The Conformational Analysis of Saturated Heterocycles. Part L.[1] Computer Program for Strain Energy Minimisation in Six-membered Rings and Recalculation of Conformational Equilibria

By **I. D. Blackburne, R. P. Duke, Richard A. Y. Jones,* A. R. Katritzky,*** and **K. A. F. Record,** School of Chemical Sciences, University of East Anglia, Norwich NOR 88C

Computer programs are developed which allow (*a*) the calculation of ring geometry including vector angles for dipole-moment components and (*b*) the energy minimisation of bond and torsion angle strain.

Conformational equilibria are recalculated for 1-alkylpiperidines, 1,3-dialkylhexahydropyrimidines, 3-alkyltetrahydro-1,3-oxazines, 5-alkyldihydro-1,3,5-dithiazines, and 1,3,5-trialkylhexahydro-1,3,5-triazines. The previous conclusions are little, for the most part insignificantly, affected.

As our studies [2-8] of the conformations of saturated six-membered rings have progressed to less-symmetrical rings containing several heteroatoms, geometrical difficulties in the interpretation of dipole moments have increased. Two types of problems were encountered: (i) the plain calculation of angles between component dipole vectors in unsymmetrical rings and (ii) the question of allowance for torsional strain, and the minimisation of total bond-angle and torsional strain. The present paper describes our proposed solution of this problem, and consequent recalculations for the conformational equilibria previously reported. The approach used has been based on a well-developed classical mechanical model [9] but extends the range of molecules studied into experimentally untested polyheterocyclic systems.

Strain Energy Minimisation.—A ring consisting of n atoms is characterised by $3n$—6 independent parameters. For a six-membered ring existing in the chair form, the 12 independent parameters may be chosen from the $3n$ internal co-ordinates: 6 bond lengths, 6 bond angles, and 6 torsional angles. We have chosen the 6 bond angles and 6 bond lengths as the independent parameters, and have devised a program to express the 18 Cartesian co-ordinates of the ring atoms in these terms.[10]

The total strain energy of a given conformation, equation (1), is the sum of several components: E_θ is the

$$E_{\text{total}} = E_\theta + E_\omega + E_{\text{R}} - E_{\text{A}} + E_l \qquad (1)$$

angle strain, E_ω the torsional strain, E_{R} and E_{A} the repulsive and attractive non-bonded interactions, and E_l the bond-length distortion strain. The strain energy for a structure with known geometry is calculated by applying the appropriate potential functions, and forming the sum of their various contributions. This approximate structure is then altered so as to minimise the energy, using the method of conjugate gradients.[11,12] As we assume invariant bond lengths (see later), this requires the minimisation of a function of up to six variables.

As a second approach we have used the method of steepest descent to find the strain-energy minimum.[9] In this method, the derivatives are estimated by changing each angle in turn by a given amount, and recalculating the energy for each of these six modified conformations, thus requiring the evaluation of the energies of seven conformations including the original. Each of the original bond angles is next changed by an amount proportional to the partial derivative and a new energy is calculated. The angles are modified in this way until the total energy no longer decreases. A new set of partial derivatives is then calculated and the angles of the ring are then changed in this sense. These processes are then continued until an energy minimum is reached. We recognise this as a local, and not a global energy minimum.

If the structure contains symmetry elements, the symmetrically related atoms are changed simultaneously in calculating the steepest descent partial derivatives. In the conjugate gradient method certain symmetry elements can be kept, and this decreases computational time.

The two methods used do not require the formal evaluation of derivatives, and may locate false minima. They do, however, locate nearly identical minima, which suggests that they represent approximations to

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[1] Part XLIX, M. J. Cook, R. A. Y. Jones, A. R. Katritzky, M. Moreno-Mañas, A. C. Richards, A. J. Sparrow, and D. L. Trepanier, preceding paper.

[2] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, R. J. Wyatt, R. J. Bishop, and L. E. Sutton, *J. Chem. Soc.* (*B*), 1970, 127; W. Fedeli, R. A. Y. Jones, A. R. Katritzky, F. Mazza, P. G. Mente, and A. Vaciago, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1969, **46**, 733; R. A. Y. Jones, A. R. Katritzky, and P. G. Mente, *J. Chem. Soc.* (*B*), 1970, 1210.

