Conformational Analysis. XXIII. 1,3-Dioxolanes[1,2]

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Abstract: Two series, one of 2,4-di- and one of 2,*r*-4,*cis*-5-trialkyl-substituted 1,3-dioxolanes, have been studied through acid-catalyzed equilibration of diastereoisomers and by nuclear magnetic resonance spectroscopy. Free-energy differences between diastereoisomers are small, and nearly constant within each series spanning the ranges 0.3–0.5 kcal/mol for the dialkyl series and 0.2–0.7 kcal/mol for the trialkyl series in favor of the *cis*-2 or *syn*-2 substituents. Exceptions are 2-*t*-butyl-*r*-4,*cis*-5-diisopropyl-1,3-dioxolane (+0.22 kcal/mol), 2-isopropyl-*r*-4,*cis*-5-di-*t*-butyl-1,3-dioxolane (+0.01 kcal/mol), and the corresponding 2-*t*-butyl homolog (+0.92 kcal/mol) (in favor of the *anti* isomer). The data suggest a highly flexible five-membered ring with only the most bulky substituents showing signs of specific steric interactions.

Conformational analysis[3] of five-membered ring systems, although of considerable interest because of the widespread occurrence of such systems in nature (*e.g.*, in carbohydrates, steroids, alkaloids, nucleic acids, and certain amino acids), has progressed much more slowly than the corresponding analysis of the six-membered homologs, largely due to the complications caused by the conformational mobility of five-membered rings.[4-9]

Until recently it had been considered that "envelope" (**1**) or "half-chair" (**2**) forms[8,10,11] were adequate models for a description of the conformation of a given five-membered ring system since these two forms were postulated as the most stable forms in much of the pioneering work on five-membered rings (cyclopentane and its derivatives).[4-14] In subsequent work on 1,3-dioxolanes, it was similarly assumed, *a priori*, that one or the other of the two forms should be the thermodynamically most stable.[15-17] It is now becoming

1 2

increasingly clear, however, that this approach represents an oversimplification and that many five-membered systems have a large number of minimum-energy conformations which are often somewhere in between the two prototype forms **1** and **2**.[18]

In cyclopentane, there is little if any energy difference between the envelope and half-chair (or, for that matter, any of the intermediate conformations).[19] The molecule is thus in a rapid state of conformational flux through what is known as "pseudorotation."[6,7] Internal substitution of the five-membered ring with a heteroatom seems to introduce small energy barriers (0.05–0.3 kcal/mol) in the pseudorotation circuit,[6-9,20] but conformational change is still quite facile. External substitution of the five-membered ring has a similar effect.[21] Presumably, a single small substituent or even two of them, while preventing complete pseudorotation (which may lead to conformations in which the substituents become sterically compressed), may still permit wide conformational oscillation about rather flat energy minima ("pseudolibration").[21] As the substituents become larger or more numerous, however, their own steric requirements seem to confine the ring to certain definite energy minima[21] whose position, in the pseudorotation circuit of the ring, is dictated, however, by the steric requirement of the substituent rather than that of the ring, so that they are not necessarily associated with any specific conformation of the ring.

At the inception of this investigation, quantitative information regarding preferred conformations of five-

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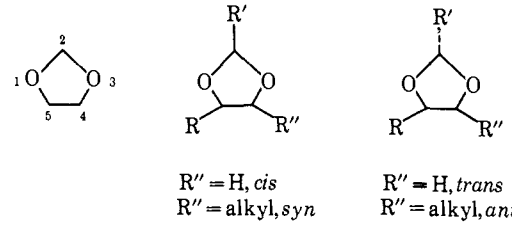
membered ring systems was limited largely to cyclopentane derivatives.[6,8,10,11] The work in the heterocyclic area was confined largely to nmr spectroscopy,[16,17,22-24] although certain systems had been investigated by X-ray diffraction,[25-27] dipole moment study,[18,28] and infrared and Raman spectroscopy.[28b] Few free-energy differences between diastereoisomeric five-membered ring systems have been measured with precision.[29-33]

Recent equilibration studies, used in conjunction with nmr spectroscopy, proved to be a powerful tool in the conformational analysis of substituted 1,3-dioxanes.[34] It was hoped that the same type of study, applied to the 1,3-dioxolane system, would lead to a better understanding of the conformation of five-membered rings in general.

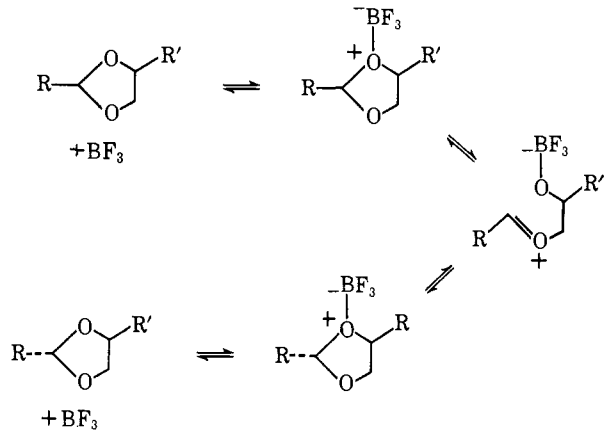
The 1,3-dioxolane system (Chart I) has a number of advantageous properties from the point of view of conformational study. Thus, since 1,3-dioxolanes are

Chart I



cyclic acetals, they are readily synthesized with a wide variety of substituents at the 2, 4, and 5 positions from appropriately substituted and generally readily available aldehydes or ketones and 1,2-glycols. Secondly, in the cases where diastereoisomers (*cis–trans* or *syn–anti* isomers; *cf.* Chart I) exist, such isomers are generally readily equilibrated[17a,22,30-32,35-39] by means of anhydrous acid, probably through the type of reversible ring opening depicted in Chart II. Since chemical

Chart II



equilibration is one of the most reliable and accurate methods of conformational study,[3b] facile attainment of equilibrium provides a distinctly attractive feature of the 1,3-dioxolane system. Moreover, the nmr spectra of 1,3-dioxolanes (useful for configurational and conformational assignments of structure), although generally not first order, are often readily interpretable by computer analysis[16,22,40-44] since the spin system at position 2 (acetal position) is usually quite distinct, and independent of the spin system at positions 4, 5 (ether positions).

Results and Discussion

The 1,3-dioxolanes used in the present study were prepared by acid-catalyzed condensation of alkyl-substituted ethylene glycols with appropriate aldehydes. In most cases the glycols were synthesized from the corresponding olefins by peroxidation with performic acid, followed by hydrolysis. Diastereoisomers were separated by preparative gas chromatography (glpc) and characterized by elemental analysis, nmr and ir spectra, and refractive indices. Equilibration of the isomers was effected in ether solution using a catalytic amount of boron trifluoride etherate; in each case equilibrium was approached from both sides using appropriate *cis* (or *syn*)-rich and *trans* (or *anti*)-rich mixtures. Equilibrated samples were analyzed by glpc to obtain equilibrium constants and, from them, free-energy differences between isomers.

