

Conformational Analysis. XVI. 1,3-Dioxanes<sup>1,2</sup>Ernest L. Eliel and Sr. M. Carmeline Knoeber, Ad.PP.S.<sup>2</sup>*Contribution from the Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556. Received December 7, 1967*

**Abstract:** A series of conformationally biased 2-, 4-, and 5-alkyl-1,3-dioxanes has been studied through acid-catalyzed equilibration of diastereoisomers and by nuclear magnetic resonance spectroscopy. The preferences of the alkyl substituents for the equatorial (over the axial) position are substantially different from corresponding preferences in cyclohexane and depend on the location in the dioxane ring. Quantitatively, these preferences (in kilocalories/mole) are Me-2,  $\geq 3.55$ ; Me-4, 2.9; Me-5, 0.8; Et-5, 0.7; *i*-Pr-5, 1.0; Ph-5, 1.0; *t*-Bu-5, 1.4. The data are rationalized in terms of the shape of the 1,3-dioxane ring and the "size" of the free electron pair on oxygen. The preference of the 1,3-dioxane ring for the chair over the skew-boat conformation is estimated to be at least 4 kcal/mol.

Conformational equilibria of the type shown in Figure 1 have been studied extensively in cyclohexane<sup>3,4</sup> and a number of  $-\Delta G^\circ$  values ( $=RT \ln K$ ) or "conformational energies" have been tabulated for a wide variety of substituents,<sup>3,5</sup> including values for the methyl (1.70 kcal/mol), ethyl (1.75 kcal/mol), and isopropyl (2.15 kcal/mol) groups. For the *t*-butyl group it is known experimentally only that the conformational energy is in excess of 4.4 kcal/mol; recent calculations<sup>6</sup> suggest a value of 5.4 kcal/mol.

In contrast, relatively little is known about conformational preferences in saturated heterocyclic systems. It has often been assumed that, in six-membered rings, such preferences may be taken to be the same as in cyclohexane; what limited information is available indicates, however, that this assumption is, in general, not valid. For example, an alkoxy group in position 2 of tetrahydropyran prefers the axial position for reasons related to dipole interactions<sup>7</sup> and a hydroxyl group in position 5 in a 1,3-dioxane prefers the axial position for reasons of hydrogen bonding.<sup>8</sup>

Even when polar effects do not come into play and the conformational preference is controlled by steric factors only, one would not expect an exact parallel between cyclohexane and its heterocyclic analogs, for the bond distances and bond angles in saturated six-membered heterocyclic rings and in cyclohexane are not the same, the angle bending force constants and possibly also the torsional potentials differ, and last but not least the heterocyclic rings have unshared

pairs of electrons in certain positions where cyclohexane has hydrogen substituents. It is because of these potentially interesting differences that we have launched a research program to investigate the conformational preferences in a number of substituted heterocycles.

For one of the first representatives, we chose 1,3-dioxane (Figure 2). This system has a number of advantageous properties from the point of view of conformational study. Thus, since 1,3-dioxanes are acetals or ketals, they are readily synthesized with a wide variety of substituents in the 2, 4, 5, and 6 positions from appropriately substituted and generally readily available aldehydes or ketones and 1,3-glycols. Secondly, in the cases where diastereoisomers (*cis-trans* isomers) exist, it might be expected that such isomers would be readily equilibrated by means of anhydrous acid through the type of reversible ring-opening process depicted in Figure 3. This possibility of facile equilibration is quite important, for chemical equilibration is perhaps the most accurate and certainly one of the most reliable methods of conformational study.<sup>9</sup> A third advantage of the 1,3-dioxane system is the fact that nmr spectra (useful for configurational and conformational assignments of structure) in this system are often readily interpretable, inasmuch as the chemical shifts of the protons in positions 2 (acetal position), 4,6 (ether position), and 5 (hydrocarbon position) are usually quite distinct so that, in contrast to the situation in cyclohexane, well-defined spectra are generally obtained. A fourth advantage of the 1,3-dioxane system is that it affords three distinct sites of substitution (C<sub>2</sub>, C<sub>4,6</sub>, and C<sub>5</sub>), thus permitting a larger number of conformational studies than a more symmetrical system with a resulting greater amount of useful information. Finally, the 1,3-dioxane system shares with other heterocyclic systems the interesting feature of possessing atoms with unshared pairs. Thus an axial substituent in the 5 position will be *syn*-axial not with two axial hydrogens (as in cyclohexane) but with two unshared pairs of electrons.

At the inception of this investigation, conformational

(1) Paper XV: E. L. Eliel and M. C. Reese, *J. Am. Chem. Soc.*, **90**, 1560 (1968).

(2) (a) From the Ph.D. Dissertation of Sr. M. C. Knoeber, University of Notre Dame, 1967. We acknowledge support of this work under grants from the National Science Foundation (G-20555) and the Air Force Office of Scientific Research (AF-AFOSR-772). (b) Preliminary publication: *J. Am. Chem. Soc.*, **88**, 5347 (1966).

(3) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1965.

(4) E. L. Eliel, *Angew. Chem.*, **77**, 784 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 761 (1965).

(5) J. A. Hirsch, in "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1967.

(6) N. L. Allinger, J. A. Hirsch, M. A. Miller, I. Tyminski, and F. A. VanCattedge, *J. Am. Chem. Soc.*, **90**, 1199 (1968).

(7) E.g., C. B. Anderson and D. T. Sepp, *Chem. Ind. (London)*, 2054 (1964); C. A. Giza, Ph.D. Dissertation, University of Notre Dame, Notre Dame, Ind., 1967. In the present investigation we have found that in 2-methoxy- and 2-ethoxy-1,3-dioxane, the alkoxy group prefers the axial position by 0.35 kcal/mol at 25°.

(8) Cf. N. Baggett, M. A. Bukhari, A. B. Foster, L. Lehmann, and J. M. Webber, *J. Chem. Soc.*, 4157 (1963).

(9) Regarding the various available methods, see ref 4. For limitations of the once popular kinetic method of conformational study, see E. L. Eliel and F. J. Biros, *J. Am. Chem. Soc.*, **88**, 3334 (1966), and J. L. Mateos, C. Perez, and M. Kwart, *Chem. Commun.*, 125 (1967). Regarding limitations of the more versatile nmr method, see E. L. Eliel and R. J. L. Martin, *J. Am. Chem. Soc.*, **90**, 682 (1968), S. Wolfe and J. R. Campbell, *Chem. Commun.*, 872 (1967), and M. L. Stien, R. Ottinger, J. Reisse, and G. Chiurdoglu, *Tetrahedron Letters*, 1521 (1968).

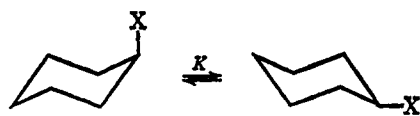


Figure 1.



Figure 2.

information on the 1,3-dioxane system was quite limited.<sup>10a</sup> There is, in fact, still no fundamental study of the 1,3-dioxane structure, but in the last 3 years, several nmr studies of 1,3-dioxanes have become available.<sup>10b,11-16</sup> Even more recently,<sup>17,18</sup> results of the configurational equilibration of alkyl-substituted 1,3-dioxanes have been published, the most recent article<sup>18</sup> having been submitted almost simultaneously with our own preliminary communication on the subject.<sup>2b</sup>

## Results

**2-Alkyl Series.** Equilibrium between equatorial and axial 2-alkyl groups lies very much on the side of the equatorial conformation. It was therefore quite difficult to obtain a pair of epimers which differed in the conformation of the 2-alkyl substituent. As will be discussed below, all of the *trans*-2,4- and *cis*-2,5-dialkyldioxanes prepared in the present investigation exist quite predominantly in the conformation in which the 2-alkyl group is equatorial and the 4- or 5-alkyl group axial; this includes 2-methyl-5-*t*-butyl-1,3-dioxane. The problem of the conformational preference in the 2 position was finally attacked by an examination of the epimeric 2-*cis*-4,6-trimethyl-1,3-dioxanes (Figure 4) available from acetaldehyde and *meso*-2,4-pentanediol. The *cis*-2 isomer I clearly exists in the conformation in which all methyl groups are equatorial. The *trans*-2 isomer II could exist in the conformation in which the 2-methyl group is axial, in the conformation

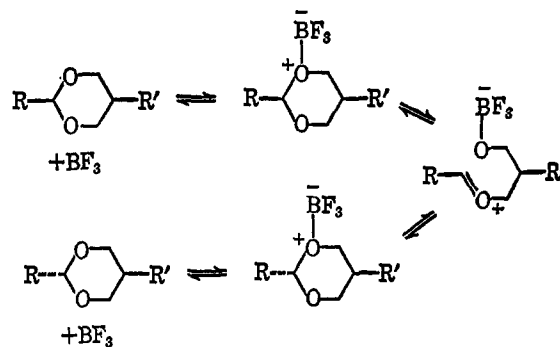


Figure 3.

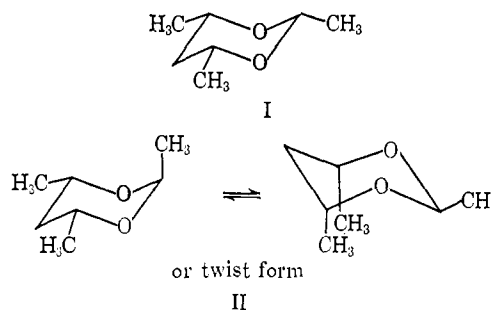


Figure 4. 2,4,6-Trimethyldioxanes.

in which the 4- and 6-methyl groups are *syn*-axial, or in a twist-boat conformation. The second possibility (methyls in 4- and 6-axial) is excluded by the nmr spectrum on the following grounds: (a) The coupling constants  $J_{4,5e}$  and  $J_{4,5a}$  are 3.9 and 10.9 cps, respectively. These are typical coupling constants for axial protons and quite incompatible with the presence of equatorial protons in positions 4 and 6 (*cf.* Table III). (b) The chemical shift of the 4,6-methyl groups is 65.0 cps. Shifts of equatorial methyl at  $C_{4,6}$  range from 64.4 to 69.8 cps (excluding unsaturated compounds) whereas those of axial methyl range from 76.9 to 77.5 cps (Table V). If anything, the 4,6-methyl groups of II are somewhat on the high-field side of the average. (c) The chemical shift of the 2-methyl group, 79.2 cps, is at too low a field for an equatorial methyl (range 67.5–71.7 cps for 2-monomethyl compounds; *cf.* Table V). It is a little more difficult to exclude categorically the possibility that II exists in the skew-boat (twist) form, but the evidence cited above that its nmr spectrum is “normal” (*i.e.*, entirely compatible with that of model compounds for which there is no reason to believe that they exist as skew-boats) strongly militates against such a form. In particular, it appears highly unlikely that a twist form would show “normal”  $H_4-H_5$  coupling constants (see Table III); rather, it might be expected to show coupling constants quite different from those of chair forms and intermediate in magnitude between  $J_{a,a}$  and  $J_{a,e}$ .<sup>19</sup> The following additional argument<sup>13c</sup> has been made *against* the existence of II in the twist form: if II existed in that form because of strong *syn*-axial

(19) *Cf.* H. Booth and G. C. Gidley, *Tetrahedron Letters*, 1449 (1964); K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961); also ref 12b. For a review of abnormal conformations in six-membered rings, see D. L. Robinson and D. W. Theobald, *Quart. Rev. (London)*, **21**, 314 (1967). It must be conceded that the observed coupling constants might be compatible with a nonflexible classical boat conformation made rigid by steric constraints.

(10) (a) For an early study of the 1,3-dioxane inversion barrier, see H. Friebolin, S. Kabuss, W. Maier, and A. Lüttringhaus, *Tetrahedron Letters*, 683 (1962); (b) H. G. Schmid, H. Friebolin, S. Kabuss, and R. Mecke, *Spectrochim. Acta*, **22**, 623 (1966).

(11) (a) J. Delmau, M. Davidson, G. Parc, and M. Hellin, *Bull. Soc. Chim. France*, 241 (1964); (b) C. Barbier, M. Davidson, and J. Delmau, *ibid.*, 1046 (1964); (c) J. Delmau and C. Barbier, *J. Chem. Phys.*, **41**, 1106 (1964); (d) J. Delmau, *Rev. Inst. Franc. Petrole Ann. Combust. Liquides*, **20**, 94 (1965); *Chem. Abstr.*, **62**, 14066c (1965); (e) C. Barbier, J. Delmau, and J. Ranft, *Tetrahedron Letters*, 3339 (1964); (f) J. Delmau and J. Duplan, *ibid.*, 559 (1966); (g) J. Delmau and J. Duplan, *ibid.*, 2693 (1966); (h) J. Delmau, *Compt. Rend. Congr. Natl. Soc. Savantes Sect. Sci.*, **90**, 123 (1964); *Chem. Abstr.*, **64**, 17387d (1966); (i) J. Delmau, J.-C. Duplan, and M. Davidson, *Tetrahedron*, **23**, 4371 (1967).

(12) (a) M. Anteunis, D. Tavernier, and F. Borremans, *Bull. Soc. Chim. Belges*, **75**, 396 (1966); (b) D. Tavernier and M. Anteunis, *ibid.*, **76**, 157 (1967); (c) M. Anteunis, E. Coene, and D. Tavernier, *Tetrahedron Letters*, 4579 (1966).

(13) (a) J. E. Anderson and J. C. D. Brand, *Trans. Faraday Soc.*, **62**, 39 (1966); (b) J. E. Anderson, *Tetrahedron Letters*, 4713 (1965); (c) J. E. Anderson, F. G. Riddell, and M. J. T. Robinson, *ibid.*, 2017 (1967).

(14) Yu. Yu. Samilov and R. M. Aminova, *Zh. Strukt. Khim.*, **5**, 207 (1964); *J. Struct. Chem. USSR*, **5**, 189 (1964).

(15) K. C. Ramey and J. Messick, *Tetrahedron Letters*, 4423 (1965).

(16) W. J. Mijs, *Rec. Trav. Chim.*, **86**, 220 (1967).

(17) J. E. Anderson, F. G. Riddell, J. P. Fleury, and J. Morgen, *Chem. Commun.* 128 (1966).

(18) F. G. Riddell and M. J. T. Robinson, *Tetrahedron*, **23**, 3417 (1967).

