SMITH, WILLIAM FRANCIS. Transannular Effects in Cage Compounds. The Alcohol-Ketal Exchange Reaction of 3-methoxy-4-oxahexacyclo$[5.4.1.0.^{2,6}0.^{3,10}0.^{5,9}0.^{8,11}]$dodecane. (1974) Directed by: Dr. James C. Barborak. Pp.92

The transannular effects in a homologous series of dimethoxy cage alochols were studied by use of physical methods such as infrared and nmr spectra. It was shown that a pronounced transannular effect occurred in these cage compounds which manifested itself as an increasingly stronger hydrogen bond between the hydroxyl proton and the *endo*-methoxyl oxygen as the number of carbon atoms increases in the C_n bridge. The occurrence of transannular effects in these compounds was also supported by an intramolecular alcohol-ketal exchange reaction and molecular mechanics calculations.

In Part II, an intermolecular acid catalyzed alochol-ketal exchange reaction occurring in the cage compound 3-methoxy-4-oxahexacyclo$[5.4.1.0.^{2,6}0.^{3,10}0.^{5,9}0.^{8,11}]$ dodecane was examined. This reaction proceeded under surprisingly harsh conditions which can be attributed to the generation of a non-planar carbonium ion at the cage site. This reaction may have utility as a means of protecting the alcohol group under very acidic conditions.

Transannular Effects in Cage Compounds.
The Alcohol-Ketal Exchange Reaction
of 3-methoxy-4-oxahexacyclo
$[5.4.1.0^{2,6}0.^{3,10}0.^{5,9}$
$0.^{8,11}]$dodecane

by

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Approved by

James Barborak
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APPROVAL PAGE

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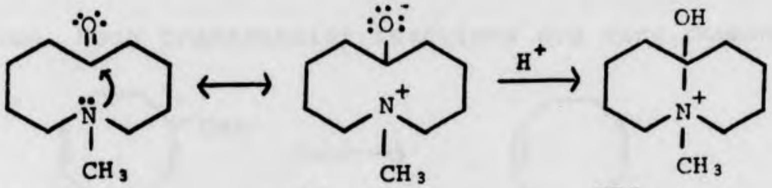
Part I

INTRODUCTION

Transannular effects are a well known phenomenon which have been shown to exist in four to eleven membered rings.[1] These effects are far reaching and can be used to explain such properties as the non-planarity of cyclopentane and cyclobutane. Transannular effects can be divided into two classes, physical and chemical, and can be measured in terms of spectroscopy, dipole moments, heats of hydrogenation, rates of reactions, and X-radiation.[2]

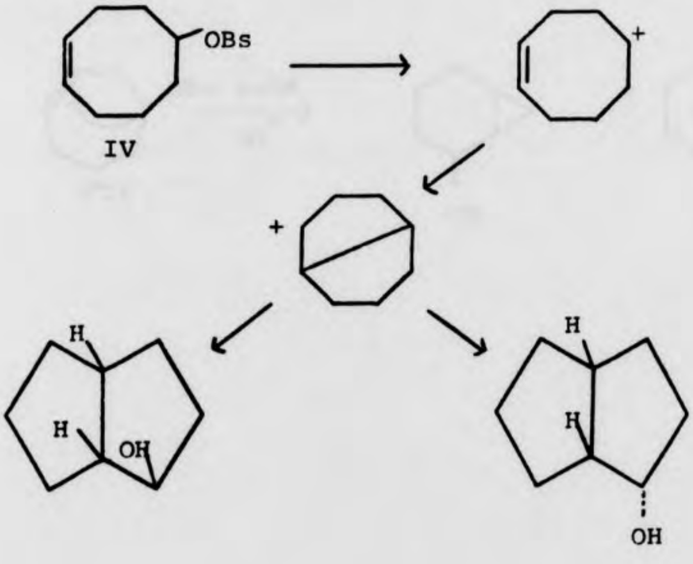
An excellent example of a transannular interaction is shown in the case of 1-methyl-1-azacyclo-6-decanone (I).[3]



I II III

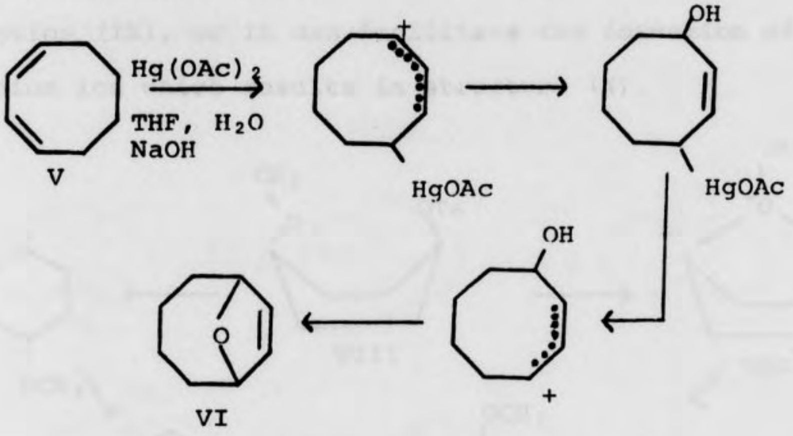
There is a great deal of spectral and dipole evidence which indicates an intense cross-ring interaction between the lone pair of electrons of the nitrogen atom and the adjacent carbon atom of the carbonyl group. This suggests resonance structure II in which there is bonding between the nitrogen and carbon atoms. Protonation of I in fact occurs on the oxygen atom, giving rise to a full transannular bond between the carbon and nitrogen as indicated by structure III.

Transannular reactions are the culmination of intense transannular interactions and have received a great deal of attention in recent years. Transannular reactions are most frequently observed under conditions which favor carbonium ion formation; however, carbene and free radical transannular reactions are known.[4] An example of a transannular reaction proceeding via a carbonium ion mechanism is given in the case of the solvolysis of 4-cyclo-octenylbrosylate (IV).[5] Here a transannular reaction occurs through interaction of the C_1 and C_5 carbon atoms via a carbonium ion mechanism. Molecular models show that the 1 and 5 carbons lie close to each other in this cyclic system. Such transannular reactions are very common.

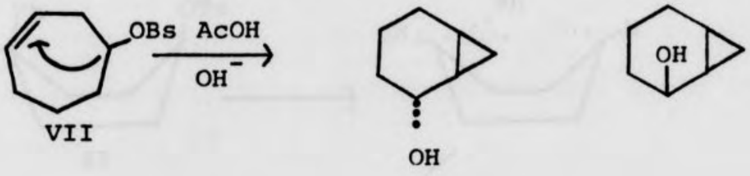


IV

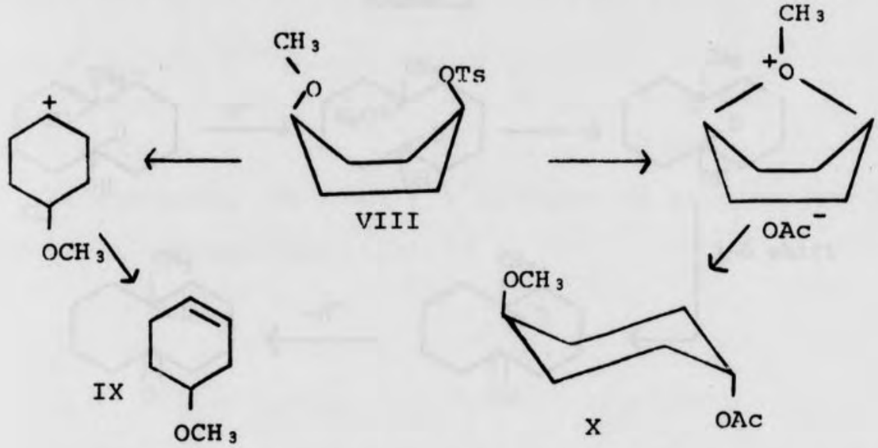
Organometallic mercuration reactions are known to proceed via transannular mechanisms. The major product of the treatment of 1,3-cyclooctadiene (V) is 9-oxabicyclo [4.2.1]non-7-ene (VI).[6]



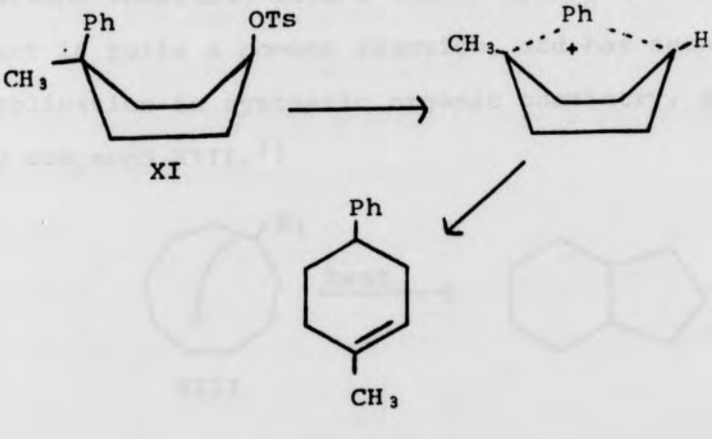
Similarly, compound VII undergoes a transannular carbonium ion reaction.[7] This reaction proceeds via a homoallylic cation.



An excellent example of a transannular effect is seen in the acetolysis of 4-methoxy-cyclohexyl tosylate (VIII).[8] Here the methoxy group can either help stabilize a developing carbonium ion which then undergoes an elimination reaction (IX), or it can facilitate the formation of an oxonium ion which results in structure (X).

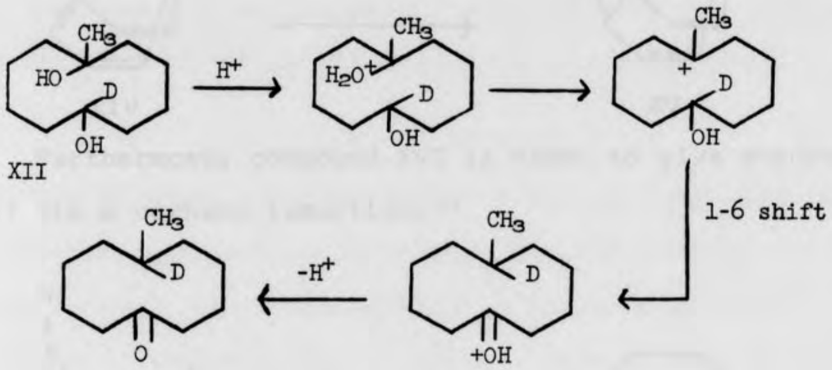


Transannular 1,4-phenyl shifts have been reported in six membered rings (XI).[9]

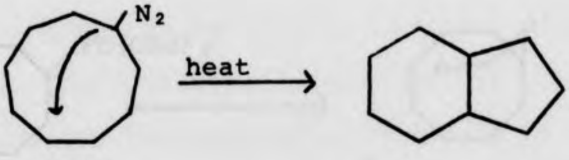


In addition, transannular hydride shifts have been reported as in the case of compound XII. Here a hydride shift is seen across the cyclo-decane ring between the 1 and 6 carbons.[10] This has been demonstrated by the use of a deuterium labeling technique as shown in scheme I.

Scheme I

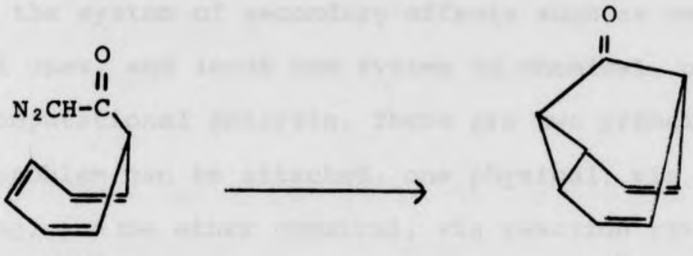


Transannular reactions are also known to proceed via carbene insertion into a carbon-hydrogen bond. This in fact is quite a common reaction, and has seen rather wide application in synthetic organic chemistry, as is indicated by compound XIII.[11]



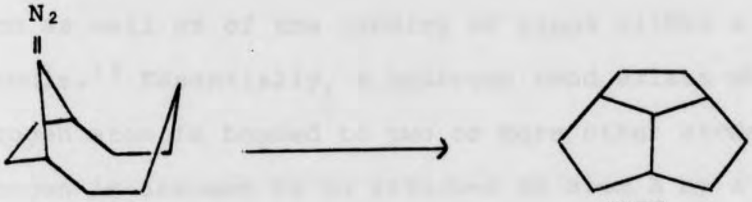
XIII

An excellent example of a transannular carbene insertion is seen by the reaction of cycloheptatrien-7-yl-diazomethyl ketone (XIV) with copper powder to give barbaralone (XV).[12]



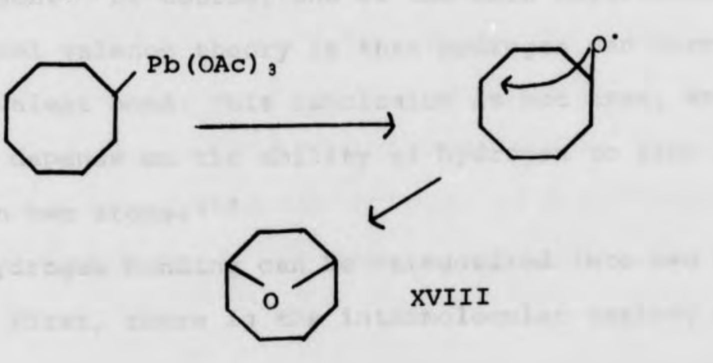
XIV XV

Furthermore, compound XVI is known to give structure XVII via a carbene insertion.[13]



XVI XVII

Radical transannular reactions are also known. The intermediate radical generated from certain Pb-alcoholate esters can attack the H atom in the 4 position to give 1,4-epoxycyclo-octane (XVIII).[14]



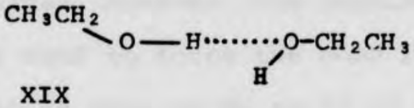
XVIII

It is a primary aim of this thesis to study transannular effects in systems whose geometry is fixed in such a way that the effect is not influenced by a host of variables. Rigidity in the structures chosen for study frees the system of secondary effects such as conformational ones, and lends the system to chemical, physical, and computational analysis. There are two principal ways this problem can be attacked, one physical, via hydrogen bonding, and the other chemical, via reaction rates.

PHYSICAL METHODS

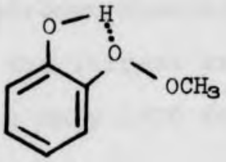
The concept of the hydrogen bond has been most useful in the explanation of many cases of molecular association as well as of the closing of rings within a molecule.[15] Essentially, a hydrogen bond exists when a hydrogen atom is bonded to two or more other atoms. The hydrogen is assumed to be attached to atom A by a normal covalent bond and attached to atom B by a weaker hydrogen bond.[16] It is probably safe to say that hydrogen bonding is essentially an electrostatic attraction between a partial positive hydrogen and an electron-rich atom such as oxygen.[17] Of course, one of the main assertions of classical valence theory is that hydrogen can form only one covalent bond. This conclusion is not true, and "life itself depends on the ability of hydrogen to link itself between two atoms."[18]

Hydrogen bonding can be categorized into two main types. First, there is the intermolecular variety as in the case of ethanol acetic acid (XIX). Here, the hydrogen bond links two separate molecules together to form a dimeric species. The second type of hydrogen bonding is the intramolecular variety. In this case, the hydrogen bond



XIX

exists between two atoms within the same molecule. An excellent example of this is seen in guaiacol where the hydroxyl hydrogen is hydrogen bonded to the oxygen of the adjacent methoxy group (XX).[19]



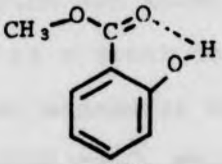
XX

The characteristics of a hydrogen bond, of course, vary from molecule to molecule. There is good reason to believe that hydrogen bonding is much more than simply an exaggerated electrostatic dipole-dipole interaction, because the length of the hydrogen bond indicates considerable overlap of van der Waals radii.[20] A typical hydrogen bond distance is 2.7 angstroms, as in the case of the intermolecular hydrogen bond in formic acid.[21] An intramolecular hydrogen bond occurs usually when the hydrogen of the donor group and the acceptor site is between 1.4 and 2.5 angstroms. It was once thought that hydrogen bonds required linear geometry; however, this requirement is not as stringent as suspected. The hydrogen bond itself is non-directional when looked at from the viewpoint of either an electrostatic attraction or overlap of the spherical 1s orbital. However, the repulsion from the other atoms will tend to force the bond into a linear arrangement if it is free to do so.[22] If one talks about intramolecular hydrogen bonds, then cyclic structures must be mentioned. Hydrogen bond formation is particularly favorable in six membered rings, seven membered rings are known, and five membered rings are rare.[23] There is a case of intramolecular hydrogen bonding consisting of a 16 membered ring, one of the largest known.[24] Hydrogen bonds are very weak, being only 1/20 to 1/50 as strong as the most familiar chemical bonds, and have bond energies of three to seven kilocalories/mole.[25] In most systems capable of intramolecular hydrogen bonding, at least two types of equilibria may be involved, one being the formation of an intramolecular hydrogen bond, the other being the intermolecular association of either of two individual molecules.[26] However, very strongly intramolecularly bonded substances such as methyl salicylate show little if any self-association.

There are a variety of ways to detect and study hydrogen bonding. Recourse has usually been to comparison of such properties as association in non-polar solvents, solubility, melting points, and volatility of analogous compounds.[27] Pauling and Brochway studied hydrogen bonding between formic acid molecules by X-ray diffraction in 1934.[28] Intramolecular hydrogen bonds in phenols were studied by optical methods, while freezing point measurements have been used to demonstrate the degree of association in suspected hydrogen bonded molecules.[29] Intermolecular hydrogen bonding in a chemical system changes the number, mass, shape, and electronic structure of the participants, while intramolecular hydrogen bonds affect only the electronic structure of the molecule.[30]

Probably the two most powerful tools for studying hydrogen bonding are infrared and nuclear magnetic resonance spectroscopy. Most researchers would agree that infrared spectroscopy is the better of the two tools; however, nmr spectroscopy does have some very real advantages. Probably the greatest advantage of infrared is the fact that it is an extremely sensitive tool to very small concentrations. Thus, one can work with small amounts of sample and very low concentration ranges.

