PREFACE

Interest in the conformations of cyclic systems with more than six atoms in the ring became considerable when the difficulties of synthesis of such compounds, and their abnormal reactions, were reported. However, the classical methods of conformational analysis, which were used to solve many problems associated with six-membered rings, have not been applied as extensively in larger rings and have yielded only very limited information. The present work describes the application of some more recent techniques, involving nuclear magnetic resonance spectroscopy (N.M.R.), to studies of conformations in seven- and eight-membered rings. New evidence supporting the crown conformation of cycloöctane is presented.

The author wishes to thank his research director, Dr. F.A.L. Anet, for his guidance and encouragement, and in particular for his timely suggestions which led to the combination of several recently developed techniques in this work. Thanks are also due to Dr. Anet for operating the N.M.R. spectrometer, to Mrs. S. Osgerby for preparing 2,2,6,6-tetradeuterio-4-deuteroxycyclohexanone, and to fellow research workers for helpful discussions and assistance.

The kind assistance of two research chemists of the National Research Council of Canada is gratefully acknowledged.

Dr. F.P. Lossing carried out the mass spectrographic analysis. Dr. L.C. Leitch supplied the sample of deuterated cyclohexane.

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Part I

In order to obtain coupling constants in a seven-membered ring, 3,3,4,4,5,5,6,6-octadeuteriocycloheptyl acetate was prepared in several steps from 2,2,6,6-tetradeuterio-4-deuteroxycyclohexanone, available from a previous investigation. The N.M.R. spectrum of the acetate showed no "freezing out" of conformational isomers down to -110°. Analysis of the $(AB)_2X$ spectrum at 20° and at -95° indicated an unexpected variation of the geminal H-H coupling constant, J_{AB}, with temperature, as well as variation of the vicinal couplings.

Part II

Massively deuterated 1,5-cycloöctadiene was prepared from hexadeuterio-1,3-butadiene by acetophenone- catalysed photolysis to give a mixture of dimers, followed by pyrolysis of this mixture at 190°. Chromatographic separation of the 1,5-cycloöctadiene and catalytic reduction of this compound with deuterium gas yielded a massively deuterated cycloöctane containing large proportions of the desired mono- and di-protonated compounds, C_8HD_{15} and $C_8H_2D_{14}$. Proton magnetic resonance spectra of this product, in vinyl chloride with deuterium spin decoupling, were obtained between -50° and -148°. At -135° two sharp lines, of relative chemical

shift 18.8 c.p.s., were obtained. These became broader at higher temperatures, coalesced at -111.5°, and finally gave a single sharp line. The signal shapes allowed calculation of rates of the inversion process between -101° and -119°. The activation energy of this process was found to be 7.7 kcal./mole, the free energy of activation, 8.1 kcal./mole, and the entropy of activation, -4.6 e.u.

Diimide reduction of fully deuterated 1,5-cycloöctadiene yielded a cycloöctane containing two pairs of protons, each pair in a cis vicinal relationship, at the 1,2 and 5,6 positions. The proton spectrum at -135° showed an additional small splitting, but was otherwise quite similar to the spectrum of massively deuterated cycloöctane. The spectrum was interpreted, using the Karplus relationship, as evidence favouring the crown conformation.

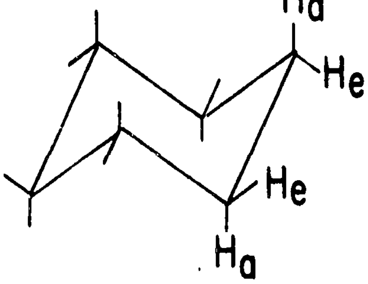
No significant additional results were obtained from an analysis of cycloöctane by spectral moments.

INTRODUCTION

a) General

The term "conformation" denotes a unique spatial arrangement of the atoms in a given configuration. In cyclic structures, the number of possible stable conformations is severely limited, making an analysis to determine which are present relatively easy. Such analysis can be of great value, since it has been found that physical and chemical properties are related to preferred molecular conformations.

The first significant studies in this direction dealt with the cyclohexane ring. It had long been recognized that this ring could exist, with no appreciable distortion of bond lengths or bond angles, in either of two conformations, the chair (I) or the boat (II). After 1940, evidence in favour of the chair form accumulated from several different methods of investigation; the decreased stability of the boat was ascribed to strong non-bonded interactions of eclipsed substituents. Electron diffraction studies by Hassell and co-workers (1) demonstrated the different properties of the two distinct substituent positions, axial and equatorial, of the chair form (H_a and H_e in I). Interconversion between chair conformations was found to have an activation energy too small to allow the isolation of the separate conformational isomers. Extensive studies, notably by Barton and co-workers, on fused six-membered rings confirmed and extended the work on simple



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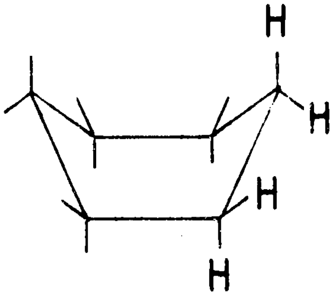

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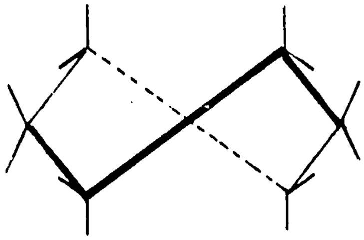


IIa

systems. In some cases, ring fusion prevented interconversion of conformers and allowed comparison of the behaviour of a substituent in a purely axial or purely equatorial conformation. From similar considerations, a systematic chemistry of fused cyclohexane systems was built up (2, 3, 4); this replaced the empirical rules that had previously been developed to explain the observed reactivities and products in such systems. The most stable conformation is generally that in which the largest number of rings are in the chair form, and the largest number of substituents occupy equatorial positions. Rates of reaction of ring substituents are often highly dependent on conformation, because of certain spatial relationships necessary to form the transition state.

Exceptions to the usual rules are known; in such cases the abnormal conformation can be explained by special structural features of the molecule. An example is trans-1,3-di-t-butylcyclohexane, which exists in the boat form (5). The chair form would have an axial t-butyl group, with resultant very large steric repulsion between this group and the axial hydrogens. This destabilization of the chair causes a boat structure to be the most stable; the strong interactions between eclipsed vicinal hydrogens in the regular boat (II) can be decreased in a twisted boat form (IIa).

Attempts to determine the conformations of larger rings are more recent, although interest in the subject developed early as a result of attempts to explain the difficulties in synthesis of these compounds. The larger rings pose problems quite unlike those encountered in six-membered systems. The seven-membered ring, and especially the "medium" rings of eight to twelve members, have large strain energies when compared to the corresponding straight-chain species (6). The ease with which the medium rings undergo transannular reactions (7) further demonstrates the presence of abnormal effects in these rings; substituents on opposite sides appear to be crowded close together. These rings cannot exist in an essentially strain-free conformation, as cyclohexane can. The stable conformations are those in which the strain energy is minimized. A sharp energy minimum, corresponding to one definite spatial arrangement, is not necessarily present; instead, the minimum could correspond to a limited range of conformations, free to interconvert by pseudorotation. Interpretation of such systems is difficult. The use of molecular models does not yield much information since non-bonded repulsions cannot easily be represented.

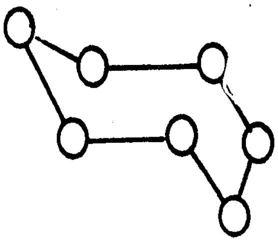
Other difficulties arise. The number of possible conformations increases greatly with increasing ring size. Hendrickson considered four possible conformationsin his calculations on cycloheptane (8). Also, in a given conformation there may be several types of substituents. Hendrickson has calculated that cycloheptane in its most stable conformation contains seven distinct substituent positions (8,9). Fortunately, cycloöctane is believed to be much less complex. In yet larger rings, however, the number of possibilities vastly increases. Although conformational analysis is highly significant when applied to most cyclic compounds, it loses its special usefulness in very large rings which are almost as flexible as the corresponding open-chain compounds. Analysis of such systems has not yet been attempted.

Some information concerning the conformations of saturated seven- and eight-membered ring systems has been obtained by classical chemical methods. Now, new techniques are available which allow knowledge inaccessible by classical methods to be obtained. One of these, nuclear magnetic resonance spectroscopy (N.M.R.), has wide scope and is quite easy to apply. N.M.R. procedures relevant to the present study are discussed in a separate section.

b) The Seven-Membered Ring

The seven-membered ring can be considered in the light of recent calculations by Hendrickson on the conformational stabilities of cycloheptane (8) and simple derivatives (9). In these, the most detailed which have been reported, semi-empirical expressions were used to relate the effects of all known geometric variables to energy. Since good agreement with experimental results was obtained in calculations on cyclopentane and cyclohexane, it is reasonable to assume the validity of calculations, by the same method, on cycloheptane. The ring was found to exist in two conformational families, based on III and IV, analogous to the chair and boat forms of cyclohexane. The chair is of lower energy. Both have serious axial H-H interactions, which are minimized in the corresponding more stable twist-chair (V) and twist-boat (VI) forms. Many different substituent positions exist; there are two main types, analogous to axial and equatorial in cyclohexane. Bond angles are slightly distorted. Even with bulky substituents at low temperatures, no "freezing out" of conformational isomers is expected because of very low energy barriers to pseudorotation.

Chemical methods have indicated the flexible nature of this ring. For example, both the cis- and the trans-1,2-cycloheptanediols easily form cyclic ketals, whereas only the cis-1,2-cyclohexanediol can form the ketal under the same conditions (10). Recently, Huffman and Engle studied the deamination of the cis- and trans-2-amino-cycloheptanols (11). The product distributions were explained by assuming flexibility of the ring; this was necessary to satisfy the



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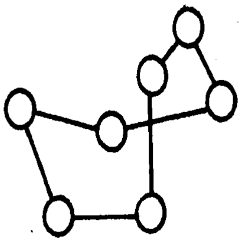

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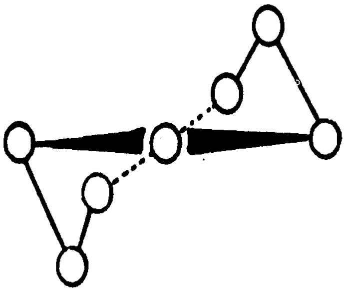

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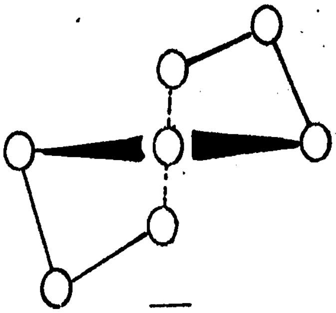

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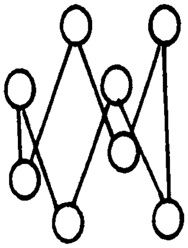

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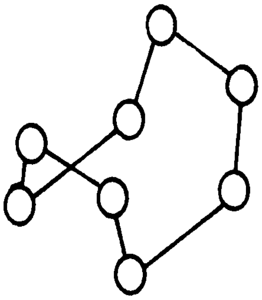

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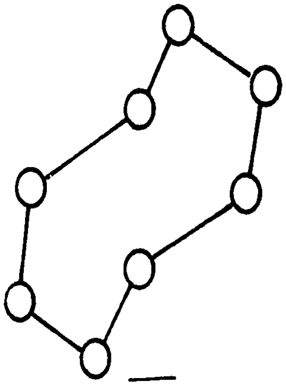

IX

known steric requirements of the deamination reaction. The present study of cycloheptyl acetate was carried out as an attempt to ascertain the conformations present, and the degree of ring flexibility, in this cycloheptane derivative.

c) The Eight-Membered Ring

No calculations similar in detail or reliability to those on cycloheptane have been carried out on an eight-membered system. The three conformations of cyclooctane which have been seriously considered are the crown (VII), tub (VIII), and chair (IX). Of these, only the crown appears to be free of the most serious strains due to large diaxial and eclipsed vicinal non-bonded interactions. However, repulsive non-bonded interactions can in some cases be minimized by deformation or skewing to yield modified structures which are energetically more favourable. Calculations performed by Allinger, based on rotational energy barriers, favoured the skewed crown form (12). A more detailed treatment by Pauncz and Ginsberg indicated that the crown was the regular form of lowest energy, but predicted that angular deformation in the chair would yield a more stable form; the effects of skewing were not considered (13). Neither method of calculation considered all the relevant variables.

Most conclusions based on experimental work have favoured the crown or skewed crown conformation. Infrared studies have been carried out. Chiurdoglu and co-workers investigated the methylene scissoring frequencies; their results indicated the skewed crown structure (14). Bellis and Slowinski studied the infrared and Raman spectra in great detail; in one region of the spectrum, the observed lines were not consistent with the theoretical spectrum of the crown form (15). They proposed the tub conformation as the most probable, but did not exclude a distorted crown form. Both investigations indicated that a single conformation was present. An electron diffraction study was inconclusive; the crown form was the most compatible with the results, but it was not possible to exclude a mixture of rotational isomers containing a high proportion of the crown (16). An X-ray diffraction investigation of the closely related azacycloöctane hydrobromide indicated a skewed crown structure (17).

There is strong chemical evidence that a crown conformation is involved in the reactions of substituted cycloöctanes. Cope and co-workers have demonstrated both 1,5 and 1,3 concerted hydride shifts in cycloöctene oxide (18). These results are difficult to explain on the basis of any conformation other than the crown. Allinger and Hu carried out a catalytic equilibration study on the cis and *trans* isomers of 1,3-dimethylcyclooctane (19). The isomers were found to have similar stabilities. This result excluded the tub conformation because in this form the *cis* isomer would be much less stable than the *trans*, as a result of one methyl group being in a highly hindered axial position. The solvolysis of the *cis*- and *trans*-5-*t*-butylcyclooctyl tosylates is readily interpreted in terms of a crown structure (20). The proposed reaction sequence is shown in Fig. 1. The different product ratios obtained from the *cis* and *trans* isomers (XII: XIII ratios of 4:1 and 1:2, respectively) suggest that a competitive path, involving elimination of the tosyl group with anchimeric assistance from the C5 hydrogen, as in X, is possible in the *cis* isomer. A similar intermediate is not formed in the case of the *trans* isomer XI because the geometry is unfavourable. The reasoning rests on the assumption, amply verified in six-membered rings, that the steric interactions of the *t*-butyl group are so large that only the conformation in which this group is equatorial can be present in significant amount (21). The conformation proposed is not the regular crown but a 'stretched' or 'skewed' crown in which there are three similar but distinct types of carbon atoms, and hence three types each of axial and equatorial substituents. This complication does not seriously affect the reasoning involved.

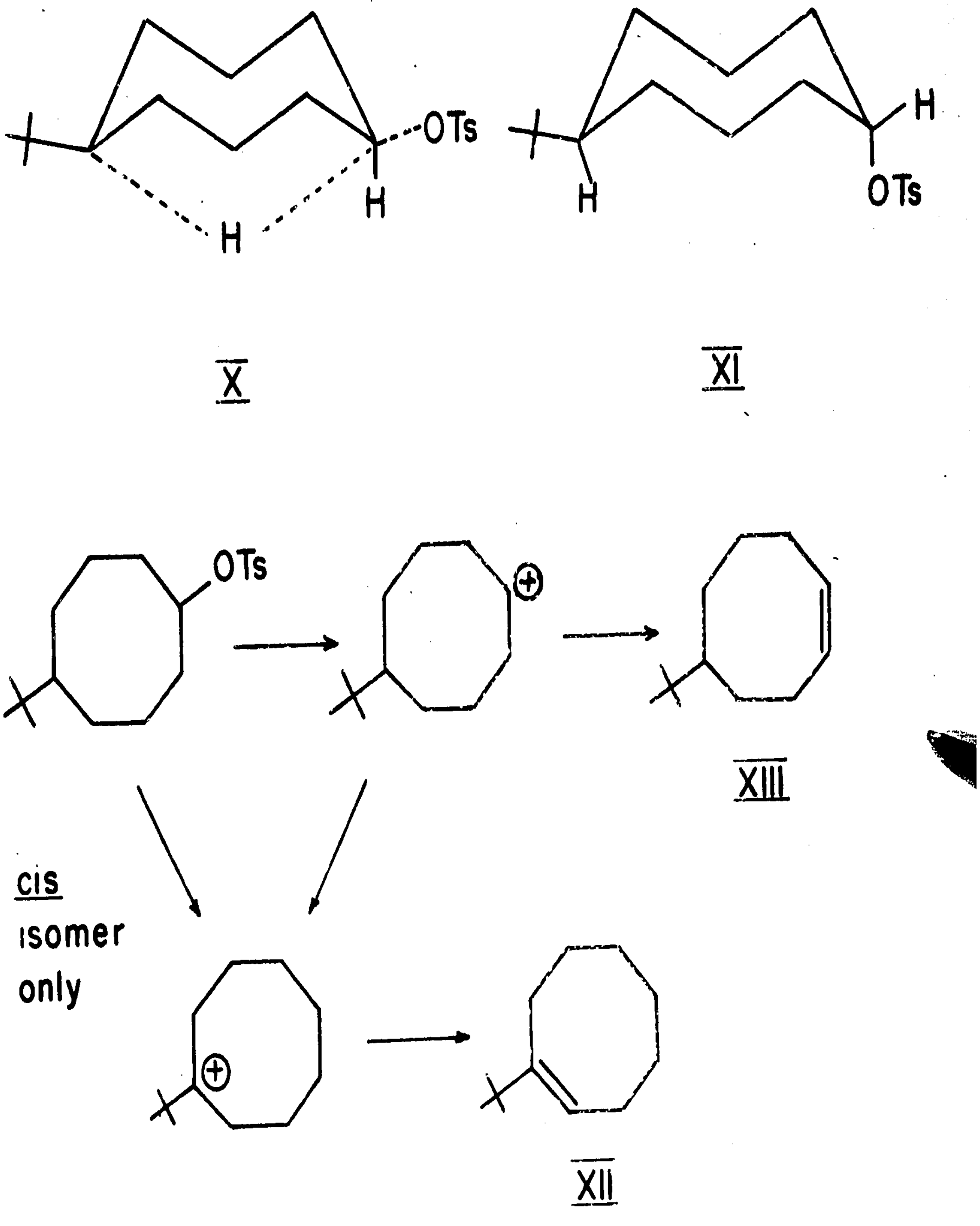

Figure 1. Solvolysis of the 5-*t*-butylcycloöctyl tosylates.