Configurational Assignment. The configurational assignments for the 1,3-dioxolanes are extrapolated from the known configurations of the *cis*- and *trans*-2,4-dimethyl-1,3-dioxolanes, which were originally assigned[36] by comparison of physical properties with those of the corresponding dimethylcyclopentanes.[12,29] Later, the configurations of the 2,4-dimethyl-1,3-dioxolanes were more definitely established through synthesis of the *cis* isomer (**7**) by degradation of 1,6-anhydrogalactose.[31,37] Since the yields in some of the steps of this correlation are quite low, and since a contrary assignment was subsequently made on the basis of nmr spectroscopy,[17a,44a] we decided to establish

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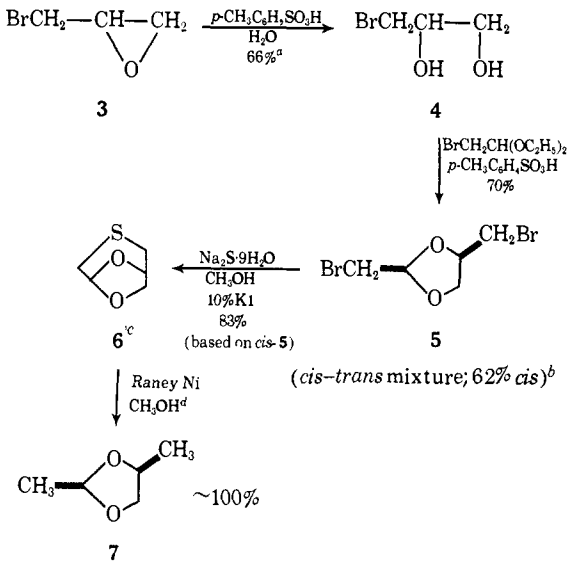
the configuration of *cis*-**7** by an independent synthesis shown in Scheme I. Compound **6** is clearly *cis* bridged;

Scheme I



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the transformation of **6** to **7** proceeded in quantitative yield to give a homogeneous material (glpc evidence) which was unaltered by prolonged refluxing with Raney nickel. The physical properties of the material confirmed the previous chemical assignment of configuration.[31,36,44a]

Knowledge of the correct configurations of the 2,4-dimethyl-1,3-dioxolanes, combined with the fact that the *cis* isomer is thermodynamically more stable, has the lower refractive index, and displays an upfield chemical shift for the C-2 proton (in comparison with the *trans* isomer), permits configurational assignments for all of the other 1,3-dioxolanes in this study to be made by correlation. It is seen (Table I) that in all but three cases, the compound of greater thermodynamic stability has the upfield H(2) chemical shift[2b] and (with one additional exception: the diastereoisomeric 2,4-di-*t*-butyl-1,3-dioxolanes), the lower refractive index; the isomer of lesser $\nu_{H(2)}$ (and generally lower $n^{20}D$) is therefore assigned the *cis* (disubstituted 1,3-dioxolanes) or *syn* (trisubstituted 1,3-dioxolanes) configuration by analogy with the 2,4-dimethyl case (Table I).[2b] It was also found, in those cases where the chemical shift of the 2-alkyl substitutent was determined, that its nmr signal (where R(2) = Me, *i*-Pr, or *t*-Bu) in a *cis* or *syn* isomer is invariably downfield from the corresponding signal in the *trans* or *anti* isomer (Table I).

Equilibrium Studies

2,4-Dialkyl Series. The most striking fact about the free-energy differences (presented in Table II) obtained for the diastereoisomeric 2,4-dialkyl-1,3-dioxolanes is that they are all within 0.25 kcal/mol of each other.

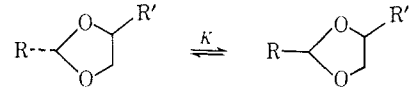
(44a) NOTE ADDED IN PROOF. This assignment has since been withdrawn; *cf.* ref 34b.

Table I. Refractive Indices and Chemical Shifts[a] in Substituted 1,3-Dioxolanes

Dioxolane	More stable isomer[b] $n^{20}D$	$\nu_{H(2)}$	$\nu_{R(2)}$[d]	Less stable isomer[c] $n^{20}D$	$\nu_{H(2)}$	$\nu_{R(2)}$[d]
2,4-Me_2	1.3940	294.7	76.8	1.3960	302.7	74.4
2-Et-4-Me	1.4035	285.7		1.4055	291.3	
2-*i*-Pr-4-Me	1.4083	273.8	54.6	1.4103	278.4	53.5
2-*t*-Bu-4-Me	1.4128	267.2	53.1	1.4150	271.9	51.8
2-Me-4-Et	1.4041	307.0	79.8	1.4060	312.8	77.6
2-Me-4-*i*-Pr	1.4090	296.2	77.0	1.4106	301.9	74.6
2-Me-4-*t*-Bu	1.4138	294.8	77.0	1.4167	301.8	74.3
2-Et-4-*t*-Bu	1.4192	284.9		1.4205	290.9	
2,4-*t*-Bu_2	1.4235[e]	266.0	55.2	1.4211[e]	271.0	52.0
2,4,5-Me_3[f]	1.4005	292.5	76.4	1.4035	313.3	71.0
2-Et-4,5-Me_2[f]	1.4103	283.4		1.4120	299.7	
2-*i*-Pr-4,5-Me_2[f]	1.4142	270.5	54.9	1.4165	285.0	52.7
2-*t*-Bu-4,5-Me_2[f]	1.4183	264.0	53.4	1.4204	278.3	50.7
2-Ph-4,5-Me_2[f]	1.5070	338.8		1.5080	359.9	
2-Me-4,5-Et_2[f]	1.4153	297.4	77.2	1.4173	311.6	72.6
2-*t*-Bu-4,5-Et_2[f]		267.4	54.2		276.6	52.1
2-Et-4,5-*i*-Pr_2[f]		282.2			304.6	
2,4,5-*i*-Pr_3[f]		261.8			285.0	
2-*t*-Bu-4,5-*i*-Pr_2[f,g]	1.4310	281.0	52.1	1.4300	257.6	56.6
2-Me-4,5-*t*-Bu_2[f]		293.8	82.0		325.0	71.0
2-Et-4,5-*t*-Bu_2[f]	1.4410	277.3		1.4423	307.2	
2-*i*-Pr-4,5-*t*-Bu_2[f,g]	1.4414	290.0	53.5	1.4386	257.6	58.3
2,4,5-*t*-Bu_3[f,g]	1.4425	287.9	52.4	1.4405	255.0	58.0

[a] Nmr signals refer to carbon tetrachloride solutions and are in cycles per second downfield from TMS at 60 Mcps. Blanks indicate data were not determined. [b] *cis* or *syn* isomer except where noted. [c] *trans* or *anti* isomer except where noted. [d] Refers to the methyl signal of the Me, *i*-Pr, or *t*-Bu group. [e] These diastereoisomers constitute the only case in this table where the refractive index is lower for the *trans* rather than the *cis* isomer. [f] In all cases the 4,5 substituents are in a *cis* relationship. [g] These three cases are the only ones in this table where the thermodynamically more stable isomer is *anti*, rather than *syn*, as suggested by reversal of the $n^{20}D$, $\nu_{H(2)}$, and $\epsilon_{R(2)}$ data.

Table II. Equilibria in 2,4-Dialkyl-1,3-dioxolanes



T (*trans*) C (*cis*)

Entry	R	R'	K[a]	$\Delta G°_{25}$,[b] kcal/mol	Formula C	Formula T
1	Me	Me	1.59 ± 0.03	−0.276 ± 0.006	**7**	**8**
2	Et	Me	1.55 ± 0.01	−0.260 ± 0.004	**9**	**10**
3	*i*-Pr	Me	1.50 ± 0.06	−0.239 ± 0.010	**11**	**12**
4	*t*-Bu	Me	1.59 ± 0.07	−0.274 ± 0.013	**13**	**14**
5	Me	Et	1.60 ± 0.06	−0.279 ± 0.011	**16**	**17**
6	Me	*i*-Pr	1.73 ± 0.03	−0.323 ± 0.007	**19**	**20**
7	Me	*t*-Bu	2.28 ± 0.07	−0.490 ± 0.016	**22**	**23**
8	Et	*t*-Bu	2.4[c]	−0.5	**24**	**25**
9	*t*-Bu	*t*-Bu	2.00 ± 0.10	−0.409 ± 0.021	**26**	**27**

[a] Glpc area ratio corrected by thermal response ratio ± error propagated (through calculations) from all measured quantities (see: Y. Beers, "Introduction to the Theory of Error," Addison-Wesley, Reading, Mass., 1957, p 28). [b] Error is that propagated from all measured quantities. [c] Ratio of H(2) signals in the nmr spectrum of the equilibrium mixture; approximate value. Reference 34b reports the following values: entry 1, K = 1.56; 2, 1.52; 3, 1.53; 4, 1.59; 7, 1.57; 8, 1.56; 9, 1.53. Evidently there is good agreement with the present results when R' = Me but not when R' = *t*-Bu.

