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The Effect of Stereoelectronic Control and Long Range Interaction on the Stability of Bicyclic Enolate Anions

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THE EFFECT OF STEREOELECTRONIC CONTROL AND LONG RANGE INTERACTION ON THE STABILITY OF BICYCLIC ENOLATE ANIONS

by

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I. INTRODUCTION

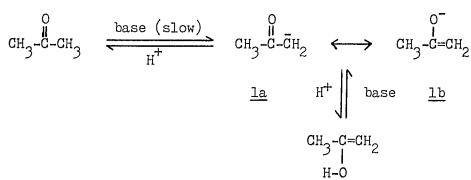
Enolate anions are among the most widely used intermediates in synthetic organic chemistry. Alkylations, Grignard reactions, aldol condensations and Claisen condensations are only a few of the many reactions that may proceed by means of such intermediates.

While numerous studies have been reported in connection with the factors affecting the formation, stabilization and reactions of enolate anions derived from open-chain or cyclic ketones, little is known about enolates of bicyclic ketones. The present investigation was initiated in order to identify and study the major factors that may affect the formation and stability of bicyclic enolates.

II. HISTORICAL

A. Structural Effects on the Base-Catalyzed Hydrogen-Deuterium Exchange of Certain Bicyclo[2.2.1] Ketones.

It is well known[1] that carbonyl groups activate hydrogen atoms bonded to carbon atoms next to the carbonyl function. The acidity of the C-H bond in these substances is due to a combination of the electron withdrawing ability of the carbonyl oxygen as well as the ability of this substituent to delocalize the negative charge remaining when the proton has been removed.



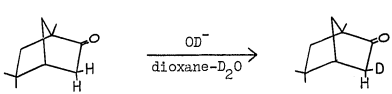
The anions 1a,b, usually called enolate anions, which should be distinguished from an enol such as 2, may be derived from a ketone, as shown above, or from other carbonyl compounds. It is an important intermediate in many types of organic reactions.

In view of the importance of this intermediate in synthetic organic chemistry, considerable effort has been made by chemists

to determine the factors affecting the formation of enolate anions and their subsequent reactions with electrophiles. These studies generally have involved open chain or cyclic ketones with relatively little work having been done with bicyclic ketones. Indeed, the only bicyclic ketones whose enolization-ketonization reactions have been studied are those involving a [2.2.1] system.

A review of the enolization and subsequent ketonization reactions of the various bicyclo[2.2.1] ketones which have a bearing on the present study will be presented in this section.

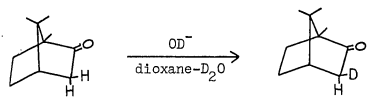
There has recently been considerable interest and controversy in the investigation of base catalyzed hydrogen-deuterium exchange in bicyclic ketones regarding both rates and stereochemistry. The stereochemistry of these exchanges has proved to be very interesting. Thomas and Willhalm[2] established by nuclear magnetic resonance (nmr) that isofenchone 3 can be specifically



3

monodeuterated in the exo position. This was not unexpected, since a large body of evidence indicates that the exo face of a bicyclo[2.2.1]heptane is more accessible to attack by external reagents than the endo face. However, Meinwald[3] found that when the isomeric ketone 4 with a methyl group in the syn position

at C_7 blocking the exo face was used, exo exchange still occurred.



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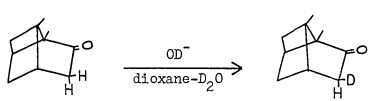
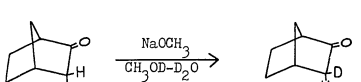
He also reported similar stereospecific hydrogen-deuterium exchange in even greater degree with carvonecamphor 5.



5

Previous to this work, Jerkunica[4] et.al. had reported that when they heated bicyclo[2.2.1]heptan-2-one (6) in CH_3OD/D_2O with $NaOCH_3$ as base for 12 hours at 100°C only one of the two alpha hydrogens exchanged with deuterium. However, when he used bicyclo[2.2.1]hept-5-en-2-one(7) he exchanged both hydrogens while using identical conditions. In direct contrast to this, Tidwell[5]



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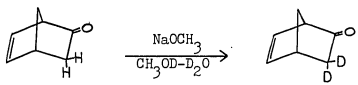

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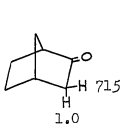
has recently reported that the rates of NaOD catalyzed hydrogen-deuterium exchange of these ketones were the exact opposite

Relative Rates of NaOD Catalyzed Exchange[5]



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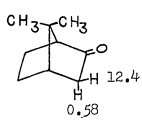

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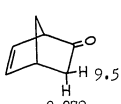

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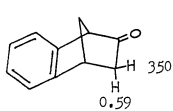


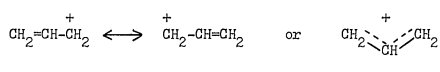
10

as those indicated by Jerkunica. He found that the bicyclo-[2.2.1]heptan-2-one (6) exchanged about 75 times faster than its unsaturated counterpart, bicyclo[2.2.1]hept-5-en-2-one (7). In all cases, Tidwell observed a strong preference for exo

exchange ranging from about 25:1 for the exo hindered trimethyl compound 4 and up to 750:1 for the bicyclo[2.2.1]heptan-5-one (6). This strong exo preference is in agreement with cation ionization rates where the exo:endo ionization for norbornyl brosylate is 1600,[6] and there is a 5000:1 preference for exo hydration of the norbornyl cation.[6] In addition, free radical chlorination of norbornane has been shown to favor formation of exo over endo norbornyl chloride by about 20:1.[7] Nevertheless, the very large exo/endo rate difference for hydrogen-deuterium exchange, as observed by Tidwell, is surprising and the stereospecificity observed as yet is unexplained.

B. Homoconjugative and Homoaromatic Stabilization Effects in Certain Enolate and Related Anions

The stabilization of systems containing a p-orbital which is associated with a positive charge (zero electrons),[8] a negative charge (two electrons),[9] or a radical (one electron)[10] by an adjacent unsaturated site has been known for a long time. Carbonium ions, carbanions, and radicals can interact and be stabilized by vinyl, aryl or ethynyl groups attached to them. This is represented by the following examples 11, 12, and 13 with a vinyl group:



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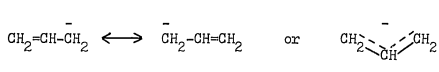

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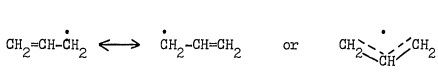

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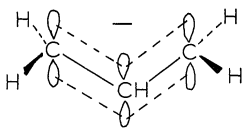
This stabilization originates by the utilization of the p-orbital in question with the neighboring p-orbitals of the unsaturated center as shown below for the allylic anion 14.



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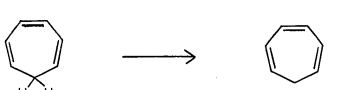
Charge stabilization can be achieved by aromaticity as well as the allylic type just mentioned. For example, cyclopentadiene (15) readily loses one proton to form the aromatic cyclopentadienyl anion 16 . This stabilization arises from the attainment

pK_a=15

15

6 π electrons
Aromatic

16



pK_a=36

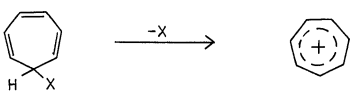
17

8 π electrons
Anti- Aromatic

18

of a completely conjugated planar cyclic 6 π electron system complying with Huckel's[11,12] 4n+2 rule. The large difference

in the pKa's of cyclopentadiene[13] (15) and cycloheptatriene[14] (17) is believed to be due to the difference in the number of the electrons in the cyclic anions. Other well known unusually stable charged cyclic species are the tropylium cation[15] 19 (6 π electrons) the cyclopropenyl cation[16] 20 (2 π electrons) and the cyclooctatetraene dianion[17] 21 (10 π electrons). These species are



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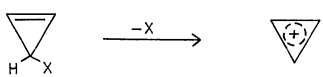

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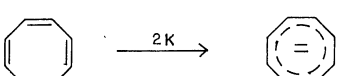

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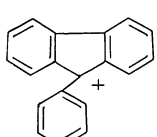
believed to achieve their unusual stability by the attainment of a favorable number of electrons leading to resonance stabilization.

While aromaticity might be considered a special stability

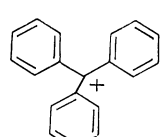
associated with planar, cyclic conjugated $4n+2$ π electron systems, as compared to their linear counterparts, a newer concept, that of antiaromaticity,[18] can be defined as decreased stabilization when compared to the linear systems. Both theoretical[19] and experimental[19] evidence have increasingly shown that $4n$ π electron planar, cyclic conjugated systems are destabilized or antiaromatic. For instance, the well known difficulty in forming the 4 π electron cyclobutadiene[20] is ascribed to this instability.

Just as charged species can be stabilized by aromaticity, so they also can be destabilized by antiaromaticity. Breslow[21] has shown that the cyclopentadienyl cation 22 is less stable than the closely related triphenyl cation 23 probably because of the destabilization of the 4 π electron cyclic system.



$pK_{R^+} = -10.8$

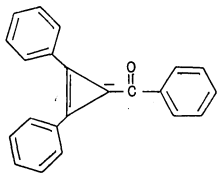
22



$pK_{R^+} = -6.6$

23

Breslow[22] has also demonstrated the destabilization of the cyclopropenyl anion 24. The unusually high pKa of cyclohepta-



24

triene (17) is undoubtedly due to the formation of the 8 π electron antiaromatic cycloheptatrienyl anion[14] 18.

In all of the cases mentioned up to this point, the carbon atom bearing the charge was directly adjacent to the unsaturated site or sites and connected to it by a σ bond as shown by 25 and 26.

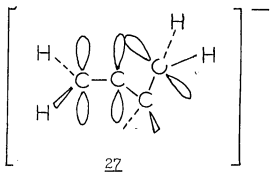
25

26

However, as a result of extensive work done in the last forty years by a number of workers,[23a-e] but especially by Winstein and his group,[24] a new concept has developed. It was determined that when geometry conditions were favorable, overlap of orbitals on carbon atoms between which a directly connecting σ bond was not present, could also lead to stabilization. This type of conjugation, where an intervening saturated carbon atom cannot

insulate the charge from the unsaturated site is called homoconjugation. It was so called by Winstein[25] to show that it is a homolog of regular conjugation.

While the well known allylic conjugation achieves its maximum stabilization where the p-orbital associated with the charge is parallel to the p-orbitals of the original olefinic group, a homoallylic system achieves maximum stabilization when the orbital associated with the charge is disposed perpendicularly to the orbitals of the olefinic group[25] as shown in 27.



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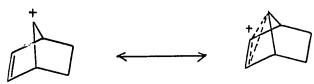
This type of overlap is not true end-to-end σ-type bonding nor is it side-to-side overlap as in π bonding but it has aspects of both types.

This type of stabilization (homoconjugation) with suitably chosen substrates, can also lead to cyclic delocalization[26a-c] as in the 7-norbornenyl cation. This cyclic homo stabilization has been termed homoaromaticity[24] and the example below would be a bishomoaromatic cyclopropenyl cation. The bis designation is used when there is non-classical stabilization on two sides of the cyclopropenyl system. The tremendous rate accel-



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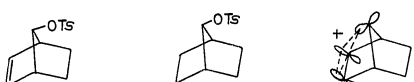
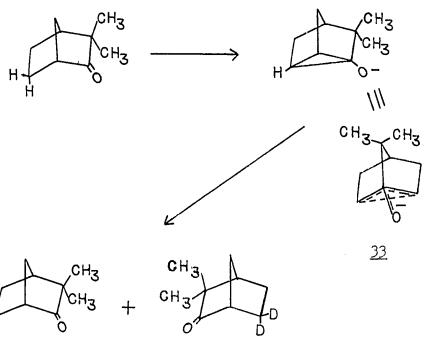
eration (10^{11}) in the solvolysis of anti-norbornen-7-yl toluene-p-sulfonate (29) compared to its saturated analog 30 was attributed by Winstein[27a-c] to the interaction of the developing positive charge with the $C_{5,6}$ olefinic group as depicted in 31.



29 30 31

The possibility of homoconjugation or homoaromaticity in systems with a negative charge, i.e., carbanions, has only recently been investigated. The first authentic example of homoconjugation involving carbanions was reported in 1962 by Nickon and Lambert[28] who observed that when optically active camphenilone (32) was treated with potassium t-butoxide in t-butanol-O-d at 185°, the system underwent hydrogen-deuterium exchange at C_6. They found that the rate of exchange at C_6 and racemization of the molecule were about the same and explained these

results on the basis of the symmetrical homoenolate anion 33.



