THE STUDY OF RING INVERSIONS BY NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

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CONFORMATIONAL analysis of cyclohexane derivatives has only become fully established since 1945,[1] but one of the basic tenets, the rapid interconversion among various conformations, was recognised as possible by Sachse[1a,b] in 1890 when he made the first suggestion of a non-planar conformation for cyclohexane. Recently the thermodynamic constants for such interconversions, "ring inversions" in cyclohexane and other cyclic compounds, have become available using nuclear magnetic resonance (n.m.r.) spectroscopy. It is the purpose of this Review, after showing the basis and the scope of the n.m.r. technique, to discuss the results so far obtained, and the conclusions which can be drawn about conformational mobility in ring compounds.

It is well to point out first that there are recent determinations of barriers to inversion by other techniques. Several examples of optical isomerism due to the fixed conformation of a ring are known.[2] In such compounds, ring inversion causes racemisation, so that the rate of loss of optical activity can be related to the rate of ring inversion. This approach is suitable where the barrier is somewhat more than 20 kcal./mole, that is, higher than can be measured by n.m.r. By use of ultrasonic techniques the barrier to ring inversion in methylcyclohexane has been determined.[3] This method may prove valuable in future, for it can be applied only to unsymmetrical systems, whereas the n.m.r. technique is more readily applied to symmetrically substituted molecules.

The Technique

The way in which n.m.r. spectroscopy can be applied to the study of fast reactions is best illustrated by an example. The n.m.r. spectrum of the *N*-methyl groups of *NN*-dimethylacetamide is a doublet of chemical shift[4]

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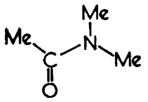
[1] Historical details and general background information on conformational analysis can be found in (*a*) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, 1965; (*b*) M. Hanack, "Conformation Theory," Academic Press, New York, 1965. Background information on nuclear magnetic resonance spectroscopy can be found in (*c*) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, 1959.

[2] (*a*) K. Mislow, S. Hyden, and H. Schaefer, *J. Amer. Chem. Soc.*, 1962, **84**, 1449; (*b*) K. Mislow and M. A. W. Glass, *ibid.*, 1961, **83**, 2780; (*c*) K. Mislow and H. B. Hopps, *ibid.*, 1962, **84**, 3018; (*d*) K. Mislow and H. D. Perlmutter, *ibid.*, p. 3591; (*e*) W. Tochterman and H. Kuppers, *Angew. Chem.*, 1965, **77**, 173.

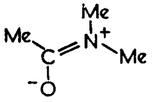
[3] J. E. Piercy and S. V. Subrahmanyam, *J. Chem. Phys.*, 1965, **42**, 4011.

[4] Throughout this Review, "chemical shift" means the relative chemical shift of the signals implied by the context measured at 60 Mc./sec. operating frequency.

4·8 cycles/sec. at room temperature.[5] This arises since, because of the mesomerism (I)↔(II), and the resultant partial-double-bond character of



(I)



(II)

the carbon–nitrogen bond, there are two environments for an *N*-methyl group, either *cis* or *trans* to the carbonyl function. As the temperature is raised, the two *N*-methyl signals broaden and collapse to a single line which becomes sharp on further heating. Raising the temperature increases the rate of rotation about the carbon–nitrogen bond until this rate becomes so high that only an averaged signal is observed. A diagrammatic representation of the *N*-methyl signal as the temperature is raised is shown in Fig. 1.

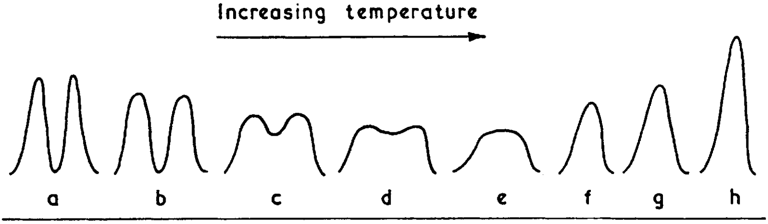


FIG. 1. *Diagrammatic representation of the* N-*methyl proton spectrum of* NN-*dimethyl-acetamide at various temperatures.*

The technique can be extended to cyclohexane inversion in the following manner. Cyclohexane is accepted[1a,b] to exist as a rapidly exchanging mixture of equal-energy chair forms. In the exchange, each proton changes from an axial to an equatorial position, or *vice-versa*. The process is rapid at room temperature, so that a single line is observed for the n.m.r. spectrum of cyclohexane. Below about −65°, two separate signals can be observed, these being ascribed to the axial and equatorial protons in any molecule, for ring inversion is now much slower. However, in any frozen conformation of cyclohexane, each proton will be coupled to other protons in the molecule, so that the resultant low-temperature spectrum is very complex.

