and filtered by suction. Crude VI (4.88 g, 12.4 mmol, 85%) was obtained as a yellow powder. Recrystallization from acetone yielded colorless prisms of pyrazoline VI, mp 180° dec; ν^{KBr}: 3030, 2940, 2820, 1535, 1485, 1422, 1284, 1245, 1049, 1019, and 749 cm^{-1}; nmr ($CDCl_3$): δ 6.62–7.91 (8 H, $H_{1'-8'}$) complex, 6.58 (2 H, $H_{2,3}$) AB multiplet, 5.50 (1 H, H_7) doublet (triplet), J = 6.3 (1) cps, 4.49 (1 H, H_8) broad singlet, 3.85 (3 H, OCH_3) sharp singlet, 3.58 (3 H, OCH_3) sharp singlet, 3.52 (1 H, H_5) broad singlet, 2.32 (1 H, H_6) doublet (doublet), J = 6.3 (2) cps, 1.72 (2 H, $H_{11s,11a}$) AB multiplet; uv (dioxane) λ_{max} mμ (ϵ): 271 (26,990), 258 (23,200), 281 (24,720), 293 (13,280), and 299 (9520).

Anal. Calcd for $C_{26}H_{22}N_2O_2$: C, 79.16; H, 5.62; N, 7.10; O, 8.11; mol wt, 394. Found: C, 79.32; H, 5.65; N, 7.42; O, 7.61; mol wt, 382.

Preparation of III. VI (0.72 g, 1.83 mmol) was heated in a 100-ml round-bottomed flask at 190° for 15 min in the presence of 20 ml of *trans*-decalin. The solvent was removed by rotary-vacuum evaporation, and 35 ml of hot EtOH was added to the residue. Crystallization afforded 0.35 g (0.96 mmol, 52%) of yellow needles. Recrystallization from 95% EtOH yielded white needles, mp 151–152°; ν^{CCl_4}: 3030, 2980, 2920, 2830, 1600, 1490, 1440, 1252, 1178, 1075, 1055, 1015, and 745 cm^{-1}; nmr: δ 6.72–8.00 (8 H, $H_{1'-8'}$) complex, 6.69 (2 H, $H_{2,3}$) singlet, 4.10 (2 H, $H_{6,7}$) broad singlet, 3.84 (6 H; OCH_3) sharp singlet, 2.96 (1 H, H_{11b}) doublet, J = 9.6 cps, 2.21 (2 H, $H_{5,8}$) broad singlet, 1.70 (1 H, H_{11a}) doublet, J = 9.6 cps; uv (cyclohexane) λ_{max} mμ (ϵ): 277 (17,400), 293 (17,100), and 304 (14,400).

Anal. Calcd for $C_{26}H_{22}O_2$: C, 85.21; H, 6.05; O, 8.74; mol wt, 366. Found: C, 85.38; H, 6.30; O, 8.32; mol wt, 359.

Acknowledgment. This work has been supported in part by the National Aeronautics and Space Administration on Grant NsG-603.

Nuclear Magnetic Resonance Spectroscopy. Conformational Equilibria and Equilibration of 4,4-Difluoropiperidine. Measurement of the N–H Inversion Rate in a Six-Membered Ring[1]

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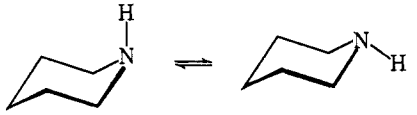
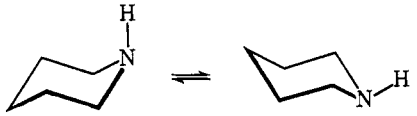
Abstract: Fluorine magnetic resonance spectroscopy has been used to measure the rates of inversion of 4,4-difluoropiperidine. The activation energy (E_a) was found to be 13.9 and 13.5 kcal/mol in methanol and chloroform, respectively. In acetone, N–H nitrogen inversion was found to be slow on the nmr time scale with an E_a of about 10 kcal/mol. The free-energy difference between the forms with the N–H hydrogen axial and equatorial appears to be 0.42 kcal/mol with uncertain sign.

