

Conformational Abnormalities in Cyclohexane Chemistry

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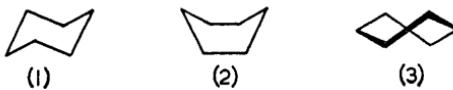
1 Introduction

The conformational analysis of cyclohexane and its derivatives has hitherto depended upon the assumption that such entities preferentially adopt the chair conformation.¹ That this assumption is valid for unrestricted cyclohexane derivatives has been verified by a wealth of physical evidence.^{2,3} Barton and Cookson,² however, recognised the need for caution when applying the concepts of conformational analysis to heavily substituted cyclohexane derivatives. The conformational situation in these molecules may be substantially modified by strong intramolecular forces which may compel the cyclohexane ring to adopt an abnormal conformation, *viz.*, a boat or twist conformation in preference to the normal chair.

This Review is not comprehensive but rather selects examples to illustrate the physical techniques which have revealed the existence of conformational abnormalities, the types of abnormality encountered, and how these arise. Any limitations inherent in the application of these techniques are also pointed out.

2 Energy Considerations

Sachse concluded that theoretically cyclohexane might exist in two isomeric forms.⁴ These are currently known as the chair form (1) and the flexible form which can adopt either a classical boat conformation (2) or a twist conformation (3).



In the thermodynamically favoured chair conformation the non-bonded interactions are minimised by the complete staggering of the C-H bonds. The severe boat conformation, on the other hand, is destabilised by two eclipsed

¹ D. H. R. Barton, *Experientia*, 1950, **6**, 316; *Experientia, Suppl. II*, 1955, 121; *J. Chem. Soc.*, 1953, 1027.

² D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, 1956, **10**, 44.

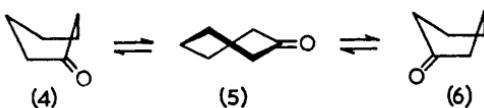
³ (a) E. L. Eliel, 'Stereocchemistry of Carbon Compounds', McGraw-Hill, New York, 1962; (b) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis', Interscience, New York, 1965.

⁴ H. Sachse, *Ber.*, 1890, **23**, 1363; *Z. phys. Chem. (Leipzig)*, 1892, **10**, 203.

ethane-type interactions and a 1,4 non-bonded interaction between the 'flagpole' hydrogen atoms. The calculated energy difference between the boat and chair conformations ranges from 5.25 to 8.0 kcal./mole,^{5,6} which is in close agreement with the value of 5.9 ± 0.6 kcal./mole determined experimentally.⁷

Although Sachse referred to the flexible form of cyclohexane as the boat isomer he had envisaged it as a supple entity.⁴ Unfortunately this was overlooked until recently. Unlike the chair isomer which is locked in a potential well, the flexible isomer can pass continuously through an infinite number of configurations without concomitant angle strain.⁵ Midway between the conversion of one severe boat conformation into another by rotation about the C-C bonds, a minimum-energy conformation is attained. This conformation, known as the twist conformation (3), is energetically attractive because both the 1,4 non-bonded interaction between the 'flagpole' hydrogen atoms and the eclipsed ethane-type interactions of the severe boat conformation are partially relieved. Theoretical estimates of the energy of the twist conformation of cyclohexane relative to the chair conformation range from 4.0 to 5.33 kcal./mole,⁵ agreeing with the values of 4.79 ± 0.94 kcal./mole⁸ and 5.5 kcal./mole⁹ determined experimentally.

The relatively large energy difference between the chair and flexible conformations of cyclohexane prevents the adoption of flexible forms except in special circumstances. In cyclohexanone, however, the situation is otherwise. Certain arrangements (4 and 6) of the flexible form of cyclohexanone have only *one* eclipsed ethane-type interaction, and the 1,4 non-bonded interaction between the 'flagpole' hydrogen atoms. Both of these interactions can be partially alleviated by rotation about the C-C bonds towards the twist conformation (5). As a result the energy of the flexible form of cyclohexanone is less than that of the flexible form of cyclohexane.



The effect of the carbonyl group, therefore, is to reduce the energy difference between the chair and flexible forms of cyclohexanone to something less than 5 kcal./mole. The calculated energy difference of 2.7 kcal./mole^{5a,10} is in excellent

⁵ (a) N. L. Allinger, *J. Amer. Chem. Soc.*, 1959, **81**, 5727; (b) P. Hazebroek and L. J. Oosterhoff, *Discuss. Faraday Soc.*, 1951, **10**, 87; (c) K. E. Howlett, *J. Chem. Soc.*, 1957, 4353; (d) J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1961, **83**, 4537.

⁶ C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488.

⁷ N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, 1960, **82**, 2393 (see however ref. 3b, p. 470).

⁸ J. L. Margrave, M. A. Frisch, R. G. Bautista, R. L. Clarke, and W. S. Johnson, *J. Amer. Chem. Soc.*, 1963, **85**, 546.

⁹ 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.

¹⁰ N. L. Allinger, J. Allinger, and M. A. DaRooge, *J. Amer. Chem. Soc.*, 1964, **86**, 4061.

agreement with the experimentally determined values, 2.39 ± 0.38 kcal./mole¹¹ and 2.8 kcal./mole.¹² This energy difference is small enough to be outweighed by interactions between bulky substituents and consequently flexible forms are far more common among cyclohexanone than among cyclohexane derivatives.

3 Physical Techniques

Conformational abnormalities in cyclohexane derivatives are usually disclosed by the application of physical techniques. In some cases abnormal conformations of compounds have been specified exactly by the use of *X*-ray diffraction. This technique is unfortunately laborious to apply and is restricted to the study of compounds in the solid state. The conformation of a compound in solution, which is perhaps of greater interest to the organic chemist, may differ from that in the solid state. Organic chemists, therefore, use a number of techniques which involve the study of dilute solutions. The results obtained from combinations of these techniques (discussed briefly below) generally agree although in some cases a decision as to the exact conformation of a particular compound cannot always be made.¹³

Dipole-moment studies, which are still used extensively in the solution of conformational problems, provided the first indication of conformational abnormality in cyclohexane derivatives.¹⁴ Since dipole moments are vectors, the shape of a molecule is reflected in its observed dipole moment. The dipole moment expected for all plausible conformations of a molecule can be calculated with the aid of Dreiding models or in simple cases by vectorial analysis provided the absence of dipole-dipole interactions is assumed. If, within the experimental error, one of the calculated dipole moments agrees with that observed for the molecule, its conformation can be defined.

