CONFORMATIONAL EFFECTS IN COMPOUNDS WITH SIX-MEMBERED RINGS—II

CONFORMATIONAL EQUILIBRIA IN MONOSUBSTITUTED AND CIS-1,3-DISUBSTITUTED CYCLOHEXANES

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Abstract—Conformational equilibria in methyl-, ethyl-, isopropyl-, methoxycarbonyl-, and carboxy-cyclohexane and several *cis*-1,3-di-substituted cyclohexanes, and the chair-boat equilibrium in cylco-hexane itself, have been studied quantitatively by determining equilibrium constants, by indirect as well as direct methods, for model chemical reactions, namely the epimerization of derivatives of 5-alkylcyclohexane-1,3-dicarboxylic acids. The conformational equilibria in cyclohexanecarboxylic acid and its esters are very similar, contrary to previous estimates, and it is unnecessary to assume a large effect for the difference in solvation of the acid and its esters. *trans*-5-t-Alkylcyclohexane-*cis*-1,3-dicarboxylic acids and *cis*-3-amino-*trans*-5-isopropylcyclohexane-*cis*-1-carboxylic acid change conformation during ionization.

THE stereoisomers of 5-alkylcyclohexane-1,3-dicarboxylic acids and their derivatives, which we have prepared,[1] are suitable material for studies of certain conformational equilibria. In the following discussion, the free energy, enthalpy, and entropy differences for conformational changes in both monosubstituted cyclohexanes (I; $X \neq Y = H$) and *cis*-1,3-disubstituted cyclohexanes (I; $X, Y \neq H$) will be symbolized by $\Delta F_{(e \to a)}$ (I), etc. For several reasons this seems preferable, for our purposes, to the use of "A_X value"[2] or "conformational free energy, ΔF_X"[3] for the substituent X $[A_X = \Delta F_X = -\Delta F_{(e \to a)}$ (I; $X \neq Y = H$)], and to the use of "X"[2] or "Z"[4] values for the repulsion between substituents X and Y in (I; $X, Y \neq H$). The term "A value (or conformational energy) of the group X" is a convenient tool, but it implies incorrectly that it is an inherent property of the group X and this concept can easily lead to mistaken conclusions about multi-substituted cyclohexanes (cf. later discussion concerning the isopropyl group). Furthermore, in subsequent papers of this series we require symbolism for derivatives of cyclohexanone and heterocyclic systems. The value of "X" (or "Z") can only be derived from observable free energy differences by assuming that the diaxial repulsions between the group X or Y and the nearby axial hydrogen atom are the same as in the monosubstituted cyclohexanes with axial X or axial Y. This assumption may be seriously wrong if the repulsion between X and Y is large or if X or Y is an unsymmetrical group, and there does not seem to be a clearly satisfactory way of testing its validity.

Equilibria between the esters (IIb, c, or d; IIIb, c, or d; and IVb, c, or d) can be determined directly by epimerization in the appropriate alcohols under relatively mild conditions. These quantitative results, together with qualitative evidence for the preferred conformations in doubtful cases, can be used to calculate the conformational

[1] B. J. Armitage, G. W. Kenner and M. J. T. Robinson, Part I *Tetrahedron* **20**, 723 (1964).
[2] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.* **77**, 5562 (1955).
[3] E. L. Eliel and R. G. Haber, *J. Amer. Chem. Soc.* **81**, 1249 (1959).
[4] D. S. Noyce and L. J. Dolby, *J. Org. Chem.* **26**, 3619 (1961).

equilibria in methyl-, ethyl-, isopropyl-, methoxy- and isopropoxy-carbonyl, and *cis*-1,3-dimethoxycarbonyl-cyclohexane if it is assumed that there are no interactions in the esters to invalidate them as models. The absence of significant differences in the acid dissociation constants of the acids (IIa and IVa; R ≠ t-Alkyl; Table 9) is sufficient to establish that inductive effects of the alkyl groups are less than ±0·1 kcal mole⁻¹ for the ionization of the acids and interactions between alkyl and ester groups seem certain to be smaller. It should be noted, however, that there are small differences in the ratios of apparent retention times for esters of the acids (IIa and IVa) for different O-alkyl groups. For example, the ratio of apparent retention times for esters of the acids (IVa; R = Me and IIa; R = Me) falls from 1·38/1·40 through 1·82/1·87 to 2·51/2·68 for methyl, ethyl and isopropyl esters. Since the ratio of apparent retention times is equal to the ratio of partition coefficients (for the distribution of the esters between gas and stationary phase) which in turn is equal to the ratio of the equilibrium constants (for the epimerization in the gas and in the stationary phase), it is apparent that the effect of solvation by the stationary phase, and presumably by other solvents, on the epimerization equilibrium is not the same for the various sets of O-alkyl esters. Although this implies that the various sets of stereoisomeric esters with the same 5-alkyl substituent cannot all be *exact* models for the conformations of the alkylcyclohexane the resulting systematic errors are small compared with random experimental errors.

Carboxylic acids and their anions may be epimerized directly, but only under conditions which are not even remotely near the range of conditions we wished to study. Esterification–hydrolysis equilibria, however, can be established in aqueous alcoholic solvents which are hardly different in character from the alcohols suitable for epimerizing esters, while acid dissociation constants measure the equilibria between acids and their anions. Combination of data for the epimerization of esters with esterification equilibrium and acid dissociation constants gives, indirectly, free energy differences for epimerization of carboxylic acids and anions. Although solvation effects are undoubtedly important for anions we believe that differential solvent effects in hydrolyxic solvents will be small for esters and acids and that the variations in solvents used in this work are not important. This tenet is contrary to the tentative explanation, which we shall show to be unecessary, given for the supposed large difference between the conformational equilibria in cyclohexanecarboxylic acid and its esters,[5] but it is supported by the direct comparison of carboxyl and ester groups reported later in this paper.

EXPERIMENTAL

PMR spectra were measured for solutions in deuterochloroform at 60 Mc. on a Varian A-60 spectrometer. Acid dissociation constants were determined in 50% and 78·5% aqueous 2-methoxy-ethanol by a procedure based on Simon's method.[6]

Epimerization equilibria. Samples (ca. 2–3 ml) of a 1% solution of an ester in the appropriate dry alcoholic 0·2 M sodium alkoxide, sealed in ampules, were heated in vapour baths (56° to 140°) for 1–14 days. The ampules were either crushed in acetic or benzoic acid at the vapour bath temp or chilled in ice and then crushed in acetic acid. The mixtures of esters were isolated (extraction with CCl₄) and the solutions were washed, dried, concentrated, and analysed by gas chromatography. Each equilibrium was approached from both extremes to give identical mixtures of esters without detectable hydrolysis.

⁵ E. L. Eliel, H. Haubenstock and R. V. Acharya, *J. Amer. Chem. Soc.* **83**, 2351 (1961).
⁶ W. Simon, *Helv. Chim Acta* **41**, 1835 (1958).

Esterification equilibria. Samples (ca. 2–3 ml) of a 2% solution of an acid (IIa, IIIa, or IVa; R = t-Bu) in aqueous methanol (1:1 by volume) containing 1% H_2SO_4, sealed in ampules, were heated at 78° for 7 days. Runs for 14 days confirmed that equilibrium had been reached. Each tube was crushed (in sat. Na_2HPO_4 aq.; 10 ml), and the mixture was acidified (pH = 4) and extracted with ether. The extracts were treated with a small excess of diazoethane, concentrated under red. press., diluted CCl_4, dried (Na_2SO_4) and analysed by gas chromatography.

