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CONFORMATIONAL ANALYSIS—XXVIII

FOUR-COMPONENT EQUILIBRIA IN 1,3-DIOXANES. RING DEFORMATIONS AND THE CHAIR-TWIST FREE ENERGY DIFFERENCE[1]

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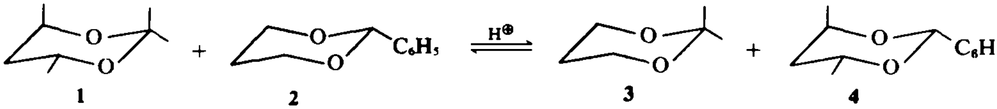
Abstract—Four-component equilibria in substituted 1,3-dioxanes were applied to the determination of conformational energies not accessible by conventional equilibration, with the following conclusions: 1. The difference in free energy between the chair and twist forms of 2,2,*trans* - 4,6 - tetramethyl - 1,3 - dioxane is 7·4 kcal/mol. 2. Equatorial Me substituents at C-4,6 exert a palpable buttressing effect on the corresponding axial substituents. 3. Equatorial substituents at C-2 exert a similar buttressing effect on the geminal axial substituent. 4. The effect of equatorial t-Bu substitution or *gem*-dimethyl substitution at C-5 on conformational energy seems to be of minor importance. The more complex effects of equatorial 4-t-Bu substitution are discussed.

INTRODUCTION

It occurred to us that the scope of the equilibration method of determining conformational energies[3] could be enlarged by the study of four-component systems (Fig 1) to complement the more conventional investigations of two-component equilibria (Figs 1, 2). The former type of equilibration sometimes offers advantages over the latter; in fact, as will be shown in the sequel, one may gain insights from the investigation of four-component equilibria which could not be obtained from two-component systems. Investigation of four-component equilibria has proved advantageous under the following sets of circumstances: 1. When an equilibrium of the type shown in Fig 2 is extremely one-sided ($K > 2{,}000$) it cannot be determined accurately or may be altogether inaccessible.[4] In such instances an equilibrium of the type shown in Fig 1, in which the large (and unknown) interaction on one side is counterbalanced by similarly large, but known, interactions on the other side, may be substituted. 2. Four-component equilibria provide what is perhaps a unique means of evaluating subtle difference between interactions of various substituents with the rest of the ring system. Four-component equilibria of this type are summarized in Tables 1–3. 3. Equilibria of the type shown in Fig 2 involve diastereoisomers which are not always readily accessible in pure form. Four-component equilibria, in contrast, may be established between compounds which either present no diastereoisomerism at all or in which one diastereoisomer is so much more stable than the others that it is obtained in essentially pure form in a thermodynamically controlled synthesis.

Four-component equilibria present somewhat different experimental problems than two-component ones. Since bimolecular reactions must be involved, it is necessary to use higher concentrations of reagents than has been customary in the past (*ca* 2M in ether in each dioxane or 4M overall). At these concentrations, equilibrium with Amberlyst-15 (beaded polystyrenesulfonic acid) as a catalyst is established in several weeks at room ture provided there is at least one substituent at C-2 in the 1,3-dioxane. Equilibria involving formals (e.g., Figs 3, 4) are established very slowly, and a concurrent unimolecular decomposition of one of the components often becomes extensive; for this reason equilibria involving formals were avoided whenever possible. Attainment of equilibrium is fastest when the substitutent at C-2 is phenyl or



$$\Delta G° = -0{\cdot}28 \pm 0{\cdot}01 \text{ kcal/mol}$$

Fig 1.

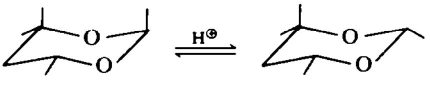
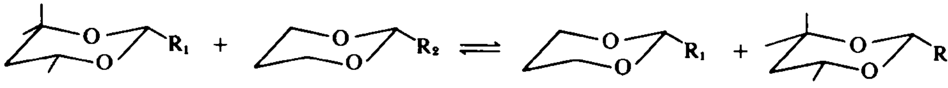


Fig 2.

when there are two substitutents at C-2 (as in a ketal) because of the obvious stabilization of the oxocarbonium ion which must be an intermediate in the equilibration (whose detailed mechanism is otherwise unknown). Since in the equilibrium A +

