+; \text{NH}_4^+ + \text{H}_2\text{O} \rightarrow \text{NH}_3 + \text{H}_3\text{O}^+) \), break down nanojars into trinuclear species, as indicated by the \([\text{Cu}_3\text{O}(\text{pz})_3(\text{NO}_3)_2]^- \) \((m/z \ 531.9)\) and \([\text{Cu}_3\text{O}(\text{pz})_2(\text{NO}_3)_3]^- \) \((m/z \ 526.8)\) ions observed by ESI-MS(–), as well as the \([\text{Cu}_3\text{O}(\text{pz})_3]^+ \) \((m/z \ 407.9)\) ion observed by ESI-MS(+). The breakdown occurs even with extremely weak acids, such as Mg\(^{2+}\)(aq) and Ca\(^{2+}\)(aq) (pK\(_a\) 11.2 and 12.7, respectively); however, nanojars reassemble and precipitate out upon addition of excess water to the corresponding THF solutions. Stronger acids, such as Fe\(^{3+}\)(aq), Hg\(^{2+}\)(aq), and Al\(^{3+}\)(aq) (pK\(_a\) 2.2, 3.4 and 5.0, respectively), lead to complete breakdown of the nanojars to Cu\(^{2+}\) and pyrazole, so that only mononuclear species, such as \([\text{Cu(NO}_3]_3]^- \) \((m/z \ 248.9)\), \([\text{Cu(NO}_3)_2]^- \) \((m/z \ 188)\) and \([\text{CuO(NO}_3]^- \) \((m/z \ 142)\), are observed in the ESI-MS(–) spectra of the resulting solutions. As shown above (Scheme 3.12), these reactions are reversible, and addition of sufficient amounts of a strong base restores the nanojars. Nanojars are not affected by Tl\(^+\)(aq), Sr\(^{2+}\)(aq), Ba\(^{2+}\)(aq), Li\(^+\)(aq), Na\(^+\)(aq), K\(^+\)(aq), and Bu\(_4\)N\(^+\)(aq) nitrates (pK\(_a\) of the hydrated metal cations is 13.2, 13.2, 13.4, 13.6, 13.9, and 14.0, respectively; Bu\(_4\)NOH is a strong base similar to NaOH).
Other weak acids, such as alkylcarboxylic acids (pK_a ≈ 5), phenol (pK_a 10.0), alkanethiols (pK_a 10.4–10.7), and even methanol (pK_a 15.5), also lead to breakdown of the nanojars. Indeed, ESI-MS of (Bu_4N)_2[CO_3⊂{Cu(OH)(pz)}_n] (n = 27, 29, 31) in CH_3CN/CH_3OH (2:1) shows nanojars in which an HO_– group is substituted by CH_3O_–, [CO_3⊂{Cu_n(OCH_3)(OH)(OH)_{n-1}(pz)_{n-1}}]^{2–} (n = 27, m/z 2029.0; n = 29, m/z 2176.9; n = 31, m/z 2324.4). At higher methanol concentrations (CH_3CN/CH_3OH = 1:1), both an HO_– and a pz_– group are substituted by CH_3O_– and [CO_3⊂{Cu_n(OCH_3)_{2}(OH)_{n-1}(pz)_{n-1}}]^{2–} species are observed (n = 27, m/z 2011.0; n = 29, m/z 2158.9; n = 31, m/z 2306.4). Upon further substitution, the nanojars break down to small fragments, so that in a neat CH_3OH solution no nanojar species can be detected, even when freshly prepared. On standing, the initially blue methanolic solution of nanojars gradually turns colorless and deposits an insoluble, brown solid. Ethanol (pK_a 15.9) and higher alcohols (pK_a ≥ 16.0), which have lower acidity than water (pK_a 15.7), dissolve the nanojars without decomposition, as attested by ESI-MS in ethanol and isopropanol, which show only intact nanojars, [CO_3⊂{Cu(OH)(pz)}_n]^{2–}.

Scheme 3.12: pH-dependent equilibrium between Cu^{2+} ions and pyrazole, trinuclear copper pyrazolate complex, and nanojars (only the one with n = 27 is shown). The stepwise formation of nanojars with increasing amounts of base is reversible upon lowering the pH. Reproduced with permission, from reference 106.

3.2.1.2 Synthesis and study of the properties of sulfate-nanojars

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Upon mixing a solution of copper(II) nitrate and pyrazole in tetrahydrofuran (THF) with a solution of Bu_4NOH and (Bu_4N)_2SO_4 in THF (29:29:58:1 molar ratio), a deep-blue, clear solution is
instantly obtained, which produces a blue precipitate in quantitative yield upon the addition of excess water (method A). Electrospray ionization mass spectrometry, ESI-MS(–), identifies the product as a mixture of sulfate-incarcerating nanojars, \([SO_4\subset\{Cu(OH)(pz)\}_n]^{2–}\) (Cu\(_n\)SO\(_4\), \(n = 27\sim 33\); \(n = 27\), \(m/z\) 2040.0; \(n = 28\), \(m/z\) 2113.4; \(n = 29\), \(m/z\) 2187.9; \(n = 30\), \(m/z\) 2261.4; \(n = 31\), \(m/z\) 2334.9; \(n = 32\), \(m/z\) 2409.9; \(n = 33\), \(m/z\) 2483.3; \(m/z\) values represent the mono-isotopic mass of the most abundant peak within the isotope pattern; all observed values match calculated values (Figure 3.28A and Appendix B). If the reaction is carried out using copper(II) sulfate, pyrazole, NaOH, and Bu\(_4\)NOH (molar ratio of 29:29:56:2) in THF, a slightly different distribution of nanojars is obtained (method B), with larger amounts of Cu\(_{28}\)SO\(_4\) and negligible amounts of Cu\(_{30}\)SO\(_4\) and Cu\(_{33}\)SO\(_4\) (Figure 3.28B). The different outcome in the latter case is attributed to the insolubility of the copper(II) sulfate and NaOH reagents in THF, which also results in a longer time (three days) being needed to complete the reaction.

Sulfate-incarcerating nanojars of different sizes have different solubility in toluene. Although a mixture of nanojars is initially completely soluble in toluene, the smaller nanojars slowly crystallize out of the solution. Thus, when \((Bu_4NO)_2[SO_4\subset\{Cu(OH)(pz)\}_n]\) (obtained using method B) is dissolved in toluene, a clear, deep-blue solution is obtained first. Within minutes, a dark-blue powder starts settling out, which after filtration and rinsing with toluene is identified by ESI-MS(–) as Cu\(_{28}\)SO\(_4\), with small amounts of Cu\(_{27}\)SO\(_4\) (Figure 3.28C). The filtrate, in turn, contains the larger Cu\(_{29}\)SO\(_4\) and Cu\(_{31}\)SO\(_4\) nanojars, with small amounts of Cu\(_{27}\)SO\(_4\), Cu\(_{28}\)SO\(_4\), and Cu\(_{32}\)SO\(_4\) (Figure 3.28D). In addition, a sample of Cu\(_{31}\)SO\(_4\) is also obtained by using Pb(NO\(_3\))\(_2\) as an additive (see section 3.2.1.2.2).

3.2.1.2.1 Effect of the amount of Bu\(_4\)NOH on the size distribution and yield of sulfate-nanojars

As discussed above, replacing most of the Bu\(_4\)NOH base by NaOH (just enough Bu\(_4\)NOH to provide two Bu\(_4\)N\(^+\) counterions per nanojar) leads to a different nanojar distribution. To further assess whether the amount of available Bu\(_4\)N\(^+\) counterions has an effect on the size distribution of the resulting nanojars, a pair of experiments was carried out, wherein Bu\(_4\)NOH was used either in substoichiometric amount, or in excess. Based on ESI-MS(–) analysis of the nanojar mixtures obtained under otherwise identical reaction conditions, it becomes evident that, in the latter case, the Cu\(_{27}\), Cu\(_{28}\), and Cu\(_{29}\) nanojars are considerably more abundant, relative to the Cu\(_{31}\) nanojar, than in the former case (Figure 3.29).
Figure 3.28: ESI-MS(–) spectra (in CH$_3$CN) of the sulfate-incarcerating nanojars $[SO_4\subset\{Cu(OH)(pz)\}_a]^2^-$ ($n = 27$–$33$) from Cu(NO$_3$)$_2$, pyrazole, Bu$_4$NOH and (Bu$_4$N)$_2$SO$_4$ (29:29:58:1 molar ratio) in THF (A), from CuSO$_4$, pyrazole, NaOH and Bu$_4$NOH (29:29:56:2 molar ratio) in THF (B), the fraction crystallized out of toluene (C), and the fraction soluble in toluene (D). Reproduced with permission, from reference 107.
Regardless of their size, all nanojars require two singly charged Bu4N+ counterions. However, whereas \((\text{Bu}_4\text{N})_2[\text{SO}_4 \subset \{\text{Cu(OH)}(\text{pz})\}_{31}]\) requires 2.0 equivalents of Bu4N+ for 31 equivalents of copper, \((\text{Bu}_4\text{N})_2[\text{SO}_4 \subset \{\text{Cu(OH)}(\text{pz})\}_{27}]\) requires 2.3 equivalents of Bu4N+ for 31 equivalents of copper.

If Bu4NOH is completely left out of the reaction (only NaOH is used as a base), the resulting sulfate nanojar mixture is impurified with significant amounts of carbonate nanojars, Cu₃CO₃ (see Figure 3.30A), and the yield decreases from \(~81\%\) to \(~21\%\). Although even high-purity, fresh, commercially available NaOH and Bu₄NOH contain small amounts of carbonate (up to \(~0.5\%\) in NaOH, unspecified amount in Bu₄NOH), the sulfate nanojar mixture is either free of carbonate nanojars (when obtained via method B)
\(^{107}\) or contains negligible amounts of carbonate nanojars, (when obtained via method A).
\(^{107}\) Furthermore, if NaOH is replaced by KOH (which
contains up to 2% carbonate) in method (B), an approximately equal mixture of the carbonate- and sulfate-incarcerating nanojars is obtained (Figure 3.31A).

If Bu₄NOH is left out (only KOH is used as base), more carbonate nanojars than sulfate nanojars are obtained (see Figure 3.30B), and the yield decreases to ~13%. We conclude that the presence of Bu₄N⁺ is beneficial in forming THF-soluble nanojars, instead of an intractable side-product, assumed to be \([\text{Cu(\(\mu\)-OH)(\(\mu\)-pz)})\]₇¹ and that the amount of Bu₄NOH employed has an influence on the yield of the reaction, the size distribution of sulfate nanojars, and the amount of carbonate nanojar impurities.

Figure 3.30: ESI-MS(–) spectra (in CH₃CN) of the reaction product of CuSO₄, pyrazole and NaOH (up to 0.5% Na₂CO₃) in THF (A), and CuSO₄, pyrazole and KOH (up to 2% K₂CO₃) in THF (B). Reproduced with permission, from reference 107.
3.2.1.2.2 Effect of lead salts on sulfate-nanojar size and purity

Interestingly, if PbSO₄ is added to the reaction of CuSO₄, pyrazole, KOH (containing K₂CO₃), and Bu₄NOH (29:29:29:56:2 molar ratio), a pure sulfate nanojar mixture is obtained, with absolutely no traces of carbonate (Figure 3.31B). Yet, when excess PbSO₄ (100-fold) is stirred with carbonate nanojars, (Bu₄N)₂[CO₃⊂{Cu(µ-OH)(µ-pz)}₈] (n = 27, 29 − 31) in wet THF (similar to the self-assembly reaction conditions), no reaction occurs and the carbonate nanojars are recovered intact after stirring for 3 days. We conclude that, during the nanojar self-assembly reaction, PbSO₄ (K_{sp} = 2.53 \times 10^{-8} in H₂O at 25 °C)十一 sequesters all carbonate before it is incarcerated by nanojars, and forms almost one million times less-soluble PbCO₃ (K_{sp} = 7.40 \times
In the reaction of CuCO₃·Cu(OH)₂, PbSO₄, pyrazole, NaOH, and Bu₄NOH (29:29:58:54:4 molar ratio), however, PbSO₄ is unable to sequester all carbonate, and a mixture of sulfate- and carbonate-incarcerating nanojars is obtained (see section 3.2.1.3; Anion exchange studies: carbonate binding vs. sulfate binding by nanojars). This result can be attributed to the much lower solubility of CuCO₃·Cu(OH)₂ (Ksp = 7.08 × 10⁻⁹) compared to Na₂CO₃ or (Bu₄N)₂CO₃, as well as to the intimate proximity of carbonate to copper in the former compound. A very different result is obtained when Pb(NO₃)₂ is used instead of PbSO₄ during nanojar self-assembly. The reaction of CuSO₄, pyrazole, NaOH, Bu₄NOH, and Pb(NO₃)₂ in a 31:31:60:2:31 molar ratio results in only one single nanojar: (Bu₄N)₂[SO₄⊂{Cu(OH)(pz)}₃₁] (Figure 3.31C). Here, Pb(NO₃)₂ plays a dual role: first, it acts as a carbonate scavenger, and second, it provides acidity. Because of hydrolysis, Pb²⁺(aq) is a weak acid (pKₐ = 7.6). Whereas PbSO₄ is very poorly soluble (4.4 mg/100 mL H₂O at 25 °C) and its saturated aqueous solution is practically neutral, Pb(NO₃)₂ is highly soluble (59.7 g/100 mL H₂O at 25 °C) and its aqueous solution is acidic. In a slightly acidic medium, the smaller species of [SO₄⊂{Cu(OH)(pz)}ₙ]²⁻ (n = 27–30) are not stable and transform to Cu₃₁SO₄. Isolation of the product by pouring a THF solution in water leads to the precipitation of Cu₃₁SO₄, and small amounts of Cu₃₂SO₄. (Bu₄N)₂ [SO₄⊂{Cu(OH)(4-Mepz)}₃₁] was obtained similarly, using 4-methylpyrazole instead of pyrazole. Note that, as Pb(NO₃)₂ dissolves during the reaction, the Pb²⁺ ions react with the excess sulfate and precipitate as PbSO₄, eliminating any free Pb(NO₃)₂ from the final mixture. When stirred with Pb(NO₃)₂ in THF, all nanojars, including Cu₃₁SO₄, break down completely to the trinuclear complex [Cu₃(µ-OH)(µ-pz)₃(NO₃)₃]⁻ (as shown by ESI-MS). To prove that the observed effect is due to Pb²⁺, the experiment was repeated with Ba(NO₃)₂ (the pKₐ of Ba²⁺(aq) is equal to 13.4) instead of Pb(NO₃)₂: all nanojars were recovered unchanged after 15 days of stirring under identical conditions. PbSO₄, even in large excess (100 equiv per nanojar), is also unable to break down any of the nanojars, and, despite its solubility (Ksp = 2.53 × 10⁻⁸) being over 5 orders of magnitude higher than that of PbCO₃ (Ksp = 7.40 × 10⁻¹⁴), it is unable to exchange carbonate from Cu₆CO₃ to sulfate.
3.2.1.2.3 Breakdown of the sulfate-nanojar mixture into only \( \text{Cu}_{31} \) upon treatment with ammonia

The results discussed in this section were originally published in *Chem. - Eur. J.* 2016, 22, 5499−5503.\(^{105}\) Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission. Sulfate nanojars \((\text{Bu}_4\text{N})_2[\text{SO}_4\{\text{Cu(OH)}(\text{pz})\}_n]\) \((n = 27, 28, 29, 31)\), in contrast to the analogues CO\(_3\)-incarcerating nanojars, were recovered unchanged from a pyridine solution after standing for six weeks. However, NH\(_3\) led to the complete decomposition of the smaller nanojars, and similarly to the carbonate analogue, gave the most stable nanojar in this case pure \((\text{Bu}_4\text{N})_2[\text{SO}_4\{\text{Cu(OH)}(\text{pz})\}_{31}]\) (Figure 3.32).

![Figure 3.32: ESI-MS(−) spectrum of the \((\text{Bu}_4\text{N})_2[\text{SO}_4\{\text{Cu(OH)}(\text{pz})\}_n]\) nanojars in CH\(_3\)CN. Top: as-synthesized \((n = 27, 28, 29, 31)\); bottom: after standing in THF solution saturated with NH\(_3\) for 7 days \((n = 31)\). Reproduced with permission, from reference 105.](image-url)
3.2.1.3 Anion exchange studies: carbonate binding vs. sulfate binding by nanojars

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It has been demonstrated earlier that nanojars are selective for anions with large hydration energies, such as SO$_4^{2–}$ ($\Delta G^\circ_h = -1064$ kJ/mol), and do not form at all with anions with small hydration energies, such as NO$_3^{–}$ ($\Delta G^\circ_h = -289$ kJ/mol) and ClO$_4^{–}$ ($\Delta G^\circ_h = -229$ kJ/mol). It is then expected that CO$_3^{2–}$, with a ca. 25% larger hydration energy ($\Delta G^\circ_h = -1324$ kJ/mol) than sulfate, would be bound significantly stronger by nanojars. We have also shown that sulfate- and carbonate-incarcerating nanojar mixtures (Cu$_{27}$–Cu$_{31}$) are selectively broken down by NH$_3$ to Cu$_{27}$CO$_3$ and Cu$_{31}$SO$_4$, respectively. This result was attributed to the better size match between the smaller carbonate ion and the smallest Cu$_{27}$ nanojar, and between the larger sulfate ion and the larger Cu$_{31}$ nanojar, respectively. The solution-phase thermal stability results, based on the variable-temperature NMR studies described above, further demonstrate that the Cu$_{8+14+9}$ nanojar provides the best fit for the sulfate ion, followed by the Cu$_{8+13+8}$ nanojar.

To assess the carbonate versus sulfate binding preference of nanojars, we first conducted a pair of anion competition experiments. In one experiment, sulfate-incarcerating nanojars Cu$_n$SO$_4$ ($n = 27, 28, 29, 31, 32$) were stirred in THF with an approximately equimolar amount of (Bu$_4$N)$_2$CO$_3$ (soluble in THF). A drastic change in the relative amounts of Cu$_{27}$SO$_4$ and Cu$_{28}$SO$_4$ nanojars is immediately observed. As indicated by ESI-MS (Figure 3.33), most of the Cu$_{28}$SO$_4$ nanojars transformed into Cu$_{27}$SO$_4$ nanojars. At the same time, a peak at $m/z$ 622.2, corresponding to $[(\text{Bu}_4\text{N})\text{Cu}_2(\text{pz})_2(\text{CO}_3)_2]$–, is also detected. These observations indicate that the Cu$_{10}$ ring shrinks to a Cu$_9$ ring as the $[\text{SO}_4\subset\{\text{Cu}(\text{OH})(\text{pz})\}_6+12+10]^2$– nanojar (Cu$_{28}$SO$_4$) converts to $[\text{SO}_4\subset\{\text{Cu}(\text{OH})(\text{pz})\}_6+12+9]^2$– (Cu$_{27}$SO$_4$), while the expelled [Cu(OH)(pz)] unit dimerizes and binds carbonate to form $[\text{Cu}_2(\text{pz})_2(\text{CO}_3)_2]^2$–. After 45 min, small amounts of $[\text{CO}_3\subset\{\text{Cu}(\text{OH})(\text{pz})\}_6+12+9]^2$– nanojars are also detected. After 10 days of stirring, the amount of Cu$_{27}$SO$_4$ and Cu$_{27}$CO$_3$ nanojars is approximately equal, while the larger nanojars appear to be unaffected. This mixture remains virtually unchanged over time, as indicated by ESI-MS after 24 days. Thus, we conclude that nanojars with $n > 27$ do not exchange the incarcerated SO$_4^{2–}$ ion with CO$_3^{2–}$ ions. The excess carbonate (not incarcerated by the Cu$_{27}$CO$_3$ nanojar) precipitates out as (Bu$_4$N)$_2$[Cu$_2$(pz)$_2$(CO$_3$)$_2$] (purple solid), which is filtered out of the solution (ESI-MS is shown in Figure 3.34A).
addition of another equivalent of (Bu4N)2CO3 to the filtrate leads to further conversion of Cu27SO4 to Cu27CO3, and diminishing of Cu28SO4. If excess (Bu4N)2CO3 is used (100 equiv), all nanojars are converted to (Bu4N)2[Cu2(pz)2(CO3)2], most of which precipitates out as a purple solid.

Figure 3.33: ESI-MS(−) spectra (in CH3CN) of (Bu4N)2[SO4⊂{Cu(OH)(pz)}n] (n = 27, 28, 29, 31): initial spectrum (A), within a few minutes after adding an equimolar amount of (Bu4N)2CO3 (B), after 45 min (C), and after 10 days (D). Inset in panel (B) shows the signal corresponding to [(Bu4N)Cu2(pz)2(CO3)2]− (m/z 622.2). Reproduced with permission, from reference 107.
Figure 3.34: ESI-MS(−) spectra (in CH₃CN) of a mixture of sulfate- and carbonate-incarcerating nanojars obtained at ambient temperature with a SO₄²⁻:CO₃²⁻ molar ratio of 1:1: when all reagents are soluble in the THF reaction medium (A), and after refluxing the THF solution for 24 h (B). Reproduced with permission, from reference 107.

