Acylpyrazolones: Synthesis, Self-Assembly and Lanthanide Metal Ion Separation

Jun Yang
Western Michigan University

Follow this and additional works at: http://scholarworks.wmich.edu/dissertations
Part of the Chemistry Commons

Recommended Citation

This Dissertation-Open Access is brought to you for free and open access by the Graduate College at ScholarWorks at WMU. It has been accepted for inclusion in Dissertations by an authorized administrator of ScholarWorks at WMU. For more information, please contact maira.bundza@wmich.edu.
ACYLPYRAZOLONES: SYNTHESIS, SELF-ASSEMBLY AND LANTHANIDE METAL ION SEPARATION

by

Jun Yang

A Dissertation
Submitted to the
Faculty of the Graduate College
in partial fulfillment of the
requirement for the
Degree of Doctor of Philosophy
Department of Chemistry

Western Michigan University
Kalamazoo, Michigan
June 2005
The central hypothesis that nanoscale self-assemblies can provide excellent metal ion recognition has been substantiated by employing acylpyrazolones and trivalent lanthanide metal ions as model systems. Several novel acylpyrazolones and their amphiphilic analogs have been designed, synthesized, and characterized. Their lanthanide metal ion recognition efficacies have been demonstrated through baseline separations of a mixture of light, middle, and heavy lanthanide metal ions by employing them in the aqueous mobile phase of high performance liquid chromatography (HPLC) with octadecylsilanized silica (ODS) as the stationary phase. The complex separation mechanism is influenced by the structures of acylpyrazolone and amphiphilic moieties, and spontaneous self-assembly of the ligand in the aqueous and on the stationary phases. Transmission electron microscopy (TEM) studies of the ligand self-assemblies in the aqueous phase in the absence and presence of lanthanide metal ions reveal spherical, dendritic, and linear (nanofibers, nanorods, and nanotubes) nanoscale structures. Such structures have also been observed when chloromethylated acylpyrazolones are stimulated to self-assemble by a base in nonaqueous solvents and when silica nanoparticles derivatized with them spontaneously self-assemble in aqueous and nonaqueous solvents.
ACKNOWLEDGMENTS

I would like to begin by thanking my advisor, Professor Subra Muralidharan for his advice, support, dedication, and patience through my research. The knowledge, enthusiastic attitude, and thoughtful ideas are the great lessons he taught me in the years of my PhD study.

Next, I gratefully acknowledge the members of my research committee, Dr. Elke Schoffers, Dr. Yirong Mo, Dr. Marc Perkovic and Dr. Brian Tripp for taking the time to review my work. I would like to thank Dr. Marc Perkovic for X-ray single crystal structure analysis of my compounds and Dr. Elke Schoffers and Dr. Yirong Mo for exciting graduate courses and many useful suggestions.

I would like to extend my grateful thanks to Dr. Hengli Ma for her help since I came here, for our productive collaboration and her help with HPLC investigations. I would also like to thank members of our research group: Ke Du, Pedro Gonzalez, Shankar Varangati, Tushara Gunasinghe, for our friendship and collaboration.

I would like to especially thank my family for their encouragement and support during my study.

This research was supported by a grant from the U.S. Department of Energy, Office of Basic Energy Sciences

Jun Yang
# TABLE OF CONTENTS

ACKNOWLEDGMENTS .................................................................................. ii

LIST OF TABLES ............................................................................................ viii

LIST OF FIGURES ......................................................................................... xii

LIST OF SCHEMES ....................................................................................... xxiv

CHAPTER

I. INTRODUCTION ...................................................................................... 1

1.1 Why is the separation of lanthanides important? .............................................. 1

1.2 Current approaches to lanthanide separation. .................................................. 2

1.3 Central hypothesis. ....................................................................................... 4

1.4 Research to substantiate the central hypothesis. .............................................. 6

1.5 Prior research on acylpyrazolones and acylisoxazolones. .............................. 7

II. EXPERIMENTAL METHODS .................................................................... 8

2.1 Nomenclature .......................................................................................... 8

2.2 Synthetic approaches ............................................................................... 9

2.3 Characterization ...................................................................................... 11
<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>III.</td>
<td>SYNTHESIS OF PYRAZOLONES AND ACYLPYRAZOLONES</td>
<td>15</td>
</tr>
<tr>
<td>3.1</td>
<td>Synthesis of the parent pyrazolones</td>
<td>15</td>
</tr>
<tr>
<td>3.2</td>
<td>Synthesis of acylpyrazolones</td>
<td>18</td>
</tr>
<tr>
<td>3.2.1</td>
<td>Synthesis of 1-phenyl-3-methyl-4-acyl-5-pyrazolone from aliphatic acyl chlorides</td>
<td>18</td>
</tr>
<tr>
<td>3.2.2</td>
<td>Synthesis of 1-phenyl-3-methyl-4-acyl-5-pyrazolone from aromatic acyl chlorides</td>
<td>22</td>
</tr>
<tr>
<td>3.3</td>
<td>Structure of the ligands and their metal ion complexes</td>
<td>23</td>
</tr>
<tr>
<td>3.4</td>
<td>Experimental procedures</td>
<td>33</td>
</tr>
<tr>
<td>IV.</td>
<td>SYNTHESIS OF AMPHIPHILIC ACYLPYRAZOLONES</td>
<td>43</td>
</tr>
<tr>
<td>4.1</td>
<td>Synthesis of 1-phenyl-3-methyl-4-(4’-PEG)-benzoyl-5-pyrazolone ligands</td>
<td>44</td>
</tr>
<tr>
<td>4.2</td>
<td>Study of the functional groups effects on the metal ion recognition properties of acyl pyrazolones</td>
<td>49</td>
</tr>
<tr>
<td>4.2.1</td>
<td>Brief introduction</td>
<td>49</td>
</tr>
<tr>
<td>4.2.2</td>
<td>Synthesis of PEG750 acylpyrazolones</td>
<td>50</td>
</tr>
<tr>
<td>4.3</td>
<td>Experimental procedures</td>
<td>55</td>
</tr>
<tr>
<td>V.</td>
<td>SYNTHESIS OF ACYLISOXAZOLONE LIGANDS</td>
<td>60</td>
</tr>
<tr>
<td>5.1</td>
<td>Brief introduction</td>
<td>60</td>
</tr>
</tbody>
</table>
CHAPTER

5.2 Synthesis of acylisoxazolones ............................................. 61

5.2.1 Synthesis of 3-phenyl-4-acyl-5-isoxazolone
from aliphatic acyl chlorides ............................................. 62

5.2.2 Synthesis of 3-methyl-4-(4’-PEG750)-benzoyl-5-isoxazolone ............................................. 66

5.3 Experimental procedures ..................................................... 67

VI. HPLC SEPARATION OF TRIVALENT LANTHANIDES WITH AMPHIPHILIC ACYLPYRAZOLONES ................................. 72

6.1 Brief introduction ............................................................... 72

6.2 HPLC separation of rare earth metal ions by using
self-assembling 1-phenyl-3-methyl-4-(4’-PEG)
benzoyl-5-pyrazolone Family Ligands ................................. 76

6.2.1 Dependence of lanthanide metal ion separation
on ligand concentration ..................................................... 77

6.2.2 Comparison of 1-phenyl-3-methyl-4-(4’-PEG2000)-
benzoyl-5-pyrazolone with 1-phenyl-3-methyl-4-
benzoyl-5-pyrazolone ..................................................... 81

6.2.3 Comparison of 3-methyl-1-phenyl-4-(4’-PEG)-
benzoyl-5-pyrazolone family ligands ................................. 83

6.3 HPLC separation with amphiphilic acylpyrazolones
with varying substituents ..................................................... 92

6.3.1 Substituent in the 1 position (R’ group) ......................... 93

6.3.2 Substituent in the 3 position (R” group) ......................... 102

6.3.3 Substituent in the 4 position (R”’ group) ......................... 107
<table>
<thead>
<tr>
<th>CHAPTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.4 Self-assemblies in the aqueous solutions of acylpyrazolones with alkyl acyl groups .......................................................... 114</td>
</tr>
<tr>
<td>6.5 Mechanism of lanthanide metal ion recognition by amphiphilic acylpyrazolones ......................................................... 136</td>
</tr>
<tr>
<td>6.6 logD vs log[HL] and logD vs pH ..................................................... 140</td>
</tr>
<tr>
<td>6.6.1 logD vs log[HL] and logD vs pH for the ligand HPMBP750 .......................................................... 140</td>
</tr>
<tr>
<td>6.6.2 logD vs log[HL] and logD vs pH for the ligand HPMVP750 .................................................................. 150</td>
</tr>
<tr>
<td>6.7 Discussion .................................................................................. 165</td>
</tr>
<tr>
<td>VII. SPONTANEOUS AND STIMULATED SELF-ASSEMBLY OF SILICA NANOPARTICLES DERIVATIZED WITH ACYLPYRAZOLONES AND ACYLISOXAZOLONES ................ 172</td>
</tr>
<tr>
<td>7.1 Introduction ................................................................................ 172</td>
</tr>
<tr>
<td>7.2 Synthesis of silica nanoparticles derivatized with acylpyrazolones and acylisoxazolones ........................................... 174</td>
</tr>
<tr>
<td>7.3 Self-assembly of derivatized silica nanoparticles ..................... 176</td>
</tr>
<tr>
<td>7.4 Experimental procedures ........................................................... 203</td>
</tr>
<tr>
<td>7.5 Discussion ................................................................................ 205</td>
</tr>
</tbody>
</table>
CHAPTER

VIII. CONCLUSIONS AND FUTURE DIRECTIONS .............................. 207

8.1 Conclusions ................................................................. 207

8.2 Future Directions ......................................................... 211

APPENDICES................................................................................. 213

A. LC-MS.............................................................................. 213

B. GC-MS........................................................................... 216

C. 1HNMR AND 1H {13CNMR........................................ 246

D. UV-VIS & EMISSION..................................................... 272

E. IR.................................................................................. 275

BIBLIOGRAPHY ................................................................. 278

REFERENCES ...................................................................... 282
LIST OF TABLES

3.1 Physical properties of the parent pyrazolones ...................................................... 17
3.2 Pyrazolone acylation by using different base ...................................................... 20
3.3 Pyrazolone acylation by using different solvent .................................................. 21
3.4 Benzoylation of PMP by using different bases ...................................................... 22
3.5 Bond lengths and bond angles of HPMCP ............................................................ 24
3.6 Bond lengths and bond angles of the cyclic compound ........................................ 26
3.7 Bond lengths and bond angles of HPMVP ........................................................... 28
3.8 Bond lengths and bond angles of HPMPnP ............................................................ 29
3.9 HPMCP copper(II) complex .................................................................................. 31
4.1 Synthesis of amphiphilic 4-benzoyl-5-pyrazolones .............................................. 56
4.2 Synthesis of amphiphilic acylpyrazolones ............................................................ 58
4.3 Synthesis of amphiphilic acylpyrazolones with PMP ............................................ 59
5.1 Base effects ............................................................................................................. 63
5.2 Solvent effects for the acylation reaction .............................................................. 66
6.1 Self-assemblies of the different amphiphilic HPMBP ligands .............................. 90
6.2 Summary of HPLC separation and nanoscale self-assemblies of pyrazolone ligands ........................................................... 131
6.3 D, N and α for 2×10^{-5}M of HPMBP750 and HPMVP750 ................................. 137
LIST OF TABLES ---- Continued

6.4 logD vs log[HL] for the ligand HPMBP750 .................................................. 141
   a. Retention time at different ligand concentrations ............................ 141
   b. D values at different ligand concentration ................................... 141
   c. logD values at different ligand concentrations ............................. 142

6.5 logD vs log[HL]: pH=2.41 ................................................................. 143

6.6 Selectivity \( \alpha \) for adjacent lanthanide metal ions ......................... 144

6.7 logD vs pH for the ligand HPMBP750 at [HL]=5x10\(^{-6}\)M ..................... 144
   a. Calculations of logD vs pH, at [HL]=5x10\(^{-6}\)M .......................... 144
   b. D value at different pH ............................................................. 145
   c. logD vs pH .............................................................................. 145

6.8 Slope of logD vs pH: [HL]=5x10\(^{-6}\)M .............................................. 147

6.9 Selectivity \( \alpha \) for adjacent lanthanide metal ions ............................. 147

6.10 logD vs pH for the ligand HPMBP750 at [HL]=2x10\(^{-5}\)M ..................... 147
   a. Calculations of logD vs pH, at [HL]=2x10\(^{-5}\)M .......................... 148
   b. D value at different pH ............................................................. 148
   c. logD vs pH .............................................................................. 148

6.11 Slope of logD vs pH: [HL]=2x10\(^{-5}\)M .............................................. 150

6.12 Selectivity \( \alpha \) for adjacent lanthanide metal ions ............................. 150
LIST OF TABLES ----- Continued

6.13 logD vs log[HL] for the ligand HPMVP750 .......................................................... 151
   a. Retention time at different ligand concentrations ................................. 151
   b. D values at different ligand concentrations ........................................... 152
   c. logD vs log[HL] ..................................................................................... 153

6.14 logD vs log[HL]: pH=2.78 ................................................................. 155

6.15 Selectivity $\alpha$ at different ligand concentration ........................................ 156

6.16 logD vs pH at [HL]=5x10^{-6} for HPMVP750 ..................................................... 157
   a. Retention time for lanthanide metal ions at different pH values
      at a ligand concentration of 5x10^{-6}M ................................................. 157
   b. D values at different pH ......................................................................... 158
   c. logD values at different pH .................................................................... 158

6.17 Slope of logD vs pH: [HL]=5x10^{-6}M ....................................................... 160

6.18 Selectivity $\alpha$ at different pH ..................................................................... 160

6.19 logD vs pH at [HL]=2x10^{-5}M for HPMVP750 ............................................ 161
   a. Retention times at different pH at [HL]=2x10^{-5}M .............................. 161
   b. D values at different pH .......................................................................... 161
   c. logD vs pH ......................................................................................... 162

6.20 Slopes of logD vs pH: [HL]=2x10^{-5}M ....................................................... 164

6.21 Selectivities $\alpha$ at different pH at ligand concentration 2x10^{-5}M .......... 164
LIST OF TABLES ----- Continued

6.22 Slope of logD vs pH with different equilibrium time .......................... 168
6.23 logK_ex for lanthanide metal ions with different equilibrium time .......... 170
7.1 SiO_2-HPMBP self-assemblies at different ligand concentrations ............. 180
7.2 SiO_2-HPPBP self-assemblies at different ligand concentrations ............. 184
7.3 SiO_2-HPMVP self-assemblies at different ligand concentration ............... 187
7.4 SiO_2-HMPBP self-assemblies at different ligand concentrations ............. 190
7.5 Self-assemblies of SiO_2-HPBI at different ligand concentrations .......... 193
7.6 Stimulated self-assemblies of chloromethyl acylpyrazolones and acylisoxazolones ................................................................. 196
7.7 Metal ion facilitated self-assembly of SiO_2-HL systems ....................... 202
LIST OF FIGURES

1.1 Phosphonic acids and phosphinic acids as extractants ........................................... 3
1.2 Acylpyrazolones and acylisoxazolones ................................................................. 5
1.3 Distribution of papers on acylpyrazolones and acylisoxazolones for the past 30 years ………………… 7
2.1 Structure of the parent pyrazolone ................................................................. 9
2.2 Structure of the acylpyrazolones ........................................................................... 9
2.3 Structure of amphiphilic acyl pyrazolone .......................................................... 10
2.4 Structure of the parent isoxazolone ............................................................... 10
2.5 Structure of the acylisoxazolone ...................................................................... 10
2.6 Structure of amphiphilic acyl pyrazolone ......................................................... 11
2.7 Arsenazo III .................................................................................................. 14
3.1 Isomers of the acylpyrazolones ........................................................................ 16
3.2 Structures of parent pyrazolones ..................................................................... 17
3.3 Synthesized acylpyrazolones ........................................................................... 18
3.4 Isomers of the acylpyrazolones ...................................................................... 23
3.5 Crystal structure of 1-phenyl-3-methyl-4-crotonoyl-5pyrazol-one ...................... 24
3.6 HPMC molecules packing in the crystal .......................................................... 24
3.7 Structure of HPMC ......................................................................................... 25
3.8 Crystal structure of the cyclic compound and the molecules packing in the crystal ........................................... 26
3.9 Crystal structure of 1-phenyl-3-methyl-4-valeryl-5-pyrazolone and the molecules packing in the crystal ........................................ 27

3.10 Chemical structure of HPMVP .......................................................... 29

3.11 Crystal structure of HPMPnP and the molecules packing in the crystal .......... 29

3.12 Chemical structure of HPMPnP .......................................................... 30

3.13 Crystal structure of HPMCP copper(II) complex ................................. 31

3.14 HPMUP copper complex ................................................................. 33

4.1 Possible polyethylene glycol derivatives .............................................. 45

4.2 HPLC separation of lanthanide metal ions with HMP750VP ..................... 46

4.3 GC-MS spectrum of 1-phenyl-3-methyl-4-(4’-chloromethyl)benzoyl -5- pyrazolone ................................................................. 48

4.4 Surfactants and related ligand derivatives ............................................. 48

4.5 Isomers of the acylpyrazolone ............................................................ 49

4.6 Structure comparison ............................................................................ 51

4.7 Changing of R” .................................................................................... 51

4.8 Changing of R’ .................................................................................... 52

4.9 Changing of R”’ ................................................................................... 52

5.1 Comparison of the isomers of acylpyrazolones and acylisoaxazolones ....... 60

5.2 Parent isoaxazolones ............................................................................ 61
LIST OF FIGURES ---- Continued

5.3 Structures of synthesized acylisoxazolones ......................................................... 62
5.4 GC-MS data of the acylation of pyrazolone ........................................................ 64
5.5 GC-MS data of the acylation of isoxazolone ....................................................... 65
5.6 Synthesized amphiphilic acylisoxazolones .......................................................... 67
6.1 HPLC instrument ................................................................................................. 72
6.2 Alltech HPLC Column Model 1666 Slurry Packer ................................................ 75
6.3 Parent HPMBP and its amphiphilic derivatives ..................................................... 76
6.4 HPLC separation with HPMBPBrj ........................................................................ 77
6.5 HPLC separation with HPMBPBrj ........................................................................ 77
6.6 HPLC separation with HPMBPBrj ........................................................................ 78
6.7 HPLC separation with HPMBP2000 ................................................................. 78
6.8 HPLC separation with HPMBP2000 ................................................................. 79
6.9 HPLC separation with HPMBP2000 ................................................................. 79
6.10 HPLC separation with HPMBP750 ................................................................. 80
6.11 HPLC separation with HPMBP750 ................................................................. 80
6.12 HPMBP and HPMBP2000 ................................................................................. 81
6.13 HPLC separation with HPMBP dissolved in PEG2000 .................................... 82
6.14 HPLC separation with HPMBP2000 ................................................................. 82
6.15 Surfactants employed ...................................................................................... 84
LIST OF FIGURES ----- Continued

6.16 HPLC chromatograms of PEG family ligands ........................................... 85  
   a. HPLC separation with HPMBPBrij ......................................................... 85  
   b. HPLC separation with HPMBP2000 ...................................................... 85  
   c. HPLC separation with HPMBP750 ....................................................... 86  
   d. HPLC separation with HPMBP550 ....................................................... 86  
   e. HPLC separation with HPMBPTriton .................................................... 87  

6.17 TEM images of HPMBPBrij ................................................................. 87  

6.18 TEM images of HPMBP2000 ................................................................. 88  

6.19 TEM images of HPMBP750 ................................................................. 88  

6.20 TEM images of HPMBP550 ................................................................. 88  

6.21 TEM images of HPMBPTriton ............................................................... 89  

6.22 Ligand self-assemblies in aqueous solution ............................................ 90  

6.23 Formation of vesicles .......................................................................... 90  

6.24 Ligands with different substituents in 1 position (R’ group) ....................... 93  

6.25 HPLC separation with HPMBP750 ....................................................... 94  

6.26 HPLC separation with HMOPMBP750 .................................................. 95  

6.27 HPLC separation with HMPMBP750 .................................................... 95  

6.28 HPLC separation with HMMBP750 ...................................................... 96  

6.29 HPLC separation with HtBuMBP750 ................................................... 97
LIST OF FIGURES ---- Continued

6.30 HPLC separation with HBnMBP750 ................................................................. 98
6.31 HPLC separation with HFPMBP750 ............................................................... 99
6.32 Influence with electron donating groups in 1 position ................................... 100
6.33 Influence with electron withdrawing groups in the
   \textit{para} position of 1-phenyl ring ................................................................. 101
6.34 Influence with electron donating groups in the
   \textit{para} position of 1-phenyl ring ................................................................. 102
6.35 Different substituent in the 3 position of the acylpyrazolone ......................... 103
6.36 HPLC separation with HPPBP750 ................................................................. 103
6.37 HPLC separation with HPNPBP750 ............................................................... 104
6.38 HPLC separation with HPEBP750 ................................................................. 105
6.39 HPLC separation with HPPrBP750 ............................................................... 106
6.40 Available compounds with different R''' group ........................................... 107
6.41 HPLC separation of with HPMB3P750 .......................................................... 108
   a. Ligand concentration: 5\times 10^{-5} \text{ M}, pH: 2.60 ....................................... 108
   b. Ligand concentration: 5\times 10^{-5} \text{ M}, pH: 2.60 ....................................... 108
6.42 HPLC separation with HPMAP750 at different pH .......................................... 109
   a. Ligand concentration: 5\times 10^{-6} \text{ M}, pH=2.29 ....................................... 109
   b. Ligand concentration: 5\times 10^{-6} \text{ M}, pH=2.38 ....................................... 109
6.43 HPLC separation with HPMPOP750 ................................................................. 110
   a. Ligand concentration: $5 \times 10^{-6}$ M, pH=4.27 ........................................ 110
   b. Ligand concentration: $1 \times 10^{-5}$ M, pH=3.28 ........................................ 110
6.44 HPLC separation with HPMBOP750 ................................................................. 111
   a. Ligand concentration: $5 \times 10^{-6}$ M, pH=3.25 ........................................ 111
   b. Ligand concentration: $5 \times 10^{-6}$ M, pH=2.94 ........................................ 111
6.45 HPLC separation with HPMVP750 at different pH ........................................... 112
   a. Ligand concentration: $5 \times 10^{-6}$ M, pH=2.63 ........................................ 112
   b. Ligand concentration: $5 \times 10^{-6}$ M, pH=2.88 ........................................ 112
6.46 TEM images of HPMBP750 ................................................................. 114
6.47 TEM images of HPMVP750 ................................................................. 115
6.48 TEM images of HPMAP750 ................................................................. 115
6.49 TEM images of HPMPOP750 ................................................................. 116
6.50 TEM images of HPMBOP750 ................................................................. 116
6.51 HPMBP750 self-assembly with the presence of MgCl$_2$ ................................. 118
   a. Ligand concentration: $5 \times 10^{-3}$ M, [MgCl$_2$]: $5 \times 10^{-4}$ M (after one week) ....... 118
   b. Ligand concentration: $5 \times 10^{-3}$ M, [MgCl$_2$]: $5 \times 10^{-3}$ M .......................... 118
   c. Ligand concentration: $5 \times 10^{-3}$ M, [MgCl$_2$]: $5 \times 10^{-3}$ M (after one week) ....... 118
6.52 HPMVP750 self-assembly with the presence of MgCl₂ ........................... 119
a. Ligand concentration: 5x10⁻³ M, [MgCl₂]: 5x10⁻⁴ M ................................ 119
b. Ligand concentration: 5x10⁻³ M, [MgCl₂]: 5x10⁻⁴ M (after one week) .......... 119
c. Ligand concentration: 5x10⁻³ M, [MgCl₂]: 5x10⁻³ M .......................... 119
d. Ligand concentration: 5x10⁻³ M, [MgCl₂]: 5x10⁻³ M (after one week) ....... 120
6.53 TEM images of HPMBP750 + Sm³⁺ ......................................................... 120
6.54 TEM images of HPMBP2000 + Sm³⁺ ....................................................... 121
6.55 TEM images of HPMBPBrij + Sm³⁺ ......................................................... 121
6.56 TEM images of HPMBP550 + Sm³⁺ ......................................................... 121
6.57 TEM images of HPMVP750 + Sm³⁺ ......................................................... 122
6.58 TEM images of HPMBP750 + C₁₈ silica gel .......................................... 123
6.59 TEM images of HPMBP750 + C₁₈ silica gel + Sm³⁺ .............................. 123
6.60 TEM images of HPMVP750 + C₁₈ silica gel .......................................... 123
6.61 TEM images of HPMVP750 + C₁₈ silica gel + Sm³⁺ .............................. 124
6.62 HPLC separation with HPMBP+Brij35p ............................................... 126
6.63 HPLC separation with HPMBP+PEG2000 ......................................... 126
6.64 HPLC separation with HPMBP+PEG750 ......................................... 127
6.65 HPLC separation with HPMBP+PEG550 ......................................... 127
6.66 HPLC separation with HPMVP+PEG750 ......................................... 128
LIST OF FIGURES ----- Continued

6.67 TEM images of HPMBP+PEG550 ......................................................... 129
6.68 TEM images of HPMBP+PEG750 ......................................................... 130
6.69 TEM images of HPMVP+PEG750 ......................................................... 130
6.70 Lanthanide metal ion separation mechanism ..................................... 138
6.71 logD vs log[HL] for La\(^{3+}\) ................................................................. 142
6.72 logD vs log[HL] for Ce\(^{3+}\) ................................................................. 142
6.73 logD vs log[HL] for Nd\(^{3+}\) ................................................................. 142
6.74 logD vs log[HL] for Sm\(^{3+}\) ................................................................. 142
6.75 logD vs log[HL] for Ho\(^{3+}\) ................................................................. 143
6.76 logD vs pH for La\(^{3+}\) ................................................................. 146
6.77 logD vs pH for Ce\(^{3+}\) ................................................................. 146
6.78 logD vs pH for Nd\(^{3+}\) ................................................................. 146
6.79 logD vs pH for Sm\(^{3+}\) ................................................................. 146
6.80 logD vs pH for Ho\(^{3+}\) ................................................................. 146
6.81 logD vs pH for La\(^{3+}\) ................................................................. 149
6.82 logD vs pH for Ce\(^{3+}\) ................................................................. 149
6.83 logD vs pH for Nd\(^{3+}\) ................................................................. 149
6.84 logD vs pH for Sm\(^{3+}\) ................................................................. 149
6.85 logD vs pH for Ho\(^{3+}\) ................................................................. 149
6.86 logD vs log[HL] for La$^{3+}$ ................................................................. 154
6.87 logD vs log[HL] for Ce$^{3+}$ ................................................................. 154
6.88 logD vs log[HL] for Pr$^{3+}$ ................................................................. 154
6.89 logD vs log[HL] for Nd$^{3+}$ ................................................................. 154
6.90 logD vs log[HL] for Sm$^{3+}$ ................................................................. 154
6.91 logD vs log[HL] for Eu$^{3+}$ ................................................................. 154
6.92 logD vs log[HL] for Ho$^{3+}$ ................................................................. 154
6.93 logD vs pH for La$^{3+}$ ....................................................................... 158
6.94 logD vs pH for Ce$^{3+}$ ....................................................................... 158
6.95 logD vs pH for Pr$^{3+}$ ....................................................................... 159
6.96 logD vs pH for Nd$^{3+}$ ....................................................................... 159
6.97 logD vs pH for Sm$^{3+}$ ....................................................................... 159
6.98 logD vs pH for Eu$^{3+}$ ....................................................................... 159
6.99 logD vs pH for Ho$^{3+}$ ....................................................................... 159
6.100 logD vs pH for La$^{3+}$ ..................................................................... 162
6.101 logD vs pH for Ce$^{3+}$ ..................................................................... 162
6.102 logD vs pH for Pr$^{3+}$ ..................................................................... 162
6.103 logD vs pH for Nd$^{3+}$ ..................................................................... 162
6.104 logD vs pH for Sm$^{3+}$ ..................................................................... 163
6.105 logD vs pH for Eu$^{3+}$ ................................................................. 163
6.106 logD vs pH for Ho$^{3+}$ ................................................................. 163
6.107 Equilibration of the C$_{18}$ stationary phase with HPMVP750, pH=2.51 ........ 167
6.108 Equilibration of the C$_{18}$ stationary phase with HPMVP750, pH=2.65 ........ 167
6.109 Slope vs time for La$^{3+}$ .............................................................. 168
6.110 Slope vs time for Ce$^{3+}$ .............................................................. 168
6.111 Slope vs time for Pr$^{3+}$ .............................................................. 169
6.112 Slope vs time for Nd$^{3+}$ .............................................................. 169
6.113 Slope vs time for Sm$^{3+}$ .............................................................. 169
6.114 Slope vs time for Eu$^{3+}$ .............................................................. 169
6.115 Slope vs time for Ho$^{3+}$ .............................................................. 168
6.116 The factors that determine the HPLC separation .................................... 171
7.1 Structure of silica nanoparticle .......................................................... 174
7.2 TEM images of silica nanoparticles ....................................................... 175
7.3 Derivatization of SiO$_2$ nanoparticle with acylpyrazolones or acylisoxazolones .............................................................. 175
7.4 Isomers of acylpyrazolone ................................................................. 176
7.5 Acylpyrazolone derivatized SiO$_2$ nanoparticles ...................................... 177
7.6 Acylisoxazolone derivatized SiO$_2$ nanoparticles ...................................... 177
LIST OF FIGURES ----- Continued

7.7 Structure of SiO$_2$-HPMBP ................................................................. 177
7.8 TEM images of SiO$_2$-HPMBP at 1 : 1 ratio ........................................ 178
7.9 TEM images of SiO$_2$-HPMBP at 2 : 1 ratio ........................................ 178
7.10 TEM images of SiO$_2$-HPMBP at 5 : 1 ratio ........................................ 179
7.11 TEM images of SiO$_2$-HPMBP at 10 : 1 ratio ..................................... 179
7.12 Structure of SiO$_2$-HPPBP ................................................................. 180
7.13 TEM images of SiO$_2$-HPPBP at 4 : 1 ratio ........................................ 181
7.14 TEM images of SiO$_2$-HPPBP at 5 : 1 ratio ........................................ 181
7.15 Self-assemblies of 1µm polystyrene particles [77] ............................. 181
7.16 TEM images of SiO$_2$-HPPBP at 6 : 1 ratio ........................................ 182
7.17 TEM images of SiO$_2$-HPPBP at 7 : 1 ratio ........................................ 182
7.18 TEM images of SiO$_2$-HPPBP at 10 : 1 ratio ....................................... 182
7.19 Structure of SiO$_2$-HPMVP ................................................................. 185
7.20 TEM images of SiO$_2$-HPMVP at 1 : 1 ratio ........................................ 185
7.21 TEM images of SiO$_2$-HPMVP at 5 : 1 ratio ........................................ 186
7.22 TEM images of SiO$_2$-HPMVP at 10 : 1 ratio ..................................... 186
7.23 Structure of SiO$_2$-HMPBP ................................................................. 187
7.24 TEM images of SiO$_2$-HMPBP at 1 : 1 ratio ........................................ 188
7.25 TEM images of SiO$_2$-HMPBP at 2 : 1 ratio ........................................ 188
LIST OF FIGURES ----- Continued

7.26 TEM images of SiO$_2$-HMPBP at 5 : 1 ratio ........................................... 189
7.27 TEM images of SiO$_2$-HMPBP at 10 : 1 ratio ........................................... 189
7.28 Structure of SiO$_2$-HPBI ................................................................. 190
7.29 TEM images of SiO$_2$-HPBI at 1 : 1 ratio ........................................... 191
7.30 TEM images of SiO$_2$-HPBI at 2 : 1 ratio ........................................... 191
7.31 TEM images of SiO$_2$-HPBI at 5 : 1 ratio ........................................... 192
7.32 Silica nanoparticles before and after reaction with NaHCO$_3$ in dry THF ........ 194
7.33 TEM images of HPMCMBP ................................................................. 194
7.34 TEM images of HPPCMBP ................................................................. 195
7.35 TEM images of HPCMBI ................................................................. 195
7.36 TEM images of SiO$_2$-HPPBP + Cu$^{2+}$ ........................................... 198
7.37 TEM images of SiO$_2$-HPPBP + Sm$^{3+}$ ........................................... 198
7.38 TEM images of SiO$_2$-HPMBP + Cu$^{2+}$ ........................................... 199
7.39 TEM images of HPMVP-SiO$_2$ + Cu$^{2+}$ ........................................... 199
7.40 TEM images of HMPBP-SiO$_2$ + Cu$^{2+}$ ........................................... 199
7.41 TEM images of SiO$_2$-HPBI + Cu$^{2+}$ ........................................... 200
### LIST OF SCHEMES

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Synthesis of the pyrazolones and acylpyrazolones</td>
<td>15</td>
</tr>
<tr>
<td>3.2</td>
<td>Acylation of pyrazolones</td>
<td>19</td>
</tr>
<tr>
<td>3.3</td>
<td>Benzylation of PMP</td>
<td>22</td>
</tr>
<tr>
<td>3.4</td>
<td>Cyclization of HPMCP</td>
<td>25</td>
</tr>
<tr>
<td>4.1</td>
<td>Synthesis of amphiphilic acylpyrazolones</td>
<td>43</td>
</tr>
<tr>
<td>4.2</td>
<td>Synthetic method for family 2 in Figure 4.1</td>
<td>46</td>
</tr>
<tr>
<td>4.3</td>
<td>Synthesis of family 3 ligands in Figure 4.1</td>
<td>47</td>
</tr>
<tr>
<td>4.4</td>
<td>Synthesis of 1-phenyl-3-R''-4-(4'-methylPEG750)-benzoyl-5-pyrazolone</td>
<td>53</td>
</tr>
<tr>
<td>4.5</td>
<td>Synthesis of 1-R’-3-methyl-4-(4'-methylPEG750)-benzoyl-5-pyrazolone</td>
<td>54</td>
</tr>
<tr>
<td>4.6</td>
<td>Synthesis of 1-phenyl-3-methyl-4-R”’-5-pyrazolone</td>
<td>54</td>
</tr>
<tr>
<td>5.1</td>
<td>Synthetic approach to acylisoxazolone</td>
<td>61</td>
</tr>
<tr>
<td>5.2</td>
<td>Synthesis of acylisoxazolone</td>
<td>63</td>
</tr>
<tr>
<td>5.3</td>
<td>Synthesis of acylisoxazolones</td>
<td>65</td>
</tr>
<tr>
<td>5.4</td>
<td>Synthesis of amphiphilic ligands</td>
<td>67</td>
</tr>
</tbody>
</table>
CHAPTER I

INTRODUCTION

1.1 Why is the separation of lanthanides important?

The lanthanide elements are usually defined as those in which the 4f-orbitals are progressively filled located at bottom of periodic table below transition metals; the definition includes the elements Ce (Cerium) to Lu (Lutetium). The element La (lanthanum) is the prototype of the series and for practical purpose is usually included.

Lanthanide contraction: There is a steady decrease in metallic and ionic radii of the lanthanides as the series is traversed from La to Lu. The reason for this has been explained as an electrostatic effect due to the imperfect screening by the f-electrons as the nuclear charge is increased [1]. Because of lanthanide contraction, the middle and heavy lanthanides have very close chemical properties so that the separation of lanthanides is still a challenging problem.

The investigation of methods for the separation of lanthanides dates back to the Manhattan Project during World War II. Nuclear wastes contain many metals including radioactive lanthanides. Removal of radioactive lanthanides from nuclear wastes and converting medium and high level wastes to low level wastes is more manageable and less expensive to dispose. The lanthanide metals are also widely used in many fields [2],
such as: 1) catalytic converters; for example: CeO$_2$ is used as ceramic support for the platinum metal components of the catalyst or used as an oxygen reservoir due to the ability to exist as Ce$_2$O$_3$ under reduction conditions and CeO$_2$ under oxidizing conditions; 2) electronic applications; for example: Eu phosphors are used in CRT TV screens and Nd-YAG lasers; 3) pigments; and 4) lanthanide complexes are used as catalysts in synthetic chemistry, so the recycling of lanthanides from wastes and separation of each individual metal ion is valuable and important.

1.2 Current approaches to lanthanide separation.

The separation of metal ions, especially closely related ones such as the trivalent lanthanides, by single stage methods poses daunting challenges even to the most selective of extractants [3]. Therefore, the use of multistage methods is necessary for their separation. Multistage methods consist of solid-liquid and liquid-liquid partition, with the former involving solid supports such as silica and cross-linked organic polymers, derivatized, coated, or impregnated with a ligand which serves to separate metal ions by complexation in a conventional liquid chromatographic mode. The latter involves two bulk liquid phases with the extractant dissolved in the organic phase [4]. Current approaches are derived from these two basic methods.

a. **Solvent extraction:** Solvent extraction is the most widely used method for lanthanides separation. The success of solvent extraction in the production of high
purity metals for nuclear defense and energy programs, together with the development of a variety of selective metal ion extractants, has led to the widespread application of solvent extraction in hydrometallurgical separations and in nuclear processing and waste treatment applications [5]. The advantage of this method is that the large amount of metals can be isolated in high purity. The disadvantages of this method include: 1) high cost; 2) complicated separation processes; and 3) acidic high level liquid waste. In the rare earth industry, acidic phosphonic acids and phosphinic acids are major extractants for the separation of lanthanides. The structures are shown in Figure 1.1.

Figure 1.1 Phosphonic acids and phosphinic acids as extractants.

\[
\begin{align*}
\text{phosphoric acid} & : \quad R \text{OPO}_3\text{OH} \\
\text{phosphonic acid} & : \quad R \text{OPO}_2\text{OH} \\
\text{phosphinic acid} & : \quad R \text{P} = \text{O} \text{OH}
\end{align*}
\]

R: alkyl group

b. **Membrane-based [6] and supercritical fluid [7]** processes: for metal ions separation are newer developments and are the subjects of intense research interest. Numerous applications of these techniques have been proposed and many are likely to receive considerable attention in the future.

c. **Chromatographic methods**: Methods such as centrifugal partition chromatography, countercurrent chromatography and high performance liquid chromatography are being investigated [8,9]. The advantages of these methods include: 1) small
instruments; 2) ease of operation; and 3) low cost. The disadvantage of these methods is that only small amounts of metals can be separated. So these methods are widely used in lab scale research.

In this thesis, high performance liquid chromatography (HPLC) is the method used for lanthanides separation. On lab scale, most reported work was focused on the extraction by using different ligands; there are very few reports that use HPLC [9,10] to perform the separation of lanthanides because well-known efficient ligands used in solvent extraction cannot dissolve in water and most of these ligands are effective only at low or high pH values which is not suitable for silica supports. Our research focus has been to identify a family of ligands that are soluble in the aqueous phase that can provide efficient separation of trivalent lanthanides in the pH range 2-3 where metal ions do not form hydroxide species.

