Tetrahedron. Vol. 30, pp. 1971 to 1978. Pergamon Press 1974. Printed in Great Britain

CONFORMATIONAL EQUILIBRIA IN COMPOUNDS WITH 6-MEMBERED RINGS

M. J. T. ROBINSON*
Dyson Perrins Laboratory, University of Oxford

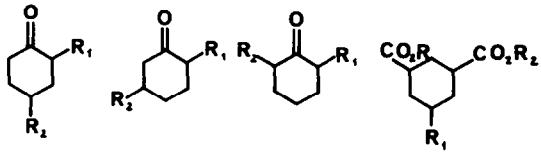
(*Received in the UK 5 February* 1974)

INTRODUCTION

Cyclohexane and other non-aromatic 6-membered ring compounds are probably more numerous and more important than all other saturated cyclic compounds taken together. Bond and torsion angles in cyclohexane and many of its heterocyclic analogues, furthermore, are sufficiently close to 'normal' values for there to be a close correspondence between saturated 6-membered ring and acyclic compounds. It is understandable, therefore, why interest in conformational equilibria in cyclohexane and its analogues has been so widespread.

The work described in this paper is mainly concerned with conformational equilibria in the liquid phase. Conformational equilibria in isolated molecules in the gas phase, although more difficult to measure, will be easier to understand or predict and it is therefore desirable to study the solvation of conformers in order to relate gas and liquid phase equilibria. Some early results of our studies of solvation effects in conformational equilibria will be given later in this paper.

My interest in conformational effects and equilibria in compounds with one or two 6-membered rings arose during earlier work on steroids. It seemed clear that the complex origins of differences in reactivity associated with differing configurations of the ring systems in such compounds, e.g., the regioselectivity in the enolisation of 3-oxo-5α and -5-β-steroids, could only be unravelled by working with simpler ring systems. Anancomeric derivatives of *cis*- and *trans*-decalin were chosen for study. In the course of synthesising various decalones it became obvious that the monocyclic intermediates, various 2,4-, 2,5-, and 2,6-dialkylcyclohexanones (**1–3**)[1,2] were themselves of great interest (see particularly, Klyne[3]). The presence of a carbonyl group next to one (or both) alkyl-substituted carbon atoms allowed equilibrium within each group of stereoisomers to be reached under mild conditions, while the development of gas chromatography made the necessary analyses possible. At the same time a synthesis of a range of cyclohexane 1,3-dicarboxylic acids (**4**; R_2=H) and their derivatives,[4] originally intended for a quite different purpose, provided the basis for a related study of derivatives of cyclohexane based on the epimerisation of alkoxycarbonyl groups.



1 **2** **3** **4**

Before describing the results obtained from the compounds **1** to **4** I will outline the general considerations that have guided our work on conformational equilibria.

Methods for studying conformational equilibria in solution

The general 'rigidity' of the chair conformer of cyclohexane, its low energy relative to the twist conformer, and the high barrier separating the two chair conformers of a substituted cyclohexane makes it reasonable to characterise the equilibrium between two chair conformers by thermodynamic parameters† $\Delta G^\circ_{e\to a}$, etc, with the twist conformer negligible for many purposes.

Methods of studying conformational equilibria with N conformers reduce to solving one or more ($\leq N-1$) equations such as (1) for n_i (n_i is the mole fraction of the ith conformer: $\Sigma n_i = 1$):[5]

$$P = \sum_1^N n_i P_i \qquad (1)$$

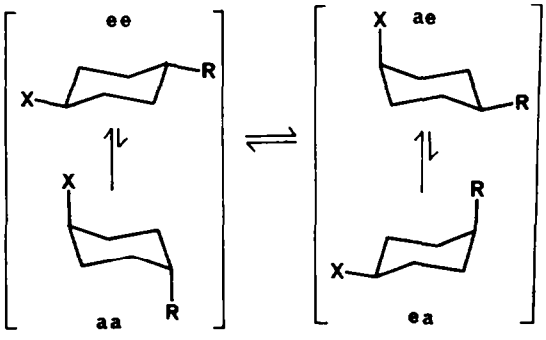
where P is the numerical value of some property *P* of the compound and P_i are the corresponding values for the N-conformers. It is not common in practice for N to be greater than 2 except for

†It is not always recognised that such parameters are not really appropriate when the barriers between conformers are low. In such cases an appreciable proportion of the molecules have an energy greater than the barrier in the relevant vibration/internal rotation mode; such molecules cannot be said to be a part of one or the other conformer.

special cases, e.g., where two (out of three) conformers (2 and 3, say) are enantiomeric so that an additional equation, $n_2 = n_3$, is available. I will be mainly considering equilibria of these general types, although large errors can be caused by the neglect of minor conformers.