We will now give a qualitative picture of the theory which governs the derivation of reaction parameters from n.m.r. spectra; a full description is readily available in the literature.[6]

Provided that the rate of sweeping through a signal is slow, the shape observed for a particular signal is determined by certain time-dependent

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[5] "NMR Spectra Catalog," Varian Associates, Palo Alto, 1963, vol. II, spectrum 421.

[6] (*a*) See ref. 1*c*, ch. 10; (*b*) L. H. Piette and W. A. Anderson, *J. Chem. Phys.*, 1959, **30**, 899.

processes. Thus, for a hydrogen nucleus, there is a finite lifetime in either of the possible spin states,[1c] and the signal shape depends on the relaxation time for an exchange between these spin states. In practice, where there is no exchange process of the type we are considering here, the signal shape is determined not by this relaxation time, but by the homogeneity of the magnetic field. We can nonetheless derive a relaxation time T_0 from the observed shape, this T_0 corresponding to the homogeneity, but not being precisely defined. Likewise, for a molecule undergoing exchange, we can obtain an experimental relaxation time T_e, from the shape of exchange-modified signals.

If, then, we include in a sample a compound undergoing an exchange process, and a reference compound, we can measure T_e and T_0. We can then calculate[6] the value of τ, the average lifetime of a molecule in either conformation (that is in either chair form in the case of cyclohexane) by using these relaxation times and the chemical shift, when exchange is slow (Fig. 1a), of the signals whose coalescence is being studied. Since the ring inversion is a zero-order reaction, the rate constant for the process is the inverse of the average lifetime τ.

If values of this rate constant are measured at several temperatures, thermodynamic parameters for the inversion can be derived using the Eyring or Arrhenius equations.

It is also possible to obtain values of relaxation times by the spin-echo technique.[7] Allerhand and Gutowsky[8] have recently developed the application of this technique to the measurement of rate processes, and have used it to study the inversion of two ring compounds, though there are earlier pioneering examples of such applications.[9,10] For the ring inversion of cyclohexane, the high-resolution method and the spin-echo method have given values of the free energy of activation ΔG^* which agree well,[8c] though there are differences in the enthalpies and entropies of activation (ΔH^* and ΔS^*) found. It has however been pointed out[8c] that systematic errors affect ΔS^* and ΔH^* much more markedly than ΔG^*.

Allerhand and Gutowsky[8a,8c] have given a critical comparison of the two techniques. They point out that the temperature range over which high-resolution technique can be applied is limited to that in which the contribution to relaxation from the exchange process is larger than the n.m.r. spectrometer's error in measuring the reference relaxation time. This almost invariably limits measurements to a temperature range of about 30°. In effect, the spin-echo technique allows a much more accurate determination of relaxation times, so that there is a much wider range over which the

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[7] See ref. 1*c*, section 3.7.

[8] (*a*) A. Allerhand and H. S. Gutowsky, *J. Chem. Phys.*, 1964, **41**, 2115; (*b*) A. Allerhand and H. S. Gutowsky, *ibid.*, 1965, **42**, 1587; (*c*) A. Allerhand, F.-M. Chen, and H. S. Gutowsky, *ibid.*, p. 3040; (*d*) A. Allerhand and H. S. Gutowsky, *ibid.*, p. 4203.

[9] L. W. Reeves and E. J. Wells, *Discuss. Faraday Soc.*, 1962, **34**, 177; see also M. Bloom, L. W. Reeves, and E. J. Wells, *J. Chem. Phys.*, 1965, **42**, 1615.

[10] S. Meiboom, Paper presented at symposium on High Resolution Nuclear Magnetic Resonance, Boulder, Colorado, July, 1962.

exchange contribution to the experimental relaxation time is measurable. Thus Allerhand, Chen, and Gutowsky can reasonably claim[8c] that the spin-echo results are 'probably more reliable than others'.

At the coalescence temperature (Fig. 1e), the rate constant for inversion is independent of the relaxation time T_0 provided that T_0 is fairly large, so that, knowing the chemical shift of the two signals coalescing, one can obtain a value of the rate constant for inversion. From this, knowing the temperature, one can calculate a value of the free energy of activation ΔG^*, using the Eyring equation. Since ΔH^* and ΔS^* values, even from the most careful analysis, may be subject to errors, it might seem at first sight that there is little to be gained by a full analysis. However, comparisons of ΔG^* should be made at the same temperature, and since errors in ΔH^* and ΔS^* are self-compensating,[8c] ΔG^* values obtained by extrapolation or intrapolation of results from a full analysis allow this comparison.

A large proportion of reports give barriers derived from temperatures of coalescence, especially when there is only a passing interest in actual values or where values are difficult to obtain. When systematic examination of a series is being made, a full analysis, despite its certain limitations, is obviously necessary.

Throughout this Review, when the "barrier to ring inversion" is mentioned, it is the free energy of activation for the ring inversion process that is meant, unless otherwise indicated.

Technical Details and Difficulties

There are two principal difficulties which hamper systematic investigations of ring inversions. These are complex spectra and low barriers to inversion.

