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CONFORMATIONAL EFFECTS IN COMPOUNDS WITH SIX-MEMBERED RINGS—VI

CONFORMATIONAL EQUILIBRIA IN 5-ALKYL-1,3-DIOXANES

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Abstract—Conformational equilibria in 5-alkyl-1,3-dioxanes have been studied by determining the equilibria between stereoisomeric pairs of 2,5-disubstituted-1,3-dioxanes in which the 2-substituent (t-butyl or *p*-nitrophenyl) was large enough to act as a conformational locking group; the results were independent of the 2-substituent. The more fully studied 2-t-butyl series gave enthalpy and entropy differences for the conformations of 5-methyl, 5-ethyl and 5-isopropyl-1,3-dioxanes which were smaller than those for the analogous alkylcyclohexanes, in agreement with the difference in van der Waals radii of oxygen atoms and methylene groups. *cis*-2,5-Di-t-butyl-1,3-dioxane has an axial 5-t-butyl group. The enthalpy and entropy differences vary with the size of the alkyl group in an irregular manner which is not consistent with the usual assumptions made in the conformational analysis of chair–chair equilibria in 6-membered rings and which shows the inadequacy of considering only free energies.

THE use of equilibria between separable stereoisomers as models for equilibria between rapidly interconverting conformations has been particularly valuable for the study of cyclohexane derivatives[1c, f] despite the paucity of accurately reversible reactions and doubts about the possible influence of the bulky conformation holding groups which are commonly used. Although some epimerization equilibria for acyclic compounds and for cyclic compounds with other than 6-membered rings have been measured[1d] the results are not easy to interpret quantitatively and 6-membered heterocyclic systems appear to be the most suitable for detailed study by this method at present. We selected 5-alkyl-1,3-dioxanes I (Fig. 1) for several reasons. Firstly, 1,3-dioxanes are readily prepared from 1,3-diols and aldehydes so that the conformation holding group at C-2 may be varied by changing the aldehyde and it becomes comparatively easy to determine whether the nature of this group seriously influences the results. It was expected, furthermore, that nuclear magnetic resonance spectra would be useful for determining the configuration of the products and for quantitative analysis. In the third place the required stereochemical equilibria should be readily achieved without side reactions in acidic media. Finally, the strain energies for axial groups were expected to be smaller in 5-alkyl-1,3- dioxanes than in alkylcyclohexanes and an accuracy high enough to allow tests of some common assumptions in conformational analysis could be expected.

[1] E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis*. Interscience, New York (1965); [a] p. 44; [b] p. 46; [c] pp. 58–70; [d] pp. 200, 209; [e] p. 249; [f] pp. 436–442.

Preliminary experiments showed that two series of 2,5-disubstituted-1,3-dioxanes were particularly suitable for study. When the conformation holding group was a 2-t-butyl substituent each pair of stereoisomers, all of which were liquids except *trans*-2,5-di-t-butyl-1,3-dioxane, were readily separated by gas chromatography and were sufficiently cleanly interconverted by 0·5–1·0M trifluoroacetic acid* in chloroform for measurements to be made over a wide temperature range (−33° to +60°); 2,5-di-t-butyl-1,3-dioxane slowly formed small amounts of byproducts (see below).

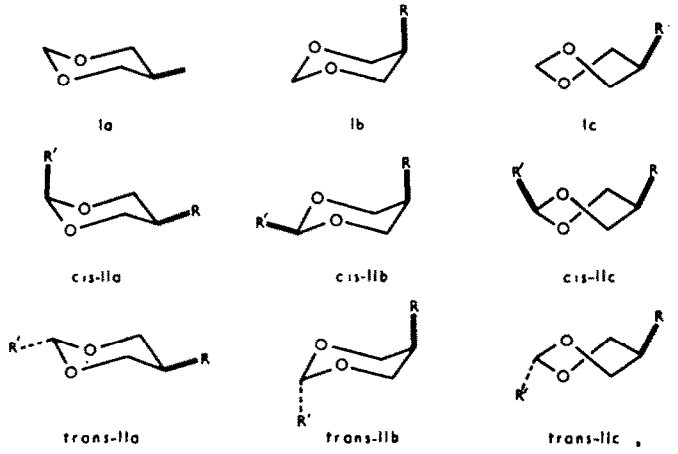

FIG. 1.