One might very well expect infrared to be a good tool in hydrogen bonding studies. Consider the well known case of the strong intramolecular hydrogen bond in methyl salicylate (XXI). The O-H bond is depicted as a vibrating



XXI

spring, with the frequency of vibration proportional to the strength of the spring. The strength of the spring is, of course, related to the electron density centered between the hydrogen and oxygen atom of the hydroxyl group. Now, as the hydrogen bond is formed between the oxygen atom of the carbonyl group and the hydrogen atom of the hydroxyl group, any delocalization of electrons to the carbonyl oxygen forms at the expense of the concentration of electrons in the O-H bond. This can only weaken the O-H bond, thus causing a lowering of its stretching frequency and hence a shift of the infrared spectrum to a lower wave number. These shifts may range from about 30 cm^{-1} to several hundred cm^{-1}.[31] As has already been pointed out, it is acceptable to talk of the hydrogen bond in terms of a delocalization of electrons over the three atoms involved.[32] Indeed, molecular orbital calculations have been made using this assumption. Clearly, then, it is easy to rationalize the importance of infrared spectroscopy to hydrogen bonding studies.

How is a hydrogen bond detected in a molecule? First, molecular models may give some insight into the possibility of a hydrogen bond existing. Then, a comparison can be made between the structure in question and that of other molecules which are known to have hydrogen bonds. In addition, in view of a great deal of previous research, it has been shown that monomeric alcohols and phenols absorb at about 3590 to 3650 cm^{-1}, while hydrogen bonded alcohols and phenols absorb between 3200 and 3600 cm^{-1} with sometimes a broadening of the absorption.[33] The same effect is seen in monomeric and hydrogen bonded carboxylic acids. A good example of this is seen in *o*-nitrophenol which is intramolecularly hydrogen bonded and absorbs at 3350 cm^{-1}.[34] Also, it is well known that vapor state alcohols (essentially no hydrogen bonds) absorb at 3700 cm^{-1}, whereas the pure liquid state is found to absorb at 3400 cm^{-1} (hydrogen bonded).[35]

Thus, if an alcohol in which hydrogen bonding is possible has an absorption in the region of 3200 to 3600 cm^{-1}, this would strongly suggest a hydrogen bond. In addition, if one could collect a series of closely related molecules, which were capable of a hydrogen bond, and whose internal differences were minimal, then a shift in the infrared spectrum of the hydroxyl group would indicate a varying degree of hydrogen bond formation.

Infrared spectroscopy can also distinguish between intermolecular and intramolecular hydrogen bonds, because intermolecular bonds are affected by an increase in concentration, whereas intramolecular bonds are unaffected.

Nuclear magnetic resonance spectroscopy has been used to study such molecular interactions as charge-transfer, dipolar interactions, and hydrogen bonding, and can provide some insight into the details of the mechanisms involved.[36] In addition, hydrogen bonding association constants have been determined as a function of concentration in CCl_4 solutions of methanol and ethanol by the use of nmr.[37] However, the limited sensitivity of nmr spectroscopy impedes its application to dilute solutions or gases.[38] The great advantage of the nmr is that it is sensitive to very weak hydrogen bonding interactions which may be very difficult to detect by infrared spectroscopy. For example, the existence of a weak hydrogen bond between the hydrogen atoms of the methyl groups in dimethylacetylene and toluene and the oxygen atoms of alkoxy groups underlines the sensitivity of proton chemical shifts to very weak specific interactions.[39]

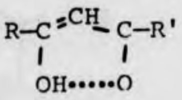
Thus it can be seen how the nmr would be sensitive to a hydrogen bonding effect. If we consider a hydrogen bonded system (XXII), the formation of a hydrogen bond (A---H) most certainly modifies the electron density around the proton and hence its shielding. If A is an

A---H——B

XXII

electronegative atom such as oxygen, electron density would be expected to decrease around the hydrogen atom, or in other words, the hydrogen atom is deshielded. This causes a displacement downfield due to a hydrogen bond formation.[40] The nmr can, like the infrared, differentiate between intramolecular and intermolecular hydrogen bonds. As might be predicted, nmr is insensitive to concentration for an intramolecular hydrogen bond. In addition, nmr is also insensitive to temperature on thermodynamic grounds for an intramolecular bond.[41]

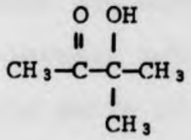
Nuclear magnetic resonance has been used as a measure of hydrogen bond strength in studying hydrogen bonding in beta-diketones (XXIII).[42] The hydrogen bonding exists between the hydroxyl hydrogen and the oxygen atom of the carbonyl group. As increasingly larger "R" groups are substituted into the enol and the shift of the hydroxyl proton noted, it is found that as the "R" groups increase in size, the hydroxyl proton signal is shifted downfield. Evidently, as the "R" groups become bulkier, they force the carbonyl group and the hydroxyl group closer together forming a stronger hydrogen bond. This is entirely reasonable and demonstrates the significance of the downfield shift as a measure of the strength of the hydrogen bond.



XXIII

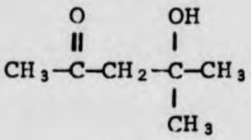
Another example of nmr as a measure of hydrogen bond strength was performed by Cronan.[43] He studied the intramolecular hydrogen bonding in ketones as given by structures XXIV and XXV. Clearly, one would predict that hydrogen bonding would be stronger in structure XXIV due to the hydroxyl proton and carbonyl group being much closer to one another. This would mean that the OH signal should appear further downfield. This is in fact the case.

The chemical shift of the hydroxyl proton is 242 Hz (from TMS) and 235 Hz for XXIV and XXV respectively.



$$CH_3-\overset{\overset{O}{\|}}{C}-\underset{\underset{CH_3}{|}}{\overset{\overset{OH}{|}}{C}}-CH_3$$

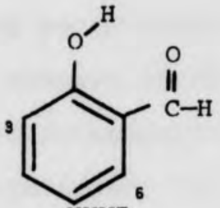
XXIV



$$CH_3-\overset{\overset{O}{\|}}{C}-CH_2-\underset{\underset{CH_3}{|}}{\overset{\overset{OH}{|}}{C}}-CH_3$$

XXV

A further example of the nmr as a hydrogen bond tool is seen in the case of salicylaldehyde (XXVI).[44] It is found that the downfield shift is greater with substituents in the six position rather than in the three position. Upon examination, this is reasonable because of the greater steric interaction between the hydroxyl group and the substituents.



XXVI

An examination of Drieding models reveals that the distance between a methyl group and the hydroxyl group is 2.2 angstroms. The distance between the methyl and aldehyde proton is 1.6 angstrom. Thus, groups in the six position are capable of forcing the carbonyl group closer to the hydroxyl, causing a downfield shift. In addition, H-bonding is greater with methyl than methoxy substituents, due to the greater effective size of the methyl group, as the preferred orientation of the methoxy group has the O-CH_3 bond directed away from neighboring substituents.

There has been extensive use of the nmr in studying intramolecular hydrogen bonding. The basic idea that the downfield shift of the hydrogen bonded proton is a measure of hydrogen bond strength has many cases which correlate fact and theory. This method of studying hydrogen bonds, coupled with infrared methods, has been employed in the present work.

CHEMICAL METHODS

Transannular effects can be studied by means other than physical methods such as hydrogen bonding. Chemical methods can be employed such as measuring the rate of a reaction which may be influenced by transannular effects.

The classic example of this is the acetolysis of anti-7-norbornenyl toluenesulfonate (XXVII) and 7-norbornyl toluenesulfonate (XXVIII).[45]

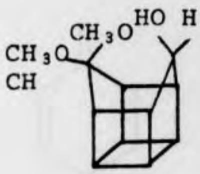
XXVII

XXVIII

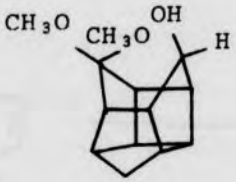
XXIX

The anti-7-tosylate is solvolyzed over a billion times faster than its saturated analog. The explanation for this difference in reaction rate is the transannular participation of the "pi" cloud of the double bond with the developing charge of the carbonium ion. The "pi" cloud delocalizes the charge and thereby stabilizes the resulting carbonium ion, thus serving to increase the rate of reaction (XXIX).

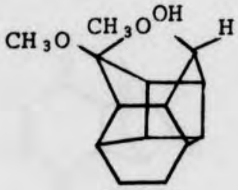
In attempting to study transannular effects in ring systems, the use of rigid structures is highly desirable. This greatly limits the number of variables to be considered, such as conformational ones, and lends itself to a more direct approach to the study of transannular effects. To this end, a major portion of the laboratory research covered by this work was devoted to the attempted synthesis of a series of dimethoxy cage alcohols (XXX-XXV). The



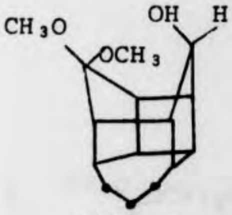
XXX



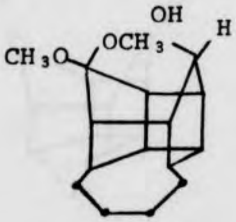
XXXI



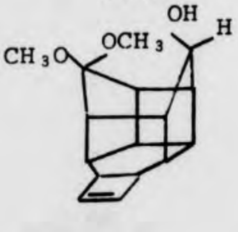
XXXII



XXXIII

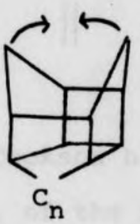


XXXIV



XXXV

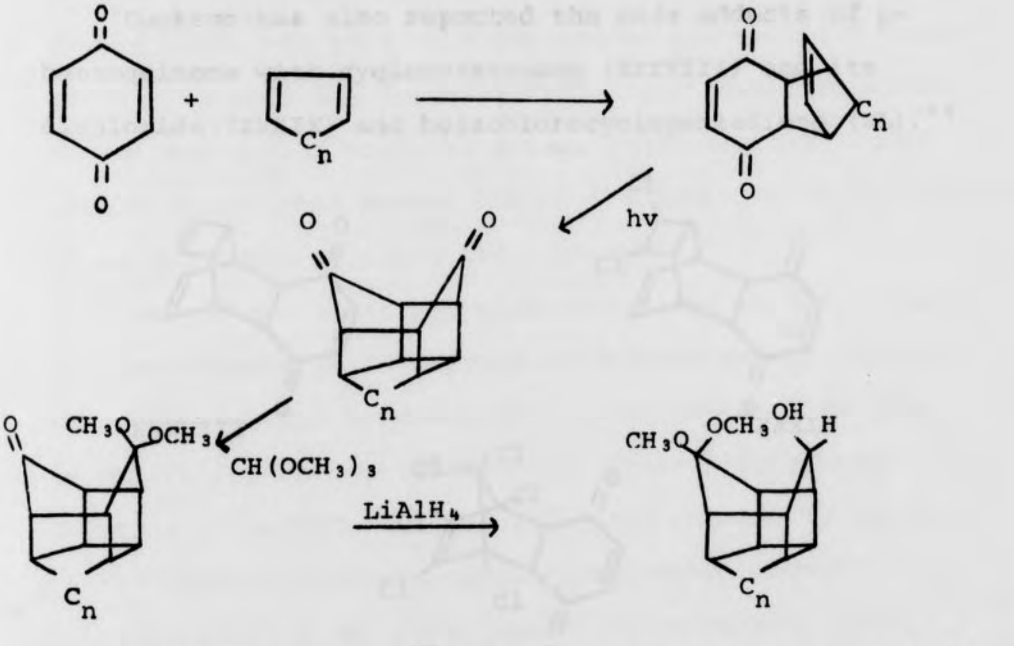
rigidity of these structures is apparent, and it is the transannular effects occurring between the 1-2 methylene carbons (see Appendix) to which this thesis is directed (XXXVI). These effects will be studied as carbon atoms are inserted into the C_n position of the cage skeleton (see Appendix for an explanation of the C_n notation), (XXXVI).



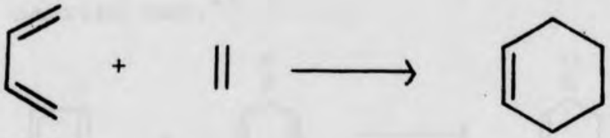
XXXVI

The synthesis of the C_n series of dimethoxy cage alcohols followed the general reaction sequence given below (scheme 2).

Scheme 2



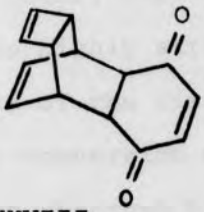
The first step of the synthesis is a rather straightforward Diels-Alder reaction of a conjugated diene (XXXVII) with a dienophile to give a cyclic six membered olefin. Diels-Alder reactions of this general type are extremely



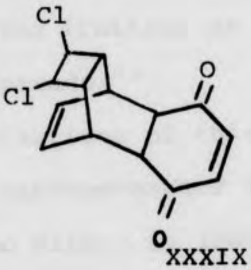
XXXVII

well known. R.C. Cookson has reported the specific case, used in this work, of the reaction of *p*-benzoquinone with cyclopentadiene ($C_n=1$), and 1,3 cyclohexadiene ($C_n=2$).[46] The reaction was first observed, however, in 1906 by Albrecht, but he misassigned the structure.[47] It has been well established that the *endo* adduct is produced as the major product.

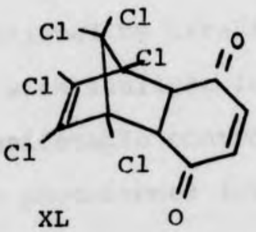
Cookson has also reported the *endo* adducts of *p*-benzoquinone with cyclooctatraene (XXXVIII) and its dichloride (XXXIX) and hexachlorocyclopentadiene (XL).[48]



XXXVIII

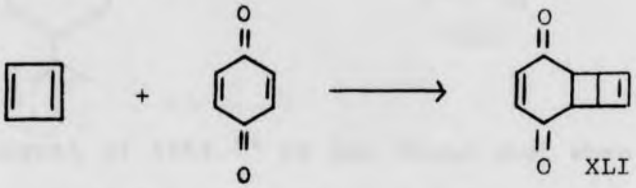


XXXIX



XL

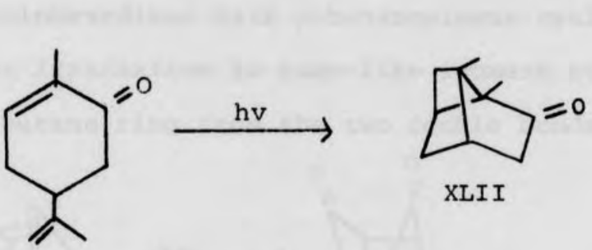
Furthermore, the Diels-Alder reaction of *p*-benzoquinone with cyclobutadiene (C_n=0) to give the C_o adduct has been carried out.[49]


XLI

The second step in the synthesis is less familiar than the previous Diels-Alder reaction. This involves the intramolecular isomerization of the C_n Diels-Alder adduct to its corresponding cage compound. It is quite reasonable to expect that if two double bonds were close enough to each other in an organic molecule, and if one of the double bonds was part of a conjugated system which would serve to absorb the incoming radiation, then interaction of the two double bonds to give a photochemical isomer should occur. This method has proven fruitful as a synthetic route to highly strained cage compounds.[50]

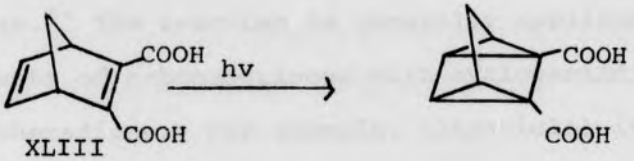
One of the first photoisomerizations of this nature was the conversion of carvone to carvonecamphor (XLII). This was observed by Ciamician and Silber in 1908. The isomerization was achieved by irradiating an alcohol solution of carvone with sunlight for periods up to one year.[51] However, considerable controversy reigned over the structure of the photoisomer for quite some time.

Probably the first authentic report of an intramolecular photoisomerization was reported by Cristol and



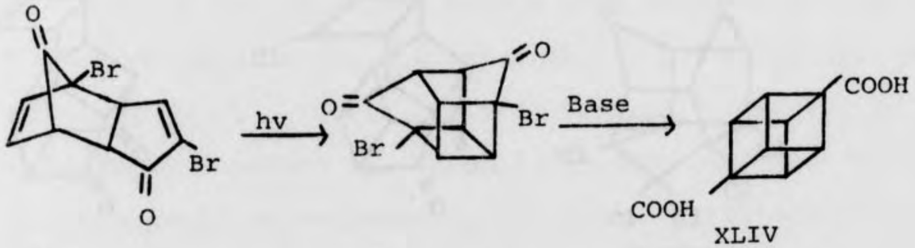
XLII

Snell in August of 1954.[52] It was found that when a solution of bicyclo[2.2.1.]heptadiene-2,3-dicarboxylic acid (XLIII) in absolute ether was irradiated for 8-12 hours a photoisomerization occurred.



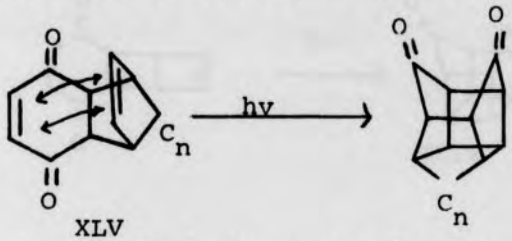
XLIII

The first tactical synthesis of the cubane carbon skeleton (XLIV) was achieved by Eaton in 1964 in another example of an intramolecular cyclization reaction to achieve a cage precursor of cubane.[53]



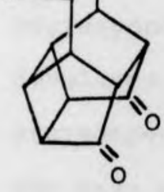
XLIV

In the synthesis of the dimethoxy alcohols to be used in this work, the *endo* adducts of cyclopentadiene and 1,3-cyclohexadiene with *p*-benzoquinone cyclize on ultraviolet irradiation to cage-like isomers by formation of a cyclobutane ring from the two double bonds (XLV).