1.3 Central hypothesis.

Nanoscale structures often have unique properties that are different from individual atoms, molecules and bulk structures. We hypothesized that organized nanoscale molecular self-assemblies are capable of providing excellent metal ion selectivities, especially for closely related ones, such as the trivalent lanthanide metal ions. Our approach to test the central hypothesis is to employ amphiphilic ligands that spontaneously self-assemble into nanoscale structures in the aqueous phase and exploit
such structures for the recognition of lanthanide metal ions. This research work represents the first systematic approach to the recognition of trivalent lanthanide metal ions using nanoscale self-assemblies.

The ligands that have been employed in our studies are amphiphilic acylpyrazolones and acylisoxazolones. The structures of the acylpyrazolones and acylisoxazolones are shown in Figure 1.2 [9, 10]. For the acylpyrazolones and acylisoxazolones, R’, R” and R’” can be alkyl, alkenyl or aromatic groups. In the case of amphiphilic acylpyrazolones and acylisoxazolones, R’” is alkyl or aromatic with a given number of oxyethylene groups as described in Chapters III, IV and V.

**Figure 1.2 Acylpyrazolones and acylisoxazolones.**

<table>
<thead>
<tr>
<th>Acylpyrazolones</th>
<th>Acylisoxazolones</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td><img src="image2.png" alt="Structure" /></td>
</tr>
<tr>
<td>pKa: 4.0</td>
<td>pKa: 1~2</td>
</tr>
</tbody>
</table>

Important ligands properties that make them excellent for the separation of trivalent lanthanides are: 1) low pKₐ values that allow complexation under acidic conditions [9, 10]; 2) high stability constants for lanthanide metal ions that allow the selectivity for lanthanides [9, 10]; 3) solubility of amphiphilic ligands in the aqueous phase makes them suitable for the HPLC separation.
1.4 Research to substantiate the central hypothesis.

The objectives of this research to substantiate the central hypothesis are: 1) design of nanoscale self-assembling acylpyrazolone ligands; 2) synthesize self-assembling ligands; 3) characterize the nature of their self-assemblies in the aqueous phase; 4) investigate their efficacies for efficient baseline separation of trivalent lanthanides; 5) elucidate the mechanism of the recognition of lanthanides by amphiphilic ligands and 6) discern the role of this nanoscale self-assemblies in metal ion recognition.

It is evident from the structures in Figure 1.2 that:

a. A synthetic route can be devised to obtain the ligands with a variety of substituent groups R’, R” and R”’.

b. Hydrophilic amphiphilic ligands can be obtained by derivatization in the 4 position of the acylpyrazolone and acylisoxazolone structures with oxyethylene groups.

c. The ligand structures can be systematically varied to discern their influence on the structures of nanoscale self-assemblies.

d. The self-assemblies can also be generated on other substrates, such as silica nanoparticle and titanium nanoparticles to obtain novel nanoscale structures that can be employed for lanthanide metal ion recognition.
1.5 Prior research on acylpyrazolones and acylisoxazolones.

Acylpyrazolones have been previously investigated for the separation of transition and lanthanide metal ions [11]. They have been mainly used by solvent extraction to separate Fe(III) [12], Cu(II), Zn(II), Co(II) and Ni(II); lanthanide [13] and actinide metal ions [14]. A literature search was performed by Scifinder Scholar and revealed the distribution of papers for the past 30 years (Figure 1.3).

**Figure 1.3 Distribution of papers on acylpyrazolones and acylisoxazolones for the past 30 years.**

![Number of papers on acylpyrazolones and acylisoxazolones published in the last 30 years](image)

While acylpyrazolone ligands have been used in the past for lanthanide separation by solvent extraction, their selectivity has been only modest at best [8, 9]. As shown in Figure 1.3, the number of papers published for the acylpyrazolone ligands during the past 30 years is about 200. This offers opportunities for developing this family of ligands for nanoscale self-assemblies for metal ions recognition.
CHAPTER II

EXPERIMENTAL METHODS

General synthetic methods for acylpyrazolones and acylisoxazolones, their nomenclature and their characterization methods are described in this Chapter.

2.1 Nomenclature.

All ligands are denoted by abbreviations for convenience. The pyrazolone (Figure 2.1) is denoted by P and the isoxazolone (Figure 2.4) is denoted by I; the acylpyrazolone and acylisoxazolone with an ionizable proton start with H and for all compounds, the letters preceding P and I indicate the substituents in the 1, 3 and 4 positions. Abbreviations are listed below:

P: pyrazolone; Bn: benzyl;
I: isoxazolone; MOP: 4-methoxyphenyl;
M: methyl; MP: 4-methylphenyl
E: ethyl; tBu: tert-butyl;
Pr: propyl; V: valeryl;
Pn: pentenoyl; CM: chloromethyl;
B: benzoyl; 550: polyethylene glycol 550; (see
P: phenyl; Chapter IV)
NP: nitrophenyl; 750: polyethylene glycol 750; (see
A: acetyl; Chapter IV)
C: crotonyl; Brij: Brij35p; (see Chapter IV)
D: decanoyl; Tr: triton X-100; (see Chapter IV)
U: undecenoyl;

For example: The compound 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone is denoted by HPMBP and the numbering is indicated in Figure 2.1
2.2 Synthetic approaches.

(a) Synthesis of parent pyrazolones.

Figure 2.1 Structure of the parent pyrazolone.

This parent pyrazolone with different R’ and R” groups has been synthesized by using β-ketoesters (with R” group) and hydrazines (with R’ group) under reflux condition in ethanol solvent for 48-72 hours. After reaction, the precipitate was recrystallized from ethanol to obtain the pure compound. This is described in detail in Chapter III.

(b) Synthesis of acylpyrazolones.

Figure 2.2 Structure of acylpyrazolones.

Acylpyrazolones have been synthesized in high yields by using equal molar concentration of the parent pyrazolone and an acyl chloride in anhydrous THF in the presence of a base (triethyl amine, calcium hydroxide, sodium methoxide, etc.) as described in Chapter III. Acylpyrazolones with a CH₂Cl group in the 4 position were also synthesized through this approach and are described in Chapter III.

(c) Synthesis of amphiphilic acylpyrazolones.
First, the acylpyrazolone with CH$_2$Cl group on R’’’ was synthesized and isolated. The target amphiphilic acylpyrazolones have been obtained by reacting this intermediate with the sodium salt of polyethylene glycol in anhydrous THF under reflux condition for 8-12 hours. This is described in detail in **Chapter IV**.

(d) Synthesis of the parent isoxazolone.

**Figure 2.4 Structure of the parent isoxazolone.**

Isoxazolone with different R’’ groups have been synthesized by using a β-ketoester (with R’’ group) and hydroxyl amine hydrochloride under reflux condition in ethanol for 48-72 hours. The crude reaction mixture was recrystallized from ethanol to obtain the pure compound. This is described in detail in **Chapter V**.

(e) Synthesis of acyl isoxazolones.

**Figure 2.5 Structure of the acylisoxazolone.**

Acylisoxazolones have been synthesized in high yields by using an equimolar
concentration of the parent isoxazolone and an acyl chloride in anhydrous THF in the presence of a base (triethyl amine, calcium hydroxide, sodium methoxide, etc.) as described in Chapter III. The acylisoxazolones with a CH₂Cl group in the 4 position are also synthesized through this approach and described in Chapter IV.

(f) Synthesis of amphiphilic acyl isoxazolones.

Figure 2.6 Structure of amphiphilic acylpyrazolone.

\[
\begin{align*}
&\text{O} \\
&\text{N} \\
&\text{R''} \\
&\text{O} \\
&\text{OH} \\
&\text{R'''} \text{OCH}₂\text{CH}_₂ \text{R''''} \\
&\text{OH}
\end{align*}
\]

The acyl isoxazolone with a CH₂Cl group on the R'''' group in the 4 position was synthesized and isolated. The target amphiphilic acyl isoxazolone have been obtained by reacting this compound with the sodium salt of polyethylene in anhydrous THF under reflux condition for 8-12 hours. This is also described in detail in Chapter V.

2.3 Characterization.

All the parent pyrazolones, isoxazolones, acylpyrazolones and acyl isoxazolones were characterized by GC-MS, \(^1\)H-NMR and \(^1\)H\(^{13}\)C-NMR. The amphiphilic acylpyrazolones are mixtures due to the parent polyethylene glycols being mixtures differing in the number of oxyethylene -(OCH₂CH₂)- group. Selected amphiphilic pyrazolones were analyzed by LC-MS to determine their molecular weight distribution. In addition, they were also characterized by their UV-VIS spectra. NMR characterization
is difficult for this family of ligands as the -OCH$_2$CH$_2$- protons essentially dominate the entire spectra. The self-assemblies of amphiphilic acylpyrazolones and acylisoxazolones have been characterized by transmission electronic microscopy (TEM). The metal ion recognition efficacies of all the ligands have been characterized by high performance liquid chromatography (HPLC). X-ray structures of acylpyrazolones that could be obtained as single crystals have been determined.

The thermometer used for melting point determination was not calibrated. However, the melting point of pure naphthalene was determined to be 81 °C, which agrees with the literature value 80.3 °C [15].

**GC-MS: HP 6890 SERIES GC SYSTEM.**

**HP 5973 MASS SELECTIVE DETECTOR.**

Column: 5% diphenyl and 95% dimethyl siloxane copolymer.

ID/dimensions: BPX5/30 m x 0.25 mm.

Carrying gas: Helium.

Flow rate: 2.0 mL/min;

Front Inlet temperature: 250 °C.

Oven temperature: initial: 60 °C; end: 300 °C; heating rate: 20 °C/min.

**NMR: JEOL JNM-ECP400 FT NMR SYSTEM.**

**Eclipse 400 FT-NMR Spectrometer with Delta NMR Software.**

All NMR experiments were carried out in chloroform-$d$ or DMSO-$d_6$.

**X-ray single crystal: ENRAF NONIUS DELFT, DIFFRACTIS 586 X-ray system.**
**Refine:** SHELXL-97

George M. Sheldrick Release 97-2

**Solution:** Sir92 Altomare, A; Casecarano, G.; Giacovazzo, C.; Gualdiard, A [16].

**TEM images**

The TEM images of all the aqueous solution samples have been collected by:

**JEOL JEM1230 Transmission Electron Microscope**

Accelerating Voltage = 80 KV.

Gatan digital camera & digital micrograph software.

Samples on formvar membrane covered copper grids.

**HPLC determination.**

HPLC data were collected by Perkin Elmer Series 200, with UV-VIS detector.

Stationary phase: 3 µm, C$_{18}$ silica gel.

Buffer solutions: chloroacetic acid buffer of ionic strength 0.01 for pH range 2-3, or formic acid buffer of ionic strength 0.01 for pH range 3-4[17].

Total ionic strength: 0.1. (adjusted with NaClO$_4$)

Sample loop size: 20 µl.


Mobile phase: Ligand dissolved in aqueous solution at the desired pH; ionic strength=0.1, adjusted with NaClO$_4$.

Flow rate: 1 mL/min;

Metal ion detection: postcolumn derivatization of the metal ion with Arsenazo III
(Figure 2.7) at pH 3.45; detection wavelength 656 nm; indicator flow rate 0.5 mL/min;

**Figure 2.7 Arsenazo III.**

![Figure 2.7 Arsenazo III.](image)

**LC-MS determination.**

The LC-MS data were collected on a Shimadzu LCMS-2010EV High-Performance Liquid Chromatograph/Mass Spectrometer.

Software: LCMS Solution.

Stationary phase: 5 µm, C\textsubscript{18} silica gel.

Sample introduction: Auto injection.

Mobile phase: H\textsubscript{2}O/MeOH (gradient).

Flow rate: 0.6 mL/min.

Ionization: APCI (atmospheric pressure chemical ionization).

**UV-VIS spectrum: Perkin Elmer UV-VIS Spectrometer Lambda 20.**

**Emission Spectrum: Perkin Elmer Luminescence Spectrometer LS50B.**

**IR: BRUKER, EQUINOX 55.**
SYNTHESIS OF PYRAZOLONES AND ACYLPYRAZOLONES

Synthetic methods for the pyrazolones and acylpyrazolones have been reported in the literature [18, 19]. The two key steps are shown in Scheme 3.1 below:

Scheme 3.1 Synthesis of the pyrazolones and acylpyrazolones.

By this method, many pyrazolones and acylpyrazolones have been successfully synthesized and characterized and are listed in Figures 3.1 and 3.2 and Tables 3.1-3.3. Pyrazolones in Figure 3.1 which have been synthesized for the first time in this research are denoted “New” and the others have been previously reported in the literature [20-23].

3.1 Synthesis of the parent pyrazolones.

Most of these parent pyrazolones have been used to synthesize herbicides [22, 23]. Acylpyrazolones have not been extensively employed in metal ion separation [24]. In order to investigate the relationship between metal ion recognition efficacies and the structure of acylpyrazolone ligands, many parent pyrazolones with different R’ and R” substituents have been synthesized and characterized for this research.
Acylpyrazolone shown in Figure 3.1 clearly can have a keto and enol structure and in the latter the –OH group is either on the pyrazolone ring or on the substituent in the 4 position.

**Figure 3.1 Isomers of the acylpyrazolones.**

The extent of keton-enol tautomerization and the position of the –OH group will be influenced by resonance, inductive and steric effects \[10\]. These effects will be influenced by substituents (electron donating or withdrawing) in the 1, 3 and 4 positions. It is likely that extent of keto-enol tautomerization and the position of the –OH group would influence lanthanide metal ion chelation and efficacies of metal ion recognition and separation of the acylpyrazolones.

As shown in Scheme 3.1, pyrazolones with variable R’ (1 position) and R’’ (3 position) have been synthesized by using β-ketoesters (with R’’ group) and hydrazines (with R’ group) under reflux condition in ethanol solvent for 48-72 hours. After the reaction, the precipitate was first filtered and washed with a small amounts of ethanol (3 times). Then the solid was recrystallized from ethanol to obtain the pure compound. Reaction times and product yields depended on the nature of the β-ketoester and hydrazines. Different pyrazolones shown in Figure 3.2 were synthesized and their physical properties are summarized in Table 3.1.
Figure 3.2 Structures of parent pyrazolones.

All the pyrazolones were characterized by $^1$H NMR, $^{13}$C-NMR and GC-MS, and detailed procedures are given at the end of this chapter.

Table 3.1 Physical properties of the parent pyrazolones.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Melting point $^{(\circ C)}$</th>
<th>Color</th>
<th>GC-MS (FW)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMP</td>
<td>129-130</td>
<td>Light Yellow</td>
<td>174</td>
<td>*</td>
</tr>
<tr>
<td>NPMP</td>
<td>93-95</td>
<td>Brown</td>
<td>219</td>
<td>64</td>
</tr>
<tr>
<td>FPMP</td>
<td>264-266</td>
<td>Yellow</td>
<td>242</td>
<td>78</td>
</tr>
<tr>
<td>MMP</td>
<td>&gt;250</td>
<td>Red</td>
<td>112</td>
<td>55</td>
</tr>
<tr>
<td>tBuMP</td>
<td>liquid</td>
<td>Light yellow</td>
<td>154</td>
<td>81</td>
</tr>
<tr>
<td>BnMP</td>
<td>141-143</td>
<td>White</td>
<td>188</td>
<td>71</td>
</tr>
<tr>
<td>PEP</td>
<td>121-123</td>
<td>White</td>
<td>188</td>
<td>43</td>
</tr>
<tr>
<td>PPrP</td>
<td>108-110</td>
<td>White</td>
<td>202</td>
<td>75</td>
</tr>
<tr>
<td>MOPMP</td>
<td>212-215</td>
<td>Light Brown</td>
<td>204</td>
<td>61</td>
</tr>
<tr>
<td>MPMP</td>
<td>192-195</td>
<td>White</td>
<td>188</td>
<td>76</td>
</tr>
<tr>
<td>PPP</td>
<td>135-137</td>
<td>Orange</td>
<td>236</td>
<td>83</td>
</tr>
<tr>
<td>PNPP</td>
<td>264-268</td>
<td>Yellow</td>
<td>281</td>
<td>85</td>
</tr>
</tbody>
</table>

*: commercially available.
3.2 Synthesis of acylpyrazolones.

Various pyrazolones were converted to their acyl derivatives as outlined in Scheme 3.1.

3.2.1 Synthesis of 1-phenyl-3-methyl-4-acyl-5-pyrazolone from aliphatic acyl chlorides

The traditional method to synthesize acylpyrazolone employs a very strong base for the condensation of pyrazolone and acetyl chlorides [25]. While this approach works reasonably well for saturated acyl groups, we observed that it is not suitable for those with unsaturation and yields of the desired acylpyrazolones were lowered by the formation of several by-products. We have investigated different bases, solvents and reaction conditions that are suitable for a variety of saturated and unsaturated acyl groups. Their structures are shown in Figure 3.3.

Figure 3.3 Synthesized acylpyrazolones.

Aliphatic acyl chlorides employed in the synthesis include acetyl chloride (C$_2$H$_3$ClO), crotonoyl chloride (C$_4$H$_5$ClO), valeryl chloride (C$_5$H$_7$ClO), pentenoyl chloride
(C₅H₇ClO), decanoyl chloride (C₁₀H₁₉ClO) and undecenoyl chloride (C₁₁H₁₉ClO). The solvents employed include: THF, dioxane and dichloroethane. The bases used in these reactions include sodium hydroxide (NaOH), calcium hydroxide (Ca(OH)₂) and triethyl amine (Et₃N).

a. Effect of base on acylation reaction.

Sodium hydroxide (NaOH), calcium hydroxide (Ca(OH)₂) and tri-ethyl amine (Et₃N) are very commonly used as bases for alkylation or acylation reactions. The choice of the base used in the reaction depends on the acidity of the hydrogen in the 4 position of the pyrazolone.

The solvent THF that has been frequently employed in literature methods was used to investigate the influence of the nature of the base on the yield of the target molecule. The solvent was dried by reflux with sodium metal (Na) and benzophenone (PhCOPh). The preparation of the acylpyrazolone derived from PMP is shown in Scheme 3.2.

Scheme 3.2 Acylation of pyrazolones.
The yields and conditions of these reactions using different bases are shown in Table 3.2.

**Table 3.2 Pyrazolone acylation by using different base.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NaOH, 0°C 4hs</td>
</tr>
<tr>
<td>HPMAP</td>
<td>32</td>
</tr>
<tr>
<td>HPMCP</td>
<td>&quot;</td>
</tr>
<tr>
<td>HPMVP</td>
<td>26</td>
</tr>
<tr>
<td>HPMPnP</td>
<td>&quot;</td>
</tr>
<tr>
<td>HPMDP</td>
<td>42</td>
</tr>
<tr>
<td>HPMUP</td>
<td>28</td>
</tr>
</tbody>
</table>

*: "\" indicates that the desired product was obtained in very low yield and mixed with several other unidentified products.

From the above table, it is clear that triethylamine (Et$_3$N) provided good yields under mild conditions. The yields of this reaction using calcium hydroxide (Ca(OH)$_2$) for unsaturated acyl chlorides were very poor. This was due to the polymerization of the unsaturated carbon-carbon double bond (C=C) [26]. For example in the case of crotonoyl chloride, when Ca(OH)$_2$ was employed, a very sticky dark oily polymerization product was formed. This was also observed for pentenoyl chloride and undecenoyl chloride.

When sodium hydroxide was used, the yields of the reaction decreased even further as NaOH absorbed water and even trace amounts of water adversely affected the final yield of this reaction. This was most likely due to the hydrolysis of acyl chlorides to their acids which did not react with the parent pyrazolone.

The above experiments indicated that triethylamine (Et$_3$N) was the best choice for the
reaction with aliphatic acyl chlorides and was employed in the generation of other acylpyrazolones.

b. Solvent effects.

The influence of the nature of the solvents was investigated by employing Et$_3$N as the base. Acyl chlorides are generally very reactive towards protic solvents such as water, methanol, ethanol, and the solvent must be dried rigorously. The parent PMP is insoluble in non-polar solvent such as hexane or toluene. Here, THF, dioxane and dichloroethane were studied at room temperature for their influence on the acylation reaction to yield acylpyrazolones. Reaction yields are summarized in Table 3.3.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dichloroethane</td>
</tr>
<tr>
<td>HPMAP</td>
<td>*</td>
</tr>
<tr>
<td>HPMCP</td>
<td>*</td>
</tr>
<tr>
<td>HPMVP</td>
<td>26</td>
</tr>
<tr>
<td>HPMPnP</td>
<td>35</td>
</tr>
<tr>
<td>HPMDP</td>
<td>33</td>
</tr>
<tr>
<td>HPMUP</td>
<td>24</td>
</tr>
</tbody>
</table>

*: “\*” indicates that the desired product was obtained in very low yield and mixed with several other unidentified products.

These results indicate that THF and dioxane are the ideal choice for this acylation reaction.
3.2.2 Synthesis of 1-phenyl-3-methyl-4-acyl-5-pyrazolone from aromatic acyl chlorides.

Base effect

Although there are many publications describing the use of acylpyrazolones as ligands for transition metal ion separation, most of the reports deal with aromatic acylpyrazolones [27, 28]. Aliphatic acylpyrazolones in terms of their synthesis and separation efficacies for different metal ion families have not been investigated. Different acyl groups may be expected to influence metal ion recognition properties of acylpyrazolones. We have investigated both aromatic and aliphatic acylpyrazolones in this work and details of the mechanism of separation are discussed in CHAPTER VI. The synthesis of HPMBP from PMP and the effect of different bases on this synthesis are given below.

**Scheme 3.3 Benzoylation of PMP.**

![Scheme 3.3 Benzoylation of PMP.](image)

Three bases listed in Table 3.4 were investigated here for acylation of PMP

<table>
<thead>
<tr>
<th>Base</th>
<th>Reaction Condition</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaOH</td>
<td>0°C, 4hs</td>
<td>34</td>
</tr>
<tr>
<td>Ca(OH)_2</td>
<td>0°C, 4hs</td>
<td>92</td>
</tr>
<tr>
<td>Et_3N</td>
<td>rt, 4hs</td>
<td>72</td>
</tr>
</tbody>
</table>

**Table 3.4 Benzoylation of PMP by using different bases.**
From the data shown in the table above, calcium hydroxide is the best choice for acylation with benzoyl chloride. Aromatic acyl chlorides are generally reactive due to conjugation from the aromatic ring to the carbonyl group, they will not polymerize in the presence of base. The poor yield with NaOH could be due to the hygroscopic nature of this base. Triethyl amine, being a weaker base, needs a higher temperature than Ca(OH)\(_2\) which also gave a lower yield.

### 3.3 Structure of the ligands and their metal ion complexes.

#### a. Structures of the ligands.

X-ray structures of single crystals of free acylpyrazolones and their metal complexes were performed to gain an understanding of their molecular structures in terms of bond angles, bond lengths and the position of the –OH group in the free ligand as shown in Figure 3.4.

**Figure 3.4 Isomers of acylpyrazolones.**

Acylpyrazolones such as crotonoyl pyrazolone, valeryl pyrazolone, pentenoyl pyrazolone, undecynoyl pyrazolone and benzoyl pyrazolone were investigated to discern the influence of the nature of the R groups on resonance and the orientation of the –OH group. Crystal structure results are shown in figures and tables below:
Figure 3.5 Crystal structure of 1-phenyl-3-methyl-4-crotonoyl-5pyrazol-one.

Figure 3.6 HPMCP molecules packing in the crystal.

Table 3.5 Bond lengths and bond angles of HPMCP.

<table>
<thead>
<tr>
<th>INTRAMOLECULAR BOND LENGTHS (H omitted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bond length limits based on covalent radii</td>
</tr>
<tr>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>N(1) - N(2) 1.4012(9)  N(1) - C(12) 1.413(1)</td>
</tr>
<tr>
<td>N(1) - C(5) 1.364(1)  N(2) - C(3) 1.316(1)</td>
</tr>
<tr>
<td>O(3) - C(7) 1.334(1)  O(4) - C(5) 1.272(1)</td>
</tr>
<tr>
<td>C(4) - C(5) 1.417(1)  C(4) - C(7) 1.365(1)</td>
</tr>
<tr>
<td>C(4) - C(3) 1.405(1)  C(12) - C(13) 1.364(1)</td>
</tr>
<tr>
<td>C(12) - C(17) 1.374(1)  C(7) - C(8) 1.453(1)</td>
</tr>
<tr>
<td>C(13) - C(16) 1.375(1)  C(14) - C(15) 1.355(1)</td>
</tr>
<tr>
<td>C(15) - C(16) 1.343(1)</td>
</tr>
</tbody>
</table>
INTRAMOLECULAR BOND ANGLES (H omitted)

<table>
<thead>
<tr>
<th>Bond length limits based on covalent radii</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(2) - N(1) - C(12)</td>
</tr>
<tr>
<td>C(12) - N(1) - C(5)</td>
</tr>
<tr>
<td>C(5) - C(4) - C(7)</td>
</tr>
<tr>
<td>C(7) - C(4) - C(3)</td>
</tr>
<tr>
<td>N(1) - C(12) - C(17)</td>
</tr>
<tr>
<td>N(1) - C(5) - O(4)</td>
</tr>
<tr>
<td>O(4) - C(5) - C(4)</td>
</tr>
<tr>
<td>O(3) - C(7) - C(8)</td>
</tr>
<tr>
<td>N(2) - C(3) - C(4)</td>
</tr>
<tr>
<td>C(4) - C(3) - C(6)</td>
</tr>
<tr>
<td>C(12) - C(13) - C(14)</td>
</tr>
<tr>
<td>C(12) - C(17) - C(16)</td>
</tr>
<tr>
<td>C(14) - C(15) - C(16)</td>
</tr>
</tbody>
</table>

The X-ray structure indicates that the predominant isomer of 1-phenyl-3-methyl-4-crotonoyl-5-pyrazolone is as shown in Figure 3.7 where the –OH group is outside the pyrazolone ring.

**Figure 3.7 Structure of HPMCP.**

![Structure of HPMCP](image)

When the trans-crotonoyl pyrazolone (HPMCP; yellow crystal) was heated in a THF/water mixture, it cyclized as shown in Scheme 3.4.

**Scheme 3.4 Cyclization of HPMCP.**

![Scheme 3.4 Cyclization of HPMCP](image)
This cyclization is catalyzed by acid as indicated by rapid cyclization of HPMCP in THF with excess acid at room temperature. The cyclization can be avoided in nonprotic solvents such as ethyl acetate and petroleum ether. The crystal structure of this compound is shown in Figure 3.8.

**Figure 3.8 Crystal structure of the cyclic compound and the molecules packing in the crystal.**

---

**Table 3.6 Bond lengths and bond angles of the cyclic compound.**

<table>
<thead>
<tr>
<th>INTRAMOLECULAR BOND LENGTHS (H omitted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bond length limits use covalent radii + 0.00A</td>
</tr>
<tr>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>O(1) - C(6)</td>
</tr>
<tr>
<td>N(2) - N(1)</td>
</tr>
<tr>
<td>N(1) - C(9)</td>
</tr>
<tr>
<td>C(9) - C(10)</td>
</tr>
<tr>
<td>C(5) - C(7)</td>
</tr>
<tr>
<td>C(14) - C(13)</td>
</tr>
<tr>
<td>C(13) - C(12)</td>
</tr>
<tr>
<td>C(3) - C(2)</td>
</tr>
<tr>
<td>C(2) - C(1)</td>
</tr>
<tr>
<td>-----------------------------------------</td>
</tr>
</tbody>
</table>

26
The crystal structure of 1-phenyl-3-methyl-4-valeryl-5-pyrazolone is shown in Figure 3.9.

**Figure 3.9** Crystal structure of 1-phenyl-3-methyl-4-valeryl pyrazol-5-one and the molecules packing in the crystal.
Table 3.7 Bond lengths and bond angles of HPMVP.

INTRAMOLECULAR BOND LENGTHS (H omitted)

<table>
<thead>
<tr>
<th>Bond Length</th>
<th>Value</th>
<th>Bond Length</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1) - C(2)</td>
<td>1.398(4)</td>
<td>C(1) - C(6)</td>
<td>1.386(3)</td>
</tr>
<tr>
<td>C(1) - N(2)</td>
<td>1.432(3)</td>
<td>C(2) - C(3)</td>
<td>1.382(4)</td>
</tr>
<tr>
<td>C(3) - C(4)</td>
<td>1.388(4)</td>
<td>C(4) - C(5)</td>
<td>1.387(4)</td>
</tr>
<tr>
<td>C(5) - C(6)</td>
<td>1.391(3)</td>
<td>C(7) - C(9)</td>
<td>1.434(4)</td>
</tr>
<tr>
<td>C(7) - C(10)</td>
<td>1.485(3)</td>
<td>C(7) - N(1)</td>
<td>1.319(3)</td>
</tr>
<tr>
<td>C(8) - C(9)</td>
<td>1.392(3)</td>
<td>C(8) - N(2)</td>
<td>1.349(3)</td>
</tr>
<tr>
<td>C(8) - O(1)</td>
<td>1.323(3)</td>
<td>C(9) - C(11)</td>
<td>1.425(4)</td>
</tr>
<tr>
<td>C(11) - C(12)</td>
<td>1.499(3)</td>
<td>C(11) - O(2)</td>
<td>1.261(3)</td>
</tr>
<tr>
<td>C(12) - C(13)</td>
<td>1.530(4)</td>
<td>C(13) - C(14)</td>
<td>1.487(4)</td>
</tr>
<tr>
<td>C(14) - C(15)</td>
<td>1.272(6)</td>
<td>N(1) - N(2)</td>
<td>1.400(3)</td>
</tr>
</tbody>
</table>

INTRAMOLECULAR BOND ANGLES (H omitted)

<table>
<thead>
<tr>
<th>Bond Angle</th>
<th>Value</th>
<th>Bond Angle</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(2) - C(1) - C(6)</td>
<td>120.5(2)</td>
<td>C(2) - C(1) - N(2)</td>
<td>120.7(2)</td>
</tr>
<tr>
<td>C(6) - C(1) - N(2)</td>
<td>118.8(2)</td>
<td>C(1) - C(2) - C(3)</td>
<td>119.2(2)</td>
</tr>
<tr>
<td>C(2) - C(3) - C(4)</td>
<td>121.3(3)</td>
<td>C(3) - C(4) - C(5)</td>
<td>118.7(2)</td>
</tr>
<tr>
<td>C(4) - C(5) - C(6)</td>
<td>121.3(2)</td>
<td>C(1) - C(6) - C(5)</td>
<td>119.1(2)</td>
</tr>
<tr>
<td>C(9) - C(7) - C(10)</td>
<td>129.2(2)</td>
<td>C(9) - C(7) - N(1)</td>
<td>111.5(2)</td>
</tr>
<tr>
<td>C(10) - C(7) - N(1)</td>
<td>119.3(2)</td>
<td>C(9) - C(8) - N(2)</td>
<td>108.6(2)</td>
</tr>
<tr>
<td>C(9) - C(8) - O(1)</td>
<td>126.2(2)</td>
<td>N(2) - C(8) - O(1)</td>
<td>125.2(2)</td>
</tr>
<tr>
<td>C(7) - C(9) - C(8)</td>
<td>103.9(2)</td>
<td>C(7) - C(9) - C(11)</td>
<td>135.9(2)</td>
</tr>
<tr>
<td>C(8) - C(9) - C(11)</td>
<td>120.1(2)</td>
<td>C(9) - C(11) - C(12)</td>
<td>122.0(2)</td>
</tr>
<tr>
<td>C(9) - C(11) - O(2)</td>
<td>118.2(2)</td>
<td>C(12) - C(11) - O(2)</td>
<td>119.8(2)</td>
</tr>
<tr>
<td>C(11) - C(12) - C(13)</td>
<td>114.6(2)</td>
<td>C(12) - C(13) - C(14)</td>
<td>112.0(2)</td>
</tr>
<tr>
<td>C(13) - C(14) - C(15)</td>
<td>127.0(4)</td>
<td>C(7) - N(1) - N(2)</td>
<td>105.8(2)</td>
</tr>
<tr>
<td>C(1) - N(2) - C(8)</td>
<td>131.1(2)</td>
<td>C(1) - N(2) - N(1)</td>
<td>118.7(2)</td>
</tr>
<tr>
<td>C(8) - N(2) - N(1)</td>
<td>110.2(2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The predominant isomer of 1-phenyl-3-methyl-4-valeryl-5-pyrazolone is as shown in Figure 3.10 and has the –OH group on the pyrazolone ring.
The crystal structure of 1-phenyl-3-methyl-4-pentenoyl-5-pyrazolone is shown in Figure 3.11.

### Figure 3.10 Structure of HPMVP.

![Structure of HPMVP](image)

### Figure 3.11 Crystal structure of HPMPnP and the molecules packing in the crystal.

![Crystal structure of HPMPnP](image)

### Table 3.8 Bond lengths and bond angles of HPMPnP.

**INTRAMOLECULAR BOND LENGTHS (H omitted)**

<table>
<thead>
<tr>
<th>Bond Length</th>
<th>C(1) - C(2)</th>
<th>C(2) - C(3)</th>
<th>C(3) - C(4)</th>
<th>C(4) - C(5)</th>
<th>C(5) - C(7)</th>
<th>C(5) - O(1)</th>
<th>C(6) - C(7)</th>
<th>C(6) - N(1)</th>
<th>C(6) - O(2)</th>
<th>C(7) - C(8)</th>
<th>C(8) - C(9)</th>
<th>C(8) - N(2)</th>
<th>C(10) - C(11)</th>
<th>C(10) - C(15)</th>
<th>C(10) - N(1)</th>
<th>C(12) - C(13)</th>
<th>C(14) - C(15)</th>
<th>N(1) - N(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>1.110(10)</td>
<td>1.439(10)</td>
<td>1.531(7)</td>
<td>1.449(7)</td>
<td>1.445(7)</td>
<td>1.273(6)</td>
<td>1.371(7)</td>
<td>1.354(6)</td>
<td>1.324(5)</td>
<td>1.427(6)</td>
<td>1.460(7)</td>
<td>1.323(6)</td>
<td>1.393(6)</td>
<td>1.398(6)</td>
<td>1.404(6)</td>
<td>1.381(7)</td>
<td>1.370(7)</td>
<td>1.420(5)</td>
</tr>
</tbody>
</table>
INTRAMOLECULAR BOND ANGLES (H omitted)

Bond length limits use covalent radii + 0.20A

<table>
<thead>
<tr>
<th>Bond angles and lengths</th>
<th>143.7(12)</th>
<th>114.2(5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)-C(2)-C(3)</td>
<td>116.9(5)</td>
<td>123.4(5)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(5)</td>
<td>120.6(5)</td>
<td>115.9(5)</td>
</tr>
<tr>
<td>C(7)-C(6)-N(1)</td>
<td>108.7(4)</td>
<td>127.4(5)</td>
</tr>
<tr>
<td>N(1)-C(6)-O(2)</td>
<td>123.9(5)</td>
<td>120.7(4)</td>
</tr>
<tr>
<td>C(5)-C(7)-C(8)</td>
<td>133.3(5)</td>
<td>109.9(4)</td>
</tr>
<tr>
<td>C(7)-C(8)-N(2)</td>
<td>118.7(4)</td>
<td>118.3(5)</td>
</tr>
<tr>
<td>C(9)-C(8)-N(2)</td>
<td>119.8(4)</td>
<td>121.8(4)</td>
</tr>
<tr>
<td>C(11)-C(10)-C(15)</td>
<td>120.1(5)</td>
<td>122.3(5)</td>
</tr>
<tr>
<td>C(12)-C(13)-C(14)</td>
<td>117.4(4)</td>
<td>121.2(4)</td>
</tr>
<tr>
<td>C(10)-C(15)-C(14)</td>
<td>120.7(5)</td>
<td>132.0(4)</td>
</tr>
<tr>
<td>C(6)-N(1)-N(2)</td>
<td>108.9(4)</td>
<td>119.1(4)</td>
</tr>
<tr>
<td>C(8)-N(2)-N(1)</td>
<td>106.5(4)</td>
<td></td>
</tr>
</tbody>
</table>

The predominant isomer of 3-methyl-4-pentenoyl-1-phenyl pyrazol-5-one is one in which the enol group is on the pyrazolone ring as shown in Figure 3.14.

Figure 3.12 Structure of HPMPnP.

b. Structures of the metal ion complexes.

The structures of Cu(II) complexes of HPMCP and HPMUP are shown in Figures 3.13 and 3.14.
Figure 3.13 Crystal structure of HPMCP copper(II) complex.

Table 3.9 HPMCP copper(II) complex.

<table>
<thead>
<tr>
<th>INTRAMOLECULAR BOND LENGTHS (H omitted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bond length limits use covalent radii + 0.00Å</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
<th>Bond</th>
<th>Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu(1) - O(2)</td>
<td>1.9156(11)</td>
<td>Cu(1) - O(4)</td>
<td>1.9203(12)</td>
</tr>
<tr>
<td>Cu(1) - O(1)</td>
<td>1.9155(11)</td>
<td>Cu(1) - O(3)</td>
<td>1.8900(12)</td>
</tr>
<tr>
<td>O(2) - C(11)</td>
<td>1.268(2)</td>
<td>O(4) - C(25)</td>
<td>1.250(2)</td>
</tr>
<tr>
<td>O(1) - C(9)</td>
<td>1.254(2)</td>
<td>O(3) - C(23)</td>
<td>1.272(2)</td>
</tr>
<tr>
<td>N(3) - C(23)</td>
<td>1.384(2)</td>
<td>N(3) - C(15)</td>
<td>1.413(2)</td>
</tr>
<tr>
<td>N(1) - C(9)</td>
<td>1.366(2)</td>
<td>N(1) - C(1)</td>
<td>1.421(2)</td>
</tr>
<tr>
<td>N(4) - C(21)</td>
<td>1.328(2)</td>
<td>N(2) - C(7)</td>
<td>1.325(2)</td>
</tr>
<tr>
<td>C(9) - C(8)</td>
<td>1.445(2)</td>
<td>C(1) - C(2)</td>
<td>1.365(2)</td>
</tr>
<tr>
<td>C(1) - C(6)</td>
<td>1.368(2)</td>
<td>C(11) - C(8)</td>
<td>1.403(2)</td>
</tr>
<tr>
<td>C(11) - C(12)</td>
<td>1.497(2)</td>
<td>C(7) - C(8)</td>
<td>1.428(2)</td>
</tr>
<tr>
<td>C(7) - C(10)</td>
<td>1.486(2)</td>
<td>C(25) - C(22)</td>
<td>1.417(2)</td>
</tr>
<tr>
<td>C(25) - C(26)</td>
<td>1.471(2)</td>
<td>C(23) - C(22)</td>
<td>1.440(2)</td>
</tr>
<tr>
<td>C(22) - C(21)</td>
<td>1.427(2)</td>
<td>C(15) - C(20)</td>
<td>1.379(2)</td>
</tr>
<tr>
<td>C(15) - C(16)</td>
<td>1.368(2)</td>
<td>C(2) - C(3)</td>
<td>1.382(2)</td>
</tr>
<tr>
<td>C(12) - C(13)</td>
<td>1.292(2)</td>
<td>C(6) - C(5)</td>
<td>1.391(2)</td>
</tr>
<tr>
<td>C(20) - C(19)</td>
<td>1.354(2)</td>
<td>C(21) - C(24)</td>
<td>1.482(2)</td>
</tr>
<tr>
<td>C(26) - C(27)</td>
<td>1.296(2)</td>
<td>C(27) - C(28)</td>
<td>1.467(3)</td>
</tr>
<tr>
<td>C(16) - C(17)</td>
<td>1.356(2)</td>
<td>C(13) - C(14)</td>
<td>1.471(2)</td>
</tr>
<tr>
<td>C(3) - C(4)</td>
<td>1.357(2)</td>
<td>C(18) - C(19)</td>
<td>1.390(2)</td>
</tr>
<tr>
<td>C(18) - C(17)</td>
<td>1.326(2)</td>
<td>C(4) - C(5)</td>
<td>1.350(2)</td>
</tr>
</tbody>
</table>
The crystal structure indicates that the bond lengths of C(23)-O(3) (on the pyrazolone ring) and C(25)-O(4) (outside the pyrazolone ring) are similar in the complex compared to C(5)-O(4) (on the ring) and C(7)-O(3) (outside the ring) in the free ligand being different by 0.06 Å. The results show that the complex has a square planar geometry.
and the crotonoyl side chains are present on the same side of the square planar structure with a mirror plane about the Z-axis.

