Heterocyclic Conformational Analysis

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Conformational analysis, which now ranks amongst the most important branches of organic stereochemistry, may be said to have started in 1950 with the classical paper by Barton[1] in which some fundamental relationships between the conformations and chemical reactivity of certain molecules were pointed out. The fundamental tenet of conformational analysis as suggested by Barton and Cookson[2] is that the chemical and physical properties of organic molecules depend not only on their gross structure and stereochemistry but also on the conformations they prefer to adopt. The intense work stimulated by these suggestions has led to a reasonable understanding of the behaviour of alicyclic compounds and for background material the reader may consult several recent texts on the subject.[3,4,5] Recently more attention has been directed towards the conformational analysis of heterocyclic systems, which not only displays many points in common with that of alicyclic systems but also provides many interesting and instructive points of difference.

The overall similarities between heterocyclic and alicyclic conformational analyses are important. In general, six-membered heterocyclic compounds, like cyclohexane derivatives, prefer chair conformations with equatorial substituents. This has been demonstrated by a wide variety of physical techniques. For example, piperidine,[6] piperazine,[7] *NN'*-dimethyl- and *NN'*-dichloropiperazine[7,8] have chair conformations of geometry closely analogous to that of cyclohexane. 1,4-Dioxan,[7,9–11] 1,4-dithian,[10,12,13] 1,3,5-trioxan,[13–15] and 1,3,5-trithian[10,13] and

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* Present address: Department of Chemistry, The University, Stirling, Scotland.

[1] D. H. R. Barton, *Experientia*, 1950, **6**, 316.

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

[3] M. Hanack, 'Conformation Theory', Academic Press, New York, 1965.

[4] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis', Interscience, New York, 1964.

[5] E. L. Eliel, *Angew. Chem.*, 1965, **77**, 784.

[6] (*a*) J. W. Visser, J. Manassen, and J. L. De Vries, *Acta Cryst.*, 1954, **7**, 288; (*b*) M. Przybylska and W. H. Barnes, *Acta Cryst.*, 1953, **6**, 377.

[7] M. Davies and O. Hassel, *Acta Chem. Scand.*, 1963, **17**, 1181.

[8] P. Anderson and O. Hassel, *Acta Chem. Scand.*, 1949, **3**, 1180.

[9] L. E. Sutton and L. O. Brockway, *J. Amer. Chem. Soc.*, 1935, **57**, 473.

[10] O. Hassel and H. Viervoll, *Acta Chem. Scand.*, 1947, **1**, 149.

[11] (*a*) D. A. Ramsey, *Proc. Roy. Soc.*, 1947, *A*, **190**, 562; (*b*) F. E. Malherbe and H. J. Bernstein, *J. Amer. Chem. Soc.*, 1952, **74**, 4408.

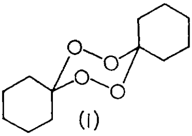
[12] H. J. Dothie, *Acta Cryst.*, 1953, **6**, 804; (*b*) R. E. Marsh, *Acta Cryst.*, 1955, **8**, 91.

[13] K. E. Calderbank and R. J. W. Le Fèvre, *J. Chem. Soc.*, 1949, 199.

[14] N. F. Moermann, *Rec. Trav. chim.*, 1937, **56**, 161.

[15] D. A. Ramsey, *Trans Faraday Soc.*, 1948, **44**, 289.

their derivatives[16–18] have chair conformations. Even the highly hetero-substituted dimeric cyclohexane peroxide (1) has the heterocyclic ring in the chair form.[19] α-Tristhioacetaldehyde (2) with an axial methyl group is less stable than the *β*-isomer (3),[18] and α-paraldehyde (4) is about 3 kcal./mole less stable than its *β*-isomer (5).[20] As with the corresponding cyclohexanes, 1,4-dioxan-*cis*-2,5- and -*trans*-2,6-dicarboxylic acids are less stable than their all equatorial isomers.[21]



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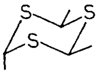

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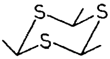

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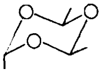

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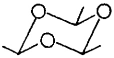

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These great similarities should not hide the striking differences that exist between the forces controlling alicyclic and heterocyclic conformations. Five obvious differences need to be considered. First, torsional interactions along heteroatom–carbon bonds differ from those along carbon–carbon bonds. Secondly, non-bonded interactions are different in heterocyclic and alicyclic systems. Thirdly, the presence of hetero-atoms increases the importance of dipolar interactions. Fourthly, the force constants for bond-angle deformation of hetero-atoms are different from those of carbon and, finally, internal hydrogen bonding between hydroxyl groups and hetero-atoms can influence the preferred conformations. This Review will be mainly concerned with the consequences of these effects but will also consider in detail the results available for a few specific systems.