[3] R. A. Y. Jones, A. R. Katritzky, and M. Snarey, *J. Chem. Soc.* (*B*), 1970, 131.

[4] R. A. Y. Jones, A. R. Katritzky, and M. Snarey, *J. Chem. Soc.* (*B*), 1970, 135.

[5] R. A. Y. Jones, A. R. Katritzky, and D. L. Trepanier, *J. Chem. Soc.* (*B*), 1971, 1300.

[6] R. A. Y. Jones, A. R. Katritzky, D. L. Ostercamp, K. A. F. Record, and A. C. Richards, *J.C.S. Perkin II*, 1972, 34.

[7] R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, K. A. F. Record, and B. B. Shapiro, *J. Chem. Soc.* (*B*), 1971, 1302; R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, and B. B. Shapiro, *ibid.*, p. 1308; R. A. Y. Jones, A. R. Katritzky, and P. G. Lehman, *ibid.*, p. 1316; R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, A. C. Richards, and R. Scattergood, *J.C.S. Perkin II*, 1972, 41.

[8] B. J. Hutchinson, R. A. Y. Jones, A. R. Katritzky, K. A. F. Record, and P. J. Brignell, *J. Chem. Soc.* (*B*), 1970, 1224.

[9] K. B. Wiberg, *J. Amer. Chem. Soc.*, 1965, **87**, 1070.

[10] For full details see R. P. Duke, Ph.D. Thesis, University of East Anglia, 1971, and K. A. F. Record, Ph.D. Thesis, University of East Anglia, 1970. Copies of both these programs, written in Fortran, are available on request.

[11] R. Fletcher and C. M. Reeves, *Computer J.*, 1964, **7**, 149.

[12] For full details see R. P. Duke, Ph.D. Thesis, University of East Anglia, 1971.

the true minimum. The convergence of the conjugate gradient method is more rapid, and the following discussion is in terms of the results obtained by this method.

Potential Functions.—(a) *Bond-length distortion*. The change in energy with bond-length distortion for small displacements may be evaluated from equation (2),

$$\Delta V = \tfrac{1}{2}k_r(r - r_0)^2 \qquad (2)$$

where r_0 is the equilibrium bond length, and k_r is the stretching-force constant. The force constant k_r for a C–C bond is near 5×10^5 dyn cm^{-1} from vibrational spectral data.[13] However, following Hendrickson [14] we neglect this contribution and treat bond lengths as invariant, because the energy required to change them appreciably is much greater than the energy required to change valence angles or torsional angles. The bond lengths used [15] are: C–C 1·54, C–N 1·47, C–O 1·43, and C–S 1·81 Å.

(b) *Bond-angle distortion*. The energy associated with the bending of a single bond angle from its strain-free value is given by equation (3) where k_θ is the bending

$$E_\theta = \tfrac{1}{2}k_\theta(\theta - \theta_0)^2 \qquad (3)$$

$$V = \tfrac{1}{2}\Sigma k_\theta(\Delta\theta_i)^2 \qquad (4)$$

force constant and θ_0 is the strain-free bond angle.[14] Hence the total bond-angle strain is given by equation (4).

Hendrickson [14] used Westheimer's [16] force constants, which are 0·32, 0·55, and 0·8 mdyn Å rad^{-2} for the H–C–H, C–C–H, and C–C–C respectively, and combined these to obtain a single equivalent force constant of 0·9 mdyn Å rad^{-2} for C–CH$_2$–C bending (*cf*. ref. 9). Other values for the bending force constants for C–C–C are 0·97 (ref. 17) and 0·86 (ref. 18) mdyn Å rad^{-2} from normal mode analysis of cyclohexane, and 0·90 mdyn Å rad^{-2} from normal mode analysis of n-alkanes.[19] The calculated potential is not very sensitive to the value of the force constant used.[20] For C–C–C we used 0·9 mdyn Å rad^{-2} (ref. 19).

Less work relevant to the calculation of force constants has been done on molecules incorporating heteroatoms. No literature information is directly relevant to the nitrogen systems, though Hendra and Powell [21] suggested from a comparison of values for amines and alcohols that the bending force constants for C–C–N and C–N–C should be 0·9 and 1·38 mdyn Å rad^{-2}, respectively. Normal mode analysis of aliphatic ethers [22] and of a number of oxans [18] has indicated respectively 1·18 and 1·15 mdyn Å rad^{-2} for C–C–O and 1·31 and 1·02 mdyn Å rad^{-2} for C–O–C. In similar fashion the C–S–C force constant has been reported variously [23] as 1·02 and 1·42 mdyn Å rad^{-2}. For X–C–Y systems no data was available. Since, over a small range, the calculated geometries were insensitive to the actual values of the force constants used, selection of values was made by interpolation of the available data. These are collected in Table 1.