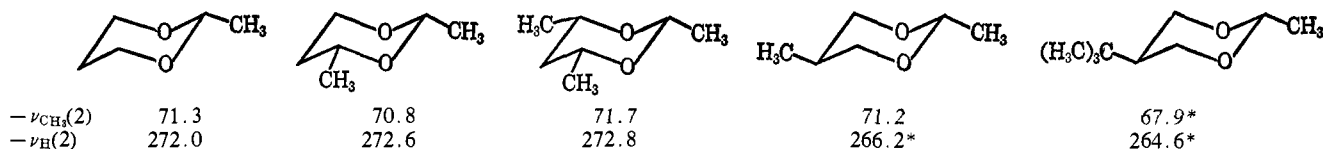


Figure 5. Asterisks indicate that these figures suggest some distortion in the model (to be discussed later).

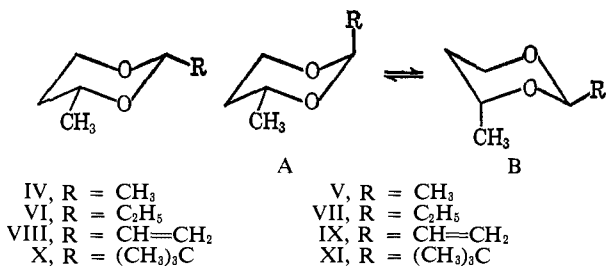
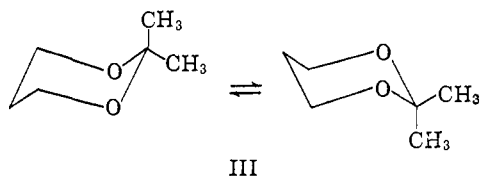


Figure 6.

CH<sub>3</sub>-H-H interaction in the chair, so should 2,2-dimethyldioxane (III), for the same reason. However, it has been shown<sup>18a</sup> that the nmr spectrum of III, at very low temperature (below -126°), becomes that of an individual conformer whereas above that temperature it is the averaged spectrum of the two (equivalent) conformations in equilibrium with each other. Since it is unlikely that pseudo-rotation of a twist form (which would be expected to involve a very low energy barrier) can be "frozen out" at -126°, the low-temperature nmr spectrum of III is uniquely compatible with a chair conformation and it might thus be expected that II also exists as a chair.<sup>20</sup>



Experimentally, the equilibrium constant between I and II was found to be 402, corresponding to  $-\Delta G^\circ = 3.55$  kcal/mol. As will be shown below, this number must be considered a minimum value. In part this may be due to experimental difficulties: equilibria of 99.7:0.3 are obviously not easy to measure accurately, and compound II was one of only two dioxanes in this investigation which were not obtained in a state of analytical purity so that a response ratio for the gas chromatography was not available.<sup>21</sup>

(20) Perhaps a *caveat* is in order here: since the twist form has the higher entropy, its concentration increases fairly rapidly with temperature. Thus even if only the chair form can be seen in the low-temperature nmr spectrum, appreciable amounts of the twist conformation may coexist at room temperature, and the twist form may actually become predominant at higher temperatures. The magnitude of the increase depends, of course, on the thermodynamic parameters of the chair-twist equilibrium and, if these are unknown, the argument based on low-temperature nmr becomes somewhat uncertain.

(21) It would probably have been hopeless to attempt to isolate the amount of II present at equilibrium. That we were able to isolate II and other compounds present in very low equilibrium concentrations at all is thanks to a suggestion of Dr. J. Sicher (Prague) to interrupt the dioxane-forming reaction between the aldehyde and the 1,3-diol long before conversion to products is complete. Under such conditions, partial kinetic rather than thermodynamic control of reaction products results and, along with considerable amounts of (easily removable) unchanged aldehyde and glycol, an enhanced amount of the less stable of the two dioxane epimers is obtained (see also ref 18).

If the equilibrium between I and II lies all the way on the side of I, it may thus be concluded that 2-methyl-1,3-dioxane exists virtually exclusively in the conformation in which the methyl group is equatorial (as distinct from the carbocyclic analog methylcyclohexane which exists only to the extent of about 95% in this conformation). Both the chemical shift of the methyl protons and that of the acetal proton are compatible with this interpretation, as may be seen through a comparison with conformationally biased (or "anconomeric"<sup>12a</sup>) analogs (Figure 5).

The relatively high instability of an axial substituent in the 2 position of a 1,3-dioxane explains a number of observations in the literature regarding six-membered cyclic ketals (2,2-disubstituted 1,3-dioxanes).<sup>22a,c-e</sup> Thus it is found that, whereas glycerol forms about equal amounts of the dioxolane (five-membered ring) and the 1,3-dioxane (six-membered ring) with acetaldehyde under equilibrium conditions, it forms almost exclusively the five-membered dioxolane with acetone.<sup>22c</sup> Since, except for a small *gem*-dialkyl effect,<sup>22b</sup> there is no reason to assume that the dioxolane derived from acetone is particularly stable, it appears that the difference is due mainly to the instability of the dioxane derived from acetone resulting from its axial 2 substituent. The observation that 2,2-dialkyldioxanes are hydrolyzed (in acid) faster than corresponding dioxolanes whereas without the geminal disubstitution the five-membered dioxolanes are generally hydrolyzed faster<sup>22d</sup> may be ascribed to the same cause, as may the observation<sup>22e</sup> that 2,2,4-trimethyl-1,3-dioxane is subject to an unusually rapid cleavage by LiAlH<sub>4</sub>-AlCl<sub>3</sub>.

It had already been observed by Friebolin and co-workers<sup>10</sup> that the ring-inversion barrier for 2,2-dimethyl-1,3-dioxane is considerably lower than the corresponding barrier in 1,3-dioxane itself or 5,5-dimethyl-1,3-dioxane, and this observation had been explained in terms of ground-state compression by the axial 2-methyl group. More recent results<sup>13a</sup> indicate a difference between 2,2-dimethyl-1,3-dioxane and other 1,3-dioxanes of 1.2-3.4 kcal/mol in barrier height (depending on the compound with which comparison is made); in the light of the present findings, this suggests that not all of the ground-state compression is relieved in the transition state; if it were, the difference in barrier should be of the order of 3.5-4 kcal/mol.

**4-Alkyl Series.** The *cis*- and *trans*-2-alkyl-4-methyl-1,3-dioxanes shown in Figure 6 were prepared from 1,3-butanediol and appropriate aldehydes. Through

In the case of II, even this "enhanced" amount was only 1.3% of the total dioxane and while we were able to isolate enough material (by preparative gas chromatography) for an nmr spectrum, the sample was not obtained analytically pure and a glpc response ratio was not established but was assumed to be unity (*cf.* Table VIII).

(22) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962: (a) p 200; (b) p 197; (c) G. Aksnes, P. Albriktsen, and J. Juvvik, *Acta Chem. Scand.*, **19**, 920 (1965); (d) O. Cedar, *Arkiv Kemi*, **6**, 523 (1954); (e) U. E. Diner and R. K. Brown, *Can. J. Chem.*, **45**, 1297 (1967).

partial kinetic control<sup>21</sup> in the acetal formation followed by fractional distillation, fractions containing from 6 to 15% of the less stable (*trans*) isomer were obtained from which the pure *trans* isomer (and sometimes also the pure *cis* isomer<sup>23</sup>) were isolated by preparative gas chromatography. Equilibration was effected by means of boron trifluoride etherate in ether<sup>24</sup> with the results shown in Table I.

**Table I.** Equilibria in 2-Alkyl-4-methyl-1,3-dioxanes

Equilibrium	<i>K</i>	$-\Delta G^{\circ}_{25}$ , kcal/mol
IV/V	138 $\pm$ 6 <sup>a</sup>	2.92 $\pm$ 0.02
VI/VII	108 $\pm$ 14	2.77 $\pm$ 0.08
VIII/IX	101 $\pm$ 4	2.73 $\pm$ 0.02
X/XI	127 $\pm$ 8	2.87 $\pm$ 0.04

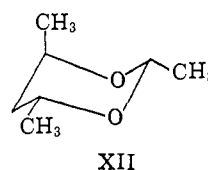
<sup>a</sup> Response ratio not available; response ratio for ethyl case (1.10) used instead. The effect of using a smaller response ratio would be to increase *K* and  $-\Delta G^{\circ}$ .

As a first approximation it appears that the position of all the equilibria shown in Figure 6 is the same; in particular, there is no palpable difference between the 2-*t*-butyl and 2-methyl compounds.<sup>25</sup> It may be concluded that all compounds of the 2,4-*trans* series exist in conformation B with the 4-methyl group axial and the 2-alkyl group equatorial and that the  $-\Delta G^{\circ}$  value of 2.9 kcal/mol in Table I represents the conformational free energy of a 4-methyl substituent. Nmr data are compatible with this supposition: the chemical shifts of the 4-methyl groups in V (77.5 cps), VII (76.9 cps), and XI (77.9 cps) are virtually the same and quite distinct from the typical shift of an equatorial 4-methyl group (63.8–69.8 cps; see Table V). The signal of the 4-methyl group of IX occurs at slightly lower field, 74.1 cps, probably due to a deshielding effect of the double linkage.

The fact that the chemical shift of the methyl substituent in 4-methyl-1,3-dioxane (69.3 cps) is well within the range of equatorial 4-methyl groups (63.8–

69.8 cps or 67.7–69.8 cps if one omits the probably distorted compounds with axial 2 substituents; *cf.* Table V) confirms that this compound exists very largely in the conformation with equatorial methyl. The previous suggestion,<sup>11c</sup> based on (inherently inaccurate) nmr arguments that the preference is only 93:7 must no doubt be revised upward.<sup>11i</sup>

The conclusion that V exists nearly entirely in conformation B is not completely consistent with the conformational energies of the respective methyl groups: Me-2, 3.55 kcal/mol and Me-4, 2.9 kcal/mol. With these energies, V should exist in conformation B to the extent of about 75% and in conformation A to the extent of 25%. This, in turn, should have the following consequences. (a) Because of the entropy of mixing, there should be a palpable lowering of  $-\Delta G^{\circ}$  for V below the value for XI (to about 2.7 kcal/mol). (b) The chemical shift of the 4-methyl group should be displaced about a quarter of the way to that of an equatorial group (*ca.* 69 cps), *i.e.*, it should be *ca.* 75.5 cps rather than 77.5 cps (using 77.5 cps as an approximate value for axial 4-methyl; *cf.* Table V). (c) The 2-methyl group should be somewhat displaced from the normal equatorial position (67.5–71.7 cps, Table V) toward the axial position (77.1–80.6 cps). However, the signal is actually found at 68.2 cps. (d) The acetal proton (H<sub>2</sub>) should be displaced toward the equatorial position (308 cps in compound II). The signal actually occurs at 293.5 cps and, at first sight, would appear to be displaced downfield from the "normal" position of 271–273 cps (Table VI, entries 5–8). However, most of the 2-methyl compounds in Table VI are not suitable models for, unlike VB (Figure 6), they do not have a *syn*-axial methyl group. A suitable model is compound XII, prepared from *dl*-2,4-pentanediol and acetaldehyde;<sup>26</sup> its acetal proton is centered at 292.9 cps, very close to the corresponding signal in V.



(23) To obtain the *cis* isomer, it is preferable to carry out the acetal formation under conditions of thermodynamic control, refluxing 3 hr or more. Under those conditions, less than 1% of the *trans* isomer remains. In view of the extreme position of equilibrium in 2,4- and 2,4,6-substituted 1,3-dioxanes it is not surprising that in several previous syntheses of such compounds, only a single isomer was observed, *e.g.*, R. Lukes, J. Jařy, and J. Nemeć, *Collection Czech. Chem. Commun.*, **27**, 735 (1962); J. Kovář, J. Šteřkova, and J. Jary, *ibid.*, **30**, 2793 (1965); S. J. Angyal and J. A. Mills, *Rev. Pure Appl. Chem.*, **2**, 192 (1952). Our own research project was almost abandoned, as, for a long period, we were unable to secure the less stable diastereoisomers!

(24) Riddell and Robinson<sup>18</sup> found this catalyst unsatisfactory in chloroform solvent and used trifluoroacetic acid instead. We detected no effect on changing BF<sub>3</sub> concentration (always kept below 10 mol %) on the position of 2,5-di-*t*-butyl-1,3-dioxane equilibrium in ether (see Experimental Section), and the equilibrium was the same as that established over an Amberlyst (Rohm & Haas cross-linked polystyrene-sulfonic acid resin) catalyst. The difference is probably due to the fact that in ether, but not in chloroform, most of the BF<sub>3</sub> is complexed with solvent rather than solute.

(25) The slightly smaller *K* for ethyl and vinyl appears to be real. It is tempting to assume that an appreciable amount of the *trans*-vinyl compound IX exists in the conformation with axial vinyl; the resulting entropy of mixing for IX would diminish the free energy difference between VIII and IX. However, the strong similarity of the nmr spectra of 2-vinyl-1,3-dioxane and its *cis*-4-methyl analog VIII in the vinyl region (–305 to –380 cps) suggests that the parent compound exists very largely with equatorial vinyl. (The spectrum of the axial vinyl compound IX is quite different in the vinyl region.) In any case, there is no obvious reason why the ethyl compound also should have a slightly smaller  $-\Delta G^{\circ}$ , for whereas arguments can be made for an axial vinyl group (planar!), no corresponding argument can readily be made for axial ethyl.

It follows from this discussion that compound V must exist largely in conformation B, and while no accurate quantitative apportionment can be calculated from the data, it is estimated that the ratio VB:VA is in excess of 5:1 and quite possibly as high as 10:1 or even higher. This means that VA is less stable than VB by at least 1 kcal/mol and since VA, in turn, is 2.9 kcal/mol less stable than IV, the conformational energy of an axial methyl group in position 2 is probably in excess of 4 kcal/mol, rather than the approximate equilibrium value of 3.55 kcal/mol.

**5-Alkyl Series.** A number of 2,5-dialkyl-1,3-dioxanes were synthesized from various aldehydes and 2-alkyl-1,3-propanediols, the latter, in turn, prepared by lithium aluminum hydride reduction of alkylmalonic esters. The equilibrium positions in this series are summarized in Table II. Several compounds of this series have also been equilibrated by Riddell and

(26) Y. Fujiwara and S. Fujiwara, *Bull. Chem. Soc. Japan*, **37**, 1010 (1964).