Eq(s) (1) can be solved if P_i are either known or can be estimated in some way. In fact P_i are only known accurately if all *must* be equal or are proportional to integers directly related to the structures of the compound studied. These conditions are rarely satisfied in practice and the corresponding methods (see later) were not available in our early work. When P_i must be estimated indirectly several methods, differing greatly in their sensitivity to systematic errors, are possible. If P can be measured with precision over a wide temperature range then n_1 and n_2 can be replaced by functions of the energy difference, etc., between the conformers and curve fitting will give values of P_i and the energy difference. This is often used with acyclic compounds (e.g., 2 - alkyl - 1,3 - dioxanes and some allenes, see *Alkylcyclohexanones and related compounds* below), for which few methods are available. The uncertain temperature dependence of the properties P_i may introduce serious systematic errors and it is in any case uncommon to obtain sufficiently precise data with cyclic compounds for this type of method to give more than qualitative results for ring inversion equilibria.

Six-membered rings in chair conformations do have the important advantage that the ring can be 'locked' by substituents, notably t-butyl, relatively far from the centre of interest and, hopefully, having no other effect. Such anancomeric molecules may be used as 'models' for the conformers:

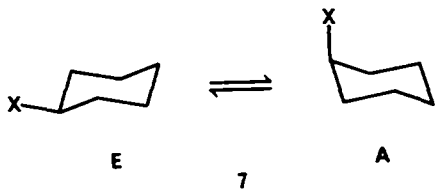


5 6

By rearranging Eq (1) one obtains for 7E and 7A:

$$'K = \frac{n_a}{n_e} = \frac{P_e - P}{P - P_a} \simeq \frac{P'_e - P}{P - P'_a} \qquad (2)$$

where the unobservable P_e and P_a are approximated



by P'_e and P'_a obtained from the models **5** and **6**. Since K in Eq (2) is evaluated from a ratio of differences its value is very sensitive to systematic errors in the assumptions $P_e = P'_e$, etc.[6] If possible one wishes to avoid Eq (2) and use **5** and **6** more directly by taking the stereochemical equilibrium **5**⇌**6** as a model for the conformational equilibrium 7E⇌7A. For this to be possible either substituent X or the locking group(s) R must be cleanly epimerisable. Clearly this is generally the case with ketones such as **1**–**3** but is more limited for **5**⇌**6** unless X or R are rather special, as in the esters **4**(R_2 = Alkyl). In effect we now use two equations (in which the properties P are concentrations):

$$[5]_{equil} = [5_{ee}] + [5_{aa}] \simeq C(n_e + n_a e^{-(E_R/RT)}) \qquad (3)^*$$

$$[6]_{equil} = [6_{ea}] + [6_{ae}] \simeq C(n_e e^{-(E_R/RT)} + n_a)$$

where E_R is the increase in free energy associated with R becoming axial. If E_R is large, then the equations (3) may be simplified and combined to give (4):

$$K = n_a/n_e \simeq [6]_{equil}/[5]_{equil} \qquad (4)$$

The approximations implicit in (4) turn out to be acceptable in practice if polar interactions and twist conformers can be neglected.

It is at once obvious that Eq (4) is better than (2) because (a) it uses the ratio of two numbers rather than the ratio of two differences and (b) free energy differences (which are directly related to concentrations) are much less sensitive to minor changes in shape and to long distance interactions than are many of the properties P, e.g., rate constants, NMR chemical shifts, used with Eq (2). An additional, almost completely overlooked, advantage is that **5** and **6** may be used as models for determining solvent effects on the equilibrium 7E⇌7A *without re-establishing the chemical equilibrium* **5**⇌**6** *in every solvent* (see *Solvent effects* below).

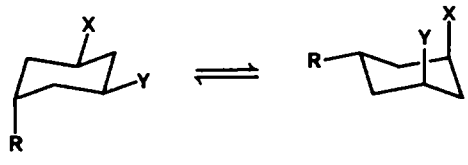
Mono- and di-substituted cyclohexanes, and 5 - alkyl - 1,3 - dioxanes

The epimerisation equilibria for the esters **4**(R_2 = Alkyl)[4] gave results in good general agreement with other published results for alkyl- and alkoxycarbonylcyclohexane.[7] By combining results from epimerisation, esterification, and ionisation equilibria we obtained the first accurate estimates of $\Delta G^0_{e\to a}$ for 7(X = CO_2H or CO_2^-), and thereby re-

*Eqs (3) may, of course be used without simplification if E_R is known.

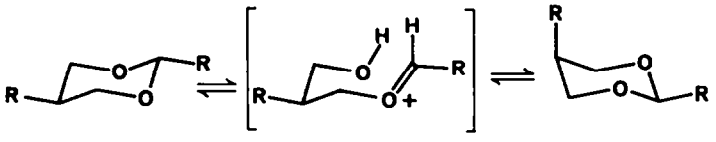
moved the anomalous difference earlier found for CO_2H and CO_2R.[8]

The results for the esters **4** were combined with other equilibrium data to give free energy differences for conformational equilibria in some *cis* - 1,3 - disubstituted cyclohexanes (**8**; R = H or Alkyl), including the amusing aminoacid **8**(R = i-Pr; $X = NH_3^+$; $Y = CO_2^-$) that changes from $\mathbf{8}_{aa}$ to $\mathbf{8}_{ee}$ when protonated, and for the chair twist equilibrium in cyclohexane.