Two distinct methods have been developed in the application of nuclear magnetic resonance spectroscopy to the study of conformational abnormality. The first of these utilises the Karplus equation (1) which relates the coupling constant (*J*) between two vicinal protons to the dihedral angle (ϕ) between them.¹⁵ It has been shown experimentally that the values of *x* and *y* vary with the substituents in the system under consideration, while the value of *z* approximates to zero.¹⁶ On this basis it is possible to calculate the dihedral angle between vicinal

$$\left. \begin{array}{l} J = x \cos^2 \phi - z \quad 0^\circ \leq \phi \leq 90^\circ \\ J = y \cos^2 \phi - z \quad 90^\circ \leq \phi \leq 180^\circ \end{array} \right\} \quad (1)$$

protons to an accuracy of $\pm 2^\circ$. The conformation is then given by the Dreiding model which most readily accommodates the calculated dihedral angles.

¹¹ N. L. Allinger and H. M. Blatter, *J. Amer. Chem. Soc.*, 1961, **83**, 994.

¹² N. L. Allinger and F. M. Karkowski, *Tetrahedron Letters*, 1965, No. 26, 2171.

¹³ M. Fétizon, M. Golffier, and P. Laszlo, *Bull. Soc. chim. France*, 1965, 3486.

¹⁴ C. G. Le Févre and R. J. W. Le Févre, *J. Chem. Soc.*, 1935, 1696; 1956, 3549.

¹⁵ M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11; M. Karplus and D. H. Anderson, *J. Chem. Phys.*, 1959, **30**, 6.

¹⁶ K. L. Williamson, *J. Amer. Chem. Soc.*, 1963, **85**, 516; K. L. Williamson, C. A. Langford, and C. R. Nicholson, *ibid.*, 1964, **86**, 762; D. H. Williams and N. S. Bhacca, *ibid.*, p. 2742; A. C. Huitric, J. B. Carr, W. F. Trager, and B. J. Nist, *Tetrahedron*, 1963, **19**, 2145.

The second method is essentially empirical and depends on small changes in the nuclear magnetic resonance chemical shifts of methyl groups. For a large number of 3-keto-steroids the resonance frequency of the C(19) angular methyl protons can be predicted provided the steroid exists in the all-chair conformation.¹⁷ If the A ring is forced to assume a twist conformation the angular methyl group will move into the diamagnetic anisotropy cone of the 3-keto-group and hence the C(19) protons will resonate at a higher field than expected.¹⁸

Infrared spectroscopy has proved a valuable technique in the study of conformational abnormality. It has been possible to detect slight flattenings of cyclohexanone rings from shifts in the carbonyl absorption frequencies.¹⁹ The discovery of intramolecular hydrogen bonding in several compounds has indicated deformation,²⁰ and the configurational assignment of halogen atoms in α -halogeno-ketosteroids has also been important.²¹

The combination of infrared spectroscopy with Raman spectroscopy and appropriate selection rules has revealed the total structures of simple symmetrical molecules. For example, the twist conformation of cyclohexane-1,4-dione has been established in this way.²²

Optical rotatory dispersion²³ and circular dichroism²⁴ techniques stand out in the study of conformational distortion, because minute deformations in cyclic systems containing carbonyl groups markedly affect their optical rotatory dispersion and circular dichroism curves. Deformations alter the asymmetric environment of the carbonyl group and it is this which determines the sign and amplitude of the Cotton effect. For most molecules which display a Cotton effect, the sign and amplitude for any conformational arrangement can be predicted qualitatively by use of the octant²⁵ or reverse octant rules.²⁶ A com-

¹⁷ R. F. Zürcher, *Helv. Chim. Acta*, 1963, **46**, 2054; 1961, **44**, 1380; J. N. Shoolery and M. T. Rogers, *J. Amer. Chem. Soc.*, 1958, **80**, 5121.

¹⁸ W. J. Wechter, G. Slomp, F. A. MacKellar, R. Wiechert, and U. Kerb, *Tetrahedron*, 1965, **21**, 1625.

¹⁹ (a) J. O. Halford, *J. Chem. Phys.*, 1956, **24**, 830; (b) S. Bory, M. Fétizon, P. Laszlo, and D. H. Williams, *Bull. Soc. chim. France*, 1965, 2541.

²⁰ (a) R. D. Stolow, P. M. McDonagh, and M. M. Bonaventura, *J. Amer. Chem. Soc.*, 1964, **86**, 2165; (b) R. D. Stolow and M. M. Bonaventura, *J. Amer. Chem. Soc.*, 1963, **85**, 3636; (c) R. D. Stolow, *J. Amer. Chem. Soc.*, 1961, **83**, 2592; 1964, **86**, 2170; (d) J. Klinol and A. Vystrčil, *Chem. and Ind.*, 1963, 738; (e) M. Svoboda, M. Tichý, J. Fajkoš, and T. Sicher, *Tetrahedron Letters*, 1962, No. 16, 717.

²¹ (a) D. H. R. Barton, D. A. Lewis, and J. F. McGhie, *J. Chem. Soc.*, 1961, 767; (b) D. I. Cropp, B. B. Dewhurst, and J. S. E. Holker, *Chem. and Ind.*, 1961, 209; (c) Y. Mazur and F. Sondeheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 5220; (d) C. Djerassi, N. Finch, and R. Mauli, *J. Amer. Chem. Soc.*, 1959, **81**, 4997; (e) C. Djerassi, N. Finch, R. C. Cookson, and C. W. Bird, *J. Amer. Chem. Soc.*, 1960, **82**, 5488.

²² (a) N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, 1961, **83**, 5028; (b) M. V. Blatt, G. Srinivasan, and P. Neelakantan, *Tetrahedron*, 1965, **21**, 291.

²³ C. Djerassi, 'Optical Rotatory Dispersion—Applications to Organic Chemistry', McGraw-Hill, New York, 1960; P. Crabbé, 'Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry', Holden-Day, San Francisco, California, 1965.

²⁴ L. Velluz, M. Legrand, and M. Grosjean, 'Optical Circular Dichroism', Academic Press, New York, 1965.

²⁵ W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013.