It has been calculated[11] that for cyclohexane itself, below the temperature of coalescence, the spectrum should comprise many hundreds of lines. Thus it is not correct to apply the theory derived for the collapse of a doublet, even though the lines observed group themselves into two broad bands.[12] In the case of cyclohexane the difficulty has been overcome by examining undecadeuterocyclohexane with irradiation at the deuterium frequency to remove hydrogen–deuterium coupling.[13,14] In the majority of cases however, deuterated compounds are not readily available and proton decoupling of the protio-compound is impracticable.

Another difficulty occurs when examining monosubstituted cyclic compounds. The substituent has an energy preference for the equatorial

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[11] J. I. Musher, *J. Chem. Phys.*, **35**, 1159.

[12] F. R. Jensen, D. S. Noyce, C. H. Sederholm, and A. J. Berlin, *J. Amer. Chem. Soc.*, 1960, **82**, 1256; 1962, **84**, 386. See also, comment thereon in reference 8*c*.

[13] F. A. L. Anet, M. Ahmad, and L. D. Hall, *Proc. Chem. Soc.*, 1964, 145. See correction in a footnote in reference 16*a*.

[14] F. A. Bovey, F. P. Hood III, E. W. Anderson, and R. L. Kornegay, *Proc. Chem. Soc.*, 1964, 146; *J. Chem. Phys.*, 1964, **41**, 2041.

position,[1a,b] so that even with other factors favourable, the more complex treatment[15] for the collapse of an *unsymmetrical* doublet ought to be used.

The second great difficulty is that of low barriers to inversion. It is theoretically possible to slow down inversion to obtain splitting of signals by cooling to a sufficiently low temperature; the lower the barrier to inversion, the lower the temperature required. With reference to cyclohexyl compounds again, few have barriers significantly higher than that of cyclohexane in which the coalescence temperature is about −65°,[13,14] so that temperatures much lower than this must be accessible. The lowest temperature at which high resolution proton spectra have been recorded is about −170°.[16,17] This places a lower limit of about 5 kcal./mole on barriers which can be measured at present.

In addition there are difficulties at such low temperatures. The reference signal becomes broad, so that in some examples, *e.g.*, trioxan,[18] where splitting is not observed at the lowest attainable temperatures this may be due to a small chemical shift obscured by poor homogeneity rather than to a low barrier.

At these low temperatures, the choice of solvent may prove to be another difficulty. In general mixed solvents have not proved very satisfactory. For temperatures below −120°, certain tetrahalogenomethanes with two different halogen atoms, *e.g.*, CCl_3F or vinyl chloride, have been found most useful.[16,17,19] In general, a suitable solvent should have a low freezing point, good solvent properties at low temperatures, and a relatively simple proton n.m.r. spectrum.

It is noteworthy that there is little information on the effects of solvents on barriers to ring inversion. In other kinetic processes studied by n.m.r. the solvent has been shown to have a large effect,[20] particularly when the molecule studied contains polar functions. Analogous effects would be expected in polar ring compounds, and in 3,3,6,6-tetramethyl-1,2-dioxan a range of 3 kcal./mole in the barrier to inversion in various solvents has been found.[21] It is unfortunate that the best solvents may owe this quality to their polar nature and that this may influence the results found.

Results

Cyclohexane and its Derivatives.—The inversion of six-membered rings is of particular interest to the organic chemist, and the inversion of the

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[15] F. A. Bovey, E. W. Anderson, F. P. Hood, and R. L. Kornegay, *J. Chem. Phys.*, 1964, **40**, 3099.

[16] (*a*) F. A. L. Anet and M. Z. Haq, *J. Amer. Chem. Soc.*, 1965, **87**, 3147; (*b*) F. R. Jensen and C. H. Bushweller, *ibid.*, p. 3285.

[17] F. R. Jensen and L. A. Smith, *J. Amer. Chem. Soc.*, 1964, **86**, 956.

[18] J. E. Anderson and J. C. D. Brand, *Trans. Faraday Soc.*, in the press.

[19] F. A. L. Anet and J. S. Hartman, *J. Amer. Chem. Soc.*, 1963, **85**, 1204.

[20] See, for example, A. Loewenstein, J. F. Neumer, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1960, **82**, 3599.

[21] H. Friebolin, S. Kabuss, and H. Schmid, personal communication.

parent, cyclohexane, has been much studied.[8c,10,12,13,14,22–24] In the period 1960—1962 the first five papers appeared,[12,22–24] each describing in greater or lesser detail the broadening and resolution into two parts of the single n.m.r. absorption line of cyclohexane on cooling to about +100°. By virtue of the complexity of the spectrum mentioned above, the derived equations were not strictly applicable, and only approximate values of parameters could be determined. In 1962, Meiboom[10] reported values of these parameters derived from an early application of the spin-echo technique.