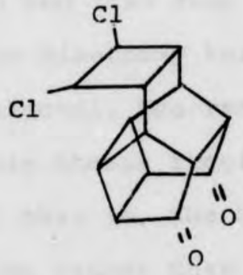


XLV

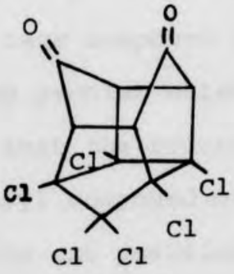
There is little doubt as to the formation of the cage skeleton, as the high stretching frequency of the carbonyl group is consistent with its absorption in strained cyclopentanones.[54] The reaction is generally applicable to *endo* adducts of *p*-benzoquinone with cyclopentadiene or 1,3-cyclohexadiene. For example, ultraviolet irradiation converts, into exactly analogous cage isomers, the adducts of benzoquinone with cyclooctatraene (XLVI) and its dichloride (XLVII) and hexachlorocyclopentadiene (XLVIII).[55]



XLVI

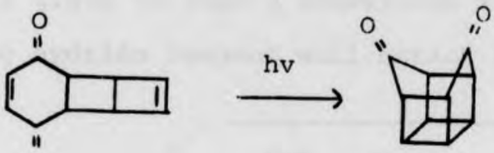


XLVII



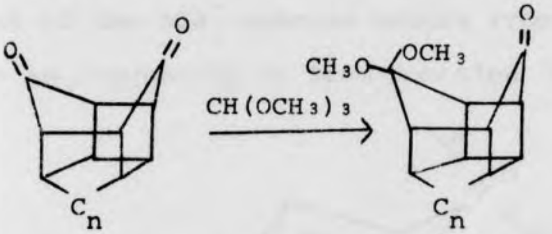
XLVIII

Similarly, the adduct of cyclobutadiene and *p*-benzoquinone yields the expected cage compound (XLIX).[56]



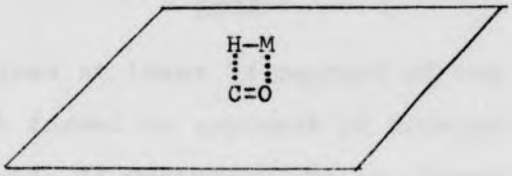
XLIX

The third step in the reaction sequence is the formation of the cage ketal (L) from the reaction of the cage dione with trimethylorthoformate. This is a general method for the preparation of ketals involving an exchange reaction of ketones with alkyl orthoformates.[57]



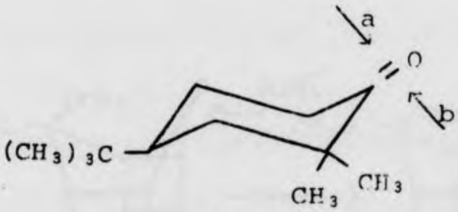
L

The fourth and last step in the synthesis is the reduction of the dimethoxy ketone cage compound to its corresponding alcohol. The research problem which will be developed in this thesis requires that the reduction be stereospecific; that is, the hydroxyl compound must be in the *endo* position rather than in the *exo* position. This problem is not as overwhelming as might first be expected. Lithium aluminum hydride reductions have been known to be considerably stereospecific under optimum conditions. The reacting species in lithium aluminum hydride is the AlH_4^- ion (probably polymeric). This species attacks a planar carbonyl group to form a transition state (LI).[58] The incoming hydride reagent will attack the planar carbonyl



LI

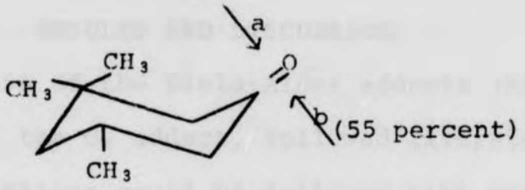
group from its least hindered side. An excellent example of this steric hindrance is seen in the case of the reduction of 2,2-dimethyl-4-*t*-butyl cyclohexanone (LII).[59] Attack of the AlH_4^- species occurs from position "a" 20 times as frequently as from position "b." This is due to



LII

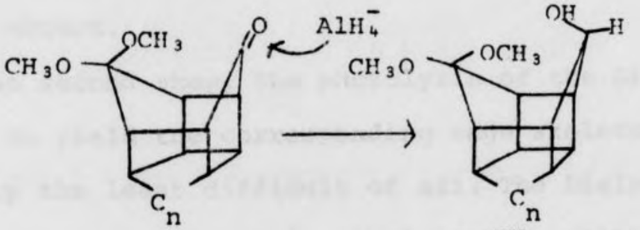
hindrance from the two methyl groups which restrict attack from position "b." Conversely, in the case of 3,3,5-trimethylcyclohexanone (LIII), it is observed that 55 percent of the yield is due to attack from side "b" in this case.

A striking case of steric hindrance is found in the 11-keto steroids whose reduction with lithium aluminum



LIII

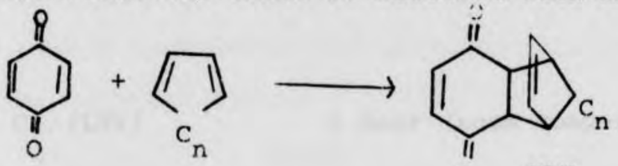
hydride gives at least 78 percent of the less stable 11-beta-ol formed by approach of hydride from the less hindered side.[61] Certainly, in the dimethoxy ketones to be synthesized in the present work, the two methoxy groups and the large cage structure itself provide a formidable example of steric hindrance (LIV). This would leave only an outside approach available to an incoming AlH_4^- species, yielding the *endo* alcohol (LV).



LV

RESULTS AND DISCUSSION

The synthesis of the Diels-Alder adducts (XLV), with the exception of the C_3 adduct, followed literature procedures. The reactions could be followed with nmr.



XLV

The most interesting aspect of this synthetic problem was the rates of adduct formation (Table 1).

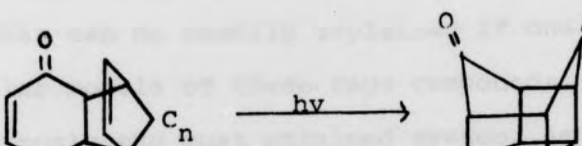
This decrease in the rate of Diels-Alder reactions can be adequately explained in terms of the relative energy of reactants and products. As expected, the C_0 reaction goes with the greatest facility due to its great internal strain and antiaromatic character, while 1,3-cyclooctadiene fails to react because of excessive strain in the adduct.

The second step, the photolysis of the Diels-Alder adduct to yield the corresponding cage skeleton (LX), was probably the least difficult of all. The Diels-Alder adducts were photolyzed in ethyl acetate using a quartz photolysis apparatus with a pyrex filter and a Hanovia 450 watt medium pressure lamp. The reaction was followed by nmr, by noting the disappearance of the olefinic peaks of the adduct. The cage skeletons for C_0, C_1, C_2, C_3, and C_x were readily obtained in this manner.

TABLE 1

Rates of Diels-Alder Reactions

Diene	C_n Notation	Approximate reaction time for a 60 percent yield
	C_0 (XLI)	20 minutes (0°C)
	C_1 (LVI)	1 hour (room temperature)
	C_2 (LVII)	24 hours (55°C)
	C_3 (LVIII)	2.5 weeks (80°C)
	C_4 (LIX)	no reaction
	C_x (XXXVIII)	4 hours (130°C)



LX

One interesting aspect of this step relates the nmr's of these photolysis compounds and the resulting strain induced into the cage skeleton. One interpretation of nmr is that bond strain shifts nmr spectra downfield.[62] Therefore, one might expect a reduction in the maximum chemical shift (from TMS) in going from the C_0 to the C_3 cage skeleton. This correlates directly with the amount of strain energy in each of the systems. This can be seen by reference to Table 2.

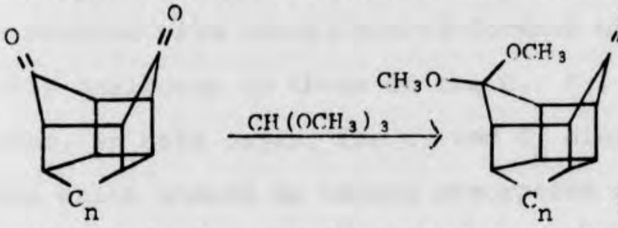
TABLE 2

Maximum Chemical Shift Observed in Cage Compounds

Cage Compound	Maximum Chemical Shift Observed (ppm downfield from TMS)
C_0 (XLIX)	3.7 ppm
C_1	3.3 ppm
C_2 (LXII)	3.0 ppm
C_3 (LXIII)	3.3 ppm
C_x (LXVI)	3.1 ppm

The cage skeleton with the highest downfield absorption (most strained bond) is C_0 with δ 3.7. The C_1 compound sees a reduction to δ 3.3, while C_2 recedes to δ 3.0. This can be readily explained if one refers to molecular models of these cage compounds. The C_0 system is obviously the most strained system. As a carbon atom is inserted into the C_n position of the cage, bond strain is reduced. Additional reduction in bond strain is noted for the insertion of a second carbon atom into the C_n position. With theinsertion of a third carbon in a molecular model, the cage skeleton itself is severely distorted and bond strain is increased. This could explain the sudden rise in the maximum downfield absorption for the C_3 compound. A molecular model will show that the degree of strain in the C_x compound approaches that of the C_2 compound. Consequently, it is seen that, experimentally, the C_0 compound is the most strained system (highest maximum chemical shift), while the C_2 compound has the least strain (lowest maximum chemical shift).

The formation of the C_0, C_1, and C_2 monoketals was very straightforward, going without incident. The cage diketone was simply stirred overnight with a 5 percent excess of trimethylorthoformate in methanol to give the monosubstituted ketal (L). This was evidenced by methoxy



L

absorptions in the nmr and a strong carbonyl absorption in the infrared. The reluctance of the dione to form the diketal could be attributed to the steric hindrance due to formation of the first ketal group.

An interesting point is demonstrated by Table 3. The chemical shift between the two ketal methoxy groups becomes increasingly smaller in proceeding from the C_0 compound to the C_2 compound. Eventually, the difference in the chemical shift is not discernible for the C_2 compound,

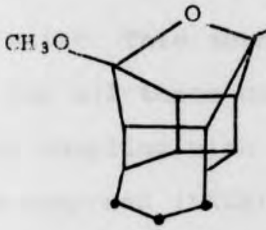
TABLE 3

Chemical Shift Difference between the Methoxy Groups in Cage Dimethoxy Ketones

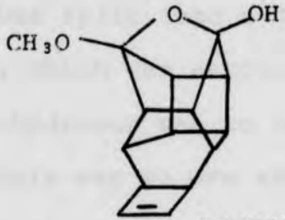
Cage Dimethoxy Ketone	Chemical Shift of Methoxy Groups (from TMS)	Change in Chemical Shift between Groups
C_0 (LXIV)	196 Hz, 189 Hz	7 Hz
C_1 (LXV)	187 Hz, 183 Hz	2 Hz
C_2 (LXVI)	188 Hz	0 Hz

and the two methoxy groups appear as one absorption. The explanation for this observation is not obvious.

While the synthesis of the C_0, C_1, and C_2 dimethoxy ketones was straightforward, the synthesis failed for the C_3 and C_x compounds at this point. The C_3 and C_x compounds were reacted with trimethylorthoformate under conditions exactly analogous to those of the C_0, C_1, and C_2 diones. However, in both cases, the C_3 and C_x diones gave compounds which showed no ketone absorption in the infrared, but showed a pronounced but broad alcohol absorption at 3360 cm^{-1} for the C_3 compound and 3350 cm^{-1} for the C_x compound. The nmr's of these compounds showed a sharp methoxy singlet at δ 3.5 for C_3 and C_x, representing three hydrogen atoms. There was also a single intense lower field peak, equivalent to one hydrogen at δ 4.6 for C_x and δ 4.2 for C_3. This peak varied in position with the concentration of the nmr sample. All evidence, in addition to elemental analysis data, points to formation of mixed ketals of the sort given by structures LXVII and LXVIII. All attempts to synthesize the dimethoxy ketones for C_3 and C_x were fruitless. A variety of reaction conditions were tried, including the use of trimethylorthoformate as the reaction solvent. Mixed ketals (LXVII and LXVIII) were obtained as the only isolable products.

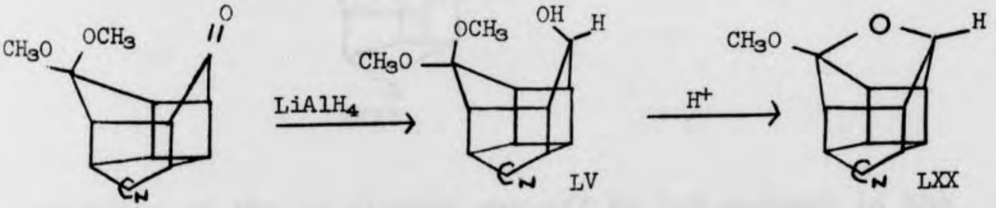


LXVII

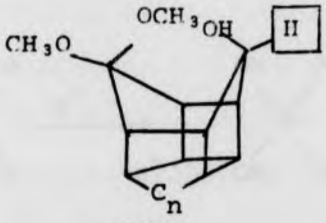


LXVIII

Finally, the reduction of the three dimethoxy ketones (C_0, C_1, and C_2) with $LiAlH_4$, in diethyl ether, provided the corresponding *endo* dimethoxy alcohols (LV). The reaction proceeded smoothly provided care was taken to avoid acidic conditions which caused a closure reaction.

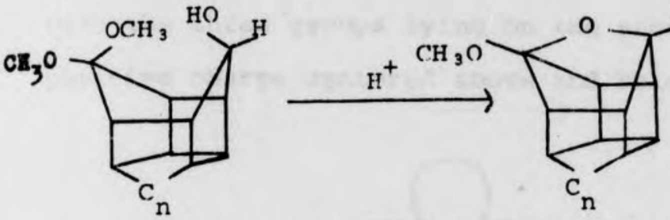


The structural evidence for these alcohols was based on nmr and infrared spectroscopy, and elemental analysis. In the infrared spectra, intense alcohol absorptions were obtained with the disappearance of the ketone absorption for all three alcohols. In the nmr, it was expected that since the alcohol was in the *endo* position, the magnetic field experienced by the two methoxy groups would be very different, giving rise to two separate methoxy absorptions for each of the three compounds. This was, in fact, observed for all three compounds. In addition, a hydroxyl proton should have been seen downfield in all cases and did exist. This absorption was split into a doublet in the nmr for all three compounds, which was entirely reasonable, since coupling with the *exo*-hydrogen was to be expected in this compound (LXIX). That this was so was shown by deuterium substitution in this position, which resulted in the hydroxyl signal being reduced to a sharp singlet. The elemental analyses of the C_1 and C_2 dimethoxy alcohols were consistent with those compounds. The elemental analysis of the C_0 alcohol was off by 0.8 percent in the hydrogen analysis, probably due to difficulties encountered in purification of the alcohol.



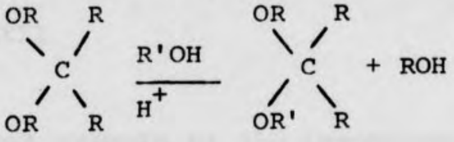
LXIX

Another piece of convincing evidence for the compounds lies in the transannular alcohol-ketal exchange reaction of the dimethoxy alcohols to provide the corresponding closure products (LXX).



LXX

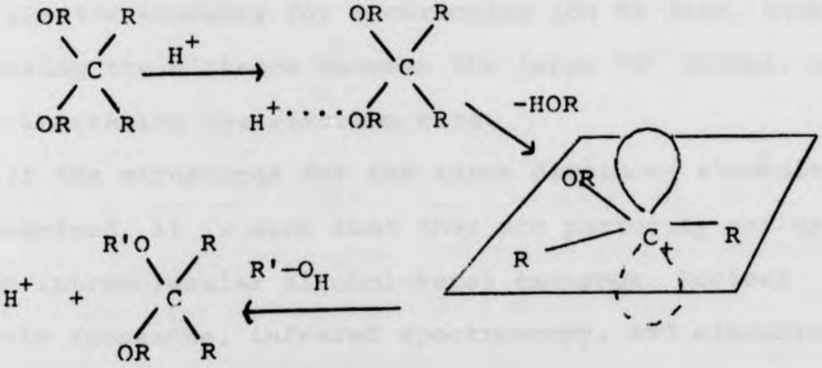
Exchange reactions of this type are well known and take place between a ketal (LXXI) and an excess of alcohol with acid catalyst. These reactions usually proceed very



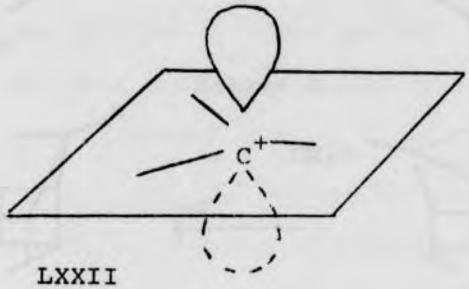
LXXI

rapidly and there is a wealth of evidence to indicate a carbonium ion mechanism (Scheme 3).[63]

Scheme 3



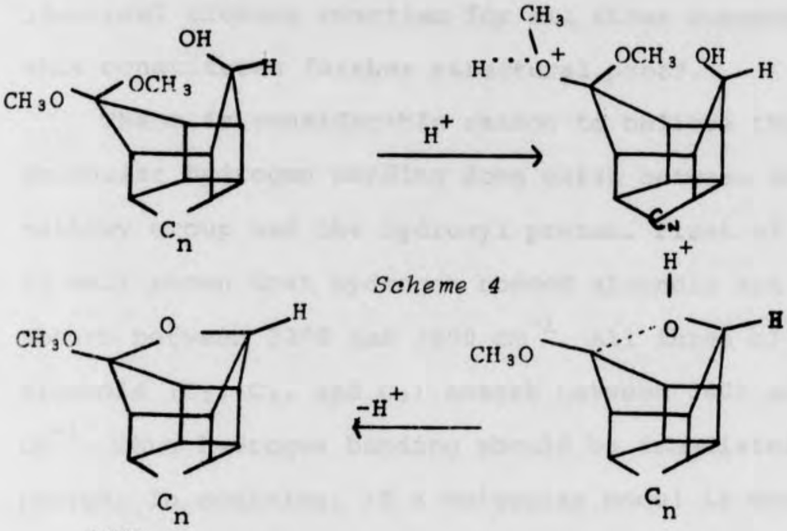
The usual factors which govern carbonium ion mechanisms can be expected to control these reactions. One such factor which is of paramount importance is the ability of the carbonium ion to achieve a trigonal planar structure with the three groups lying on the same plane and the positive charge centered above and below the plane (LXXII).