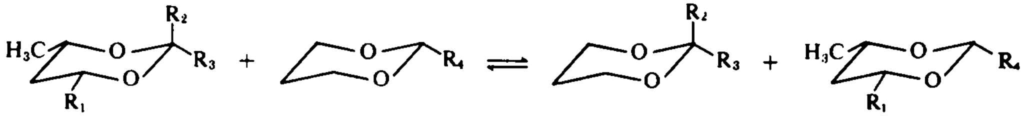
Table 1



Equilibrium #	R_1	R_2	K	$-\Delta G°$ (kcal/mol)
1	CH_3	C_6H_5	1·29 ± 0·02	0·12 ± 0·01
2	CH_3CH_2	C_6H_5	1·16 ± 0·01	0·09 ± 0·01
3	$(CH_3)_2CH$	C_6H_5	1·40 ± 0·02	0·20 ± 0·01
4	$(CH_3)_3C$	C_6H_5	1·34 ± 0·02	0·17 ± 0·01
5	C_6H_5	H	1·56 ± 0·02	0·26 ± 0·01
6	CH_3	H	*a*	0·38 ± 0·01
7	CH_3CH_2	H	*b*	0·35 ± 0·01
8	$(CH_3)_2CH$	H	*c*	0·45 ± 0·01
9	$(CH_3)_3C$	H	*d*	0·43 ± 0·01

[a] Calc'd as $\Delta G^\circ_1 + \Delta G^\circ_5$. [b] Calc'd as $\Delta G^\circ_2 + \Delta G^\circ_5$. [c] Calc'd as $\Delta G^\circ_3 + \Delta G^\circ_5$. [d] Calc'd as $\Delta G^\circ_4 + \Delta G^\circ_5$.

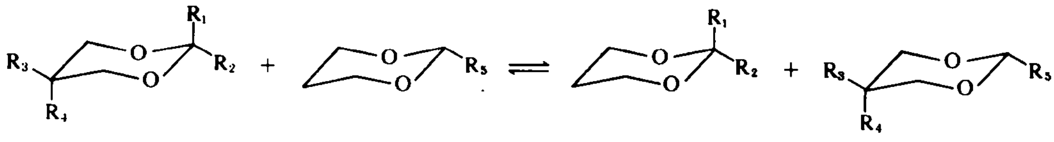
Table 2



Equilibrium #	R_1	R_2	R_3	R_4	K	$-\Delta G°$ (kcal/mol)
10	H	CH_3	CH_3	C_6H_5	1·21 ± 0·03	0·11 ± 0·02
11	CH_3	CH_3	CH_3	C_6H_5	3·48 ± 0·07	0·74 ± 0·01
12	H	H	C_6H_5	H	1·01 ± 0·01	0·01 ± 0·01
13	CH_3	H	C_6H_5	H	1·14 ± 0·01	0·08 ± 0·01
14	H	CH_3	CH_3	H	*a*	0·12 ± 0·02
15	CH_3	CH_3	CH_3	H	*b*	0·82 ± 0·01

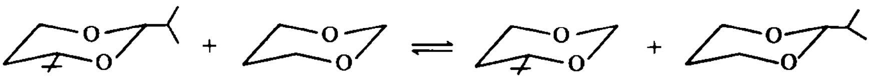
[a] Calc'd as $\Delta G^\circ_{10} + \Delta G^\circ_{12}$. [b] Calc'd as $\Delta G^\circ_{11} + \Delta G^\circ_{13}$.

Table 3



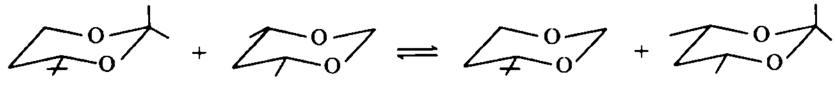
Equilibrium #	R_1	R_2	R_3	R_4	R_5	K	$-\Delta G°$ (kcal/mol)
16	H	CH_3	$(CH_3)_3C$	H	C_6H_5	0·66 ± 0·01	−0·24 ± 0·01
17	CH_3	CH_3	$(CH_3)_3C$	H	C_6H_5	0·91 ± 0·01	−0·06 ± 0·01
18	H	CH_3	$(CH_3)_3C$	H	H	1·18 ± 0·01	0·10 ± 0·01
19	CH_3	CH_3	$(CH_3)_3C$	H	CH_3	*a*	0·18 ± 0·02
20	CH_3	CH_3	CH_3	CH_3	C_6H_5	0·93 ± 0·02	−0·04 ± 0·01
21	CH_3	CH_3	CH_3	CH_3	H	0·86 ± 0·01	−0·07 ± 0·01
22	H	CH_3	CH_3	CH_3	H	0·89 ± 0·01	−0·07 ± 0·01

[a] Calc'd as $\Delta G^\circ_{17} - \Delta G^\circ_{16}$.



$\Delta G^\circ = -0{\cdot}23 \pm 0{\cdot}01$ kcal/mol

Fig 3.



$\Delta G^\circ_{(calc)} = 1{\cdot}21 \pm 0{\cdot}02$ kcal/mol

Fig 4.