The ESI-MS of the violet mother liquor shows peaks attributable exclusively to [(Bu₄N)ₓ+1Cu₂(pz)₂(CO₃)₂(HCO₃)ₓ]⁻ (x = 0−5, m/z 622.2–2139.6), [(Bu₄N)₃{Cu₂(pz)₂(CO₃)₂}²]⁻ (m/z 1488.6), and [(Bu₄N)ₓ(HCO₃)ₓ+1]⁻ clusters (x = 0−11, m/z 61.0–3399.1) (Figure 3.34B). If the solution obtained after stirring the CuₓSO₄ nanojars with 100 equiv of (Bu₄N)₂CO₃ in THF for 18 h is alternatively poured into excess water, the precipitated product analyzes as approximately equal amounts of Cu₂⁷CO₃ and Cu₃₁SO₄ nanojars, with a small amount of Cu₂₉CO₃. This result shows that, upon precipitation with water, the dinuclear complex reverts to nanojars, affording the most stable nanojar with each anion.
In another experiment, carbonate-incarcerating nanojars CuₙCO₃ (n = 27, 29–31) were reacted in THF with an approximately equimolar amount of (Bu₄N)₂SO₄ (soluble in THF). Within minutes, ESI-MS shows that, besides the major set of peaks corresponding to the original nanojars, a new set of peaks appear, corresponding to nanojars in which one pyrazolate ion is substituted by an SO₄²⁻ ion: [(Bu₄N)CO₃\{Cuₙ(OH)ₙ₋₁(pz)ₙSO₄\}]²⁻ (n = 27, m/z 2158.1; n = 29, m/z 2306.0; n = 30, m/z 2379.5; n = 31, m/z 2453.0) (Figure 3.35). This type of reactivity was not observed in the previous experiment. As in the previous experiment, a dinuclear species, [(Bu₄N)Cu₂(pz)₂(SO₄)₂]⁻ (m/z 694.1), is also detected, along with trace amounts of [SO₄\{Cu(OH)(pz)ₙ\}]²⁻ (n = 28, m/z 2113.4; n = 31, m/z 2334.9; n = 32, m/z 2409.9). After 1 day, in addition to the peaks described above, a new nanojar peak is observed at m/z 2471.0, corresponding to [(Bu₄N)SO₄\{Cu₃₁(OH)₃₁(pz)₃₀SO₄\}]²⁻. Also, an increased amount of [SO₄\{Cu(OH)(pz)₃₁\}]²⁻ is observed, along with dinuclear complexes [(Bu₄N)Cu₂(pz)₂(SO₄)(CO₃)]⁻ (m/z 658.1) and [(Bu₄N)Cu₂(pz)₂(CO₃)₂]⁻ (m/z 622.2). After 6 days, the abundance of Cu₃₁SO₄ is slightly larger than that of Cu₃₁CO₃; similarly, the abundance of [(Bu₄N)SO₄\{Cu₃₁(OH)₃₁(pz)₃₀SO₄\}]²⁻ is larger than that of [(Bu₄N)CO₃\{Cu₃₁(OH)₃₁(pz)₃₀SO₄\}]²⁻. In addition, a new peak is observed at m/z 1566.2, corresponding to [SO₄\{Cu₃₁(OH)₃₁(pz)₃₀SO₄\}]³⁻. After 12 days, the peak at m/z 2453.0 is no longer observed, and Cu₃₁SO₄ is much more abundant than Cu₃₁CO₃.
Figure 3.35: ESI-MS(−) spectra (in CH$_3$CN) of (Bu$_4$N)$_2$[CO$_3$⊂{Cu(OH)(pz)}$_n$] (n = 27, 29, 30, 31) (A), within a few minutes after adding an equimolar amount of (Bu$_4$N)$_2$SO$_4$ (B), after 1 day (C), after 6 days (D), after 12 days (E) and after 18 days (F). Insets show the signals corresponding to [(Bu$_4$N)Cu$_2$(pz)$_2$(SO$_4$)$_2$]$^-$ (m/z 694.1), [(Bu$_4$N)Cu$_2$(pz)$_2$(SO$_4$)(CO$_3$)]$^-$ (m/z 658.1) and [(Bu$_4$N)Cu$_2$(pz)$_2$(CO$_3$)$_2$]$^-$ (m/z 622.2), as well as [SO$_4$⊂{Cu$_{31}$(OH)$_{31}$(pz)$_{30}$SO$_4$}]$^{3−}$ (m/z 1566.2). Reproduced with permission, from reference 107.
Also, the abundance of the dinuclear species has flipped, favoring [(Bu₄N)Cu₂(pz)₂(CO₃)₂]⁻ over [(Bu₄N)Cu₂(pz)₂(SO₄)₂]⁻. The trend continues, and after 18 days, only a small amount of Cu₃1CO₃ is left. Beyond this point, no further changes are observed over time. If excess (Bu₄N)₂SO₄ is used (100 equiv), no precipitate forms (in contrast to the (Bu₄N)₂CO₃ experiment), and the ESI-MS(–) spectrum of the solution after 5 days is dominated by HSO₄⁻ ions (m/z 97.0) and tetrabutylammonium sulfate clusters, such as [(Bu₄N)₂₋ₓ(SO₄)ₓ]⁻ (x = 2, m/z 918.8; x = 3, m/z 1499.3; x = 4, m/z 2080.8; x = 5, m/z 2661.3; x = 6, m/z 3241.8). The ESI-MS(+) spectrum is similarly dominated by peaks corresponding to [(Bu₄N)₂₋ₓ(SO₄)ₓ]⁺ (x = 0, m/z 242.3; x = 1, m/z 822.8; x = 2, m/z 1403.3) ions. When the solution is poured into excess water, a blue precipitate forms, the ESI-MS(–) spectrum of which shows almost exclusively [CO₃₋{(Cu(OH)(pz))ₙ}]₂⁻ (n = 27, 29, 31, 31) nanojars, with a small amount of [SO₄₋{(Cu(OH)(pz))₃₁}]₂⁻.

Next, we conducted a series of experiments with both sulfate and carbonate ions present in a 1:1 molar ratio during nanojar self-assembly. Depending on the source of the carbonate and sulfate ions, varying relative amounts of carbonate- and sulfate-incarcerating nanojars were observed (Figure 3.36). Using Cu(NO₃)₂, CuSO₄, pyrazole, NaOH, Na₂CO₃ and Bu₄NOH in a 29:1:30:56:1:2 molar ratio in THF, for instance, leads exclusively to sulfate-incarcerating nanojars, [SO₄₋{(Cu(OH)(pz))₃₁}]₂⁻, along with the trinuclear complex [Cu₃(µ-OH)(µ-pz)₃(NO₃)₃]⁻. In contrast, the reaction of Cu(NO₃)₂, Na₂SO₄, pyrazole, NaOH, Na₂CO₃ and Bu₄NOH (29:29:29:29:2 molar ratio) yielded a mixture of carbonate-incarcerating nanojars, [CO₃₋{(Cu(OH)(pz))ₙ}]₂⁻ (n = 27, 29, 31), exclusively. A mixture of CuSO₄, pyrazole, NaOH, Na₂CO₃ and Bu₄NOH (29:29:56:29:2 molar ratio), or CuCO₃·Cu(OH)₂, PbSO₄, pyrazole, NaOH and Bu₄NOH (29:29:58:54:4 molar ratio) in THF leads to a mixture of carbonate- and sulfate-incarcerating nanojars: the carbonate nanojars dominate in the former case, while sulfate nanojars are more abundant in the latter case. Finally, when all reagents, including the sulfate and carbonate sources are soluble (Cu(NO₃)₂, pyrazole, Bu₄NOH, (Bu₄N)₂SO₄ and (Bu₄N)₂CO₃ in a 29:29:58:56:1:1 molar ratio in THF), a nanojar mixture overall slightly favoring sulfate over carbonate is obtained (Figure 3.36). The composition of the mixture also reveals that the Cu₂⁸, Cu₃₁, Cu₃₂, and Cu₃₃ nanojars strongly favor sulfate, whereas the Cu₂⁷ nanojar strongly favors carbonate, and the Cu₂⁹ and Cu₃₀ nanojars have a comparable preference for sulfate and carbonate.
Figure 3.36: ESI-MS(−) spectra (in CH3CN) of the reaction product in THF of Cu(NO3)2, CuSO4, pyrazole, NaOH, Na2CO3 and Bu4NOH (29:1:30:56:1:2) (A), Cu(NO3)2, Na2SO4, pyrazole, NaOH, Na2CO3 and Bu4NOH (29:29:29:56:29:2) (B), CuSO4, pyrazole, NaOH, Na2CO3 and Bu4NOH (29:29:56:29:2) (C), and CuCO3·Cu(OH)2, PbSO4, pyrazole, NaOH and Bu4NOH (29:29:58:54:4) (D). The SO42−:CO32− molar ratio is 1:1 in all reactions. Reproduced with permission, from reference 107.
3.2.1.4 Synthesis of nanojars highly selective for carbonate- vs. sulfate-anions

The results discussed in this section were originally published in *Chem. Commun.* 2017, 53, 1029–1032,108 and reproduced by permission of The Royal Society of Chemistry. Nanojars of the formula \([\{\text{Cu(OH)(pz)\}_n\text{anion}\}]^{2–}\) (pz = pyrazolate anion; \(n = 27–33\)), have been shown to bind both dinegative \(\text{CO}_3^{2–}\) and \(\text{SO}_4^{2–}\) anions: carbonate is bound almost exclusively by odd-membered nanojars (\(n = 27, 29, 31\)), whereas sulfate is bound by both even- and odd-membered nanojars (\(n = 28, 29, 31\)). Consequently, we sought to use a tethered bis(pyrazole) ligand to favor the formation of even-membered nanojars (\(n = 28\)) and gain selectivity for \(\text{SO}_4^{2–}\) over \(\text{CO}_3^{2–}\). The ligand 1,2-bis(1\(H\)-pyrazol-3-yl)ethane (LH\(_2\)) where prepared by two methods (see section 2.2.1.4), and used for the synthesis of the even-membered nanojars by two ways; either by transforming the copper complexes precursors to nanojars, or by the direct synthesis from starting materials by using LH\(_2\).

3.2.1.4.1 Synthesis and characterization of Cu\(_4(\mu_3-\text{OH})_2(\mu_3-\text{pzCH}_2\text{CH}_2\text{pz})_2(\text{NO}_3)_2\) \(66\)

Reaction of LH\(_2\) (HpzCH\(_2\)CH\(_2\)pzH) with Cu(NO\(_3\))\(_2\) and NaOH (1:2:3 molar ratio) in THF (Scheme 3.13) produces a dark-blue (\(\lambda_{\text{max}} = 609\) nm, \(\varepsilon = 208\) M\(^{-1}\) cm\(^{-1}\) in CH\(_2\)Cl\(_2\); Figure 3.37) tetranuclear complex Cu\(_4(\mu_3-\text{OH})_2(\mu_3-\text{pzCH}_2\text{CH}_2\text{pz})_2(\text{NO}_3)_2\) \(66\), isolated as \(66(\text{H}_2\text{O})_2(\text{THF})\).

The ESI-MS spectrum in CH\(_3\)CN shows peaks at \(m/z\) 730.8 and 606.8 in the negative and positive modes, respectively, corresponding to \([\text{Cu}_4\text{O(\text{OH})(pzCH}_2\text{CH}_2\text{pz})_2(\text{NO}_3)_2]^-\) and \([\text{Cu}_4\text{O(\text{OH})(pzCH}_2\text{CH}_2\text{pz})_2]^+\) (see Appendix B). Only one set of peaks is observed in the \(^1\)H NMR spectrum in DMSO-\(d_6\) at 25 °C, at 132.39 ppm (OH protons), 52.07 and 46.05 ppm (4- and 5-pz protons), 0.22 and 2.40 ppm (CH\(_2\)Cl\(_2\) protons)(Figure 3.38). This implies that in solution, the symmetry of the molecule is determined by two orthogonal mirror planes, and that the two protons of the CH\(_2\) groups are magnetically inequivalent.

Integration of the THF peaks at 1.76 and 3.60 ppm (recorded at 150 °C, where the H\(_2\)O peak does not overlap) indicates the presence of one THF molecule per complex (see Appendix A). The composition of \(66(\text{H}_2\text{O})_2(\text{THF})\) is also confirmed by elemental analysis\(^{108}\) and thermogravimetry (see Appendix D). Variable-temperature \(^1\)H NMR spectroscopy (see Appendix C) shows that the pyrazole proton signals shift upfield with increasing temperature (to 43.98 and 39.15 ppm at 150 °C), whereas the OH and CH\(_2\) proton signals shift downfield (to 172.81, 0.64
and 1.04 ppm, respectively, at 150 °C). The tertranuclear complex Cu₄(µ₃-OH)₂(µ₃-pzCH₂CH₂pz)₂(NO₃)₂ 66, were characterized as well by X-ray crystallography (see section 3.2.4.4.6).

Scheme 3.13: Synthesis of complexes 66, 67 and 68 from LH₂ (Bu₄N⁺ and NO₃ counterions not shown for clarity). Complex 68 (n = 28) forms in mixture with other nanojars, [Cuₙ(OH)ₙ(pzCH₂CH₂pz)ₙ/₂(CO₃)]²⁻ (n = 26, 28, 30). Reproduced with permission, from reference 108.
Figure 3.37: UV−vis spectra of the tetranuclear complexes 66 (red line) and 67 (violet line) (2.600 × 10⁻³ M in CH₂Cl₂), and the mixture of nanojars containing 68 (blue line) (6.500 × 10⁻⁴ M in CH₂Cl₂). Reproduced with permission, from reference 108.

Figure 3.38: Variable-temperature ¹H NMR spectra of 66(H₂O)₂(THF). Only the regions between 125–175 ppm (OH proton), 35–55 pm (pz protons) and (−3) to 1 ppm (CH₂CH₂ protons) are shown for clarity. Reproduced with permission, from reference 108.
The novel complex based on the tethered bis(pyrazole) ligand \([pzCH_2CH_2pz]^2−\) (L) stand in stark contrast with the corresponding complexes obtained with the parent pyrazole (pz) ligand. For instance, when Hpz is reacted with Cu(NO_3)_2 and NaOH (2:2:3 molar ratio) in THF, a trinuclear complex, Cu_3(μ_3-OH)_2(μ-pz)_2(NO_3)_2(H_2O),^{106} is preferentially obtained instead of a tetranuclear complex analogous to 66 under otherwise identical reaction conditions (Figure 3.39).

![Figure 3.39: Contrast between the products of the reaction of Cu(II) and pyrazole (molar ratio 1:1) with and without an ethylene group tethering pairs of pyrazolate units. Reproduced with permission, from reference 108.](image)

3.2.1.4.2 Synthesis and characterization of Bu_4N[Cu_4(μ_4-OH)(μ_3-pzCH_2CH_2pz)_4] 67

The tetranuclear complex Bu_4N[Cu_4(μ_4-OH)(μ_3-pzCH_2CH_2pz)_4], prepared by the addition of LH_2, NaOH and Bu_4NOH to the THF solution of 66(H_2O)_2(THF) (2:2:1:1 molar ratio) (Scheme 3.13), produces a new, dark-violet (λ_{max} = 558 nm, ε = 332 M^{-1} cm^{-1} in CH_2Cl_2; Figure 3.37). This complex can also be obtained directly from Cu(NO_3)_2, LH_2, NaOH and Bu_4NOH (4:4:8:1 molar ratio) in THF. The ESI-MS(−) spectrum of 67 shows one single signal at m/z 911.0, corresponding
to \([\text{Cu}_4(\text{OH})(\text{pzCH}_2\text{CH}_2\text{pz})_4]^-\) (see Appendix B). The \(^1\text{H}\) NMR peaks (DMSO-\(d_6\), 400 MHz, 25 °C) of \(\textbf{67}\) are very broad (61.71 ppm, \(w_{1/2} = 1.4\) kHz; 43.51 ppm, \(w_{1/2} = 2.0\) kHz; 0.92 ppm, \(w_{1/2} = 0.25\) kHz). The tertranuclear complex \(\text{Bu}_4\text{N}[\text{Cu}_4(\mu_4-\text{OH})(\mu_3-\text{pzCH}_2\text{CH}_2\text{pz})_4]\) \(\textbf{67}\), were characterized by X-ray crystallography as well (see section 3.2.4.4.7).

In the absence of the ethylene tether between pairs of pyrazoles ligands, the hypothetical complex \(\text{Bu}_4\text{N}[\text{Cu}_4(\mu_4-\text{OH})(\mu_3-\text{pz})_8]\), analogous to \(\textbf{67}\), is inaccessible by reacting Hpz, Cu(NO\(_3\))\(_2\), NaOH and \(\text{Bu}_4\text{NOH}\) in 8:4:8:1 molar ratio. Instead, polymeric \([\text{Cu}(\mu-\text{pz})_2]_\infty\) is obtained (Figure 3.40).\(^{71}\)

Figure 3.40: Contrast between the products of the reaction of Cu(II) and pyrazole (molar ratio 1:2) with and without an ethylene group tethering pairs of pyrazolate units. Reproduced with permission, from reference 108.
Although not observed as a discrete molecule, a \([\text{Cu}_4(\mu\text{-pz})_8]\) moiety has no inherent factors (such as steric hindrance or bonding restraints) preventing its existence. Indeed, this unit has been observed as part of the extended 3D metal–organic framework of \(\text{Cu}_3(\text{BTP})_2\), with the trivalent ligand 1,3,5-tris(pyrazol-4-yl)benzene (H\(_3\)BTP).\(^{149}\) On the other hand, an analysis of the crystal structure of \([\text{Cu}(\mu\text{-pz})_2]_\infty\)\(^{150}\) reveals that an ethylene tether between two pz units does prevent the formation of a linear \([\text{Cu}(\mu_3\text{-pzCH}_2\text{CH}_2\text{pz})]_\infty\) polymer, due to geometric constrain. Therefore, it becomes clear that the reason why \([\text{Cu}_4(\mu_4\text{-OH})(\mu_3\text{-pzCH}_2\text{CH}_2\text{pz})]_\infty\) cannot be obtained, is that the ethylene tether prevents the system from accessing the apparently more favorable, polymeric form.

### 3.2.1.4.3 Synthesis and characterization of nanojars \([\text{Cu}_n(\text{OH})_n\text{pzCH}_2\text{CH}_2\text{pz}]_{n/2}(\text{CO}_3)\)^{2–} (n = 26, 28, 30)

Addition of \(\text{NaOH}, \text{Bu}_4\text{NOH}\) and \(\text{Na}_2\text{CO}_3\) to the THF solution of \(66(\text{H}_2\text{O})_2(\text{THF})(12:2:1:7\) molar ratio) (Scheme 3.13), produces another new, dark-blue product (\(\lambda_{\text{max}} = 608\) nm, \(\varepsilon = \sim 2.5 \times 10^3\) M\(^{-1}\) cm\(^{-1}\) in \(\text{CH}_2\text{Cl}_2\); Figure 3.37). Variable-temperature \(^1\text{H NMR}\) and ESI-MS(–) analysis reveals that this product consists of a mixture of nanojars, containing mainly \([\text{Cu}_n(\text{OH})_n\text{pzCH}_2\text{CH}_2\text{pz}]_{n/2}(\text{CO}_3)\)^{2–} (n = 26, \(m/z\) 2117.6; n = 28, \(m/z\) 2278.5 [\(68,\) Scheme 3.13]; n = 30, \(m/z\) 2439.0) and \([\text{Cu}_{28}(\text{OH})_{27}\text{pzCH}_2\text{CH}_2\text{pz}]_{14}(\text{pzCH}_2\text{CH}_2\text{pzH})(\text{CO}_3)]\) \(^{2–}\) (\(m/z\) 2350.1) (see Figure 3.41 and Appendices B and Appendix C). A similar mixture of nanojars is obtained directly from \(\text{Cu}(\text{NO}_3)_2\), \(\text{LH}_2\), \(\text{Bu}_4\text{NOH}\) and \(\text{(Bu}_4\text{N})_2\text{CO}_3\) (28:14:56:1 molar ratio), or from \(\text{Cu}(\text{NO}_3)_2\), \(\text{LH}_2\), \(\text{NaOH}, \text{Bu}_4\text{NOH}\) and \(\text{Na}_2\text{CO}_3\) (28:14:54:2:1 molar ratio) in THF.

![Figure 3.41: ESI-MS(–) spectra (in CH\(_3\)CN) of the mixture of nanojars \([\text{Cu}_n(\text{OH})_n\text{pzCH}_2\text{CH}_2\text{pz}]_{n/2}(\text{CO}_3)\)^{2–} (n = 26, 28, 30). Reproduced with permission, from reference 108.](image-url)
The smallest nanojar known to date $[\text{Cu}_{26}(\text{OH})_{26}(\text{pzCH}_2\text{CH}_2\text{pz})_{13}(\text{CO}_3)]^{2-}$, becomes available by using the tethered ligand L, whereas the analogous $[\{\text{Cu(OH)}(\text{pz})\}_{26}(\text{CO}_3)]^{2-}$ has never been observed with the parent pyrazole ligand. The mixture of nanojars obtained with (pzCH₂CH₂pz) also contains $[\text{Cu}_{28}(\text{OH})_{28}(\text{pzCH}_2\text{CH}_2\text{pz})_{14}(\text{CO}_3)]^{2-}$ and $[\text{Cu}_{30}(\text{OH})_{30}(\text{pzCH}_2\text{CH}_2\text{pz})_{15}(\text{CO}_3)]^{2-}$ in large amounts, whereas $[\{\text{Cu(OH)}(\text{pz})\}_{28}(\text{CO}_3)]^{2-}$ remains elusive and $[\{\text{Cu(OH)}(\text{pz})\}_{30}(\text{CO}_3)]^{2-}$ is a very minor component of the nanojar mixture obtained with pyrazole.

Perhaps the most striking result of the conversion of the parent pyrazole ligand to the tethered ligand pzCH₂CH₂pz is the selectivity of the corresponding nanojars for the incarceration of CO₃²⁻, not SO₄²⁻, contrary to expectations. $[\text{Cu}_n(\text{OH})_n(\text{pzCH}_2\text{CH}_2\text{pz})_{n/2}(\text{CO}_3)]^{2-}$ nanojars are easily obtained from a mixture of Cu(NO₃)₂, LH₂, NaOH, Bu₄NOH and Na₂CO₃ (28:14:54:2:28 molar ratio) in THF. In contrast, no reaction is observed when CuSO₄ is used instead of Cu(NO₃)₂/Na₂CO₃, under otherwise identical reaction conditions. In fact, despite the large excess of SO₄²⁻ ions, CO₃-incarcerating nanojars start forming slowly in the latter mixture after exposure to air, as CO₂ slowly diffuses and converts to CO₃²⁻. This result is unexpected, as nanojars based on the parent pyrazole ligand have comparable propensity to bind the CO₃²⁻ and SO₄²⁻ anions,¹⁰⁷ and only the odd-membered ones bind CO₃²⁻ significantly (Figure 3.42).
Figure 3.42: Contrast between the Cu$_{28}$-nanojars formed with SO$_4^{2-}$ and CO$_3^{2-}$ with and without an ethylene group tethering pairs of pyrazolate units. Reproduced with permission, from reference 108.
3.2.2 Study the self-assembly mechanism of nanojars

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To study the intermediates and the mechanism of the self-assembly of pyrazole with Cu$^{2+}$ and OH$^{-}$ ions into nanojars, we use a set of complementary techniques including mass spectrometry, pH titration, UV–vis and NMR spectroscopies, chemical synthesis, and single-crystal X-ray diffraction. The results reveal a pH-dependent equilibrium between Cu$^{2+}$ ions and pyrazole, a trinuclear copper pyrazolate complex, and nanojars.

3.2.2.1 Mass spectrometry monitoring of the self-assembly mechanism

The reaction of copper nitrate and pyrazole with NaOH (1:1:2 molar ratio) in the presence of sodium carbonate in THF was monitored by ESI-MS(−) (Figure 3.43). The reaction mixture (which does not dissolve the NaOH and Na$_2$CO$_3$ reactants or the NaNO$_3$ byproduct) was sampled periodically.

Before the addition of any base, the equimolar mixture of Cu(NO$_3$)$_2$ and pyrazole (Hpz) gives rise to peaks corresponding to mononuclear [Cu(NO$_3$)$_2$]$^-$ ($m/z$ 186.9), [Cu(NO$_3$)$_3$]$^-$ ($m/z$ 248.9) and [CuO(NO$_3$)]$^-$ ($m/z$ 140.9) as major species along with a significant peak at $m/z$ 526.8 corresponding to [Cu$_3$O(pz)$_2$(NO$_3$)$_3$]$^-$ ($m/z$ values represent monoisotopic mass of the most abundant peak within the isotope pattern; all observed values match calculated values). The presence of the latter complex indicates that pyrazole is partially deprotonated even in the absence of a base. This suggests that a solution of copper nitrate should become more acidic upon addition of pyrazole, as some H$_3$O$^+$ ions should form along with the trinuclear complex, which is indeed the case (see section 3.2.2.2). As soon as NaOH/Na$_2$CO$_3$ is added (not soluble in THF), the abundance of the mononuclear species decreases whereas the abundance of the trinuclear species increases. After 25 min of stirring, the mononuclear species are mostly replaced by trinuclear species, as indicated by peaks corresponding to [Cu$_3$O(pz)$_2$(NO$_3$)$_3$]$^-$ ($m/z$ 526.8) and [Cu$_3$(OH)$_3$(pz)$_2$(NO$_3$)$_2$]$^-$ ($m/z$ 499.8) and smaller amounts of [Cu$_3$(OH)$_3$(pz)(NO$_3$)$_2$]$^-$ ($m/z$ 432.8), [Cu$_3$(OH)$_4$(pz)$_3$]$^-$ ($m/z$ 459.9), [Cu$_3$(OH)$_4$(pz)$_2$(NO$_3$)(H$_2$O)]$^-$ ($m/z$ 472.9), [Cu$_3$(OH)$_3$(pz)$_3$(NO$_3$)]$^-$ ($m/z$ 504.9) and [Cu$_3$O(pz)$_3$(NO$_3$)$_2$]$^-$ ($m/z$ 531.8). After 45 min, in addition to the trinuclear species, tetrnuclear [Cu$_4$O$_2$(pz)$_2$(NO$_3$)$_3$]$^-$ ($m/z$ 605.7), [NaCu$_4$O$_2$(OH)(pz)$_3$(NO$_3$)$_2$]$^-$ ($m/z$ 650.8), and [Na$_2$Cu$_4$O$_3$(pz)$_4$(NO$_3$)]$^-$ ($m/z$ 677.8), as well as hexanuclear [Cu$_6$O$_2$(pz)$_5$(NO$_3$)$_3$(OH)]$^-$ ($m/z$ 951.7),
Most intriguingly, peaks corresponding to sodium nitrate clusters, $[\text{Na}_x(\text{NO}_3)_{x+1}]^-$ ($x = 0$–22; $m/z$ 62.0–1931.5) start appearing at this point, together with traces of intermediates $[\{\text{Cu}_3(\text{OH})_3(\text{pz})_3\}_{a/3}(\text{NaNO}_3)_y\text{CO}_3]^2-$ ($n = 27, 29, 31; y = 1–13; m/z$ 2064.5–2869.8) and nanojars $[\text{CO}_3\{\text{Cu}(\text{OH})(\text{pz})\}_n]^2-$ ($n = 27, m/z$ 2022.0; $n = 29, m/z$ 2169.9; $n = 31, m/z$ 2317.4). The presence of sodium nitrate clusters is unexpected, as NaNO$_3$ is insoluble in both THF and CH$_3$CN, as indicated by the absence of any sodium nitrate clusters in the ESI-MS spectra of THF or CH$_3$CN stirred with NaNO$_3$. It is also important to notice that after the peaks of the $[\{\text{Cu}_3(\text{OH})_3(\text{pz})_3\}_{a/3}(\text{NaNO}_3)_y\text{CO}_3]^2-$ intermediates disappear and the nanojars are fully formed (after $\sim$4 h of stirring), the peaks corresponding to NaNO$_3$ clusters can no longer be observed in the ESI-MS spectra. Therefore, we conclude that the NaNO$_3$ clusters detected by ESI-MS are formed during sample injection as the $[\{\text{Cu}_3(\text{OH})_3(\text{pz})_3\}_{a/3}(\text{NaNO}_3)_y\text{CO}_3]^2-$ intermediates eliminate NaNO$_3$ and transform to the final products, $[\text{CO}_3\{\text{Cu}(\text{OH})(\text{pz})\}_n]^2-$.