2-Aryl-5-alkyl-1,3-dioxanes are readily prepared for many different aryl groups but since we did not intend to use gas chromatography for analysis the conveniently crystalline 2-*p*-nitrophenyl compounds were chosen for detailed study. Only the *trans*-isomers were isolated in a pure condition but it was possible to obtain mixtures containing up to 40% of the *cis*-isomers, which could be identified readily from the NMR spectra of the mixtures. The relatively sharp singlets due to the C-2 protons were used for quantitative analysis by integration but the poor reproducibility of successive integrals except for spectra run at room temperature discouraged us from making a study of the temperature dependence of the equilibria except for 2-*p*-nitrophenyl-5-methyl-1,3-dioxane (II; R = Me, R′ = $C_6H_4NO_2$).

EXPERIMENTAL

NMR spectra were measured on a Varian A 60 spectrometer and were calibrated with sidebands generated by a Muirhead-Wigan D-8090-A oscillator. Mass spectra were measured with an A.E.I. MS 9 spectrometer.

1,3-Diols. 2-Alkylpropane-1,3-diols were prepared by reducing alkylmalonic esters with LAH in THF.

1,3-Dioxanes. The following general method, scaled down for diols available only in small quantities, was used with minor variations for all the 1,3-dioxanes. An aldehyde (1 mole) and a 1,3-diol (1·1 moles)

* The variation in the concentration of this catalyst did not change the equilibrium at room temperature, whereas boron trifluoride-ether altered the equilibrium. Hydrogen chloride was too volatile to be used in this instance, although it was very convenient in sealed samples for nuclear magnetic resonance spectral analysis.

TABLE 1. ANALYTICAL DATA FOR 1,3-DIOXANES

Substituents 2-	5-	Formula	C Found	C Req.	H Found	H Req.	M.p. (B.p.)
t-Bu	Me[a]	$C_9H_{18}O_2$	68·05	68·31	11·21	11·47	(44–46°/14 mm)
	Et[a]	$C_{10}H_{20}O_2$	69·90	69·72	11·66	11·70	(64°/14 mm)
	i-Pr[a]	$C_{11}H_{22}O_2$	70·63	70·92	11·60	11·90	(75–76°/14 mm)
	t-Bu[b]	$C_{12}H_{24}O_2$	71·68	71·95	11·79	12·08	80°
p-$NO_2C_6H_4$	Me[b]	$C_{11}H_{13}NO_4$	59·30	59·18	5·90	5·89	55°
	Et[b]	$C_{12}H_{15}NO_4$	61·09	60·75	6·36	6·37	77°
	i-Pr[b]	$C_{13}H_{17}NO_4$	62·41	62·14	7·11	6·82	116°
	t-Bu[b]	$C_{14}H_{19}NO_4$	63·62	63·38	7·29	7·22	80°

[a] Mixture of stereoisomers. [b] *trans* stereoisomer.

TABLE 2. EQUILIBRIUM CONSTANTS FOR THE EPIMERIZATION OF 2-T-BUTYL-5-ALKYL-1,3-DIOXANES (*cis* ⇌ *trans*) IN CHLOROFORM

5-Alkyl group	Temp.	% *cis*	Equilibrium constant
Me	+56°	20·05	3·99
	40	19·25	4·20
	23	18·20	4·49
	0	16·15	5·20
	−33	13·45	6·43
Et	+60	28·80	3·47
	40	22·40	3·67
	35	20·75	3·82
	23	19·75	4·07
	0	18·30	4·46
	−33	15·85	5·31
i-Pr	+60	15·60	5·36
	40	14·70	5·81
	35	14·15	6·07
	23	12·90	6·75
	0	11·35	7·81
	−33	9·71	10·30
t-Bu	+56	7·48	12·37
	40	5·74	16·43
	23	4·68	20·35
	0	3·72	25·9
	−33	2·58	37·8