Torsional Strain

In ethane the energy barrier to internal rotation is about 3 kcal./mole.[22] When one carbon atom is replaced by a hetero-atom the barrier changes significantly; 1·1 kcal./mole for methanol,[23] 1·3 kcal./mole for methanethiol,[24] and 2·0 kcal./mole for methylamine.[25] Just as the figures for rotational barriers in alicyclic hydrocarbons have been used for empirical calculations of chair–boat energy differences in cyclohexane,[26] so these figures have been used for the same estimation in the case of heterocycles.[27] These estimations, which lead to a lowering of the chair–boat energy difference for each hetero-atom introduced, make the explicit assumption that the rotational barrier does not change with substituents providing that they are neither large nor polar. This assumption is evidently

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[16] K. Hayasaki, *J. Chem. Soc. Japan*, 1955, **76**, 284.
[17] M. Baron and D. P. Hollis, *Rec. Trav. chim.*, 1964, **83**, 391.
[18] E. Campaigne, N. F. Chamberlain, and B. E. Edwards, *J. Org. Chem.*, 1962, **27**, 135.
[19] P. Groth, *Acta Chem. Scand.*, 1964, **18**, 1301.
[20] F. G. Riddell, unpublished observations.
[21] R. K. Summerbell and J. R. Stevens, *J. Amer. Chem. Soc.*, 1954, **76**, 731, 6401.
[22] D. R. Lide, *J. Chem. Phys.*, 1958, **29**, 1426.
[23] E. V. Ivash and D. M. Dennison, *J. Chem. Phys.*, 1953, **21**, 1804.
[24] T. Kotima, *J. Phys. Soc. Japan*, 1960, **15**, 1284.
[25] T. Itoh, *J. Phys. Soc. Japan*, 1956, **11**, 264.
[26] N. L. Allinger, *J. Amer. Chem. Soc.*, 1959, **81**, 5727.
[27] Ref. 4, p. 244.

incorrect, for the barrier in dimethyl ether is 2·7 kcal./mole[28] and in trimethylamine 4·4 kcal./mole.[29] Taking either of these figures, we can calculate an energy difference for the heterocycles comparable with or greater than that accepted for cyclohexane. In any event, no experimental value is available for the chair–boat energy difference in any heterocycle and a decision as to the magnitude of such quantities must await reliable measurements.

When two hetero-atoms are adjacent in an acyclic molecule, the barrier to internal rotation is much greater than for ethane. For hydrogen peroxide, measurements on the far-infrared spectrum indicate a barrier of 7·0 kcal./mole in the *cis* configuration.[30] Calculations on hydrazine give a value of 11·5 kcal./mole, which is probably a little high, but nonetheless indicates an actual barrier considerably greater than that for ethane.[31] The high barriers to rotation about N–N and O–O bonds are undoubtedly a leading factor in the high barriers to ring inversion in certain tetrahydro-piperazines,[32] in diacetone peroxide,[33] and in certain other compounds.[33b]

Non-Bonded Interactions

The non-bonded interactions between an axial alkyl substituent on cyclohexane and the two β axial hydrogen atoms largely determine the conformational preference of that substituent. It is accepted that large groups have a greater preference for the equatorial conformation than small groups. Thus a t-butyl group ($-\Delta G > 4{\cdot}0$ kcal./mole), which is physically larger than methyl ($-\Delta G =$ *ca.* 1·7 kcal./mole), has the greater preference for the equatorial position.

In an *N*-alkylpiperidine the *N*-substituent may occupy either the equatorial or axial position. Interconversion of the two conformations by nitrogen inversion is an easier process ($\Delta E^* < 10$ kcal./mole) than ring inversion ($\Delta E^* > 10$ kcal./mole), enabling the *N*-alkyl group to change its orientation without the intervention of ring inversion. The position of the equilibrium between the two conformations may be said to be determined by the relative sizes of the *N*-substituent and the lone pair. (By size of the lone pair in this context is meant its preference for the equatorial position relative to the other *N*-substituent.)† Indeed the 'size of the lone pair' is a central issue in discussing non-bonded interactions in heterocycles. We first consider the case of the simple unhindered heterocycles such as the piperidines (6, 7), and then consider some of the more complex and more hindered molecules that have been studied.

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† The position of a conformational equilibrium is determined by size only if there is an appreciable difference in crowding between the axial and equatorial positions. This is probably not the case for piperidine. The use of the word 'size' in the context of the conformational equilibrium in piperidine therefore invites, and has led to, confusion.

[28] P. H. Kasai and R. J. Myers, *J. Chem. Phys.*, 1959, **30**, 1096.

[29] D. R. Lide, jun., and D. E. Mann, *J. Chem. Phys.*, 1958, **28**, 572.

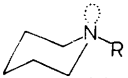
[30] R. H. Hunt, R. A. Leacock, C. W. Peters, and K. T. Hecht, *J. Chem. Phys.*, 1965, **42**, 1931.

[31] A. Veillard, *Theor. Chim. Acta*, 1966, **5**, 413.

[32] (*a*) J. C. Brelière and J. M. Lehn, *Chem. Comm.*, 1965, 426; (*b*) R. Daniels and K. Roseman, *Tetrahedron Letters*, 1966, 1335; (*c*) J. E. Anderson and J. M. Lehn, personal communication.

[33] (*a*) R. W. Murray, P. R. Story, and M. L. Kaplan, *J. Amer. Chem. Soc.*, 1966, **88**, 526; (*b*) G. Claeson, G. Androes, and M. Kalvin, *J. Amer. Chem. Soc.*, 1961, **83**, 4357.

In 1958, Aroney and Le Fèvre studied the molecular polarisability of certain piperidines in benzene, and concluded that 'the volume requirement of a "lone" electron pair on nitrogen exceeds that of a covalently-bound hydrogen and seems to approach in order of magnitude that of a methyl group, an idea that was foreshadowed by Barton and Cookson.[2,34] The novel implication of this statement, and its rather unfortunate wording, has led to much original and interesting work.



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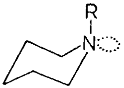

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Allinger, Katritzky, and Sutton and their co-workers studied the dipole moments of 4-*p*-chlorophenylpiperidine and its *N*-methyl derivative. They found energy differences of 1·7 kcal./mole for methyl and 0·4—0·5 kcal./mole for hydrogen, favouring the equatorial conformations.[35,36] Similar values were found for methyl and hydrogen in substituted piperazines. The conclusion that a lone pair has a small steric requirement was drawn.