On the basis of these observations, the following mechanism is proposed (Scheme 3.14). As the NaOH pellets gradually react with the THF solution of copper nitrate and pyrazole, the trinuclear complex $[\text{Cu}_3(\mu_3-\text{OH})(\mu-\text{pz})_3(\text{NO}_3)_2(\text{H}_2\text{O})]\text{69a}$ forms. This complex was isolated and characterized in detail (see sections 3.2.4.4.8). Further reaction of this complex with NaOH leads to replacement of the H$_2$O molecule and NO$_3^-$ ions with HO$^-$ ions, forming $[\text{Cu}_3(\mu_3-\text{OH})(\mu-\text{pz})_3(\text{OH})_x(\text{NO}_3)_3-x]^-$ ($x = 1, m/z$ 549.9 70; $x = 2, m/z$ 504.9 71; $x = 3, m/z$ 459.9 72) species (species wherein the OH group is deprotonated or pyrazolate is replaced by nitrate are also observed in the mass spectra). These species are unstable: unsupported, terminal Cu$^{II}$–OH groups are virtually absent in copper–pyrazole chemistry. Of the $\sim$500 crystal structures in the current Cambridge Structural Database (CSD) containing a $[\text{Cu}(\text{OH})(\text{pz})]$ moiety, only three have terminal Cu$^{II}$–OH groups. In two of these, the terminal Cu$^{II}$–OH group is supported by intramolecular H-
bonding$^{151,152}$ whereas in the third one it is supported by steric crowding around the OH group$^{153}$ the rest contain far more common bridging $\mu_2$-OH and/or $\mu_3$-OH groups.

Figure 3.43: Time-dependent ESI-MS(–) spectra of a solution (in CH$_3$CN) sampled periodically from a mixture of Cu(NO$_3$)$_2$·2.5H$_2$O, pyrazole, NaOH and Na$_2$CO$_3$·H$_2$O (1:1:2:1 molar ratio) stirred in THF. The spectrum at time zero is of the solution of the first two, THF-soluble reactants, just before the addition of the insoluble sodium hydroxide and carbonate. Reproduced with permission, from reference 106.
In other copper(II) complexes, terminal Cu–OH groups are similarly stabilized by hydrogen bonding\textsuperscript{154,155,156,157} and/or steric crowding\textsuperscript{158,159,160,161,162,163} which prevent bridging/oligomerization.

In the next step, the unstable species \textbf{70}, \textbf{71}, and \textbf{72} form transient tetranuclear and hexanuclear species. For example, \([\text{Cu}_6(\text{OH})_3(\text{pz})_6(\text{NO}_3)_4]^-\textbf{73}\), detected at \textit{m/z} 1082.7, can be viewed as two trinuclear \([\text{Cu}_3(\mu_3-\text{OH})(\mu-\text{pz})_3(\text{NO}_3)_2]^-\) units bridged by a \(\mu\)-OH group. Also, the first carbonate-incorporating species, \([\text{Cu}_6(\text{OH})_2(\text{H}_2\text{O})(\text{pz})_6(\text{NO}_3)_3(\text{CO}_3)]^-\), is observed at \textit{m/z} 1081.7.

As more and more NaOH reacts, increasing numbers of trinuclear units end up bridged together, forming large intermediates with the formula \([\{\text{Cu}_3(\text{OH})_3(\text{pz})_3\}_x(\text{NaNO}_3)_y(\text{Na}_2\text{CO}_3)_z]\textbf{74}\). These intermediates are short lived and will eliminate NaNO\(_3\) while transforming into the final products Na\(_2\)[CO\(_3\)⊂{Cu(OH)(pz)}\(_n\)] (\(n = 27, 29, 31\)). It is important to notice that the oligomeric intermediates \([\text{Cu}_3(\text{OH})_3(\text{pz})_3]_x\), based on trinuclear repeating units, have the same composition as the nanojars, \([\text{Cu}(\text{OH})(\text{pz})]_n\) (\(n = 3x\)) (Scheme 3.15).

Scheme 3.15: Illustration of the relationship between trinuclear \([\text{Cu}(\text{OH})(\text{pz})]_3\) units and \([\text{Cu}(\text{OH})(\text{pz})]_x\), rings of identical composition found in nanojars (a ring combination with \(x = 6\) and 12 is shown). Reproduced with permission, from reference 106.

Although the exact structure of the intermediates \textbf{74} cannot be established, their existence is unequivocally demonstrated by the following experiment. Mixing an aqueous solution of copper nitrate and pyrazole with an aqueous solution of NaOH (with small amounts of Na\(_2\)CO\(_3\)) in a 1:1:2
molar ratio under vigorous stirring leads to the immediate, quantitative precipitation of a dark-blue solid (intermediate 74). If this solid is stirred in its mother liquor for several days, it slowly changes color to purple, as it transforms into the polymeric \([\text{trans-Cu}({\mu-\text{OH}})({\mu-\text{pz}})]_{\infty}\). This material is completely insoluble in THF and in other solvents. In contrast, a completely different outcome is observed if the dark-blue solid (intermediate 74) is immediately filtered out of the solution upon its precipitation. Although initially completely insoluble (indicating that this material contains neither the trinuclear intermediate nor the nanojars), when stirred with THF, it slowly dissolves and yields a mixture of nanojars \(\text{Na}_2[\text{CO}_3\subset\{\text{cis-Cu}({\mu-\text{OH}})({\mu-\text{pz}})}\}_n]\) \(n = 27, 29, 31\). It becomes apparent that in order for the intermediates 74 to convert to nanojars, the reaction medium must dissolve the final product. Indeed, if a THF solution of \(\text{Bu}_4\text{NOH}\) (NaOH is insoluble in THF) is added at once to a vigorously stirred THF solution of copper nitrate and pyrazole, nanojars instantly form (as evidenced by ESI-MS). Immediately upon the addition of the \(\text{Bu}_4\text{NOH}\) solution, the reaction is quenched by pouring the deep-blue solution into a large amount of water under stirring. The blue solid formed is filtered out immediately, rinsed with water, and dried. This product, when added to THF, dissolves instantly and completely, and nanojars \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset\{\text{Cu(OH)}(\text{pz})\}_n]\) \(n = 27, 29, 31\) are identified in the resulting solution by ESI-MS. When the reaction with \(\text{Bu}_4\text{NOH}\) is carried out in \(\text{H}_2\text{O}\), similar results are obtained as with NaOH: a dark-blue precipitate forms upon mixing the aqueous solutions of \(\text{Bu}_4\text{NOH}\) and copper nitrate/pyrazole, which after immediate filtration from the solution, followed by rinsing with water and drying, is at first insoluble in THF. Upon continued stirring, the product slowly dissolves in THF and fully transforms into nanojars \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset\{\text{Cu(OH)}(\text{pz})\}_n]\) \(n = 27, 29, 31\), as shown by ESI-MS. It is conceivable that when the reaction is carried out in THF with soluble \(\text{Bu}_4\text{NOH}\), the intermediate \([\text{Cu}_3(\text{OH})_3(\text{pz})_3]_x\) has a size comparable to that of the final nanojars \((x = n/3)\), and being soluble in THF, it quickly converts to the final product. In contrast, if the reaction is carried out in \(\text{H}_2\text{O}\), in which neither the intermediate nor the nanojars are soluble, a polymeric intermediate (large \(x\)) is produced, which is also insoluble in THF. This polymeric intermediate will slowly break down and transform into THF-soluble nanojars upon stirring with THF.
3.2.2.2 pH titration and UV–vis. monitoring of the self-assembly mechanism

An aqueous solution of Cu(NO₃)₂ is acidic, due to the hydrolysis of the hydrated Cu²⁺ ion (pKₐ = 7.5).¹⁴⁶ Pyrazole is a very weak base (N: pKₐ 11.43) and a very weak acid (N–H: pKₐ = 14.21),¹⁶⁴ and its aqueous solution is practically neutral. Upon addition of an equimolar amount of pyrazole to an aqueous Cu(NO₃)₂ solution (1.72 × 10⁻² M), the pH drops from 4.55 to 3.88, accompanied by a change in the wavelength of the absorbance maximum (λ_max) from 800 to 768 nm. These changes indicate not only that pyrazole (Hpz) binds to copper but also that it partially deprotonates yielding H₃O⁺ ions, along with pyrazolate ion (pz⁻) in the resulting product(s). The presence of a trinuclear copper pyrazolate species in this solution is clearly established by ESI-MS (see section 3.2.2.1). Upon addition of increasing amounts of NaOH (with traces of Na₂CO₃) to this solution, the pH gradually increases (Figure 3.44, Table 3.6), while λ_max continually shifts toward lower wavelengths (Figure 3.45, Table 3.6). At a Cu:Hpz:NaOH molar ratio of 3:3:4, the absorbance reaches a maximum at λ_max = 668 nm at a pH of 6.23. At this point, the soluble, trinuclear complex [Cu₃(µ₃-OH)(µ-pz)₃(NO₃)₂(H₂O)] ⁶⁹a is fully formed. As more NaOH is added to the solution, the pH slowly increases, and the absorbance gradually decreases, accompanied by precipitation of a dark-blue solid (filtered out of the solution prior to the measurements). When a Cu:Hpz:NaOH molar ratio of 3:3:6 is reached, the absorbance at 668 nm drops to zero and the pH becomes neutral. At this point, all [Cu₃(OH)(pz)₃(NO₃)₂(H₂O)] ⁶⁹a is converted to the insoluble [{Cu₃(OH)₃(pz)₃}(NaNO₃)ₓ(Na₂CO₃)ᵧ]₇₄. Addition of further amounts of NaOH to the colorless solution leads to an abrupt increase in pH, indicating that no other species are left in solution that would react with NaOH. The two inflection points on the pH titration curve at Cu:Hpz:NaOH molar ratios of 3:3:4 and 3:3:6, along with the accompanying UV–vis spectral changes, suggest the reaction sequence shown in Scheme 3.12. As demonstrated below, nanojars can be transformed back to the trinuclear copper pyrazolate complex and ultimately to Cu²⁺ ions and pyrazole upon addition of increasing amounts of acids.
Figure 3.44: pH titration curve (A) and accompanying absorbance change at 668 nm (B) of an aqueous solution of copper nitrate and pyrazole (1.72 × 10⁻² M each) with increasing amounts of NaOH (containing Na₂CO₃) from a Cu:Hpz:NaOH molar ratio of 3:3:0 to 3:3:9. At 4 equivalents of NaOH, the trinuclear complex Cu₃(OH)(pz)_3(NO₃)₂(H₂O) is fully formed, whereas at 6 equivalents of NaOH the trinuclear complex is fully transformed into insoluble [Cu(OH)(pz)]₆, which is filtered out of the solution prior to the measurements. Reproduced with permission, from reference 106.

Figure 3.45: Electronic absorption spectra obtained during the titration of an aqueous solution of copper nitrate and pyrazole (1.72 × 10⁻² M each) with NaOH (containing Na₂CO₃) from a Cu:Hpz:NaOH molar ratio of 3:3:0 to 3:3:4 (traces a to h in A) and from 3:3:4 to 3:3:6 (traces h to q in B). [Cu(OH)(pz)]₆ is insoluble and is filtered out of the solution. Spectra from the titration of the copper nitrate/pyrazole solution with HNO₃ to a Cu:Hpz:HNO₃ molar ratio of 3:3:1 (trace b’ in A; pH = 2.34) and 3:3:18 (trace c’ in A; pH = 1.08) are also shown. Reproduced with permission, from reference 106.
Table 3.6: pH and visible absorbance measurements during the titration of Cu(NO₃)₂/pyrazole (3:3 molar ratio) with NaOH. Reproduced with permission, from reference 106.

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3.2.2.3 Stepwise synthesis of nanojars

To obtain further proof of the identity of the trinuclear complex intermediate in the formation of the nanojars, a reaction using Cu(NO₃)₂, pyrazole, and NaOH in a 3:3:4 molar ratio is carried out in tetrahydrofuran (THF). After filtering out the insoluble NaNO₃ byproduct and evaporating the solvent, the isolated product (near-quantitative yield) is identified as pure [Cu₃(µ₃-OH)(µ-pz)₃(NO₃)₂(H₂O)] 69a with no trace of nanojars, based on single-crystal X-ray diffraction, ESI-MS, UV–vis, and ¹H NMR (see sections 3.2.4.1.3 and 3.2.4.4.8).

Next, we demonstrate that the trinuclear intermediate 69a is fully convertible to nanojars. Upon stirring 69a with 2 equiv of NaOH (and small amounts of Na₂CO₃) in THF, the color of the solution changes from dark green-blue to deep blue and a NaNO₃ precipitate is filtered out. After evaporation of the solvent, the product is identified as pure nanojars Na₂[CO₃{Cu(OH)(pz)}ₙ] (n = 27, 29, 31) based on ESI-MS, ¹H NMR, and single-crystal X-ray diffraction studies.¹⁰⁵ Thus, we observe a clean transformation of the intermediate to nanojars, as no trinuclear complex nor any other copper complex is detectable in the final product (Figure 3.46).

![Figure 3.46: ESI-MS(−) evidence for the clean synthesis of either trinuclear complex or nanojars based on the Cu:Hpz:NaOH ratio employed. The lower spectrum corresponds to the product obtained from the isolated trinuclear complex upon treatment with 2 equivalents of NaOH. Reproduced with permission, from reference 106.](image-url)
3.2.3 Liquid–liquid extraction of anions from water into organic solvents

3.2.3.1 Extraction of carbonate-anions

The results discussed in this section were originally published in *Dalton Trans.* 2016, 45, 8327–8339, and are reproduced by permission of The Royal Society of Chemistry. The carbonate ion (CO$_3^{2-}$) is in a pH-dependent equilibrium with the bicarbonate ion (HCO$_3^-$) and CO$_2$. At neutral pH, virtually no CO$_3^{2-}$ ion is found in aqueous solution, while above pH $\sim$ 12, carbonate is found exclusively as CO$_3^{2-}$. Given its very large hydration energy ($\Delta G^{\circ}_h = 1315$ kJ mol$^{-1}$), the CO$_3^{2-}$ ion is difficult to extract from water, compared to HCO$_3^-$ ($\Delta G^{\circ}_h = 368$ kJ mol$^{-1}$). Herein we show that nanojars are excellent hosts for the solvent extraction of carbonate at pH 8–14. The industrial solvent Isopar-L is chosen as the organic extraction medium, which is a relatively harmless, colorless and odorless mixture of C$_{11}$–C$_{13}$ isoalkanes, with low vapor pressure (0.3 mmHg at 20 °C, bp $\sim$189–209 °C, compared to hexane: 132 mmHg, bp 69 °C). Carbonate is extracted quantitatively from a 1.0 mM aqueous Na$_2$CO$_3$ solution at pH 8–14 by stirring with a mixture of 4-R- pyrazole (R = n-butyl or n-octyl), copper nitrate and NaOH (1:1:2 molar ratio) in Isopar-L, whereby nanojars Na$_2$[CO$_3$$\subset$(Cu(OH)(4-R-pz))$_n$], identified by ESI-MS(−), are separated into the organic phase. As the nanojar forms, it creates a highly hydrophilic cavity that encloses the carbonate ion, surrounded by a highly hydrophobic outer layer, which fully isolates the ion and provides solubility in the hydrophobic solvent. The incarcerated anion can be released as bicarbonate and/or CO$_2$ upon stripping the organic phase with a dilute nitric acid solution.

3.2.3.2 Extraction of sulfate-anions

The results discussed in this section are reprinted with permission, from *Inorg. Chem.* 2016, 55, 10666–10679. Copyright 2016 American Chemical Society. To demonstrate the extraction of SO$_4^{2-}$ ions from aqueous media, a sulfate solution was prepared by mixing aqueous solutions of CuSO$_4$ and KOH/Bu$_4$NOH, which was then stirred with a solution of pyrazole in CH$_2$Cl$_2$.Cu(OH)$_2$, which initially precipitates from the aqueous solutions, serves both as a copper source and base, and it quickly dissolves into the organic phase as it reacts with pyrazole to form nanojars, while incarcerating the sulfate ion. After separation of the organic phase and evaporation of the solvent, ESI-MS(−) shows that the product is Cu$_n$SO$_4$ ($n = 27–33$), with small amounts of Cu$_n$CO$_3$ ($n = 27, 29, 31$) (Figure 3.47A).
In another setup, a 1:1 molar mixture of aqueous SO\textsubscript{4}\textsuperscript{2−} and CO\textsubscript{3}\textsuperscript{2−} ions was employed, by stirring an aqueous solution of (Bu\textsubscript{4}N)\textsubscript{2}SO\textsubscript{4}, (Bu\textsubscript{4}N)\textsubscript{2}CO\textsubscript{3}, and Bu\textsubscript{4}NOH with a THF solution of Cu(NO\textsubscript{3})\textsubscript{2} and pyrazole. The THF phase separated from the aqueous phase after the addition of NaNO\textsubscript{3}. Evaporation of the solvent provides a mixture of sulfate- and carbonate-incarcerating nanojars in comparable amounts (Figure 3.47B). When a large excess of sulfate is used (Na\textsubscript{2}SO\textsubscript{4}/Na\textsubscript{2}CO\textsubscript{3} molar ratio = 125:1 in the aqueous phase), mostly sulfate nanojars (Cu\textsubscript{n}SO\textsubscript{4}, n = 27−33) are obtained, and carbonate is also extracted (exclusively as Cu\textsubscript{27}CO\textsubscript{3}) (Figure 3.47C).

Figure 3.47: ESI-MS(−) spectra (in CH\textsubscript{3}CN) demonstrating extraction of sulfate by nanojars from water into CH\textsubscript{2}Cl\textsubscript{2}, using CuSO\textsubscript{4}, pyrazole, KOH and Bu\textsubscript{4}NOH in a 28:28:56:2 molar ratio (A), into THF, using Cu(NO\textsubscript{3})\textsubscript{2}, pyrazole, Bu\textsubscript{4}NOH, (Bu\textsubscript{4}N)\textsubscript{2}SO\textsubscript{4} and (Bu\textsubscript{4}N)\textsubscript{2}CO\textsubscript{3} in a 29:29:58:1:1 molar ratio (B), and into THF, using Cu(NO\textsubscript{3})\textsubscript{2}, pyrazole, NaOH, Bu\textsubscript{4}NOH, Na\textsubscript{2}SO\textsubscript{4} and Na\textsubscript{2}CO\textsubscript{3} in a 29:29:56:2:125:1 molar ratio (C). Reproduced with permission, from reference 107.
3.2.4 Characterization of nanojars and other copper complexes

3.2.4.1 $^1$H NMR spectroscopy and mass spectrometry studies of nanojars and other copper complexes

3.2.4.1.1 $^1$H NMR of carbonate-nanojars

The results discussed in this section were originally published in Chem. - Eur. J. 2016, 22, 5499–5503. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

The isolation of pure (Bu$_4$N)$_2$[CO$_3$\{Cu(OH)(pz)\}$^{6+12+9}$], as well as of the (Bu$_4$N)$_2$[CO$_3$\{Cu(OH)(pz)\}$^{6+12+9}$] + (Bu$_4$N)$_2$[CO$_3$\{Cu(OH)(pz)\}$^{7+13+9}$] + (Bu$_4$N)$_2$[CO$_3$\{Cu(OH)(pz)\}$^{8+13+8}$] mixture, allowed the full interpretation of the intricate $^1$H NMR spectrum of the as-synthesized mixture of CO$_3$ nanojars. The spectrum of pure (Bu$_4$N)$_2$[CO$_3$\{Cu(OH)(pz)\}$^{6+12+9}$] (Figure 3.48) showed twelve paramagnetically shifted resonances, eight in the $\delta = 21–38$ ppm window (pyrazolate protons) and four in the $(-29)–(-69)$ ppm window (OH protons; Table 3.7). The four sets of pyrazole peaks integrate to 9:6:6:6, allowing the assignment of individual Cu$_x$ ring protons. Within each pair, the first value corresponds to the pz-4-$H$ proton, and the second one to the pz-3,5-$H_2$ protons. Thus, all pyrazolates of the Cu$_6$ ring and Cu$_9$ ring, respectively, are equivalent in solution (in contrast to the crystal). For the Cu$_{12}$ ring, two sets of peaks, of equal integrated intensities, were observed, due to the different magnetic field environments associated with the Cu$_6$ and Cu$_9$ rings. As can be seen in Figure 3.77, pyrazolato and OH groups of the Cu$_{12}$ ring in (Bu$_4$N)$_2$[CO$_3$\{Cu(OH)(pz)\}$^{6+12+9}$] alternate in up and down orientations relative to the mean plane of the Cu atoms, with six pyrazoles pointing toward the Cu$_6$ ring, and six pyrazoles pointing toward the Cu$_9$ ring. Assignment of resonances to each set of pyrazoles was confirmed by $^1$H–$^1$H COSY NMR data (Figure 3.49). Peak widths at half-heights ($w_{1/2}$), as well as longitudinal (spin–lattice, $T_1$), and transverse (spin–spin, $T_2$) relaxation times are summarized in Table 3.7.
Figure 3.48: $^1$H NMR spectra (400 MHz, 20 °C) of Cu$_{27}$ nanojar (Bu$_4$N)$_2$[CO$_3$⊂{Cu(OH) (pz)}$_{6+12+9}$] (top), Cu$_{27}$/Cu$_{29}$ nanojar mixture (Bu$_4$N)$_2$[CO$_3$⊂{Cu(OH) (pz)}$_{6+12+9}$] + (Bu$_4$N)$_2$[CO$_3$⊂{Cu(OH)(pz)}$_{7+13+9}$] + (Bu$_4$N)$_2$[CO$_3$⊂{Cu(OH)(pz)}$_{8+13+8}$] (center), and of the as-synthesized nanojar mixture (bottom) in DMSO-$d_6$, showing pyrazole protons (left) and OH protons (right). Reproduced with permission, from reference 105.