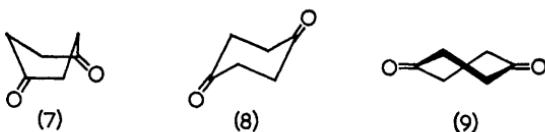
²⁶ C. Djerassi, W. Klyne, T. Norin, G. Ohloff, and E. Klein, *Tetrahedron*, 1965, **21**, 163.

parison between observed and predicted amplitudes can then reveal departures from chair forms. So far, however, no entirely satisfactory quantitative treatment of rotatory dispersion has been evolved.²⁷

4 Monocyclic Compounds

As a result of studies on cyclohexane derivatives, Kumler and Huitric²⁸ concluded that six-membered carbocyclic compounds most likely to exist in the flexible form were those containing two or more atoms in the ring with sp^2 hybridisation, and those with one such atom in the ring and a strong dipole on an adjacent atom. These two conditions, or in some cases simply severe non-bonded interactions, can be recognised in many six-membered carbocyclic compounds known to possess a flexible or boat conformation.

Cyclohexane-1,4-dione is by far the simplest illustration of the first condition. On the basis of the observed dipole moment (1.31 D in benzene) earlier workers¹⁴ considered that cyclohexane-1,4-dione existed as an equilibrium mixture consisting of 20% of the boat form (7) and 80% of the chair form (8).



In 1959, Allinger^{5a} calculated that the chair, boat, and twist conformations of cyclohexane-1,4-dione have comparable energies (within 0.2 kcal./mole) and suggested that the twist conformer (9) might contribute to the equilibrium mixture rather than the boat conformer (7).

The spectroscopic evidence, presented by Allinger^{22a} and Srinivasan^{22b} and their co-workers from a comparison of the Raman and infrared spectra, although not entirely in agreement, nevertheless permitted the conclusion that cyclohexane-1,4-dione exists not as an equilibrium mixture in solution but rather as a single conformer and that this could not be the chair conformer (8). The suggestion was therefore that cyclohexane-1,4-dione exists either in the boat conformation (7) or the twist conformation (9) and that on the basis of dipole-moment measurements the latter conformation is the most likely in solution.

A decision between the boat conformer (7) and the twist conformer (9) was made by an X-ray analysis of cyclohexane-1,4-dione.²⁹ This showed that in the solid state, cyclohexane-1,4-dione exists as a twist conformer with the two carbonyl bonds making an angle of 154° with each other. The dipole moment

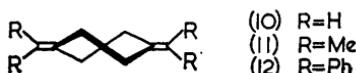
²⁷ (a) W. Moffitt and A. Moscowitz, *J. Chem. Phys.*, 1959, **30**, 648; (b) C. Beard, C. Djerassi, J. Sicher, F. Sipoš, and M. Tichý, *Tetrahedron*, 1963, **19**, 919; (c) J. C. Tai and N. L. Allinger, *J. Amer. Chem. Soc.*, 1966, **88**, 2179.

²⁸ (a) W. D. Kumler and A. C. Huitric, *J. Amer. Chem. Soc.*, 1956, **78**, 3369; (b) 1956, **78**, 1147; (c) 1956, **78**, 614.

²⁹ P. Groth and O. Hassel, *Acta Chem. Scand.*, 1964, **18**, 923; A. Mossel and C. Romers, *Acta Cryst.*, 1964, **17**, 1217; P. Groth and O. Hassel, *Proc. Chem. Soc.*, 1963, 218; A. Mossel, C. Romers, and E. Havinga, *Tetrahedron Letters*, 1963, No. 19, 1247.

calculated for this conformation is 1.27 D, suggesting a twist conformation in solution (cf. $\mu_{\text{expt}} = 1.31$ D in benzene). The similarity of the infrared spectra of the compound in the solid state and in solution supports this conclusion. Several derivatives of cyclohexane-1,4-dione have also been shown to possess twist conformations.³⁰

Nuclear magnetic resonance and dipole moment studies³¹ have shown that 1,4-dimethylenecyclohexane (10) and its *exo*-tetramethyl (11) and *exo*-tetraphenyl (12) analogues exist in the twist conformation of the flexible form in solution. This is to be expected since these compounds also satisfy Kumler and Huitric's first condition for flexibility.



Hexamethylcyclohexane-1,3,5-trione, another system which satisfies Kumler and Huitric's first condition, also exists predominantly in the twist conformation.³²

The second condition which Kumler and Huitric suggested for the existence of flexible forms in six-membered carbocyclic compounds was based on the dipole moments of α -halogeno-cyclohexanones. The suggestion was^{28a} that both α -bromo- and α -chloro-cyclohexanones existed to some extent in the twist conformation. There is now, however, substantial evidence to refute these suggestions. All available data (based on infrared, ultraviolet,³³ and optical rotatory dispersion studies³⁴) are consistent only with equilibrium mixtures containing interconvertible chair conformations. When Kumler and Huitric's second condition is accompanied by severe steric interactions, however, abnormal conformations often occur. Although most examples of this type occur in polycyclic systems (to be discussed below) one monocyclic example is known.

Ourisson and his co-workers³⁵ synthesised 2,6-dibromo-3,3,5,5-tetramethylcyclohexanone and demonstrated by considerations of angular deformation energy and X-ray studies that the six-membered ring is slightly distorted from the normal chair conformation. 3,3,5,5-Tetramethylcyclohexanone itself is also distorted from the chair conformation but to a lesser extent. This reveals the

³⁰ P. Groth and O. Hassel, *Acta Chem. Scand.*, 1965, **19**, 1733; 1964, **18**, 1327; P. Groth and O. Hassel, *Tetrahedron Letters*, 1964, No. 2, 65; P. Groth, *Acta Chem. Scand.*, 1966, **20**, 579; R. D. Stolow and C. B. Boyce, *J. Amer. Chem. Soc.*, 1961, **83**, 3722; R. D. Stolow and M. M. Bonaventura, *Tetrahedron Letters*, 1964, No. 2, 95.

³¹ F. Lautenschaeger and G. F. Wright, *Canad. J. Chem.*, 1963, **41**, 1972.

³² J. Dale, *J. Chem. Soc.*, 1965, 1028.

³³ E. J. Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 2301; J. Allinger and N. L. Allinger, *Tetrahedron*, 1958, **2**, 64; N. L. Allinger, J. Allinger, L. A. Freiberg, R. F. Czaja, and N. A. Le Bel, *J. Amer. Chem. Soc.*, 1960, **82**, 5876.