In the meantime, Hendrickson[25] had made calculations on the energies of the possible conformations of cyclohexane, and had presented a plausible picture of the path of ring inversion, through the structures shown in Fig. 2. The plausibility of the pathway is enhanced by the reasonable agreement between his calculated values for activation enthalpies and enthalpy differences, and those found by experiment.[8c,13,15,26,27]

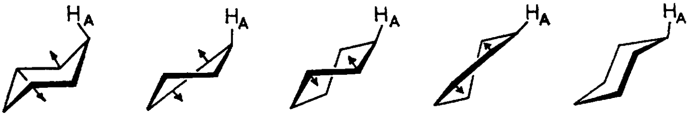

FIG. 2. *Diagram of the path suggested by Hendrickson for the inversion of six-membered rings.*[25]

The difficulties arising from the complex low-temperature spectrum were removed in work by Anet,[13] Bovey,[14] and their co-workers published in 1964. They studied [$^2H_{11}$]cyclohexane, with deuterium decoupling to give a single- and double-line spectrum at high and low temperatures respectively. At the same time Allerhand and Gutowsky were developing the spin-echo technique[8a–d] and in early 1965 they reported a study of both cyclohexane and [$^2H_{11}$]cyclohexane.[8c] From these three studies it was clear that the free energy of activation for ring inversion is close to 10·3 kcal./mole. Values of the enthalpy of activation range from 9·1 to 10·5 kcal./mole, the spin-echo technique giving the lower value. The corresponding range of values for the entropy of activation is —5·8 to +1·4 e.u. Calculations based on symmetry considerations alone suggest an entropy of activation of +4·9 e.u:[12] this is outside the range of experimental values, and thus there are additional factors involved.

There are no reported values of barriers to inversion in alkylcyclohexanes. This may be due to a combination of low barriers and therefore low coalescence temperatures, and very unequal populations of the two

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[22] R. K. Harris and N. Sheppard, *Proc. Chem. Soc.*, 1961, 418.

[23] W. B. Moniz and J. A. Dixon, *J. Amer. Chem. Soc.*, 1961, **83**, 1671.

[24] N. Muller and W. C. Tosch, *J. Chem. Phys.*, 1962, **37**, 1167.

[25] J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1961, **83**, 4537.

[26] N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, 1960, **82**, 2393.

[27] W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *J. Amer. Chem. Soc.*, 1961, **83**, 606.

chair conformations in the monosubstituted cases. 1,1-Dimethylcyclohexane would seem to be very suitable for study, but Harris and Sheppard[22] found that at −120° the methyl signal is still a singlet. Muller and Tosch[24] confirmed this, but found that the complex signal of the ring protons broadens on cooling to −75°, then sharpens on further cooling, which suggests that the conformational exchange is slow at such low temperatures. The failure to resolve the methyl signal may be due to a very small chemical shift as Harris and Sheppard have suggested,[22] and as is supported by unpublished results of the Freiburg group.[21]

For *cis*-1,2-, *cis*-1,4-, and *trans*-1,3-dimethylcyclohexane, Muller and Tosch[24] found that exchange is slow at −120°. In all cases the maximum broadening was observed about −70°, which suggests that generally, in the simple alkyl cyclohexanes, the barriers to inversion are similar to those in cyclohexane itself.

Cyclohexyl halides have received considerable attention. Bovey, Hood, Anderson, and Kornegay[15] have fully studied cyclohexyl fluoride using the ^{19}F-spectrum with spin decoupling of adjacent protons. With equations modified for the unequal numbers of fluorine atoms in axial and equatorial positions, they found the barriers to inversion slightly lower than in cyclohexane. For the other halides[28a,29] and for cyclohexanol[29] barriers have been obtained from temperatures of coalescence, and appear to be slightly larger than for cyclohexane, but the difference is probably not significant. Methoxy- and ethoxy-cyclohexane are reported to invert rapidly even at −110°.[28b]

Of the disubstituted cases that have been investigated,[8d,22,24,28b,30–32] the dimethylcyclohexanes have been discussed above. For both *cis*-1,2-[28b] and *trans*-1,3-dihalocyclohexanes[30] the barrier is close to that of the parent compound. Jonáš, Allerhand, and Gutowsky[31] have examined the inversion of 1,1-difluorocyclohexane both by the high resolution and spin-echo techniques.[8d,32] They found the barrier to be less than that in cyclohexane by 0·7 kcal./mole.

Several polysubstituted cyclohexanes have been studied.[33–35] Here the most interesting results are those of Tiers[33] on the ring inversion of perfluorocyclohexane, followed from the ^{19}F-spectrum. Because of the large chemical shift involved, rate measurements could be made over a much wider temperature range, 93°. The free energy of activation is slightly smaller than in cyclohexane, and since the entropy of activation is high

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[28] (*a*) L. W. Reeves and K. O. Strømme, *Canad. J. Chem.*, 1960, **38,** 1241; (*b*) L. W. Reeves and K. O. Strømme, *Trans. Faraday Soc.*, 1961, **57,** 390.