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The information available concerning the conformations of eight-membered ketones has recently been re-interpreted in terms of crown structures (22). Thus the crown appears to be well established as the dominant conformation in eight-membered ring systems.

d) Some Relevant N.M.R. Techniques

The introduction of nuclear magnetic resonance spectroscopy (N.M.R.) allowed a more direct approach to some conformational problems. Many reviews of N.M.R. are available (23-26). Early in its application to organic chemistry, Lemieux and co-workers showed that the chemical shifts of substituents in polysubstituted six-membered rings depended on their conformational positions, and further, that the magnitude of the coupling of vicinal protons depended on the conformational relationship between them (27). These empirical conclusions were very soon applied in the determination of configurations (28,29). Karplus supplied a theoretical basis for the variations of coupling constants by approximate valence bond calculations of electron-coupled spin interactions (30). The magnitude of the vicinal coupling was found to vary with dihedral angle as in Fig. 2; good agreement with the experimental data was obtained. Suitable model compounds, yielding coupling constants for a wide range of dihedral angles, further support the relationship (31,32).

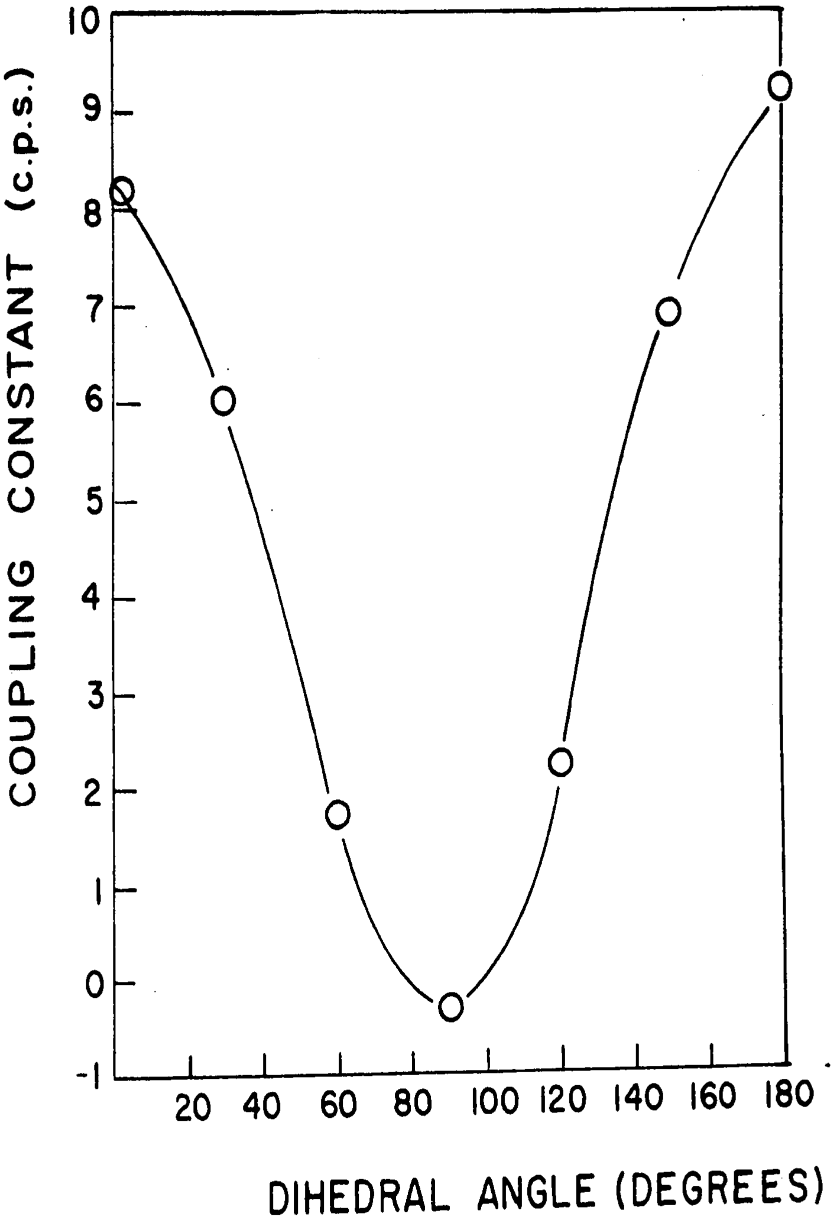

Fig.2 The Karplus relationship

In early work, configurations were determined by application of the accepted rules of conformational stability in the interpretation of N.M.R. spectra. The converse, conformational analysis of compounds of known configuration, also appears feasible. From the observed coupling constants, dihedral angles may be estimated in favourable cases; this can greatly reduce the number of possible conformations and simplify analysis. Unfortunately, application of this method is limited to systems in which vicinal coupling constants can be determined. This requires a relatively simple N.M.R. spectrum, either first order, in which coupling constants may be obtained directly, or consisting of simple patterns of strongly coupled multiplets, in which case analysis is more difficult but still possible. Many sugar derivatives are suitable because relatively few protons, often well chemically shifted from each other, are present on the ring. Simpler alicyclic compounds, such as the saturated hydrocarbons and their mono- and disubstituted derivatives, are less suitable. Fewer peaks are obtained in the spectra, but strong coupling among many protons of similar chemical shift yields very complex spectra which cannot be analysed. Use of the Karplus relationship in such cases requires a device for simplification of the spectra.

The work of Lemieux and co-workers opened a second possible approach to conformational analysis. Axial and equatorial substituents were found to give rise to signals chemically shifted from each other. If similar separate resonances could be detected in simpler systems, the proportions of conformers present could be determined by the relative areas of the peaks. However, rapid interconversion between conformers at room temperature has been found to average the signals; to observe them separately, it has been necessary to slow down the rate process.

Another possible approach to the study of conformation is the determination of the rates of interchange of the stable forms. Classical methods of chemical kinetics, depending on a net chemical change in a system over a period of time, are not applicable. A kinetic approach did not become practicable until the development of methods for the study of processes involving no permanent chemical change. One such method, quite easy to apply, makes use of N.M.R. spectra and depends on the observed shape of the signals obtained from nuclei, on sites chemically shifted from each other, which are undergoing mutual exchange. Signal shape changes with exchange rate, in a regular fashion, if the mean lifetimes of nuclei on the sites are of the order of magnitude of the inverse frequency separation which would be observed between the peaks in the absence of an exchange process. If the rate of exchange is much greater than this, i.e., if the lifetime on a site is small, the signals are averaged together to give a single line. On the other hand, if the rate of exchange is much less, the separate signals appear, with their normal chemical shifts and any fine structure expected due to spin-spin interactions. The theoretical considerations and early applications have been reviewed ((23), Ch. 10, 14); a new review will be available shortly (33).

The changes in signal shape are related to rates by mathematical treatments similar to that of Gutowsky and Saika (34). The rate process involved can be intermolecular, e.g. proton exchange between an acid and water, or intramolecular, e.g. rotation about a bond. The first investigation of an intramolecular process, by Gutowsky and Holm, proved the existence of restricted rotation about the central C-N bond of dimethylamides, and provided kinetic data on the process (35). Many similar rate investigations have been successful. Of special interest are the additional methods of obtaining kinetic data from the spectrum, developed by Piette and Anderson (36) and by Loewenstein and Meiboom (37,38). The relative merits of these methods in the present investigation will be discussed. A more general but quite complex method of analysis, applicable to complex spin-coupled chemical shift multiplets, has recently been put forward (39). Other methods, not applicable in the present investigation, have been applied. One of these utilizes the coalescence of spin-spin doublets rather than chemical shift doublets (40,41). More specialized procedures make use of quadrupole interactions (42) or the presence of paramagnetic species (43). N.M.R. has also been used as a device in classical kinetic analysis, to observe slower exchange processes by the use of an isotopically enriched material; changes in peak intensities can be observed over a period of time (44, 45).

Ring inversion appears well suited to kinetic analysis by N.M.R. If the usual range of relative chemical shifts is present, the mean lifetimes which can be measured are quite short, of the order of 10^{-2} to 10^{-4} seconds. Early evidence (1) indicated a rapid rate process in the cyclohexane ring. Axial and equatorial substituents, which interconvert in the ring inversion process, have different chemical shifts. Thus the fundamental requirements for an N.M.R. investigation of rates are fulfilled. In mono-substituted compounds, the α-proton is the most suitable for investigation since it is usually well chemically shifted from all other protons. However, early investigations yielded only a single broad peak for this proton. Interconversion is rapid at room temperature and averages the signals; the broadening results from complex unresolved coupling patterns in each of the two signals which are averaged. It has proved possible, by the development of techniques for obtaining spectra at very low temperatures (36), to resolve the signal into its axial and equatorial components. These, however, consisted of broad bands of unresolved multiplets, and did not allow the determination of accurate rate data. Unfortunately, kinetic analysis, like analysis based on the Karplus relationship, is severely limited by requirements for simple spectra.

The limitations described have led to great interest in techniques leading to simplified spectra. One such technique, double irradiation, is effective only when applied to a nucleus well chemically shifted from its neighbours; hence it has not been important in the study of the strongly coupled systems in question. On the other hand, techniques of deuteration which have recently been developed are very useful. These rest on the fact that deuterium is "transparent" in the proton magnetic resonance spectrum. The only observed effects are small coupling and quadrupole interactions with nearby protons, which normally cause only a broadening of these proton signals. Even these small effects can be removed by double irradiation at the deuterium resonance frequency. Thus a compound is available which, although it is essentially the same chemically as the non-deuterated compound, has a simplified N.M.R. spectrum. An early application was the practice of using D_2O as a solvent for compounds containing acidic protons; the easy replacement of these protons by deuterium simplified the spectra. The related device of inclusion of deuterium in certain known positions in a molecule as part of its synthesis, in order to obtain simpler spectra, has been applied in conformational analysis. Examples will be discussed. An additional, different deuteration procedure has been reported by Tiers and co-workers (46). Aromatic spectra were simplified by random replacement of hydrogen by deuterium until 75-95% of deuterium was present. Most of the residual protons were surrounded by deuterium, and hence were coupled only to deuterium. The proton spectra showed only the small splittings and line broadening characteristic of proton-deuterium interactions and hence allowed the determination of the true chemical shift values. In the absence of deuterium these compounds yield highly complex spectra. This thesis describes the first application of this massive deuteration method to conformational analysis, in conjunction with spin decoupling of the deuterium to yield sharp singlets for the residual protons.

e) Applications of N.M.R. to Conformational Analysis

Extensive studies of ring conformations by N.M.R. have been carried out in the six-membered series. Some examples involving simple cyclohexane derivatives can illustrate the scope of the methods available.

The proportions of axial and equatorial conformers in cyclohexyl bromide were estimated from the chemical shift of the α-proton resonance (47). The cis- and trans-4-t-butyl compounds were synthesised to yield chemical shift values for the α-protons of the "pure" conformers (21). Proportions of conformers in the simple bromide were estimated by assuming an averaging of the "pure" chemical shifts. Mono- and dihalogenated cyclohexanes have also been examined at low temperatures to allow direct observation of separate axial and equatorial resonances as broad bands (48,49,87). The spectrum of one dihalogenated compound was simplified by deuteration adjacent to an α-proton to yield separate sharp singlets for the conformers at low temperature (50). Generally the halogens showed only a slight preference for equatorial positions; in some dihalogenated compounds a diaxial form is more stable.

Because the relative chemical shift between the α-proton's axial and equatorial conformers is quite small in cyclohexanol and its esters, a good separation of α-proton signals was not obtained at low temperatures. Analysis of the acetate might prove feasible since at low temperatures the acetate peak should separate into axial and equatorial components. A similar case in a more complex system has been reported (51). Until now, however, detailed study of cyclohexanol and its esters has required selective deuteration of the ring. In this laboratory, Anet synthesized 3,3,4,4,5,5-hexadeuteriocyclohexanol and its acetate; the remaining ring protons yielded well-resolved $(AB)_2X$ patterns, slightly broadened by coupling with deuterium (52). Analysis by coupling constants was carried out. Synthesis of the corresponding *cis* and *trans* pentadeuterated 4-*t*-butylcyclohexanols supplied models for the 'pure' axial and equatorial hydroxyl conformers. Coupling constants in these were much as expected from the Karplus relationship; these were related to the coupling constants in the simple alcohol to yield an estimate of the proportion of conformers. The acetate was analysed from the separate axial and equatorial α-proton resonances which could be distinguished at -110°. Calculation of the room temperature equilibrium was based on the observed low temperature coupling constants. The first part of the present work is an attempt to extend this remote deuteration technique to the analogous seven-membered alcohol.

A different selective deuteration approach was utilized by Lewin and Winstein (53). In a series of *cis*- and *trans*-2,2,6,6-tetradeuterio-4-alkylcyclohexanols, the 1-proton signal appeared as a sharp singlet. 1-Proton chemical shift data from the *cis*- and *trans*-4-*t*-butyl model compounds were applied in the estimation of proportions of

conformers in the series. This adjacent deuteration technique has also been used, by Reeves and co-workers, in a low temperature study of cyclohexyl esters (54). Sharp α-proton singlets, corresponding to the two conformers, were used to estimate proportions of conformers; rate analysis appears feasible but was not attempted.

A few six-membered heterocycles have been investigated successfully (55,56,57), one by the use of a deuteration technique (56). However, detailed information has not been obtained from N.M.R. spectra of alkylcyclohexanes (58). The α-proton is not appreciably chemically shifted from nearby protons and cannot be observed separately. A recent study of methylcyclohexane by ultrasonic relaxation indicates that, although it cannot be investigated by N.M.R., a similar process of rapid interconversion between conformers is taking place (59).

Thus N.M.R. studies have supported the belief that conformers of simple six-membered rings interconvert readily. Kinetic analysis has yielded activation energies of the order of 10 kcal./mole for the process. In most cases the expected preference of bulky substituents for equatorial positions has been observed. One limitation to the extension of conformational analysis by N.M.R. is the difficulty of synthesis of many of the deuterated compounds which are

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Thus N.M.R. studies have supported the belief that conformers of simple six-membered rings interconvert readily. Kinetic analysis has yielded activation energies of the order of 10 kcal./mole for the process. In most cases the expected preference of bulky substituents for equatorial positions has been observed. One limitation to the extension of conformational analysis by N.M.R. is the difficulty of synthesis of many of the deuterated compounds which are

required to obtain useful spectra.

Cyclohexane, the parent compound of the six-membered series, is of special interest. Having only two kinds of substituents, it is less complex than its derivatives. However, as in its simple derivatives, analysis of the spectrum has been hampered by strong coupling among the many protons of similar chemical shift. The room temperature spectrum consists of a single sharp line, in accord with the expected rapid interconversion of chair conformers. Jensen and co-workers reported that separate axial and equatorial resonances could be identified below -66° (60). A rough doublet was obtained, but further smaller spin-spin interactions gave rise to a very complex, incompletely resolved pattern. Because of the complexity, only an approximate rate determination, based on the coalescence temperature T_c, was attempted. Harris and Sheppard carried out measurements of line widths near the fast exchange limit as a basis for calculations; a straight line Arrhenius plot was obtained (61). Tiers obtained similar results by the same method in his investigation of the closely related perfluorocyclohexane, C_6F_{12} (62). A very clear coalescence pattern has been observed in the fluorine resonance spectrum of 1,1-difluorocyclohexane (63).

The approximations involved in the kinetic analysis of cyclohexane cast doubt on the results. Even approximate analysis depended on the presence of only small apparent couplings in the system, which allowed the signal to be considered as arising from a simple chemical shift doublet.

There have been few applications to conformational analysis in the medium rings. Harris and Sheppard (61) reported broadening of the single peak of cyclooctane below -100°, but no resolution into components down to -113°. The present work shows that a simple rate process, similar to that in cyclohexane, occurs; however, the coupling pattern is less favourable and does not allow even an approximate rate analysis. Deuteration is necessary to obtain simple spectra. Allinger and Greenberg (20) obtained chemical shift values of the 1-protons in the <u>cis</u>- and <u>trans</u>-isomers of the 4- and 5-<u>t</u>-butylcyclooctyl acid phthalates. These were interpreted in terms of the crown conformation; the isomers in which the 1-proton would be axial were found to yield signals for this proton which were considerably chemically shifted to higher field. These relative chemical shifts of axial and equatorial 1-protons (0.32 τ in the 5- and 0.24 τ in the 4-<u>t</u>-butyl compounds) are in accord with the results of studies on cyclohexane derivatives, in which axial ring hydrogens were found to occur at higher field. Additional studies have involved unsaturated eight- and nine-membered rings; they are not directly related to the present investigation (64,65).

PART I

A STUDY OF CYCLOHEPTYL ACETATE

EXPERIMENTAL

2,2,6,6-Tetradeuterio-4-acetoxycycloheptanone

2,2,6,6-tetradeuterio-4-deuteroxycyclohexanone (XIV) (5.3 g., available from a previous investigation) was acetylated with acetic anhydride (17.2 ml.) and sodium acetate (0.38 g.). Reduced pressure distillation yielded 6.0 g. (80%) of the 4-acetoxy compound (bp. 78-80°/1mm.). This was added, under anhydrous conditions, to boron trifluoride etherate (3.5 g.) in ether (125 ml.) in a one-liter three-necked flask under nitrogen. An ethereal solution of diazomethane, prepared from N-nitroso-N-methylurea and dried 30 minutes over potassium hydroxide pellets, was added until V.P.C. analysis by peak areas (Pye Argon Chromatograph, Versamid column (F and M. Scientific Corporation), 135°) showed 74% of the seven-membered analogue in the reaction mixture, along with 7% of unreacted starting material and 15% of analogous eight-membered compound. Approximately 300 mole per cent of diazomethane was required. Reduced pressure fractionation of the mixture did not yield pure fractions; the best fraction (1.7 g., b.p. 91-94°/1mm. ; 90% of the desired seven-membered compound) was used in the following step.