Gas chromatography of esters. Dilute solutions (1–5%, 0·5–5 µl) of mixtures of esters in "AnalaR" CCl_4 were analysed in vapour jacketed (at 132°) columns (0·4 × 175 cm) packed with celite (G-CEL, Gas Chromatography Ltd., 80–100 mesh, acid and alkali washed, and treated with hexamethyl-disilazine) coated with mannitol hexa-2-cyanoethyl ether (1–1·5%).[7] The argon ionization detector and amplifier were supplied by Gas Chromatography Ltd. Each mixture was analysed at least 5 times.

The retention times of the esters of all the *cis*-dicarboxylic acids and of the esters of the *trans* diacids (IIIa; R = H) and (IIIa; R = t-Bu) were obtained using authentic samples. The esters of the remaining *trans* acids were assumed to be the third component in each epimerization mixture (Tables 1 and 2). The gas chromatographic detector was found to be equally sensitive to stereoisomeric esters where these were available pure and this was assumed to hold for all sets of stereoisomers. Because reproducible analyses could not be obtained for mixtures of esters of the acids with a 5-(1,1-diethyl-propyl) substituent, quantitative study of their epimerization equilibria was not possible.

TABLE 1. RELATIVE APPARENT RETENTION TIMES[a] OF ESTERS OF 5-ALKYLCYCLOHEXANE-1,3-DICARBOXYLIC ACIDS ON MANNITOL HEXA-(2-CYANOETHYL) ETHER AT 132° (161°)

5-Alkyl group	Acid		
	IIa	IIIa	IVa
Methyl esters:			
H	1·37	1·00	
Me	1·40	1·09	1·38
Et	2·76	1·84	2·60
i-Pr	2·82	1·90	2·33
t-Bu	3·36	2·27	1·98
	(2·59)	(1·82)	(1·68)
CMe₂Et	5·40	3·58	2·95
Ethyl esters:			
Me	1·87	1·29	1·82
t-Bu	4·65	3·45	2·68
Isopropyl esters:			
Me	2·68	1·81	2·51
Et	4·14	2·77	3·74
i-Pr	5·50	3·80	4·48

[a] Relative to the ester (IIIb; R = H) = 1·00 at 132°, or at 161° for relative apparent retention times given in brackets.

TABLE 2. RELATIVE APPARENT RETENTION TIMES[a] OF DIMETHYL 5-T-BUTYLCYCLOHEXANE-1,3-DICARBOXYLATES ON SUCROSE ACETATE ISOBUTYRATE

Temperature (°C)	Relative apparent retention times		
	IIb	IIIb	IVb
132	1·00	0·61	0·50
158	1·00	0·68	0·61
187	1·00	0·73	0·69
208	1·00	0·75	0·75

[a] Apparent retention time of the ester IIb taken as 1·00 at each temp.

[7] H. A. Bruson, U.S.P. 2,401,607 (1946); *Chem. Abstr.* 41, 5450² (1946).

Table 3. Relative apparent retention times[a] of dimethyl, methyl ethyl, and diethyl esters of 5-t-butycylclohexane-1,3-dicarboxyclic acids on mannitol hexa(2-cyanoethyl) ether at 132°

Ester	Acid		
	IIa; R = t-Bu	IIIa; R = t-Bu	IVa; R = t-Bu
b-Dimethyl	3·36	2·27	1·98
g-Methyl ethyl	3·83	2·60	2·20
i-Methyl ethyl		2·70	
c-Diethyl	4·65	3·45	2·68

[a] Relative to the ester (IIIb; R = H) = 1·00.

Table 4. Percentage compositions and equilibrium constants for the epimerization of methyl and isopropyl esters of 5-alkylclohexane-1,3-dicarboxylic acids

5-Alkyl group	T(°C)[a]	Acid IIa	IIIa	IVa	K_1[b]	K_2[c]
		Methyl esters in methanol:				
H	63	75·4%	24·6%		3·07	
	78	74·2	25·8		2·89	
	110	71·8	28·2		2·52	
	139	69·7	30·3		2·30	
i-Pr	78	72·1	25·7	2·2%	2·80	32·8
	110	69·2	27·8	3·0	2·49	23·2
	148	66·3	30·0	3·7	2·20	17·9
t-Bu	56	75·5	24·2	0·29	3·13	260
	78	73·4	26·2	0·39	2·83	188
	100	72·0	27·5	0·52	2·61	139
	110	71·3	28·1	0·62	2·53	116
	139	69·0	30·2	0·81	2·29	85·2
CMe₂Et	63	71·4	28·2	0·40	2·53	178
	110	67·6	31·6	0·83	2·14	81·4
	139	65·6	33·3	1·10	1·97	59·6
		Isopropyl esters in isopropyl alcohol:				
Me	56	65·1	29·9	5·0	2·18	13·1
	78	62·7	31·6	5·7	1·97	11·1
	132	57·9	35·1	7·0	1·65·	8·2
Et	56	66·9	29·2	3·9	2·30	17·2
	78	64·7	30·8	4·5	2·10	14·5
	132	60·0	34·4	5·6	1·73	10·7
i-Pr	56	63·5	34·0	2·5	1·88	25·6
	78	61·2	35·6	3·2	1·72	19·4
	132	56·1	39·5	4·4	1·42	12·7

[a] Bath temperature, $\pm 1°$.

[b] Equilibrium constant for the reaction (IIIb) → (IIb) (methyl esters) or (IIId) → (IId) (isopropyl esters).

[c] Equilibrium constant for the reaction (IVb) → (IIb) (methyl esters) or (IVd) → (IId) (isopropyl esters).

TABLE 5. ENTHALPY AND ENTROPY DIFFERENCES FOR THE EPIMERISATION OF ESTERS OF
5-ALKYLCYCLOHEXANE-1,3-DICARBOXYLIC ACIDS

5-Alkyl group	II → III		II → IV	
	ΔH (kcal mole^{-1})	ΔS (cal. deg.$^{-1}$ mole^{-1})	ΔH (kcal mole^{-1})	ΔS (cal. deg.$^{-1}$ mole^{-1})
	Methyl esters:			
H	$+1\cdot06 \pm 0\cdot06$	$-0\cdot95 \pm 0\cdot3$		
i-Pr	$+1\cdot02 \pm 0\cdot06$	$+0\cdot9 \pm 0\cdot3$	$+2\cdot6 \pm 0\cdot2$	$-0\cdot4 \pm 0\cdot3$
t-Bu	$+1\cdot01 \pm 0\cdot04$	$+0\cdot8 \pm 0\cdot2$	$+3\cdot6 \pm 0\cdot3$	$-0\cdot2 + 0\cdot6$
CMe$_2$Et	$+0\cdot91 \pm 0\cdot12$	$+0\cdot8 \pm 0\cdot4$	$+4\cdot0 \pm 0\cdot7$	$+1\cdot5 \pm 1\cdot2$
	Isopropyl esters:			
Me	$+0\cdot99 \pm 0\cdot06$	$-1\cdot4 \pm 0\cdot2$	$+1\cdot60 \pm 0\cdot16$	$-0\cdot3 \pm 0\cdot5$
Et	$+0\cdot99 \pm 0\cdot06$	$+1\cdot4 \pm 0\cdot3$	$+1\cdot65 \pm 0\cdot15$	$-0\cdot7 \pm 0\cdot4$
i-Pr	$+0\cdot99 \pm 0\cdot06$	$+1\cdot8 \pm 0\cdot4$	$+2\cdot4 + 0\cdot3$	$-0\cdot1 \pm 0\cdot7$

TABLE 6. ESTERIFICATION EQUILIBRIA COMPOSITIONS AND EQUILIBRIUM CONSTANTS FOR THE
ESTERIFICATION OF 5-t-BUTYLCYCLOHEXANE-1,3-DICARBOXYLIC ACIDS IN 50% AQUEOUS
METHANOL AT 78°.