dissolved in CH_2Cl_2 (250 ml) containing toluene-*p*-sulphonic acid (0·01 mole) were heated and stirred with anhyd $CuSO_4$ (100 g) for 2 hr. The CH_2Cl_2 soln was decanted through a short column of alumina and, together with CH_2Cl_2 washings, was distilled through a fractionating column or concentrated to a small volume according to the volatility of the product. Substantially stereochemically pure samples of 2-t-butyl-5-methyl, -5-ethyl, and -5-isopropyl-1,3-dioxane were isolated by PGC with silicone oil as the stationary phase. The mass spectra of the individual stereoisomers were consistent with the expected mol wts and structures. The *trans* isomers of 2,5-di-t-butyl- and the 2-*p*-nitro-phenyl-5-alkyl-1,3-dioxanes were obtained by fractional crystallization, often at low temperatures, and by hand sorting of crystals. Analytical data are given in Table 1.

Epimerization equilibria for 2-t-butyl-5-alkyl-1,3-dioxanes. A soln of a 1,3-dioxane (10% w/v) Chf containing sufficient trifluoracetic acid (between 0·5M at 60° and 1·0M at −33°; checks at room temp showed that the equilibrium was not influenced by the concentration of the catalyst) to give a convenient half-life for the epimerization was maintained at the chosen temp by a vapour jacket or ice bath or liquid ammonia bath. From time to time small samples were transferred to a soln of Et_3N in Chf maintained at the same temp in the thermostat. The neutralized soln was immediately injected into the gas chromatograph and after the relative concentrations had become constant 5 or 6 further samples were analysed (Table 2).

The analyses were carried out with $\frac{1}{8}$" diam columns packed with 5% silicone oil on celite in a Beckman GC 2A gas chromatograph with a flame ionization detector. The analyses were based on peak heights and relative retention times together with a correction factor[2] determined for the 5-isopropyl derivatives by using standard mixtures made up by weight. Owing to the greater volatility of the 5-methyl and 5-ethyl compounds it was not found possible to prepare such standard mixtures for these compounds and this introduces a very small uncertainty into the entropy differences for the epimerizations (Table 4).

Epimerization equilibria for 2-p-nitrophenyl-5-alkyl-1,3-dioxanes. A freshly prepared soln of a 2-*p*-nitrophenyl-1,3-dioxane (10% w/v) in Chf in an NMR sample tube was saturated with dry HCl, thermostated at the temp at which the spectrum was to be measured and then quickly transferred to the spectrometer probe immediately the temp of the latter had been checked. Quantitative analyses were based on integration of the signals due to the C-2 protons (at least 12 scans), while the rest of the spectrum provided a check on the absence of side reactions (Table 3).

TABLE 3. EQUILIBRIUM CONSTANTS FOR THE EPIMERIZATION OF 2-NITROPHENYL-5-ALKYL-1,3-DIOXANES (*cis* ⇌ *trans*) IN CHLOROFORM

5-Alkyl group	Temp.	% *cis*	Equilibrium constant
Me	+52	20·9	3·78
	30	18·9	4·30
	−5	18·4	4·43
	−31	12·9	6·74
Et	+30	21·3	3·48
i-Pr	+30	14·8	5·74

RESULTS AND DISCUSSION

The preparations of the 1,3-dioxanes (II) used in this work were interesting in one respect. The first formed mixtures of products were always richer in the less stable *cis* isomers (up to 40%) than were the equilibrium mixtures resulting from prolonged reaction times and this facilitated isolation of the *cis* isomers of II (R = Me, Et or i-Pr; R′ = t-Bu) by gas chromatography. A similar result observed in the preparation

[2] N. W. J. Pumphrey, *Thesis* Liverpool (1964).

of II (R = O·COPh; R′ = Ph)[3] has been attributed,[4] without detailed explanation, to dipole-dipole interactions but any such explanation can not apply in the present examples, nor to the high selectivity often observed in kinetically controlled preparations of 2,4-disubstituted 1,3-dioxolanes.[5, 6]

Although there is no doubt that the chair conformation of 1,3-dioxane is more stable than any arrangement of the boat conformation[7] (the magnitude of the energy difference will be discussed below) there have been no direct structural studies of any of the 1,3-dioxanes of interest in this work. We have calculated, therefore, some of the distances between non-bonded atoms for axial 2- and 5-methyl and 5-t-butyl groups in 1,3-dioxanes together with some analogous distances in cyclohexane