Table II. Equilibria in 2,5-Dialkyl-1,3-dioxanes

Entry	R	R'	K	-ΔG° <sub>25</sub> , kcal/mol	Formula	
					C	T
1	CH <sub>3</sub>	CH <sub>3</sub>	5.11 ± 0.04	0.97 ± 0.01	XIII	XIV
2	CH <sub>3</sub>	(CH <sub>3</sub> ) <sub>3</sub> C	3.86 ± 0.12	0.80 ± 0.02 (0.89 <sup>a</sup> )	XV	XVI
3	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	3.44 ± 0.03	0.73 ± 0.01	XVII	XVIII
4	C <sub>2</sub> H <sub>5</sub>	(CH <sub>3</sub> ) <sub>3</sub> C	3.08 ± 0.07	0.67 ± 0.01 (0.81 <sup>a</sup> )	XIX	XX
5	(CH <sub>3</sub> ) <sub>2</sub> CH	(CH <sub>3</sub> ) <sub>3</sub> C	5.25 ± 0.10	0.98 ± 0.01 (1.10 <sup>a</sup> )	XXI	XXII
6	C <sub>6</sub> H <sub>5</sub>	(CH <sub>3</sub> ) <sub>3</sub> C	5.71 ± 0.23	1.03 ± 0.02	XXIII	XXIV
7	(CH <sub>3</sub> ) <sub>3</sub> C	(CH <sub>3</sub> ) <sub>3</sub> C	9.88 ± 0.15	1.36 ± 0.01 (1.7 <sup>a</sup> )	XXV	XXVI
8	(CH <sub>3</sub> ) <sub>3</sub> C	(CH <sub>3</sub> ) <sub>2</sub> CH	10.75 ± 0.17	1.40 ± 0.01	XXVII	XXVIII
9	(CH <sub>3</sub> ) <sub>3</sub> C	C <sub>6</sub> H <sub>5</sub>	10.22 ± 0.08	1.38 ± 0.01	XXIX	XXX
10	(CH <sub>3</sub> ) <sub>3</sub> C	C <sub>2</sub> H <sub>5</sub>	11.22 ± 0.32	1.43 ± 0.02	XXXI	XXXII
11	(CH <sub>3</sub> ) <sub>3</sub> C	CH <sub>3</sub>	11.86 ± 0.24	1.46 ± 0.01	XXXIII	XXXIV

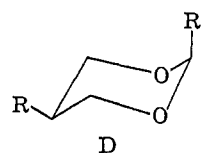
<sup>a</sup> Data from ref 18.

Robinson,<sup>18</sup> and their experimental results and ours are in general agreement. The equilibria in this series are generally not as one-sided as those in the 2,4 and 2,4,6 series, and isolation of the two pure isomers by gas chromatographic separation is therefore relatively easy.

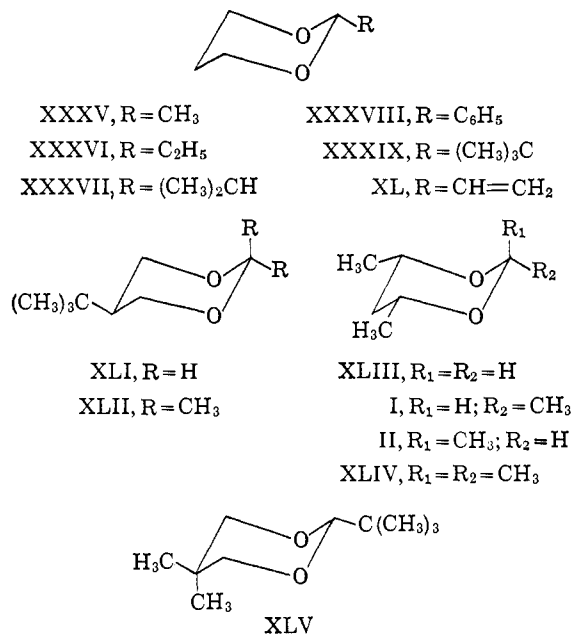
Since the equilibria shown in Table II are in no case extreme, and since it has already been shown that the conformational energy of even a methyl substituent in position 2 is at least 3.55 kcal/mol, it is clearly justifiable to assume that all these equilibria involve movement of the 5 substituent between the equatorial and the axial position. It is thus seen that the conformational energies of *all* alkyl groups in the 5 position are considerably smaller than corresponding values in cyclohexane, as the following summary shows (cyclohexane values<sup>5</sup> in parentheses): CH<sub>3</sub>, 0.80–0.97 (1.70); C<sub>2</sub>H<sub>5</sub>, 0.67–0.73 (1.75); (CH<sub>3</sub>)<sub>2</sub>CH, 0.98 (2.15); C<sub>6</sub>H<sub>5</sub>, 1.03 (3.0); (CH<sub>3</sub>)<sub>3</sub>C, 1.36–1.46 (>4.4). This point will be returned to later. There are a few minor (and, at present, unexplained) anomalies and peculiarities in the values in Table II: the slight but systematic deviation of our values from those of Riddell and Robinson,<sup>18,27</sup> the slight variation of *K* with R' (compare entries 1 with 2; 3 with 4; and 7, 8, 9, 10, and 11 with each other), and the consistently smaller value for ethyl as compared with methyl (entries 1 and 2 compared to 3 and 4, including the literature values in parentheses<sup>18</sup>). Of these anomalies, we believe that only that relating to the smaller conformational energy of ethyl *vs.* methyl is significant (because of its consistency), but we have no explanation to offer at the moment.

The fairly consistent -ΔG° values for the 2-alkyl-5-*t*-butyl series regardless of the 2 substituent suggest that all the *trans*-2-alkyl-5-*t*-butyl compounds in fact exist in conformation C (top of Table II). In order to exclude the alternative conformation D, and also a skew-boat conformation, we have examined the nmr spectra of the compounds listed in Table II as well as several others. Table III lists the 4,5 coupling constants for these compounds and Table IV lists chem-

ical shifts of *t*-butyl groups. It should be noted that



the *cis*-2-alkyl-5-*t*-butyl compounds, XXV, XXVII, XXIX, XXXI, and XXXIII, have virtually the same



coupling constants  $J_{4e,5e}$  and  $J_{4a,5e}$  (entries 23–27 of Table III) and chemical shifts for the 5-*t*-butyl groups (entries 20–24 of Table IV).<sup>28</sup> This finding confirms the hypothesis, reached on the basis of the equilibrium data (Table II), that all the *cis*-2-alkyl-5-*t*-butyl-1,3-dioxanes have the same conformation.<sup>29</sup> The fact

(28)  $J_{4e,5e}$  for compound XXIX (entry 25) is, in fact, slightly different, possibly due to a long-range effect of the phenyl group. Long-range deshielding effects of phenyl groups on *chemical shifts* of *t*-butyl substituents in positions 2 or 5 are clearly seen (Table IV) in the case of compounds XXIII, XXIV, and XXX (entries 5, 11, and 15).

(29) Incidentally, the nmr data also confirm the configurational assignment of compounds XXV, XXVII, XXIX, XXXI, and XXXIII

(27) These differences may be due to difference in solvent: CHCl<sub>3</sub> in ref 18, ether in our work.

Table III. Coupling Constants,  $J_{4,5}$ , in 1,3-Dioxanes (cps)<sup>a</sup>

Entry	Compd <sup>b,e</sup>	R	R'	Config	$J_{4e,5e}$	$J_{4a,5e}$	$J_{4e,5a}$	$J_{4a,5a}$
1	XIV	CH <sub>3</sub>	CH <sub>3</sub>	<i>trans</i>			4.6	11.1
2	XVI	CH <sub>3</sub>	(CH <sub>3</sub> ) <sub>3</sub> C	<i>trans</i>			4.3	10.1
3	XVIII	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	<i>trans</i>			4.4	10.8
4	XX	C <sub>2</sub> H <sub>5</sub>	(CH <sub>3</sub> ) <sub>3</sub> C	<i>trans</i>			4.7	12.7
5	XXII	(CH <sub>3</sub> ) <sub>2</sub> CH	(CH <sub>3</sub> ) <sub>3</sub> C	<i>trans</i>			4.9	10.2
6	XXIV	C <sub>6</sub> H <sub>5</sub>	(CH <sub>3</sub> ) <sub>3</sub> C	<i>trans</i>			4.6	10.2
7	XXVI	(CH <sub>3</sub> ) <sub>3</sub> C	(CH <sub>3</sub> ) <sub>3</sub> C	<i>trans</i>			4.7	12.1
8	XXVIII	(CH <sub>3</sub> ) <sub>3</sub> C	(CH <sub>3</sub> ) <sub>2</sub> CH	<i>trans</i>			4.6	11.3
9	XXX	(CH <sub>3</sub> ) <sub>3</sub> C	C <sub>6</sub> H <sub>5</sub>	<i>trans</i>			4.7	11.3
10	XXXII	(CH <sub>3</sub> ) <sub>3</sub> C	C <sub>2</sub> H <sub>5</sub>	<i>trans</i>			4.4	11.2
11	XXXIV	(CH <sub>3</sub> ) <sub>3</sub> C	CH <sub>3</sub>	<i>trans</i>			5.6	10.6
12	XLI	(CH <sub>3</sub> ) <sub>3</sub> C	H				4.5	11.2
							(4.2) <sup>c</sup>	(10.2) <sup>c</sup>
13	XXXV	H	CH <sub>3</sub>		1.4	2.0	5.1	11.2
						(2.7) <sup>d</sup>		
14	XXXVI	H	C <sub>2</sub> H <sub>5</sub>		1.5	2.0	4.9	10.6
15	XXXVII	H	(CH <sub>3</sub> ) <sub>2</sub> CH		1.5	2.3	5.6	11.8
16	XXXVIII	H	C <sub>6</sub> H <sub>5</sub>		1.5	2.0	5.5	11.2
17	XXXIX	H	(CH <sub>3</sub> ) <sub>3</sub> C		1.4	3.0	5.3	10.1
					(1.3) <sup>c</sup>	(2.7) <sup>c</sup>	(5.9) <sup>c</sup>	(10.8) <sup>c</sup>
18	XLIII			<i>cis</i>		3.1		9.5
						(ca. 3, <sup>d</sup> 3.7) <sup>c</sup>		(9.9) <sup>c</sup>
19	II			<i>trans-cis</i>		3.9		10.2
20	XLIV			<i>cis</i>		3.2		10.9
21	XXI	(CH <sub>3</sub> ) <sub>2</sub> CH	(CH <sub>3</sub> ) <sub>3</sub> C	<i>cis</i>	2.3	3.0		
22	XXIII	C <sub>6</sub> H <sub>5</sub>	(CH <sub>3</sub> ) <sub>3</sub> C	<i>cis</i>	1.4	3.8		
23	XXV	(CH <sub>3</sub> ) <sub>3</sub> C	(CH <sub>3</sub> ) <sub>3</sub> C	<i>cis</i>	1.1	3.9		
24	XXVII	(CH <sub>3</sub> ) <sub>3</sub> C	(CH <sub>3</sub> ) <sub>2</sub> CH	<i>cis</i>	1.4	4.3		
25	XXIX	(CH <sub>3</sub> ) <sub>3</sub> C	C <sub>6</sub> H <sub>5</sub>	<i>cis</i>	2.0	4.2		
26	XXXI	(CH <sub>3</sub> ) <sub>3</sub> C	C <sub>2</sub> H <sub>5</sub>	<i>cis</i>	1.1	3.9		
27	XXXIII	(CH <sub>3</sub> ) <sub>3</sub> C	CH <sub>3</sub>	<i>cis</i>	1.3	4.0		

<sup>a</sup> Obtained by first-order analysis. <sup>b</sup> Compounds XIII-XXXIV are identified in Table II. <sup>c</sup> Data given in ref 12a. Ranges of other values in ref 12a (in cycles per second):  $J_{4e,5e} = 1.31-1.76$ ;  $J_{4e,5a} = 2.85-4.4$ ;  $J_{4e,5a} = 3.34-5.90$ ;  $J_{4a,5a} = 9.0-11.63$ . In ref 13c:  $J_{4e,5e} = 1.2-1.9$ ;  $J_{4a,5e} = 2.5-3.1$ ;  $J_{4e,5a} = 5.0-6.6$ ;  $J_{4a,5a} = 10.0-12.0$ . <sup>d</sup> Data from ref 11i. <sup>e</sup> See text for formulas of compounds XXXV-XLV.

that both coupling constants  $J_{4,5}$  are small (less than 5 cps) excludes the conformation in which the 5-*t*-butyl group is equatorial and the 5-H atom axial, for in this conformation there should be a large (>10 cps)  $J_{aa}$ . *A priori* it would be entirely possible that the *cis*-2-alkyl-5-*t*-butyl compounds existed as skew-boats in which both the (bulky, see above) 2-alkyl and the potentially bulky 5-*t*-butyl group would avoid the axial positions. On the basis of the nmr data, however, this possibility also may be ruled out. The coupling constants  $J_{4,5}$  of the 5-*t*-butyl compounds are not only too small to be compatible with a twist conformation (expected<sup>19</sup> coupling constants, 5-7 cps; observed, 1.1-2.0 and 3.9-4.3 cps) but, more importantly, they are quite similar to those of the *cis*-5-isopropyl- and *cis*-5-phenyl-2-*t*-butyl-1,3-dioxane (XXI and XXIII; Table III, entries 21 and 22) which are not likely to be in the twist form. Even more convincingly, these coupling constants are also similar to those of the 2-alkyl-1,3-dioxanes XXXV-

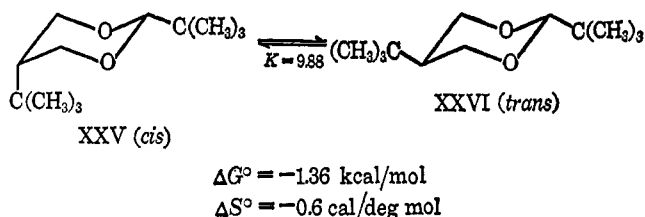
as *cis* and of their diastereoisomers XXVI, XXVIII, XXX, XXXII, and XXXIV as *trans*. Thus the assumption that diequatorial (*trans*) configurations are more stable than diastereoisomeric equatorial-axial (*cis*) configurations (in analogy with the situation in cyclohexane), which has been implicitly made in the earlier discussion and in Table II, is completely confirmed by the nmr data. Any conformational argument made with respect to an equatorial-axial 2,5 (or 2,4) isomer may also be construed to mean that this isomer is *cis* in the 2,5 series (or *trans* in the 2,4 series). The earlier discussion regarding the conformation of II also serves to confirm its configuration as *trans*; hence I is *cis*. While we have not included in the discussion arguments regarding the conformation of the various *e,e* isomers, their conformation and hence configuration is also completely and compellingly supported by the nmr data, in particular by the large  $J_{4a,5a}$  coupling constants for compounds XIV, XVI, XVIII, XX, XXII, XXIV, XXVI, XXVIII, XXX, XXXII, and XXXIV. See also ref 15.