33

The bishomoaromatic carbanion 34 was proposed as an intermediate by J. M. Brown[29] in 1965 to explain the large ($10^{4.5}$) acceleration in the base catalyzed hydrogen-deuterium exchange at C_4 of bicyclo[3.2.1]octadiene (35) as compared to bicyclo-[3.2.1]oct-2-ene (36), its saturated analog. This bishomocyclopentadiene anion is analogous to the aromatic cyclopentadiene anion.

34 35 36

Subsequently, Winstein[30] was able to generate anion 34 in sufficient quantities to study its nmr spectrum. He observed that the vinylic protons, H_6 and H_7 of anion 34, had undergone a substantial upfield shift (2.3 ppm) relative to the starting diene. This clearly established that delocalization of charge to the olefinic bond had indeed occurred.

Recently, the anions of a number of related systems were generated and studied kinetically and/or spectroscopically.[31a-c] The monoanion 37 of bicyclo[3.2.2]nonatriene (38) was formed and its nmr spectrum showed that delocalization had occurred across

37

38

both vinylic bridges. The question of whether this carbanion existed as a symmetrical intermediate with simultaneous delocalization to both bridges or whether there was a rapid (on nmr time scale) bridge flipping, as in 39 and 40, has not been answered.

39 40

In 1970 Breslow[32] suggested that the bishomoantiaromatic analog of the cyclopropenyl anion (24) might be the cause of a slight destabilization in the 7-norbornenyl anion 41. Breslow thought that even though the rate of base catalyzed H-D exchange in 7-anti-cyanonorbornene (42) was faster than that of 7-anti-cyanonorbornane (43), there might still be some net destabilization. He observed that there was a greater charge stabilization and consequent rate increase when comparing 3-cyanocyclopentene to cyanocyclopentane than with the aforementioned norbornyl systems.

41

42

43

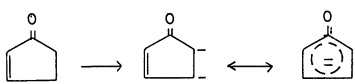
This model cyclopentene system would be an indication of the stabilizing effect of the double bond on the carbanion. Since there was a lesser rate increase in the bicyclo[2.2.1] system, he concluded that there might be some antiaromatic destabilization.

Very recently, Trimitsis and Crowe[33] have found that the carbanion generated from 2,4-diphenylbicyclo[3.2.1]oct-6-en-3-one did not homoconjugate with the olefinic double bond. This was the first attempt to see if a carbanion stabilized by a carbonyl group would homoconjugate. However, this anion is stabilized not only by the carbonyl group but also by the phenyl ring making the charge very stable at this position. Interestingly, when the

dianion 44 of this species was formed, it was found to be a 6 π electron bishomoaromatic system as shown by its nmr. The H_6

44

and H_7 vinylic protons were observed to move upfield 1.1 ppm relative to the starting ketone. This clearly showed charge delocalization to the vinylic group to form the bishomoaromatic analog of the aromatic cyclopentenone dianion 45.



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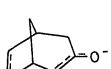
III. Statement of Problem

In view of the controversy associated with some of the results presented in the previous two sections, it was felt that a more thorough and definitive study concerning the factors affecting the formation and stability of bicyclic enolate anions was desirable. For this purpose a series of bicyclic ketones and some model cyclic ketones were prepared and their enolization was carefully studied. In particular the present investigation sought to examine the effect of the following three factors on the formation and stability of bicyclic enolates:

(a) The effect of ring strain on the enolization of bicyclic ketones.

(b) The effect of stereoelectronic control on the enolization-ketonization of bicyclic ketones.

(c) Possible stabilization of bicyclic enolate anions by means of long-range interactions as in 46.



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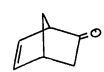
IV. RESULTS

The ketones 6, 7, and 47-53, used in the present study, were either prepared by literature methods with some modifications or were purchased and used directly. The compounds can be divided into four groups: bicyclo[2.2.1] ketones 6 and 7, bicyclo[3.2.1] ketones 47, 48, and 49, bicyclo[2.2.2] ketones 50 and 51, and cyclic ketones 52 and 53.

6



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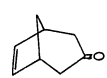
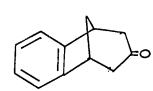
47



48



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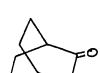
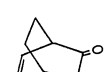


50

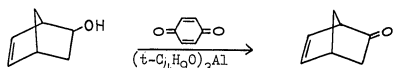


51

52

53

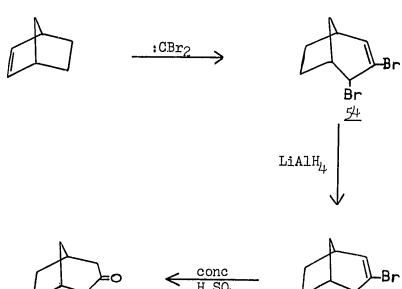
Preparation of the bicyclo[2.2.1]hept-5-en-2-one (7) was accomplished by an Oppenauer oxidation of the bicyclo[2.2.1]hept-5-en-2-ol following the procedure of Cristol and Freeman.[34]



7

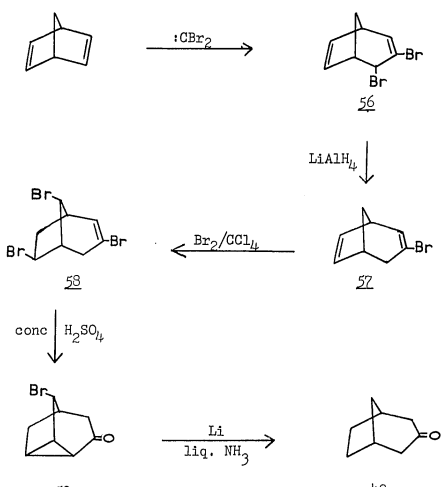
The preparation of the [3.2.1] ring system was somewhat more elaborate. The saturated analog, bicyclo[3.2.1]octan-3-one (47), was synthesized by the method of Kraus[35] and others[36] as shown in Scheme I. The bicyclo[3.2.1]oct-6-en-3-one (48), was synthesized

Scheme I



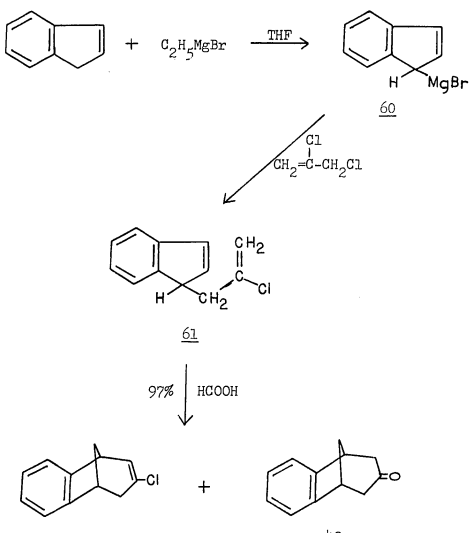
by an almost analogous method, as illustrated in Scheme II, a procedure first reported by Lebel and Liesemer.[37] This compound was somewhat difficult to purify and was finally obtained pure by sublimation followed by silica gel column chromatography and subsequent recrystallization from pentane. The preparation of the

Scheme II



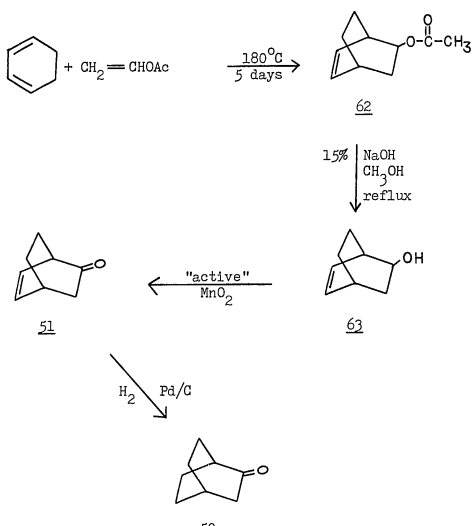
6,7-benzobicyclo[3.2.1]oct-6-en-3-one (49) was accomplished by the method of Lansbury and Nienhouse,[38] as shown in Scheme III. The final mixture of products can be readily separated by column chromatography on alumina.

Scheme III



The bicyclo[2.2.2] systems, 50 and 51, were prepared according to the methods of Hine[39] and Mislow,[40] as shown in Scheme IV. The

Scheme IV



initial Diels-Alder reaction was reported by Hine while Mislow extended this by oxidation to the ketones. All of the aforementioned compounds gave infrared (ir), nmr and melting points as

reported in the literature.

The rates of hydrogen-deuterium exchange were determined by a well-known nmr integration method.[41,42] The ratio of the area of the reacting alpha hydrogen site to that of a separated unreacting, unactivated position provides a measure of the extent of exchange occurring between hydrogen and deuterium in the molecule. By taking successive integrations at timed intervals the rate of disappearance of the alpha hydrogens can be followed. The exchange reaction can also be followed by integrating the increasing HOD signal. This is also valid[42] where unequivalent protons are exchanging in the same molecule since their rate differences were quite large and it was possible to separate the two rates. The increase in the HOD signal was used when overlap of signals of other protons in a particular molecule made it difficult to determine accurately the decreasing ratio by observing the decrease in the signal of the alpha hydrogens. In some instances both methods were used and there was good agreement between the two.

The peaks used as an internal standard for the bicyclic systems were either the downfield absorptions in those compounds containing unsaturated functions or the bridgehead protons which also were sufficiently separated from the remainder of absorption in the molecule. In the cyclic systems the t-butyl group was a convenient reference in the case of t-butyl cyclohexanone; in cyclohexanone the remaining six proton absorptions could be separated from the exchangeable alpha hydrogens.

Data were treated by the method of least squares using a Wang calculator. Observed pseudo-first order rate constants were obtained from a plot of log (a-x) vs. time. Division of the first order rate constants by the base concentration gave the second order rate constants. The temperature of the nmr probe was recorded, $37^{\circ} \pm 1^{\circ}$, before each run and was essentially invariant. Reactants were thermostated for about 30 minutes prior to the beginning of each run. They were then mixed and immediately put into the nmr probe. The time was recorded upon mixing and the run was begun.

Reactions were followed for at least two half-lives and were essentially linear throughout this period. The data obtained are recorded in Table 1. A representative graph, with a computer plotted least squares line, is shown for a number of compounds.

Table 1

Second Order Rate Constants of NaOD
Catalyzed Deuterium Exchange in DMSO-d_6/D_2O
at 37.0° ± 1.0°, k_2[a,b] in l, mol^{-1}, sec^{-1}

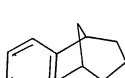
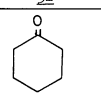
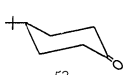
	Exo	Endo	Exo/Endo
 6	9.5×10^{-2}	0.21×10^{-2}	45
 7	4.3×10^{-2}		
 47	$105. \times 10^{-2}$[c]	(very slow)[d]	large
 48	$120. \times 10^{-2}$	0.55×10^{-2}	218
 49	$135. \times 10^{-2}$	1.3×10^{-2}	103

Table 1 (cont.)

	Exo	Endo	Exo/Endo
 50	120. x 10^{-2}	same	one
 51	31. x 10^{-2}	same	one
 52	36. x 10^{-2}		
 53	110. x 10^{-2}[e]	20. x 10^{-2}[f]	5.5

a. average of 2-4 trials (± 10%)
b. obtained by dividing the observed first order rate constants by base concentration
c. corrected for statistical factors
d. solubility problems at base concentrations necessary for the exchange of these hydrogens precluded the accurate determination of this rate. It is at least as slow as the endo rate of 48.
e. axial
f. equatorial

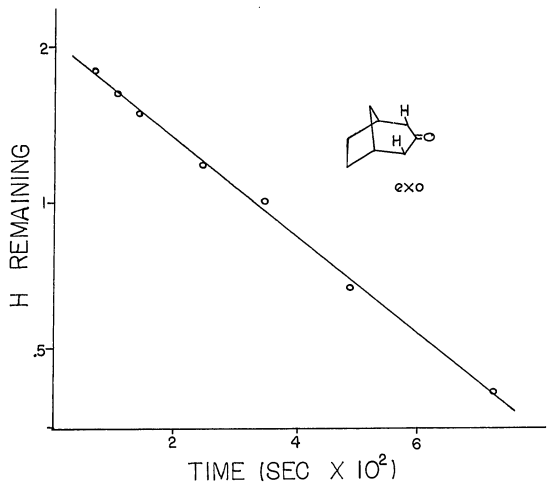


Figure 1. Typical first order plot of the base catalyzed exo hydrogen-deuterium exchange in bicyclo[3.2.1]octan-3-one (47), $k_{obs} = 2.37 \pm .08 \times 10^{-3}$, [NaOD] = 1.2×10^{-3} M.