$B \rightleftarrows C + D$ two of the components, say A and C, are frequently considerably more volatile than the other two, B and D, (e.g., when B and D are phenyl-substituted dioxanes) it often provided desirable to determine the ratios C/A and B/D separately; K was then computed as (C/A) × (D/B). Equilibria were approached from both sides and it is satisfying that, although the individual ratios C/A and D/B varied widely, depending on the initial concentrations of reagents, their products, i.e., the equilibrium constants K, were constant within reasonable standard deviations.

RESULTS AND DISCUSSION

Fig 1 summarizes what is perhaps the most interesting application of the four-component method: the determination of the chair-twist free energy difference in 1,3-dioxane. The experimental instability of 2,2 - *trans* - 4,6 - tetramethyl - 1,3 - dioxane (**1**) can be evaluated from the position of equilibrium and the known interactions present in the other compounds involved in the equilibration. Equilibration of **1** with 2 - phenyl - 1,3 - dioxane (**2**) gives 2,2 - dimethyl - 1,3 - dioxane (**3**) with an axial Me-2 interaction of *ca* 4 kcal/mol[4] and *r* - 2 - phenyl- *cis* - 4, *trans* - 6 - 1,3 - dioxane (**4**) with an axial Me-4 interaction of 3·1 kcal/mol.* Since ΔG° for the process shown in Fig 1 is −0·3 kcal/mol, the conformational free-energy of **1** must be 7·4 kcal/mol (4·0 + 3·1 + 0·3).

The chair form of **1** would have the following interactions: Me-2/H-4, *ca* 2 kcal/mol (one-half the axial Me-2 interaction[4]); Me-4/H-6, *ca* 0·85 kcal/mol (one-half the axial Me interaction in cyclohexane) or *ca* 1·1 kcal/mol (Me-4/H-2,6—one-half Me-2/H-4 interaction in 1,3-dioxane, i.e., 3·1 − 2·0 kcal/mol); Me-2/Me-4, $\gg$ 3·7 kcal/mol, which is the corresponding interaction in cyclohexane[7] where the Me-Me *syn*-axial distance is much greater (the interaction has been "evaluated" as 8·9 kcal/mol in 1,3-dioxane[8]). Thus the total interaction energy is $\gg$ 6·55 or $\gg$ 6·8 kcal/mol, perhaps as large as 11·75 or 12 kcal/mol, and since the experimental instability is only *ca* 7·4 kcal/mol, **1** should exist largely in the twist form. This has recently been confirmed by Pihlaja *et al.*[9]

Pihlaja[10] has reported 7·1 kcal/mol as the enthalpy difference between the chair and twist forms of **1**, and both he[10] and one of us[11] were at first surprised about the near equality of ΔG° and ΔH° which implies $\Delta S^\circ_{\text{chair-twist}} \approx 0$. However, it has since been shown[9] that **1** exists in essentially a single, nearly rigid twist conformation[6] (Fig 5), located in a relatively deep energy well and capable of only limited pseudolibration, so that the lack of entropy gain in going to this conformation is entirely reasonable.[12]

Although the 7·4 kcal/mol value for the twist form of **1** probably requires some adjustment if it is to be compared to the chair-twist enthalpy difference in 1,3-dioxane itself, since there is presumably some residual methyl/hydrogen interaction in the twist form of **1** due to a pseudoaxial methyl group (*cf* Fig 5),† it is clear that the chair-twist free-energy difference in 1,3-dioxane is considerably

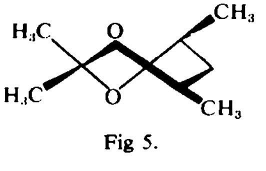


Fig 5.

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*This is the experimental ΔG° value[5] for 2 - isopropyl - 4 - methyl - 1,3 - dioxane (K = 163 ± 5) corrected for the conformational inhomogeneity of the 2 - isopropyl group (K = 1,134[4]) which is used instead of the earlier value of 2·9 kcal/mol derived from 2 - t - butyl - 4 - methyl - 1,3 - dioxane.[6]

†The magnitude of this interaction is difficult to assess and, as it is probably partially offset by the fact that the assumed value of *ca* 4 kcal/mol for the Me-2 interaction in **3** is too small (since it has not been corrected for buttressing) so we have chosen to disregard it.

larger than the corresponding value (5·9 kcal/mol in cyclohexane.[13] This conclusion is supported by the values for the chair-twist enthalpy difference which were recently deduced from microcalorimetric[14] (8·8 kcal/mol) and mass spectral[15] measurements (8·5 kcal/mol).