Table IV. Chemical Shifts of *t*-Butyl Groups<sup>a</sup>

Entry	Compd	Shift (conformation)	
		2- <i>t</i> -Bu (e)	5- <i>t</i> -Bu
1	XXXIX	50.3	
		(48.0) <sup>b</sup>	
2	XVI	50.3	
3	XX	50.5	
4	XXII	49.8	
5	XXIV	54.9	
6	X	51.6	
7	XI	50.6	
8	XV	50.6	
9	XIX	52.2	
10	XXI	50.5	
11	XXIII	55.0	
12	XXVI	48.9	53.0 (e)
13	XLV	52.6	
14	XXVIII		52.6 (e)
15	XXX		55.1 (e)
16	XXXII		52.5 (e)
17	XXXIV		52.6 (e)
18	XLI		53.7 (e) <sup>c</sup>
			(52.2) <sup>b</sup>
19	XLII		54.4
20	XXV	49.7	62.7 (a)
21	XXVII		63.1 (a)
22	XXIX		62.9 (a)
23	XXXI		63.1 (a)
24	XXXIII		62.3 (a)

<sup>a</sup> Shifts in cycles per second downfield from tetramethylsilane at 60 Mcps. <sup>b</sup> Data from ref 12a. <sup>c</sup> About 10% axial contribution, see text.

XXXIX (Table III, entries 13-17) which cannot be reasonably assigned a skew-boat conformation, both on *a priori* grounds and on the basis of their (perfectly

Figure 7. 2,5-Di-*t*-butyl-1,3-dioxane equilibrium.

normal)  $J_{4e,5a}$  and  $J_{4a,5a}$  coupling constants. In summary, there is a completely self-consistent argument that *all* the compounds so far discussed exist in the chair conformation, although, as will be discussed later, some of the chairs may be somewhat deformed.

An additional argument against the existence of XXV (Figure 7) in the skew-boat conformation comes from considerations of entropy. The standard entropy change for the process shown in Figure 7 was measured by both Riddell and Robinson<sup>18</sup> and ourselves through studies of equilibrium as a function of temperature. The English authors<sup>18</sup> found  $-0.5 \pm 1.7 \text{ cal/deg mol}$  and we found  $-0.6 \pm 0.1 \text{ cal/deg mol}$ .<sup>30</sup> If the *cis* isomer existed as a flexible (skew-boat) form, one would expect its entropy to be several entropy units (cal/deg mol) higher than that of the *trans* isomer (chair),<sup>31</sup> and the small entropy difference (Figure 7) thus militates against the skew-boat (flexible) conformation for the *cis* isomer XXV.

In accordance with the foregoing arguments, 5-*t*-butyl-1,3-dioxane (XLI) and 5-*t*-butyl-2,2-dimethyl-1,3-dioxane (XLII) should exist in the conformation with axial *t*-butyl to the extent of about 10% at room temperature ( $-\Delta G^\circ = 1.4 \text{ kcal/mol}$ ). The data in Table IV (entries 18 and 19) bear this out: the *t*-butyl signals in XLI and XLII are at a slightly lower field than the typical signals for equatorial *t*-butyl (excepting the 5-phenyl compound), and the difference of about 1–1.5 cps is approximately what one would expect (one-tenth the difference between equatorial and axial *t*-butyl, which amounts to 10–11 cps). The coupling constants (Table III, entry 12) seem to be less sensitive to the presence of the minor conformation.

## Discussion

In the absence of available structural information on 1,3-dioxane, it may be assumed that the C–C distance and C–C–C angle are similar as in cyclohexane<sup>32</sup> (1.53 Å and 111.5°, respectively) and the C–O distance and C–O–C angle are similar as in dimethyl ether<sup>33</sup> (1.41 Å and 111.7°). A model constructed with these dimensions turns out to be a puckered chair or “super-chair” in the O<sub>1</sub>–C<sub>2</sub>–O<sub>3</sub> region and a flattened chair in

(30) Regarding the exact method and precision of the measurement, *cf.* ref 1.

(31) Regarding the situation in cyclohexane, see N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.*, **82**, 2393 (1960). It must be pointed out that there is a slight uncertainty in transferring an argument for a high entropy in the flexible form from cyclohexane to 1,3-dioxane, since some of the entropy advantage of the skew-boat over the chair form in cyclohexane may be due to the high symmetry (resulting in a low entropy of symmetry) of the chair form. The chair form in 1,3-dioxane is much less symmetrical. However, the situation is analogous in the *trans*-1,3-di-*t*-butylcyclohexane actually investigated by Allinger and Freiberg.

(32) M. Davis and O. Hassel, *Acta Chem. Scand.*, **17**, 1181 (1963).

(33) U. Blukis, P. H. Kasai, and R. J. Myers, *J. Chem. Phys.*, **38**, 2753 (1963). However, somewhat different values have been found for 1,4-dioxane in ref 32.

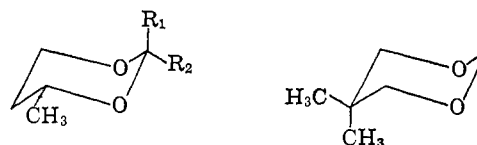
the C<sub>4</sub>–C<sub>5</sub>–C<sub>6</sub> region. As a result of the puckering as well as of the short C–O (as compared to C–C) bond, an axial substituent at C<sub>2</sub> is closer to the *syn*-axial hydrogens at C<sub>4</sub> and C<sub>6</sub> than it would be in cyclohexane. (Riddell and Robinson<sup>18</sup> have calculated distances of 1.94 and 2.29 Å, respectively, between the hydrogen of an axial methyl group and the *syn*-axial ring hydrogen in dioxane and in cyclohexane.) It is therefore not surprising that an axial methyl group in position 2 of 1,3-dioxane has a much larger conformational energy ( $\geq 3.6 \text{ kcal/mol}$ ) than an axial methyl in cyclohexane (1.7 kcal/mol). Because of the strong compression of the hydrogen atoms at a distance of 1.94 Å

Table V. Nmr Shifts of Methyl Groups in 1,3-Dioxanes

Entry	Compd <sup>a</sup>	Me-2 shift, cps		Me-4 shift, cps	
		e	a	e	a
1	XXXV	71.3 (70.8 <sup>a</sup> )			
2	IV	70.8		68.6	
3	V	68.2 <sup>b</sup>			77.5 <sup>b</sup>
4	XIV	71.2			
5	XIII	71.4			
6	I	71.7		67.7	
7	XII	67.5		68.8	77.0
8	XXXIV	67.9			
9	XXXIII	69.1			
10	II		79.2	65.0	
11	XLIV	75.6	80.6	64.4	
12	XLII	74.1 <sup>b</sup>	78.0 <sup>b</sup>		
13	LI		77.1	64.7	
14	LII	70.4		63.8	
15	LIII			69.3 (70.2 <sup>a</sup> )	
16	VI			69.0	
17	VIII			71.4	
18	X			69.8	
19	XLIII			68.2 (70.2, <sup>a</sup> 67.2 <sup>c</sup> )	
20	VII				76.9
21	IX				74.1
22	XI				77.9
23	III	78.0 (av) <sup>d</sup>			
24	XLIX			73.5 (av) <sup>d</sup>	
25	LXVIII	74.1 (av) <sup>d</sup>		66.1 (av) <sup>d</sup>	

<sup>a</sup> Reference 11i. <sup>b</sup> Not completely conformationally homogeneous. <sup>c</sup> Reference 12a. <sup>d</sup> Two equivalent conformations; averaged spectrum. <sup>e</sup> See text for formulas of compounds LI–LIV.

in the undeformed molecule, it is very likely that in the trimethyldioxane II the axial methyl group bends outward and the chair is deformed from the “super-chair” to a more regular chair conformation. Unfortunately one cannot easily obtain definitive evidence



LI, R<sub>1</sub> = CH<sub>3</sub>; R<sub>2</sub> = C<sub>2</sub>H<sub>5</sub>

LII, R<sub>1</sub> = C<sub>2</sub>H<sub>5</sub>; R<sub>2</sub> = CH<sub>3</sub>

LIII, R<sub>1</sub> = R<sub>2</sub> = H

for such a deformation, but the very low-field position of the H<sub>2</sub> proton in II (308 cps) may be an indication. (In 4-methyldioxane and *cis*-4,6-dimethyldioxane, resonance of the equatorial H<sub>2</sub> proton occurs at 292.0 and 292.3 cps; *cf.* Table VI, entries 12 and 13.

Table VI. Nmr Shifts of Acetal Protons ( $H_2$ ) in 1,3-Dioxanes

Entry	Compd	Shift, cps	
		$H_{2a}$	$H_{2e}$
1	LIII	272.6 (271.3, <sup>a</sup> 274.2 <sup>b</sup> )	292.3 (290.1, <sup>a</sup> 293.4 <sup>b</sup> )
2	XLIII	271.7 (271.4, <sup>a</sup> 275.4 <sup>b</sup> )	292.0 (291.0, <sup>a</sup> 295.2 <sup>b</sup> )
3	XLI	264.0 <sup>c</sup>	289.1 <sup>c</sup>
4	II	<i>d</i>	308.0
		$H_{2a}$	2e substituent
5	XXXV	272.0 (273.0 <sup>b</sup> )	CH <sub>3</sub>
6	IV	272.6	CH <sub>3</sub>
7	I	272.8	CH <sub>3</sub>
8	XIII	271.0	CH <sub>3</sub>
9	XIV	266.2	CH <sub>3</sub>
10	XXXIII	273.5	CH <sub>3</sub>
11	XXXIV	264.6	CH <sub>3</sub>
12	V	293.5 <sup>a</sup>	CH <sub>3</sub> <sup>e</sup>
13	XII	292.9	CH <sub>3</sub> <sup>e</sup>
14	XXXVI	259.5	C <sub>2</sub> H <sub>5</sub>
15	VI	263.0	C <sub>2</sub> H <sub>5</sub>
16	XVII	259.7	C <sub>2</sub> H <sub>5</sub>
17	XVIII	253.2	C <sub>2</sub> H <sub>5</sub>
18	XXXI	261.9	C <sub>2</sub> H <sub>5</sub>
19	XXXII	252.1	C <sub>2</sub> H <sub>5</sub>
20	VII	280.8	C <sub>2</sub> H <sub>5</sub> <sup>e</sup>
21	XXXVII	246.5	(CH <sub>3</sub> ) <sub>2</sub> CH
22	XXVII	248.5	(CH <sub>3</sub> ) <sub>2</sub> CH
23	XXVIII	242.0	(CH <sub>3</sub> ) <sub>2</sub> CH
24	XXXVIII	321.0	C <sub>6</sub> H <sub>5</sub>
25	XXIX	325.5	C <sub>6</sub> H <sub>5</sub>
26	XXX	312.4	C <sub>6</sub> H <sub>5</sub>
27	XXXIX	239.5	(CH <sub>3</sub> ) <sub>3</sub> C
28	X	240.1	(CH <sub>3</sub> ) <sub>3</sub> C
29	XV	238.5	(CH <sub>3</sub> ) <sub>3</sub> C
30	XVI	237.5	(CH <sub>3</sub> ) <sub>3</sub> C
31	XIX	240.4	(CH <sub>3</sub> ) <sub>3</sub> C
32	XX	233.6	(CH <sub>3</sub> ) <sub>3</sub> C
33	XXI	240.5	(CH <sub>3</sub> ) <sub>3</sub> C
34	XXII	231.0	(CH <sub>3</sub> ) <sub>3</sub> C
35	XXV	239.7	(CH <sub>3</sub> ) <sub>3</sub> C
36	XXVI	231.5	(CH <sub>3</sub> ) <sub>3</sub> C
37	XLV	232.7	(CH <sub>3</sub> ) <sub>3</sub> C
38	XXIII	247.4	(CH <sub>3</sub> ) <sub>3</sub> C
39	XXIV	242.8	(CH <sub>3</sub> ) <sub>3</sub> C
40	XI	256.7	(CH <sub>3</sub> ) <sub>3</sub> C
41	XLIX		H (av) 284.2 <sup>e</sup>
42	1,3-Dioxane		282.6

<sup>a</sup> Reference 57. <sup>b</sup> Reference 11i. <sup>c</sup> Not conformationally homogeneous. <sup>d</sup> Axial methyl substituent. <sup>e</sup> *syn*-Axial methyl group in addition.

The downfield shift in II is probably not due just to the presence of an extra methyl group at C<sub>2</sub>, apart from deformation, for the effect of an equatorial methyl group on the shift of an axial H<sub>2</sub> proton is small.<sup>11i</sup> Thus in 2-methyl-1,3-dioxane, *cis*-2,4-dimethyl-1,3-dioxane, and *cis,cis*-2,4,6-trimethyldioxane (Table VI, entries 5–7), the H<sub>2</sub> proton is found at 272.0–272.8 cps whereas in the earlier mentioned 2-unsubstituted compounds 4-methyldioxane and *cis*-4,6-dimethyldioxane (Table VI, entries 1 and 2) the axial H<sub>2</sub> proton is found at 272.6 and 271.7 cps.) An additional indication for chair deformation in the dioxanes with axial 2 substituents (II, XLIV, and the two diastereoisomeric 2,4-dimethyl-2-ethyl-1,3-dioxanes XLVIII and XLIX) comes from the comparatively high-field positions of their 4-methyl protons (63.8–65.0 cps; *cf.* Table V, entries 10, 11, 13, and 14), compared to the “normal” position of 67.7–69.8 cps (Table V).

The much greater preference of the methyl group in 2-methyl-1,3-dioxane as compared to that in methylcyclohexane for the equatorial conformation has its

parallel in the acyclic analogs methyl ethyl ether and *n*-butane. Whereas *n*-butane has an *gauche:anti* ratio of about two at room temperature,<sup>3</sup> the microwave spectrum of methyl ethyl ether<sup>34</sup> suggests that the compound exists almost exclusively in the *anti* conformation. Here again, because of the smaller C–O (as compared to C–C) bond distance, the distance between the marked hydrogens, *HCH*<sub>2</sub>*CH*<sub>2</sub>*OCH*<sub>2</sub>*H*, in the *gauche* form (Figure 8) would be so short as to give rise to a marked steric repulsion.

It is interesting that the position of equilibrium among the 2,4,6-trimethyl-1,3,5-trioxanes (paraldehyde stereoisomers, Figure 9) is less extreme than that in the corresponding dioxanes (I and II). The equilibrium constant of  $57.4 \pm 16.0$ , after correction for the symmetry number of 3 of the *cis* isomer, corresponds to  $\Delta G^{\circ}_{25} = 3.05$  kcal/mol.<sup>35</sup> Although the C–O–C bond distances and bond angles in 1,3,5-trioxane are

(34) L. Pierce, personal communication.

(35) F. G. Riddell (unpublished results, quoted in *Quart. Rev.* (London), 21, 364 (1967)) reports 3 kcal/mol.



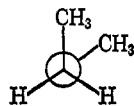


Figure 8.