8

Although considerably later our study of 5 - alkyl - 1,3 - dioxane follows much the same technique.[9] In this case the equilibrium is established by opening and reclosing the ring:



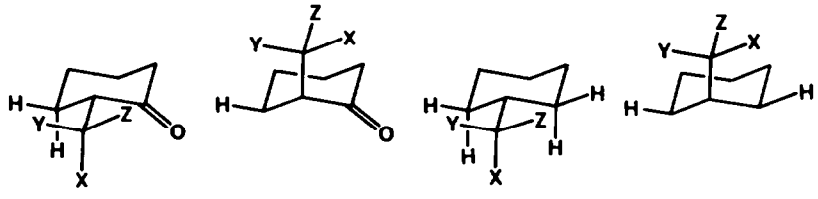
This system gave the striking result that whereas any alkyl group would serve as a conformation locking group R_2 at position 2 even t-butyl could quite easily become axial at position 5, thereby demonstrating how sensitive 1,3-diaxial interactions can be to the shape and constitution of a ring in the chair conformation. This work was carried out almost simultaneously with Eliel and Knoeber's,[10] and Eliel has gone on to study a wide range of substituents in this fascinating ring system.

Alkylcyclohexanones and related compounds

The epimerisation equilibria for the ketones **1**–**3**[1,2,11,12] and subsequent follow-up work has yielded many interesting results. Conformational equilibria in 3 - methyl- and 4 - methyl - cyclohexanone were much as expected but for the 2 - alkylcyclohexanones were surprising (Table 1). I will discuss first the results for 2 - methylcyclohexanone and consequent work before returning to the other 2 - alkylcyclohexanones.

The free energy difference $\Delta G^0_{e\to a}$ for 2 - methylcyclohexanone **9a** was *higher* than for methylcyclohexane (contrast with the original 2-alkylketone effect[3]), although the probably flattening of the ring relative to cyclohexane had been expected to reduce steric repulsions between 2- and 6-axial substituents. We related this anomaly to (a) the strongly preferred conformation of propionaldehyde[13] (Fig 1) with C-methyl eclipsing C=O (similar results are obtained for other acyclic ketones and aldehydes) and (b) the high reactivity (in nuucleophilic additions) and low thermodynamic stability of cyclohexanone.[14] These special features of carbonyl compounds can be accounted for if hyperconjugation between axial or similar C–H groups (but *not* equatorial C–H groups) and carbonyl double bonds stabilise ketones and aldehydes.

An alternative explanation for the conformational preferences in ketones and aldehydes, alkyl-oxygen *attraction* (exactly the opposite of the original 2-alkylketone effect!) when an alkyl group eclipses C=O, accounts neither for the low stability and high reactivity of cyclohexanone nor for the



9 **10**

	a:	b:	c:	d:	e:	f:	g:
X =	H	H	H	Me	H	Me	Me
Y =	H	H	Me	H	Me	Me	H
Z =	H	Me	H	H	Me	H	Me

Fig 1. Conformations of 2-methyl-, 2-ethyl- and 2-isopropyl-cyclohexanone and of the parent hydrocarbons. At first approximation X and Z are equidistant from the oxygen atom in 9E but the deviation of the ring from idealised geometry with perfectly staggered bonds probably brings Z closer than X to O in 9E.

absence of any effect of the supposed attraction on, e.g., enthalpies and free energies of hydrogenation of ketones.[14] The latter could result from equally strong attractive skew interactions between alkyl groups and *singly* bonded oxygen. Accordingly we studied rotameric equilibria in 2 - alkyl - 1,3 - dioxanes (Fig 3) and in 3 - alkyl - 1,1 - diphenylallenes[15] (Fig 2). The results for the dioxanes were consistent only with *repulsive* skew interactions between methyl and singly bonded oxygen. In contrast the allenes, with a double bond but no oxygen, qualitatively resembled the aldehydes, suggesting that the vital factor in the latter is the double bond and *not* the oxygen atom. When C-methyl eclipses C=X (Fig 2) there may be appreciable steric repulsion offsetting the effect of hyperconjugation. This seems to be very important in imines (Fig 2, X=N–R)[16,17] and related compounds (e.g., X=NOMe[16,17] or N.NMe$_2$[16]) because only in the diazoalkanes (X=N$_2$) does the C-methyl rather than the C–H eclipse the C=N.[17]

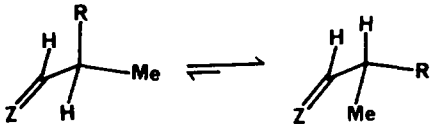


Fig 2. Rotameric equilibria at an sp^3-sp^2 carbon-carbon bond: C-methyl rather than C–H prefers to eclipse the C=Z when Z = O, C=CPh$_2$, and N$_2$, but not when Z = N–R, N–OMe, and N–NMe$_2$.