Type of ester[a]	Parent acid		
	IIa; R = t-Bu	IIIa; R = t-Bu	IVa; R = t-Bu
b-Dimethyl	57·8%	60·2	51·2
g + i-Methyl ethyl	36·9	34·7	41·5
g		18·1[b]	
i		16·6[b]	
c-Diethyl	5·3	7·3	5·1
Equilibrium constants:[c]			
First carboxyl group	$3\cdot5 \pm 0\cdot2(K_E)$	$3\cdot25(K_E$ assumed) $3\cdot55 \pm 0\cdot1(K_A)$	$2\cdot8 \pm 0\cdot1(K_A')$
Second carboxyl group	$3\cdot14 \pm 0\cdot05(K_E)$	$3\cdot3 \pm 0\cdot1(K_E)$ $3\cdot65 \pm 0\cdot1(K_A)$	$2\cdot47 \pm 0\cdot04(K_A')$

[a] Diethyl ester results from dicarboxylic acid and methyl ethyl ester results from monomethyl ester in the equilibrium mixture.

[b] Calculated assuming $K_E = 3\cdot25$ for an equatorial carboxyl group.

[c] K_E, K_A, and K_A' are the relative esterification equilibrium constants for equatorial, unhindered axial, and hindered axial carboxyl groups (see text).

RESULTS AND DISCUSSION

Alkyl groups

The results from epimerization of esters of the acids (IIa, IIIa and IVa) are given in Table 5, and the derived enthalpy and entropy differences for conformational equilibria in mono-substituted cyclohexanes are given in Table 7. The calculations were based on the following principles. Only the conformation (V), having all the substituents equatorial, need be considered for the esters (IIb and IId), so that these provide a good model for alkylcyclohexanes with the alkyl group equatorial. On the other hand, the esters (IVb and IVd) have three conformations (VII, VIII, IX) which may be of comparable stability and only one, (VIII), has the alkyl group axial. In

Table 7. Conformational equilibria in monosubstituted derivatives of cyclohexane

Substituent	$\Delta F_{(e \to a)}{}^a$ kcal mole^{-1}	$\Delta H_{(e \to a)}$ kcal mole^{-1}	$\Delta S_{(e \to a)}$ cal. deg.$^{-1}$ mole^{-1}	Ref.
Me	1·6 (calc)			8
	1·8 (calc)			9
	1·5 (100°)			4
	1·5			10
	1·74			11
	1·60			11
	1·87			12
	1·6$_7$	1·6$_0$	−0·2$_5$	This paper
Et	1·80			12
	1·74			11
	1·77			11
	1·9	1·8	−0·4	13
	1·86 (calc)^b	1·71 (calc)^b	−0·51 (calc)^b	13
	1·8$_6$	1·6$_5$	−0·7	This paper
i-Pr	3·3			2
	3·5 (100°)			4
	2·12			12
	2·6$_2$	2·5	−0·4	This paper^c
	2·4$_3$	2·4	−0·1	This paper^d
	1·87 (calc)^b	1·51 (calc)^b	−1·2 (calc)^b	This paper
CO$_2$Me	1·05			14
	1·1$_5$	1·0$_0$	−0·5	This paper
CO$_2$Et	1·24 (100°)			12
	1·0 − 1·2			5
	1·05			14
	1·1			15
CO$_2$i-Pr	0·9$_8$	0·9$_9$	+0·1	This paper
CO$_2$H	1·6			16
	1·6 − 1·9			17
	1·95 (195°)			18
	1·2$_0$ (78°)			This paper
CO$_2{}^-$	2·4			17
	2·2			16
	1·9			This paper

^{a} At 25° unless otherwise stated.

^{b} Calculated assuming 0·9 kcal mole^{-1} for each skew interaction so that for methylcyclohexane $\Delta F_{(e \to a)} = \Delta H_{(e \to a)} = 1·8$ kcal mole^{-1}, $\Delta S_{(e \to a)} = 0$ (see text).

^{c} From experiments with methyl esters.

^{d} From experiments with isopropyl esters.

[8] W. G. Dauben and K. S. Pitzer, *Steric Effects in Organic Chemistry* (Edited by M. S. Newman) Wiley, New York (1956).

[9] C. W. Beckett, K. S. Pitzer and R. Spitzer, *J. Amer. Chem. Soc.* **69**, 2488 (1947).

[10] E. L. Eliel and M. N. Rerick, *J. Amer. Chem. Soc.* **82**, 1367 (1960).

[11] A. H. Lewin and S. Winstein, *J. Amer. Chem. Soc.* **84**, 2464 (1962).

[12] N. L. Allinger, L. A. Freiberg and S-E. Hu, *J. Amer. Chem. Soc.* **84**, 2836 (1962).

[13] N. L. Allinger and S-E. Hu, *J. Amer. Chem. Soc.* **84**, 370 (1962).

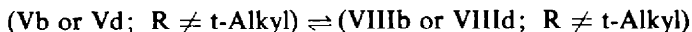[14] N. L. Allinger and R. J. Curby, *J. Org. Chem.* **26**, 933 (1961).

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

[16] M. Tichý, J. Jonáš and J. Sicher, *Coll. Czech. Chem. Comm.* **24**, 3434 (1959).

[17] R. D. Stolow, *J. Amer. Chem. Soc.* **81**, 5806 (1959).

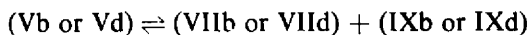[18] H. E. Zimmerman and H. J. Giallombardo, *J. Amer. Chem. Soc.* **78**, 6259 (1956).

order to isolate the equilibrium

$$(Vb \text{ or } Vd; \; R \neq t\text{-Alkyl}) \rightleftharpoons (VIIIb \text{ or } VIIId; \; R \neq t\text{-Alkyl})$$

which is the model for an alkylcyclohexane, it is necessary to make a correction for that part of the esters (IVb or IVd; $R \neq t$-Alkyl) existing in conformations VII and IX. This has been done by supposing that conformation VIII may be neglected when R is a t-alkyl group so that the equilibrium

$$(IIb; \; R = t\text{-Bu}) \rightleftharpoons (IVb; \; R = t\text{-Bu})$$
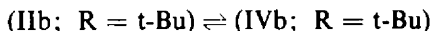
is a satisfactory model for the equilibrium

$$(Vb \text{ or } Vd) \rightleftharpoons (VIIb \text{ or } VIId) + (IXb \text{ or } IXd)$$

when R is not a t-alkyl group. The resulting correction is small even for the isopropyl group.