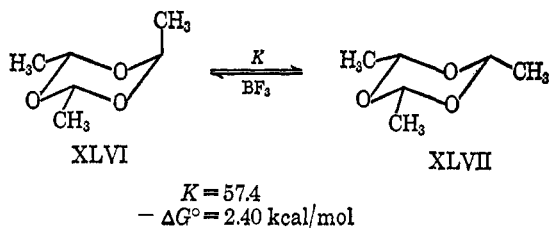


Figure 9.

probably nearly the same as in 1,3-dioxane, the symmetry of the former molecule removes the uneven puckering of the ring ("super-chair" quality of the 2 position in the dioxane mentioned earlier), and the axial bonds in the trioxane are not quite as close to each other at the outer extremity as the axial bonds in the 2 and 4 positions of the dioxane.

The interaction of an axial methyl group in the 4 position of 1,3-dioxane (conformational energy 2.9 kcal/mol) is less severe than in the 2 position. Since the 4 and 6 positions are separated by a methylene group (C-C distance 1.53 Å) whereas the 2 and 4 positions are separated by an oxygen (C-O distance 1.41 Å) it is easy to understand why the interaction between an axial group at C<sub>4</sub> and the *syn*-axial hydrogen at C<sub>6</sub> is less important than that between an axial group at C<sub>2</sub> and the *syn*-axial hydrogen at C<sub>4</sub>. The difference is also clearly seen in a Dreiding model. It follows that an axial substituent in the 4 position has only one very serious *syn*-axial interaction (with H<sub>2a</sub>) and one much less serious one (with H<sub>6a</sub>) whereas the axial substituent in the 2 position has *two* severe *syn*-axial interactions (with H<sub>4a</sub> and H<sub>6a</sub>).

The conformational energies of alkyl groups in the 5 position of 1,3-dioxanes (Table II) are substantially lower than corresponding values in cyclohexane. The difference is most dramatic for the 5-*t*-butyl group (Figure 7) which has a conformational energy of only 1.4 kcal/mol whereas in cyclohexane the corresponding figure is in excess of 4.4 kcal/mol.<sup>5,36</sup> Three causes may contribute to the large difference. First, as has already been indicated, the ring is flattened in the C<sub>4-5-6</sub> region; as a result the *axial* substituent leans outward and its distance from the sterically interacting ring atoms is increased. It has been calculated<sup>18</sup> that the distance between the nearest hydrogen on an axial methyl group in position 5 and the ring oxygens is 2.95 Å. In contrast, the distance between the methyl hydrogen pointing into the ring in axial methylcyclohexane and the ring carbon atom at C<sub>3</sub> is 2.6 Å.<sup>37</sup> Secondly, and because of the same flat-

(36) Recently the conformational energy of *t*-butyl has been calculated<sup>6</sup> to be 5.4 kcal/mol. The calculation is very sensitive to the exact parameters and energy minimization scheme employed; a previous calculation (N. L. Allinger, M. A. Miller, F. A. VanCatledge, and J. A. Hirsch, *J. Am. Chem. Soc.*, 89, 4345 (1967)) gave a value of 12.3 kcal/mol. Although *trans*-1,3-di-*t*-butylcyclohexane exists largely as the twist form<sup>31</sup> recent infrared studies<sup>6</sup> indicate that the chair form with axial *t*-butyl also contributes appreciably to the conformational equilibrium of this species.

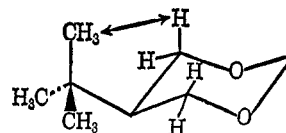


Figure 10.

tening of the ring, when the equatorial 5 substituent is *t*-butyl, there will be an increase in the *syn*-axial interactions between it and the axial hydrogens at C<sub>4</sub> and C<sub>6</sub> (Figure 10). Thirdly, there is very likely a diminution of the axial interactions because, where in cyclohexane there are axial hydrogens in positions 1 and 3, in 1,3-dioxane there are, instead, electron pairs on oxygen. It has been argued on theoretical grounds<sup>38</sup> that the presence of unshared pairs should not, in any way, modify the "bulk" of a given atom (oxygen in our case, although the original calculation was carried out for nitrogen); in other words, the atom has the same van der Waals radius when approached from the side of the pair than when approached from a side away from the pair. If one assumes, in addition, that the van der Waals radii of the first-row elements carbon, nitrogen, oxygen, and fluorine are all approximately the same,<sup>39</sup> then the difference in interaction of an axial group with C-H on one hand and O: on the other (assuming the same distance from C and O) would be equal to the interaction between the axial group in question and the *syn*-axial H. In the case where the axial group is alkyl, the interaction (of the carbons and hydrogens of the alkyl group) with the *syn*-axial hydrogen is certainly repulsive, and therefore the interaction with O: would be expected to be less than that with C-H.<sup>40</sup> Thus one would predict that an axial substituent in position 5 in a 1,3-dioxane should suffer less repulsion than an axial substituent in cyclohexane simply on the basis of the replacement of the *syn*-axial hydrogens by electron pairs.

On the experimental side, we feel that especially the dramatic difference between the *cis-trans* equilibrium in 2,5-di-*t*-butyl-1,3-dioxane (Figure 7,  $\Delta G^{\circ}_{25} = 1.4$  kcal/mol) and 1,3-di-*t*-butylcyclohexane<sup>31</sup> ( $\Delta G^{\circ} = 4.4$  kcal/mol; at that the *trans* isomer exists largely in the twist form<sup>6</sup>) must have the small steric requirement of the electron pair on oxygen as a contributing factor.<sup>41</sup> The methyl carbon and nearest hydrogen of the 5-*t*-butyl group are so close to the ring oxygens that repulsion should be very sizable if the axial electron pair contributed to it.<sup>42</sup>

(37) These are distances in models with normal bond angles. Energy minimization, through deformation of bond and torsional angles, will no doubt change the nonbonded distances in the actual molecules.

(38) N. L. Allinger and J. C. Tai, *J. Am. Chem. Soc.*, 87, 1227 (1965).

(39) The values given in ref 3, p 452, vary slightly, ranging from 1.35 Å for fluorine to 1.70 Å for carbon, the oxygen value being 1.40 Å. Later calculations<sup>6</sup> suggest a somewhat smaller radius for carbon (1.55-1.65 Å). No detailed calculations for oxygen compounds are available, so there is no way to judge the adequacy of the 1.40-Å radius for oxygen in this context.

(40) The situation is not necessarily the same with other axial atoms or groups. For example, for axial chlorine it has been calculated (ref 3, p 455) that the interaction with the *syn*-axial hydrogen is attractive. Omission of this hydrogen (*i.e.*, replacement by an electron pair) might, in this case, lead to a *disfavoring* of the axial conformation.

(41) It might also be recalled that the evidence described earlier conclusively indicates that *cis*-2-methyl-5-*t*-butyl-1,3-dioxane (XXXIII) exists virtually exclusively with equatorial methyl and axial *t*-butyl.

(42) We assume that the electron pairs and C-O bonds are sp<sup>3</sup> hybridized and approximately tetrahedrally disposed. The equality of the C-O-C and C-C-C bond angles (*vide supra*) supports this view.

It must nevertheless be conceded that in the absence of meaningful *a priori* calculations (for which there is, at present, no adequate background), and in the absence of detailed structural data on 1,3-dioxane itself and 1,3-dioxanes with axial substituents in position 5, no conclusive apportionment of the small experimental conformational energy of alkyl groups in that position can be made. There is certainly some relief of the interaction of the *axial* substituent with various ring atoms due to ring flattening and, in the case of *t*-butyl, there is also an increase of the interaction of the equatorial substituent with ring atoms due to the causes embodied in Figure 10 (*vide supra*), but it seems unlikely that these two factors alone can account for the remarkably small conformational energy of the 5-alkyl substituents and it is thus highly probable that the "small size" of the electron pair is also causally involved,<sup>43</sup> where by "small size" we mean either an intrinsically small space requirement, or a high polarizability, or both.

In this connection, a few additional observations are of interest. As seen in Table III,  $J_{4e,5a}$  is distinctly smaller, on the average,<sup>44</sup> for dioxanes with equatorial substituents in position 5 (entries 1–12) than for those devoid of equatorial substituents. We interpret this to mean<sup>44</sup> that repulsion between the equatorial 5 substituent and parts of the ring (especially the hydrogens at positions 4 and 6) leads to an increased puckering or diminished flattening of the 4–5–6 region of the chair. This puckering would increase the  $H_{4e}H_{5a}$  torsional angle from a value well below 60° toward 60° and would thus, according to the Karplus equation, lead to a diminution of  $J_{4e,5a}$  as observed. On the other hand, comparison of  $J_{4a,5e}$  for the compounds devoid of substituents in position 5 (Table III, entries 13–18, average  $J_{4a,5e} = 2.40$  cps) with those with an axial sub-

stituent in position 5 (entries 21–27, average  $J_{4a,5e} = 3.87$  cps) shows substantial enhancement of  $J_{4a,5e}$  by an axial *t*-butyl or phenyl substituent in position 5 and a lesser one by isopropyl in position 5. This probably means that 1,3-dioxanes with bulky axial substituents in position 5 are further flattened in the 4–5–6 region of the chair; such flattening will diminish the  $H_{4a}H_{5e}$  torsional angle and thus, according to the Karplus equation, enhance the coupling constant.

**Nmr Spectra of 1,3-Dioxanes.** In addition to the above-mentioned effects of deformation of the 1,3-dioxane chair by substituents at axial 2 and equatorial and axial 5 positions, the spectra of dioxanes without particular distorting influences are of interest. In cyclohexane, typical coupling constants<sup>45</sup> span the following ranges:  $J_{aa} = 9.5$ – $12.5$  cps;  $J_{ee} = 3.0$ – $4.5$  cps;  $J_{ee}$  (rather limited data) = 2–3 cps. Inspection of Table III indicates that  $J_{4a,5a}$  couplings are in the normal range whereas  $J_{4e,5a}$  coupling constants, especially for the 2-alkyldioxanes, entries 13–17, tend to be high, thus supporting the conclusion reached earlier on the basis of models that the 4–5–6 region of the 1,3-dioxane chair is flattened. Such flattening leads to a diminution of the  $H_{4e}H_{5a}$  torsional angle<sup>46</sup> from 55° and, in accordance with the Karplus equation,  $J_{ee}$  should increase.<sup>47</sup> It is also clear from Table III that  $J_{4a,5e} < J_{4e,5a}$ . Since the torsional angles here are the same, there must be other reasons for this inequality. It has been pointed out by Booth<sup>48</sup> that the coupling constant of a proton located *anti* to an electronegative substituent is usually smaller than normal.  $H_{5e}$  is *anti* to the ring oxygens and should therefore have abnormally small coupling constants. This explains why  $J_{4a,5e} < J_{5a,4e}$ , why  $J_{4a,5e}$  is below the normal minimum of 3.0 cps for a  $J_{ae}$  in the undeformed dioxanes XXXV–XXXIX (Table III, entries 13–17),<sup>49</sup> and also why the  $J_{4e,5e}$  coupling constants in 1,3-dioxanes are anomalously low, well below the range of 2–3 cps normal in cyclohexanes (see Table III). However, in the case of  $J_{4e,5e}$ , there appears to be a contributing factor in ring flattening; this increases the  $H_{4e}$ – $H_{5e}$  torsional angle above 60° and thus also decreases the coupling constant.<sup>50</sup>

In concluding this section, attention is drawn to an accidental degeneracy which is found in the nmr spectra of some *cis*-2,5-dialkyl-1,3-dioxanes resulting from equality or near equality of the chemical shifts of the equatorial and axial protons at C<sub>4</sub> (or C<sub>6</sub>). In general, axial protons at C<sub>4</sub> and C<sub>6</sub> (and also axial protons at C<sub>2</sub>) absorb at higher field than equatorial protons, similar to what is found in cyclohexane. (As a result of deshield-

(43) Perhaps a more direct piece of evidence for the lesser steric requirement of a pair of electrons as compared to a hydrogen atom comes from a comparison of the *syn*-axial CH<sub>3</sub>–OH interaction (1.9–2.4 kcal/mol) with the corresponding CH<sub>3</sub>–CH<sub>3</sub> interaction (3.6 kcal/mol) (ref 3, p 52). It is of interest to compute the conformational enthalpy of an axial 5-*t*-butyl group in a 1,3-dioxane on that basis. Such a group will have two CH<sub>3</sub>–O interactions (taken as 2 kcal/mol each), and two methyl *gauche* interactions (0.85 kcal/mol each) for a total of 5.7 kcal/mol. The equatorial *t*-butyl group (Figure 9) has two methyl *gauche* and one methyl *syn*-axial interaction (1.7 kcal/mol) for a total of 3.4 kcal/mol; the computed difference is thus 5.7 – 3.4 = 2.3 kcal/mol, somewhat more than the observed 1.5 kcal/mol, but considerably less than the minimum value in cyclohexane of 4.4 kcal/mol. (For a similar calculation in cyclohexane, which gives a value of 5.4 kcal/mol for the conformational enthalpy of axial *t*-butyl, see S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, 77, 5562 (1955).) The difference between the computed and observed value, ca. 0.8 kcal/mol, may be ascribed to the two above-mentioned causes *other than* the small size of the pair: extra compression of the equatorial group and relief of compression in the axial group as a result of the flattening of the 1,3-dioxane ring in the 4–5–6 region.

(44) Since the coupling patterns in the 4–5–6 region of most of the dioxanes investigated are complicated, the coupling constants had to be extracted by a sometimes quite laborious, albeit first-order analysis. In two cases (*cis*- and *trans*-2,5-*t*-butyl-1,3-dioxanes (XXV and XXVI)), the spectra were reconstituted from the calculated shifts and spin coupling constants by means of a computer program (MARIP, kindly provided by Dr. Gerhard Binsch). The calculated spectra were in excellent agreement with the experimental ones (see Experimental Section) with all coupling constants within 0.1 cps. It would, however, be overoptimistic to assume that the first-order calculations for all the compounds give equally good results; in fact, work of other investigators (ref 13c and M. Anteunis, personal communication) suggest that they do not and, in particular, that the  $J_{4e,5a}$  values in Table III are generally too low by about 1 cps. While the systematic difference between the 2,5-*trans* isomers (entries 1–12, average  $J_{4e,5a} = 4.67$  cps) and the 2,5-*cis* isomers (entries 13–17, average  $J_{4e,5a} = 5.28$  cps) is probably significant, speculations regarding deformation of the ring (*vide infra*) based on small variations of the coupling constants are put forward with some reserve.

(45) A. C. Huitric, J. B. Carr, W. F. Trager, and B. J. Nist, *Tetrahedron*, 19, 2145 (1963); H. Booth, *ibid.*, 20, 2211 (1964).