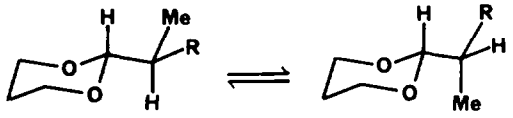


Fig 3. Rotameric equilibria in 2-alkyl-1,3-dioxanes: C-methyl tends to *avoid* skew interactions with C-oxygen single bonds (similar results were obtained for 2-alkyl-1,3-dioxolanes).[15]

The decrease in $\Delta G^0_{e\to a}$ along the series 2-methyl-, 2-ethyl-, and 2 - isopropyl - cyclohexanone (Fig 1) can be explained qualitatively[2,11,12] by (a) *one* relatively *un*hindered position (i.e., less steric repulsion than in the skew Me–C–C–CH$_2$– present in the analogous hydrocarbon 10A) for a β-methyl when ethyl or isopropyl is axial (Fig 3, X in 9A; physically this is similar to the origin of the 3-alkylketone effect[3]) and (b) *two* relatively hindered positions for β-methyl when ethyl or isopropyl is equatorial (Fig 1; X and Z in 9E), the methyl groups in isopropyl being unable to avoid both. Quantitatively the decreases in $\Delta G^0_{e\to a}$ may be used to evaluate two parameters for skew interactions in Me–C–C–CO.[2] These parameters were then used to account for (a) reversal of sign of the Cotton effects of aldehydes and methylketones MeEtCH(CH$_2$)$_n$COR (R=H or Me) between n = 0 and n = 1, the first explanation[18] of this long-standing anomaly,[19] and (b) the absence of a marked conformational preference in 2-ethylbutanal,[2,20] in contrast to propionaldehyde.

This analysis of 2-alkylcyclohexanones involved the assumption that methyl groups at Y and Z in 9E (Fig 1) were *equally* hindered by the carbonyl group. It followed, therefore, that the stabilities of the rotamers of 2(e) - isopropylcyclohexanone should be in the order

$$9Ee > 9Ef > 9Eg,$$

This sequence conflicts with an interpretation of

Table 1. Free energy ($\Delta G^\circ_{e\to a}$), enthalpy ($\Delta H^\circ_{e\to a}$) and entropy ($\Delta S^\circ_{e\to a}$) differences for alkylcyclohexanones and free energy differences for alkylcyclohexanes

Cyclohexanone	$\Delta G^\circ_{e\to a}$ kcal/mole^{-1} (298K)	$\Delta H^\circ_{e\to a}$ kcal/mole^{-1}	$\Delta S^\circ_{e\to a}$ cal/deg.$^{-1}$	$\Delta G^\circ_{e\to a}$ (Parent hydrocarbon) kcal/mole^{-1}	Ref.
2-Me	+2·0	+2·1	+0·3	+1·7	2
	1·6	1·6	+0·1		11
	1·8	1·9$_5$	+0·4		12
3-Me	1·3	1·4	−0·3		1
	1·3$_5$	1·3$_5$	(0)[a]		11
4-Me	1·8	1·9	+0·4		1
2-Et	1·1	1·3	+0·6	1·8	2
	1·1	1·1	(0)[a]		11
	1·3	1·3	+0·2		12
2-i-Pr	0·6	0·4$_5$	−0·5	2·2	11
	0·5$_5$	0·3	−0·6		12

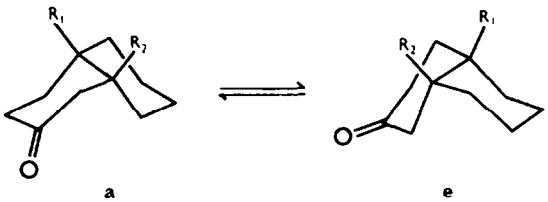
[a] Assumed

the circular dichroism of 2α - isopropyl - 5α - cholestan - 3 - one[21] and this intriguing discrepancy remains unresolved.

Conformational equilibria in decalones were first considered in detail by Klyne[3] and many of his interpretations and predictions based on the 'alkyl-ketone effects' have been verified. *cis*-2-Decalones, however, have provided some problems in the past[22] and continue to do so. Fortunately it is now possible to get reliable experimental results because conformational equilibria in *cis*-decalones can be frozen out readily on the NMR timescale (contrast with cyclohexanones). One of the most reliable, though not very sensitive, methods for solving Eq (1) is NMR integration of spectra of compounds in which the conformational equilibrium is 'frozen'. When each conformer gives one or more well separated bands Eq (1) can be put into the form:

$$P(1)/P(2) = n_1 . N_2/n_2 . N_1 \qquad (5)$$

where N_1 and N_2 are the numbers of protons per molecule responsible for the characteristic bands with integrated intensities P(1) and P(2). The results for **11** (R_1=Me; R_2=H) confirm earlier conclusions[2,3,22] that **11a** is more stable than **11e**. The



11

equilibrium in **11** (R_1=H; R_2=Me), however, is found to favour **11a** strongly ($\Delta G^0_{193} = 0.7$ kcal/mole^{-1}) although the equilibrium would be expected to be quite finely balanced as it is in the corresponding methyl ketal.[23] This anomaly is at present not explained.