The second application of the four-component method was in confirming what we should like to call "Allinger buttressing", since it was first pointed out by Allinger's group[16] that an equatorial alkyl group at C-3 in a cyclohexane buttresses the geminal axial hydrogen by decreasing the C—C—H valency angle from 109·5° to 107·7°, by increasing the angle bending force constant ($\omega_{C-C-H} > \omega_{H-C-H}$), and by pressing on the axial hydrogen. In turn, this leads to an increase in the *syn*-axial interaction of this hydrogen atom with an axial substitutent at C-1. This type of buttressing accounts for the known[17] fact that $\Delta G^\circ_{e\text{-}a}$ values for the substituent in substituted cyclohexyl compounds are larger when the holding group (e.g. t-butyl, $OAlCl_2$) is in the 3-position than when it is in the 4-position. The results of our first series of experiments investigating buttressing effects of this type are shown in Table 1, entries 1–4, where the axial H-2 is differentially buttressed by an equatorial phenyl or alkyl group at C-2 with a resulting effect on the compression of the 2-axial hydrogen with the axial Me group on C-4. From these data and the experimentally determined buttressing energy of phenyl compared to hydrogen (entry 5) one may, by the application of Hess's law, calculate the buttressing energy caused by an equatorial alkyl substituent at C-2, i.e., the increase in buttressing which results when the equatorial H-2 is replaced by an alkyl or a phenyl group (entries 5–9).

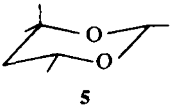
As the data in Table 1 show, the effect is palpable for all groups studied and increases in the series Ph < Me ~ Et < i-Pr ~ t-Bu. This order is reasonable if it is granted that the effect is one partly of angle deformation and partly of steric compression. The steric factor is least in phenyl, which in a 2-phenyl-1,3-dioxane is either oriented horizontally[18] ("perpendicular conformation"[19]) or rotates freely;[20] it is about equal in Me and Et, the latter probably having its terminal Me group oriented *anti* to H-2, and it is larger, but equally so, in isopropyl and t-Bu, both of which must have at least one *β*-Me group *gauche* to H-2.

A related, and in fact considerably more pronounced, buttressing effect is seen in the series shown in Table 2. Equilibrium 11 shows that the axial Me group (R_2) at C-2 prefers the *syn*-axial position in the unbuttressed 2,2-dimethyl compound over that in the doubly buttressed *cis*-4,6-dimethyl compound by 0·74 kcal/mol, whereas the preference with respect to the singly buttressed compound (entry 10) is only 0·11 kcal/mol. The calculated equilibria (based on 10/12 and 11/13) show that the effect is not an artifact of phenyl substitution; equilibria 12 and 13 (Table 2) represent fairly good "null experiments" with an expected and observed ΔG° of near zero.

There are two points to be discussed in relation to the data in Table 2. First, it should be noted that there is a disproportionately large increase in buttressing energy resulting from the addition of a second buttressing substituent (entries 11 *vs* 10 and 15 *vs* 14). This is reasonable if one considers the fact that the axial Me groups (R_2) against which the *syn*-axial protons (H-4, H-6) abut, are themselves buttressed by an equatorial Me group (R_3) and therefore cannot readily minimize *syn*-axial non-bonded interactions by bending outward. When the first buttressing substituents is introduced (at C-4), the axial Me group at C-2 may, however, minimize some of the resulting increase in non-bonded interactions by bending away from the buttressed *syn*-axial hydrogen (at C-4) and toward the as yet unbuttressed one (at C-6), which should be both further away (angular effect) and more easily bent outward (steric effect). The introduction of the second buttressing substituent precludes this possibility, and the two buttressing substituents would then in effect reinforce one another, resulting in a large increase in buttressing energy.

Secondly, it may be noted that the buttressing energy is considerably greater when the two *syn*-axial protons are located at C-4 and C-6 and buttressed against an axial substituent at C-2 than when they are located at C-2 and C-6 and similarly buttressed against an axial substituent at C-4 (Table 1, entry 6). This is in fact quite reasonable: because of the puckering of the 1,3-dioxane ring in the O—C—O region,[18] an axial Me group on C-2 leans into the ring more than an axial Me group on C-4, and for this reason, the Me-2/H-4 *syn*-axial distance is less than the Me-4/H-2 *syn*-axial distance. Therefore, the buttressing energy resulting from the extra compression of an axial hydrogen at C-4 (or C-6) with an axial Me group at C-2 caused by the addition of an equatorial substituent at C-4 should be greater than the buttressing energy resulting from the extra compression of an axial hydrogen at C-2 with an axial Me group on C-4 caused by the addition of an equatorial substituent at C-2.