The crystal structure of the Cu(II) complex of 4-undecenoyl pyrazolone clearly shows the undecenoyl group present on opposite sides of the square planar structure due to the large steric hindrance.

**Figure 3.14 HPMUP copper complex.**

---

### 3.4 Experimental procedures.

**(a) Synthesis of parent pyrazolones.**

The general synthetic method is given for NPMP as the example. 4.16 ml \((3.27 \times 10^{-2} \text{mol})\) of ethyl acetoacetate was added to 50 ml of ethanol in a round bottom flask; 5.55 g \((3.27 \times 10^{-2} \text{mol})\) of 4-nitro-phenyl hydrazine was introduced and refluxed with stirring for 24 hours. The solvent was rotary evaporated, filtrated and the solid product was washed with ethanol 3 times and recrystallized from ethanol. The pure compound was obtained with 76\% of yield (5.4 g).
The melting points and $^1$H and $^{13}$C [$^1$H] (400 MHz) data for the various pyrazolones and acylpyrazolones are given below. The molecular formula of these compounds and their structures were also established by their characteristic GC-MS analysis. Elemental (C, H, N) analysis was not performed.

**NPMP:** 3-methyl-1-(4'-nitro)-phenyl pyrazol-5-one $C_{10}H_9N_3O_3$

GC-MS: FW: 219; melting point: 93-95 °C, $^1$H NMR in $d_6$-DMSO (δ, ppm): δ = 7.53(t), ortho-$CH$ on the phenyl ring; δ = 7.31(t), meta-$CH$ on the phenyl ring; δ = 5.73(s), -COH=CH- (in the pyrazolone ring); δ = 2.36(s), Ph-CH$_2$; δ = 2.24(s), Pyrazolone-CH$_3$; $^{13}$C-NMR: δ = 156.00, HO-C=C; δ = 148.18, -N=C-CH$_3$; δ = 137.70, ->C-N< (on the phenyl ring); δ = 133.31, ortho-$CH$ on the phenyl ring; δ = 130.20, meta-$CH$ on the phenyl ring; δ = 123.16, para-CH on the phenyl ring; δ = 90.43, N=C=CH-; δ = 21.17, Ph-CH$_3$; δ = 13.08, N=C-CH$_3$;

**FPMP:** 3-methyl-1-(4'-trifluoromethyl)-phenyl pyrazol-5-one $C_{11}H_9F_3N_2O$

GC-MS: FW: 242; melting point: 264-266°C, $^1$H NMR: δ = 7.53(t), ortho-$CH$ on the phenyl ring; δ = 7.31(t), meta-$CH$ on the phenyl ring; δ = 5.73(s), -COH=CH- (in the pyrazolone ring); δ = 2.36(s), Ph-CH$_2$; δ = 2.24(s), Pyrazolone-CH$_3$; $^{13}$C NMR: δ = 156.00, HO-C=C; δ = 148.18, -N=C-CH$_3$; δ = 137.70, ->C-N< (on the phenyl ring); δ = 133.31, ortho-$CH$ on the phenyl ring; δ = 130.20, meta-$CH$ on the phenyl ring; δ = 123.16, para-CH on the phenyl ring; δ = 90.43, N=C=CH-; δ = 21.17, Ph-CH$_3$; δ = 13.08,
N=C-CH₃;

**MMP:** 1-methyl-3-methyl pyrazol-5-one C₅H₈N₂O

GC-MS: FW: 112; melting point: >250°C, ¹H NMR: δ = 7.53 c(t), ortho-CH on the phenyl ring; δ = 7.31(t), meta-CH on the phenyl ring; δ = 5.73(s), -COH=CH- (in the pyrazolone ring); δ = 2.36(s), Ph-CH₃; δ = 2.24(s), Pyrazolone-CH₃; ¹³C NMR: δ = 156.00, HO-Ç=C; δ = 148.18, -N=Ç-CH₃; δ = 137.70, >C-N< (on the phenyl ring); δ = 133.31, ortho-ÇH on the phenyl ring; δ = 130.20, meta-ÇH on the phenyl ring; δ = 123.16, para-ÇH on the phenyl ring; δ = 90.43, N-C=ÇH--; δ = 21.17, Ph-CH₃; δ = 13.08, N=C-CH₃;

**tBuMP:** 1-ß-butyl-1-methyl pyrazol-5-one C₈H₁₄N₂O (liquid)

GC-MS: FW: 154; ¹H NMR: δ = 7.53 c(t), ortho-ÇH on the phenyl ring; δ = 7.31(t), meta-ÇH on the phenyl ring; δ = 5.73(s), -COH=CH- (in the pyrazolone ring); δ = 2.36(s), Ph-CH₃; δ = 2.24(s), Pyrazolone-CH₃; ¹³C NMR: δ = 156.00, HO-Ç=C; δ = 148.18, -N=Ç-CH₃; δ = 137.70, >C-N< (on the phenyl ring); δ = 133.31, ortho-ÇH on the phenyl ring; δ = 130.20, meta-ÇH on the phenyl ring; δ = 123.16, para-ÇH on the phenyl ring; δ = 90.43, N-C=ÇH--; δ = 21.17, Ph-CH₃; δ = 13.08, N=C-CH₃;

**BnMP:** 1-benzyl-3-methyl pyrazol-5-one C₁₁H₁₂N₂O

GC-MS: FW: 188; melting point: 141-143°C, ¹H NMR: δ = 7.36-7.28(m), H on the
phenyl ring; \( \delta = 5.97(s), -\text{COH}=\text{CH}- \) (in the pyrazolone ring); \( \delta = 5.21(s), \text{Ph-CH}_2\text{-N}; \delta = 2.23(s), \text{Ph-CH}_3; \) \(^{13}\text{C NMR: } \delta = 155.60, \text{HO-}=\text{C}; \delta = 146.51, -\text{N}=\text{C-CH}_3; \delta = 136.11, >\text{C}-\text{N}< \) (on the phenyl ring); \( \delta = 129.38, \text{ortho-CH} \) on the phenyl ring; \( \delta = 128.42, \text{meta-CH} \) on the phenyl ring; \( \delta = 88.25, \text{N-C}=\text{C-CH}_3; \delta = 21.17, \text{Ph-CH}_3; \delta = 13.08, \text{N=C-CH}_3; \)

**MOPMP:** 3-methyl-1-(4’-methoxyl)-phenyl pyrazol-5-one C\(_{11}\)H\(_{12}\)N\(_2\)O\(_2\)

\(^{1}\text{H NMR: } \delta = 7.53(t), \text{ortho-CH} \) on the phenyl ring; \( \delta = 7.31(t), \text{meta-CH} \) on the phenyl ring; \( \delta = 5.73(s), -\text{COH}=\text{CH}- \) (in the pyrazolone ring); \( \delta = 2.36(s), \text{Ph-CH}_3; \delta = 2.24(s), \text{Pyrazolone-CH}_3; \) \(^{13}\text{C NMR: } \delta = 156.00, \text{HO-}=\text{C}; \delta = 148.18, -\text{N}=\text{C-CH}_3; \delta = 137.70, >\text{C}-\text{N}< \) (on the phenyl ring); \( \delta = 133.31, \text{ortho-CH} \) on the phenyl ring; \( \delta = 130.20, \text{meta-CH} \) on the phenyl ring; \( \delta = 123.16, \text{para-CH} \) on the phenyl ring; \( \delta = 90.43, \text{N-C}=\text{CH}-; \delta = 21.17, \text{Ph-CH}_3; \delta = 13.08, \text{N=C-CH}_3; \)

**MPMP:** 3-methyl-1-(4’-methyl)-phenyl pyrazol-5-one C\(_{11}\)H\(_{12}\)N\(_2\)O

\(^{1}\text{H NMR: } \delta = 7.53(t), \text{ortho-CH} \) on the phenyl ring; \( \delta = 7.31(t), \text{meta-CH} \) on the phenyl ring; \( \delta = 5.73(s), -\text{COH}=\text{CH}- \) (in the pyrazolone ring); \( \delta = 2.36(s), \text{Ph-CH}_3; \delta = 2.24(s), \text{Pyrazolone-CH}_3; \) \(^{13}\text{C NMR: } \delta = 156.00, \text{HO-}=\text{C}; \delta = 148.18, -\text{N}=\text{C-CH}_3; \delta = 137.70, >\text{C}-\text{N}< \) (on the phenyl ring); \( \delta = 133.31, \text{ortho-CH} \) on the phenyl ring; \( \delta = 130.20, \text{meta-CH} \) on the phenyl ring; \( \delta = 123.16, \)
para-\text{CH} on the phenyl ring; \( \delta = 90.43 \), N-C=\text{CH}-; \( \delta = 21.17 \), Ph-\text{CH}_3; \( \delta = 13.08 \), N=C-\text{CH}_3;

**PPP:** 1-phenyl-3-phenyl pyrazol-5-one C\(_{15}\)H\(_{12}\)N\(_2\)O

GC-MS: FW: 236; melting point: 135-137\(^\circ\)C, \(^1\text{H}\) NMR: \( \delta = 7.53(t) \), ortho-\text{CH} on the phenyl ring; \( \delta = 7.31(t) \), meta-\text{CH} on the phenyl ring; \( \delta = 5.73(s) \), -COH=\text{CH}- (in the pyrazolone ring); \( \delta = 2.36(s) \), Ph-\text{CH}_3; \( \delta = 2.24(s) \), Pyrazolone-\text{CH}_3; \(^{13}\text{C}\) NMR: \( \delta = 156.00 \), HO-C=C; \( \delta = 148.18 \), -N=C-\text{CH}_3; \( \delta = 137.70 \), >C-N< (on the phenyl ring); \( \delta = 133.31 \), ortho-\text{CH} on the phenyl ring; \( \delta = 130.20 \), meta-\text{CH} on the phenyl ring; \( \delta = 123.16 \), para-\text{CH} on the phenyl ring; \( \delta = 90.43 \), N-C=\text{CH}-; \( \delta = 21.17 \), Ph-\text{CH}_3; \( \delta = 13.08 \), N=C-\text{CH}_3;

**PNPP:** 1-phenyl-3-(4’-nitro)-phenyl pyrazol-5-one C\(_{15}\)H\(_{11}\)N\(_3\)O\(_3\)

GC-MS: FW: 281; melting point: 264-268\(^\circ\)C, \(^1\text{H}\) NMR: \( \delta = 7.53(t) \), ortho-\text{CH} on the phenyl ring; \( \delta = 7.31(t) \), meta-\text{CH} on the phenyl ring; \( \delta = 5.73(s) \), -COH=\text{CH}- (in the pyrazolone ring); \( \delta = 2.36(s) \), Ph-\text{CH}_3; \( \delta = 2.24(s) \), Pyrazolone-\text{CH}_3; \(^{13}\text{C}\) NMR: \( \delta = 156.00 \), HO-C=C; \( \delta = 148.18 \), -N=C-\text{CH}_3; \( \delta = 137.70 \), >C-N< (on the phenyl ring); \( \delta = 133.31 \), ortho-\text{CH} on the phenyl ring; \( \delta = 130.20 \), meta-\text{CH} on the phenyl ring; \( \delta = 123.16 \), para-\text{CH} on the phenyl ring; \( \delta = 90.43 \), N-C=\text{CH}-; \( \delta = 21.17 \), Ph-\text{CH}_3; \( \delta = 13.08 \), N=C-\text{CH}_3;
(b) Synthesis of acylpyrazolones.

The general synthetic method is indicated with HPMUP as the example. 5 g of 1-phenyl-3-methyl-5-pyrazolone was dissolved in 50 ml THF and cooled in an ice bath. After the temperature reached 5 °C, 5ml triethylamine was added and stirred. 6.44 ml of undecenoyl chloride was added dropwise and stirred for about 4 hours. The reaction solution was added to 100 ml 1N HCl solution and extracted with 30 ml CH₂Cl₂ three times. The extractants were combined and washed with water three times and dried over Na₂SO₄. The solvent was evaporated and the product was recrystallized from THF/H₂O. The recrystallization was performed by dissolving the crude product in the minimum volume of THF and heated to reflux, adding H₂O dropwise until the solution turned cloudy and then adding a drop of THF to render the solution clear. The product 8.4 g (yield: 86%) was obtained from the solution upon standing.

HPMAP: Acetyl-pyrazolone C₁₂H₁₂N₂O₂, GC-MS: FW=214; yellow needles, melting point: 51-54 °C. ¹H NMR: δ = 7.82, ortho-CH on the phenyl ring; δ = 7.43, meta-CH on the phenyl ring; δ = 7.28, para-CH on the phenyl ring; δ = 2.46, -CO-CH₃; δ = 2.45, Ar-CH₃. ¹³C-NMR: δ = 194.46, -CO-CH₃; δ = 160.52, HO-ₓₓC-ₓₓC; δ = 147.78, -N=ₓₓC-ₓₓC; δ = 137.32, >ₓₓC-N< (on the phenyl ring); δ = 129.20, ortho-CH on the phenyl ring; δ = 126.68, meta-CH on the phenyl ring; δ = 120.75, para-CH on the phenyl ring; δ = 104.33, >ₓₓCH-CO-; δ = 26.74, -CO-CH₃; δ = 15.68, N=ₓₓC-ₓₓC.
HPMDP: Decanoyl-pyrazolone C_{19}H_{26}N_{2}O_{2}, GC-MS: FW=314; white crystals, melting point: 37-40 °C. \(^1\)H NMR: \(\delta = 7.82\), ortho-CH on the phenyl ring; \(\delta = 7.43\), meta-CH on the phenyl ring; \(\delta = 7.28\), para-CH on the phenyl ring; \(\delta = 2.72\), -CO-CH\(_2\); \(\delta = 2.46\), Ar-CH\(_3\); \(\delta = 1.73\), -CO-CH\(_2\)-CH\(_2\)-; \(\delta = 1.22-1.45\), -(CH\(_2\))\(_6\)-; \(\delta = 0.87\), -(CH\(_2\))\(_6\)-CH\(_3\). \(^{13}\)C NMR: \(\delta = 197.46\), -CO-CH\(_3\); \(\delta = 160.94\), HO-\(\text{C}=\text{C}\); \(\delta = 147.50\), -N=\(\text{C}\)-CH\(_3\); \(\delta = 137.38\), >C-N< (on the phenyl ring); \(\delta = 129.16\), ortho-CH on the phenyl ring; \(\delta = 126.57\), meta-CH on the phenyl ring; \(\delta = 120.70\), para-CH on the phenyl ring; \(\delta = 103.86\), >CH-CO-; \(\delta = 39.02\), -CO-CH\(_2\)-; \(\delta = 31.94\), -CO-CH\(_2\)-CH\(_2\)-; \(\delta = 29.52\), -CO-CH\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_2\)-; \(\delta = 29.49\), -CO-CH\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_2\)-; \(\delta = 29.35\), -CO-CH\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_2\)-; \(\delta = 29.48\), -CO-CH\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_2\)-; \(\delta = 29.35\), -CO-CH\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_2\)-; \(\delta = 24.82\), -CH\(_2\)-CH\(_2\)-CH\(_3\); \(\delta = 22.75\), -CH\(_2\)-CH\(_2\)-CH\(_3\); \(\delta = 15.88\), N=C-CH\(_3\); \(\delta = 14.20\), -CH\(_2\)-CH\(_2\)-CH\(_3\).

HPMVP: Valeryl-pyrazolone C_{15}H_{18}N_{2}O_{2}, GC-MS: FW=258; white needles, melting point: 59-61 °C. \(^1\)H NMR: \(\delta = 7.82\), ortho-CH on the phenyl ring; \(\delta = 7.43\), meta-CH on the phenyl ring; \(\delta = 7.28\), para-CH on the phenyl ring; \(\delta = 2.73\), -CO-CH\(_2\); \(\delta = 2.46\), Ar-CH\(_3\); \(\delta = 1.72\), -CO-CH\(_2\)-CH\(_2\)-; \(\delta = 1.42\), -CH\(_2\)-CH\(_3\); \(\delta = 0.96\), -CH\(_2\)-CH\(_3\). \(^{13}\)C NMR: \(\delta = 197.44\), -CO-CH\(_3\); \(\delta = 160.94\), HO-\(\text{C}=\text{C}\); \(\delta = 147.49\), -N=\(\text{C}\)-CH\(_3\); \(\delta = 137.38\), >C-N< (on the phenyl ring); \(\delta = 129.15\), ortho-CH on the phenyl ring; \(\delta = 126.57\), meta-CH on the phenyl ring; \(\delta = 120.69\), para-CH on the phenyl ring; \(\delta = 103.85\), >CH-CO-; \(\delta = 38.71\), -CO-CH\(_2\)-; \(\delta = 26.86\), -CO-CH\(_2\)-CH\(_2\)-; \(\delta = 22.59\), -CH\(_2\)-CH\(_2\)-CH\(_3\); \(\delta = 15.87\), N=C-CH\(_3\); \(\delta = 13.97\), -CH\(_2\)-CH\(_2\)-CH\(_3\).
**HPMCP:** Crotonoyl-pyrazolone C$_{14}$H$_{14}$N$_2$O$_2$, GC-MS: FW=242; yellow needles, melting point: 75-77 °C. $^1$H NMR: $\delta$ = 7.88, ortho-CH on the phenyl ring; $\delta$ = 7.41, meta-CH on the phenyl ring; $\delta$ = 7.24, para-CH on the phenyl ring; $\delta$ = 7.22, -CH=CH-CO-; $\delta$ = 6.54, -CH=CH-CO-; $\delta$ = 2.47, Ar-CH$_3$; $\delta$ = 2.49, CH$_2$-CH=CH-. $^{13}$C NMR: $\delta$ = 178.65, -CO-CH=CH-; $\delta$ = 165.30, HO-CC=C<; $\delta$ = 147.26, -N=C-CH$_3$; $\delta$ = 145.28, -CO-CH=CH-; $\delta$ = 137.75, >C-N< (on the phenyl ring); $\delta$ = 129.06, ortho-CH on the phenyl ring; $\delta$ = 125.91, meta-CH on the phenyl ring; $\delta$ = 124.49, -CO-CH=CH-; $\delta$ = 119.91, para-CH on the phenyl ring; $\delta$ = 103.71, >CH-CO-; $\delta$ = 19.13, -CO-CH$_3$; $\delta$ = 16.45, N=C-CH$_3$.

**HPMUP:** Undecenoyl-pyrazolone C$_{21}$H$_{28}$N$_2$O$_2$, GC-MS: FW=340; white thin plate crystals, melting point: 40-42 °C. $^1$H NMR: $\delta$ = 7.89, ortho-CH on the phenyl ring; $\delta$ = 7.49, meta-CH on the phenyl ring; $\delta$ = 7.31, para-CH on the phenyl ring; $\delta$ = 5.80, CH$_2$=CH-; $\delta$ = 4.93, CH$_2$=CH-; $\delta$ = 2.84, -CO-CH$_2$-; $\delta$ = 2.47, Ar-CH$_3$; $\delta$ = 2.04, C$_2$H$_3$-CH$_2$-; $\delta$ = 1.72, -CO-CH$_2$-CH$_2$-; $\delta$ = 1.27-1.48, -(CH$_2$)$_5$-; $^{13}$C NMR: $\delta$ = 197.39, -CO-CH=CH-; $\delta$ = 160.94, HO-CC=C<; $\delta$ = 147.46, -N=C-CH$_3$; $\delta$ = 139.21, >C-N< (on the phenyl ring); $\delta$ = 7.40, -CH$_2$-CH=CH$_2$; $\delta$ = 129.15, ortho-CH on the phenyl ring; $\delta$ = 126.54, meta-CH on the phenyl ring; $\delta$ = 120.65, para-CH on the phenyl ring; $\delta$ = 114.27, -CH$_2$-CH=CH$_2$; $\delta$ = 103.85, >CH-CO-; $\delta$ = 39.01, -CO-CH$_2$-; $\delta$ = 33.87, -CO-CH$_2$-CH$_2$-; $\delta$ = 29.47, -CO-CH$_2$-CH$_2$-CH$_2$-CH$_2$-; $\delta$ = 29.40, -CO-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-; $\delta$ = 29.15, -CO-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-; $\delta$ = 29.89, -CH$_2$-CH$_2$-CH=CH$_2$; $\delta$ = 24.76,
-CH₂-CH₂-CH=CH₂; δ = 15.88, N=C-CH₃.

**HPMPnP: Pentenoyl-pyrazolone C₁₅H₁₆N₂O₂**, GC-MS: FW=256; white crystals, melting point: 58-59 °C. ¹H NMR: δ = 7.82, ortho-CH on the phenyl ring; δ = 7.44, meta-CH on the phenyl ring; δ = 7.28, para-CH on the phenyl ring; δ = 5.88, CH₂=CH-; δ = 5.08, CH₃=CH-; δ = 2.84, -CO-CH₂-; δ = 2.47, Ar-CH₃; δ = 2.49, C₂H₃-CH₂. ¹³C NMR: δ = 197.48, -C=O-CH=CH-; δ = 160.54, HO-C=C<; δ = 147.49, -N=C-CH₃; δ = 137.41, >C-N< (on the phenyl ring); δ = 136.93, -CH₂-CH=CH₂; δ = 129.17, ortho-CH on the phenyl ring; δ = 120.66, para-CH on the phenyl ring; δ = 115.26, -CH₂=CH=CH₂; δ = 103.81, >CH-CO-; δ = 38.05, -CO-CH₂-; δ = 28.22, -CO-CH₂-CH₂-; δ = 15.84, N=C-CH₃.

**HPMBP: benzoyl-pyrazolone C₁₅H₁₆N₂O₂**, GC-MS: FW=256; light yellow crystals, melting point: 58-59 °C. ¹H NMR: δ = 7.82, ortho-CH on the phenyl ring; δ = 7.44, meta-CH on the phenyl ring; δ = 7.28, para-CH on the phenyl ring; δ = 5.88, CH₂=CH-; δ = 5.08, CH₃=CH-; δ = 2.84, -CO-CH₂-; δ = 2.47, Ar-CH₃; δ = 2.49, C₂H₃-CH₂. ¹³C NMR: δ = 197.48, -C=O-CH=CH-; δ = 160.54, HO-C=C<; δ = 147.49, -N=C-CH₃; δ = 137.41, >C-N< (on the phenyl ring); δ = 136.93, -CH₂-CH=CH₂; δ = 129.17, ortho-CH on the phenyl ring; δ = 120.66, para-CH on the phenyl ring; δ = 115.26, -CH₂=CH=CH₂; δ = 103.81, >CH-CO-; δ = 38.05, -CO-CH₂-; δ = 28.22, -CO-CH₂-CH₂-; δ = 15.84, N=C-CH₃.
Cyclic compound: $\text{C}_{14}\text{H}_{14}\text{N}_{2}\text{O}_{2}$, GC-MS: FW=242; white tiny crystals, melting point: 88-90 °C. $^1$H NMR: $\delta = 7.74$, ortho-$\text{CH}$ on the phenyl ring; $\delta = 7.45$, meta-$\text{CH}$ on the phenyl ring; $\delta = 7.29$, para-$\text{CH}$ on the phenyl ring; $\delta = 4.87$, -O-$\text{CH}<;$ $\delta = 2.58$, >CH-$\text{CH}_2$-CO-; $\delta = 2.46$, Ar-$\text{CH}_2$; $\delta = 1.58$, CH$_2$-CH<. $^{13}$C NMR: $\delta = 186.29$, -CO-$\text{CH}_3$; $\delta = 158.77$, -O-$\text{C}=\text{C}<;$ $\delta = 148.49$, -N=$\text{C}-\text{CH}_3$; $\delta = 137.46$, >C-N< (on the phenyl ring); $\delta = 129.22$, ortho-$\text{CH}$ on the phenyl ring; $\delta = 126.87$, meta-$\text{CH}$ on the phenyl ring; $\delta = 120.99$, para-$\text{CH}$ on the phenyl ring; $\delta = 103.06$, >CH-CO-; $\delta = 80.53$, >CH-$\text{CH}_3$; $\delta = 43.91$, -CO-$\text{CH}_2$-; $\delta = 20.63$, N=C-$\text{CH}_3$; $\delta = 14.15$, >CH-$\text{CH}_3$. 

42
CHAPTER IV

SYNTHESIS OF AMPHIPHILIC ACYLPYRAZOLONES

The general equation for the synthesis of the amphiphilic acylpyrazolones is shown in Scheme 4.1.

Scheme 4.1 Synthesis of amphiphilic acylpyrazolones.

Pyrazolones with different R’ and R” have been synthesized by using β-ketoesters (with R” group) and hydrazines (with R’ group) as described in Chapter III. Acylpyrazolones with a CH₂Cl group in the 4 position were synthesized in high yields by using equal molar concentration of the parent pyrazolone and acyl chloride in anhydrous THF in the presence of calcium hydroxide. The target amphiphilic acylpyrazolones have been obtained by reacting the chloromethyl-acylpyrazolone with the sodium salt of polyethylene glycol in anhydrous THF under reflux for 8-12 hours.
4.1 Synthesis of 1-phenyl-3-methyl-4-(4’-PEG)-benzoyl-5-pyrazolone ligands.

Acylpyrazolones discussed in Chapter III are all soluble in polar organic solvents, so they can be used as the extractant for rare earth metal ions and transition metal ions in organic solvents [29-31]. The ligand 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone (HPMBP) has been extensively investigated in the past 30 years for the separation of transition and lanthanide metal ions by solvent extraction. It was also used with crown ethers [32, 33] in order to improve selectivity in metal ion separations. Our goal as stated in the central hypothesis is to generate nanoscale structures in the aqueous phase for metal ion recognition, especially lanthanide metal ions. Such systems are also “green” as the use of the toxic organic solvents can be avoided and separation from aqueous solutions where metal ions are present can be employed in small and large scales.

We have synthesized acylpyrazolones that are soluble in water by attaching polyethylene oxides to the aliphatic and aromatic groups in the 4 position.

Polyethylene oxide was chosen to synthesize amphiphilic acylpyrazolones due to their properties below [34].

1. They are soluble in water and most organic solvents.
2. Both low molecular weight and high molecular weight precursor compounds are commercially available.
3. They have a free terminal –OH form which Na salt can be generated for the synthesis.
4. They have good thermal stability.
5. Copolymers of ethylene oxide are commercially available.
Polymers of polyethylene oxides, namely the polyethylene glycols were used in our study for the synthesis of amphiphilic acylpyrazolones. A literature survey indicated that while several publications on the synthesis of acylpyrazolones have appeared [10, 35-36], no report on the synthesis of aqueous soluble analogs have been reported. Our research represents the first studies to obtain amphiphilic acylpyrazolones.

There are three possible ways to attach the surfactant side chains to the acylpyrazolone core structures as shown in Figure 4.1.

Figure 4.1 Possible polyethylene glycol derivatives.

The structure contains both hydrophilic (OCH₂CH₂) and hydrophobic pyrazolone moieties making them amphiphilic. Such compounds solvents self-assemble to form micelles, vesicles and other structures in aqueous and nonaqueous [37-41]. These structures have nanoscale dimensions and have properties distinct from individual molecules and bulk materials. It is these unique properties that, as stated in the central hypothesis, we hope to exploit for the recognition of trivalent lanthanide metal ions.
Scheme 4.2 Synthetic method for family 2 in Figure 4.1.

The metal ion recognition efficacies of the above ligands were studied by HPLC employing the procedure in Chapter II. The selectivities of the above ligands are very poor as shown by the example in Figure 4.2 for the ligand HMP750VP and they were not pursued further. The family of ligands where the polyethylene glycol is attached to the acyl group in the 4 position (3 in Figure 4.1) provided the best results as discussed in detail in Chapter VI. This family of ligands is more readily synthesized than family 2.

Figure 4.2 HPLC separation of lanthanide metal ions with HMP750VP.
Acylpyrazolones with a terminal chloromethyl group (-CH$_2$Cl) can be readily converted to hydrophilic ligands. Several types of hydrophilic side chains can be introduced onto the acylpyrazolone structure by the method [35] that is shown below in Scheme 4.3.

**Scheme 4.3 Synthesis of family 3 ligands in Figure 4.1.**

![Scheme 4.3](image)

As discussed in CHAPTER III, acyl chlorides with a terminal CH$_2$Cl group can be reacted with different pyrazolones employing Ca(OH)$_2$ as base. The GC-MS analysis of the product indicates that it is a very high yield reaction. The gas chromatogram and the mass spectral fragmentation pattern for 1-phenyl-3-methyl-4-(4'-chloromethyl)benzoyl-5-pyrazolone is shown in Figure 4.3. The parent ion peaks of 326 and 328 are due to the $^{35}$Cl and $^{37}$Cl isotopes which occur in a 3:1 natural abundance ratio.

The isolated and recrystallized chloromethyl pyrazolone was reacted with the sodium salt of polyethylene glycol in THF. The final product was obtained with very good yield. Most of the ligands are red waxy solids, except for 1-phenyl-3-methyl-4-(4'PEG550) -benzoyl-5-pyrazolone (HPMBP550), which is a red liquid.
Figure 4.3 GC-MS data for 1-phenyl-3-methyl-4-(4′-chloromethyl)benzoyl-5-pyrazolone.

The structures of different acylpyrazolone PEG ligands are shown in Figure 4.7.

Figure 4.4 Surfactants and related ligand derivatives.

PEG550  n = 13
PEG750  n = 17
PEG2000 n = 45
Brij35p  n = 27
Triton X-100  n = 17
4.2 Study of the functional groups effects on the metal ion recognition properties of acylpyrazolones.

4.2.1 Brief introduction.

As Figure 4.5 shows, the predominant resonance structure of the acylpyrazolone will depend on the properties of $R'$, $R''$ and $R'''$. The X-ray crystal structures of acylpyrazolones in Chapter III support this aspect. It is thus important to understand the effect of substituents on the metal ion recognition efficacies of amphiphilic acylpyrazolones. An additional impetus of this study is the lack of information in the literature on acylpyrazolones with a variety of substituents. The acylpyrazolone extensively investigated is HPMBP. Some additional compounds such as 3-methyl-1-phenyl-pyrazol-5-one (PMP) [42-44], 1-methyl-3-methyl-pyrazol-5-one and 3-methyl-1-(4’-chloro)-phenyl-pyrazol-5-one have also been reported. Most of these parent pyrazolones were used to synthesize the herbicides [45, 46]. There are few reports for the synthesis of acylpyrazolones and their application in metal ion separation [47].

Figure 4.5 Isomers of the acylpyrazolone.

When the group $R'$; $R''$ and $R'''$ changed, the electron distribution on atoms 1; 2; 3; 4 and 5 will dramatically change, so that it makes the hydroxyl group either on the five membered pyrazolone ring or outside the ring. The acidity of the hydroxyl group (-OH) will be very different if they are on different structures, and also, the complexing ability
of the ligands with metal ions will also be different due to this reason. The functional
groups R’, R” and R”’ were systematically varied to identify the best combination of
substituents for the optimum selectivities of lanthanide metal ions. The substituents and
the polyethylene glycol influence their metal ion recognition efficacies and
self-assembling characteristics of amphiphilic acylpyrazolones as discussed in Chapter 6.

4.2.2 Synthesis of PEG750 acylpyrazolones.

For structure analysis of these compounds, the electronic effect is the most critical
factor to be considered. The electronic effects include:

1. resonance effect;
2. inductive effect. (depends on electronegativity)

As a result of these two electronic effects, different functional groups will show
different effects on the electron density distribution of the neighboring chemical bonds.
Electron donating and electron withdrawing groups have been investigated to understand
the electronic effects.

1. Electron donating groups; such as –OR, -OH, -NHR, -R, etc.
2. Electron withdrawing groups; such as –NO2, CF3, -CN, -CO-, etc.

In addition, steric hindrance can also influence the properties of these compounds
[48]. The compounds in Figure 4.6 have been examined as examples to understand the
interplay of these features.
The first compound: 1-phenyl-3-methyl-4-(4’-methylPEG750)-benzoyl-5-pyrazolone (HPMBP750) has very good selectivity for lanthanide metal ions separation by HPLC studies (Chapter VI). The second acylpyrazolone HMP750VP has poor metal ion recognition efficacy. These experimental results show that a different acylpyrazolone core structure will dramatically change the metal ion recognition properties.

The ligands in Figure 4.7-4.9 were synthesized to elucidate the influence of the substituents R’, R” and R”’ on metal ion recognition efficacies of this acylpyrazolones. The polyethylene glycol moiety was PEG750 and was not varied in these studies.

**Figure 4.7 Changing of R”**.

In this group only the substituent in the 3 position is changed while the phenyl group on the nitrogen atom remained.
The substituents in the 1 position were changed while those in the 3 and 4 positions were the same.

Here the substituent in the 4 position was changed while those in the 1 and 3 positions were the same in each ligand.

1 Synthesis of 1-phenyl-3-R’’-4-(4’methylPEG750)-benzoyl-pyrazol-5-one.

The synthetic route is shown in Scheme 4.4 below:
Scheme 4.4 Synthesis of 1-phenyl-3-R"'-4-(4'-methylPEG750)-benzoyl-5-pyrazolone.

\[
\text{R''} \text{O} \text{Et} + \text{PhNHNH}_2 \xrightarrow{\text{EtOH reflux}} \text{N} \text{N} \text{R''} \text{O} \text{Et} \xrightarrow{\text{base}} \text{N} \text{N} \text{R''} \text{O} \text{Cl} \xrightarrow{\text{NaOPEG}_{750}} \text{N} \text{N} \text{R''} \text{O} \text{PEG}_{750} \text{Cl}
\]

Phenyl hydrazine can be reacted with many types of \( \beta \)-ketoesters [49] and obtain many parent pyrazolone structures that have different substituent groups in the 3 position. This reaction always provides very good yields for the final product and generally, the product can be purified by recrystallization from ethanol. Some physical properties of the parent pyrazolones are shown in Table 3.1.

2 Synthesis of 1-R'-3-methyl-4-(4'methylPEG750)-benzoyl-pyrazol-5-one

The way to change substituents on the nitrogen atom is to use different hydrazines. Several types of hydrazines are commercial available, which have been utilized in synthesizing the desired N-substituted pyrazolones.

The synthetic route is shown in Scheme 4.5 below:
Scheme 4.5 Synthesis of 1-R’-3-methyl-4-(4’-methylPEG750)-benzoyl-5-pyrazolone.

Different parent pyrazolones were synthesized and their physical properties are shown in Chapter III, Table 3.1. These ligands were prepared for HPLC studies to evaluate their efficiencies for lanthanide metal ion recognition.

3 Synthesis of 1-phenyl-3-methyl-4-R’’’(-OPEG750)-5-pyrazolone.

1-Phenyl-3-methyl-5-pyrazolone was chosen to synthesize the amphiphilic acylpyrazolones with different acyl groups and PEG groups. All the amphiphilic acylpyrazolones are new compounds and not reported in the literature. The synthetic route is shown in Scheme 4.6.
Acyl chlorides used here include: 3-chloromethyl benzoyl chloride \((\text{ClCOC}_6\text{H}_4\text{m-CH}_2\text{Cl})\); 4-chloromethyl benzoyl chloride \((\text{ClCOC}_6\text{H}_4\text{p-CH}_2\text{Cl})\); 2-chloroacetic chloride \((\text{ClCOCH}_2\text{Cl})\); 3-chloropropionyl chloride \((\text{ClCOC}_2\text{H}_4\text{Cl})\); 4-chlorobutyryl chloride \((\text{ClCOC}_3\text{H}_6\text{Cl})\) and 5-chlorovaleryl chloride \((\text{ClCOC}_4\text{H}_8\text{Cl})\).

4.3 Experimental procedures.

(a) Reagents and physical methods

THF was distilled from sodium metal. All reagents were purchased from Sigma-Aldrich. The thermometer for melting points determination was uncorrected. The solvent for all NMR was \(d_6\)-DMSO.

(b) Synthesis of 1-phenyl-3-methyl-4-(4’-chloromethyl)-benzoyl-5-pyrazolone (HPMCMBP)

A 2.3g \((1.32\times10^{-2}\text{mol})\) of 1-phenyl-3-methyl-5-pyrazolone dissolved in 50 mL dry THF the solution was cooled to 0°C in an ice bath and 1g Ca(OH)\(_2\) was added to the cooled solution. It was stirred for 5 minutes followed by the dropewise addition of a solution of 2.5g \((1.32\times10^{-2}\text{mol})\) 4-chloromethyl-benzoyl chloride in 10 mL dry THF and stirred overnight. The orange red solution was filtrated to remove CaCl\(_2\) and excess Ca(OH)\(_2\). The solvent was evaporated to obtain a yellow solid, which was recrystallized from ethyl acetate/hexane. This provided 3.9g of pure compound (yield 90.3%). Mp: > 250°C. \(^1\)H
NMR (in d-chloroform): $\delta$: 7.69-7.11, protons on the phenyl ring; $\delta$: 4.61, Ph-CH$_2$-Cl; $\delta$: 2.35, Ar-CH$_3$.

(c) Synthesis of amphiphilic 4-benzoyl-5-pyrazolones.

The general procedure involved dissolving 0.0132 moles (based on average molecular weight) of polyethylene glycol companied in 100 mL of freshly distilled dry THF and reacting with thin plates of Na overnight at room temperature. The solution was filtered to remove excess Na and was added slowly to a solution of 3.9g (0.0119 moles) of 1-phenyl-3-methyl-4-(4’-chloromethyl)-5-pyrazolone in 30 mL THF and the mixture was refluxed for 12 hours. The filtrate was rotary evaporated to obtain the PEG-acylpyrazolone as a waxy solid. The following Table 4.1 summarizes the different PEG compounds employed, their amounts based on average molecular weight, and the yield of the amphiphilic acylpyrazolones.