Changing the 2 substituent has no effect at all (within the limits of experimental error) and the effect of changing the 4 substituent, though palpable, is minor. This indicates that 1,3-nonbonded interactions in these

Table III. Equilibria in 2,4,*cis*-5-Trialkyl-1,3-dioxolanes

A(*anti*) S(*syn*)

R	R′	K^a	$\Delta G°_{25}$,[b] kcal/mol	Formula S	Formula A
Me	Me	3.28 ± 0.14	−0.703 ± 0.031	**30**	**31**
Et	Me	2.85 ± 0.12	−0.621 ± 0.027	**32**	**33**
i-Pr	Me	2.73 ± 0.12	−0.595 ± 0.027	**34**	**35**
t-Bu	Me	2.69 ± 0.17	−0.587 ± 0.038	**36**	**37**
Ph	Me	1.91 ± 0.03	−0.384 ± 0.008	**38**	**39**
Me	Et	3.30 ± 0.14	−0.708 ± 0.032	**41**	**42**
t-Bu	Et	2.2[c]	−0.5	**43M**[d]	**43M**[d]
Et	*i*-Pr	2.5[c]	−0.5	**45M**[d]	**45M**[d]
i-Pr	*i*-Pr	2.05 ± 0.19	−0.426 ± 0.040	**46**	**47**
t-Bu	*i*-Pr	0.688 ± 0.043	+0.222 ± 0.014	**48**	**49**
Me	*t*-Bu	2.3[c]	−0.5	**51M**[d]	**51M**[d]
Et	*t*-Bu	1.35 ± 0.07	−0.179 ± 0.010	**52**	**53**
i-Pr	*t*-Bu	0.980 ± 0.054	+0.0122 ± 0.0007	**54**	**55**
t-Bu	*t*-Bu	0.212 ± 0.019	+0.919 ± 0.083	**56**	**57**

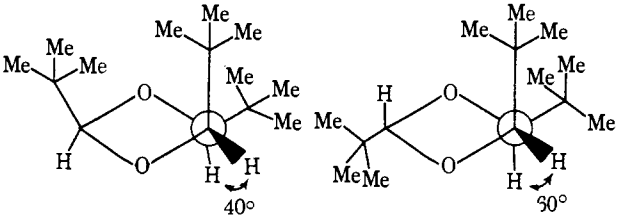
[a] Glpc area ratio corrected by thermal response ratio ± error propagated (through calculations) from all measured quantities. [b] Error is that propagated from all measured quantities. [c] Ratio of H(2) signals in the nmr spectrum of the equilibrium mixture; approximate value. [d] M = mixture; separation of isomers by glpc was not achieved.

compounds are quite small, insensitive to the nature of the 2- and almost insensitive to that of the 4-alkyl substituent (where R and R′ may be Me, Et, *i*-Pr, or *t*-Bu). It also suggests that the preferred conformation or conformations of the ring for all of the *cis* isomers are probably nearly the same, and for all of the *trans* isomers are likewise nearly the same, although the conformation or conformations preferred for the *cis* isomers may differ from those preferred for the *trans*. In all cases the *cis* isomers are thermodynamically favored over the corresponding *trans* isomers. This has been explained[45] on the basis of an unfavorable steric interaction of a pseudoaxial substituent at C-2 with a pseudoaxial hydrogen at C-4 (envelope conformation) in the *trans* isomer. Our data (Table II) would rather suggest that in the predominant conformation the substituent at C-4 is pseudoaxial and that at C-2 pseudoequatorial, so that the salient interaction is between the C-4 substituent and H-2. Accordingly, the interaction is insensitive to the C-2 substituent (first four entries in Table II) but increases as the bulk of the C-4 substituent increases (entries 1, 5, 6, and 7), either because of the increased *syn*-axial interaction or because the molecule is forced into a less favorable conformation. The favoring of the *cis* isomers cannot be due to entropy effects, for only a small entropy difference (0.26 ± 0.04 eu) has been found in the case of the 2,4-dimethyl-1,3-dioxolanes.[46]

2,4,*cis*-5-Trialkyl Series. The free-energy differences (presented in Table III) for the diastereoisomeric 2,4,-*cis*-5-trialkyl-1,3-dioxolanes are all very nearly equal when R′ is Me, regardless of the bulk of R (except for R = Ph). The same is true for R′ = Et and R = Me or *t*-Bu. It is only when R′ becomes *i*-Pr or *t*-Bu that any significant change in the free-energy differences occurs as R changes from Me or Et to *i*-Pr and finally to *t*-Bu.

The *syn* isomers are the thermodynamically more stable ones except for the 2-*t*-Bu-*r*-4-*cis*-5-di-*i*-Pr- and the 2,*r*-4-*cis*-5-tri-*t*-Bu-1,3-dioxolanes,[47] for which the *anti* diastereoisomers become favored. This inversion of thermodynamic stability probably arises from unfavorable 1,3-transannular nonbonded interactions. For example, when R′ = *t*-Bu, one of the six methyl groups pertaining to the *t*-butyl substituents at C-4 and C-5 must point into the ring, and is forced close to the methyl groups of the 2 substituent (R) when the latter is *t*-butyl (Chart III). The cases R′ = *t*-Bu, R = Et or *i*-Pr and R = R′ = *i*-Pr are intermediate in thermodynamic stability between the R = Me and R = *t*-Bu cases undoubtedly because all but a few rotational conformations are sterically disfavored in the *syn* isomers.

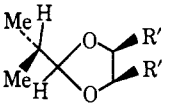
Chart III



40° 60°

56 57

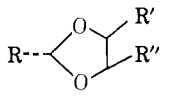
The coupling constants between H(2) and the isopropyl methine proton for the case R = *i*-Pr increase from 4.4 for R′ = Me to 7.5 for R′ = *t*-Bu (Table IV) in the *syn* series, suggesting that the isopropyl group is increasingly forced into the rotational conformation in which the methyl groups point away from the ring (as in **58**) and H(2) and the methine proton are *anti*.[48]



58

(45) R. U. Lemieux in "Molecular Rearrangements," P. deMayo, Ed., Wiley-Interscience, New York, N. Y., 1964, p 728.
(46) P. Salomaa, *Ann. Univ. Turku, Ser. A*, 46 (1961).
(47) Regarding the use of *r* (Beilstein nomenclature) see E. L. Eliel and F. W. Nader, *J. Amer. Chem. Soc.*, **92**, 584 (1970). See also International Union of Pure and Applied Chemistry, Information Bulletin No. 35, June 1969.
(48) S. L. T. Thuan and J. Wiemann, *Bull. Soc. Chim. Fr.*, 4550 (1968).

Table IV. Coupling Constants (cps) between H(2) and the Isopropyl Methine Proton



Dioxolane R	R′	R″	*J* (*cis* or *syn*)	*J* (*trans* or *anti*)
i-Pr	Me	H	4.4	4.5
i-Pr	Me	Me	4.4	5.0
i-Pr	*i*-Pr	*i*-Pr	6.9	5.7
i-Pr	*t*-Bu	*t*-Bu	7.5	6.2
			Change: 3.1	Change: 1.7

The smaller overall change in coupling constants in the *anti* series where R = *i*-Pr (J = 5.0 for R′ = Me, J = 6.2 for R′ = *t*-Bu) indicates that the average rotational conformation of R (*i*-Pr) does not change much throughout this series; however, for R′ = R″ = Me the isopropyl group is actually more restrained in the *anti* series than in the *syn* series (or in either of the 2,4-disubstituted 1,3-dioxolane diastereoisomers) as indicated by the coupling constant of 5.0 (taking J = 4.4 as the value for "freely" rotating R). The reasons for this are probably the same which make the *anti* isomer the less stable (more compressed?) in all but the very highly substituted dioxolanes.