The opposite view, that the lone pair is larger than a covalently-bound hydrogen atom, has been consistently expressed by Aroney and Le Fèvre. In 1964, they pointed out that their earlier observations could have been influenced by association of the solutes with benzene, but from Kerr-constant measurements on morpholine and *N*-methylmorpholine in both cyclohexane and benzene, remained convinced that the order from smallest to largest is N–H, lone pair, *N*-methyl.[37]

Recent criticisms[38] of the use of Kerr-constant measurements in conformational analysis are not entirely justified.[39] Statements that the calculations involved are lengthy, and references to computer programmes, do not carry the correct implication. Although the solution of a cubic equation is required to locate the principal polarisability axes in a three-dimensional structure, molar Kerr constants for specified structures can generally be calculated quite quickly by use of logarithms or a desk calculator.[40] In addition, the statement that only one piece of information can be obtained about a molecule by this method is incorrect, for in the course of measuring a molar Kerr constant, one also has to measure the molecular refraction, the molecular polarisation, and the dipole moment.

Lambert and Keske recently examined the low-temperature nuclear magnetic

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[34] M. J. Aroney and R. J. W. Le Fèvre, *J. Chem. Soc.*, 1958, 3002.

[35] (*a*) N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *Tetrahedron Letters*, 1964, 3345; (*b*) N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *J. Amer. Chem. Soc.*, 1965, **87**, 1232.

[36] R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, and A. R. Katritzky, *Proc. Chem. Soc.*, 1964, 257.

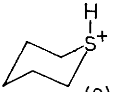
[37] M. J. Aroney, C. Y. Chen, R. J. W. Le Fèvre, and J. D. Saxby, *J. Chem. Soc.*, 1964, 4269.

[38] Ref. 4, p. 180.

[39] R. J. W. Le Fèvre, personal communication.

[40] R. J. W. Le Fèvre, *Adv. Phys. Org. Chem.*, 1965, **3**, 55.

resonance (n.m.r.) spectra of [3,3,5,5-$^2H_4$]piperidine and its *N*-methyl derivative,[41] explaining the large geminal chemical shift difference between the C(2, 6) protons in the *N*-methyl case by an axial lone pair and the smaller geminal chemical shift difference for the N–H case by an equatorial lone pair. The same authors have examined the n.m.r. spectra of thian and selenan in FSO_3H–SO_2 at $-30°$.[42] The proton on the hetero-atom shows a triplet of triplets, the couplings being 12 and 4 c./sec. The larger coupling, which is presumably between two axial protons, indicates an axial proton on the hetero-atom (8, 9). The gegen-ion FSO_3^- seems not to be bound to the equatorial position because the ^{19}F spectrum shows resonances only for unbound solvent down to $-80°$.



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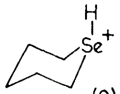

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A recent re-examination[43] of the evidence based on the 4-*p*-chlorophenylpiperidines[37,38] suggests that the energy differences are much lower than originally thought. Indeed, a value of 1·7 kcal./mole for the axial–equatorial energy difference of an *N*-methyl group would seem somewhat high (the value corresponds to that currently accepted for methylcyclohexane). The barrier to nitrogen inversion in simple amines is only around 8 kcal./mole, implying that an axial *N*-methyl group should be easily distorted somewhat from a truly axial position, minimising non-bonded interactions, and that one would therefore expect a lower value than in methylcyclohexane. Calculations along these lines provide reasonable agreement with more recent experimental data.[43]

The most conclusive evidence on piperidine itself comes from a recent microwave study,[44] in which the strongest spectrum has been shown to come from the chair conformation with N–H axial. At the time of reviewing no line of the N–H equatorial form has been identified, although it may be present in considerable abundance.

It has been pointed out[38] that in the case of piperidine, an equatorial hydrogen on nitrogen is at just about the van der Waals distance from the four adjacent α hydrogen atoms, and that an axial hydrogen on nitrogen is at a similar distance from the two axial β hydrogens. Thus as a first approximation one might expect little conformational preference for the hydrogen on nitrogen. However, in the latter case the 1,3 geometrical relationship of the bonds which the axial hydrogen on nitrogen has with the two axial β hydrogens is different from that which it has with the gauche α hydrogens in both conformations. As the distances involved are very probably in the attractive region of the van der Waals curve,[45]

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[41] J. B. Lambert and R. G. Keske, *J. Amer. Chem. Soc.*, 1966, **88**, 620.

[42] J. B. Lambert, personal communication.

[43] R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, A. R. Katritzky, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1967, 493.

[44] C. C. Costain, P. J. Buckley, and J. E. Parkin, personal communication.

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

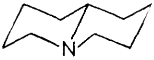
slight differences in attractions with differing bond geometry may, as a second-order effect, affect the conformation of the hydrogen on nitrogen.

It seems clear from the bulk of the reliable experimental evidence, that in simple heterocycles an unhindered hydrogen on the hetero-atom prefers the axial conformation.

Note added in proof: It has, however, been found that gaseous piperidine shows two bands in the NH first overtone region which can be ascribed to the NH equatorial and NH axial conformations by consideration of their contours. An Arrhenius plot of the ratio of band absorbances indicates an enthalpy difference of 0·5 ± 0·3 kcal./mole favouring the NH equatorial conformation. (R. W. Baldock and A. R. Katritzky, personal communication.)