TABLE 1

Angle force constants (k_θ, mdyn Å rad^{-2})

X	C–C–X	C–X–C	X–C–X	X–C–Y
C	0·9 (0·9,[a] 0·97,[b] 0·86,[c] 0·90 [d])	0·9	0·9	
N	1·0 (0·9 [e])	1·0 (1·38 [e])	1·2	1·3 (Y = S)
O	1·2 (1·18,[d] 1·15 [c])	1·1 (1·02,[c] 1·31 [d])	1·6 (1·66 [c])	1·4 (Y = N)
S	1·1	1·2 (1·02,[f] 1·42 [g])	1·4	1·5 (Y = O)

[a] Ref. 14. [b] Ref. 17. [c] Ref. 18. [d] Ref. 22. [e] Ref. 21. Ref. 23*a*. [g] Ref. 23*b*.

(c) *Equilibrium bond angles*. The bond angles used (Table 2) are taken from corresponding three-membered units, *e.g.* C–O–C 111·5° from dimethyl ether, as listed by Sutton.[15]

TABLE 2

Equilibrium bond angles

Angle	Equilibrium bond angle (θ_0°)
CCC	112·4 [a]
CCN	110·0 [a]
CCO	110·0 [a]
CCS	113·0 [a]
CNC	112·1 [b]
COC	111·5 [a]
CSC	99·0 [c]
NCN	110·0 [d]
OCO	110·0 [d]
SCS	110·0 [d]
NCO	110·0 [d]
NCS	110·0 [d]

[a] 'Interatomic Distances,' ed. L. E. Sutton, Chemical Society Special Publication, No. 11, London, 1958, p. M139. [b] N. L. Allinger, J. A. Hirsch, and M. A. Miller, *Tetrahedron Letters*, 1967, 3729. [c] L. Pierce and M. Hayashi, *J. Chem. Phys.*, 1961, **35**, 479. [d] Assumed value.

(d) *Torsional distortion*. As Bixon and Lifson pointed out,[20] this mode of distortion expends the least amount of energy in a cyclic structure and consequently large torsional angle changes may be found.

Bixon and Lifson pointed out that, on the basis of the enthalpy difference between *gauche* isomers of the higher n-alkanes,[24] an unsymmetrical barrier might be expected. The potential barriers for rotation in cyclohexane are considered [25] to be quite high. It is certain

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[13] E. B. Wilson, J. C. Decins, and P. C. Cross, 'Molecular Vibrations,' McGraw-Hill, New York, 1955, p. 175.

[14] J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1964, **86**, 4854.

[15] 'Interatomic Distances Supplement,' ed. L. E. Sutton, *Chem. Soc. Special Publ.*, No. 18, 1965.

[16] F. H. Westheimer, 'Steric Effects in Organic Chemistry,' ed. M. S. Newman, John Wiley and Sons, New York, 1956, ch. 12.

[17] M. Larnaudie, *J. Phys. Rad.*, 1954, **15**, 365.

[18] H. M. Pickett and H. L. Strauss, *J. Amer. Chem. Soc.*, 1970, **92**, 7281.

[19] R. G. Snyder and J. H. Schachtschneider, *Spectrochim. Acta*, 1965, **21**, 169.

[20] M. Bixon and S. Lifson, *Tetrahedron*, 1967, **23**, 769.

[21] P. J. Hendra and D. B. Powell, *Spectrochim. Acta*, 1962, **18**, 299.

[22] R. G. Snyder and G. Zerbi, *Spectrochim. Acta*, 1967, **23***A*, 391.

[23] (*a*) H. Siebert, *Z. anorg. Chem.*, 1952, **271**, 65. (*b*) D. W. Scott and M. Zaki El-Sabban, *J. Mol. Spectroscopy*, 1969, **30**, 317.

[24] N. Sheppard and C. J. Szasz, *J. Chem. Phys.*, 1949, **17**, 86.