<table>
<thead>
<tr>
<th>Compound</th>
<th>PEG compound</th>
<th>Amount used in synthesis (g)</th>
<th>Yield (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMBPBrij</td>
<td>Brij35p</td>
<td>16.0</td>
<td>20.0</td>
</tr>
<tr>
<td>HPMBP2000</td>
<td>PEG2000</td>
<td>26.5</td>
<td>30.0</td>
</tr>
<tr>
<td>HPMBP750</td>
<td>PEG750</td>
<td>10.0</td>
<td>14.0</td>
</tr>
<tr>
<td>HPMBP550</td>
<td>PEG550</td>
<td>7.30</td>
<td>11.5</td>
</tr>
<tr>
<td>HPMBPTriton</td>
<td>Triton X-100</td>
<td>8.32</td>
<td>12.0</td>
</tr>
</tbody>
</table>
(d) Synthesis of amphiphilic acylpyrazolones with 4-chloromethylbenzoyl chloride as the acyl group and PEG750 as the lipophilic group.

Pyrazolone (0.0132 moles) was dissolved in 60 mL of dry freshly distilled THF in a 150 mL three necked round bottom flask immersed in an ice bath and stirred for 5 minutes. A 0.98 g of Ca(OH)$_2$ was added to this solution and stirred for 15 minutes. A 10 mL solution of 2.5 g (0.0132 moles) of 4-chloromethyl-benzoyl chloride was added dropwise to this solution and stirred for 4 hours. The solution was filtrated to remove CaCl$_2$ and excess Ca(OH)$_2$. The acylpyrazolone was characterized by GC-MS, which indicated the product with the correct molecular weight and >90% purity. To this 50 mL of solution containing 10 g (0.01325 moles based on average molecular weight) of Na salt of PEG750 prepared as described in section (c) (previous synthesis) was added and heated to reflux for 12 hours. The solution was filtrated to remove NaCl and the filtrate was rotary evaporated to obtain the amphiphilic acylpyrazolone as a waxy solid. The different chloromethyl acylpyrazolones, their quantities and the yields of the amphiphilic acylpyrazolones are listed in Table 4.2.
Table 4.2 Synthesis of amphiphilic acylpyrazolones.

<table>
<thead>
<tr>
<th>Product</th>
<th>Amount of starting chloromethyl acylpyrazolone used (g)</th>
<th>GC-MS of the starting intermediate (molecular weight and purity (%))</th>
<th>Yield of amphiphilic acylpyrazolone (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMBP750</td>
<td>2.50</td>
<td>326/328; 92.7</td>
<td>14</td>
</tr>
<tr>
<td>HFPMBP750</td>
<td>3.20</td>
<td>\</td>
<td>14</td>
</tr>
<tr>
<td>HMMBP750</td>
<td>1.48</td>
<td>224/226, 50</td>
<td>7.0</td>
</tr>
<tr>
<td>HtBuPMBP750</td>
<td>2.04</td>
<td>264/266; &gt;95</td>
<td>13</td>
</tr>
<tr>
<td>HBnMBP750</td>
<td>2.49</td>
<td>340/342, 50</td>
<td>8.0</td>
</tr>
<tr>
<td>HMOPMBP750</td>
<td>2.70</td>
<td>356/358; 72</td>
<td>10</td>
</tr>
<tr>
<td>HMPMBP750</td>
<td>2.49</td>
<td>340/342; 65</td>
<td>9.0</td>
</tr>
<tr>
<td>HPPBP750</td>
<td>3.12</td>
<td>406/408, 88</td>
<td>13</td>
</tr>
<tr>
<td>HPNPBP750</td>
<td>3.70</td>
<td>\</td>
<td>11</td>
</tr>
<tr>
<td>HPEBP750</td>
<td>2.67</td>
<td>340/342, 70</td>
<td>10</td>
</tr>
<tr>
<td>HPPrBP750</td>
<td>2.49</td>
<td>354/356; 81</td>
<td>10</td>
</tr>
</tbody>
</table>

(e) Synthesis of amphiphilic acylpyrazolones with 1-phenyl-3-methyl-5-pyrazolone.

A 2.3 g (1.32x10^-2 mol) of 1-phenyl-3-methyl-5-pyrazolone was dissolved in 50 mL dry THF the solution was cooled to 0°C in an ice bath and 1g Ca(OH)₂ was added to the cooled solution. It was stirred for 5 minutes, a solution of 1.32x10^-2 mol of
chloromethyl-acyl chloride in 10 mL dry THF was added dropwise and stirred overnight. The solution was filtrated to remove CaCl$_2$ and excess Ca(OH)$_2$. The acylpyrazolone was characterized by GC-MS, which indicated the product with the current molecular weight and >90% purity. To this 50 mL of solution containing 10g (0.01325 moles based on average molecular weight) of Na salt of PEG750 prepared as described in section (c) (previous synthesis) was added and heated to reflux for 12 hours. The solution was filtrated to remove NaCl and the filtrate was rotary evaporated to obtain the amphiphilic acylpyrazolone as a waxy solid. The different 4 substituted acylpyrazolones, their quantities and the yields of the amphiphilic acylpyrazolones are listed in Table 4.3.

Table 4.3 Synthesis of amphiphilic acylpyrazolones with PMP.

<table>
<thead>
<tr>
<th>Product</th>
<th>Acyl chloride (g)</th>
<th>GC-MS of the starting intermediate (molecular weight and purity (%))</th>
<th>Yield (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMB3P750</td>
<td>2.50</td>
<td>326/328; 97</td>
<td>14</td>
</tr>
<tr>
<td>HPMAP750</td>
<td>1.49</td>
<td>250/252; 57.7</td>
<td>6.0</td>
</tr>
<tr>
<td>HPMPOP750</td>
<td>1.68</td>
<td>264/266; 40.1</td>
<td>6.0</td>
</tr>
<tr>
<td>HPMBOP750</td>
<td>1.86</td>
<td>278/280; 43.3</td>
<td>6.0</td>
</tr>
<tr>
<td>HPMVP750</td>
<td>2.05</td>
<td>292/294; 41.5</td>
<td>5.0</td>
</tr>
</tbody>
</table>
5.1 Brief introduction

Acylisoxazolone is another β-diketone ligand and has properties different from acylpyrazolones [51-55]. A literature search resulted in a total of 21 publications for isoxazolones and 4 publications for acylisoxazolones. Isoxazolones offer a unique opportunity for a new family of ligands for metal ion recognition and nanoscale self-assemblies. For example, isoxazolones are more polar than pyrazolones as indicated by their shorter retention time on a nonpolar stationary phase in GC-MS experiments and higher solubility in dioxane compared to pyrazolone. pKₐ values of acylisoxazolones are also considerably lower (as much as 3 pKₐ units) compared to acylpyrazolones [48, 51-54].

Figure 5.1 Comparison of the isomers of acylpyrazolones and acylisoxazolones.

It is evident from the isomers that the higher electronegativity of O compared to N would result in a lower pKa value for the enolic –OH in acylisoxazolones compared to
acylpyrazolones. We have synthesized isoxazolones, acylisoxazolones and amphiphilic acylisoxazolones with PEG moieties similar to acylpyrazolones to examine their metal ion recognition efficacies.

5.2 Synthesis of acylisoxazolones.

The parent isoxazolones can be synthesized by using β-ketoesters and hydroxyl amine (HONH$_2$·HCl) with good yields [54]. The acylation reaction discussed in Chapter III for pyrazolones can be employed for isoxazolones to obtain the acylisoxazolone ligands. The reactions are shown in Scheme 5.1 below:

**Scheme 5.1 Synthetic approach to acylisoxazolone.**

Two types of β-ketoesters were used in our synthesis namely ethyl acetoacetate and ethyl 3-oxo-3-benzyl propionate. The isoxazolones obtained are shown in Figure 5.1.

**Figure 5.2 Parent isoxazolones.**

These isoxazolones were used to synthesize acylisoxazolones as described below.
5.2.1 Synthesis of 3-phenyl-4-acyl-5-isoxazolone from aliphatic acyl chlorides.

As in the case of acylpyrazolones, literature reports on acylisoxazolones have employed strong bases like Ca(OH)$_2$ [48, 50, 54]. We pointed out in Chapter 3 that using a strong base will considerably lower the yields of acylpyrazolones if the acyl chlorides have an olefinic bond. Since our goal was to develop a general synthetic scheme that can be employed for the synthesis of acylisoxazolones with saturated and unsaturated aliphatic acyl groups in the 4-position, we investigated different solvents and temperatures to obtain the optimum yields.

The structures of our target acylpyrazolone compounds are shown in Figure 5.2 below:

**Figure 5.3 Structures of synthesized acylisoxazolones.**

![Structures of synthesized acylisoxazolones](image)

Aliphatic acyl chlorides that have been used are valeryl chloride ($\text{C}_5\text{H}_9\text{ClO}$), pentenoyl chloride ($\text{C}_8\text{H}_7\text{ClO}$), decanoyl chloride ($\text{C}_{10}\text{H}_{19}\text{ClO}$) and undecenoyl chloride ($\text{C}_{11}\text{H}_{19}\text{ClO}$). The solvents include THF, dioxane and dichloroethane and the bases used were calcium hydroxide ($\text{Ca(OH)}_2$) and triethylamine ($\text{Et}_3\text{N}$).
a. Effect of base on the acylation of isoxazolones.

As described in Chapter III, calcium hydroxide (Ca(OH)$_2$) and triethylamine (Et$_3$N) were used for the synthesis of acylisoxazolones in THF. The solvent was distilled over Na and benzophenone (PhCOPh). The reaction is shown in Scheme 5.3 and the results are summarized in Table 5.1.

Scheme 5.2 Synthesis of acylisoxazolone.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
+ & \quad \text{Cl}_\text{R} \\
\text{base} & \quad \text{O} \\
\text{THF} & \\
\end{align*}
\]

\[R = \text{C}_4\text{H}_9, \text{C}_4\text{H}_7, \text{C}_9\text{H}_{19}, \text{C}_{10}\text{H}_{19}\]

Table 5.1 Base effects.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction yield (%)</th>
<th>Ca(OH)$_2$, 0$^\circ$C, 4hs</th>
<th>Et$_3$N, rt, 4hs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPVI</td>
<td>55</td>
<td>\</td>
<td>\</td>
</tr>
<tr>
<td>HPPOI</td>
<td>42</td>
<td>\</td>
<td>\</td>
</tr>
<tr>
<td>HPDI</td>
<td>40</td>
<td>\</td>
<td>\</td>
</tr>
<tr>
<td>HPUI</td>
<td>33</td>
<td>\</td>
<td>\</td>
</tr>
</tbody>
</table>

*: “\” means yield was very low.

It is clear from this table that no acylisoxazolones were obtained with Et$_3$N or with Ca(OH)$_2$; the yields were considerably lower than those for acylpyrazolones as described in Chapter III. Reaction mixtures where Et$_3$N was employed as base when analyzed by
GC-MS indicated that the isoxazolones have undergone ring opening reactions evident by the presence of several GC peaks and corresponding mass spectra. In an independent experiment we observed that mixing isoxazolone with Cu(II) acetate in methanol immediately reduced Cu(II) to Cu(I). It is possible that an adduct formation between the keto oxygen of isoxazolone and Et$_3$N occurs with the subsequent formation of ring opening products.

A comparison of the GC-MS analysis of valerylpyrazolone and valerylisoxazolone synthesized with Ca(OH)$_2$ is made in Figures 5.3 and 5.4. It is evident that the PMP reacts cleanly with valeryl chloride with only a minor amount of PMP remaining upon completion of the synthesis. In the case of the isoxazolone, no starting compounds are present when the synthesis is complete and the acylisoxazolone HMVI is not the only product obtained. Another product that was not identified but could be removed by recrystallization was obtained as may be seen from the GC data.

Figure 5.4 GC-MS data for the acylation of pyrazolone.
b. Solvent effects.

The influence of the solvents THF and dioxane on the synthesis of acylisoxazolones with Ca(OH)$_2$ as the base was studied, the results are compared in Table 5.2, and the reaction is shown in Scheme 5.4 below.

Scheme 5.3 Synthesis of acylisoxazolones.
Table 5.2 Solvent effects for the acylation reaction.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction yield (%)</th>
<th>Dioxane, C_4H_8O_2</th>
<th>THF, C_4H_8O</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPVI</td>
<td>53</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>HPPOI</td>
<td>45</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>HPDI</td>
<td>38</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>HPUI</td>
<td>36</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

Both THF and dioxane are suitable for the synthesis of acylisoxazolones. It may be seen that the yields are not as high as in the case of acylpyrazolones and the yields for alkenyl R groups are much poorer compared to alkyl R groups. This may be due to the susceptibility of the olefinic bond to strong bases like Ca(OH)_2, which may lead to side products.

5.2.2 Synthesis of 3-methyl -4-(4’-PEG750)-benzoyl isoxazolone.

Amphiphilic acylisoxazolones were synthesized in an analogous procedure to acylpyrazolones. The synthesis of acylisoxazolones with PEG 750 in the 4 position is shown in Scheme 5.5. The two compounds synthesized by this procedure with different substituents in the 3 position are shown in Figure 5.5.
Scheme 5.4 Synthesis of amphiphilic ligands.

\[
R'' \text{O} \text{O} + \text{HONH}_2\text{HCl} \xrightarrow{\text{heat, EtOH}} \text{N}^{R''} \text{O} \text{H}
\]

\[
\text{N}^{R''} \text{OH} + \text{Cl} \text{R}'''' \text{O} \text{Cl} \xrightarrow{\text{Ca(OH)}_2, \text{THF}} \text{N}^{R''} \text{O} \text{R}'''' \text{Cl}
\]

\[
\text{N}^{R''} \text{OH} \text{R}'''' \text{Cl} \xrightarrow{\text{NaOPEG}_{750}} \text{N}^{R''} \text{O} \text{R}'''' \text{OPEG}_{750}
\]

Figure 5.6 Synthesized amphiphilic acylisoxazolones.

5.3 Experimental procedures.

a. Reagents and physical methods

THF was distilled from sodium metal. All reagents were purchased from Sigma-Aldrich.

The thermometer for melting point determination is uncorrected.

The solvent for all NMR was DMSO-\text{d}6.
b. Synthesis of isoxazolones.

Synthesis of 3-methyl-5-isoxazolone. Hydroxyl amine hydrochloride 10 g (0.144 mol) was added into 250 mL round bottom flask with 100 mL ethanol. A 18.2 mL (0.144 mol) of ethyl acetoacetate was added to this under stirring and the mixture was refluxed for 48 hours. The solid product was collected by filtration and washed 3 times with 10 mL of ethanol. It was recrystallized from ethanol and the pure compound was obtained with a yield of 68%. $^1$HNMR: phenyl protons: δ = 7.70-7.30; -OH proton (enol form): δ = 11.76; -CO-CH$_2$-: δ = 2.31(t); -CO-CH$_2$-CH$_2$-: δ = 1.52(m); -CO-(CH$_2$)$_2$-CH$_2$-CH$_3$: δ = 1.16(m), -CO-(CH$_2$)$_3$-CH$_3$: δ = 0.73(t).

Synthesis of 3-phenyl-isoxazolone. Hydroxyl amine hydrochloride 10 g (0.144 mol) was added into 250 mL round bottom flask with 100 mL ethanol. A 24.9 mL (0.144 mol) of ethyl 3-oxo-3-benzyl-propionate ester was added to this under stirring and the mixture was refluxed for 60 hours. The solid product was collected by filtration and washed 3 times with 10 mL of ethanol. It was recrystallized from ethanol and the pure compound was obtained with a yield of 68%. Melting point: 153-155 °C, $^1$HNMR: phenyl protons: δ = 7.68-7.47(m); -CO-CH$_2$- (on the isoxazolone ring): δ = 3.81(s).

c. Synthesis of acylisoxazolones.

The general synthetic method is given with HMVI as the example. A 5 g weight of
3-phenyl-5-isoxazolone was dissolved in 30mL dry THF in a 100 mL round bottom flask, cooled in ice bath followed by the addition of 2.3 g (3.1x10^-2 mol) of calcium hydroxide (Ca(OH)₂) and stirred for 5 minutes. A 3.7 mL (3.1x10^-2 mol) volume of valeryl chloride was added and stirred for 4 hours. The solution was filtered and the solvent was removed by rotary evaparate. The product was recrystallized from ethyl acetate/hexane. The pure compound was obtained with 55% yield.

The melting points and ¹H and ¹³C{¹H} data for the acylisoxazolones are given below. The molecular formula of these compounds and their structures were also established by their characteristic GC-MS analysis. Elemental (C, H, N) analysis was not performed.

**Synthesis of 3-phenyl-4-valeryl isoxazolone** GC-MS: FW=245. ¹H NMR:  phenyl protons: δ = 7.70-7.30; -OH proton (enol form): δ = 11.76; -CO-CH₂-: δ = 2.31(t); -CO-CH₂-CH₂-: δ = 1.52(m); -CO-(CH₂)₂-CH₂-CH₃: δ = 1.16(m), -CO-(CH₂)₃-CH₃: δ = 0.73(t).

**Synthesis of 3-phenyl-4-pentenoyl isoxazolone** GC-MS: FW=243. ¹H NMR: phenyl protons: δ = 7.70-7.30; -OH proton (enol form): δ = 11.76; CH₂=CH-: δ = 5.88; δ = CH₂=CH₂: 5.08; -CO-CH₂-: δ = 2.84; C₂H₅-CH₂: δ = 2.49.

**Synthesis of 3-phenyl-4-decanoyl isoxazolone**, GC-MS: FW=301. ¹H NMR: phenyl protons: δ = 7.70-7.30; -OH proton (enol form): δ = 11.76; -CO-CH₂-: δ = 2.72; -CO-CH₂-CH₂-: δ = 1.73; -(CH₂)₆-: δ = 1.22-1.45; -(CH₂)₆-CH₂-: δ = 0.87.
Synthesis of 3-phenyl-4-undecenoyl isoxazolone, GC-MS: FW=327. $^1$H NMR: phenyl protons: $\delta = 7.70-7.30$; -OH proton (enol form): $\delta = 11.76$; CH$_2$=CH-: $\delta = 5.80$; CH$_2$=CH-: $\delta = 4.93$; -CO-CH$_2$: $\delta = 2.84$; C$_2$H$_3$-CH$_2$: $\delta = 2.04$; -CO-CH$_2$-CH$_2$: $\delta = 1.72$; -(CH$_2$)$_2$: $\delta : 1.27-1.48$.


Synthesis of 3-phenyl-4-(4’-chloromethyl)-benzoyl-5-isoxazolone A 2.13 g (1.32x10$^{-2}$ mol) amount of 3-phenyl-5-isoxazolone was dissolved in 50 mL dry THF, cooled in an ice bath, and 1 g (1.32x10$^{-2}$ mol) of calcium hydroxide (Ca(OH)$_2$) was added. After stirring for 5 minutes, 2.5 g (1.32x10$^{-2}$ mol) of 4-chloromethyl benzoyl chloride was added and stirred for 4 hours. The solution was filtered and the filtrate was carried to the next step.

Synthesis of 3-phenyl-4-(4’-methyl-PEG750)-benzoyl-5-isoxazolone A 10 g quantity of PEG 750 was dissolved in 100 mL dry THF and an excess of sodium metal was added to make the Na salt of PEG750. The reaction was carried out overnight. The solution was filtered and combined with the solution of the chloromethyl compound obtained above and refluxed for 12 hours. The THF solution was centrifuged to remove NaCl and the solvent was evaporated to obtain the yellow waxy HPBI750.
e. Synthesis of 3-methyl-4-(4’-methyl-PEG750)-benzoyl isoxazolone.

Synthesis of 3-methyl-4-(4’-chloromethyl)-benzoyl-5-isoxazolone A 1.31 g (1.32x10^{-2} mol) amount of 3-methyl-5-isoxazolone was dissolved in 50 mL dry THF, cooled in an ice bath, and 1 g (1.32x10^{-2} mol) of calcium hydroxide (Ca(OH)₂) was added. After stirring for 5 minutes, 2.5 g (1.32x10^{-2} mol) of 4-chloromethyl benzoyl chloride was added and stirred for 4 hours. The solution was filtered and the filtrate was carried to the next step.

Synthesis of 3-phenyl-4-(4’-methyl-PEG750)-benzoyl-5-isoxazolone A 10 g quantity of PEG 750 was dissolved in 100mL dry THF and an excess of sodium metal was added to make the Na salt of PEG750. The reaction was carried out overnight. The solution was filtered and combined with the solution of the chloromethyl compound obtained above and refluxed for 12 hours. The THF solution was centrifuged to remove NaCl and the solvent was evaporated to obtain the yellow waxy HMBI750.
6.1 Brief introduction.


The Perkinelmer HPLC instrument used in lanthanide metal ion separation studies is shown in Figure 6.1.

Figure 6.1 HPLC instrument.
HPLC determination.

The HPLC data were collected by Perkin Elmer Series 200, with UV-VIS detector.

Loop size: 20 µl

Quantinary pump: Perkin Elmer Series 200,

UV-Vis detector: Perkin Elmer Series 200 UV-Vis detector,

Postcolumn derivatization pump: Altex A100,

Sample introduction: Manual injection;

Stationary phase: 3 µm, 100 Å, C18 silica gel;

The conditions that are used for the experiment include:

Mobile phase: Ligand dissolved in aqueous solution at the desired pH; Ionic strength=0.1, adjusted with NaClO4;

Ligand concentration of PEG ligands were calculated using average molecular weight.

Flow rate: 1mL/min;

Buffer solutions: chloroacetic acid buffer of ionic strength 0.01 for pH range 2-3, or formic acid buffer of ionic strength 0.01 for pH range 3-4 [17];

Total ionic strength: 0.1; (adjusted with NaClO4)

Metal ion detection: Postcolumn derivatization of the metal ion with Arsenazo III (Figure 2.7) at pH: 3.45, detection wavelength: 656 nm, indicator flow rate: 0.5 mL/min [9];

Data collection was performed with PerkinElmer TOTAL CHROM Workstation,
b. Column.

The HPLC columns were packed by using the Alltech HPLC Column Model 1666 Slurry Packer (Figure 6.2), which is a self-contained unit designed to pack columns. The materials that were used for packing a column include:

1. A 125 mm of length of the column with inner diameter 4.6 mm and outer diameter 6.25 mm (1/4 inch);

2. The solvent employed is HPLC grade methanol;

3. The C\textsubscript{18} silica gel particle size is 3 \textmu m, 100 Å.

First, the column and the end fittings were assembled with the reservoir and made sure there was enough gas pressure and solvent to pack. A 2.0 g weight of C\textsubscript{18} silica gel was added in a 30 mL beaker with 20 mL of HPLC grade methanol. This mixture was kept in the ultrasonic bath for 5 minutes and added to the reservoir through a glass stick. The reservoir was sealed. A nitrogen gas at an inlet pressure of 8,000 psi with a regulator was applied and the air supply valve was turned to “ON” position. The nitrogen pressure regulator was moved clockwise to obtain a pressure of 7500 psi and the prime valve was opened until there was the methanol flow, then the prime valve was closed and the solvent flow needle valve was opened to the maximum.
Figure 6.2 Alltech HPLC Column Model 1666 Slurry Packer.

1. Air Supply Pressure Gauge;  2. Air Supply ON/OFF;  3. Air Pressure Regulator;  
4. Solvent Pressure Gauge;  5. Pressurizing Solvent Selector;  6. Prime Valve;  
7. Solvent Flow Needle Valve ON/OFF.

After consuming 500-600 mL of methanol, the solvent flow needle valve was turned to “OFF” position. The air supply was turned to “OFF” position and then the air pressure regulator was adjusted anticlockwise to “0”. The reservoir was opened and methanol was removed. The column was disconnected from the reservoir, the silica gel was smoothed with a spatula and the end fittings were attached.
6.2 HPLC separation of rare earth metal ions by using self-assembling 1-phenyl-3-methyl-4-(4’-PEG)benzoyl-5-pyrazolone family ligands.

In Chapter IV, the synthesis of 1-phenyl-3-methyl-4-(4’-PEG)benzoyl-5-pyrazolone family ligands were described. These ligands in comparison to HPMBP are soluble in the aqueous phase and self-assemble to form various structures as described in section 6.2.3. The structures of these ligands are shown in Figure 6.3:

Figure 6.3 Parent HPMBP and its amphiphilic derivatives.

These ligands were all dissolved in water and the solutions were used as the mobile phase in HPLC separation studies. Comparison was also made by dissolving HPMBP in a ten fold excess of PEG550, PEG750, PEG200 and Brij35p. HPLC studies were performed to discern the influence of the following on the separation of the lanthanide metal ions.

1. Ligand concentration.
2. pH of the mobile phase.
3. Ionic strength of the solution.
4. Structure of the ligand.
6.2.1 Dependence of lanthanide metal ion separation on ligand concentration.

The results of HPLC separations of lanthanide metal ions are shown in the following figures. The ligand concentrations and pH are listed for each figure. The total ionic strength was adjusted to 0.1 with NaClO₄. The buffer was chloroacetic acid plus NaOH which had an ionic strength of 0.01 [17].

1. 1-phenyl-3-methyl-4-(4’brij35p)benzoyl-5-pyrazolone.

**Figure 6.4** HPLC separation with HPMBPBrij. Ligand concentration: 2x10⁻⁵ M; pH=2.52.

![Graph showing HPLC separation](image)

**Figure 6.5** HPLC separation with HPMBPBrij. Ligand concentration: 1x10⁻⁵ M; pH=2.57.

![Graph showing HPLC separation](image)
Figure 6.6 HPLC separation with HPMBPBrij. Ligand concentration: $5 \times 10^{-6}$ M; pH=2.44.

It can be seen from these separations the best separation was obtained with a ligand concentration of $5 \times 10^{-6}$ M.

2. 1-phenyl-3-methyl-4-(4’-PEG2000)benzoyl-5-pyrazolone.

Figure 6.7 HPLC separation with HPMBP2000. Ligand concentration: $2 \times 10^{-5}$ M; pH=2.20.
Figure 6.8 HPLC separation with HPMBP2000. Ligand concentration: $1 \times 10^{-5}$ M; pH=2.16.

While good separation was achieved at all HPMBP2000 concentrations, the concentration $5 \times 10^{-6}$ M was clearly better than the higher concentrations.

Figure 6.9 HPLC separation with HPMBP2000. Ligand concentration: $5 \times 10^{-6}$ M; pH=2.23.
3. 1-phenyl-3-methyl-4-(4’-PEG750)benzoyl-5-pyrazolone.

Figure 6.10 HPLC separation with HPMBP750. Ligand concentration: 1x10^{-5} M; pH=2.25.

Figure 6.11 HPLC separation with HPMBP750. Ligand concentration: 5x10^{-6} M; pH=2.35.

The two concentrations employed for HPMBP750 again indicate that the concentration of 5x10^{-6} M provided the best separation of lanthanide metal ions.
Interesting differences among the different PEG amphiphilic ligands of HPMBP were noticed in the above separations. These differences will be rationalized in section 6.2.3.

6.2.2 Comparison of 1-phenyl-3-methyl-4-(4’-PEG2000)benzoyl-5-pyrazolone with 1-phenyl-3-methyl-4benzoyl-5-pyrazolone.

The structures of these two ligands are shown in Figure 6.12.

**Figure 6.12 HPMBP and HPMBP2000.**

![Figure 6.12 HPMBP and HPMBP2000.](image)

The stability constants for a given metal ion can be expected to be similar and the metal ions selectivities as a result can also be expected to be similar for these two ligands. Their solubilities in the aqueous phase are markedly different with HPMBP2000 being readily soluble while HPMBP being insoluble. The ligand HPMBP however will dissolve in the aqueous phase in the presence of excess PEG2000. The HPLC separations of the lanthanide metal ions were compared with HPMBP2000 and HPMBP dissolved in the aqueous phase in the presence of excess PEG2000. The chromatogram for the latter is shown in Figure 6.13.
Figure 6.13 HPLC separation with HPMBP dissolved in PEG2000. Ligand concentration: $5 \times 10^{-6}$ M; pH=2.63.

It may be seen that a mixture of HPMBP and PEG2000 is also capable of separating the lanthanide metal ions but at a much lower efficiency compared to HPMBP2000. This
lower efficiency results in incomplete separation even for light lanthanides. Clearly in this case the PEG2000 chemically bonded to HPMBP compared to the mixture of the ligand and PEG2000 provides much better separation.

6.2.3 Comparison of 3-methyl-1-phenyl-4-(4’-PEG)benzoyl-5-pyrazolone family ligands.

Polyethylene glycols are widely used surfactants to solubilize organic compounds dissolve in aqueous solutions. Because of the activity of the hydroxyl group, polyethylene glycols are usually chemically bonded with the organic compounds so that the compounds will be soluble in water and this method is widely used in biochemistry [56].

The surfactants that were adopted in our research include: PEG 550, PEG750, PEG2000, Brij35p and Triton X-100. The chemical structures of these surfactants are shown in Figure 6.15.

Surfactants PEG 550, PEG750 and PEG2000 have methyl group (CH$_3$-) as the end group, Brij35p has the linear C$_{12}$H$_{25}$ non-polar chain as the end group and Triton X-100 has the branched bulky group (tertc$_8$H$_{17}$) as the end group. The different end groups may be expected to influence the adsorptivities of the surfactants on the C$_{18}$ stationary phase and self-assembly in the aqueous phase.
The separation of the lanthanide metal ions under identical condition of ligand concentration $5 \times 10^{-6}$ M and pH 2.2-2.4 are compared in Figures 6.16 ae. These chromatograms indicate the following:

1. The selectivities and efficiencies of separation are very different.

2. HPMBP ligand with **PEG750** and **PEG2000** provide excellent separations of a mixture of light, middle and heavy lanthanide metal ions. The separation efficiency for HPMBP750 is better than for HPMBP2000.

3. HPMBP Brij separates the same mixture of lanthanide metal ions at a much lower efficiency than HPMBP750 and HPMBP2000.

4. HPMBP550 and HPMBP Triton provide very poor separation as mentioned above. These differences may stem from the differences in the nature of the self-assemblies of these ligands in the aqueous phase and the stationary phase. A more detailed discussion is provided in a later section in this chapter.
Figure 6.16 HPLC chromatograms of PEG family ligands.

a. HPLC separation with HPMBPBrj.

![HPLC chromatogram with HPMBPBrij](image)

b. HPLC separation with HPMBP2000.

![HPLC chromatogram with HPMBP2000](image)
c. HPLC separation with HPMBP750.

![Graph](image)

La1Ce1Pr1.5Nd2Sm3.6Eu3.6Ho5-100103-0.000005N6pH2.35

<table>
<thead>
<tr>
<th>Element</th>
<th>Retention Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>La</td>
<td>2.47</td>
</tr>
<tr>
<td>Ce</td>
<td>3.43</td>
</tr>
<tr>
<td>Pr</td>
<td>4.70</td>
</tr>
<tr>
<td>Nd</td>
<td>5.87</td>
</tr>
<tr>
<td>Sm</td>
<td>15.77</td>
</tr>
<tr>
<td>Eu</td>
<td>21.40</td>
</tr>
<tr>
<td>Ho</td>
<td>31.70</td>
</tr>
</tbody>
</table>

d. HPLC separation with HPMBP550.

![Graph](image)

La1Ce1Nd2.5Sm3.5Ho5.5-100105-0.000005N9pH2.54

<table>
<thead>
<tr>
<th>Element</th>
<th>Retention Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>La</td>
<td>2.17</td>
</tr>
<tr>
<td>Ce</td>
<td>2.70</td>
</tr>
<tr>
<td>Nd</td>
<td>3.33</td>
</tr>
<tr>
<td>Sm</td>
<td>7.00</td>
</tr>
<tr>
<td>Ho</td>
<td>14.27</td>
</tr>
</tbody>
</table>
e. HPLC separation with HPMBPTriton.

The nature of the self-assemblies of the amphiphilic HPMBP ligands in the aqueous phase were examined by TEM. The images obtained with 5x10^{-3} M aqueous solution of these ligands are displayed in Figures 6.17-6.21.

**Figure 6.17 TEM images of HPMBPBrij.**
Figure 6.18 TEM images of HPMBP2000.

Figure 6.19 TEM images of HPMBP750.

Figure 6.20 TEM images of HPMBP550.
The TEM images reveal three types of self-assemblies:

1. Long branched linear structures.
2. Star shaped dendritic structures.
3. Spherical structures resembling vesicles.

The star shaped dendritic structures are formed by all ligands. The spherical structures are formed in ligands with PEG550, PEG750 and Triton X-100. The linear structures are formed in ligands with PEG550, PEG750 and Brij35p.

The formation of these structures could be rationalized by the formation of micelle and vesicle self-assemblies as displayed in Figure 6.22 and 6.23. The types of aggregation for each ligand are summarized in Table 6.1.
Figure 6.22 Ligand self-assemblies in aqueous solution.

\[
\text{Self-Assembly}
\]

\[
\begin{align*}
\text{PEG550} & : \text{HO} & -O- & n & \text{-Me} \\
\text{PEG750} & : \text{HO} & -O- & n & \text{-C}_{12}H_{25} \\
\text{PEG2000} & : \text{HO} & -O- & n & \text{-C}_{t}H_{17} \\
\text{Brij35p} & : \text{HO} & -O- & n & \text{-Me} \\
\text{Triton X-100} & : \text{HO} & -O- & n & \text{-C}_{12}H_{25}
\end{align*}
\]

\[
L = \text{Ligand site}
\]

\[
\begin{align*}
R & = \text{Brij, PEG, Triton X-100} \\
\text{a} & \rightarrow \text{b}
\end{align*}
\]

Figure 6.23 Formation of vesicles.

Table 6.1 Self-assemblies of the different amphiphilic HPMBP ligands.

<table>
<thead>
<tr>
<th>ligand</th>
<th>Shape of Self-assemblies</th>
<th>Size</th>
<th>Shape of Self-assemblies</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type c (from Type a)</td>
<td></td>
<td>Type d (from Type b)</td>
<td></td>
</tr>
<tr>
<td>HPMBPBrij</td>
<td>Linear</td>
<td>&gt;100µm</td>
<td>Dendritic</td>
<td>&lt;1µm</td>
</tr>
<tr>
<td>HPMBP2000</td>
<td>Linear</td>
<td>&gt;100µm</td>
<td>Dendritic</td>
<td>&lt;1µm</td>
</tr>
<tr>
<td>HPMBP750</td>
<td>/</td>
<td>/</td>
<td>Dendritic</td>
<td>&lt;1µm</td>
</tr>
<tr>
<td>HPMBP550</td>
<td>Linear</td>
<td>&gt;100µm</td>
<td>Dendritic</td>
<td>&gt;1µm</td>
</tr>
<tr>
<td>HPMBPTriton</td>
<td>Spherical</td>
<td>0.3-0.4µm</td>
<td>Dendritic</td>
<td>&lt;1µm</td>
</tr>
</tbody>
</table>

90
1. Formation of micelle type self-assemblies: This is due to ligand site aggregation (type a and b) due to intermolecular hydrogen bonding between the carbonyl group and the hydroxyl group which is a strong interaction and is thermodynamically favored. The micelles could have either the R group or ligand L on the surface.

2. Formation of vesicle type, star shaped and linear structures: These are the result of type c and d aggregation involving the following types of interactions:
   a. van der Waal’s interaction between the hydrophobic side chains R resulting in tail to tail self-assembly and vesicle structures with the polar ligand group on the surface of the vesicle. These would be derived from micelles with R group on the surface. This leads to vesicles with a nonpolar bilayer region.
   b. Intermolecular hydrogen bonding between the L groups on the surface of micelles and free ligands to yield vesicles where the R group of the surfactants is on the surface. This leads to vesicles with a polar bilayer region.
   c. Further self-assemblies of the L groups and R groups on the surface of the vesicles leading to star shaped dendritic structures. This can also lead to multilamellar type vesicles, namely, vesicle inside a vesicle. Such structures are normally encountered with lipids.
   d. The linear fibrous structures are also formed by the van der Waal’s interaction between the R groups and the intermolecular hydrogen bonding between the ligand groups. These are dense structures where most likely the R to R and L to
L assembly alternates. That is, $LR\cdots RL\cdots LR\cdots RL$. Such a self-assembly is a function of the nature of $R$ and the number of oxyethylene groups. Branched $R$ groups do not form linear structures as indicated by Triton X-100. It is interesting to note that PEG 750 which is linear like. PEG550, PEG750 and Brij35p does not form linear structures. This may be due to preference for forming spherical and dendritic structures over linear structures.

Structures of this type identified for the amphiphilic acylpyrazolone ligands have been observed by other studied in the literature. Spherical vesicle type structures have been identified by Johnsson for polyethylene glycols themselves [57]. Macrocyclic amphiphilic ligands and alkylquinoline ligands and terpyridyl ligands derivatized with polyethylene glycols have also been shown to form various types of spherical and linear structures [58-61]. Our studies have examined the same acylpyrazolone ligands with various PEG groups substituted in the 4 position. While precedence for the self-assembly of amphiphilic ligands exists in the literature [62], our studies indicate the dependence of the self-assembly on the subtle changes in the nature of the PEG group.

6.3 HPLC separation with amphiphilic acylpyrazolones with varying substituents.

The influence of the nature of the substituents in the 1, 3 and 4 position of the acylpyrazolone on the separation of lanthanide metal ions was also investigated. The
nature of the PEG group was PEG750 and was not changed in these studies. The studies with HPMBP clearly indicated that PEG750 provided the best separation among the various PEG groups.

6.3.1 Substituents in 1 position (R’ group).

The various ligands with different R’ groups in the 1 position employed in HPLC separation are displayed in Figure 6.24. The substituents in the 3 and 4 positions were methyl and benzoyl respectively.

**Figure 6.24 Ligands with different substituents in 1 position (R’ group).**

![Chemical structures](image)

The best separation for each ligand is shown in the following figures, which was obtained after optimization of pH and ligand concentration.
Separation results for this ligand can be summarized as:

1. Baseline separation of light lanthanide metal ions $\text{La}^{3+}$, $\text{Ce}^{3+}$, $\text{Pr}^{3+}$ and $\text{Nd}^{3+}$ was obtained.

2. Selectivity for the middle lanthanide metal ions $\text{Sm}^{3+}$ and $\text{Eu}^{3+}$ is good but the resolution is poorer compared to the light lanthanides. This is due to the poorer chromatographic efficiency which does not result in baseline separation.

3. The selectivity and resolution for the heavy lanthanide metal ions is poor. The reasons for the above observations will be described under mechanism of separation section 6.4.
Figure 6.26 HPLC separation with HMOPMBP750. Ligand concentration: $5 \times 10^{-6}$ M, pH = 2.17.

The separation results for this ligand are:

1. Poor efficiency for all metal ions.
2. Good selectivity for light lanthanide metals.
3. Very low selectivity for middle and heavy lanthanide metals.

Figure 6.27 HPLC separation with HMPMBP750. Ligand concentration: $2 \times 10^{-6}$ M, pH = 2.01.
The separation results of this ligand are:

1. Poor selectivity and efficiency.
2. Requires low pH (high acidity);
3. Very poor selectivity for middle and heavy lanthanide metals.