The position in the more hindered cases is more complex and seems to indicate a 'small' lone pair. Katritzky and his co-workers, who studied the isomeric methylquinolizidines,[46] concluded that the nitrogen lone pair is smaller than a covalently bound hydrogen atom. More recent work by Aaron[47] and also Katritzky *et al.*[48] has produced evidence that the *trans* form of quinolizidine (10) is around 4·5 kcal./mole more stable than the *cis* (11), whereas the quaternary salts (12, 13) have an energy difference (3·0 kcal./mole) nearer that of the isomeric decalins (2·7 kcal./mole). The large energy difference between the two forms of the free base can be accounted for in terms of a small lone pair removing or diminishing non-bonded interactions, and is considerably greater than that predicted by the methods criticised previously[27] (2·6 kcal./mole).

Epimerisation equilibria on the decahydroquinolines (14, 15) led Katritzky's group to the conclusion that a free lone pair is smaller than a covalently bound



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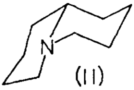

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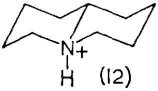

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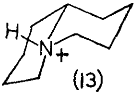

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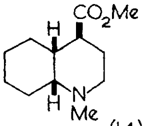

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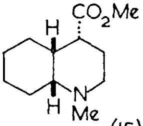

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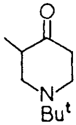

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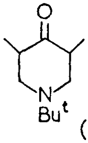

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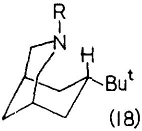

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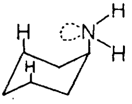

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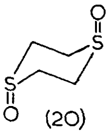

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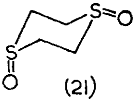

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[46] T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 1962, 2637.

[47] H. S. Aaron, *Chem. and Ind.*, 1965, 1338.

[48] C. D. Johnson, R. A. Y. Jones, A. R. Katritzky, C. R. Palmer, K. Schofield, and R. J. Wells, *J. Chem. Soc.*, 1965, 6797.

hydrogen, but that both of these are smaller than a solvated lone pair.[49] A study of *N*-t-butyl-3-methyl- and 3,5-dimethyl-4-piperidone (16, 17) by the same group has shown that it is slightly easier to place a 3- (or 5-) methyl group axial in this system than a 2-methyl group axial in cyclohexanone. The conclusion that in the non-hydrogen-bonding solvent employed, carbon tetrachloride, the interactions between axial methyl and axial lone pair are weaker than the corresponding methyl–hydrogen interactions in the methylcyclohexanones was drawn.[50]

When one considers the approach of a hindering substituent along the axis of a lone pair or N–H bond, theory and experiment are in accord. Allinger and Tai performed calculations on the approach of a helium atom to ammonia, either along the lone pair or along an N–H bond.[51] They found, both by a simple van der Waals treatment, and by more detailed quantum mechanical calculations, that the repulsion energy is much less along the axis of the lone pair than along that of the N–H bond.

Experimental verification of this work is provided by the work of Pumphrey and Robinson,[52] who found that the 3-azabicyclononanes (18) exist in the two-chair, *N*-substituent *exo* (equatorial) conformation (as drawn in diagram 18). Here, the 3-*endo* position is extremely hindered by the 7-*endo* hydrogen, which is on or near the axis of the lone pair.

Two examples from alicyclic chemistry show examples of 'small' lone pairs. The variation in the free-energy difference for the conformational equilibrium in cyclohexylamine with change in solvent[53] is most readily understood if the axial amino-substituent prefers the orientation with the unshared pairs of electrons directed into the ring (19). Analogously, the unshared pair of electrons on the oxygen atom of an axial hydroxyl group in its preferred orientation occupy the more hindered position,[54] and this preference increases with increase in steric hindrance.[55]

It seems that by thoughts directed along the lines of conventional conformational analysis, a property has been ascribed to the lone pair that it does not possess; size. The terms steric requirement, volume requirement, and size are all unfortunate terms in this instance and should be used with extreme caution when talking about the readily polarised lone pair on an easily deformable nitrogen atom. In fact, all that one can ever measure in experiments purporting to demonstrate a 'volume requirement' for the lone pair is the axial or equatorial preference of some other group.

In sulphoxides and sulphites the sulphur atom has an approximately tetrahedral geometry, enabling the doubly-bonded oxygen atom to adopt either the equatorial or axial position when these groups are incorporated in six-membered

[49] K. Brown, A. R. Katritzky, and A. J. Waring, *Proc. Chem. Soc.*, 1964, 257.
[50] P. J. Brignell, A. R. Katritzky, and P. L. Russell, *Chem. Comm.*, 1966, 723.
[51] N. L. Allinger and J. C. Tai, *J. Amer. Chem. Soc.*, 1965, **87**, 1227.
[52] N. W. J. Pumphrey and M. J. T. Robinson, *Chem. and Ind.*, 1963, 1903.
[53] Ref. 4, p. 439.
[54] A. R. H. Cole and P. R. Jeffries, *J. Chem. Soc.*, 1956, 4391.
[55] N. W. J. Pumphrey and M. J. T. Robinson, unpublished work, quoted in ref. 52.

rings. *X*-Ray studies on the α (20)[56] and β (21)[57] isomers of 1,4-dithian-1,4-dioxide indicate a preference for the oxygen to occupy the axial conformation. The n.m.r. spectrum of the α isomer is complex, consistent with a single conformation, whereas the β isomer shows only one line at room temperature.[58]