After subtracting the Cu$_{27}$ peaks from the $^1$H NMR spectrum of the Cu$_{27}$ + Cu$_{29}$ mixture obtained by pyridine etching (Figure 3.48), Cu$_{29}$ peaks were assigned as follows: Cu$_{7+13+9}$ nanojar, 33.93 and 29.84 ppm (Cu$_9$ ring), 30.86 and 27.45 ppm (Cu$_7$ ring), 27.10 and 22.00 ppm (Cu$_{13}$ ring); Cu$_{8+13+8}$ nanojar, 28.55 and 25.60 ppm (Cu$_{13}$ ring), 25.88 and 21.20 ppm (two Cu$_8$ rings). Finally, by subtracting all Cu$_{27}$ and Cu$_{29}$ peaks, Cu$_{31}$ peaks can be assigned in the spectrum of the as-synthesized mixture of nanojars. As opposed to the Cu$_{27}$ and Cu$_{29}$ nanojars, the Cu$_{31}$ nanojar displayed much broader resonances. Thus, only one peak can be distinguished clearly, at 22.65 ppm (Cu$_{14}$ ring). Broad peaks (overlapped with Cu$_{27}$ and Cu$_{29}$ peaks) are evident at 37.6, 33.3,
31.2, 29.7, 28.4 and 27.3 ppm. Cu$_{30}$ nanojar peaks could not be assigned, because the abundance of this species is very low.

Table 3.7: $^1$H NMR data (400 MHz) for (Bu$_4$N)$_2$[CO$_3$$\subset$[Cu(OH)(pz)]$_{6+12+9}$] in DMSO-$d_6$. Reproduced with permission, from reference 105.

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<th>Peak [ppm]</th>
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<th>$T_2$ (esd) [ms]</th>
<th>Assignment</th>
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<tr>
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<td>21</td>
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<td>19.5(0.4)</td>
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The relatively sharp NMR signals of (Bu$_4$N)$_2$[CO$_3$$\subset$[Cu(OH)(pz)]$_{6+12+9}$] suggest strong antiferromagnetic coupling between the Cu atoms of each Cu$_x$ ring (average Cu···Cu 3.294(1) Å; Cu-O-Cu 117.9(2)$^\circ$). Pyrazolato and O(H) ligands are indeed known to mediate such coupling.$^{52,167}$ Variable-temperature (VT) NMR indicates that the largest spin density resides on the Cu$_9$ ring, because its resonances show the largest hyperfine shifts and fastest relaxation, as well as the most pronounced temperature-dependent shifts (see Figure 3.50 and Appendix C). The localization of the unpaired electron density on the Cu$_9$ ring becomes even more pronounced at low temperatures, because the signals of the Cu$_9$ protons shift in opposite direction to the Cu$_6$ and Cu$_{12}$ protons, and broaden until they vanish. Variation of the hyperfine shifts in solvents with different donor numbers is also documented (Table 3.8).
Figure 3.49: $^1$H–$^1$H COSY NMR spectrum of (Bu$_4$N)$_2$[CO$_3$⊂{Cu(OH)(pz)}$_{6+12+9}$]. Reproduced with permission, from reference 105.

Figure 3.50: Temperature-dependent $^1$H NMR spectra of (Bu$_4$N)$_2$[CO$_3$⊂{Cu(OH)(pz)}$_{6+12+9}$] in toluene-$d_8$. The numbers 6, 9, and 12 correspond to the different Cu$_x$ rings in [CO$_3$⊂{Cu(OH)(pz)}$_{6+12+9}$]$^{2-}$. Reproduced with permission, from reference 105.
Table 3.8: $^1$H NMR data for nanojars (Bu$_4$N)$_2$[CO$_3$⊂{Cu(OH)(pz)}$_{6+12+9}$], (Bu$_4$N)$_2$[CO$_3$⊂{Cu(OH)(pz)}$_{7+13+9}$] and (Bu$_4$N)$_2$[CO$_3$⊂{Cu(OH)(pz)}$_{8+13+8}$] in different solvents (donor number, $^{168}$kcal/mol) at 25 ºC. Reproduced with permission, from reference 105.

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</tr>
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<td>28.55</td>
<td>28.34</td>
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3.2.4.1.2 Variable-temperature $^1$H NMR and mass-spec characterization of sulfate-nanojars

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The $^1$H NMR spectrum of the as-synthesized mixture of sulfate-incarcerating nanojars (method B) in DMSO-$d_6$ is very complex, as it contains six overlapping sets of peaks corresponding to Cu$_{6+12+9}$SO$_4$, Cu$_{6+12+10}$SO$_4$, Cu$_{7+13+9}$SO$_4$, Cu$_{8+13+8}$SO$_4$, Cu$_{8+14+9}$SO$_4$ and Cu$_{8+14+10}$SO$_4$ nanojars (Figure 3.51 and Figure 3.52). Within each Cu$_x$-ring ($x = 6–14$, except 11), all pyrazole and OH groups are magnetically identical, respectively, with the exception of the Cu$_{12}$-ring, which shows two sets of signals for both the pyrazole and the OH protons in the Cu$_{6+12+9}$SO$_4$ and Cu$_{6+12+10}$SO$_4$ nanojars. The pyrazole units have two magnetically distinct set of protons: one at the 4-position and one at the 3,5-positions (with 1:2 integrated intensities). Thus, the nanojars described above display 8, 8, 6, 4, 6, and 6 pyrazole proton peaks, respectively, in the 21–41 ppm window, and 4, 4, 3, 3, and 3 OH proton peaks, respectively, in the window between –25 ppm and –59 ppm. At room temperature, the assignment of each individual peak in this mixture is impossible, because of severe (sometimes complete) overlap. The isolation of three different fractions (Cu$_{27}$/Cu$_{28}$, Cu$_{29}$/Cu$_{31}$, Cu$_{31}$/Cu$_{32}$), combined with variable-temperature measurements over a 25–150 °C range (see Appendix C), permitted the assignment of all 59 peaks (except the one of the OH proton of the Cu$_{14}$-ring of the Cu$_{8+14+10}$SO$_4$ nanojar, which is likely overlapped with the corresponding peak of the same size ring of the Cu$_{8+14+9}$SO$_4$ nanojar).
Figure 3.51: Variable-temperature $^1$H NMR spectra of the mixture of six different sulfate-incarcerating nanojars in DMSO-$d_6$, showing pyrazole proton signals in the 21–41 ppm window. Reproduced with permission, from reference 107.
Figure 3.52: Variable-temperature $^1$H NMR spectra of the mixture of six different sulfate-incarcerating nanojars in DMSO-$d_6$, showing OH proton signals in the ($-25$)–($-59$) ppm window. Reproduced with permission, from reference 107.
We have previously shown that (i) because of the paramagnetic Cu(II) atoms, the peaks corresponding to pyrazole and OH protons are drastically shifted downfield and upfield, respectively, and (ii) their chemical shift values are temperature-dependent. Fortuitously, the chemical shift of certain peaks displays much larger temperature dependence than those of others. Monitoring the position of each peak in the 60 variable-temperature $^1$H NMR spectra collected allows the observation of individual peaks that are overlapped at a given temperature, but are clearly separated at a certain different temperature (see Figure 3.53 and Table 3.9).

Comparison of the $^1$H NMR spectra of the Cu$_{6+12+9}$SO$_4$ nanojar with the corresponding ones of the carbonate-encapsulating analogue Cu$_{6+12+9}$CO$_3$ indicates that, with the exception of the Cu$_{12}$-ring pyrazole protons, which show a difference of <0.3 ppm, all other proton signals have a significantly different chemical shift (2−3 ppm difference for Cu$_6$- and Cu$_9$-ring pyrazole protons, and 3−15 ppm difference for OH protons). These differences indicate that the incarcerated anion (sulfate versus carbonate) has a significant influence on spin density distribution within nanojars.

The Cu$_{6+12+10}$SO$_4$ nanojar, which has not been observed before with carbonate, displays signals that are more paramagnetically shifted than those of the Cu$_{6+12+9}$SO$_4$ nanojar (see Figure 3.51 and Figure 3.52, as well as Appendix C). For instance, the pyrazole signals of the Cu$_{10}$-ring are found at 40.27 and 34.50 ppm, compared to 34.83 and 31.03 ppm in the case of the Cu$_9$-ring, whereas the OH signal of the Cu$_{10}$-ring is located at −57.75 ppm, compared to −52.95 ppm in the case of the Cu$_9$-ring.
Figure 3.53: Temperature-dependent variation of the chemical shift of different Cu$_n$-ring protons in the various sulfate-nanojars in DMSO-$_d_6$, illustrating the influence of the size of the ring on chemical shift, as well as the difference in chemical shift for the same Cu$_n$-ring in different nanojars. Reproduced with permission, from reference 107.
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In fact, the signals of the Cu_{10}-ring are the most paramagnetically shifted among all Cu_{n}-rings observed within sulfate-incarcerating nanojars, and they display the strongest temperature dependence (6, 5, and 12 ppm shift for the pyrazole 4- and 3,5-protons and OH proton, respectively, upon going from 25 °C to 150 °C, compared to 5, 4, and 5 ppm, respectively, for the Cu_{9}-ring). The Cu_{6}- and Cu_{12}-ring signals in the Cu_{27}- and Cu_{28}-nanojars display a much smaller shift with temperature (Cu_{6}-ring: 1–2 and 2 ppm for the pyrazole and OH protons, respectively; Cu_{12}-ring: 0.2–0.4 and 0.5–3 ppm for the pyrazole and OH protons) (Figure 3.54).

Figure 3.54: Temperature-dependent variation of the chemical shift of different Cu_{n}-ring protons in the Cu_{6+12+9}CO_{3}, Cu_{6+12+9}SO_{4} and Cu_{6+12+10}SO_{4} nanojars in DMSO-\text{d}_6, illustrating the influence of incarcerated anion and size of the ring on chemical shift (also see Figure 3.53). Reproduced with permission, from reference 107.

The temperature-dependent variation of the chemical shift of different Cu_{n}-ring protons in the various sulfate nanojars in DMSO-\text{d}_6, illustrating not only the influence of the size of the ring on chemical shift, but also the difference in chemical shift for the same Cu_{n}-ring in different nanojars, is shown in Figure 3.53. As the Cu_{6+12+9}/Cu_{6+12+10} nanojar mixture is heated in DMSO-\text{d}_6, a gradual
decrease of the Cu$_{6+12+10}$ signals are observed, while new signals, corresponding to Cu$_{8+13+8}$ and Cu$_{8+14+9}$ nanojars, appear. Upon cooling back to 25 °C, mixture of Cu$_{6+12+9}$, Cu$_{6+12+10}$, Cu$_{7+13+9}$, Cu$_{8+13+8}$ and Cu$_{8+14+9}$ nanojars is obtained, confirmed also by ESI-MS spectrometry (Figure 3.55).

Similarly to the carbonate analogues, two different Cu$_{29}$-nanojars, Cu$_{7+13+9}$SO$_4$ and Cu$_{8+13+8}$SO$_4$ are obtained with sulfate (see Figure 3.51 and Figure 3.52, as well as Appendix C). In the as-synthesized mixture at room temperature, Cu$_{7+13+9}$SO$_4$ is much more abundant than Cu$_{8+13+8}$SO$_4$. Upon heating in DMSO-$d_6$, however, the former transforms to the latter, which, in turn, transforms to Cu$_{8+14+9}$SO$_4$ at even higher temperatures (greater than $\sim 100$ °C). At 150 °C, the mixture that initially contained mostly Cu$_{7+13+9}$SO$_4$ and Cu$_{8+14+9}$SO$_4$, and small amounts of Cu$_{6+12+9}$SO$_4$, Cu$_{6+12+10}$SO$_4$, Cu$_{8+13+8}$SO$_4$, Cu$_{8+14+10}$SO$_4$ nanojars, displays only two sets of peaks, corresponding to Cu$_{8+14+9}$SO$_4$ and a small amount of Cu$_{8+13+8}$SO$_4$ nanojars (Figure 3.56).
Figure 3.56: ESI-MS(−) spectra (in CH$_3$CN) of the nanojar fraction containing Cu$_{29}$SO$_4$ and Cu$_{31}$SO$_4$ (and small amounts of Cu$_{27}$SO$_4$, Cu$_{28}$SO$_4$ and Cu$_{32}$SO$_4$) before heating (A) and after heating to 150 °C in DMSO-$d_6$ (B). Reproduced with permission, from reference 107.

The Cu$_8$- and Cu$_{13}$-ring signals show much less variation with temperature than the Cu$_9$- and Cu$_{10}$-ring signals, and are more similar to the Cu$_{12}$-ring signals (Cu$_8$-ring: 0.5 and 4 ppm for the pyrazole and OH protons, respectively; Cu$_{13}$-ring: 0.2−0.5 and 1.5 ppm for the pyrazole and OH protons, respectively). In the Cu$_{6+12+9}$ nanojar, the incarcerated anion has less influence than in the Cu$_{6+12+9}$ nanojar: differences of 0.2−1 ppm (pyrazole protons) and 2−5 ppm (OH protons) are observed between Cu$_{8+13+8}$SO$_4$ and Cu$_{8+13+8}$CO$_3$.$^{105}$ Notably, the crystal structures of the two nanojars are virtually identical (see sections 3.2.4.4.11 and 3.2.4.4.15).

As with the carbonate-incarcerating analogues, Cu$_{8+14+9}$SO$_4$ shows the broadest signals among the nanojars of different sizes (see Figure 3.51 and Figure 3.52, as well as Appendix C). At room temperature, the pyrazole proton signals of the Cu$_9$-ring, as well as those of the OH protons of both the Cu$_8$- and Cu$_9$-rings are too broad to be observed. In contrast to the carbonate analogue, however, Cu$_{8+14+9}$SO$_4$ is stable at higher temperatures, and the corresponding signals appear much
sharper at 150 °C. At this temperature, tiny amounts of Cu$_{8+13}$SO$_4$ decomposition product are also observed as confirmed by ESI-MS as well (Figure 3.57).

![ESI-MS spectra](image)

**Figure 3.57**: ESI-MS (−) spectra (in CH$_3$CN) of the nanojar fraction containing Cu$_{31}$SO$_4$ and small amounts of Cu$_{32}$SO$_4$ before heating (A) and after heating to 150 °C in DMSO-$d_6$ (B). Reproduced with permission, from reference 107.

Assignment of the NMR signals corresponding to protons in the pyrazole 4- and 3,5-positions was easily done earlier on a pure Cu$_{27}$CO$_3$ sample at room temperature, as an integrated ratio of 1:2 was unambiguously obtained for distinct peaks. Although overlapping prevents the quantitative integration of certain peaks in Cu$_n$SO$_4$ mixtures at a given temperature, the assignment of individual peaks is possible thanks to the different temperature dependence of the chemical shift of those peaks. Nevertheless, we verified the assignment of the 4- and 3,5-protons by substituting the 4-position of the pyrazole ligands in Cu$_{31}$SO$_4$ with a methyl group. Thus, nanojars (Bu$_4$N)$_2$[SO$_4$]+=Cu(OH)(4-Mepz)$_{31}$] were prepared using 4-methylpyrazole instead of pyrazole. The $^1$H NMR peaks corresponding to the pyrazole 4-position are absent in the substituted nanojar.
(see Appendix C), while the peaks corresponding to the equivalent 3- and 5-positions have almost identical chemical shifts to those in the unsubstituted nanojar (see Appendix C).

### 3.2.4.1.3 $^1$H NMR and mass spectrometry characterization of [Cu$_3$($\mu$$_3$-OH)(µ-pz)$_3$(NO$_3$)$_2$ (H$_2$O)] $^{69a}$ and [Cu$_3$($\mu$$_3$-OH)(µ-pz)$_3$(NO$_3$)$_2$(CH$_3$CN)] $^{69b}$

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In the ESI-MS(+) spectrum of $^{69a}$ in CH$_3$CN, the base peak observed at $m/z$ 407.9 corresponds to [Cu$_3$O(pz)$_3$]$^+$ (due to loss of H$_2$O, NO$_3^-$ and HNO$_3$ upon ionization); smaller peaks attributable to [Cu$_4$O$_2$(pz)$_4$]$^+$ ($m/z$ 553.8), [Cu$_5$O$_2$(pz)$_5$]$^+$ ($m/z$ 683.8), [Cu$_6$(OH)$_2$(pz)$_6$(NO$_3$)$_3$]$^+$ ($m/z$ 1003.7) and [[Cu$_6$(OH)$_2$(pz)$_6$(NO$_3$)$_3$]$_2$(NO$_3$)]$^+$ ($m/z$ 2069.4) are also present. In the ESI-MS(–), the base peak observed at $m/z$ 526.8 corresponds to [Cu$_3$O(pz)$_2$(NO$_3$)$_3$]$^-$; a smaller peak attributable to [Cu$_3$(OH)$_3$(pz)$_2$(NO$_3$)$_3$]$^-$ ($m/z$ 499.8), as well as traces of [Cu$_3$(OH)$_4$(pz)$_3$]$^-$ ($m/z$ 459.9), [Cu$_3$O(pz)$_3$(NO$_3$)$_3$]$^-$ ($m/z$ 531.9), [Cu$_4$O$_2$(pz)$_2$(NO$_3$)$_3$]$^-$ ($m/z$ 605.7), [Cu$_4$O$_2$(pz)$_4$(NO$_3$)$_2$]$^-$ ($m/z$ 677.8), [Cu$_6$O$_2$(pz)$_4$(NO$_3$)$_5$]$^-$ ($m/z$ 991.6) and [Cu$_6$O$_2$(pz)$_5$(NO$_3$)$_4$]$^-$ ($m/z$ 996.6) are also identified. Importantly, no traces of nanojars could be detected in either negative or positive mode. The $^1$H NMR spectrum of $^{69a}$ shows two peaks in a 1:2 integrated ratio at 40.90 and 35.19 ppm in (CD$_3$)$_2$CO at 25 °C, attributable to the pyrazolate protons in the 4 and 3,5 positions, respectively (Figure 3.58).
Figure 3.58: $^1$H NMR spectrum (400 MHz, (CD$_3$)$_2$CO, 25 °C) of [Cu$_3$(µ$_3$-OH)(µ-pz)$_3$(NO$_3$)$_2$(H$_2$O)] 69a. Reproduced with permission, from reference 106.

The observed signals are relatively sharp for a paramagnetic complex, suggesting strong antiferromagnetic coupling between the Cu(II) centers. Similar values are obtained with recrystallized 69b (40.99 and 35.13 ppm in (CD$_3$)$_2$CO at 25 °C). These results show that in contrast to the solid-state structure, in solution the complex assumes 3-fold symmetry, as a result of fast exchange of the nitrate ions with the water 69a or acetonitrile 69b moieties. Complex 69b retains its 3-fold symmetry in (CD$_3$)$_2$CO solution down to −100 °C (Figure 3.59). 69a, however, partially dimerizes in (CD$_3$)$_2$CO solution, as suggested by the appearance of a second set of peaks. The ratio of dimer to trinuclear complex increases as the temperature is lowered (Figure 3.59). Dimerization leads to a decrease of the unpaired electron density on the complex, resulting in the upfield shift of the peaks, along with lowering the symmetry from $C_{3v}$ to $C_{2h}$, resulting in a larger number of peaks.
Figure 3.59: Variable-temperature $^1$H NMR spectra of $[\text{Cu}_3(\mu_3-\text{OH})(\mu-\text{pz})_3(\text{NO}_3)_2(\text{H}_2\text{O})]$ (69a, left) and $[\text{Cu}_3(\mu_3-\text{OH})(\mu-\text{pz})_3(\text{NO}_3)_2(\text{CH}_3\text{CN})]$ (69b, right) in (CD$_3$)$_2$CO. Peaks corresponding to the trinuclear complexes are indicated in blue, those of the dimer in red, those of H$_2$O in cyan, and those of CH$_3$CN in violet. Reproduced with permission, from reference 106.

The proposed structure of the dimer with bridging H$_2$O molecules is shown in Figure 3.60. Similar structures, with carboxylate bridges instead of water and carboxylate or pyrazole ligands instead of nitrate, have been characterized crystallographically. The variable-temperature $^1$H NMR studies also provide proof for the coordinated H$_2$O or CH$_3$CN molecules in 69a and 69b, respectively: as the temperature is lowered, the corresponding peaks display increasing hyperfine shifts and shorter relaxation times (evidenced by downfield shifts and broadening), similar to the pyrazolate peaks.
3.2.4.2 $^1$H NMR spectroscopic and mass spectrometric studies of thermal stability of nanojars

The results discussed in this section are reprinted with permission, from *Inorg. Chem.* 2016, 55, 10666–10679. Copyright 2016 American Chemical Society. As evidenced by the $^1$H NMR experiments in DMSO solution described in (section 3.2.4.1.2), certain nanojars are more stable at high temperature than others. Thus, nanojars that are stable at room temperature, such as Cu$_{6+12+9}$SO$_4$, Cu$_{6+12+10}$SO$_4$, Cu$_{7+13+9}$SO$_4$ and Cu$_{8+14+10}$SO$_4$, transform in solution to more robust Cu$_{8+13+8}$SO$_4$ and Cu$_{8+14+9}$SO$_4$ nanojars upon increasing the temperature. The higher stability of the latter two complexes could be attributed to a tighter accommodation of the sulfate ion guest within the nanojar host, which will form at higher temperatures on the expense of both smaller and larger nanojars. Similarly, the carbonate ion finds a better fit in the smaller nanojars, as Cu$_{6+12+9}$CO$_3$ and Cu$_{8+13+8}$CO$_3$ are more resistant to heating than Cu$_{7+13+9}$CO$_3$ and Cu$_{8+14+9}$CO$_3$. After refluxing a mixture of Cu$_n$SO$_4$ and Cu$_n$CO$_3$ in THF (b.p. 66 °C) for 24 h, only Cu$_{31}$SO$_4$, Cu$_{29}$SO$_4$, Cu$_{27}$CO$_3$ and Cu$_{25}$CO$_3$ survive, as shown by ESI-MS (Figure 3.34B); $^1$H NMR indicates that both Cu$_{29}$ nanojars (Cu$_{7+13+9}$ and Cu$_{8+13+8}$) are still present, with both sulfate and carbonate (Figure 3.61).
Figure 3.61: $^1$H NMR spectrum (in DMSO-$d_6$) of a mixture of sulfate- and carbonate-incarcerating nanojars with a $\text{SO}_4^{2-} : \text{CO}_3^{2-}$ molar ratio of 1:1 (all reagents soluble in the THF reaction medium), after refluxing the THF solution for 24 hours (pyrazole signals in the 21–41 ppm window). Reproduced with permission, from reference 107.

In contrast, all nanojars are considerably more stable at higher temperatures in the solid state: the ESI-MS spectrum of a mixture of $\text{Cu}_n\text{SO}_4$ and $\text{Cu}_n\text{CO}_3$ is almost unchanged after heating at 140 °C for 24 h in an oven under air. Furthermore, thermogravimetric analysis shows that, regardless of nanojar size or incarcerated anion (sulfate or carbonate), thermal decomposition accompanied by weight loss does not occur up to 205–210 °C under N$_2$ (see Appendix D).
3.2.4.3 Mass-spectrometric study of carbonate- and sulfate-nanojars


ESI-MS(−) of the as-prepared mixtures of (Bu₄N)₂[anion{Cu(OH)(pz)}ₙ] (anion = CO₃²⁻ or SO₄²⁻) nanojars (by the room temperature self-assembly of Cu²⁺, OH⁻ and pyrazole, see Figure 3.26 and Figure 3.32) in CH₃CN, at cone voltages no greater than 40 V, reveals in each case the presence of multiple [anion{Cu(OH)(pz)}ₙ]²⁻ nanojars (Figure 3.62).

