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(18) We wish to thank Drs. O. Bastiansen and V. Mastryukov for instructive comments on this point.

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Figure 1. The 251-MHz ^{1}H NMR spectra of chloromethyl methyl ether in $CHFCl_2/CHF_2Cl$ (1:3).

Generalized Anomeric Effect and Barrier to Internal Rotation about the Oxygen–Methylene Bond in Chloromethyl Methyl Ether

Sir:

The anomeric effect,[1] although first recognized in carbohydrates, has a wide significance in organic chemistry and has been extensively studied by both experimental and theoretical methods.[2] In its generalized form,[3] the effect causes a preference for gauche over anti arrangements in compounds of the type C–X–C–Y, where X = O, N, or S, and Y = O, N, or halogen. The magnitude of the anomeric effect appears to be generally of the order of 0.5 to 3 kcal/mol. We thought that the presence of the generalized anomeric effect in halomethyl methyl ethers should lead to enhanced barriers to rotation. Although the barrier to rotation about the O–CH$_3$ bond in chloromethyl methyl ether has been measured to be 1.84 kcal/mol,[4] the barrier to rotation about the O–CH$_2$Cl bond has not been reported. We now present variable temperature NMR measurements on chloromethyl methyl ether (I), bis-(chloromethyl) ether, and fluoromethyl methyl ether.

The ^{1}H spectrum of chloromethyl methyl ether (I)[5] in $CHFCl_2/CHF_2Cl$ (1:3) (Figure 1) shows a clear dynamic NMR effect below −170 °C. The methylene protons give rise to a distinct symmetrical doublet at −182 °C. At still lower temperature the lines become very broad because of dipole–dipole relaxation effects in the increasingly viscous solution. Since the line width at −182 °C is of the order of 50 Hz, spin–spin coupling between the diastereotopic methylene protons cannot be observed.

The presence of two methylene proton resonances at low temperatures is consistent with the gauche conformation, in agreement with most other physical data.[4,6] A line-shape calculation with an exchange rate constant of 250 s^{-1}, a T_2 corresponding to $1/\pi T_2$ = 50 Hz, and a chemical shift difference of 120 Hz reproduced the observed methylene resonance at −180 °C. From the absolute rate theory a free-energy barrier ($\Delta G^{\ddagger}$) of 4.2 kcal/mol is obtained.

There are two possible mechanisms for the interconversion of the two chiral gauche forms, I-G and I-G′. In one mechanism, the process takes place via the plane symmetrical eclipsed form (I-E), and in the other via the plane-symmetrical anti form (I-A). The eclipsed geometry is probably a transition state, but the anti form might be either an energy minimum or maximum. Steric repulsions in the form having the methyl group and chlorine atom eclipsed should be substantial; furthermore the orientation of the lone pairs with respect to the carbon–chlorine bond is unfavorable. Thus, this mechanism is probably unimportant because it involves a barrier which is
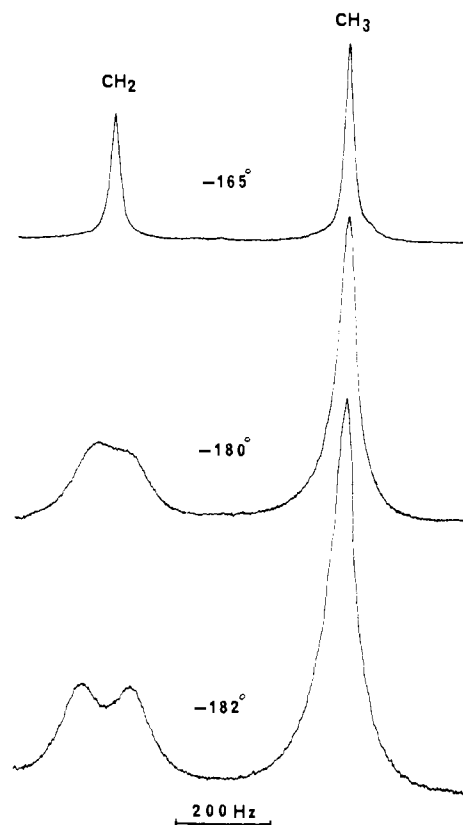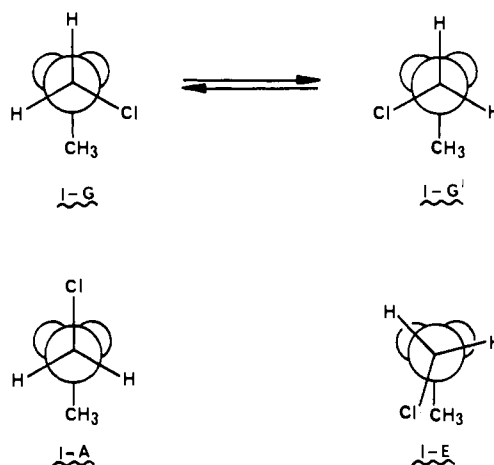