(46) Cf. R. A. Wohl, *Chimia*, 18, 219 (1964). In cyclohexane, since the bond angles are 111.5° rather than tetrahedral,<sup>32</sup> the torsional angle between adjacent equatorial bonds is 65° and that between adjacent equatorial and axial bonds is already diminished to 55°. Presumably, a further flattening occurs in 1,3-dioxane. See also ref 12a.

(47) The torsional angle between adjacent axial bonds will simultaneously diminish from 180°. However,  $J_{aa}$  is not very sensitive to small decreases of this angle.

(48) H. Booth, *Tetrahedron Letters*, 411 (1965); see also ref 12a.

(49) Deformation, *i.e.*, ring flattening, may bring the coupling constants "back to normal;" cf. entries 18–27. Since even in the absence of a 5-axial substituent which produces additional flattening, the dioxane ring is flatter in the C<sub>4</sub>–5–6 region than cyclohexane (*vide supra*), one would, as explained earlier, expect  $J_{4a,5e}$  to be larger than  $J_{ae}$  in cyclohexane, were it not for the *anti* effect of the electronegative atom.<sup>48</sup>

(50) While this effect alone could be invoked to explain the smallness of  $J_{4e,5e}$ , it cannot explain the small  $J_{4a,5e}$ ; cf. footnote 49.

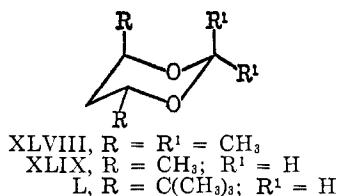


Figure 11.

ing by oxygen, the situation is reversed for the protons at C<sub>5</sub>, alkyl groups at C<sub>5</sub>, and alkyl groups at C<sub>2</sub>.) However, when there is an axial substituent (methyl, ethyl, or phenyl, compounds XIII, XV, XVII, XIX, and XXIII) in position 5, it may deshield H<sub>4a</sub> and shield H<sub>4e</sub>,<sup>51</sup> and the result is a coincidence or near coincidence in the shift of the two protons.<sup>52</sup> It has sometimes been stated in the literature that the deceptively simple spectra which result when  $\nu_{H_{4e}} = \nu_{H_{4a}}$  are, in fact, the result of rapid conformational inversion of two nearly equally populated conformations,<sup>53</sup> but this is undoubtedly not true for 2-alkyl-substituted dioxanes because of the large preference of the 2 substituent for the equatorial conformation. In the case of *cis*-2-*t*-butyl-5-phenyl-1,3-dioxane (XXIII), although H<sub>4e</sub> and H<sub>4a</sub> were not resolved, the signal of H<sub>5</sub> actually showed independent couplings with the two H<sub>4</sub> protons ( $J = 1.8$  and  $3.4$  cps). (In the case of the *cis*-5-methyl and -ethyl compounds, H<sub>3e</sub> is lost under the alkyl peaks.)

#### The Chair-Skew-boat Equilibrium in 1,3-Dioxane.

The enthalpy difference between the chair and the twist form in cyclohexane has been determined by various methods<sup>54a</sup> to amount to *ca.* 5.5 kcal/mol; since the skew-boat exceeds the chair in entropy by about 5 cal/deg mol, this suggests a free-energy advantage of the chair form of *ca.* 4 kcal/mol at room temperature. It had at one time been suggested<sup>54b</sup> that the corresponding enthalpy advantage of the chair in 1,3-dioxane might be only 2.2 kcal/mol, the argument being that, whereas the figure in cyclohexane was about twice the value of the ethane barrier (2.7–3 kcal/mol), the value in 1,3-dioxane should be of the order of twice the methanol barrier (1.1 kcal/mol). Later it was pointed out, however,<sup>55</sup> that the chair-skew-boat difference in 1,3-dioxane is related not to the barrier in methanol but to that in dimethyl ether which is 2.7 kcal/mol,<sup>56</sup> similar to the barrier in ethane. Thus it might be predicted that the chair-skew-boat difference in 1,3-dioxane should be similar to that in cyclohexane.

Experimentally it has now been found that *trans*-4-methyl-2-*t*-butyl-1,3-dioxane (XI) (axial 4-methyl) is less stable than the *cis* isomer (equatorial 4-methyl) by 2.9 kcal/mol and, even more pertinently, that *trans*-2,4,6-trimethyl-1,3-dioxane (II) (axial 2-methyl) is less stable than the equatorial *cis*,*cis* isomer I by

(51) Similar effects in cyclohexanes are well known; see, for example, E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Letters*, 741 (1962).

(52) See also ref 11i.

(53) *E.g.*, N. Baggett, B. Dobinson, A. B. Foster, J. Homer, and L. F. Thomas, *Chem. Ind.* (London), 106 (1961); A. B. Foster, A. H. Haines, J. Homer, J. Lehmann, and L. F. Thomas, *J. Chem. Soc.*, 5005 (1961).

(54) Reference 3: (a) p 38; (b) p 249.

(55) See Riddell, ref 35. See also ref 13c and 18.

(56) P. H. Casai and R. J. Myers, *J. Chem. Phys.*, 3, 1096 (1959). For a possible explanation for the large difference between the methanol and dimethyl ether barriers, *cf.* J. Dale, *Tetrahedron*, 22, 3373 (1966).

at least 3.55 kcal/mol. Moreover, very strong evidence has been adduced that both XI and II exist as chairs or distorted chairs rather than skew boats. It thus appears that the skew-boat form in 1,3-dioxane is at least 4 kcal/mol less stable than the chair, and since this represents a  $\Delta G^{\circ}_{25}$  value, the situation is probably not very different from cyclohexane for which  $\Delta G^{\circ}_{25}$  chair  $\rightarrow$  skew-boat is about 4.4 kcal/mol. We are presently trying to find 1,3-dioxanes for which nmr evidence suggests a skew-boat conformation, including compounds for which equilibrium experiments can be carried out. A skew-boat conformation probably exists in 2,2-*trans*-4,6-tetramethyl-1,3-dioxane (XLVIII, Figure 11, strong CH<sub>3</sub>CH<sub>3</sub> *syn*-axial compression in the chair); it may be significant that the averaged  $J_{4,5}$  in this compound<sup>57</sup> is 6.5 cps whereas in *trans*-4,6-dimethyl-1,3-dioxane (XLIX, Figure 11), which undoubtedly exists in the chair form, the corresponding averaged constant is 5.6 cps (in our hands; 5.4 cps reported<sup>12b</sup>). *trans*-4,6-Di-*t*-butyl-1,3-dioxane (L, Figure 11) synthesized by Anteunis and Tavernier<sup>12b</sup> probably exists in the twist form also (for an axial *t*-butyl group in the 4 position, unlike one in the 5 position, is likely to be excessively compressed); its averaged  $J_{4,5}$  is 7.8 cps.

It had been claimed<sup>11g</sup> that 4-methyl-4-*t*-butyl-1,3-dioxane (which, in the chair form, has a single axial methyl group at position 4) exists in the skew-boat conformation, but in the light of contrary evidence<sup>12b,13c,53</sup> that claim has now been withdrawn.<sup>59,59a</sup>

#### Experimental Section

Nmr spectra were recorded by Mr. Donald Schifferl on a Varian HR-60 instrument; samples were 15–20% solutions in carbon tetrachloride; shifts are reported in cycles per second (cps) downfield from tetramethylsilane at 60 Mcps. Infrared spectra were recorded on a Perkin-Elmer Infracord instrument. Complete tracings of all nmr and most infrared spectra may be found in the Ph.D. Dis-

(57) A similar value was found by M. Anteunis (personal communication).

(58) The nmr data collected in the present work (Tables III and VI) provide additional indication that the nmr spectrum of 4-methyl-4-*t*-butyl-1,3-dioxane corresponds to the chair conformation. The coupling constants of 1.2, 5.0, 4.0, and 12.0<sup>11g,13c</sup> are within the normal range of  $J_{4e,5e}$ ,  $J_{4e,5a}$ ,  $J_{4a,5e}$ , and  $J_{4a,5a}$  (Table III), respectively. The small difference in chemical shift between H<sub>2a</sub> and H<sub>2e</sub><sup>11g</sup>—6 cps *vs.* a "normal" value of 23 cps—can be explained readily if it is taken into account that H<sub>2a</sub> is *syn*-axial with the 4-methyl group; as seen from comparison of *cis*-2,4-dimethyl-1,3-dioxane with the *trans* isomer (Table VI, entries 6 and 12) the *syn*-axial methyl group produces a downfield shift of H<sub>2a</sub> of about 20 cps and H<sub>2a</sub> and H<sub>2e</sub> should therefore be close together; in fact, one cannot assume with any confidence that the higher field proton in this case is the axial one. If, in fact, they are reversed, this would explain why the *high*-field (equatorial!) proton engages in long-range coupling with H<sub>3e</sub> (W arrangement in the chair). Finally, the observation<sup>11g</sup> that the chemical shift between H<sub>3e</sub> and H<sub>3a</sub> is 60 cps (instead of the usual 36 cps) is not anomalous either if it is taken into account that in a 1,3-dioxane, H<sub>3a</sub> is upfield from H<sub>3e</sub>. It has been calculated<sup>11g</sup> that the effect of the methyl and *t*-butyl groups at C<sub>4</sub> should shift H<sub>3a</sub> upfield relative to H<sub>3e</sub> by about 20 cps. Clearly, in a 1,3-dioxane the effect of this displacement will be to increase (from 36 cps to a calculated 56 cps, in good agreement with the observed 60 cps) rather than to decrease the difference between  $\nu_{3a}$  and  $\nu_{3e}$ .

(59) Reference 13c, footnote 17.

(59a) NOTE ADDED IN PROOF. After submission of the present paper, a completely independent thermochemical investigation of some substituted 1,3-dioxanes was published.<sup>60</sup> The conformational enthalpy differences (in the liquid phase) which can be computed from the thermochemical data<sup>60</sup>—Me-2 (e  $\rightarrow$  a),  $4.1 \pm 0.5$  kcal/mol; Me-4 (e  $\rightarrow$  a),  $2.4 \pm 0.5$  kcal/mol—are in excellent agreement with the data obtained in the present work (by a completely different procedure!) on the reasonable assumption that  $\Delta S^{\circ} \approx 0$  for the change of a methyl substituent from the equatorial to the axial position in a dioxane chair.

(60) K. Pihlaja and J. Heikkilä, *Acta Chem. Scand.*, 21, 2390, 2430 (1967).

Table VII. 1,3-Dioxanes Prepared under Conditions of Thermodynamic Control

1,3-Dioxane	No.	Yield, %	Bp, °C (mm)	$n_D^{20}$	$I_r,^a \mu$	Calcd, %		Found, %	
						C	H	C	H
2-Me	XXXV	41	104–105 <sup>b</sup> (735)	1.4178	7.13, 8.02, 8.70, 9.02, 11.60				
2-Et	XXXVI	74	127–128 <sup>c</sup>	1.4214	8.08, 8.70, 9.08, 10.23				
2- <i>i</i> -Pr	XXXVII	70	142–143	1.4251	6.82, 8.02, 8.70, 9.01, 10.02, 10.88	64.58	10.84	64.73	10.92
2-Ph	XXXVIII	49	48–49 <sup>d,e</sup>		6.91, 7.22, 7.85, 8.72, 9.08, 9.92, 10.01				
2- <i>t</i> -Bu	XXXIX <sup>e</sup>	58	147–149	1.4270	8.63, 8.88, 9.53, 9.95	66.63	11.18	66.83	11.12
2-Vinyl	XL	48	136–139 <sup>e</sup>	1.4441	8.06, 8.72, 9.09, 10.10, 10.69				
5- <i>t</i> -Bu	XLI <sup>e</sup>	75	66 (18)	1.4381	6.65, 8.38, 8.47, 8.62, 9.24, 11.19	66.63	11.18	66.69	11.25
2,2-Me <sub>2</sub>	III	41	124–125 <sup>f</sup>	1.4206	7.32, 8.0, 8.32, 9.08, 10.29, 12.02				
5,5-Me <sub>4</sub>	LIV	25	124–126 <sup>b</sup>	1.4248	8.52, 9.02, 9.59, 10.59, 10.73				
<i>cis</i> -4,6-Me <sub>4</sub>	XLIII	71	114–116 <sup>g</sup>	1.4136	8.27, 8.83, 9.32, 9.67				
<i>trans</i> -4,6-Me <sub>2</sub>	XLIX	64	<i>h</i>	1.4221	7.27, 8.32, 8.61, 9.43, 9.80	62.04	10.41	62.03	10.27
2- <i>cis</i> -4- <i>trans</i> -6-Me <sub>3</sub>	XII	61	50 (60) <sup>i</sup>	1.4232	7.21, 8.49, 8.62, 9.0				
<i>cis</i> -2,4-Me <sub>2</sub>	IV	46	117–118	1.4138	7.19, 8.42, 8.78, 8.99	62.04	10.41	61.43	10.44
2,2-Me <sub>2</sub> -5- <i>t</i> -Bu	XLII	70	76 (18)	1.4359	7.29, 8.27, 9.19, 11.78	69.72	11.70	69.52	11.71
5,5-Me <sub>2</sub> -2- <i>t</i> -Bu	XLV	72	58.0– 58.5 <sup>o</sup>		6.88, 8.95, 9.59, 10.25	69.72	11.70	69.74	11.67
2,2- <i>cis</i> -4,6-Me <sub>4</sub>	XLIV	76	56–58 <sup>i</sup> (18)	1.4173	7.25, 7.90, 8.45, 8.88, 9.95				
2,2- <i>trans</i> -4,6-Me <sub>4</sub>	XLVIII	38	111–112	1.4117	7.28, 8.13, 8.68, 9.72	66.63	11.18	66.59	11.08
2,5- <i>trans</i> -Me <sub>2</sub>	XIV	79 <sup>j</sup>	118–125 <sup>j</sup>	1.4142	7.12, 8.70, 9.06, 9.67, 11.50	62.04	10.41	61.99	10.43
2,5- <i>cis</i> -Me <sub>2</sub>	XIII	79 <sup>j</sup>	118–125 <sup>j</sup>	1.4145	7.13, 8.02, 8.69, 10.07, 11.62	62.04	10.41	61.93	10.35
2,5- <i>trans</i> -Et <sub>2</sub>	XVIII	84 <sup>j</sup>	60–62 (18) <sup>j</sup>	1.4261	6.82, 8.61, 9.19, 9.78, 10.59,	66.63	11.18	66.79	10.86
2,5- <i>cis</i> -Et <sub>2</sub>	XVII	84 <sup>j</sup>	60–62 (18) <sup>j</sup>	1.4279	6.78, 8.58, 9.93, 10.68	66.63	11.18	66.93	11.14
<i>trans</i> -2-Me-5- <i>t</i> -Bu	XXXIV	85 <sup>j</sup>	70–72 (14) <sup>j</sup>	1.4339	7.13, 8.68, 9.02, 9.87	68.31	11.47	68.53	11.37
<i>cis</i> -2-Me-5- <i>t</i> -Bu	XXXIII	85 <sup>j</sup>	70–72 (14) <sup>j</sup>	1.4340	7.12, 8.0, 8.68, 9.28, 9.92	68.31	11.47	68.21	11.34
<i>trans</i> -2-Et-5- <i>t</i> -Bu	XXXII	86 <sup>j</sup>	81–90.5 (26) <sup>j</sup>	1.4375	6.82, 8.58, 9.19, 10.58	69.72	11.70	69.64	11.73
<i>cis</i> -2-Et-5- <i>t</i> -Bu	XXXI	86 <sup>j</sup>	81–90.5 (26) <sup>j</sup>	1.4391	6.82, 7.18, 8.70, 9.28, 9.98	69.72	11.70	69.81	11.84
<i>trans</i> -2- <i>i</i> -Pr-5- <i>t</i> -Bu	XXVIII	67 <sup>j</sup>	83–90 (10) <sup>j</sup>	1.4381	8.68, 9.10, 9.58	70.92	11.90	70.93	11.87
<i>cis</i> -2- <i>i</i> -Pr-5- <i>t</i> -Bu	XXVII	67 <sup>j</sup>	83–90 (10) <sup>j</sup>	1.4408	6.81, 8.0, 8.56, 9.20, 9.89	70.92	11.90	70.82	11.92
<i>trans</i> -2- <i>t</i> -Bu-5-Me	XVI	76 <sup>j</sup>	162–166 <sup>j,k</sup>	1.4251	6.85, 8.52, 8.89, 10.08 <sup>l</sup>	68.31	11.47	68.53	11.48
<i>cis</i> -2- <i>t</i> -Bu-5-Me	XV	76 <sup>j</sup>	162–166 <sup>j,k</sup>	1.4262	6.85, 8.52, 8.89, 10.08 <sup>l</sup>	68.31	11.47	68.15	11.37
<i>trans</i> -2- <i>t</i> -Bu-5-Et	XX	66 <sup>j</sup>	180–185 <sup>j,m</sup>	1.4291	6.82, 7.22, 8.18, 8.82, 9.08, 9.65, 9.75, 10.24	69.72	11.70	70.00	11.98
<i>cis</i> -2- <i>t</i> -Bu-5-Et	XIX	66 <sup>j</sup>	180–185 <sup>j,m</sup>	1.4317	8.73, 8.86, 9.38, 9.92, 10.51	69.72	11.70	70.03	11.66
<i>trans</i> -2- <i>t</i> -Bu-5- <i>i</i> -Pr	XXII	83 <sup>j</sup>	85–90 (18) <sup>j,n</sup>	1.4338	6.78, 7.15, 8.74, 9.17, 9.46, 10.18	70.92	11.90	70.89	11.87
<i>cis</i> -2- <i>t</i> -Bu-5- <i>i</i> -Pr	XXI	83 <sup>j</sup>	85–90 (18) <sup>j,n</sup>	1.4359	6.75, 8.48, 8.78, 9.37, 9.52, 9.90, 10.50	70.92	11.90	70.89	11.88
<i>cis</i> -2,4-Me <sub>2</sub> -2-Et	LII	60 <sup>j</sup>	41–42.5 (10) <sup>j</sup>	1.4239	7.29, 7.90, 8.5, 8.98	66.63	11.8	66.49	11.41
<i>trans</i> -2,4-Me <sub>2</sub> -2-Et	LI	60 <sup>j</sup>	41–42.5 (10) <sup>j</sup>	1.4250	7.23, 8.35, 8.93, 10.28	66.63	11.18	66.69	11.38