![Figure 3.62: ESI-MS(−) spectra of the as-synthesized CO₃²⁻ (lower) and SO₄²⁻ (upper) nanojar mixtures at 40 V in CH₃CN. Insets show shrunken daughter nanojars at 100 V (numbers indicate parent nanojar). Reproduced with permission, from reference 105.](image)

In the case of carbonate, dinegative Cu₂⁷ (m/z 2023), Cu₂⁹ (m/z 2171), Cu₃₀ (m/z 2244) and Cu₃₁ (m/z 2318) nanojars are observed, while with sulfate, Cu₂⁷ (m/z 2041), Cu₂₈ (m/z 2115), Cu₂₉ (m/z 2189) and Cu₃₁ (m/z 2336) nanojars are detected. Accurate mass data, as well as predicted and observed isotopic patterns are presented in the (Table 3.10 and Appendix B).
Table 3.10: Accurate mass data for the carbonate- and sulfate-nanojars by ESI-MS(−). In each case, the most abundant peak from the isotope pattern is used for comparing predicted and observed \(m/z\) values. Reproduced with permission, from reference 105.

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<td>([\text{CO}<em>3{\text{Cu(OH)(pz)}}</em>{27}]^{2-})</td>
<td>(\text{Cu}<em>{27}\text{C}</em>{82}\text{H}<em>{108}\text{N}</em>{54}\text{O}_{30})</td>
<td>2021.9646</td>
<td>2021.9650</td>
</tr>
<tr>
<td>([\text{CO}<em>3{\text{Cu(OH)(pz)}}</em>{29}]^{2-})</td>
<td>(\text{Cu}<em>{29}\text{C}</em>{85}\text{H}<em>{112}\text{N}</em>{56}\text{O}_{31})</td>
<td>2169.9258</td>
<td>2169.9153</td>
</tr>
<tr>
<td>([\text{CO}<em>3{\text{Cu(OH)(pz)}}</em>{30}]^{2-})</td>
<td>(\text{Cu}<em>{30}\text{C}</em>{88}\text{H}<em>{116}\text{N}</em>{58}\text{O}_{32})</td>
<td>2243.4070</td>
<td>2244.3972</td>
</tr>
<tr>
<td>([\text{CO}<em>3{\text{Cu(OH)(pz)}}</em>{31}]^{2-})</td>
<td>(\text{Cu}<em>{31}\text{C}</em>{94}\text{H}<em>{124}\text{N}</em>{62}\text{O}_{34})</td>
<td>2316.8879</td>
<td>2316.8809</td>
</tr>
<tr>
<td>([\text{SO}<em>4{\text{Cu(OH)(pz)}}</em>{27}]^{2-})</td>
<td>(\text{Cu}<em>{27}\text{C}</em>{81}\text{H}<em>{108}\text{N}</em>{54}\text{O}_{31}\text{S})</td>
<td>2039.9480</td>
<td>2039.9636</td>
</tr>
<tr>
<td>([\text{SO}<em>4{\text{Cu(OH)(pz)}}</em>{28}]^{2-})</td>
<td>(\text{Cu}<em>{28}\text{C}</em>{84}\text{H}<em>{112}\text{N}</em>{56}\text{O}_{32}\text{S})</td>
<td>2113.4290</td>
<td>2113.4290</td>
</tr>
<tr>
<td>([\text{SO}<em>4{\text{Cu(OH)(pz)}}</em>{29}]^{2-})</td>
<td>(\text{Cu}<em>{29}\text{C}</em>{87}\text{H}<em>{116}\text{N}</em>{58}\text{O}_{33}\text{S})</td>
<td>2186.9099</td>
<td>2186.9063</td>
</tr>
<tr>
<td>([\text{SO}<em>4{\text{Cu(OH)(pz)}}</em>{31}]^{2-})</td>
<td>(\text{Cu}<em>{31}\text{C}</em>{93}\text{H}<em>{124}\text{N}</em>{62}\text{O}_{35}\text{S})</td>
<td>2334.8713</td>
<td>2334.8789</td>
</tr>
</tbody>
</table>

At sampling cone voltages higher than 40 V, the peaks corresponding to \([\text{CO}_3\{\text{Cu(OH)(pz)}\}_n]^{2-}\) nanojars in the \(m/z\) 2010–2330 window gradually disappear, while a peak at \(m/z\) 198, along with a new group of peaks in the \(m/z\) 1550–2010 window appear. At 100 V, no parent nanojars, but only daughter species are observed (Figure 3.62). Although the \(m/z\) = 198 peak could easily be assigned to \([\text{Cu}^+\text{(pz)}_2]^-\), the origin of the peaks in the \(m/z\) 1550–2010 window was not readily apparent. Tandem mass spectrometry experiments were carried out on each parent \([\text{CO}_3\{\text{Cu(OH)(pz)}\}_n]^{2-}\) peak (Appendix E). The results show that the nanojars shrink by losing neutral \(\text{Cu}_5\text{(OH)}_{10}\text{(Hpz)}_{10-y}\text{(H}_2\text{O})_{(n+y-20)}/2\) fragments (\(y = 4–12; y\) has the same parity as \(n\)). Thus, four to five shrunken nanojars of the formula \([\text{Cu}_{n-5}\text{O}_{(n-y)/2}\text{(pz)}_{n+y-10}\text{CO}_3]^{2-}\) were produced by each parent nanojar (Table 3.11). The corresponding sulfate nanojars lose \(\text{Cu}_3\text{(OH)}_6\text{(Hpz)}_{8-y}\text{(H}_2\text{O})_{(n+y-14)}/2\) fragments (\(y = (-1)–8\)), and produce \([\text{Cu}_{n-3}\text{O}_{(n-y+2)/2}\text{(pz)}_{n+y-8}\text{SO}_4]^{2-}\) daughter nanojars (Appendix E). In addition to these major peaks, minor peaks attributed to \([\text{Cu}_{n-5}\text{O}_{(n-y)/2}\text{(OH)}\text{(pz)}_{n+y-11}\text{CO}_3]^{2-}\) and \([\text{Cu}_{n-3}\text{O}_{(n-y+2)/2}\text{(OH)}\text{(pz)}_{n+y-9}\text{SO}_4]^{2-}\), respectively, are also observed.
Table 3.11: Carbonate- and sulfate-nanojar species observed by ESI-MS(–) at different cone voltages (40 V – parent nanojar; 100 V – daughter nanojars). See also Appendix E. Reproduced with permission, from reference 105.

<table>
<thead>
<tr>
<th>Parent nanojar ((m/z))</th>
<th>Daughter nanojars ((m/z))</th>
<th>Parent nanojar ((m/z))</th>
<th>Daughter nanojars ((m/z))</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{CO}<em>3{\text{Cu(OH)}(pz)}</em>{27}]^{2-}) ((2022.93))</td>
<td>([\text{CO}<em>3{\text{Cu}</em>{22}\text{O}<em>{11}(pz)</em>{22}}]^{2-}) ((1554.79))</td>
<td>([\text{CO}<em>3{\text{Cu}</em>{22}\text{O}<em>{10}(pz)</em>{24}}]^{2-}) ((1613.86))</td>
<td>([\text{SO}<em>4{\text{Cu}</em>{24}\text{O}<em>{14}(pz)</em>{20}}]^{2-}) ((1593.28))</td>
</tr>
<tr>
<td>([\text{CO}<em>3{\text{Cu}</em>{22}\text{O}<em>{9}(pz)</em>{26}}]^{2-}) ((1672.93))</td>
<td>([\text{CO}<em>3{\text{Cu}</em>{22}\text{O}<em>{8}(pz)</em>{28}}]^{2-}) ((1732.00))</td>
<td>([\text{CO}<em>3{\text{Cu}</em>{22}\text{O}<em>{7}(pz)</em>{30}}]^{2-}) ((1791.07))</td>
<td>([\text{SO}<em>4{\text{Cu}</em>{24}\text{O}<em>{13}(pz)</em>{22}}]^{2-}) ((1652.35))</td>
</tr>
<tr>
<td>([\text{CO}<em>3{\text{Cu}</em>{24}\text{O}<em>{10}(pz)</em>{28}}]^{2-}) ((1811.55))</td>
<td>([\text{CO}<em>3{\text{Cu}</em>{24}\text{O}<em>{9}(pz)</em>{30}}]^{2-}) ((1870.62))</td>
<td>([\text{CO}<em>3{\text{Cu}</em>{24}\text{O}<em>{12}(pz)</em>{24}}]^{2-}) ((1733.17))</td>
<td>([\text{SO}<em>4{\text{Cu}</em>{25}\text{O}<em>{15}(pz)</em>{20}}]^{2-}) ((1633.05))</td>
</tr>
<tr>
<td>([\text{CO}<em>3{\text{Cu}</em>{24}\text{O}<em>{11}(pz)</em>{26}}]^{2-}) ((1752.47))</td>
<td>([\text{CO}<em>3{\text{Cu}</em>{24}\text{O}<em>{10}(pz)</em>{28}}]^{2-}) ((1811.55))</td>
<td>([\text{CO}<em>3{\text{Cu}</em>{24}\text{O}<em>{13}(pz)</em>{24}}]^{2-}) ((1751.20))</td>
<td>([\text{SO}<em>4{\text{Cu}</em>{25}\text{O}<em>{12}(pz)</em>{26}}]^{2-}) ((1810.27))</td>
</tr>
<tr>
<td>([\text{CO}<em>3{\text{Cu}</em>{25}\text{O}<em>{10}(pz)</em>{30}}]^{2-}) ((1910.39))</td>
<td>([\text{CO}<em>3{\text{Cu}</em>{25}\text{O}<em>{9}(pz)</em>{32}}]^{2-}) ((1969.46))</td>
<td>([\text{SO}<em>4{\text{Cu}</em>{25}\text{O}<em>{16}(pz)</em>{20}}]^{2-}) ((1731.90))</td>
<td>([\text{SO}<em>4{\text{Cu}</em>{26}\text{O}<em>{15}(pz)</em>{22}}]^{2-}) ((1731.90))</td>
</tr>
<tr>
<td>([\text{CO}<em>3{\text{Cu}</em>{25}\text{O}<em>{11}(pz)</em>{28}}]^{2-}) ((1851.32))</td>
<td>([\text{CO}<em>3{\text{Cu}</em>{25}\text{O}<em>{10}(pz)</em>{30}}]^{2-}) ((1910.39))</td>
<td>([\text{SO}<em>4{\text{Cu}</em>{26}\text{O}<em>{14}(pz)</em>{24}}]^{2-}) ((1790.97))</td>
<td>([\text{SO}<em>4{\text{Cu}</em>{26}\text{O}<em>{13}(pz)</em>{26}}]^{2-}) ((1850.04))</td>
</tr>
<tr>
<td>([\text{CO}<em>3{\text{Cu}</em>{25}\text{O}<em>{12}(pz)</em>{30}}]^{2-}) ((1969.46))</td>
<td>([\text{CO}<em>3{\text{Cu}</em>{25}\text{O}<em>{9}(pz)</em>{32}}]^{2-}) ((1969.46))</td>
<td>([\text{SO}<em>4{\text{Cu}</em>{26}\text{O}<em>{16}(pz)</em>{20}}]^{2-}) ((1731.90))</td>
<td>([\text{SO}<em>4{\text{Cu}</em>{26}\text{O}<em>{12}(pz)</em>{28}}]^{2-}) ((1909.11))</td>
</tr>
</tbody>
</table>
Table 3.11: Continued.

<table>
<thead>
<tr>
<th>Parent nanojar (m/z)</th>
<th>Daughter nanojars (m/z)</th>
<th>Parent nanojar (m/z)</th>
<th>Daughter nanojars (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[CO₃{Cu(OH)}(pz)}₃]²⁻ (2318.18)</td>
<td>[CO₃{Cu₂₆O₁₃(pz)}₂]²⁻ (1832.02)</td>
<td>[SO₄{Cu₂₈O₁₇(pz)}₂]²⁻ (1811.44)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[CO₃{Cu₂₆O₁₂(pz)}₂]²⁻ (1891.09)</td>
<td>[SO₄{Cu₂₈O₁₆(pz)}₂]²⁻ (1870.52)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[CO₃{Cu₂₆O₁₁(pz)}₂]²⁻ (1950.16)</td>
<td>[SO₄{Cu₂₈O₁₅(pz)}₂]²⁻ (1929.59)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>[SO₄{Cu₂₈O₁₃(pz)}₂]²⁻ (2047.73)</td>
<td></td>
</tr>
</tbody>
</table>

3.2.4.4 Crystallographic studies of organic compounds, nanojars and other copper complexes

3.2.4.4.1 1,6-Bis(pyrazol-3(5)-yl)hexane

The results discussed in this section were originally published in RSC Adv. 2015, 5, 24081–24093,¹¹¹ and are reproduced by permission of The Royal Society of Chemistry.

The unexpected insolubility of 1,6-bis(pyrazol-3(5)-yl)hexane in most common solvents, as well as the difficulty in completely removing water from it, even after heating in high vacuum, prompted us to carry out single-crystal X-ray diffraction studies to elucidate its solid state structure. Crystals of 1,6-bis(pyrazol-3(5)-yl)hexane hydrate were grown by slow cooling of a hot aqueous solution to which a small amount of methanol was added. Within the crystal lattice of 1,6-bis(pyrazol-3(5)-yl)hexane, the bridging hexylene unit is fully extended and the two pyrazole moieties are at a dihedral angle of 63.9(1)° (Figure 3.63).
The pyrazole N–H hydrogen atoms are located on the N-atom adjacent to the bridging hexylene unit, and are involved in hydrogen-bonding with the solvent water molecule (Table 3.12). The two H-atoms of H$_2$O, in turn, are involved in hydrogen-bonding to the other pyrazole N-atom. Besides the hydrogen-bonded network within the resulting two-dimensional layer (Figure 3.64), edge-to-face interactions are observed between neighboring pyrazole (pz) units, with closest contact of 2.961(3) Å (C11−H11⋯N2′), C11−H11/centroid (pz) distance of 3.183(3) Å, centroid (pz)–centroid (pz) distance of 5.262(2) Å, and pz–pz dihedral angle of 63.9(1)°.

Table 3.12: Summary of hydrogen bonding data for 1,6-bis(pyrazol-3(5)-yl)hexane hydrate (with esds, except fixed/riding hydrogens). Reproduced with permission, from reference 111.

<table>
<thead>
<tr>
<th>D−H⋯A</th>
<th>D−H (Å)</th>
<th>H⋯A (Å)</th>
<th>D⋯A (Å)</th>
<th>D−H−A (°)</th>
<th>Symmetry operator for A</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1−H1o⋯N4′</td>
<td>0.86(2)</td>
<td>1.95(2)</td>
<td>2.807(3)</td>
<td>175(2)</td>
<td>−x+1, −y+2, −z+1</td>
</tr>
<tr>
<td>O1−H2o⋯N1′</td>
<td>0.84(2)</td>
<td>1.98(2)</td>
<td>2.818(3)</td>
<td>177(3)</td>
<td>−x, −y, −z+1</td>
</tr>
<tr>
<td>N2−H2n⋯O1′</td>
<td>0.86</td>
<td>1.97</td>
<td>2.826(2)</td>
<td>171</td>
<td>x, y−1, z</td>
</tr>
<tr>
<td>N3−H3n⋯O1′</td>
<td>0.86</td>
<td>1.98</td>
<td>2.838(3)</td>
<td>175</td>
<td>x+1, y, z</td>
</tr>
</tbody>
</table>
Figure 3.64: Hydrogen-bonding network (green dashed lines) within a layer of 1,6-bis(pyrazol-3(5)-yl)hexane hydrate. Reproduced with permission, from reference 111.

Further edge-to-face pyrazole interactions are observed in-between the layers (Figure 3.65), with closest contact of 2.901(4) Å (C2–H2⋯C12′), C2–H2/centroid (pz) distance of 3.169(3) Å, centroid (pz)–centroid(pz) distance of 5.159(2) Å, and pz–pz dihedral angle: 63.9(1)°. Such a 2D layered structure is unusual for NH–pyrazoles with no additional donor atoms, which typically self-assemble either into discrete cyclic motifs (dimers, trimers, tetramers, hexamers), or 1D catemers, via intermolecular N–H/N hydrogen bonds.\textsuperscript{171}
1,6-Bis(pyrazol-3(5)-yl)hexane is only soluble in highly polar solvents, such as methanol, ethanol, dimethylformamide, dimethylsulfoxide, nitromethane and nitrobenzene, and is slightly soluble in cold water (solubility increases significantly in hot water). Its very poor solubility in other organic solvents (isopropanol, acetonitrile, ethyl acetate, acetone, tetrahydrofuran, diethyl ether, dichloromethane, chloroform, hydrocarbons), even at reflux temperatures, is surprising, given that 3(5)-propylpyrazole (half of the 1,6-bis(pyrazol-3(5)-yl)hexane molecule) is readily soluble in all common solvents, including hexane. The water of crystallization provides increased lattice enthalpy, by forming an extended hydrogen-bonded 2D network with the 1,6-bis(pyrazol-3(5)-yl)hexane units, which concurs with the difficulty in drying 1,6-bis(pyrazol-3(5)-yl)hexane. Furthermore, the extensive H-bonding interactions within the lattice are in accord with the poor solubility of the compound in solvents of medium or low polarity. THP-protected 1,6-bis(pyrazol-3(5)-yl)hexane, which lacks the N–H hydrogen bond donor, is readily soluble in common organic
solvents (even in hexane, slightly), and similarly to all other 3(5)-alkylpyrazoles studied here, it does not have affinity for water.

3.2.4.4.2 5-n-Hexadecyl-1-(tetrahydropyran-2-yl)pyrazole

The results discussed in this section were originally published in RSC Adv. 2015, 5, 24081–24093, and are reproduced by permission of The Royal Society of Chemistry. Crystals of 5-n-hexadecyl-1-(tetrahydropyran-2-yl)pyrazole were grown by slow evaporation of a methanolic solution containing a small amount of water. Two crystallographically independent molecules are found within the asymmetric unit of 5-n-hexadecyl-1-(tetrahydropyran-2-yl)pyrazole (Figure 3.66).

Figure 3.66: Crystal structure (thermal ellipsoid plot, 50% probability level) of 5-n-hexadecyl-1-(tetrahydropyran-2-yl)pyrazole, showing the two crystallographically independent molecules (from different asymmetric units, for clarity). Reproduced with permission, from reference 111.

The C_{16} chains are fully extended, a common feature of crystal structures of molecules possessing long hydrocarbon chains. An analysis of the Cambridge Structural Database reveals that it is the ratio between the size/number of the aliphatic chains and the size of the polar part of the molecule/structure that determines the conformation of the chain. When the size of the chain(s) dominates, a fully extended conformation of the chain, which maximizes the London dispersion forces between neighboring chains, provides a significant contribution to the overall crystal lattice enthalpy. The result is a layered structure, wherein the nonpolar chains and the more polar part of the molecule each aggregate separately to form alternating 2D layers (Figure 3.67). When the size
of the polar part of the molecule (which might include counterions) dominates, the long hydrophobic chains might not be fully extended and densely packed, but can assume different bent conformations to fill the crystal lattice voids determined by the dominant polar interactions.\textsuperscript{172}

Figure 3.67: Packing diagram of 5-n-hexadecyl-1-(tetrahydropyran-2-yl)pyrazole (view down the \textit{b} axis), showing a layered structure. Reproduced with permission, from reference 111.

3.2.4.4.3 Bis(3-amino-1\textit{H}-pyrazol-4-yl)-1\textit{H}-pyrazol-3-yl-methane (HpzCH(HpzNH\textsubscript{2})\textsubscript{2}) 21

The results discussed in this section are reprinted with permission, from \textit{J. Org. Chem.} 2017, \textbf{82}, 10549–10562.\textsuperscript{112} Copyright 2017 American Chemical Society.

Single crystals of bis(3-amino-1\textit{H}-pyrazol-4-yl)-1\textit{H}-pyrazol-3-yl-methane 21 are grown by slow evaporation of an ethanol/water solution. X-ray diffraction data are collected at room temperature from a single-crystal mounted atop a glass fiber with cyanoacrylate glue. The high-quality diffraction data collected allows for the unambiguous assignment of N–H hydrogen atoms in 21, which is situated on a general position within the triclinic lattice (Figure 3.68). Thus, the position of the N atoms and their protonation state as well as the connectivity between the pyrazole rings are established unequivocally on the basis of the H-bond network formed by 21 with its neighboring molecules (Figure 3.69). Hydrogen bonding data are summarized in Table 3.13.
Figure 3.68: Thermal ellipsoid plot (50% probability level) of the crystal structure of bis(3-amino-1H-pyrazol-4-yl)-1H-pyrazol-3-yl-methane 21. Reproduced with permission, from reference 112.

Table 3.13: Summary of the hydrogen-bonding data for bis(3-amino-1H-pyrazol-4-yl)-1H-pyrazol-3-yl-methane 21. Reproduced with permission, from reference 112.

<table>
<thead>
<tr>
<th>D–H⋯A</th>
<th>D–H (Å)</th>
<th>H⋯A (Å)</th>
<th>D⋯A (Å)</th>
<th>D–H–A (°)</th>
<th>Symmetry operator for A</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2–H2N…N3#</td>
<td>0.858(15)</td>
<td>2.090(16)</td>
<td>2.923(2)</td>
<td>164(2)</td>
<td>−x, −y, −z</td>
</tr>
<tr>
<td>N3–H3B…N1#</td>
<td>0.885(15)</td>
<td>2.201(16)</td>
<td>3.061(2)</td>
<td>164(2)</td>
<td>x+1, y, z</td>
</tr>
<tr>
<td>N5–H5N…N6#</td>
<td>0.901(15)</td>
<td>2.036(16)</td>
<td>2.936 (2)</td>
<td>177(2)</td>
<td>−x, −y, −z+1</td>
</tr>
<tr>
<td>N6–H6A…N7#</td>
<td>0.893(15)</td>
<td>2.143(16)</td>
<td>3.006(2)</td>
<td>162(2)</td>
<td>−x, −y+1, −z+1</td>
</tr>
<tr>
<td>N8–H8N…N4#</td>
<td>0.873(14)</td>
<td>2.102(15)</td>
<td>2.939(2)</td>
<td>161(2)</td>
<td>x−1, y+1, z</td>
</tr>
</tbody>
</table>
3.2.4.4.4 (1E,7E)-1,8-bis(dimethylamino)octa-1,7-diene-3,6-dione ((CH₃)₂NCHCHCOCH₂)₂

The results discussed in this section through section 3.2.4.4.7 were originally published in Chem. Commun. 2017, 53, 1029–1032,¹⁰⁸ and are reproduced by permission of The Royal Society of Chemistry.

X-ray quality single-crystals of (1E, 7E)-1,8-bis(dimethylamino)octa-1,7-diene-3,6-dione are grown from an ethyl acetate solution by hexane vapor diffusion (Figure 3.70).
3.2.4.4.5 1,2-Bis(1H-pyrazole-3-yl)ethane

Single-crystals of 1,2-bis(1H-pyrazole-3-yl)ethane are obtained by slow evaporation of an EtOH/H$_2$O solution (Figure 3.71 and Figure 3.72).
Figure 3.72: Crystal packing diagram of 1,2-bis(1H-pyrazole-3-yl)ethane. Hydrogen bonding: 
N2···N1*: 2.923(1) Å; N2–H2N: 0.88(1) Å; H2N···N1*: 2.08(1) Å; N2–H2N···N1*: 159(1)°. Symmetry operator (*): −x, y−1/2, −z+1/2. Reproduced with permission, from reference 108.

