and ΔS_i is largest for proton transfer from the hydronium ion, for only in this case is the bimolecular lowering of $\Delta S^{\pm}$ of opposite sign to the contribution made by solvation and only here, therefore, can the bimolecular effect not be masked by incomplete changes in solvation.

Nonequilibrium Transition-State Solvation. It has been suggested recently[2] that proton transfer from an acid to a substrate may not be a truly adiabatic process because the reactants may not be in continuous equilibrium with the solvent as they pass through the transition state. The dielectric relaxation time of water, 10^{-10} to 10^{-11} sec,[35] is greater than the time required for a proton jump to occur between suitably oriented and activated molecules, 10^{-12} to 10^{-13} sec.[36] This would imply that the reorganization of solvent, and therefore solvation, cannot keep up with proton transfer in aqueous solution. Additional evidence for this hypothesis has been adduced from entropies of activation: it is argued[2a] that $\Delta S^{\pm}$ for a number of rate-determining proton transfers in water is more negative than expected and that this is because desolvation of the proton does not take place before the transition state is reached.

The explanation of the difference in $\Delta S^{\pm}$ for proton transfer to 1,3-dimethoxybenzene and 1,3,5-trimethoxybenzen presented above would seem to negate this argument. In addition, the general parallelism between the activation parameters of Table VI and corresponding quantities for the equilibrium ionization of the catalyst acids is inconsistent with nonequilibrium transition-state solvation, for the ionization processes are not time dependent and cannot be subject to nonadiabatic effects of this type. The correspondence between equilibrium and kinetic parameters, on the other hand, is not perfect, and this does leave room for some nonequilibrium transition-state solvation. The presently available data, therefore, while suggesting an adiabatic kinetic situation, do not resolve the issue completely. It is hoped that a comparison of activation parameters for aromatic protonation with corresponding quantities for the more closely related equilibrium process, equilibrium aromatic protonation,[28] might be more definitive, and experiments are therefore being conducted to supply the necessary information.

(35) J. B. Hasted, *Progr. Dielectrics*, **3**, 101 (1961).
(36) T. Ackermann, *Z. Physik. Chem.*, **27**, 34 (1961).

Experimental Section

Materials. 1,3,5-Trimethoxybenzene-2-*t* was prepared from 2,4,6-trimethoxyphenyllithium by the method already described.[3] 1,3-Dimethoxybenzene-4-*t* was synthesized by adding an equivalent amount of tritiated water to a solution of 2,4-dimethoxyphenylmagnesium bromide prepared from 2,4-dimethoxybromobenzene and magnesium in tetrahydrofuran at 65°. The resulting mixture was hydrolyzed with saturated aqueous ammonium chloride, and the product was removed and was purified to constant specific activity by fractional distillation. When aqueous acid was used to perform this hydrolysis instead of ammonium chloride solution, the product was found to contain varying amounts (of the order of 5%) of the isomeric 1,3-dimethoxybenzene-2-*t*. This could easily be detected by kinetic experiments: plots of log (aromatic radioactivity) *vs.* time began to show curvature after a few half-lives, and suitable analysis of the data showed that two parallel detritiation reactions were occurring. The slower of the two rate constants obtained in this way was identical with that measured using an authentic sample of 1,3-dimethoxybenzene-2-*t* prepared by the reaction of tritiated water with 2,6-dimethoxyphenyllithium.

All other materials were reagent grade chemicals available commercially. Buffer solutions were prepared by weight from the pure components, and perchloric acid solutions were assayed by standard acidimetric methods. Corrections for concentration changes produced by changes in volume were made in the case of reactions carried out at temperatures different from that at which the solutions were prepared.

Kinetic Procedure. Kinetics were measured by the two methods already described.[1b,3] The initial-rate method was used for the experiments with 1,3-dimethoxybenzene in dilute acids at 25° and for the experiments with 1,3,5-trimethoxybenzene in phosphate buffers; the other method was used for all other determinations. The reactions at 96° were conducted in sealed ampoules; those at the lower temperatures, in glass-stoppered flasks. Bath temperatures were controlled to ±0.02° and were measured with a platinum resistance thermometer which had been calibrated by the National Bureau of Standards.

The Protonation Site of a Sulfonamide and the Stereochemistry of Proton Exchange

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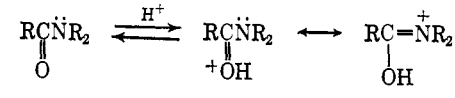
Abstract: Variable-temperature nmr studies of N-methyl-5-chloro-1,2-benzisothiazoline 1,1-dioxide (compound E in text) in fluorosulfonic acid prove unequivocally that (a) protonation occurs on the nitrogen of the sulfonamide and (b) the nitrogen proton of the conjugate acid of E exchanges with retention of configuration. The results are discussed in terms of the electronic structure of sulfonamides.