Enthalpy–entropy studies for the 2,*r*-4,*cis*-5-trimethyl- and 2,*r*-4,*cis*-5-tri-*t*-butyl-1,3-dioxolanes[47] (see Experimental Section) yielded the thermodynamic values $\Delta H^\circ = -0.763 \pm 0.043$ kcal/mol ($H^\circ_{syn} < H^\circ_{anti}$), $\Delta S^\circ = -0.33 \pm 0.02$ eu ($S^\circ_{syn} < S^\circ_{anti}$) and $\Delta H^\circ = -1.32 \pm 0.11$ kcal/mol ($H^\circ_{anti} < H^\circ_{syn}$), $\Delta S^\circ = -0.91 \pm 0.02$ eu ($S^\circ_{anti} < S^\circ_{syn}$), respectively. These results (along with ΔS° determined for the 2,4-dimethyl-1,3-dioxolanes)[46] demonstrate that entropy differences between stereoisomers are not dominating in the conformational analysis of substituted 1,3-dioxolanes.

In many cases it was found that the preparation of the diastereoisomeric mixtures gives an at least partially kinetically controlled product ratio rather different from the equilibrium controlled product ratio. In most cases the thermodynamically favored isomer is even more favored kinetically, unlike in 1,3-dioxanes (*cf.* Experimental Section, Table VII).[34,49]

Nmr Spectra of 1,3-Dioxolanes. The nmr spectra of substituted 1,3-dioxolanes have been previously investigated especially by Anteunis and his coworkers.[17,22] Typical H(4)–H(5) vicinal coupling constants span the following ranges: $J_{4\text{-}cis\text{-}5}$ = 5.4–7.5 cps and $J_{4\text{-}trans\text{-}5}$ = 5.9–8.5 cps,[16,17b,22,42] corresponding to torsional angles of 35–50° (*cis*) and 125–140° (*trans*), respectively (values taken from a Karplus curve modified for 1,3-dioxolanes).[16,50] Inspection of Table V indicates that the $J_{4,5}$ couplings (for the 1,3-dioxolanes in the present study) are in the "normal" ranges (with "normal" dihedral angles in the ranges 35–50° or 125–140°), with the exception of the couplings for the 2,*r*-4,*cis*-5-tri-*t*-butyl-1,3-dioxolanes,[51] which fall slightly outside of the normal range. The coupling constants in the tri-*t*-butyl-1,3-dioxolanes indicate a torsional angle of H(4) and H(5) of roughly 40° for the *syn* (**56**) and roughly 60° for the *anti* (**57**) isomer, respectively. These angles are in accordance with those expected on the basis of the free-energy difference between the isomers. Thus the *anti* (thermodynamically more stable) isomer can be maximally staggered (which is to be expected for minimization of vicinal interaction between the *t*-butyl groups) at the 4 and 5 positions, with a dihedral angle of 60°, without interference from the 2-*t*-butyl group, whereas the expected maximal 4,5 staggering in the *syn* (thermodynamically less stable) isomer would give rise to severe nonbonded transannular interaction between the methyl groups of the 2-*t*-butyl substituent and the methyl groups of the 4- (or 5-)*t*- butyl substituent so that staggering in the *syn* isomer is less than maximal and corresponds to an angle of 40°.[52] (These conclusions assume that the

Table V. Coupling Constants (cps) in Substituted 1,3-Dioxolanes[a]

Compd	$J^{cis}_{H(4)H(5)}$	$J^{trans}_{H(4)H(5')}$	$J^{gem}_{H(5)H(5')}$
cis-2,4-Ph_2[b]	7.04[c]	6.93[c]	−7.72
trans-2,4-Ph_2[b]	6.39[c]	7.51[c]	−8.14
cis-2,4-Me_2	6.6[c,d]	7.2[c,d]	−7.3[d]
trans-2,4-Me_2[e]	*e*	*e*	*e*
cis-2-*t*-Bu-4-Me	6.50[c,d]	6.98[c,d]	−7.18[d]
trans-2-*t*-Bu-4-Me[e]	*e*	*e*	*e*
cis-2,4-*t*-Bu_2	6.8[c,f]	5.8[c,f]	−7.0[f]
cis-2-Me-4-*t*-Bu[g]			
trans-2-Me-4-*t*-Bu	7.0[c,f]	7.1[c,f]	−8.7[f]
syn-2-Ph-4,5-Me_2	5.8[h]		
anti-2-Ph-4,5-Me_2	5.8[h]		
syn-2,4,5-*t*-Bu_3	7.9[i]		
anti-2,4,5-*t*-Bu_3	5.2[i]		

[a] Obtained by computer analysis on a Univac 1107 computer using the EXAN II (S. Castellano and J. S. Waugh, *J. Chem. Phys.*, **34**, 295 (1961)) and/or FREQINT IV programs (this is a modified version of a program kindly provided by Dr. A. A. Bothner-By), except in the last four cases. [b] Prepared (mixture of diastereoisomers) in 76% yield, bp 145–154° (0.1 mm) (lit.[30] 140° (12 mm)). [c] J_{cis} could not be distinguished from J_{trans}. [d] Complete solution of the $ABCX_3$ spectrum was achieved by using the solution to the ABC portion which was obtained for the decoupled Me(4)–H(4) spectrum. [e] Constants similar to those in *cis*. [f] From the spectrum at 220 Mcps. [g] H(4), H(5), H(5′) are isochronous. [h] From ref 42. [i] From the spectrum of those molecules containing ^{13}C nuclei.

(49) (a) Recently a stereospecific synthesis of the *syn* diastereoisomers of three 2,*r*-4,*cis*-5-trisubstituted 1,3-dioxolanes was reported[48] using 70% phosphoric acid as the reaction medium. Repetition of one of the preparations (2,*r*-4,*cis*-5-tri-*i*-Pr-1,3-dioxolane) in this study essentially confirmed the report (92% of the *syn* and 8% of the *anti* isomer was obtained). The reasons for the high stereoselectivity in these largely kinetically controlled reactions are not clear. (b) D. R. Garrison, M. May, H. F. Ridley, and D. J. Triggle (*J. Med. Chem.*, **12**, 130 (1969)) report preparation ratios of 4:1 (*syn*:*anti*) and 3:1 (*cis*:*trans*) for diastereoisomeric mixtures of 2-methyl-4-*cis*-5-chloromethyl- and 2-methyl-4-(methyl-*cis*-chloromethyl)-1,3-dioxolane, respectively.

(50) The calculation of specific torsional angles from coupling constants in five-membered rings is probably a dangerous procedure. It has been pointed out by V. Tabacik (*Tetrahedron Lett.*, 555, 561 (1968)) that coupling constants should properly be integrated over the whole rotation circuit of conformationally mobile molecules rather than just summed over the most stable conformations. In five-membered rings where the energy wells are not so deep and pseudorotation or pseudolibration may lead to rather wide conformational circuits, Tabacik's objection should be particularly pertinent and the classical procedure of assuming that the averaging of one, two, or three conformations with their appropriate torsional angles can be made to explain the observed coupling constants may be quite bad.

(51) These couplings were determined from the ABX spectra of the molecules containing carbon-13 nuclei (natural abundance); see, for example, N. Sheppard and J. J. Turner, *Proc. Roy. Soc.*, **252**, 506 (1959).

(52) The previously raised objection to the calculation of torsional angles (ref 50) is not so important in the case of the 4,5-di-*t*-butyl compounds, since the conformation of these compounds appears to be quite biased so that there is a pronounced energy minimum and a very short pseudolibration circuit.

ring in these compounds is not distorted in some unusual manner such that the modified Karplus curve[16] cannot be used in assessing dihedral angles).[53]

Some of the compounds exhibited across-the-ring long-range coupling (*cf.* Table VI);[54] however, since

Table VI. Long-Range Coupling Constants in 1,3-Dioxolanes[a]

Compd	$J_{2,4}$
trans-2-Me-4-*i*-Pr	0.36
trans-2-Me-4-*t*-Bu	0.40
trans-2-Et-4-*t*-Bu	≤0.15
trans-2,4-Ph_2	0.43
4-Me[b]	$J_{2,4}$ (and/or $J_{2,5}$)[c] range: 0.1–0.9
4-Et[b]	
4-*i*-Pr[b]	
4-*t*-Bu[b]	
4-*cis*-5-di-Me[b]	
4-*cis*-5-di-Et[b]	

[a] In cycles per second; compounds in this table are the only ones in this study which were observed to exhibit long-range (across-the-ring) coupling. (The limit of observation is *ca.* 0.1 cps.) [b] Compounds unsubstituted at C-2. [c] In all cases the coupling is between the *syn*-2-proton (with respect to the 4- or 4,5-alkyl substituents) only, the assignment at C-2 being based on relative chemical shifts (*cf.* Table I). In the case of the first three compounds, the coupling is with H(4), which was located in the case of *trans*-2,4-dimethyl-1,3-dioxolane by methyl decoupling and in the above three cases by analogy of shift; in the fourth compound H(5) seems to be involved. Coupling patterns in the other six were complex and were not analyzed.

no consistent pattern was discerned, the significance of the couplings is not clear.