The entropy and enthalpy differences for the conformational equilibria in methyl-, ethyl-, and isopropyl-cyclohexane are in general agreement with other recently published values, collected in Table 7. Most of the newer values of $\Delta F_{(e \rightarrow a)}$ (isopropyl-cyclohexane) are much lower than Winstein and Holness[2] early measurement, which has since been corrected, but two observations have been interpreted as evidence for a high value. Cole and Jefferies[19] concluded from its hydroxyl group stretching frequency that neoisomenthol must be predominantly in the conformations (X; $R_1 = OH$, $R_2 = Me$) with the hydroxyl group axial and therefore with the isopropyl group equatorial. This was supposed to imply that $\Delta F_{(e \rightarrow a)}$ (isopropylcyclohexane) is greater than $\Delta F_{(e \rightarrow a)}$ (*cis*-3-methyl-cyclohexanol) $\simeq 3 \cdot 5$ kcal mole^{-1}. Noyce and Dolby[4] compared the free energy changes for the lactonisation of *cis*-3-hydroxycyclohexanecarboxylic acid and its *cis*-4-isopropyl derivative, assuming that the lactonisation was accompanied by a change of conformation of the acid, e.g. from $XI(R_1 = OH, R_2 = CO_2H)$ to $X(R_1 = OH, R_2 = CO_2H)$. Both groups of authors assumed that the repulsion between the *cis* hydroxyl (or lactone oxygen atom) and isopropyl groups is the same in the two sets of chair conformations* (XI and XII) because the distance between the atoms directly attached to the ring is unchanged, but this assumption is mistaken. When the isopropyl group is equatorial, it can adopt an orientation, as in conformation (Xa; $R_1 = OH$, $R_2 = Me$), in which there is only a weak skew interaction between the hydroxyl (or lactone oxygen atom) and methyl groups of the isopropyl substituent [cf. the large interaction in $Xb(R_1 = OH, R_2 = Me)$]. When the isopropyl group is axial, however, it can not adopt an orientation with one of the methyl groups turned into the ring, since this would be nearly as bad as an axial t-butyl group, and the only other orientation, e.g. as in the conformation (XIa; $R_1 = OH$, $R_2 = Me$), involves a repulsion between the hydroxyl and methyl groups comparable with the *cis*-1,3-diaxial interaction between the methyl and hydroxyl groups in $X(R_1 = OH, R_2 = Me)$. It is obvious, therefore, that although the atoms of the vicinal groups directly attached to the ring
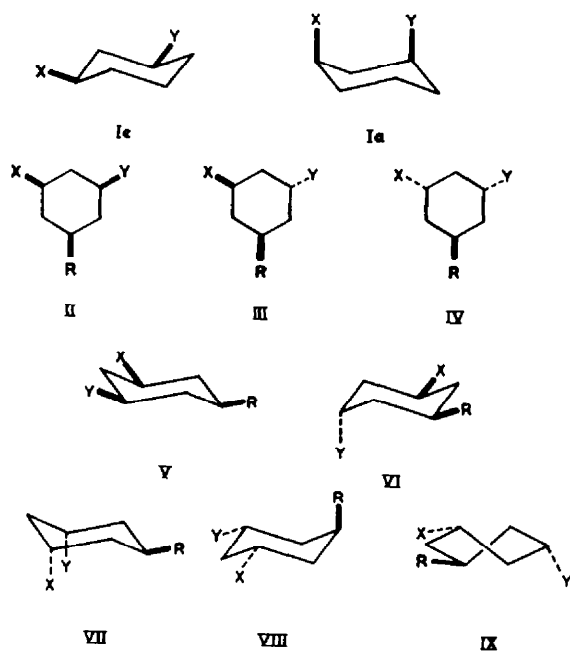
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* There appears to be no collective noun for a number of conformations, less than the total possible for a given compound, but the increasing interest in alkyl groups such as ethyl and isopropyl which can adopt more than one orientation makes such a term necessary and 'set of conformations' is suggested; Hendrickson[20] has already used set in a similar sense.

[19] A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.* 4391 (1956); A. R. H. Cole, P. R. Jefferies and G. T. A. Müller, *Ibid.* 1222 (1959).
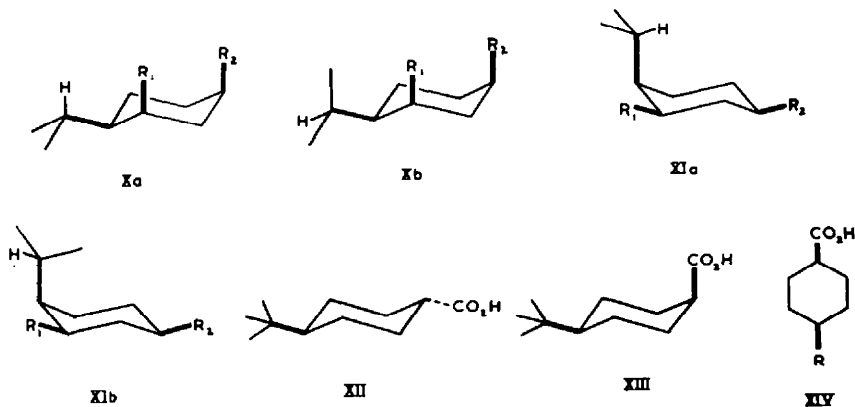
[20] J. B. Hendrickson, *J. Amer. Chem. Soc.* **83**, 4537 (1961).

are, at least approximately, the same distance apart in the sets of conformations (X; R_1 = OH, R_2 = Me and XI; R_1 = OH, R_2 = Me) the repulsion between the two vicinal groups will be very different in the most stable conformation of each set. Similar arguments apply to the lactonization of the acid (XI; R_1 = OH, R_2 = CO_2H). The error introduced by the assumption discussed above is some $1 - 2$ kcal mole^{-1}.

A point of general importance in conformational analysis arises from a comparison of the experimental results for alkylcyclohexanes in Table 7 with the values

a; X = Y = CO_2H
b; X = Y = CO_2Me
c; X = Y = CO_2Et
d; X = Y = CO_2iPr
e; X = Y = CO_2^-
f; X = CO_2H, Y = CO_2Me
g; X = CO_2Et, Y = CO_2Me
h; X = CO_2Me, Y = CO_2H

i; X = CO_2Me, Y = CO_2Et
j; X = $\overset{+}{N}H_3$, Y = CO_2^-
k; X = $\overset{+}{N}H_3$, Y = CO_2H
l; X = Y = NH_2
m; X = Y = $\overset{+}{N}H_3$

calculated using assumptions commonly made when considering the relative stabilites of the conformations of alkyl derivatives of cyclohexane. This has already been done for methyl- and ethyl-cyclohexane,[13] using 0·9 kcal mole^{-1} for the value for a 'skew butane' interaction and assuming that different conformations have the same entropy, and we have carried out the calculation for isopropylcyclohexane. Ethyl and isopropyl groups, unlike methyl, have three distinguishable staggered arrangements for both axial and equatorial groups, with differing enthalpies and consequently differing populations from which the weighted averages for the axial and equatorial sets of conformations may be calculated. The assumption that the enthalpies of the various conformations of an alkylcyclohexane may be obtained by adding up the appropriate number of supposedly identical interactions leads unambiguously to the prediction that $\Delta H_{(e \to a)}$ for alkylcyclohexanes, but not the free energy differences, will decrease in the order methyl > ethyl > isopropyl; qualitatively this result does not depend on the value assumed for a "skew butane" interaction, nor on the assumption that the various conformations have the same entropy, within wide limits. The experimental values are not sufficiently accurate to show with certainty the difference predicted for methyl- and ethyl-cyclohexane, so that good agreement may be claimed,[13] but the results for isopropylcyclohexane are about 50–60 % higher than the calculated value. This large discrepancy contrasts sharply with the satisfactory agreement between experimental and calculated enthalpy differences for isomeric dimethylcyclohexanes and for *cis*- and *trans*-decalin but it is not an isolated example of the failure of such simple calculations. For example, the three conformations of 2,3-dimethylbutane are equally stable[21] although the two gauche conformations have three skew butane interactions and the meso conformation has only two. We will defer further discussion of this problem until we have more accurate data about the differences in the conformational equilibria in alkylcyclohexanes.