It has been shown with the aid of nmr spectroscopy that amides in strong acid protonate at the oxygen, thereby producing a resonance-stabilized cation in which the positive charge is distributed between the oxygen and nitrogen.[1] Sulfonamides might likewise



(1) R. J. Gillespie and T. Birchall, *Can. J. Chem.*, **41**, 148 (1963).

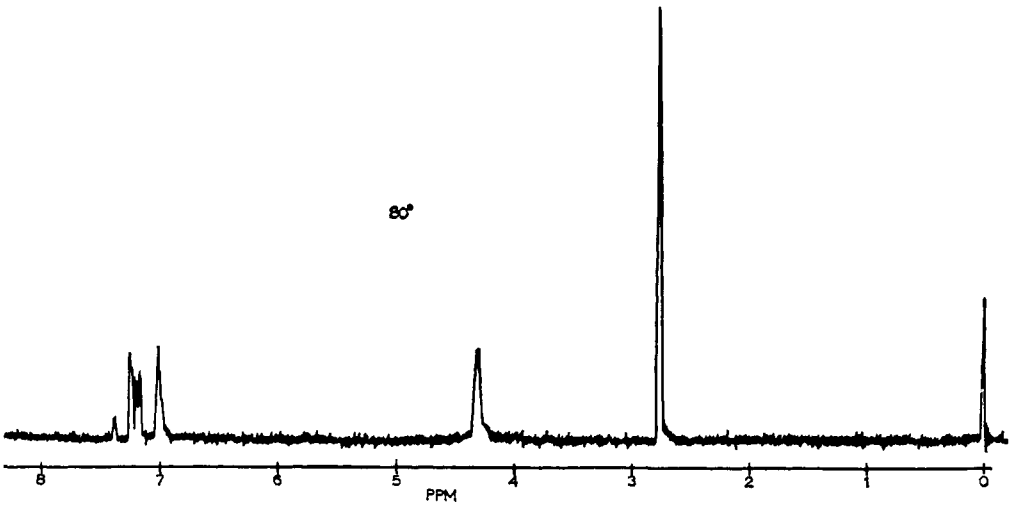
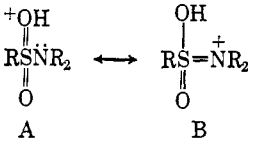


Figure 1. Nuclear magnetic resonance spectra of N-methyl-5- chloro-1,2-benzisothiazoline 1,1-dioxide in fluorosulfonic acid at 80°.

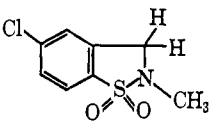
be expected to protonate at the oxygen if the same sulfur d orbital overlaps with the unshared pair of electrons of both oxygen and nitrogen, that is, if resonance contributor B is important. Alternatively, one d orbital of sulfur could interact with the oxygen electrons and a second d orbital with those of nitrogen, precluding resonance stabilization of the type indicated below. The system is in this case not analogous to amides, and thus protonation at nitrogen is a possibility.



A B

Previous work bearing on this question is twofold. In a kinetic study of ours it was shown that the oxygens of a sulfonamide of a primary amine are extremely poor intramolecular nucleophiles even in basic solutions where the sulfonamide is anionic.[2] This suggests that electron density (and hence nucleophilicity) is not imparted by resonance from the nitrogen to the oxygen, and that therefore nitrogen is a likely protonation site. More direct experiments were carried out by Birchall and Gillespie[3] who examined nmr spectra of N,N-dimethyl-*p*-toluenesulfonamide (C) and N-methyl-*p*-toluenesulfonamide (D) in fluorosulfonic acid. The N–CH_3's of C were found to be a doublet and the N–CH_3 of D a poorly resolved triplet. It was concluded from this that N-protonation is taking place (the doublet of C and the triplet of D arising from spin–spin coupling by one and two nitrogen protons, respectively). We must point out, however, that definite conclusions about the protonation site of sulfonamides are in fact not possible from the data of Birchall and Gillespie because oxygen protonation could also lead to the observed spectral patterns. In such a case the doublet of C would be due to magnetically nonequivalent methyl groups and the triplet of D to two superimposed doublets.