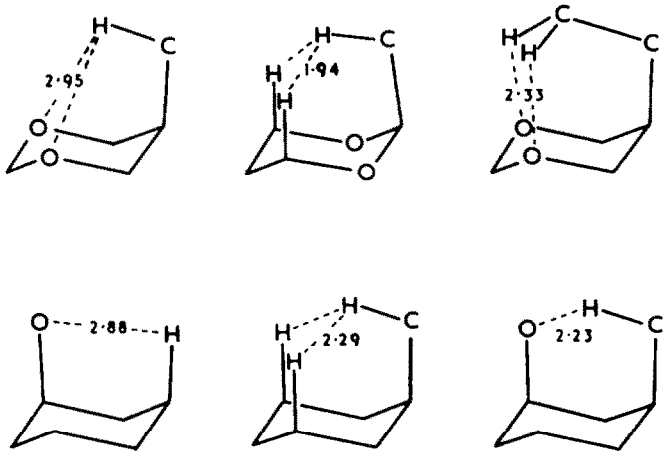

FIG. 2.

derivatives (Fig. 2). Because we have not attempted to minimize strain energies the comparisons between the two ring systems have only qualitative significance.

In calculating the distances given in Fig. 2* the C–O bond length (1.417Å), unlike the C—C (1.537 Å) and C—H (1·096 Å) bond lengths,[8] was taken to be that found in dimethyl ether, for which microwave[9] and electron diffraction[10] measurements agree excellently, rather than the slightly larger value recommended by Sutton.[8]

* The distances for the cyclohexane derivatives are considerably longer than those commonly quoted, e.g. in Ref. 1*b*, which are based on ideal tetrahedral bond angles. Small changes in bond angles have large effects on distances between axial substituents.

[3] M. Bergmann and N. M. Carter, *Z. physiol. Chem.* **191**, 211 (1930).
[4] N. Baggett, J. S. Brimacombe, A. B. Foster, M. Stacey and D. H. Whiffen, *J. Chem. Soc.* 2574 (1960).
[5] F. S. Al-Jeboury, N. Baggett, A. B. Foster and J. M. Webber, *Chem. Comm.* 222 (1965).
[6] F. G. Riddell and M. J. T. Robinson, unpublished results.
[7] M. Hanack, *Conformation Theory*, (translated by H. C. Neumann) p. 308. Academic Press, New York and London (1965).
[8] L. E. Sutton, *Interatomic Distances Supplement*, The Chemical Society, London (1965).
[9] P. H. Kasai and R. J. Myers, *J. Chem. Phys.* **30**, 1096 (1959); U. Blukis, P. H. Kasai and R. J. Myers, *Ibid.* **38**, 2753 (1963).
[10] K. Kimura and K. Kubo, *J. Chem. Phys.* **30**, 151 (1959).

The bond angles were assumed to be 111·5° for ∠CCC[11] and ∠COC,[9, 10] and 109·5° for ∠HCH.

An axial Me group is nearer to the syn-axial hydrogen atoms when it is at C-2 in a 1,3-dioxane (the shortest H–H distances are 1·94 Å) than in a cyclohexane (2·29 Å) and we can be certain that either a 2-t-butyl or a 2-*p*-nitro phenyl group will be an effective conformation holding group in 1,3-dioxanes.* The two shortest methyl–hydrogen to oxygen distances in 5(ax)-methyl-1,3-dioxane (Ib; R = Me) (2·95 Å) are comparable with the sum of the van der Waals radii (1·20–1·52 Å),[14] so that when we began this research there was no certainty that the Me group in 5-methyl-1,3-dioxane would tend to be equatorial, although analogy with cyclohexanol (Fig. 2) suggested that some preference would be found. Preliminary experiments showed that a clear preference did in fact exist and the NMR spectra established that the 5-alkyl groups were equatorial in the more stable *trans* isomers of II,[6] for all the 5-alkyl substituents studied. The shortest H–O distances in 5(ax)-t-butyl-1,3-dioxane (2·33 Å) are appreciably longer than the formally analogous separation (2·23 Å) in diaxial-*cis*-3-methylcyclohexanol, which is probably less readily distorted, and it is not surprising that the 5-t-Bu group is axial in *cis*-II(R = R′ = t-Bu) (see below).