The conformations assumed by piperidine and N-substituted piperidine rings are of substantial chemical and biochemical interest. A number of X-ray studies have indicated that the chair form is favored for the piperidine ring.[3] The degree of preference for equatorial *vs.* axial positioning of the N–H hydrogen in piperidine is a matter of considerable controversy and of special significance, involving as it does what can be taken as a judgment of the relative steric sizes of hydrogen or a lone pair of electrons. Kerr constant measurements have been interpreted to indicate that the form with the N–H hydrogen *axial* predominates to the extent of 80% or more,[4,5] although recent dipole moment measurements have been taken to indicate a preference for the equatorial location of the N–H hydrogen to the extent of 0.46 kcal/mol.[6] A convincing reversal of the latter assignment has been proposed recently on the basis of nuclear magnetic resonance and infrared evidence.[7]

An important and interesting question with piperidine and piperidine derivatives is the rate of inversion of the nitrogen (eq 1) relative to the rate of inversion of the ring (eq 2). A study of the temperature dependence


(1)


(2)

of the ^{19}F resonances of N-fluoroperfluoropiperidine[8] indicates that either inversion of the N-fluoro nitrogen is fast on the nmr time scale even at −115°, at which temperature ring inversion is quite slow, or else nitrogen inversion is at least somewhat faster than ring inversion

(1) Supported by the National Science Foundation.

(2) Participant in the Northwestern–Khartoum Universities Exchange Program for 1966–1967.

(3) See E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, p 245.

(4) M. Aroney and R. J. W. Le Fèvre, *J. Chem. Soc.*, 3002 (1958); M. J. Aroney, C.-Y. Chen, R. J. W. Le Fèvre, and J. D. Saxby, *ibid.*, 4269 (1964).

(5) M. Hanack, "Conformational Theory," Academic Press Inc., New York, N. Y., 1965, p 303; see also D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 73 (1956).

(6) N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *Tetrahedron Lett.*, 3345 (1964); *J. Amer. Chem. Soc.*, **87**, 1232 (1965). See also N. L. Allinger and J. C. Tai, *ibid.*, **87**, 1227 (1965).

(7) (a) J. B. Lambert, R. G. Keske, R. E. Carhart, and A. P. Jovanovich, *ibid.*, **89**, 3761 (1967); J. B. Lambert, *ibid.*, **89**, 1836 (1967); (b) see also commentary by N. L. Allinger, J. A. Hirsch, and M. A. Miller, *Tetrahedron Lett.*, 3729 (1967).

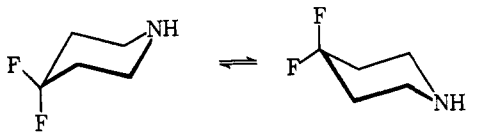
(8) L. W. Reeves and E. J. Wells, *Discussions Faraday Soc.*, **34**, 177 (1962); J. Lee and K. G. Orrell, *Trans. Faraday Soc.*, **63**, 16 (1967).

and there is a marked axial or equatorial conformational preference for the N-fluoro group.[8,9] Similar observations have been reported for piperidine-3,3,5,5-d_4 and its N-methyl and N-*t*-butyl analogs[9] as well as for N,N'-dimethylpiperazine and hexahydro-1,3,5-trimethyl-1,3,5-triazine.[10] The point here is a subtle one—namely, that the rate of nitrogen inversion will only be easily determined in a symmetrical cyclic compound, if it is *slower* than the rate of ring inversion and there is, in addition, a significant amount of the conformer with the less favorable position of the nitrogen substituent. The latter condition appears not to have been surely met for the N-fluoro and N-methyl compounds already studied, as mentioned above, but would be for piperidine itself because, with piperidine, there is on the order of 20% of the less favorable conformer present. The situation for piperidine is, however, rendered complex by the possibility of intermolecular N–H exchange which, if much faster than inversion, will preclude measurement of the nitrogen inversion rates. The general pattern of nitrogen inversions which are slow on the nmr time scale will be discussed later.

