The Proton Magnetic Resonance Spectra of Six-membered Cyclic Acetals. Part III.[1] The Vicinal Coupling Constants of Alkyl-substituted 1,3-Dioxans existing in Non-chair Conformations

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The ^1H n.m.r. spectra of several 1,3-dioxans known to exist in non-chair conformation have been recorded in carbon tetrachloride, methylene chloride, benzene, or nitrobenzene solutions at 60 and 220 MHz. In all cases the values of the vicinal coupling constants are almost independent of temperature, and in several cases large (>10 Hz) vicinal coupling constants, indicative of anancomeric twisted boat conformations are observed. The results lead to conclusions concerning the preferred boat conformations of the 1,3-dioxan ring, and the preferred orientations of substituents under this circumstance.

It has recently become well established that 1,3-dioxans that would have a 2,4-*syn*-diaxial interaction between two alkyl groups in a chair conformation assume non-chair, probably twisted boat, conformations. Heat of formation data[2-4] has shown that *trans*-2,2,4,6-tetramethyl-1,3-dioxan has a non-chair conformation. ^1H N.m.r. studies have confirmed this and also led to the same conclusion for 2,2-*r*-4-*c*-5-*t*-6-pentamethyl-1,3-dioxan.[1,5,6] Two of us have recently investigated the ^{13}C n.m.r. spectra of some 1,3-dioxans.[7] A study of substituent effects upon ring carbon chemical shifts showed that a 2,4-*syn*-diaxial interaction forces a 1,3-dioxan ring into a non-chair conformation.[7] The above results are corroborated by the molecular rotation measurements of Tocanne who reported non-chair conformations for several similar compounds.[8]

Despite the wealth of evidence for non-chair conformations, no work has yet been forthcoming on the details of the conformations of these non-chair compounds. Such information is, in principle, obtainable from vicinal proton–proton coupling constants. The vicinal coupling constants for the chair form of a 1,3-

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[1] Part II, K. Pihlaja and P. Ayras, *Acta Chem. Scand.*, 1970, **24**, 531.

[2] K. Pihlaja and J. Heikkila, *Acta Chem. Scand.*, 1967, **21**, 2390.

[3] K. Pihlaja and J. Heikkila, *Acta Chem. Scand.*, 1967, **21**, 2430.

[4] K. Pihlaja and S. Luoma, *Acta Chem. Scand.*, 1968, **22**, 2401.

[5] E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, 1968, **90**, 3444.

[6] K. Pihlaja and P. Ayras, *Acta Chem. Scand.*, 1970, **24**, 204.

[7] G. M. Kellie and F. G. Riddell, *J. Chem. Soc.* (*B*), 1971, 1030.

[8] J. Tocanne, *Bull. Soc. chim. France*, 1970, 750.

dioxan ring are well known,[9] and vary little with substitution pattern. Although values for couplings in boat conformations of 1,3-dioxan are not known the generalisation arising from the Karplus equations can be applied. Thus large couplings >10 Hz are indicative of a *trans* periplanar or eclipsed arrangement and small couplings <1 Hz are indicative of approximately 90° dihedral angles. Intermediate values indicate values for the torsional angles between (say) 20 and 70° and 110 and 160°. We report here the coupling patterns in the 60 and 220 MHz spectra of several 1,3-dioxans known to exist in non-chair conformations. In several cases the values of the coupling constants enable definite conclusions to be drawn about the preferred non-chair conformations of the molecules, and a scheme is presented enabling *a priori* selection of the probable conformation to be made.

EXPERIMENTAL

The n.m.r. spectra were recorded on Perkin-Elmer R10 60 MHz spectrometers in Stirling and Turku and on the S.R.C. 220 MHz spectrometer in Runcorn. In general 10% v/v solutions were used. Spectra were calculated using the program LAOCOON III on an Elliot 4130 computer.

2,2,4,4,5-*Pentamethyl*-1,3-*dioxan* was prepared by the conventional method from 2,3-dimethylbutane-1,3-diol (b.p. 146—148° at 760 mmHg, n_D^{20} 1·4273).

2,2-*Bis*(*trideuteriomethyl*)-4,4,6-*trimethyl*-1,3-*dioxan* was prepared by a similar route to that described previously [7] using hexadeuterioacetone as starting material.

