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CONFIGURATIONAL EQUILIBRIA IN 2, 4, 5-TRISUBSTITUTED 1, 3-DIOXOLANES

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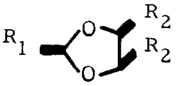
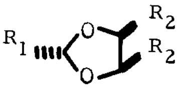
A recent report (1) of the stereospecific synthesis of some alkyltrisubstituted 1, 3-dioxolanes prompts us to communicate some of our findings regarding the preparation and properties of certain 2, 4-*cis*-5-trisubstituted 1, 3-dioxolanes.

Somewhat unexpectedly we have found that 1, 2 as well as 1, 3 non-bonded interactions are relatively small in these compounds. The evidence regarding 1, 2-interactions is that the diastereoisomeric *syn*(I) and *anti*(II) 2-alkyl-4-*cis*-5-trisubstituted-1, 3-dioxolanes, including the *syn*(Ia) and *anti*(IIa) 2, 4-*cis*-5-tri-*t*-butyl-1, 3-dioxolanes, are easily prepared (2). The fact that I and II, in many cases, exhibit only small differences in thermodynamic stability (Table 1) bears on the small magnitude of 1, 3-interactions.



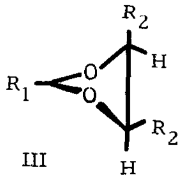
I



II

Ia, IIa: $R_1 = R_2 = (CH_3)_3C$

The *syn* isomers are the thermodynamically more stable ones except for the 2-*t*-Bu-4-*cis*-5-di-*i*-Pr- and the 2, 4-*cis*-5-tri-*t*-Bu-1, 3-dioxolanes, for which the *anti* diastereomers become favored. This may be explained on the basis of transannular interactions. To minimize vicinal interaction of the groups at the 4 and 5 positions, the rings probably adopt a half-chair conformation III (3). In general, the *syn* configuration in which R_1 and one of the R_2's are pseudoequatorial is preferred in analogy with the situation in 1, 3-dimethylcyclopentane (4, 5) and 2, 4-dialkyldioxolanes (6). However when R_2= *t*-Bu, one of the six methyl groups must point into the ring, and when R_1= *t*-Bu also, the *syn* configuration is then disfavored by transannular steric interactions. (The cases R_2= *t*-Bu,



III

R_1= Et or *i*-Pr and R_2=R_1 = *i*-Pr are intermediate because all but a few rotational conformations are sterically disfavored) (7).

Table 1. Equilibrium Ratios and Free Energy Differences (at 25°) for Diastereoisomeric 2-Alkyl-4-*cis*-5-trisubstituted-1, 3-dioxolanes (in Ether).

Dioxolane[a] R_1	R_2	Equilib. Ratio[b, c]	ΔG^o kcal/mol	Dioxolane[a] R_1	R_2	Equilib. Ratio[b, c]	ΔG^o kcal/mol
Me	Me	77:23	-0.70	Et	*i*-Pr	71:29[d]	-0.5
Et	Me	74:26	-0.62	*i*-Pr	*i*-Pr	67:33	-0.43
i-Pr	Me	73:27	-0.60	*t*-Bu	*i*-Pr	41:59	+0.22
t-Bu	Me	73:27	-0.59	Me	*t*-Bu	70:30[d]	-0.5
Ph	Me	66:34	-0.38	Et	*t*-Bu	58:42	-0.18
Me	Et	77:23	-0.71	*i*-Pr	*t*-Bu	50:50	+0.01
t-Bu	Et	69:31[d]	-0.5	*t*-Bu	*t*-Bu	18:82	+0.92

(a) Preparations yielded diastereoisomer mixtures ranging from 95:5 to 47:53 in composition with the more stable isomer generally predominating (Exception: Ia:IIa, preparation ratio 83:17). In ref. 1, a single diastereoisomer (I) is reported to be formed (under different conditions). (b) Corrected for response ratio (0.98 to 1.05). (c) I:II. (d) By NMR. Other ratios by glpc.

Assignment of *syn* and *anti* geometry to the isomers is based upon the correlation of several physical properties with configuration, using the *cis*- and *trans*-2, 4-dimethyl-1, 3-dioxolanes of known configuration (8) as reference compounds. The NMR signal of the 2-proton for all the isomers assigned the *syn* configuration is invariably at higher field than the corresponding signal of the *anti* isomers within any given series (Figure 1). Also, the *syn* isomers invariably have a lower refractive index than the corresponding *anti* isomers (9), in agreement with other reports for alkyl-1, 3-dioxolanes (10-12).