There are NMR data which support the concept of buttressing. In *cis*-2,4,4,6-tetramethyl-1,3-dioxane (**5**) $J_{5a,6a} = 8\cdot5$ Hz and $J_{5e,6a} = 6\cdot1$ Hz while the corresponding values in Δ-2-*cis*-4,*trans*-6-trimethyl-1,3-dioxane (**6**) are 11·7 Hz and 2·6 Hz respectively, indicating that there is considerable outward displacement of the 6-axial proton in the tetramethyl compound relative to the trimethyl



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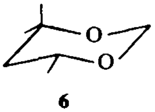

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compound.* The entire deformation cannot be due simply to an angular effect resulting from the introduction of an equatorial Me group since Geise[21] has shown by electron diffraction studies that the ring geometry is essentially the same in cyclohexane and methylcyclohexane and Buys and Eliel[22] have shown that the introduction of an equatorial substituent at C-2 does not significantly alter the geometry of the 1,3-dioxane ring in the C-4,5,6 region as evidenced by constancy of coupling constants. The deformation is therefore best explained on the basis of a buttressing of the axial Me group at C-4 resulting from the introduction of the equatorial Me substituent at C-2. This should result in both an increase in the *syn*-axial non-bonded interactions and an increase in the reluctance of the now buttressed axial Me group to bend outward. As a net result, then, one would expect an increase in the outward deformation of the *syn*-axial proton at C-6, which in this instance is manifested by an increase in J_{5e6a} and a decrease in J_{5a6a}.

J_{4a5a} in *cis*-4,6-dimethyl-1,3-dioxane has been reported as 9·5–10·0 Hz[6,23] whereas the value in 1,3-dioxane is 12·4 Hz.[20,22] Such a decrease in J_{4a5a} in the dimethyl compound could result from either an inward or outward deformation of the 4,6-axial protons from their position in 1,3-dioxane. But the value of 10·6–10·9 Hz[6,23] reported for J_{4a5a} in 2,2-*cis*-4,6-tetramethyl-1,3-dioxane suggests that the 4,6-axial protons were deformed inward in the 4,6-dimethyl compound, and were then "pushed" back outward (nearer to their position in 1,3-dioxane) by the introduction of the axial Me group at C-2 in the tetramethyl compound. Again, this observation is in complete harmony with the concept of buttressing proposed above.

If this phenomenon is a general one, and it appears that it is, then one must conclude that the conformational energies for 2-substituents in the 1,3-dioxane system which have been determined by equilibration of 2-substituted *cis*-4,6-dimethyl compounds are too large, because neither of the *syn*-axial hydrogens can easily escape the compression of the axial substituent by outward bending. Indeed the expected trend can be found in the values determined for the gas-phase conformational energies of the Me group in variously substituted polymethylcyclohexanes. The value of 1·91 kcal/mol[24,25] in 1,4-dimethylcyclohexane, where there is no buttressing of a hydrogen *syn*-axial to the Me group, is slightly smaller than the value of 1·96 kcal/mol[24,25] found in the 1,3-dimethyl compound where there is one buttressed *syn*-axial hydrogen, and is significantly smaller than the value of 2·05 kcal/mol[26] found in the 1,3,5-trimethyl compound in which both *syn*-axial hydrogens are buttressed. The values determined for buttressing energies in 1,3-dioxanes by the above four-component studies may well represent upper limits, since, as stated, in our studies all the axial methyl groups were themselves buttressed by an equatorial Me group, and the buttressing of one Me group by another is expected to be more important than the steric buttressing of an H atom by a Me group. Nevertheless, because of the shorter *syn*-axial distances, buttressing energies should be larger in 1,3-dioxanes than in cyclohexanes, and the effects of buttressing on earlier determined conformational energies[3b] cannot be ignored.

In light of this conclusion, we decided to extend our study to an investigation of the potential of a 4-t-Bu substituent as a holding group for conformational studies in 2-substituted 1,3-heterocycles. Of course, such a study was also of interest because the effect of 3-t-Bu substitution on conformational preferences in cyclohexanes is rather well understood[27] and it was hoped that several direct analogies would emerge. Such, however, was not the case.

We have found[5,28] that the preference of a 2-i-Pr substituent in 1,3-dioxane for the equatorial position is over 1 kcal/mol less in the 4-t-Bu substituted compound than in the *cis*-4,6-dimethyl substituted compound (Fig 6). Obviously this must result from a destabilization of the equatorial i-Pr group, a stabilization of the axial one, or a combination of the two in the 4-t-Bu substituted compound relative to the *cis*-4,6-dimethyl substituted compound.

We are able to rule out the possibility of a large destabilization of the equatorial 2-i-Pr group by the 4-t-Bu substituent by the four-component equilibrium shown in Fig 3. Although the i-Pr group is slightly less comfortable in the 4-t-Bu compound than in 2-isopropyl-1,3-dioxane, the small decrease in stability observed is quite insufficient to explain the greatly reduced equatorial preference of the 2-i-Pr group in 4-t-butyl-2-isopropyl-1,3-dioxane.