³⁴ N. L. Allinger, J. Allinger, L. E. Geller, and C. Djerassi, *J. Org. Chem.*, 1960, **25**, 6; 1961, **26**, 3521; C. Djerassi, K. M. Wellman, and E. Bunnenberg, *J. Amer. Chem. Soc.*, 1963, **85**, 1876; C. Djerassi, L. E. Geller, and E. J. Eisenbraun, *J. Org. Chem.*, 1960, **25**, 1.

³⁵ C. Sandris and G. Ourisson, *Bull. Soc. chim. France*, 1956, 958; 1958, 1524; B. Waegell and G. Ourisson, *ibid.*, 1961, 2443.

greater flexibility of the α -halogeno-cyclohexanone system compared with cyclohexanone itself. It is noteworthy that nuclear magnetic resonance, infrared, and ultraviolet spectral studies suggest that 2,2,6,6-tetramethylcyclohexanone adopts either a flattened chair or a twist conformation.^{19b} This ambiguity obviously warrants further investigation.

It is well known that t-butyl groups tend to avoid axial orientations.³⁶ Accordingly *trans*-1,3-di-t-butylcyclohexane and *trans*-2,4-di-t-butylcyclohexanone might be expected to adopt flexible conformations since these forms allow the t-butyl groups to assume equatorial orientations. Originally these compounds were thought to exist in classical boat forms but it has now been suggested that they adopt twist forms. The basis for this suggestion is derived from equilibration studies of these compounds with their respective *cis* isomers.^{7,11} The determined energy differences are comparable with those determined for other chair-twist interconversions. The *cis* isomers of these compounds can exist in chair conformations with both t-butyl groups equatorial whereas the chair conformations of the *trans* isomers possess one t-butyl group in a destabilising axial position and one in an equatorial position.

Provided the substituents are bulky a similar situation exists in *cis*-1,4-disubstituted cyclohexanes in general. The diaxial interactions present in chair conformations of such compounds are avoided by the adoption of flexible conformations since these permit the large axial substituents to assume equatorial-like orientations. Nuclear magnetic resonance studies utilising the Karplus equation, for example,³⁷ have shown that *cis*-4-t-butyl-1-phthalimidocyclohexane and *cis*-4-t-butyl-1-succinimidocyclohexane consist of rapidly interconvertible twist conformations together with a small contribution from the chair conformation, and it has been suggested that *cis*-4-t-butyl-1-phenylcyclohexane also exists as a conformational equilibrium mixture with contributions from twist conformations.³⁸

Optical rotatory dispersion has revealed that twist conformations make minor contributions to the conformational equilibria which exist in *cis*-2-t-butyl-5-methylcyclohexane,³⁹ *cis*-2-methyl-4-t-butylcyclohexanone,^{27b} *cis*-2,4-dimethylcyclohexanone,^{27b} and 2-methylcyclohexanone.⁴⁰ Since the theoretical interpretation of the optical rotatory dispersion curves is very similar in all these cases only the evidence for twist conformations in the *cis*-2,4-dialkylcyclohexanones will be considered here.

The octant rule²⁵ predicts a negligible Cotton effect for the chair form of (+)-*cis*-2-methyl-4-t-butylcyclohexanone (13). The observed positive Cotton effect amplitude, $\alpha = +17.5$ (where α is defined as the difference between the molecular rotation, $[\phi]_L$, at the extremum of longer wavelength minus the

³⁶ S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, 1955, **77**, 5562; E. L. Eliel and C. A. Lukach, *ibid.*, 1957, **79**, 5986; E. L. Eliel and R. S. Ro, *ibid.*, 1957, **79**, 5992, 5995.

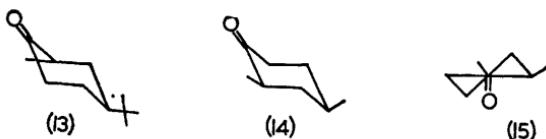
³⁷ H. Booth and G. C. Gidley, *Tetrahedron Letters*, 1964, No. 23, 1449.

³⁸ E. W. Garisch, jun. and D. B. Patterson, *J. Amer. Chem. Soc.*, 1963, **85**, 3228.

³⁹ C. Djerassi, E. J. Warawa, J. M. Berdahl, and E. J. Eisenbraun, *J. Amer. Chem. Soc.*, 1961, **83**, 3334.

⁴⁰ C. Djerassi, C. Beard, T. Elliot, and R. C. C. Tao, *J. Amer. Chem. Soc.*, 1962, **84**, 874.

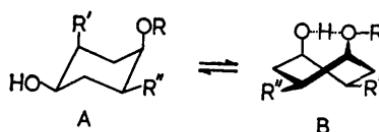
molecular rotation, $[\phi]_s$, at the extremum of shorter wavelength divided by 100), was taken therefore to indicate some conformational distortion from the classical chair conformation. In order to determine whether this deformation was caused by the t-butyl group the optical rotatory dispersion curve of the antipodal (−)-*cis*-2,4-dimethylcyclohexanone (14) was recorded, $\alpha = -16.5$. It was therefore concluded that the conformational distortion was not necessarily associated with the bulk of the C(4) substituent but rather with the presence of two 1,3-diequatorial alkyl groups. Contrary to earlier predictions from the octant rule, Djerassi found that an equatorial methyl group α to a carbonyl function in a chair form cyclohexanone makes a molecular amplitude contribution of *ca.* 9 to the Cotton effect. Conformations apart from the chair forms (13) and (14) must contribute, therefore, to the molecular amplitudes of the *cis*-2,4-dialkylcyclohexanones.



Conformers containing axial alkyl groups are unlikely to be present because of their high energy and part of the Cotton-effect amplitudes must be associated with contributions from non-chair conformations. Twist conformers (*e.g.*, 15) would lead to amplitude values of the correct sign but the only factor which might be responsible for distortions to such forms, namely the interaction between the equatorial methyl group and the carbonyl group, is negligible.¹¹ Moreover, the quantitative molecular amplitude contribution for a twist conformation has yet to be obtained and therefore the extent to which these forms contribute to the conformational equilibrium cannot be precisely estimated. Clearly therefore our understanding even in such simple molecules is far from adequate.

Stolow *et al.*^{20a,b,c} synthesised a number of *cis,cis,cis*-2,5-dialkylcyclohexane-1,4-diols and examined their infrared spectra. All the compounds in dilute carbon tetrachloride solution showed absorptions attributable to intramolecular hydrogen bonding. Inspection of Dreiding models indicated that this was compatible only with the existence of twist conformations. The relative absorbance in the 3490 cm^{-1} region was in fact taken as a measure of the twist population for each diol. The twist contribution increased with the size of the alkyl groups as shown in the Table.