Conclusion

The results of both our extensive equilibration studies and the less extensive investigation of nmr spectra confirm, once again, that the five-membered ring found in 1,3-dioxolanes is highly flexible. The fact that even *meso*-1,2-di-*t*-butylethylene glycol forms dioxolanes with aldehydes as branched as trimethylacetaldehyde with relative ease indicates that both vicinal and transannular (1,3) interactions in the 1,3-dioxolane system must be small. The small energy differences between *cis*- and *trans*- or *syn*- and *anti*-substituted compounds (Tables II and III) and the generally small variations in nmr coupling constants (Table V) are readily interpretable in terms of a very flexible ring whose conformation adjusts itself easily to the steric requirements of the substituents. Evidently both stereoisomers in each series take up conformations in which there is little compression involving the 2-alkyl substituent, since $\Delta G°$ (*trans* ⇌ *cis*) in all but the most highly substituted cases is almost independent of the 2 substituent. Nevertheless, the energy minima, or pseudorotational circuits (presumably avoiding compression of the 2 substituent), for the *trans* or *anti* isomers are slightly different, and somewhat higher in average energy level, than the corresponding minima or circuits for the *cis* or *syn* isomers, except in the case of **49**, **55**, and **57**.

The conformational situation in most of the dioxolanes here studied is fundamentally different from that found in 1,3-dioxanes[34] and in cyclohexane.[3] In six-membered rings one deals with a ring of essentially well-defined conformation, namely the chair form (since the pseudorotating flexible form is higher in energy by well over 5 kcal/mol[3b]). The substituents on the chair must thus assume either the equatorial or the axial position and both the energetics and the spectral properties of equatorially and axially substituted cyclohexanes are substantially different. In 1,3-dioxolane, there is no corresponding minimum energy conformation of the ring as such and therefore also no predetermined conformation for a given substituent. A notable exception is *cis*-4,5-di-*t*-butyl-1,3-dioxolane (**50**); in this compound the bulky substituents apparently confine the ring to a very small part of the pseudorotation circuit and the molecule has something resembling a definitive conformation (although even here the ring conformation is somewhat affected by the size and configuration of the C-2 substituent). Therefore, in 2-alkyl-*r*-4,*cis*-5-di-*t*-butyl-1,3-dioxolanes (**51–57**), unlike in all the other series, one finds a progression of $\Delta G°$ (*anti* ⇌ *syn*) as the 2 substituent is changed from methyl to ethyl to isopropyl to *t*-butyl (last four entries in Table III), similarly as one would find in an alkyl-substituted, conformationally anchored, cyclohexane, such as 2-alkyl-*trans*-decalin.[55]

In those dioxolanes where no pronounced configurational preference exists, we cannot be certain whether we are simply dealing with readily adjustable energy wells, or whether there are actually long flat spots in the energy of the pseudorotation circuit with no pronounced energy minima at all. The latter situation has been observed in the 3-methylcyclopentanols,[29] in cyclopentyl monohalides,[56] and in *trans*-1,2-dichloro- (but not dibromo-) cyclopentane.[21]

There is some indication on this matter from the infrared spectra of the compounds here studied. The dioxolanes with methyl and ethyl substituents only (notably **9**, **10**, **15**, **16**, **17**, **28**, **29**, **30**, **31**, **61**) show rather broad bands and the spectra of diastereoisomers (*e.g.*, **9**/**10**, **16**/**17**, **28**/**29**, **30**/**31**) are extremely similar. These compounds presumably undergo a wide pseudorotation (or at least pseudolibration) circuit. At the other extreme, disubstituted dioxolanes with a *t*-butyl group at C(4), **21–27**, and trisubstituted dioxolanes with *t*-butyl groups at C(4) and C(5), **50**, **52–57**, display rather narrow infrared bands and the infrared spectra of diastereoisomers are quite distinct. These compounds probably have discrete energy wells; for **52–57** this fact was independently arrived at as explained above. A number of the remaining cases are intermediate between the above two categories in the

(53) The 4-*cis*-5-di-*t*-butyl-1,3-dioxolane derivatives all exhibited temperature-dependent broadening of the *t*-butyl signals (while the H(2) and H(4,5) signals remained moderately sharp), but no fine structure in the signals was discernible at temperatures down to −105°. DL-*cis*-3,4-*cis*-3′,4′-Tetramethyl-2,5,2′,5′-tetraoxospiro[4.4]nonane (see Experimental Section) was prepared with a view toward obtaining the corresponding tetra-*t*-butyl compound and investigating its low-temperature nmr spectrum; however, the synthesis of the homolog was not achieved.

(54) M. Barfield, *J. Chem. Phys.*, **41**, 3825 (1964). See J. C. Jochims and G. Taigel, *Chem. Ber.*, **103**, 448 (1970), for a case related to the present one.

(55) The referee has drawn our attention to a previously reported case of a "stiff" furanose ring fused to a 1,4-dioxane ring in which two adjacent *trans*-hydroxyl groups are fixed at a dihedral angle of about 150° to such a degree that periodate cleavage becomes very slow: R. U. Lemieux and R. Nagarajan, *Can. J. Chem.*, **42**, 1270 (1964).

(56) (a) J. Reisse, L. Nagels, and G. Chiurdoglu, *Bull. Soc. Chim. Belg.*, **74**, 162 (1965). (b) See, however, I. O. C. Ekejiuba and H. A. Hallam, *Spectrochim. Acta, Part A*, **26**, 59, 67 (1970); see, also, *J. Chem. Soc., B*, 209 (1970).

appearance of the infrared spectra; these compounds may well have somewhat wide but perhaps not entirely flat energy minima.

Experimental Section

Nmr spectra were recorded on a Varian A-60-A instrument; samples generally were 30–50% solutions in carbon tetrachloride or carbon disulfide (low-temperature spectra).[57] Infrared spectra were recorded on a Perkin-Elmer Infracord instrument. Complete tracings of all nmr and most ir spectra may be found in the Ph.D. Dissertation of W. Edward Willy[2a] (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 305° coupled to a 1-mV Honeywell Elektronik Model 15 recorder equipped with a disk integrator. Columns were 1/8 in. in diameter and 35 ft in length. All analyses were corrected for detector response. Preparative gas chromatographic separation was effected on a Varian-Aerograph Model 1520B instrument with a 65 ft × 3/8 in. aluminum column using a helium flow rate of 200 ml/min. Samples were collected in 4 mm (o.d.) U-tubes containing a small amount of anhydrous potassium carbonate, and immersed in liquid nitrogen. With one exception (chromatography over 5% TCEP on 60–80 Chromosorb G of the 2-phenyl-4,-*cis*-5-dimethyl-1,3-dioxolanes), the columns were packed with Chromosorb G (70–80 mesh analytical; 45–60 mesh preparative) coated with 5.5% Carbowax 20M and 0.5% potassium hydroxide.