While we were not able to investigate directly the effect of 4-t-Bu substitution on an axial 2-i-Pr group, we were able to show (Fig 4) that an axial substituent at C-2 (at least the axial Me of a *gem*-dimethyl) is considerably more stable in the 4-t-Bu compound than in the *cis*-4,6-dimethyl compound. This effect will be discussed in more detail in a forthcoming publication.[28]

Extension of our study of substituent effects by the four-component equilibration method to 5-t-Bu and 5,5-dimethyl substituted dioxanes led to the findings shown in Table 3. Although the use of the 4-t-Bu substituent as a holding group[29] for conformational studies in cyclohexyl systems has been widely criticized,[30–37] with most of the more recent criticism stemming from Cornubert's[38] original sug-

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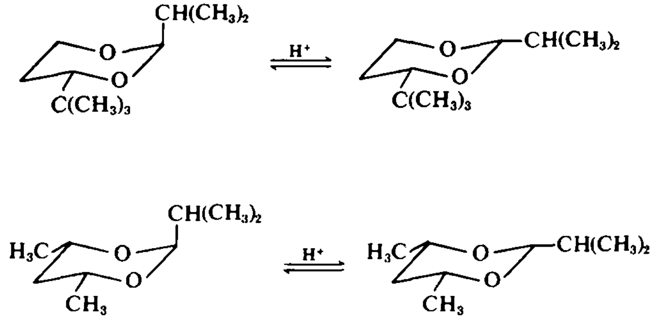
*These coupling constants were arrived at by computer refinement of first-order input. Computer program LAME (J. D. Swalen, *Progress in NMR Spectroscopy* **1**, 205 (1966)) was provided by Dr. G. Binsch and the calculations carried out on the Univac 1107 computer at the University of Notre Dame.



$\Delta G° = -2{\cdot}70 \pm 0{\cdot}02$ kcal/mol[5,28]

$\Delta G° = -4{\cdot}17 \pm 0{\cdot}05$ kcal/mol[4]

Fig 6.

gestion that one of the Me groups of the 4-t-Bu substituent buttresses the axial hydrogens at C-3 and C-5 resulting in an increase in steric compression on an axial substituent at C-1, our data show that the effect is of marginal importance even in a system as compressed as 1,3-dioxane. The data in Table 3 suggests that 5-t-Bu buttressing may be palpable if one compares the 2,2-dimethyl series with the 2-Me series (Equilibria 16 and 17) but that it is overwhelmed by another effect operating in the opposite direction which is most notable in the 2-Me series and still predominates slightly over supposed "Cornubert buttressing" even in the 2,2-dimethyl series. The origin of this "other" effect, which prevents Equilibrium 16 from serving as a null experiment, is unfortunately not clear; however, comparison of Equilibria 16 and 18 indicates that this effect is an artifact of phenyl substitution. If, as has been suggested[20] an equatorial phenyl at C-2 ordinarily rotates freely, one might imagine that a deformation caused by the 5-t-Bu group could affect the rotational freedom of the 2-phenyl substituent resulting in an entropic loss and an overall destabilization of the 5 - t - butyl - 2 - phenyl - 1,3 - dioxane. This is, of course, highly speculative. Fortunately, one can "remove" the effect of phenyl substitution by algebraic subtraction of Equilibrium 16 from Equilibrium 17 to yield Equilibrium 19 in Table 3.

Although Equilibrium 19 does show that a 5-t-Bu substituent destabilizes an axial group at C-2 (at least the axial Me of a *gem*-dimethyl) and that Cornubert's suggestion is thus apparently correct, the magnitude of the effect seems to be quite small even in a compound as compressed as a 2-axially substituted 1,3-dioxane. This might, however, have been expected in light of recent X-ray diffraction studies[39–44] which indicate that while the distance between the hydrogens on one of the Me groups of the t-Bu substituent and the adjacent axial hydrogens may be slightly less than the combined van der Waals radii, there is usually an accompanying slight flattening of the ring. Although the results of all the X-ray studies are not in agreement on these points, it is reasonable to assume that these effects will largely offset one another. Local ring flattening resulting from t-Bu substitution has also been predicted from molecular mechanics calculations.[45]