The dipole moments of various 4-substituted thian 1-oxides are in accord with an axial oxygen atom.[59] In 1963, Johnson and McCants reported the isomerisation of various sulphoxides by differing methods and at different temperatures, finding values of between 0·6 and 1·3 kcal./mole for the free-energy preference for an axial oxygen atom.[60]

Lambert and Keske recently reported the low-temperature n.m.r. spectrum of the parent oxide and found a value of 0·17 kcal./mole for the axial preference at −90°.[61] In this case, one conformation shows a large geminal chemical-shift difference (0·87 p.p.m.) for the α protons whereas the other conformation is normal (0·48 p.p.m.). The large chemical-shift difference occurs in the conformation with the axial lone pair, as seems to be the case in the piperidines,[41] and may well be a general criterion for conformations containing axial lone pairs.[42] Various authors appear to have wrongly assigned the conformations of several cyclic sulphoxides.[62]

The case of the cyclic sulphites is more complex. Conflicting conformational assignments have been made,[63,64] and at the time of reviewing the position is not clear. Various authors suggest that an axial oxygen atom is preferred,[64] but more recent work seems to show that trimethylene sulphite itself may have a twisted boat conformation.[65]

Note added in proof: The most recent evidence, however, uniformly confirms the chair conformation. The crystal structure of trimethylene sulphite at low temperatures (C. Altona, H. J. Geise, and N. C. Romers, *Rec. Trav. Chim.*, 1966, **85**, 1197) and the infrared spectra and dipole moments of derivatives (H. F. van Woerden and E. Havinga, *Rec. Trav. Chim.*, 1967, **86**, 341, 353) are entirely consistent with an axial oxygen in a chair conformation being strongly preferred.

Differing explanations have been put forward to explain these results,[42,60,66]

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[56] H. M. M. Shearer, *J. Chem. Soc.*, 1959, 1394.

[57] H. Montgomery, *Acta Cryst.*, 1960, **13**, 381.

[58] C. Y. Chen and R. J. W. Le Fèvre, *Austral. J. Chem.*, 1963, **16**, 917.

[59] (*a*) J. C. Martin and J. J. Uebel, *J. Amer. Chem. Soc.*, 1964, **86**, 2936; (*b*) C. R. Johnson, *J. Amer. Chem. Soc.*, 1963, **85**, 1020.

[60] C. R. Johnson and D. McCants, *J. Amer. Chem. Soc.*, 1964, **86**, 2935.

[61] J. B. Lambert and R. G. Keske, *J. Org. Chem.*, 1966, **31**, 3429.

[62] (*a*) H. B. Henbest and S. A. Khan, *Proc. Chem. Soc.*, 1964, 56; (*b*) R. Riemschneider and V. Wurscherpfennig, *Z. Naturforsch.*, 1962, **17b**, 516; (*c*) W. Otting and F. A. Neugebauer, *Chem. Ber.*, 1962, **95**, 540.

[63] (*a*) P. B. D. de la Mare, W. Klyne, D. J. Millen, J. G. Pritchard, and D. Watson, *J. Chem. Soc.*, 1965, 1813; (*b*) J. G. Pritchard and R. L. Vollmer, *J. Org. Chem.*, 1963, **28**, 1545; (*c*) P. C. Lauterbur, J. G. Pritchard, and R. L. Vollmer, *J. Chem. Soc.*, 1963, 5307.

[64] (*a*) D. G. Hellier, J. G. Tillet, H. F. Van Woerden, and R. F. M. White, *Chem. and Ind.*, 1963, 1956; (*b*) R. S. Edmundson, *Tetrahedron Letters*, 1965, 1649; (*c*) C. G. Overberger, T. Kurtz, and S. Yaroslavsky, *J. Org. Chem.*, 1965, **30**, 4363; (*d*) M. F. Van Woerden, *Tetrahedron Letters*, 1966, 2407.

[65] G. Wood and M. Miskow, *Tetrahedron Letters*, 1966, 4433.

[66] M. J. T. Robinson, personal communication.

the most widely accepted being the presence of a large lone pair on sulphur,[42,60] despite the formal positive charge carried by that atom.

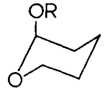
Dipolar Effects

The most striking of all the dipolar effects found in heterocyclic molecules is the anomeric effect. As early as 1905, Jungius found that equilibrium mixtures of certain pyranose acetates contained as much as 90% of the α isomer.[67] This observation was supplemented by the work of Freudenberg and Soff, in 1936, who found 88% α isomer,[68] and more recently, by the work of many other authors.[69] In modern conformational terms, these observations imply a preference for an axial 2-methoxy- or 2-acetoxy-substituent in a tetrahydropyran ring (22).

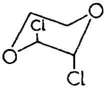
In 1955 Edward suggested that dipolar forces were responsible not only for the slower rate of hydrolysis of the axial methoxy- and acetoxy-(α)-isomers, but also for the axial preference of these groups.[70]

In 1964, Anderson and Sepp equilibrated the isomers of both 2-methoxy- and 2-acetoxy-4-methyltetrahydropyran.[71] They found the position of the equilibrium to vary with solvent in the manner expected for a dipolar effect, and were able to assign an experimental value of 1·3 kcal./mole for the dipolar interaction in non-polar solvents. This value falls as low as 0·9 kcal./mole in aqueous methanol.

