

## Anomeric Effect in Compounds with Five-membered Rings

### Comparison of Equilibrium Data for Isomeric Tetrahydrofuran and Tetrahydropyran Derivatives

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The free energy differences between the *cis-trans* isomeric 2,5-dimethoxytetrahydrofurans and 2,6-diethoxytetrahydropyrans were measured in different solvents. The obtained data revealed a stabilizing anomeric effect in the studied tetrahydrofuran derivatives. The possible conformations of 2,5-dimethoxytetrahydrofurans are discussed on the basis of the observed anomeric effects. A synthetic method has been described for the preparation of 2,6-dialkoxytetrahydropyrans. The method makes use of kinetic results on vinyl ether and acetal hydrolysis.

In a previous kinetic study of the hydrolysis of 2-alkoxytetrahydrofurans and 2-alkoxytetrahydropyrans,<sup>1</sup> it was found that there exists a linear relationship between inductive polar effects of different alkoxy groups ( $\text{CH}_3\text{O}$ ,  $\text{CH}_3\text{CH}_2\text{O}$ ,  $(\text{CH}_3)_2\text{CHO}$ ,  $\text{ClCH}_2\text{CH}_2\text{O}$ , and  $\text{CH}_3\text{OCH}_2\text{CH}_2\text{O}$ ) and the corresponding rate coefficients. Thus it can be concluded that conformational differences between different substituents in the two series of compounds are negligible. This implies that each alkoxy substituent has nearly the same conformation in both series of compounds. However, to get a better picture of conformational effects in the alkoxy-substituted tetrahydropyran and tetrahydrofuran derivatives, the relative stabilities of isomeric dialkoxy-substituted derivatives were studied in this work. 2,5-Dialkoxytetrahydrofurans and 2,6-dialkoxytetrahydropyrans were chosen as model compounds as their free energy differences can easily be measured by equilibration methods.

#### EXPERIMENTAL

*Syntheses.* 2,5-Dimethoxy-2,5-dihydrofuran was prepared by a standard method<sup>2</sup> from furan, bromine, and methanol. The product was purified by repeated distillation. B.p. 52–54°C/13.5 torr,  $n_D^{20}$  1.4348. The collected fraction was a mixture of *cis* and *trans* isomers.

2,5-Dimethoxytetrahydrofuran was synthesized by hydrogenating 2,5-dimethoxy-2,5-dihydrofuran for 2 h in methanol.<sup>3</sup> The pressure was 20 atm and the temperature 25°C. After two fractionations in a Todd assembly the following best fractions were collected. One fraction b.p. 62°C/40 torr,  $n_D^{20}$  1.4187,  $d_4^{20}$  1.0262, and  $(R)_D$  32.50 (calc. 32.47) contained 98.0 % of the more volatile isomer I and 2.0 % of the less volatile isomer II. Another fraction b.p. 63°C/40 torr,  $n_D^{20}$  1.4174,  $d_4^{20}$  1.0252, and  $(R)_D$  32.45 contained 3.1 % of isomer I and 96.9 % of isomer II. NMR spectra were measured with Perkin Elmer R-10 spectrometer on 10 % solutions of the fractions in carbon tetrachloride with tetramethyl silane as standard substance. The following chemical shifts ( $\delta$ -values, ppm) were recorded for the methine protons: 4.96 for isomer I and 4.92 for isomer II. Aito *et al.*<sup>4</sup> have shown on the basis of the chemical shifts, which are in accordance with those measured in this work, that the more volatile isomer I has the *trans* configuration and isomer II the *cis* configuration.