The chair conformation in these molecules is destabilised by the 1,3-diaxial interactions shown in the diagram (Table, A). In the twist conformation, however, the alkyl groups are able to assume equatorial-like orientations, and extra stability also accrues from the formation of the intramolecular hydrogen bond (Table, B).

Twist contributions in *cis,cis,cis*-2,5-dialkylcyclohexane-1,4-diols

R	R'	R''	Twist contribution (%)		Ref.
			Me	Pr ^t	
H	Me	Me	5	20c	
H	Me	Pr ^t	13	20c	
H	Me	But ^t	14	20c	
H	Pr ^t	Pr ^t	80	20c	
H	cyclohexyl	cyclohexyl	80	20a	
H	But ^t	But ^t	98	20c	
H	t-pentyl	t-pentyl	98	20a	
Me	But ^t	But ^t	98	20b	

5 Bicyclic Compounds

Although electron-diffraction studies⁴¹ have shown *cis*- and *trans*-decalins to exist in double-chair conformations, a recent theoretical treatment^{42a} of the decalins has indicated that flexible conformations or flattened chair conformations are energetically feasible, especially in the case of *cis*-decalins. Nevertheless few examples of bicyclic systems containing non-chair conformations have been reported. This may reflect the difficulties encountered in handling these systems.

The fact that nuclear magnetic resonance evidence^{42b} indicates that a number of *cis*-decal-2-ones exist in double-chair conformations does not eliminate the possibility of slight unsymmetrical distortions. Indeed optical rotatory dispersion and circular dichroism measurements^{42c} revealed the presence of distortion in such molecules but the results were misleadingly interpreted in terms of twist-chair conformations. This illustrates the conflicting conclusions which are sometimes drawn from the application of closely related physical techniques in the investigation of conformation.

Despite the foregoing evidence for double-chair conformations it is still conceivable that both rings in the decalins could exist in abnormal conformations because the decalin systems are not as conformationally restricted as polycyclic systems. Further studies might prove extremely rewarding.

Djerassi, Mauli, and Zalkow⁴³ have demonstrated that *trans*-tetrahydroeremophilone (16) is unstable with respect to its *cis* isomer. The instability of the *trans* isomer was attributed to the acute 1,3-diaxial interaction between the

⁴¹ M. I. Davis and O. Hassel, *Acta Chem. Scand.*, 1964, **18**, 813.

⁴² (a) P. Geneste and G. Lamaty, *Tetrahedron Letters*, 1964, No. 47, 3545; *Bull. Soc. chim. France*, 1964, 2439; R. Bucourt and D. Hainaut, *ibid.*, 1965, 1366; 1966, 501; (b) D. R. Elliott, M. J. T. Robinson, and F. G. Riddell, *Tetrahedron Letters*, 1965, No. 22, 1693; (c) C. Djerassi, J. W. Chamberlain, D. Eland, T. Toda, and G. Stork, *J. Amer. Chem. Soc.*, 1964, **86**, 465.

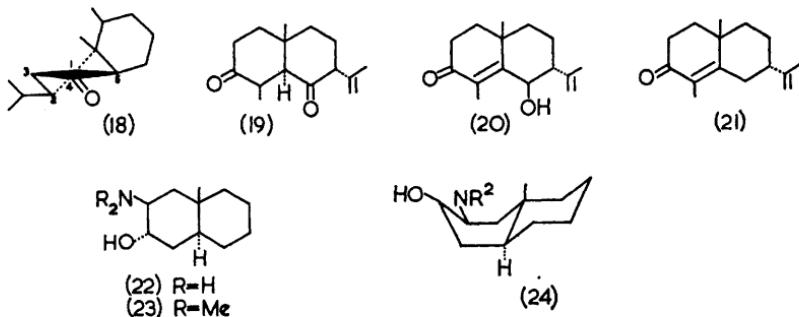
⁴³ C. Djerassi, R. Mauli, and L. H. Zalkow, *J. Amer. Chem. Soc.*, 1959, **81**, 3424.

β -oriented isopropyl group and the angular methyl group which can be partially relieved in the boat-chair conformation (cf. 16 and 17).



Optical rotatory dispersion⁴⁴ has confirmed that the A ring in this compound is not a normal chair and suggests the twist rather than the boat form of the flexible conformation. Thus the octant rule²⁵ predicts a small negative Cotton-effect amplitude for both the double-chair (16) and the boat-chair (17) conformations, but the observed amplitude is abnormally large ($\alpha = -109$) and can only be explained by the twist-chair conformation (18). This conformation, a small step from Djerassi's boat-chair conformation, would also relieve the 1,3-interaction between the angular methyl group and the 2β -isopropyl group.

Similarly it has been suggested⁴⁵ that the abnormally large Cotton-effect amplitude ($\alpha = +442$) and the strong circular dichroism ($\Delta \xi_{298} + 9.97$) of (+)-4 β ,7 β (H)-eudesm-11-en-3,6-dione (19) could be rationalised by assuming a twist conformation for the B ring in this compound relieving non-bonded interactions of the isopropenyl group. The optical rotatory dispersion curves of the related compounds (+)-6 β -hydroxy-7 β (H)-eudesma-4,11-dien-3-one (20) and (+)-7 β (H)-eudesma-4,11-dien-3-one (21) are similar to those of the 8 α -steroids. Since the 8 α -steroids possess either ring B or C as a boat⁴⁶ it seems likely⁴⁵ that these eudesmane derivatives (20 and 21) also possess ring B as a full or partial boat which would relieve the steric compression expected in all chair conformations.



The infrared spectra of the amino-alcohol (22) and the dimethylamino-alcohol (23) display both bonded and free hydroxyl absorption bands. This is consistent only with a conformational equilibrium in the A rings of these compounds between boat and chair conformations.^{20e} The geometrical requirements for

⁴⁴ C. Djerassi and W. Klyne, *Proc. Nat. Acad. Sci. U.S.A.*, 1962, **48**, 1093.

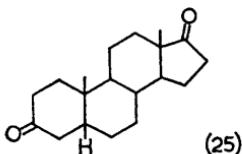
⁴⁵ D. W. Theobald, *Tetrahedron*, 1963, **19**, 2261.