Cyclohexanones with polar substituents

Although 2-halocyclohexanones have been extensively studied cyclohexanones with other polar substituents have been relatively neglected. We have been interested in methoxyl and acetoxyl substituents.

The difference in $\Delta G^0_{e\to a}$ for methoxycyclohexane (**13**) (0·6 kcal/mole^{-1}) and 2 - methoxycyclohexanone (**12**) would be expected to be even *larger* than the difference for ethylcyclohexane (1·8 kcal/mole^{-1}) and 2 - ethylcyclohexanone (1·3 kcal/mole^{-1}). This is because the two substituents are similarly shaped and skew interactions in the fragment Me–O–C–CH_2 (~ 1·5 kcal/mole^{-1}) and unavoidable in any rotamer of **13** (Fig 4) are larger than in Me–C–C–CH_2 (~ 0·8 kcal/mole^{-1}), present in ethylcyclohexane (Fig 1). Such skew interactions are almost completely relieved in one rotamer of **12A** (Fig 4) and **10A**. It was surprising, therefore, to find that semi-quantitative results for the epimerisation equilibrium in 2 - methoxy - *trans* - 1 - decalone[24] suggest that the $\Delta G^0_{e\to a}$ values for **12** and **13** are almost the same. In studying **12** itself we have had to use equation (2) with ($J_{2,3\text{-}cis} + J_{2,3\text{-}trans}$) as the property *P*.[25] Surprisingly $\Delta G^0_{e\to a}$ (**12**) is ~ 0 (the most favourable situation for the use of Eq (2)) and is essentially *independent* of solvent polarity. Presumably the methoxyl group in **12E** avoids rotamer *a* (Fig 4) (electric dipoles almost parallel) and adopts the sterically more hindered *b* or *c* with favourable electrostatic interactions that just balance those in **12A** (only one rotamer is shown because both electrostatic interactions—electric dipoles antiparallel—and steric hindrance are minimised in the same rotamer).

2-Acetoxycyclohexanone (**14**) is even more interesting. In 2β - acetoxy - 3 - oxo 5α - steroids the A-ring adopts a twist conformation and Williamson and Johnson suggested that this could be caused by a large 1,3-diaxial repulsion between acetoxyl and the 19-methyl groups when the A-ring is in a chair conformation.[26] We have found, again using vicinal

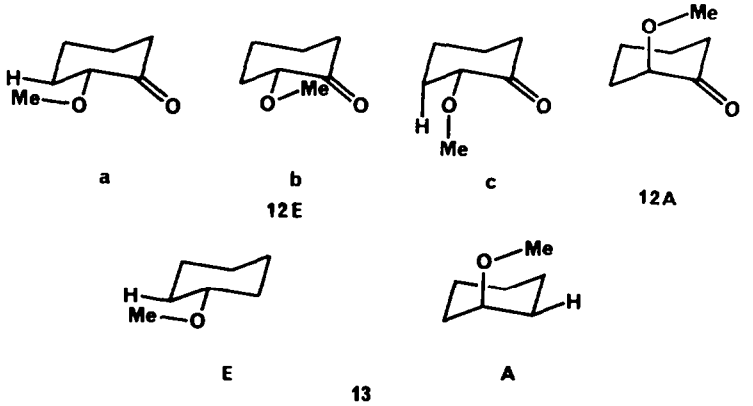
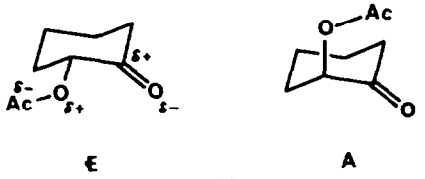


Fig 4. Some of the rotamers of 2-methoxycyclohexanone (**12**) (only the most favourable rotamer of **12A** is shown) and methoxycyclohexane (**13**).

coupling constants in Eq (2), that 2 - acetoxycyclohexanone (**14**) exists almost exclusively with the acetoxyl group equatorial, $\Delta G^0_{e\to a} = 2{\cdot}5 \pm 0{\cdot}5$ kcal/mol^{-1} (a very unfavourable case for the use of Eq (2)!).[25] The small difference between P ($= J_{2,3\text{-}cis} + J_{2,3\text{-}trans}$) and P'_e ($= J_{2a,3e} + J_{2a,3a}$ for *cis* - 2 - acetoxy - 4 - t - butylcyclohexanone) is essentially independent of solvent polarity and may therefore be mainly due to the error in assuming $P_e = P'_e$. This is because the only apparent explanation for the large difference in the conformational equilibria in **14** and cyclohexyl acetate ($\Delta G^0_{e\to a} = 0{\cdot}6$ kcal/mol^{-1}) is electrostatic interactions between the two polar groups in **14** and such interactions should vary with the polarity of the solvent.