Romers and his co-workers studied *trans*-2,3- and *trans*-2,5-dichloro-1,4-dioxan (23, 24) by a variety of physical techniques.[72] They have shown that the molecules prefer chair forms with axial halogen atoms. Booth and Ouellette, in a recent attempt to measure the anomeric effect in 2-chloro- and 2-bromo-



R = Me or Ac
(22)



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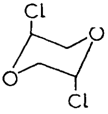

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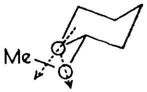

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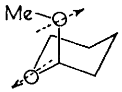

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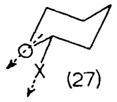

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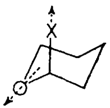

(28)

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[67] C. L. Jungius, *Z. phys. Chem.*, 1905, **52**, 97.

[68] K. Freudenberg and K. Soff, *Ber.*, 1936, **69**, 1245.

[69] Amongst others, see (*a*) W. A. Bonner, *J. Amer. Chem. Soc.*, 1959, **81**, 1448; (*b*) E. P. Painter, *J. Amer. Chem. Soc.*, 1953, **75**, 1137; (*c*) C. T. Bishop and F. P. Cooper, *Can. J. Chem.*, 1963, **41**, 2743.

[70] J. T. Edward, *Chem. and Ind.*, 1955, 1102.

[71] C. B. Anderson and D. T. Sepp, *Chem. and Ind.*, 1964, 2054.

[72] (*a*) C. Altona, C. Romers, and E. Havinga, *Tetrahedron Letters*, 1959, **10**, 16; (*b*) C. Altona, C. Knobler, and C. Romers, *Acta Cryst.*, 1963, **16**, 1217; (*c*) C. Altona, C. Knobler, and C. Romers, *Rec. Trav. chim.*, 1963, **82**, 1089; (*d*) C. Altona and C. Romers, *Rec. Trav. chim.*, 1963, **82**, 1080.

tetrahydropyran, could only observe the halogen-axial form.[73] Solvent polarity appeared to have little effect on the conformational equilibrium.

The origin of the anomeric effect is somewhat different in the cases of oxygen- and halogen-substituted tetrahydropyrans. In the case of 2-methoxytetrahydropyran, the two conformations (25) and (26) are undoubtedly the most favoured equatorial and axial conformations respectively, on the basis of both dipolar and non-bonded interactions. In (25), the two ether dipoles are approximately perpendicular, giving rise to a negligible dipolar interaction, whilst in (26), they are almost antiparallel, giving rise to a strong dipolar stabilisation. [It should be noted that the ether dipole moments involved approximately bisect the C–O–C angles. The implication in certain publications that the substituent dipole goes along the C(2)–oxygen bond is incorrect.] Previous calculations of the magnitude of the anomeric effect may not be valid because of an error in the accepted formula for calculation of such dipolar effects.[74] A more recent estimation gives a calculated value of about 1·7 kcal./mole;[20] tetrahedral geometry was assumed and a dipole moment used for each ether unit of 1·25 D. The agreement of this value with experiment is reasonable if the approximations employed are considered.

For the halogeno-compounds the orientation of the halogen dipole is fixed, and it can readily be seen that dipolar interactions are stronger with an equatorial (27) than with an axial (28) halogen. The magnitude of the effect in this case is expected to be larger than with oxygen because the dipoles are closer. Calculations are however more difficult because one cannot justify any chosen point of action for the halogen dipole.

Angle Deformation

It is generally accepted that deformation of bond angles is one of the easiest ways of distributing strain throughout a molecule.[75] The currently accepted pathway to ring inversion of six-membered rings occurs through a four-atom coplanar transition state in which much of the potential energy of the molecule must be in the form of angle strain.[76] Since the publication of a recent Review on ring inversions,[76] It has become increasingly clear that replacement of carbon in a six-membered ring by nitrogen or sulphur raises the barrier to ring inversion,[41,77,78] whereas oxygen appears to lower it.[79] Thus, for example, *NN'*-dimethylpiperazine has a free energy of activation for ring inversion of 12·6 kcal./mole at a coalescence temperature of −8·5°.[78] The accepted value for cyclohexane is about 10·3 kcal./mole.

The apparent failure to observe coalescences in the variable-temperature

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[73] G. E. Booth and R. J. Ouellette, *J. Org. Chem.*, 1966, **31**, 544.

[74] J. M. Lehn and G. Ourisson, *Bull. Soc. chim. France*, 1963, 113.

[75] F. H. Westheimer, 'Steric Effects in Organic Chemistry', ed. M. S. Newman, J. Wiley and Sons, New York, 1956, pp. 524–555.

[76] J. E. Anderson, *Quart. Rev.*, 1966, **19**, 426.

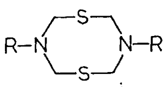
[77] J. M. Lehn and F. G. Riddell, unpublished results.

[78] R. K. Harris and R. A. S. Spragg, *Chem. Comm.*, 1966, 314.

[79] J. E. Anderson and J. C. D. Brand, *Trans. Faraday Soc.*, 1966, **62**, 517.

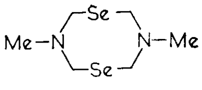
n.m.r. spectra of certain heterocycles does not necessarily indicate either a low barrier to ring inversion or the presence of boat conformations, but may simply arise from a small chemical-shift difference between the protons being observed.[76,78]

The most striking example of hetero-atoms raising the barrier to ring inversion occurs in the eight-membered systems (29) and (30), where free energies of activation of 13—15 kcal./mole have been reported.[80] The observed value for cyclo-octane is 8·1 kcal./mole.[81]



(29)

R=Me,Et,Pr^i,Ph



(30)

Hydrogen Bonding

Whereas the conformational equilibrium in cyclohexanol favours the equatorial form by about 0·7 kcal./mole,[82] the position of this equilibrium is reversed in many heterocycles owing to intramolecular hydrogen bonding. In many sugars this may be the principal factor determining the conformation.