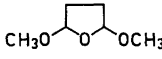
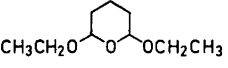
2,6-Diethoxytetrahydropyran was prepared by alcoholysis of 2-ethoxy-2,3-dihydropyran. 2-Ethoxy-2,3-dihydropyran was recently found<sup>5</sup> to hydrolyze in water by three routes: (A) as a vinyl ether, (B) as an acetal with a rate-determining *exo*-carbon-oxygen bond fission, and (C) as an acetal with a rate-determining ring opening. It was calculated from the kinetic data that the ratio of the contributions of A and B is about 2 to 1 and that the contribution of route C is negligible. It was also shown that the ratio is nearly the same for the alcoholysis reaction. The ethanolysis by route B leads to the original substrate. Ethanolysis of the type A yields the desired 2,6-diethoxytetrahydropyran and reaction C the diacetal of glutaraldehyde. The contribution of reaction C can be minimized by reducing the temperature because the rate of acetal hydrolysis decreases more rapidly (by a factor of three for every ten degrees) than that of vinyl ether hydrolysis (temperature coefficient about 2). On the basis of these results, the synthesis of 2,5-diethoxytetrahydropyran was carried out as follows. An equimolar mixture of 2-ethoxy-2,3-dihydropyran (64 g) and ethanol (23 g) was cooled to 0°C. Hydrochloric acid (0.3 ml concentrated acid in 5 ml of abs. ethanol) was dropped into the cooled mixture with vigorous stirring. When the progress of the reaction was followed by gas chromatography, it was found that the reaction went to completion in 3 h. The amount of the diacetal of glutaraldehyde formed was negligible. The reaction mixture was neutralized with sodium ethoxide at 0°C and fractionated in a Todd precise fractionation assembly. The following best samples were collected in fractionation of the isomers. Fraction I, b.p. 59.8–61.2°C/5.0 torr,  $n_D^{20}$  1.4288,  $d_4^{20}$  0.9651,  $(R)_D$  46.53 (calc. 46.45); the amount of the less volatile isomer II in this fraction was 1.5 %. Fraction II, b.p. 68°C/6.5 torr,  $n_D^{20}$  1.4313,  $d_4^{20}$  0.9665,  $(R)_D$  46.69. This fraction contained only 0.5 % of the more volatile isomer I. The methine protons of isomer I resonated in the magnetic field 4.66 ( $\delta$ -value, ppm), and isomer II in the field 4.41. NMR data for the substituted tetrahydropyrans<sup>6</sup> showed that axial anomeric methine protons resonate in a higher field than equatorial methine protons. Thus we can conclude that isomer I has the *trans* configuration and isomer II the *cis* configuration because as is the case of 2-alkoxy-4-methyltetrahydropyrans,<sup>6</sup> the contribution of the conformer with axial ethoxy groups is negligible in the *cis* configuration as a result of serious 1,3-diaxial interaction. Eliel and Giza<sup>7</sup> have recently proposed the same conformations for these isomers.

*Equilibrations.* A solution containing 2.5 % of a tetrahydrofuran or a tetrahydropyran derivative and a small amount of *p*-toluenesulfonic acid was kept at 25°C until the equilibrium had been reached. Equilibrations were carried out on the following solvents: benzene, carbon tetrachloride, diethyl ether, methanol, ethanol, nitrobenzene, water, 2,5-dimethoxytetrahydrofuran, and 2,6-diethoxytetrahydropyran. When hydrolyzing or alcoholyzing agents were used as solvents, the content of substrate was 5 %. The equilibrium mixture was analyzed with a Perkin Elmer F 11 gas chromatograph equipped with a silicone gum column. The composition of the mixture was calculated from the areas of the peaks of the isomers. To make sure that equilibrium had been reached, samples that had been neutralized with diethylamine before injection were analyzed on successive days.

## EQUILIBRIUM DATA

The equilibrium proportions of the isomeric 2,5-dimethoxytetrahydrofurans and 2,6-diethoxytetrahydropyrans are shown with their standard errors in Table 1. The accuracy of the equilibrium data is poorest in those cases

Table 1. Equilibrium data for isomeric 2,5-dimethoxytetrahydrofurans and 2,6-diethoxytetrahydropyrans in different solvents at 25°C.