We have also studied 4 - methoxycyclohexanone but in that compound interest centres on solvent effects on the equilibrium (see below), while 3 - methoxycyclohexanone was investigated by Chamberlain and Whitham.[27]



14

N-*Substituted piperidines*

Conformational equilibria at the N atom in piperidine and its N-substituted derivatives (Fig 5) have been investigated by many methods without general agreement being reached. The central problem for N–H and N-alkyl is the rapidity of inversion at the nitrogen atom (N-halogen is much more convenient in this respect, see below). The basicity of nitrogen, however, makes possible the simplest method for studying conformational equilibria, i.e., the conversion of each conformer into a corresponding stereoisomeric form of another compound

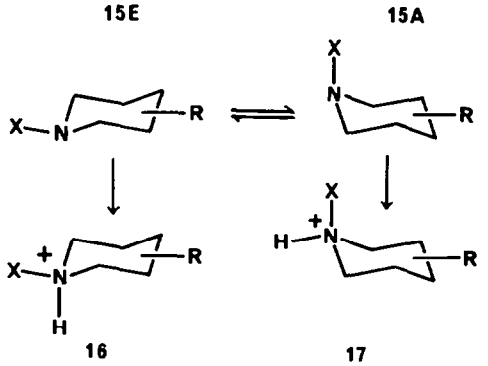


Fig 5. Measurement of the very mobile conformational equilibrium in an N-alkylpiperidine by rapid, stereospecific protonation with a strong scid. When X = F or Cl the equilibrium is readily 'frozen' out on the NMR timescale.

by a reaction (protonation by a strong acid) that is fast (so that the Curtin–Hammett Principle does *not* apply), stereospecific, and irreversible.[28] Under these conditions

$$P(1)/P(2) = n_1/n_2 \qquad (5)$$

where P(i) is the concentration of the *i*th stereoisomeric product formed from the *i*th conformer. For simple piperidines only NMR integration is at present a feasible method of analysis for the mixture of products.

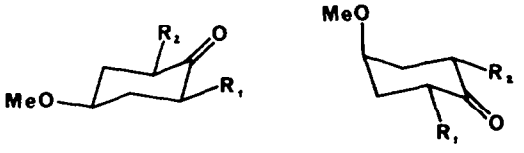
Booth's original method, direct mixing of a liquid amine with excess of a strong acid, has been criticised[29] and defended[30] for its original application to N–H but we have now found that it is definitely invalid for N-methyl. When a liquid N-methylpiperidine (**15**; e.g., R = *cis*-2,6-Me$_2$) is mixed with trifluoroacetic acid the ions **16** and **17** are formed in relative amounts quite close to the equilibrium concentrations for aqueous acid. When the amine diffuses through air or an inert solvent to the surface of concentrated sulphuric acid, so that individual molecules are protonated irreversibly and can not exchange protons with free amine as in liquid-liquid mixing, the results are strikingly different and give $\Delta G^0_{e\to a}$ (**15**; X=Me) $\nless 1{\cdot}4$ kcal/mole^{-1} at 25°.[31] These results conflict sharply with those $\ngtr 0{\cdot}7$ kcal mole^{-1} obtained by Katritzky,[32] using electric dipole moments in Eq (2), but are consistent with equilibria in **15** (X=F[33] or Cl[17]) determined by NMR integration at low temperatures. We conclude that the equilibrium **15E**⇌**15A** is in general as much in favour of equatorial X as the equilibrium 7E⇌7A (provided X is not an unsaturated group that can conjugate with the unshared pair of nitrogen in **15**).

Solvent effects

Solvent effects on conformational equilibria in 6-membered rings are of interest in themselves and also serve to relate equilibria in solution, for which much experimental data is available, to equilibria in the gas phase, to which the results of 'molecular mechanics' and other calculations apply. Unfortunately most methods for studying conformational equilibria are either so laborious or inaccurate, or both, as well as being subject to severe limitations in scope, that significant solvent effects have for the most part only been measured (or even sought) for conformers differing greatly in electric dipole moments. Since equilibria between anancomeric stereoisomeric compounds are widely used as models for conformational equilibria one may as well use differences in the solvation energies of such compounds as models for the differential solvation effects on conformers. In principle one simply measures partition coefficients for pairs of stereoisomers between immiscible fluid phases. In practice we have used GLC in two ways. The direct and experimentally simple method is to use ratios

of corrected retention times (with suitable precautions to eliminate undesirable surface effects[34]) as a measure of the ratios of partition coefficients* for the compounds between the gas and involatile stationary liquid phases. The second method, which we are currently developing,[35] uses the high sensitivity of GLC to analyse samples of vapour in equilibrium with solutions of known composition.