[25] V. W. Laurie, *Accounts Chem. Res.*, 1970, **3**, 331.

that the torsional barrier is indeed unsymmetrical, but it is not clear in which sense this will be (whether distortion to $\omega > 60°$ will in fact be more difficult than distortion to $\omega < 60°$ (where ω is the dihedral angle between the two ring bonds). Since the uncertainties in the degree of asymmetry are large, and for the sake of simplicity, a symmetrical threefold sinusoidal barrier has been used, following Bixon and Lifson [20] and others.[9,26,27] This is described by equation (5), where

$$E_\omega = \tfrac{1}{2}k_t(1 + \cos 3\omega) \text{ kcal mol}^{-1} \qquad (5)$$

the torsional distortional energy (E_ω) is defined by the sinusoidal function and by the observed barrier height in the 'three heavy atom' system (K_t kcal mol^{-1}). The 'three heavy atom' systems were chosen because, as Bixon and Lifson found,[20] the propane barrier gives good agreement between the strain energy minimised angles and the observed values for cyclohexane.[28] The values of barriers to rotation [29] for the three-atom systems used in our calculations are given in Table 3.

TABLE 3

Barriers to rotation of three-membered units [29]

Segment	Barrier (K_T) (kcal mol^{-1})
C–C–C	3·4
C–O–C	2·7
C–N–C	3·6
C–S–C	2·1

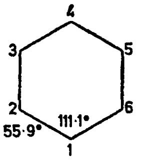
(e) *Non-bonded interactions.* It is difficult to assess accurately the contribution to the total strain energy from non-bonded interactions especially in heterocyclic systems. To some extent they are already allowed for

TABLE 4

Bond and torsional angles and Cartesian co-ordinates

Cartesian co-ordinates of atoms (Å) [b]

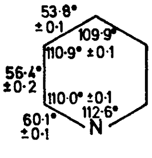
Cyclohexane [a]



(1)

	X	Y	Z
1	0·0000	0·0000	0·0000
2	−1·1317	0·7986	−0·6731
3	−1·3168	2·1712	0·0007
4	0·0000	2·9698	0·0000
5	1·1321	2·1712	0·6725
6	1·3168	0·7986	0·0000

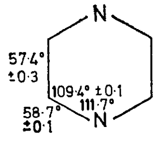
Piperidine



(2)

	X	Y	Z
1	0·0000	0·0000	0·0000
2	−1·0595	0·7240	−0·7170
3	−1·3014	2·0916	−0·0595
4	0·0000	2·9128	0·0000
5	1·1076	2·0917	0·6860
6	1·2793	0·7240	0·0000

Piperazine



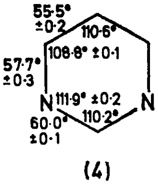
(3)

	X	Y	Z
1	0·0000	0·0000	0·0000
2	−1·0639	0·7429	−0·6908
3	−1·2685	2·1066	0·0058
4	0·0000	2·8494	0·0000
5	1·0670	2·1066	0·6859
6	1·2685	0·7429	0·0000

TABLE 4 (*Continued*)

Cartesian co-ordinates of atoms (Å) [b]

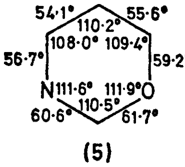
Hexahydropyrimidine



(4)

	X	Y	Z
1	0·0000	0·0000	0·0000
2	−1·0548	0·7614	−0·6845
3	−1·3111	2·0556	−0·0250
4	0·0000	2·8630	0·0000
5	1·1197	2·0556	0·6826
6	1·2575	0·7614	0·0000

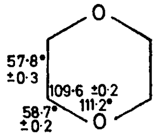
Tetrahydro-1,3-oxazine



(5)

	X	Y	Z
1	0·0000	0·0000	0·0000
2	−1·0534	0·7465	−0·7029
3	−1·3222	2·0440	−0·0552
4	0·0000	2·8316	0·0000
5	1·0934	1·9887	0·6824
6	1·2241	0·7393	0·0000

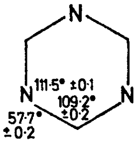
Tetrahydro-1,4-dioxan



(6)

	X	Y	Z
1	0·0000	0·0000	0·0000
2	−1·0262	0·7255	−0·6823
3	−1·2323	2·0932	0·0059
4	0·0000	2·8187	0·0000
5	1·0294	2·0932	0·6774
6	1·2323	0·7255	0·0000