3.2.4.4.6 \( \text{Cu}_4(\mu_3\text{-OH})_2(\mu_3\text{-pzCH}_2\text{CH}_2\text{pz})_2(\text{NO}_3)_2(\text{C}_5\text{H}_5\text{N})_5 \) 66

Single-crystals of \( \text{Cu}_4(\mu_3\text{-OH})_2(\mu_3\text{-pzCH}_2\text{CH}_2\text{pz})_2(\text{NO}_3)_2(\text{py})_5 \) are obtained by \( \text{iPr}_2\text{O} \) vapor diffusion to a pyridine solution of \( \text{Cu}_4(\mu_3\text{-OH})_2(\mu_3\text{-pzCH}_2\text{CH}_2\text{pz})_2(\text{NO}_3)_2(\text{H}_2\text{O})_2(\text{THF}) \) 66. A preliminary X-ray crystal structure from the poorly diffracted crystal is described here (see), which unambiguously establishes the molecular structure of \( \text{Cu}_4(\mu_3\text{-OH})_2(\mu_3\text{-pzCH}_2\text{CH}_2\text{pz})_2(\text{NO}_3)_2(\text{py})_5 \). The molecule is comprised of two Cu3 triangles sharing an edge at a dihedral angle of 135.05(8)° (Figure 3.73). The resulting bent-rhombus shaped Cu4-core is held together by two \( \mu_3\text{-OH} \) groups (located 0.667(10) and 0.700(12) Å above the Cu3 mean-planes, respectively; average Cu–O bond length: 1.980(11) Å) and two \( \mu_3 \)-bridging pzCH2CH2pz ligands (average Cu–N bond length: 1.963(15) Å).

210
Figure 3.73: Crystal structure of Cu$_4$(μ$_3$-OH)$_2$(μ$_3$-pzCH$_2$CH$_2$pz)$_2$(NO$_3$)$_2$(py)$_5$ 66. Weak Cu–O bonds and H-bonds are shown with dashed lines. Reproduced with permission, from reference 108.

The Cu···Cu separations along the outer edges of the Cu$_4$ core average 3.308(3) Å, whereas the central Cu···Cu distance along the common edge is significantly shorter (3.003(3) Å). The two central Cu atoms have a distorted square planar geometry with pyridine ligands in the axial positions. The two outer Cu atoms both have a pyridine ligand in their basal/equatorial plane, and nitrate O atom in their axial position. One of these two Cu atoms displays slightly distorted square-pyramidal coordination geometry, whereas the other Cu atom has an additional, weakly coordinating pyridine ligand and is therefore hexacoordinate, with an elongated, distorted octahedral geometry. The two nitrate ions form H-bonds to the two μ$_3$-OH groups. A complex with a related Cu$_4$(μ$_3$-OH)$_2$(μ$_4$-Cl) core is known. 173

3.2.4.4.7 Bu$_4$N[Cu$_4$(μ$_4$-OH)(μ$_3$-pzCH$_2$CH$_2$pz)$_4$] 67

Two crystallographically independent molecules are found in the solid-state structure of Bu$_4$N[Cu$_4$(μ$_4$-OH)(μ$_3$-pzCH$_2$CH$_2$pz)$_4$] (crystallized by Et$_2$O vapor diffusion to a CH$_2$Cl$_2$ solution), each located on an inversion center, which gives rise to crystallographically imposed planar Cu$_4$(μ$_4$-OH) cores. The ligands pzCH$_2$CH$_2$pz of one of the two units are disordered over two positions about the inversion center (Figure 3.74).
Figure 3.74: Thermal ellipsoid plot (50% probability) of Bu₄N[Cu₄(μ₄-OH)(μ₃-pzCH₂CH₂pz)₄]. Reproduced with permission, from reference 108.

Structural description is based on the non-disordered unit (Figure 3.75). The four Cu atoms form a slightly distorted square (Cu···Cu distances: 3.170(1) and 3.220(1) Å; Cu–Cu–Cu angles: 91.46(3) and 88.54(3)°). Two pairs of ligand pzCH₂CH₂pz are bound on each side of the Cu₄(μ₄-OH) core. The pyrazole moieties form angles of 52.2(2)–59.6(2)° with the Cu₄(μ₄-OH) core (average: 55.1(2)°). The Cu centers are square-pyramidal, with four pyrazole N atoms in the basal positions and a hydroxide O atom in the axial positions. The Cu atom chelated by two pzCH₂CH₂pz ligands has slightly shorter bond lengths (average Cu2–N: 1.981(6) Å; Cu2–O1: 2.2304(8) Å) than the Cu atom coordinated by the terminal pyrazole N atoms (average Cu1–N: 2.018(6) Å; Cu1–O1: 2.2879(9) Å).
Figure 3.75: Crystal structure of Bu₄N[Cu₄(µ₄-OH)(µ₃-pzCH₂CH₂pz)₄] 67. Only one of the two crystallographically independent moieties of Bu₄N[Cu₄(µ₄-OH)(µ₃-pzCH₂CH₂pz)₄], and no counterion or H-atoms are shown for clarity. Reproduced with permission, from reference 108.

3.2.4.4.8 [Cu₃(µ₃-OH)(µ-pz)₃(NO₃)₂(CH₃CN)] 69b

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The crystal structure of the trinuclear complex [Cu₃(µ₃-OH)(µ-pz)₃(NO₃)₂(CH₃CN)] 69b, obtained by diethyl ether vapor diffusion into an acetonitrile solution of [Cu₃(µ₃-OH)(µ-pz)₃(NO₃)₂(H₂O)] 69a, is shown in Figure 3.76 (see Appendix D for thermogravimetric analysis of 69b). The complex, crystallized in the chiral space group P4₃2₁2, is located on a C₂ axis running through the linear CH₃CN molecule and symmetrically bisecting the pyrazolate moiety on the opposite side of the trinuclear unit. The Cu₃(µ-pz)₃ framework is nearly planar, with the pyrazolate moieties twisted by 3.8(1)° and 7.2(2)° relative to the Cu₃(pz)₃ mean plane. The µ₃-OH unit is located 0.509(4) Å above this mean plane and is disordered (50/50) about the C₂ axis. The nitrate ion, located on a general position, is also disordered over two positions (50/50). To date, only one of the structurally characterized Cu₃(µ-pz)₃ frameworks has nitrate as sole terminal ligand for the Cu centers;¹⁷₄ all others contain pyrazole¹⁶⁷,¹⁷₅,¹⁷₆,¹⁷₇ or pyridine¹⁷₈ ligands in addition to the nitrate ions. In [Cu₃(µ₃-OH)(µ-pz)₃(NO₃)₂(CH₃CN)], the coordinating O atom of the nitrate ion forms a longer, axial bond to the CH₃CN bound Cu atom of an adjacent trinuclear unit (O₂–Cu₁’, 2.403(12) Å), whereas another O atom of the same nitrate ion forms a hydrogen bond with the µ₃-OH group of the same adjacent trinuclear unit (O₃···O₁’, 1.967(10) Å). Interatomic distances are similar to related
of trinuclear copper pyrazolate complexes.\textsuperscript{167,174,175,176,177,178} Within the crystal lattice, the trinuclear units are found in a helical arrangement around the \(4_3\) screw axis (Figure 3.76).

![Image of crystal structure](image.png)

**Figure 3.76:** (Left) Crystal structure of Cu\(_3(\mu_3\text{-OH})(\mu\text{-pz})_3(\text{NO}_3)_2(\text{CH}_3\text{CN})\) \(69b\). Only one position of the disordered nitrate (50/50) and hydroxide ions (50/50) is shown for clarity. Symmetry code: (a) \(y, x, -z\). Bond lengths (Å): Cu\(_1\)–O\(_1\), 2.011(4); Cu\(_1\)–N\(_1\), 1.952(3); Cu\(_1\)–N\(_5\), 2.027(4); Cu\(_2\)–O\(_1\), 2.042(5); Cu\(_2\)–N\(_2\), 1.919(3); Cu\(_2\)–N\(_3\), 1.927(3); Cu\(_2\)–O\(_2\), 1.922(12). (Right): helical arrangement of the trinuclear units around the crystallographic \(4_3\) screw axis (C–H hydrogens, nitrate and acetonitrile units not shown). Reproduced with permission, from reference 106.

3.2.4.4.9 \((\text{Bu}_4\text{N})_2[\text{CO}_3\{\text{Cu(OH)}(\text{pz})\}_{6+12-9}](\text{C}_7\text{H}_8)(\text{C}_6\text{H}_{12})_5\)

The results discussed in this section through section 3.2.4.4.11 were originally published in *Chem. - Eur. J.* \textbf{2016}, 22, 5499–5503.\textsuperscript{105} Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

Single crystals were grown by hexane or cyclohexane vapor diffusion into a toluene solution of the nanojars. One of the two \text{Bu}_4\text{N}\(^+\) counterion molecules is completely disordered over two positions (50/50). Four of the five cyclohexane solvent molecules are disordered over two positions (50/50); the toluene solvent molecule is also disordered over two positions (67/33). The
nanojar crystallizes in a triclinic (P$\overline{1}$) lattice with one toluene and five cyclohexane solvent molecules. The nanojar, located on a general position, consists of three [Cu(OH)(pz)]$_x$ rings (Cu$_6$, $x = 6$; Cu$_{12}$, $x = 12$; Cu$_9$, $x = 9$) surrounding a CO$_3^{2-}$ ion, and has pseudo-$C_{3v}$ symmetry (Figure 3.77 and Figure 3.78).

Figure 3.77: Top- and side-views of the crystal structures of (Bu$_4$N)$_2$[CO$_3$(Cu(OH)(pz))$_{6+12+9}$], (Cu$_6$–cyan; Cu$_9$–red; Cu$_{12}$–violet; Carbonate is orange; H-bonds and weak Cu···O interactions are illustrated with green and black dashed lines, respectively). Reproduced with permission, from reference 105.

The Cu$_6$ and Cu$_9$ rings form three shorter (average O···O 2.754(5) Å) and nine longer (average O···O 2.872(5) Å) hydrogen bonds, respectively, with the incarcerated CO$_3^{2-}$ ion (Table 3.14 and Figure 3.79 – Figure 3.82). Thus, the neutral nanojar binds the CO$_3^{2-}$ ion by twelve hydrogen bonds (O···O 2.746(5)–2.915(5) Å; average 2.842(5) Å), four to each of the three carbonate O atoms (Figure 3.83). The OH groups of the Cu$_{12}$ ring, in turn, form alternating H bonds with the two smaller rings (average O···O 2.761(5) Å), so that the Cu$_6$ and Cu$_9$ rings each accept six H bonds from the Cu$_{12}$ ring (Cu$_6$ 2.716(5)–2.772(5) Å, average O···O 2.742(5) Å; Cu$_9$ 2.754(6)–2.824(5) Å, average 2.780(5) Å) (Figure 3.84 and Figure 3.85).
The overall H bonding pattern in (Bu₄N)₂[CO₃{Cu(OH)(pz)}₆+12+9] is shown in Figure 3.86. Although all six Cu atoms of the Cu₆ ring of the nanojar form axial Cu–O interactions with the Cu₁₂ ring (Cu⋯O 2.375(4)–2.487(4) Å; average 2.414(4) Å), only six Cu atoms of the Cu₀ ring are involved in Cu⋯O contacts less than 3.00(8) Å (Cu⋯O 2.352(4)–3.068(4) Å; average 2.713(4) Å). The other three Cu atoms of the Cu₀ ring are at distances of over 3.176(4) Å from O atoms of the Cu₁₂ ring, and are not considered to contribute significantly to bonding. Likewise, none of the Cu atoms of the Cu₁₂ ring have nearby O atoms to interact with. Overall, there are twelve Cu⋯O distances < 3.00(8) Å in-between Cuₙ rings, with an average of 2.564(4) Å.
Table 3.14: Summary of hydrogen bonding (H···A < r(A) + 2.00 Å and <DHA > 110º) in (Bu₄N)₂[CO₃{Cu(OH)(pz)}₆₋₁₂₊₉] (with esd’s except fixed and riding H). O1–O6: 6-membered ring; O7–O18: 12-membered ring; O19–O27: 9-membered ring; O28–O30: carbonate. Reproduced with permission, from reference 105.

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Figure 3.79: Top- and side-views of the 6-membered ring in (Bu4N)2[CO3{Cu(OH)(pz)}6+12+9], showing hydrogen-bonding (green dashed lines) to the carbonate ion. C–H hydrogen atoms are omitted for clarity. Reproduced with permission, from reference 105.

Figure 3.80: Top- and side-views of the 9-membered ring in (Bu4N)2[CO3{Cu(OH)(pz)}6+12+9], showing hydrogen-bonding (green dashed lines) to the carbonate ion. C–H hydrogen atoms are omitted for clarity. Reproduced with permission, from reference 105.
Figure 3.81: Top-views of the 12-membered ring in (Bu4N)2[CO3{Cu(OH)(pz)}6+12+9]. C–H hydrogen atoms are omitted for clarity. Reproduced with permission, from reference 105.

Figure 3.82: Top- and side-views of the 6- and 9-membered rings in (Bu4N)2[CO3{Cu(OH)(pz)}6+12+9] hydrogen-bonding (green dashed lines) to the carbonate ion. C–H hydrogen atoms are omitted for clarity. Color code: Cu–dark blue; O–red; N–light blue; C–black; H–pink. Reproduced with permission, from reference 105.
Figure 3.83: Top- and side-views of the hydrogen-bonding pattern (green dashed lines) to the carbonate ion in \((\text{Bu}_4\text{N})_2[\text{CO}_3\{\text{Cu(OH)(pz)}\}]_{6+12+9}\). C–H hydrogen atoms are omitted for clarity. Reproduced with permission, from reference 105.

Figure 3.84: Top- and side-views of the 6- and 12-membered rings in \((\text{Bu}_4\text{N})_2[\text{CO}_3\{\text{Cu(OH)(pz)}\}]_{6+12+9}\), showing hydrogen-bonding (green dashed lines) and axial Cu-O interactions (black dashed lines for Cu–O distances <2.50 Å) between the two. C–H hydrogen atoms are omitted for clarity. Color code: Cu–dark blue; O–red; N–light blue; C–black; H–pink. Reproduced with permission, from reference 105.
Figure 3.85: Top- and side-views of the 9- and 12-membered rings in (Bu₄N)₂[CO₃{Cu(OH)(pz)}₆₊₁₂₊₉], showing hydrogen-bonding (green dashed lines) and axial Cu-O interactions (black dashed lines for Cu···O distances < 2.50 Å: Cu₁₉···O₁₈, Cu₂₂···O₁₀, Cu₂₅···O₁₄) between the two. C–H hydrogen atoms are omitted for clarity. Color code: Cu—dark blue; O—red; N—light blue; C—black; H—pink. Reproduced with permission, from reference 105.

Figure 3.86: Top- and side-views of the overall hydrogen-bonding pattern (green dashed lines) in (Bu₄N)₂[CO₃{Cu(OH)(pz)}₆₊₁₂₊₉], converging at the central carbonate ion. Reproduced with permission, from reference 105.
Single crystals were grown by hexane or cyclohexane vapor diffusion into a toluene solution of the nanojars. In the nanojar, a terminal CH$_3$ group of each of the two Bu$_4$N$^+$ counterions is disordered over two positions (70/30). Two toluene solvent molecules are disordered over two positions (50/50), and another two are disordered with a hexane solvent molecule (50/50). Within the monoclinic (P2$_1$/n) lattice of (Bu$_4$N)$_2$[CO$_3${Cu(OH)(pz)}$_{7+13+9}$], the nanojar consisting of Cu$_7$, Cu$_{13}$, and Cu$_9$ rings is crystallized with one hexane and four toluene solvent molecules, and is located on a general position (Figure 3.87 and Figure 3.88).

Figure 3.87: Top- and side-views of the crystal structures of (Bu$_4$N)$_2$[CO$_3${Cu(OH)(pz)}$_{7+13+9}$], (Cu$_x$ rings: Cu$_7$–olive; Cu$_9$–red; Cu$_{13}$–blue; carbonate is orange; H-bonds and weak Cu···O interactions are illustrated with green and black dashed lines, respectively). Reproduced with permission, from reference 105.

The Cu$_7$ ring forms six H bonds (O···O 2.843(5)–2.956(5) Å; average 2.897(5) Å), whereas the Cu$_9$ ring forms three shorter (O···O 2.753(5)–2.894(5) Å; average 2.809(5) Å) and five longer (O···O 2.961(6)–3.140(5) Å; average 3.054(5) Å) H bonds with the incarcerated CO$_3^{2–}$ ion (Table 3.15, Figure 3.89 – Figure 3.92).
Thus, in (Bu4N)2[CO3{Cu(OH)(pz)}7+13+9], only eight of the fourteen H bonds formed by the neutral nanojar with the CO32– ion are within an O···O distance range of 2.75(1)–2.92(1) Å (Figure 3.93), in contrast to (Bu4N)2[CO3{Cu(OH)(pz)}6+12+9], in which all twelve H bonds are within that range. As a result, the average H-bonding distance to carbonate in (Bu4N)2[CO3{Cu(OH)(pz)}7+13+9] (O···O: 2.934(5) Å) is significantly longer than in (Bu4N)2[CO3{Cu(OH)(pz)}6+12+9] (O···O: 2.842(5) Å). The central Cu13 ring forms six H bonds to the Cu7 ring (O···O 2.692(5)–2.918(5) Å; average 2.808(5) Å) and seven H bonds to the Cu9 ring (O···O 2.708(5)–3.051(5) Å; average 2.828(5) Å) (Figure 3.94 and Figure 3.95). The overall H-bonding pattern in (Bu4N)2[CO3{Cu(OH)(pz)}7+13+9] is shown in Figure 3.96.
Table 3.15: Summary of hydrogen bonding (H···A < r(A) + 2.00 Å and <DHA > 110º) in (Bu$_4$N)$_2$[CO$_3${Cu(OH)(pz)}$_7$]$_{+13}$ (with esds except fixed and riding H). O1–O7: 7-membered ring; O8–O20: 13-membered ring; O21–O29: 9-membered ring; O30–O32: carbonate. Reproduced with permission, from reference 105.

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<td>O17–H170···O28</td>
<td>0.83(2)</td>
<td>1.90(2)</td>
<td>2.708(5)</td>
<td>165(6)</td>
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<tr>
<td>O18–H180···O5</td>
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<td>1.87(2)</td>
<td>2.692(5)</td>
<td>168(6)</td>
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<td>O19–H190···O29</td>
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<td>3.051(6)</td>
<td>157(6)</td>
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<td>O20–H200···O21</td>
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<td>2.04(3)</td>
<td>2.861(6)</td>
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<tr>
<td>O21–H210···O31</td>
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<td>2.31(3)</td>
<td>3.107(5)</td>
<td>160(6)</td>
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<tr>
<td>O22–H220···O31</td>
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<td>2.752(5)</td>
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<td>O23–H230···O31</td>
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<td>3.140(5)</td>
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<td>O26–H260···O30</td>
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<tr>
<td>O29–H290···O32</td>
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<td>2.19(4)</td>
<td>2.960(6)</td>
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The Cu7 and Cu9 rings of (Bu4N)2[CO3{Cu(OH)(pz)}7+13+9] form seven and six Cu···O contacts < 3.00(8) Å, respectively, with O atoms of the Cu13 ring (Cu7 ring, Cu···O 2.351(4)–2.836(4) Å, average 2.534(4) Å; Cu9 ring, Cu···O 2.325(4)–2.891(4) Å; average 2.553(4) Å). All other Cu atoms, including the ones of the Cu13 ring, are at distances larger than 3.188(4) Å from the closest non-bonding O atoms. Overall, there are thirteen Cu···O distances < 3.00(8) Å in-between the Cu rings, with an average of 2.548(4) Å.

Figure 3.89: Top- and side-views of the 7-membered ring in (Bu4N)2[CO3{Cu(OH)(pz)}7+13+9], showing hydrogen-bonding (green dashed lines) to the carbonate ion. C–H hydrogen atoms are omitted for clarity. Reproduced with permission, from reference 105.
Figure 3.90: Top- and side-views of the 13-membered ring in (Bu$_4$N)$_2$[CO$_3${Cu(OH)(pz)}$_7$]$^{13+9}$]. C–H hydrogen atoms are omitted for clarity. Reproduced with permission, from reference 105.

Figure 3.91: Top- and side-views of the 9-membered ring in (Bu$_4$N)$_2$[CO$_3${Cu(OH)(pz)}$_7$]$^{13+9}$], showing H-bonding (green dashed lines for O···O distances <3.00(5) Å, grey dashed lines for O···O distances 3.00(5)–3.20(5) Å) to the carbonate ion. C–H hydrogen atoms omitted for clarity. Reproduced with permission, from reference 105.
Figure 3.92: Top- and side-views of the 7- and 9-membered rings in (Bu₄N)₂[CO₃{Cu(OH)(pz)}₇+13+9] hydrogen-bonding (green dashed lines for O⋯O distances <3.00(5) Å, grey dashed lines for O⋯O distances 3.00(5)−3.20(5) Å) to the carbonate ion. C−H hydrogen atoms are omitted for clarity. Color code: Cu−dark blue; O−red; N−light blue; C−black; H−pink. Reproduced with permission, from reference 105.

Figure 3.93: Top- and side-views of the hydrogen-bonding pattern (green dashed lines for O⋯O distances 3.00(5)−3.20(5) Å) to the carbonate ion in (Bu₄N)₂[CO₃{Cu(OH)(pz)}₇+13+9]. Reproduced with permission, from reference 105.
Figure 3.94: Top- and side-views of the 7- and 13-membered rings in (Bu₄N)₂[CO₃{Cu(OH)(pz)}₇+13+9], showing hydrogen-bonding (green dashed lines for O···O distances <3.00(5) Å, grey dashed lines for O···O distances 3.00(5)−3.20(5) Å) and axial Cu-O interactions (black dashed lines for Cu···O distances <2.50 Å) between the two. C−H hydrogen atoms are omitted for clarity. Color code: Cu−dark blue; O−red; N−light blue; C−black; H−pink. Reproduced with permission, from reference 105.

Figure 3.95: Top- and side-views of the 9- and 13-membered rings in (Bu₄N)₂[CO₃{Cu(OH)(pz)}₉+13+9], showing hydrogen-bonding (green dashed lines for O···O distances <3.00(5) Å, grey dashed lines for O···O distances 3.00(5)−3.20(5) Å) and axial Cu-O interactions (black dashed lines) between the two. C−H hydrogen atoms are omitted for clarity. Color code: Cu−dark blue; O−red; N−light blue; C−black; H−pink. Reproduced with permission, from reference 105.
3.2.4.4.11  \((\text{Bu}_4\text{N})_2[\text{CO}_3\{\text{Cu(OH)(pz)}\}_{8+13+8}^+13+8]\) \((\text{C}_7\text{H}_8)(\text{C}_6\text{H}_{14})\)

Single crystals were grown by hexane or cyclohexane vapor diffusion into a toluene solution of the nanojars. In the nanojar, a terminal CH$_3$ group of the symmetry-related Bu$_4$N$^+$ counterions is disordered over two positions (50/50). The toluene solvent molecules are disordered with hexane solvent molecules (50/50). Nanojar \((\text{Bu}_4\text{N})_2[\text{CO}_3\{\text{Cu(OH)(pz)}\}_{8+13+8}^+13+8]\) crystallizes in a monoclinic (C2/c) lattice with one hexane and one toluene solvent molecule, and consists of one Cu$_{13}$- and two Cu$_8$ rings (Figure 3.97 and Figure 3.98). The nanojar is located on a twofold rotation axis (C$_2$), which runs through the C atom of the incarcerated carbonate ion, symmetrically bisecting the latter. Each Cu$_8$ ring forms six H bonds to the carbonate ion (O···O 2.792(7)–3.072(7) Å; average 2.905(7) Å); only eight of the twelve H bonds have O···O distances<2.92(1) Å (compared to twelve in \((\text{Bu}_4\text{N})_2[\text{CO}_3\{\text{Cu(OH)(pz)}\}_{6+12+9}^+13+9]\); Table 3.16, Figure 3.99–Figure 3.102). The average H bonding distance to carbonate in \((\text{Bu}_4\text{N})_2[\text{CO}_3\{\text{Cu(OH)(pz)}\}_{8+13+8}^+13+8]\) is 2.90(1) Å.
Figure 3.97: Top- and side-views of the crystal structures of (Bu$_4$N)$_2$[CO$_3$Cu(OH)(pz)]$_{8+13+8}$ (Cu$_8$ rings: Cu$_8$–magenta; Cu$_{13}$–blue; Carbonate is orange; H-bonds and weak Cu···O interactions are illustrated with green and black dashed lines, respectively). Reproduced with permission, from reference 105.