The fluorine resonances of 4,4-difluoropiperidine[11] were used in the present research to study the rates of ring and nitrogen inversion. The general applicability and utility of fluorine as a "tracer" for hydrogen in studies of conformational equilibria and equilibration now seem to be on a reasonably sound basis.[12]

Experimental Results and Discussion

The temperature dependence of the ^{19}F spectrum of 4,4-difluoropiperidine (**1**) was investigated in chloroform, methanol, and acetone at temperatures from −88 to +35°. At 35°, the fluorine resonance in all of the solvents is a relatively sharp binomial quintet (Figure 1) showing no chemical shift difference between the axial and equatorial fluorines as the result of rapid conformational equilibration (eq 3).[12] The multiplicity of the fluorine resonances arises from coupling



(3)

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with the adjacent hydrogens and is an example of a "deceptively simple" AA'(XX')$_2$ system. Exactly the same type of spectrum is observed with 1,1-difluorocyclohexane[12a,b,13] with the average H–F coupling which corresponds to the spacing of the quintet being 13.5 Hz for **1** and 12 Hz for 1,1-difluorocyclohexane.

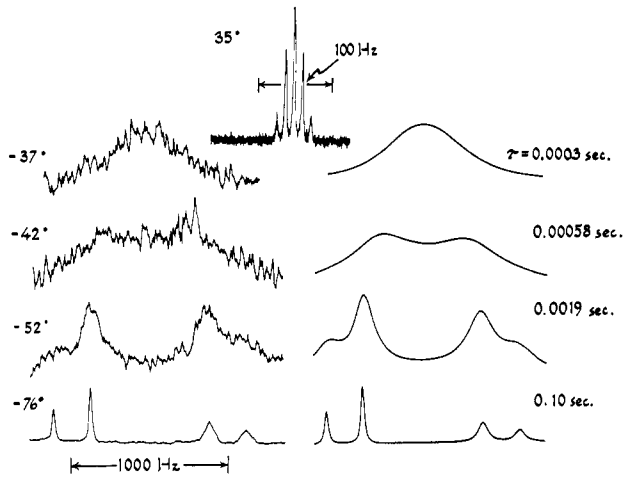


Figure 1. Illustrative experimental fluorine nmr spectra (left and center) of 4,4-difluoropiperidine in chloroform as a function of temperature at 56.4 MHz. Spectra calculated as a function of the mean lifetime before ring inversion are on the right. Note that the scale of the 35° spectrum is much larger than the other spectra which are all on the same scale.

As the temperature is reduced, the ^{19}F resonance lines of **1** broaden as the result of slowing of the rate of the equilibration of eq 3 and, below −40°, the typical distorted AB pattern of axial (upfield) and equatorial (downfield) *gem*-fluorines emerge (Figure 1).[12] The behavior in chloroform and methanol is similar and quite analogous to that of 1,1-difluorocyclohexane.[12a,b] Different behavior is observed in acetone, and this will be discussed separately. The chemical shift difference between the axial and equatorial fluorines in chloroform was found to be 970 Hz—significantly larger than the value of 884 Hz obtained for 1,1-difluorocyclohexane. While the significance of such differences is not yet completely clear,[12a,b] there is a clear pattern of influence by 4-substituents, primarily on the chemical shift of *equatorial fluorines*. The general effect is to produce an upfield shift, an equatorial 4-substituent appearing to produce a rather larger shift than the same substituent in an axial position.[12b] The over-all result in any case is a smaller chemical shift difference, which may well be a steric effect because both chlorine and methyl act in the same way. The enhanced chemical shift for **1** may reflect some sort of long-range shielding, or perhaps a sort of negative steric hindrance effect (relative to hydrogen) by the unshared electron pair. The geminal F–F couplings are wholly normal for six-membered carbocyclic rings, 234 Hz.[12a,b]

The rate of ring inversion of **1** was determined as a function of temperature by comparison of the experimental line shapes with line shapes calculated as a function of the mean lifetime τ before exchange, by the procedure outlined previously.[12a,b] An illustrative set of curves for solutions of **1** in chloroform is shown in Figure 1. Activation parameters were obtained in the usual way. Interestingly, and perhaps surprisingly, because of the substantial differences in the nature of the solvents, E_a was the same in chloroform and methanol to within the experimental error. An E_a of 14.5 ± 0.5

(9) However, see the very recent work of J. J. Delpuech and M. N. Deschamps [*Chem. Commun.*, 1188 (1967)] and of J. L. Sudmeier and G. Occupati [*J. Amer. Chem. Soc.*, **90**, 154 (1968)] for elegant demonstrations of how rates of nitrogen inversion can be determined for N-methyl-*cis*-2,6-dimethylpiperidine at 33° and N,N'-dimethylpiperazine at 44° by use of the technique of M. Saunders and F. Yamada, *J. Amer. Chem. Soc.*, **85**, 1882 (1963). The systems are rather different from the ones considered in this paper in that there is no ring inversion effect on the spectra.