⁴⁶ C. Djerassi, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6377.

intramolecular hydrogen bond formation are not realised in all-chair conformations but are satisfied by boat-chair conformations (24). The driving forces in the deformation are undoubtedly the interactions which exist between the 2β -substituents and the angular methyl groups in the double-chair conformations of these amino-alcohols (22 and 23). These interactions are relieved in the boat-chair conformations (24), which are also stabilised by the intramolecular hydrogen bonds.

6 Polycyclic Compounds

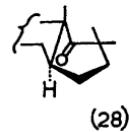
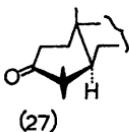
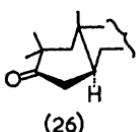
Until 1953 the steroids and triterpenoids had been thought of as rigid all-chair systems. During the last decade, however, the various methods already mentioned have shown that abnormal conformations occur widely in these polycyclic systems. The major cause of conformational distortion is usually the non-bonded interactions which would occur between substituents in all-chair conformations.



The first demonstration that the conformations of steroids were not 'fixed' came from dipole-moment measurements on 5β -androstane-3,17-dione (25). Nace and Turner⁴⁷ observed that this compound had a dipole moment of 3.5 D in benzene solution. An all-chair conformation of the compound has a calculated moment of 3.04 D. The difference between the observed and calculated values suggested a conformational equilibrium containing approximately 16% of the compound with the A ring in the boat conformation; this has a calculated dipole moment of 5.28 D. The measurement of dipole moments has since been extensively and successfully employed in the investigation of conformational distortions in both the steroids and triterpenoids.

For example, by this method Allinger and DaRooge⁴⁸ demonstrated that the A rings in 2,2- and 4,4-dimethyl-3-keto-steroids exist as flattened chair forms (26, 27), as does ring D in the 17,17-dimethyl-D-homo-17 α -keto-steroids¹⁰ (28) and ring A in 2β -bromo-, 2,2-dibromo-, and 2ζ -chloro- 2ζ -bromo-cholestane-3-one.⁴⁹

The same deformation occurs in the triterpenoid 28-cyanolupan-3-one (29).

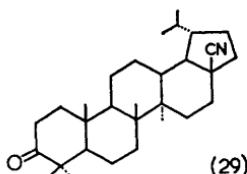


⁴⁷ H. R. Nace and R. B. Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 4063.

⁴⁸ N. L. Allinger and M. A. DaRooge, *J. Amer. Chem. Soc.*, 1962, **84**, 4561; *Tetrahedron Letters*, 1961, No. 19, 678.

⁴⁹ A. K. Bose, M. S. Manhas, and E. R. Malinowski, *J. Amer. Chem. Soc.*, 1963, **85**, 2795.

The dipole moment observed for this compound was interpreted originally in terms of an A ring conformational equilibrium between a chair form (70%) and an unspecified distorted boat form (30%).⁵⁰ Recently, however, dipole-moment determinations at different temperatures^{49,51} have shown that the compound exists as a single conformer in which ring A adopts a flattened chair conformation.



It is generally recognised that conformation cannot always be specified on the basis of the results obtained from a single physical technique. In most cases the flattened chair conformations revealed by dipole-moment studies have in fact been confirmed by the use of other physical techniques such as optical rotatory dispersion,^{10,48,52} circular dichroism,⁵² and infrared⁵³ and nuclear magnetic resonance spectroscopy,^{49,51,54} or at least results from these are consistent with the dipole-moment studies. Despite the seemingly overwhelming evidence for flattened chair conformations an element of controversy remains, for Holker and Whalley⁵⁵ believe that the optical rotatory dispersion curves of the 3-keto- triterpenoids and the 4,4-dimethyl-3-keto-steroids are best rationalised in terms of the octant rule if these compounds have ring A in a twist conformation. However, it has already been mentioned that the amplitudes of such forms cannot be assessed accurately at present. It is difficult to see what further evidence can resolve this dispute (except perhaps *X*-ray analysis), and this in itself illustrates the limitations of our methods for investigating the conformations of these molecules.

The kinetically controlled bromination of 2α -methylcholestan-3-one gives a 2-bromo-2-methylcholestan-3-one. On the basis of the infrared and ultraviolet spectra which indicated the presence of an axial bromine atom, the compound was assumed to be 2β -bromo- 2α -methylcholestan-3-one (30).^{21c} Although the axial halogeno-ketone rule,⁵⁶ a special case of the more general octant rule, predicted a strongly positive Cotton effect for the compound with this conformation, the observed Cotton effect was negative.^{21d,e} This apparent contradiction was rationalised by assuming the initial bromination product to be 2α -bromo- 2β -methylcholestan-3-one (31), with the A ring as a chair. The 1,3-diaxial inter-

⁵⁰ J.-M. Lehn, J. Levisalles, and G. Ourisson, *Tetrahedron Letters*, 1961, No. 19, 682.

⁵¹ J.-M. Lehn, J. Levisalles, and G. Ourisson, *Bull. Soc. chim. France*, 1963, 1096.

⁵² M. Uskoković, M. Gut, E. N. Trachtenberg, W. Klyne, and R. I. Dorfman, *J. Amer. Chem. Soc.*, 1960, **82**, 4965; P. Witz, H. Hermann, J.-M. Lehn, and G. Ourisson, *Bull. Soc. chim. France*, 1963, 1101.

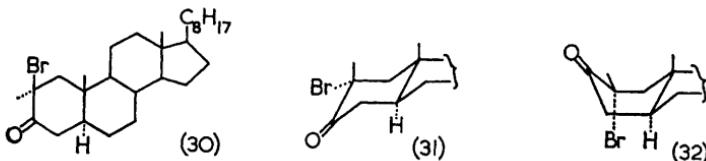
⁵³ J. Klinot and A. Vystrčil, *Coll. Czech. Chem. Comm.*, 1966, **31**, 1079.

⁵⁴ J.-M. Lehn and G. Ourisson, *Bull. Soc. chim. France*, 1963, 1113; C. W. Shoppee, T. E. Bellas, R. E. Lack, and S. Sternhell, *J. Chem. Soc.*, 1965, 2483; R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.*, 1963, 806.

⁵⁵ J. S. E. Holker and W. B. Whalley, *Proc. Chem. Soc.*, 1961, 464.

⁵⁶ C. Djerassi and W. Klyne, *J. Amer. Chem. Soc.*, 1957, **79**, 1056; C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 1216.