Our last series of experiments were designed to investigate the somewhat related suggestion of Lambert[46] that 4,4-dimethyl substitution in cyclohexane tends to increase the axial stability of a halogen substituent at C-1 by 0·03–0·10 kcal/mol. Our data (Equilibria 20–22) are clearly in agreement, but the effect, as in Lambert's case, is quite marginal. However, the fact that we observe less stabilization of an axial Me group than previously observed[46] for an axial halogen substituent leads us to question the explanation[46] of the effect. It was proposed[46] that the change in the exocyclic bond angle about C-4 from about 111° in cyclohexane to about 109° in the 4,4-dimethyl compound should result in a slight puckering of the C(3)—C(4)—C(5) portion of the ring and a bending away of the 3,5-axial protons from the ring center. Not only is this difficult to visualize; but it is also inconsistent with existing data. Recent electron diffraction data[47] show that, as a result of the introduction of the axial Me group, 1,1-dimethylcyclohexane is, as expected, considerably flatter (torsional angle $\tau_{av} = 51{\cdot}7°$) than either cyclohexane ($\tau_{av} = 55{\cdot}9°$[21]) or methylcyclohexane ($\tau_{av} = 55{\cdot}3°$[21]). When considered on the basis of ring flattening our results become quite consistent with those of Lambert's group.[46] Because the 2,4-*syn*-axial distance in 1,3-dioxane is considerably shorter than the corresponding 1,3-*syn*-axial distance in cyclohexane, and also because a Me group is larger than a halogen atom, a similar deformation of the ring would be expected to result in a larger stabilization in our system than in Lambert's. This is not the case. The deformation is probably not similar, nor should it be if ring flattening is involved. Introduction of an axial Me group into the cyclohexane ring should engender more flattening of the ring than the introduction of an axial Me group at C-5 in 1,3-dioxane, since the flattening of the ring results, at least in part, from an attempt to relieve the *syn*-axial interactions experienced by an axial substituent in this way. As the *syn*-axial interactions are not as large for an axial Me group at C-5 in 1,3-dioxane ($\Delta G° = 0{\cdot}85$ kcal/mol[23]) as they are for an axial Me group in cyclohexane (*ca* 1·75 kcal/mol[48]) the 1,3-dioxane ring should be flattened proportionately less than the cyclohexane ring by the introduction of an axial Me group. If considered in light of this argument, the data for the 5,5-dimethyl 1,3-dioxane system and the 4,4-dimethylcyclohexane systems are compatible.

In summary, our data show that geminal buttressing effects can be quite substantial especially when both protons *syn*-axial to a test group are buttressed in this fashion. Vicinal buttressing effects (e.g., buttressing by a 5-t-Bu substituent) and remote substituent effect (e.g., by 5,5-dimethyl substitution), on the other hand, seem to be of minor importance in their effect on conformational equilibria.

EXPERIMENTAL

Reaction products and equilibration mixtures were analyzed on F & M Scientific Corporation Model 810-29 or 810-19 dual thermal conductivity Research Chromatographs, or a Hewlett–Packard Model 5254 dual thermal conductivity Research Chromatograph. The F & M instruments were equipped with Honeywell Brown Electronik Model 15 1·0 mv recorders and the Hewlett-Packard instrument with a Mosley Model 7127A 1·0 mv recorder. All recorders were equipped with Disc Instrument Company peak area integrators. Detector temperatures were maintained between 230 and 300°; the injector block was maintained at 230°.

Purification of all compounds was effected by preparative GLC on a Nester–Faust Model 850 Prepkromatic Automatic Preparative Gas Chromatograph or Varian Aerograph Series 1520 and 2700 Preparative Chromatographs. Elemental analyses were performed by either Midwest Microlab, Indianapolis, Ind. or Galbraith Laboratories, Knoxville, Tenn.

NMR spectra were recorded on Varian A-60A, JEOLCO C60HL, and Varian XL-100 spectrometers on solns of 5 to 25% v/v or w/v in CCl_4, using TMS as a standard.

The preparation and purification of 2,2,4 - *trans* - 6 - tetramethyl - 1,3 - dioxane, 2 - phenyl - 1,3 - dioxane, 2,2 - dimethyl-1,3-dioxane, 2-methyl-1,3-dioxane, 2-ethyl-1,3 - dioxane, 2 - isopropyl - 1,3 - dioxane, 2 - t - butyl - 1,3 - dioxane, *cis* - 2,2,4,6 - tetramethyl - 1,3 - dioxane, 2,2 - dimethyl - 5 - t - butyl - 1,3 - dioxane, *trans* - 2 - methyl - 5 - t - butyl - 1,3 - dioxane and *trans* - 2 - phenyl - 5 - t - butyl - 1,3 - dioxane have been described elsewhere.[6] The

Table 4. Yield and properties of substituted 1,3-dioxanes

Substituents	Yield %	B.p., °C (mm)	Analysis or Literature Reference		
cis-2-Ph-4,4,6-tri-Me	45	64–65(0·6)		*a*	
cis-2,4,4,6-tetra-Me	48	138–139		*b*	
cis-2-Et-4,4,6-tri-Me	89	154–155		C	H
			Calc'd	68·30	11·47
			Found	68·49	11·64
cis-2-i-Pr-4,4,6-tri-Me	64	76–77(22)		*c*	
cis-2-t-Bu-4,4,6-tri-Me[d]	40	49–50(5·0)		C	H
			Calc'd	71·68	12·04
			Found	71·62	12·22
2,4,4-tri-Me	91	130–131		*e*	
cis-2-Ph-4-Me	87	78–80(0·3)		*f*	
r-2-Ph-*trans*-4-*cis*-6-di-Me	85	143–144(18)		*g*	
2-Ph-5,5-di-Me	82	133–135(15)		*h*	
2,5,5-tri-Me	56	128–130		*i*	
cis-2-i-Pr-4-t-Bu	84[j,k]	*l*		C	H
			Calc'd	70·91	11·91
			Found	71·26	11·97

[a] A. Franke and E. Gigerl, *Monatsh. Chem.* **49**, 8 (1928) report b.p. 124°/9 mm. Analysis: Calc'd for $C_{13}H_{18}O_2$: C, 75·72; H, 8·73. Found: C, 75·76; H, 8·85.