In order to interpret the conformational equilibria in 5-ethyl- and 5-isopropyl-1,3-dioxane it is desirable to know whether *cis*-II(R = t-Bu; R′ = t-Bu or $C_6H_4NO_2$) has an axial 5-t-butyl group as in *cis*-IIb or is in a boat conformation like *cis*-IIc. Unfortunately the relative stability of the boat and chair conformations of 1,3-dioxane has not yet been measured accurately. The enthalpy difference, $\Delta H_{ch \rightarrow bt}$ (I; R = H), has been estimated[1c] to be twice the barrier to internal rotation in kcal/mole) in methanol (1·11 kcal/mole),[15] i.e. ~2 kcal/mole, following the simple approximation successfully used for cyclohexane,[16] in which the strain energy of the boat conformation is roughly twice the barrier to internal rotation in ethane.† This approximation is, however, less certain for oxygen compounds because barriers to internal rotation about C—O bonds in CH_3–OX molecules, unlike C—C bonds in CH_3–CH_2X, are sensitive to the nature of the group X. Low barriers have been found in methanol[15]

* There is a smaller difference in chemical shifts for the axial and equatorial protons at C-4 and C-6 in *cis*-II (R large) than in the *trans* isomers[6] and this is attributable to the well known tendency for alkyl groups to deshield a vicinal hydrogen atom when it is s-*trans* but to shield it when it is gauche.[12] There is no justification for supposing, as has sometimes been done,[13] that such diminished chemical shift differences are evidence for an equilibrium between two chair conformations both present in substantial amounts in *cis*-II (R large).

† The only evidence which may be used to support a low value for $\Delta G_{ch \rightarrow bt}$(I; R = H) is the intramolecular hydrogen bonding in *trans*-2-alkyl-5-hydroxy-1,3-dioxanes.[4, 17] The published intensity data and some very uncertain assumptions, which are not worth detailing, lead to $\Delta G_{ch \rightarrow bt}$(I; R = H) ≃ + 2 kcal./mole. This result is very sensitive to errors in the intensity data and in the assumptions so that we attach little weight to it, and other evidence points to a much higher value.

[11] M. Davis and O. Hassel, *Acta Chem. Scand.* **13**, 1737 (1959).
[12] H. Booth, *Tetrahedron* **22**, 615 (1966).
[13] N. Baggett, B. Dobinson, A. B. Foster, J. Homer and L. F. Thomas, *Chem. & Ind.* 106 (1961).
[14] A. Bondi, *J. Phys. Chem.* **68**, 441 (1964).
[15] J. D. Swalen, *J. Chem. Phys.* **23**, 1739 (1955).
[16] C. W. Beckett, K. S. Pitzer and R. Spitzer, *J. Am. Chem. Soc.* **69**, 2488 (1947).
[17] B. Dobinson and A. B. Foster, *J. Chem. Soc.* 2338 (1961).

and methyl formate (1·19)[18] but relatively high ones in methyl hypochlorite (3·06)[19] and, most pertinently, dimethyl ether (2·72).[9] Because special factors probably affect barriers to the rotation of OH groups dimethyl ether should be a far more appropriate model than methanol for the torsion strain in cyclic ethers and acetals. This is strongly supported by the similarity between the barriers to ring inversion, to which torsion strain makes a major contribution,[20] in cyclohexane ($\Delta G^{\ddagger} = +10{\cdot}3$ kcal/mole)[21] and in 1,3-dioxane ($\Delta G^{\ddagger} = +9{\cdot}7$ kcal/mole).[22] From this we conclude that the chair-boat *equilibrium* should be comparable in these two ring systems, contrary to earlier estimates.[1c] In preliminary experiments we have found that the boat conformation of 1,3-dioxane is at least 3 kcal/mole less stable than the chair.[6] Since the observed free energy differences for the epimerization of the 1,3-dioxanes II (Table 4) are all $\leqslant 1{\cdot}7$ kcal/mole we will assume that boat conformations such as *cis*- and *trans*-IIc can be neglected. Furthermore the calculations summarized in Fig. 2 show that conformations with axial 2-t-butyl or 2-*p*-nitrophenyl groups, i.e. *cis*-IIa and *trans*-IIb, may also be neglected and the epimerization equilibria *trans*-II $\rightleftharpoons$ *cis*-II are models for the conformational equilibria Ia $\rightleftharpoons$ Ib, even when R = t-Bu. The conclusion that *cis*-II(R = t-Bu, R′ = t-Bu or $C_6H_4NO_2$) has an axial 5-t-Bu group is consistent with the variation in the differences in chemical shifts of the C-4 protons in the series of compounds *cis*-II(R = Me, Et, i-Pr or t-Bu, R′ = t-Bu or $C_6H_4NO_2$).[6]