Figure 3.98: Ball-and-stick representation (top- and side-views) of (Bu$_4$N)$_2$[CO$_3$Cu(OH)(pz)]$_{8+13+8}$. C–H hydrogen atoms are omitted for clarity. Color code: Cu–dark blue; O–red; N–light blue; C–black; H–pink. Reproduced with permission, from reference 105.
Table 3.16: Summary of hydrogen bonding (H···A < r(A) + 2.00 Å and <DHA > 110°) in (Bu₄N)₂[CO₃{Cu(OH)(pz)}₈+13+8] (with esds except fixed and riding H). O1–O5 and O13–O15: 8-membered ring; O6–O12: 13-membered ring; O16–O17: carbonate. Symmetry operator for O5’: −x, y, −z+3/2. Reproduced with permission, from reference 105.

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The central Cu₁₃ ring forms five H bonds to each Cu₈ ring (average O···O 2.766(6) Å; Figure 3.103). The overall H-bonding pattern is shown in Figure 3.104. In compound (Bu₄N)₂[CO₃{Cu(OH)(pz)}₈+13+8], seven Cu atoms of each Cu₈ ring form axial Cu–O interactions shorter than 3.00(5) with the Cu₁₃ ring (Cu···O 2.340(4)–2.993(4) Å, average 2.573(4) Å). The other Cu atoms, including the ones of the Cu₁₃ ring, are at distances larger than 3.201(4) from the closest non-bonding O atoms. Overall, there are fourteen Cu···O distances < 3.00(5) Å, with an average of 2.574(4) Å.
Figure 3.99: Top- and side-views of the 8-membered ring in (Bu₄N)₂[CO₃⊂{Cu(OH)(pz)}₈+13+8], showing hydrogen-bonding (green dashed lines for O⋯O distances <3.00(5) Å, grey dashed lines for O⋯O distances 3.00(5)−3.20(5) Å) to the carbonate ion. C−H hydrogen atoms are omitted for clarity. Reproduced with permission, from reference 105.

Figure 3.100: Top- and side-views of the 13-membered ring in (Bu₄N)₂[CO₃⊂{Cu(OH)(pz)}₈+13+8], with the carbonate ion at the center. C−H hydrogen atoms are omitted for clarity. Reproduced with permission, from reference 105.
Figure 3.101: Top- and side-views of the two 8-membered rings in \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset\{\text{Cu(OH)}(\text{pz})\}_{8+13+8}]\) hydrogen-bonding (green dashed lines for O···O distances <3.00(5) Å, grey dashed lines for O···O distances 3.00(5)−3.20(5) Å) to the carbonate ion. C−H hydrogen atoms are omitted for clarity. Color code: Cu−dark blue; O−red; N−light blue; C−black; H−pink. Reproduced with permission, from reference 105.

Figure 3.102: Top- and side-views of the hydrogen-bonding pattern (green dashed lines) to the carbonate ion in \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset\{\text{Cu(OH)}(\text{pz})\}_{8+13+8}]\). Reproduced with permission, from reference 105.
Figure 3.103: Top- and side-views of the 8- and 13-membered rings in (Bu$_4$N)$_2$[CO$_3$⊂{Cu(OH)(pz)}$_{8+13+8}$], showing hydrogen-bonding (green dashed lines for O···O distances <3.00(5) Å, grey dashed lines for O···O distances 3.00(5)−3.20(5) Å) and axial Cu-O interactions (black dashed lines for Cu···O distances <2.50 Å: Cu$_3$···O9, Cu$_5$···O12, Cu$_{14}$···O8) between the two. C−H hydrogen atoms are omitted for clarity. Color code: Cu−dark blue; O−red; N−light blue; C−black; H−pink. Reproduced with permission, from reference 105.

Figure 3.104: Top- and side-views of the overall hydrogen-bonding pattern (green dashed lines) in (Bu$_4$N)$_2$[CO$_3$⊂{Cu(OH)(pz)}$_{8+13+8}$], converging at the central carbonate ion. Reproduced with permission, from reference 105.
3.2.4.4.12 \((\text{Et}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}(\text{H}_2\text{O})_2]\)

The results discussed in this section through section 3.2.4.4.14 were originally published in *Dalton Trans.* 2016, 45, 8327–8339,104 and are reproduced by permission of The Royal Society of Chemistry.

The nanojar in \((\text{Et}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}(\text{H}_2\text{O})_2]\), which consists of three \([\text{Cu(OH)(pz)}]_x\) rings with \(x = 8, 13\) and 8, is similar to the one found in \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\);105 however, the difference in counterion size (\(\text{Et}_4\text{N}^+\) vs. \(\text{Bu}_4\text{N}^+\)) does induce significant changes in the molecular structure of the nanojar (Figure 3.105). Furthermore, despite a seemingly very similar overall crystal packing, the position of the nanojars relative to the crystal’s symmetry elements is altered in \((\text{Et}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\) compared to \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\). In \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\), the nanojar is located on a two-fold rotation axis \((C_2)\), which runs through the C-atom of the incarcerated carbonate ion, symmetrically bisecting the latter. In \((\text{Et}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\), the nanojar is also located on a two-fold rotation axis, but unlike in \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\), the \(C_2\) axis does not bisect the carbonate ion symmetrically, although it still runs through its central C-atom. As a result, the incarcerated carbonate ion in \((\text{Et}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\) is disordered over two positions (50/50). Similarly to \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\), each \(\text{Cu}_8\) ring forms six H-bonds to the carbonate ion (for one \(\text{Cu}_8\) ring, \(O\cdots O: 2.81(1)–3.12(1)\ \text Å\); average: 2.90(1) \text Å; for the other \(\text{Cu}_8\) ring, \(O\cdots O: 2.68(1)–3.01(1)\ \text Å\); average: 2.90(1) \text Å). As in \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\), only eight of the twelve H-bonds to carbonate in \((\text{Et}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\) have \(O\cdots O\) distances <2.92(1) \text Å. The average H-bonding distance to carbonate is identical in \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\) and \((\text{Et}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\) (2.90(1) \text Å). The central \(\text{Cu}_{13}\) ring forms five H-bonds to each \(\text{Cu}_8\) ring (average \(O\cdots O: 2.752(6)\ \text Å\) in \((\text{Et}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\), 2.766(6) \text Å in \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\)). The presence of two water molecules (symmetry-related) in \((\text{Et}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\) has significant consequences on the structure of the nanojar (no water is found in \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset \{\text{Cu(OH)(pz)}\}_{29}]\)). Each \(\text{H}_2\text{O}\) molecule is hydrogen-bonded to two \(\text{OH}\) groups across the \(\text{Cu}_8\) ring (O19⋯O5: 2.851(6), O19⋯O2: 3.039(7) \text Å).
As a result, those two OH groups are pulled closer to each other (O2⋯O5: 4.981(6) Å), compared to the corresponding distance in (Bu4N)2[CO3{Cu(OH)(pz)}29] (O⋯O: 5.596(6) Å), which lacks the bridging H2O molecules. In fact, O2 and O5 are indeed the two most likely O-atoms to bind a bridging H2O molecule, since those two O-atoms are not involved in significant H-bonding with the Cu13 ring (O⋯O: 3.326(6) and 3.317(6) Å in (Et4N)2[CO3{Cu(OH)(pz)}29]; 3.245(6) and 3.324(6) Å in (Bu4N)2[CO3{Cu(OH)(pz)}29]). The distance between the two bonded Cu atoms
across the ring also decreases from 8.254(1) Å in (Bu₄N)₂[CO₃⊂{Cu(OH)(pz)}₂₉] to 7.846(1) Å in (Et₄N)₂[CO₃⊂{Cu(OH)(pz)}₂₉].

In both (Et₄N)₂[CO₃⊂{Cu(OH)(pz)}₂₉] and (Bu₄N)₂[CO₃⊂{Cu(OH)(pz)}₂₉], seven Cu-atoms of each Cu₈ ring form axial Cu–O interactions shorter than 3.00(5) Å with the Cu₁₃ ring ((Et₄N)₂[CO₃⊂{Cu(OH)(pz)}₂₉], Cu⋯O: 2.367(5)–3.041(5) Å, average: 2.575(4) Å; (Bu₄N)₂[CO₃⊂{Cu(OH)(pz)}₂₉], Cu⋯O: 2.340(4)–2.993(4) Å, average: 2.573(4) Å). The other Cu atoms, including the ones of the Cu₁₃ ring, are at distances larger than 3.201(4) Å from the closest non-bonding O-atoms. Overall, there are fourteen Cu⋯O distances <3.00(5) Å in each nanojar, with an average of 2.574(4) Å.

3.2.4.4.13 (Bu₄N)₂[CO₃⊂{Cu₃₀(OH)₃₀(pz)₁₅(3,5-Me₂pz)₁₅(H₂O)}]

Within the triclinic (Pī) crystal lattice of (Bu₄N)₂[CO₃⊂{Cu₃₀(OH)₃₀(pz)₁₅(3,5-Me₂pz)₁₅(H₂O)}], the nanojar is located on a general position (with pseudo-mirror symmetry) and consists of three rings, [Cu(OH)(pz)]₇, [Cu(OH)(3,5-Me₂pz)]₁₄ and [Cu₉(OH)₉(pz)₈(3,5-Me₂pz)(H₂O)] (Figure 3.106–Figure 3.116). The encapsulated carbonate ion is found disordered over three positions (55/28/17), around the axis perpendicular to the central carbon atom. In each orientation, the carbonate ion is bound by twelve hydrogen bonds (average O⋯O: 2.90(2) Å), six each from the Cu₇ and Cu₉ rings, four to each of the three carbonate O-atoms.
Figure 3.106: Top- and side-views of the crystal structure of (Bu4N)2[CO3⊂{Cu30(OH)30(pz)15(3,5-Me2pz)15(H2O)}]. Color scheme: Cu7 olive; Cu9 red; Cu14 orange; CO32− lime-green; H bonds and weak Cu⋯O interactions green and black dashed lines, respectively; Cu–O bonds to the coordinated H2O molecule red/white stripes. Only the major component of the disordered units, and no C–H and H2O hydrogens, counterions or solvent molecules are shown. Reproduced with permission, from reference 104.

The Cu7 and Cu9 rings each accept seven H-bonds from the Cu14 ring (Cu7 ring, O⋯O: 2.787(5)–3.123(5) Å, average: 2.976(5) Å; Cu9 ring, O⋯O: 2.750(5)–3.050(5) Å, average: 2.910(5) Å). Thus, the fourteen OH groups of the Cu14 ring form alternating H-bonds with the Cu7 and Cu9 rings (average O⋯O: 2.943(5) Å). The presence of a water molecule within the nanojar is apparently the consequence of the steric hindrance caused by the methyl groups of the 3,5-Me2pz unit within the Cu9 ring. Thus, the H2O molecule fills the void created between the Cu9 and Cu14 rings, as the Cu2(μ-3,5-Me2pz) moiety moves away from the two neighboring pyrazole units of the Cu9 ring (Figure 3.106, right). This H2O molecule bridges the pair of Cu-atoms linked by the only 3,5-Me2pz unit of the Cu9 ring (Cu28⋯O31: 2.431(6), Cu29⋯O31: 2.450(7) Å), and donates a very short hydrogen bond to an adjacent OH-group of the Cu14 ring (O16–H16o⋯O31: 2.482(9) Å). The overall H-bonding pattern in (Bu4N)2[CO3⊂{Cu30(OH)30(pz)15(3,5-Me2pz)15(H2O)}] is shown in Figure 3.115.
The Cu7 and Cu9 rings form seven and six Cu⋯O contacts <3.000(1) Å, respectively, with O-atoms of the Cu14 ring (Cu7-ring, Cu⋯O: 2.516(4)–2.809(4) Å, average: 2.618(4) Å; Cu9 ring, Cu⋯O: 2.407(4)–2.984(5) Å; average: 2.541(4) Å). Two Cu-atoms of the Cu9 ring (bridged by the 3,5-Me2pz ligand) bind the bridging H2O molecule, which donates a H-bond to the Cu14 ring. All other Cu atoms, including the ones of the Cu14 ring, are at distances larger than 3.545(4) Å from the closest non-bonding O atoms. Overall, there are thirteen Cu⋯O distances <3.000(1) Å in-between Cu8-rings, with an average of 2.548(4) Å.

Figure 3.107: Top- and side-views of (Bu4N)2[CO3⊂{(Cu30(OH)30(pz)15(3,5-Me2pz)15(H2O))}] (for clarity, only the major component of the disordered units is shown). H-bonds are shown as green dashed lines, and weak Cu–O bonds as black dashed lines. Reproduced with permission, from reference 104.
Figure 3.108: Top- and side-views of the Cu\textsubscript{7} ring in (Bu\textsubscript{4}N\textsubscript{2})\textsubscript{2}[CO\textsubscript{3} \{Cu\textsubscript{30}(OH)\textsubscript{30}(pz)\textsubscript{15}(3,5-Me\textsubscript{2}pz)\textsubscript{15}(H\textsubscript{2}O)\}]], showing hydrogen-bonding (green dashed lines for O···O distances <3.00(5) Å, grey dashed lines for O···O distances 3.00(5)−3.20(5) Å) to the carbonate ion (only the major component of the disordered units is shown). Reproduced with permission, from reference 104.

Figure 3.109: Top- and side-views of the Cu\textsubscript{14} ring in (Bu\textsubscript{4}N\textsubscript{2})\textsubscript{2}[CO\textsubscript{3} \{Cu\textsubscript{30}(OH)\textsubscript{30}(pz)\textsubscript{15}(3,5-Me\textsubscript{2}pz)\textsubscript{15}(H\textsubscript{2}O)\}]], with the carbonate ion at the center (only the major component of the disordered units is shown). Reproduced with permission, from reference 104.
Figure 3.110: Top- and side-views of the Cu\textsubscript{9} ring in (Bu\textsubscript{4}N)\textsubscript{2}[CO\textsubscript{3}\subset\{Cu\textsubscript{30}(OH)\textsubscript{30}(pz)\textsubscript{15}(3,5-Me\textsubscript{2}pz)\textsubscript{15}(H\textsubscript{2}O)\}], showing hydrogen-bonding (green dashed lines for O⋯O distances <3.00(5) Å, grey dashed lines for O⋯O distances 3.00(5)–3.20(5) Å) to the carbonate ion (only the major component of the disordered units is shown). Cu–O bonds to the H\textsubscript{2}O molecule are shown with black dashed lines. Reproduced with permission, from reference 104.

Figure 3.111: Top- and side-views of the Cu\textsubscript{7} and Cu\textsubscript{9} rings in (Bu\textsubscript{4}N)\textsubscript{2}[CO\textsubscript{3}\subset\{Cu\textsubscript{30}(OH)\textsubscript{30}(pz)\textsubscript{15}(3,5-Me\textsubscript{2}pz)\textsubscript{15}(H\textsubscript{2}O)\}], showing hydrogen-bonding (green dashed lines for O⋯O distances <3.00(5) Å, grey dashed lines for O⋯O distances 3.00(5)–3.20(5) Å) to the carbonate ion (only the major component of the disordered units is shown). Cu–O bonds to the H\textsubscript{2}O molecule are shown with black dashed lines. Reproduced with permission, from reference 104.
Figure 3.112: Top- and side-views of the Cu$_7$ and Cu$_{14}$ rings in (Bu$_4$N)$_2$[CO$_3$$\subset$$\{Cu_{30}(OH)_{30}$ (pz)$_{15}(3,5$-Me$_2$pz)$_{15}$(H$_2$O)$\}]$, showing hydrogen-bonding (green dashed lines for O···O distances <3.00(5) Å, grey dashed lines for O···O distances 3.00(5)−3.20(5) Å) and axial Cu-O interactions (black dashed lines for Cu···O distances <2.50 Å) (only the major component of the disordered units is shown). Reproduced with permission, from reference 104.

Figure 3.113: Top- and side-views of the Cu$_9$ and Cu$_{14}$ rings in (Bu$_4$N)$_2$[CO$_3$$\subset$$\{Cu_{30}(OH)_{30}$ (pz)$_{15}(3,5$-Me$_2$pz)$_{15}$(H$_2$O)$\}]$, showing hydrogen-bonding (green dashed lines for O···O distances <3.00(5) Å, grey dashed lines for O···O distances 3.00(5)−3.20(5) Å) and axial Cu-O interactions (black dashed lines for Cu···O distances <2.50 Å) between the two (only the major component of the disordered units is shown). Reproduced with permission, from reference 104.
Figure 3.114: Top- and side-views of the hydrogen-bonding pattern (green dashed lines for O···O distances <3.00(5) Å, grey dashed lines for O···O distances 3.00(5)–3.20(5) Å) to the carbonate ion in (Bu4N)2[CO3⊂{Cu30(OH)30(pz)15(3,5-Me2pz)15(H2O)}] (only the major component of the disordered carbonate ion is shown). Reproduced with permission, from reference 104.

Figure 3.115: Top- and side-views of the overall hydrogen-bonding pattern (green dashed lines for O···O distances <3.00(5) Å, grey dashed lines for O···O distances 3.00(5)–3.20(5) Å) in (Bu4N)2[CO3⊂{Cu30(OH)30(pz)15(3,5-Me2pz)15(H2O)}], converging at the central carbonate ion (only the major component of the disordered carbonate ion is shown). Reproduced with permission, from reference 104.
Figure 3.116: Space-filling representations (two different top- and side-views) of \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset\{\text{Cu}_{30}^\text{OH}_{30}(\text{pz})_{15}(3,5-\text{Me}_2\text{pz})_{15}(\text{H}_2\text{O})\}]\) (only the major component of the disordered units is shown). Reproduced with permission, from reference 104.

3.2.4.4.14 \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset\{\text{Cu}_{30}^{\text{OH}}_{30}(\text{pz})_{16}(3,5-\text{Me}_2\text{pz})_{14}\}]\)

Only very small crystals of \((\text{Bu}_4\text{N})_2[\text{CO}_3\subset\{\text{Cu}_{30}(\mu-\text{OH})_{30}(\mu-\text{pz})_{10}(\mu-3,5-\text{Me}_2\text{pz})_{14}\}]\) could be obtained, which diffracted poorly; therefore, only preliminary data are presented here (monoclinic, P2/n, \(a = 23.864(4) \, \text{Å}\), \(b = 14.830(2) \, \text{Å}\), \(c = 31.070(4) \, \text{Å}\), \(\beta = 95.138(10)\), \(V = 10952(3) \, \text{Å}^3\), \(Z = 2\)). Although the severely disordered solvent molecules and \(\text{Bu}_4\text{N}^+\) counterions
are not modeled, the identity of the nanojar is established unambiguously, and all Cu-atoms are refined anisotropically ($R_1 = 16\%$, $R_w = 20\%$). The nanojar $(\text{Bu}_4\text{N})_2[\text{CO}_3\subset\{\text{Cu}_{30}(\mu-\text{OH})_{30}(\mu-pz)_{16}(\mu-3.5\text{-Me}_2\text{pz})_{14}\}]$, (Figure 3.117) consisting of one $[\text{Cu(OH)}(3.5\text{-Me}_2\text{pz})]_{14}$ and two $[\text{Cu(OH)}(pz)]_{8}$ rings, is located on a two-fold rotation axis ($C_2$), which runs perpendicular to the encapsulated carbonate ion, disordered accordingly over two positions (50/50). The position of the nanojar and encapsulated carbonate ion relative to the $C_2$ axis is clearly different than in $(\text{Et}_4\text{N})_2[\text{CO}_3\subset\{\text{Cu(OH)}(pz)\}]_{8+13+8}$ and $(\text{Bu}_4\text{N})_2[\text{CO}_3\subset\{\text{Cu(OH)}(pz)\}]_{8+13+8}$, in which the $C_2$ axis is located in the plane of the carbonate ion. The central Cu$_{14}$ ring is made up by 3,5-dimethylpyrazolate ligands, while the two Cu$_8$ side rings contain only non-substituted pyrazole ligands.

![Figure 3.117: Top- and side-views of the crystal structure of $(\text{Bu}_4\text{N})_2[\text{CO}_3\subset\{\text{Cu}_{30}(\mu-\text{OH})_{30}(\mu-pz)_{16}(\mu-3.5\text{-Me}_2\text{pz})_{14}\}]$. Color scheme: Cu$_8$–magenta; Cu$_{13}$–orange; CO$_3^{2-}$ lime-green (only one position of the disordered carbonate, and no H atoms, counterions or solvent molecules are shown). Reproduced with permission, from reference 104.](image)

The CO$_3^{2-}$ ion is bound by a total of nine H bonds in each disordered position (O⋯O: 2.63(9)–2.97(9) Å, average: 2.87(8) Å), four from one Cu$_8$ ring and five from the other, with each O atom having three H bonds. Each Cu$_8$ ring forms six H bonds with the Cu$_{14}$ ring (O⋯O: 2.73(5)–2.96(5) Å, average: 2.87(5) Å). The two Cu$_8$ rings form six and eight Cu⋯O contacts <3.00(7) Å,
respectively, with O-atoms of the Cu_{14} ring (one Cu_{8} ring, Cu⋯O: 2.52(3)–2.76(3) Å, average: 2.56(3) Å; other Cu_{8} ring, Cu⋯O: 2.43(3)–3.10(3) Å; average: 2.67(3) Å). All other Cu atoms, including the ones of the Cu_{14} ring, are at distances larger than 3.13(3) Å from the closest non-bonding O atoms. Overall, there are fourteen Cu⋯O distances <3.00(7) Å, with an average of 2.61(3) Å.

3.2.4.4.15 (Bu_{4}N)_{2}[SO_{4}^{2–}\{\text{Cu(OH)(pz)}\}_{8+13+8}]\cdot2C_{4}H_{8}O_{2}

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Single crystals of (Bu_{4}N)_{2}[SO_{4}^{2–}\{\text{Cu(OH)(μ-pz)}\}_{8+13+8}]\cdot2C_{4}H_{8}O_{2} are grown by hexane vapor diffusion to an ethyl acetate (C_{4}H_{8}O_{2}) solution of a sulfate-incarcerating nanojar mixture. Once removed from the mother liquor, the crystals are extremely sensitive to solvent loss under ambient conditions and are quickly mounted under a cryostream (100 K) to prevent decomposition. (Cu_{29}SO_{4}) crystallizes in a monoclinic (C2/c) lattice with two ethyl acetate solvent molecules, and consists of one Cu_{13} ring and two Cu_{8} rings (see Figure 3.118 and Figure 3.119). The nanojar is located around a two-fold rotation axis (C_{2}), which runs through the S atom of the incarcerated sulfate ion, from the side of the nanojar. The SO_{4}^{2–} ion is severely disordered about the special position (only the disorder about the C_{2} axis was modeled). The OH protons of the two Cu_{8} rings form a multitude of hydrogen bonds with the incarcerated, disordered sulfate ion, with O⋯O distances ranging from 2.624(15) Å to 3.023(16) Å, while the OH protons of the central Cu_{13} ring form five hydrogen bonds with each of the two Cu_{8} rings (O⋯O: 2.715(4)–2.834(5) Å; average: 2.774(5) Å). Seven Cu atoms of each Cu_{8} ring form axial Cu⋯O interactions shorter than 3.00(5) Å with the Cu_{13} ring (Cu⋯O: 2.348(4)–3.024(3) Å). The other Cu atoms, including those of the Cu_{13} ring, are at distances larger than 3.186(3) Å from the closest nonbonding O atoms. Overall, there are 14 Cu⋯O distances of <3.00(5) Å, with an average of 2.582(3) Å. The structure of Cu_{8+13+8}SO_{4} closely resembles that of the analogous Cu_{8+13+8}CO_{3}, as illustrated in Figure 3.97.
Figure 3.118: Top and side views of the crystal structure of (Bu4N)2[SO42−{(Cu(OH)(pz)}8+13+8}. (Color scheme: Cu8–magenta; Cu13–blue; S yellow; O–red. C–H hydrogen atoms, counterions and solvent molecules are not shown) Reproduced with permission, from reference 107.