Carboxylic acid and ester groups

The epimerization equilibria for esters of the acids (IIa and IIIa) are concordant for each alkoxycarbonyl group and give almost identical values of $\Delta H_{(e \to a)}$ for the methyl and isopropyl esters of cyclohexanecarboxylic acid. The agreement with published results for the ethyl ester is good (Table 7). The ratios of apparent retention times shows that solvation effects also are similar for the various esters. These results imply that the methoxy and isopropoxy groups are far enough away from the ring not to interact with it, as would be expected from the known preferred arrangement of the atoms in an ester group, and provide additional circumstantial evidence that the interactions between alkyl and ester groups are unimportant in these cyclohexane derivatives. Since an alkoxycarbonyl group is far from being axially symmetrical it must be appreciably more restricted in rotation when it is axial than when it is equatorial in order to minimise repulsion between the oxygen atoms and the nearby axial hydrogen atoms. This may explain the small unfavourable entropy difference of about 0·5 cal. deg.$^{-1}$ mole^{-1} for methyl cyclohexanecarboxylate, although no effect is apparent for the isopropyl ester.

The absence of a significant difference between the values of $\Delta H_{(e \to a)}$ for different esters of cyclohexanecarboxylic acid did not appear to be consistent with the relatively large reported difference between the values of $\Delta F_{(e \to a)}$ for the acid and for its esters

[21] J. K. Brown and N. Sheppard, *J. Chem. Phys.* **19**, 976 (1951).

(Table 7).   Hitherto all but one of the determinations of $\Delta F_{(e \to a)}$ for the acid have been made by comparing the dissociation constants of conformationally homogenous acids, e.g. XII and XIII, and inhomogeneous acids, e.g. XIV.   If it is assumed that 4-alkyl substituents exert no inductive effect so that acids such as XII and XIII are exact models for the conformations of the acid (XIV), then

$$\Delta F_{(e \to a)} \text{ (XIV; } R = H) - \Delta F_{(e \to a)} \text{ (R-cyclohexane)}$$
$$= -RT \ln (K_e - K)/(K - K_a)$$

where K is the dissociation constant of the acid (XV) and K_e and K_a are the dissociation constants of the acids (XIII and XIV).   The method fails for cyclohexanecarboxylic acid itself[17] because K and K_e are almost identical but it has been applied to *cis*-4-methylcyclohexanecarboxylic acid (XIV; $R = Me$) directly[16] and in a modified form.[17]   The results are very sensitive to experimental errors and to systematic errors arising from any imperfection in the acids (XII and XIII) as models for the conformations of XIV.   The only other reported determination of $\Delta F_{(e \to a)}$ (cyclohexane-carboxylic acid) is due to Zimmerman and Giallombardo[18] who found a free energy difference $+1.95$ kcal mole^{-1} for the epimerization of 4-phenylcyclohexanecarboxylic acid at 195° with no solvent.   Because this was done incidentally to other work the result may be less accurate than is implied by the error (± 0.3 kcal mole^{-1}) which we have calculated from the accuracy claimed for the analytical method used, and in any case the conditions are very different from all the other experiments.   Eliel *et al.*[5] have suggested that the difference in $\Delta F_{(e \to a)}$ between cyclohexanecarboxylic acid and its esters, if it is real, might be explained by steric hindrance to the solvation of axial groups if a carboxylic acid is more strongly solvated than its esters.   Qualitatively both ideas are reasonable but quantitatively the result would be expected to be small. The difference in $\Delta F_{(e \to a)}$ between cyclohexanecarboxylic acid and its anion is only 0.7 kcal mole^{-1}.[16,17]   (in 80% 2-methoxyethanol) and the difference would between the acid and its esters be expected to be much smaller, perhaps only 0.1 kcal mole^{-1}. In order to measure such a small difference with certainty it was desirable to compare carboxylic acids and their esters directly rather than to attempt to determine the separate values of $\Delta F_{(e \to a)}$ with sufficient accuracy.   For this purpose esterification-hydrolysis equilibria were measured for acids with conformationally fixed carboxyl groups.

Using the acids (IIa; $R = $ t-Bu, IIIa; $R = $ t-Bu and IVa; $R = $ t-Bu) we have measured the following series of equilibria in aqueous methanol:
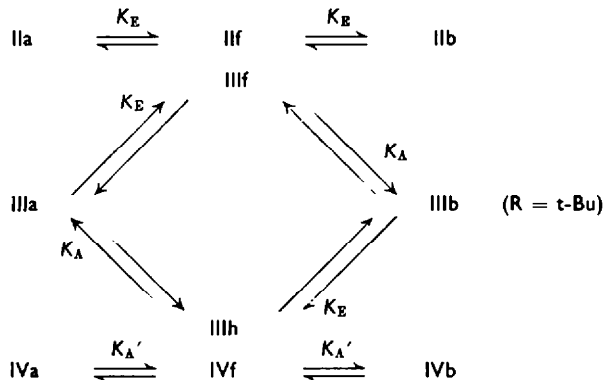
The equilibrium mixtures of acids and mono- and di-methyl esters were quantitatively esterified with diazoethane and the resulting mixtures of dimethyl, methyl ethyl, and diethyl esters were analysed by gas chromatography. Because water and methanol were present in large excess the esterification equilibrium constant for each acid is proportional to the ratio [methyl ester]/[ethyl ester], which may be called the relative equilibrium constant K_E, K_A or K'_A depending on whether the carboxyl group is equatorial, axial, or hindered and axial. The methyl ethyl esters (IIIg; R = t-Bu and IIIi; R = t-Bu) could not be separated by gas chromatography but since

$$([IIIg] + [IIIi])/[IIIc] = ([IIIf] - [IIIh])/[IIIa] \ (R = t\text{-}Bu)$$

$$= K_E + K_A$$

and

$$[IIIb]/[IIIc] = [IIIb]/[IIIa] \ (R = t\text{-}Bu)$$

$$= K_A K_E$$

K_A and K_E may be readily calculated. Alternatively an experimental value of K_E derived from the acid (IIa; R = t-Bu) may be assumed to hold for the equatorial carboxyl group in IIIa. Because the values of K_E agree well we are satisfied that K_A is sufficiently accurate. Because K_A and K_E are proportional to the true esterification equilibrium constants the difference in $\Delta F_{(e \to a)}$ for cyclohexanecarboxylic acid and its methyl ester is given by

$$\Delta F_{(e \to a)} (C_6H_{11}CO_2H) - \Delta F_{(e \to a)} (C_6H_{11}CO_2Me) = RT \ln K_A/K_E$$

$$= +0.05 \pm 0.02 \ \text{kcal mole}^{-1} \ \text{at} \ 78°.$$

Since esterification equilibria are very insensitive to change in temperature[22] it is very probable that this small free energy difference is appropriate at 25° and it seems certain that previous estimates of $\Delta F_{(e \to a)}$ for the acid were substantially in error and that there is no need to postulate large differences in the effects of solvation on the conformational equilibria in cyclohexanecarboxylic acid and its esters.

cis-1,3-Disubstituted cyclohexanes

Most of the free energy and enthalpy differences for conformational equilibria in cis-1,3-disubstituted cyclohexanes given in Table 8 depend on the measurements of epimerization equilibrium for the esters (IIb; R = t-Bu and IVb; R = t-Bu). The low concentration of the latter made accurate measurements relatively difficult so that the widest possible temperature range was used, the lower limit being set by the rate at which equilibrium was reached and the upper by the vapour pressure of methanol. Although the upper limit of temperature could have been raised by choice of a higher alcohol, the increased difficulty of analysing the mixtures of esters would have offset the advantages; such difficulties severely limit the accuracy possible even with the methyl esters of the homologous acids with a 5-(1,1-dimethylpropyl) group and quantitative analysis of the esters (IIb, IIIb, and IVb; R = CEt₃) has not been successful so far (Experimental). The interpretation of the results for the equilibrium (IIb; R = t-Bu) ⇌ (IVb; R = t-Bu) is much less straightforward than for the lower homologues because the ester (IVb; R = t-Bu) may exist in a boat conformation to an appreciable extent. That the chair conformation (VII) predominates in the ester

⁺² M. Berthelot and P. de St. Gilles, *Ann. Chim. Phys.* [3], **66**, 5 (1862).