We present in this paper nmr spectra of fluorosulfonic acid solutions of N-methyl-5-chloro-1,2-benzisothiazoline 1,1-dioxide (E). An unquestionable decision concerning the protonation site of a sulfonamide is possible with this compound. If nitrogen is protonated, then its inversion is inhibited and the methylene protons become nonequivalent. Oxygen protonation would, if anything, accelerate inversion; however, this mode of protonation also leads to magnetic nonequivalence of the methylene protons because of the resulting asymmetry of the sulfonyl group. Nevertheless, the protonation site of E can be elucidated because nitrogen protonation should produce spin–spin coupling between the NH and the CH_2 and CH_3, whereas oxygen protonation should not result in coupling (the protons are separated by five bonds). It is important to understand the difference between an acyclic sulfonamide, like N,N-dimethyltoluenesulfonamide, and the cyclic compound E. In the acyclic case, one is not sure whether methyl splitting in strong acid is due to magnetic nonequivalence or to spin–spin coupling (as would arise from O- and N-protonation, respectively). In E it should be possible to observe magnetic nonequivalence and spin–spin coupling as separate and distinct phenomena.



E

Experimental Section

Materials. N-Methyl-5-chloro-1,2-benzisothiazoline 1,1-Dioxide (E). This compound was synthesized by a procedure already described in the literature[4,5] (see diagram). It had mp 175–177° (lit.[4] mp 175.5–177.5°) and an nmr in agreement with structure E (Figure 1). The presence of the chlorine atom in the starting material (K & K Laboratories *m*-chlorobenzyl bromide) is necessary to direct chlorosulfonation to the desired site.

Fluorosulfonic Acid. Baker & Adamson fluorosulfonic acid (called fluosulfonic acid) was distilled through a glass column under nitrogen. A small center cut was collected and thereafter stored and transferred in a drybox.

(2) F. M. Menger and C. L. Johnson, *Tetrahedron*, **23**, 19 (1967).
(3) T. Birchall and R. J. Gillespie, *Can. J. Chem.*, **41**, 2642 (1963).
(4) Y. Nitta, M. Shindo, T. Takasur, and C. Isone, *Yakugaku Zasshi*, **84**, 493 (1964); *Chem. Abstr.*, **65**, 8291g (1964).
(5) We thank Mr. Howard Brock, Ford Undergraduate Career Scholar, for carrying out two steps in this synthesis.

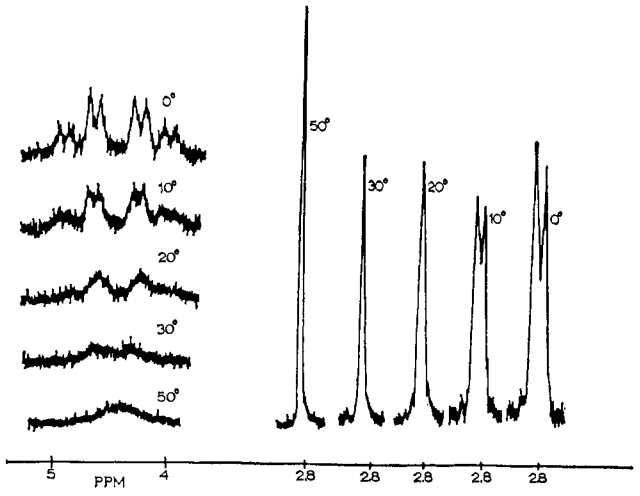
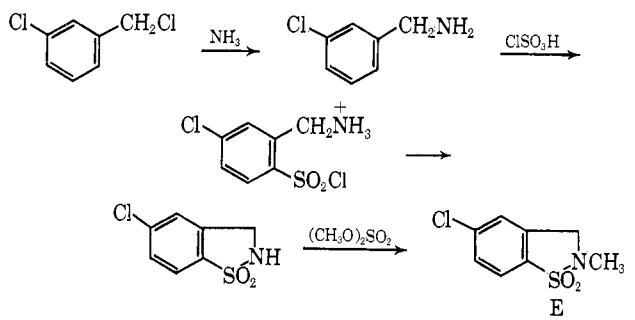


Figure 2. Nuclear magnetic resonance spectra of N-methyl-5-chloro-1,2-benzisothiazoline 1,1-dioxide in fluorosulfonic acid at several temperatures. The spectrum amplitude setting is not the same in all the spectra.

Stability of E in FSO_3H. The stability of E in FSO_3H was established by dissolving 114 mg of E in the acid and warming it to 70° for 12 min. When the colorless solution was poured onto ice, a precipitate formed. This was separated by filtration and dried under vacuum. The material weighed 96 mg (84%) and had a melting point and infrared spectrum identical with those of E.

Nmr Spectra. The nmr spectra were obtained using a Varian A-60 spectrometer fitted with a variable-temperature probe.[6] TMS was used as an internal standard.