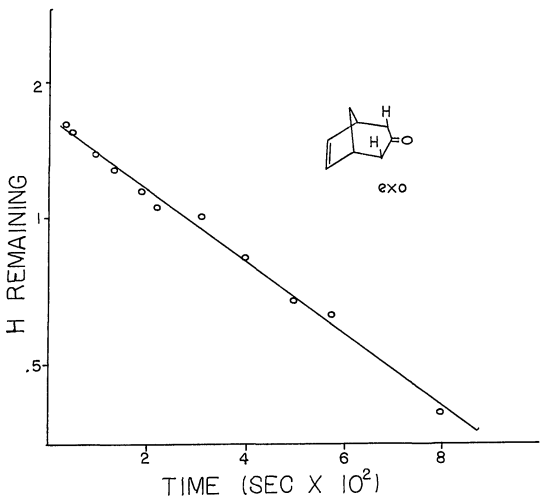


Figure 2. Typical first order plot of the base catalyzed exo hydrogen-deuterium exchange in bicyclo[3.2.1]oct-6-en-3-one (48), $k_{obs} = 2.48 \pm .08 \times 10^{-3}$, [NaOD] = 1.1×10^{-3} M.

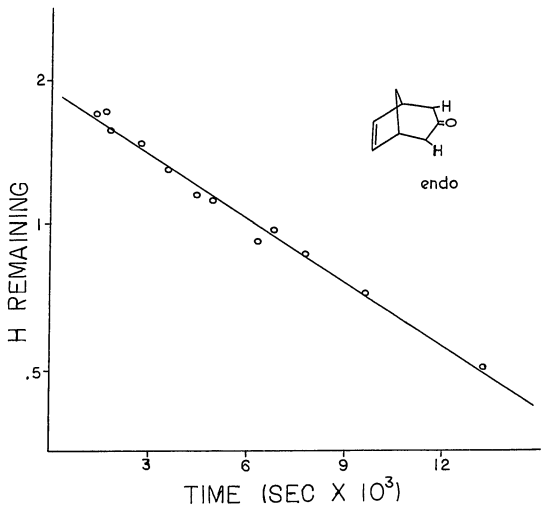


Figure 3. Typical first order plot of the base catalyzed endo hydrogen-deuterium exchange in bicyclo[3.2.1]oct-6-en-3-one (48), $k_{obs} = 1.13 \pm .07 \times 10^{-4}$, [NaOD] = 2.1×10^{-2} M.

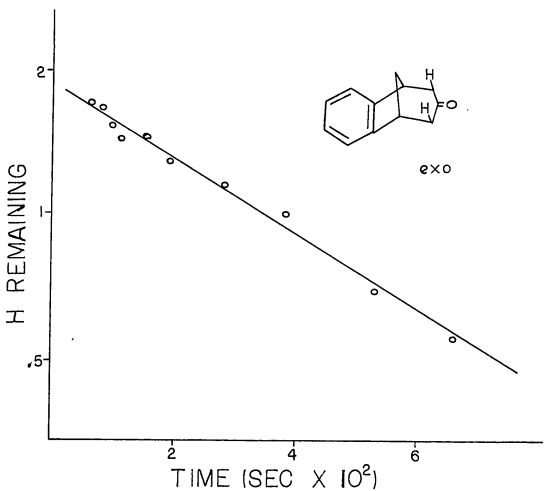


Figure 4. Typical first order plot of the base catalyzed exo hydrogen-deuterium exchange in 6,7-benzobicyclo[3.2.1]oct-6-en-3-one (49), $k_{obs} = 1.90 \pm .08 \times 10^{-3}$, [NaOD] = 6.9×10^{-4} M.

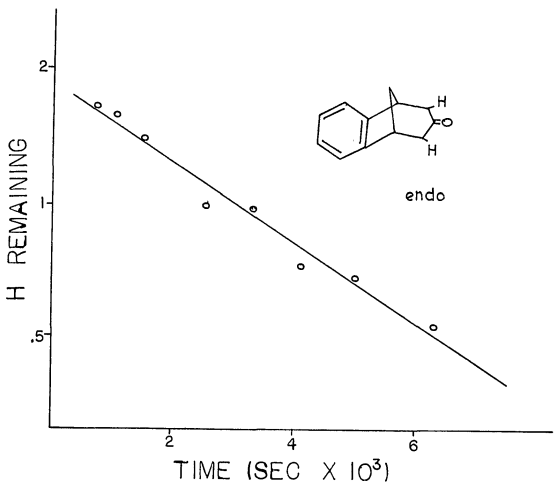


Figure 5. Typical first order plot of the base catalyzed endo hydrogen-deuterium exchange in 6,7-benzobicyclo[3.2.1]oct-6-en-3-one (49), $k_{obs} = 1.93 \pm .10 \times 10^{-4}$, $[NaOD] = 7.4 \times 10^{-3}$ M.

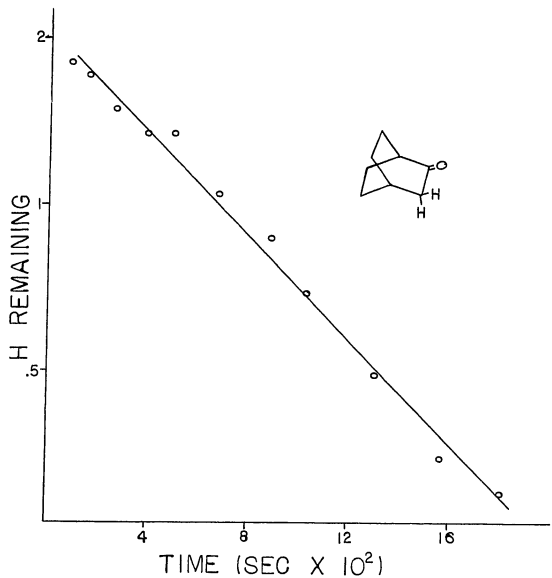


Figure 6. Typical first order plot of the base catalyzed hydrogen-deuterium exchange in bicyclo[2.2.2]octan-2-one (50), $k_{obs} = 1.06 \pm .05 \times 10^{-3}$, [NaOD] = 9.1×10^{-4} M.

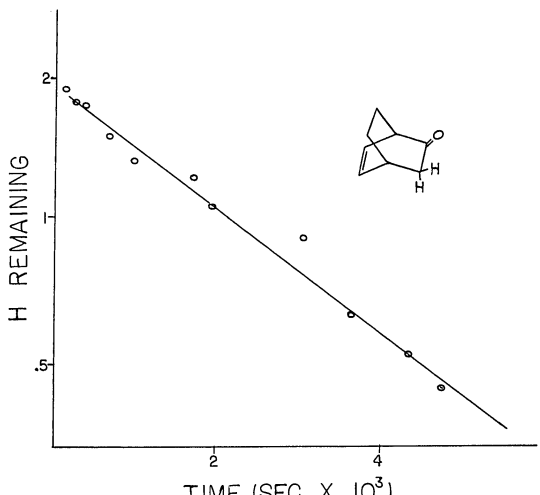


Figure 7. Typical first order plot of the base catalyzed hydrogen-deuterium exchange in bicyclo[2.2.2]oct-5-en-2-one (51), $k_{obs} = 3.56 \pm .09 \times 10^{-4}$, [NaOD] = 9.7×10^{-4} M.

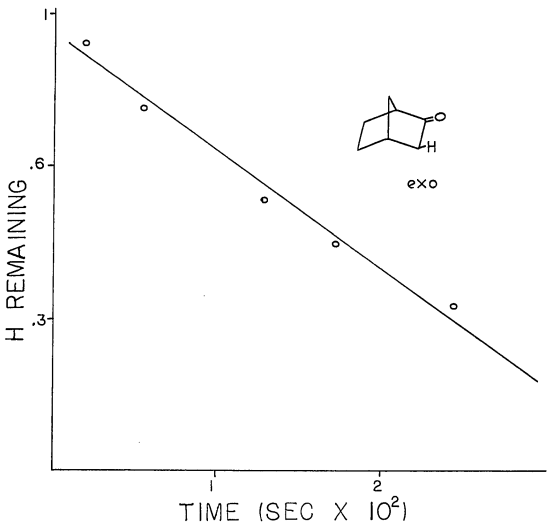


Figure 8. Typical first order plot of the base catalyzed exo hydrogen-deuterium exchange in bicyclo[2.2.1]heptan-2-one (6), $k_{obs} = 4.20 \pm .02 \times 10^{-2}$, $[NaOD] = 4.1 \times 10^{-1}$ M.

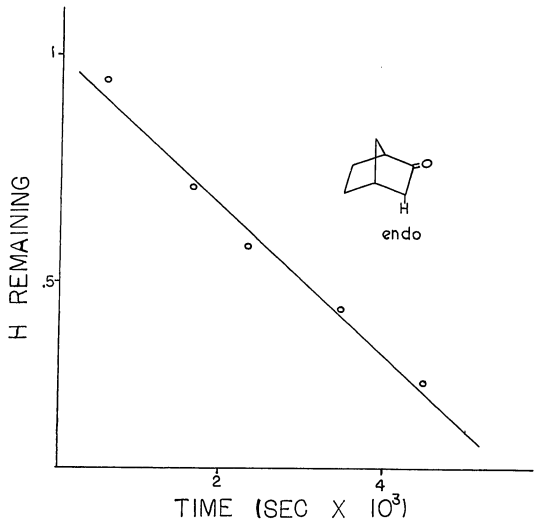


Figure 9. Typical first order plot of the base catalyzed endo hydrogen-deuterium exchange in bicyclo[2.2.1]heptan-2-one (6), $k_{obs} = 2.25 \pm .15 \times 10^{-4}$, [NaOD] = 1.1×10^{-1} M.

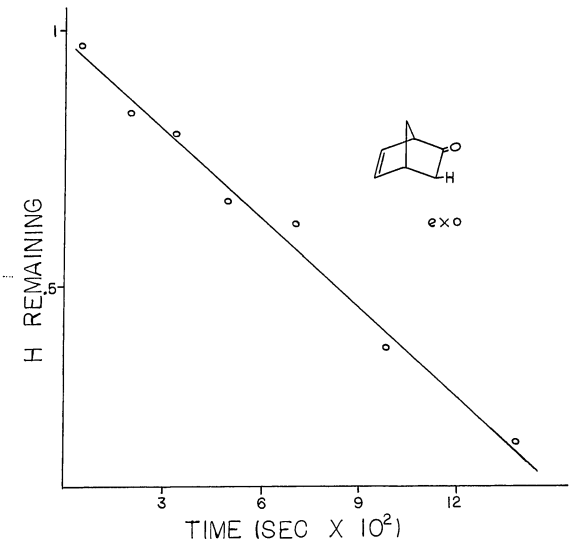


Figure 10. Typical first order plot of the base catalyzed exo hydrogen-deuterium exchange in bicyclo[2.2.1]hept-5-en-2-one (2), $k_{obs} = 9.21 \pm .47 \times 10^{-4}$, $[NaOD] = 2.1 \times 10^{-2}$ M.

V. DISCUSSION

A number of factors are involved in the differences in rates of hydrogen-deuterium exchange observed in bicyclic ketones. These are related to the ease of formation of the carbanion and resulting enolate. In the accepted theory[43] for the base catalyzed halogenation of ketones, the rate and product determining step of the reaction is the base catalyzed formation of the enolate anion. This reaction is followed by a rapid halogenation of the enolate anion. The same mechanism is considered to be valid for the base catalyzed deuteration of ketones[44] (see Historical p. 2).

The results presented in the previous section indicate that there are three major factors affecting the base-catalyzed hydrogen-deuterium exchange of bicyclic ketones. These are (a) ring strain, (b) stereoelectronic control, and (c) homoconjugative effects.

The first part of the discussion will examine the effect of the first two factors while the second part of the discussion will deal with the effect of the third factor in the base catalyzed H-D exchange of bicyclic ketones.

A. The Effect of Ring Strain and Stereoelectronic Control on the Base Catalyzed Hydrogen-Deuterium Exchange of Certain Cyclic and Bicyclic Ketones.

The first observation which can be made from Table 1 is that the rates of H-D exchange of the bicyclo[2.2.1] system are much

slower than those of the [3.2.1] or [2.2.2] systems. If t-butyl cyclohexanone is taken as a standard it becomes obvious that the [2.2.1] systems are slow rather than the other two being fast. This is due to strain in the [2.2.1] system.

The differences in the geometry caused by variations in ring size and differing bond angles in bicyclic ketones will lead to enolate stabilization or destabilization. This will then contribute to speeding up or slowing down the rate of hydrogen-deuterium exchange.