3,3,4,4,5,5,6,6-Octadeuteriocycloheptanol

The above mixture of tetradeuterated ketoacetates (1.7 g.) was refluxed two hours with sodium carbonate (1.7 g.) and deuterium oxide (11 ml.); most of the deuterium oxide was distilled off, to yield chiefly 2,2,6,6,7,7-hexadeuterio-4-deuteroxycycloheptanone, of 97% theoretical deuteration. To this, a deuterated mixture, prepared by exchange with deuterium oxide, of hydrazine hydrochloride (3.8 g.), sodium hydroxide (2.5 g.), and diethylene glycol (4 ml.), was added. After two hours of reflux the mixture was distilled at 230°. Both the distillate and the residue were extracted with ether, dried over $MgSO_4$, and the ether removed. Yield of distillate, 0.6 g., containing 93% of the seven-membered alcohol by V.P.C. analysis. Yield of residue, 0.3 g., containing 96% of the seven-membered alcohol.

The residue and distillate were purified by preparative V.P.C. (carbowax, 130°). The identity of the deuterated cycloheptanol was confirmed since it had the same retention time as an authentic non-deuterated sample. Yield, 0.3 g. of 3,3,4,4,5,5,6,6-octadeuteriocycloheptanol.

3,3,4,4,5,5,6,6-octadeuteriocycloheptyl acetate

The deuterated cycloheptanol (0.08 g.) was acetylated by reflux with acetic anhydride (0.44 g.) in pyridine (1 ml.). Carbon tetrachloride (5 ml.) was then added; the solution was washed with 10% HCl, 10% $NaHCO_3$, and with water until neutral, and dried over magnesium sulphate. Most of the carbon tetrachloride was removed under reduced pressure; the remaining liquid was transferred directly to an N.M.R. sample tube, and carbon disulphide added.

Integration of N.M.R. peak areas showed the presence of an excess of 2.8 protons per molecule over the theoretical; thus the introduction of deuterium was accomplished with only 65% isotopic purity.

N.M.R.

The N.M.R. spectra were obtained on a Varian V-4302 60 Mc./sec. high resolution spectrometer, with approximately 1% of tetramethylsilane as an internal standard. Calibrations were carried out by the usual side-band modulation technique. A deuterium spin decoupler, manufactured by N.M.R. Specialties, was used. Integration of peak areas was carried out with a Varian model V 3521 Integrator. Simultaneous irradiation of the low-field multiplet was carried out, using the Varian Integrator, by the double side band method of Freeman and Whiffen (66). The device for obtaining low sample temperatures is described in Part II of this thesis.

Spectra at 20° and -95° were obtained in approximately 10% solution in carbon disulphide. Analyses to determine coupling constants and chemical shifts were carried out washed with 10% HCl, 10% $NaHCO_3$, and with water until neutral, and dried over magnesium sulphate. Most of the carbon tetrachloride was removed under reduced pressure; the remaining liquid was transferred directly to an N.M.R. sample tube, and carbon disulphide added.

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Spectra at 20° and -95° were obtained in approximately 10% solution in carbon disulphide. Analyses to determine coupling constants and chemical shifts were carried out independently on each of three deuterium decoupled spectra at 20° and at -95°.

RESULTS

N.M.R. spectra of non-deuterated and 3,3,4,4,5,5,6,6-octadeuterated cycloheptyl acetate are shown in Fig. 3. Even the 1-proton of the non-deuterated compound gave rise to only a broad unresolved band, while in the deuterated compound (XV) considerable fine structure appeared. At both 20° and -95°, the low field (1-proton) multiplet of XV showed resolution into triplets of a triplet, as expected for the X proton of an $(AB)_2X$ pattern. There was no indication of a "freezing-out" of conformational isomers at -95°. The high field part of the spectrum changed considerably with temperature, but all the expected peaks were not resolved.

The inability to observe the $(AB)_2X$ pattern in the high field multiplet of XV was the result of several factors. The acetate peak interfered with part of the multiplet. Coupling and quadrupole interactions of the β-protons with adjacent deuterium broadened the signals and prevented the resolution of some closely spaced lines. Signals due to the large proportion of isotopic impurity, shown to be present in the remote methylene groups, appeared in the same region of the spectrum; analysis was complicated by the necessity of determining which of the observed peaks were part of the $(AB)_2X$ pattern.

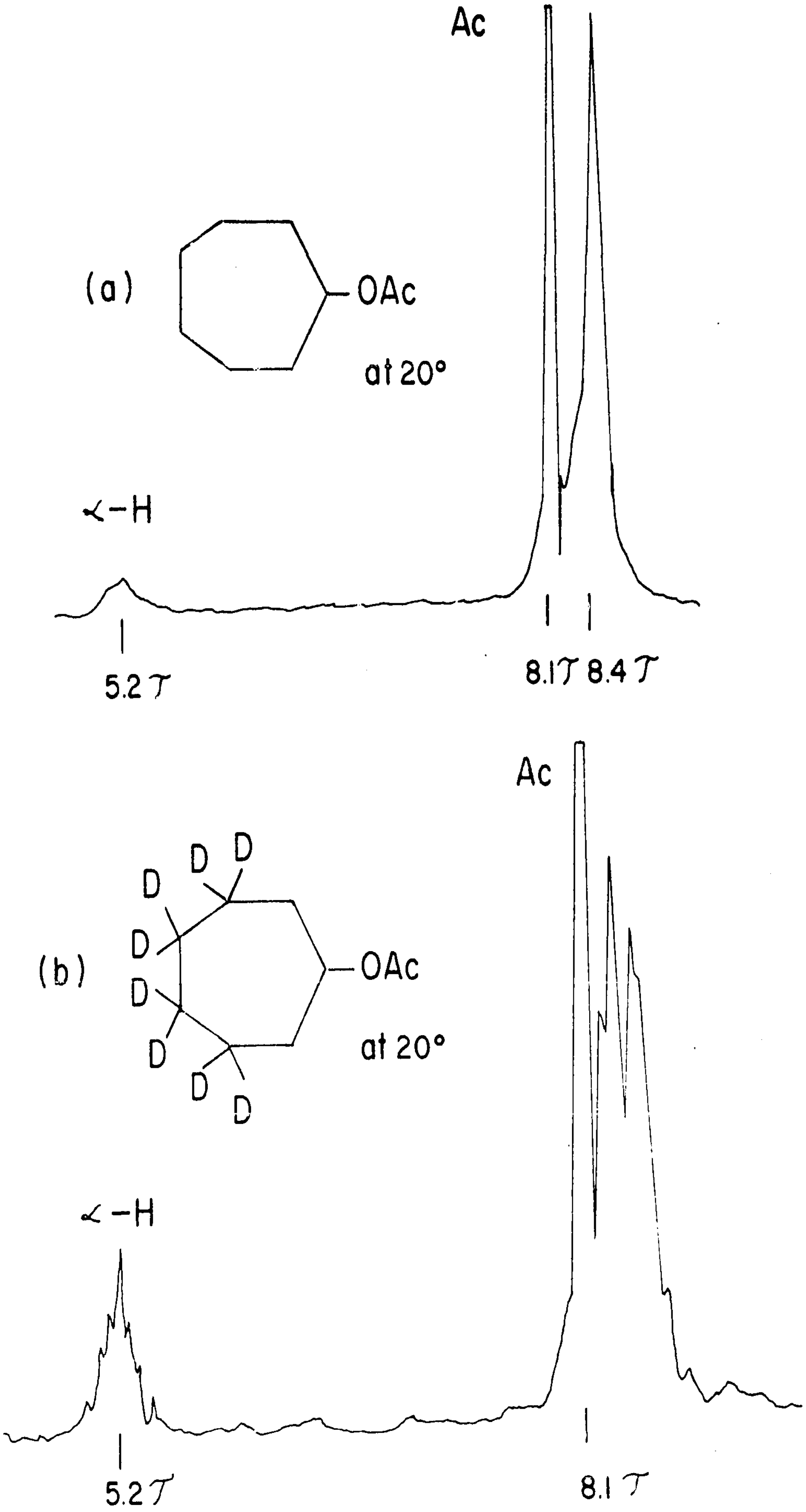


Figure 3. Cycloheptyl acetate spectra.

It was not possible to eliminate the interference of the acetate peak or the isotopic impurity peaks. However, double irradiation at the deuterium resonance frequency eliminated the interactions with deuterium and allowed resolution of additional lines. The deuterium decoupled spectra showed considerable changes between 20° and -95° (Fig. 4a, 5a); both were sufficiently well resolved to permit analysis of the $(AB)_2X$ pattern, in spite of interference from the isotopic impurity peaks which decreased the accuracy of the results.

Because of uncertainties in peak assignments in the high field multiplets, an independent analysis was desired. This proved possible by a second simplification of the spectrum. Simultaneous irradiation of the low-field (α-proton) multiplet, while observing the deuterium decoupled high field portion of the spectrum, yielded an AB pattern for the two non-equivalent β-protons A and B (Fig. 4c, 5c). These patterns, while recognizable, were seriously distorted by the isotopic impurity, which caused the two central peaks to be of unequal intensity. One of the outer peaks was covered by the acetate peak. Because of the interference from unrelated signals, calculations from these spectra yielded only rough estimates of J_{AB} and ν_{AB}. The estimates, however, were useful in analysing the $(AB)_2X$ patterns since they indicated

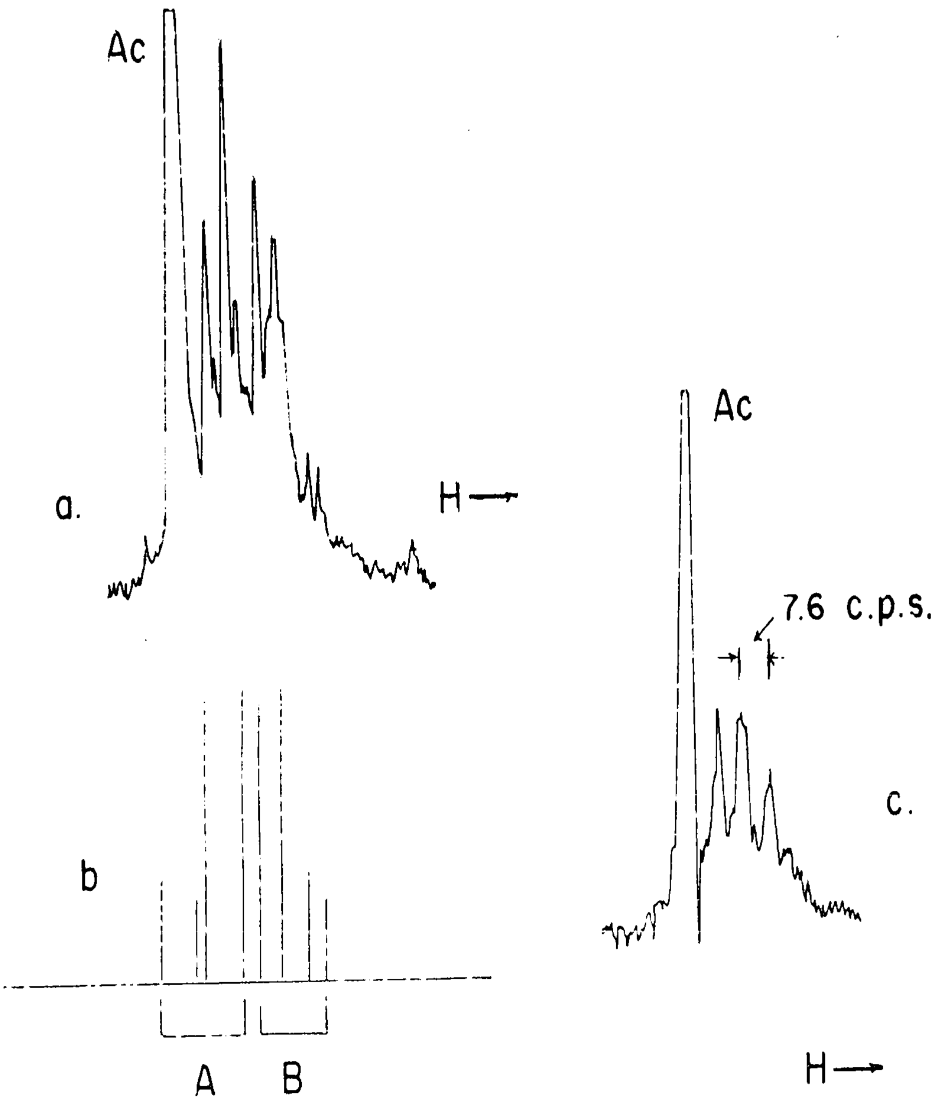


Figure 4. The deuterium decoupled high field multiplet of the deuterated cycloheptyl acetate XV (20°).

a) observed
b) calculated
c) with additional α-proton decoupling.

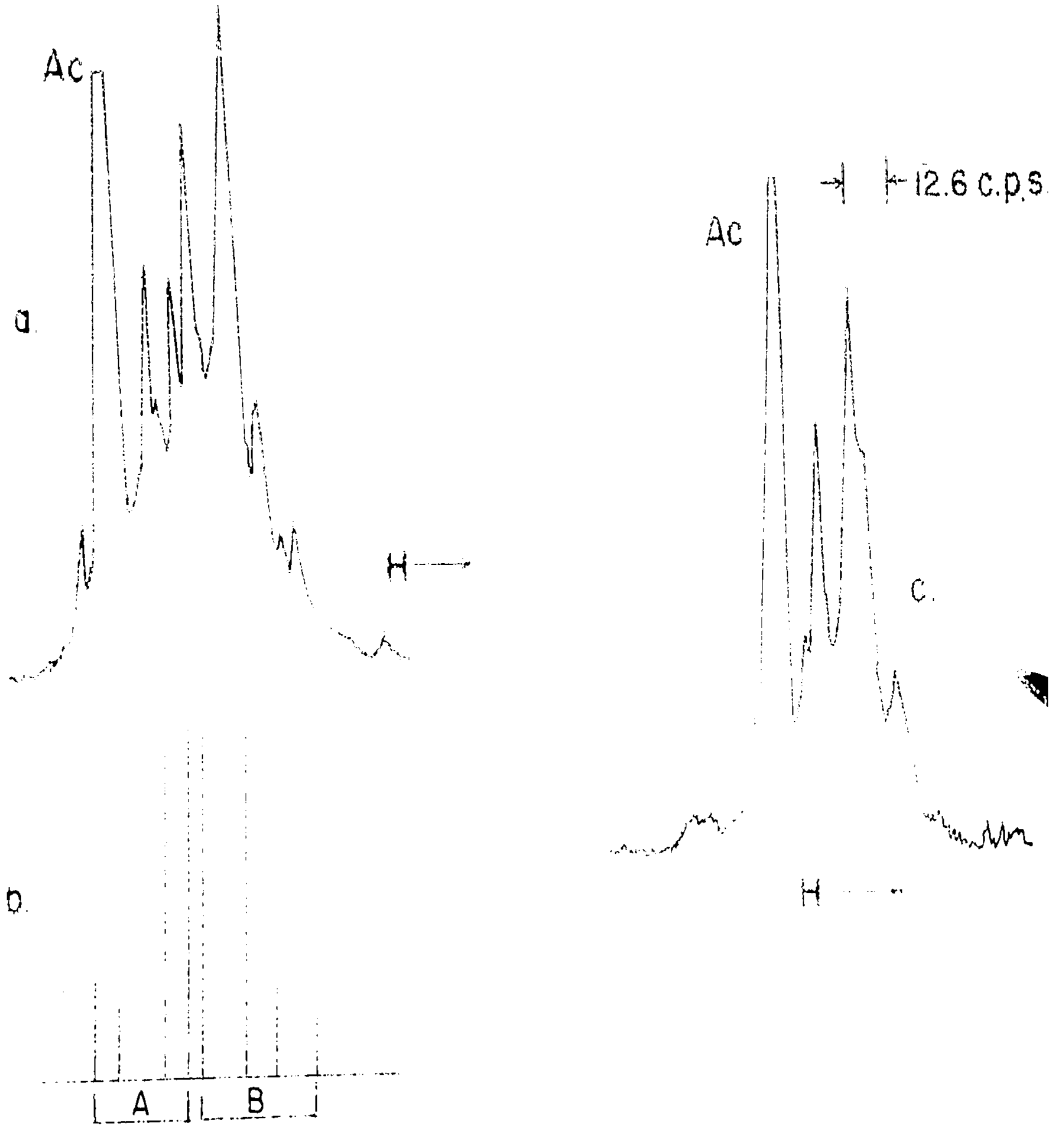


Figure 5. The deuterium decoupled high field multiplet of the deuterated cycloheptyl acetate XV (-95°)

a) observed
b) calculated
c) with additional α-proton decoupling.

the size of the spacings to be expected in the $(AB)_2X$ quartets. These approximate values of J_{AB} changed greatly with temperature (Table I).

Table I

Analysis of α-Proton Decoupled Spectra of the Deuterated Cycloheptyl Acetate XV.

	20°	-95°
J_{AB} (c.p.s.)	7.6	12.6
ν_{AB} (c.p.s.)	11.8	17.8

The $(AB)_2X$ pattern can be analysed easily; it is very similar to the well-known ABX pattern for which a simple solution is possible (67). Mixing of states occurs only between A and B protons bonded to the same carbon atom. This gives rise to an X multiplet which is made up of two combined multiplets of the ABX case, as shown in Fig. 6. The net result is the pattern of three 1:2:1 triplets as in Fig. 6. In the present case, although these triplets overlapped, all the lines could be identified. The information obtained from the X multiplets is shown in Table II. Much more precise measurements were obtained at -95° than at 20°; the reason for the low precision at 20° is not known.