We have used the conformational equilibrium in 4-methoxycyclohexanone (**18**; $R_1 = R_2 = Me$) as a test system for the first method.[35] This equilibrium shows considerable sensitivity to solvent polarity[36] and can be readily studied in a wide range of solvents using vicinal coupling constants in Eq (2). Such measurements give differences between one non-viscous solvent and another but can not be applied in the gas phase. Gas–liquid solvation energy differences ($\delta\Delta G°$: a positive value implies that the conformer with an equatorial group in the more strongly solvated) were determined by GLC using *two* pairs of model compounds, **18**($R_1 = R_2 =$ Me) and **18**($R_1 = Me$, $R_2 = H$) and extrapolating to **18**($R_1 = R_2 = H$).* The GLC stationary phases were



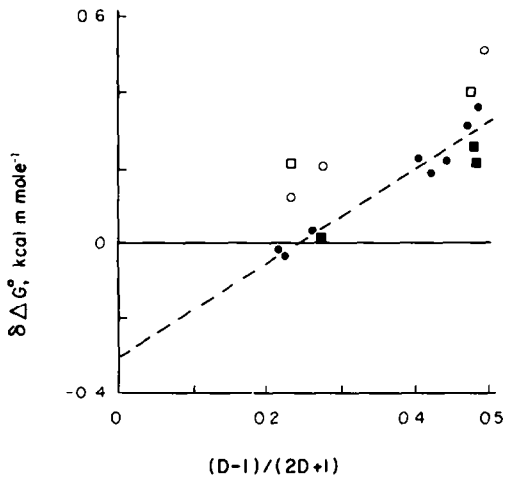
E A

18

too viscous to be used directly for high resolution NMR spectroscopy. By using mixtures of silicone oil and hexamethyldisiloxane, which have similar solvent characteristics, and extrapolating to 100% silicone oil it was possible to bring the GLC and NMR results on to the same scale. The results (a small selection of solvents is given in Fig 6) for 'normal' solvents, i.e., excluding aromatic and hydroxylic solvents) show a reasonably smoothe dependence on dielectric constant, with aromatic and hydroxylic solvents being more effective in stabilising **18**E than would be expected from their dielectric constants. A surprising feature is that there is almost *no* differential solvation in passing from the gas phase to low polarity solvents like silicone oil, although a simple extrapolation from the normal solvents would suggest a difference of at least 0·2 kcal/mole^{-1} between the gas phase and silicone oil. The stationary phases (a) silicone oil or squalane (aliphatic non-polar), (b) benzylbiphenyl† (aromatic non-polar), (c) cyanosilicone gum XE 60

*Solvation energies for individual compounds may, of course be obtained from retention data but many of the sources of error in such measurements cancel out when two very similar compounds are directly compared.

†Me groups interact sufficiently strongly with an adjacent CO group for it to be necessary to use two pairs of models.



Solvents: ○ Aromatic or hydroxylic ● 'normal'
Glc phases: □ Aromatic or hydroxylic ■ 'normal'

Fig 6. Solvent dependence of the conformational equilibrium in 4-methoxycyclohexanone (relative to the gas phase, for which $\Delta G°_{\text{gas}} = -0{\cdot}55$ kcal mole^{-1} at 25°). N.B. Dielectric constants D for some stationary phases were estimated indirectly and may be seriously in error for the two polar phases cyanosilicone gum XE 60 and sucrose acetate isobutyrate.

or sucrose acetate isobutyrate (dipolar aprotic), and (d) diglycerol* (hydroxylic) exemplify four of the common classes of solvent. Accordingly it is simple to determine solvent effects on a conformational equilibria, for which models are available, at a semiquantitative level for a wide range of substituents. We have concentrated in the first instance on the ordinarily neglected pairs of conformers with very similar electric dipole moments.

Some of the differences in solvation (Table 2) are immediately surprising, e.g., $\delta\Delta G°$ is *less* for hydroxyl than for methoxyl, and the very weakly polar

Table 2. A selection of differences* ($\delta\Delta G°$) in solvation energies in a non-polar (silicone oil) and in a polar (cyanosilicone gum XE 60) stationary phase for pairs of stereoisomers (**5** and **6**) used as models for conformers (**7E** and **7A**)

	$\delta\Delta G°$/cal mole^{-1}			
	R = t-Bu		R = *cis*-3,5-Me_2	
Substituent X	Silicone oil	XE 60	Silicone oil	XE 60
Me	−84	−102	−150	−161
CN	+135	+250		
OH	54	198		+125
OMe	220	339	+155	300
NMe_2	380	590		

*A positive value implies that X is more solvated when equatorial

dimethylamino group shows the *largest* sensitivity to solvation. The results for cyano ($\delta\Delta G^\circ$ = 0·250 kcal. mole^{-1} in XE 60), given that $\Delta G^\circ_{e\to a}$ = 0·15 kcal/mole^{-1}, for **7** (X = CN) in t-butyl alcohol,[7] implies that the axial cyano is the preferred conformation in the gas phase, a unique result for a cyclohexane derivative at present.