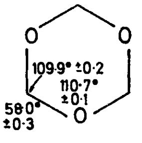
Hexahydro-1,3,5-triazine



(7)

	X	Y	Z
1	0·0000	0·0000	0·0000
2	−1·0584	0·7776	−0·6603
3	−1·2649	2·0774	0·0057
4	0·0000	2·8263	0·0000
5	1·0763	2·0773	0·6645
6	1·2475	0·7776	0·0000

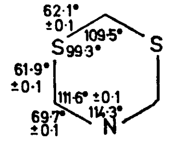
1,3,5-Trioxan



(8)

	X	Y	Z
1	0·0000	0·0000	0·0000
2	−1·0367	0·7378	−0·6525
3	−1·2187	1·9997	0·0058
4	0·0000	2·7479	0·0000
5	1·0344	1·9997	0·6443
6	1·2250	0·7378	0·0000

Dihydro-1,3,5-dithiazine



(9)

	X	Y	Z
1	0·0000	0·0000	0·0000
2	−1·0495	0·6880	−0·7656
3	−1·5691	2·2192	0·0415
4	0·0000	3·1205	0·0000
5	1·2397	2·2192	0·9628
6	1·2991	0·6880	0·0000

[a] Convergence to 0·05° variation in bond angles (at apices). Dihedral (torsional) angles are given midway along relevant bonds. [b] Co-ordinates for tetrahydro-1,3-dioxan and tetrahydro-1,3-dithian were also calculated.

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[26] H. M. Seip, *Acta Chem. Scand.*, 1969, **23**, 2741.

[27] N. C. Cohen, *Tetrahedron*, 1971, **27**, 789.

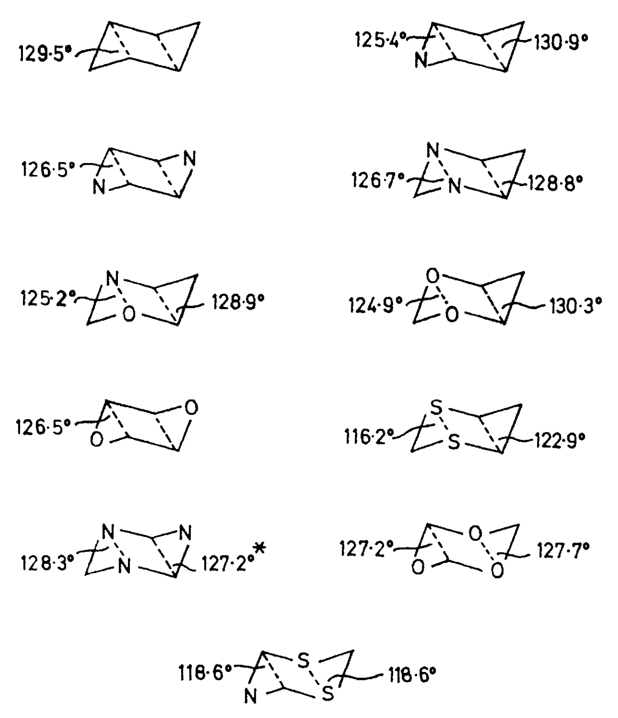
[28] H. R. Buys and H. J. Geise, *Tetrahedron Letters*, 1970, 2991.

[29] J. P. Lowe, *Progr. Phys. Org. Chem.*, 1968, **6**, 1.

in that the force constants for angle bending and torsional twisting, derived from spectroscopic measurements, undoubtedly contain contributions from non-bonded interactions. Thus Allinger *et al.*,[30] who have specifically included terms for non-bonded interactions in their strain-energy calculations, use abnormally low values for bending and torsional force constants. Since we cannot readily assess the extent of the redundancy nor can we easily parameterise the total non-bonded interactions we have chosen to omit a separate term for them; Seip [26] found that this term made little difference to the five-membered ring molecules that he was studying.

RESULTS

The bond and torsional angles and Cartesian co-ordinates given in Table 4 were calculated with the ICL 1905E computer at the University of East Anglia using the potential functions and parameters given above. The results obtained from the conjugate gradient program GEOMIN are given.[10] The angles between planes, calculated from the atom co-ordinates, are given in the Figure.