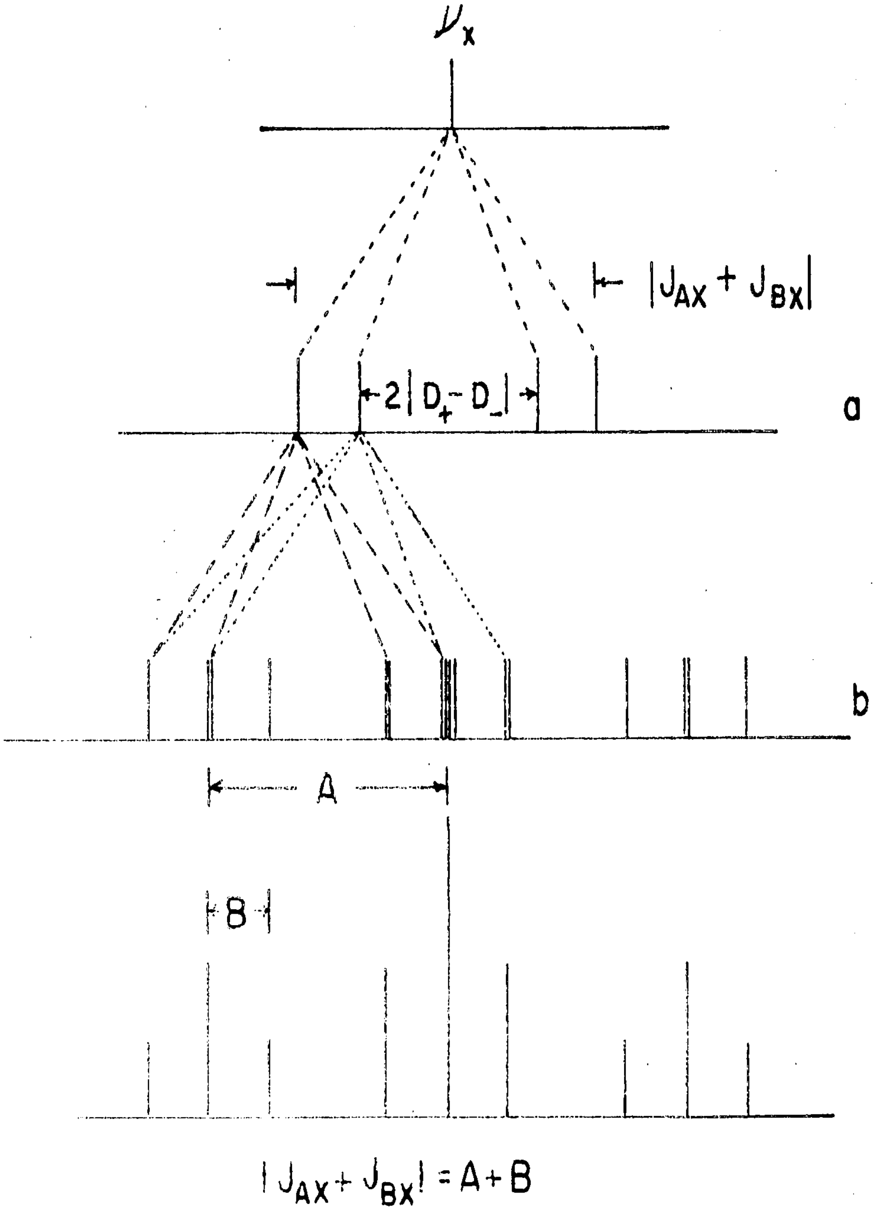


Figure 6. The X multiplet of an $(AB)_2X$ spectrum in which J_{AX} and J_{BX} have the same sign.

a) interaction with the first AB

b) interaction with the second AB.

Table II

Analysis of the Low Field (X) Multiplets of XV

	20°	-95°
A (c.p.s.)	7.5 ± 0.5	7.87 ± 0.2
B (c.p.s.)	4.7 ± 0.4	5.02 ± 0.1
$\vert J_{AX} + J_{BX} \vert$ (c.p.s.)	12.2 ± 0.9	12.8 ± 0.3
$\vert D_+ - D_- \vert$ (c.p.s.)	1.4 ± 0.4	1.43 ± 0.2

The analysis of the AB part of an $(AB)_2X$ spectrum is identical to the analysis of the AB part of an ABX. The procedure outlined by Wiberg and Nist (67) was followed. Some peak separations equal to J_{AB} were submerged by the large acetate peak; however, since this spacing occurs four times in an AB multiplet, quite accurate values of J_{AB} were obtained. An extraneous peak due to isotopic impurity could be identified; attempts to include it in the $(AB)_2X$ calculations yielded coupling constants obviously in error. The assignment of a spectrum at -95° is shown in Table III. Quite good agreement of calculated and observed peak spacings was obtained at this temperature. However, due to the distortions caused by isotopic impurity, no attempt was made to correlate calculated and observed intensities. Observed intensities appeared to be of approximately the correct magnitude. The results obtained from analysis of spectra at both 20° and -95° are shown in

Table III

Calculation of an $(AB)_2$ Multiplet of XV (-95°)

	Observed (Fig. 5a)			Calculated^c (Fig. 5b)			
peaks (c.p.s. from T.M.S.)	peak spacings (c.p.s.)	selection of quartets I	selection of quartets II	peaks (c.p.s. from $1/2(v_A+v_B)$)	peak spacings (c.p.s.)	discrepancy^d (c.p.s.)	intensity
76.2				+21.0			0.34
	7.5				8.1	0.6	
83.7		14.1		+16.1			0.43
	6.6				6.0	0.6	
90.3			14.7	+ 6.9			1.66
	8.1				8.1	0.0	
98.4				+ 2.0			1.57
	2.4				2.4	0.0	
100.8				- 0.4			1.66
	2.4				4.9	0.1	
$(103.2)^a$							
	2.4	$(\quad)^b$					
105.7				- 8.5			1.57
					9.2		
$(\quad)^b$	13.5		13.5	-14.5		0.6	0.34
					4.9		
119.2				-22.6			0.43
						1.9	

a extraneous peak

b hidden by acetate peak

c from: $J_{AB} = 14.1$ c.p.s., $J_{AX} = 6.0$ c.p.s., $J_{BX} = 7.0$ c.p.s., $v_{AB} = 16.6$ c.p.s.

d absolute values of the discrepancies of calculated and observed peak spacings.

detail in Table IV; the average values of chemical shifts and coupling constants are shown in table V. Whereas chemical shifts did not change appreciably with temperature, the coupling constants were quite strongly temperature-dependent. The calculated spectra (Fig. 4b, 5b) were rather similar in appearance; some of the changes with temperature in the observed spectra were caused by the spectral behaviour of the isotopic impurity.

Table V

Analysis of the Spectrum of the Deuterated Cycloheptyl Acetate XV

	20°	-95°
J_{AB} (c.p.s.)	10.8 ± 0.3	13.9 ± 0.3
J_{AX} ″	8.2 ± 2.0	5.2 ± 1.0
J_{BX} ″	4.0 ± 2.0	7.8 ± 1.0
ν_{AB} ″	17.9 ± 1.5	18.1 ± 1.0
ν_{X}	5.20 τ	5.34 τ
$\nu_{acetate}$	8.12 τ	8.09 τ
ν_{A}	8.22 τ	8.20 τ
ν_{B}	8.51 τ	8.50 τ

Table IV

$(AB)_2$ Mutiplets of XV

	20°			-95°		
	A	B	C	A	B	C
Peak	81.8	78.1	81.4	76.2	76.9	75.6
positions	84.9	81.9	84.5	83.7	84.7	83.5
(c.p.s.	92.3	89.0	91.9	90.3	90.1	90.3
from	95.4	93.7	96.2	98.4	98.5	97.9
T.M.S.)	100.1	98.7	100.8	100.8	102.2	100.5
	(102.8)[a]	(101.2)	(103.2)	(103.3)	(104.2)	-
	107.1	105.8	108.2	105.7	106.9	105.8
	(121.9)	(120.0)	(122.2)	119.2	121.1	118.5
J_{AB} (c.p.s.)	10.5	10.9	11.1	14.1	13.7	13.9
J_{AX} "	8.4	8.6	7.2	6.0	4.8	4.3
J_{BX} "	3.8	3.6	5.0	7.0	8.2	8.6
ν_{AB} "	17.3	18.8	17.1	16.6	19.4	18.6
ν_A (τ)	8.21	8.23	8.21	8.21	8.18	8.21
ν_B (τ)	8.50	8.54	8.49	8.49	8.50	8.53
discrepancy[b] (c.p.s.)	5.3	3.3	6.3	1.9	2.0	4.2

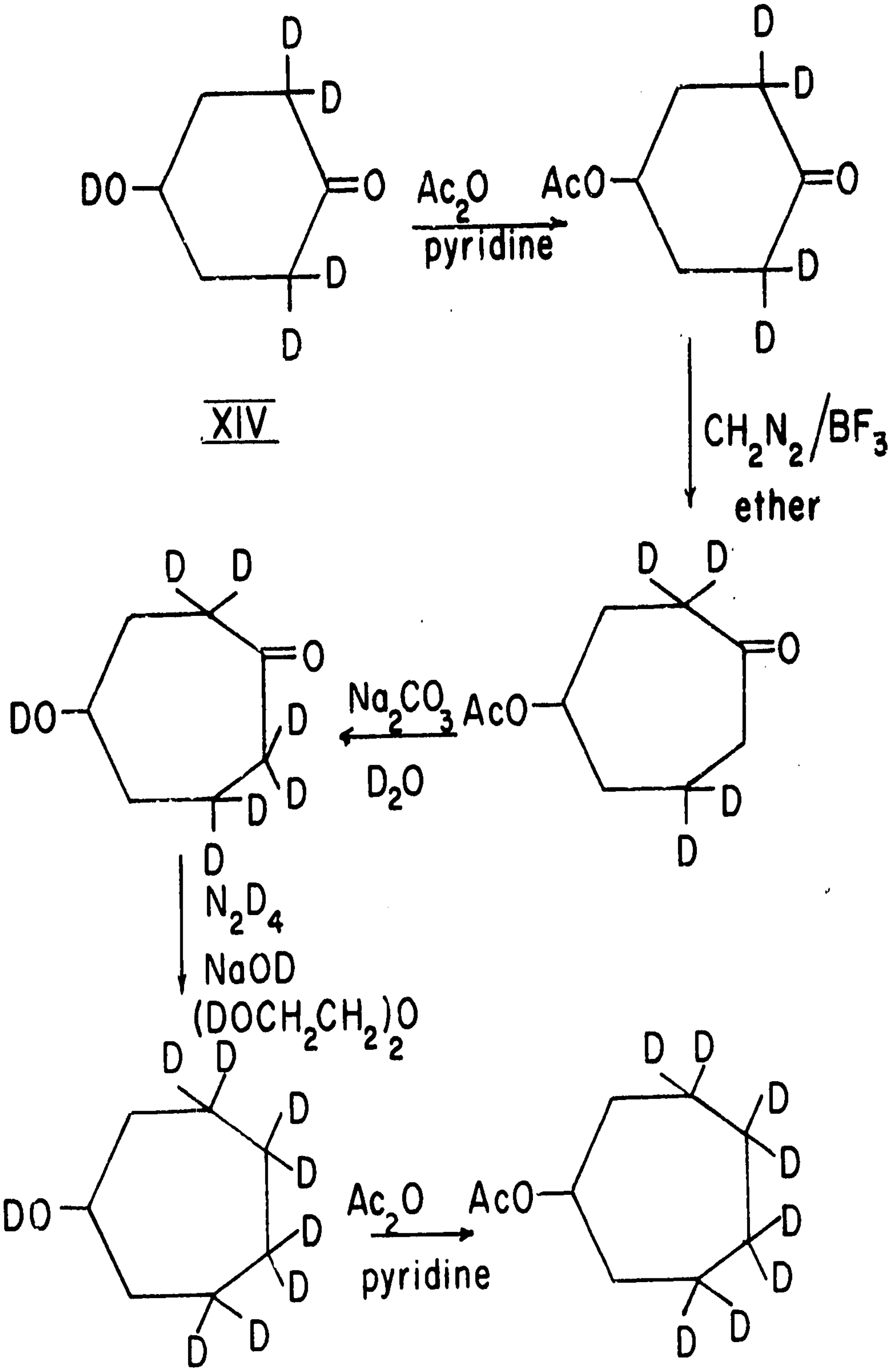
[a] extraneous peaks are bracketed.

[b] total discrepancy between calculated and observed peak spacings in a multiplet.

DISCUSSION

The difficulties involved in the analysis of N.M.R. spectra of simple alicyclic compounds have been discussed. In the cyclohexane series, the complex spectra have in some cases been simplified by deuteration techniques. One of these, the remote deuteration technique developed by Anet (52) in this laboratory, appears suitable for extension to larger rings. It allows the determination of vicinal and geminal coupling constants. Provided that coupling constants of the pure conformers can be determined, either by "freezing out" of the conformers or by the use of suitable model compounds, the dihedral angles may be estimated using the Karplus relationship. Because 3,3,4,4,5,5,6,6-octadeuteriocycloheptyl acetate (XV) did not undergo a "freezing out" of conformers down to -110°, no conformational analysis was attempted. This result, however, confirms the recent calculations of Hendrickson (9) which indicated high flexibility of cycloheptane rings even in the presence of bulky substituents. A more limited investigation of XV was carried out; the spectra at 20° and -95° were analysed to determine chemical shifts and coupling constants.

XV was synthesized from 2,2,6,6-tetradeuterio-4-deuteroxycyclohexanone (XIV), available from Anet's previous investigation (52), as shown in Fig. 7. XIV had been synthesized from quinitol by mono-acetylation, chromium



XIV

XV

Figure 7. The synthesis of 3,3,4,4,5,5,6,6-octadeuterio-cycloheptyl acetate.

trioxide oxidation of the remaining hydroxyl group, and deuterium exchange α to the carbonyl group.

In most cases, remote deuteration is more difficult than adjacent deuteration because exchange of hydrogen for deuterium is most readily carried out adjacent to a suitable functional group. In the present synthesis, however, the presence of a ketone function as a second functional group in the 4-position of the six-membered ring made possible a simple reaction sequence. The ketone allowed base-catalysed deuterium exchange α to it, and ring enlargement with diazomethane to give a cycloheptane derivative. After the completion of these procedures, the ketone could be removed by a Wolff-Kishner reduction using deuterated reagents; this yielded cycloheptanol with the desired pattern of deuterium substitution.

The ring enlargement was carried out most conveniently by diazomethane in the presence of boron trifluoride (68). However the insertion of a methylene group into a ketone by reaction with diazomethane has the inherent disadvantage that one pure product, resulting from insertion of a single methylene group, is not obtained. This initial product is itself reactive towards diazomethane and yields higher homologs. In the present ring enlargement reaction, therefore, a mixture of the six, seven, and eight-membered compounds was obtained; this was not easily separated. Wolff-Kishner reduction was carried out directly on the mixture; the alcohols obtained could be separated by preparative vapour phase chromatography.

The low isotopic purity (65% deuteration) obtained was not inherent in the method, but probably resulted from insufficient deuteration of the reagents used in the Wolff-Kishner reduction. In spite of the low isotopic purity, analysis of the $(AB)_2X$ spectrum of XV was possible. The inaccuracies involved, however, were considerable. Further studies, involving a series of compounds of higher isotopic purity, would be desirable to confirm the results. The present work should be considered as merely a preliminary investigation into coupling in seven-membered rings.

The variation of J_{AB}, the geminal H-H coupling constant, with temperature was supported by independent calculations on three spectra at each temperature. The values of J_{AB} at a single temperature agreed to within 0.6 c.p.s., while the mean value of J_{AB} at -95° was 3.1 c.p.s. larger than the mean value at 20°. Because the variation of J_{AB} with temperature is considerably larger than the experimental error, the effect can be regarded as genuine. The result is of interest in the light of theoretical treatments of geminal coupling constants by Gutowsky and co-workers (69,70). It has been discovered that their calculations (69) are based on an incorrect expression for angular dependence of the coupling constant. However, they are probably correct in their prediction (70) that geminal coupling should not be temperature-dependent as a result of contributions from excited vibrational states due to C-H bending. The temperature-dependent effect observed in cycloheptyl acetate is probably the result of special properties of the seven-membered ring.

The marked temperature dependence of the vicinal coupling constants J_{AX} and J_{BX} (Table V) is also interesting, and provides an additional indication of unusual effects in this system. Although the values of J_{AX} and J_{BX} are less accurate than the J_{AB} values, the changes with temperature exceed the estimated experimental error.

The temperature dependence of the coupling constants in cycloheptyl acetate could be due to significantly different proportions of conformers at the two temperatures studied. In most cycloheptane derivatives, several conformers of similar energy should be present (9). Because of the small energy differences of the conformers, their proportions in the equilibrium mixture could change considerably over the temperature range involved. This would result in different averaged values of the dihedral angles, and hence different vicinal couplings, at the two temperatures. Also the conformations could have different degrees of bond angle deformation; thus the geminal couplings, highly dependent on bond angle (69), would also change with temperature.

Because of the number of possible conformations in cycloheptane derivatives, it is difficult to deduce anything about the pure conformers. In a fused seven-membered system, some evidence has been presented indicating that axial ring hydrogens absorb at higher field than the corresponding equatorial ones (71), but no similar results in simple systems have been reported. The present study at -95° appears to support this relationship. At this temperature the β-proton B, which absorbed at highest field, coupled more strongly with the α-proton, X. As in the cyclohexane system, the Karplus relationship suggests that this strong coupling resulted from the predominance of vicinal diaxial relationships; this would indicate that the axial β-proton absorbed at higher field. However, at 20° the higher field β-proton (B) coupled less strongly than the lower field β-proton (A). The predominance of a different conformer at 20° could explain this change, but the system is too complex, and the available information too limited, to allow definite conclusions.

The present investigation does not definitely establish any relationship between conformational position and chemical shift of ring protons in the seven-membered ring. The variations of coupling constants with temperature are, however, in accord with the predicted existence of several conformations of similar energy in cycloheptane derivatives. An extension of this work to other derivatives and other temperatures would be of interest and might lead to a novel approach to the study of conformations in seven-membered systems.

PART II

RING INVERSION IN CYCLOOCTANE

EXPERIMENTAL

A. Synthesis

Thermal isomerization of *trans*-1,2-divinylcyclobutane

Trans-1,2-divinylcylobutane (b.p. 109-110°, pure by V.P.C. analysis) was prepared by acetophenone-catalysed photodimerization of butadiene (72), followed by fractional distillation. Pyrolysis of a portion (0.10 g.) in a sealed tube at 200° for 12 hours under nitrogen yielded a C_8 product consisting of approximately equal amounts of 1,5-cycloöctadiene and 4-vinylcyclohexene, along with a small amount of polymer. None of the starting material remained. Analysis was carried out by vapour phase chromatography (V.P.C.) as described in the following section. Similar pyrolysis at 145° gave a similar product ratio, but only 50% of the starting material had reacted after 12 hours; 85% had reacted after 72 hours.