LXXII

An excellent example of the importance of carbonium ion effects is seen in the work of Kreevoy and Taft.[64] It was found that the rate of carbonium ion generation in ketal hydrolysis depends on the size of the "R" group of the carbonium ion. As the "R" groups get bulkier, there is a greater tendency for a carbonium ion to form, thus increasing the distance between the large "R" groups, and hence increasing the reaction rate.

If the structures for the three dimethoxy alcohols are examined, it is seen that they are perfectly set up for an intramolecular alcohol-ketal exchange. Nuclear magnetic resonance, infrared spectroscopy, and elemental analysis show that this reaction does indeed take place for all three dimethoxy alcohols. As expected, this would proceed via a carbonium mechanism to yield the closure product (LXX) (Scheme 4).



Scheme 4

LXX

The nmr spectrum of the C_1 closure product shows a very characteristic absorption due to the *exo*-hydrogen atom attached to the methylene carbon of the cage skeleton (Fig. 1). The acid catalyzed reaction products of both the C_0 and C_2 compounds show remarkably similar absorptions in the same nmr region. This absorption (Fig. 1) was followed by a single methoxy absorption in the nmr at approximately δ 3.1 in all cases. In addition, the alcohol absorption in the infrared spectrum disappeared for all

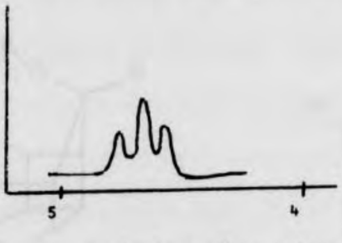
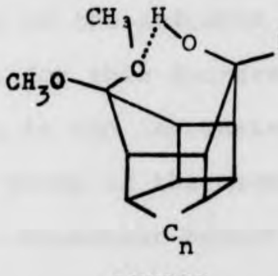


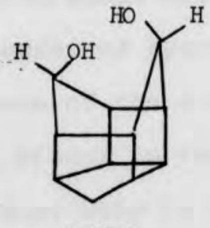
Fig. 1. The nmr triplet for closure products.

three compounds as closure took place. This suggests an identical closure reaction for all three compounds, and thus constitutes further structural proof.

There is considerable reason to believe that intramolecular hydrogen bonding does exist between the *endo* methoxy group and the hydroxyl proton. First of all, it is well known that hydrogen bonded alcohols and phenols absorb between 3200 and 3600 cm^{-1}. All three of the cage alcohols (C_0, C_1, and C_2) absorb between 3400 and 3500 cm^{-1}. Thus hydrogen bonding should be immediately suspected. In addition, if a molecular model is examined, it is seen that the oxygen atom of the *endo* methoxy group and the hydroxyl proton are in an ideal position to form a seven membered cyclic hydrogen bond (LXXIII). In addition, it has been shown that one of the strongest known hydrogen bonds exists in structure LXXIV.[65]



LXXIII



LXXIV

Probably the best evidence of an intramolecular hydrogen bond is seen in the infrared data collected from a 0.375 M cage alcohol solution in carbon tetrachloride (Table 4). There is a decided shift to lower wave numbers as the length of the C_n bridge is increased. This would

TABLE 4

Hydroxyl Infrared Absorptions (cm^{-1}) of the C_0, C_1, and C_2 Cage Alcohols

Cage Compound	Concentration	Alcohol Absorption
C_0 (XXX)	0.375 M	3465 cm^{-1}
C_1 (XXXI)	0.375 M	3455 cm^{-1}
C_2 (XXXII)	0.375 M	3445 cm^{-1}

indicate a higher degree of hydrogen bond formation as one proceeds from the C_0 to the C_2 cage compound. Intermolecular hydrogen bonding may be eliminated since the absorptions were concentration independent for all three alcohols. A feasible explanation for the alteration of the hydroxyl bond, then, is a hydrogen bond which forms at the expense of the oxygen-hydrogen bond of the hydroxyl group, thereby weakening it, and shifting its absorption to lower wave numbers in the infrared spectrum. One model which would account for this increase in the degree of hydrogen bonding is the increasing convergence of the 1-2 methylene carbon atoms of the cage as the C_n bridge is increased in length. Molecular models indicate that this is in fact the case.

Another convincing piece of evidence is the nmr data for equal concentrations of a carbon tetrachloride solution of each of the three cage alcohols (Table 5). It is seen that the hydroxyl proton is shifted further downfield as carbon atoms are inserted into the C_n position. This

TABLE 5

Hydroxyl nmr Absorptions (Hz from TMS) of the

C_0, C_1, and C_2 Cage Alcohols

Cage Compound	Concentration	Chemical Shift (from TMS)
C_0 (XXX)	0.635 M	268 Hz
C_1 (XXXI)	0.635 M	287 Hz
C_2 (XXXII)	0.635 M	322 Hz

clearly supports the idea of the 1-2 methylene carbons of the cage converging upon one another. A downfield shift of the hydroxyl hydrogen would be expected as it experiences the increased deshielding effect of the converging oxygen atom of the *endo*-methoxy group. In addition, nmr supports the concept of an intramolecular hydrogen bond. A downfield shift in the hydroxyl signal should appear as the methylene carbons converge, and the hydroxyl proton, closer to the methoxy oxygen, is in a better position to hydrogen bond. The hydrogen bond will deshield the proton and shift the signal downfield.

A third piece of evidence which will support the idea of the cage methylene carbons converging upon one another is molecular mechanics (force field) calculations.[66] The worth of these calculations has been shown in their ability "to estimate the structures and enthalpies of molecules with a degree of accuracy rivaling that of experimental methods."[67] Such quantities as bond lengths, bond angles, heats of formation, and relative strain are calculated with a remarkable degree of accuracy. It is concluded by molecular mechanics advocates that "in principle, molecular mechanics must be considered to be competitive with experimental determination of the structures and enthalpies of molecules."[68] The results of the molecular mechanics calculations for the C_0, C_1, and C_2 hydrocarbons are given in Table 6. It is clearly shown that the methylene carbons converge on one another as carbon atoms are inserted into the C_n position.

TABLE 6

Molecular Mechanics Calculations on the

C_0, C_1, and C_2 Hydrocarbon Skeletons

Cage Hydrocarbon	Relative Strain	Heats of Formation Kcal/mole	Distance between *Endo* Methylene H atoms (angstrom)	Distance between 1-2 Methylene C atoms (angstrom)
C_0 (LXXV)	87.89	60.35	2.353	2.784
C_1 (LXXVI)	52.29	19.62	2.254	2.751
C_2 (LXXVII)	52.90	15.10	2.150	2.705

In summary, then, the three dimethoxy cage alcohols have been synthesized. All three of these compounds readily underwent similar transannular, alcohol-ketal exchange reactions to form their respective closure products. There was a wealth of evidence which pointed to the formation of an intramolecular hydrogen bond in the three dimethoxy cage alcohols. This hydrogen bond was intensified as carbon atoms were inserted into the C_n

position of the dimethoxy alcohols. This led to the conclusion that the methylene carbon sites of the cage converge on one another as increasing numbers of carbon atoms are inserted into the C_n position. These results are supported by molecular mechanics calculations.

EXPERIMENTAL

All nmr spectra were run on a Varian T-60 nmr. Infrared data were obtained on a Perkin Elmer 457 grating spectrophotometer using Beckman NaCl cells. A limited number of infrared spectra were run on a Beckman R-54 spectrophotometer. Melting points were obtained by using a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories of Knoxville, Tennessee.

Synthesis of cis-3,4-dichlorocyclobutene[69]

"Dry chlorine gas is admitted into a solution of 104 g of cyclooctatetraene and 150 ml of dry carbon tetrachloride contained in a tared 500 ml three-necked flask equipped with a gas inlet tube, a low-temperature thermometer, and a calcium chloride drying tube. The reaction mixture is maintained between -28° and -30°C throughout the addition, which is then terminated after 71 g of chlorine has been added. After the addition, which takes approximately one hour, the reaction mixture is allowed to warm to 0°C and 50 g of powdered sodium carbonate is added and the contents then shaken gently for several minutes. This treatment removes any HCl which may have been produced during the reaction. The mixture is then filtered directly into a 1-liter round bottomed flask containing 135 g of dimethyl acetylenedicarboxylate. A condenser is fitted to the flask and the solution is heated at gentle reflux for three hours. The solvent is then removed under reduced pressure. The crude Diels-Alder adduct, which will slowly solidify on standing, is used directly in the next step.

"The crude Diels-Alder adduct is transferred to a 500-ml pressure-equalizing dropping funnel which is attached to a 1-liter three-necked round-bottomed flask; the latter is immersed in an oil bath maintained at 200°C and is equipped with a distillation head, condenser, and receiving flask. The pressure inside the equipment is reduced to 20 mm. A magnetic stirrer in the pyrolysis flask is started, the Diels-Alder adduct is then added slowly to the hot flask and the pyrolysate collected in the receiving flask. The distillation temperature during the pyrolysis varies from 135° to 152°C, depending on the rate of addition of the Diels-Alder adduct. After the addition is complete, the pyrolysate is then redistilled at 12-15 mm, all the material boiling below 140°C being collected; this distillate consists mainly of a mixture of dichlorocyclobutene and 1,4 dichlorobutadiene, the residue being mainly dimethylphthalate. A final distillation in which the fraction boiling at 70-71°C at 55 mm yields 49-52 g of pure *cis*-3,4-dichlorocyclobutene. The forerun consists mainly of 1,4-dichlorobutadiene."

Synthesis of Cyclobutadieneiron Tricarbonyl[70]

"In a well-ventilated hood a 500 ml three-necked flask is immersed in an oil bath and fitted with a condenser and a mechanical stirrer, a T-piece is inserted through a rubber stopper placed in the top of the condenser, one lead of the T-piece being connected to a nitrogen supply and the other to a gas bubbler. *Cis*-3,4-dichlorocyclobutene, 20 g, and 125 ml of anhydrous benzene are added to the flask and the apparatus is flushed with nitrogen. Diiron enneacarbonyl, 25 g, is then added, the flow of N_2 is stopped, and the mixture is heated to 50-55°C with stirring. After about 15 minutes, the initial rapid evolution of carbon monoxide becomes greatly diminished and a further 8 g of $Fe_2(CO)_9$ is added. Additional 8-g quantities of $Fe_2(CO)_9$ are added at intervals governed by the rate of carbon monoxide evolution. The addition is continued until no more carbon monoxide is liberated and the reaction mixture stirred at 50°C for an additional hour. Approximately 140 g of $Fe_2(CO)_9$ is required for the complete conversion of the dichlorocyclobutene, the total reaction time being about six hours.

"The contents of the flask are then filtered with suction through Celite and the residue, while kept in the Buchner funnel, is thoroughly washed with pentane until the washings are colorless. The pentane and much of the benzene are evaporated from the combined filtrates by means of a water aspirator.

"The residual liquid is then transferred to a flask equipped with a fairly efficient fractionating column and distilled under reduced pressure. Benzene is removed first followed by considerable quantities of iron pentacarbonyl; when the $Fe(CO)_5$ has been removed, the pressure is reduced further and cyclobutadieneiron tricarbonyl is collected as a pale yellow oil, b.p. 47°C at 3 mm. The yield is approximately 45%."

Synthesis of the C_0 *Diels-Alder Adduct:*[71] *endo*-tricyclo[4.4.0.$0^{2,5}$]deca-3,8-dien-7,10-dione

Approximately 12.8 g of cyclobutadieneiron tricarbonyl was reacted with 6.4 g of freshly sublimed quinone in 50 ml of acetone and the reaction was cooled to 0°C in an ice bath. Approximately 160 g of ceric ammonium nitrate was added in small portions to the vigorously stirred solution. Addition of the oxidant was complete in one hour. The reaction mixture was poured into ice cold brine and extracted three times with a total volume of 200 ml of diethyl ether. The ether extracts were washed with water and then dried with $MgSO_4$. The ether was removed at aspirator pressures and 30°C to yield a dark oil which was chromatographed with benzene on silica gel. A total of 4.3 g (54% yield) of adduct was obtained which was recrystallized from diethyl ether and melted at 77 to 78°C.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) showed two olefinic peaks at δ 6.8 and δ 6.2 which integrate 1 to 1. In addition, there was a rather broad peak at δ 3.8 which integrated 1 to 2 with the olefinic peaks.

Infrared Spectrum

The infrared spectrum was obtained in chloroform solution and exhibited the following absorptions: 870 cm^{-1} (w); 894 (vw); 935 (w); 967 (w); 1039 (w); 1120 (w); 1258 (w); 1294 (w); 1550 (w); 1602 (w); 1677 (s); 3040 (w).

Synthesis of the C_0 Cage Dione: pentacyclo[4.4.0.0.^{2,5}0.^{3,9}0^{4,8}]deca-7,10-dione

The C_0 adduct (4.3 g) was photolyzed in 200 ml of ethyl acetate for 1.5 hours using a Hanovia 450 watt, medium pressure lamp. The photolysis reaction was continued until no olefinic peaks remained in the nmr. The photoproduct precipitated out during the reaction. The ethyl acetate was removed at aspirator pressure and 30°C to give 4.78 g of a solid residue. This material was recrystallized from acetone at -20°C to give 2.5 g of cage dione which melted at 218-223°C. This reaction gave a 61% yield.

Nuclear Magnetic Resonance Spectrum

The nmr spectrum agreed with that previously reported for this structure. The nmr (CCl_3D) consisted of a set of two absorptions at δ 3.72 and δ 3.3.

Synthesis of the C_0 Cage Ketal: 10,10-dimethoxy-pentacyclo[4.4.0.^{2,5}0.^{3,9}0^{4,8}]decan-7-one

Approximately 2.5 g of cage dione was reacted with 1.82 g of trimethylorthoformate in 35 ml of anhydrous methanol. A few mg of *p*-toluenesulfonic acid was added as a catalyst. The reaction was allowed to proceed for 18 hours at room temperature with vigorous stirring. The methanol was distilled off at aspirator pressure and 30°C to yield 2.70 g of unpurified product. The product was then washed twice with 15 ml portions of diethyl ether to give 1.85 g of product (45% yield).

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) was characterized by a single, broad, aliphatic absorption at δ 3.5. In addition the nmr displayed two rather sharp singlet absorptions at δ 3.2 and δ 3.3 which were assigned to the two methoxy groups.

Infrared Spectrum

The infrared spectrum was run in CCl_3H and displayed the following characteristic absorptions: 3000 cm^{-1} (s); 2840 (w); 1735 (s); 1460 (w); 1325 (s); 1145 (m); 1105 (m); 890 (m); 940 (w); 910 (w); 1020 (w).

Synthesis of the C_0 Dimethoxy Alcohol: 7,7-dimethoxy-pentacyclo[4.4.0.0.^{2,5}0.^{3,9}0.^{4,8}]decan-10-ol

Approximately .92 g of dimethoxy ketone was stirred into 50 ml of anhydrous ether in a dropping funnel. Then 0.17 g of $LiAlH_4$ was dissolved in 30 ml of anhydrous ether in a dropping funnel. This solution was then introduced into a 100 ml three-necked flask and cooled to 0°C under dry N_2 gas. The dimethoxy ketone was added slowly to the reaction flask and was added over a period of 15 minures. The reaction was allowed to proceed for one hour at 0°C and one hour at room temperature. One ml of water was added at 0°C to slowly decompose the excess $LiAlH_4$. The solution underwent a color change from a slight green to brown upon addition of the water. The solution was filtered and the brown residue was washed with CCl_3H. The clear filtrate was poured into water and extracted four times with diethyl ether. The ether layer was dried with anhydrous Na_2CO_3. The ether was removed at 30°C and aspirator pressure to yield 0.54 g (59%) of a clear liquid which later crystallized to form white crystals. The infrared indicated a strong alcohol absorption and the nmr indicated a characteristic doublet alcohol signal and two sharp methoxy absorptions. The white crystals were recrystallized three times (58% yield) from pentane at -30°C, and melted at 27.5° to 29.5°C. This compound exhibited the sweet characteristic smell of compounds of this sort.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_4) of this compound exhibited the characteristic doublet alcohol signal at δ 4.5 and two intense methoxy absorptions at δ 3.3 and δ 3.0.

Infrared Spectrum

The infrared spectrum was run in CCl_3H and yielded the following absorptions: 3455 cm^{-1} (s); 2980 (s); 2870 (w); 2840 (w); 1460 (m); 1445 (m); 1340 (m); 1280 (s); 1300 (s); 1120 (w); 1100 (s); 1055 (s); 1025 (s); 1010 (w); 970 (w); 935 (m).

Synthesis of the C_0 Cage Closure Product: 3-methoxy-4-oxahexacyclo[5.4.0.0.^{2,6}0.^{3,10}0.^{5,9}0^{8,11}]undecane

Approximately 0.15 g of dimethoxy alcohol was dissolved with a trace of acid in a small heart-shaped evaporation flask and allowed to stand over a twenty-hour period at room temperature. The solution was evaporated to yield 0.12 g of an oil which crystallized (83%). The product was recrystallized twice from pentane and Dry Ice.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) exhibited a peak which was very characteristic of compounds of this type at δ 5.1. There was a single methoxy absorption at δ 3.6 and a broad aliphatic absorption at δ 3.3.

Elemental Analysis ($C_{11}H_{12}O_2$)

The experimentally determined values showed 72.04% carbon and 6.03% hydrogen. The calculated result was 74.98% carbon and 6.86% hydrogen.