[29] W. C. Neikam and B. P. Dailey, *J. Chem. Phys.*, 1963, **38,** 445.

[30] H. M. van Dort and T. J. Sekuur, *Tetrahedron Letters*, 1963, 1301.

[31] K. Nagarajan and J. D. Roberts, unpublished results quoted in J. D. Roberts, *Angew. Chem.*, 1963, **75,** 20.

[32] J. Jonáš, A. Allerhand, and H. S. Gutowsky, *J. Chem. Phys.*, 1965, **42,** 3396.

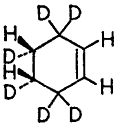
[33] G. V. D. Tiers, *Proc. Chem. Soc.*, 1960, 389.

[34] S. Brownstein, *Canad. J. Chem.*, 1962, **40,** 870.

[35] R. K. Harris and N. Sheppard, *Mol. Phys.*, 1964, **7,** 595.

and negative, —10·7 e.u., the enthalpy of activation is much smaller than in cyclohexane. Tiers has attributed this to fluorine–fluorine interactions' raising the energy of the ground-state chair conformation. Brownstein[34] has examined the acetates of three configurational isomers of inositol (1,2,3,4,5,6-hexahydroxycyclohexane), and finds the enthalpies of activation are low for these compounds also, probably for the same reasons as in perfluorocyclohexane.

There are two other obvious systems which fall into this section, and whose barriers to inversion are of interest, cyclohexanones and cyclohexenes. There is no report of a barrier to inversion of cyclohexanone, but $[^2H_9]$cyclohexanone appears to be inverting rapidly even at —140°,[36] which would place an upper limit of about 7·7 kcal./mole on the barrier to inversion. Anet and Haq have recently studied the ring inversion of cyclohexene using the compound (III) with deuterium decoupling.[16a] The coalescence temperature is as low as —164° and the barrier is therefore about 5·3 kcal./mole. They discuss the path the inversion may take and suggest a conformation with five carbon atoms in one plane as the most likely transition state. The barrier to inversion of 4-bromocyclohexene is slightly larger than for the parent compound,[16b] but the derivative (IV), a tetrahydropyridazine, presents a marked contrast. Lehn[37] has found the barrier to inversion to be about 19 kcal./mole, probably owing to the multiple interactions of bulky substituents in a near-planar transition state.



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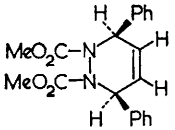


(IV)

Thus the information that an n.m.r. study of ring inversions gives about the conformations of simple cyclohexanes is limited. One useful conclusion is that in all cases ring inversion is rapid at ordinary temperatures. In cyclohexane, for example, the average time spent in any conformation is less than 10^{-4} sec. at room temperature. Experimental results bear out Hendrickson's picture of the path of inversion[25] quite satisfactorily. The majority of substituted cyclohexanes studied, however, have barriers close to that of the parent compound and perhaps not significantly different from it. Further examples will no doubt be investigated, but there are factors which make it doubtful whether a systematic study will be possible.

If, for example, one considers unsymmetrical cyclohexane derivatives, then that conformation with more "large" groups equatorial will predominate. A free-energy difference of only 1·5 kcal./mole between these conformations is sufficient for there to be more than 95% of the more stable

[36] J. E. Anderson, D. D. MacNicol, and B. D. Batts, unpublished results.

[37] J. C. Breliere and J. M. Lehn, *Chem. Comm.*, 1965, 426.

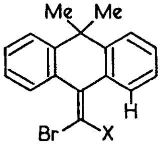
isomer at low temperates, so that even if inversion is slow, the signals due to the less stable isomer will not be readily observed.

One could hope to obtain a molecule suitable for study by ensuring that in both possible conformations there is an approximately equal "weight" of axial and equatorial substituents. This is the position obtaining in perfluorocyclohexane and in the inositol acetates mentioned above, but if the substituents involved are much "larger" than fluorine or the acetate group, then 1,3-diaxial interactions will be of such magnitude as either to lower the barrier towards and perhaps below the present limit of measurability, or to make flexible boat conformations energetically probable. The latter is the case in *trans*-1,3-di-t-butylcyclohexane[26] and hexamethylcyclohexane-1,3,5-trione[38] which might otherwise be suitable for study by the n.m.r. method.

Six-membered Heterocyclic Rings.—The inversion of six-membered rings containing one or more hetero-atoms has given more detailed information on the factors which affect barriers to inversion. Reeves and his co-workers have reported free energy values for the barrier to inversion in one piperazine[39] and one piperidine[9] derivative. From two studies of 1,2-dioxans and 1,2-dithians,[40–42] it is clear that the replacement of two adjacent methylene groups by oxygen or sulphur atoms raises the barrier to inversion.