<sup>a</sup> Major ir bands above 6  $\mu$ . Liquids neat, solids in CCl<sub>4</sub>. <sup>b</sup> C. S. Rondstedt, *J. Org. Chem.*, **26**, 2247 (1961), reports bp 109–110° (760 mm),  $n_D^{25}$  1.4119 for XXXV, bp 126.5° (760 mm),  $n_D^{25}$  1.4190 for LIV. <sup>c</sup> A. C. Bellaart, *Rec. Trav. Chim.*, **81**, 457 (1962), reports bp 132–133,  $n_D^{20}$  1.4219 for XXXVI, bp 143–144°,  $n_D^{20}$  1.4439 for XL. <sup>d</sup> E. D. Bergmann and A. Kaluszner, *Rec. Trav. Chim.*, **78**, 337 (1959), report mp 47–49°. <sup>e</sup> Compound mentioned in ref 12a without analysis. <sup>f</sup> C. J. Salmi and V. Ramniko, *Ber.*, **72B**, 600 (1939), report bp 124.0–124.2° (758 mm),  $n_D^{20}$  1.42007. <sup>g</sup> F. Aftalion, D. Lumbroso, M. Hellin, and G. Coussemant, *Bull. Soc. Chim. France*, 1958 (1965), report bp 125°,  $n_D^{20}$  1.4135. <sup>h</sup> Kugelrohr distillation, boiling point not determined. <sup>i</sup> P. Maroni, Y. Maroni-Barnaud, and L. Cazaux, *Compt. Rend.*, **257**, 1715 (1962), report bp 43° (20 mm),  $n_D^{25}$  1.4173 for XII, bp 42° (20 mm),  $n_D^{25}$  1.4152 for XLIV. <sup>j</sup> For mixture of stereoisomers. <sup>k</sup> Reference 18 reports bp 44–46° (14 mm). <sup>l</sup> Accidental coincidence of major bands, ir spectra different. <sup>m</sup> Reference 18 reports bp 64° (14 mm). <sup>n</sup> Reference 18 reports bp 75–76° (14 mm). <sup>o</sup> Melting point.

Table VIII. 1,3-Dioxanes Prepared under Conditions of Kinetic Control

1,3-Dioxane	No.	Time, <sup>a</sup> min	Yield, %	Bp, °C (mm)	<i>n</i> <sub>D</sub> <sup>20</sup>	Ir, <sup>b</sup> μ	Calcd, % C	H	Found, % C	H
<i>cis</i> -2-Vinyl-4-Me	VIII	5	29 <sup>c</sup>	<i>d</i>	1.4384	8.53, 8.95, 9.95, 10.55	65.60	9.44	65.69	9.41
<i>trans</i> -2-Vinyl-4-Me	IX	5	29 <sup>c</sup>	<i>d</i>	1.4419	7.95, 8.52, 8.75, 8.86, 9.05, 10.20	65.60	9.44	65.81	9.58
<i>trans</i> -2,4-Me <sub>2</sub>	V	30	51 <sup>c</sup>	118–124 <sup>c</sup>	1.4208	7.12, 7.93, 8.68, 9.09	62.04	10.41	62.13	10.49
<i>cis</i> -2-Et-4-Me	VI	30	<i>d</i>	139	1.4190	7.22, 8.45, 8.78, 8.85, 8.95, 10.08, 11.10	64.58	10.83	64.58	11.09
<i>trans</i> -2-Et-4-Me	VII	30	<i>d</i>	145–145.5	1.4257	7.99, 8.69, 8.88, 10.28	64.58	10.84	64.88	10.65
<i>cis</i> -2- <i>t</i> -Bu-4-Me	X	5	52 <sup>c</sup>	140–156 <sup>c</sup>	1.4214	8.50, 8.83, 9.22, 9.34, 9.96	68.31	11.47	68.53	11.56
<i>trans</i> -2- <i>t</i> -Bu-4-Me	XI	5	52 <sup>c</sup>	140–156 <sup>c</sup>	1.4286	8.69, 8.83, 9.55, 9.89, 10.20	68.31	11.47	68.18	11.54
<i>cis</i> -2-Ph-5- <i>t</i> -Bu	XXIX	3	73 <sup>c</sup>	34.5–35.5 <sup>i</sup>		7.22, 8.05, 8.73, 9.30, 9.77, 14.36	76.32	9.15	76.08	8.86
<i>trans</i> -2-Ph-5- <i>t</i> -Bu	XXX	3	73 <sup>c</sup>	67.5–68 <sup>i</sup>		7.25, 8.02, 8.69, 9.18, 14.36	76.32	9.15	76.34	9.03
<i>cis</i> -2- <i>t</i> -Bu-5-Ph	XXIII	4	67 <sup>c</sup>	76–79 (0.5) <sup>c</sup> 30–34 <sup>i</sup>		8.80, 9.25, 9.48, 9.92, 14.27	76.32	9.15	76.38	9.27
<i>trans</i> -2- <i>t</i> -Bu-5-Ph	XXIV	4	67 <sup>c</sup>	76–79 (0.5) <sup>c</sup> 37.5–38 <sup>i</sup>		8.71, 9.08, 9.57, 10.23, 14.27	76.32	9.15	76.48	9.12
<i>cis</i> -2,5-Di- <i>t</i> -Bu	XXV	3	86 <sup>c</sup>	47.5–48.5 <sup>i</sup>		8.13, 8.62, 9.10	71.95	12.08	71.95	11.93
<i>trans</i> -2,5-Di- <i>t</i> -Bu	XXVI	3	86 <sup>c</sup>	80–80.5 <sup>c,i</sup>		6.84, 8.15, 8.62, 9.0, 9.42, 10.15	71.95	12.08	71.67	11.97
2- <i>cis</i> -4- <i>cis</i> -6-Me <sub>3</sub>	I	2.25	52 <sup>c</sup>	122–123 <sup>c</sup>	1.4132 <sup>f</sup>	<i>d</i>				
2- <i>trans</i> -4- <i>trans</i> -6-Me <sub>3</sub>	II	2.25	42 <sup>c</sup>	122–123 <sup>c</sup>	<i>d</i>	<i>d</i>	64.58	10.84	63.13 <sup>g</sup>	10.77
Paraldehyde ( <i>cis</i> )	XLVI	15	19 <sup>c</sup>	115–124 <sup>c</sup>	1.4045 <sup>h</sup>	7.19, 7.48, 8.45, 9.05, 10.52				
Paraldehyde ( <i>trans</i> )	XLVII	15	19 <sup>c</sup>	115–124 <sup>c</sup>	1.4082 <sup>h</sup>	7.18, 8.5, 8.63, 9.0, 9.20, 10.52				

<sup>a</sup> Reaction time in minutes. <sup>b</sup> Major ir bands above 6 μ. Liquids neat, solids in CCl<sub>4</sub>. <sup>c</sup> For mixture of stereoisomers. <sup>d</sup> Not determined. <sup>e</sup> Lit.<sup>18</sup> mp 80°. <sup>f</sup> Reported (Table VII, footnote *i*): *n*<sub>D</sub><sup>25</sup> 1.4119. Nmr spectrum identical with that reported in ref 26. <sup>g</sup> Not enough sample available for accurate C analysis. However, the nmr spectrum was entirely in accord with the assigned structure. <sup>h</sup> E. C. Craven, H. Jowitt, and W. R. Ward, *J. Appl. Chem.* (London), **12**, 526 (1962), report *n*<sub>D</sub><sup>20</sup> 1.4048 for *cis* isomer, *n*<sub>D</sub><sup>20</sup> 1.4082 for *trans* isomer. The nmr spectra were identical with those reported by J. L. Jungnickel and C. A. Reilly, *J. Mol. Spectry.*, **16**, 135 (1965). <sup>i</sup> Melting point.

sertation of Sr. M. Carmeline Knoeber, University of Notre Dame, Notre Dame, Ind., 1967 (available on interlibrary loan). Elemental analyses were obtained by Midwest Microlab, Indianapolis, Ind. Analytical gas chromatographic analyses were carried out on an F & M Instrument and Research Inc. Model 810-29 instrument equipped with a thermal conductivity detector maintained at 300° coupled to a 1-mV Honeywell Elektronik Model 15 recorder equipped with a disk integrator. Columns were 1/8 in. in diameter and 9–30 ft in length. With two exceptions (see below), all analyses were corrected for detector response (see Table IX). Preparative gas chromatographic separation was effected on a Wilkens (Varian) Aerograph Autoprep Model A-700 instrument with 3/8 in. aluminum columns, 10, 20, or 30 ft in length using a helium flow rate of 200 cc/min. Samples were injected on column and were collected in receivers containing a small amount of anhydrous sodium carbonate, protected by drying tubes and immersed in a Dry Ice-acetone bath. Details of glpc conditions may be found in the above dissertation.

**Starting Materials.** The aldehydes, ketones, 1,3-propanediol, and 1,3-butanediol used in this investigation were commercially available; 2-methyl-, 2-ethyl-, and 2-phenyl-1,3-propanediol were prepared by lithium aluminum hydride reduction of the corresponding diethyl alkylmalonates (see below). *meso*- and *dl*-2,4-pentane-diols were prepared by sodium borohydride reduction of acetylacetone and were separated *via* their cyclic sulfites by fractional distillation through a 4-ft Podbielniak distillation column.<sup>61a</sup>

**Diethyl *t*-Butylmalonate.** Diethyl isopropylidenemalonate, bp 110–115° (9–10 mm), *n*<sub>D</sub><sup>20</sup> 1.4490 (lit.<sup>61b</sup> bp 111–113° (9 mm)), was prepared in 49% yield by condensation of diethyl malonate with acetone.<sup>61b</sup> The material was found to be 90% pure by glpc and was satisfactory for the next step, the addition of methylmagnesium iodide,<sup>62</sup> which was modified, with resulting increase in yield, by cuprous chloride catalysis of 1,4 addition.<sup>63</sup> Methylmagnesium iodide was prepared in the usual way in a 500-ml three-necked, round-bottomed flask from 6.8 g (0.28 g-atom) of magnesium in 200 ml of dry ether and 39.9 g (0.28 mol) of methyl iodide. After completion of the Grignard reaction, the dark solution was cooled in an ice-salt bath to about –20° and then 1.0 g cuprous chloride was added, followed by dropwise addition of a solution of 40 g (0.20 mol) of diethyl isopropylidenemalonate in 40 ml of dry ether. The latter addition took 40 min, the solution being stirred mechanically and the temperature held below 0°. The mixture was allowed to warm to room temperature, stirred for an additional hour, poured onto 100 g of crushed ice, and acidified with 10% sulfuric acid. The aqueous phase was separated and extracted four times with 100 ml of ether each. The combined ether extracts were washed with water and aqueous sodium thiosulfate, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 43.9

(1963); (b) A. C. Cope and E. M. Hancock, *J. Am. Chem. Soc.*, **60**, 2644 (1938).