Foster and his co-workers have studied hydrogen bonding in several 5-hydroxy-1,3-dioxans.[83] In the parent compound, the equilibrium favours the axial conformation by 1·04 kcal./mole. In the *trans*-2-substituted compounds (31, 32, 33), a substantial amount of a hydrogen bonded form is present, the amount being only slightly affected as the 2-substituent is changed from methyl to ethyl to isopropyl to phenyl, and its free energy being only about 0·7 kcal./mole greater than the non-bonded form. These results can be interpreted either in terms of a diaxial form (32) or a boat form (33) for the bonded conformation. If the diaxial form is the observed hydrogen bonded species, then the axial–equatorial free-energy difference can be estimated to be *ca.* 1·7 kcal./mole. In the case of the boat conformation, no reliable chair-boat energy difference can be calculated because of the differing dipolar and steric interactions and probably differing hydrogen bond strengths for (31), (32) and (33).

Luttringhaus and his group have found the axial conformation of 5-hydroxy-1,3-dithian (34) to be favoured by 0·5 kcal./mole,[84] and Abraham and Thomas that of the 2,2-dimethyl derivative (35) to be favoured by 0·8 kcal./mole.[85] The infrared spectrum of 5-hydroxy-*cis*-2-phenyl-1,3-dithian shows the presence of only bound hydroxyl. The *trans* isomers show absorptions of both bound and free hydroxyls, indicating a diequatorial–diaxial equilibrium favouring the diequatorial conformation by 0·85 kcal./mole.[85] The acetylated derivative of

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[80] J. M. Lehn and F. G. Riddell, *Chem. Comm.*, 1966, 803.

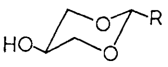
[81] F. A. L. Anet and J. S. Hartman, *J. Amer. Chem. Soc.*, 1963, **85**, 1204.

[82] E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, 1962, 97.

[83] N. Baggett, M. A. Bukhari, A. B. Foster, J. Lehmann, and J. M. Weber, *J. Chem. Soc.*, 1963, 4157.

[84] A. Luttringhaus, S. Kabuss, H. Prinzbach, and F. Langenbucher, *Annalen*, 1962, **653**, 195.

[85] R. J. Abraham and W. A. Thomas, *J. Chem. Soc.*, 1965, 335.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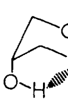
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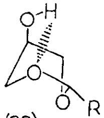
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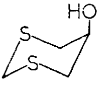
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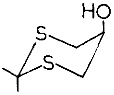
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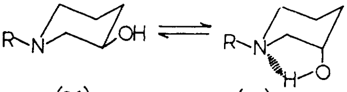
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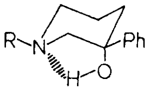
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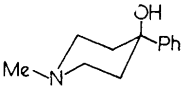
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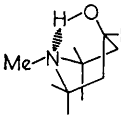
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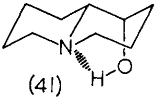
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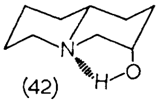
(42)

the *trans* isomer exists almost exclusively in the diequatorial conformation.

3-Hydroxypiperidine and its *N*-methyl derivative (36, 37) show the presence of both free and bound hydroxyls from the infrared spectrum.[86] The analogous 3-phenyl-3-hydroxypiperidines (38) show only bound hydroxyl, the combined equatorial preference of phenyl and the hydrogen-bonding possibilities of hydroxyl favouring the hydroxyl–axial conformation very strongly.

N-Methyl-4-piperidinol shows no evidence of internal hydrogen bonding and presumably exists as (39).[87] Not surprisingly, *N*,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol is forced into the boat conformation (40). This avoids two axial methyls and an axial hydroxyl or phenyl on the same side of the ring in a chair conformation, and the presence of an internal hydrogen bond is observed from the infrared spectrum.[87]

The use of hydrogen bonds in structural assignments is neatly shown by the work of Aaron and his group on the epimeric 1- and 3-hydroxyquinolizidines, for which only one epimer in each instance (41, 42) can show an intramolecular hydrogen bond.[88]

Some Specific Examples

1,3-Dioxans.—Amongst the most studied of the simpler heterocyclic systems is 1,3-dioxan. Derivatives are easily prepared either by condensation of the appropriate diol with a ketone or aldehyde, or by the Prins reaction. Stereoisomers at the 2-position can readily be epimerised by dilute acids in non-hydroxylic media. 1,3-Dioxans show simple n.m.r. spectra and hence are readily studied by this method.

Delmau and his co-workers have extensively studied the n.m.r. spectra of

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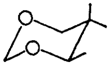
[86] G. Hite, E. E. Smissman, and R. West, *J. Amer. Chem. Soc.*, 1960, **82**, 1207.

[87] R. E. Lyle, *J. Org. Chem.*, 1957, **22**, 1280.