Figure 3.119: Space-filling representation of [SO42−{(Cu(OH)(pz)}8+13+8}]2−. Reproduced with permission, from reference 107.
Solvent- and catalyst-free, green protection methodology we have developed, showed that a variety of functional groups, including –OH, –SH, –COOH, –CONH₂ and heterocyclic polyamines, can be quantitatively protected with the inexpensive 3,4-dihydro-2H-pyran (DHP). The conversion of the protecting reaction was found to be influenced by the following variables: acidity of the substrate, miscibility of substrate and DHP, amount of DHP employed, nucleophilicity of the atom to be protected, steric hindrance, reaction time and reaction temperature.

One-pot telescoping synthesis methodology of mono- and dialkylpyrazoles, provides high overall yields of pyrazole derivatives, in addition to many other advantages such as minimizing of the use of solvents/reagents, greatly diminishing waste production, eliminating the use of highly toxic or explosive materials, easily scalable and versatility to allow for the synthesis of various other 3,5-disubstituted pyrazoles (symmetrical and unsymmetrical) such as alkyl, halogen, hydroxyl, amino, azido, carbonyl, and organo-element substituents.

Study of the intriguing reactivity of amino- and hydroxypyrazole derivatives toward aldehydes and ketones under either neutral or acidic conditions, provided not only an understanding of the mechanism of the reactions, but also a variety of novel bis- and non-scorpionate tris(pyrazolyl) methane ligands. The study showed that the conversion and outcome of the reaction can be affected by different factors, such as presence or absence of the acid catalyst, ratios between aldehydes/ketones and amines, aldehydes vs ketones, effect of the aliphatic vs aromatic substituents, and effect of the steric hindrance.

The selective C-4 deuteration of the pyrazole nucleus activated by NH₂ or OH groups at the C-3(5) position by D₂O was studied, either in the presence or absence of an acid catalyst or with heat, and a convenient procedure for large-scale deuteration was developed. The study showed that both the reaction conditions and the substituents of the pyrazole substrates influence the rate of the deuteration reaction.
Computational studies showed that in contrast to the methyl-substituted, six-membered aromatic molecules, which deprotonate at the substituted methyl group and produces exocyclic benzylic carbanions stabilized by $\pi$-conjugation, methyl-substituted, five-membered aromatic rings deprotonate at an endocyclic CH group. Diminished $\pi$-conjugation, reduced bond angles and strengthened induction of C$_{sp}^{2}$ versus C$_{sp}^{3}$ in five-membered ring are collectively responsible for deprotonation of an endocyclic carbon rather than of the ‘benzylic’ position.

It has also been shown that the resistance of 5-alkyl-1-(tetrahydropyran-2-yl)-1H-pyrazole isomer to deprotonation by $^n$BuLi, previously attributed to the “adjacent lone pair effect”, is mainly due not to electron pair repulsion, but rather to reduced $\pi$-resonance and weaker electrostatic interactions within the pyrazole ring.

The stability of nanojars is determined by the size match between nanojar host and the anion guest: the smaller carbonate ion fits best inside the smallest nanojar (Cu$_{27}$), whereas the larger sulfate ion prefers the largest nanojar (Cu$_{31}$). Therefore, the less stable sulfate and carbonate nanojars in the [anion⊂Cu(OH)(pz)$_{n}$]$_{2}^{2-}$ (n = 27 – 31) series selectively break down in the presence of pyridine or NH$_{3}$, and self-assemble back into the more stable ones under the given conditions. For instance, NH$_{3}$ leads to the most stable pure [CO$_{3}^{2-}$⊂Cu(OH)(pz)$_{27}$] and [SO$_{4}^{2-}$⊂Cu(OH)(pz)$_{31}$] nanojars, whereas pyridine provides a mixture of [CO$_{3}^{2-}$⊂Cu(OH)(pz)$_{27}$] and [CO$_{3}^{2-}$⊂Cu(OH)(pz)$_{29}$]. Furthermore, Pb(NO$_{3}$)$_{2}$, which provides acidity because of hydrolysis during the nanojar-forming reaction, leads to the most stable pure [SO$_{4}^{2-}$⊂Cu(OH)(pz)$_{31}$].

Further knowledge of the stability of various nanojars with different anions is made available by anion exchange studies. Cu$_{27}$SO$_{4}$ is the only nanojar that exchanges its incarcerated SO$_{4}^{2-}$ anion with CO$_{3}^{2-}$ in THF solution (molar ratio of anions is 1:1). In contrast, only Cu$_{31}$CO$_{3}$ exchanges CO$_{3}^{2-}$ to SO$_{4}^{2-}$ under identical conditions. It can be concluded that, although sulfate or carbonate may be thermodynamically preferred by nanojars of certain sizes (SO$_{4}^{2-}$ bound most strongly by the large Cu$_{31}$ nanojar and most weakly by the small Cu$_{27}$ nanojar, and vice versa for CO$_{3}^{2-}$), there is a considerable kinetic barrier for exchanging an already incarcerated anion.

In contrast to the unprecedented stability of nanojars to highly alkaline media such as 10 M NaOH, nanojars are unstable under acidic pH, and even very weak acids break down nanojars
to trinuclear copper pyrazolate complexes and ultimately to its original components, copper ions and pyrazole. These properties are ideal for recycling the nanojars as extracting agents of anions with large hydration energies from alkaline aqueous media. The extracted anion is conveniently recovered under slightly acidic conditions, and the nanojars are then fully reassembled when the pH is made alkaline again.

The mechanism of self-assembly of nanojars from pyrazole, Cu(NO₃)₂ and NaOH in the presence of Na₂CO₃ is proposed based on mass spectrometric, UV–vis and NMR spectroscopic, pH titration and crystallographic studies. When the reaction is carried out in THF, the insoluble NaOH and Na₂CO₃ will gradually react with the copper pyrazolate trinuclear intermediate [Cu₃(μ₃-OH)(μ-pz)₃(NO₃)₂(H₂O)], which forms first. As more NaOH reacts, the nitrate ions are gradually replaced by hydroxide ions. The resulting [Cu₃(μ₃-OH)(μ-pz)₃(OH)ₓ(NO₃)₃-x]⁻ (x = 1–3) intermediates, which have unstable terminal Cu–OH groups, react with each other to form OH-bridged units, [Cu₃(μ₃-OH)(μ-pz)₃(NO₃)₂]₂(μ-OH) and then [{Cu₃(μ₃-OH)(μ-pz)₃(μ-OH)₂}ₓ(NaNO₃)₃(Na₂CO₃)₂] oligomers. In these oligomers, the Cu₃(OH)₃(pz)₃ repeating units have the same composition as the [Cu(OH)(pz)]ₙ (n = 3x) nanojars and are rearranged to the final products, Na₂[CO₃{Cu(μ-OH)(μ-pz)}ₙ] (n = 27, 29, 31), while eliminating the last amounts of NaNO₃. When carried out in water, in which all reactants are soluble, the reaction is very fast and an insoluble, polymeric [{Cu₃(OH)₃(pz)₃}ₓ(NaNO₃)₃(Na₂CO₃)₂]∞ intermediate forms instantly. If it is further stirred in water, the intermediate slowly transforms into intractable [trans-Cu(μ-OH)(μ-pz)]∞ and eliminates NaNO₃ and Na₂CO₃.

The formation of the trinuclear intermediate at a Cu:Hpz:NaOH molar ratio of 3:3:4 also confirmed by pH titration and UV–vis monitoring of the accompanying absorbance changes. This intermediate transform cleanly into nanojars upon addition of two more equivalents of NaOH (at a Cu:Hpz:NaOH molar ratio of 3:3:6).

We have shown that if pairs of pyrazole ligands are locked together by an ethylene tether, a variety of novel coordination architectures which are inaccessible with a given ligand, can be obtained. For example, when the ligand 1,2-bis(1H-pyrazol-3-yl)ethane (H₂L), is employed, the tetranuclear complexes Cu₄(μ₃-OH)₂(μ₃-L)₂(NO₃)₂ and Bu₄N[Cu₄(μ₄-OH)(μ₃-L)₄] are obtained. In contrast, the trinuclear complex Cu₃(μ₃-OH)₂(μ-pz)₂(NO₃)₂(H₂O) or the polymeric complex [Cu(μ-
pz)₂ are produced when the simple, non-tethered pyrazole is the ligand. In addition, using H₂L in the synthesis of nanojars provides total selectivity for carbonate over sulfate anions.

In the future, in order to achieve high selectivity for different anions, we need to obtain rigidified oligopyrazole ligands, and use them to prepare nanojars. Such nanojars, are expected to provide hydrogen bonds with specific lengths and orientations, and to optimally fit the geometry of the targeted oxoanions (i.e. lengths and orientations of the element-oxygen bonds within those anions).
REFERENCES


179. A related structure (monoclinic, P2\textsubscript{1}/n), in which one pyrazolato anion of the Cu\textsubscript{9}-ring is substituted by a bridging acetato anion, was reported earlier: G. Mezei, P. Baran, R. G. Raptis Angew. Chem. 2004, 116, 584–587; reference 58.

Appendix A

$^1$H NMR and $^{13}$C NMR spectral data of selected compounds
$^1$H NMR spectrum of bis(3(5)-aminopyrazol-4-yl)-pyrazol-3(5)-yl-methane 21 in DMSO-$d_6$. Reproduced with permission, from reference 112.

$^{13}$C NMR of bis(3(5)-aminopyrazol-4-yl)-pyrazol-3(5)-yl-methane 21 in DMSO-$d_6$. Reproduced with permission, from reference 112.
$^1$H NMR of $N$-(4-((1H-Pyrazol-3-yl)methylene)-4H-pyrazol-3-yl)-1-(1H-pyrazol-3-yl)methanimine 19 in DMSO-$d_6$. Reproduced with permission, from reference 112.

$^{13}$C NMR of $N$-(4-((1H-Pyrazol-3-yl)methylene)-4H-pyrazol-3-yl)-1-(1H-pyrazol-3-yl)methanimine 19 in DMSO-$d_6$. Reproduced with permission, from reference 112.
$^1$H NMR of 3(5)-aminopyrazole-$d_4$ in D$_2$O. Reproduced with permission, from reference 114.

$^{13}$C NMR spectrum of 3(5)-aminopyrazole-$d_4$ in D$_2$O. Reproduced with permission, from reference 114.
\( ^1\text{H} \text{NMR monitoring of the deuteration of 5-amino-1-methylpyrazole 55 in D}_2\text{O with 100 mol \% DCl at 25 °C. Reproduced with permission, from reference 114.} \)

\( ^1\text{H} \text{NMR monitoring of the deuteration of 3(5)-amino-5(3)-phenylpyrazole 60 in CD}_3\text{OD with 100 mol \% DCl at 25 °C. Reproduced with permission, from reference 114.} \)
$^1$H NMR spectrum (400 MHz, DMSO-$d_6$, 150 °C) of Cu$_4$(μ$_3$-OH)$_2$(μ$_3$-pzCH$_2$CH$_2$pz)$_2$(NO$_3$)$_2$(H$_2$O)$_2$ (THF) 66, showing the 1:1 stoichiometry between complex 66 and THF. Reproduced with permission, from reference 108.
Appendix B

Predicted and observed isotopic patterns of selected compounds
Predicted (blue) and observed (red) isotopic patterns for [(Bu4N)Cu2(pz)2(CO3)2]− (A), [(Bu4N)Cu2(pz)2(CO3)(SO4)]− (B), [(Bu4N)Cu2(pz)2(SO4)2]− (C), [SO4⊂{Cu(OH)(pz)}30]2− (D), [SO4⊂{Cu(OH)(pz)}32]2− (E) and [SO4⊂{Cu(OH)(pz)}33]2− (F). Reproduced with permission, from reference 107.
Predicted (blue) and observed (red) isotopic patterns for \([\text{Cu}_4\text{O(OH)}(\text{pzCH}_2\text{CH}_2\text{pz})_2(\text{NO}_3)_2]^-\) (A), \([\text{Cu}_4\text{O(OH)}(\text{pzCH}_2\text{CH}_2\text{pz})_2]^+\) (B), \([\text{Cu}_4(\text{OH})(\text{pzCH}_2\text{CH}_2\text{pz})_4]^-\) (C), \([\text{Cu}_{26}(\text{OH})_{26}(\text{pzCH}_2\text{CH}_2\text{pz})_{13}(\text{CO}_3)]^{2-}\) (D), \([\text{Cu}_{28}(\text{OH})_{28}(\text{pzCH}_2\text{CH}_2\text{pz})_{14}(\text{CO}_3)]^{2-}\) (E) and \([\text{Cu}_{30}(\text{OH})_{30}(\text{pzCH}_2\text{CH}_2\text{pz})_{15}(\text{CO}_3)]^{2-}\) (F). Reproduced with permission, from reference 108.
Predicted (green) and observed (red) isotopic pattern for $[\text{CO}_3 \subset \{\text{Cu(OH)(pz)}\}_{27}]^{2-}$ (A); $[\text{CO}_3 \subset \{\text{Cu(OH)(pz)}\}_{7+13+9}]^{2-}$ and $[\text{CO}_3 \subset \{\text{Cu(OH)(pz)}\}_{8+13+8}]^{2-}$ (B); $[\text{CO}_3 \subset \{\text{Cu(OH)(pz)}\}_{30}]^{2-}$ (C); $[\text{CO}_3 \subset \{\text{Cu(OH)(pz)}\}_{31}]^{2-}$ (D); $[\text{SO}_4 \subset \{\text{Cu(OH)(pz)}\}_{27}]^{2-}$ (E); $[\text{SO}_4 \subset \{\text{Cu(OH)(pz)}\}_{28}]^{2-}$ (F); $[\text{SO}_4 \subset \{\text{Cu(OH)(pz)}\}_{29}]^{2-}$ (G); $[\text{SO}_4 \subset \{\text{Cu(OH)(pz)}\}_{31}]^{2-}$ (H). Reproduced with permission, from reference 105.
Appendix C

Variable-temperature $^1$H NMR spectroscopy of selected compounds
Variable-temperature $^1$H NMR spectra (in DMSO-$d_6$) of Cu$_4$(µ$_3$-OH)$_2$(µ$_3$-pzCH$_2$CH$_2$pz)$_2$(NO$_3$)$_2$(H$_2$O)$_2$(THF) 66. Only the regions between 125–175 ppm (OH proton), 35–55 pm (pz protons) and (−3)–1 ppm (CH$_2$CH$_2$ protons) are shown for clarity. Reproduced with permission, from reference 108.
Variable-temperature $^1$H NMR spectra (in DMSO-$d_6$) of the mixture of nanojars $(\text{Bu}_4\text{N})_2 [\text{Cu}_n(\text{OH})_a(\text{pzCH}_2\text{CH}_2\text{pz})_{n/2}(\text{CO}_3)]$ ($n = 26, 28, 30$) 68 (pyrazole signals in the 21–45 ppm window). Reproduced with permission, from reference 108.
Variable-temperature $^1$H NMR spectra (in DMSO-$d_6$) of the mixture of nanojars (Bu$_4$N)$_2$[Cu$_n$ (OH)$_m$(L)$_n$(CO$_3$)] ($n = 26, 28, 30$) (OH signals in the $(-28)–(-70)$ ppm window). Reproduced with permission, from reference 108.
Variable-temperature $^1$H NMR spectra of (Bu$_4$N)$_2$[SO$_4$⊂{Cu(OH)(pz)}$_{28}$] with small amounts of (Bu$_4$N)$_2$[SO$_4$⊂{Cu(OH)(pz)}$_{27}$] in DMSO-$d_6$ (pyrazole signals in the 21−41 ppm window). Reproduced with permission, from reference 107.
Variable-temperature $^1$H NMR spectra of (Bu$_4$N)$_2$[SO$_4$⊂{Cu(OH)(pz)}$_{28}$] with small amounts of (Bu$_4$N)$_2$[SO$_4$⊂{Cu(OH)(pz)}$_{27}$] in DMSO-$d_6$ (OH signals in the (–25)–(–59) ppm window). Reproduced with permission, from reference 107.
Variable-temperature $^1$H NMR spectra of (Bu$_4$N)$_2$[SO$_4$·$\{\text{Cu(OH)(pz)}\}_{29}$] and (Bu$_4$N)$_2$[SO$_4$·$\{\text{Cu(OH)(pz)}\}_{31}$], with small amounts of Cu$_{27}$SO$_4$, Cu$_{28}$SO$_4$ and Cu$_{32}$SO$_4$ in DMSO-$d_6$ (pyrazole signals in the 21–41 ppm window). Reproduced with permission, from reference 107.
Variable-temperature $^1$H NMR spectra of (Bu$_4$N)$_2$[SO$_4$-$\{\text{Cu(OH)(pz)}\}_{29}$] and (Bu$_4$N)$_2$[SO$_4$-$\{\text{Cu(OH)(pz)}\}_{31}$], with small amounts of Cu$_{27}$SO$_4$, Cu$_{28}$SO$_4$ and Cu$_{32}$SO$_4$ in DMSO-$d_6$ (OH signals in the (−25)−(−59) ppm window). Reproduced with permission, from reference 107.
Variable-temperature $^1$H NMR spectra of (Bu$_4$N)$_2$[SO$_4$\{Cu(OH)(pz)\}]$_{31}$ with small amounts of (Bu$_4$N)$_2$[SO$_4$\{Cu(OH)(pz)\}]$_{32}$ in DMSO-$d_6$ (pyrazole signals in the 21–41 ppm window). Reproduced with permission, from reference 107.
Variable-temperature $^1$H NMR spectra of (Bu$_4$N)$_2$SO$_4$$\subset$[Cu(OH)(pz)]$_{31}$ with small amounts of (Bu$_4$N)$_2$SO$_4$$\subset$[Cu(OH)(pz)]$_{32}$ in DMSO-$d_6$ (OH signals in the (–25)–(–59) ppm window). Reproduced with permission, from reference 107.
$^1$H NMR spectra of pure (Bu$_4$N)$_2$[SO$_4\cdot$Cu(OH)(pz)$_3$]$_1$ in DMSO-$d_6$ at 25 °C and 100 °C, showing pyrazole proton signals in the 21−35 ppm window. Insets show the corresponding OH proton signals. Small peaks corresponding to Cu$_{8+13+8}$SO$_4$ decomposition product are observed at high temperature. Reproduced with permission, from reference 107.
Variable-temperature $^1$H NMR spectra of $(\text{Bu}_4\text{N})_2[\text{SO}_4\subset\{\text{Cu(OH)(4-Mepz)}\}]_{31}$ with small amounts of $(\text{Bu}_4\text{N})_2[\text{SO}_4\subset\{\text{Cu(OH)(4-Mepz)}\}]_{32}$ in DMSO-$d_6$ (pyrazole signals in the 21–41 ppm window). Reproduced with permission, from reference 107.
Variable-temperature $^1$H NMR spectra of (Bu$_4$N)$_2$(CO$_3$)[$\text{Cu(OH)(pz)}$]$_{6+12+9}$ in toluene-$d_8$ (left: pyrazole protons; right: OH protons; red–Cu$_9$ ring; cyan–Cu$_6$ ring; violet –Cu$_{12}$ ring). Reproduced with permission, from reference 105.
Variable-temperature $^1$H NMR spectra of (Bu$_4$N)$_2$[CO$_3$\{Cu(OH)(pz)\}_{6+12+9}]$ in DMSO-$d_6$ (red – Cu$_9$ ring; cyan–Cu$_6$ ring; violet–Cu$_{12}$ ring; magenta–Cu$_{13}$ ring; blue–Cu$_8$ ring). Peaks corresponding to (Bu$_4$N)$_2$[CO$_3$\{Cu(OH)(pz)\}_{8+13+8}]$ are observed at temperatures above 110 °C, indicating that (Cu$_{6+12+9}$) converts to (Cu$_{8+13+8}$) at high temperatures. Reproduced with permission, from reference 105.
Variable-temperature $^1$H NMR spectra of the as-synthesized mixture of CO$_3$ nanojars in DMSO-$d_6$, evidencing the otherwise hard to observe, broad peaks of the Cu$_{31}$ nanojar. These peaks sharpen as the temperature increases, but then diminish above ~60 °C, as the Cu$_{8+14+9}$ nanojar breaks down to the Cu$_{8+15+8}$ nanojar. Reproduced with permission, from reference 105.
Appendix D

Thermogravimetric analysis of selected compounds
Thermogravimetric curve of Cu₃(μ₃-OH)(μ-pz)₃(NO₃)₂(CH₃CN) 69b (Figure 3.76), heated at 5 °C/min under N₂. Calculated loss of the CH₃CN molecule: 7.15%; observed: 7.2%. Reproduced with permission, from reference 106.

Thermogravimetric curve of Cu₃(μ₃-OH)(μ-pz)₃(NO₃)₂(H₂O) 69a, heated at 5 °C/min under N₂. Calculated loss of the H₂O molecule: 3.27%; observed loss by the same temperature as in the case of 69b (135 °C): 7.4%. Reproduced with permission, from reference 106.
Thermogravimetric curves for the Cu$_{27}$CO$_3$, Cu$_{28}$SO$_4$ (with small amounts of Cu$_{27}$SO$_4$) and Cu$_{31}$SO$_4$ (with small amounts of Cu$_{32}$SO$_4$) heated at a rate of 5 °C/min under N$_2$. Cu$_{28}$SO$_4$ retains a toluene solvent molecule at room temperature under vacuum, which is lost on heating above ~50 °C (1.9%). Reproduced with permission, from reference 107.

Thermogravimetric curve of Cu$_4$(μ$_3$-OH)$_2$(μ$_3$-pzCH$_2$CH$_2$pz)$_2$(NO$_3$)$_2$(H$_2$O)$_2$(THF) 66, heated at 3 °C/min under N$_2$. Calculated loss of the THF molecule: 8.58%; observed: 8.6%. Calculated loss of the THF and the two H$_2$O molecules: 12.86%; observed: 12.9%. Reproduced with permission, from reference 108.
Appendix E

Tandem mass spectrometry of nanojars
Tandem mass spectrum of $[\text{CO}_3\subset\{\text{Cu(OH)(pz)}\}_{27}]^{2-}$ (A); $[\text{CO}_3\subset\{\text{Cu(OH)(pz)}\}_{7+13+9}]^{2-}$ and $[\text{CO}_3\subset\{\text{Cu(OH)(pz)}\}_{8+13+8}]^{2-}$ (B); $[\text{CO}_3\subset\{\text{Cu(OH)(pz)}\}_{30}]^{2-}$ (C); $[\text{CO}_3\subset\{\text{Cu(OH)(pz)}\}_{31}]^{2-}$ (D); $[\text{SO}_4\subset\{\text{Cu(OH)(pz)}\}_{27}]^{2-}$ (E); $[\text{SO}_4\subset\{\text{Cu(OH)(pz)}\}_{28}]^{2-}$ (F); $[\text{SO}_4\subset\{\text{Cu(OH)(pz)}\}_{29}]^{2-}$ (G); $[\text{SO}_4\subset\{\text{Cu(OH)(pz)}\}_{31}]^{2-}$ (H). Reproduced with permission, from reference 105.
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