(IVb; R = t-Bu) is suggested by its PMR spectrum. The axial protons α to equatorial ester groups in esters of the acids (IIa and IVa; R ≠ t-Alkyl) are not resolved from the other ring protons $(7 \cdot 6-9 \cdot 0\tau)$ but the ester (IIIb; R = t-Bu) shows a band due to one equatorial α-proton at $7 \cdot 17\tau$ (half width 7–8 c.p.s.), while the ester (IVb; R = t-Bu) shows a band due to two α-protons at $7 \cdot 35\tau$, the half-width of the band (8–9

TABLE 8. FREE ENERGY, ENTHALPY AND ENTROPY DIFFERENCES FOR CONFORMATIONAL
EQUILIBRIA IN cis-1,3-DISUBSTITUTED CYCLOHEXANES (Ie—Ia)

Substituents X, Y	$\Delta F_{298^\circ K}$ (kcal mole^{-1})	ΔH (kcal mole^{-1})	ΔS (cal. deg.$^{-1}$ mole^{-1})
2 CO_2Me	$3 \cdot 9^a$	$2 \cdot 9^a$	$-3 \cdot 4^a$
	$3 \cdot 8^b$	$3 \cdot 3^b$	$-1 \cdot 7^b$
	$3 \cdot 7^c$	$3 \cdot 5^c$	$-0 \cdot 9^c$
2 CO_2H	$3 \cdot 5^d$		
2 CO_2^-	$\sim 8^e$		
NH_3^+, CO_2^-	$2 \cdot 0$		
NH_3^+, CO_2H	$3 \cdot 6$		

^{a} 4·2, ^{b} 4·4, ^{c} 4·6 kcal mole^{-1} assumed for the free energy of the boat conformation of cyclohexane relative to the chair in order to allow for the conformational equilibrium in the ester (IVb; R = t-Bu) (See text). ^{d} Based on assumption b for the diester. ^{e} Based on the free energy difference for the diacid and on the observed pK_a values for the acid (IIa; R = t-Bu) and the calculated sum of the pK_a values for the acid (IVa; R = t-Bu) in the conformation (VIIa; R = t-Bu).

c.p.s.) being consistent with equatorial protons on a ring in a chair conformation. The small difference in chemical shift between the equatorial α-protons in the two esters may be due to the ester (IVb; R = t-Bu) existing partly in the boat conformation (IXb; R = t-Bu) or simply to a difference in the orientation of the axial ester groups. The predominance of the conformation (VIIb; R = t-Bu) in the ester (IVb; R = t-Bu) at low temperatures is also indicated by ratios of apparent retention times of the esters (IIb, IIIb, and IVb). Although quantitatively the retention times do not change regularly with increase in the size of the 5-alkyl group, the qualitative relationships are consistent with the idea that the order of increasing retention times for each group of stereoisomers depends on the importance of conformations with equatorial ester groups for which solvation by the stationary phase will be greater than for axial ester groups. Thus the retention times increase in the order (IIIb) < (IVb) < (IIb) when the 5-alkyl group is primary or secondary but are in the order (IVb) < (IIIb) < (IIb) when it is tertiary. This interpretation is strongly supported by the temperature dependence of the retention times for the esters with a 5-t-butyl group. Wheras the ratio of corrected retention times for the esters (IIb; R = t-Bu and IIIb; R = t-Bu) varies little, as would be expected if each remains predominantly in a single conformation, the retention time on a polar stationary phase for the ester (IVb; R = t-Bu) relative to its stereoisomers increases with temperature until at about 200° it equals the ester (IIIb; R = t-Bu). The change is apparent even over a very restricted range of temperature with mannitol hexa-(2-cyanoethyl) ether, which could not be used as the stationary phase at much above 160°, while sucrose acetate isobutyrate could be used at much higher temperatures (Table 2). This change is very satisfactorily explained by a change from the conformation (VIIb; R = t-Bu) with

axial ester groups at low temperatures to increasing amounts of the conformation (IXb; R = t-Bu) with boat-equatorial ester groups at higher temperatures, provided that the change in conformation is accompanied by considerable increases in both enthalpy *and* entropy in order to get a relatively rapid change in the necessarily small free energy difference. Allinger and Freiberg[23] have shown that an increase in entropy may accompany an isomerisation involving a change of conformation from chair to boat, although the cause of this change is nor entirely clear, and the boat conformation (IXb; R = t-Bu) would be expected to be only a little less stable than the chair (VIIb; R = t-Bu). The alternative possibility that the change of conformation is from VIIb(R = t-Bu) to VIIIb (R = t-Bu) is very unlikely because no favourable entropy change would be expected, but in the absence of any direct evidence for the strain energy caused by an axial t-butyl group, except for a lower limit of about 4–5 kcal mole^{-1} implied by Allinger and Freiberg's results,[23] the presence of a small proportion of the conformation (VIIIb; R = t-Bu) can not be ruled out.

The importance of the appreciable amount of the boat conformation (IXb; R = t-Bu) in the ester (IVb; R = t-Bu) lies in its effect on the enthalpy difference for the isomerization (IIb; R = t-Bu to IVb; R = t-Bu), because the measured value is a weighted average of those appropriate to each conformation of IVb(R = t-Bu). When the various conformations of a compound have similar entropies the enthalpy of the compound is only slightly higher than that of the most stable conformation because the conformations with a high enthalpy are present in only small amounts, but when one of the conformations has a high enthalpy partly balanced by a high high entropy then the average enthalpy may be considerably higher than that of the most stable conformation and with rise in temperature will approach a value near that of the high entropy conformation. It is to be expected, therefore, that the enthalpy difference for the isomerization of IIb(R = t-Bu) to IVb(R = t-Bu) will increase with temperature but our experimental data are not precise enough to show any curvature in a plot of the logarithms of the equilibrium constants against the reciprocal of the absolute temperature over the temperature range studied, although the curvature should become rapidly discernible if measurements can be extended to about 200° and if our interpretation of the gas chromatographic retention times is correct. In order to calculate the entropy and enthalpy changes for the chair to chair conformational equilibrium in dimethyl cyclohexane-1,3-dicarboxylate from the results for the esters (IIb; R = t-Bu and IVb; R = t-Bu) it is necessary to assume values of the enthalpy and entropy differences for the isomerizations of the ester (IIb; R = t-Bu) to the conformations (VIIIb; R = t-Bu and IXb; R = t-Bu) of the ester (IVb; R = t-Bu). For want of better data we will assume that the conformation (VIIIb; R = t-Bu) is so unstable that it may be neglected. If we use Hendrickson's calculated value (+5·3 kcal mole^{-1})[21] for the enthalpy and our measured values (+4·2–+4·6 kcal mole^{-1} at 25°, see below) for the free energy of the boat conformation of cyclohexane relative to the chair the results given in Table 8 for the equilibrium (Ie; X = Y = CO$_2$Me) $\rightleftharpoons$ (Ia; X = Y = CO$_2$Me) are obtained. The entropy values in particular are very sensitive to the assumed free energy difference for the chair-boat equilibrium and the largest negative value (ΔS = −3·4 cal. deg.$^{-1}$ mole^{-1}) seems far too large to be accounted for by the mutual