The variations in ring size between the bicyclo[2.2.1] ring system and the other two systems studied, the [2.2.2] and the [3.2.1] are quite pronounced. The [2.2.1] bicyclic system is a severely strained system[45] in comparison with the other two. The internal bond angles are constricted to less than the 109° angle preferred by a tetrahedral carbon. The introduction of a 120° sp^2 bonded carbon of the carbonyl into this system adds to the internal strain of the molecule. It has been suggested[46] that this decrease in internal angles would enhance the s character of the external orbitals and would then lead to increased acidity of the alpha hydrogens. However, other results[47] do indicate that the increased strain in the formation of the enolate is a more important factor.

In both the [3.2.1] and [2.2.2] bicyclic systems the alpha hydrogens are positioned on a six membered ring. As such they are less subject to internal ring strain. The [2.2.2] bicyclic ring is known[48] to be almost strain free and would not be subject

to excessive strain during enolate formation. While models do indicate that the [3.2.1] system is a slightly more rigid structure, it is actually no more than a bridged cyclohexanone. As such it is locked into the chair conformation and has bond angles essentially identical to those of the chair cyclohexanone.[49]

This system would also not experience any excess strain upon formation of the carbanion-enolate anion system.

It therefore becomes apparent that the slower rate observed with the bicyclo[2.2.1]heptan-2-one (6) and its unsaturated analog, bicyclo[2.2.1]hept-5-en-2-one (7) is due to internal ring strain. This internal strain causes difficulty in the formation of the enolate anion and therefore slows down the rate of hydrogen-deuterium exchange relative to the less strained bicyclic systems. This substantiates earlier data[47] stressing the importance of the ease of enolate formation. As can be seen in Table 1, the rates of H-D exchange in the [2.2.2] and [3.2.1] bicyclic systems are quite close to each other and also to the cyclic compounds, cyclohexanone and t-butyl cyclohexanone. This is to be expected since they all incorporate a relatively strain free six membered ring.

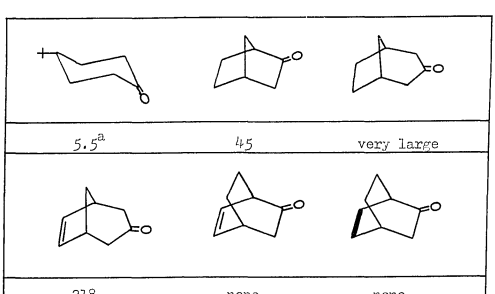
A second observation, as shown in Table 2, is that the exo/endo rate is not the same in the [2.2.1], [2.2.2], and [3.2.1] systems. Instead, the following trend is observed. The [3.2.1]

exo/endo preference is greater than the [2.2.1] and there is no preference in either the saturated or unsaturated bicyclo[2.2.2] ketones.

As observed by Tidwell,[5] there is a surprisingly large preference for exo exchange in the bicyclo[2.2.1] saturated and unsaturated systems. Our results confirmed Tidwell's observations with these ketones. However, with the [3.2.1] and [2.2.2] bicyclic systems, even more surprising results were found. In the bicyclo-[3.2.1] system a preference for exo exchange was found which was even greater than that found in the [2.2.1] system. This might not have been expected since an inspection of models of these systems seems to indicate a greater steric preference for the exo face of the [2.2.1] system than that seen for the [3.2.1] system.

Table 2

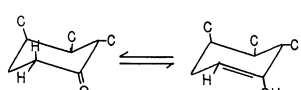
Exo/Endo Rate Ratios



a. ax/eq

The finding of only one rate for removal of both hydrogens in the bicyclo[2.2.2]oct-5-en-2-one (51) was very surprising. Here models show a distinct steric preference for the face bridged by the vinylic group vs. the saturated bridge. This ketone has also been shown to discriminate between faces regarding endo/exo attacks during $NaBH_4$ reduction of bicyclo[2.2.2]oct-5-en-2-one[50] (51). The observation of one rate for bicyclo[2.2.2]-octan-2-one (50) was expected since this molecule has a plane of symmetry through C_1, C_2, C_3, and C_4 with identical alpha hydrogens (Fig. 11).

These results can be best rationalized on the basis of the theory of stereoelectronic control. The principle of stereoelectronic control in enolization-ketonization reactions was first proposed by Corey and Sneen[51] in 1956. They studied the stereochemistry of enolization of 3-acetoxy-cholestan-7-one to the 3-acetoxy-cholest-6-en-7-ol and of the ketonization of this enol using a deuterium tracer. This steroidal system contains a



cyclohexanone ring frozen in the chair conformation.

They observed that the axial hydrogen at C_6 was lost 1.2 times as fast as the equatorial hydrogen upon hydrogen bromide catalyzed enolization in chloroform solution. For the reverse

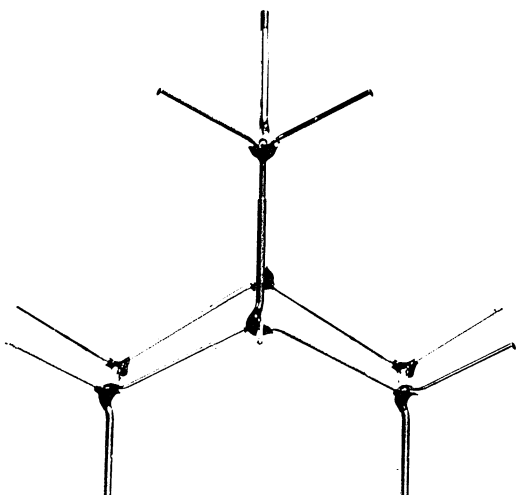
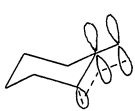


Figure 11. Model showing the angle of *exo* and *endo* hydrogens in relation to the carbonyl in bicyclo[2.2.2]octan-2-one (50).

reaction, ketonization, an axial hydrogen was gained 1.5 times faster than an equatorial one. These axial and equatorial rates, being in reasonably good agreement, led Corey to state that despite steric interference in the axial position, axial attack was more preferable than equatorial attack. Correction for the steric factor gave the result that the stereoelectronic factor favors axial attack by a factor of about 12.

On the basis of these and earlier bromination experiments,[52] they proposed that the orienting influence responsible for the stereochemical preference was stereoelectronic in nature. Of the two carbon-hydrogen bonds alpha to the carbonyl function, it is the axial bond which is closest to being perpendicular to the carbon-oxygen double bond and best situated for overlap with the π orbitals of the exocyclic double bond.



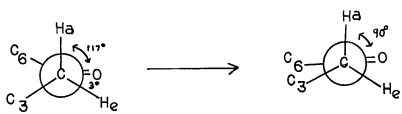
axial interaction
(bonding)

equatorial interaction
(non-bonding)

These ideas have subsequently led to the principle of maximum overlap of reacting orbitals.[53] By this principle, a reagent attacks an unsaturated function in such a way as to give maximum possible overlap between the reacting orbital of the reagent and the orbital of the unsaturated function. Since the electron

density of a π bond is greatest perpendicular to the plane of the sp^2 atoms involved in the bond, the reactant must approach the reaction center from this direction. According to the principle of microscopic reversibility,[53] if the reaction is reversed, the reactant will leave in the same direction. Toromanoff[54] has stressed that the stereoelectronic principle of perpendicular attack is a very general one and can be applied to a variety of unsaturated groups: carbonyl functions, olefinic and enolic double bonds, α, β-unsaturated carbonyl functions, allylic structures, etc.

In a simple chair cyclohexanone (Fig. 12), the principle of perpendicular attack and departure predicts that the axial position will be favored. It is the axial position which most closely approaches this perpendicularity in the enolization-ketonization process. Enolization of the carbonyl function requires a hydrogen at C-2 to assume a position perpendicular to the plane of the carbonyl function. A study of bond angles shows that the axial hydrogen at C-2 can assume this position with much less overall distortion in the molecule than the equatorial hydro-



gen. The enol or enolate ion is therefore formed preferentially

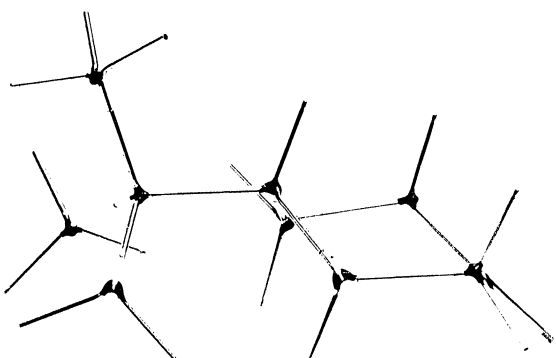
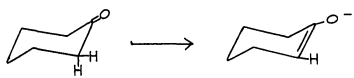
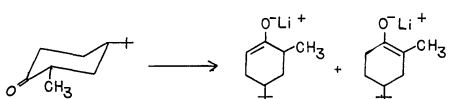


Figure 12. Model showing the angle of axial and equatorial hydrogens in relation to the carbonyl in t-butyl cyclohexanone (53).

by loss of the axial hydrogen. In the reverse process (formation of the ketone), the proton becomes attached to C-2 of the enolate in such a way that it finally occupies an axial position.

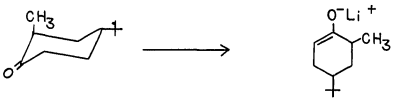


Additional evidence supporting stereoelectronic control in removal of an axial vs. an equatorial hydrogen comes from the recent work of Caine and his coworkers[55]. In a study of the stereochemistry of methylation of the lithium enolate of 2-methyl-4-t-butyl cyclohexanone, they determined the composition of the enolates formed from the cis and trans isomers. They found that under conditions of kinetic control the cis isomer 64 which has



64 86% 14%

two axial hydrogens gave a mixture of the two possible enolates. There was about a 6:1 preference for proton removal from the less substituted alpha carbon. This would be expected since the alpha methyl substituent would destabilize the carbanion formation. When the trans isomer 65 was used in which there is only one available axial hydrogen, only one enolate was formed. As



65

noted by the authors, this would appear to be a manifestation of a stereoelectronic preference for axial hydrogen removal.

With these observations in mind, we proceeded to apply the theory of stereoelectronic control to the present results. The finding that there are two distinct rates of H-D exchange in a simple cyclohexanone known to be frozen in the chair conformation, as in t-butyl cyclohexanone, confirms the importance of stereoelectronic control in proton removal. t-Butyl cyclohexanone should be an ideal substrate on which to determine hydrogen-deuterium exchange rates. This system should have minimum steric interference and there should be no question about conformational changes, as the equatorial t-butyl position is well established.

The finding that there are two distinct rates of hydrogen-deuterium exchange in t-butyl cyclohexanone is not surprising. This would have been predicted by Corey's stereoelectronic concept.[51] However, as noted earlier, Corey predicted a possible rate preference of up to 12 for axial attack. Although this was not totally realized, the rate preference of 5.5 found for the deuterium-hydrogen exchange at the axial position in t-butyl cyclohexanone approaches Corey's maximum prediction. Additional

evidence for stereoelectronic control in the preferential removal of an axial hydrogen, which had been postulated earlier,[56] was obtained by isolation of a dideuterated product enriched more than three to one in the exo position. The identification of the axial hydrogens in t-butyl cyclohexanone was readily accomplished by the use of a shift reagent. It has been reported[57] that the use of benzene as a solvent for nmr studies enables differentiation of axial and equatorial hydrogens in steroidal and other cyclohexanones. However, we were not able to satisfactorily differentiate them by this method. Instead, the resolving agent, 2,2,4,4-tetramethylheptan-3,5-dione Europium (II), very adequately separated the alpha hydrogen absorptions from the remainder of the molecule and also distinctly separated the axial and equatorial hydrogens as shown in the nmr spectra (Fig. 13a). A sample of selectively deuterated t-butyl cyclohexanone was prepared by allowing a mixture of t-butyl cyclohexanone in DMSO with 4.2×10^{-3}M NaOD/D_2O to react at room temperature for five minutes. After rapid isolation and drying, an nmr spectrum taken with the shift reagent, 2,2,4,4-tetramethylheptan-3,5-dione Europium (II), showed that the axial hydrogen had been preferentially exchanged by about three to one. Further substantiation of this was noted in a similar experiment carried out in dioxane. With this solvent system a preference for axial exchange was found to be greater than 5:1. This is strongly indicative of stereoelectronic control favoring that position which can most easily come

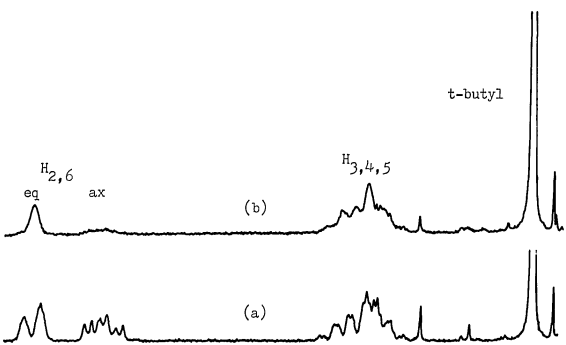


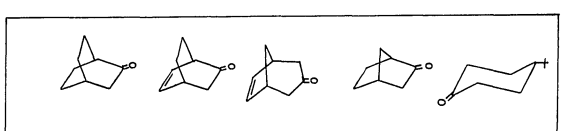
Figure 13. Nmr spectra (a) t-butyl cyclohexanone (53) in CCl_4 with shift reagent; (b) 53 after 30 min in NaOD/D_2O-dioxane.

into conjugation with the π orbitals of the carbon-oxygen double bond. The removal of two hydrogens from t-butyl cyclohexanone followed by a slower removal of the remaining two hydrogens is in direct contrast to that of cyclohexanone. The H-D exchange of cyclohexanone was followed linearly with no appreciable change in slope until more than 3.5 hydrogens were removed.