V.P.C. analysis of butadiene dimers

A Pye Argon Chromatograph with an Apiezon column operating at 60° was used in the analysis of C_8 diolefins. The conditions yielded suitable retention times, none greater than 20 minutes. The four peaks involved were identified easily. The 4-vinylcyclohexene peak was confirmed by comparison with an authentic sample (Matheson Coleman and Bell). The two peaks of similar retention times, due to the *cis*- and *trans*-1,2-divinylcyclobutanes formed in the photochemical reaction of butadiene (72), could be characterized by the behaviour of the photochemical reaction mixture on reflux at 120°. One peak (the *trans*) remained unchanged while the other (the *cis*) was replaced by a new peak of considerably longer retention time. This was in accord with the reported (73) isomerization of the *cis* isomer to 1,5-cycloöctadiene, and allowed identification of the 1,5-cycloöctadiene peak as well as both of the *cis*- and *trans*-1,2-divinylcyclobutane peaks.

Hexadeuterio-1,3-butadiene (74,75)

Sodium iodide (1g.) and cupric chloride (6.1 g., crystallized from deuterium oxide to exchange the water of hydration) were dissolved in deuterium oxide (47 g., 99.7%). The solution was added to a mixture of dry dioxane (300 ml.) and zinc dust (130 g., Fisher) in a one-liter three-necked flask equipped with mechanical stirrer, dropping funnel, and reflux condenser. The mixture was refluxed 1/2 hour, and the apparatus flushed with nitrogen for a few minutes. Hexachloro-1,3-butadiene (87.0 g., Eastman, practical grade) was added dropwise, over 1-1/2 hours, to maintain a moderate reflux. The gas evolved was collected in a trap cooled by liquid nitrogen. The spent reaction mixture was flushed with a slow stream of nitrogen. The crude product (7 ml.) was a clear, colourless liquid at -10°.

Photodimerization (72)

The crude hexadeuterio-1,3-butadiene was distilled directly into a quartz tube. Acetophenone (1.8 ml.) and a small crystal of hydroquinone were added; the mixture was cooled to -78°, flushed with dry nitrogen, and sealed. Irradiation for 52 hours with a Hanovia Type L 450 watt U.V. lamp yielded:

(a) dimeric products (3 ml.), boiling range 100-160°. V.P.C. analysis showed several components, the chief ones being the *trans*- and *cis*-1,2-divinylcyclobutanes, in an approximately 6:1 ratio.

(b) unreacted material (2 ml.) of boiling point near 0°. By I.R. and N.M.R. analysis, the material was a mixture of olefinic and acetylenic components.

(c) a yellow polymer.

Thermal Isomerization

The dimer fraction described above was pyrolysed under nitrogen in a sealed tube at 190° for 12 hours. V.P.C. analysis of the product indicated the presence of a mixture of 1,5-cycloöctadiene and 4-vinylcyclohexene in approximately equal amounts, as well as several minor components which were not investigated. The deuterated 1,5-cycloöctadiene was separated by preparative vapour phase chromatography (diisodecyl phthalate, 140°) and purified by bulb-to-bulb distillation. A further V.P.C. analysis showed only the desired single peak. Yield 0.15 g.; the infrared spectrum showed C-D absorption at 2095, 2140, 2190 and 2250 cm.$^{-1}$.

Reduction with deuterium gas

Adam's catalyst (0.097 g.) was added to the deuterated 1,5-cyclooctadiene (0.15 g.). The mixture was degassed in a vacuum line and deuterium gas was introduced. An excess pressure of 8 p.s.i. of deuterium gas was maintained for 12 hours, with shaking of the sample tube. The product was dried with sodium shavings and distilled under high vacuum to yield deuterated cyclooctane (0.09 g.). The infrared spectrum showed no olefinic C-D absorption. Mass spectrographic analysis indicated the following composition: C_8D_{16}, 39.9%; C_8HD_{15}, 36.1%; $C_8H_2D_{14}$, 16.1%; $C_8H_3D_{13}$, 5.29%; $C_8H_4D_{14}$, 2.21%.

An independent determination of the percentage of hydrogen was carried out by integration of the proton magnetic resonance signal. Comparison with a standard solution of chlorodibromomethane indicated the presence of 0.8 ± 0.3 protons per molecule.

Diimide reduction of deuterated 1,5-cycloöctadiene

Deuterated 1,5-cycloöctadiene (0.08 g.), p-toluenesulphonylhydrazine (0.99 g., Aldrich), and diglyme (1.6 ml.) were refluxed together for one hour; a brown discoloration appeared and a solid separated. Carbon disulphide (5 ml.) and water (5 ml.) were added; the solid dissolved again. The carbon disulphide layer was separated, washed with 5% HCl, 5% NaOH, and with water until neutral, and dried over magnesium sulphate. Bulb-to-bulb distillation yielded approximately 1 ml. of clear, colorless liquid, which was transferred directly to an N.M.R. sample tube; most of the carbon disulphide was then removed by a slow stream of dry nitrogen.

8. N.M.R. Studies

All proton magnetic resonance spectra were obtained on a Varian V-4302 60 Mc./sec. high-resolution N.M.R. spectrometer. Approximately 1% of tetramethylsilane (T.M.S.) was used as an internal standard. Calibration to determine chemical shifts was carried out by the usual side-band modulation technique. A slightly modified procedure was applied to the spectra used in some calculations. The C^{13} satellite of the T.M.S. peak (59.1 c.p.s. from T.M.S.) occurred at slightly higher field than the cycloöctane spectrum. This was used, along with a side-band at lower field, for calibration. The strength of the main T.M.S. peak was too great, relative to the weak C_8HD_{15} signal, th allow accurate calibration from it. Double irradiation at the deuterium resonance frequency was carried out by means of a spin decoupler manufactured by N.M.R. Specialties.

A low temperature device similar to that described by Piette and Anderson (35) was used to cool the spinning sample tube to the required temperature. An electric current was passed through a heating element in a large Dewar filled with liquid nitrogen, and the evolved cold nitrogen gas was directed through a jacket around the spinning sample tube. The temperature of the sample could be varied by adjustment of the current in the heating element. A copper-constantan thermocouple, checked at the freezing point of toluene (-95°) and found to be accurate to within 1°, was placed inside the jacket and used to monitor the sample temperature. Corrections for the difference between the monitored temperature and the true sample temperature were determined by placing a second thermocouple directly in a sample tube containing only solvent.

Approximate values of the transverse relaxation time T_2 were estimated from the decay envelope of the T.M.S. peak, observed on the oscilloscope, at various temperatures. Very accurate T_2 values, such as are obtained by the use of a fast-response (Sanborn) recorder, were not required in the methods of calculation used in this work.

All of the cycloöctane spectra used as a basis for rate calculations were obtained in approximately 10% solution in vinyl chloride. This solvent remained liquid at a sufficiently low temperature to allow the true low temperature spectrum to be recorded. Even at very low temperatures cycloöctane was quite soluble in vinyl chloride, and yielded a solution of low viscosity. Cyclohexane spectra were obtained in 10% solution in carbon disulphide.

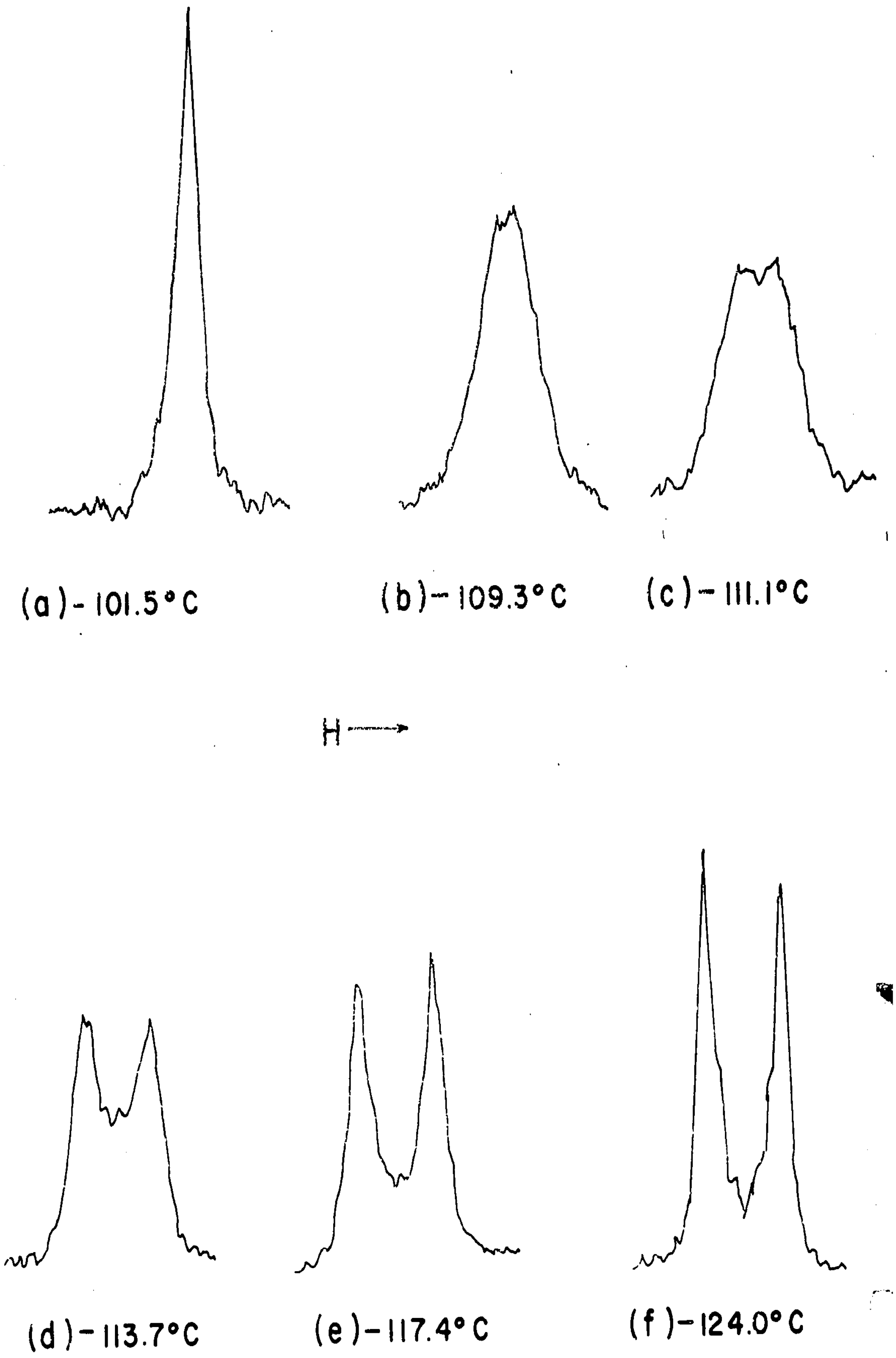
The moment method of spectral analysis was applied to non-deuterated cyclohexane and cycloöctane. The low temperature spectra, at -100^{0} and -135^{0}, respectively, were taken under especially careful control of conditions to insure a pure absorption mode, homogeneous field, and linear sweep. Special care was taken to obtain correct intensities by setting the radio-frequency power well below its saturation value. Intensities were determined from a millimeter grid superimposed on the spectrum. Six spectra of each compound were treated; on each, from 40 to 90 readings of intensity, spaced 1 mm. apart, were obtained. An I.B.M. 650 Computer, programmed to calculate moments and used previously for a similar calculation in this laboratory (76), was used for the calculation.

RESULTS

(a) The Massively Deuterated Cycloöctane

The cycloöctane, "C_8HD_{15}", prepared by massive deuteration, yielded a single broad peak at room temperature in carbon disulphide and at -50° in vinyl chloride. This became quite sharp when double irradiation was applied at the deuterium resonance frequency of about 9.2 Mc./sec. As the temperature was lowered below -100°, the sharp line broadened and separated into two distinct peaks (Fig. 8), the shapes of which corresponded to the simplest exchange process in which two sites exist , with equal populations and lifetimes, and no spin-spin coupling is present. The coalescence temperature was -111.5° ± 0.5°. At -135° the two peaks were quite sharp (Fig. 9-(3)) and no further separation occurred at lower temperatures. The chemical shift difference was 18.8 ± 0.1 c.p.s.; the peaks occurred at 8.41 and 8.72 on the τ scale. The low temperature spectrum of non-deuterated cycloöctane is shown in Fig. 9-(1). The triplet, in which the two small satellite peaks are separated by 29.4 ± 0.4 c.p.s., does not correspond to any well-known strongly coupled system.

Chemical shifts were negligibly dependent on temperature or solvent. The centre of the spectrum of


(a) - 101.5°C (b) - 109.3°C (c) - 111.1°C

(d) - 113.7°C (e) - 117.4°C (f) - 124.0°C

Figure 8. Changes in the signal shape of massively deuterated cyclooctane near T_c.

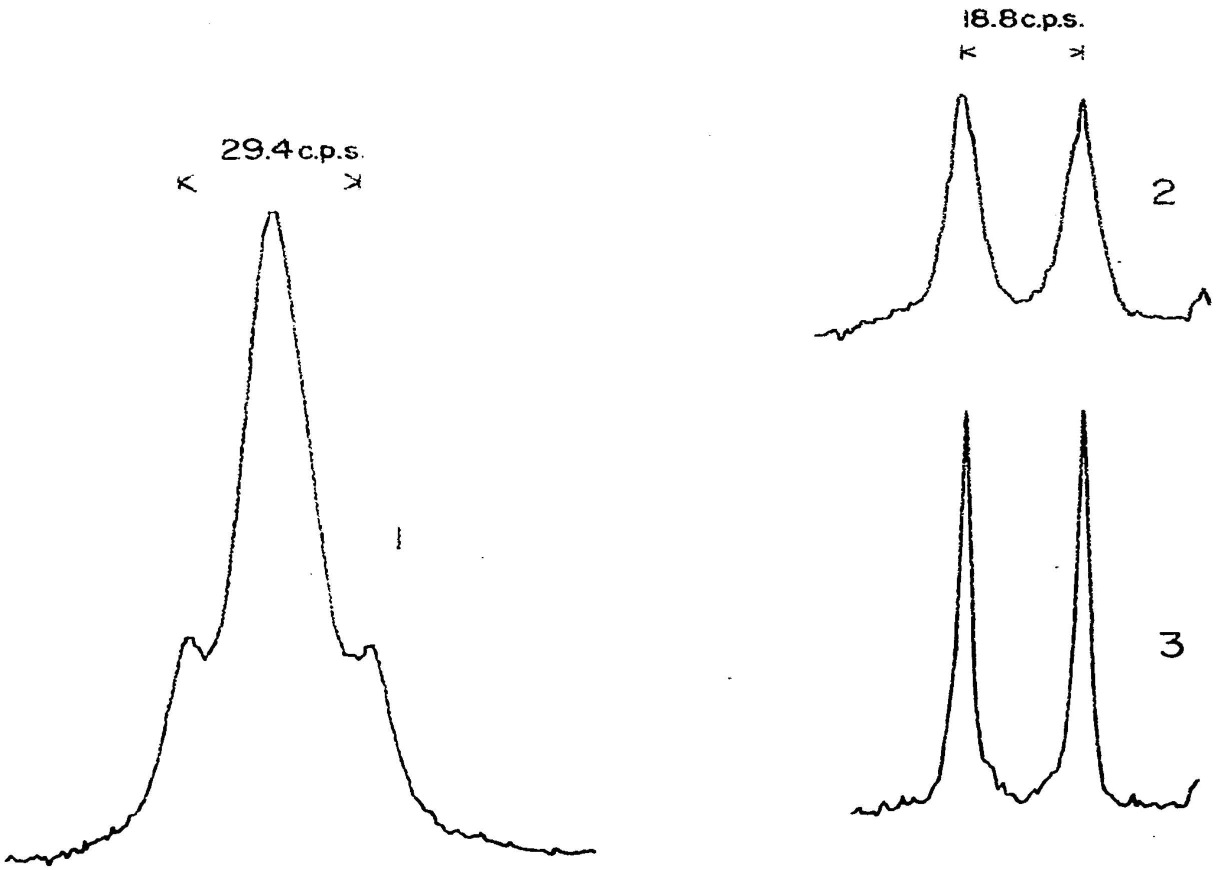


FIG. 9. — CYCLO-OCTANE at -135°
(1) C_8H_{16}, (2) $C_8D_{15}H$, (3) $C_8D_{15}H$, D decoupled

C_8HD_{15} in vinyl chloride was shifted slightly to higher field at -148° (8.56 τ) than at -50° (8.52 τ). Spectra obtained in vinyl chloride, carbon disulphide and difluorodichloromethane at a given temperature were essentially identical, except within a few degrees of the temperature at which either solvent or solute crystallized. This indicates that the rate process observed is purely intramolecular and is not affected significantly by the solvent. All the proton magnetic resonance spectra of C_8HD_{15} were quite weak (Fig. 8 shows the high noise level) as a result of the small percentage of hydrogen present in the molecule and the necessity of working in dilute solution.

At temperatures below the coalescence temperature T_c, rates were calculates by the method of Gutowsky and Holm (35). This is based on measurement of the separation of the peak maxima near coalescence. The relevant equation in the present simple case, assuming negligible dipole-dipole broadening, is

$$\tau = \left[\frac{1}{2\pi^2 \nu_{AB}{}^2 \left[1 - \left(\frac{\nu_e}{\nu_{AB}}\right)^2\right]}\right]^{1/2}, \qquad [1]$$

in which: ν_e (c.p.s.) is the observed peak separation

ν_{AB} (c.p.s.) is the peak separation at slow exchange (i.e., the true chemical shift)

2τ is the lifetime of a proton on either site in the molecule.

The results are summarized in Table VI. Gutowsky and Holm developed a graphical method of determining corrections for T_2; this was found to be suitable for the present analysis. Since T_2 was estimated to be 0.21 sec. in the temperature range involved, the corrections to log $\frac{1}{2\tau}$ were small and were estimated directly from Fig. 3 of reference (35). These corrections were plotted against $10^3/T$, the best straight line was drawn, and the corrections actually used in Table VI were determined from this line. The measurement of peak separations very near T_c involved large errors because here the high noise level made it difficult to locate the maxima accurately.