[b] P. Mastagli, P. Lambert, and G. Francois, *Bull. Soc. Chim. Fr* 764 (1957) report b.p. 139–140°.

[c] F. Blicke and H. Raffelson, *J. Am. Chem. Soc.* **74**, 1730 (1952) report b.p. 68°/25 mm.

[d] IR: 1477(m), 1192 (s), 1152 (s), 1085 (s), 992 (s), 877 cm^{-1} (s). NMR: 0·88 (s, 9H), 1·03–1·42 (m, 11H), 3·47–3·98 (m, 1H), 4·27 ppm (s, 1H).

[e] G. Schneider, O. Kovacs, and M. Chinori, *Acta. Univ. Szeged., Acta. Phys. Chem.* **10**, 95 (1964) report b.p. 129°.

[f] *Id., Ibid*, report b.p. 105/5 mm.

[g] J. Kovar, J. Staffkova, and J. Jarry, *Collection Chech. Chem. Commun.* **30**, 2793 (1965) report b.p. 120°/14 mm.

[h] *Id. Ibid*, report b.p. 140°/17 mm.

[i] C. S. Rondestvedt, *J. Org. Chem.* **26**, 2247 (1961) reports b.p. 130–131°.

[j] IR: 1464 (m), 1361 (m), 1248 (m), 1125 (m), 1067 (m), 1028 (m), 992 (m), 888 cm^{-1} (m). NMR: 0·87 (s, 9H), 0·88 (d, J = 6·2, 6H), 0·92–2·08 (m, 3H), 2·99–4·08 (m, 3H), 4·16 ppm (d, J = 4·5, 1H).

[k] The preparation, by a new method, of 4,4-dimethyl-1,3-pentanediol will be reported in a future publication. For a previous preparation, see Ref 51.

[l] Distilled with a microdistillation apparatus.

properties of these compounds, notably NMR and IR spectra were as reported previously. 2 - Phenyl - *cis* - 4,6 - dimethyl - 1,3 - dioxane has also been reported in a previous paper.[4] 2,2,5,5 - Tetramethyl - 1,3 - dioxane was a gift from Dr. W. F. Bailey;[20] 1,3 - dioxane and 4 - methyl - 1,3 - dioxane were commercially available. *cis* - 4,6 - Dimethyl - 1,3 - dioxane was available from the doctoral research of Sr. M. C. Knoeber.[49]

The remaining 1,3-dioxanes were prepared from the corresponding aldehydes or ketones and 1,3-diols, using *p*-toluenesulfonic acid as catalyst and benzene as solvent; water was removed azeotropically according to the method of Salmi,[50] and the solution was neutralized by stirring with excess anhydrous potassium carbonate prior to work-up. Products not previously reported[4,6,20,49] are shown in Table 4.

4 - t - Butyl - 1,3 - dioxane was prepared by the general procedure of Aftalion[52] from 4,4 - dimethyl - 1,3 - pentanediol and aqueous formaldehyde. The steam distilled product was dried and purified by preparative GLC (75% yield by GLC). IR: 1477 (m), 1575 (m), 1172 (m), 1005 (s), 1098 (s), 1042 (s), 998 (m), 963 (m), 914 (m), 876 (m), 838 cm^{-1} (m). NMR: 0·87 (s, 9H), 1·06–2·10 (m, 2H), 3·12 (dd, J = 10·5, J = 3·0, 1H), 3·49–4·25 (m, 2H), 4·54 (d, J = 6·0, 1H), 4·96 ppm (d, J = 6·0, 1H). (Found: C, 67·10; H, 11·22. Calc'd for $C_8H_{16}O_2$: C, 66·62; H, 11·19%).

Equilibrium studies. Equilibrations were effected in anhydrous diethyl ether with Amberlyst-15 (beaded polystyrenesulfonic acid) as catalyst in sealed ampoules under an atmosphere of N_2. Solns were *ca* 4M in combined dioxane concentration and equilibrium was generally established in 6–8 weeks. Each equilibrium constant reported is the average of 12–20 determinations; in all cases, area ratios, as determined by analytical GLC, were corrected for response ratios. The errors stated are standard deviations.

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