considerably greater than 4 kcal/mol.[7] The second mechanism does not involve large nonbonded repulsions; at one stage there is eclipsing of a hydrogen and a methyl group, but the lone pair is eclipsed with the carbon–chlorine bond and this should provide some stability due to the "cis effect".[3] In the anti form, steric repulsion effects should be absent, but electronic and dipole effects are unfavorable. The observed barrier of 4.2 kcal/mol is appreciably higher than that expected for the second mechanism, if only steric repulsions are considered. A rough estimate of the steric barrier is 2 kcal/mol,[8] and thus the anomeric effect on the barrier to rotation of the O–CH$_2$ bond is ~2 kcal/mol.

We have also examined the ^{1}H NMR spectra of bis(chloromethyl) ether and fluoromethyl methyl ether,[9] but we did not observe any splitting of the methylene resonances down to −180 °C. Dimethoxymethane itself cannot be studied by dynamic NMR because the C_2 symmetry of the gauche conformation makes the methylene protons indistinguishable.[10]

Equilibration data on 2-chloro-4-methyltetrahydropyran show that an axial chlorine is *stabilized* by 2.2 kcal/mol when compared with a similarly placed equatorial chlorine.[11] Chlorocyclohexane, on the other hand, is more stable with the chlorine equatorial, and has $\Delta G° = 0.5$ kcal/mol.[12] From these data, the anomeric effect can be estimated to be $2.2 + 0.5 = 2.7$ kcal/mol. CNDO calculations[2d] on chloromethyl methyl ether indicate that the gauche form is more stable than the anti form by ~2 kcal/mol and that the barrier to internal rotation about the oxygen–methylene bond is slightly larger than 2 kcal/mol.[13] Thus, both experimental and theoretical data show that the magnitude of the anomeric effect in α-chloro ethers has a value of 2–3 kcal/mol.

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(7) The short C–O bond length and the small C–O–C bond angle should increase substantially the methyl–chlorine repulsions in the eclipsed form as compared to the situation in 1-chloropropane. The methyl–chlorine repulsion in eclipsed 1-chloropropane should be a little larger than the methyl–methyl repulsion in eclipsed butane (J. E. Anderson and H. Pearson, *J. Am. Chem. Soc.*, **97**, 764–769 (1975), footnote 5); eclipsed butane is estimated to be 6 kcal/mol higher in energy than gauche butane (E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis". Interscience Publishers, New York, N.Y., 1965, p 9).

(8) The steric barrier might be expected to be similar to the barrier to rotation of the methyl group in I.

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(10) 1,3-Dioxacycloheptane (1,3-dioxepane) can have an arrangement similar to gauche dimethoxymethane in a ring system which is basically very flexible. However, neither the ^{1}H nor the ^{13}C spectrum of this compound showed any dynamic NMR effect down to -180 °C.

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Pyrimidine *S*-Nucleoside Photorearrangement. New Access to Pseudonucleosides

Sir:

Because of their biological importance, considerable effort has been directed toward the synthesis of pseudonucleosides (*C*-nucleosides)[1] during the past several years.[2] In the conventional preparation of these substances the crucial step is the introduction, with appropriate stereochemical control, of a functionalized carbon unit at the anomeric center of a suitably derivatized pentose. This newly introduced substituent serves to elaborate the nitrogenous heterocyclic portion of the molecule.[2] However, direct coupling of the aglycone with the carbohydrate moiety is possible in a few cases.[3] Since such single-step synthesis—even with moderate yield—might be preferred, we have devised in the *S*-nucleoside series a new rearrangement prone to generalization, which ends up in the formation of a pseudonucleoside.

From our recent observation that 4-benzylthiopyrimidin-2-ones undergo a photoreaction leading to 5-benzylpyrimidin-2-ones,[4] we were prompted to investigate the photochemistry of some 4-glycosylthiopyrimidines. We expected to obtain by photorearrangement their 5-glycosyl isomer.

Interest in a pyrimidine amenable to further chemical transformations which may provide a variety of useful pyrimidine derivatives led us to select 4-mercapto-2-methylthiopyrimidine (1) as a substrate. Its *S*-benzyl derivative 2a (oil)[5] was prepared and exposed to light[6] resulting in the formation of 1 and 3a (mp 170–172 °C) in 30 and 60% yield, re-