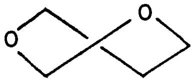
2,2,4,4,5,6-*Hexamethyl*-1,3-*dioxan* was prepared as a mixture of both diastereoisomers, by a method similar to that employed for 2,2,4,4,6-pentamethyl-1,3-dioxan, using 2,2-dimethoxypropane and 2,4-dimethylpentane-2,4-diol (b.p. 48° at 5 mmHg). The isomers were not separable by spinning-band distillation.

These compounds had ^1H and ^{13}C n.m.r. spectra and i.r. spectra in accord with their structures. All other compounds were prepared by conventional methods and had physical properties in agreement with the literature. We acknowledge a generous gift of *trans*-2,4,4,6-tetramethyl-1,3-dioxan from Mr. J. Powers and Professor E. L. Eliel.

Spectral Analysis.—The spectra examined in this work consist of spin–spin multiplets of the AB, AMX, ABX, or AA′XX′ types with extra couplings on one or more protons due to the methyl substituents. For the ABX spectra full ABX analyses were performed although the extra couplings from the alkyl groups were always treated on a first order basis. It is worth noting in passing that, for an ABX spectrum, only when $\Delta AB/J_{AB}$ is large (say $>2{\cdot}0$) can an estimate of J_{AX} and J_{BX} be made from the X resonance. This condition is never met in the 60 MHz spectra recorded in this work. The analyses of spectra were confirmed by comparison of observed spectra with those generated by the LAOCOON III program.

DISCUSSION AND RESULTS

Before proceeding to a discussion of our results we shall present a qualitative scheme we have developed for the prediction of the preferred conformation of alkyl groups in twist-boat 1,3-dioxan rings. Although the scheme arose from our results, our results are best interpreted in the light of it. We make no pretence that our scheme explains all the facts about the spectra of each compound. It does however account for the overall features of spectra in this series for those compounds where boat conformations predominate.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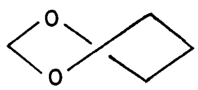
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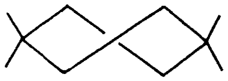
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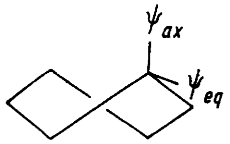

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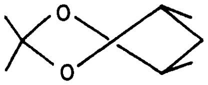
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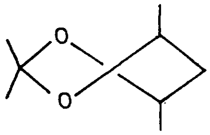
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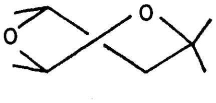
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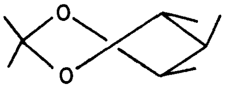
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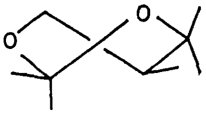
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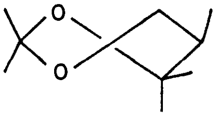
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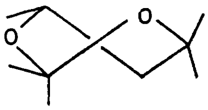
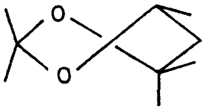

(VIa)


(VIb)

There are two basic types of twisted boat conformation for a 1,3-dioxan ring. We shall call these the 1,4-twist (Ia) with O(1) and C(4) at the ' stem and stern ' position, and the 2,5-twist (Ib) with C(2) and C(5) at these positions. The relative free-energies are determined principally by non-bonded interactions, torsion strain, angle strain, and dipolar effects. Torsion strain effects should be marginally smaller in a 1,4-twist conformation,

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[9] See for example, H. R. Buys, and E. L. Eliel, *Tetrahedron Letters*, 1970, 2779.

TABLE 1

Chemical shifts of ring hydrogens (τ) *

Compound	2-H	4,6-H	5-H
2,2-r-4-*c*-5-*t*-6-Penta-Me		6·02 6·69	*a*
2,2-*trans*-4,6-Tetra-Me		6·13	8·51
2,2,4,4-*cis*-5,6-Hexa-Me		6·26	*b*
2,2,4,4-*trans*-5,6-Hexa-Me		5·74	*b*
2,2,4,4,5-Penta-Me		6·47 6·53	8·25
2,2-Bis(trideuterio-Me)-4,4,6-tri-Me		6·04	8·64 8·73
2,4,4,6-*trans*-Tetra-Me	4·99	5·98	8·38 8·44

* All shifts recorded at 33·5 °C as 10% v/v CCl_4 solutions.

