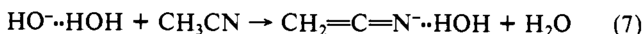
diffuse, should be less favorably solvated. The reaction involving **1** should also be considerably endothermic. Structure **3** is the first intermediate for hydrolysis; the charge, localized on the imide nitrogen, should be a better hydrogen bond acceptor than that of **1** or **2**. The net effect of solvation is to slow all reactions due to reactant solvation, but to stabilize **3** the most.

Why does $HO^{-}\cdot\cdot HOH$ not deprotonate acetonitrile in the gas phase? The basicity of the monosolvated hydroxide is lower than that of the bare hydroxide by the hydrogen bond strength of 25 kcal/mol,[5] making reaction 6 endothermic by 6.3 kcal/mol.[1d]

$$HO^{-}\cdot\cdot HOH + CH_3CN \rightarrow CH_2{=}C{=}N^{-} + 2H_2O \quad (6)$$



$$HO^{-}\cdot\cdot HOH + CH_3CN \rightarrow CH_2{=}C{=}N^{-}\cdot\cdot HOH + H_2O \quad (7)$$

Deprotonation with solvation of the product, as in reaction 7, is about 7 kcal/mol exothermic, if a estimate of ca. 13 kcal/mol for the hydrogen bond strength in the product is made.[2] The observed process (5) is likewise ca. 7 kcal/mol exothermic, based on the 13.8 kcal/mol bond strength of $HOH\cdot\cdot{}^{-}CN$.[5] We speculate that the controlling factor is the amount of charge developed on the potential solvation site in the transition state. The cyano group stabilizes adjacent anions primarily by polar effects, with little charge developed on the nitrogen due to resonance delocalization.[9] Cyanide, however, involves a localized charge more suitable for solvation. To the extent that localized charge is developed on the product anion in the transition state, solvation should favor that transition state, all other things such as total exothermicity being equal. We do not observe "hidden" proton transfer in the gas phase, since $HO^{-}\cdot\cdot HOH$ does not incorporate any deuterium when in the presence of CD_3CN in the ICR spectrometer.

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Search for Oxygen Scrambling during Ethanolysis of [*ether*-^{17}O]-*endo*-2-Norbornyl Mesylate. The True Exo/Endo Rate Ratio and the Nature of the Rate-Controlling Steps

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Few facts in organic chemistry have inspired so much research as the large ratio of solvolysis rates of the epimeric 2-norbornyl pair of substrates. Oddly enough, in spite of all that has been written about the topic,[1] the magnitude of this ratio is subject to a possibly major uncertainty in the rate constant of one of the isomers. Thus, while the ratio of solvolysis rates was originally described[2] to be 350, it was later raised[3] several fold when racemization of the exo substrate was found to be several times faster than solvolysis; this process is of course a more sensitive indicator of ionization than the appearance of solvolysis products. The reason is that the endo isomer cannot racemize as a consequence

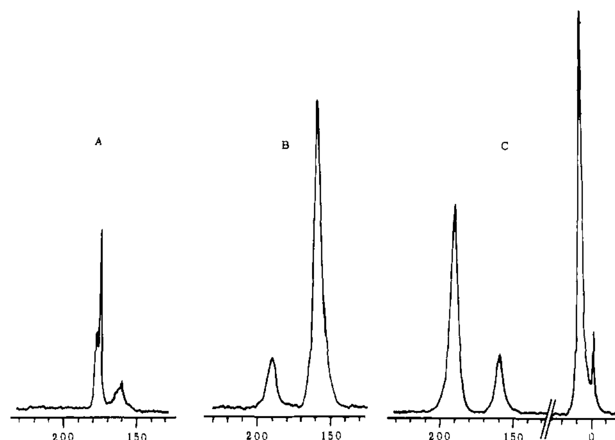

Figure 1. ^{17}O NMR spectra of *endo*-2-norbornyl mesylate in ethanol, with external water reference: (A) Natural abundance 20% solution in ethanol, showing base-line separation of the broad ether signal and sharp sulfone signal, a small amount of methanesulfonic acid is visible just upfield of the latter (600 000 transients, 500-μs delay time). (B) Ether-labeled ester 3 h after dissolution in ethanol at 75 °C, with some $Pr(NO_3)_3$ added to shift the acid liberated (100 000 transients). (C) The same solution after 64 h, with additional shift reagent and with solvent and reference shown. The sharp sulfonyl signal at 173.5 is clearly not detectible.

of heterolysis to an ion pair and return. Should there nevertheless be substantial endo return, we would have an exaggerated notion of how large the rate ratio really is.