**Figure 6.28 HPLC separation with HMMPB750.** Ligand concentration: $2 \times 10^{-4}$ M, pH=4.71.

The separation results of this ligand are:

1. Very poor selectivity for all lanthanide metal ions.
2. No separation at low pH;
3. Requires high pH even for partial separation;
4. It’s a very weak ligand for lanthanide metal ions.
The separation results of this ligand are:

1. Very poor selectivity for lanthanide metal ions,

2. Requires relatively high pH for any separation to be noticed and no separation occurs at low pH,

3. Weak ligand for lanthanide metal ions.
The separation results of this ligand are:

1. No selectivity for lanthanide metal ions,
2. No retention of metal ions at low pH,
3. Partial retention at high pH but there is no separation,
4. A very weak ligand for lanthanide metal ions.
The separation results of this ligand are:

1. Very poor selectivity for lanthanide metal ions,

2. No metal ion retention at low pH,

3. Higher retention at high pH but very poor selectivity for light, middle and heavy lanthanides.

4. Weak ligand for lanthanide metal ions.

From the above results, we can conclude:

1. None of the ligands separate the lanthanide metal ions as well as the acylpyrazolone with the phenyl group in the 1 position. Both substitution on the phenyl group and substitution of the phenyl group with alkyl groups adversely affect the selectivity and separation of metal ions. A major reason for this may be the description of the
self-assembly of the ligands on the C18 stationary phase. This is discussed further under the mechanism of separation in section 6.4. Further the predominant resonance structure for the ligand is one in which the C=C double bond of the βdiketone structure is in the pyrazolone ring leading to good stability for the lanthanide metal complexes.

2. When electron donating group is substituted in 1 position, the stability constant for the lanthanide metal ions could be much lower compared to the acylpyrazolone with phenyl group in the 1 position. The lower stability constants could require high pH for complexation to occur and for separation.

Figure 6.32 Influence with electron donating groups in 1 position.

![Figure 6.32 Influence with electron donating groups in 1 position.](image)

The low stability constant may be the result of the electron donating group lowering the electron density on the nitrogen in 1 position and increasing the electron density on the carbonyl carbon in 5 position of the pyrazolone ring. This would lead to a resonance structure shown above where the double bond of the βdiketone moiety has outside the pyrazolone ring. This would lead to lower stability constant.

3. When electron withdrawing group (EWD) is present in the para position of 1-phenyl ring, the electron density on the positions a and b will be increased, leading to reduced electron delocalization of the pyrazolone ring. The phenyl group will exhibit
electron donating property to the pyrazolone ring and decrease polarity of the OH group. This in turn will lead to low lanthanide metal ion stability constants and poor metal ion selectivity.

**Figure 6.33 Influence with electron withdrawing groups in the *para* position of 1-phenyl ring.**

These ligands show the very weak complexation with metal ions and generally, they need high pH (pH > 4) similar to the electron donating alkyl groups discussed above.

4. When an electron donating group (EDG) is present in the *para* position of the phenyl ring, (Figure 6.33) electron density on positions a, b will increase and the electron delocalization from the pyrazolone ring to the phenyl ring will increase. This will increase the stability constant of the lanthanide metal complexes. Such ligands as shown in Figure 6.24 will provide separation at a very low pH. The selectivity however is a function of the differences in the stability constants of the adjacent metal ions. The difference may become smaller compared to the acylpyrazolone with un-substituted phenyl group. This is discussed further under mechanism of separation in section 6.4.
We can conclude the following for the influence of the nature R’ group:

1. Phenyl group at 1 position gives the best selectivity for lanthanide metal ions.

2. Other groups decrease the selectivity and efficiency of the separation.

3. Electron donating groups (Me, tBu, CF₃C₆H₄, etc) require high pH and high ligand concentration even for poor to moderate separation.

4. Electron withdrawing groups (MeOC₆H₄, MeC₆H₄, etc) require low pH and low ligand concentration. Their selectivities are not as good as phenyl group probably due to smaller differences in the stability constants of adjacent metal ions.

6.3.2 Substituent in the 3 position (R” group).

The influence of the substituent in the 3 position was also examined. The structures of ligands employed in these studies are displayed in Figure 6.34 and in these ligands the substituents in the 1 position was phenyl and the 4 position was benzoyl with PEG 750 in the para position.
Figure 6.35 Different substituent in the 3 position of the acylpyrazolone.

Figure 6.36 HPLC separation with HPPBP750. Ligand concentration: 5x10^{-6} M, pH=2.04.

The separation results for this ligand are:

1. Good selectivity for lanthanide metal ions,
2. Poor efficiency and as a result of poor resolution of adjacent metal ions,
3. Requires low pH to obtain separation in a reasonable time,
4. It is a stronger ligand than HPMBP750.
The separation results for this ligand are:

1. No selectivity for lanthanide metal ions,
2. Poor efficiency,
3. Requires high PH to get adequate retention on the column,
4. It is a much weaker ligand compared to HPMBP750.
The separation results for this ligand are:

1. Good selectivity and resolution for light lanthanide metal ions La\(^{3+}\), Ce\(^{3+}\), Pr\(^{3+}\) and Nd\(^{3+}\) was obtained,

2. Selectivity for the middle lanthanide metal ions Sm\(^{3+}\) and Eu\(^{3+}\) is good but the resolution is poorer compared to the light lanthanides. This is due to the poorer chromatographic efficiency which does not result in baseline separation,

3. The selectivity and resolution for the heavy lanthanide metal ions is poor. This ligand is as good as HPMBP750.
The separation results for this ligand are:

1. Good selectivity for lanthanide metal ions,
2. The resolution is poorer compared to HPMBP750 and HPEBP750,

We may conclude from these studies that:

1. Methyl group in the 3 position gives the best selectivity for lanthanide metal ions,
2. The ligand with ethyl group or propyl group in the 3 position exhibits the similar selectivity and poorer efficiency compared to HPMBP750.
3. Other substituents decrease the selectivity and efficiency of the separation.
6.3.3 Substituent in the 4 position (R”’ group).

The nature of the acyl substituent in the 4 position of the acylpyrazolone was also investigated. The substituent in the 1 and 3 position were phenyl and methyl respectively and the PEG group on the acyl group was PEG750. The ligands examined are shown in Figure 6.39.

Figure 6.40 Available compounds with different R”’ group.

By using the above structures, we can compare the aliphatic acyl groups and aromatic acyl groups; the effects from the surfactant if on the different position of the phenyl ring of the benzoyl group, and also the electron effects from substitute groups.

As discussed in Chapter 3, when there is an α, β-unsaturated acyl group on the 4 position, the crystal structure shows that the hydroxyl (-OH) is outside the ring. When an aliphatic (not α,β-unsaturated) group is on the 4 position, the hydroxyl group is on the pyrazolone ring. The pKa value and complex stability constant will be very different and metal ion recognition properties will depend on the position of the ionizable OH group. The pH and ligand concentration were optimized for the best separation chromatograms are displayed in the following figures.
Figure 6.41 HPLC separation with HPMB3P750.

a. Ligand concentration: $5 \times 10^{-5}$ M, pH: 2.60.

b. Ligand concentration: $5 \times 10^{-5}$ M, pH: 2.60.

The separation results from Figure 6.40 (a) and (b) are:

1. Poor selectivity for light, middle and heavy lanthanide metal ions.

2. Poor resolution.

This result clearly shows that when position of the PEG group is changed, the
selectivity and efficiency are dramatically decreased. This may stem from poor adsorption and self-assembly of the ligand on the C\textsubscript{18} stationary phase and electronic effects due to the position of the PEG group.

Figure 6.42 HPLC separation with HPMA\textsubscript{P}750 at different pH.

a. Ligand concentration: 5x10\textsuperscript{-6} M, pH=2.29.

![HPLC separation graph](image1)

b. Ligand concentration: 5x10\textsuperscript{-6} M, pH=2.38.

![HPLC separation graph](image2)

1. The ligand has good selectivity for lanthanide metal ions,
2. Poor efficiency leading to poor resolution.

**Figure 6.43** HPLC separation with HPMPOP750.

a. Ligand concentration: $5 \times 10^{-6}$ M, pH=4.27.

b. Ligand concentration: $1 \times 10^{-5}$ M, pH=3.28.

1. This ligand exhibits very poor selectivity for lanthanide metal ions,

2. Poor efficiency leading to incomplete resolution.
Figure 6.44 HPLC separation with HPMBOP750.

a. Ligand concentration: $5 \times 10^{-6}$ M, pH=3.25.

b. Ligand concentration: $5 \times 10^{-6}$ M, pH=2.94.

1. This ligand has good selectivity for lanthanide metal ions,

2. Poor efficiency and as a result poor resolution of adjacent lanthanide metal ions,

4. Requires a slightly higher pH than HPMBP750 for separation,

5. It is a slightly weaker ligand than HPMBP750.
Figure 6.45 HPLC separation with HPMVP750 at different pH.

a. Ligand concentration: $5 \times 10^{-6}$ M, pH=2.63.

b. Ligand concentration: $5 \times 10^{-6}$ M, pH=2.88.

The separation results of this ligand are:

1. Very good selectivity for lanthanide metal ions,
2. Very high efficiency,
3. Very good separation for middle and heavy lanthanides,
4. It is better than HPMBP750 in terms of selectivity, efficiency and resolution.

The foregoing studies lead to the following conclusions:

1. HPMBP750 and HPMVP750 possess the best metal ion recognition efficacies for trivalent lanthanide metal ions.

2. HPMVP750 and HPMBP750 have similar selectivities for the light and middle lanthanide metal ions. The ligand HPMVP750 has higher selectivity for the heavy lanthanides compared to HPMBP750.

3. In the ligand HPMBP750 substituents on the phenyl ring in 1 position as well as changing the nature of the substituent in the 3 position lead to poor selectivities.

4. If the position of the PEG750 group is changed on the benzoyl ring in the 4 position of HPMBP750, essentially no selectivity for the lanthanide metal ions is observed.

5. When the alkyl chain length of HPMVP750 for the alkyl group in the 4 position is changed, the selectivity for the lanthanide metal ions and the efficiencies of separation are dramatically changed. The methyl (1 carbon atom after carbonyl) and valeryl (4 carbon atoms after carbonyl) have much better selectivities than those ligands with 2 and 3 carbon atoms after the carbonyl group. The ligand HPMVP750 has the best selectivity, efficiency and resolution for light, middle and heavy lanthanides.
6.4 Self-assemblies in the aqueous solutions of acylpyrazolones with alkyl acyl groups.

The TEM images of aqueous solutions of the different acylpyrazolones with alkyl groups in the 4 position were examined to gain an understanding of their self-assembling behavior and its influence on their metal ion selectivities. The ligand HPMBP750 only forms spherical and dendritic self-assemblies as shown in Figure 6.45.

Figure 6.46 TEM images of HPMBP750.

The ligand HPMVP750 almost exclusively forms nanotubes as shown in Figure 6.46 with some spherical vesicle type structures. This may indicate that this ligand has the most ordered structures on the C_{18} stationary phase. Such structures like the nanotubes in solution may be two dimensional analogs containing ordered layers of HPMVP750 on the C_{18} surface. The ligand HPMVP750 because of the alkyl chain compared to the benzoyl group of HPMBP750 can form a more closely packed monolayers on C_{18}. As will be discussed in the section on the mechanism of separation, further aggregation is also most likely more ordered and closely packed for HPMVP750 compared to HPMBP750. As shown in Figure 6.47, it forms square and rectangular aggregates with no evidence of
linear, spherical and dendritic aggregates. The behavior of HPMAP 750 is most likely analogous to HPMVP750 in that it forms compact self-assemblies. In the case of HPMAP750, these compact self-assemblies are truncated to form rectangular and square shaped structures while in the HPMVP750, they continue to grow to form nanotubes. This may stem from the difference in the number of carbon atoms in the acyl groups, namely, 2 in the case of HPMAP750 and 5 in the case of HPMVP750. The self-assembly of HPMAP750 on C_{18} stationary phase is most likely different from HPMVP750 resulting in the observed differences in lanthanide metal ion separation.

**Figure 6.47 TEM images of HPMVP750.**

![TEM images of HPMVP750](image1)

**Figure 6.48 TEM images of HPMAP750.**

![TEM images of HPMAP750](image2)
Figure 6.49 TEM images of HPMPOP750.

Figure 6.50 TEM images of HPMBOP750.

The ligands HPMPOP750 and HPMBOP750 (Figure 6.49 and 6.50 respectively) with 3 and 4 carbon atoms respectively in the acyl group are different from HPMAP750 and HPMVP750. The ligand HPMPOP750 forms spherical, dendritic and linear structures while HPMBOP750 forms spherical structures that are linked by films resembling neural network. The poor selectivity of HPMPOP750 is difficult to understand based on the structures of self-assemblies in the aqueous phase as they are similar to those of HPMBP550 and HPMBPBrij, which have good selectivities for the lanthanide metal ions. The ligand HPMBOP750 has moderate selectivity for the lanthanide metal ions may have a complex adsorption behavior on $C_{18}$ analogous to its solution structures. It must be kept
in mind that these amphiphilic ligands are complex mixtures with varying oxyethylene chain lengths.

This is analogous to naturally occurring lipids such as EggPC which is a complex mixture of anionic and zwitterionic lipids with varying alkyl chain lengths without and with C=C double bonds [63]. EggPC forms complex vesicle structures in the aqueous phase with small and large unilamellar and multilamellar structures. Under the right condition, it forms linear structures as well.

An observation in the behavior of lipids like EggPC that is worth employing with the amphiphilic acylpyrazolones is the effect of MgCl$_2$ on their self-assembly. The self-assembled structures in the presence of MgCl$_2$ of the amphiphilic acylpyrazolones HPMBP750 and HPMVP750 that have the best selectivities for lanthanide metal ions were examined by TEM. A $5 \times 10^{-3}$M concentration of the ligands was equilibrated with $5 \times 10^{-4}$M and $5 \times 10^{-3}$M MgCl$_2$ to discern the type of self-assemblies that are formed. The TEM structures for HPMBP750 are shown in Figure 6.50 and those for HPMVP750 are shown in Figure 6.51. The low concentration of MgCl$_2$ yielded spherical structures for both ligands. These structures for freshly prepared mixtures of HPMVP750 with MgCl$_2$ are analogous to multivesicle vesicles often formed by synthetic and natural lipids. At the high MgCl$_2$ concentrations dense spherical structures are formed by HPMBP750, which are linked by nanofibers. In the case of HPMVP750, the multivesicles vesicles form linear chains. In addition, both HPMBP750 and HPMVP750 form dense structures probably due to the further aggregation of the spherical and linear structures [64-73].
Figure 6.51 HPMBP750 self-assembly with MgCl$_2$.

a. Ligand concentration: $5 \times 10^{-3}$ M, $[\text{MgCl}_2]$: $5 \times 10^{-4}$ M (after one week)

In the case of HPMBP750, the only spherical aggregation was observed after one week, which means the aggregation under this condition is low.

b. Ligand concentration: $5 \times 10^{-3}$ M, $[\text{MgCl}_2]$: $5 \times 10^{-3}$ M

c. Ligand concentration: $5 \times 10^{-3}$ M, $[\text{MgCl}_2]$: $5 \times 10^{-3}$ M (after one week)
Figure 6.52 HPMVP750 self-assembly with the presence of MgCl$_2$.

a. Ligand concentration: $5 \times 10^{-3}$ M, [MgCl$_2$]: $5 \times 10^{-4}$ M.

b. Ligand concentration: $5 \times 10^{-3}$ M, [MgCl$_2$]: $5 \times 10^{-4}$ M (after one week).

c. Ligand Concentration: $5 \times 10^{-3}$ M, [MgCl$_2$]: $5 \times 10^{-3}$ M.
d. **Ligand Concentration:** $5 \times 10^{-3}$ M, $[\text{MgCl}_2]$: $5 \times 10^{-3}$ M (after one week).

It is also important to understand the nature of self-assemblies formed in solution when lanthanide metal ions are present. The structures obtained in the presence of the middle series lanthanide metal ion $\text{Sm}^{3+}$ for acylpyrazolones were examined by TEM. The structures formed for HPMBP750, HPMBP2000, HPMBPRrij and HPMBP550 are displayed in Figures 6.52-6.55 respectively. The self-assemblies formed in the presence of $\text{Sm}^{3+}$ for HPMVP750 are shown in Figure 6.56. In all cases, $\text{Sm}^{3+}$ leads to large spherical vesicle type structures and nanotubes. The spherical structures are very dense and appear to be multivesicle vesicles. In a few cases, branched linear structures are also formed. The lanthanide metal ions appear to selectively lead to spherical and linear structures of multivesicle vesicles, nanotubes, nanofibers and nano-rods respectively.

**Figure 6.53 TEM images of HPMBP750 + Sm$^{3+}$.**
Figure 6.54 TEM images of HPMBP2000 + Sm$^{3+}$. 

Figure 6.55 TEM images of HPMBPBrij + Sm$^{3+}$. 

Figure 6.56 TEM images of HPMBP550 + Sm$^{3+}$. 

TEM studies to understand the nature of self-assemblies on C₁₈ stationary phase in the absence and presence of Sm³⁺ were performed. The TEM images of HPMBP750 on the surface of spherical C₁₈ particles in the absence and presence of Sm³⁺ are displayed in Figures 6.57 and 6.58. The TEM images of HPMVP750 on C₁₈ particles in the absence and presence of Sm³⁺ are displayed in Figures 6.59 and 6.60. In case of both HPMBP750 and HPMVP750, the adsorption of the ligand is evident by the halo around the spherical C₁₈ particles. This halo of adsorbed ligand gets larger in the presence of Sm³⁺. It is difficult to determine any fine structures in the halo region of the adsorbed ligand. This will require high resolution transmission in electron microscopy (HRTEM) studies. In addition, spectroscopic techniques and small angle neutron diffraction will also provide a greater detail of these adsorbates. Such studies will be undertaken in the future.
Figure 6.58 TEM images of HPMBP750 + C\textsubscript{18} silica gel.

Figure 6.59 TEM images of HPMBP750 + C\textsubscript{18} silica gel + Sm\textsuperscript{3+}.

Figure 6.60 TEM images of HPMVP750 + C\textsubscript{18} silica gel.
The summary of the HPLC separations and the nanoscale self-assemblies of the various amphiphilic acylpyrazolone ligands are given in Table 6.2. The studies to date while supporting the central hypothesis that high metal ion selectivities can be achieved with nanoscale self-assemblies of a ligand like amphiphilic acylpyrazolones, also indicate the complex nature of interactions that one finds in such systems. This is analogous to naturally occurring lipids like EggPC. The metal ion recognition observed for individual amphiphilic ligand is the result of self-assembly in solution and on C18 surface and complex formation and dissociation. Another interesting observation from Table 6.2 is that the pKa values of all ligands for which pKa values were measured by pH titration are between 8 and 9. The pKa value of the acylpyrazolones determined in H2Oethanol and H2Odioxane mixtures and corrected for dielectric constant is about 4.[74, 75] The PEG compounds such as PEG750 and Brij35p have pKa values of about 8 from titration studies performed here. Clearly the pKa values of the amphiphilic ligands are dominated by the pKa values of the PEG group on the acyl substituent. The PEG compounds due to
the large number of oxyethylene groups are associated with protons which have an average pKa value of about 8.

Separation with mixtures of acylpyrazolones and PEG compounds were also performed to fully understand the role of PEG groups chemically bonded to acylpyrazolones compared to being simply present as a mixture. Two ligands HPMBP and HPMVP were dissolved in different PEG surfactants such as: PEG550, PEG750, PEG2000 and Brij35p and the lanthanide metal ion separations studied by HPLC with C18 stationary phase. In these studies, $5 \times 10^{-6}$ M of the ligand was dissolved in 5 to 10 fold excess of the PEG surfactant. Unlike ligands with chemically bonded PEG moieties where lanthanide metal ion separations could be obtained with $2 \times 10^{-6}$ M of the ligand, this dissolution procedure required higher concentration of ligand and a large excess of PEG surfactant. This has practical limitations in addition to separation not always being effective.

The separation of lanthanides with HPMBP plus Brij35p mixture is shown in Figure 6.61, with HPMBP + PEG2000 mixture in Figure 6.62, with HPMBP + PEG750 mixture in Figure 6.63, with HPMBP + PEG550 mixture in Figure 6.64 and with HPMVP + PEG750 mixture in Figure 6.65.
Figure 6.62 HPLC separation with HPMBP+Brij35p.

Figure 6.63 HPLC separation with HPMBP+PEG2000.
Figure 6.64 HPLC separation with HPMBP+PEG750.

La1Ce1Pr1.5Nd2Sm3.6Eu3.6Ho5-100108-0.000005N16pH2.18
Ligand : Surfactant = 1 : 5

Figure 6.65 HPLC separation with HPMBP+PEG550.

La1Ce1Pr1.5Nd2Sm3.6Eu3.6Ho5-100109-0.000005N16pH2.05
Ligand : Surfactant = 1 : 5
The separation with HPMBP dissolved in Brij35p and PEG2000 are much poorer than HPMBPBrij and HPMBP2000 (requires low pH and more surfactant respectively). However the separation with HPMBP dissolved in PEG750 and PEG550 are just as selective and efficient as HPMBP750 and better than the separation with HPMBP550. The separation with HPMVP dissolved in PEG750 is much poorer than the separation with HPMVP750.

It may also be seen from the chromatograms of the mixtures that they require much longer time to achieve separation at lower pH values compared to the amphiphilic ligands. These results indicate that while simple mixtures of ligands and surfactants may in some instances be as effective or even superior to amphiphilic ligands derivatized with PEG moieties, a systematic understanding of factors influencing the selectivities and efficiencies of separation by nanoscale self-assemblies would be much harder to obtain with mixtures compared to amphiphilic ligands.
The TEM images of the ligand and surfactant mixtures were examined for comparison with those of amphiphilic ligands. The TEM images of HPMBP+PEG550 are shown in Figure 6.66, the TEM images of HPMBP+PEG750 are shown in Figure 6.67, the TEM images of HPMVP+PEG750 are shown in Figure 6.68. The mixture HPMBP + PEG550 in the absence and presence of Sm$^{3+}$ only has spherical vesicle type structures that form aggregates. This is in contrast to HPMBP550 which forms spherical, dendritic and linear structures (Figure 6.19). The mixture HPMBP + PEG750 has dendritic structures and no linear structures like HPMBP750 (Figure 6.18) and unlike HPMBP750 lacks spherical structures. There is a major difference between HPMVP + PEG750 and HPMVP750 (Figure 6.47) with the latter compound predominantly forming nanotubes and the mixture are not exhibiting any definite structure. Amphiphilic ligands are a better choice than ligand and surfactant mixtures in terms of the condition required for separation and for gaining a fundamental understanding of influence of the structure of ligands and their nanoscale self-assemblies on metal ion recognition.

**Figure 6.67 TEM images of HPMBP+PEG550.**
Figure 6.68 TEM images of HPMBP+PEG750.

Figure 6.69 TEM images of HPMVP+PEG750.
Table 6.2 Summary of HPLC separation and nanoscale self-assemblies of pyrazolone ligands.

<table>
<thead>
<tr>
<th>Compound</th>
<th>pKa</th>
<th>HPLC Separation (Best Condition for Separation)</th>
<th>TEM of Ligand</th>
<th>TEM of Ligand + Metal</th>
<th>TEM of Ligand on C\textsubscript{18} Surface</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMBPBrij</td>
<td>8.71</td>
<td>Separation of 7 metals, not base line separation (5x10\textsuperscript{-6} M, pH2.44)</td>
<td>Linear structure, 1-10 µm</td>
<td>Spherical structure, 1-10 µm</td>
<td>Halo around C\textsubscript{18} particle</td>
</tr>
<tr>
<td>HPMBP2000</td>
<td>8.17</td>
<td>Separation of 7 metals, nearly base line separation (5x10\textsuperscript{-6} M, pH2.23)</td>
<td>Linear structure, &gt;100 µm</td>
<td>Spherical structure, 200-300 nm</td>
<td>Halo around particles 1-5 µm</td>
</tr>
<tr>
<td>HPMBP750</td>
<td>8.32</td>
<td>Separation of 7 metals, base line separation, except Sm, Eu (5x10\textsuperscript{-6} M, pH2.35)</td>
<td>Spherical structure, 30-50 nm</td>
<td>Spherical structure, 200-300 nm</td>
<td></td>
</tr>
<tr>
<td>HPMBPTriton</td>
<td>8.74</td>
<td>Separation of 3 metals, Head separation, (1x10\textsuperscript{-5} M, pH2.31)</td>
<td>Spherical structure, 300-500 nm</td>
<td>Spherical structure, 200-300 nm</td>
<td></td>
</tr>
<tr>
<td>HPMBP550</td>
<td>8.62</td>
<td>Separation of 5 metals, incomplete separation, (5x10\textsuperscript{-6} M, pH2.54)</td>
<td>Linear structure, 10-100 µm</td>
<td>Spherical structure, 0.2-200 nm</td>
<td>Halo around particles 0.5-1 µm</td>
</tr>
<tr>
<td>Compound</td>
<td>pKa</td>
<td>HPLC Separation</td>
<td>TEM of Ligand</td>
<td>TEM of Ligand + Metal</td>
<td>TEM of Ligand on C_{18} Surface</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------</td>
<td>------------------------------------------------------</td>
<td>----------------------------------------------------</td>
<td>----------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Best Condition for Separation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPMBP+Brij35p</td>
<td>1:5</td>
<td>Good separation for 5 ions, not base line separation</td>
<td>Spherical structure with dendritic structure inside, 0.5-5 µm</td>
<td>Cross-linked linear, 10-100µm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(La, Ce, Nd, Sm, Ho)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incomplete for 7 ions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(La, Ce, Pr, Nd, Sm Eu, Ho)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5x10^{-6}M, pH2.30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPMBP+PEG2000</td>
<td>1:5</td>
<td>Poor separation for 7 ions</td>
<td>Plates, &gt;100 µm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(La, Ce, Pr, Nd, Sm Eu, Ho)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Better than</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>HPMBP+Brij35p</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5x10^{-6}M, pH2.38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPMBP+PEG750</td>
<td>1:5</td>
<td>Good separation for 7 ions, nearly base line separation</td>
<td>Dendritic structure, 5-10 µm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(La, Ce, Pr, Nd, Sm Eu, Ho)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Better than</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>HPMBP+PEG2000, not as good as HPMBP750</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5x10^{-6}M, pH2.18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPMBP+PEG550</td>
<td>1:5</td>
<td>Good separation for 7 ions, base line separation</td>
<td>Spherical structure, 50-200 nm</td>
<td>Spherical structure, 100-500 nm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(La, Ce, Pr, Nd, Sm Eu, Ho)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Better than</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>HPMBP750</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5x10^{-6}M, pH2.18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>pKa</td>
<td>HPLC Separation (Best Condition for Separation)</td>
<td>TEM of Ligand</td>
<td>TEM of Ligand + Metal</td>
<td>TEM of Ligand on C\textsubscript{18} Surface</td>
</tr>
<tr>
<td>---------------</td>
<td>--------</td>
<td>---------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------</td>
<td>-----------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>HPMB3P750</td>
<td></td>
<td>Separation of 3 metals, Head separation, (5x10\textsuperscript{-5} M, pH2.60)</td>
<td>Spherical structure, 50-200 nm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPMVP750</td>
<td>8.57</td>
<td>Good separation for 8 ions, base line separation (La, Ce, Pr, Nd, Sm Eu, Tb, Lu)</td>
<td>Linear tube, &gt;100 µm</td>
<td>Spherical structure, 50-100 nm</td>
<td>Linear rod structure, 10-100 µm</td>
</tr>
<tr>
<td></td>
<td>9.18 in</td>
<td>Better than HPMBP+PEG550 (5x10\textsuperscript{-6} M, pH2.88)</td>
<td></td>
<td></td>
<td>Halo around C\textsubscript{18} surface 0.5-2 µm</td>
</tr>
<tr>
<td>HPMAP750</td>
<td></td>
<td>Separation of 8 metals, Incomplete separation, (La, Ce, Pr, Nd, Sm Eu, Tb, Lu)</td>
<td>Spherical structure, 20-50 nm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Better than HPMBP+PEG550 (5x10\textsuperscript{-6} M, pH2.38)</td>
<td>Spherical structure, 20-50 nm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPMPOP750</td>
<td></td>
<td>No Separation (5x10\textsuperscript{-6} M, pH4.27)</td>
<td>Spherical structure, 20-50 nm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Better than HPMBP+PEG550 (5x10\textsuperscript{-6} M, pH4.27)</td>
<td>Spherical structure, 20-50 nm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPMBOP750</td>
<td></td>
<td>Separation of 3 metals, nearly baseline separation, (5x10\textsuperscript{-6} M, pH2.94)</td>
<td>Spherical structure, 50-500 nm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>pKa</td>
<td>HPLC Separation (Best Condition for Separation)</td>
<td>TEM of Ligand</td>
<td>TEM of Ligand + Metal</td>
<td>TEM of Ligand on C&lt;sub&gt;18&lt;/sub&gt; Surface</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------</td>
<td>-----------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>HMOPMBPBrij</td>
<td></td>
<td>Separation for 5 ions not base line separation (La, Ce, Nd, Sm, Ho) (1.25x10&lt;sup&gt;-6&lt;/sup&gt; M, pH2.98)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMOPMBP750</td>
<td></td>
<td>Separation for 5 ions not base line separation (La, Ce, Nd, Sm, Ho) (2.5x10&lt;sup&gt;-6&lt;/sup&gt; M, pH2.17)</td>
<td>Linear structure, &gt;100 µm</td>
<td></td>
<td>Dendritic structure, &gt;100 µm</td>
</tr>
<tr>
<td>HMMBP750</td>
<td></td>
<td>Poor separation of Ho from La &amp; Sm. No separation for La &amp; Sm (2 x10&lt;sup&gt;-4&lt;/sup&gt; M, pH4.71)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPPBP750</td>
<td></td>
<td>Separation for 5 ions poor separation (La, Ce, Nd, Sm, Ho) (5x10&lt;sup&gt;-6&lt;/sup&gt; M, pH2.04)</td>
<td>Linear structure, 10-100 µm</td>
<td></td>
<td>Spherical structure, 20-50 nm</td>
</tr>
<tr>
<td>HPNPBP750</td>
<td></td>
<td>No separation (5x10&lt;sup&gt;-5&lt;/sup&gt; M, pH4.24)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>pKa</td>
<td>HPLC Separation (Best Condition for Separation)</td>
<td>TEM of Ligand</td>
<td>TEM of Ligand + Metal</td>
<td>TEM of Ligand on C&lt;sub&gt;18&lt;/sub&gt; Surface</td>
</tr>
<tr>
<td>-----------</td>
<td>-----</td>
<td>-------------------------------------------------</td>
<td>---------------</td>
<td>-----------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>HFPMBP750</td>
<td></td>
<td>Poor separation of Ho from La &amp; Sm. No separation for La &amp; Sm (2 x10&lt;sup&gt;-5&lt;/sup&gt; M, pH4.70)</td>
<td></td>
<td>Linear structure, 10-100 µm</td>
<td>Spherical structure, 50-100 nm</td>
</tr>
<tr>
<td>HMPMBP750</td>
<td></td>
<td>Separation for 5 ions poor separation (La, Ce, Nd, Sm, Ho) (5x10&lt;sup&gt;-6&lt;/sup&gt; M, pH1.96)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBnMBP750</td>
<td></td>
<td>No Separation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HtBuMBP750</td>
<td></td>
<td>Poor separation of La from Sm &amp; Ho. No separation for Sm &amp; Ho (1 x10&lt;sup&gt;-4&lt;/sup&gt; M, pH4.61)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.5 Mechanism of lanthanide metal ion recognition by amphiphilic acylpyrazolones

When the column is equilibrated with ligand solution, the ligand absorbs on C_{18} leading to monolayer formation. As will be discussed subsequently, the self-assembly of ligands on C_{18} is also a complex phenomenon much like the self-assembly in the aqueous phase. Similarly, ligands adsorbed on the column will also complex the metal ions. The complexation of the metal ions as indicated in Figure 6.69 is a pH dependent process. Metal complexation may be viewed as an ionexchange process in which H^+ are displaced by metal ions. It is evident that the complexation of the metal ion in the mobile phase and on the C_{18} column is a competitive process which ultimately leads to the separation of the metal ions. This process, unlike in simple systems where self-assembly is absent, invariably can be expected to be influenced by the spontaneous self-assembly of the amphiphilic acylpyrazolone ligands in the aqueous phase and on the C_{18} surface. The central hypothesis of this research is that nanoscale self-assemblies in the aqueous and on the C_{18} stationary phases would provide excellent metal ion selectivities. The results from HPLC separation and the mechanism of separation proposed substantiate this hypothesis.

Additional factors that influence the separation of metal ions by the self-assemblies of the amphiphilic acylpyrazolones are the stability constants of the metal complexes and the kinetics of complex formation and dissociation. The stability constant influences retention time and as a result the distribution constant D (also known as capacity factor) of the metal ion between the mobile phase and stationary phase. This in turn affects the selectivity \( \alpha \) between adjacent lanthanide ion pairs (\( \alpha = \)
D₂/D₁, D₂ and D₁: distribution constants of the more and less retained metal ion respectively. The kinetics of complex formation and dissociation influence the efficiency of separation (chromatographic band width). As may be seen from the various chromatograms displayed, the efficacies of separation decrease from the light to heavy lanthanide metal ions. Table 6.3 contains an example of D, N and α for 2x10⁻⁵ M of HPMBP750 and HPMVP750.

Table 6.3 D, N and α for 2x10⁻⁵ M of HPMBP750 and HPMVP750.

<table>
<thead>
<tr>
<th>Metal ion</th>
<th>HPMBP750</th>
<th>HPMVP750</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>D</td>
</tr>
<tr>
<td>La</td>
<td>156</td>
<td>0.571</td>
</tr>
<tr>
<td>Ce</td>
<td>77</td>
<td>1.159</td>
</tr>
<tr>
<td>Pr</td>
<td>\</td>
<td>\</td>
</tr>
<tr>
<td>Nd</td>
<td>73</td>
<td>2.629</td>
</tr>
<tr>
<td>Sm</td>
<td>25</td>
<td>10.100</td>
</tr>
<tr>
<td>Eu</td>
<td>\</td>
<td>\</td>
</tr>
<tr>
<td>Ho</td>
<td>17</td>
<td>25.041</td>
</tr>
</tbody>
</table>

D = (tᵣ₋ₜ₀)/t₀ ,  \[t₀=1.70\text{min}; \text{from the retention time of Na}_2\text{Cr}_2\text{O}_7]\ ;

N = 16(tᵣ/W)² ;  \[α = D₂/D₁ \] ;

In order to gain an understanding of the mechanism of lanthanide metal ion recognition by amphiphilic acylpyrazolones, separation experiments were conducted as a function of ligand concentration (5x10⁻⁶ M - 2.5x10⁻⁵ M) at a constant pH=2.41.
for HPMBP750 and pH=2.78 for HPMVP750 and as a function of pH at two different ligand concentrations 5x10^{-6} M and 2x10^{-5} M. The results of these studies are presented in the following sections in the form of tables and figures. A detailed compilation of the ligand dependence and pH dependence data is included here to underscore the complexity of these dependences as indicated by the mechanism in Figure 6.70.

**Figure 6.70 Lanthanide metal ion separation mechanism.**

The complexity of the separation and hence metal ion recognition by the amphiphilic ligands can be better discerned by considering a simple model for the distribution of the metal ion from the aqueous mobile phase to the C_{18} stationary phase. In this simple model, the ligand does not aggregate in the aqueous phase, the
complexation of metal ion occurs in the aqueous phase and the complex distributes to the $C_{18}$ stationary phase. This is depicted in equation 1 where the subscripts $a$ and $s$ represent aqueous and $C_{18}$ stationary phases.

$$M^{3+} + 3HL(a) \rightleftharpoons K_{ex} ML_3(s) + 3H^+(a)$$

The equilibrium constant $K_{ex}$ is given by equation 2.

$$K_{ex} = \frac{[ML_3]_s [H^+]^3}{[M^{3+}]_a [HL]^3}(a)$$

The ratio $[ML_3]_a/[M^{3+}]_a$ is the distribution constant $D$ for a given metal ion. $K_{ex}$ can be rewritten in terms of $D$ and written as a logarithmic expression, equation 3.

$$\log K_{ex} = \log D - 3pH - 3\log [HL]$$

This can be rewritten as equation 4 for the dependence of $\log D$ on $\text{pH}$ and ligand concentration.

$$\log D = \log K_{ex} + 3pH + 3\log [HL]$$

In this simple model, $\log D$ measured from chromatographic capacity factors will have linear dependence on $\text{pH}$ with slope 3 at constant ligand concentration and linear dependence on $\log[HL]$ at constant $\text{pH}$ with slope 3. Further the equilibrium constant $K_{ex}$ can be obtained from the intercept.

Examining the plots of $\log D$ vs $\log[HL]$ clearly reveals a much more complex behavior than the one predicted by the simple model, most likely the complex mechanism indicated in Figure 6.69. The ligand dependence at very low concentration (below $1.5 \times 10^{-5}$ M) actually has a small negative slope indicating that the metal ions are less strongly retained with increasing ligand concentration. As the ligand...
concentration is increased above $1.5 \times 10^{-5}$ M the distribution constant increases with slope from 0.7-1.3 for La$^{3+}$ - Ho$^{3+}$ in the case of HPMBP750 and 0.7-2.5 for La$^{3+}$ - Ho$^{3+}$ in the case of HPMVP750.

The dependence of the distribution constant on pH was performed at low ligand concentration $5 \times 10^{-6}$ M and high ligand concentration $2 \times 10^{-5}$ M to parallel the ligand dependence studies. The slopes of logD vs pH plots at $5 \times 10^{-6}$ M range from 0.9-2.6 for La$^{3+}$ - Ho$^{3+}$ in the case of HPMBP750 and 0.7-2.5 for La$^{3+}$ - Ho$^{3+}$ in the case of HPMVP750.

At the higher ligand concentration, $2 \times 10^{-5}$ M, the slopes range from 3.5-7.1 for La$^{3+}$ - Ho$^{3+}$ in the case of HPMBP750 and 3.2-8.7 in the case of HPMVP750. The selectivity $\alpha$ for adjacent lanthanide metal ions in the separation are also listed for HPMBP750 and HPMVP750 and these values range from 1.3-4. These $\alpha$ values indicate the excellent metal ion recognition efficacies of these ligands.

6.6 logD vs log[HL] and logD vs pH.

6.6.1 logD vs log[HL] and logD vs pH for the ligand HPMBP750.

a. logD vs log [HL].

The dependence of the distribution constant D as a function of ligand concentration HL at a pH=2.41 was analyzed by plotting logD as a function of log[HL] in the ligand concentration range $5 \times 10^{-6}$ M-$2 \times 10^{-5}$ M. The pH condition for the determination of logD vs log[HL] was 2.41 and the ligand concentration range is from
5x10^{-6} M to 2.5x10^{-5} M. For each lanthanide metal ion, the results are shown in Figures 6.71-6.75 and the calculations are shown in Table 6.4.

Table 6.4 logD vs log[HL] for the ligand HPMBP750.

Table 6.4a Retention time at different ligand concentrations.