Synthesis of the C_1 Diels-Alder Adduct: endo-tricyclo [6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione

Approximately 409 g of *p*-benzoquinone was reacted with 256.5 g of recently prepared cyclopentadiene in ethanol. The cyclopentadiene was added slowly by means of a dropping funnel to the vigorously stirred mixture. Considerable quantities of heat were liberated and the reaction vessel took on a rather dark color. The reaction was allowed to cool on the bench top and later stored in the refrigerator to induce crystallization of the yellow adduct. The crystals were collected by vacuum filtration and recrystallized from methanol (charcoal) to yield 495 g of a yellow crystalline adduct (74% yield). The crystals melted at 67.5° to 72.0°C.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) showed two olefinic peaks at δ 6.4 and δ 5.8 which integrated 1 to 1. In addition, there were three aliphatic peaks at δ 3.3, δ 3.1, and δ 1.3 which integrated 1:1:1.

Synthesis of the C_1 Cage Dione: pentacyclo[6.2.1.$0.^{2,7}0.^{4,10}0^{5,9}$]undecan-3,6-dione

Approximately 100 g of the C_1 Diels-Alder adduct was photolyzed in a Hanovia, 450 watt, medium pressure photolysis apparatus. Six hundred ml of ethyl acetate was used as the solvent. After about 2.5 hours, a white solid appeared in the photolysis apparatus. The nmr showed that the olefinic peaks of the adduct had disappeared. The white solid was filtered with charcoal over Celite and recrystallized from ethyl acetate. Seventy-nine g of cage dione was obtained (79%). The compound melted at 245-246°C.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) showed no olefinic peaks but a rather broad absorption from δ 2.6 to δ 3.3. In addition, there was an absorption at δ 1.9.

Infrared Spectrum

The infrared spectrum was run in CCl_4 and showed the following absorptions: 3000 cm^{-1} (s); 2890 (w); 1765 (vs); 1450 (w); 1300 (w); 1280 (w); 1270 (w); 1220 (m); 1195 (m); 1120 (m); 1065 (m).

Synthesis of the C_1 Cage Ketal: 6,6-dimethoxy-pentacyclo[6.2.1.$0.^{2,7}0.^{4,10}0^{5,9}$]undecan-3-one

Thirty-five g of the C_1 dione was reacted with 22.4 g of $CH(OCH_3)_3$ (5% excess) in 120 ml of methanol. A few mg of *p*-toluenesulfonic acid was added as a catalyst. The reaction was allowed to proceed for 20 hours at room temperature. The reaction mixture was then poured into 200 ml of a 10% $NaHCO_3$ solution to neutralize the acid. The resulting solution was extracted four times with 100 ml portions of water and then dried with K_2CO_3. The resulting solution was evaporated at 30°C and aspirator pressures to remove the CH_2Cl_2 and yielded a yellow oil which crystallized. The solid material was recrystallized from hexane to give 39 g (68% yield) of cage dimethoxy ketone which melted at 69° to 70°C.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) indicated two very sharp methoxy absorptions at approximately δ 3.1 which integrate 1 to 1.

There was a rather broad absorption at δ 2.5 to δ 3.9, and a quartet at δ 1.4 to δ 2.9.

Infrared Spectrum

The infrared spectrum was obtained in chloroform and yielded the following absorptions: 3000 cm^{-1} (s); 2880 (w); 2845 (m); 1740 (s); 1460 (m); 1335 (s); 1280 (w); 1180 (w); 1115 (s); 1070 (s); 1020 (m); 940 (m); 905 (m); 860 (m).

Elemental Analysis ($C_{13}H_{16}O_3$)

The calculated values were 70.80% carbon and 7.28% hydrogen. The experimental values were 71.06% carbon and 7.54% hydrogen.

Synthesis of the C_1 *Dimethoxy Alcohol:* 6,6-dimethoxypentacyclo[6.2.1.0.^{2,7}0.^{4,10}0^{5,9}]undecan-3-ol

Five grams of dimethoxy ketone was reacted with 0.431 g of $LiAlH_4$. The $LiAlH_4$ was dissolved in 20 ml of anhydrous ether in a three-necked flask under N_2 at 0°C. The ketone was dissolved in 50 ml of anhydrous ether in a dropping funnel. The ketone solution was added slowly to the $LiAlH_4$ and addition was complete in thirty-two minutes. During addition, the temperature never exceeded 3.9°C. After one hour, 5.7 ml of water was added slowly (over 15 minutes). During the water addition, the temperature never exceeded 16°C. The reaction mixture was filtered and the filtrate dried with K_2CO_3. The ether was removed at 30°C and aspirator pressure. A clear oil (3.6 g, 72% yield) remained, which crystallized on cooling to give white crystals which were recrystallized from pentane at -30°C. The compound melted at 39° to 41°C.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_4) spectrum showed a doublet alcohol absorption at δ 4.7. In addition, two methoxy signals appeared at δ 3.3 and δ 3.1 and integrated 1 to 1. Another broad absorption appeared at δ 2.5 and a quartet appeared at δ 1.4.

Infrared Spectrum

The infrared spectrum was run in CCl_4 and yielded the following absorptions: 3455 cm^{-1} (s); 2980 (s); 2880 (m); 2840 (w); 1460 (m); 1435 (m); 1340 (m); 1300 (s); 1280 (m); 1265 (w); 1240 (w); 1170 (w); 1120 (s); 1100 (s); 1055 (s); 1025 (m); 1010 (m); 970 (m); 955 (m); 910 (w).

Synthesis of the C_1 Cage Closure Product: 3-methoxy-4-oxahexacyclo[5.4.1.0.^{2,6}0.^{3,10}0.^{5,9}0^{8,11}]dodecane

One g of C_1 dimethoxy alcohol was allowed to stand in 20 ml of methanol with a trace of HCl for twenty-four hours. The methanol was evaporated to yield .77 g (89% yield) of a clear oil. This oil was purified by vacuum distillation, collecting the fraction which distilled at 108°C and .75 mm of pressure.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) showed a characteristic absorption at δ 4.7 and a single methoxy absorption at δ 3.5. A rather broad absorption appeared at δ 2.7. A quartet appeared at δ 1.8 and the integration complied with the desired structure.

Infrared Spectrum

The infrared spectrum was run in CCl_3H and yielded the following absorptions: 2980 cm^{-1} (s); 2870 (m); 2850 (m); 1450 (m); 1340 (s); 1315 (m); 1305 (m); 1295 (m); 1280 (m); 1260 (m); 1245 (w); 1200 (m); 1170 (w); 1160 (w); 1140 (m); 1120 (m); 1080 (m); 1040 (m); 1020 (m); 980 (m); 960 (m); 920 (m); 910 (m); 860 (m).

Elemental Analysis ($C_{13}H_{14}O_2$)

The calculated values were 77.20% carbon and 6.93% hydrogen. The experimental values were 74.89% carbon and 7.28% hydrogen.

Synthesis of the C_2 Diels-Alder Adduct: endo-tricyclo[6.2.2.$0^{2,7}$]undeca-4,9-dien-3,6-dione

Sixty-six g of *p*-benzoquinone was reacted with 49 g of 1,3-cyclohexadiene in 150 ml of ethanol. The reaction mixture was heated to 60°C and stirred vigorously for twenty-four hours. The reaction mixture was cooled in ice to yield a yellow crystalline solid which was removed by vacuum filtration. The solid was recrystallized twice from ethanol and the nmr indicated that it was the adduct. Fifty-four g (55% yield) of purified adduct was obtained.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) showed two olefinic peaks at δ 6.5 and δ 6.1 which integrate 1 to 1. There was a broad aliphatic peak at δ 3.0 and a quartet at δ 1.5. The integration complied with the desired structure.

Infrared Spectrum

The infrared spectrum was run in CCl_4 and gave the following results: 1680 cm^{-1} (s); 1660 (w); 1305 (w); 1180 (w); 1100 (w); 1070 (w); 890 (w); 870 (w); 835 (w).

Synthesis of the C_2 Cage Dione: pentacyclo[6.2.2.0.^{2,7}0.^{4,10}0.^{5,9}]dodecan-3,6-dione

Forty-one g of the C_2 Diels-Alder adduct was photolyzed using a Hanovia, 450 watt, medium pressure, ultraviolet lamp equipped with a pyrex filter. The photolysis was run for two hours and a white crystalline solid formed. Another two hours of photolysis showed no more olefinic absorptions in the nmr. The white crystals were removed by vacuum filtration and were recrystallized from ethyl acetate (charcoal) to give 8.1 g of photoproduct (20% yield) which melted at 251° to 254°C.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) showed no olefinic peaks. There were four pronounced peaks at δ 3.1, δ 2.6, δ 2.2, and δ 1.8. The integration complied with the desired structure (2:1:1:2).

Infrared Spectrum

The infrared spectrum was obtained in CCl_3H and yielded the following results: 2940 cm^{-1} (w); 2905 (w);

2870 (w); 1745 (s); 1460 (w); 1240 (w); 1140 (w); 1050 (m); 830 (w). This is in agreement with the Cookson synthesis.

The Synthesis of the C_2 Cage Ketal: 6,6-dimethoxypentacyclo[$6.2.2.0.^{2,7}0.^{4,10}0^{5,9}$]dodecan-3-one

The C_2 cage dione (7.85 g) was reacted with 4.66 g of trimethylorthoformate in 27 ml of methanol. A few mg of *p*-toluenesulfonic acid was added as a catalyst. The reaction was allowed to proceed for 24 hours at room temperature. The reaction mixture was poured into dilute $NaHCO_3$ solution and extracted five times with dichloromethane. The dichloromethane layer was washed three times with 250 ml portions of tap water. Upon evaporation about 5 g of a yellowish oil remained (50%). The oil was chromatographed over silica gel using hexane to give 2 g of purified C_2 dimethoxy ketone. The compound was still an oil but much clearer and colorless. The nmr and infrared spectra complied with the expected structure. Evidently, both methoxy absorptions merged into a single absorption.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) indicated a very intense (6 protons) methoxy absorption at δ 3.2. There was a very broad absorption from δ 3.0 to δ 2.5. There was a sharper absorption at δ 1.7. The integration complied with the desired structure.

Infrared Spectrum

The infrared spectrum was run in CCl_4 and yielded the following results: 2970 cm^{-1} (w); 2950 (m); 2920 (w); 2880 (w); 2840 (w); 1755 (s); 1465 (w); 1335 (w); 1320 (w); 1240 (w); 1195 (w); 1185 (w); 1145 (m); 1115 (m); 1080 (s); 1050 (w); 950 (w); 920 (w).

Synthesis of the C_2 Dimethoxy Alcohol: 6,6-dimethoxy-pentacyclo[6.2.2.0.^{2,7}0.^{4,10}0^{5,9}]dodecan-3-ol

The cage ketal (1.43 g) was reacted with 0.232 g of lithium aluminum hydride. The C_2 cage ketal was dissolved in 20 ml of anhydrous ether in a dropping funnel. The $LiAlH_4$ was dissolved in 30 ml of anhydrous ether in a thr three-necked flask at 0°C and under dry N_2 gas. Heat was evolved as the cage compound was slowly added to the $LiAlH_4$ solution. The reaction was allowed to proceed for 112.5 minutes and the temperature never exceeded 4°C. Approximately 1.3 ml of water was added slowly (over 6 minutes) after 112.5 minutes of reaction time, and the temperature never exceeded 10°C during water addition. At 135 minutes the reaction mixture was filtered by vacuum filtration and the resulting solution was dried with anhydrous potassium carbonate. The ether was removed by evaporation at 30°C and aspirator pressure to yield 1.2 g (80% yield) of a whitish oil which crystallized. The nmr indicated two sharp methoxy absorptions and a doublet alcohol signal. The infrared showed an alcohol absorption and no ketone. The compound was recrystallized three times from pentane at Dry Ice temperatures. A white crystalline solid was obtained which melted at 56.5° to 57.0°C.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_4) showed a characteristic doublet hydroxyl proton at δ 5.4. There were two methoxy absorptions at δ 3.1 and δ 3.3 which integrated 1 to 1. There were two broad absorptions at δ 2.5 and δ 1.5. The integration complied with the desired structure.

Infrared Spectrum

The infrared spectrum was run in CCl_4 and yielded the following results: 3440 cm^{-1} (s); 2960 (s); 2870 (m); 2840 (w); 1465 (w); 1290 (m); 1270 (m); 1175 (m); 1145 (m); 1105 (s); 1065 (m); 1045(w); 940 (w); 920 (w); 890 (w).

Elemental Analysis ($C_{14}H_{20}O_3$)

The experimental analysis of this compound yielded 71.33% carbon and 8.52% hydrogen. The calculated values were 71.16% carbon and 8.53% hydrogen.

Synthesis of the C_2 Closure Product: 5-methoxy-4-oxahexacyclo$[5.4.2.0.^{3,10}0.^{2,6}0.^{5,9}0^{8,11}]$tridecane

Approximately 0.3 g of the C_2 dimethoxy alcohol was allowed to stand in 2 ml of methanol with a trace of HCl for twenty-four hours. The methanol was evaporated to yield 0.28 g (87% yield) of a clear, colorless oil.

Nuclear Magnetic Resonance Spectrum

A characteristic triplet signal appeared at δ 4.6 and a single methoxy absorption appeared at δ 3.4. A rather broad absorption appeared at δ 2.5 and δ 1.6.

Synthesis of 1,3-cycloheptadiene[72]

Approximately 200 g of 1,3,5-cycloheptatriene was purified by chromatographing over alumina and then distilling at atmospheric pressure. Then 128.11 g of the heptatriene was reacted with 64.4 g of sodium in liquid ammonia at -30°C. The sodium was added over a 40-minute period to the liquid ammonia-triene mixture. Five hundred ml of pet ether and 37 g of NH_4Cl were added after the sodium addition was complete and the liquid ammonia solution was allowed to warm and evaporate over a twenty-four-hour period in a good hood. Then 500 ml of water was added after the NH_3 had evaporated. Two layers separated and the water layer was removed and washed three times with 75 ml portions of pet ether. The ether layer was then washed twice with water and dried with $MgSO_4$. The pet ether was removed by distillation at atmospheric pressure. The fraction boiling at 115° to 120°C was collected to give 46.5 g of a clear liquid which the nmr verified as the 1,3-cycloheptadiene.

Nuclear Magnetic Resonance Spectrum

The nmr (neat) showed an intense olefinic absorption at δ 1.7 and δ 1.3. The integration complied with the required structure.

Synthesis of the C_3 Diels-Alder Adduct: endo-tricyclo [6.3.2.0^{2,7}]trideca-4,12-dien-e,6-dione

Recently sublimed *p*-benzoquinone (56.1 g, 5% excess) was added to 46.30 g of the diene in 300 ml of purified ethanol. The temperature of the reaction mixture was brought to 50°C with vigorous stirring. The reaction was followed by nmr and allowed to proceed for a period of 2.5 weeks. At the end of this time, the reaction mixture was poured into 500 ml of water and extracted four times with 250 ml portions of ether. The ether layer was washed with two portions of water and was then evaporated at 40°C and aspirator pressure to give 78 g of a blackish residue (77% yield). The blackish material was recrystallized from ethanol using charcoal to give pale yellowish crystals which melted at 77° to 79°C.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) was characterized by a sharp singlet absorption at δ 6.8 and a complex absorption at δ 6.1, both of which were olefinic in nature. Aliphatic absorptions occurred at δ 3.3 and δ 1.7. The integration complied with the desired structure (1:1:2:3).

Infrared Spectrum

The infrared spectrum was run in CCl_3H and yielded the following absorptions: 2940 cm^{-1}; 2860 (m); 1670 (s); 1450 (w); 1380 (w); 1280 (w); 1190 (m).

Elemental Analysis ($C_{13}H_{14}O_2$)

The calculated values for this compound were 77.20% carbon and 6.98% hydrogen. The experimental values were 77.07% carbon and 6.78% hydrogen.

Synthesis of the C_3 Cage Dione: pentacyclo[6.3.2.0.^{2,7}0.^{4,12}0.^{5,13}]tridecan-3,6-dione

The C_3 adduct (13.88 g) was photolyzed in 200 ml of ethyl acetate for 1.5 hours. The ethyl acetate was removed at 40°C and aspirator pressure to yield 12.76 g (90% yield) of a yellowish crystalline solid. The solid was washed with small portions of ether which took out much of the color to give 7 g of white crystals. The crystals were then recrystallized from ethanol to yield a compound which melted at 160-162°C.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) showed no olefinic peaks. There were five pronounced absorptions in the aliphatic region at δ 3.2, δ 2.8, δ 2.6, δ 2.1, and δ 1.9.

Infrared Spectrum

The infrared spectrum was run in CCl_3H and yielded the following results: 3020 cm^{-1} (m); 2940 (w); 2880 (w); 1760 (s); 1060 (m).

Elemental Analysis ($C_{13}H_{14}O_2$)

The calculated values of the elemental analysis were 77.20% carbon and 6.98% hydrogen. The experimental values were 77.40% carbon and 7.00% hydrogen.

Synthesis of the C_3 Mixed Ketal: 9-methoxy-14-oxahexacyclo[7.4.1.0.^{2,8}0.^{3,12}0.^{7,11}0^{10,15}]tetradecan-1-ol

The C_3 dione (0.81 g) was dissolved in 11 ml of anhydrous methanol (0.05% water) and mixed with 0.45 g of trimethylorthoformate (5% excess). A few mg of *p*-toluenesulfonic acid was added as a catalyst. On addition of the acid, a noticeable clearing took place. Reaction was allowed to stand for twenty-four hours with vigorous stirring at room temperature. The reaction mixture was then poured into dilute $NaHCO_3$ solution and extracted four times with 30 ml portions of drum diethyl ether. The ether layer was washed twice with 30 ml portions of water and then the ether was removed at 30°C and aspirator pressure. Approximately 0.6 g of product (70% yield) was obtained, which was recrystallized from 30% ether/hexane to give white crystals which melted at 80° to 83°C.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) showed an alcohol absorption at δ 4.9 and a methoxy absorption at δ 3.4 which integrated 1 to 3 with the alcohol absorption. Two rather sharp peaks occurred at δ 2.7 and δ 1.6 and were of equal intensity. The integration complied with the desired structure.