(62) S. Wideqvist, *Arkiv Kemi Mineral. Geol.*, **B23**, 1 (1946); *Chem. Abstr.*, **41**, 1615 (1947).

(63) J. Munch-Petersen, *J. Org. Chem.*, **22**, 170 (1957).

(61) (a) J. G. Pritchard and R. L. Vollmer, *J. Org. Chem.*, **28**, 1545

Table IX. Equilibration Results

Compd	Time, days	Column		Ret time, min		Area ratio	Response ratio
		Code	Temp, °C	C	T		
I/II	3	<i>a</i>	98	13	27	402.0 ± 34.7	<i>b</i>
IV/V	5	<i>c</i>	98	10	17	152.1 ± 5.7	<i>d</i>
VI/VII	12	<i>a</i>	97	8	16	119.0 ± 14.3	1.104 ± 0.023
VIII/IX	6	<i>c</i>	85	19	24	103.9 ± 3.6	1.029 ± 0.012
X/XI	10	<i>c</i>	72	12	23	133.8 ± 8.1	1.054 ± 0.011
XIII/XIV	12	<i>c</i>	72	14	17	5.167 ± 0.031	1.012 ± 0.009
XV/XVI	75	<i>e</i>	62	19	21	4.100 ± 0.115	1.062 ± 0.005
XVII/XVIII	8	<i>e</i>	91	17	24	3.543 ± 0.020	1.029 ± 0.008
XIX/XX	17	<i>e</i>	108	13	17	3.144 ± 0.045	1.020 ± 0.019
XXI/XXII	99	<i>e</i>	90	10	16	5.475 ± 0.097	1.043 ± 0.002
XXIII/XXIV	34	<i>c</i>	150	30	34	5.708 ± 0.229	0.999 ± 0.002
XXV/XXVI	24	<i>c</i>	125	8	12	9.853 ± 0.137	0.997 ± 0.016
XXVII/XXVIII	6	<i>e</i>	118	8	14	10.35 ± 0.15	0.963 ± 0.024
XXIX/XXX	16	<i>f</i>	178	11	18	10.64 ± 0.08	1.041 ± 0.004
XXXI/XXXII	9	<i>a</i>	122	14	27	11.11 ± 0.31	0.990 ± 0.010
XXXIII/XXXIV	5	<i>e</i>	118	9	17	12.24 ± 0.23	1.032 ± 0.007
XLVI/XLVII	2-8	<i>c</i>	88	17	22	50.54 ± 16.05	0.880 ± 0.004

<sup>a</sup> TCEP, 20% on Chromosorb P, 45-60 mesh, 12-ft length. <sup>b</sup> Not determined, assumed to be unity. <sup>c</sup> TCEP, 6% on Chromosorb G, 60-80 mesh, 30-ft length. <sup>d</sup> Not determined, assumed to be 1.10 (value for VI/VII). <sup>e</sup> As *c*, but 18-ft length. <sup>f</sup> Carbowax 20M, 20% on Chromosorb W, 60-80 mesh, 4-ft length.

Table X

Acid	Concentration	<i>K</i>	-Δ <i>G</i> <sup>o</sup> , kcal/mol
BF <sub>3</sub>	0.2 <i>M</i> (40 mol %)	9.64 ± 0.16	1.34 ± 0.01
BF <sub>3</sub>	0.1 <i>M</i> (20 mol %)	10.31 ± 0.13	1.41 ± 0.01
BF <sub>3</sub>	ca. 10 mol %	9.88 ± 0.15	1.36 ± 0.01
Amberlyst 15	ca. 1 mol	9.52 ± 0.09	1.33 ± 0.01
	ca. 0.1 mol	9.57 ± 0.17	1.34 ± 0.01

g of crude product. Distillation through a spinning-band column yielded 37.4 g (87%) of a single fraction, bp 109-114° (17 mm), *n*<sub>D</sub><sup>20</sup> 1.4238 (lit.<sup>64</sup> 78-83° (1.6 mm), *n*<sub>D</sub><sup>20</sup> 1.4250).

**2-*t*-Butyl-1,3-propanediol.** To a solution of 5.6 g (0.155 mol) of lithium aluminum hydride in 200 ml of ether contained in a 100-ml three-necked, round-bottomed flask equipped with stirrer, pressure-equalized dropping funnel, and condenser protected by a drying tube was added dropwise 27.9 g (0.129 mol) of diethyl *t*-butylmalonate in 200 ml of dry ether. Addition with stirring took 1 hr, and the mixture was then boiled for an additional 3 hr before being cooled and hydrolyzed by addition of 5.7 ml of water followed by 5.7 ml of 15% aqueous sodium hydroxide and 17.1 ml of water. After stirring for an additional hour, the precipitate was filtered and washed three times with 100-ml portions of ether. The combined ether solutions were dried over anhydrous magnesium sulfate and concentrated. The residue crystallized on cooling and was recrystallized from ether-petroleum ether (bp 30-60°) to give 11.3 g (67%) of needles, mp 57-58° (lit.<sup>64</sup> 58-59°). Additional material (1.6 g) was recovered from the mother liquors.

Other diethyl alkylmalonates were reduced similarly, including diethyl isopropylmalonate obtained by hydrogenation of the isopropylidene compound (*vide supra*) over 10% palladium-on-carbon catalyst in a Parr hydrogenator at 45 psi in ethanol solvent. The constants of the 2-alkyl-1,3-propanediols were as follows: 2-methyl-1,3-propanediol, bp 111-114° (17 mm), *n*<sub>D</sub><sup>20</sup> 1.4447 (lit.<sup>65</sup> bp 83.5-84° (3 mm), *n*<sub>D</sub><sup>25</sup> 1.4430); 2-ethyl-1,3-propanediol, bp 119-121° (17 mm), *n*<sub>D</sub><sup>20</sup> 1.4473 (lit.<sup>65</sup> bp 83-86° (1-2 mm), *n*<sub>D</sub><sup>25</sup> 1.4471); 2-isopropyl-1,3-propanediol, bp 123-127° (10 mm), *n*<sub>D</sub><sup>20</sup> 1.4473 (lit.<sup>66</sup> bp 148-148.5° (18 mm), *n*<sub>D</sub><sup>20</sup> 1.4505); 2-phenyl-1,3-propanediol, mp 50-51.5° (lit.<sup>65</sup> mp 48.5-49°).

**1,3-Dioxanes.** Except for 1,3-dioxane itself and the 2-methyl homolog, which were commercially available, the 1,3-dioxanes were prepared from the appropriate diol and carbonyl compound by the general procedure of Salmi<sup>67</sup> under conditions of either thermodynamic or partial kinetic control. One example will be described for each preparation.

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**Thermodynamic Control.** In a 100-ml, round-bottomed flask fitted with a Dean-Stark trap and a Friedrich condenser protected with a drying tube a solution of 7.6 g (0.1 mol) of 1,3-propanediol, 4.4 g (0.1 mol) of acetaldehyde, and a catalytic amount of *p*-toluenesulfonic acid in 80 ml of benzene was boiled until no more water was collected in the trap (2 hr). The cooled solution was washed twice with 50-ml portions of 10% aqueous sodium hydroxide and once with 50 ml of brine, dried over anhydrous magnesium sulfate, concentrated, and distilled to give 4.2 g (41%) of 2-methyl-1,3-dioxane. The yield is low undoubtedly because of loss of acetaldehyde; higher yields were obtained in other cases. Results are listed in Table VII which also gives physical constants including salient IR bands.

**Partial Kinetic Control.** A solution of 40 g (0.44 mol) of 1,3-butanediol and a catalytic amount of *p*-toluenesulfonic acid in 100 ml of benzene was brought to boil in the apparatus described in the previous paragraph. Acetaldehyde (38.7 g, 0.88 mol) was added and boiling continued for 30 min. Even though water was still being formed, the reaction was stopped and the product worked up as above to give 26 g (51%) of 2,4-dimethyl-1,3-dioxane, bp 118-124°, which, according to glpc analysis on a 1/8 in. × 30 ft 6% tricyanoethoxypropane (TCEP) on Chromosorb G column (at 98°), consisted of three fractions constituting 92.6, 1.0, and 6.4% of the total (retention times 10, 13, and 17 min). The third fraction was separated by preparative glpc using a 3/8 in. × 20 ft 20% TCEP on Chromosorb P column at 85° (retention times of the three fractions 32, 45, and 60 min) and appeared to be homogeneous *trans*-2,4-dimethyl-1,3-dioxane by analytical glpc and nmr analysis. (The first fraction was a mixture of the *cis* isomer and *cis*-2,4,6-trimethyltrioxane (paraldehyde), and the second fraction was probably *trans*-2,4,6-trimethyltrioxane. The *cis*-2,4-dimethyl-1,3-dioxane was more readily obtained under conditions of thermodynamic control but could not be completely freed of paraldehyde.) Dioxanes prepared by the kinetic method are listed in Table VIII.

**Equilibrations.** For each pair of stereoisomeric 1,3-dioxanes four mixtures (two initially richer in *cis* isomer and two richer in *trans* isomer than the equilibrium mixture as ascertained by preliminary experiments) were equilibrated. In general, ca. 0.07 g (0.5 mmol) of dioxane was dissolved in 1.0 ml of dry ether (to give an approximately 0.5 *M* solution) in a 10-ml, oven-dried, glass-stoppered flask to which was added one drop (containing ca. 8.3 mg or 0.06 mol) of boron trifluoride etherate from a calibrated

capillary pipet. The mole ratio of  $\text{BF}_3$  to dioxane was 1:10. The solutions were placed in a desiccator at room temperature; periodically aliquots were quenched with ethanolic sodium ethoxide or solid sodium or potassium carbonate and then analyzed by glpc on  $\frac{1}{8}$  in.  $\times$  12 ft (or 18 ft, or 30 ft in some cases) TCEP columns. The 12-ft column was 20% TCEP on Chromosorb P (45–60 mesh), the other two 6% TCEP on Chromosorb G (60–80 mesh). The results are tabulated in Table IX. In one case (noted), a 4-ft 20% Carbowax 20M on Chromosorb W (60–80 mesh) column was used. In all but two cases (noted) glpc response ratios were established by analyzing known mixtures of diastereoisomers on the same column and under the same circumstances under which the actual analyses were performed. Analysis results were considered only after each mixture had come to equilibrium, *i.e.*, after successive analyses of products from both *cis*-rich and *trans*-rich mixtures gave the same result, within the limits of experimental error. At least two and often three or four analyses of each mixture were effected, so that the total number of samples analyzed for each compound varied between 8 and 20. The experimental data are summarized in Table IX and the calculated  $K$  and  $\Delta G^\circ$  values as shown in Tables I and II.

**Equilibration of 2,5-Di-*t*-butyl-1,3-dioxane. Effect of Catalyst Concentration.** Solutions (0.5 *M*) of samples containing 98% *trans* isomer or 70% *trans* isomer were treated with variable amounts of boron trifluoride etherate. The same samples were also equilibrated by shaking them with a washed Amberlyst 15 (Rohm & Hass cross-linked polystyrenesulfonic acid resin) catalyst. The results shown in Table X were obtained (analyses as previously described).

**Entropy Determination.** The equilibration was carried out in the usual way at 25.0, 39.8, and 50.1° in a thermostat. The respective equilibrium constants were  $K_{25.0} = 9.88 \pm 0.15$ ;  $K_{39.8} = 8.695 \pm 0.07$ ;  $K_{50.1} = 8.076 \pm 0.14$ . On drawing a least-square plot by means of a computer, these data yielded  $\Delta H^\circ = -1.54 \pm 0.03$  kcal/mol (from the slope of the line) and  $\Delta S^\circ = -0.63 \pm 0.01$  cal/deg mol (from the intercept). The errors given are statistical errors of the plot, but, since only three points were taken, are probably not very meaningful.

**Computer Analysis of 2,5-Di-*t*-butyl-1,3-dioxane Nmr Spectra.** Table XI gives the computer output of the chemical shifts and coupling constants for the *cis* (XXV) and *trans* (XXVI) isomers using the MARIP program and employing as input the chemical

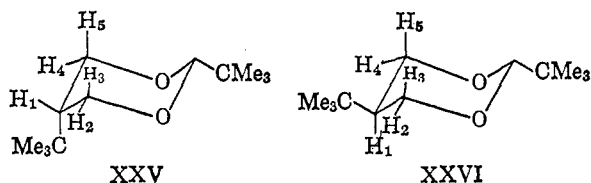


Table XI

Proton	Shielding parameters, cps at 60 Mcps			
	<i>cis</i> isomer		<i>trans</i> isomer	
	First-order (input)	Computed (output)	First-order (input)	Computed (output)
H <sub>1</sub>	56.2		94.0	93.2
H <sub>2</sub>	256.1	257.2	244.6	245.5
H <sub>3</sub>	223.3	222.2	206.2	205.5
H <sub>4</sub>	256.1	257.2	244.6	245.5
H <sub>5</sub>	223.3	222.3	206.2	205.5
Spin-spin coupling constants, cps				
$J_{1,2}$	1.1	1.1	4.7	4.7
$J_{1,3}$	3.9	3.8	12.1	12.2
$J_{1,4}$	1.1	1.1	4.7	4.7
$J_{1,5}$	3.9	3.8	12.1	12.2
$J_{2,3}$	-12.2	-12.2	-12.1	-12.2
$J_{2,4}$	0	0	0	0
$J_{2,5}$	0	0	0	0
$J_{3,4}$	0	0	0	0
$J_{3,5}$	0	0	0	0
$J_{4,5}$	-12.2	-12.2	-12.2	-12.2

shifts and coupling constants obtained from the spectra by first-order analysis. The good agreement between the first-order and computer-approximated data suggests that first-order analysis is satisfactory in these instances.

**Reduction of 2-Vinyl-4-methyl-1,3-dioxanes.** Since the configuration of these compounds, unlike that of all the other dialkyldioxanes, could not be directly inferred from the nmr spectra, samples were hydrogenated to the 2-ethyl-4-methyl-1,3-dioxanes of known configuration. A 92:8 mixture of VIII and IX (3.15 g) was dissolved in 50 ml of anhydrous ether and hydrogenated in a 500-ml pressure bottle in the presence of 50 mg of 10% Pd-C at 45.5 psi hydrogen absorption, being complete after 5 min. The solution was filtered and subjected to gas chromatographic analysis which showed two peaks in a ratio of 91.9:8.1, retention times 7 and 13 min. Identical retention times were shown by a 87:13 mixture of *cis*- and *trans*-4-methyl-2-ethyl-1,3-dioxanes (VI and VII) whereas the starting materials VIII and IX had retention times of 16 and 21 min, respectively, under the same column conditions.

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