There has been a full study of the 1,3-dioxans (V; A = B = oxygen),[18,21,42,43] 1,3-dithians (V; A = B = sulphur),[21,43] and 1,3-thioxans (V; A = sulphur, B = oxygen).[21,42] The parent compounds in these series have barriers similar to that in cyclohexane. In the 1,3-dioxan series, results[18,43] show that introduction of two methyl groups into the 2-position lowers the barrier to inversion. The 1,3-dioxan ring is smaller than the cyclohexane ring since carbon–oxygen bonds are shorter than carbon–carbon bonds, so that the axial methyl group has strong 1,3-interactions with two hydrogen atoms, and the energy of the ground state is raised, *i.e.*, the barrier to inversion is lowered. The 5,5-dimethyl deriva-

(V)



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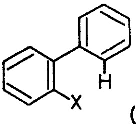

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[38] J. Dale, *J.*, 1965, 1028.

[39] L. W. Reeves and K. O. Strømme, *J. Chem. Phys.*, 1961, **34**, 1711.

[40] G. Claeson, G. M. Androes, and M. Calvin, *J. Amer. Chem. Soc.*, 1960, **82**, 4428; 1961, **83**, 4357.

[41] A. Lüttringhaus, S. Kabuss, W. Maier, and H. Friebolin, *Z. Naturforsch.*, 1961, **16***b*, 761; H. Friebolin and W. Maier, *ibid.*, 1961, **16***a*, 1640.

[42] H. Schmid, H. Friebolin, S. Kabuss, and R. Mecke, *Spectrochim. Acta*, in the press.

[43] H. Friebolin, S. Kabuss, W. Maier, and A. Lüttringhaus, *Tetrahedron Letters*, 1962, 683.

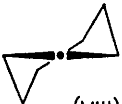
tive, in which the axial methyl group now interacts with two much smaller oxygen lone pairs, has a barrier similar to that of the parent compound, while the 2,2,5,5-tetramethyl compound has a barrier of intermediate value. The effects of substituents are less clearly marked in the dithian and thioxan series[21,43] in which steric compression is less because of long carbon–sulphur bonds.

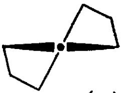
Lastly, there is a considerable body of results on the inversion of annellated six-membered rings. It is difficult to draw any general conclusions from these studies, for no systematic investigations have been carried out. *cis*- and *trans*-Decalin[22,23] and derivatives,[44] and *cis*- and *trans*-perhydroindane[23] are saturated systems that have been studied. 9,10-Dihydrophenanthrene has been shown to have a low barrier to inversion.[45]

Curtin, Carlson, and McCarty have studied the series (VI) in detail,[46] determining ΔG^*, ΔH^*, ΔS^*, and finding agreement between the barriers to inversion in this series, and the barriers to rotation in the series (VII), which, as they point out, is analogous.

Rings Smaller than Six-membered.—There has been no n.m.r. study of the inversion of rings smaller than six-membered. In cyclopropane the protons are identical. In the favoured conformations of cyclobutane and cyclopentane[1a,b] there are different kinds of protons, but the barriers to interconversion of conformations are much smaller than can be measured by n.m.r.

Seven-membered Rings.—There is no report of a study of cycloheptane, for which Hendrickson[25] has calculated that there are two stable conformations, the twist-chair (VIII), and the slightly less-favoured twist-boat (IX).


(VIII)


(IX)


(X)


(XI)

Both forms are flexible and, in contrast with cyclohexane, the interconversions of "axial" and "equatorial" positions in the twist-chair can be achieved by pseudorotation,[47] which can be defined as a change in conformation of a ring compound involving only a small barrier, a barrier which arises from non-bonded interactions rather than bond-angle strain, *i.e.*, pseudorotation is the flexing of a flexible system. The barrier involved in pseudorotation will normally be smaller than can be measured by n.m.r.

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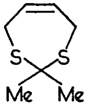
[44] F. G. Riddell and M. J. T. Robinson, *Chem. Comm.*, 1965, 227.

[45] M. Oki, H. Iwamura, and N. Hayakawa, *Bull. Chem. Soc. Japan*, 1963, **36**, 1542; 1964, **37**, 1865.

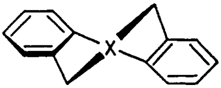
[46] D. Y. Curtin, C. G. Carlson, and C. G. McCarty, *Canad. J. Chem.*, 1964, **42**, 565.

[47] J. E. Kilpatrick, J. S. Pitzer, and R. Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2483.