Infrared Spectrum

The infrared spectrum was run in CCl_3H solution and yielded the following results: 3350 (s) cm^{-1}; 2940 (s); 2860 (w); 1450 (m); 1350 (s); 1320 (s); 1270 (m); 1365 (m); 1160 (m); 990 (w); 960 (w); 940 (w); 920 (s); 870 (w); 850 (w); 830 (w).

Synthesis of the C_x Diels-Alder Adduct: tetracyclo [6.4.2.0.^{2,7}0.^{9,12}]tetradeca-4,10,13-trien-9,12-dione

Recently sublimed *p*-benzoquinone (19.23 g) was reacted with 9.43 g of cyclooctatetrene (5% excess) in 160 ml of orthodichlorobenzene (b.p. 179°C). The reaction was brought to 130°C and allowed to proceed for four hours with vigorous stirring. The solvent was removed at 80°C and aspirator pressure to give a black oily residue which later crystallized. The solid was recrystallized from ethanol to give 10 g of fine yellow crystals (25% yield).

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3H) showed two absorptions, at δ 3.2 and δ 2.8, which integrated 1 to 1. Two olefinic absorptions appeared, at δ 6.7 and δ 5.9, which integrated 1 to 2.

Synthesis of the C_x Cage Dione: hexacyclo[6.4.2. 0.^{2,7}0.^{4,14}0.^{5,13}0.^{9,12}]tetradec-10-en-6,3-dione

Fifteen grams of the C_x cage adduct was photolyzed in ethyl acetate by means of a Hanovia, 450 watt, medium pressure lamp. The photolysis was continued for approximately two hours, after which the ethyl acetate was removed by rotovaping at 30°C and aspirator pressures to yield 15 g (100% yield) of a white crystalline solid which melted at 194°C. A good recrystallization solvent for this compound was not found.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) showed an intense olefinic absorption at δ 6.3 and two rather broad peaks at δ 3.0 and δ 2.4.

This was in agreement with the Cookson synthesis.

Infrared Spectrum

The infrared spectrum was run in CCl_3H and showed the following absorptions: 2990 cm^{-1} (w); 2920 (w); 1760 (s); 1735 (w).

Synthesis of the C_x Mixed Ketal Cage Compound: 10-methoxy-15-oxaheptacyclo[$8.4.1.0.^{2,7}0.^{3,13}0.^{4,7}0.^{8,12}0^{11,14}$]pentadec-5-en-1-ol

The C_x cage dione (2.7 g) was reacted with 20 ml of pure trimethylorthoformate in a 50 ml three-necked flask. The reaction was allowed to continue at room temperature for twenty hours with vigorous stirring. A few mg of *p*-toluenesulfonic acid was added as a catalyst at the beginning of the reaction. A yellowish solid precipitated after about ten hours of reaction time. At the end of the reaction, the excess trimethylorthoformate was removed at 40°C and aspirator pressure to give 3.81 g (85% yield) of a yellowish solid. The solid was recrystallized from ethyl acetate (charcoal) to give a white solid which melted at 198° to 200°C.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3H) showed a sharp olefinic peak at δ 6.15 and an alcohol peak at δ 4.5 which integrated 2 to 1. A sharp methoxy absorption appeared at δ 3.5 and a broad absorption appeared at δ 2.5. The integration complied with the desired structure.

Infrared Spectrum

The infrared spectrum was run in CCl_3H and yielded the following absorptions: 3350 cm^{-1} (w); 2980 (m); 1350 (w); 1360 (w); 1340 (w); 1310 (w); 1270 (w); 1140 (s); 1070 (w); 970 (w); 910 (m); 890 (w); 850 (w).

Elemental Analysis ($C_{15}H_{16}O_3$)

The calculated values for this compound were 73.75% carbon and 6.60% hydrogen. The experimental values were 74.07% carbon and 6.99% hydrogen.

Infrared Hydrogen Bond Determination

A 0.375 M solution of the C_0, C_1, and C_2 dimethoxy alcohols was obtained using reagent grade (unopened bottle) CCl_4. The solutions were made in a 2.00 ml volumetric flask and masses were obtained by using a Mettler analytical balance accurate to 0.001 g. The infrared spectra were run on a Perkin-Elmer 457 grating spectrophotometer, using dual Beckman NaCl cells with a CCl_4 blank. The spectra were obtained within ten minutes after the solutions were made up. Three spectra were obtained for each of the three solutions. In addition, spectra were obtained for each of the three compounds using concentrations other than 0.375 M. In all cases, the absorptions were found to be concentration independent. This leads to the conclusion that the hydrogen bonding was essentially intramolecular in nature.

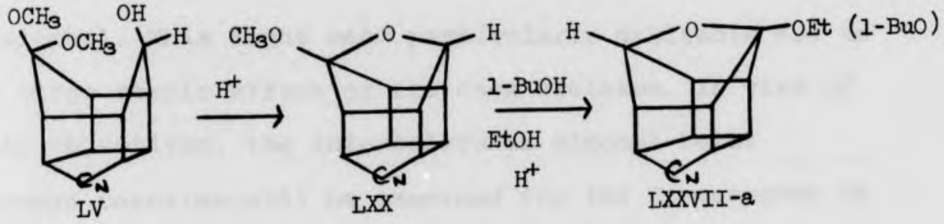
Nuclear Magnetic Resonance Hydrogen Bond Determination

A 0.635 M solution of each of the three dimethoxy alcohols (C_0, C_1, and C_2) was obtained using reagent grade CCl_4 (unopened bottle). The solutions were made in 2.00 ml volumetric flask and masses were obtained on a Mettler analytical balance accurate to 0.001 g. The nmr spectra were run on a Varian T-60 nmr after temperature stabilization had been achieved. All spectra were run at the same temperature. Three spectra were obtained for each of the three solutions and were run within ten minutes after the solutions were made up. The same nmr tube and spin rate were used for all nmr spectra.

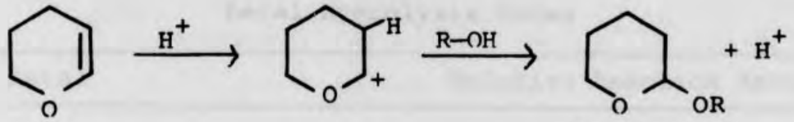
Part II

INTRODUCTION

An example of an alcohol-ketal exchange reaction has already been presented in Part I, represented by the C_0, C_1, and C_2 *endo*-alcohols (LV) giving rise to closure products (LXX). This is an intramolecular alcohol-ketal exchange which typically proceeds almost spontaneously via a carbonium ion mechanism, when small amounts of acid are introduced into a solution of the dimethoxy cage alcohol.



The product molecule (LXX) is also a ketal and therefore capable of an exchange with still another alcohol molecule (LXXVII-a), thus constituting an intermolecular ketal exchange. Exchange reactions of this type are important as a means of protecting the alcohol group in certain synthetic routes. For example, dihydropyran (LXXVIII) reacts readily with alcohols in the presence of an acid catalyst to give cyclic acetals such as structure LXXIX.[73] The alcohol can easily be regenerated at some future time by mild acid hydrolysis of the acetal.



LXXVIII LXXIX

Similarly, in this work, it is conceivable that the C_1 closure product (LXX, n=1) could act as an effective protector group in undergoing an exchange reaction with an alcohol. This might seem particularly desirable due to the large steric effect of the cage skeleton. In view of these objectives, the intermolecular alcohol-ketal exchange reaction will be examined for the C_1 compound in Part II of this thesis.

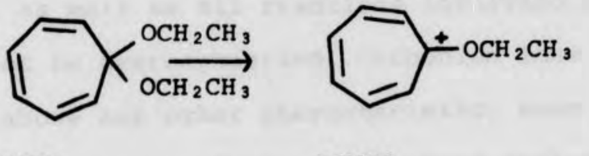
There are many examples of intermolecular ketal hydrolysis reactions which proceed through carbonium ion mechanisms exactly analogous to that of alcohol-ketal exchange reactions. Examples of some ketals which hydrolyze via carbonium ion mechanisms are given in Table 7 with their respective relative reaction rates.[74]

That alcohol-ketal hydrolysis reactions proceed through carbonium ions is demonstrated by the large relative reaction rate for the hydrolysis of tropone diethyl ketal (LXXX) to its ketone (LXXXI).[75] The ease with which this reaction proceeds is expected because the intermediate is the aromatic tropylium cation, known to be extremely stable.

TABLE 7

Ketal Hydrolysis Rates

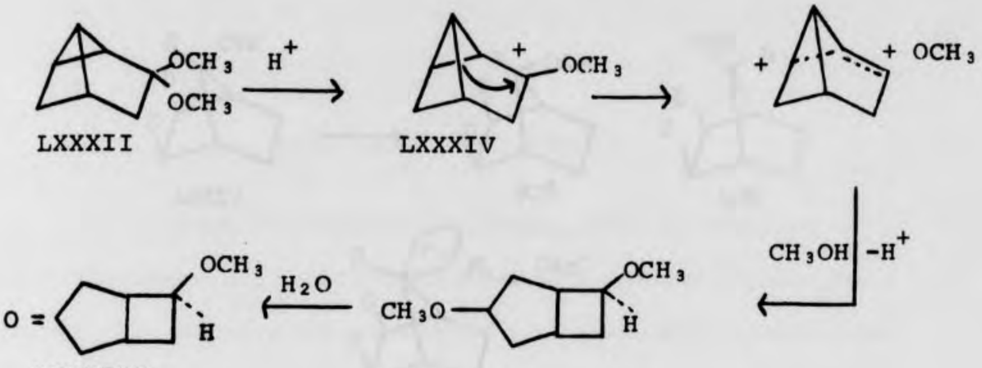
Ketal	Relative Reaction Rate
$(CH_3)_2C(OC_2H_5)_2$	549
$(CH_3)_3CCH_2C(OC_2H_5)_2CH_3$	6715
$(CH_3)_3CC(OC_2H_5)_2CH_3$	59,854
$CH_2(CH_2)_2C(OC_2H_5)_2$	1
$CH_2(CH_2)_3C(OC_2H_5)_2$	239
$CH_2(CH_2)_4C(OC_2H_5)_2$	70
$CH_2(CH_2)_5C(OC_2H_5)_2$	2139



LXXX LXXXI

Another example of a ketal proceeding through a carbonium ion mechanism is the acid catalyzed rearrangement of 3,3-dimethoxy-tricyclo[3.2.0.0^{2,7}]heptane (LXXXII) to give 6-methoxy-bicyclo[3.2.0]heptan-3-one (LXXXIII).[76] This reaction involves the initial protonation of the methoxyl oxygen, followed by loss of the methoxyl group as methanol, to give the carbonium ion (LXXXIV).

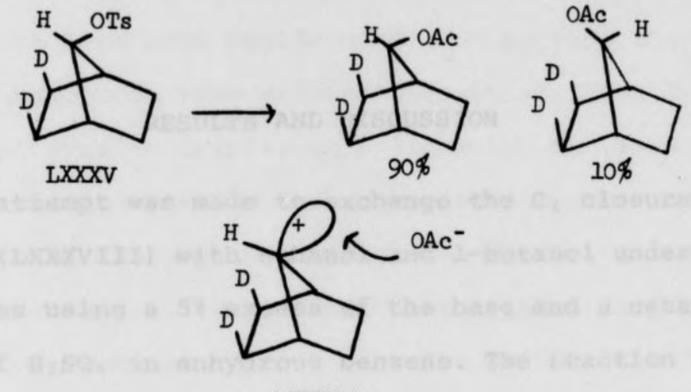
Interestingly, this reaction requires rather forceful conditions (10% sulfuric acid in methanol and two hours of reaction time). It has been suggested that this



is due to the fact that the resulting carbonium ion (LXXXIV) can achieve a planar configuration only with a considerable increase in bond angle strain.

The importance of planarity in alcohol-ketal exchange reactions, as well as all reactions involving carbonium ions, cannot be overemphasized. Carbonium ions prefer planarity above any other characteristic, even when this may cause a distortion from optimum bond angles (C-C less than 120°).[77]

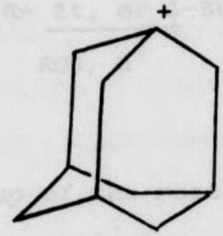
The concept of a non-planar carbonium ion is, of course, not unreasonable, and has been proposed in the acetolysis of *exo, exo*-2,3-dideuterio-anti-7-tosyloxybicyclo[2.2.1]heptane (LXXXV) which recently was reported to give a mixture of two compounds with 90% retention of stereochemistry.[78] The explanation for this is a non-planar carbonium ion (LXXXVI). This would allow attack of the OAc^- group from only one side to yield a stereospecific product.



LXXXV

LXXXVI

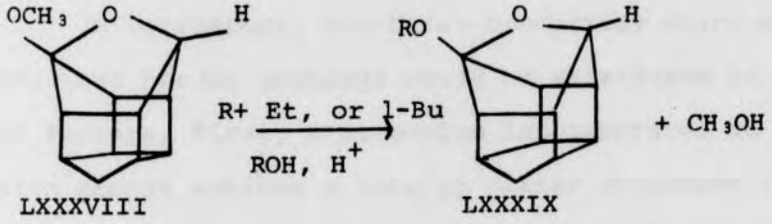
In addition, the adamantyl cation is well known and can obviously not achieve planarity (LXXXVII).[79]



LXXXVII

RESULTS AND DISCUSSION

An attempt was made to exchange the C_1 closure product (LXXXVIII) with ethanol and 1-butanol under mild conditions using a 5% excess of the base and a catalytic amount of H_2SO_4 in anhydrous benzene. The reaction was allowed to proceed for three hours at reflux temperatures (LXXXIX).

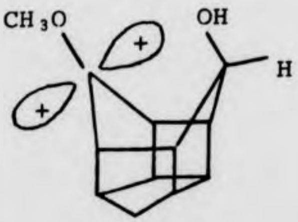


The workup of the reaction showed that no exchange had taken place. Only after the reaction was attempted under surprisingly vigorous conditions, using pure alcohol as solvent, 1 g of H_2SO_4 as catalyst, and refluxing for twenty-four hours with vigorous stirring, did the exchange finally occur. This was very unusual, since exchange reactions of this nature were known to proceed with facility, as did the intramolecular version for the C_0, C_1, and C_2 dimethoxy alcohols.

The ethanol and 1-butanol exchange products were both clear, colorless, viscous liquids which could be readily purified by vacuum distillation. Both products could be made in good yields of 77% or better. The nmr's of these compounds were rather interesting. Both exhibited the characteristic triplet at δ 4.6 which had become closely associated with closure products of this type. The 1-butanol exchange product showed an absorption at δ 3.6 which integrated 2 to 1 with the triplet at δ 4.6. The ethanol exchange product showed a quartet at δ 3.8 and a triplet at δ 1.3. The elemental analysis of these compounds complied with the empirical formulas of both compounds.

In retrospect, the harsh conditions which were required for the exchange could be attributed to a series of factors. First, a carbonium ion generated at a cage site cannot achieve a totally planar structure (XC). In the case of the intramolecular version of this exchange, the carbonium ion can achieve a planar structure, and thus the exchange proceeds vigorously.

XC



XCI

In addition, due to the non-planarity, the oxygen atom cannot stabilize the positive carbonium ion by resonance. This would represent an "orthogonal olefin-like" situation which is contrary to good resonance stabilization. Furthermore, the electronegative oxygen atom exhibits an electron withdrawal effect adjacent to the carbonium ion site; this intensifies the positive charge and tends to destabilize the system. In summary, then, all effects in this system tend to produce an unstable intermediate carbonium ion. This could possibly explain the harsh conditions required to force this reaction to completion.

This reaction may prove useful as a means of protecting the alcohol group under strongly acidic conditions.

EXPERIMENTAL

Synthesis of the Ethanol Exchange Product: 3-ethoxy-4-oxahexacyclo[5.4.1.0.^{2,6}0.^{3,10}0.^{5,9}0^{8,11}]dodecane

One gram of the C_1 closure product was reacted with 30 ml of an acidic ethanol solution (1 g H_2SO_4/50 ml ethanol) at reflux for twenty-four hours. The solution was poured into a dilute $NaHCO_3$ solution and extracted twice with benzene. The benzene was removed at 40°C and aspirator pressure to give 0.96 g of a clear oil (80% yield). The product was then purified twice by distillation at 2 mm pressure and 105°C.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) showed a characteristic triplet at δ 4.6. A quartet appeared at δ 3.7 and a broad absorption at δ 2.6. A quartet and a triplet appeared at δ 1.7 and δ 1.3 respectively. The integration complied with the desired structure.

Infrared Spectrum

The infrared spectrum was run in CCl_3H and showed the following absorptions: 2990 cm^{-1} (s); 28880 (w); 1380 (m); 1340 (s); 1320 (w); 1305 (w); 1295 (m); 1280 (m); 1260 (w); 1150 (m); 1120 (m); 1080 (w); 1045 (w); 1020 (m); 960 (w); 910 (m); 870 (w).

Elemental Analysis ($C_{13}H_{16}O_2$)

The elemental analysis calculated values were 76.46% carbon and 7.90% hydrogen. The experimental values were 76.48% carbon and 7.91% hydrogen.

Synthesis of the l-Butanol Exchange Product: 3-(n-butoxy)-4-oxahexacyclo[5.4.1.0.^{2,6}0.^{3,10}0.^{5,9}0^{8,11}]dodecane

One gram of C_1 closure product was dissolved in 30 ml of an acidic 1-butanol solution (1 g H_2SO_4/50 ml 1-butanol solution) and allowed to reflux for twenty-four hours with vigorous stirring. The solution was then poured into a $NaHCO_3$ solution and extracted twice with benzene. The benzene was removed at 40°C and aspirator pressure to give 1.3 g of a clear oil (77% yield). The liquid was readily purified by distilling at 2 mm pressure and 120°C.

Nuclear Magnetic Resonance Spectrum

The nmr (CCl_3D) showed a characteristic triplet absorption at δ 4.7. A complex absorption appeared at δ 3.6 and a broad absorption appeared at δ 2.7. A complex absorption appeared at δ 1.5 and δ 0.9. The integration complied with the desired structure.

