Does an Anomeric Effect raise the Barrier to Conformational Change?

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Ring inversion of 2,2-dimethoxyoxane occurs with $\Delta G^\ddagger$ = 8.7 kcal/mol (1 kcal = 4.18 kJ), significantly lower than in other six-membered rings.

Conformational equilibria are subject to an anomeric effect,[1] whereby conformations with an electronegative substituent axial are more stable. However, there has been no attempt to assess any anomeric effect on rates of conformational equilibration. Deslongchamps[2] has suggested that the anomeric effect might increase the barrier to conformational change. This is an interesting suggestion, worth testing. We here report that we find no evidence for such an increase but rather a slight decrease.

Historically the anomeric effect arose in molecules at the aldehyde level of oxidation. However, the preference for one conformer unnecessarily complicates the situation for kinetics. We need a molecule with two conformers of equal energy. Also, the barrier must be measurable by n.m.r. spectroscopy. Such a molecule is 2,2-dimethoxyoxane (**1**),[3] at the carboxylic-acid level of oxidation. This is especially appropriate since Deslongchamps' suggestion[2] was in the context of tetrahedral intermediates in imidate and amide hydrolyses, and it has important implications for his theory of stereoelectronic control.[4]

Line-shape analysis of the two separate methoxy peaks of (**1**) at 170 and 172 K (coalescence temperature *ca.* 176 K, limiting peak separation = 25 Hz at 360 MHz) indicates that $\Delta G^\ddagger$ for ring inversion is 8.68 ± 0.03 kcal/mol (36.3 ± 0.1 kJ/mol). This value is significantly lower than that for cyclohexane (10.5 kcal/mol),[5] oxane (10.3 kcal/mol),[6] or 1,1-dimethoxycyclohexane (10.8 kcal/mol),[7] and quite close to that reported for 2,2-dimethoxy-5,5-dimethyl-1,3-dioxane (*ca.* 8.6 kcal/mol).[8] Figure 1 depicts this comparison more graphically than the $\Delta G^\ddagger$ values, determined in separate samples. It is a set of variable-temperature ^{1}H n.m.r. spectra of a mixture of (**1**) and cyclohexane in CS_2. Even at the lowest temperature (*ca.* 190 K) attainable without a variable-temperature probe,[9] the methoxy peaks of (**1**) have broadened only slightly (but detectably), while the axial and equatorial peaks of cyclohexane are well separated. Figure 1 shows clearly that ring inversion in cyclohexane is slower than in (**1**), although only at lower temperature can the full decoalescence of (**1**) be seen.

We therefore conclude that the anomeric effect does not raise the barrier to conformational change in (**1**), relative to other six-membered rings. Instead, the barrier seems to be reduced by 1.4—2.1 kcal/mol, depending on which reference is chosen. The exact extent of the reduction is difficult to

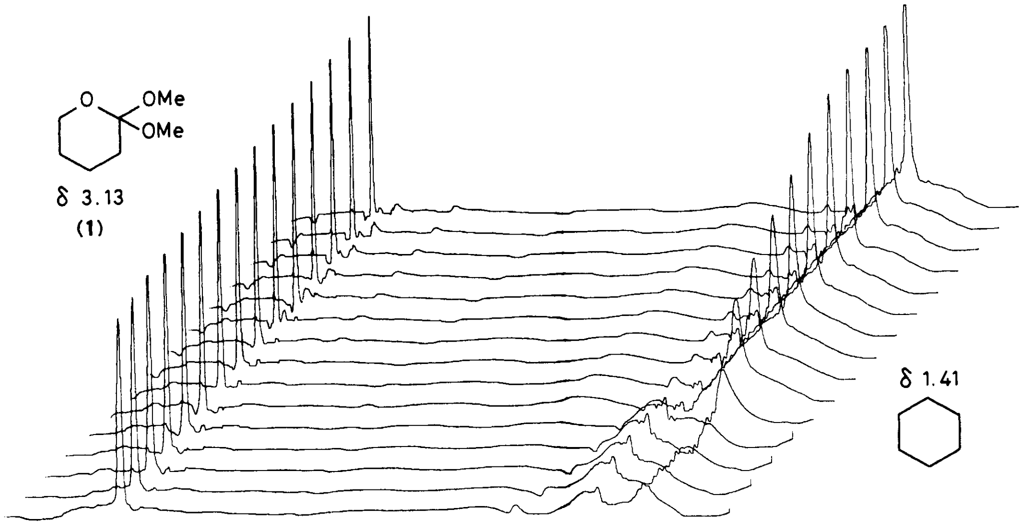

Figure 1. Variable-temperature (v.t.) 360 MHz ^{1}H n.m.r. spectra of 2,2-dimethoxyoxane (**1**) and cyclohexane in CS_2. These spectra were taken without a v.t. probe,[9] by inserting a precooled sample and pulsing every 6 s using Fourier transform n.m.r. spectroscopy.

assess, since some of the observed reduction may be due to alleviation of the axial methoxy-hydrogen repulsion. Nevertheless, this cannot be large, as judged by its effects on the equilibrium in methoxycyclohexane (0.55 kcal/mol)[10] and on the barrier in dimethoxycyclohexane (−0.3 kcal/mol).[5,7]

It is difficult to rationalize convincingly so small an effect. However, the reduction in the barrier is consistent with the same n–σ* mixing as is considered[1] to be responsible for the anomeric effect on equilibria. In the eclipsed half-chair conformation that is the transition state for rotation about the O–C(OMe)$_2$ bond, there is better overlap between the 2p lone pair on the ring oxygen and the π combination of C–OMe σ* MOs. In contrast, analysis[11] of dipole–dipole repulsions suggests that they would increase in that transition state, so this result is another piece of evidence[1] against dipole–dipole repulsions as responsible for the anomeric effect.

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