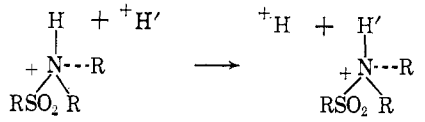
Results and Discussion

The nmr spectrum of sulfonamide E in $DCCl_3$ has a methylene singlet at τ 5.76 (slightly broadened because of coupling with an aromatic proton) and a sharp methyl singlet at τ 7.12. This indicates that the sulfonamide nitrogen inverts so rapidly that the two methylene protons are not distinct, which is hardly surprising in view of the findings that inversion of *n*-alkylpyrrolidines is too rapid to measure by nmr at −77°[7] and that a sulfonyl group accelerates nitrogen inversion.[8]

The spectra of E in fluorosulfonic acid at various temperatures are given in Figures 1 and 2. At 50 ± 3° the CH_2 group is a broad resonance spread over about 35 cps. The CH_3 peak is quite sharp. Lowering the temperature to 37 ± 0.2° causes the CH_2 peak to begin to resolve into a quartet structure, but the CH_3 remains unchanged as a singlet. At 20° the quartet for the CH_2 is distinct (spin–spin coupling of 15 cps) and still there is no observable splitting of the CH_3. The CH_3 begins to split only at 11 ± 0.2° at which temperature the CH_2 quartet displays a second splitting. Finally at 0 ± 3° the CH_2 resonance is clearly an octet (second coupling 5.5 cps) and that of the CH_3 a sharp doublet (J = 4.5 cps). Warming the sample to a high temperature (80°) causes the spectrum to return to that found in $DCCl_3$.

The results prove unequivocally that nitrogen is the protonation site. This conclusion is demanded by the splitting of the methylene quartet and the methyl singlet into an octet and doublet, respectively. The observation that protonation of E occurs on nitrogen rather than on oxygen suggests that an oxygen-protonated sulfonamide would not be resonance stabilized in the way that conjugate acids of amides presumably are. Amides differ from sulfonamides in that the former have a central sp^2-hybridized carbon with but *one* p orbital available for overlap, while sulfonamides have a sulfur with *several* empty d orbitals This permits oxygen and nitrogen $p\pi$–$d\pi$ overlap involving two orthogonal sulfur d orbitals, so that the unshared pair of electrons of nitrogen contributes little to the basicity of the oxygen. The large S–O bond order (1.80) in $SO_2(NH_2)_2$[9] and the free rotation about the N–S bond of sulfinamides[10] are consistent with this description.

It is particularly interesting that at 20° the proton resides on the nitrogen of E long enough to inhibit inversion (thereby affecting magnetic nonequivalence of the methylene protons and giving rise to a quartet) and yet no spin–spin coupling between the nitrogen proton and the methylene or methyl is evident. The only reasonable explanation for this finding is that the nitrogen proton is exchanging (and hence destroying spin–spin coupling) in such a manner that the magnetic nonequivalence of the methylene protons is maintained. *This means that proton exchange is occurring with retention of configuration.*[11] Only at lowered temperatures, below 11°, is the lifetime of the nitrogen proton sufficiently long to cause the methylene quartet and the methyl singlet to split into an octet and doublet. The stereochemical behavior of the proton exchange thus classifies it as an S_E2 reaction. It may be that the observed stereochemistry is the



result of the bifunctional fluorosulfonic acid molecule accepting and delivering a proton in a cyclic concerted process.[12]

Acknowledgment. We greatly appreciate support from the McCandless Fund of Emory University.

(6) We are very grateful to Professor John R. Dyer for making these facilities available to us.

(7) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, **80**, 5203 (1958).

(8) F. A. L. Anet, R. D. Trepka, and D. J. Cram, *ibid.*, **89**, 357 (1967).

(9) R. J. Gillespie and E. A. Robinson, *Can. J. Chem.*, **41**, 2074 (1963).

(10) R. M. Moriarty, *Tetrahedron Letters*, 509 (1964).

(11) A similar result has been found for protonated dibenzylmethylamine: M. Saunders and F. Yamada, *J. Am. Chem. Soc.*, **85**, 1882 (1963).

(12) It is interesting (although perhaps not directly relevant) that an optically active sulfone, which is isoelectronic with a protonated sulfonamide, exchanges its labile hydrogen many times faster than it racemizes: E. J. Corey and E. T. Kaiser, *ibid.*, **83**, 490 (1961); D. J. Cram, D. A. Scott, and W. D. Nielson, *ibid.*, **83**, 3696 (1961).