The results obtained for the hydrogen-deuterium exchange rates with bicyclic systems strongly indicate that stereoelectronic control may also be responsible for the exo/endo rate preferences noted in bicyclic ketones. A study of Dreiding models shows that the angle of the alpha hydrogen to the plane of the carbonyl differs greatly from one bicyclic system to the next.

Table 3

Angle of Alpha Hydrogen to Carbonyl Group



exo	63°	63°	113°	56°	117° a
endo	63°	63°	7°	54°	3° b

a. axial
b. equatorial

As can be seen from Table 3, the angles of the alpha hydrogens are equal in both of the bicyclo[2.2.2] ketones (Fig. 11 and 14). The bicyclo[3.2.1] ketones are different, however. With this

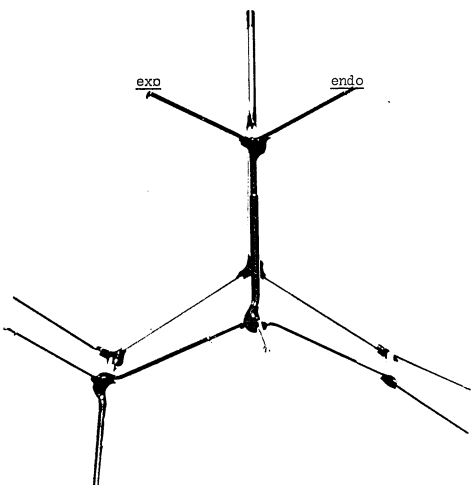


Figure 14. Model showing the angle of exo and endo hydrogens in relation to the carbonyl in bicyclo[2.2.2]oct-5-en-2-one (51).

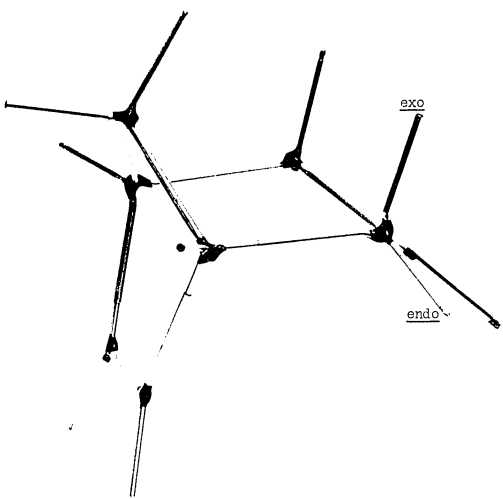


Figure 15. Model showing the angle of exo and endo hydrogens in relation to the carbonyl in bicyclo[3.2.1]oct-6-en-3-one (48).

system the six membered ring is a bridged chair rather than a skew or twist as in the [2.2.2] system. This causes a large difference in the angles of the exo (113°) and endo (7°) hydrogens (Fig. 15) in relationship to the carbonyl. According to the principle of stereoelectronic control, that bond which can most easily come into conjugation with the carbonyl is preferred. As the equal angles show (Fig. 14), the bicyclo[2.2.2]oct-5-en-2-one (51) should therefore not show any stereoelectronic preference for exo vs. endo hydrogen-deuterium exchange. As shown in the graph (Fig. 7) the rate of exchange was linear for more than 1.5 protons removed. In order to attain the enolate-like transition state the carbon-hydrogen bond must rotate 27° with either the endo or exo hydrogen in the [2.2.2] system. This indicates that both alpha hydrogens can attain this geometry with the same facility and therefore stereoelectronically one should not be preferable over the other. The observation of one rate of exchange for both hydrogens would appear to indicate that stereoelectronic control is governing the rate of removal of these hydrogens since sterically they should be distinctly different. With the bicyclo-[2.2.2]octan-2-one (50) the angles of the alpha hydrogens are also equal. However, in this symmetric molecule the rates of alpha hydrogen-deuterium exchange would be expected to be equal since the environments of the two protons are identical. Although the results are consistent, here it is not possible to tell if stereoelectronic control is operative or not as the same results should be obtained in either case.

The bicyclo[3.2.1] systems present an interesting example of stereoelectronic control. As noted in Table 3, the exo hydrogen of bicyclo[3.2.1]oct-6-en-3-one (48) has an angle of about 113° with the plane of the carbonyl. The endo hydrogen, in contrast, forms only a 7° angle (Fig. 15). This would allow the exo hydrogen to overlap much more readily than the endo hydrogen which is almost parallel to the carbon-oxygen double bond. It has been stated by Zimmerman[58] that where stereoelectronic factors are operative, "the stereoelectronic driving force will either cooperate with or oppose the driving force due to steric hindrance to approach." The net stereochemical outcome will then depend, of course, on the magnitude of the steric effects relative to the stereoelectronic driving force. For all three [3.2.1] compounds, a very large exo/endo hydrogen-deuterium exchange preference was found. In all of these cases, the angles clearly show that the exo hydrogen has the preferred orientation. In addition, steric effects would likely favor the exo position although models do not indicate as great a preference for exo attack as is seen with the [2.2.1] system. It thus appears that the large exo/endo rate preference for H-D exchange noted in bicyclo[3.2.1] ketones is an interesting example of cooperation between steric driving forces and stereoelectronic driving forces. From the rates obtained with the [2.2.2] and [3.2.1] systems, it is indicated that the stereoelectronic driving force is a significant factor in these systems. In summary, where the angles are the same, equal rates

are obtained. Where the angles show a distinct preference for exo exchange, a much faster rate for exo exchange is found.

An alternative argument based only on steric effects might be mentioned. It has been suggested[58] that the orbitals of bicyclo[2.2.2]oct-5-en-2-one (57) exercise an appreciable steric effect on the endo position. This might then fortuitously cause equal exo and endo exchange rates. This argument, however, can not be extended to the [3.2.1] system. If this same steric effect was operative here, one would also expect about equal exo-endo rates, rather than the very large exo preference which was found.

Although strong evidence for stereoelectronic control is found in the relatively strain free [2.2.2] and [3.2.1] systems where the formation of the enolates are not hindered, the same evidence is not as conclusive in the strained bicyclo[2.2.1] system. A study of the models shows that the exo and endo bond angles are about the same (Fig. 16). However, the results which were obtained in the present study agree with those previously reported by Tidwell and indicate a distinct preference for exo hydrogen-deuterium exchange. There are two substantial reasons, however, why this result is not unexpected. First, the steric preference for exo attack in the bicyclo[2.2.1] system is well documented.[60] Secondly, and perhaps most importantly, as previously indicated, the strain introduced in forming the enolate anion is quite pronounced. As such, the element of stereoelectronic control, which is associated with the formation of an enolate anion, would also be greatly hindered. In the face of

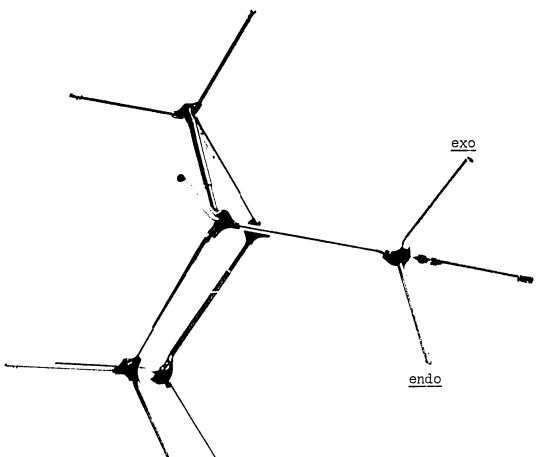


Figure 16. Model showing the angle of exo and endo hydrogens in relation to the carbonyl in bicyclo[2.2.1]heptan-2-one (6).

this it is not surprising that the steric driving force is more dominant than stereoelectronic control. Additionally, the slower rate of exchange found in the bicyclo[2.2.1] ketones would enhance any steric preference for the exo side of the molecule. This is an example of the selectivity principle[61] which states that the slower a reaction becomes, the more selective it becomes. Obviously, then, a faster reaction becomes less selective.

Another example of diminished selectivity is seen when comparing the H-D exchange rates which were obtained in DMSO-d_6-D_2O with those previously reported by Tidwell.[5] The solvent which he employed is the less polar, more weakly solvating dioxane-D_2O system. This system will not give base catalyzed H-D exchange rates as fast as one would get with DMSO-D_2O. This rate enhancement is characteristic of the polar aprotic solvent, dimethyl sulfoxide.[62] The resultant loss in selectivity is borne out by the decreased exo/endo preference which was obtained with the bicyclo[2.2.1]heptan-2-one (6) in DMSO-d_6-D_2O.

Another interesting observation can be made by comparing the rate of H-D exchange of the endo hydrogen of the bicyclo[2.2.1]-heptan-2-one (6) with the endo rates obtained with the three bicyclo[3.2.1] ketones. As can be seen from Table 1, the rates of the endo hydrogens in the [3.2.1] system are only slightly faster than those of the [2.2.1] system. This is quite different from the exo rates where, as stated earlier, the [2.2.1] rates are much slower. This fact can once again be explained by means of stereoelectronic control. From Table 3 it can be seen that

the endo alpha hydrogens in the [3.2.1] system are much more poorly disposed for conjugation than any of the other hydrogens which were studied. It is probable that the rate of these endo hydrogens is almost as slow as the more strained [2.2.1] endo hydrogen because of their nearly parallel disposition to the carbonyl. Although the strain in forming the [2.2.1] enolate anion is great, the angle of the endo hydrogen is much closer to the preferred 90° configuration (54°) than the [3.2.1] endo hydrogens (7°). As such, this [2.2.1] endo carbon-hydrogen bond can take part in p - π overlap much more readily and more easily achieve the perpendicular configuration necessary for enolate formation. This increased stereochemical preference apparently makes up for the added strain and accounts for almost equal rates.

A question which might be asked is why the equatorial hydrogens of t-butyl cyclohexanone are not as slow to exchange as the comparable [3.2.1] endo hydrogens. This is probably due to two major differences in these systems. The bicyclic system has a greater steric hindrance for the endo position and is also a more rigid molecule. This increased rigidity will make the large deformation necessary for the endo hydrogen to be removed more difficult and will additionally slow its rate of H-D exchange. Although these reasons are perhaps not totally satisfying, ultimately the answers lie in the inherent differences between cyclic and bicyclic systems.

Recently, the importance of stereoelectronic control, although widely accepted, has come under attack. Fishman[63] has

suggested that the steric and stereoelectronic control factors are quite often in conflict with each other and it can be difficult to assess the contribution made by each one. Bordwell and his coworkers[64] published a report in 1968 dealing with the base catalyzed hydrogen-deuterium exchange rates of cyclohexanone and some 4,4-disubstituted cyclohexanones. His results, carried out in methanol-O-d at 25° with sodium methoxide as the basic catalyst were as shown in Table 4 .

Table 4

Base Catalyzed Hydrogen-Deuterium Exchange Rates of 4,4-Disubstituted Cyclohexanones, k in M^{-1} sec^{-1}.[64]

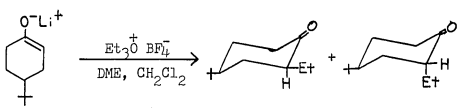
	k	rel. rate
	1.05×10^{-1}	1.0
	3.4×10^{-1}	3.3
	8.9×10^{-2}	0.9
	5.7×10^{-2}	0.5

The results appear to show that substituents in the 4-axial position do not slow down the rate of proton abstraction at the 2 position when compared with the unsubstituted cyclohexanone as might be expected if there is a steric effect hindering the removal of the axial hydrogen. Bordwell[64] claimed that the failure of either a 4-axial phenyl or 4-axial methyl group to retard the rate of removal of a porton from the C-2 position "casts doubt on the importance of stereoelectronic control."