Other means of searching for return are available. As is known from Goering's painstaking researches,[4] the only general one is oxygen scrambling when the leaving group is an oxy anion such as a sulfonate. This requires that the anion within the pair be able to undergo rotation about the C–S bond at a rate not very much slower than the pair collapse. In all of the known cases of return in which a search for such scrambling has been made, it has been found and always at a rate equal to or only moderately less than return. Thus, oxygen scrambling is clearly a very useful cue. Until recently, its use was based on sampling, isolation, degradation, the use of ^{18}O and mass spectrometry;[5] however, we recently showed that the process can easily be followed in situ by means of NMR if ^{17}O is used.[6] Return in the *exo*-brosylate during ethanolysis was confirmed. We have now applied the same tool to the *endo*-mesylate during ethanolysis at 75 °C; we were forced to the change in anion because the two oxygen atoms in the *endo*-brosylate were found to have virtually identical chemical shifts (both within 0.1 of 161.5 ppm in ethanol at 75 °C; ethanol itself is at 7.3 ppm relative to external water at that temperature).[7a,b]

The natural-abundance spectrum of the mesylate in ethanol at 75 °C shows signals at 158.3 and 173.5 ppm; ether-labeled material[8] confirms our assumption on the basis of line widths that

(1) Much of the literature on this subject is quoted by: Brown, H. C. "The Non-Classical Ion Problem"; Plenum Press: New York, 1977; with comments by Schleyer, P. v. R. For recent summaries, see the December issue of: *Acc. Chem. Res.* **1983**.

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(5) One major experimental advance had been the introduction of whole molecule mass spectrometry to analyze the reisolated substrate: Paradisi, C.; Bunnett, J. F. *J. Am. Chem. Soc.* **1981**, *103*, 946. Their experiment led to the unexpected finding that 2-adamantyl tosylate, the arch example of a secondary substrate ionizing by a purely k_c process, is subject to major return during solvolysis.

(6) Chang, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1983**, *105*, 3708. For another NMR method potentially applicable in this field, see: Risley, J. M.; Van Etten, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 252. It rests on the ^{18}O isotope shift of ^{13}C resonances.

(7) (a) We confirm that this is slightly different from the 25 °C value of 6 ppm; Crandall, J. K.; Centeno, M. A. *J. Org. Chem.* **1979**, *44*, 1183. (b) The change from brosylate to mesylate has little effect on the exo and endo ethanolysis rates and virtually none on the ratio of the two: Brown, H. C.; Ravindranathan, M.; Chloupek, F. J.; Rothberg, I. *J. Am. Chem. Soc.* **1978**, *100*, 3143. (c) For another extensive search for possible solvent assistance, see: Harris, J. M.; Mount, D. L.; Raber, D. J. *Ibid.* **1978**, *100*, 3139.

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these peaks represent the ether and sulfone oxygens, respectively. The free methanesulfonic acid peak appears at 176.2 ppm. The ethanolysis was conducted as before; once again, the signal of the acid liberated was shifted away from the region of interest by metering in praseodymium nitrate as a shift reagent. The kinetics, followed to two half-lives, behaved in excellent first-order fashion; $k_1 = 6.18 \times 10^{-6}$ s^{-1}, with a correlation coefficient of 0.999. Throughout this period, only an ether ^{17}O signal was seen; even at the conclusion of the experiment, no sulfonyl ^{17}O was observed even though this signal is naturally about 8 times sharper than the ether signal (a factor of 2 due to statistics, and another of 4 because of line width). We estimate that even 0.5% scrambling would have been observed (see Figure 1). This is in startling constrast to the *exo*-brosylate; unsolvolyzed material remaining after two half-lives in that case is completely scrambled.[6] It is clear that the reluctance of norbornyl ions to capture nucleophiles on the endo side continues undiminished even if the species to be bound is the nearest neighbor anion that had just departed. As Brown has often pointed out,[1] the leaving anion must be poorly solvated as it begins its journey into the U-shaped cationic cavity. By one possible extension of this reasoning, ionization could lead to a highly crowded endo pair stage from which return might be efficient; clearly, such an extrapolation is not justified.

The facts observed here must be seen in the light of recently reached agreement that the *endo*-sulfonates solvolyze without significant solvent assistance.[7a,b] They lead to several interesting conclusions. The first of these is that the correct value of the exo/endo solvolysis rate ratio is indeed of the order of 10^3. The only possible doubt rests on the notion that return might occur without oxygen scrambling; this notion is, however, without laboratory precedent as noted above. Second, the *exo*- and *endo*-2-norbornyl substrates clearly have different rate-controlling steps in solvolysis: formation of an ion pair in endo and dissociation of the pair in exo. The data permit the statement that in the endo energy profile, the maximum representing the ionization exceeds any other by at least 3 kcal/mol. The third conclusion is that the argument for charge delocalization in the transition state for exo solvolysis that was based on its unusually large volume[13] is now much stronger than before, since it was subject to the caveat that an "earlier" location along the reaction coordinate might be responsible. Now that the reverse of this possibility has been demonstrated, there is no longer a viable alternative to the interpretation that it is due to charge dispersal.