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

hindrance of the two axial ester groups, so that the higher values of the enthalpy difference are probably more reliable. Similarly the experimental data for the equilibria between the acids (IIa; R = t-Bu and IVa; R = t-Bu) and between the monomethyl esters (IIf; R = t-Bu and IVf; R = t-Bu) may be corrected for the conformational equilibria in the less stable isomers. It is interesting to note the small but significant* differences between axial ester and carboxyl groups in diaxial-1,3-interactions. Although $\Delta F_{(e \to a)}$ is slightly larger for cyclohexanecarboxylic acid than for its methyl ester, the reverse is true for cyclohexane-1,3-dicarboxylic acid and its dimethyl ester. A plausible explanation is that the methoxyl groups in the di-ester (Ia; X = Y = CO_2Me) are close enough for mutual repulsion with a consequent increase in enthalpy or decrease in orientational freedom, or both, relative to the acid. We have also studied a small group of cis-3-amino-5-alkylcyclohexanecarboxylic acids, mainly in order to interpret the epimerization equilibria for the di-anions (IIe; R = t-Bu and IVe; R = t-Bu) (see below) but with results of interest in their own right. The diaxial 1,3-interaction between a carboxyl and an ammonium ($-NH_3^+$) group would be expected to be comparable with or rather larger than that between two carboxyl groups while the net repulsion in the related zwitterion should be greatly reduced by electrostatic attraction. An amino acid (IVj) with a suitably sized 5-alkyl substituent, R, therefore, should have different conformations at different acidities if

$$\Delta F_{(e \to a)} \,(\text{I};\ X = NH_3^+,\ Y = CO_2^-) < \Delta F_{(e \to a)} \,(\text{R-cyclohexane}) < \Delta F_{(e \to a)}$$

$$(\text{I};\ X = NH_3^+\ Y = CO_2H).$$

This has been observed in the acid (IVj; R = i-Pr). If the amino acid (IIj; R — t-Bu) has the conformation (Vj; R = t-Bu), and the amino acid (IVj; R = t-Bu) is predominantly in the conformation (VIIj; R = t-Bu), assuming that there may be some of the boat conformation (IXj; R = t-Bu) but that the other chair conformation (VIIIj; R = t-Bu) may be neglected, then the observation that the dissociation constant for the protonation of the acid (IVj; R = i-Pr) lies between those for the acids (IIj; R = t-Bu; pK_a = 6·04 and IVj; R = t-Bu; pK_a = 4·84) implies that the isopropyl acid changes conformation when the carboxylate group is protonated (Fig. 1). By trial and error it is found that the equilibrium constant for the conformational change (VIIj; R = i-Pr) → (VIIIj; R = i-Pr) is 0·34 ± 0·13 and for (VIIk; R = i-Pr) → (VIIIk; R = i-Pr) is 5·4 ± 2·0, and when the corresponding free energy differences are added to $\Delta F_{(e \to a)}$ for isopropylcyclohexane values of $\Delta F_{(e \to a)}$ are obtained for cis-3-aminocyclohexanecarboxylic acid and its conjugate acid (Table 8).

The conformational equilibrium in cyclohexane

Because solvation makes the carboxylate group a comparatively bulky group and electrostatic repulsion would be expected to be important in the ion (IVe; R = t-Bu) in the conformation (VIIe; R = t-Bu), we had expected that ionization of the acids (IVa; R = t-alkyl) would be associated with a change of conformation of the ring. The following comparison of the experimental equilibrium constants for the ionization of these acids to the di-anions with a value calculated assuming that the acids and di-anions are both in the conformation (VII) shows that the di-anions must

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* These differences are significant because they depend only on the esterification-hydrolysis equilibria and are not affected by the relatively large errors in the absolute values of $\Delta F_{(e \to a)}$.

be in either the boat conformation (IXe; R = t-alkyl) or have the t-alkyl groups axial. The latter appears to be very improbable since the dissociation constants only change slightly when the 5-t-alkyl group increases in size from t-butyl to 1,1-diethylpropyl. The equilibria between the anions (IIe; R = t-Alkyl and IVe; R = t-Alkyl) are therefore models for the boat-chair conformational equilibrium in cyclohexane.
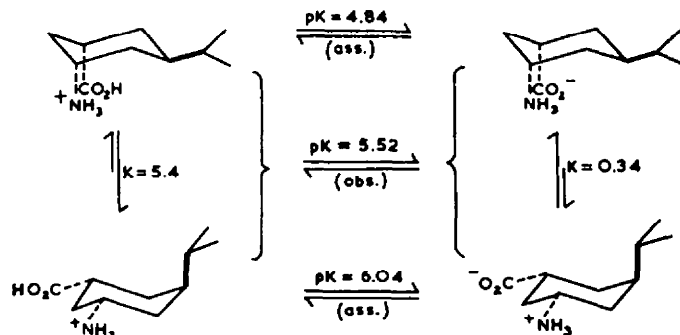

FIG. 1. Conformational and ionization equilibria in *cis*-3-amino-*trans*-5-isopropyl-cyclohexane-*cis*-1-carboxylic acid and its conjugate acid.

The equilibrium constant for the ionization of the acid (IVa; R = t-Bu) to the di-anion (VIIe; R = t-Bu; $pK_1 + pK_2$) may be estimated to be approximately

$$2[pK(IVf;\ R = t\text{-}Bu)] + [pK(IVf;\ R = t\text{-}Bu) - pK(IVk;\ R = t\text{-}Bu)] = 18\cdot6$$

The first term is the hypothetical sum of the dissociation constants of the acid (IVa; R = t-Bu) in the absence of electrostatic repulsion in the di-anion. The monomethyl ester is taken as a model for the first dissociation constant because the low observed pK_1 for the acid (IVa; R = t-Bu) is probably due to weak hydrogen bonding in the mono-anion as well as to the statistical factor, neither of these special effects being relevant to the equilibrium between the acid and its di-anion. The second term is a measure of the electrostatic repulsion in the di-anion (VIIe; R = t-Bu) assuming that this is similar in magnitude to the attraction in the zwitterion (IVj; R = t-Bu) and assuming that both the ion (IVk; R — t-Bu) and the zwitterion are in conformation (VII). Neither of these assumptions is correct but the errors introduced tend to cancel. Since the calculated value of pK_2 for the acids (IVa; R = t-alkyl) is $18\cdot6 - pK_1 = 11\cdot65$, assuming that the di-anions have the conformation (VII), whereas the observed values are more than 2 units less, we conclude that the di-anions adopt a boat conformation almost exclusively.

The free energy difference for the isomerization of the ion (IIc; R = t-alkyl to IVe; R = t-alkyl) is the sum of the free energy differences for the chain of equilibria (IIe) ⇌ (IIa) ⇌ (IIb) ⇌ (IVb) ⇌ (IVa) ⇌ (IVe) for R = t-alkyl. We have already argued that differences in hydroxylic solvents should be relatively unimportant for the neutral molecules, so that the data for epimerization in methanol and esterification in aqueous methanol may be carried over to aqueous 2-methoxyethanol in which the acid dissociation constants were measured.