Above T_c, kinetic analysis was based on the width at half-height of the single broad line. The equations involved were developed by Gutowsky and Holm (35) but were not applied to their rate determinations. In the present simple case, with the assumption of large T_2, the expression is

$$\tau = \left[\frac{2\nu^2}{\frac{1}{2}\pi^2 \nu_{AB}{}^4 + 4\pi^2 \nu_{AB}{}^2 \nu^2 - 8\pi^2 \nu^4}\right]^{1/2} \qquad [2]$$

in which 2ν (c.p.s.) is the band width at half-height. This equation is also applicable immediately below T_c, and was applied to a few spectra in this region which did not show a clean separation of peaks because of the high noise level. T_2 was estimated to be 0.40 sec. at -100° and 0.32 sec. at

Table VI

Cyclooctane Inversion Rates from Separation of Maxima

T (°C)	$10^3/T°K$	ν_e c.p.s.	Rate ($\frac{1}{2\tau}$) (sec^{-1})	log $\frac{1}{2\tau}$ ($T_2=\infty$)	correction ($T_2 \neq \infty$)	log $\frac{1}{2\tau}$ ($T_2=0.21$ sec.)	Number of spectra measured
-117.8	6.435	17.8	13.51	1.131	-0.045	1.086	1
-117.4	6.418	17.6	14.86	1.172	-0.043	1.129	5
-115.6	6.345	16.6	19.73	1.295	-0.036	1.259	5
-115.0	6.321	16.1	21.61	1.335	-0.034	1.301	2
-113.7	6.270	15.0	25.21	1.402	-0.029	1.373	4
-113.0	6.242	11.9	32.36	1.510	-0.026	1.484	3
-112.6	6.227	9.0	36.69	1.565	-0.025	1.540	1
-112.4	6.219	11.3	33.41	1.524	-0.029	1.373	1

Table VI

Cycloöctane Inversion Rates from Separation of Maxima

T (^{o}C)	$10^3/T^{o}K$	ν_e c.p.s.	Rate ($\frac{1}{2\tau}$) (sec^{-1})	log $\frac{1}{2\tau}$ ($T_2=\infty$)	correction ($T_2 \neq \infty$)	log $\frac{1}{2\tau}$ (T_2=0.21 sec.)	Number of spectra measured
-117.8	6.435	17.8	13.51	1.131	-0.045	1.086	1
-117.4	6.418	17.4	14.86	1.172	-0.043	1.129	5
-115.6	6.345	16.6	19.73	1.295	-0.036	1.259	5
-115.0	6.321	16.3	21.61	1.335	-0.034	1.301	2
-113.7	6.270	15.0	25.21	1.402	-0.029	1.373	4
-113.0	6.242	11.9	32.36	1.510	-0.026	1.484	3
-112.6	6.227	9.0	36.69	1.565	-0.025	1.540	1
-112.4	6.219	11.3	33.41	1.524	-0.029	1.373	1

-108°. The corrections required for these T_2 values were quite small but extremely difficult to calculate. A graphical method could be developed, but in this case the following complex expression, a modification of equation (10-23) of reference (23), was used:

$$v = -K\frac{[(1+\mathcal{T}/T_2)\,P + QR]}{P^2 + R^2} \qquad [3]$$

in which $P = \mathcal{T}[\frac{1}{T_2^2} - w^2 + \frac{1}{4}\nu_{AB}{}^2] + \frac{1}{T_2}$.

$Q = -\mathcal{T}w.$

$R = -w - \frac{2w\mathcal{T}}{T_2}$

v is the intensity of absorption.

w is the frequency (radians/sec.) relative to an origin at the band centre

ν_{AB} is in radians/sec.

Application of equation 3 leads to equation 4, a quartic in $\mathcal{T}$:

$$\frac{\mathcal{T}^2[\frac{1}{T_2^3} + \frac{w^2}{T_2} + \frac{\nu_{AB}{}^2}{4T_2}] + \mathcal{T}[\frac{2}{T_2^2} + \frac{\nu_{AB}{}^2}{4}] + \frac{1}{T_2}}{\mathcal{T}^2[\frac{1}{T_2^4} + w^4 + \frac{\nu_{AB}{}^4}{16} + \frac{2w^2}{T_2^2} + \frac{\nu_{AB}{}^2}{2T_2^2} - \frac{w^2\nu_{AB}{}^2}{2}] + \mathcal{T}[\frac{2}{T_2^3} + \frac{2w^2}{T_2} + \frac{\nu_{AB}{}^2}{2T_2}] + \frac{1}{T_2^2} + w^2}$$

$$= \frac{\mathcal{T}^2[\frac{1}{T_2^3} + \frac{\nu_{AB}^2}{4T_2}] + \mathcal{T}[\frac{2}{T_2^2} + \frac{\nu_{AB}^4}{4}] + \frac{1}{T_2}}{2\mathcal{T}^2[\frac{1}{T_2^4} + \frac{\nu_{AB}^4}{16} + \frac{\nu_{AB}^2}{2T_2^2}] + 2\mathcal{T}[\frac{2}{T_2^3} + \frac{\nu_{AB}^2}{2T_2}] + \frac{2}{T_2^2}} \qquad [4]$$

Equation 4 reduces to equation 2 if $\frac{1}{T_2} = 0$. Because of the difficulty of calculations involving equation 4, solutions were obtained at only two temperatures. Approximate corrections for the remaining temperatures were obtained by intrapolation. The correction factors, $(\log \frac{1}{2\mathcal{T}})_{eq.\ 4} - (\log \frac{1}{2\mathcal{T}})_{eq.\ 2}$, were plotted against $10^3/T$; a third point corresponding to T_c was included, at which the correction was assumed to be negligible. A curve passing through the three points was used to estimate corrections for spectra taken at the remaining temperatures. The rate data calculated by the line broadening method are shown in Table VII.

A further rate determination was possible at T_c where, for infinite T_2,

$$\mathcal{T} = \frac{\sqrt{2}}{2\pi\ \nu_{AB}} \quad . \qquad [5]$$

This yielded a rate constant $(\frac{1}{2\mathcal{T}})$ of 41.9 sec^{-1}. However, the observed coalescence temperature, -111.5°, shown in the Arrhenius plot (Fig. 10) is not the temperature which would be observed if T_2 were in fact infinite. The true T_c for infinite T_2 was estimated from the Arrhenius plot to be -110°.

Table VII

Cycloöctane Inversion Rates from Line Broadening

T ($^\circ$C)	$10^3/T^\circ K$	2ν (c.p.s.)	Rate $(\frac{1}{2\tau})$ (sec^{-1})	Log $\frac{1}{2\tau}$ ($T_2=\infty$)	Correction ($T_2 \neq \infty$)	log $\frac{1}{2\tau}$ ($T_2 \neq \infty$)	Number of spectra measured
-100.7	5.797	4.55	128.8	2.110	0.077^a	2.187	1
-101.1	5.811	4.68	121.1	2.083	0.072	2.155	1
-101.5	5.824	4.90	118.8	2.075	0.072	2.147	2
-103.5	5.893	5.19	98.50	1.993	0.050	2.043	1
-103.7	5.900	5.86	90.40	1.957	0.048	2.005	2
-104.4	5.924	7.80	81.69	1.912	0.042	1.954	1
-106.3	5.992	9.73	69.20	1.840	0.028	1.868	3
-106.5	5.999	10.42	67.64	1.830	0.027	1.857	1
-107.8	6.046	13.33	54.93	1.740	0.020^a	1.759	3
-108.2	6.061	14.51	51.93	1.716	0.017	1.732	1
-108.9	6.086	15.95	48.30	1.684	0.013	1.696	2

Continued on next page.

Table VII - Continued.

T (^{o}C)	$10^3/T^{o}K$	2ν (c.p.s.)	Rate ($\frac{1}{2\tau}$) (sec^{-1})	log $\frac{1}{2\tau}$ ($T_2=\infty$)	Correction ($T_2 \neq \infty$)	log $\frac{1}{2\tau}$ ($T_2 \neq \infty$)	Number of spectra measured
-109.3	6.101	17.50	44.88	1.652	0.010	1.662	2
-110.7	6.154	19.55	40.13	1.603	0.003	1.606	2
-111.1	6.169	20.43	38.17	1.582	0.001	1.583	3
-112.4	6.219	23.35	31.10	1.493	0.000	1.493	2
-112.6	6.227	22.70	32.77	1.515	0.000	1.515	2

a Calculated by equation 4.

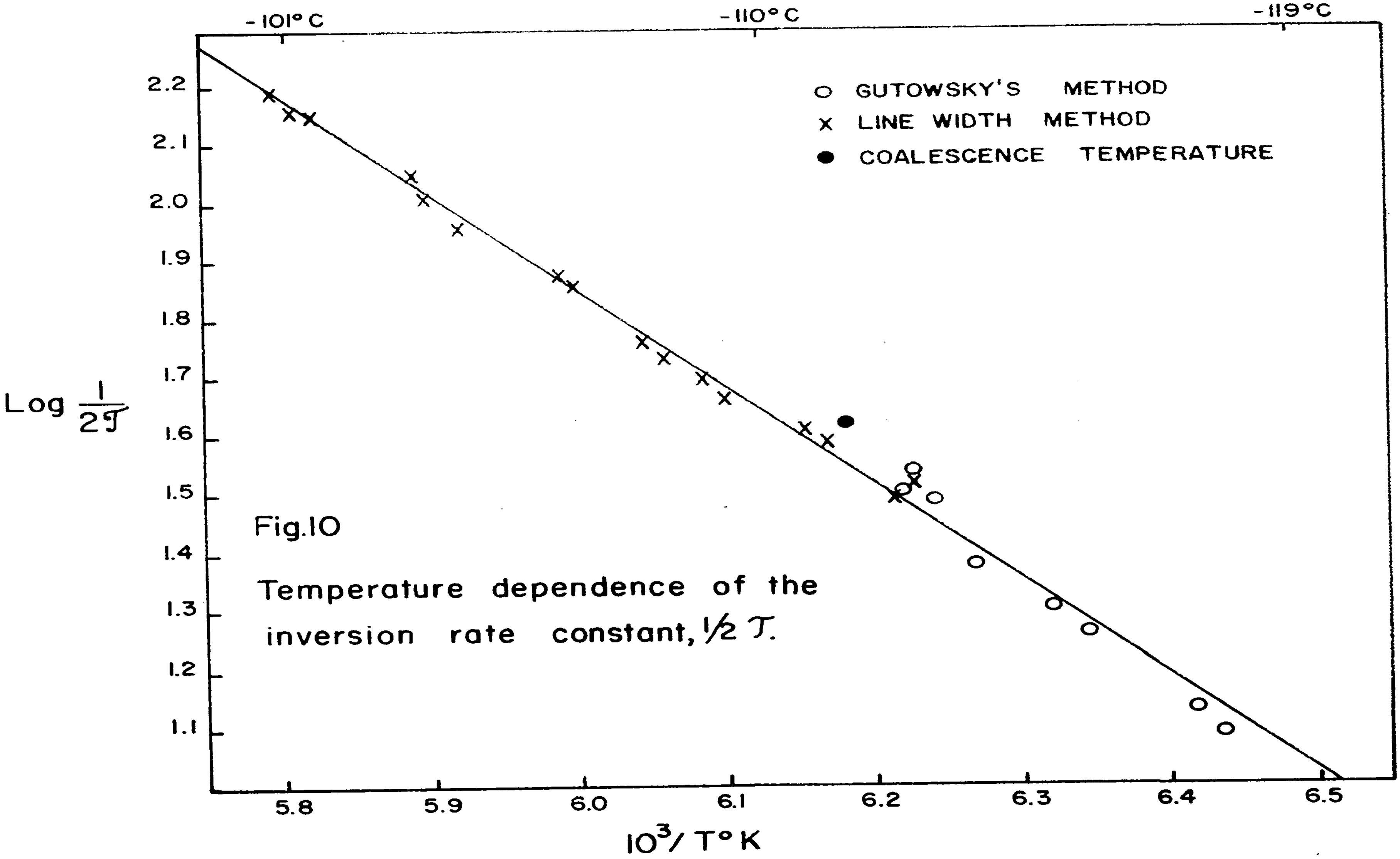


Fig.10

Temperature dependence of the inversion rate constant, $1/2\tau$.

The Arrhenius plot, including all the rate data, yielded a good straight line (Fig. 10). As expected from the difficulties in measurement, rates determined by maxima separations very near T_c, are seen to be less accurate. A least squares analysis was carried out to yield values of the Arrhenius activation energy E_a and the frequency factor A, according to the equation

$$k = \frac{1}{2\tau} = A\, e^{-E_a/RT} \qquad [6]$$

For comparison, separate least squares analyses were carried out on the values obtained from line broadening, and those obtained from maxima separations well below T_c. As shown in Table VIII, the two methods agreed quite well.

Table VIII

Reaction Parameters by Least Squares Analysis

	all data	line broadening	maxima separation
Slope	-1.687	-1.612	-1.688
E_a(kcal./mole)	7.72	7.38	7.73
log A	11.97	11.52	11.97
A (sec^{-1})	$8.8\text{x}10^{11}$	$3.3\text{x}10^{11}$	$9.2\text{x}10^{11}$

Thus the Arrhenius activation energy is 7.72 ± 0.30 kcal./mole, and the frequency factor is 8 x 10^{11} $sec.^{-1}$ The free energy of activation, $\Delta F^{\neq}$, was calculated to be 8.15 ± 0.30 kcal./mole, from Eyring's equation (77),

$$k = K \frac{kT}{h} e^{-\Delta F^{\neq}/RT} , \qquad [7]$$

at the coalescence temperature, -110°. The transmission coefficient, K, was assumed to be unity. The enthalpy of activation, $\Delta H^{\neq}$, was 7.40 ± 0.30 kcal./mole, and the entropy of activation was -4.6 ± 3.5 e.u. The values of $\Delta F^{\neq}$ and $\Delta S^{\neq}$ assume a simple rate process, not involving a stable intermediate. If, however, a stable intermediate exists, a statistical correction to these values is required (56). The modified calculation, involving a transmission coefficient of one-half, yields a $\Delta F^{\neq}$ of 7.92 kcal./mole, and a $\Delta S^{\neq}$ of -3.2 e.u.

Spectra at -148°, the lowest temperature attainable in vinyl chloride solution, showed additional fine structure in the form of two very small peaks, within the major peaks and separated from them by 5.7 ± 0.7 c.p.s. (Fig. 11). This indicates the presence of an AB coupling pattern in a small proportion of the molecules; the additional smaller peaks outside the major peaks could be swamped by the high noise level. The spacing corresponds to a coupling constant of 20 ± 5 c.p.s.

A preliminary investigation was carried out, for comparison, on a sample of deuterated cyclohexane supplied by Dr. L.C. Leitch. Similar behaviour was observed. The low temperature spectrum (-100°) consisted of two sharp singlets

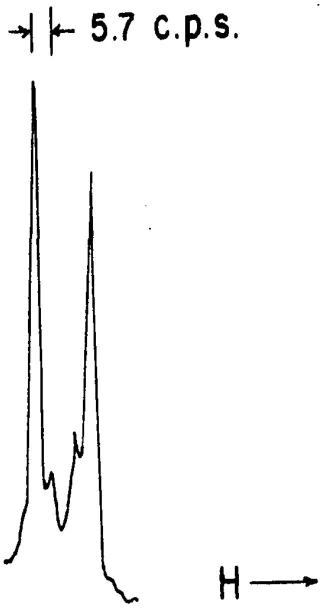


Figure 11. Massively deuterated cycloöctane at -148°.

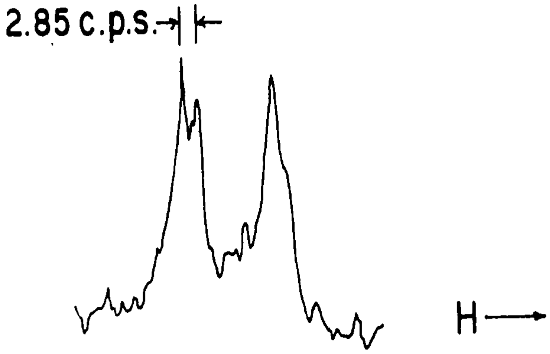


Figure 12. The cycloöctane formed by diimide reduction, at -135°.

separated by 28.6 ± 0.1 c.p.s. However, the proportion of hydrogen present as isotopic impurity was too low to allow calculation of rate data. In the region of coalescence, the broadened lines were barely distinguishable above the noise.

(b) The Diimide Reduction Product

The deuterium decoupled low temperature spectrum of the cycloöctane obtained by diimide reduction is shown in Fig. 12. The signal was quite weak, despite the presence of approximately five protons per molecule, because only a small amount of the compound was prepared; a very dilute solution was used. However, the spectrum is adequate to yield the desired information. A small splitting of 2.34 ± 0.4 c.p.s. is apparent in the low field peak. This is obscured in the high field peak; however, a similar degree of broadening in this peak indicates unresolved fine structure. Chemical shifts of the two main peaks were the same as those obtained from C_8HD_{15}. Fig. 12 clearly indicates the absence of any large coupling between non-equivalent protons.

(c) Moment Analysis

In the case of both chair cyclohexane and crown cycloöctane, the equations for the reduced second, third, and fourth moments, i.e., these moments taken from an origin where the first moment is zero, reduce to the relatively simple forms

$$M_2 = \frac{(\nu_{AB})^2}{4}$$

$$M_3 = 0$$

$$M_4 = M_2^2 + M_2(J_{gem}^2 + 2J_{cis}^2)$$

where J_{gem} is the geminal coupling constant, J_{cis} is the cis vicinal coupling constant and 1,3 coupling is assumed to be negligible. These are easily derived from equations (6-89), (6-90) and (6-91) of reference (23). They allow the calculation of the relative chemical shift of the two substituent positions, and the root mean square of the coupling constants between non-equivalent protons, as follows:

$$\nu_{AB} = 2\, M_2^{1/2} \qquad [8]$$

$$J_{gem}^2 + 2\, J_{cis}^2 = \frac{M_4 - M_2^2}{M_2} \qquad [9]$$

The computed values for M_2, M_3 and M_4, and the corresponding values for ν_{AB} and $[J_{gem}^2 + 2\, J_{cis}^2]^{1/2}$, are shown in Table IX. Large errors are evident. The results show a distinct trend with sweep rate; the lower the sweep rate, the smaller ν_{AB} and $[J_{gem}^2 + 2\, J_{cis}^2]^{1/2}$ become. Values of the third moment, M_3, are not grouped about the theoretical zero value.