Angles between ring planes, calculated from atom co-ordinates of Table 4. * For hexahydro-1,3,5-triazine, angle between equatorial lone pairs = 106·9°, between axial lone pairs = 1·6°, angle between axial and equatorial lone pairs = 112·0°

DISCUSSION

For cyclohexane, for which electron-diffraction data have been reported, the calculated values of bond and torsional angles are very close to the experimentally observed ones (Table 5). Considering the variation reported in electron-diffraction data for piperazine [31,32] and 1,3,5-trioxan,[31,33] the angles calculated for these and for 1,4-dioxan are also in good agreement with the experimentally observed values. The calculations on other molecules have used the same parameters, or parameters from similar sources, and therefore should give reasonable representations of the molecules studied.

TABLE 5

Comparison of experimental and calculated parameters for six-membered rings

	Calculated		Experimental		
	Bond angle (°)	Torsional angle (°)	Bond angle (°)	Torsional angle (°)	Ref.
Cyclohexane					
	CCC 111·1	55·9	111·05 ± 0·15	55·9 ± 0·3	*a*
Piperazine					
	CNC 111·7	58·7 ± 0·1	112·6 ± 0·5		*b*
			109·0 ± 0·8		*c*
	CCN 109·4 ± 0·1	57·4 ± 0·3	109·8 ± 0·5		*b*
			110·4 ± 0·8		*c*
1,4-Dioxan					
	COC 111·2	58·8 ± 0·2	112·5 ± 0·5		*b*
	CCO 109·6 ± 0·2	57·8 ± 0·3	109·2 ± 0·5		*b*
1,3,5-Trioxan					
	COC 110·7 ± 0·1	58·0 ± 0·3	110 ± 1·0		*d*
			109·2 ± 1·0		*e*
	OCO 109·9 ± 0·2	58·0 ± 0·3	110 ± 2·0		*d*
			111·0 ± 0·7		*c*

[a] Ref. 28. [b] Ref. 31. [c] Ref. 32. [d] S. Kimura and K. Aoki, *J. Chem. Soc. Japan*, Pure Chem. Sect., 1951, **72**, 169. [e] Ref. 33.

The results suggest that substitution of carbon in the cyclohexane ring by nitrogen or oxygen leads to some puckering at the substituted end of the ring. The effect of the small sulphur valency angle and the long C–S bond is to pucker the ring severely at the S–C–S plane in 1,3-dithian (Figure).

The previously reported dipole moment results for the *N*-alkyl axial–equatorial equilibria in 1-alkyl-4-aryl-piperidines,[34] 1,3-dialkylhexahydropyrimidines,[3] 3-alkyl-tetrahydro-1,3-oxazines,[5] 1,3,5-trialkylhexahydro-1,3,5-triazines,[4] 5-alkyldihydro-1,3,5-dithiazines,[35] and 1-alkyl-4-t-butylpiperazines [36] have been calculated, making the same assumptions used in the original work, except that the strain-energy minimised geometry has been used. The original and recalculated results are summarised in Table 6.

For the 1-alkyl-4-t-butylpiperazines, the diaxial and diequatorial conformers are almost centrosymmetric and probably possess very small dipole moments arising

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[30] N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and E. A. van Catledge, *J. Amer. Chem. Soc.*, 1968, **90**, 1199.

[31] M. Davis and O. Hassel, *Acta Chem. Scand.*, 1963, **17**, 1181.

[32] A. Yokozeki and K. Kuchitsu, *Bull. Chem. Soc. Japan*, 1971, **44**, 2352.

[33] A. H. Clark and T. G. Hewitt, *J. Mol. Structure*, 1971, **9**, 33.

[34] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1970, 122.

[35] L. Angiolini, R. P. Duke, R. A. Y. Jones, and A. R. Katritzky, *Chem. Comm.*, 1971, 1308; *J.C.S. Perkin II*, 1972, 674.