Although the sums $pK_1 + pK_2$ for the dissociation of the acids (IIa; R = t-Bu and IVa; R = t-Bu) change by $+2\cdot36$ and $+2\cdot32$ units in passing from 50% to 78·5% 2-methoxyethanol (Table 9), the *difference* between these sums, which alone affects the

2

TABLE 9. APPARENT DISSOCIATION CONSTANTS[a] OF 5-ALKYLYCYCLOHEXANE-1,3-DICARBOXYLIC
ACIDS AT 25° IN 2-METHOXYETHANOL/WATER[b]

5-Alkyl substituent		IIa	IIIa	IVa
H	pK_1	6·84	6·99	—
	pK_2	8·24	8·53	
	ΔpK	1·40	1·54	
Me	pK_1	6·86		6·81
	pK_2	8·29	—	8·25
	ΔpK	1·43		1·44
i-Pr	pK_1	6·86		6·88
	pK_2	8·29	—	8·32
	ΔpK	1·43		1·44
t-Bu	pK_1	6·87 (5·78)[c]	7·11 (5·99)[c]	6·95 (6·02)[c]
	pK_2	8·30 (7·03)[c]	8·68 (7·37)[c]	8·87 (7·48)[c]
	ΔpK	1·43 (1·25)[c]	1·57 (1·38)[c]	1·94 (1·46)[c]
	ΣpK	15·17 (12·81)[c]		15·82 (13·50)[c]
CMe₂Et	pK_1	6·92		7·01
	pK_2	8·30	—	9·02
	ΔpK	1·40		2·01
	ΣpK	15·22		16·03
CEt₃	pK_1	6·89		6·88
	pK_2	8·29	—	9·24
	ΔpK	1·40		2·36
	ΣpK	15·18		16·12

[a] pK ± 0·07. [b] 78·5% 2-methoxyethanol. [c] 50% 2-methoxyethanol/water as solvent.

TABLE 10. APPARENT DISSOCIATION CONSTANTS[a] OF SOME *cis*-1,3-DISUBSTITUTED
5-ALKYLCYCLOHEXANES AT 25° IN 2-METHOXYETHANOL/WATER[b]

Substituents	pK II	pK IV
R = t-Bu, X = $\overset{+}{N}H_3$, Y = CO_2^-	pK 6·04 (5·16)[c]	4·84 (4·29)[c]
R = i-Pr, X = $\overset{+}{N}H_3$, Y = CO_2^-	pK —	5·52 (4·93)[c]
R = H, X = Y = $\overset{+}{N}H_3$[d]	pK_1 7·56 (8·01)[c] pK_2 9·63 (9·93)[c] ΔpK 2·07 (1·92)[c]	—
R = Me, X = Y = $\overset{+}{N}H_3$[d]	pK_1 7·51 (7·99)[c] pK_2 9·61 (9·90)[c] ΔpK 2·10 (1·91)[c]	—
R = t-Bu, X = Y = $\overset{+}{N}H_3$[d]	pK_1 7·54 (7 96)[b] pK_2 9·61 (9·86)[c] ΔpK 2·07 (1·90)[c]	(6·83)[c] e (>10)[c] (>3·17)[r]
R = t-Bu, X = CO_2H, Y = CO_2Me	pK 7·18 (6·02)[c]	7·78 (6·76)[c]

[a] pK ± 0·07. [b] 78·5% 2-methoxyethanol. [c] 50% 2-methoxyethanol/water as solvent. [d] Dipicrate salt. [e] Dipicrate insufficiently soluble for measurements.

calculation of the free energy difference for the reaction (IIe; R = t-Bu) → (IVe; R = t-Bu), is unchanged (−0·04 units) within experimental error. This signifies that the large differences in solvation of carboxylic acids and their anions are the same in a cyclohexane whether the carboxyl group is equatorial on a chair ring or pseudo-equatorial on a twisted boat ring and therefore IIe(R = t-Bu) and IVe(R = t-Bu) are valid models for the conformational equilibrium in cyclohexane. Furthermore the epimerization and esterification equilibria should be insensitive to the size of the 5-t-alkyl substituent, which remains equatorial on a chair form ring, so that the results for the 5-t-butyl acids may be used for the other acids for which data is either less accurate or not available. Therefore the change of free energy when cyclohexane is converted from the chair into the boat conformation is given by

$$\Delta F(\text{chair} \rightarrow \text{boat}) \simeq \Delta F(\text{IIe} \rightarrow \text{IVe}; \ R = \text{t-alkyl})$$

$$= \Delta F(\text{IIb} \rightarrow \text{IVb}; \ R = \text{t-Bu}) \qquad \text{(epimerization)}$$

$$-RT[\ln K(\text{IIa}; \ R = \text{t-Bu}) + \ln K^{-1}(\text{IVa}; \ R = \text{t-Bu})] \qquad \text{(esterification)}$$

$$-RT[-(pK_1 + pK_2)(\text{IIa}; \ R = \text{t-alkyl}) + (pK_1 + pK_2)$$

$$(\text{IVa}; \ R = \text{t-alkyl})] \qquad \text{(acid dissociation)}$$

$$= 3·6 - 0·3 + 0·9 = +4·2 \ \text{kcal mole}^{-1} \ (R = \text{t-Bu})$$

$$= 3·6 - 0·3 + 1·1 = +4·4 \qquad (R = \text{CEtMe}_2)$$

$$= 3·6 - 0·3 + 1·3 = +4·6 \qquad (R = \text{CEt}_3)$$

The three values are in fair agreement with Allinger and Freiberg's results extrapolated to 25° (Table II). The small differences are due to the increase in the value of pK_2 for the acids (IVa; R = t-alkyl) as the size of the alkyl group increases and there are two obvious causes which will explain part of the differences, at least. Allinger and Freiberg's use of 1,3-di-t-butylcyclohexane[23] has been criticized on the grounds that repulsions between the t-butyl groups and the ring may be larger when the ring is in

TABLE 11. FREE ENERGY, ENTHALPY AND ENTROPY DIFFERENCES FOR THE CHAIR-BOAT CONFORMATIONAL EQUILIBRIUM IN CYCLOHEXANE

$\Delta F_{298}{}^{\circ}K$ (kcal. mole^{-1}) (Obs.)	ΔH (kcal. mole^{-1}) (Obs.) (Calc.)		ΔS (cal. deg.$^{-1}$) mole^{-1} (Obs.)	Reference
		+5·3		21
+4·9[a]	+5·9		+3·5	23
	+5·5			24
+4·2				This paper
+4·4				This paper
+4·6				This paper

[a] Extrapolated from experimental results for higher temperatures.

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

a boat conformation (*trans* isomer) than when it is in a chair (*cis* isomer).[24] Such an effect would be expected to increase with larger alkyl groups but the rather small increase we observe suggests that the effect is quite small for t-butyl so that our lowest estimate is probably the best. Another much less probable explanation is that the anion (IVe; R = t-Bu) exists to a substantial extent in the conformation (VIII) so that the free energy of the ion (IVe; R = t-Bu) is lowered by an additional entropy of mixing term. The conformation ((VIII) should be less important for the ion IVe(R = CMe_2Et) and neglible for the ion IVe(R = CEt_3). In the absence of any reliable estimate of the instability caused by an axial t-butyl group it is not possible to calculate this entropy of mixing but it is most unlikely to be important.

The high basicity of the amine (IVe; R = t-Bu; $pK_2 > 10$) suggests that there is significant hydrogen bonding between the axial amino and ammonium groups in the mono-ion, otherwise this base should be weaker than the diequatorial amine (III; R = t-Bu).[16] This special stabilization in the mono-ion, rather than greater electrostatic repulsion in the ion IVm(R = t-Bu) than in the ion IIm(R = t-Bu), probably accounts for the difference between the first dissociation constants of the diammonium ions so that this difference does not imply that ion IVm(R = t-Bu) is in a chair conformation with axial ammonium groups. On the contrary, analogy with the di-anions IVe(R = t-alkyl) suggests strongly that the di-cation IVm(R = t-Bu) exists in a boat conformation.