[a] Resonance obscured by alkyl peaks. [b] Mixture of stereoisomers. Only C(4,6) resonances umabiguously assigned.

TABLE 2

Coupling constants for compounds examined

Compound	T/°C [a]	Solvent	$^2J_{5.5}$ [b,c]	$^2J_{6.6}$ [b,c]	$^3J_{5.6(1)}$ [b,c]	$^3J_{5.6(2)}$ [b,c]	$^3J_{5.Me}$ [b,c]	$^3J_{6.Me}$ [b,c]
2,2-*r*-4-*c*-5-*t*-6-Penta-Me	+33·5	CCl_4 [g]			7·8	5·3	6·35	6·5, 6·3
	+70·0	CH_2Cl_2			7·9	5·3	6·35	6·5, 6·3
	+33·5	CH_2Cl_2			7·9	5·3	6·35	6·5, 6·3
	0·0	CH_2Cl_2			7·9	5·3	6·35	6·5, 6·3
	−35·0	CH_2Cl_2			7·9	5·3	6·35	6·5, 6·3
	−55·0	CH_2Cl_2			7·9	5·3	6·35	6·5, 6·3
	+32·2	Benzene			7·7	5·3		
	+51·8	Benzene			7·6	5·3		
	+71·6	Benzene			7·9	5·4		
	+91·5	Benzene			7·8	5·3		
2,2-*trans*-4,6-Tetra-Me	+33·5	CCl_4 [g]	−13·0		8·0 [f] (7·4)	6·8 [f] (7·4)		6·3 [f] (6·3)
	+33·5	CH_2Cl_2			7·5	7·5		
	−20·0	CH_2Cl_2			7·5	7·5		
	−50·0	CH_2Cl_2			7·5	7·5		
	+70·0	CH_2Cl_2			7·5	7·5		
2,2,4,4-*cis*-5,6-Hexa-Me	+33·5	CCl_4			2·4		*e*	6·4
	0·0	CH_2Cl_2			2·4			6·4
	+60·0	CH_2Cl_2			2·5			6·4
	+80·0	CH_2Cl_2			2·5			6·4
2,2,4,4-*trans*-5,6-Hexa-Me	+33·5	CCl_4				9·7	*e*	6·1
	0·0	CH_2Cl_2				9·7		6·1
	+60·0	CH_2Cl_2				9·8		6·1
	+80·0	CH_2Cl_2				9·7		6·1
2,2,4,4,5-Penta-Me	+33·5	CCl_4		−11·8 [d]	10·3 [d]	4·9 [d]	6·0	
	+33·2	Benzene		11·9 [d]	10·1 [d]	5·0 [d]		
	+51·8	Benzene		12·0 [d]	10·0 [d]	5·3 [d]		
	+71·6	Benzene		12·1 [d]	9·9 [d]	5·4 [d]		
	+91·5	Benzene		11·8 [d]	9·9 [d]	5·3 [d]		
2,2-Bis(trideuterio-Me)-4,4,6-tri-Me	+33·5	CCl_4 [g]	−12·9 [d]		10·9 [d] (8·4)	2·5 [d] (5·6)		6·0 [d]
2,2,4,4,6-Penta-Me	+33·2	Benzene			9·0	5·0		6·0
	+51·8	Benzene			8·4	5·6		6·0
	+71·6	Benzene			8·0	6·2		6·0
	+91·5	Benzene			7·7	6·4		6·0
	+33·2	Nitrobenzene			9·3	4·8		
	+91·5	Nitrobenzene			9·3	4·8		
	+121·0	Nitrobenzene			9·3	4·8		
	+151·0	Nitrobenzene			9·2	4·8		
	+180·0	Nitrobenzene			9·3	4·8		
2,4,4,6-*trans*-Tetra-Me	+33·5	CCl_4 [g]	−14·1 [d]		11·8 [d]	4·4 [d]		6·3 [d]

[a] ±1·0 °C. [b] Values in Hz; ±0·1 Hz. [c] All couplings are first order values unless otherwise noted. [d] Values obtained from ABX analysis, all other couplings are first order splittings. [e] Mixture of stereoisomers. Only C(6) resonances unambiguously assigned. [f] Values found to give a good approximation to the experimental spectrum (see text). [g] Values from 220 MHz spectra.

but this effect is likely to be small in relation to the large non-bonded interactions in these compounds.