<table>
<thead>
<tr>
<th>[HL], M</th>
<th>log[HL]</th>
<th>Retention Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>La</td>
</tr>
<tr>
<td>5x10^{-6}</td>
<td>-5.30103</td>
<td>2.63</td>
</tr>
<tr>
<td>1x10^{-5}</td>
<td>-5</td>
<td>2.47</td>
</tr>
<tr>
<td>1.5x10^{-5}</td>
<td>-4.82391</td>
<td>2.43</td>
</tr>
<tr>
<td>2x10^{-5}</td>
<td>-4.69897</td>
<td>2.5</td>
</tr>
<tr>
<td>2.5x10^{-5}</td>
<td>-4.60206</td>
<td>2.73</td>
</tr>
</tbody>
</table>

D=(t_r-t_0)/t_0  
t_0=1.70 (from Na_2Cr_2O_7 retention time)

Table 6.4b D values at different ligand concentration.

<table>
<thead>
<tr>
<th>[HL], M</th>
<th>log[HL]</th>
<th>D(La)</th>
<th>D(Ce)</th>
<th>D(Nd)</th>
<th>D(Sm)</th>
<th>D(Ho)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5x10^{-6}</td>
<td>-5.30103</td>
<td>0.547059</td>
<td>1.194118</td>
<td>2.764706</td>
<td>9.058824</td>
<td>20.92353</td>
</tr>
<tr>
<td>1x10^{-5}</td>
<td>-5</td>
<td>0.452941</td>
<td>0.9</td>
<td>1.958824</td>
<td>6.252941</td>
<td>12.98235</td>
</tr>
<tr>
<td>1.5x10^{-5}</td>
<td>-4.82391</td>
<td>0.429412</td>
<td>0.764706</td>
<td>1.605882</td>
<td>5.041176</td>
<td>10.94118</td>
</tr>
<tr>
<td>2x10^{-5}</td>
<td>-4.69897</td>
<td>0.470588</td>
<td>0.805882</td>
<td>1.723529</td>
<td>5.864706</td>
<td>12.57059</td>
</tr>
<tr>
<td>2.5x10^{-5}</td>
<td>-4.60206</td>
<td>0.605882</td>
<td>1.217647</td>
<td>2.747059</td>
<td>10.58824</td>
<td>22.01765</td>
</tr>
</tbody>
</table>
Table 6.4c logD values at different ligand concentrations.

<table>
<thead>
<tr>
<th>[HL], M</th>
<th>log[HL]</th>
<th>logD(La)</th>
<th>logD(Ce)</th>
<th>logD(Nd)</th>
<th>logD(Sm)</th>
<th>logD(Ho)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$5 \times 10^{-6}$</td>
<td>-5.30103</td>
<td>-0.26197</td>
<td>0.077047</td>
<td>0.441649</td>
<td>0.957072</td>
<td>1.320635</td>
</tr>
<tr>
<td>$1 \times 10^{-5}$</td>
<td>-5.069897</td>
<td>-0.34396</td>
<td>-0.04576</td>
<td>0.291995</td>
<td>0.796084</td>
<td>1.113353</td>
</tr>
<tr>
<td>$1.5 \times 10^{-5}$</td>
<td>-4.82391</td>
<td>-0.36713</td>
<td>-0.11651</td>
<td>0.205714</td>
<td>0.702532</td>
<td>1.039064</td>
</tr>
<tr>
<td>$2 \times 10^{-5}$</td>
<td>-4.69897</td>
<td>-0.32736</td>
<td>-0.09373</td>
<td>0.236419</td>
<td>0.768246</td>
<td>1.099356</td>
</tr>
<tr>
<td>$2.5 \times 10^{-5}$</td>
<td>-4.60206</td>
<td>-5.30103</td>
<td>0.085521</td>
<td>0.438868</td>
<td>1.024824</td>
<td>1.342771</td>
</tr>
</tbody>
</table>

Figure 6.71 logD vs log[HL] for La$^{3+}$.  
Figure 6.72 logD vs log[HL] for Ce$^{3+}$.  
Figure 6.73 logD vs log[HL] for Nd$^{3+}$.  
Figure 6.74 logD vs log[HL] for Sm$^{3+}$.  

142
Figure 6.75 logD vs log[HL] for Ho$^{3+}$.

Table 6.5 logD vs log[HL]: pH=2.41.

<table>
<thead>
<tr>
<th>Metal ion</th>
<th>Concentration range (M)</th>
<th>Slope</th>
<th>Concentration range (M)</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>La</td>
<td>5x10$^{-6}$-1.5x10$^{-5}$</td>
<td>-0.226</td>
<td>1.5x10$^{-5}$-2.5x10$^{-5}$</td>
<td>0.657</td>
</tr>
<tr>
<td>Ce</td>
<td>5x10$^{-6}$-1.5x10$^{-5}$</td>
<td>-0.406</td>
<td>1.5x10$^{-5}$-2.5x10$^{-5}$</td>
<td>0.876</td>
</tr>
<tr>
<td>Pr</td>
<td>\ / \ / \ / \ /</td>
<td>\ / \ / \ /</td>
<td>\ / \ / \ /</td>
<td>\ / \ / \ /</td>
</tr>
<tr>
<td>Nd</td>
<td>5x10$^{-6}$-1.5x10$^{-5}$</td>
<td>-0.495</td>
<td>1.5x10$^{-5}$-2.5x10$^{-5}$</td>
<td>1.013</td>
</tr>
<tr>
<td>Sm</td>
<td>5x10$^{-6}$-1.5x10$^{-5}$</td>
<td>-0.534</td>
<td>1.5x10$^{-5}$-2.5x10$^{-5}$</td>
<td>1.409</td>
</tr>
<tr>
<td>Eu</td>
<td>\ / \ / \ / \ /</td>
<td>\ / \ / \ /</td>
<td>\ / \ / \ /</td>
<td>\ / \ / \ /</td>
</tr>
<tr>
<td>Ho</td>
<td>5x10$^{-6}$-1.5x10$^{-5}$</td>
<td>-0.601</td>
<td>1.5x10$^{-5}$-2.5x10$^{-5}$</td>
<td>1.327</td>
</tr>
</tbody>
</table>

The selectivities for the adjacent lanthanide metal ions in the separation are listed in Table 6.6.
Table 6.6 Selectivity $\alpha$ for adjacent lanthanide metal ions.

<table>
<thead>
<tr>
<th>[HL], M</th>
<th>log[HL]</th>
<th>$\alpha$(Ce/La)</th>
<th>$\alpha$(Nd/Ce)</th>
<th>$\alpha$(Sm/Nd)</th>
<th>$\alpha$(Ho/Nd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$5\times10^{-6}$</td>
<td>-5.30103</td>
<td>2.182796</td>
<td>2.315271</td>
<td>3.276596</td>
<td>2.30974</td>
</tr>
<tr>
<td>$1\times10^{-5}$</td>
<td>-5</td>
<td>1.987013</td>
<td>2.176471</td>
<td>3.192192</td>
<td>2.076199</td>
</tr>
<tr>
<td>$1.5\times10^{-5}$</td>
<td>-4.82391</td>
<td>1.780822</td>
<td>2.1</td>
<td>3.139194</td>
<td>2.170362</td>
</tr>
<tr>
<td>$2\times10^{-5}$</td>
<td>-4.69897</td>
<td>1.7125</td>
<td>2.138686</td>
<td>3.40273</td>
<td>2.14343</td>
</tr>
<tr>
<td>$2.5\times10^{-5}$</td>
<td>-4.60206</td>
<td>2.009709</td>
<td>2.256039</td>
<td>3.85439</td>
<td>2.079444</td>
</tr>
</tbody>
</table>

b. logD vs pH.

Table 6.7 logD vs pH for the ligand HPMBP750 at [HL]=5x10^{-6} M.

Table 6.7a Calculations of logD vs pH, at [HL]=5x10^{-6} M.

<table>
<thead>
<tr>
<th>pH</th>
<th>Retention Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>La</td>
</tr>
<tr>
<td>2.11</td>
<td>2.6</td>
</tr>
<tr>
<td>2.16</td>
<td>2.67</td>
</tr>
<tr>
<td>2.21</td>
<td>2.8</td>
</tr>
<tr>
<td>2.26</td>
<td>2.93</td>
</tr>
<tr>
<td>2.31</td>
<td>3.07</td>
</tr>
</tbody>
</table>

$D = (t_r - t_0)/t_0$, $t_0=1.70$ (from Na$_2$Cr$_2$O$_7$ retention time)
Table 6.7b D value at different pH.

<table>
<thead>
<tr>
<th>pH</th>
<th>D(La)</th>
<th>D(Ce)</th>
<th>D(Nd)</th>
<th>D(Sm)</th>
<th>D(Ho)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.11</td>
<td>0.529412</td>
<td>0.923529</td>
<td>1.941176</td>
<td>6.041176</td>
<td>11.78235</td>
</tr>
<tr>
<td>2.16</td>
<td>0.570588</td>
<td>1.041176</td>
<td>2.217647</td>
<td>7.276471</td>
<td>14.11765</td>
</tr>
<tr>
<td>2.21</td>
<td>0.647059</td>
<td>1.217647</td>
<td>2.747059</td>
<td>9.000000</td>
<td>17.15882</td>
</tr>
<tr>
<td>2.26</td>
<td>0.723529</td>
<td>1.394118</td>
<td>3.452941</td>
<td>11.68824</td>
<td>21.95882</td>
</tr>
<tr>
<td>2.31</td>
<td>0.805882</td>
<td>1.705882</td>
<td>4.394118</td>
<td>18.27647</td>
<td>43.25294</td>
</tr>
</tbody>
</table>

Table 6.7c logD vs pH.

<table>
<thead>
<tr>
<th>pH</th>
<th>logD(La)</th>
<th>logD(Ce)</th>
<th>logD(Nd)</th>
<th>logD(Sm)</th>
<th>logD(Ho)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.11</td>
<td>-0.27621</td>
<td>-0.03455</td>
<td>0.288065</td>
<td>0.781122</td>
<td>1.071232</td>
</tr>
<tr>
<td>2.16</td>
<td>-0.24368</td>
<td>0.017524</td>
<td>0.345892</td>
<td>0.861921</td>
<td>1.149762</td>
</tr>
<tr>
<td>2.21</td>
<td>-0.18906</td>
<td>0.085521</td>
<td>0.438868</td>
<td>0.954243</td>
<td>1.234488</td>
</tr>
<tr>
<td>2.26</td>
<td>-0.14054</td>
<td>0.144299</td>
<td>0.538189</td>
<td>1.067749</td>
<td>1.341609</td>
</tr>
<tr>
<td>2.31</td>
<td>-0.09373</td>
<td>0.231949</td>
<td>0.642872</td>
<td>1.261892</td>
<td>1.636016</td>
</tr>
</tbody>
</table>

Using the data in the above Table 6.7, the LogD vs pH for each studies lanthanide metal ions at ligand concentration 5x10^-6 M are shown below:
The slopes of these plots are listed in Table 6.8 and the selectivities $\alpha$ are given in Table 6.9.
### Table 6.8 Slope of logD vs pH: [HL]=5x10^{-6} M.

<table>
<thead>
<tr>
<th>Metal ion</th>
<th>pH range</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>La</td>
<td>2.11-2.31</td>
<td>0.936</td>
</tr>
<tr>
<td>Ce</td>
<td>2.11-2.31</td>
<td>1.320</td>
</tr>
<tr>
<td>Pr</td>
<td>\ / \ /</td>
<td>\ / \ /</td>
</tr>
<tr>
<td>Nd</td>
<td>2.11-2.31</td>
<td>1.804</td>
</tr>
<tr>
<td>Sm</td>
<td>2.11-2.31</td>
<td>2.335</td>
</tr>
<tr>
<td>Eu</td>
<td>\ / \ /</td>
<td>\ / \ /</td>
</tr>
<tr>
<td>Ho</td>
<td>2.11-2.31</td>
<td>2.643</td>
</tr>
</tbody>
</table>

### Table 6.9 Selectivity $\alpha$ for adjacent lanthanide metal ions.

<table>
<thead>
<tr>
<th>pH</th>
<th>$\alpha$(Ce/La)</th>
<th>$\alpha$(Nd/Ce)</th>
<th>$\alpha$(Sm/Nd)</th>
<th>$\alpha$(Ho/Sm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.11</td>
<td>1.744444</td>
<td>2.101911</td>
<td>3.112121</td>
<td>1.950341</td>
</tr>
<tr>
<td>2.16</td>
<td>1.824742</td>
<td>2.129944</td>
<td>3.281167</td>
<td>1.940178</td>
</tr>
<tr>
<td>2.21</td>
<td>1.881818</td>
<td>2.256039</td>
<td>3.276231</td>
<td>1.906536</td>
</tr>
<tr>
<td>2.26</td>
<td>1.926829</td>
<td>2.476793</td>
<td>3.385009</td>
<td>1.878712</td>
</tr>
<tr>
<td>2.31</td>
<td>2.116788</td>
<td>2.575862</td>
<td>4.159304</td>
<td>2.366592</td>
</tr>
</tbody>
</table>

At a ligand concentration of 2x10^{-5} M, logD vs pH calculations are shown in Table 6.10 and for each metal ion, the result is shown in Figures 6.80-6.84.

### Table 6.10 logD vs pH for the ligand HPMBP750 at [HL]=2x10^{-5} M.

<table>
<thead>
<tr>
<th>pH</th>
<th>logD Ce/La</th>
<th>logD Nd/Ce</th>
<th>logD Sm/Nd</th>
<th>logD Ho/Sm</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.11</td>
<td>1.744444</td>
<td>2.101911</td>
<td>3.112121</td>
<td>1.950341</td>
</tr>
<tr>
<td>2.16</td>
<td>1.824742</td>
<td>2.129944</td>
<td>3.281167</td>
<td>1.940178</td>
</tr>
<tr>
<td>2.21</td>
<td>1.881818</td>
<td>2.256039</td>
<td>3.276231</td>
<td>1.906536</td>
</tr>
<tr>
<td>2.26</td>
<td>1.926829</td>
<td>2.476793</td>
<td>3.385009</td>
<td>1.878712</td>
</tr>
<tr>
<td>2.31</td>
<td>2.116788</td>
<td>2.575862</td>
<td>4.159304</td>
<td>2.366592</td>
</tr>
</tbody>
</table>
Table 6.10a Calculations of logD vs pH, at [HL]=2x10^{-5} M.

<table>
<thead>
<tr>
<th>pH</th>
<th>Retention Time (min)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>La</td>
<td>Ce</td>
<td>Nd</td>
<td>Sm</td>
<td>Ho</td>
<td></td>
</tr>
<tr>
<td>2.04</td>
<td>\</td>
<td>2.47</td>
<td>3.13</td>
<td>5.77</td>
<td>9.33</td>
<td></td>
</tr>
<tr>
<td>2.1</td>
<td>2.4</td>
<td>2.9</td>
<td>4.2</td>
<td>10.5</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>2.15</td>
<td>2.67</td>
<td>3.67</td>
<td>6.17</td>
<td>18.87</td>
<td>44.27</td>
<td></td>
</tr>
<tr>
<td>2.2</td>
<td>3.27</td>
<td>5.7</td>
<td>11.3</td>
<td>43.53</td>
<td>108.57</td>
<td></td>
</tr>
</tbody>
</table>

D=(t_r-t_0)/t_0, \ t_0=1.70 (from Na_2Cr_2O_7 retention time)

Table 6.10b D value at different pH.

<table>
<thead>
<tr>
<th>pH</th>
<th>D(La)</th>
<th>D(Ce)</th>
<th>D(Nd)</th>
<th>D(Sm)</th>
<th>D(Ho)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.04</td>
<td>\</td>
<td>0.452941</td>
<td>0.841176</td>
<td>2.394118</td>
<td>4.488235</td>
</tr>
<tr>
<td>2.10</td>
<td>0.411765</td>
<td>0.705882</td>
<td>1.470588</td>
<td>5.176471</td>
<td>11.35294</td>
</tr>
<tr>
<td>2.15</td>
<td>0.570588</td>
<td>1.158824</td>
<td>2.629412</td>
<td>10.10000</td>
<td>25.04118</td>
</tr>
<tr>
<td>2.20</td>
<td>0.923529</td>
<td>2.352941</td>
<td>5.647059</td>
<td>24.60588</td>
<td>62.86471</td>
</tr>
</tbody>
</table>

Table 6.10c logD vs pH.

<table>
<thead>
<tr>
<th>pH</th>
<th>logD(La)</th>
<th>logD(Ce)</th>
<th>logD(Nd)</th>
<th>logD(Sm)</th>
<th>logD(Ho)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.04</td>
<td>\</td>
<td>-0.34396</td>
<td>-0.07511</td>
<td>0.379145</td>
<td>0.652076</td>
</tr>
<tr>
<td>2.10</td>
<td>-0.38535</td>
<td>-0.15127</td>
<td>0.167491</td>
<td>0.714034</td>
<td>1.055108</td>
</tr>
<tr>
<td>2.15</td>
<td>-0.24368</td>
<td>0.064017</td>
<td>0.419859</td>
<td>1.004321</td>
<td>1.398655</td>
</tr>
<tr>
<td>2.20</td>
<td>-0.03455</td>
<td>0.371611</td>
<td>0.751822</td>
<td>1.391039</td>
<td>1.798407</td>
</tr>
</tbody>
</table>
Figure 6.81 logD vs pH for La$^{3+}$.  

Figure 6.82 logD vs pH for Ce$^{3+}$.

Figure 6.83 logD vs pH for Nd$^{3+}$.  

Figure 6.84 logD vs pH for Sm$^{3+}$.  

Figure 6.85 logD vs pH for Ho$^{3+}$.

The calculated slopes are shown in Table 6.11 and the selectivities are given in Table 6.12.
Table 6.11 Slope of logD vs pH: [HL]=2x10^{-5} M.

<table>
<thead>
<tr>
<th>Metal ion</th>
<th>pH range</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>La</td>
<td>2.04-2.20</td>
<td>3.508</td>
</tr>
<tr>
<td>Ce</td>
<td>2.04-2.20</td>
<td>4.429</td>
</tr>
<tr>
<td>Pr</td>
<td>\</td>
<td>\</td>
</tr>
<tr>
<td>Nd</td>
<td>2.04-2.20</td>
<td>5.133</td>
</tr>
<tr>
<td>Sm</td>
<td>2.04-2.20</td>
<td>6.258</td>
</tr>
<tr>
<td>Eu</td>
<td>\</td>
<td>\</td>
</tr>
<tr>
<td>Ho</td>
<td>2.04-2.20</td>
<td>7.126</td>
</tr>
</tbody>
</table>

Table 6.12 Selectivity $\alpha$ at different pH values at ligand concentration 2x10^{-5} M.

<table>
<thead>
<tr>
<th>pH</th>
<th>$\alpha$(Ce/La)</th>
<th>$\alpha$(Nd/Ce)</th>
<th>$\alpha$(Sm/Nd)</th>
<th>$\alpha$(Ho/Sm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.03</td>
<td>\</td>
<td>1.857143</td>
<td>2.846154</td>
<td>1.874693</td>
</tr>
<tr>
<td>2.1</td>
<td>1.714286</td>
<td>2.083333</td>
<td>3.52</td>
<td>2.193182</td>
</tr>
<tr>
<td>2.15</td>
<td>2.030928</td>
<td>2.269036</td>
<td>3.841163</td>
<td>2.479324</td>
</tr>
<tr>
<td>2.2</td>
<td>2.547771</td>
<td>2.4</td>
<td>4.357292</td>
<td>2.554865</td>
</tr>
</tbody>
</table>

6.6.2 logD vs log[HL] and logD vs pH for the ligand HPMVP750.

a. logD vs log [HL].

The logD vs log[HL] plots were generated at a pH=2.78 in the range of ligand concentrations of 5x10^{-6} M to 2.5x10^{-5} M. The results are shown in Figures 6.85-6.91 and the calculations are shown in Table 6.13.
Table 6.13 logD vs log[HL] for the ligand HPMVP750.

Table 6.13a Retention times at different ligand concentrations.

<table>
<thead>
<tr>
<th>[HL], M</th>
<th>log[HL]</th>
<th>Retention Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>La</td>
</tr>
<tr>
<td>5x10^-6</td>
<td>-5.30103</td>
<td>2.43</td>
</tr>
<tr>
<td>1x10^-5</td>
<td>-5</td>
<td>2.43</td>
</tr>
<tr>
<td>1.5x10^-5</td>
<td>-4.82391</td>
<td>2.43</td>
</tr>
<tr>
<td>2x10^-5</td>
<td>-4.69897</td>
<td>2.5</td>
</tr>
<tr>
<td>2.5x10^-5</td>
<td>-4.60206</td>
<td>2.7</td>
</tr>
</tbody>
</table>

D=(t-t_0)/t_0,  t_0=1.70 (from Na_2Cr_2O_7 retention time)
Table 6.13b D values at different ligand concentrations

<table>
<thead>
<tr>
<th>[HL], M</th>
<th>log[HL]</th>
<th>D(La)</th>
<th>D(Ce)</th>
<th>D(Pr)</th>
<th>D(Nd)</th>
<th>D(Sm)</th>
<th>D(Eu)</th>
<th>D(Ho)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0x10^{-6}</td>
<td>-5.30103</td>
<td>0.429412</td>
<td>0.941176</td>
<td>1.747059</td>
<td>2.570588</td>
<td>9.705882</td>
<td>13.64706</td>
<td>27.07647</td>
</tr>
<tr>
<td>1.0x10^{-5}</td>
<td>-5.00000</td>
<td>0.429412</td>
<td>0.882353</td>
<td>1.511765</td>
<td>2.135294</td>
<td>7.158824</td>
<td>10.15882</td>
<td>17.47059</td>
</tr>
<tr>
<td>1.5x10^{-5}</td>
<td>-4.82391</td>
<td>0.429412</td>
<td>0.864706</td>
<td>1.488235</td>
<td>2.1</td>
<td>7.1</td>
<td>10.11765</td>
<td>17.25294</td>
</tr>
<tr>
<td>2.0x10^{-5}</td>
<td>-4.69897</td>
<td>0.470588</td>
<td>0.941176</td>
<td>1.588235</td>
<td>2.252941</td>
<td>7.764706</td>
<td>11.11765</td>
<td>19.27647</td>
</tr>
<tr>
<td>2.5x10^{-5}</td>
<td>-4.60206</td>
<td>0.588235</td>
<td>1.394118</td>
<td>2.276471</td>
<td>3.335294</td>
<td>12.29412</td>
<td>18.15882</td>
<td>33.33529</td>
</tr>
<tr>
<td>[HL], M</td>
<td>log[HL]</td>
<td>logD(La)</td>
<td>logD(Ce)</td>
<td>logD(Pr)</td>
<td>logD(Nd)</td>
<td>logD(Sm)</td>
<td>logD(Eu)</td>
<td>logD(Ho)</td>
</tr>
<tr>
<td>-----------</td>
<td>---------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>5.0x10^{-6}</td>
<td>-5.30103</td>
<td>-0.36713</td>
<td>-0.02633</td>
<td>0.242308</td>
<td>0.410033</td>
<td>0.987035</td>
<td>1.135039</td>
<td>1.432592</td>
</tr>
<tr>
<td>1.0x10^{-5}</td>
<td>-5.00000</td>
<td>-0.36713</td>
<td>-0.05436</td>
<td>0.179484</td>
<td>0.329458</td>
<td>0.854842</td>
<td>1.006843</td>
<td>1.242308</td>
</tr>
<tr>
<td>1.5x10^{-5}</td>
<td>-4.82391</td>
<td>-0.36713</td>
<td>-0.06313</td>
<td>0.172672</td>
<td>0.322219</td>
<td>0.851258</td>
<td>1.00508</td>
<td>1.236863</td>
</tr>
<tr>
<td>2.0x10^{-5}</td>
<td>-4.69897</td>
<td>-0.32736</td>
<td>-0.02633</td>
<td>0.200915</td>
<td>0.35275</td>
<td>0.890125</td>
<td>1.046013</td>
<td>1.285028</td>
</tr>
<tr>
<td>2.5x10^{-5}</td>
<td>-4.60206</td>
<td>-0.23045</td>
<td>0.144299</td>
<td>0.357262</td>
<td>0.523134</td>
<td>1.089697</td>
<td>1.259088</td>
<td>1.522904</td>
</tr>
</tbody>
</table>
Figure 6.86 logD vs log[HL] for La\textsuperscript{3+}.

Figure 6.87 logD vs log[HL] for Ce\textsuperscript{3+}.

Figure 6.88 logD vs log[HL] for Pr\textsuperscript{3+}.

Figure 6.89 logD vs log[HL] for Nd\textsuperscript{3+}.

Figure 6.90 logD vs log[HL] for Sm\textsuperscript{3+}.

Figure 6.91 logD vs log[HL] for Eu\textsuperscript{3+}.

Figure 6.92 logD vs log[HL] for Ho\textsuperscript{3+}.
The slopes for low and high ligand concentrations are given in Table 6.14 and the separation factors are given in Table 6.15.

Table 6.14 \( \log D \) vs \( \log[HL] \): pH=2.78.

<table>
<thead>
<tr>
<th>Metal ion</th>
<th>Concentration range (M)</th>
<th>Slope</th>
<th>Concentration range (M)</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>La</td>
<td>5x10^{-6}-1.5x10^{-5}</td>
<td>0</td>
<td>1.5x10^{-5}-2.5x10^{-5}</td>
<td>0.700</td>
</tr>
<tr>
<td>Ce</td>
<td>5x10^{-6}-1.5x10^{-5}</td>
<td>-1.780</td>
<td>1.5x10^{-5}-2.5x10^{-5}</td>
<td>1.761</td>
</tr>
<tr>
<td>Pr</td>
<td>5x10^{-6}-1.5x10^{-5}</td>
<td>-0.209</td>
<td>1.5x10^{-5}-2.5x10^{-5}</td>
<td>1.617</td>
</tr>
<tr>
<td>Nd</td>
<td>5x10^{-6}-1.5x10^{-5}</td>
<td>-0.268</td>
<td>1.5x10^{-5}-2.5x10^{-5}</td>
<td>1.655</td>
</tr>
<tr>
<td>Sm</td>
<td>5x10^{-6}-1.5x10^{-5}</td>
<td>-0.439</td>
<td>1.5x10^{-5}-2.5x10^{-5}</td>
<td>2.059</td>
</tr>
<tr>
<td>Eu</td>
<td>5x10^{-6}-1.5x10^{-5}</td>
<td>-0.426</td>
<td>1.5x10^{-5}-2.5x10^{-5}</td>
<td>2.199</td>
</tr>
<tr>
<td>Ho</td>
<td>5x10^{-6}-1.5x10^{-5}</td>
<td>-0.632</td>
<td>1.5x10^{-5}-2.5x10^{-5}</td>
<td>2.455</td>
</tr>
</tbody>
</table>
Table 6.15 Selectivity $\alpha$ at different ligand concentration.

<table>
<thead>
<tr>
<th>[HL], M</th>
<th>Log[HL]</th>
<th>$\alpha$(Ce/La)</th>
<th>$\alpha$(Pr/Ce)</th>
<th>$\alpha$(Nd/Pr)</th>
<th>$\alpha$(Sm/Nd)</th>
<th>$\alpha$(Eu/Sm)</th>
<th>$\alpha$(Ho/Eu)</th>
<th>$\alpha$(Ho/Sm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$5 \times 10^{-6}$</td>
<td>-5.30103</td>
<td>2.191781</td>
<td>1.85625</td>
<td>1.47138</td>
<td>3.775744</td>
<td>1.406061</td>
<td>1.984052</td>
<td>2.789697</td>
</tr>
<tr>
<td>$1 \times 10^{-5}$</td>
<td>-5</td>
<td>2.054795</td>
<td>1.713333</td>
<td>1.412451</td>
<td>3.352617</td>
<td>1.419063</td>
<td>1.719745</td>
<td>2.440427</td>
</tr>
<tr>
<td>$1.5 \times 10^{-5}$</td>
<td>-4.82391</td>
<td>2.013699</td>
<td>1.721088</td>
<td>1.411067</td>
<td>3.380952</td>
<td>1.425021</td>
<td>1.705233</td>
<td>2.429992</td>
</tr>
<tr>
<td>$2 \times 10^{-5}$</td>
<td>-4.69897</td>
<td>2</td>
<td>1.6875</td>
<td>1.418519</td>
<td>3.446475</td>
<td>1.431818</td>
<td>1.733862</td>
<td>2.482576</td>
</tr>
<tr>
<td>$2.5 \times 10^{-5}$</td>
<td>-4.60206</td>
<td>2.37</td>
<td>1.632911</td>
<td>1.465116</td>
<td>3.686067</td>
<td>1.477033</td>
<td>1.835763</td>
<td>2.711483</td>
</tr>
</tbody>
</table>
b. logD vs pH for HPMVP750.

The logD vs pH results were studied at two ligand concentration conditions: $5 \times 10^{-6}$ M and $2 \times 10^{-5}$ M, since HPMVP750 has good separation efficacies at these two concentrations.

At ligand concentration $5 \times 10^{-6}$ M, the retention time for each metal ion shown in Table 6.16 and for each metal ion, the result is shown in Figures 6.92-6.98.

### Table 6.16 logD vs pH at [HL]=$5 \times 10^{-6}$ for HPMVP750.

#### Table 6.16a Retention time for lanthanide metal ions at different pH values at a ligand concentration of $5 \times 10^{-6}$ M.

<table>
<thead>
<tr>
<th>pH</th>
<th>La</th>
<th>Ce</th>
<th>Pr</th>
<th>Nd</th>
<th>Sm</th>
<th>Eu</th>
<th>Ho</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.73</td>
<td>2.27</td>
<td>2.87</td>
<td>3.6</td>
<td>4.43</td>
<td>11.37</td>
<td>14.47</td>
<td>25.17</td>
</tr>
<tr>
<td>2.78</td>
<td>2.33</td>
<td>3</td>
<td>3.87</td>
<td>4.83</td>
<td>13.1</td>
<td>16.7</td>
<td>28.47</td>
</tr>
<tr>
<td>2.83</td>
<td>2.37</td>
<td>3.13</td>
<td>4.3</td>
<td>5.4</td>
<td>15.93</td>
<td>20.13</td>
<td>35.03</td>
</tr>
<tr>
<td>2.88</td>
<td>2.43</td>
<td>3.37</td>
<td>4.77</td>
<td>6.13</td>
<td>19.53</td>
<td>24.83</td>
<td>43.2</td>
</tr>
</tbody>
</table>

$D=\frac{(t_t-t_0)}{t_0}$, $t_0=1.70$ (from $\text{Na}_2\text{Cr}_2\text{O}_7$ retention time)
Table 6.16b D values at different pH.

<table>
<thead>
<tr>
<th>pH</th>
<th>D(La)</th>
<th>D(Ce)</th>
<th>D(Pr)</th>
<th>D(Nd)</th>
<th>D(Sm)</th>
<th>D(Eu)</th>
<th>D(Ho)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.73</td>
<td>0.335294</td>
<td>0.688235</td>
<td>1.117647</td>
<td>1.605882</td>
<td>5.688235</td>
<td>7.511765</td>
<td>13.80588</td>
</tr>
<tr>
<td>2.78</td>
<td>0.370588</td>
<td>0.764706</td>
<td>1.276471</td>
<td>1.841176</td>
<td>6.705882</td>
<td>8.823529</td>
<td>15.74706</td>
</tr>
<tr>
<td>2.83</td>
<td>0.394118</td>
<td>0.841176</td>
<td>1.529412</td>
<td>2.176471</td>
<td>8.370588</td>
<td>10.84118</td>
<td>19.60588</td>
</tr>
<tr>
<td>2.88</td>
<td>0.429412</td>
<td>0.982353</td>
<td>1.805882</td>
<td>2.605882</td>
<td>10.48824</td>
<td>13.60588</td>
<td>24.41176</td>
</tr>
</tbody>
</table>

Table 6.16c logD values at different pH.

<table>
<thead>
<tr>
<th>pH</th>
<th>logD(La)</th>
<th>logD(Ce)</th>
<th>logD(Pr)</th>
<th>logD(Nd)</th>
<th>logD(Sm)</th>
<th>logD(Eu)</th>
<th>logD(Ho)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.73</td>
<td>-0.47457</td>
<td>-0.16226</td>
<td>0.048305</td>
<td>0.205714</td>
<td>0.754978</td>
<td>0.875742</td>
<td>1.140064</td>
</tr>
<tr>
<td>2.78</td>
<td>-0.43111</td>
<td>-0.11651</td>
<td>0.106011</td>
<td>0.265095</td>
<td>0.826456</td>
<td>0.945642</td>
<td>1.197199</td>
</tr>
<tr>
<td>2.83</td>
<td>-0.40437</td>
<td>-0.07511</td>
<td>0.184524</td>
<td>0.337753</td>
<td>0.922756</td>
<td>1.035076</td>
<td>1.292386</td>
</tr>
<tr>
<td>2.88</td>
<td>-0.36713</td>
<td>-0.00773</td>
<td>0.256689</td>
<td>0.415955</td>
<td>1.020702</td>
<td>1.133727</td>
<td>1.387599</td>
</tr>
</tbody>
</table>

Figure 6.93 logD vs pH for La$^{3+}$.  
Figure 6.94 logD vs pH for Ce$^{3+}$.  

\[ y = 0.6981x - 2.3775 \]  
\[ R^2 = 0.9924 \]  

\[ y = 1.0125x - 2.9307 \]  
\[ R^2 = 0.98 \]  

\[ y = 1.0125x - 2.9007 \]  
\[ R^2 = 0.9875 \]  

158
The slopes of these plots are given in Table 6.17 and the selectivities in Table 6.18.
Table 6.17 Slope of logD vs pH: [HL]=5x10^{-6} M.

<table>
<thead>
<tr>
<th>Metal ion</th>
<th>pH range</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>La</td>
<td>2.73-2.88</td>
<td>1.432</td>
</tr>
<tr>
<td>Ce</td>
<td>2.73-2.88</td>
<td>1.013</td>
</tr>
<tr>
<td>Pr</td>
<td>2.73-2.88</td>
<td>1.407</td>
</tr>
<tr>
<td>Nd</td>
<td>2.73-2.88</td>
<td>1.407</td>
</tr>
<tr>
<td>Sm</td>
<td>2.73-2.88</td>
<td>1.787</td>
</tr>
<tr>
<td>Eu</td>
<td>2.73-2.88</td>
<td>1.727</td>
</tr>
<tr>
<td>Ho</td>
<td>2.73-2.88</td>
<td>1.676</td>
</tr>
</tbody>
</table>

Table 6.18 Selectivity $\alpha$ at different pH.

<table>
<thead>
<tr>
<th>pH</th>
<th>$\alpha$(Ce/La)</th>
<th>$\alpha$(Pr/Ce)</th>
<th>$\alpha$(Nd/Pr)</th>
<th>$\alpha$(Sm/Nd)</th>
<th>$\alpha$(Eu/Sm)</th>
<th>$\alpha$(Ho/Eu)</th>
<th>$\alpha$(Ho/Sm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.73</td>
<td>2.052632</td>
<td>1.623932</td>
<td>1.436842</td>
<td>3.542125</td>
<td>1.320579</td>
<td>1.837901</td>
<td>2.427094</td>
</tr>
<tr>
<td>2.78</td>
<td>2.063492</td>
<td>1.669231</td>
<td>1.442396</td>
<td>3.642173</td>
<td>1.315789</td>
<td>1.784667</td>
<td>2.348246</td>
</tr>
<tr>
<td>2.78</td>
<td>2.134328</td>
<td>1.818182</td>
<td>1.423077</td>
<td>3.845946</td>
<td>1.295151</td>
<td>1.808464</td>
<td>2.342235</td>
</tr>
<tr>
<td>2.88</td>
<td>2.287671</td>
<td>1.838323</td>
<td>1.442997</td>
<td>4.024831</td>
<td>1.297252</td>
<td>1.794207</td>
<td>2.327538</td>
</tr>
</tbody>
</table>

The logD vs pH studies were performed at a ligand concentration of 2x10^{-5} M. The retention time for the metal ions at different pH values are given in Table 6.19. The D and logD values are also given in Table 6.19b and 6.19c. The plots of logD vs pH for the different metal ions are displayed in Figure 6.100-6.106.
Table 6.19 $\log D$ vs pH at $[\text{HL}]=2\times10^{-5}\text{M}$ for HPMVP750.

Table 6.19a Retention times at different pH at $[\text{HL}]=2\times10^{-5}\text{M}$.

<table>
<thead>
<tr>
<th>pH</th>
<th>La</th>
<th>Ce</th>
<th>Pr</th>
<th>Nd</th>
<th>Sm</th>
<th>Eu</th>
<th>Ho</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.56</td>
<td>2.3</td>
<td>2.73</td>
<td>3.33</td>
<td>4.07</td>
<td>9.17</td>
<td>12.97</td>
<td>23.9</td>
</tr>
<tr>
<td>2.59</td>
<td>2.37</td>
<td>3.03</td>
<td>4.1</td>
<td>5.13</td>
<td>14.1</td>
<td>21.43</td>
<td>44.97</td>
</tr>
<tr>
<td>2.62</td>
<td>2.53</td>
<td>3.67</td>
<td>5.33</td>
<td>7.13</td>
<td>23.63</td>
<td>36.9</td>
<td>75.5</td>
</tr>
<tr>
<td>2.65</td>
<td>2.87</td>
<td>4.53</td>
<td>7.23</td>
<td>10.13</td>
<td>39.33</td>
<td>64.13</td>
<td>\</td>
</tr>
</tbody>
</table>

$D=(t_r-t_0)/t_0$, $t_0=1.70$ (from Na$_2$Cr$_2$O$_7$ retention time)

Table 6.19b $D$ values at different pH.

<table>
<thead>
<tr>
<th>pH</th>
<th>D(La)</th>
<th>D(Ce)</th>
<th>D(Pr)</th>
<th>D(Nd)</th>
<th>D(Sm)</th>
<th>D(Eu)</th>
<th>D(Ho)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.56</td>
<td>0.352941</td>
<td>0.605882</td>
<td>0.958824</td>
<td>1.394118</td>
<td>4.394118</td>
<td>6.629412</td>
<td>13.05882</td>
</tr>
<tr>
<td>2.59</td>
<td>0.394118</td>
<td>0.782353</td>
<td>1.411765</td>
<td>2.017647</td>
<td>7.294118</td>
<td>11.60588</td>
<td>25.45294</td>
</tr>
<tr>
<td>2.62</td>
<td>0.488235</td>
<td>1.158824</td>
<td>2.135294</td>
<td>3.194118</td>
<td>12.9</td>
<td>20.70588</td>
<td>43.41176</td>
</tr>
<tr>
<td>2.65</td>
<td>0.688235</td>
<td>1.664706</td>
<td>3.252941</td>
<td>4.958824</td>
<td>22.13529</td>
<td>36.72353</td>
<td>\</td>
</tr>
</tbody>
</table>
Table 6.19c logD vs pH.