TABLE 4. FREE ENERGY, ENTHALPY AND ENTROPY DIFFERENCES FOR THE EPIMERIZATION OF 2-SUBSTITUTED-5-ALKYL-1,3-DIOXANES.
trans → *cis*

5-Alkyl group	ΔH (kcal/mole)	ΔS (cal/deg/mole)	ΔG_{303}, (kcal/mole)
	2-t-butyl:		
Me	+0·86 ± 0·09	−0·1 ± 0·3	+0·89
Et	+0·74 ± 0·08	−0·2 ± 0·3	+0·81
i-Pr	+1·13 ± 0·10	+0·1 ± 0·3	+1.10
t-Bu	+1·9 ± 0·5	+0·5 ± 1·7	+1·7
	2-*p*-Nitrophenyl:		
Me	+0·98 ± 0·17	+0·4 ± 0·6	+0·87
Et			+0·75
i-Pr			+1·05

The results for the epimerization equilibria in the 2-t-butyl series (Table 4) were satisfactorily precise except for the 2,5-di-t-butyl derivatives, which formed by-products at a rate of the order of 1–2% of the initial rate of epimerization. If the

[18] R. F. Curl, *J. Chem. Phys.* **30**, 1529 (1959).
[19] J. S. Rigden and S. S. Butcher, *J. Chem. Phys.* **40**, 2109 (1964).
[20] J. B. Hendrickson, *J. Am. Chem. Soc.* **83**, 4537 (1961).
[21] A. Allerhand, F. Chen and H. S. Gutowsky, *J. Chem. Phys.* **42**, 3040 (1965).
[22] J. E. Anderson and J. C. D. Brand, *Trans. Farad. Soc.* **62**, 39 (1966); H. Friebolin, S. Kabuss, W. Maier and A. Luttringhaus, *Tetrahedron Letters* 683 (1962).

by-products were formed more rapidly from one epimer than the other the systematic errors in the free energy differences would be small but could cause relatively large uncertainties in the enthalpy and entropy differences. The poor reproducibility of the integration on the available spectrometer made us limit the study of the 2-*p*-nitrophenyl series but there is satisfactory agreement between the two series so far as comparison can be made.

A comparison between chair-chair equilibria in 5-alkyl-1,3-dioxanes and alkylcyclohexanes[1, 23, 24] shows the expected qualitative differences. The smaller enthalpy and free energy differences (Table 5) for the dioxanes are mainly attributable to the smaller van der Waals radius of oxygen compared with a methylene group but the difference between C—C and C—O bond lengths also help to decrease the repulsions experiences by axial 5-alkyl groups in 1,3-dioxanes. The variation in enthalpy differences with increasing size of the group are qualitatively similar in the two series, the increase between ethyl and isopropyl being particularly significant. If we assume that the total strains in individual conformations are additive functions of the separate interactions and that only entropies of mixing need to be considered[23, 24] then the results for 5-methyl- and 5-t-butyl-1,3-dioxane may be used to calculate $\Delta H_{e\to a}$ and $\Delta S_{e\to a}$ for the 5-ethyl and 5-isopropyl derivatives.* The agreement between the observed and calculated values may be said to be good for the Et group but for the

TABLE 5. CONFORMATIONAL EQUILIBRIA IN 5-ALKYL-1,3-DIOXANES AND ALKYLCYCLOHEXANES (EQUATORIAL → AXIAL); ENTHALPIES AND FREE ENERGIES IN KCAL/MOLE AND ENTROPIES IN CAL/MOLE/DEG.