A consideration of substituent positions shows three basic types of position available. All four positions at stem and stern (Ic) are equivalent and relatively free from non-bonded repulsions. On the other four ring atoms there are pseudo-axial (*ψax*) and pseudo-equatorial (*ψeq*) positions available (Id). One would expect a single methyl group to prefer the less hindered pseudo-equatorial orientation rather than the pseudo-axial. It is also reasonable to suppose that *gem*-dimethyl groups will prefer stem–stern positions, where they avoid one methyl group being in a hindered pseudo-axial position.* If we have a 2,2,4,4-tetramethyl substitution pattern one methyl group must occupy a hindered pseudo-axial position whichever twisted boat conformation is chosen.

Although our analysis up to now has been in terms of static twist-boat conformations it must not be overlooked that these forms may oscillate over part of ‘pseudorotation’ circuit. Small oscillations of this nature do not upset the subsequent arguments we present. We are now in a position to predict probable

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* Some quantitative backing for this argument comes from Hendrickson's calculations on twist boat conformations of cyclohexanes (J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1967, **89**, 7043).

preferred conformations for 1,3-dioxans known to exist in non-chair conformations.

trans-2,2,4,6-Tetramethyl-1,3-dioxan should exist with the 2,2-*gem*-dimethyl group [(IIa) and (IIb)] in the stem–stern position of a 2,5-twist. Of the two possible conformations now available (IIa) will be preferred as (IIb) has two pseudo-axial methyl groups. The spectrum of the ring protons confirms this. One would expect an AA′XX′ spectrum with additional splittings from the methyl group. A much simpler (deceptively simple) spectrum is observed with a triplet (J 7·4 Hz) for the C(5) protons and a quartet of triplets (J 7·4 and 6·2 Hz) for the C(4,6) protons. This situation can only arise in the AA′XX′ case when J_{AX} is roughly equal to $J_{AX'}$. In the case of this compound one expects roughly equal values for these couplings as the dihedral angles involved are roughly 30 and 150°. The calculated spectrum with J_{AX} 8·0, $J_{AX'}$ 6·8, and J_{AMe} 6·2 Hz confirms this interpretation. The 7·4 Hz vicinal coupling we observe must be the average of J_{AX} and $J_{AX'}$, therefore $J_{AX} + J_{AX'} = 14{\cdot}8$ Hz. For other 4,6-*trans* disubstituted 1,3-dioxans which occur in chair conformations Anteunis found the sum of these vicinal couplings to be about 10·8 Hz.[10] However for 4,6-*trans*-di-t-butyl-1,3-dioxan, which almost certainly has a non-chair conformation, he observed a value of 15·5 Hz. The agreement of this value with ours provides further evidence for a non-chair conformation in our compound.

Eliel[11] found a ΔG value of 7·2 kcal/mol between conformers for this compound by use of his four component equilibrium method. He expressed surprise that this value was close to the heat of combustion value of 7·1 kcal/mol found by one of us,[4] as he had anticipated a large entropy contribution from a ‘ flexible form ’. It is now clear that one would not expect a sizeable entropy contribution to ΔG as there is essentially only one non-chair conformation involved.

The argument becomes even more convincing for *trans*-2,4,4,6-tetramethyl-1,3-dioxan. For this compound our scheme predicts a 1,4-twist with pseudo-equatorial methyl groups at C(2) and C(4) (III). This conformation is confirmed by the 220 MHz spectrum. The vicinal couplings from the ABX analysis are 11·8 and 4·4 Hz. The larger value can only arise for a conformation with two protons in a *trans* arrangement about the C(5)–C(6) bond. This is the case for conformation (III). The observed and calculated (LAOCOON III) spectra of the C(5) and C(6) protons at 220 MHz are shown in Figure 1. It is important to note, in connection with previous work on this compound,[12] that the geminal C(5) chemical shift difference is 13·2 Hz at 220 MHz and therefore only 3·6 Hz at 60 MHz. First-order analysis of the C(6) proton signal is not appropriate in either case, and reported temperature variations in the apparent couplings on the C(6) proton[11] could be due to small variations in the C(5) geminal chemical shift difference.