Infrared Spectrum

The infrared spectrum was run in CCl_3H and showed the following absorptions: 2970 cm^{-1} (s); 2880 (m); 1460 (m); 1340 (s); 1320 (w); 1310 (w); 1290 (w); 1280 (m); 1260 (w); 1160 (m); 1080 (m); 1010 (s); 960 (w); 920 (m); 870 (m).

Elemental Analysis ($C_{15}H_{20}O_2$)

The calculated values were 77.55% carbon and 8.68% hydrogen. The experimental values were 77.62% carbon and 8.70% hydrogen.

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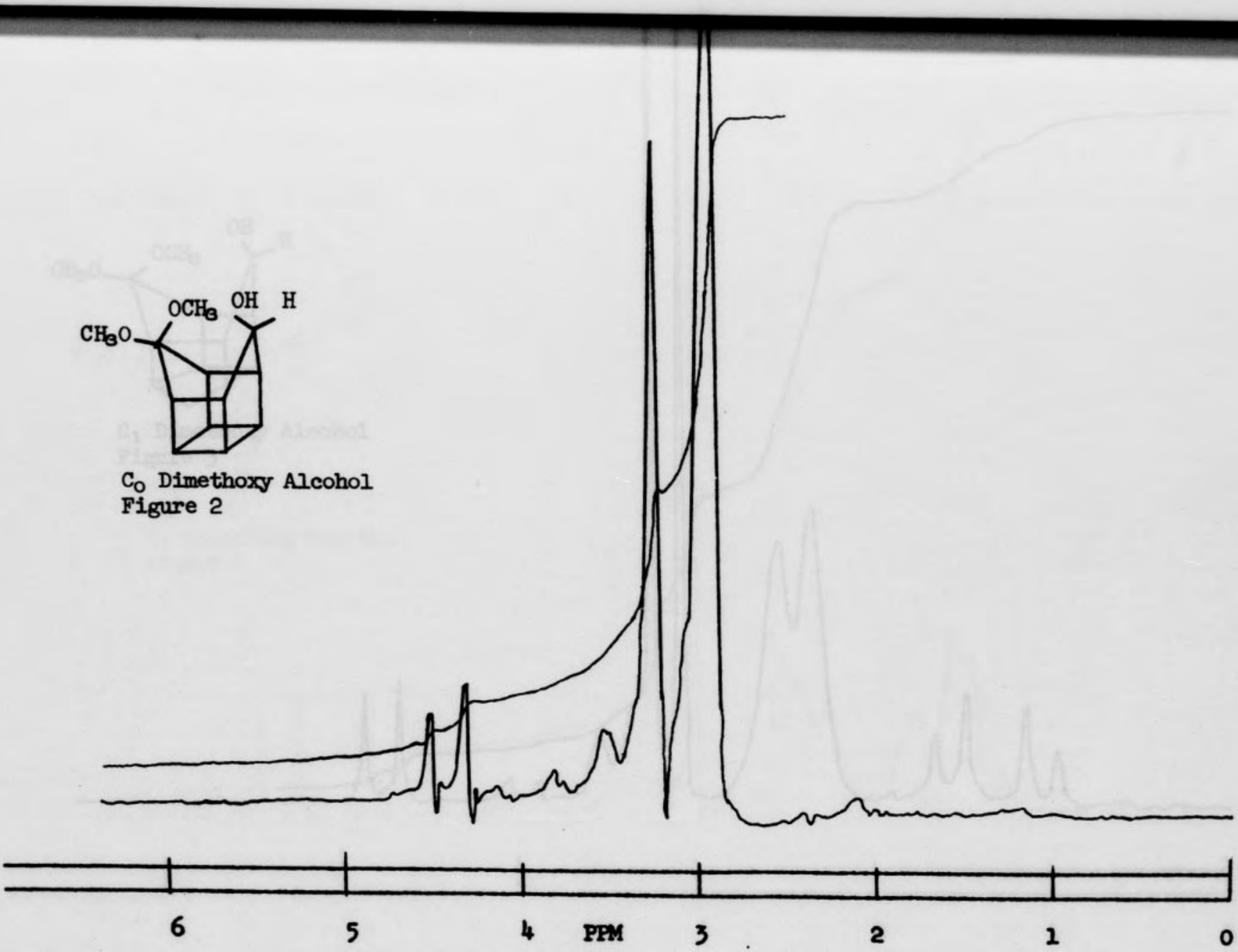
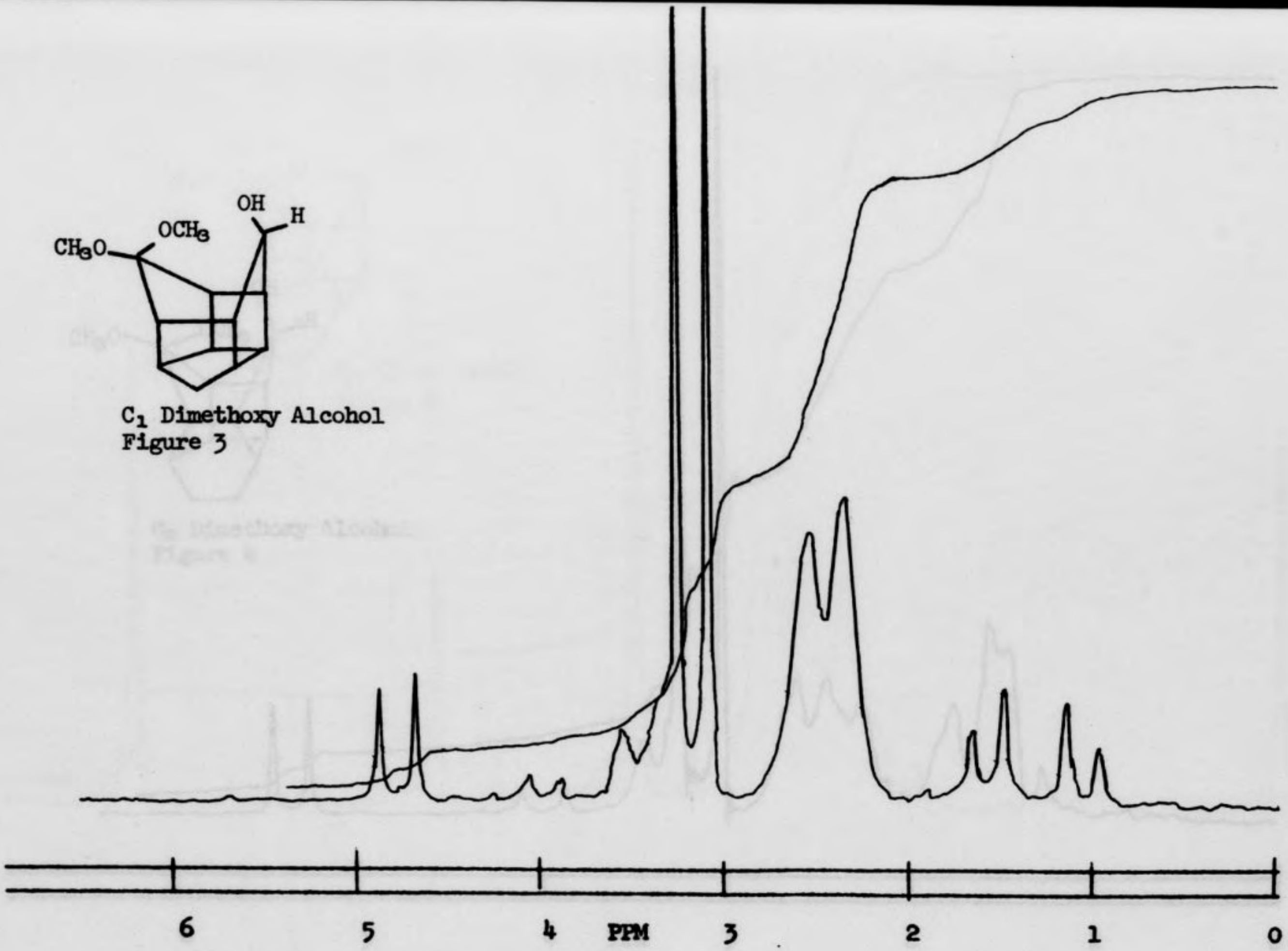
APPENDIX



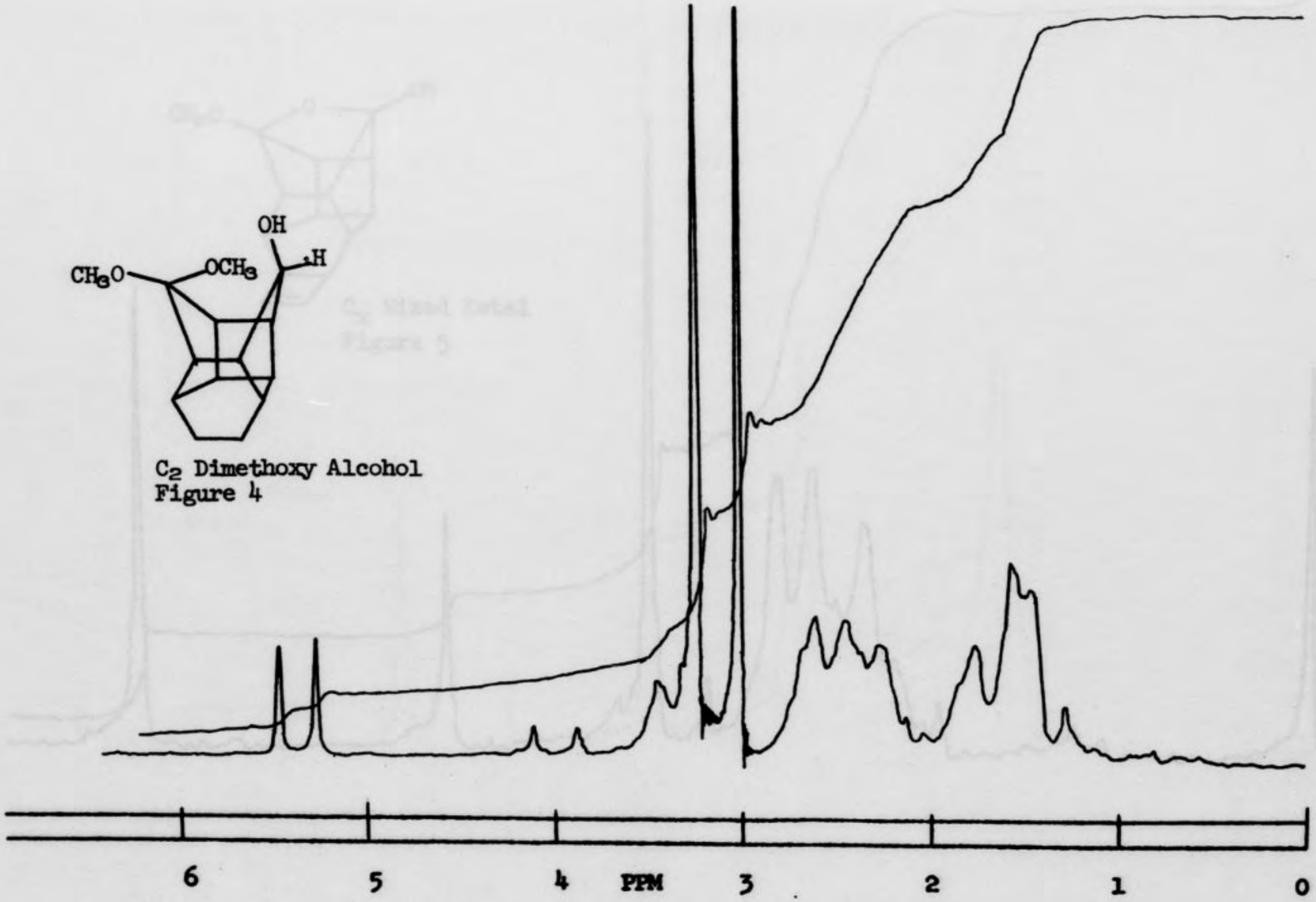
C_o Dimethoxy Alcohol
Figure 2

nmr Spectrum (T-60)



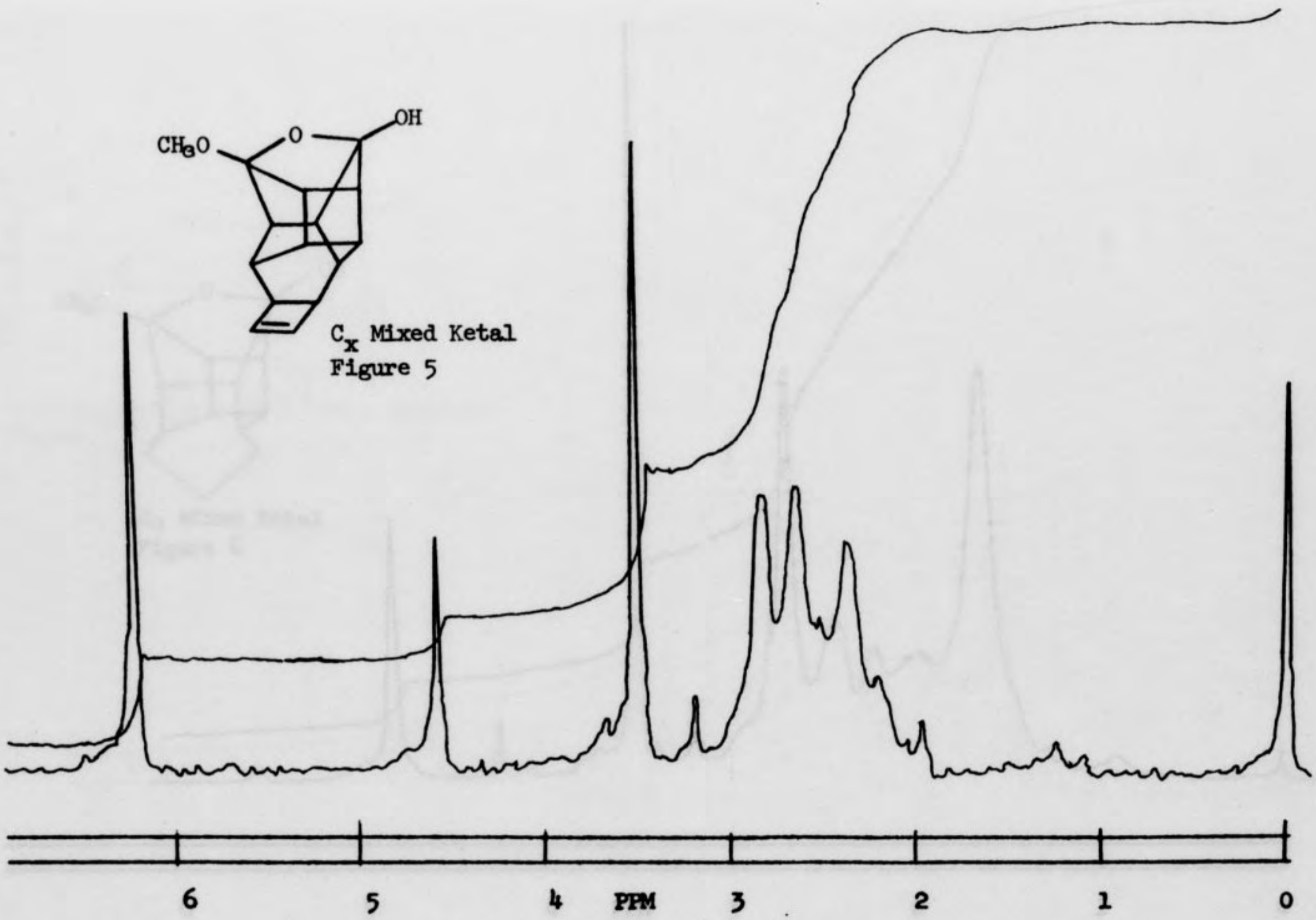
C_1 Dimethoxy Alcohol
Figure 3

nmr Spectrum (T-60)



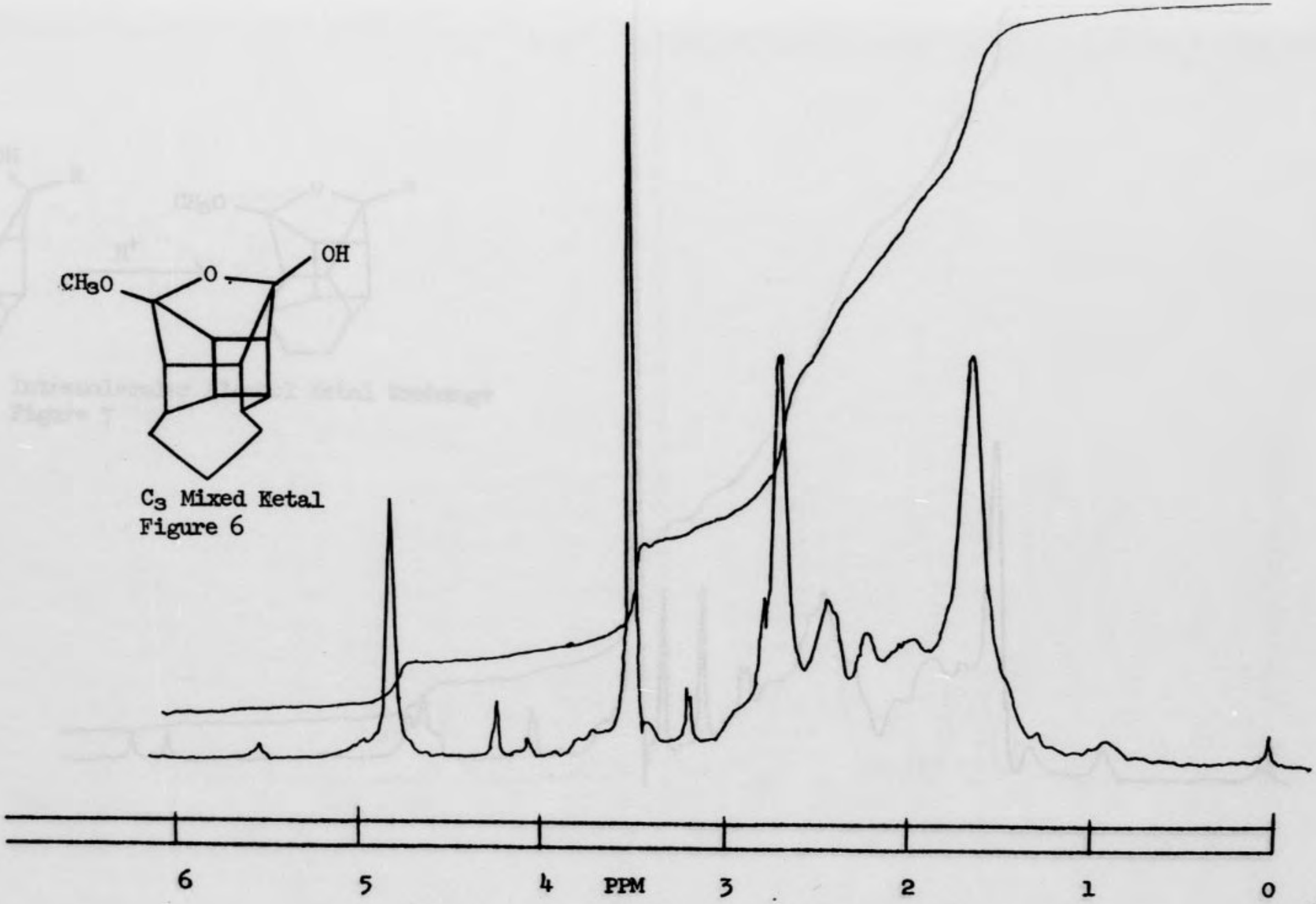
C_2 Dimethoxy Alcohol
Figure 4

nmr Spectrum (T-60)