1,2-Diols. The physical properties of the alkyl-substituted 1,2-diols prepared according to the general procedure of Brändström[58] were as follows: 3,3-dimethyl-1,2-butanediol, 70% (yield), bp 82–84° (6 mm), mp 43–45° (lit.[58] bp 95–115° (8 mm), mp[59] 45°); 3-methyl-1,2-butanediol, 37%, bp 88–92° (5 mm), n^{20}D 1.4411 (lit.[60] bp 84–85° (25 mm)); *meso*-3,4-hexanediol, 79%, mp 87–88.5° (lit.[61,62] 88°; 90–90.5°); and *meso*-2,5-dimethyl-3,4-hexanediol, 81%, mp 168–170° (lit.[52,63] 168.5°; 175°).

nteso-**2,2,5,5-Tetramethyl-3,4-hexanediol.** According to the method of Newman and Arkell,[64] pivaloin was prepared in 90% yield. Reduction of the pivaloin with sodium borohydride by the method of Dale[65] yielded 49% *meso*-2,2,5,5-tetramethyl-3,4-hexanediol, mp 119.5–121° (lit.[65,66] 125°; 121–122°).

1,2-Butanediol. To 50 ml of 91% formic acid contained in a 250-ml three-necked flask fitted with a dropping funnel and a glass stirrer was added 24.0 g (0.333 mol) of 1,2-butylene oxide (Baker Chem. Co.) over a period of 0.5 hr at a rate such that the temperature was maintained (with an ice bath) at 45–55°. The mixture was heated at reflux for 2 hr, and was then distilled (aspirator vacuum) directly from the reaction flask until no more distillate was obtained (25 ml). The residue was transferred to a 200-ml one-necked flask, and 45 g of 33% aqueous sodium hydroxide was added, with cooling, from a dropping funnel. The funnel was replaced with a condenser, and the mixture was boiled for 1 hr. Phenophthalein indicator was added, and the cooled mixture was neutralized with concentrated hydrochloric acid. The neutral solution was extracted four times with 20-ml portions of chloroform (extraction number and volume of lower phase: 1, 35 ml; 2, 23 ml; 3, 21 ml; 4. 20 ml). The combined extracts were distilled and two fractions were taken: (1) chloroform, bp 62–65° (736 mm); (2) 15.0 g (50%) of product, bp 201–203° (736 mm), n^{20}D 1.4390 [lit.[59] bp 92–94° (18 mm)].

1,3-Dioxolanes, General Procedure. The preparation of *cis*-4,5-diisopropyl-1,3-dioxolane is described as a representative example. To 3.7 g (0.025 mol) of *meso*-2,5-dimethyl-3,4-hexanediol, 0.8 g (0.025 mol) of paraformaldehyde, and 35 ml of methylene chloride[67] contained in a 100-ml flask fitted with a water trap (for solvents heavier than water) and condenser was added 0.2 g of *p*-toluenesulfonic acid. The mixture was boiled for 3 hr, at which time 0.45 ml (theoretical 0.46 ml) of water had collected in the trap. The mixture was then distilled directly from the reaction flask[68] without neutralization of the acid, and two fractions were taken: (1) 32 ml (methylene chloride), bp 41–45° (747 mm); (2) 3.4 g (85%) of product, bp 171–173° (747 mm). The product was stored over anhydrous potassium carbonate.

The physical properties of the 1,3-dioxolanes prepared are reported in Table VII.

2,4,*cis*-5-Triisopropyl-1,3-dioxolanes. Preparation according to Thuan and Wiemann[48] yielded 81% product (mixture of diastereoisomers), bp 200–203° (739 mm), n^{25}D 1.426 (lit.[48] 1.427), with a *syn*:*anti* isomer ratio of 92:8 (lit.[48] 100:0).

2,4-Bisbromomethyl-1,3-dioxolanes. To 50.8 g (0.258 mol) of bromoacetaldehyde diethyl acetal (Aldrich Chem. Co.) in 60 ml of cyclohexane contained in a 200-ml flask fitted with a Dean-Stark trap and a condenser was added 40.0 g (0.258 mol) of 1-bromo-2,3-propanediol (prepared by the method of Winstein and Goodman[69] in 66% yield, bp 125–130° (20 mm), n^{25}D 1.5180 (lit.[69] 64%, bp 106–110° (4 mm), n^{25}D 1.5133–1.5144); the distilled product was highly acidic). The mixture was boiled for 3 hr, at which time 24.0 ml (expected 24.3 ml on the basis of previous experience which showed that only 80% of the ethanol is recovered) of ethanol (lower phase) had collected in the trap (which contained 1 ml of water to begin with). All cyclohexane was then distilled and the flask residue was washed twice with 100-ml portions of saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered into a 50-ml flask, and distilled (short path distillation with aspirator vacuum). There was obtained 47.0 g (70%) of colorless product, bp 115–120° (20 mm) [lit.[70] bp 118–120° (10 mm)].

2,8-Dioxa-6-thiabicyclo[3.2.1]octane. To 45.6 g (0.190 ml) of sodium sulfide nonahydrate in 100 ml of methanol contained in a 500-ml three-necked flask fitted with a glass stirrer, a condenser, and a nitrogen bubbler was added 38.0 g (0.146 mol) of bis-2,4-bromomethyl-1,3-dioxolane (62:38 *cis*:*trans* mixture) and 2.4 g (0.015 mol) of potassium iodide. The mixture was boiled for 4 days, and was then distilled to remove all of the methanol. Water (1 l.) was added to the flask residue which was then extracted twice with 1 l. portions of chloroform. The combined extracts were dried over anhydrous magnesium sulfate, filtered, and distilled. From the product fraction was obtained 10 g (83%) of pale orange material, bp 118–120° (20 mm) [lit.[71] 62%, bp 47–49° (0.1 mm)].

Anal. Calcd for $C_5H_8O_2S$: C, 45.43; H, 6.10; S, 24.26. Found: C, 45.50; H, 6.15; S, 24.25.

Under the same reaction conditions (except with the absence of potassium iodide) bis-2,4-chloromethyl-1,3-dioxolane (prepared from chloroacetaldehyde dimethyl acetal and 1-chloro-2,3-propanediol) reacted very sluggishly to the extent of about 20%.

***cis*-2,4-Dimethyl-1,3-dioxolane.** To a methanolic slurry (7 ml of nickel as measured under water, washed four times with 10-ml portions of absolute methanol) of Raney nickel (No. 28, W. R. Grace & Co.) contained in a 25-ml flask fitted with a condenser was added 407 mg (3.07 mmol) of 2,8-dioxa-6-thiabicyclo[3.2.1]octane in 1 ml of methanol and 126 mg (3.07 mmol) of sodium hydroxide dissolved in 1 ml of methanol. The mixture was boiled for 15 min, at which time glpc analysis (20-ft 5% SF-96 column at 150°) indicated that all of the starting material had disappeared, and that the only product (glpc analysis on a 35-ft 5.5% Carbowax 20M column at 100°) was *cis*-2,4-dimethyl-1,3-dioxolane which was collected by preparative glpc (20-ft 20% Carbowax 20M column at 100°). The nmr spectrum of the product exhibited, *inter alia*, a quartet at 294.8 cps (downfield from TMS at 60 Mcps in carbon tetrachloride solution), and was identical with the spectrum of the ther-

(57) Tabulations of the coupling constants and chemical shifts of H(2), R(2), and R(4) in compounds 7–27 and **61** and of H(2), R(2), R(4,5), and H(4,5) in compounds **28–57** have been deposited as Document No. NAPS-00901 with the ASIS National Auxiliary Publications Service, c/o CCM Information Corp., 909 3rd Ave., New York, N. Y. 10022. A copy may be secured by citing the document number and by remitting $1.00 for microfiche or $3.00 for photocopies. Advance payment is required. Make checks or money orders payable to: ASIS–NAPS.