Extending the argument further leads to the spectrum of 2,2-*r*-4-*c*-5-*t*-6-pentamethyl-1,3-dioxan. Our scheme predicts that the conformation (IV) should be preferred for this molecule, a conformation very similar to (IIa). A first order AMX analysis of this spectrum is valid as the same splittings are observed at 60 and 220 MHz. The splittings do not vary appreciably with temperature indicating the probable preponderance of one boat conformation. The couplings are qualitatively correct for (IV) and similar enough to those of (II) to confirm our earlier speculations.

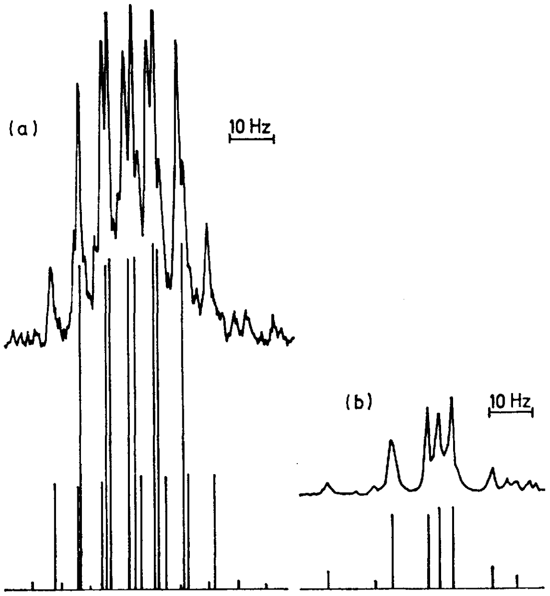

FIGURE 1 (a) Observed and calculated 220 MHz C(6)-H spectrum of *trans*-2,4,4,6-tetramethyl-1,3-dioxan. (b) Observed and calculated 220 MHz C(5)-H spectrum of *trans*-2,4,4,6-tetramethyl-1,3-dioxan

For 2,2,4,4,5-pentamethyl-1,3-dioxan there will be, as we discussed earlier, a competition between the 2 and 4 geminal groups for the stem–stern positions. The ‘ best ’ 1,4-twist predicted on our scheme is (Va) and the ‘ best ’ 2,5-twist is (Vb).

The observed vicinal couplings (10·3 Hz and 4·9 Hz) are only consistent with a preponderance of (Va). The invariance of the couplings with temperature, and their magnitude, suggests a strongly biased equilibrium in favour of (Va).

In the 220 MHz spectrum of 2,2,4,4,6-pentamethyl-1,3-dioxan in a variety of solvents the C(5) protons are always obscured beneath the methyl peaks, making it impossible to analyse the spectra. We therefore prepared the 2,2-bis(trideuteriomethyl) derivative which in carbon tetrachloride solution showed six of the eight lines of the AB [C(5)] portion of the spectrum. For this compound the two predicted twist boat conformations

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[10] D. Tavernier and M. Anteunis, *Bull. Soc. chim. belges*, 1967, **76**, 157.

[11] E. L. Eliel, Symposium on Conformational Analysis, Brussels, 1969, *Pure Appl. Chem.*, 1971, **25**, 509.

[12] E. L. Eliel and F. W. Nader, *J. Amer. Chem. Soc.*, 1970, **92**, 3050.

are (VIa) (1,4-twist) and (VIb) (2,5-twist). The values of the vicinal coupling constants (10·9 and 2·5 Hz) are consistent with a preponderance of (VIa). Again the 1,4-twist is seen to be preferred to the 2,5-twist. The changes observed, with temperature, in the apparent vicinal couplings are consistent either with an equilibrium between (VIa) and (VIb), or more probably with temperature variations in the (small at 60 MHz) C(5) chemical shift causing apparent couplings to alter. Observed and calculated 220 MHz spectra at ambient temperature are shown in Figure 2.