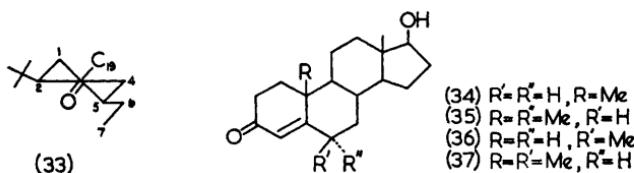
action between the C(2) and C(10)-methyl groups and the electrostatic interaction between the bromine atom and the carbonyl dipole must then cause a conformational flip to the boat form of 2α -bromo- 2β -methylcholestan-3-one (32). This conformation accommodates all the experimental data. The axial orientation of the bromine atom agrees with the spectral data, and the axial halogeno-ketone rule predicts a negative Cotton effect.



The results of this and other bromination experiments⁵⁷ prompted a reconsideration of the then accepted mechanism of Corey⁵⁸ for bromination under kinetic conditions. It is now recognised that in the presence of steric interaction the product of kinetic bromination is an equatorial and not an axial bromoketone.⁵⁹

The deformation of the A ring of this compound is a manifestation of Kumler and Huitric's second condition for ring flexibility.²⁸ That the electrostatic interaction between the equatorial bromine atom and the carbonyl dipole plays an important role in this distortion has been demonstrated by some optical rotatory dispersion studies on 2β -isopropyl- and 2β -t-butyl-cholestan-3-one.

Djerassi, Hart, and Warawa⁶⁰ have shown that 2β -t-butyl-cholestan-3-one exists as a conformational equilibrium mixture with an important contribution from the twist conformer (33). Deformation, however, is to be expected in this case since t-butyl groups tend to avoid axial orientations.³⁶ No evidence could be obtained for the presence of twist conformers in 2β -isopropylcholestan-3-one.⁶¹ Since the 1,3-homoannular diaxial interactions in these compounds are greater than those in 2α -bromo- 2β -methyl-3-keto-steroids it is obvious that the interaction between an equatorial bromine atom adjacent to a carbonyl function significantly increases ring flexibility.



Certain 6β -substituted Δ^4 -3-keto-steroids exhibit abnormal optical rotatory dispersion curves.⁶² Whereas testosterone (34), 6α -methyl-testosterone (35) and 6β -methyl-19-nortestosterone (36) have predictably normal negative Cotton-

⁵⁷ R. Mauli, H. J. Ringold, and C. Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 5944.

⁵⁸ E. J. Corey, *Experientia*, 1953, **9**, 329.

⁵⁹ R. Villotti, H. J. Ringold, and C. Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 5693.

⁶⁰ C. Djerassi, P. A. Hart, and E. J. Warawa, *J. Amer. Chem. Soc.*, 1964, **86**, 78.

⁶¹ C. Djerassi, P. A. Hart, and C. Beard, *J. Amer. Chem. Soc.*, 1964, **86**, 84.

effect curves, 6β -methyltestosterone (37) displays an inverted positive curve greatly resembling those of the 8α - Δ^4 -3-keto-steroids. Since the latter compounds were known to possess either ring B or C in a boat conformation⁶² it was originally suggested⁶² that the B ring in 6β -methyltestosterone also adopted either a full or partial boat conformation.

The inverted positive optical rotatory dispersion curves of the 6β -substituted Δ^4 -3-keto-steroids, however, have now been explained in terms of a more general conformational change in both the A and B rings, a change caused primarily by the bulk of the 6β -substituent.⁶³ (6β -Methyl-, -nitro-, -chloro-, -bromo-, and -iodo- Δ^4 -3-keto-steroids have positive Cotton effects whereas 6β -fluoro- and -hydroxy- Δ^4 -3-keto-steroids exhibit normal negative Cotton effects.)

When the 6β -substituent is at least as bulky as chlorine a strong interaction exists between this substituent and the angular methyl group. This interaction can be relieved by a lateral displacement of the 6β -substituent which in turn reverses the chirality of the C = C — C = O chromophore (38 → 39). Hence the asymmetric environment about the chromophore in the 6α - and the bulky 6β -substituted Δ^4 -3-keto-steroids are approximately mirror images. Any two epimeric 6-substituted Δ^4 -3-keto-steroids would therefore be expected to display Cotton effects of opposite sign provided the substituents are sufficiently large. Nuclear magnetic resonance spectroscopy relating to the chemical shifts of angular methyl groups has confirmed the interpretation given above.⁶⁴ Similar conformational changes also occur in 2β -substituted Δ^4 -3-keto-steroids.⁶⁵



Nuclear magnetic resonance spectroscopy, optical rotatory dispersion and circular dichroism have shown the B rings in certain 6,6-dimethylcholestane and 6,6-dimethyl-19-norandrostane derivatives to exist in twist conformations.⁶⁶ In the 6,6-dimethylcholestane derivatives the distortion of ring B is induced by interactions between the C(10) and C(6) axial methyl groups and between the C(6) equatorial methyl group and the C(4) protons. Since the former interaction is absent from the 6,6-dimethyl-19-norandrostane derivatives it appears that the C(4)-C(6) interaction is the major cause of conformational abnormality in these molecules. Such an interaction was in fact invoked by Holker and Whalley⁶⁵ when they suggested twist conformations in the A rings of 4,4-dimethyl-3-keto-steroids.

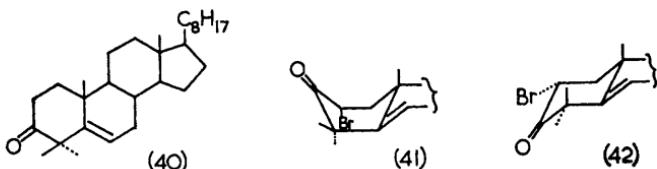
⁶² C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 4001.

⁶³ W. B. Whalley, *Chem. and Ind.*, 1962, 1024.

⁶⁴ K. Tori and K. Kuriyama, *Chem. and Ind.*, 1963, 1525.

⁶⁵ K. Kuriyama, E. Kondo, and K. Tori, *Tetrahedron Letters*, 1963, No. 2, 1485.

⁶⁶ F. Lederer and G. Ourisson, *Bull. Soc. chim. France*, 1965, 1298.