Table IX

Moment Analysis of Cyclohexane and Cycloöctane

	M_2 (c.p.s.)^2	M_3 (c.p.s.)^3	M_4 (c.p.s.)^4	ν_{AB} (c.p.s.)	$[J_{gem}^2 + 2J_{cis}^2]^{1/2}$ (c.p.s.)
Cyclohexane	206.8	227.2	89830	29.1	15.2
	-207.0	120.1	93190	30.0	16.2
	89.33	77.2	18710	32.0	17.6
	85.98	106.4	17320	30.7	17.8
	35.24	38.1	3049	30.9	18.6
	35.70	36.4	3065	31.2	18.5
Average:				30.6	17.3
Cycloöctane	52.68	-144.9	9685	23.9	18.9
	55.77	36.6	11200	23.1	18.6
	59.12	163.7	14000	24.1	20.9
	131.4	158.9	59250	22.9	17.8
	146.3	257.4	72910	22.7	17.6
	133.7	127.6	59610	22.4	17.1
Average:				23.2	18.5

DISCUSSION

(a) Ring Inversion

Detailed calculations have indicated that cycloheptane and most of its derivatives should be capable of undergoing rapid interconversion among conformers evan at low temperatures (8,9); the first part of this thesis supports these results in the case of cycloheptyl acetate. There has been little reason to assume that a similar flexibility would be present in the eight-membered ring. In this ring system kinetic analysis by N.M.R. has been attempted only on cyclo̊ctane itself. Harris and Sheppard (61) obtained only a broadened single band at their lowest temperature, -113°. An extrapolation of the line broadening process, assuming a relative chemical shift between two sites similar to that observed in cyclohexane, led these authors to estimate a coalescence temperature of -163°, an enthalpy of activation of 2.6 kcal./mole, and an entropy of activation of -30 e.u. for the exchange broadening process. This would indicate a ring flexibility similar to that of cycloheptane. However, Meiboom, from his measurements of the transverse relaxation time T_2, suggested that two separate line-broadening processes existed, both with similar activation energies of about 8 kcal./mole (78). The present work was undertaken as an attempt to clarify these contradictory findings.

It soon became apparent that cycloöctane itself could yield only very limited information. Investigation in vinyl chloride solvent at lower temperatures than those attained by Harris and Sheppard showed resolution into a triplet in which the peaks had unusual relative intensities (Fig. 9-(1)) and which remained unchanged below -135°. Clearly, since no further changes accurred at lower temperatures, the entire temperature range in which the rate process affected the appearance of the spectrum was observed. The triplet obtained below -135° was, therefore, the true low temperature spectrum of cycloöctane.

The broad signal obtained shows that at these temperatures all the protons are not equivalent. Since the spectrum does not show separate resonances of chemically different protons, strong coupling must be present among them. The signal shape does not correspond to one of the known, relatively simple multiplet patterns arising from strong coupling. This is the expected result, since mixing of states among large numbers of strongly coupled protons normally gives rise to extremely complex resonance absorption patterns (52,58). In the analogous compound cyclohexane, a fortuitous similarity of the complex pattern to a broadened doublet made possible an approximate analysis (60,61), the results of which, however, are of doubtful value. In the present case of cycloöctane, the absence of any simple pattern is not surprising, since any resemblance to a simple pattern would be coincidental.

A simple cycloöctane spectrum, capable of being analysed at low temperatures, was desired, and could be obtained by preparation of a partially deuterated cycloöctane. The mono-protonated compound C_8HD_{15} would yield the simplest possible spectrum. Under double irradiation at the deuterium resonance frequency, the single proton would be free of the effects of coupling. In addition, the proton would be distributed at random over all the substituent sites in the molecule. Hence the low temperature proton magnetic resonance spectrum should contain separate singlets for all of the chemically different substituent positions present, and the relative intensities of the singlets should indicate the populations of these positions. This information could be used to indicate the number of conformations present, and possibly, in addition, to indicate which of the proposed conformations were present. If, as was suggested by Meiboom's investigation, two separate line broadening processes were present, these might be observed as the coalescence, at different temperatures, of two different sets of lines. Thus the observation of a single non-coupled proton, which in many molecules could yield no significant information, should prove to be the source of much fundamental information in this highly symmetrical alicyclic compound, in which all substituent positions can become equivalent merely by pseudorotation or a change of conformation. For this reason, the synthesis of C_8HD_{15} was undertaken.

Non-substituted eight-membered rings can be obtained in one step from either of two simple hydrocarbons. Cycloöctatetraene can be prepared by high pressure treatment of acetylene in the presence of a suitable catalyst (79). Butadiene can be reacted, either by pyrolysis under conditions which suppress Diels-Alder dimerization (80) or in the presence of a suitable catalyst (81), to yield 1,5-cycloöctadiene. These methods did not appear suitable for preparation of the deuterated eight-membered ring. Yields are low. Deuterated acetylene can be obtained easily, but the reaction under pressure is difficult to carry out and the most suitable catalysts are difficult to prepare. Deuterated butadiene is not prepared as easily as deuterated acetylene, and the product is contaminated by other C_4 compounds (74,75). The pyrolysis of butadiene was reported to give very low yields of 1,5-cycloöctadiene. The catalytic method, which gave moderate yields, involved a difficult synthesis of the catalyst, and rigorous exclusion of moisture and impurities.

Fortunately, a simpler route to the eight-membered ring has been reported recently, as part of a study by

Hammond and co-workers concerning the ultraviolet photolysis of butadiene in the presence of various ketones as sensitizers (72). The photolysis product was found to consist of the cis- and trans-1,2-divinylcyclobutanes and 4-vinylcyclohexene, in proportions dependent on the sensitizer used. It had been reported previously that cis-1,2-divinylcyclobutane isomerized in good yield to 1,5-cycloöctadiene on reflux at 120° (73). However, since the cis- compound was the minor product (15%) in the photolysis, the overall yield from butadiene was still very low. In spite of this, the procedure appeared to be the most suitable for the small scale preparation of a deuterated eight-membered ring. Preparation of a catalyst was avoided. It was found that the other C_4 compounds, notably vinylacetylene, present as impurities in the deuterated butadiene did not react appreciably under ultraviolet irradiation and could easily be removed from the dimer fraction.

Further investigation led to a new procedure which allowed the yield of 1,5-cycloöctadiene to be greatly increased. Trans-1,2-divinylcyclobutane, the major product (80%) of photolysis when acetophenone was used as the sensitizer, was found to isomerize at 190° to give 1,5-cycloöctadiene in moderate yield. The more drastic conditions required for the isomerization of the trans, relative to the cis, can be explained on the basis of less favourable geometry in the trans compound. This rearrangement was competitive with reversion to butadiene, as evidenced by the presence of a large amount of 4-vinylcyclohexene, the Diels-Alder dimerization product of butadiene, in the pyrolysis product.

By the above procedures, summarized in Fig. 13, it was possible to prepare fully deuterated 1,5-cycloöctadiene in moderate yield by a simple synthetic route. The chief remaining problem in synthesis was reduction to the cycloöctane containing one proton. The high symmetry of the molecule suggested the possibility of avoiding the introduction of a proton in a specific manner. Because of the lack of distinctive substituents, and the rapid interconversion of conformers at room temperature which was indicated by the sharp single line in the C_8H_{16} N.M.R. spectrum, all substituent positions can, for purposes of synthesis, be considered equivalent. Protons present at random in deuterated cycloöctane would give the same N.M.R. signal as isotopically pure C_8HD_{15}, provided that no two protons were close enough in the same molecule to cause appreciable H-H coupling. This is the massive deuteration technique previously used by Tiers and co-workers (46) to simplify the spectra of aromatic compounds. These workers carried out massive deuteration by replacement of hydrogen in the final product; in the present study, it was possible to make use of the hydrogen present as an isotopic

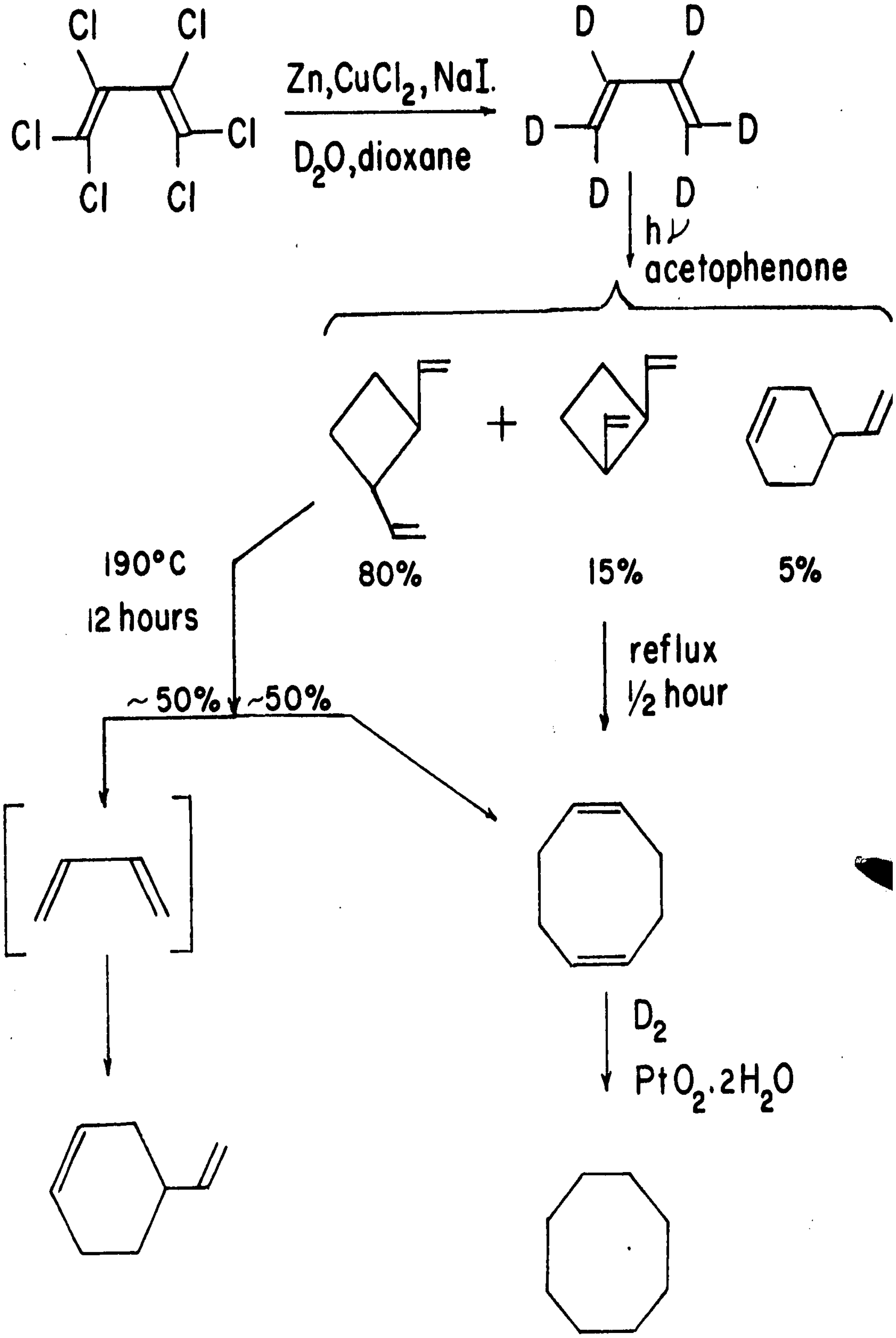


Figure 13. The synthesis of deuterated cycloöctane.

impurity in "fully deuterated" cycloöctane. Thus, the presence of considerable isotopic impurity, which is often a serious problem in syntheses involving deuterium, was put to use in the present case. Extremely high isotopic purity was not desired, because the presence of considerable hydrogen was necessary to allow a reasonably strong proton resonance signal; this allowed the steps to be carried out without special care to maintain the isotopic purity.

When the 1,5-cycloöctadiene was reduced directly to "fully deuterated" cycloöctane with deuterium gas, mass spectrographic analysis indicated the presence of 36% of the desired compound, C_8HD_{15}, as well as 39% of C_8D_{16}, which gave no proton magnetic resonance signal. The remaining 25%, cycloöctanes containing more than one proton, made very important contributions to the spectrum. Since very few molecules contained as many as four protons and coupling is negligible unless the protons are quite close, the expected random distribution allowed the effects of coupling to appear in only a small fraction of the signal. Table X illustrates that geminal coupling should appear in approximately 7% of the signal. *Cis* vicinal coupling should be present in about 15% of the signal. *Trans* vicinal coupling should not be observed if the crown conformation is present because of zero chemical shift between the *trans* protons.

Table X

Geminal Coupling in Massively Deuterated Cycloöctane

Isotopic Composition	Percentage in mixture	Contribution to signal (%)	Percentage of contribution showing geminal coupling	Percentage of total signal showing geminal coupling
C_8D_{16}	39.9	0	0	0
C_8HD_{15}	36.1	38.2	0	0
$C_8H_2D_{14}$	16.1	34.0	6.7	2.3
$C_8H_3D_{13}$	5.29	16.8	13.6	2.3
$C_8H_4D_{12}$	2.21	9.3	22.3	2.1
others (as $C_8H_5D_{11}$)	0.4	1.7	35.7	0.6
				7.3%

Rate analysis of sufficient accuracy can be carried out without considering the effects of coupling, especially since, as the temperature is raised, fine structure due to spin-spin splitting "averagesout" before the coalescence of the singlets corresponding to chemically different sites. In accord with these expectations, the spectrum at -135° (Fig. 9-(3)) showed no coupling, although it had separated into two sharp peaks; below this temperature, no further separation of the peaks could be detected. The spectrum at -148°, the lowest temperature attainable, showed small additional peaks corresponding to a residual coupling of 20 ± 5 c.p.s. (Fig. 11). For the purposes of kinetic analysis, therefore, the massively deuterated cycloöctane can be considered to have the formula C_8HD_{15}.

The simple low temperature spectrum of "C_8HD_{15}" (Fig. 9-(3)), consisting of two sharp singlets, strongly suggests that only one conformation can be present, since all proposed conformations have at least two distinct substituent positions. Fig. 8 shows clearly the simple pattern of coalescence expected for rapid proton exchange between two sites of equal populations and lifetimes. Such a pattern allows calculation of fairly accurate rate data for the process causing coalescence. The only feasible rate process in cycloöctanes is ring inversion.

In this rate investigation, the weakness of the proton resonance signal was a factor limiting the accuracy of measurements. The weak signal was expected because of the low percentage of protons in the molecule. A second limiting factor was the determination of T_2, the transverse relaxation time. T_2 is, in effect, a measure of line-broadening processes caused by magnetic field inhomogeneities in the sample. At low temperatures, the most important source of inhomogeneities is the slowing of the "tumbling" of the molecules because of high viscosity, with the resultant failure of intermolecular perturbations to average out. Thus at low temperatures T_2 is determined by the viscosity of the solution. The inhomogeneities cause broadening of all lines in the spectrum, regardless of whether additional broadening due to a rate process is involved.

In rate calculations, therefore, T_2 must be considered, in order to obtain accurate results from a coalescence pattern which is affected by the two independent line broadening processes. T_2 can be determined accurately by calculations based on the exponential decay envelope of a "sharp" line in the spectrum, i.e., a line which is involved in no additional broadening process; the T.M.S. reference peak is suitable. A fast-response (Sanborn) recorder, normally used to observe the decay envelope (36), was not available in this laboratory;

instead, approximate values of T_2 were estimated from the decay of the T.M.S. peak, as observed on the oscilloscope. These estimated values of T_2 were sufficiently accurate because the low viscosity of the vinyl chloride solution resulted in comparitively large T_2 values and hence only slight broadening of "sharp" peaks. Spectra were measured at temperatures suitable for the application of those methods of rate calculation which were the least sensitive to T_2.

The application of the methods of rate determination first put forward by Gutowsky and Holm (35) has been described. In these methods, the chief limitations on accuracy, weak spectra and approximate values of T_2, had the least effect on rate calculations. The high noise level caused serious inaccuracies only in the estimation of the coalescence temperature T_c, and in the determination of maxima separations immediately below T_c. Other methods of calculation were less suitable. Analysis below T_c, based on the ratio of the height of the central minimum to that of the peak maxima (38), was adversely affected by the low signal -to-noise ratio. Both measurements had to be taken from a poorly defined base line; also, estimation of the true positions of maxima and minima introduced large errors. The method developed by Piette and Anderson (36), based on observations of line widths at the two extremes of very slow and very fast exchange, is especially dependent on accurate T_2 measurements and hence is very unsuitable.

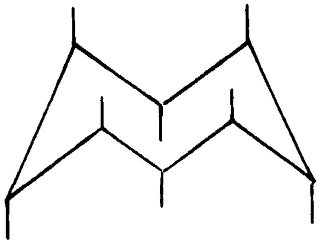
Although rate determinations by the measurement of band widths at half-height yielded accurate results, the method as applied here is unsuitable because of the laborious calculations required to include the effects of T_2. A graphical solution, similar to that used by Takeda and Stejskal (41) to correct for T_2 in the collapse of a spin-spin doublet, would be more suitable. These authors obtained a general expression for the shape of the collapsed spin-spin doublet in terms of only three variables; this made possible the graphical solution. A similar solution for the case of a chemical shift doublet is possible and would greatly simplify the rate calculations involving band widths.

The straight line relationship obtained in the Arrhenius plot of the rate data (Fig. 10) allowed a quite accurate calculation of the reaction parameters, the significance of which will be discussed further. Cyclo-öctane can be discussed on the basis of only one conformation being present, since we can ignore the extremely unlikely possibility that two different conformations, whose spectra coincide, invert at the same rate to yield the simple coalescence patterns.

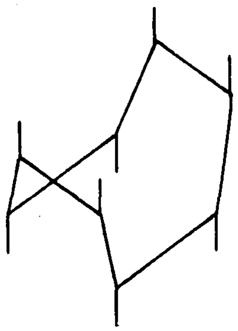
The use of the method of massive deuteration to reinvestigate the results reported on cyclohexane ring inversion (60,61) suggested itself. As described, a similar low temperature proton spectrum of two sharp singlets was obtained from "fully deuterated" cyclohexane. Although there was not enough isotopic impurity in the sample to yield a signal strong enough for rate analysis, it is obvious that the method is applicable to this compound. It is likely that the higher homologs of cycloöctane would also be suitable for treatment by this method.