(10) L. W. Reeves and K. O. Strømme, *J. Chem. Phys.*, **34**, 1711 (1961); H. S. Gutowsky and P. A. Temussi, *J. Amer. Chem. Soc.*, **89**, 4358 (1967); R. F. Farmer and J. Hamer, *Tetrahedron*, **24**, 829 (1968).

(11) This material was kindly supplied by Dr. Gilbert Berezin of the Explosives Department of E. I. du Pont de Nemours and Co.

(12) (a) See J. D. Roberts [*Chem. Brit.*, 529 (1966)] for references and discussion; (b) S. L. Spassov, D. L. Griffith, E. S. Glazer, K. Nagarajan, and J. D. Roberts, *J. Amer. Chem. Soc.*, **89**, 88 (1967); (c) R. Knorr, C. Ganter, and J. D. Roberts, *Angew. Chem.*, **79**, 577 (1967); (d) however, see also R. D. Stolow, T. W. Giants, and J. D. Roberts, *Tetradron Lett.*, in press, for examples of how *gem*-fluoro groups can change normal preferences of substituents for equatorial positioning.

(13) J. Jonas, A. Allerhand, and H. S. Gutowsky, *J. Chem. Phys.*, **42**, 3396 (1965).

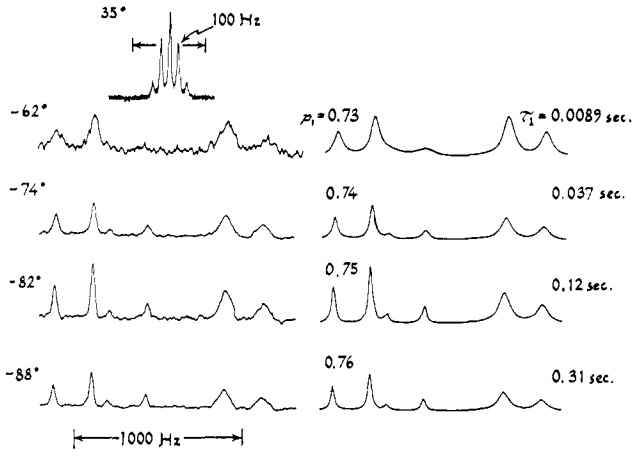
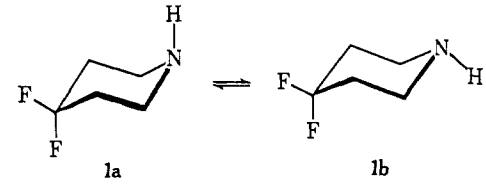


Figure 2. Illustrative experimental fluorine nmr spectra of 4,4-difluoropiperidine in acetone as a function of temperature at 56.4 MHz. Spectra calculated as a function of composition and mean lifetime before nitrogen inversion are on the right. Values of τ_1 and p_1 refer to the dominant conformer (see text). The spectrum at 35° is on a larger scale than the other spectra which are all on the same scale.

kcal/mol and a log A of 16.9 ± 1.5 have been reported[7a] for piperidine-3,3,5,5-d_4 in methanol. These values are quite comparable with the 13.9 ± 1.1 kcal/mol [log A (sec^{-1}) = 16.8] and 13.5 ± 0.2 kcal/mol [log A (sec^{-1}) = 16.0] for 1:2 v/v methanol solution and 1:1 v/v chloroform solution, respectively, which were obtained in the present work—especially when account is taken of the usual slight reduction in E_a of cyclohexane inversion through substitution of *gem*-fluorines as the result of 1,3-diaxial fluorine–hydrogen interactions.[12b] The present data shed no new light on the somewhat greater E_a values which appear to be associated with ring inversion in the saturated six-membered heterocyclic rings containing nitrogen.[7-10] It is not unreasonable to ascribe this to the ring C–N–C angles being smaller than the ring C–C–C angles. Such an explanation accords with the striking increase in the rate of inversion with cyclohexanone derivatives, wherein the keto carbon has C–C–C angles which are expected to be larger than the normal ring C–C–C angles.[14]