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Table VII

1,3-Dioxolane	No.	Yield, %	Bp, °C (1 atm)	$n^{20}D$	Calcd, % C	Calcd, % H	Found, % C	Found, % H
4-Me[a]	**61**	27	80–83	1.3985				
cis-2,4-Me_2	**7**[c]	90[b]	92–94	1.3940				
trans-2,4-Me_2	**8**[c]	90[b]	92–94	1.3960				
cis-2-Et-4-Me	**9**[d]	97[b]	113–115	1.4035	62.04	10.41	61.91	10.48
trans-2-Et-4-Me	**10**[d]	97[b]	113–115	1.4055	62.04	10.41	61.93	10.28
cis-2-*i*-Pr-4-Me	**11**[e]	92[b]	133–134	1.4083	64.58	10.84	64.56	10.61
trans-2-*i*-Pr-4-Me	**12**[e]	92[b]	133–134	1.4103	64.58	10.84	64.80	10.87
cis-2-*t*-Bu-4-Me	**13**	75[b]	138–140	1.4128	66.61	11.20	66.71	11.09
trans-2-*t*-Bu-4-Me	**14**	75[b]	138–140	1.4150	66.61	11.20	66.66	11.21
4-Et	**15**	75	113–114	1.4092	58.80	9.87	59.11	10.22
cis-2-Me-4-Et	**16**	60[b]	121–122	1.4041	62.04	10.41	62.20	10.42
trans-2-Me-4-Et	**17**	60[b]	121–122	1.4060	62.04	10.41	62.11	10.39
4-*i*-Pr	**18**	69	129–130	1.4142	62.04	10.41	61.89	10.55
cis-2-Me-4-*i*-Pr	**19**[f]	72[b]	134–135	1.4090	64.58	10.84	64.45	10.81
trans-2-Me-4-*i*-Pr	**20**[f]	72[b]	134–135	1.4106	64.58	10.84	64.74	10.66
4-*t*-Bu	**21**	92	138–139	1.4194	64.58	10.84	64.74	10.92
cis-2-Me-4-*t*-Bu	**22**	58[b]	145–147	1.4138	66.63	11.18	66.96	11.24
trans-2-Me-4-*t*-Bu	**23**	58[b]	145–147	1.4167	66.63	11.18	66.27	11.25
cis-2-Et-4-*t*-Bu	**24**	60[b]	165–166	1.4192	68.31	11.47	68.31	11.54
trans-2-Et-4-*t*-Bu	**25**	60[b]	165–166	1.4205	68.31	11.47	68.52	11.44
cis-2,4-*t*-Bu_2	**26**	59[b]	184–185	1.4235	70.92	11.90	70.71	11.65
trans-2,4-*t*-Bu_2	**27**	59[b]	184–185	1.4211	70.92	11.90	70.64	11.81
trans-4,5-Me_2	**28**[g]	74	102–103	1.3980				
cis-4,5-Me_2	**29**[h]	66	98–100	1.4059				
2-*cis*-4,*cis*-5-Me_3	**30**[i]	72[b]	110–112	1.4005				
2-*trans*-4,*trans*-5-Me_3	**31**[i]	72[b]	110–112	1.4035				
2-Et-*cis*-4,*cis*-5-Me_2	**32**	85[b]	130–132	1.4103	64.58	10.84	64.87	10.76
2-Et-*trans*-4,*trans*-5-Me_2	**33**	85[b]	130–132	1.4120	64.58	10.84	64.67	10.77
2-*i*-Pr-*cis*-4,*cis*-5-Me_2	**34**	92[b]	148–150	1.4142	66.63	11.18	66.72	11.10
2-*i*-Pr-*trans*-4,*trans*-5-Me_2	**35**	92[b]	148–150	1.4165	66.63	11.18	66.88	11.23
2-*t*-Bu-*cis*-4,*cis*-5-Me_2	**36**	97[b]	151–154	1.4183	68.31	11.47	68.21	11.41
2-*t*-Bu-*trans*-4,*trans*-5-Me_2	**37**	97[b]	151–154	1.4204	68.31	11.47	68.28	11.38
2-Ph-*cis*-4,*cis*-5-Me_2	**38**	80[b]	86 (0.1 mm)	1.5070	74.12	7.93	73.91	7.88
2-Ph-*trans*-4,*trans*-5-Me_2	**39**	80[b]	86 (0.1 mm)	1.5080	74.12	7.93	74.09	7.98
cis-4,5-Et_2	**40**	98	148–149	1.4205	64.58	10.84	64.52	10.93
2-Me-*cis*-4,*cis*-5-Et_2	**41**	80[b]	155–157	1.4153	66.63	11.18	66.41	10.97
2-Me-*trans*-4,*trans*-5-Et_2	**42**	80[b]	155–157	1.4173	66.63	11.18	66.41	10.98
2-*t*-Bu-4-*cis*-5-Et_2[b]	**43**	77[b]	190–192		70.92	11.90	70.78	11.82
cis-4,5-*i*-Pr_2	**44**	85	171–173	1.4282	68.31	11.47	68.36	11.42
2-Et-4-*cis*-5-*i*-Pr_2[b]	**45**	51[b]	195–196		70.92	11.90	71.16	12.02
2-*cis*-4,*cis*-5-*i*-Pr_3	**46**	73[b]	204–206		71.95	12.08	72.14	11.94
2-*trans*-4,*trans*-5-*i*-Pr_3	**47**	73[b]	204–206		71.95	12.08	72.30	12.22
2-*t*-Bu-*cis*-4,*cis*-5-*i*-Pr_2	**48**	79[b]	210–212	1.4300	72.84	12.23	72.93	12.06
2-*t*-Bu-*trans*-4,*trans*-5-*i*-Pr_2	**49**	79[b]	210–212	1.4310	72.84	12.23	73.11	12.14
cis-4,5-*t*-Bu_2	**50**	63	196–198	1.4450	70.92	11.90	70.71	11.90
2-Me-4-*cis*-5-*t*-Bu_2[b]	**51**	63[b]	208–209		71.95	12.08	72.24	11.99
2-Et-*cis*-4,*cis*-5-*t*-Bu_2	**52**	89[b]	214–216	1.4410	72.84	12.23	73.09	12.26
2-Et-*trans*-4,*trans*-5-*t*-Bu_2	**53**	89[b]	214–216	1.4423	72.84	12.23	73.00	12.30
2-*i*-Pr-*cis*-4,*cis*-5-*t*-Bu_2	**54**	49[b]	228–229	1.4386	73.63	12.36	73.66	12.30
2-*i*-Pr-*trans*-4,*trans*-5-*t*-Bu_2	**55**	49[b]	228–229	1.4414	73.63	12.36	73.87	12.38
2-*cis*-4,*cis*-5-*t*-Bu_3[j]	**56**	43[b]	235–237	1.4405	74.32	12.47	74.68	12.54
2-*trans*-4,*trans*-5-*t*-Bu_3[j]	**57**	43[b]	235–237	1.4425	74.32	12.47	74.52	12.50
Dioxathiabicyclooctane[k]	**59**	83	121 (20 mm)		45.43	6.10	45.50	6.15
						S, 24.26	S, 24.25	
Tetramethylspiroxolane[l]	**60**	96	217–219		57.43	8.57	57.58	8.45

[a] H. T. Clarke (*J. Chem. Soc.*, 1788 (1912)) reports bp 88–89° (755 mm), $n^{20}D$ 1.4010. [b] For mixture of stereoisomers. [c] Reference 36 reports bp 89.7° (742 mm), $n^{19}D$ 1.3950 for **7**, bp 93.5° (748 mm), $n^{19.8}D$ 1.3963 for **8**. [d] Reference 15 reports $n^{20}D$ 1.4035 for **9**, $n^{20}D$ 1.4051 for **10**; also see ref 32. [e] Reference 15 reports $n^{20}D$ 1.4083 for **11**, $n^{20}D$ 1.4099 for **12**. [f] Reference 15 reports $n^{20}D$ 1.4089 for **19**, $n^{20}D$ 1.4125 for **20**. [g] H. K. Garner and H. J. Lucas (*J. Amer. Chem. Soc.*, **72**, 5497 (1950)) report bp 95.6–95.9° (746 mm), $n^{25}D$ 1.3959. [h] Reference 17a reports bp 104°. [i] Reference 15 reports bp 109.1–109.5° (751 mm), $n^{20}D$ 1.4007 for **30**, bp 112.4° (751 mm), $n^{20}D$ 1.4038 for **31**; H. J. Backer (*Recl. Trav. Chim. Pays-Bas*, **55**, 1036 (1936)) reports bp 108–109°, $n^{18}D$ 1.4007 (mixture of stereoisomers). [j] Molecular weights were determined for each pure tri-*t*-butyl-1,3-dioxolane diastereoisomer by the Rast method (see: N. D. Cheronis, J. B. Entrikin, and E. M. Hodnett, "Semimicro Qualitative Organic Analysis," 3rd ed, Interscience, New York, N. Y., 1965, p 228) yielding values of 260 g/mol for the *syn* and 234 g/mol for the *anti* isomer, respectively. [k] 2,8-Dioxa-6-thiabicyclo[3.2.1]octane. [l] DL-*cis*-3,4-*cis*-3′,4′-Tetramethyl-2,5,2′,5′-tetraoxospiro[4.4]nonane.

modynamically more stable isomer of the diastereoisomeric 2,4-dimethyl-1,3-dioxolanes (quartet at 294.7 cps in carbon tetrachloride). Further boiling of the product (6 hr) with Raney nickel led to no change in product composition.