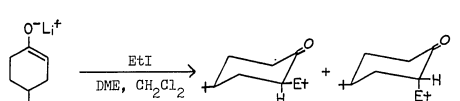
In view of the present results which indicate that there are two distinct rates of proton removal in a locked chair cyclohexanone, it would appear that Bordwell's results should be reevaluated. There are two other possible explanations which would account for only one rate of exchange for all four alpha hydrogens. First, it is distinctly possible that all four hydrogens are equivalent as a result of the large 4-axial substituent having forced the cyclohexanone into the flexible or twist form.[65] This would cause a loss of distinction between axial and equatorial hydrogens with the result that only one rate of H-D exchange would be observed. The second possibility, one which appears especially likely for the 4-methyl-4phenylcyclohexanone, is that the axial methyl group has retarded the rate of axial hydrogen exchange. This retardation, caused by the well known 1,3-diaxial interaction,[66] could have slowed the rate of axial exchange to a rate now comparable to that of the equatorial exchange and thus only one rate is observed.

Recently, considerable work has been done on the stereo-

chemistry of alkylation and protonation of enolate anions. House, Tefertiller and Olmstead[67] have reported the results of their investigations of the alkylations of the lithium enolate of t-butyl cyclohexanone. They found that approximately equal amounts of axial and equatorial alkylation products were obtained. From this they concluded that "there is no inherent factor which strongly favors the alkylation of a cyclohexanone enolate anion from that direction which will form a product with an axial alkyl substituent." House and his group have therefore concluded that the transition state for alkylation of the enolate must resemble the



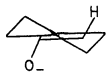
49% 51%



46% 54%

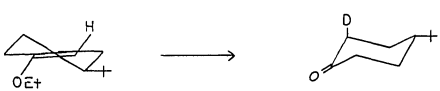
geometry of the planar enolate ion more than that of the more product-like pre-chair or twist boat as has been supposed. Models show that there are very little steric differences which would favor attack from either side so if the transition state does resemble the starting enolate anion more than the products, the

energy difference between the two transition states would be small.



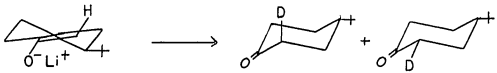
It must be pointed out that House's assumptions rest on the supposed enolate-like transition state. If the transition state is more product-like then the steric restrictions imposed by an incoming axial methyl group in the chair-like transition state could influence the product distribution to the more thermodynamically favored equatorial alkylation product. It might then be said that the reason more than 50% axial alkylation did occur was due to stereoelectronic preference to axial attack. The fact that House and his group obtained less axial alkylation with the more bulky tri-ethyl oxonium ion than with ethyl iodide would support this argument.

Indeed, House, in the previously mentioned article, also showed that deuteration of the enol ether of t-butyl cyclohexanone



in an acidic medium led to greater than 90% incorporation of the deuterium in the axial position. He also found that quenching the lithium enolate of t-butyl cyclohexanone with deuterated aqueous acetic acid resulted in 70% deuterium in the axial

position and 30% deuterium in the equatorial position. These two results would appear to indicate some form of stereochemical



70% 30%

preference for axial attack. House, on the other hand, explained these observations by making the crude assumption that about one-half of the enolate deuterated on oxygen and the other half deuterated on carbon. Since it was obvious, he said, that O deuteration yielded exclusively axial product, he felt that the C deuteration must be occurring from both directions to account for the 30% equatorial deuterium which he obtained.

B. The Effect of Homoconjugation and Antiaromaticity on the Base Catalyzed Hydrogen-Deuterium Exchange of Bicyclic Ketones.

In the previous section the effect of stereoelectronic control and ring stress has been discussed. Next, the effect of long range interactions on the base-catalyzed H-D exchange of bicyclic ketones will be considered.

As mentioned previously (Historical p. 16), 2,4-diphenylbicyclo[3.2.1]oct-6-en-3-one did not homoconjugate.[33] This is, no doubt, due to the stability of the carbanion formed in this system. Not only is the anion stabilized by the carbonyl group but also by the phenyl ring. It was felt that the unsubstituted ketone bicyclo[3.2.1]oct-6-en-3-one (48) would have a much larger tendency for homoconjugation since now the anion would be stabilized only by the carbonyl group.

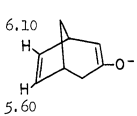
Table 5

Relative Rates of Unsaturated vs. Saturated Exo Exchange in Bicyclic Ketones

			
$\frac{k_{unsat'd}}{k_{sat'd}}$	.45	1.1	.25

A comparison of the rates of bicyclo[3.2.1]oct-6-en-3-one (48) with bicyclo[3.2.1]octan-3-one (47) indicates that there is no homoconjugation of the carbonyl stabilized carbanion in this system. The slight rate increase is that which would be expected on purely inductive grounds.[32,64]

Additional evidence against homoconjugation occurring in the enolate anion 54 of bicyclo[3.2.1]oct-6-en-3-one was found spectroscopically. An nmr spectrum of the anion of this ketone, obtained with lithium diisopropyl amide as the base in THF, showed an absorption pattern very close to that which would be predicted for the enolate anion 54. As can be seen in 54, 35 and 55, the vinylic nmr absorptions are very similar in these three closely related



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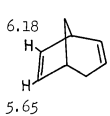

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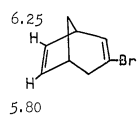
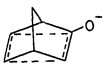


55

systems. If homoconjugation with delocalization of charge to the vinylic double bond had occurred the nmr would have shown a greater upfield shift for the vinylic hydrogens, especially H_7. It thus appears quite certain from both kinetic and spectroscopic measurements that long range stabilization of the anion was not occurring.

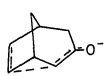
Next, the possibility of antihomoaromaticity was considered.

It has been suggested by Tidwell[5] that a possible reason for the bicyclo[2.2.1]hept-5-en-2-one (7) exchanging slower than its saturated analog, bicyclo[2.2.1]heptan-2-one (6), was due to anti-homoaromaticity in the enolate anion 56.



56

It was felt that a comparison of the rates of the [3.2.1] systems with those of the [2.2.2] systems would be an ideal way to test Tidwell's hypothesis. As can be seen in 46, the [3.2.1] enolate anion would not be able to extend the conjugation in a



46

similar manner to the antiaromatic species. However, in the bicyclo[2.2.2] systems, which like the [2.2.1] ketones are able to extend the conjugation to the bisantihomoaromatic species, an additional factor is involved. The bicyclo[2.2.2]oct-5-en-3-one (51) would introduce comparatively little strain upon formation of the enolate anion.

When the rates of H-D exchange of the bicyclo[2.2.2]oct-5-en-

2-one (51) are compared with its saturated analog, the bicyclo-[2.2.2]octan-2-one (50), a very interesting result was obtained. As can be seen in Table 5, the unsaturated ketone is about four times slower than the saturated ketone when comparing H-D exchange at the alpha position.

This somewhat unusual result (as in the [3.2.1] system, simple inductive effects would increase the rate of H-D exchange in the unsaturated ketone) becomes more enlightening when compared with our results on the [2.2.1] ketones, k unsat'd/k sat'd = 0.45, and those reported earlier by Tidwell. It appears that not only does the bicyclo[2.2.1]hept-5-en-2-one (7) exchange slower than the bicyclo[2.2.1]heptan-2-one (6), but also the bicyclo[2.2.2]oct-5-en-2-one (51) exchanges slower than its saturated analog. It can be seen that this decrease in rate is almost twice as pronounced in the [2.2.2] ring system.

It thus seems that the proposal made by Tidwell[5] concerning destabilization by a bis-antihomoaromatic enolate anion is definitely confirmed. As the [3.2.1] system aptly shows, where this destabilization is not possible, the rates of H-D exchange are slightly faster with the ketones containing the vinylic bridge. However, with the ketones which can form the bis-homocyclobutadiene

type structure, an exactly opposite result was found.

The finding that even more destabilization is occurring in the much less strained [2.2.2] ring system is just what would be expected. The formation of the enolate anion is much less strained and the attainment of a favorable orbital geometry for interaction is much more likely. It is therefore believed that the existence of an "antiaromatic" bishomocyclobutadiene type structure is most likely responsible for the observed rate deceleration in the unsaturated [2.2.2] and [2.2.1] bicyclic ketones.

VI. EXPERIMENTAL

A. General

All melting points were taken on a Thomas Hoover apparatus in open capillary tubes and are uncorrected.

Ir spectra for the compounds were recorded on a Beckman IR-8 spectrophotometer.

Nmr spectra were recorded on a Varian Associates Model A-60 spectrometer. All chemical shifts are reported in ppm relative to tetramethylsilane and all coupling constants are in hertz (Hz). Nmr data are recorded in the order: chemical shift, multiplicity (where s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet), integration, coupling constant, interpretation. Samples were run in ordinary 5 mm nmr tubes.

Gas chromatography was performed on a Varian Aerograph, Series 2700 gas chromatograph equipped with a thermal conductivity detector and 5 ft x 1/4 in SE-30 (silicone gum rubber) columns. The carrier gas was helium.

Unless otherwise noted, the starting materials were used as obtained.

B. Preparation of Starting Materials

1. Preparation of 3,4-dibromobicyclo[3.2.1]octa-2,6-diene (56).

A slurry of norbornadiene (92 g, 1.0 mole), potassium t-butox-

ide (101 g, 0.90 mole) in 350 ml of dry pentane was prepared. The slurry was stirred and kept at -15° to -20° under N_2. To this a mixture of bromoform (253 g, 1 mole) in 150 ml of pentane was added dropwise. It is important to add very slowly (addition time, 3 hours). After addition was completed, 300 ml of water was slowly added. The water layer was separated and extracted with pentane. The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent followed by vacuum distillation gave 89.5 g (38% yield) of a mixture of dibromo isomers 56. The boiling point (bp) was 62-63° at 0.005 mm (lit.[68] bp 77° at 0.05 mm); $n^{25}D$ 1.5935 (lit.[68] $n^{25}D$ 1.5964).

2. Preparation of 3-bromobicyclo[3.2.1]octa-2,6-diene (57).

A mixture of isomeric dibromobicyclooctadienes (115.1 g), prepared as described above, was added dropwise under N_2 to a stirred refluxing slurry of $LiAlH_4$ (16.50 g) in 1500 ml of dry ether. This was allowed to reflux for 13 hours. The work up procedure was done as in Fieser and Fieser[69] (for n g of $LiAlH_4$, add successively; n ml of H_2O, n ml of 15% NaOH, then 3n ml of H_2O). After filtering off the solid hydroxides, they were washed with 200 ml of ether. The ether washings were added to the original ether layer and dried over $MgSO_4$. Evaporation of the ether under reduced pressure followed by vacuum distillation gave 56.8 g (71% yield) of monobromide 57. The bp was 51-58° at 3 mm (lit.[68] bp 63° at 5 mm). $n^{25}D$ 1.5440 (lit.[67] $n^{25}D$ 1.5453).

3. Preparation of 3,7,8-tribromobicyclo[3.2.1]oct-2-ene (58).

A solution of Br_2 (61.0 g, 0.382 mole) in 70 ml of CCl_4 was added dropwise to a stirred solution of monobromide 57 (70.0 g, 0.378 mole) in 300 ml ether kept at -10° to -15°. The addition time was approximately 2 hr. An additional 300 ml of ether was added, the ether solution was washed with aqueous $NaHSO_3$ to remove excess bromine, then washed with water and dried over $MgSO_4$. Evaporation of the ether followed by addition of pentane gave 94.0 g (72% yield) of 3,7,8-tribromobicyclo[3.2.1]oct-2-ene (58) as white crystals; mp 97-99° (lit.[37] mp 100-101°).

4. Preparation of anti-8-bromotricyclo[3.2.1.$0^{2,7}$]octan-3-one (59).

3,7,8-Tribromobicyclo[3.2.1]oct-2-ene (58) (65 g) was quickly added to a cooled, stirred solution of 60 ml of water, 84 ml of concentrated H_2SO_4, and 120 ml of 95% ethanol. This was stirred and warmed on a water bath to 50° and allowed to react for 66 hr. The reaction mixture was then poured into ice water and extracted with ether. The water layer was saturated with NaCl and an additional extraction was done. The extracts were combined and dried over $MgSO_4$. Evaporation of the solvent followed by refrigeration gave 20 g (53% yield) of crude tricyclic monobromo ketone 59, which was further purified by column chromatography on silica gel. Elution with 1:1 ether-petroleum ether (bp 30-60°) gave, after evaporation and cooling, white crystals of anti-8-bromotricyclo[3.2.1.$0^{2,7}$]octan-3-one (59) with mp 54-56°

after recrystallization from ether-pentane (lit.[37] mp 54-56.5°).