Evidence for slow inversion of the amine nitrogen of **1** was obtained for acetone solutions below −60°. Above this temperature, the changes in line shapes resembled those found for methanol and chloroform solutions. However, below −60°, the typical distorted AB patterns of the axial and equatorial fluorines split into two unequal AB patterns (Figure 2). In 1:5 v/v acetone, the major pattern, corresponding to about 76% at −88°, has a *gem*-fluorine chemical shift difference of 1048 Hz and the minor pattern, 24%, of 700 Hz. The axial fluorine chemical shifts are indistinguishable, the differences being completely associated with the equatorial fluorines. The smaller shift difference, as mentioned earlier, might be ascribed to an equatorial substituent at the 4 position with respect to the fluorine—perhaps **1b**. However, before accepting this, it will be well to review the arguments as to why the spectrum of **1** below −60° in acetone can be ascribed to a superposition of the spectra of **1a** and **1b** and also why similar

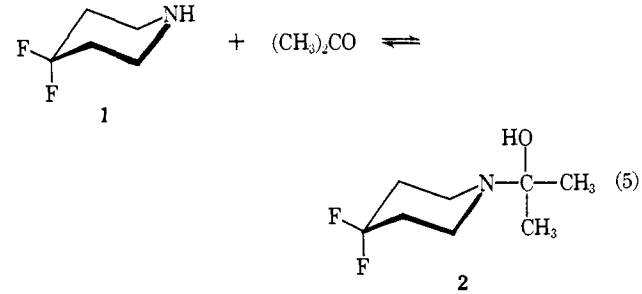
(14) R. Lack, C. Ganter, and J. D. Roberts, *J. Amer. Chem. Soc.*, in press.



1a **1b** (4)

spectra are not observed for chloroform or methanol solutions.

In the first place, it seems significant that the proportions of the species which give rise to the separate AB spectra correspond rather well (considering the differences in solvent) to the proportions of axial and equatorial N–H hydrogens as reported by others.[4-7] The seemingly most reasonable alternative is an acetone–amine complex (**2**). However, in order that the observed line shape changes occur, the equilibrium of eq 5 would have to be fast on the nmr time scale above −60°. The possibility that the equilibrium constant for formation of the complex only becomes large enough to give detectable amounts of **2** below −60° does not agree with the temperature dependence of the proportions of the species present. Although the proportion of the less-favored form appears to become less, as the temperature is raised from −88 to −60° (Figure 2), this is more the result of line-shape changes of the type characteristic of rapid rate processes and not of changes in the equilibrium constant. Furthermore, going from 1:0.6 v/v to 1:5 v/v mixtures of **1** in acetone causes no detectable change in the apparent proportions of the two forms at either −78 or −88°—behavior which would hardly be expected for equilibrium formation of **2**.



1 **2** (5)

The reason for being able to observe both the forms **1a** and **1b** in acetone but not in chloroform and methanol is conceivably (a) that acetone has a specific retarding effect on amine inversion, or (b) that inversion in methanol or chloroform may be slow but the concentration of the less favored form is too low to be detectable, or (c) that rapid intermolecular N–H exchange leads to interconversion of **1a** and **1b** in chloroform and methanol but not in acetone. The last of these possibilities appears to be correct for the following reasons. First, addition of trifluoroacetic acid (10 mol % relative to **1**) to a 1:5 v/v mixture of **1** in acetone causes averaging of the separate resonances of **1a** and **1b** at −88° as would be expected for acid catalysis of intermolecular N–H exchange. Second, when methanol is added gradually to acetone solutions of **1** at −70°, it is found for up to an equal volume of methanol to acetone, the apparent concentration of the less favored form remains essentially constant on integration. The peaks do broaden, however, as the result of exchange and the separate AB resonances cannot be observed at 1:2 v/v acetone–methanol. Third, while neat methanol

shows OH and doublet CH_3 proton resonances (J = 5 Hz) at −77°, addition of small amounts of **1** was found to lead to rapid intermolecular OH exchange and loss of the spin–spin fine structure. Clearly, **1** in methanol facilitates O–H exchange, probably by undergoing N–H exchange itself. Two final points are, first, that qualitative experiments demonstrate that acetone has no special power to reduce the rate of nitrogen inversion in 1,2,2-trimethylaziridine,[15] the temperature of the coalescence point of the aziridine *gem*-methyl resonances in acetone being in fact rather lower (67°) than in methanol (90°), and, second, that acetone does have a strong inhibiting effect on O–H exchange in water[16] and could well behave similarly with amines.