<table>
<thead>
<tr>
<th>pH</th>
<th>logD(La)</th>
<th>logD(Ce)</th>
<th>logD(Pr)</th>
<th>logD(Nd)</th>
<th>logD(Sm)</th>
<th>logD(Eu)</th>
<th>logD(Ho)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.56</td>
<td>-0.4523</td>
<td>-0.21761</td>
<td>-0.01826</td>
<td>0.144299</td>
<td>0.642872</td>
<td>0.821475</td>
<td>1.115904</td>
</tr>
<tr>
<td>2.59</td>
<td>-0.40437</td>
<td>-0.1066</td>
<td>0.149762</td>
<td>0.304845</td>
<td>0.862973</td>
<td>1.064678</td>
<td>1.405738</td>
</tr>
<tr>
<td>2.62</td>
<td>-0.31137</td>
<td>0.064017</td>
<td>0.329458</td>
<td>0.504351</td>
<td>1.11059</td>
<td>1.316094</td>
<td>1.637607</td>
</tr>
<tr>
<td>2.65</td>
<td>-0.16226</td>
<td>0.221338</td>
<td>0.512276</td>
<td>0.695379</td>
<td>1.345085</td>
<td>1.564944</td>
<td>\</td>
</tr>
</tbody>
</table>

Figure 6.100 logD vs pH for La$^{3+}$.

Figure 6.101 logD vs pH for Ce$^{3+}$.

Figure 6.102 logD vs pH for Pr$^{3+}$.

Figure 6.103 logD vs pH for Nd$^{3+}$.
Figure 6.104 logD vs pH for Sm$^{3+}$. Figure 6.105 logD vs pH for Eu$^{3+}$.

![Graph for Sm$^{3+}$](image)

![Graph for Eu$^{3+}$](image)

Figure 6.106 logD vs pH for Ho$^{3+}$.

![Graph for Ho$^{3+}$](image)

From the above results, the calculated slopes of these results are shown in Table 6.20 and the separation factors for the studied 7 lanthanide metal ions at ligand concentration [HL]=2x10$^{-5}$ M were calculated and shown in Table 6.21.
Table 6.20 Slopes of logD vs pH: [HL]=2x10^{-5} M.

<table>
<thead>
<tr>
<th>Metal ion</th>
<th>pH range</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>La</td>
<td>2.56-2.65</td>
<td>3.21</td>
</tr>
<tr>
<td>Ce</td>
<td>2.56-2.65</td>
<td>4.96</td>
</tr>
<tr>
<td>Pr</td>
<td>2.56-2.65</td>
<td>5.90</td>
</tr>
<tr>
<td>Nd</td>
<td>2.56-2.65</td>
<td>6.18</td>
</tr>
<tr>
<td>Sm</td>
<td>2.56-2.65</td>
<td>7.85</td>
</tr>
<tr>
<td>Eu</td>
<td>2.56-2.65</td>
<td>8.27</td>
</tr>
<tr>
<td>Ho</td>
<td>2.56-2.65</td>
<td>9.00</td>
</tr>
</tbody>
</table>

Table 6.21 Selectivities $\alpha$ at different pH at ligand concentration 2x10^{-5} M.

<table>
<thead>
<tr>
<th>pH</th>
<th>$\alpha$(Ce/La)</th>
<th>$\alpha$(Pr/Ce)</th>
<th>$\alpha$(Nd/Pr)</th>
<th>$\alpha$(Sm/Nd)</th>
<th>$\alpha$(Eu/Sm)</th>
<th>$\alpha$(Ho/Eu)</th>
<th>$\alpha$(Ho/Sm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.56</td>
<td>1.716667</td>
<td>1.582524</td>
<td>1.453988</td>
<td>3.151899</td>
<td>1.508701</td>
<td>1.969831</td>
<td>2.971888</td>
</tr>
<tr>
<td>2.59</td>
<td>1.985075</td>
<td>1.804511</td>
<td>1.429167</td>
<td>3.61516</td>
<td>1.591129</td>
<td>2.193107</td>
<td>3.489516</td>
</tr>
<tr>
<td>2.62</td>
<td>2.373494</td>
<td>1.84264</td>
<td>1.495868</td>
<td>4.038674</td>
<td>1.605107</td>
<td>2.096591</td>
<td>3.365253</td>
</tr>
<tr>
<td>2.65</td>
<td>2.418803</td>
<td>1.954064</td>
<td>1.524412</td>
<td>4.46382</td>
<td>1.659049</td>
<td>\</td>
<td>\</td>
</tr>
</tbody>
</table>

From the above calculation, the separation factors are also increasing with increasing of pH at high ligand concentration.


6.7 Discussion.

The mechanism in Figure 6.69 can be simplified as described in the following equations. The mechanism takes into account the formation of multiple layers of the ligand HL on C\textsubscript{18} surface. Such an assembly occurs through tail to tail and head to head association, namely SP-LH···LH···LH (SP = stationary phase), similar to that observed in solution. The SP(LH)\textsubscript{n} self-assembly can thus deprotonate and the charge balance is maintained by Na\textsuperscript{+} ions as the ionic strength is maintained at 0.1 M with NaClO\textsubscript{4}. This behavior is similar to an ion exchange resin. In addition, the lanthanide metal ion M\textsuperscript{3+} could form 1:1 (ML\textsuperscript{2+}), 1:2 (ML\textsubscript{2}\textsuperscript{+}) and 1:3 (ML\textsubscript{3}) metal:ligand complexes on the C\textsubscript{18} stationary phase.

\[
\begin{align*}
\text{SP} + n\text{HL} & \quad \rightleftharpoons \quad \text{SP-L}_n (\text{Na}^+)_n + n\text{H}^+ \\
\text{SP} + 3\text{HL} + \text{M}^{3+} & \quad \xrightleftharpoons[K_2]{K_3} \quad \text{SP-L}_3\text{M} + 3\text{H}^+ \\
\text{SP} + 2\text{HL} + \text{M}^{3+} + \text{ClO}_4^- & \quad \xrightleftharpoons[K_2]{K_1} \quad \text{SP-L}_2\text{MClO}_4 + 2\text{H}^+ \\
\text{SP} + \text{HL} + \text{M}^{3+} + 2\text{ClO}_4^- & \quad \xrightleftharpoons[K_1]{K_2} \quad \text{SP-L}\text{M(ClO}_4)_2 + \text{H}^+ \\

D_{\text{obs}} &= \frac{[\text{SP-L}_3\text{M}] + [\text{SP-L}_2\text{M}] + [\text{SP-LM}]}{[\text{M}^{3+}]} \\
D_{\text{obs}} &= K_3 [\text{HL}]^3 \frac{1}{[\text{H}^+]^3} + K_2 [\text{HL}]^2 \frac{1}{[\text{H}^+]^2} + K_1 [\text{HL}] \frac{1}{[\text{H}^+]}
\end{align*}
\]

Equation 10 indicates that the dependence of logD on log[HL] will not be a simple integer (1, 2 or 3) but could be nonintegral values depending on the extent to which the
1:1, 1:2, and 1:3 metal:ligand complexes are formed on the stationary phase SP. It is evident from the data listed in the tables for HPMBP750 in the ligand concentration range 5x10^{-6} M – 2.5x10^{-5} M that predominantly 1:1 complexes are formed for the light and middle lanthanides and 1:2 complexes are also formed for the heavy lanthanides. The dependence of logD vs pH at low ligand concentration 5x10^{-6} M is similar to the ligand dependence indicating that ligand multilayer formation on SP in equation 5 occurs to a very minor extent. However at high ligand concentration of 2x10^{-5} M logD vs pH has slopes in the range 3.5-7.1 indicating that ligand aggregation on the stationary phase (equation 1) is significant. The much higher slopes for logD vs pH compared to logD vs log[HL] are due to ligand aggregation on the stationary phase. A similar situation is encountered with HPMVP750, where the formation of 1:2 and 1:3 metal:ligand complexes occurs to a significant extent for the heavy lanthanides.

The formation of ligand aggregates by head to head and tail to tail association have been investigated by sequential equilibration of the C_{18} stationary phase with 2x10^{-5} M HPMVP750 in the pH range 2.51-2.65. The separation of La^{3+} (10^{-4} M), Ce^{3+} (1.2x10^{-4} M), Pr^{3+} (1.5x10^{-4} M), Nd^{3+} (2x10^{-4} M), Sm^{3+} (3.6x10^{-4} M), Eu^{3+} (3.6x10^{-4} M) and Ho^{3+} (5.5x10^{-4} M) were performed nine successive times under this condition. As displayed in Figure 6.107 and Figure 6.108 at pH values 2.51 and 2.65 the retention times for each metal ion increased with successive runs. Thus the D values for each metal ion increased with each successive run. The slopes of logD vs pH for each metal ion as a function of
equilibration is given in Table 6.22, where each equilibration time corresponds to a separate experiment. The plots of slope vs runtime are shown in Figures 6.108-6.114.

Figure 6.107 Equilibration of the C\textsubscript{18} stationary phase with HPMVP750, pH=2.51.

![Figure 6.107 Equilibration of the C\textsubscript{18} stationary phase with HPMVP750, pH=2.51.]

Figure 6.108 Equilibration of the C\textsubscript{18} stationary phase with HPMVP750, pH=2.65.

![Figure 6.108 Equilibration of the C\textsubscript{18} stationary phase with HPMVP750, pH=2.65.]
Table 6.22 Slope of logD vs pH with different equilibrium time.

<table>
<thead>
<tr>
<th>Equilibration time (min)</th>
<th>La$^{3+}$</th>
<th>Ce$^{3+}$</th>
<th>Pr$^{3+}$</th>
<th>Nd$^{3+}$</th>
<th>Sm$^{3+}$</th>
<th>Eu$^{3+}$</th>
<th>Ho$^{3+}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>0.9169</td>
<td>0.7682</td>
<td>1.3682</td>
<td>0.7268</td>
<td>1.7686</td>
<td>2.4903</td>
<td>2.4205</td>
</tr>
<tr>
<td>60</td>
<td>0.8892</td>
<td>0.9505</td>
<td>1.5384</td>
<td>0.9504</td>
<td>2.1351</td>
<td>2.6446</td>
<td>2.5679</td>
</tr>
<tr>
<td>120</td>
<td>0.8419</td>
<td>1.2156</td>
<td>1.7756</td>
<td>1.2156</td>
<td>2.5748</td>
<td>2.8372</td>
<td>2.7939</td>
</tr>
<tr>
<td>180</td>
<td>0.8078</td>
<td>1.3997</td>
<td>1.9333</td>
<td>1.3997</td>
<td>2.8301</td>
<td>2.9478</td>
<td>2.8360</td>
</tr>
<tr>
<td>240</td>
<td>0.7704</td>
<td>1.5352</td>
<td>2.0459</td>
<td>1.5352</td>
<td>2.9973</td>
<td>3.0197</td>
<td>2.8985</td>
</tr>
<tr>
<td>300</td>
<td>0.7433</td>
<td>1.6393</td>
<td>2.1242</td>
<td>1.6393</td>
<td>3.1530</td>
<td>3.0762</td>
<td>2.9422</td>
</tr>
<tr>
<td>360</td>
<td>0.7197</td>
<td>1.7218</td>
<td>2.1961</td>
<td>1.7218</td>
<td>3.2030</td>
<td>3.1076</td>
<td>2.9744</td>
</tr>
<tr>
<td>420</td>
<td>0.6992</td>
<td>1.7887</td>
<td>2.2409</td>
<td>1.7887</td>
<td>3.2709</td>
<td>3.1365</td>
<td>2.9992</td>
</tr>
<tr>
<td>480</td>
<td>0.6813</td>
<td>1.8443</td>
<td>2.2919</td>
<td>1.8443</td>
<td>3.3249</td>
<td>3.1594</td>
<td>3.0189</td>
</tr>
<tr>
<td>540</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.3689</td>
<td>3.1780</td>
<td>3.0349</td>
</tr>
</tbody>
</table>

Figure 6.109 Slope vs time for La$^{3+}$.

$$\text{Slope of } \log D \text{ vs pH } = y = -0.0005x + 0.9122$$

$$R^2 = 0.973$$

Figure 6.110 Slope vs time for Ce$^{3+}$.

$$\text{Slope of } \log D \text{ vs pH } = y = 0.0023x + 0.8709$$

$$R^2 = 0.9226$$
The increase in D value could be attributed to the self-assembly of the ligands on the C_{18} stationary phase, equation 5, with increasing layers of self-assembled ligands with
each run. Even though the D value continues to increase even after nine successive separations, the slopes of logD vs pH reaches a reasonably constant value with increasing equilibration times. The log of the extraction equilibrium constants $K_{ex}$ (same as $K_3$, $K_2$ and $K_1$ in equation 6, 7 and 8) as function of the equilibration times have been calculated from the intercepts of the logD vs pH plots. These values are tabulated in Table 6.23.

These values have been calculated considering that this predominant complex for La$^{3+}$ and Ce$^{3+}$ is 1:1, for Pr$^{3+}$ and Nd$^{3+}$ is 1:2 and for Sm$^{3+}$, Eu$^{3+}$ and Ho$^{3+}$ is 1:3.

<table>
<thead>
<tr>
<th>Equilibration time (min)</th>
<th>La$^{3+}$</th>
<th>Ce$^{3+}$</th>
<th>Pr$^{3+}$</th>
<th>Nd$^{3+}$</th>
<th>Sm$^{3+}$</th>
<th>Eu$^{3+}$</th>
<th>Ho$^{3+}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>1.8696</td>
<td>2.4659</td>
<td>5.8433</td>
<td>7.1659</td>
<td>10.143</td>
<td>8.4608</td>
<td>8.8726</td>
</tr>
<tr>
<td>60</td>
<td>1.9631</td>
<td>2.0431</td>
<td>5.4607</td>
<td>6.7432</td>
<td>9.2778</td>
<td>8.1300</td>
<td>8.5835</td>
</tr>
<tr>
<td>120</td>
<td>2.1259</td>
<td>1.4403</td>
<td>4.9433</td>
<td>6.1404</td>
<td>8.2691</td>
<td>7.7683</td>
<td>8.2841</td>
</tr>
<tr>
<td>180</td>
<td>2.2642</td>
<td>1.0331</td>
<td>4.6138</td>
<td>5.7335</td>
<td>7.7073</td>
<td>7.5857</td>
<td>8.1351</td>
</tr>
<tr>
<td>240</td>
<td>2.3811</td>
<td>0.7424</td>
<td>4.3888</td>
<td>5.4424</td>
<td>7.3552</td>
<td>7.4831</td>
<td>8.0580</td>
</tr>
<tr>
<td>300</td>
<td>2.4838</td>
<td>0.5253</td>
<td>4.2429</td>
<td>5.2254</td>
<td>7.1177</td>
<td>7.4224</td>
<td>8.0158</td>
</tr>
<tr>
<td>30</td>
<td>2.5742</td>
<td>0.3587</td>
<td>4.1082</td>
<td>5.0585</td>
<td>6.9493</td>
<td>7.3858</td>
<td>7.9931</td>
</tr>
<tr>
<td>420</td>
<td>2.6547</td>
<td>0.2272</td>
<td>4.0575</td>
<td>4.9272</td>
<td>6.8253</td>
<td>7.3640</td>
<td>7.9822</td>
</tr>
<tr>
<td>480</td>
<td>2.7271</td>
<td>0.1218</td>
<td>3.9470</td>
<td>4.8218</td>
<td>6.7316</td>
<td>7.3518</td>
<td>7.9787</td>
</tr>
<tr>
<td>540</td>
<td>6.6593</td>
<td>7.3461</td>
<td>7.9801</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In general, as the chromatograms indicate the equilibrium constants should increase from La$^{3+}$ to Ho$^{3+}$. The logK$_1$ value for Ce$^{3+}$ is not always larger than that for La$^{3+}$, which may be due to low D values for these metal ions. The logK$_2$ values for Pr$^{3+}$ and Nd$^{3+}$ and logK$_3$ values for Sm$^{3+}$, Eu$^{3+}$ and Ho$^{3+}$ increase as expected.

The separation of lanthanide metal ions employing the amphiphilic acylpyrazolone ligands clearly depends on the structure of the ligand, self-assembly of the ligand in the aqueous phase and self-assembly of the ligand on the C$_{18}$ stationary phase.

**Figure 6.116: The factors that determine HPLC separation.**
CHAPTER VII

SPONTANEOUS AND STIMULATED SELF-ASSEMBLY OF SILICA NANOPARTICLES DERIVATIZED WITH ACYLPYRAZOLONES AND ACYLISOXAZOLONES

7.1 Introduction.

The amphiphilic acylpyrazolones spontaneously self-assemble in the aqueous phase to form spherical, dendritic and linear (nanotubes, nanorods and nanofibers). Several of these ligands exhibit excellent selectivities for the trivalent lanthanide metal ions. Their metal ion recognition is strongly influenced by their self-assemblies. We have extended the studies on the self-assembly of amphiphilic acylpyrazolone ligands to spontaneous self-assembly of silica nanoparticles derivatized with acylpyrazolone and acylisoxazolone ligands and the stimulated self-assembly of acylpyrazolone and acylisoxazolone ligands with terminal chloromethyl group on the substituent in the 4 position.

Self-assembly of molecules, amphiphiles, supramolecular systems, nano and micron sized materials (particles, tubes and rods) can be spontaneous and/or stimulated and are fundamentally driven by (1), hydrogen bonding, (2), $\pi$-$\pi$ interaction, (3), electrostatic interaction, (4), dipole-dipole interaction, (5), van der Waal’s forces, (6), inclusion complex formation, and (7), conformational lock in chiral systems. The stimulated self-assembly of chloromethyl acylpyrazolones and acylisoxazolones and spontaneous self-assembly of SiO$_2$ nanoparticles derivatized with these ligands are driven by $\pi$-$\pi$
interaction, hydrogen bonding and van der Waal’s forces.

The spontaneous self-assembly of large (10-30 µm) silica and metal nanoparticles of various shapes on silicon wafers was reported by Whitesides [76]. Pine observed the self-assembly of 1 µm size polystyrene spheres in microemulsions to form sphere doublets, triangles, tetrahedral and various shapes of polyhedra [77]. The self-assembly of polystyrene spheres is driven by \( \pi-\pi \) interaction and van der Waal’s forces. Glotzer performed Monte Carlo simulation of nanoparticles of various shapes (spheres, disks, cubes, wheels, rods, tubes etc.) tethered (derivatized) with suitable polymers [78, 79]. Their molecular simulations indicate that derivatized nanoscale systems form spherical, cylindrical and columnar structures. They also performed simulations of self-assembly of patchy spherical nanoparticles. The patchiness of these nanoparticles were due to surface defects or the attachment of monomeric ligands [79]. The patchy nanoparticles were shown to self-assemble to form triangles, tetrahedra, square pyramids, icosohedra, rings, chains and sheets. Ranaine attached polymerizable methacryl groups by emulsion polymerization method [80]. This yielded daisy shaped and multipod-like silica polystyrene nanocomposites. The shapes of polystyrene spheres that grew on the silica core resemble the triangular, tetrahedral, icosohedral shapes observed by Pine and predicted by Glotzer. Zemb showed that salt free mixtures of cationic ionic surfactants form hollow icosohedral structures.

These systems are examples of spontaneous and stimulated self-assembly of
nano-scale systems. The self-assemblies of chloromethyl acylpyrazolones and acylisoxazolones and silica nanoparticles derivatized with these yield spherical, triangular, tetrahedral and polyhedral structures similar to those discussed above. These results are presented in this chapter.

7.2 Synthesis of silica nanoparticles derivatized with acylpyrazolones and acylisoxazolones.

The synthetic route to attach the acylpyrazolones and acylisoxazolones is very similar to that for the amphiphilic ligands. Silica nanoparticles have a porous structure with hydroxyl groups (-OH) on the surface, as is shown in Figure 7.1.

Figure 7.1 Structure of silica nanoparticle.

The TEM images of synthesized silica nanoparticles are shown in Figure 7.2.
From the above TEM images, the silica nanoparticles are fairly uniform in both shape and size and the diameter of the particles is $65 \pm 10\text{ nm}$.

Silica nanoparticles were dispersed in dry THF and sodium bicarbonate was used as the base to attach the ligands. A nucleophilic substitution reaction will occur on the chloromethyl group ($-\text{CH}_2\text{Cl}$) in the presence of base. The synthetic approach is shown in Figure 7.3.

**Figure 7.3 Derivatization of SiO$_2$ nanoparticle with acylpyrazolones or acylisoxazolones.**
The $\beta$-ketoesters were used to react with several kinds of substituted hydrazines to obtain the pyrazolone structures and the acylation reaction which was discussed in Chapter III was employed to obtain acylpyrazolones and acylisoxazolones with terminal CH$_2$Cl groups. These ligands were attached to silica nanoparticles through nucleophilic substitution reaction with NaHCO$_3$ under very mild conditions. These particles were then dispersed in H$_2$O to obtain TEM images as the TEM grids are attacked by THF.

7.3 Self-assembly of derivatized silica nanoparticles.

1. Selected ligands.

The influence of functional groups on the metal ion recognition efficacies of acylpyrazolones are discussed in Chapters III and VI.

It may be expected that the self-assembly of ligand derivatized SiO$_2$ nanoparticles will be driven by hydrogen bonding, $\pi-\pi$ interaction and van der Waal’s forces. Such interaction will be influenced by the resonance structure of the acylpyrazolone ligands displayed in Figure 7.4. As discussed before, the contribution of each resonance structure to the overall structure of the ligand is a function of the substituents R’, R” and R’’’.

Figure 7.4 Isomers of acylpyrazolone.
The choice of these ligands is towards understanding the role of π-π interaction, hydrogen bonding and van der Waal’s forces in this self-assembly analogous to the amphiphilic ligands discussed in Chapter 6. Structures of ligand derivatized nanoparticles are displayed in Figures 7.5 and 7.6.

Figure 7.5 Acylpyrazolone derivatized SiO$_2$ nanoparticles.

![Figure 7.5 Acylpyrazolone derivatized SiO$_2$ nanoparticles.](image)

Figure 7.6 Acylisoxazolone derivatized SiO$_2$ nanoparticles.

![Figure 7.6 Acylisoxazolone derivatized SiO$_2$ nanoparticles.](image)

2. Self-assemblies of acylpyrazolones derivatized silica nanoparticles.

a) 1-phenyl-3-methyl-4-(4'-methyl-Si)-benzoyl-5-pyrazolone.

The structure of this silica nanoparticle is shown in Figure 7.7.

Figure 7.7 Structure of SiO$_2$-HPMBP.

![Figure 7.7 Structure of SiO$_2$-HPMBP.](image)
The ligand derivatized nanoparticle self-assembly was examined as a function of ligand concentration. The SiO$_2$:HL ratio was varied based on the molecular weight of SiO$_2$ (MW=60) and the molecular weight of the ligand. Ratios of 1:1, 2:1, 5:1 and 10:1 were employed in the derivatization of the nanoparticles. The particles were isolated by centrifugation, washed with THF and dispersed into H$_2$O for TEM studies. The images for the different SiO$_2$:HL ratios are displayed in Figures 7.8-7.11.

**Figure 7.8**  TEM images of SiO$_2$-HPMBP at 1 : 1 ratio.

![TEM images of SiO$_2$-HPMBP at 1:1 ratio.](image1)

**Figure 7.9**  TEM images of SiO$_2$-HPMBP at 2 : 1 ratio.

![TEM images of SiO$_2$-HPMBP at 2:1 ratio.](image2)
The ligand derivatized nanoparticles aggregate to form large spherical assemblies the size of which is a function of ligand concentration employed. These self-assemblies are the result of both free ligand and derivatized particles aggregating in THF and aqueous phases. The large spherical aggregates are formed in THF during SiO$_2$ derivatization and aggregation between individual SiO$_2$-HL nanoparticles occurs in the aqueous phase. As the ligand concentration is decreased, these spherical aggregates become smaller and at 10:1 SiO$_2$: HPMBP ratio, clusters of nanoparticles are the predominant assemblies. The nature of self-assemblies formed for the different SiO$_2$:HL ratios are summarized in Table 7.1.
Table 7.1 SiO$_2$-HPMBP self-assemblies at different ligand concentrations.

<table>
<thead>
<tr>
<th>Ratio of SiO$_2$ : Ligand</th>
<th>Self-assemblies</th>
<th>Particle Size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 : 1</td>
<td>spheres</td>
<td>400 average (wide range of sizes)</td>
</tr>
<tr>
<td>2 : 1</td>
<td>sphere</td>
<td>400 average (narrow range of sizes)</td>
</tr>
<tr>
<td>5 : 1</td>
<td>spheres and clusters</td>
<td>80-100</td>
</tr>
<tr>
<td>10 : 1</td>
<td>clusters</td>
<td>65</td>
</tr>
</tbody>
</table>

b) 1-phenyl-3-phenyl-4-(4’-methyl-Si)-benzoyl-5-pyrazolone.

The structure of this kind of SiO$_2$-HL nanoparticles is shown in Figure 7.12.

Figure 7.12 Structure of SiO$_2$-HPPBP.

![Figure 7.12 Structure of SiO$_2$-HPPBP.](image)

The SiO$_2$:HL ratios investigated were 4:1, 5:1, 6:1, 7:1 and 10:1. This SiO$_2$-HL system is rich in π electrons and π-π interaction could be expected to dominate the self-assembly. The TEM images of the self-assemblies are displayed in Figures 7.13, 7.14, and 7.16-7.18. The self-assemblies of 1 µm polystyrene particles reported by Pine are displayed in Figure 7.15 for comparison.
Figure 7.13 TEM images of SiO$_2$-HPPBP at 4 : 1 ratio.

Figure 7.14 TEM images of SiO$_2$-HPPBP at 5 : 1 ratio.

Figure 7.15 Self-assemblies of 1μm polystyrene particles [77].
The self-assemblies of SiO₂-HPPBP system have similarities and differences with the SiO₂-HPMBP system. The SiO₂-HPPBP at 4:1 ratio forms very large spherical assemblies in THF which further self-assemble in H₂O as indicated in Figure 7.13. These large
spheres have SiO$_2$-HPPBP nanoparticles encapsulated. The self-assemblies at the 5:1 molar ratio are most striking as evident from Figure 7.14. Aggregates of SiO$_2$-HPPBP nanoparticles containing 2, 3, 4 and higher numbering individual particles with triangle, tetrahedral, octahedral and polyhedral structures can be seen. These self-assemblies are enclosed in a spherical shell of the chloromethylated HPPBP ligand that is formed in THF in the presence of NaHCO$_3$. The stimulated self-assembly of the chloromethylated ligand is discussed in detail in a later part of this chapter.

The structures in Figure 7.14 are analogous to those reported by Pine on the self-assembly of 1µm polystyrene spheres, which is displayed in Figure 7.15 [77]. Clearly the SiO$_2$-HPPBP and polystyrene particles self-assemble primarily through extensive $\pi$-$\pi$ interaction of the phenyl rings. In the case of SiO$_2$-HPPBP, hydrogen bonding through the $\beta$-diketone structure and van der Waal’s forces also play a role. The self-assembly motifs observed for the 5:1, SiO$_2$:HPPBP ratio have also been predicted by Glotzer for patchy spherical nanoparticles [82].

These structures are also seen at the 6:1 SiO$_2$:HPPBP ratio but to a lesser extent. Aggregation of the individual nanoparticles in the aqueous phase becomes more predominant. Similarly at the 7:1 SiO$_2$:HPPBP ratio, only very large spherical aggregation and clusters of individual nanoparticles exist. The large spherical clusters are result of encapsulation of SiO$_2$-HPPBP nanoparticles in the spherical assemblies of HPPBP. At 10:1 SiO$_2$:HPPBP ratio mainly clusters of SiO$_2$-HPPBP nanoparticles are
observed. The various structures for the SiO₂-HPPBP system are summarized in Table 7.2.

Table 7.2 SiO₂-HPPBP self-assemblies at different ligand concentrations.

<table>
<thead>
<tr>
<th>Ratio of SiO₂ : Ligand</th>
<th>Self-assemblies</th>
<th>Particle Size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 : 1</td>
<td>Large spheres and clusters</td>
<td>200-2000</td>
</tr>
<tr>
<td>5 : 1</td>
<td>Dimmers, triangular, tetrahedral, octahedral and polyhedral</td>
<td>200-2000</td>
</tr>
<tr>
<td>6 : 1</td>
<td>Polyhedral structures encapsulated in spheres and clusters</td>
<td>100-400</td>
</tr>
<tr>
<td>7 : 1</td>
<td>Polyhedral structures encapsulated in spheres and clusters</td>
<td>100-400</td>
</tr>
<tr>
<td>10 : 1</td>
<td>clusters</td>
<td>65</td>
</tr>
</tbody>
</table>

c) 1-phenyl-3-methyl-4-(5’-Si)-valeryl pyrazolone.

The structure of this SiO₂-HL nanoparticle is shown in Figure 7.19.
Figure 7.19 Structure of SiO$_2$-HPMVP.

![Structure of SiO$_2$-HPMVP](image)

The stimulated self-assembly of the chloromethyl HPMVP ligand in THF and the spontaneous self-assembly of SiO$_2$-HPMVP in THF and H$_2$O can be expected to be very different compared to HPMBP and HPPBP discussed above. This ligand has the least π electron density and the self-assembly will not be dominated by π-π interaction. Hydrogen bonding and van der Waal’s forces can be expected to contribute much more compared to HPMBP and HPPBP.

The SiO$_2$-HPMVP nanoparticles were synthesized in the SiO$_2$:HPMVP ratios 1:1, 5:1 and 10:1. TEM images were recorded to discern their self- assemblies and these are displayed in Figures 7.20-7.22.

Figure 7.20 TEM images of SiO$_2$-HPMVP at 1 : 1 ratio.
Minimum self-assembly is observed even at 1:1 SiO$_2$-HPMVP ratio as evident from Figure 7.20. Individual spheres up to 80 nm size are evident indicating that the increase in size is primarily due to the derivatization of the SiO$_2$ nanoparticles with HPMVP. Few monolayers of these ligands self-assemble leading to the 80 nm sizes. The individual SiO$_2$-HPMVP nanoparticles also do not self-assemble or form clusters in the aqueous phase. This trend is observed for the SiO$_2$-HPMVP ratio of 5:1 as well. A more interesting aggregation occurs at a SiO$_2$-HPMVP ratio of 10:1, where the SiO$_2$-HPMVP nanoparticles arrange themselves into a cylindrical pattern which is approximately 3 nanoparticles (about 180nm) in diameter. In addition, random clustering of the
SiO$_2$-HPMVP particles is also observed. The formation of the cylindrical structure parallels the formation of nanotubes in the aqueous phase by the amphiphilic HPMVP750 and by the stimulated self-assembly of chloromethyl HPMVP discussed later in this chapter. These observations are summarized in Table 7.3.

Table 7.3 SiO$_2$-HPMVP self-assemblies at different ligand concentration.

<table>
<thead>
<tr>
<th>Ratio of SiO$_2$ : Ligand</th>
<th>Self-assemblies</th>
<th>Particle Size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 : 1</td>
<td>Spheres, random aggregation</td>
<td>65-80</td>
</tr>
<tr>
<td>5 : 1</td>
<td>Spheres and clusters</td>
<td>65</td>
</tr>
<tr>
<td>10 : 1</td>
<td>Cylindrical aggregation and clusters</td>
<td>180nm diameter, 2µm length</td>
</tr>
</tbody>
</table>

d) 1-methyl-3-phenyl-4-(4’-methyl-Si)-benzoyl pyrazolone.

The structure of this SiO$_2$-HMPBP nanoparticle is shown in Figure 7.23.

Figure 7.23 Structure of SiO$_2$-HMPBP.
The SiO$_2$-HMPBP system is similar to SiO$_2$-HPMBP system with phenyl and methyl groups having switched position in HMPBP compared to HPMBP. It is interesting to determine the effect of this switching on the self-assembly of SiO$_2$-HMPBP nanoparticles.

The SiO$_2$-HMPBP nanoparticles were synthesized in the SiO$_2$:HMPBP ratio of the particle to ligand: 1:1; 2:1; 5:1 and 10:1 and the TEM images are displayed in Figures 7.24-7.27.

**Figure 7.24** TEM images of SiO$_2$-HMPBP at 1 : 1 ratio.

**Figure 7.25** TEM images of SiO$_2$-HMPBP at 2 : 1 ratio.
Figure 7.26 TEM images of SiO$_2$-HMPBP at 5 : 1 ratio.

![TEM images of SiO$_2$-HMPBP at 5 : 1 ratio.](image)

Figure 7.27 TEM images of SiO$_2$-HMPBP at 10 : 1 ratio.

![TEM images of SiO$_2$-HMPBP at 10 : 1 ratio.](image)

The SiO$_2$-HMPBP nanoparticles obtained with 1:1 SiO$_2$-HMPBP ratio have irregular shapes that only form small clusters. These irregular shapes are the result of stimulated self-assembly of chloromethyl HMPBP on SiO$_2$ nanoparticles in addition to the attachment of these ligands to the SiO$_2$ surface. Large almost transparent spheres as large as 2 µm are observed at 2:1 SiO$_2$-HMPBP ratio as shown in Figure 7.25. The SiO$_2$-HMPBP nanoparticles are encapsulated and absorbed on these spheres. This behavior is clearly different from the SiO$_2$-HPMBP system where large dense spheres are formed due to stimulated self-assemblies of chloromethylated HPMBP and SiO$_2$-HPMBP are encapsulated in these structures. These structures are absent in the SiO$_2$-HMPBP ratio
of 5:1 and 10:1 where thin films of HMPBP encapsulate linear aggregates of various lengths of SiO$_2$-HMPBP nanoparticles. The self-assembling behavior of SiO$_2$-HMPBP is much less influenced by $\pi$-$\pi$ interaction compared to SiO$_2$-HPMBP. The results for SiO$_2$-HMPBP are summarized in Table 7.4.

Table 7.4 SiO$_2$-HMPBP self-assemblies at different ligand concentrations.

<table>
<thead>
<tr>
<th>Ratio of SiO$_2$ : Ligand</th>
<th>Self-assemblies</th>
<th>Particle Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 : 1</td>
<td>Irregular shapes and some clusters</td>
<td>65 nm</td>
</tr>
<tr>
<td>2 : 1</td>
<td>Large spheres</td>
<td>2 $\mu$m</td>
</tr>
<tr>
<td>5 : 1</td>
<td>Linear and triangular assemblies</td>
<td>0.2-0.5 $\mu$m</td>
</tr>
<tr>
<td>10 : 1</td>
<td>Linear assemblies</td>
<td>1-2 $\mu$m</td>
</tr>
</tbody>
</table>

e) 3-phenyl-4-(4’-methyl-Si)-benzoyl isoxazolone.

The structure of the SiO$_2$-HPBI nanoparticle is shown in Figure 7.28.

**Figure 7.28 Structure of SiO$_2$-HPBI.**

![Structure of SiO$_2$-HPBI](image)

The HPBI ligand bears similarity to HMPBP ligand with N-methyl in HMPBP replaced by O in HPBI. The synthesis of isoxazolone and acylisoxazolone ligands
discussed in Chapter 5. The comparison of HPBI and HMPBP is important and interesting to understand the role of ligand structures on the self-assembly of nanoparticles derivatized with them.

The SiO$_2$-HPBI nanoparticles were synthesized with SiO$_2$:HPBI ratios of 1:1; 2:1 and 5:1. The TEM images are shown in Figures 7.29-7.31.

**Figure 7.29** TEM images of SiO$_2$-HPBI at 1:1 ratio.

**Figure 7.30** TEM images of SiO$_2$-HPBI at 2:1 ratio.
The SiO$_2$:HPBI ratio of 1:1 yields nanotubes of approximately 65nm in diameter and several µm in length with spherical self-assemblies adhering to the nanotubes. The spherical self-assemblies are of various diameters up to 1 µm. A closer examination of the spherical assemblies as shown in Figure 7.29 clearly reveals that they have encapsulated SiO$_2$-HPBI nanoparticles similar to SiO$_2$-HPMBP and SiO$_2$-HPPBP systems. The formation of nanotubes parallels the linear self-assemblies formed by SiO$_2$-HMPBP nanoparticles. When the concentration of the ligand is lowered to obtain SiO$_2$:HPBI ratio of 2:1, long nanotubes are no longer formed but small cylindrical self-assemblies of 0.2 µm diameter and 2 µm length are formed. These appear to be truncated nanotubes formed at the higher ligand concentration. These cylindrical structures also have SiO$_2$-HPBI nanoparticles adsorbed on their surface. The large spherical structures observed at SiO$_2$:HPBI ratio of 1:1 are present to a much smaller extent and their surface is not smooth as at the higher concentration. Small nanotubes are adsorbed on these spheres as evident from Figure 7.30. When the SiO$_2$:HPBI ratio is 5:1, irregular shapes and small clusters are observed. These observations are summarized in Table 7.5.
Table 7.5 Self-assemblies of SiO$_2$-HPBI at different ligand concentrations.

<table>
<thead>
<tr>
<th>Ratio of SiO$_2$ : Ligand</th>
<th>Self-assemblies</th>
<th>Particle Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 : 1</td>
<td>Large clusters &amp; nanotubes</td>
<td>65 nm diameter, 8 µm length</td>
</tr>
<tr>
<td>2 : 1</td>
<td>Small cylinders</td>
<td>0.2 µm diameter, 2 µm length</td>
</tr>
<tr>
<td>5 : 1</td>
<td>Small clusters, irregular shapes</td>
<td>65 nm diameter</td>
</tr>
</tbody>
</table>

2. Reaction of SiO$_2$ nanoparticles with NaHCO$_3$ in THF.

The SiO$_2$ nanoparticles were equilibrated with NaHCO$_3$ in dry THF in the absence of chloromethyl ligands at 40$^\circ$C for the same length of time as the ligand derivatization reactions. The TEM images before and after reaction with NaHCO$_3$ are displayed in Figure 7.32. The images clearly indicate that the SiO$_2$ nanoparticles are unaffected by this reaction and do not form aggregates and clusters. The self-assemblies observed for the SiO$_2$-HL systems are entirely due to the ligands employed.
Selected chloromethylated ligands 1-phenyl-3-methyl-4-(4’-chloromethyl)-benzoyl pyrazolone (HPMCMBP), 1-phenyl-3-phenyl-4-(4’-chloromethyl)-benzoyl pyrazolone (HPPCMBP) and 3-phenyl-4-(4’-chloromethyl)-benzoyl isoxazolone (HPCMBI) were reacted with NaHCO$_3$ in dry THF at 40$^\circ$C in the absence of SiO$_2$ nanoparticles for the same length of time on the nanoparticle derivatization reaction. The reaction mixture was filtered to remove NaHCO$_3$ and small volume of the THF suspension was dispersed in H$_2$O to record the TEM images. The images are displayed in Figure 7.33 for HPMCMBP, Figure 7.34 for HPPCMBP and Figure 7.35 for HPCMBI.
It is evident that all three ligands form large spherical structures on their own without the presence of SiO₂ nanoparticles. In addition, linear rod and tube structures are also founded in the case of HPMCMBP and HPCMBI, while HPPCMBP exclusively forms spherical structures of various sizes. This self-assembly is clearly stimulated by NaHCO₃ in a dry nonaqueous solvent. The spherical structures most likely are multilamellar vesicle type structures which encapsulate SiO₂-HL nanoparticles in the nanoparticle derivatization reactions described in the previous section. Further aggregation of these spherical structures occurs when the THF solution is added to an aqueous phase. In the
case of HPCMBI, a close examination of the large spherical structures reveals the presence of smaller spheres encapsulated in these structures, similar to the presence of multivesicle vesicles in the case of phospholipids. The self-assemblies of the chloromethylated ligands are summarized in Table 7.6.