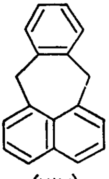
In further contrast to cyclohexane, the introduction of a double bond into cycloheptane produces a rigid conformation (X) from a flexible one (VIII). It has been shown, however, that the rigid conformation (X), and the more flexible tub-form (XI) are of approximately equal energies in some cases, *e.g.* (XII),[48a] and n.m.r. signals corresponding to the two conformations have been obtained at low temperatures. Grunwald and Price[48b] have reported another example, and have given a full discussion of the conformational interconversion processes involved. Cycloheptene itself has not been studied, but a series of benzo-derivatives have barriers about 11 kcal./mole.[49] When two of the skeletal carbon atoms are replaced by sulphur atoms, the barriers have similar values, but with two oxygen atoms the barrier is reduced.[48]



(XII)



(XIII)


(XIV)

The preferred conformation is again changed on the introduction of two double bonds into the ring,[45,50,51] usually as dibenzo-derivatives, to give bridged biphenyls whose lowest-energy conformation appears to be a pseudo-boat (XIII).[50] In the transition state of the inversion, all the atoms except X appear to be planar.[2a] Likewise in the dihydropleiadenes (XIV)[52] the transition state is taken to be a rather strained planar form, and this explains the relatively high barriers, up to 16 kcal./mole,[50,52] found in both series. Bridged biphenyls with even higher barriers have been resolved into optical isomers,[2a] and studies of their rates of racemisation have given their rates of inversion.

Cycloheptatriene is interesting. The preferred conformation is boat-shaped,[53] and interconversions of the two possible forms (XV) and (XVI) is rapid at room temperature. The spectrum of the methylene group splits only at —143°,[17,54] and the barrier to inversion is thus about 6


(XV)


(XVI)

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[48] (*a*) H. Friebolin, R. Mecke, S. Kabuss, and A. Lütteringhaus, *Tetrahedron Letters*, 1964, 1929; (*b*) E. Grunwald and E. Price, *J. Amer. Chem. Soc.*, 1965, **87**, 3139.

[49] S. Kabuss, H. Friebolin, and H. Schmid, *Tetrahedron Letters*, 1965, 469.

[50] R. J. Kurland, M. B. Rubin, and W. B. Wise, *J. Chem. Phys.*, 1964, **40**, 2426.

[51] W. Tochterman, U. Walter, and A. Mannschreck, *Tetrahedron Letters*, 1964, 2981.

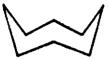
[52] P. T. Lansbury and J. F. Bieron, *J. Amer. Chem. Soc.*, 1964, **86**, 2524.

[53] M. Traetterberg, *J. Amer. Chem. Soc.*, 1964, **86**, 4265.

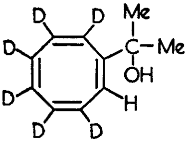
[54] F. A. L. Anet, *J. Amer. Chem. Soc.*, 1964, **86**, 458.

kcal./mole. An increase in the barrier on successive annellation of benzene rings is observed here also[51] and this has been attributed to the interaction of the *ortho*-hydrogen atoms of these rings in a planar transition state. In this series too, optically active isomers have been obtained,[2e] the asymmetry being due to hindered ring inversion.

Eight-membered Rings.—It is generally accepted that an extended crown (XVII) is the most stable conformation of cyclo-octane.[1a,b] This form is flexible, but in achieving a full cycle of pseudorotations, it can be seen from models that fairly drastic transannular interactions are encountered, so that there may be a relatively high barrier to ring inversion.



(XVII)



(XXIII)

Following earlier work by Harris and Sheppard[22] and by Meiboom,[10] this barrier was measured as 7·7 kcal./mole by Anet and Hartman,[19] using quindecadeuterocyclo-octane with deuterium decoupling.

$[^2H_{15}]$Cyclo-octatetraene is known to exist in the tub form (XVIII).[55] There are two distinct exchange processes that one might hope to study by n.m.r.,[56] bond shift (Fig. 3, path A) and ring inversion (Fig. 3, path B). In both processes the most reasonable transition state appears to be planar. Direct examination of reactions A and B is not possible since the protons in (XVIII) are equivalent. Anet[57] and Whitesides, Gwynn, and Roberts[58a] observed the ^{13}C–H satellites[1c] of the cyclo-octatetraene spectrum. Statistically one hydrogen atom in about 8% of the molecules is distinguished by being attached to a carbon-13 atom. When bond exchange

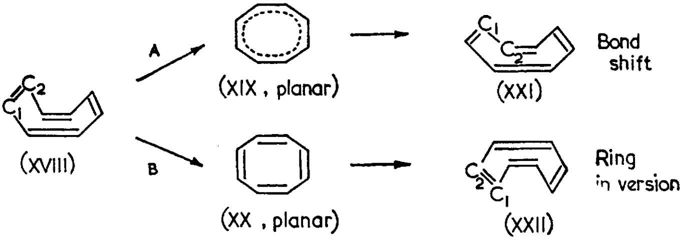


FIG. 3. *The two exchange processes taking place in cyclo-octatetraene.*

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[55] Ref. 2*d* gives leading references.

[56] F. A. L. Anet, A. J. R. Bourn, and Y. S. Lin, *J. Amer. Chem. Soc.*, 1964, **86**, 3576.

[57] F. A. L. Anet, *J. Amer. Chem. Soc.*, 1962, **84**, 671.

[58] (*a*) G. M. Whitesides, D. E. Gwynn, and J. D. Roberts, unpublished results quoted in J. D. Roberts, *Angew. Chem.*, 1963, **75**, 20; (*b*) D. E. Gwynn, G. M. Whitesides, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1965, **87**, 2862.