(b) The Conformation of Cycloöctane

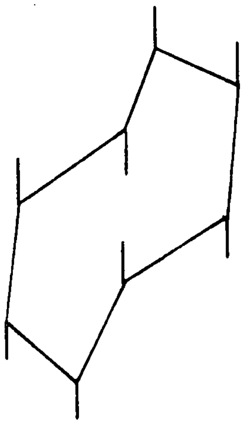
The low temperature spectrum of C_8HD_{15} suggests that one of the proposed conformations of cycloöctane is not present. The three conformations, the crown (VII), tub (VIII) and chair (IX), are re-drawn in Fig. 14 showing the axial substituents only, for simplicity. Both the crown and the tub have two distinct substituent positions; the chair has four. The crown has no eclipsed vicinal interactions, while in the tub each substituent is eclipsed with respect to a substituent on one vicinal carbon, and staggered with respect to the substituents on the other. In each case there is essentially only one type of axial and one type of equatorial substituent position. In the chair some substituents have eclipsed vicinal interactions while others do not; this doubles the total number of distinct substituent positions. Since only two peaks were



crown



tub



chair

Figure 14. Proposed conformations of cycloöctane.

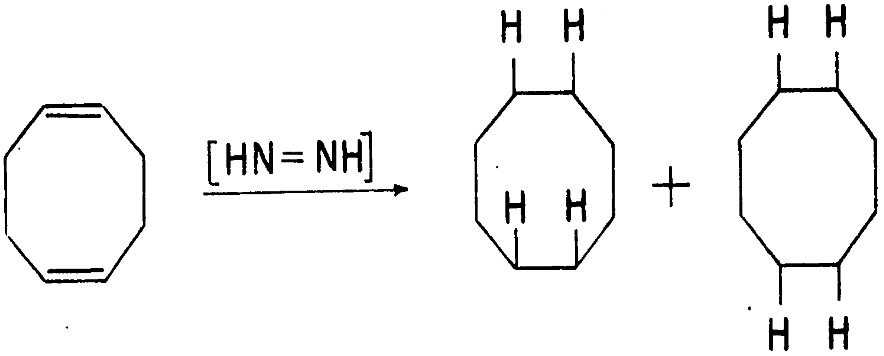
obtained in the low temperature N.M.R. spectrum, the chair conformation can be considered highly improbable.

The spectra of C_8HD_{15} could not be used to distinguish between the crown and tub conformations. To obtain additional information, it was desired to synthesize a selectively deuterated cycloöctane in which a vicinal coupling constant could be determined. This would allow a direct estimation, by the Karplus relationship, of certain features of the geometry of the molecule. The simplest results would be obtained in a molecule containing two vicinal protons, of known stereochemistry, surrounded by deuterium to eliminate all other coupling.

The recent development of the chemistry of diimide was the key to the preparation of a suitable compound. It has been shown (82,83) that diimide reduction of olefins gives exclusively cis addition of hydrogen. The reduction is easy to carry out; good yields were obtained by utilizing commercially available p-toluenesulphonylhydrazine as the diimide source (84). The previously prepared deuterated 1,5-cycloöctadiene was a suitable starting material. Mild reduction with deuterium gas to yield cycloöctene, followed by diimide reduction to give the cis-1,2-diprotonated cycloöctane, was a possible procedure. However, a synthetic step was eliminated by direct reduction of 1,5-cycloöctadiene with diimide. The desired spectrum should not be adversely affected because the two groups of cis vicinal protons introduced into the molecule are effectively isolated from each other if long range coupling is negligible. Besides the elimination of a synthetic step, a stronger spectrum should be obtained, since the resulting cyclooctane contains four protons instead of two, in the desired cis vicinal relationship. This should also help to submerge the signal from the protons which, present at random as isotopic impurity, were used previously to obtain the C_8HD_{15} spectrum.

The low temperature spectrum of the diimide reduction product is shown in Fig. 12. The absence of any large coupling is evident; a splitting of only 2.8 c.p.s. was observed in the low field peak. Thus the application of the Karplus relationship (Fig. 2) rules out very small and very large dihedral angles between non-equivalent cis protons.

It may be noted that the observed splitting could arise in either of two ways. It may be due to cis vicinal coupling. Also, in a system in which no coupling is visible it could be caused by the presence of two distinct species in which the two pairs of cis vicinal protons are cis or trans to each other. Since each double bond in 1,5-cyclooctadiene should be reduced independently by diimide, the reaction product should consist of approximately equimolar amounts of the two isomers XVI and XVII (Fig. 15).



XVI

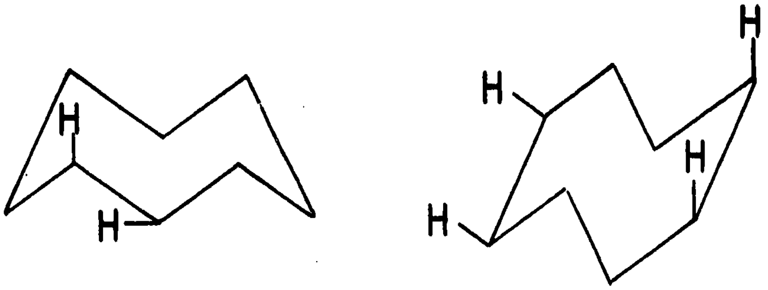
XVII

Figure 15. Diimide reduction of deuterated 1,5-cyclo-öctadiene.

The splitting could be due to the separate, almost coincident spectra of these molecules.

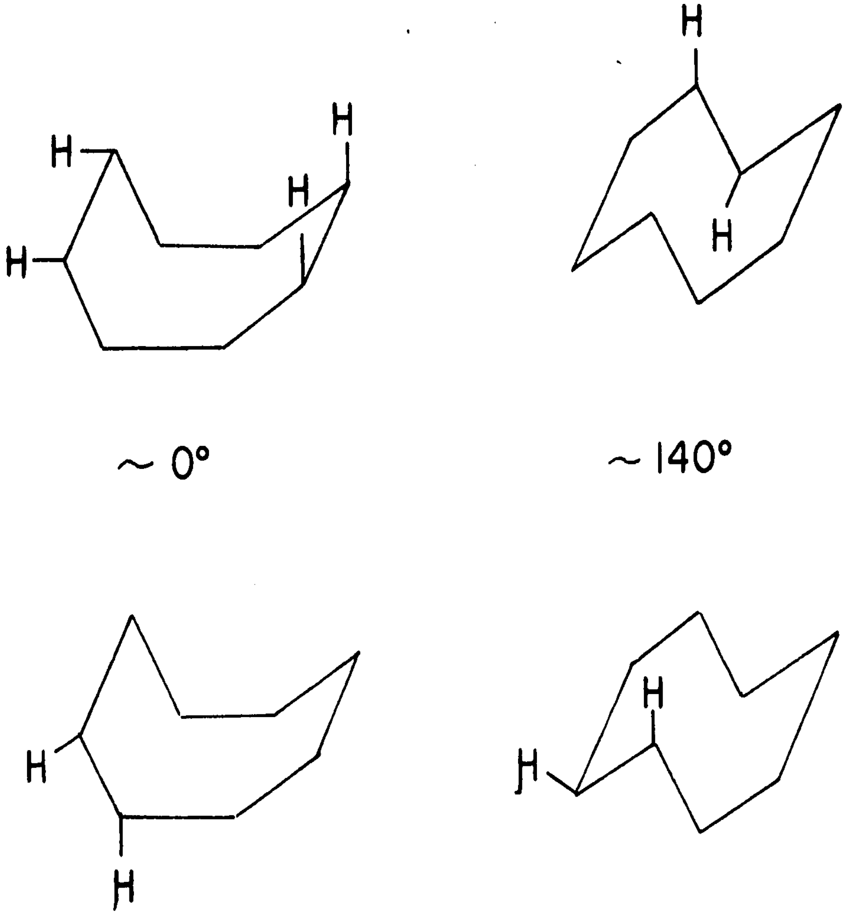
Although the origin of the splitting is not definitely known, application of the Karplus relationship supports the crown conformation. Fig. 16 shows the dihedral angles between cis vicinal protons in the various proposed conformations, as estimated from Dreiding models. The crown conformation is the simplest, since only one angle, of close to 90°, is present.

In the more complex tub and chair conformations, some cis vicinal protons are eclipsed; however, the large coupling suggested by the zero dihedral angle should not appear, since the protons involved have identical chemical shifts. In the corresponding skewed forms, however, these protons are no longer identical. They could still be sufficiently alike to give only a single peak. Even if they were sufficiently chemically shifted to show coupling, the coupling pattern would probably be averaged out. Dreiding models suggest very rapid interconversion, much more rapid than the ring inversion process, between protons which differ only as a result of skewing. This would average out the coupling pattern even well below the coalescence temperature of the ring inversion process. Thus, if either the tub or chair conformations were present, part of the signal should



~ 90° ~ 0°

crown



~ 60° ~ 60°

tub chair

Figure 16. The cycloöctane conformations, showing the dihedral angles between cis vicinal protons.

not show the effects of coupling.

In the chair form, two other cis dihedral angles of about 140° and 60° exist, as well as the angle of 0°. These should give rise to couplings of 4-7 c.p.s. and 1-3 c.p.s., respectively. The resultant spectrum should be complex, because of the presence of several different types of protons, coupled in varying degrees. Clearly, the chair conformation can be excluded, since the observed spectrum (Fig. 12) bears no relation to the spectrum expected from this conformation.

In the tub conformation, only two cis dihedral angles, of about 0° and 60°, are present in equal proportions. Half of the signal should thus be a simple chemical shift doublet showing no coupling and the remainder should show coupling of 1-3 c.p.s. This would be expected to yield either a broadened doublet or a pattern in which each peak of the doublet would be split into a closely spaced 1:2:1 triplet. The observed pattern fits these requirements much better than it fit the requirements for the chair conformation; the high field peak could be interpreted as one of the peaks of a broadened doublet. However, the low field peak is split into an approximately 1:1 doublet. Although the splitting (2.8 c.p.s.) is suitable for a 60° dihedral angle, the expected contribution of an unsplit signal is not in evidence. This speaks against the presence of a tub conformation, but the evidence against it is not as strong as the evidence against the chair conformation.

In the crown conformation, only a single coupling, very small and possibly zero, should be present. The observed splitting in the low-field peak (2.8 c.p.s.) is quite large to be caused by coupling in the case of an approximately 90° dihedral angle. The alternate explanation already mentioned, that the splitting might be due to the presence of two distinct species, could explain the splitting if the crown conformation is indeed present. Thus the observed simple splitting supports the crown conformation. However, there is not sufficient evidence to rigorously exclude the tub conformation. The definite exclusion of the chair conformation is in accord with previous evidence.

Although it was possible to use the Karplus relationship to select the most probable conformation, no accurate values of coupling constants were obtained. The largest cis vicinal coupling between non-equivalent protons is not greater than 2.8 ± 0.4 c.p.s., but it could be zero. If more information concerning the coupling constants in the molecule could be obtained, a more complete analysis would be possible and the conformation could be assigned with greater certainty. No values of coupling constants in saturated eight-membered rings have been reported to date; it is not definitely known if the Karplus relationship is accurate in these systems. Attempts were therefore made to obtain further information.

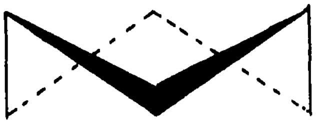
The fine structure present in the spectrum of 'C_8HD_{15}' at -148° (Fig. 11) corresponded to a coupling constant of 20 ± 5 c.p.s. in a small proportion of the molecules. This large value suggests a geminal coupling (69).

An attempt was made to obtain further information about coupling constants from analysis by the method of spectral moments developed by Anderson and McConnell (65). Moment analysis allows some data to be obtained from complex systems in which complete analysis is not possible. Its application, as described, to non-deuterated cyclohexane and cycloöctane, assuming the crown conformation of cycloöctane, led to the results in Table IX. The relative chemical shift values obtained from this method are considerably larger than those from the massive deuteration procedure. The average value for cyclohexane, 30.6 c.p.s., is 2.0 c.p.s. larger, while the average for cycloöctane, 23.2 c.p.s., is 4.4 c.p.s. larger. The dependence of the results on sweep rate, and the non-zero values of the third moment M_3, indicate that the moment analysis is of little use in the present investigation. Perhaps the recorder was not operating in the required linear fashion. No attempt was made to utilize the values of

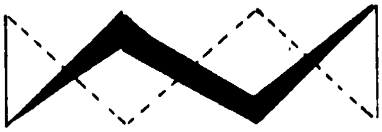
$[J_{gem}^2 + 2\ J_{cis}^2]^{1/2}$ in further estimations of cycloöctane coupling constants.

(c) Conclusion

The evidence presented in this thesis for the existence of the crown conformation of cycloöatane is in accord with the results of most previous investigations of eight membered systems. This form would also be expected by analogy with cyclohexane. Crown cycloöctane, which has an all-staggered arrangement of substituents, is a much closer analogue of chair cyclohexane than is chair cycloöctane. The analogy can be illustrated as in XVIII and XIX. However, because of increased strain in cycloöctane, this analogy is not as good as it might appear at first; the axial 1,3 distances are considerably decreased in cycloöctane (13). Derivatives of the next higher analogue, cyclodecane, have been shown to exist in a different conformation (86), probably because of even less favourable 1,3 diaxial interactions in the crown form. However, despite the hazards of attempting to draw too close a parallel, the similarity of the proposed stable conformation of cycloöctane to that of cyclohexane suggests a comparison of the ring inversion data in the two systems. Table XI summarizes this data; the closely related perfluorocyclohexane is included.



XVIII chair cyclohexane



XIX crown cycloöctane

Table XI

Kinetic Data of Ring Inversion in Cyclohexane and Cycloöctane

	$\Delta S^{\neq}$ (e.u.)	$\Delta H^{\neq}$ (kcal/mole)	$\Delta F^{\neq}$ (kcal/mole)	Reference
C_6H_{12}	-7.9^{a}	9.0 ± 0.2^{a}	10.6^{a}	(61)
C_6F_{12}	-10.2	7.5 ± 0.3	9.9	(62)
C_8H_{16}	-4.6 ± 3.5	7.4 ± 0.3	8.1	this work

[a] these values, based on an approximate treatment, may be seriously in error.

The similar values of $\Delta H^{\neq}$ and $\Delta F^{\neq}$ for the ring inversion processes in the six- and eight-membered rings are additional factors suggesting a similarity in the nature of the inversion processes in the two ring systems. This in turn suggests that the conformations are quite similar, These results could be considered to favour the crown conformation.

In the six-membered rings, the negative values of the entropy of activation, $\Delta S^{\neq}$, are of interest, in spite of the considerable errors involved in their calculation. As suggested by Harris and Sheppard (61), this indicates a rigidly defined, highly symmetrical intermediate in the inversion process. A planar intermediate fits these requirements much better than the boat intermediate which has often been assumed, for instance by Jensen and co-workers (60). However, this result appears to contradict the recent detailed calculations of Hendrickson (8) which indicate that the twist-boat (IIa) is the intermediate in ring inversion. His calculations are probably more reliable than the rate data, because of the approximations involved in determining rates from N.M.R. spectra of cyclohexane. The apparent contradiction illustrates the difficulty in attempting to deduce detailed information from small entropy values; these were calculated from a difference of two large terms, and hence large errors are likely. Cyclooctane, for which a smaller negative entropy of activation was calculated, is even more difficult to analyse. The carbon skeleton has many more degrees of freedom of internal rotation. Several processes of ring inversion, arising from different distortional modes of vibration, are conceivable. The molecule is not rigid, but appears to be free to interconvert among a family of closely related crown conformations; in the skewed crown, as described by Allinger and co-workers (22), all the carbons are not quite identical. Dreiding models show that this pseudorotation becomes highly hindered at limits where very strong 1,5-diaxial interactions occur. In the inversion process the molecule could first flip over into another conformation, in which pseudorotation is freer because transannular interactions are less. A direct inversion of the crown is also possible. Either process might occur with an entropy af activation of almost zero.

The appearance of axial ring protons at higher field in spectra of cyclohexane derivative has been attributed without proof to a small ring current effect (23). If such an effect should exist, it might be expected to be less important in a larger ring. The smaller relative chemical shift between axial and equatorial protons in cycloöctane (18.8 c.p.s. instead of 28.6 c.p.s.) might be explained on this basis. It could also be explained in terms of less rigidly defined, and hence less distinctive, substituent positions in the eight-membered ring.

There would be little value in attempting to draw further conclusions about the cycloöctane ring system, based on the limited information now available. There is strong evidence that the crown conformation is present and that the inversion of the crown takes place in cycloöctane with an activation energy of 7.7 kcal./mole.

CLAIMS TO ORIGINAL RESEARCH

1. An N.M.R. study of cycloheptyl acetate was carried out by preparation of the 3,3,4,4,5,5,6,6-octadeuterated compound. Proton spectra of this compound at 20° and -95° revealed a marked temperature dependence of both the geminal and vicinal coupling constants, while the chemical shifts did not change significantly with temperature.
2. Pyrolysis of <u>trans</u>-1,2-divinylcyclobutane was found to yield moderate amounts of 1,5-cycloöctadiene by a reaction competitive with dissociation to butadiene.
3. A method of synthesis of fully deuterated 1,5-cycloöctadiene was developed. Catalytic reduction of this compound with deuterium gas yielded fully deuterated cycloöctane of fair isotopic purity. Diimide reduction yielded a tetraprotonated cycloöctane, $C_8H_4D_{12}$, in which the vicinal protons were <u>cis</u> to each other.
4. Proton magnetic resonance spectra, with deuterium decoupling, on the isotopic impurity in "fully deuterated" cycloöctane showed coalescence of two separate sharp peaks at -111.5°. This indicated a rate process attributable to ring inversion in a single conformation. Thermodynamic data were calculated for the process.

5. Proton magnetic resonance spectra, with deuterium decoupling, on the $C_8H_4D_{12}$ formed by diimide reduction showed the absence of any large coupling. Application of the Karplus relationship indicated the existence of only the crown conformation in cycloöctane, in support of most previous evidence.

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