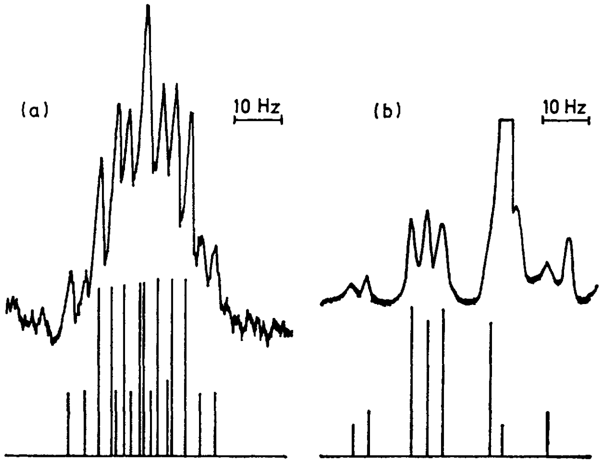

FIGURE 2 (a) Observed and calculated 220 MHz C(6)-H spectrum of 2,2-bis(trideuteriomethyl)-4,4,6-trimethyl-1,3-dioxan. (b) Observed and calculated 220 MHz C(5)-H spectrum of 2,2-bis(trideuteriomethyl)-4,4,6-trimethyl-1,3-dioxan

The observed couplings for the diastereoisomeric 2,2,4,4,5,6-hexamethyl compounds preclude the assignment of a predominant conformation. However the couplings are sufficiently different from those of unstrained chairs to confirm our assignment of non-chair conformations to these compounds.

Recently some quantitative estimates of the boat-chair energy difference in 1,3-dioxan have been made. Anteunis obtained a value of 6·2 ± 0·3 kcal/mol on the basis of some coupling-constant measurements.[13] Our experience of this approach and the assumptions and errors involved in this estimation lead us to suggest that the quoted errors (±0·3 kcal/mol) are optimistic. Pihlaja has measured the gas-phase enthalpy difference by use of appearance potentials in the mass spectrum, obtaining a value of 8·5 ± 0·5 kcal/mol.[14] The latter value agrees well with the value calculated for the gas phase of 8·3 ± 1·2 kcal/mol from the heat of formation of 2,2,4,6-tetramethyl-1,3-dioxan and a bond interaction scheme.[15]

Eliel and Nader [12] reported a standard free-energy difference >5·5 kcal/mol between the *cis*- and *trans*-isomers of 2,4,4,6-tetramethyl-1,3-dioxan. The *cis*-form certainly exists in a chair conformation, whilst we have demonstrated an anancomeric boat conformation for the *trans*-isomer. Because of the loss of entropy in the boat, the chair — boat free-energy difference should become nearly equal to the enthalpy difference (8·5 ± 0·5 kcal/mol).[4] Now there is strain in the *cis*-isomer amounting to 2·8 kcal/mol from the axial 4-methyl group. Hence a reasonable estimate of the free-energy difference between these two compounds is 8·5 — 2·8 = 5·7 ± 0·5 kcal/mol, in reasonable agreement with Eliel's estimate.

In the light of the above discussion it seems that the chair — boat enthalpy difference in 1,3-dioxan is 8·0 kcal/mol or slightly more. This value is considerably greater than that accepted for cyclohexane.

One of the outstanding features found in this work, is the existence of highly biased (anancomeric) twist-boat conformations. It has been common in certain quarters to call non-chair (or twist-boat) conformations 'flexible forms' with the implication that a wide variety of different non-chair conformations is available to such molecules. This implication is clearly misleading. When a compound is so encumbered as to be forced into a non-chair conformation hindrance between its substituents may force it into one preferred non-chair conformation.[16] This is the case with several of the compounds we have examined. The scheme we have presented in this paper allows the selection of the preferred non-chair conformations of 1,3-dioxans and should be applicable to other cyclic systems.

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[13] M. Anteunis and G. Swaelens, *Org. Magn. Resonance*, 1970, **2**, 389.

[14] K. Pihlaja and J. Jalonen, *Org. Mass Spectrometry*, in the press.

[15] K. Pihlaja, *Acta Chem. Scand.*, 1971, **25**, 451.

[16] D. J. Pasto and R. D. Rao, *J. Amer. Chem. Soc.*, 1969, **91**, 2792.