Table 7.6 Stimulated self-assemblies of chloromethyl acylpyrazolones and acylisoxazolones.

<table>
<thead>
<tr>
<th>blanks</th>
<th>Self-assemblies</th>
<th>Particle Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silica particle</td>
<td>none</td>
<td>65 nm</td>
</tr>
<tr>
<td>HPMCMBP</td>
<td>Dendritic, spherical and linear</td>
<td>0.1-1 µm</td>
</tr>
<tr>
<td>HPCMBP</td>
<td>spherical</td>
<td>0.2-2 µm</td>
</tr>
<tr>
<td>HPCMBI</td>
<td>Spherical and linear</td>
<td>50-400 nm</td>
</tr>
</tbody>
</table>

A possible mechanism for this self-assembly that leads to spherical and linear structures is given in equations 1-3. Here HL represents the ligand moiety without chloromethyl group.

\[
\text{HL–CH}_2\text{Cl} \xrightarrow{\text{NaHCO}_3, \text{Dry THF}} [\text{L–CH}_2\text{Cl}]^+ + [H^+] \quad (1)
\]

\[
[\text{CICH}_2\text{L} \ldots \text{HL–CH}_2\text{Cl}[H^+] \quad (2)
\]

\[
[\text{CICH}_2\text{LH} \ldots \text{CICH}_2\text{L} \ldots \text{HL–CH}_2\text{Cl} \ldots \text{HL–CH}_2\text{Cl}]^+[H^+] \quad (3)
\]

This self-assembly is simulated by the base NaHCO₃ to create the ion pair as
indicated in equation 1. Further association of this ion pair with monomeric ligands can occur as shown in equations 2 and 3. This self-assembly is primarily driven by hydrogen bonding. The formation of three dimensional spherical and linear structures is facilitated by π-π and van der Waal’s interactions. The HPPCMBP ligand with the highest π electron density prefers to form large spherical multilamellar type structures while HPCMBP and HPCMBI with less π electron density also form linear and multivesicle vesicle type structures.

3. Self-assemblies of SiO$_2$-HL nanoparticles in the presence of metal ions.

The self-assemblies of selected SiO$_2$-HL ligand derivatized nanoparticles in the presence of metal ions like Cu$^{2+}$ and Sm$^{3+}$ were also examined by TEM. A SiO$_2$:HL ratio of 5:1 was employed in these studies. The ligand was attached to SiO$_2$ nanoparticles in the presence of NaHCO$_3$ in dry THF. The NaHCO$_3$ was removed by filtration and a small amount of solid Cu(OAc)$_2$ (OAc=acetate) or SmCl$_3$ was added to the filtrate. It was equilibrated overnight and 0.5 mL of this solution was added to 10 mL H$_2$O and mixed well. This solution was left in the hood overnight to remove THF by evaporation. It was ultrasonicated for 2 hours before recording the TEM images by depositing the solution on a carbon grid and evaporating the solvent. In all cases, the metal ions were in large excess over the SiO$_2$-HL ligand derivatized nanoparticles.
The TEM images for SiO$_2$-HPPBP + Cu$^{2+}$ are displayed in Figure 7.36, SiO$_2$-HPPBP + Sm$^{3+}$ are displayed in Figure 7.37, SiO$_2$-HPPBP + Cu$^{2+}$ are displayed in Figure 7.38, SiO$_2$-HPPBP + Cu$^{2+}$ are displayed in Figure 7.39, SiO$_2$-HPPBP + Cu$^{2+}$ are displayed in Figure 7.40, SiO$_2$-HPPBP + Cu$^{2+}$ are displayed in Figure 7.41.

**Figure 7.36 TEM images of SiO$_2$-HPPBP + Cu$^{2+}$.**

**Figure 7.37 TEM images of SiO$_2$-HPPBP + Sm$^{3+}$.**

Different metal ions show the similar aggregation phenomenon.
Figure 7.38 TEM images of SiO$_2$-HPMBP + Cu$^{2+}$. 

Figure 7.39 TEM images of HPMVP-SiO$_2$ + Cu$^{2+}$. 

Figure 7.40 TEM images of HMPBP-SiO$_2$ + Cu$^{2+}$. 
In the case of SiO$_2$-HPPBP, the system with 3 phenyl rings and the highest $\pi$ electron density among all the ligands, large spherical and distorted spherical structures which encapsulate SiO$_2$-HL nanoparticles complexed with the metal ions are observed. The aggregation in the presence of metal ions is rather extensive compared to the SiO$_2$-HL nanoparticles themselves. The SiO$_2$-HPMBP with Cu$^{2+}$ exhibits spherical and rod shape self-assemblies. The SiO$_2$-HPMBP in the absence of Cu$^{2+}$ exhibited only spherical structures and HPMBP by itself exhibited linear structures, namely nanorods. Clearly the presence of Cu$^{2+}$ leads to a large number of nanorods. These are HPMBP nanorod self-assemblies to which Cu$^{2+}$ has complexed leading to further self-assemblies of the nanorods which are larger in length and diameter compared to the free ligand structures.

The SiO$_2$-HPMVP +Cu$^{2+}$ (Figure 7.39) also forms spherical assemblies of varying diameters and many of these spheres are linked and encapsulated into vesicle type structures formed by the free ligand. The amphiphilic ligand HPMVP750 extensively forms nanotubes and nanorods in addition to spherical assemblies in the aqueous phase in the presence and absence of metal ions. The SiO$_2$-HPMVP nanoparticles in contrast do
not at all form nanotubes and nanorods.

The SiO$_2$-HMPBP (Figure 7.40) nanoparticles in the presence of Cu$^{2+}$ lead to spheres and cylindrical structures where nanoparticles are encapsulated. The spherical aggregates are much smaller compared to the other SiO$_2$-HL systems. In addition, the individual SiO$_2$-HMPBP nanoparticles are linked to form very large linear structures. The SiO$_2$-HPBI (Figure 7.41) has very interesting nanotubes where SiO$_2$-HPBI nanoparticles are present along the inner walls. In addition, void volumes visible as white spheres are also present. These have been created by the SiO$_2$-HPBI that were originally present migrating to the outer walls of the nano-tubes. As a result we find nanotubes with spheres and void volumes on the inner walls and SiO$_2$-HPBI nanoparticles adsorbed on the outer walls. The formation of nanotubes in the presence of Cu$^{2+}$ is consistent with their formation during the synthesis of SiO$_2$-HPBI nanoparticles and the stimulated self-assembly of HPCBI ligand in the absence of SiO$_2$ nanoparticles. The observation for the metal ion facilitated self-assembly of SiO$_2$-HL nanoparticles is summarized in the Table 7.7.
<table>
<thead>
<tr>
<th>Nanoparticle systems</th>
<th>Self-assemblies</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>SiO$_2$-HPPBP+Cu$^{2+}$</td>
<td>Large spheres encapsulating</td>
<td>0.5-2 µm</td>
</tr>
<tr>
<td></td>
<td>SiO$_2$-HPPBP nanoparticles</td>
<td></td>
</tr>
<tr>
<td>SiO$_2$-HPPBP+Sm$^{3+}$</td>
<td>Large spheres encapsulating</td>
<td>0.2-1 µm</td>
</tr>
<tr>
<td></td>
<td>SiO$_2$-HPPBP nanoparticles</td>
<td></td>
</tr>
<tr>
<td>SiO$_2$-HPMBP+Cu$^{2+}$</td>
<td>Spheres, clustered spheres,</td>
<td>Spheres: 65-100nm</td>
</tr>
<tr>
<td></td>
<td>nanorods</td>
<td>nanorods: 0.2µm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diameter, 1µm length</td>
</tr>
<tr>
<td>SiO$_2$-HPMVP+Cu$^{2+}$</td>
<td>Individual and linked spheres</td>
<td>0.1-1 µm</td>
</tr>
<tr>
<td>SiO$_2$-HMPBP+Cu$^{2+}$</td>
<td>Spheres and nanorods</td>
<td>Spheres: 65-150nm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nanorods: 0.5-1µm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diameter, 0.5-2µm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>length</td>
</tr>
<tr>
<td>SiO$_2$-HPBI+Cu$^{2+}$</td>
<td>Spherical and nanotubes</td>
<td>Spheres: 65-120nm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nanotubes: 0.2µm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diameter, 5µm length</td>
</tr>
</tbody>
</table>
7.4 Experimental procedures.

The synthesis of chloromethyl acylpyrazolones are described in Chapter IV. These ligands were employed to derivatize the SiO$_2$ nanoparticles of 65 nm average diameter.

a. Synthesis of SiO$_2$-HL nanoparticles.

A 0.13 M stock solution of a given chloromethyl ligand was prepared in 100mL dry THF. Dry silica nanoparticles, 0.1 g (1.67x10$^{-3}$ moles of SiO$_2$ monomer) was added to 25 mL dry THF and ultrasonicated for 2 hours at room temperature to obtain a uniform dispersion. To this 0.14 g (1.67x10$^{-3}$ mole) NaHCO$_3$ was added followed by an appropriate volume of the ligand solution depending on the SiO$_2$: HL ratio desired. For example, in the case of HPMCBP 12.6 mL of the ligand solution was added to obtain a SiO$_2$:HPMBP ratio of 1:1. The reaction mixture of SiO$_2$ nanoparticles, ligand, and NaHCO$_3$ in dry THF was heated to 40$^\circ$C and kept for 2 hours at this temperature. The reaction mixture was filtered through cotton to remove NaHCO$_3$. A cloudy THF filtrate resulted. This was centrifuged at 1000 rpm for 5-10 minutes to remove unfiltered inorganic salts and very large aggregates of nanoparticles. The THF solution after filtration was also employed in several studies without centrifugation. The volume of this solution was brought up to 30, 35, 40 mL etc depending on the final volume obtained after filtration. A 0.5mL of the THF solution was added to 10mL H$_2$O and left in the hood overnight to remove THF. The aqueous suspension was ultrasonicated for 2 hours to obtain a uniform dispersion, which was used for obtaining TEM images. A drop of this
aqueous suspension was allowed to spread on carbon TEM grids and evaporate at room temperature. These were then mounted on the TEM stage to record the images of nanoscale self-assemblies. Reaction with SiO$_2$ nanoparticles alone were performed under these conditions as a control experiment.

**b. Complexation of SiO$_2$-HL nanoparticles with metal ions.**

A 5 mL volume of the THF solution containing a dispersion of SiO$_2$-HL described above was employed for the complexation reaction. A speck of Cu(OAc)$_2$ or SmCl$_3$ was added to this dispersion and equilibrated overnight at room temperature. A 0.5 mL volume of this solution was added to 10mL H$_2$O and left in the hood overnight to remove THF by evaporation. The aqueous suspension of nanoparticles complexed to metal ions was ultrasonicated for 2 hours to obtain a uniform dispersion. A drop of this solution was placed on the carbon TEM grid, allowed to evaporate at room temperature and the TEM images were recorded.

**c. Stimulated self-assembly of chloromethyl acylpyrazolones and acylisoxazolone.**

The self-assemblies of HPMCBP, HPPCBP and HPCBI ligands in THF stimulated by NaHCO$_3$ were investigated. An appropriate volume of the stock solution of the ligand (0.013 M) in THF corresponding to a SiO$_2$:HL ratio of 5:1 was added to 25 mL dry THF.
A weighed amount of NaHCO$_3$ corresponding to equal moles of the ligand was added to the THF solution. The mixture was brought to 40$^\circ$C and kept for 2 hours. The solution was filtered through cotton and centrifuged at 1000 rpm for 5-10 minutes to remove remaining inorganic solids and very large aggregates that may be present. A 0.5 mL volume of this solution was added to 10 mL H$_2$O and left in a hood overnight to remove THF. The solution was ultrasonicated for 2 hours and a small volume was added to the carbon grid. The images were recorded after the aqueous solution had evaporated.

7.5 Discussion

The significant results of spontaneous and stimulated self-assembly of silica nanoparticles derivatized with chloromethylated acylpyrazolones and acylisoxazolone are:

1. The self-assemblies are driven by hydrogen bonding, $\pi$-$\pi$ interaction and van der Waal’s forces as in the case of amphiphilic ligands.

2. The nature of self-assemblies formed and their size depend on the SiO$_2$:HL ratios employed.

3. The self-assemblies identified are spherical structures resembling multilamellar vesicles and multivesicle vesicles, nanotubes, nanorods and clusters of ligand derivatized nanoparticles. In many cases, the various structures encapsulate the
SiO$_2$-HL nanoparticles to yield dense self-assemblies.

4. The SiO$_2$-HL nanoparticles also self-assemble in the presence of Cu$^{2+}$ and Sm$^{3+}$ metal ions. Very large spherical assemblies with nanoparticles encapsulated are observed. Nanotubes and nanorods much larger than those formed in the absence of metal ions are found. The inside of acylisoxazolone nanotubes contain nanoparticles and void spaces when nanoparticles were originally present. These nanoparticles migrate to the outer wall of the nanotubes and are adsorbed on the wall.

5. The chloromethylated ligands can be stimulated to self-assemble to form large spheres and small nanotubes and nanorods.
8.1 Conclusions

The central hypothesis of the research undertaken, namely, organized nanoscale self-assemblies can provide excellent metal ion selectivities has been substantiated by employing amphiphilic acylpyrazolone ligands for the separation of a mixture of light, middle, and heavy lanthanide metal ions. New and novel amphiphilic acylpyrazolone ligands have been synthesized, their self-assemblies in the aqueous phase characterized, and their efficacies for recognizing trivalent lanthanide metal ions have been demonstrated by reverse phase HPLC. These ligands spontaneously form spherical, dendritic, and linear (fibers, rods, and tubes) nanoscale self-assemblies in the aqueous phase, which influence their metal ion recognition efficacies in addition to the structures of the acylpyrazolone and amphiphilic ligand moieties and the nature of self-assemblies on the octadecylsilanized silica stationary phase. The self-assembling characteristics of the acylpyrazolones is also evident when the chloromethylated ligands are attached to silica nanoparticles which spontaneously self-assemble in aqueous and nonaqueous solvents in the absence and presence of metal ions and when the chloromethylated ligands can be stimulated to form spherical, dendritic, and liner nanoscale structures by a base in nonaqueous solvents. The acylpyrazolone family of ligands (amphiphilic and chloromethylated) represents a synthetic system analogous to naturally occurring phospholipids and proteins that spontaneously form nanoscale self-assemblies.
The other important results and conclusions from this research are:

1. Facile synthetic routes to pyrazolones, acylpyrazolones, amphiphilic acylpyrazolones, and chloromethylated acylpyrazolones have been established and all the ligands have been characterized by spectroscopic techniques.

2. Single crystal x-ray structures of acylpyrazolones that could be successfully crystallized have also been performed. These studies indicate that the position of the enol group of the β-diketone moiety of the acylpyrazolone (on the ring vs. outside the ring) is a function of the substituents in the 1 and 3 positions and the nature of the acyl group.

3. A variety of substituents have been introduced into the 1,3, and 4 positions of the acylpyrazolones and various amphiphilic polyethylene glycol moieties have been attached to the acyl groups. The nature of self-assemblies and metal ion recognition efficacies of the ligands have been shown to depend on the substituents and the amphiphilic moieties.

4. Baseline separations of a mixture of lanthanide metal ions (typically $\text{La}^{3+}$, $\text{Ce}^{3+}$, $\text{Pr}^{3+}$, $\text{Nd}^{3+}$, $\text{Sm}^{3+}$, $\text{Eu}^{3+}$, and $\text{Ho}^{3+}$) have been achieved with a number of the amphiphilic acylpyrazolones by employing them in the aqueous mobile phase of HPLC separations with ODS stationary phase. The best separations in terms of efficiencies, selectivities, and resolution were obtained with 1-phenyl-3-methyl-4-(4’-PEG750)-benzoyl-5-pyrazolone (HPMBP750) and phenyl-3-methyl-4-(4’-PEG750)-valeryl-5-pyrazolone (HPMVP750).

5. The separation mechanism (and hence the metal ion recognition mechanism) is complex that is strongly influenced by ligand structure and nature of self-assemblies.
in the aqueous and stationary phases. The distribution constants (capacity factors) for the metal ions exhibit a complex dependence on the concentration of the ligand in the aqueous phase and pH. After sufficient equilibration time at high ligand concentrations (~2 x 10^{-5} M) the recognition of the light lanthanides La^{3+} and Ce^{3+} occurs primarily through their 1:1 metal:ligand complexes, of the middle lanthanides Pr^{3+} and Nd^{3+} through their 1:2 metal:ligand complexes, and the heavy lanthanides Sm^{3+}, Eu^{3+}, and Ho^{3+} through their 1:3 metal:ligand complexes. Under these conditions several monolayers of the ligand have formed on the stationary phase through assemblies of the nature SP…LH…HL…LH…HL…LH (SP = stationary phase), namely alternating head to head (LH…HL) and tail to tail (HL…LH) self-assemblies.

6. TEM images of aqueous solutions of amphiphilic acylpyrazolones reveal nanoscale structures, which are spherical, dendritic (star shaped), and linear with dimensions of tens to thousands of nanometers. The linear structures include fibers, rods, and tubes with the HPMVP750 ligand exhibiting the greatest tendency to form nanotubes. The spherical structures are multilamellar vesicle and multivesicle vesicle type structures. The dendritic structures are the result of the combination of spherical and linear structures. Linear structures are formed by head to head and tail to tail self-assemblies. Formation of these nanostructures is driven by hydrogen bonding, \( \pi-\pi \) interactions, and van der Waal’s forces. As a result their formation is affected by the nature of substituents on the acylpyrazolone moiety and the nature of PEG amphiphile on the acyl group.
7. Nanoscale structures are also formed in the presence of the lanthanide metal ions. Both the spherical and nanotube structures are much larger in the presence of lanthanide metal ions. The amphiphilic ligands also behave in an analogous manner to naturally occurring phospholipids in the presence of Mg\(^{2+}\) ions. Immediately upon the addition of Mg\(^{2+}\) ions they form multilamellar and multivesicle type structures, which unlike free ligands are linked to form much larger structures with no evidence for nanotube formation. Aging these solutions leads to more extensive self-assembly with a very large population of nanotubes in the case of HPMVP750.

8. Acylpyrazolones with terminating chloromethyl groups on the acyl groups in the 4 position can be attached to SiO\(_2\) (65 nm) nanoparticles by reaction with NaHCO\(_3\) in THF. Addition of the THF suspension of the ligand derivatized nanoparticles to H\(_2\)O results in large spherical aggregates of nanoparticles, nanorods, and nanotubes depending on the ligand employed. Such structures in much larger sizes are formed in the presence of metal ions like Cu\(^{2+}\) and Sm\(^{3+}\). These structures are similar to those formed by micron size polystyrene spheres and those predicted for patchy nanoparticles.

9. The chloromethylated ligands can be stimulated to self-assemble into spheres, nanotubes, and nanorods by NaHCO\(_3\) in THF under the same conditions as for the derivatization of silica nanoparticles. The spherical structures are multilamellar vesicle and multivesicle vesicle type structures. The self-assemblies of ligand derivatized silica nanoparticles and chloromethylated acylpyrazolones are also driven by hydrogen bonding, \(\pi-\pi\) interactions, and van der Waal’s forces.
10. A limited number of studies on the synthesis and self-assembly of amphiphilic and chloromethylated acylisoxazolones which are complementary to the acylpyrazolones have been performed. The acylisoxazolones have a distinct preference to form nanotubes compared to the acylpyrazolones. Such nanotubes are formed by spontaneous self-assembly of silica nanoparticles derivatized with the chloromethylated acylisoxazolone in the absence and presence of Cu$^{2+}$ ions and stimulated self-assembly of this ligand by NaHCO$_3$ in THF. The nanotubes formed by SiO$_2$ derivatized with this ligand have nanoparticles on their inner walls. In addition they exhibit voids on the inner walls created by the migration of the nanoparticles to the outer walls. The nanotubes thus exhibit the nanoparticles and voids on the inner walls and nanoparticles adsorbed on the outer walls.

8.2 Future Directions

This research has identified new and novel synthetic acylpyrazolone and acylisoxazolone families of ligands that form nanoscale self-assemblies spontaneously and by stimulation. The amphiphilic acylpyrazolones have excellent recognition capabilities for trivalent lanthanide ions. Many fundamental questions still need to be addressed to fully understand and exploit these novel systems. They are:

1. The nature of the self-assemblies on the reverse phase (hydrophobic) and normal phase (hydrophilic) silica surfaces need to be characterized to fully understand their metal ion recognition efficacies. Such studies could be performed with atomic force microscopy (AFM), scanning tunneling microscopy (STM), surface sensitive spectroscopic techniques (Raman scattering, surface acoustic wave spectroscopy),
fluorescence anisotropy (since the ligands are fluorescent), and small angle neutron scattering.

2. The spontaneous self-assemblies of these ligands on surfaces could be employed for nanopatterning and nanolithography for lab-on-a-chip applications for the separations and identification of lanthanide metal ions from very small volumes. This could be very useful to identify the concentration levels of radioactive lanthanides in nuclear wastes by employing very small sample volumes (nanoliter to microliter).

3. Ligands that form nanotubes are especially interesting for sensor applications and for using them as templates to build other nanotubes. For example metal ions like Cu$^{2+}$ could be bound to these nanotubes and reduced to obtain metal nanotubes and nanorods. There is great interest in applying metal nanotubes and nanorods as nanoelectrodes, catalysts, sensors, hydrogen storage etc.

4. The studies on the acylisoxazolone ligands have just been initiated in the current studies. The characterization of the metal ion recognition efficacies of these ligands and their self-assemblies and a comparison with the acylpyrazolones is fundamentally important and useful. This is especially significant as the limited studies performed here indicate a preference by these ligands to form nanotubes.

5. Self-assemblies of mixed ligands within the acylpyrazolone and acylisoxazolone families and mixtures of these ligand systems would provide valuable fundamental insights into factors driving their self-assemblies and metal ion recognition.
APPENDIX A
LC-MS
1. LC-MS of HPMBP750
2. LC-MS of HPMVP750
APPENDIX B

GC-MS
PEP

\[
\begin{align*}
C_{11}H_{12}N_2O \\
FW: 188
\end{align*}
\]

FW = 188

File : C:\HPCH\DATA\007.D
Operator :
Acquired : 10 May 2005 12:52 using AcqMethod YANG01
Instrument : GC/MS Ins
Sample Name : PEP
Misc Info :
Vial Number : 1
HPECMBP

\[ \text{C}_{19}\text{H}_{17}\text{ClN}_{2}\text{O}_{2} \]

FW = 340/342

File : C:\HFCEM1\DATA\00703.D
Operator :
Acquired : 10 May 2005 12:31 using AcqMethod YANG01
Instrument : GC/MS Ins
Sample Name: HPECMBP
Misc Info :
Vial Number: 1

![Graph showing chromatogram and mass spectrum](image-url)
PPrP

C_{12}H_{14}N_{2}O

FW = 202

FW = 202
HPPrCMBP

FW = 354/356

File    : C:\HPCHEM\1\DATA\1008II.D
Operator : 
Acquired : 15 Feb 2005 14:50 using AcqMethod YAN301
Instrument : GC/MS Ins
Sample Name: 
Vial Info : 
Vial Number: 1
MOPMP

\[ C_{11}H_{12}N_2O_2 \]

FW = 204
HMOPMCMBP

\[ C_{19}H_{17}ClN_2O_3 \]

\[ \text{FW} = 356/358 \]

: C:\HPCHEM\DATA\PYRAV.D

: 2 Dec 2003 11:23 using AcqMethod YANG01

: GC/MS Ins

: Sample Name: 1-mepoph-3-me-4-clch2benzoyl-pyrazolone

: File Info:

: Sample Number: 1
MPMP

C₁₁H₁₂N₂O

FW = 188

File : C:\HPCHEM\1\DATA\MPMP.D
Operator :
Acquired : 10 May 2005 14:30 using AcqMethod YANG01
Instrument : GC/MS Ins
Sample Name: MPMP
Misc Info :
Vial Number: 1

223
HMPMCMBP

FW = 340/342
BnMP

\[
\text{\begin{center}
\includegraphics[width=0.5\textwidth]{image.png}
\end{center}}
\]

\[\text{C}_{11}\text{H}_{12}\text{N}_{2}\text{O}\]

\[\text{FW: 188}\]

\[\text{FW} = 188\]

File : C:\HPCHEM\1\DATA\BNMP.D
Operator : 
Acquired : 10 May 2005 14:08 using AcqMethod YANG01
Instrument : GC/MS Ins
Sample Name : BnMp
Misc Info :
Vial Number : 1
HBnMCMBP

\[ \text{C}_{19}\text{H}_{17}\text{ClN}_{2}\text{O}_{2} \]

FW = 340/342
tBuMP

\[
\text{C}_9\text{H}_{14}\text{N}_2\text{O}
\]

FW = 154

File : C:\\HPCHEM\\DATA\\BUMP.D
Operator : 
Acquired : 10 May 2005 15:14 using AcqMethod YANG01
Instrument : GC/MS Ins
Sample Name : tBuMP
Misc Info : 
Vial Number : 1
MMP

\[ \text{C}_5\text{H}_8\text{N}_2\text{O} \]

FW: 112

FW = 112

---

Software: C:\\HPCHEM\DATA\PYRAIV.D

Instrument: GC/MS Ins

Sample Name: 1-me-3-me-pyrazolone

Misc Info:

Vial Number: 1

---

Graph showing the mass spectrum with peaks at m/z 55, 59, 60, 61, 62, and 63.
HMMCMBP

\[
\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{O}_2
\]

FW = 264/266

: C:\HPCHEM\1\DATA\1004A.D
rator :
quired : 27 Feb 2004 15:16 using AcqMethod YANG01
strument : GC/MS Ins
ple Name:
Molec Info :
Vial Number: 1
PPP

FW = 236

File: C:\HPCHEM\1\DATA\PPP.D
Operator:
Acquired: 10 May 2005 15:35 using AcqMethod YANG01
Instrument: GC/MS Ins
Sample Name: PPP
Misc Info:
Vial Number: 1
CFPMP

\[
\text{FW} = 242
\]

**FILE**: C:\HPCH\DATA\PYRA\D

**Acquired**: 10 Jan 2004 16:16 using AcqMethod YANG01

**Instrument**: GC/MS Ins

**Sample Name**: 1-cfipd-3-me-pyrazolone

**Misc Info**:

**Vial Number**: 1

![Diagram of CFPMP molecule with mass spectrum]
NPMP

FW = 219

C$_{10}$H$_9$N$_3$O$_3$

FW = 219

HPMCVP

\[
\text{FW} = 292/294
\]

Instrument: GC/MS Ins
Sample Name: 1-ph-3-me-(4'-5-chlorovaleryl)-pyrazolone

Misc Info:
Vial Number: 1
HPMCAP

FW = 250/252

File: C:\HPCHEM\l\DATA\YANG.D
Operator:
Acquired: 2 Oct 2003 15:53 using AcqMethod GENERAL
Instrument: GC/MS Ins
Sample Name: chloroacetyl-pyrazolone
V-ml Number: 1

Scan 958 (11,114 min): YANG.D
174

Scan 958 (11,114 min): YANG.D

m/z: 51 88 91 100 129 145 157 187 201 216 233 250

m/z: 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 355
HPMCP

FW = 242

File : C:\HPCHEM\1\DATA\JY340.D
Operator :
Acquired : 25 Jul 2001 15:44 using AcqMethod NOTHING
Instrument : GC/MS Ins
Sample Name:
Info : COMPOUND 256
Vial Number: 1

![Graph Image]
HPMVP

FW = 258

File: C:\HPCHEM\1\DATA\VALPYII1.D
Operator:
Acquired: 28 Mar 2003 11:09 using AcqMethod GENERAL
Instrument: GC/MS Ins
Suite Name:
Misc Info:
Vial Number: 1
HPMPnP

FW = 256

File : C:\HPCHSM\1\DATA\JY256.D
Operator :
Instrument : GC/MS Ins
Sample Name:
M+ or Info : COMPOUND 256
V=1 Number: 1

Abundance

TIC JY256.D

Scan 1566 (13.269 min), JY256.D

Abundance

m/z 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360 370 380 390 400 410 420 430 440 450 460 470 480 490 500 510 520 530 540 550 560 570

237
HPMDP

FW = 328

File : C:\HPCHEM\1\DATA\DECPYII1.D
Operator :
Acquired : 14 Apr 2003 13:18 using AcqMethod GENERAL
Instrument : GC/MS Ins
Sample Name:
Molec Info :
Vial Number: 1

![Graph showing abundance over time and mass-to-charge ratio](image-url)
HPMUP

FW = 340

File : C:\HPCHEM\1\DATA\HPMUP.D
Operator :
Acquired : 10 May 2005 16:38 using AcqMethod YANG01
Instrument : GC/MS Ins
Sample Name: HPMUP
Misc Info :
Vial Number: 1
HPMCMBP

FW = 326/328

file : C:\HPCHEM\1\DATA\BENPY03.D
Operator :
Acquired : 7 Oct 2003 13:19 using AcqMethod GENERAL
Instrument : GC/MS Ins
Sample Name: 4-(4'-chloromethyl)benzoyl-pyrazolone
M : Info :
Vial Number: 1
HPM3CMBP

FW = 326/328
HMPCMBP

FW = 326/328

File : C:\HPCHEM\1\DATA\BENPYX.D
Operator :
Acquired : 10 Jan 2004 15:17 using AcqMethod YANG01
Instrument : GC/MS Ins
Sample Name:
Misc Info :
Vial Number: 1
FW = 161

File : C:\HPChem\DATA\ISO.D
Operator :
Acquired : 5 Sep 2002 15:06 using AcqMethod GENERAL
Instrument : GC/MS Ins
Sample Name:
Misc Info :
Vial Number: 1
HPVI

FW = 245

File: C:\HPCHEM\DATA\VALISO.D
Operator:
Acquired: 20 Sep 2002 14:27 using AcqMethod YANG5
Instrument: GC/MS Ins
Sample Name:
Misc Info:
Vial Number: 1
PEG550

File: C:\HPCHEM\1\DATA\PEG550.D
Operator:
Acquired: 15 Feb 2005 14:22 using AcqMethod YANG01
Instrument: GC/MS Ins
Sample Name:
Misc Info:
Vial Number: 1
APPENDIX C

$^1$HNMR AND $^1$H$^{13}$CNMR
PEP

\[
\text{C}_{11}\text{H}_{12}\text{N}_{2}\text{O} \\
\text{FW:} 188
\]

\[\text{HNMR}\]

\[
\text{\{\text{H}\}^{13}\text{CNMR}}
\]
PPrP

\[
\text{C}_{12}\text{H}_{14}\text{N}_{2}\text{O}
\]

FW: 202

\[\text{\{H\}}^{13}\text{CNMR}\]

\[\text{\{H\}}^{13}\text{CNMR}\]
MOPMP

\[
\text{FW: 204}
\]

\[
C_{11}H_{12}N_{2}O_{2}
\]

\(^1\)HNMR

\[^{13}\text{CNMR}\]

\[
\{^1\text{H}\}^{13}\text{CNMR}
\]
MPMP

\[
\text{C}_{11}\text{H}_{12}\text{N}_{2}\text{O}
\]

FW: 188

\[^{1}\text{HNMR}\]

\[\{{^1}\text{H}\}^{13}\text{CNMR}\]

250
BMP

$\text{C}_{11}\text{H}_{12}\text{N}_{2}\text{O}$

FW: 188

$^1\text{HNMR}$

$^{13}\text{CNMR}$
tBuMP

\[
\text{C}_6\text{H}_{14}\text{N}_2\text{O}
\]
FW: 154

\[^1\text{HNMR}\]
MMP

\[ \text{C}_5\text{H}_8\text{N}_2\text{O} \]

FW: 112

\(^1\text{HNMR}\)

\(^{13}\text{CNMR}\)
PPP

\[ \text{C}_{15}\text{H}_{12}\text{N}_{2}\text{O} \]

FW: 236

\[^1\text{HNMR}\]

\[^{1}\text{H}^{13}\text{CNMR}\]

254
CFPMP

C$_{11}$H$_9$F$_3$N$_2$O
FW: 242

$^1$HNMR

$^1$CNMR
NPMP

$\text{C}_{10}\text{H}_9\text{N}_3\text{O}_3$

FW: 219

$^1\text{HNMR}$

$^{13}\text{CNMR}$
HPMCP

$^{1}$HNMR

$\{^{1}H\}^{13}$CNMR
HPMVP

$^1$HNMR

$^1$H$^{13}$CNMR
HPMPnP

$^{1}$$\text{HNMR}$

$^{1}$$\text{H}$$^{13}$$\text{CNR}$
HPMDP

\[
\text{HNMR}
\]

\[
\text{\{H\}\text{^{13}CNMR}}
\]
HPMUP

\[
\text{HNMR}
\]

\[
\text{CNRMR}
\]

\[
\text{CNRMR}
\]
HPMBP

\[ \text{HNMR} \]

\[ \text{Diagram of HNMR spectrum} \]
HPMCMBP

\[ \text{HNMR} \]

![HNMR spectrum](chart)

265
MI

\[
\text{C}_4\text{H}_5\text{NO}_2
\]
FW: 99

\[\text{}^{1}\text{HNMR}\]

\[\text{}^{1}\text{H}\] \text{CNMR}

\[\text{}^{1}\text{H}\] \text{CNMR}
PI

$\text{C}_9\text{H}_7\text{NO}_2$

FW: 161

$^1$HNMR

$^1$H$^{13}$CNMR
HPVI

\[ \text{HNMR} \]

\[ \{^1\text{H}\}^{13}\text{CNMR} \]
HPPnI

$\begin{align*}
\text{HNMR}
\end{align*}$
HPUI

\[ \text{HNMR} \]
APPENDIX D
UV-VIS & EMISSION
UV-VIS and emission of HPPCMBP

**UV-VIS:**

UV-Vis Spectra of ligand

Emission: cut off at 310 nm, slid width is 10 nm

Excitation & Emission Spectra of the Ligand
UV-VIS and emission of SiO$_2$-HPPBP

UV-VIS:

![UV-Vis spectra of the ligand attached silica nano-particle](image1)

Emission: excitation wavelength is 268 nm, cut off at 290 nm, slid width is 10 nm

![Excitation & Emission Spectra of the Ligand Bonded Silica Nano-particle](image2)
APPENDIX E
IR
IR of Silica nanoparticles (SiO$_2$).
IR of SiO$_2$-HPPBP

IR spectra of Ligand Attached Silica Nano-particle
BIBLIOGRAPHY

Science 306: 98.
3571.
[37] Liu, L. J., Dian-Zeng; Ji, Ya-Li; Yu, Kai-Bei (2003). Journal of Photochemistry and
Rev. 105: 1103.
Chemistry 69(14): 2835.
Chem. 97: 4729.
42.
Tokkyo Koho.
142(1-2): 129.
21(6): 797.
[52] Pettinari, C. M., Fabio; Cingolani, Augusto; Gindulyte, Asta; Massa, Lou; Rossi,
Miriam; Caruso, Francesco (2001). European Journal of Inorganic Chemistry 8:
2171.
[53] Pettinari, C. M., Fabio; Cingolani, Augusto; Gindulyte, Asta; Massa, Lou; Rossi, Miriam; Caruso, Francesco (2001). European Journal of Inorganic Chemistry 8: 2171.


[82] Zhou, D. L., Qin; Huang, Chunhui; Yao, Guangqing; Umetani, Shigeo; Matsui, Masakazu; Ying, Liming; Yu, Anchi; Zhao, Xinshe (1997). Polyhedron 16(8): 1381.
REFERENCES

[13] Zhou, Dejian; Li, Qin; Huang, Chunhui; Yao, Guangqing; Umetani, Shigeo; Matsui, Masakazu; Ying, Liming; Yu, Anchi; Zhao, Xinsheng. *Polyhedron*; 1997, 16(8), 1381.
[19] Umetani,Shigeo; Le, Quyen T.H. and Matsui, Masakazu; *Analytical Sciences*, 1997, 13, 103.
[21] Pettinari, Claudio; Marchetti, Fabio; Cingolani, Augusto; Gindulyte, Asta; Massa, Lou; Rossi, Miriam; Caruso, Francesco. *European Journal of Inorganic Chemistry*, 2001, 8, 2171.
[22] Schmitt, Monika; Van Almsick, Andreas; Preuss, Rainer; Willms, Lothar; Auler, Thomas; Bieringer, Hermann; Thuerwaechter, Felix. *PCT Int. Appl.*, 2001, 32.
[24] Sasaki, Takayuki; Umetani, Shigeo; Le, Quyen T. H.; Matsui, Masakazu; Tsurubou, Shigekazu. *Analyst (Cambridge, United Kingdom)* 1996, 121(8), 105.
[28] Cai, Qingyan; Peng, Yan; Nie, Lihua; Yao, Shouzho. *Talanta* 1995, 42(10), 1373.
[31] Oliva, Alfonso; Molinari, Aurora; Zuniga, Francisco; Ponce, Patricio. *Microchimica Acta* 2003, 142(1-2), 129.
[33] Tsurubou, Shigekazu; Mizutani, Masatoshi; Kadota, Yoshinobu; Yamamoto, Tadashi; Umetani, Shigeo; Sasaki, Takayuki; Le, Quyen T. H.; Matsui, Masakazu. *Analytical Chemistry* 1995, 67(8), 1465.
[34] F.E.Bailey, JR.; J.V. Koleske; *POLY(ETHYLENE OXIDE)*: 1976.
[35] Chiba, Peter; Holzer, Wolfgang; Landau, Marion; Bechmann, Gerhard; Lorenz, Karin; Plagens, Brigitte; Hitzler, Manuela; Richter, Elisabeth; Ecker, Gerhard. *Journal of Medicinal Chemistry* 1998, 41(21), 4001.
[40] Li, Zhibo; Kesselman, Ellina; Talmon, Yeshayahu; Hillmyer, Marc A.; Lodge, Timothy P., *Science*, 2004, (306), 98.
[44] Pettinari, Claudio; Marchetti, Fabio; Cingolani, Augusto; Gindulyte, Asta; Massa,
Lou; Rossi, Miriam; Caruso, Francesco. European Journal of Inorganic Chemistry 2001, (8), 2171.
[45] Schmitt, Monika; Van Almsick, Andreas; Preuss, Rainer; Willms, Lothar; Auler, Thomas; Bieringer, Hermann; Thuerwaechter, Felix. PCT Int. Appl. 2001, 32.
[47] Sasaki, Takayuki; Umetani, Shigeo; Le, Quyen T. H.; Matsui, Masakazu; Tsurubou, Shigekazu. Analyst (Cambridge, United Kingdom) 1996, 121(8), 1051.