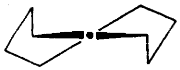
is slow, this hydrogen atom has two different neighbours, one separated from it by a single bond and coupled to it by about 12 c./sec., the other separated from it by a double bond and only weakly coupled to it. Thus at low temperatures the spectrum of this proton is a doublet which collapses at higher temperatures as the rate of bond exchange increases. Anet[57] found that the barrier to this bond exchange is 13·7 kcal./mole. Gwynn, Whitesides, and Roberts[58b] have recently reported that for the combined process of inversion and bond exchange in monofluorocyclo-octatetraene the activation energy is somewhat smaller.

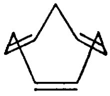
Ring inversion and bond shift have been studied in the compound (XXIII), the changes in the methyl proton and ring proton spectra being observed; the two processes can be differentiated[56] and their rates found simultaneously. Thus it was shown that the planar conformation (XX) is more stable than (XIX) by 2·4 kcal./mole, which is in the sense predicted by theoretical calculations.[56] The actual barrier to ring inversion for (XXIII) is 14·7 kcal./mole.

In two cases[2d,59] cyclo-octatetraene derivatives with two benzene rings annellated have been resolved into optical isomers, so that increased barriers to ring inversion due to annellation are observed in this series also.

cis-7,8-Dibromo-*cis*,*cis*,*cis*-cyclo-octa-1,3,5-triene has been found to have a barrier to inversion of 13 kcal./mole,[60] it being considered that the preferred conformation is still a tub.

Nine-membered and Larger Rings.—Hendrickson has calculated[61] that the most stable conformation of cyclononane is the symmetrical flexible form (XXIV), though *X*-ray evidence[62] for the hydrobromide of cyclononylamine indicates a slightly different conformation. Examination of models shows that pseudorotation renders "axial" and "equatorial" positions equivalent so that barriers to inversion are probably too small to be measured by n.m.r.


(XXIV)


(XXV)

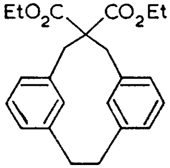
The only nine-membered ring whose inversion has been studied by n.m.r. is *cis*,*cis*,*cis*-cyclonona-1,4,7-triene[63–65] for which the conformation

[59] N. L. Allinger, W. Szkrybalo, and M. A. DaRooge, *J. Org. Chem.*, 1963, **28**, 3007.
[60] R. Huisgen and G. Bosche, *Tetrahedron Letters*, 1965, 1769.
[61] J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1964, **86**, 4854.
[62] R. F. Bryan and J. D. Dunitz, *Helv. Chim. Acta*, 1960, **43**, 1
[63] P. Radlick and S. Winstein, *J. Amer. Chem. Soc.*, 1963, **85**, 344.
[64] K. G. Untch and R. J. Kurland, *J. Amer. Chem. Soc.*, 1963, **85**, 346; *ibid.*, 1964, **86**, 5709.
[65] W. R. Roth, *Annalen*, 1964, **671**, 10.

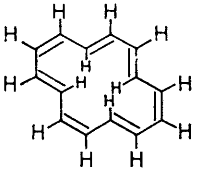
(XXV) appears to be the most stable.[65] At about −4° there are two distinct peaks for the allylic protons, but on heating to about 31° these coalesce. From this, the barrier to ring inversion is 14·5 kcal./mole.[64,65] Untch and Kurland[64] find a high negative entropy of activation for the inversion, and attribute this to a strained planar transition state. A tribenzo-derivative of cyclononatriene is known and, as expected, is found to invert slowly even at 180°.[66]

The only examples of rings larger than nine-membered which have been studied are the eleven-membered-ring compound (XXVI)[67] and two polyenes.[68a] In (XXVI) the barrier to inversion is 19 kcal./mole,[67] so this is yet another benzo-compound with a relatively high barrier.

At low temperatures, the A-isomer[68b] of [14]annulene (XXVII) shows two separate peaks corresponding to protons directed inwards and outwards.[68a] At higher temperatures, only one line is observed which indicates that protons are exchanging positions relatively rapidly. Similar results are observed for the analogous [18]annulene. From the chemical shifts of the "outer" and "inner" protons in the low-temperature spectra, there is an appreciable ring current in both molecules, so that even though the rings are inverting they are concluded to be aromatic.[68a]



(XXVI)



(XXVII)

The author acknowledges financial support from the Salters' Company.

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[66] A. S. Lindsey, *J.*, 1965; 1685.

[67] R. W. Griffin and R. A. Coburn, *Tetrahedron Letters*, 1965, 2571.

[68] (*a*) Y. Gaoni, A. Melera, F. Sondheimer, and R. Wolovsky, *Proc. Chem. Soc.*, 1964, 397; (*b*) Y. Gaoni and F. Sondheimer, *ibid.*, 1964, 299.