5. Preparation of bicyclo[3.2.1]oct-6-en-3-one (48).

A mixture of monobromoketone 52 (7.5 g, 0.037 mole) in 100 ml of ether was slowly added to a solution of lithium metal (1.30 g, 0.187 mole) in 1500 ml of liquid NH_3. Addition time was approximately 1 hr and 15 min. The reaction mixture was stirred for an additional hour. The reaction was then quenched by addition of solid NH_4Cl followed by moist ether and water. The ammonia was allowed to evaporate and the product was extracted with ether. The ether layer was washed with water and dried over $MgSO_4$. Careful distillation of the ether followed by the addition of a large volume (400 ml) of pentane, crystallized out a small amount of impurity which was filtered and discarded. Careful distillation of the pentane followed by cooling gave a white solid. Sublimation at 60° and 20 mm gave 2.5 g of bicyclo[3.2.1]oct-6-en-3-one (48), (51% yield). Ketone 48 was further purified by recrystallization from pentane; mp 100-102° (lit.[37] mp 99-100.5°). This ketone still contained an nmr detectable impurity which was ultimately removed by silica gel column chromatography. Elution with ether-petroleum ether 1:4 followed by short column distillation of the solvent and cooling gave white dry crystals; mp 102.5-103°. The nmr spectrum (CCl_4) showed: 1.75 - 2.0 ppm (complex pattern, 2H, C_8), 2.30 ppm (d, 4H, C_2, C_4), 2.88 ppm (s, 2H, C_1, C_5), 6.02 ppm (narrow multiplet, 2H, C_6, C_7). The nmr spectrum with added shift reagent (0.125 g of 2,2,4,4-tetramethylheptane-3,5-dione Europium II complex

(Resolve-Al) in 0.50 ml CCl_4 with 0.05 g ketone 48) showed: 4.0 ppm (complex pattern, 1H, C_8-Hb), 4.58 ppm (d, 1H, J=10.0 Hz, C_8, Ha), 5.0 ppm (s, 2H, C_1, C_5), 8.15 ppm (s, 2H, C_6, C_7), 9.12 ppm (doublet of doublets, 2H, $J_{1,2}$=3.5 Hz, $J_{2,2}$=17.5 Hz, C_2, C_4, exo), 9.82 ppm (d, 2H, J=17.5 Hz, C_2, C_4, endo). See Figure 17a and 17d.

6. Preparation of 3,4-dibromobicyclo[3.2.1]oct-2-ene (54).

A slurry of norbornene (40 g, 0.425 mole) with potassium t-butoxide (55 g, 0.50 mole) in 400 ml of dry pentane was prepared. To this stirred mixture, which was maintained at 25-28° with an ice bath, was added dropwise under N_2, a solution of bromoform (180 g, 0.71 mole) in 50 ml of pentane. Addition time was 2 hr. This was stirred for an additional 1.5 hr at room temperature. Careful addition of 500 ml of water was followed by separation of the hydrocarbon layer which was washed with water and dried over $MgSO_4$. Evaporation of the solvent followed by vacuum distillation at approximately 0.01 mm bp 80-90° gave 25.8 g (23% yield) 3,4-dibromobicyclo[3.2.1]oct-2-ene (54) (lit.[68] bp 80° at 0.2 mm).

7. Preparation of 3-bromobicyclo[3.2.1]oct-2-ene (55).

To a stirred refluxing slurry of $LiAlH_4$ (10.7 g) in 500 ml of dry ether under N_2 was added dropwise 25.8 g of 3,4-dibromobicyclo[3.2.1]oct-2-ene (54). This was refluxed overnight. The usual workup and vacuum distillation gave 12.35 g (68% yield) bp 52° at 2.75 mm. The ir spectrum was identical to that

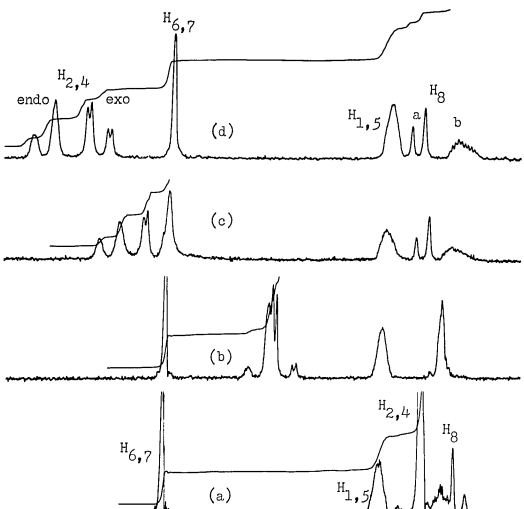


Figure 17. Nmr spectra (a) bicyclo[3.2.1]oct-6-en-3-one (48) in CCl_4; (b) 0.05 g 48 in 0.50 ml CCl_4 with 0.050 g shift reagent; (c) with 0.10 g shift reagent; (d) with 0.125 g shift reagent.

reported in the literature[68].

8. Preparation of bicyclo[3.2.1]octan-3-one (47).

To a cooled (1-5°) rapidly stirred solution of 60 ml of concentrated H_2SO_4 was added dropwise 3-bromobicyclo[3.2.1]oct-2-ene (55) (12.35 g, 0.066 mole). The flask was kept in an ice bath and stirred for an additional 30 min. The reaction mixture was then added to ice water and extracted into ether. The ether layer was washed first with aqueous saturated $NaHCO_3$, then with water and dried over $MgSO_4$. Evaporation of the ether afforded 10 g of crude ketone 47. The ketone was purified by the procedure of Kraus,[35] whereby the semicarbazone was prepared and then steam distilled. Vacuum sublimation of the product at 20 mm at 70° gave 1.7 g of bicyclo[3.2.1]octan-3-one (47), mp 138-142°, (lit.[35] mp 144-145°). The nmr spectrum (CCl_4) showed: 1.4 - 2.1 ppm (complex pattern, 6H, C_6, C_7, C_8), 2.27 ppm (m, 4H, C_2 C_4), 2.52 ppm (broad singlet, 2H, C_1, C_5). In DMSO-d_6 the spectrum showed: 0.9 - 2.1 ppm (complex pattern, 6H, C_1, C_2, C_4, C_5), 2.1 - 2.7 ppm (complex pattern, 6H, C_6, C_7, C_8).

9. Preparation of indenyl Grignard reagent 60.

Indene (58.1 g, 0.5 mole) was added dropwise to a stirred refluxing solution of ethyl magnesium bromide (prepared from 12.2 g of Mg and 54.5 g of ethyl bromide) in 200 ml of THF. This was refluxed for 30 min. The warm indenyl Grignard 60 was quickly transfered by syringe under N_2 into an addition funnel and added

dropwise to a cold (-10 to -15°) stirred solution of 2,3-dichloropropene (55.5 g, 0.5 mole) in 60 ml of THF. After the addition was completed, the reaction mixture was stirred at -10° for an additional 30 min. The addition of 100 ml of saturated NH_4Cl and then 50 ml of water gave two layers. The layers were separated and the water layer and residue were washed with THF. This was added to the organic layer and dried over $MgSO_4$. Evaporation of the solvent and vacuum distillation of 0.2 mm gave 33.6 g of 1-(2-chloroallyl)-indene (61), bp 65-72°. The ir was identical to that reported.[38]

10. Preparation of 6,7-benzobicyclo[3.2.1]oct-6-en-3-one (49).

To 900 ml of stirred refluxing 97% formic acid was added 15.3 g of 1-(2-chloroallyl)indene (61) dropwise. This mixture was refluxed for an additional hour. The reaction was cooled and one liter of ice water was added and the product extracted into ether. This was washed with aqueous saturated $NaHCO_3$ solution. The solution was then washed with water and dried over $MgSO_4$. Evaporation left a brown oil which was chromatographed on an alumina column. Elution with low boiling petroleum ether readily removed a by-product, the 3-chloro-5,6-benzobicyclo-[3.2.1]oct-2-ene. Following removal of this compound, further elution with 15% ether-petroleum ether afforded a white solid. This was recrystallized from warm petroleum ether to yield 5.0 g of 6,7-benzobicyclo[3.2.1]oct-6-en-3-one (49) mp 67-69° (lit.[38] 64-66°). The nmr spectrum (CCl_4) showed: 1.98 - 2.28 ppm (complex pattern, 2H, C_8), 2.44 ppm, (d, 4H, C_2, C_4), 3.36 ppm

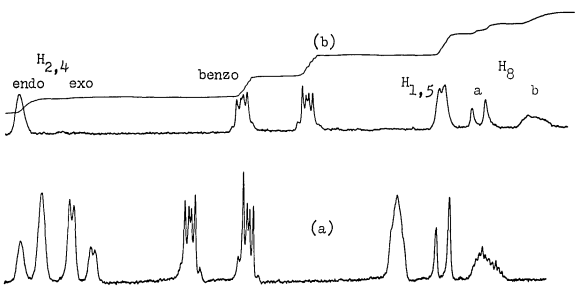


Figure 18. Nmr spectra (a) 6,7-benzobicyclo[3.2.1]-oct-6-en-3-one (42) (0.025 g) in CCl_4 (0.25 ml) with shift reagent (0.50 g); (b) Dideuteroketone 49 (0.025 g) in CCl_4 (0.25 ml) with shift reagent (0.50 g).

(m, 2H, C_1, C_5), 7.10 ppm (s, 4H, benzo). In DMSO-d_6 the nmr spectrum showed: 2.6 ppm (s, 2H, C_8), 2.40 ppm (m, 2H, C_2, C_4, endo), 2.75 ppm (d, 2H, C_2, C_4, exo), 3.40 ppm (m, 2H, C_1, C_5), 7.17 ppm (m, 4H, benzo). The nmr spectrum with shift reagent (0.25 ml CCl_4 + 0.50 g Resolve-Al + 0.025 g ketone) showed: 3.06 ppm (m, 1H, C_8-H_b), 3.70 ppm (d, 1H, J=11 Hz, C_8-Ha), 4.35 ppm (s, 2H, C_1, C_5), 6.42 ppm (m, 2H, benzo), 7.22 ppm (m, 2H, benzo), 8.78 ppm (doublet of doublets, 2H, $J_{1,2}$=3.5 Hz, C_2, C_4, exo), 9.40 ppm (d, 2H, J=17.5 Hz, C_2, C_4, endo). See Figure 18a.

11. Preparation of bicyclo[2.2.1]hept-5-en-2-one (7).

p-Benzoquinone (50.5 g, 0.468 mole) and bicyclo[2.2.1]oct-5-en-2-ol (10.0 g, 0.0910 mole) were dissolved in 1300 ml of benzene. Following removal of 400 ml of benzene by distillation from this mixture, the solution was allowed to cool and aluminum t-butoxide (17.3 g, 0.07 mole) in 150 ml of benzene was added with stirring over the course of one hour. This mixture was stirred at room temperature for eight days. The solution was washed with 5% NaOH until it was clear, followed by washings with salt solution and water and then dried over $MgSO_4$. The benzene was removed by distillation and further vacuum distillation gave 4.0 g of bicyclo-[2.2.1]hept-5-en-2-one (7) bp 85° at 25 mm (lit.[34] bp 95-97° at 93 mm). The nmr spectrum (DMSO-d_6) showed: 1.92 ppm (m, 2H, C_7), 2.08 ppm (complex pattern, 2H, C_3), 2.88 ppm (m, 1H, C_1), 3.19 ppm (m, 1H, C_4), 6.12 ppm (m, 1H, C_5), 6.58 ppm (m, 1H, C_6).

12. Preparation of bicyclo[2.2.2]oct-5-en-2-ol (63).

Cyclohexadiene (25 g, 0.312 mole) and vinyl acetate (33.6 g, 0.38 mole) with a pinch of hydroquinone were heated at 180° for five days in a stainless steel reactor. Fractional distillation afforded 14.0 g of bicyclo[2.2.2]oct-5-en-2-yl acetate (62) bp 81-82° at 5 mm (lit.[40] bp 90-91° at 9 mm) $n^{25}D$ 1.5020 (lit.[39] $n^{25}D$ 1.5020). The acetate 62 was saponified by refluxing for 2 hr with 60 ml of methanol and 40 ml of 15% NaOH. Separation of the two layers which formed, followed by ether extraction of the water layer to get additional product and then distillation of the ether gave a white solid. Recrystallization from petroleum ether gave 3.3 g mp 161-165° (lit.[40] mp 167-169°).