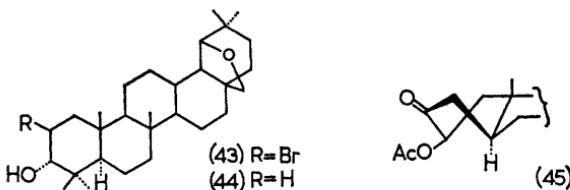
The presence of the double bond in Δ^5 -3-keto-4,4-dimethyl steroids introduces a second trigonal carbon atom into the A ring and thereby increases its flexibility. The monobromination of 4,4-dimethylcholest-5-en-3-one (40) gives a 2-bromo-compound which has been shown by infrared and ultraviolet spectroscopy to contain an axial bromine atom.^{21b} The optical rotatory dispersion curve of this bromo-ketone exhibited a reduced positive Cotton-effect amplitude when compared with the parent ketone. On this basis the bromine atom was assigned the α -configuration in a boat-form ring A (41).^{21b} The alternative chair conformation with the bromine atom in the axial 2β -configuration would be expected to exhibit an enhanced positive Cotton effect over that of the parent ketone. The chair conformation of 2α -bromo-4,4-dimethylcholest-5-en-3-one (42) would be destabilised by the interaction between the C(4) and C(10) axial methyl groups and by the electrostatic interaction between the equatorial bromine atom and the carbonyl dipole. It is to be noted that a new 1,3-diaxial interaction arises in the boat form between the bromine atom and the 4α -methyl group. Accordingly one would not expect the energy difference between the boat and chair forms to be large. In fact, nuclear magnetic resonance studies concerning the chemical shifts of the angular methyl groups have shown that the A rings in compounds of this type exist in a state of conformational equilibrium between chair and boat conformations rather than existing solely in the boat conformation.^{13,67} At low temperatures the chair conformation is favoured but at room temperature the boat form of ring A predominates. Confirmation of this should be possible by use of optical rotatory dispersion since the molecular amplitude would be expected to decrease with increasing temperature. The rate of formation of epoxides from the related 2α -bromo- 3β -hydroxy-4,4-dimethyl- Δ^5 -steroid bromohydrins (approximately one hundred times faster than expected) also demonstrates the ease with which ring A can adopt a boat conformation.⁶⁸ On this basis one might expect the conformations of these bromohydrins to be abnormal and it should be possible to establish this by investigating the hydroxyl absorption regions of their infrared spectra.

Such studies have in fact indicated the presence of a flexible conformation in ring A of 2β -bromo- $19\beta,28$ -epoxy- 3α -hydroxy- 18α -oleanane (43).^{20d} The configurations of the bromine atom and the hydroxyl group in this compound were established unequivocally by chemical means. The infrared hydroxyl

⁶⁷ B. B. Dewhurst, J. S. E. Holker, A. Lablache-Combier, M. R. G. Leeming, J. Levisalles, and J. P. Pete, *Bull. Soc. chim. France*, 1964, 3259; A. Lablache-Combier, B. Laucombe, and J. Levisalles, *ibid.*, 1965, 2595; B. Laucombe and J. Levisalles, *ibid.*, 1965, 2602; M. Gordetsky, A. Yoge, and Y. Mazur, *J. Org. Chem.*, 1966, 31, 699.

⁶⁸ B. B. Dewhurst, J. S. E. Holker, A. Lablache-Combier, and J. Levisalles, *Chem. and Ind.*, 1961, 1667.

absorption band of the corresponding 3α -ol (44) appeared at 3635 cm^{-1} while that of the bromohydrin appeared at 3583 cm^{-1} . The observed shift of $\Delta\nu = -52\text{ cm}^{-1}$ is comparable with the shifts exhibited by diequatorial and axial-equatorial bromohydrins ($\Delta\nu = -37\text{ cm}^{-1}$ and -46 to -59 cm^{-1}) though not with the shift normally associated with a diaxial bromohydrin ($\Delta\nu = -4\text{ cm}^{-1}$). The only conformation with which the observed value of $\Delta\nu$ appears compatible therefore, is the flexible conformation (probably existing in the twist form). It is likely that the $1,3$ -dialixial interactions between the 2β -bromine atom and the 4β - and 10β -methyl groups make a chair conformation for ring A energetically unfavourable.



Williamson and Johnson⁶⁹ have applied nuclear magnetic resonance spectroscopy to the study of the conformation of ring A in 2β -acetoxycholestan-3-one. The signal produced by the lone C(2) proton appeared as a quartet centred at 4.88τ . Application of a modified form of the Karplus equation¹⁵ allowed the dihedral angles between the hydrogen atoms at C(1) and C(2) to be calculated. Dreiding models indicated that these calculated dihedral angles could be most readily accommodated in the twist conformation (45).

Similar twist conformations exist in the A rings of 2β -acetoxy-3-keto-triterpenoids.⁷⁰ The principal cause of the twist conformations in these compounds is taken to be the diaxial interaction between the 2β -acetoxy-group and the angular methyl group in the conformations in which ring A is a chair. Optical rotatory dispersion evidence is consistent, but no more than consistent, with this interpretation.

7 Conclusion

It is apparent from the examples discussed that the simple yet elegant concepts of conformational analysis suggested originally by Barton^{1,2} are not always applicable to heavily substituted cyclohexane derivatives. For such molecules advances in instrumentation have revealed that the conformational situation is far from simple, and that it is almost impossible to predict which of the many available conformations will be adopted in the ground state.

The only valid generalisations which can be drawn are perhaps Kumler and Huitric's conditions for ring flexibility coupled with an additional clause relating to the destabilisation of chair conformations by severe non-bonded interactions. Cyclohexane moieties in which either of these conditions are fulfilled obviously

⁶⁹ K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, 1961, **83**, 4623.

⁷⁰ E. L. McGinnis, G. D. Meakins, J. E. Price, and M. C. Styles, *J. Chem. Soc.*, 1965, 4379.

deserve close study because conformational abnormalities are likely to be encountered.

So far there have been few if any useful *quantitative* kinetic studies upon the rates of reactions of cyclohexane derivatives known to possess abnormal ground-state conformations. The reason for this is perhaps that investigations have been primarily concerned with the disclosure of such entities rather than the study of their chemical properties. The energy differences between the classical chair conformation and what in this Review have been called abnormal conformations are usually small (*ca.* 2—5 kcal./mole) compared with the activation energies of common organic reactions (*ca.* 20 kcal./mole). This suggests that abnormal conformations, though likely to influence the rates of reactions, as in the formation of epoxides from 2α -bromo- 3β -hydroxy-4,4-dimethyl- Δ^5 -steroids already mentioned, are unlikely to provoke major mechanistic changes. In other words, the discovery of abnormal conformations should not require a radical revision of the mechanisms of organic reactions elaborated on the basis of the classical boat and chair conformations.

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