A point of general interest concerns the possible errors caused by the locking groups in model compounds. Eliel has found a small difference between *cis*-3,5-dimethyl- ($\Delta G^\circ_{e\to a}$ = 0·89 kcal/mole^{-1}) and 4-t-butyl- ($\Delta G^\circ_{e\to a}$ = 0·94 kcal/mole^{-1}) cyclohexanols as models for the conformers of cyclohexanol.[37] This small difference has been attributed to distortion of the ring by the locking groups. We find, however, that there are fairly consistent differences (40 to 70 cal/mole^{-1}) in solvation associated with these locking groups and that the difference found by Eliel is probably general and *can be entirely attributed to solvation effects.*

REFERENCES

[1]W. D. Cotterill and M. J. T. Robinson, *Tetrahedron* **20**, 765 (1964)
[2]W. D. Cotterill and M. J. T. Robinson, *Ibid.* **20**, 776 (1964)
[3]W. Klyne, *Experientia* **12**, 119 (1956)
[4]R. J. Armitage, G. W. Kenner and M. J. T. Robinson, *Tetrahedron* **20**, 723, 747 (1964)
[5]M. J. T. Robinson, *Pure Appl. Chem.* **25**, 635 (1971)
[6]E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis* pp. 71 *et seq.* Interscience, New York (1965)
[7]Data for cyclohexane derivatives have been summarised by, e.g., J. A. Hirsch, *Topics in Stereochemistry* Vol. 1, p. 199. Interscience, New York (1967)
[8]See also E. L. Eliel and M. C. Reese, *J. Am. Chem. Soc.* **90**, 1560 (1968)
[9]F. G. Riddell and M. J. T. Robinson, *Tetrahedron* **23**, 3417 (1967)
[10]E. L. Eliel and M. C. Knoeber, *J. Am. Chem. Soc.* **90**, 3444 (1968)
[11]N. L. Allinger and Blatter, *Ibid.* **83**, 994 (1963)
[12]B. Rickborn, *Ibid.* **84**, 2414 (1962)
[13]R. J. Abraham and J. A. Pople, *Mol. Phys.* **3**, 609 (1960)
[14]W. D. Cotterill and M. J. T. Robinson, *Tetrahedron Letters* 1833 (1963)
[15]F. G. Riddell and M. J. T. Robinson, *Tetrahedron* **27**, 4163 (1971)
[16]G. J. Karabatsos and N. Hsi, *Ibid.* **23**, 1079, 1089 (1967)
[17]M. J. T. Robinson, unpublished observations
[18]M. J. T. Robinson, *Chem. Ind.* 932 (1964)
[19]P. A. Levene and A. Rothen, *J. Chem. Phys.* **4**, 48 (1936)
[20]R. J. Abraham, personal communication
[21]K. H. Wellman, E. Bunnenberg and C. Djerassi, *J. Am. Chem. Soc.* **85**, 1870 (1963)
[22]See, e.g., D. R. Elliott, F. G. Riddell and M. J. T. Robinson, *Tetrahedron Letters* 1693 (1965); C. Djerassi, J. W. Chamberlain, D. Elad, T. Toda, G. Stork, *J. Am. Chem. Soc.* **86**, 465 (1964)
[23]F. G. Riddell and M. J. T. Robinson, *Chem. Comm.* 227 (1965)
[24]H. O. House and H. W. Thompson, *J. Org. Chem.* **28**, 164 (1963)
[25]A. P. Foster, M. J. T. Robinson and W. P. Russel, unpublished observations
[26]K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.* **83**, 4623 (1961)
[27]P. Chamberlain and W. H. Whitham, *J. Chem. Soc. Perkin II* 130 (1972)
[28]H. Booth, *Chem. Comm.* 802 (1968)
[29]J. McKenna and J. M. McKenna, *J. Chem. Soc.* (B)644 (1969)
[30]H. Booth and J. H. Little, *J. Chem. Soc. Perkin II* 1846 (1972)
[31]P. J. Crowley, M. J. T. Robinson and M. G. Ward, unpublished observations
[32]R. A. Y. Jones, A. R. Katritzky, A. C. Richards and R. J. Wyatt, *J. Chem. Soc.* (B) 122 (1970)
[33]Cantecuzene and J. Leroy, *J. Am. Chem. Soc.* **93**, 5263 (1971)
[34]See, e.g., J. R. Conder, D. C. Locke and J. H. Purnell, *J. Chem. Phys.* **73**, 700 (1969)
[35]D. J. Bryant, M. H. Gordon, M. J. T. Robinson and P. J. Smart, unpublished observations
[36]R. D. Stolow and T. W. Giants, *Chem. Comm.* 528 (1971)
[37]E. L. Eliel and S. H. Schroeter, *J. Am. Chem. Soc.* **87**, 5031 (1965)