[36] J.-L. Imbach, R. A. Y. Jones, A. R. Katritzky, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1967, 499.

from the different C–N–C bond angles caused by the *N*-alkyl and *N*-t-butyl substituents; the axial-equatorial conformers possess dipole moments the components of which are dependent on their angles to the C–N–C plane. This situation shows the limitation of the programs used: the effect of exocyclic substituents on the bond angles in the ring cannot easily be expressed without explicit consideration of non-bonded interactions and for the same reason the angle between the C–N–C plane and the resultant moment has to be taken from another source.[37]

TABLE 6

Recalculated results for some conformational equilibria [a]

Alkyl group(s)	Optimised geometry		Previous results	
1-Alkylpiperidines [b]	% Alkyl equatorial	ΔG°_{25} (kcal mol^{-1})	% Alkyl equatorial	ΔG°_{25} (kcal mol^{-1})
Methyl	75	0·65	73	0·59
Ethyl	85	1·03	83	0·95
Isopropyl	94	1·58	92	1·44
1,3-Dialkylhexahydropyrimidines [c]	% Alkyl groups diequatorial	ΔG°_{25} [d] for 3-alkyl (kcal mol^{-1})	% Alkyl groups diequatorial	ΔG°_{25} [d] for 3-alkyl (kcal mol^{-1})
Dimethyl	54	0·51	55	0·54
Diethyl	57	0·59	59	0·62
Di-isopropyl	*ca.* 100	$\geqslant$2·0	*ca.* 100	$\geqslant$1·8
Di-t-butyl	100	—	100	—
1-t-Butyl-3-methyl	68	0·43	69	0·47
1-t-Butyl-3-ethyl	75	0·64	75	0·65
1-t-Butyl-3-isopropyl	100	—	*ca.* 100	$\geqslant$1·5
3-Alkyltetrahydro-1,3-oxazines [e]	% Alkyl equatorial	ΔG°_{25} (kcal mol^{-1})	% Alkyl equatorial	ΔG°_{25} (kcal mol^{-1})
Methyl	57	0·18	58	0·20
Ethyl	66	0·40	68	0·43
Isopropyl			86	1·06
t-Butyl	100	—	*ca.* 100	—
1,3,5-Trialkylhexahydro-1,3,5-triazines [f]	% Mono-axial alkyl	ΔG°_{25} [g] (kcal mol^{-1})	% Monoaxial alkyl	ΔG°_{25} [g] (kcal mol^{-1})
Isopropyl	91	0·72	92	0·80 ± 0·20
t-Butyl	81	0·20	85	0·35 ± 0·12
5-Alkyldihydro-1,3,5-dithiazines [h]	% Alkyl axial	ΔG°_{25} (kcal mol^{-1})	% Alkyl axial	ΔG°_{25} (kcal mol^{-1})
Methyl, ethyl, isopropyl	100	—	100	—
t-Butyl	81	0·84	82—75	0·65—0·90 [i]

[a] In cyclohexane at 25°. [b] Using data for the 1-alkyl- and 1-alkyl-4-*p*-chlorophenyl-piperidines (ref. 34). [c] See ref. 3. [d] Corrected in the dimethyl, diethyl and di-isopropyl compounds for two-fold degeneracy of the equatorial, axial conformers.[3] [e] In benzene at 25° (ref. 5). [f] Considering the symmetrical trialkyl compounds where the equilibrium effectively contains only the triequatorial and mono-axial, diequatorial conformers (ref. 4). [g] Corrected for three-fold axis of symmetry in the triequatorial alkyl conformer (ref. 4). [h] Ref. 35. [i] See ref. 35 for a discussion of this range of values.

The recalculated results show a small increase in the estimated values of ΔG°_{25} for *N*-alkyl groups in piperidine by 0·06—0·15 kcal mol^{-1} above the values previously reported;[34] the largest increase is for the *N*-isopropyl compound. The values remain less than those for *C*-alkyl groups in cyclohexane, where the preferred values[38] are 1·7, 1·8, and 2·1 kcal mol^{-1} for methyl, ethyl, and isopropyl respectively. The conformational free-energy of an axial t-butyl group in 1,3,5-tri-t-butylhexahydro-1,3,5-triazine is found to be somewhat lower (0·20 kcal mol^{-1}) than previously estimated (0·35 kcal mol^{-1}).[4]

The results for the 1,3-dialkylhexahydropyrimidines, 3-alkyltetrahydro-1,3-oxazines, and 5-alkyldihydro-1,3,5-dithiazines are very nearly unchanged. This suggests that the original estimates of the ring geometry were not greatly in error, and also reflects the fact that in the systems chosen the calculated results were not too sensitive to the molecular geometry. We conclude that dipole-moment-derived conclusions regarding the conformations of heterocycles can be confidently accepted, and that a simple physical model satisfactorily describes the geometry of the cyclohexane ring and related heterocycles.

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