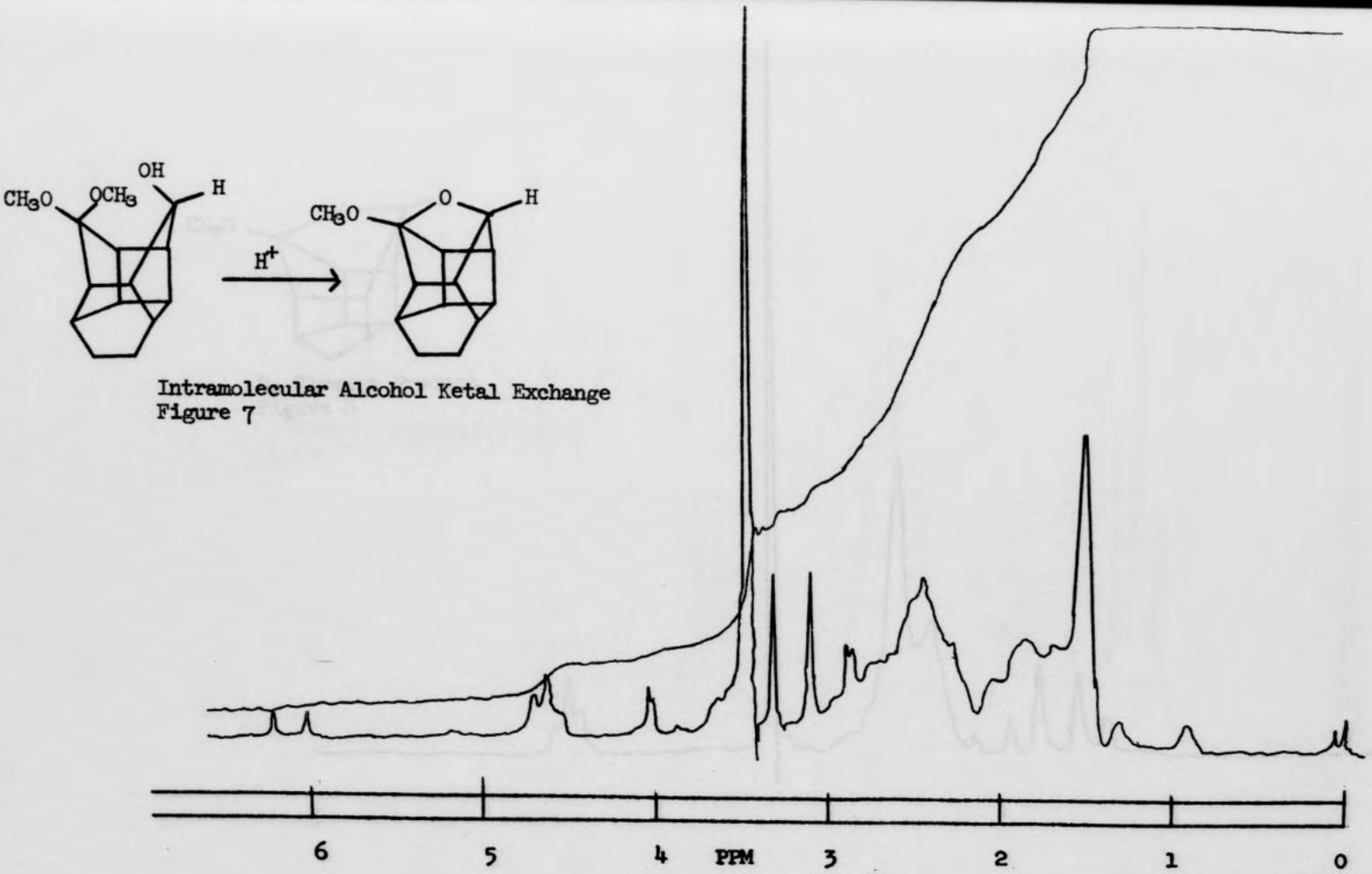
C_x Mixed Ketal
Figure 5

nmr Spectrum (T-60)



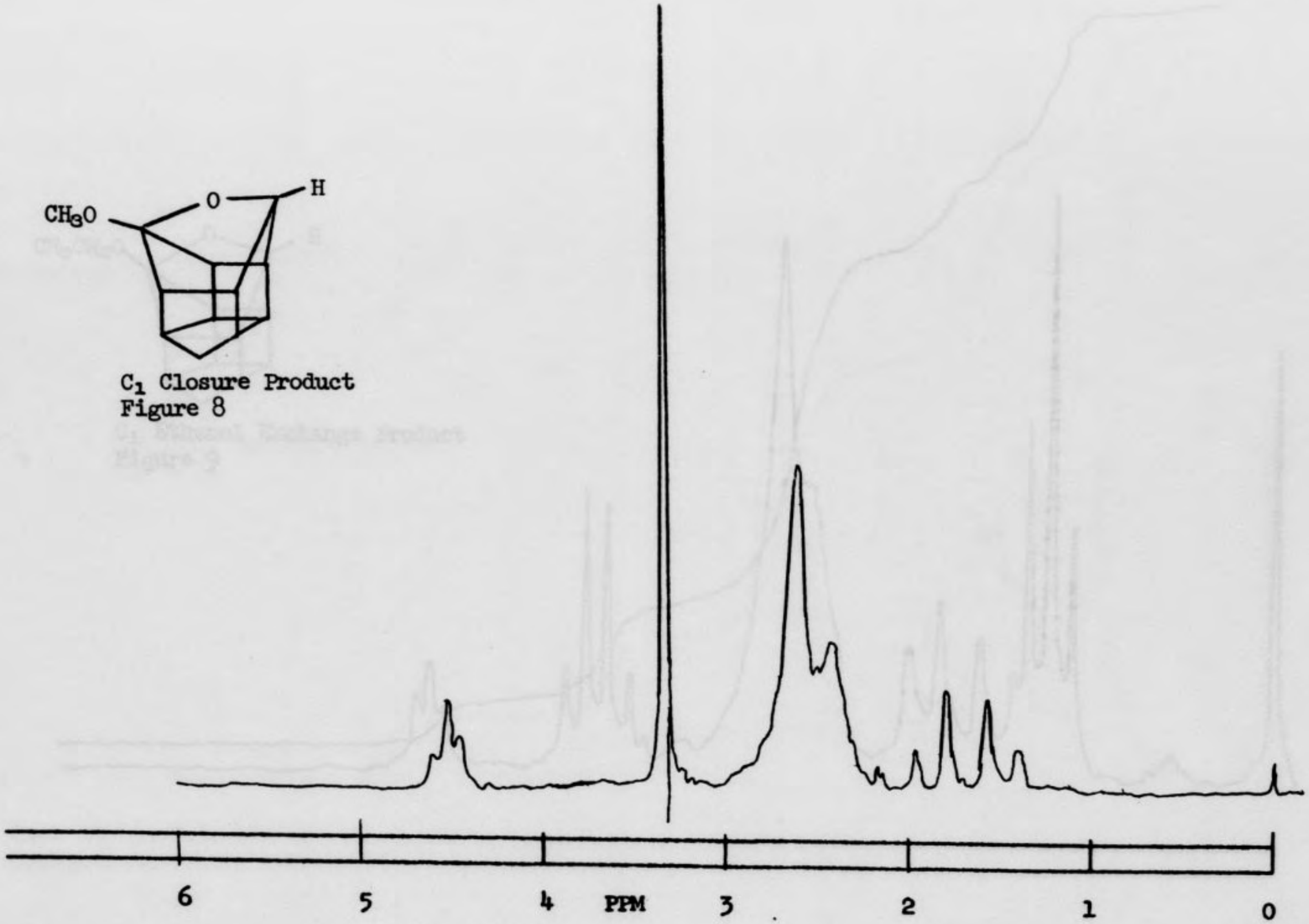
C$_3$ Mixed Ketal
Figure 6

nmr Spectrum (T-60)



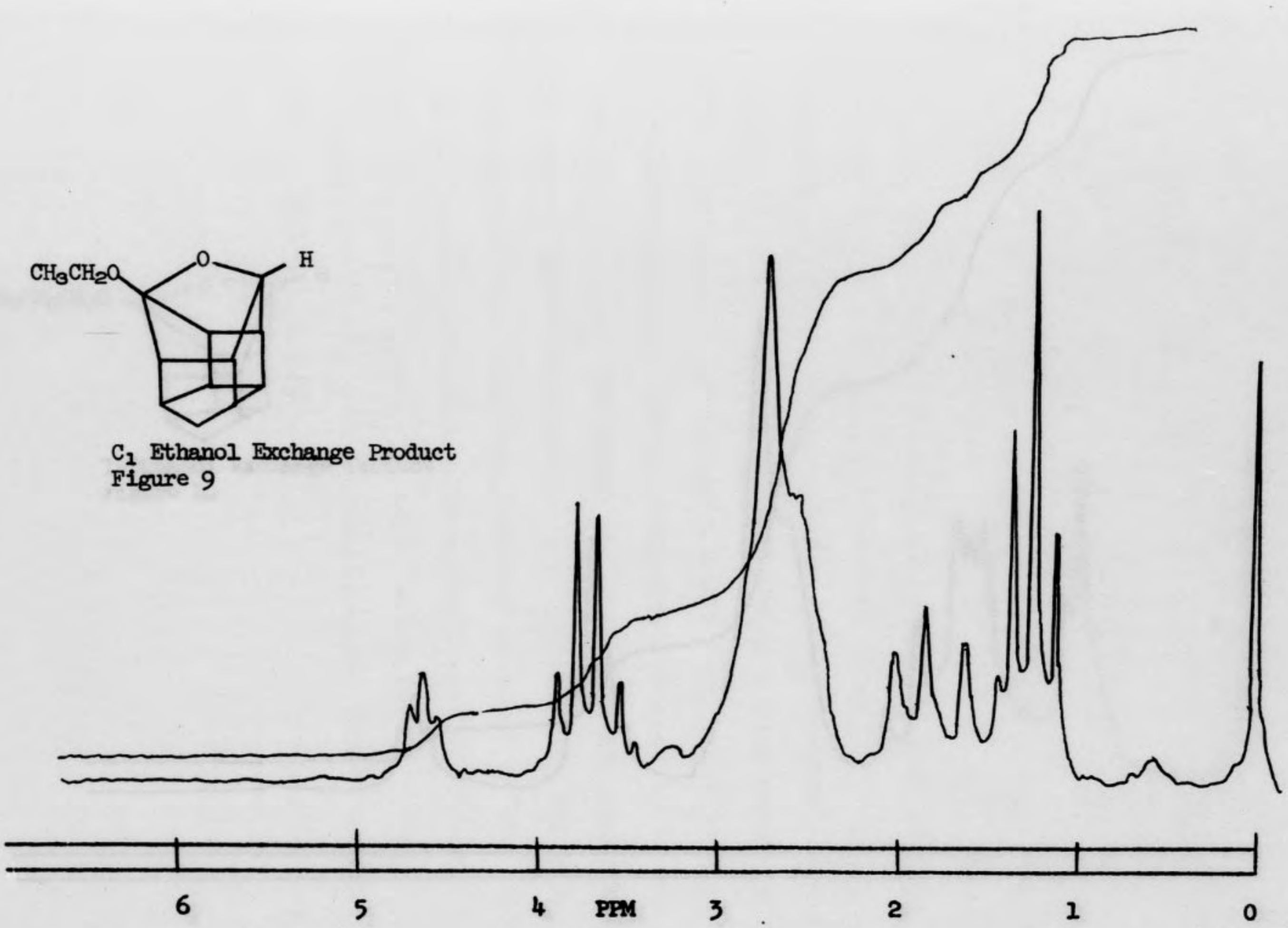
Intramolecular Alcohol Ketal Exchange
Figure 7

nmr Spectrum (T-60)



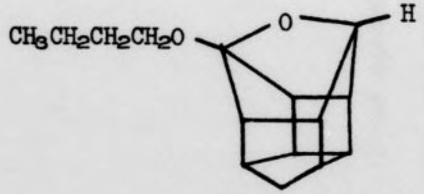
C_1 Closure Product
Figure 8

nmr Spectrum (T-60)

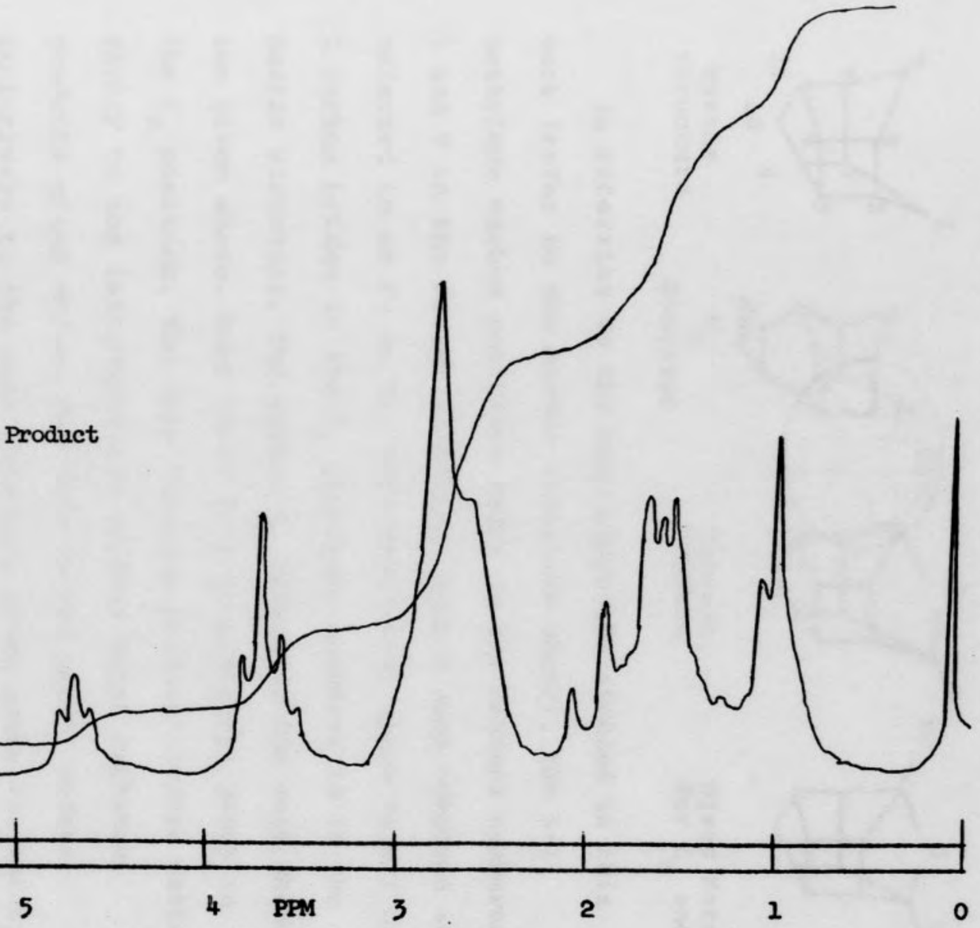


C_1 Ethanol Exchange Product
Figure 9

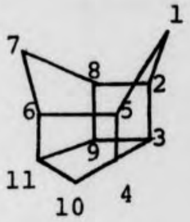
nmr Spectrum (T-60)



1-Butanol Exchange Product
Figure 10

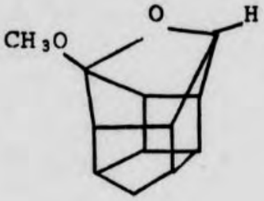


nmr Spectrum (T-60)

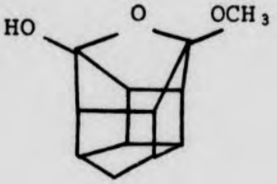


Master
Structure

C_x
Skeleton



Closure
Product



Mixed Ketal
For C_x and C_3

In referring to the cage compounds studied in this work (refer to the master structure above), the 1-2 methylene carbon positions refer to the carbons numbered 1 and 7 in the master structure. When a cage compound is referred to as C_1 or C_2, this means that there is a 1 or 2 carbon bridge in the C_n position, numbered 10 in the master structure. The symbol C_x refers to the cage skeleton given above. Here there is a cyclobutenyl group in the C_n position. The term "closure product" refers exclusively to the intramolecular alcohol-ketal exchange products given above. The term "mixed ketal" refers exclusively to the cage structure given above for the C_x and C_3 compounds only.