Registry No. ^{17}O, 13968-48-4; ^{17}O-norbornanone, 88393-12-8; norbornanone ethylene glycol ketal, 172-67-8; ^{17}O-*endo*-norbornanol, 88393-13-9; ^{17}O-*endo*-norbornanol brosylate, 88393-14-0; *endo*-norbornanol mesylate, 28627-78-3; ^{18}O-*endo*-norbornanol mesylate, 88393-15-1.

(8) The NMR spectra were measured with a 300-MHz Nicolet spectrometer operating at maximum sensitivity. For natural-abundance spectra, concentrated solutions (20%) in ethanol were used, with about a half million transients (500-μs delay delay time). For the enriched samples, 1-2% solutions were used with about 10^5 transients; the signal to noise ratio was in all cases about 80. Best simulation results were obtained with line widths of 71, 92, and 237 Hz for the sulfone, acid, and ether oxygens, respectively. ^{17}O-labeled norbornanone[9] was obtained in several 100-mg batches by the hydrolysis at 60 °C for 24 h of 200 μL of ethylene glycol ketal[10] with 25 μL of water-^{17}O (20 atom %) and 0.5 μL of concentrated HCl in sufficient dioxane to yield a homogenous solution; it was purified from traces of unreacted ketal by means of GC (Carbowax, 110 °C). Reduction to the *endo*-alcohol[11] and conversion to the brosylate[2] and mesylate[12] followed known procedures.

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Structure Determination of a Tetrasaccharide: Transient Nuclear Overhauser Effects in the Rotating Frame

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Homonuclear Overhauser effects (NOE) have been widely used in structure determination.[1] They have proven especially useful for the study of small molecules in which magnetic dipolar relaxation of the nuclei is in the extreme narrowing limit.[2] In such cases the maximum positive effect[3] that can be observed is 50%.

As spectrometer frequencies have risen and as more attention has centered on larger and more complex molecules, the situation has arisen more frequently where $\omega_0\tau_c$, the product of spectrometer angular frequency and molecular rotational correlation time, is equal to or exceeds unity. When $\omega_0\tau_c \approx 1$ no NOE occurs; when it greatly exceeds 1, as in the case of macromolecules, the NOE approaches -1 and specificity is lost due to spin diffusion.[4] Observation of the NOE at short times,[5] or of transient NOEs,[6] overcomes this difficulty in part, but at the price of observing very small effects.

We have found that the observation of transient NOEs in the rotating frame overcomes these difficulties.

We first consider a one-dimensional difference experiment. A reference spectrum, R, is generated by (1) a 90° x pulse, (2) immediate application of a spin-locking field along the y axis during a relaxation period t_{max}, (3) removal of the spin-locking field and acquisition of the free induction decay, and (4) fourier transformation. A cross-relaxation spectrum, C, is generated by the same sequence, except that immediately prior to the 90° x pulse, a selective 180° pulse is applied to one of the signals, inverting it. Finally, a difference spectrum, D, is obtained by subtracting R from C.

As an example, in Figure 1 are shown the spectra R, C, and D, obtained at 600 MHz with a sample of the tetrasaccharide, methyl *O*-(α-D-glucopyranosyluronic acid)-(1→6)-*O*-α-D-glucopyranosyl-1(1→2)-[*O*-α-L-rhamnopyranosyl-(1→3)]-α-L-rhamnopyranoside[7] (GGRR, 1). The 600-MHz proton spectrum of GGRR had been assigned by using standard 2D techniques and decoupling so that all intraring couplings could be observed and measured, establishing that each ring was predominantly in the expected lowest energy chair conformation. It was not possible, however, to observe intra- or interring NOES of the usual kind in order to confirm the sequence of sugars, presumably because $\omega\tau_c \approx 1$ under our conditions.

Observation of a transient effect in the rotating frame was successful, however. In Figure 1, the inverted peak is assigned to the anomeric proton of the rhamnosyl group (ring A), and the positive effects observable in spectrum D arise from the vicinal H_2 of ring A and H_2 and H_3 of the adjacent rhamnosyl ring B. This confirms the ring A-ring B linkage and suggests a particular conformation for the AB glycosidic linkage.

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