Compound	Solvent	Dielectric constant of the solvent <sup>14</sup> at 20°C	Equilibrium composition	
			% isomer I	% isomer II
	Benzene	2.28	63.0 ± 0.2	37.0 ± 0.2
	Diethyl ether	4.34	62.8 ± 0.2	37.2 ± 0.2
	Neat compound	—	59.2 ± 0.3	40.8 ± 0.3
	Methanol	33.62	55.2 ± 0.9	44.8 ± 0.9
	Nitrobenzene	35.74	52.4 ± 0.2	47.6 ± 0.2
	Water	80.37	42.7 ± 1.1	57.3 ± 1.1
	Carbon tetrachloride	2.24	91.7 ± 0.2	8.3 ± 0.2
	Diethyl ether	4.34	95.3 ± 0.2	4.7 ± 0.2
	Neat compound	—	87.0 ± 0.3	13.0 ± 0.3
	Ethanol	24.30	83.7 ± 0.2	16.3 ± 0.2
	Nitrobenzene	35.74	81.6 ± 0.4	18.4 ± 0.4
	Water	80.37	74.7 ± 0.4	25.3 ± 0.4

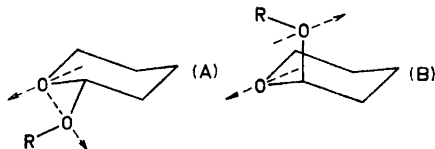
where the concentration of the substrate was very small as a result of alcoholysis (in methanol and ethanol) or hydrolysis (in water). The data in Table 1 are in accordance with the equilibrium ratios reported by Eliel and Giza<sup>7</sup> for isomeric 2,6-diethoxytetrahydropyrans in carbon tetrachloride (12.2 ± 0.1 % isomer II) and in ethanol (18.1 ± 0.2 % isomer II).

The equilibrium data show that, to prepare the more volatile isomer of 2,6-diethoxytetrahydropyran, the equilibration of the reaction mixture should be carried out in diethyl ether because in this case the proportion of the less volatile isomer is only about 4 %. In the case of 2,5-dimethoxytetrahydrofuran, the stabilities of the isomers are so much alike that the equilibrium ratios in different solvents are between 40 and 60 % and pure isomers cannot be isolated.

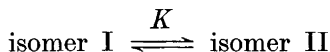
## DISCUSSION

It has been shown<sup>6-13</sup> that the anomeric effect stabilizes the axial conformations of many 2-alkoxytetrahydropyran derivatives. The proportion of axial conformer increases as the polarity of the solvent decreases. For example, Anderson and Sepp<sup>6</sup> obtained the value 1.3 kcal/mole for the stabilizing anomeric effect in 2-methoxy-4-methyltetrahydropyran in nonpolar solvents. In aqueous methanol the value is 0.9 kcal/mole. Riddell<sup>10</sup> has concluded that the anomeric effect is a result of dipole-dipole interactions, which

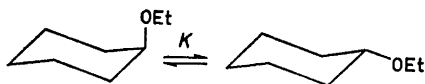
should be weaker in polar solvents as a result of increased solvation of the individual dipoles. The ether dipoles in the equatorial conformation (A) are nearly perpendicular and thus dipolar effects are negligible, whereas they are approximately antiparallel in the axial conformation (in one of its rotamers B) and give rise to a strong dipolar stabilization.



2,5-Dialkoxytetrahydrofurans and 2,6-dialkoxytetrahydropyrans are seen to be excellent model compounds for studying the anomeric effect by comparing the equilibrium data for 2,6-diethoxytetrahydropyran with the data for other pyran derivatives. As shown in the experimental part of this study, the more volatile isomer has the *trans* configuration (one axial and one equatorial ethoxy group) and the less volatile isomer the *cis* configuration (both ethoxy groups equatorial). Thus the equilibrium data for 2,6-diethoxytetrahydropyran in Table 1 reveal a typical anomeric effect because the conformer with an axial ethoxy group is more stable than the conformer which has only equatorial ethoxy groups. Furthermore, it will be seen that the contribution of the axial conformer increases with decreasing polarity of the solvent. The magnitude of the anomeric effect can be calculated from the data for 2,6-diethoxytetrahydropyran. For instance,  $\Delta G^\circ$  is 1.78 kcal/mole for the equilibrium:

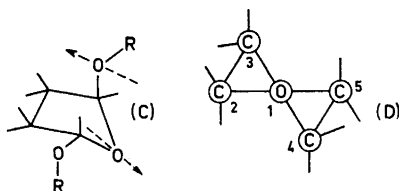


in diethyl ether. Because the *trans* isomer is a DL-pair, the term  $RT \ln 2 = 0.41$  kcal/mole, in other words the mixing entropy, must be subtracted from  $\Delta G^\circ$  to get the free energy difference between the axial and equatorial conformers. This difference is 1.37 kcal/mole. For alkoxy-substituted cyclohexanes in which there is no anomeric effect, the free energy for the equilibrium is  $-0.9$

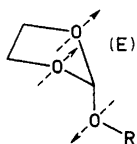


kcal/mole.<sup>15</sup> Thus the magnitude of the anomeric effect in isomer I of 2,6-diethoxytetrahydropyran is  $1.4 + 0.9$  kcal/mole = 2.3 kcal/mole. In the same way the following values are obtained for the anomeric effect in other solvents: 1.9 kcal/mole in carbon tetrachloride, 1.4–1.5 kcal/mole in ethanol, and 1.1 kcal/mole in water the most polar of the solvents. These values are slightly higher than those measured by Anderson and Sepp<sup>6</sup> for 2-alkoxy-4-methyltetrahydropyrans. The value in non-polar solvents obtained by Riddell<sup>10</sup> is 1.7 kcal/mole.

In previous studies the anomeric effect has been shown to exist only in 6-membered cyclic compounds. The equilibrium data in this work indicate, however, that the stabilizing anomeric effect must be taken into account also in 5-membered cyclic compounds. The *trans* isomer of 2,5-dimethoxytetrahydrofuran (isomer I) is more stable than the *cis* isomer in non-polar solvents. This is in contrast to what would be expected on the basis of equilibrium data for alkyl-substituted 1,3-dioxolanes,<sup>16,17</sup> because the *cis* isomers of the 2,4-dialkyl derivatives are more stable than the *trans* isomers. Furthermore, the variation of the isomer composition of 2,5-dimethoxytetrahydrofurans with the polarity of the solvent is what would be expected from dipolar effects. In a conformation in which the ether dipoles are nearly antiparallel one of the methoxy-groups must be in nearly axial position. This is the case, for instance, in the envelope structure (C) in which the ring oxygen is at the tip of the flap. Of course, the possible half-chair structures cannot be



excluded. The most stable half-chair conformation of unsubstituted tetrahydrofuran is the one in which the hetero atom is at the axis of symmetry (D) because in this case the eclipsing strain between the hydrogen atoms on the nearest carbon atoms is a minimum. The calculations of Pitzer and Donath<sup>18</sup> indicate that this conformation is more stable than the envelope structures. The difference of the anomeric effect should be negligible in this structure of the isomeric 2,5-dialkoxytetrahydrofurans. In contrast, the magnitude of the anomeric effect in a half-chair conformer in which the ring oxygen is at position 3 and the axial alkoxy group at position 4 should be comparable with that in corresponding tetrahydropyran derivatives. Thus it can be concluded that the anomeric effect has a marked influence on the proportions of different conformations of 5-membered heterocyclic compounds at equilibrium. For instance, it would be expected on the basis of the anomeric effect that the most stable conformation of 2-alkoxy-1,3-dioxolanes has the envelope structure (E), in which the alkoxy group is at the tip of the flap because in this case both the ring oxygen atoms are in positions in which the ether dipoles are antiparallel to the dipoles of the alkoxy oxygen atom. Thus, recently published results of conformational studies of these compounds<sup>19</sup> cannot be extended to alkyl-substituted 1,3-dioxolanes in which the stabilizing anomeric effect does not exist.



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