Equilibrations. Diastereoisomeric 1,3-dioxolane mixtures were equilibrated in oven-dried, sealed ampoules (2 ml) by the method of Eliel and Knoeber.[34] In general, 20–60 mg (0.2–0.25 mmol) of 1,3-dioxolane was dissolved in 0.5 ml of dry ether (to give a 0.4–0.5 *M* solution) to which was added 1 drop (containing *ca.* 3.1 mg or 0.022 mmol) of boron trifluoride etherate from a calibrated pipette. Mixtures were quenched with solid sodium methoxide and analyzed by glpc as previously described. At least two analyses of each mixture were effected, and the total number of samples analyzed for each diastereoisomeric pair was ten.

Table VIII. Equilibration Results

Compd[a]	Area ratio[b]	Response ratio[c]	Equilibrium ratio	Preparation ratio
7/8	1.57 ± 0.02	1.01 ± 0.01	61:39	60:40
9/10	1.52 ± 0.01	1.02 ± 0.00	60:40	60:40
11/12	1.49 ± 0.05	1.00 ± 0.01	60:40	64:36
13/14	1.56 ± 0.05	1.02 ± 0.03	61:39	85:15
16/17	1.62 ± 0.05	0.986 ± 0.016	62:38	60:40
19/20	1.75 ± 0.03	0.986 ± 0.010	63:37	59:41
22/23	2.27 ± 0.07	1.01 ± 0.01	70:30	67:33
24/25	2.4[d]		71:29[d]	
26/27	2.04 ± 0.10	0.977 ± 0.006	67:33	76:24
30/31	3.25 ± 0.13	1.01 ± 0.01	77:23	80:20
32/33	2.91 ± 0.11	0.982 ± 0.015	74:26	95:5
34/35	2.77 ± 0.12	0.984 ± 0.005	73:27	94:6
36/37	2.70 ± 0.07	0.999 ± 0.058	73:27	94:6
38/39	1.95 ± 0.02	1.02 ± 0.01	66:34	66:34
41/42	3.34 ± 0.08	0.989 ± 0.033	77:23	71:29
43S/43A	2.2[d]		69:31[d]	68:32[d]
45S/45A	2.5[d]		71:29[d]	66:34[d]
46/47	1.95 ± 0.12	1.05 ± 0.07	67:33	64:36
48/49	0.688 ± 0.038	0.999 ± 0.030	41:59	45:55
51S/51A	2.3[d]		70:30[d]	61:39[d]
52/53	1.33 ± 0.07	1.02 ± 0.01	58:42 (57:43)[d]	95:5
54/55	0.984 ± 0.056	0.996 ± 0.014	50:50	47:53
56/57	0.217 ± 0.018	0.978 ± 0.029	18:82	83:17

[a] S = *syn* isomer, A = *anti* isomer. [b] Error is standard deviation. [c] Error is that propagated (through calculations) from all measured quantities. [d] Ratio of H(2) signals in the nmr spectrum; separation of isomers by glpc was not achieved (except for **24/25** and **52/53**).

The experimental data are summarized in Table VIII and the calculated K and $\Delta G°$ values are shown in Tables II and III.

Entropy–Enthalpy Determination. (1) 2,4,*cis*-5-Trimethyl-1,3-dioxolane Diastereoisomers. The equilibrations were carried out, at five temperatures, as described previously, except the solvent was *p*-dioxane (Matheson Coleman and Bell, chromatoquality reagent 99+ mol %). A sample mixture to be equilibrated was sealed in the upper half of an ampoule with a breakable seal in the middle (13-mm break-seal glass tubes, Kontes Glass Co., Calif.). In the lower half was placed a 3-cm Teflon-coated stirring bar, 0.5 ml of *p*-dioxane, and a threefold mole excess of sodium methoxide (with respect to the moles of boron trifluoride in the upper half). The ampoule was then suspended in the refluxing vapor of a particular solvent chosen to give a desired temperature. After 1 week, the mixture was quenched by removing the ampoule from the constant temperature environment, breaking the seal, and placing it back into the vapor for 15 min. The ampoule was then cooled in ice–water and opened. The neutral mixture was analyzed by glpc (35-ft 5.5% Carbowax 20M column at 110°). Equilibrium constants, K = (*syn*)/(*anti*), found were K(20.0°) = 3.16 ± 0.12 (combined error from that in the response ratio and in the equilibrium constant); K(40.0°) = 2.88 ± 0.14; K(63.0°) = 2.64 ± 0.09; K(76.0°) = 2.51 ± 0.10; K(99.0°) = 2.41 ± 0.09. On drawing a least-squares plot by means of a computer, these data yielded $\Delta H°$ = −0.763 ± 0.043 kcal/mol (from the slope of the line) and $\Delta S°$ = −0.33 ± 0.02 cal/deg mol (from the intercept). The errors given are statistical errors of the plot.

(2) 2,4,*cis*-5-Tri-*t*-butyl-1,3-dioxolane Diastereoisomers. Equilibrium constants found (after 2 months) by the method described above were K(40.0°) = 5.27 ± 0.38; K(63.0°) = 4.50 ± 0.32; and K(76.0°) = 4.26 ± 0.41. On drawing a least-squares plot by means of a computer, these data yielded $\Delta H°$ = −1.32 ± 0.11 kcal/mol (from the slope of the line) and $\Delta S°$ = −0.91 ± 0.02 cal/deg mol (from the intercept) where K = (*anti*)/(*syn*). The errors given are the statistical errors of the plot, but, since only three plots were taken, are probably not statistically meaningful.

DL-*cis*-3,4-*cis*-3′,4′-Tetramethyl-2,5,2′,5′-tetraoxaspiro[4.4]nonane. To a hot (75°) mixture of 2.6 g (0.029 mol) of 96% diastereoisomerically pure *meso*-2,3-butanediol (Eastman Organic Chemicals), 2.0 g (0.015 mol) of tetramethyl orthocarbonate, and 15 ml of cyclohexane contained in a 50-ml flask fitted with a Dean-Stark trap and a condenser was added a trace of *p*-toluenesulfonic acid. The mixture was boiled for 15 min, at which time 2.8 ml (theoretical 2.4 ml) of methanol had collected in the trap. The mixture was neutralized with solid sodium bicarbonate, transferred to a 25-ml flask, and distilled. Two fractions were taken: (1) cyclohexane, bp 81–89° (741 mm); (2) 2.7 g (96%) of product: bp 217–219° (741 mm); nmr (CCl_4) δ 1.16 (m, 12, $-CH_3$), 4.21 (m, 4). *Anal.* Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.58; H, 8.45.

The corresponding *cis,trans* diastereoisomer (4%) was isolated and characterized by nmr spectroscopy (CCl_4): δ 1.33 (m, 12, $-CH_3$), 4.81 (m, 4).

Attempts to prepare the corresponding tetra-*t*-butylspiroxolane and its precursor (2,2-dimethoxy-4,*cis*-5-di-*t*-butyl-1,3-dioxolane) under the same conditions as indicated above were not successful.

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