The barrier to nitrogen inversion in trimethylamine has been estimated as 15 and 7.6 kcal/mol.[17,18] The latter value would lead to a rate which would be difficult to detect directly by the nmr method above −100°.[19] From the changes in line shape of the fluorine resonances of **1** between −88 and −60°, we estimate an E_a of about 10.5 kcal for the process of nitrogen inversion shown in eq 4. This is, of course, very much larger than the inversion barrier predicted for trimethylamine,[18] but if inversion of nitrogen proceeds most favorably through a transition state with the groups attached to nitrogen lying in a plane with approximately 120° bond angles, there is likely to be a substantial degree of angle strain associated with an inversion transition state having a planar nitrogen in a six-membered ring. On this basis, it is not surprising that the inversion of eq 4 seems to have a rate (and E_a) comparable to that of cyclohexane itself.[12b] It is also interesting in this connection that the reported[15b] proton-resonance coalescence temperatures (and therefore approximately the rates) for N–H and N–CH_3 substituted aziridines are reasonably similar.

No compelling evidence is available to help us decide whether the minor conformation in the equilibrium of eq 4 is **1a** or **1b**. The conformational free-energy difference of 0.42 kcal corresponds well to the 0.46-kcal value deduced from piperidine itself.[6,12d] The aforementioned correlation between the chemical shifts of equatorial fluorines and axial or equatorial 4-substituents suggest that the minor conformation may have the N–H hydrogen equatorial, a conclusion which has been reached for piperidine itself.[7] In this connection, it would be interesting to know the magnitude of the chemical shift difference between the fluorines in 4,4-difluoro-N-methylpiperidine at low temperatures. However, in any case, the very large difference (350 Hz) between the axial–equatorial fluorine chemical shift differences for the small structural change in going from **1a** to **1b** is surprising. Clearly, the system has a message of some significance for us but at present we do not know what it is.

(15) (a) A. Loewenstein, J. F. Neumer, and J. D. Roberts, *J. Amer. Chem. Soc.*, **82**, 3599 (1960). The E_a value of 10 ± 1 kcal reported in this paper seems low and will be checked by a complete analysis of the line shapes over a much wider temperature range. (b) The activation energies determined for inversion of the N–H nitrogen in 2,2,3,3-tetramethylaziridine and its N-deuterio analog by T. J. Bardos, C. Szantay, and C. K. Navada [*ibid.*, **87**, 5796 (1965)] also seem low, possibly because of the same reasons.

(16) (a) J. R. Holmes, D. Kivelson, and W. C. Drinkard, *J. Chem. Phys.*, **37**, 150 (1962); (b) J. Reuben, A. Tzalmona, and D. Samuel, *Proc. Chem. Soc.*, 353 (1962)

(17) J. F. Kincaid and F. C. Henriques, Jr., *J. Amer. Chem. Soc.*, **62**, 1474 (1950).

(18) G. W. Koeppl, D. S. Sagatys, G. S. Krishnamurthy, and S. I. Miller, *ibid.*, **89**, 3396 (1967).

(19) An exception is provided by the indirect method of Saunders and Yamada;[9] see also R. E. Lyle and C. R. Ellefson, *J. Amer. Chem. Soc.*, **89**, 4563 (1967).

Experimental Section

The 4,4-difluoropiperidine was used without further purification.[11] The solvents were spectroquality reagents. The ^{19}F nuclear magnetic resonance spectra were recorded at 56.4 MHz with a Varian Model A-56/60 spectrometer. A time-averaging computer, Varian Model C-1024, was used to improve the signal-to-noise ratio; in general, 4–20 scans were required. The C-1024 was calibrated by the chloroform–TMS chemical shift difference (436 Hz). The low-temperature measurements were achieved by passing precooled nitrogen through the Varian V-6057 variable-temperature accessory. The temperatures were calibrated by using the temperature dependence of the hydroxyl chemical shift of methanol and are believed to be accurate to ±1°. The theoretical spectra and the Arrhenius plots were computed by an IBM 7094 computer coupled to a Calcomp plotter.[12b]

Acknowledgment. We are deeply indebted to Dr. J. Edgar Anderson and Mr. Frank J. Weigert for many valuable suggestions and help with both the taking of the spectra and the computations of the rates.