13. Preparation of "active" MnO_2.[70]

$MnSO_4 \cdot H_2O$ (0.5 mole) in 150 ml of water and 117 ml of 40% NaOH were slowly added simultaneously to a hot stirred solution of $KMnO_4$ (96 g) in 600 ml of water. The MnO_2 precipitated as a fine brown solid. The stirring was continued for 1 hr. Solid MnO_2 was collected by filtration and repeatedly washed and centrifuged until the washings were nearly colorless. The solid was dried in an oven (110°) and ground to a fine powder before use (yield 67 g).

14. Preparation of bicyclo[2.2.2]oct-5-en-2-one (51).

Bicyclo[2.2.2]oct-5-en-2-ol (63) (1.0 g) in 30 ml of CH_2Cl_2

was made into a thick brown slurry with MnO_2 (15.0 g). This mixture was stirred at room temperature for 22 hr. Steam distillation of the brown slurry gave two layers. After separating the organic layers and washing the NaCl saturated water layer with CH_2Cl_2, the organic layers were combined and dried over $MgSO_4$. Distillation of the solvent through a short column followed by sublimation of the residue gave 0.45 g of bicyclo[2.2.2]oct-5-en-2-one (51) mp 92-94° (lit.[40] mp 91.5-93°). The nmr spectrum ($CDCl_3$) showed: 1.2 - 2.0 ppm (complex pattern, 6H, C_7, C_8), 2.04 ppm (d, 2H, C_3), 3.08 ppm (m, 2H, C_1, C_4), 6.36 ppm (m, 2H, C_5, C_6).

15. Preparation of bicyclo[2.2.2]octan-2-one (50).

Atmospheric pressure hydrogenation over 10% Pd/C was carried out on bicyclo[2.2.2]oct-5-en-2-one (51) (0.60 g) in 100 ml of ethanol. After the H_2 absorption had stopped, the solvent was distilled off and the residue sublimed. This sublimation product had a broad melting range and the product was further purified by silica gel column chromatography. Elution with ether-petroleum ether 1:5 gave pure bicyclo[2.2.2]octan-2-one (50) mp 174.5-176° (lit.[40] mp 175.5-177.5°). The nmr spectrum ($CDCl_3$) showed: 2.26 ppm (s, 4H, C_1, C_3, C_4), 1.7 ppm (s, 8H, C_5, C_6, C_7, C_8).

16. Preparation of t-butyl cyclohexanone deuterated selectively in the axial position.

To a solution of t-butyl cyclohexanone (0.50 g) in 12 ml of

dimethyl sulfoxide (DMSO) was added 4 ml of 0.0042 M NaOD/D_2O solution. After five minutes the solution was neutralized with a few drops of HCl and quickly poured into 200 ml of aqueous saturated NaCl solution which precipitated the ketone immediately. Filtration and air drying gave the axial dideuterated ketone. Nmr analysis with the use of the shift reagent Resolve-Al showed that the remaining protons were about 75% equatorial and 25% axial.

When deuteration was performed in dioxane for 30 min with a higher base concentration (0.042 M NaOD/D_2O) the nmr showed 84% of the remaining protons were in the equatorial position and only 16% remaining in the axial position. The nmr spectrum (0.50 ml CCl_4 with 0.10 g shift reagent and 0.05 g ketone) showed: 0.32 ppm (s, 9H, t-butyl), 2.77 ppm (complex pattern, 5H, C_3, C_4, C_5), 7.66 ppm (s, 2H, C_2, C_6, equatorial). See Figure 13b.

17. Exo deuteration of 6,7-benzobicyclo[3.2.1]oct-6-en-3-one (49).

6,7-Benzobicyclo[3.2.1]oct-6-en-3-one (49) (0.50 g) in 12 ml of dioxane was allowed to react with 4 ml of 0.10 M NaOD/D_2O for 1 hr at room temperature. The usual workup followed by nmr showed slightly more than two alpha hydrogens had exchanged. The use of shift reagent showed essentially all of the exo hydrogens removed with 1.6 protons remaining in the endo position. The spectrum (0.25 ml CCl_4 with 0.50 g shift reagent and 0.025 g ketone) showed: 3.38 ppm (m, 1H, C_8-Hb), 4.10 ppm, (d, 1H, J= 11 Hz, C_8-Ha), 4.63 ppm (s, 2H, C_1, C_5), 6.50 ppm (m, 2H, benzo),

7.40 ppm (m, 2H, benzo), $C_{2,4}$, exo has disappeared, 10.50 ppm (s, 2H, C_2, C_4, endo). See Figure 18b.

18. Preparation of NaOD solution.

Na (0.23 g) was weighed out in hexane. This was quickly dried and, under a N_2 atmosphere, was carefully added in portions to 25 ml of D_2O. The resultant NaOD was then standardized by titration against standard HCl. This NaOD stock solution was then used to prepare more dilute NaOD/D_2O solutions by appropriately diluting it with D_2O.

19. Preparation of bicyclo[3.2.1]oct-6-en-3-one anion (54).

The base used for the preparation of the anion was lithium diisopropyl amide, Li-N$(CH(CH_3)_2)_2$. It was prepared from n-butyllithium and diisopropyl amine. n-Butyllithium (12.7 ml, 0.022 mole) as a 1.6 M solution in hexane was syringed under N_2 into a 3-neck flask. This was stirred and cooled to 1-5° in an ice bath. Diisopropyl amine (4.25 ml, 0.033 mole) was added slowly. The flow of N_2 gas was increased and the solution was allowed to come to room temperature. As the solvent evaporated the solution became very viscous. THF (2 ml) was added to the flask and the flow of N_2 continued until this had also evaporated. When the lithium diisopropyl amide was as dry as possible 1.5 ml of THF was added and then a solution of bicyclo[3.2.1]oct-6-en-3-one (48) (0.25 g, 0.02 mole) in 0.5 ml THF was slowly added by syringe

under N_2. After stirring for 0.5 hr a portion of the solution was removed by syringe and placed into a capped nmr tube. The spectrum in THF showed that the vinylic hydrogens, H_6 and H_7, had become unequivalent. However, the similarity between the spectrum of the enolate anion 54 and some model systems, 35 and 55, indicated that charge delocalization into the vinylic bridge had not occurred.

C. Kinetic Procedure

The reactants were thermostated in a constant temperature bath at the temperature of the nmr probe, $37.0^{\circ} \pm 0.2^{\circ}$ for a minimum of 20 min before mixing. The two solutions, ketone in DMSO-d_6 and NaOD/D_2O, were then pipetted into a vial, quickly mixed and put into the nmr probe. The approximate time for this was 15 sec. The timer was begun during mixing and successive integrations were immediately taken and the times noted. The amount of hydrogen removed was determined by the ratio of the designated alpha hydrogens to some internal standard in the molecule. This internal standard was an unexchangeable proton or protons, usually the vinylic or benzo hydrogens in the unsaturated systems, or the bridgehead hydrogens in the saturated system. In some cases the rate was followed by observing the increase in the HOD signal. This is valid even when there are two rates if the rates are sufficiently different from each other. As the exo/endo rate ratios were quite large, this did not present a problem. Where

both methods were used there was good agreement between them.

In the cyclic systems, the t-butyl group was a convenient standard for the t-butyl cyclohexanone while in the cyclohexanone itself the four equivalent alpha hydrogens were sufficiently separated from the remaining six hydrogens to allow for accurate determination of the rate.

The conditions of the reactions were such that first order kinetics in base were maintained. An excess of ketone was maintained (10:1) and sufficient D_2O was used to ensure rapid deuteration. The data were treated in a least squares analysis on a Wang calculator program for log H removed vs. time. The second order rate constants were obtained by dividing the pseudo first order rate constants by the base concentration, $k_2 = k_{obs} / [B]$.

The final concentrations were determined by assuming an additivity of mixing. Mixing experiments showed only a very small volume change even with much larger amounts (10 ml).

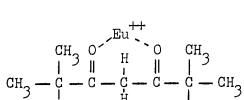
In a typical run, 0.045 g of bicyclo[3.2.1]oct-6-en-3-one (48) in 0.4 ml of DMSO-d_6 was mixed with 0.25 ml of NaOD/D_2O. The final base concentration after mixing was 5.0×10^{-3} M.

D. Determination of the Chemical Shift of Exo and Endo Hydrogens

In the spectra of the bicyclo[3.2.1] ketones the identification of the exo and endo protons was accomplished, ultimately, by the use of a shift reagent. The nmr spectrum of 6,7-benzo-[3.2.1]oct-6-en-3-one (49) in CCl_4 or chloroform did not differ-

entiate between the exo and endo hydrogens. This solvent showed an apparent doublet at 2.30 ppm which integrated for four portons. However, in DMSO-d_6 there was sufficient differentiation between them. There was a pair of doublets centered at 2.73 ppm which integrated for two hydrogens and a broad singlet at 2.42 ppm which also integrated for two hydrogens. The downfield pair of doublets was assigned to the exo hydrogens on the basis of two facts. First, the chemical shift of exo hydrogens is well known to occur downfield from endo hydrogens.[71] Secondly, an examination of Dreiding models of the bicyclo[3.2.1] system in a slightly flattened chair conformation[72] shows that the hydrogen on C_1 or C_5 should be coupled to the exo hydrogen on C_2 or C_4 with a coupling constant of about 3-4 Hz (dihedral angle 30°) while the endo hydrogen has a dihedral angle of approximately 90° resulting in no coupling. A similar assignment was made in the bicyclo[3.2.1]-oct-6-en-3-one (48).

Further, even more convincing evidence was provided by a study utilizing the shift reagent, 2,2,4,4-tetramethylheptane-3,5-dione Europium II complex.



When 6,7-benzobicyclo[3.2.1]oct-6-en-3-one (49) (0.025 g) in 0.25 ml of CCl_4 and 0.050 g of shift reagent were used, the nmr

spectrum (Fig. 18a) showed a shift of the four alpha hydrogens downfield from the remainder of the molecule and also clearly separated the two exo and two endo hydrogens. The assignment was made as before with the pair of doublets (now clearly seen) assigned to the exo hydrogens, while the doublet showing the large geminal coupling was assigned to the endo hydrogens. The endo hydrogen, as can be seen, is now further downfield which is as expected when compared with the analogous t-butyl cyclohexanone.

When the dideuterated ketone spectrum (Fig. 18b) was taken with shift reagent it was clearly seen that the exo hydrogens had been essentially totally deuterated and the endo doublet had collapsed to a singlet as expected.

The nmr spectrum of t-butyl cyclohexanone (0.050 g) with 0.10 g of shift reagent in 0.50 ml of CCl_4 showed a separation of peaks into three groups (Fig. 13a). The upfield peak (9H) t-butyl at 0.32 ppm, a set of peaks (5H) around 2.7 ppm and a multiplet (2H) at 6.64 ppm and a doublet (2H) around 7.66 ppm. The downfield doublet was assigned to the equatorial hydrogens (as recently also shown with an ytterbium shift reagent[73]) while the more highly coupled upfield multiplet was assigned to the axial hydrogens. These highly coupled axial hydrogens have both geminal and diaxial coupling as well as lesser long range couplings. The appearance of the downfield doublet in Figures 18a and 13a shows the similarity of the equatorial cyclohexanone hydrogens with the endo bicyclo[3.2.1] hydrogens. This clearly substantiates the

assignment of the exo and endo hydrogens in the bicyclo[3.2.1] ketone systems.

As seen in the spectrum of the dideuterated t-butyl cyclohexanone the axial hydrogens are greatly diminished while the equatorial doublet has collapsed to a singlet (Fig. 13b). The integration over these signals showed about 5 times as many hydrogens in the equatorial position as in the axial position accounting for a total exchange of about 2.5 hydrogens

VII. SUMMARY

The rates of the base-catalyzed hydrogen-deuterium exchange of three types of bicyclic ketones, namely the [3.2.1], [2.2.2], [2.2.1], and those of two model cyclic ketones, i.e., cyclohexanone and t-butyl cyclohexanone have been determined by means of an nmr method. Examination of the data led to the following conclusions:

(a) The ring strain inherent in certain bicyclic ketones such as bicyclo[2.2.1]heptan-2-one and bicyclo[2.2.1]-hept-5-en-2-one prevents full conjugation of the negative charge and the carbonyl group, thus greatly retarding the rates of hydrogen-deuterium exchange in these systems.

(b) The stereoselective hydrogen-deuterium exchange exhibited by some of the bicyclic and cyclic ketones studied can be explained by the theory of stereoelectronic control, first introduced by Corey.

(c) The extent of homoconjugative stabilization in enolate anions appears to be negligible. On the other hand, weak antihomoaromatic destabilization effects are evident.

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