Alkyl group		5-Alkyl-1,3-dioxane			Alkylcyclohexane		
		ΔH	ΔS	ΔG	ΔH	ΔS	ΔG
Me	Obs.	0·86	−0·1	0·89	1·7–1·9[a]	0	1·5–2·1[b]
	Ass.	0·9	0	0·9	1·8	0	1·8
Et	Obs.	0·74	−0·2	0·81	1·65[c]	−0·7[c]	1·65–2·25[b]
	Calc.	0·89	−0·14	0·93	1·71	−0·51	1·86
i-Pr	Obs.	1·13	+0·1	1·10	2·5[c]	0[c]	2·1–2·5
	Calc.	0·83	−0·76	1·06	1·53	−1·64[d]	2·01[d]
t-Bu	Obs.	1·9	+0·5	1·7	—	—	—
	Ass.	1·7	0	1·7	5·6	0	5·6

[a] Probable range of values for polar and hydroxylic solvents.

[b] Range of reasonably precise values quoted in Ref. 1*a*.

[c] Cf. Ref. 24. The values for isopropylcyclohexane, although derived from two concordant series of experiments, may be in error since the corresponding free energy difference is at the extreme limit of the range. The values found by Allinger and Hu[23] are probably seriously influenced by chair–boat equilibria at the high temperatures of the experiments and are omitted.

[d] These values differ from those previously reported. Allinger and Hu[23] used slightly different assumptions while an entropy of mixing term was wrongly calculated in Ref. 24.

[23] N. L. Allinger and S.-E. Hu, *J. Am. Chem. Soc.* **84**, 370 (1962); *J. Org. Chem.* **27**, 3417 (1962).

[24] B. J. Armitage, G. W. Kenner and M. J. T. Robinson, *Tetrahedron* **20**, 747 (1964).

i-Pr group the agreement is poor (Table 5). A similar situation appears to hold for ethyl- and isopropyl-cyclohexane, although the experimental results for the latter are as yet not accurate enough for certainty.

The differences between the observed and calculated enthalpy differences for 5-isopropyl-1,3-dioxane is qualitatively understandable. The assumption that the total strain energy of a conformation is simply the sum of a number of interactions whose magnitudes are the same in a series of related molecules may be expected to fail quite frequently. It ignores the differences in the extent to which strain may be relieved in different situations, for example, a skew interaction involving an Et group may often be relieved by a slight rotation whereas such movement in the isopropyl analogue may relieve one interaction at the expense of increasing another. The error in the entropies is less expected. The assumption that entropy differences between individual conformations may be neglected in acyclic compounds and in 6-membered ring compounds in chair conformations does not seem to have been questioned but we have found entropy differences of about 1 e.u. (equivalent to about 0·4 kcal/mole at room temperature) between conformations in some acyclic compounds,[6] and if this is common but unpredictable then simple empirical calculations of conformational energy differences will always be subject to rather large errors.

Acknowledgement—We thank D.S.I.R. for a maintenance grant (to F.G.R.).

Note added in proof. Eliel and Knoeber have independently determined free energy differences, in good agreement with our results, for epimerization equilibria in 2,5-dialkyl-1,3-dioxanes and have shown by NMR that the 5-t-butyl group is axial in *cis*-2,5-di-t-butyl-1,3-dioxane.[25]

* For example, an ethyl group can take up three distinguishable orientations, each corresponding to a potential energy minimum, in each set[24] of chair conformations (with the alkyl group either axial or equatorial).

The calculated values in Table 5 are based on $\Delta H_{e\to a}(I; R = t\text{-Bu}) = +1{\cdot}7$ kcal/mole, so that $\Delta S_{e\to a}(I; R = t\text{-Bu}) = 0$ is assumed. Since the experimental errors for the epimerization of II(R = R' = t-Bu) are rather large we repeated the calculations for other values, subject to the restriction $\Delta G_{e\to a}(I; R = t\text{-Bu}) = +1{\cdot}7$ kcal/mole, without much effect on the results calculated.

[25] E. L. Eliel and M. C. Knoeber, *J. Am. Chem. Soc.* **88**, 5347 (1966).