A detailed report of our studies on 1, 3-dioxolanes will be presented elsewhere at a later date.

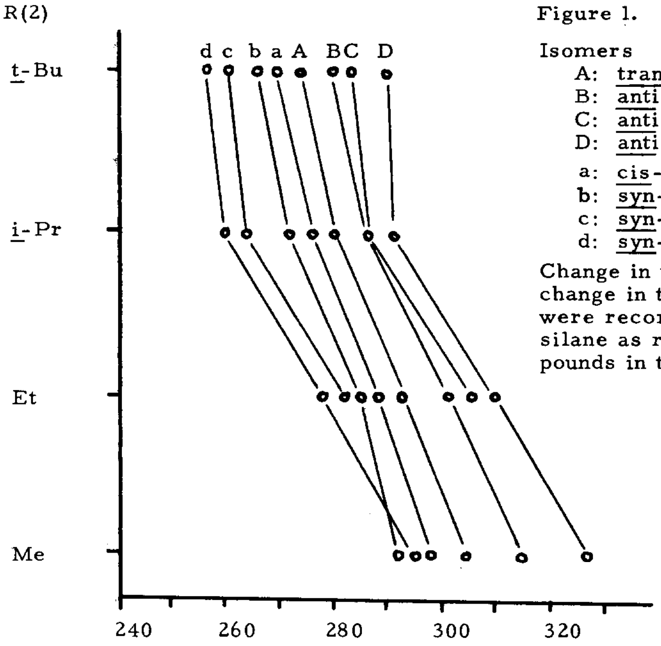


Figure 1.

Isomers
- A: trans-2-R-4-Me[a]
- B: anti-2-R-4-cis-5-Me_2
- C: anti-2-R-4-cis-5-i-Pr_2
- D: anti-2-R-4-cis-5-t-Bu_2
- a: cis-2-R-4-Me[a]
- b: syn-2-R-4-cis-5-Me_2
- c: syn-2-R-4-cis-5-i-Pr_2
- d: syn-2-R-4-cis-5-t-Bu_2

Change in the H(2) chemical shift with change in the 2-alkyl substituent. Spectra were recorded in CCl_4 with tetramethylsilane as reference. (a) The t-Bu compounds in these series are new compounds.

Acknowledgement.

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REFERENCES AND NOTES

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2. The dioxolanes were prepared from appropriate aldehydes and *meso*-diols. Equilibration of the diastereoisomeric pairs was effected by boron trifluoride etherate in ether and analysis was by glpc on 35 ft columns of Carbowax 20M. Diastereoisomeric pairs were separated by preparative gas chromatography and subjected to elemental analysis (all analyses were within the normal limits of ± 0.35%). Glpc response ratios, ir, and nmr spectra were recorded for all pure compounds. Molecular weights were determined for the tri-*t*-butyl diastereoisomers by the Rast method.

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4. *Cf.* E.L. Eliel, N.L. Allinger, S.J. Angyal and G.A. Morrison, "Conformational Analysis," Interscience Division, John Wiley & Sons, New York, *1965*, p. 202.

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6. B.E. Leggetter and R.K. Brown, *Can. J. Chem.*, **43**, 1030 (1965).

7. The coupling constants between H(2) and the isopropyl methine proton for the case R_1 = *i*-Pr increase from 4.4 for R_2 = Me to 7.5 for R_2 = *t*-Bu 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 and H(2) and the methine proton are *anti*. In the *anti* series the change is less marked: J = 5.0 for R_2 = Me, J = 6.2 for R_2 = *t*-Bu, and for R_2 = Me, the greater rotational restraint actually appears in the *anti* (pseudoaxial) isomer. Cf. ref. 1.

8. D.J. Triggle and B. Belleau, *Can. J. Chem.*, **40**, 1201 (1962).

9. The values for the *syn* and *anti* 2-Ph-4-*cis*-5-Me_2, 2-Et-4-*cis*-5-*i*-Pr_2, 2,4-*cis*-5-*i*-Pr_3, and 2-Me-4-*cis*-5-*t*-Bu_2 were not determined.

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12. The argument is actually one of correlation. Except for Ia:IIa and the other two cases shown in Table 1 with positive ΔG°, the compound of greater thermodynamic stability has the lower refractive index and the lesser H(2) chemical shift and is assigned the *syn*-configuration by analogy with the 2,4-dimethyl case.