[88] H. S. Aaron, G. E. Wicks, jun., and C. P. Rader, *J. Org. Chem.*, 1964, **29**, 2248.

many 1,3-dioxans,[89] and have analysed the spectrum of the parent compound. Using a method based on chemical shift differences, they have also assigned approximate values to certain conformational equilibria in substituted 1,3-dioxans.[89a] For example, the conformational equilibrium in 4,4,5-trimethyl-1,3-dioxan is said to favour (43) by 61·5% and in 4-methyl-1,3-dioxan to favour the equatorial conformation (44) by 93%. Not surprisingly, the errors involved in these estimations are considerable, for these values differ from those found by more exact methods in analogous systems. In particular, Eliel and Knoeber have found by a direct equilibration method a free-energy difference of about 3 kcal./mole for the two isomers of several 2-alkyl-4-methyl-1,3-dioxans.[90]



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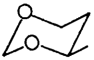

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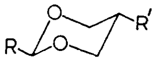
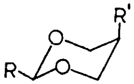


R=Me,Et,Pr^i,Bu^t

(45)



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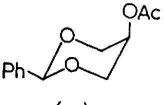

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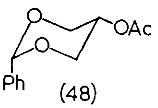

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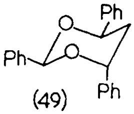

(49)

Riddell and Robinson have studied the acid-catalysed epimerisation of several 2-t-butyl- and 2-*p*-nitrophenyl-5-alkyl-1,3-dioxans (45, 46) in chloroform.[91] Enthalpy differences between the 5-equatorial and 5-axial positions of 0·86 ± 0·09, 0·74 ± 0·08, and 1·13 ± 0·10 kcal./mole were found for methyl, ethyl, and isopropyl groups respectively. A difference of 1·9 ± 0·5 kcal./mole was found between the isomers of the 2,5-di-t-butyl compound. Entropy differences in all these cases were very small. Separation of the isomers, except in the di-t-butyl case, and examination of their n.m.r. spectra, enabled the *cis* and *trans* isomers to be assigned. An axial 5-t-butyl group was tentatively assigned for the *cis*-di-t-butyl compound.

This assignment of an axial t-butyl group has been elegantly confirmed by Eliel and Knoeber,[90] who found a constant free-energy difference at 25° between the isomers (45) and (46) (R is methyl, ethyl, isopropyl, or t-butyl and R′ is t-butyl). Such constant free-energy differences are not compatible with a change in conformation of the (variable) 2-alkyl group, and hence the (constant) 5-t-butyl group must occupy the axial position in the *cis* isomers. They confirmed this conclusion by measurements of chemical shifts and coupling constant in the n.m.r. spectra of both sets of isomers.

The fact that the axial–equatorial energy differences in all the 5-alkyl-1,3-

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[89] (*a*) C. Barbier, J. Delmau, and J. Ranft, *Tetrahedron Letters*, 1964, 3339; (*b*) J. Delmau and C. Barbier, *J. Chem. Phys.*, 1964, **41**, 1106; (*c*) C. Barbier, M. Davidson, and J. Delmau, *Bull. Soc. chim. France*, 1964, 1046.

[90] E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, 1966, **88**, 5347.

[91] F. G. Riddell and M. J. T. Robinson, *Tetrahedron*, 1967, **23**, 3417.

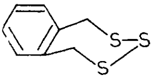
dioxans discussed above, in particular that of a 5-t-butyl group, are smaller than the corresponding values in the cyclohexanes may be taken as an indication in this instance of 'small' electron pairs on oxygen.

The n.m.r. spectrum of 5-acetoxy-*cis*-2-phenyl-1,3-dioxan shows narrow resonances for the C(4, 6) and C(5) protons.[92] On this basis, the conformational equilibrium (47) $\rightleftharpoons$ (48) was suggested. On the basis of the work described above,[90,91] this spectrum indicates a predominant amount of (47) with small ($<$ 4 c./sec.) couplings between the C(4, 6) and C(5) protons. An appreciable amount of (48) would be expected to broaden the resonances due to these protons owing to a large (10—11 c./sec.) coupling between the C(4, 6) and C(5) protons.

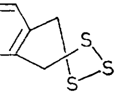
Delmau and Duplan recently suggested a boat conformation for 4-t-butyl-4-methyl-1,3-dioxan.[93] It is unlikely that this is the case. Luttringhaus and his group have observed the expected coalescence in the low-temperature n.m.r. spectrum of 4,4-dimethyl-1,3-dioxan for chair–chair interconversion.[94] Robinson has been able to show that in several *trans*-4,6-diphenyl-1,3-dioxans, one phenyl occupies the axial position in a chair conformation (49),[66] the strain in this case being greater than in that studied by Delmau and Duplan. We can thus safely conclude that 4-t-butyl-4-methyl-1,3-dioxan has a chair conformation and that the boat conformation has a free energy at least 3 kcal./mole higher than the chair.[95] The calculations criticised earlier gave a value of 2·2 kcal./mole for the enthalpy difference.

Larger Heterocyclic Systems.—There seems no reason to doubt that heterocycles of more than six atoms should adopt conformations essentially similar to those of the larger alicycles. Very little evidence is available, however, and only two pieces of work will be mentioned here, both of which support this idea. 1,2-Benzo-4,5,6-trithiacycloheptene shows an exceptionally large barrier to ring inversion.[96] The barrier is 17·4 kcal./mole at a coalescence temperature of +83° (100 Mc./sec.; n.m.r.). Below the coalescence temperature, an AB quartet and a singlet are observed in the n.m.r. spectrum of the benzylic protons. The AB quartet comes from the chair from (50) and the singlet (integrated intensity 15% at 25°) from the flexible conformation (51).

The eight-membered rings (29, 30) also show temperature-dependent n.m.r.



(50)



(51)

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spectra.[80] The observed dependence has been interpreted in terms of interconversions, either between two crown conformations, or between two families of conformations each consisting of crowns and chair–boats.

I thank Dr J. M. Lehn, Dr J. E. Anderson, and Dr M. J. T. Robinson for discussions and acknowledge financial support from the CIBA Fellowship Trust.