Iodide Reduction of Sulfilimines. 3. Evidence of a Minor Role for Catalysis by Hydrogen Bonding in the Decomposition of Sulfurane Intermediates

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Abstract: The iodide reduction of *N*-(substituted benzoyl or benzenesulfonyl)-*S*,*S*-dimethylsulfilimine ylides (aqueous solution, 25 °C, μ = 1.0 with KCl) is first order with respect to iodide concentration in the pH range 0.5–5; the order with respect to the proton is slightly >1.0. The solvent deuterium isotope effect for the reduction of *N*-(4-chlorobenzoyl)-*S*,*S*-dimethylsulfilimine ylide is k_H/k_D = 0.60. Electron-withdrawing groups in the leaving group accelerate the rate of the reaction and give a $\beta_{l.g.}$ value of −0.67. General acid catalysis is observed in the reduction reaction with Brønsted α values of 0.15 and 0.29 for 4-methoxybenzamide and 4-chlorobenzenesulfonamide leaving groups, respectively. The value of $\beta_{l.g.}$ increases with decreasing strength of the catalyzing acid and the term $p_{xy} = (\partial\beta_{l.g.}/\partial pK_a^{HA}) = (\partial\alpha/\partial pK_a^{l.g.}) \approx +0.05$. The solvent deuterium isotope effect on the general catalyzed reduction reaction is small (k_{BH}/k_{BD} = 1.32) and independent of acid strength. For the solvent-catalyzed reaction, it is suggested that the rate-limiting step involves diffusion apart of the amide anion–iodosulfonium cation pair. It is concluded, however, that the observed general catalysis *does not* arise from hydrogen bonding effects in a preassociation-type mechanism, but rather it involves proton transfer that is concerted with S–N bond cleavage.

The reduction of sulfilimine salts by iodide anion proceeds by a mechanism in which an initially formed addition product, a tetracoordinate sulfurane,[1-3] can partition by a variety of pathways to give an iodosulfonium ion, which rapidly undergoes a second reduction step to give the final products, the amine, the sulfide, and iodine.[4] In previous work,[2] we have reported that the value of the Brønsted $\beta_{l.g.}$ for the acid-catalyzed iodide anion reduction of sulfilimine ylides with sulfonyl and benzoyl leaving groups was large and positive, suggesting that the major pathway for decomposition of the sulfurane intermediate derived from strongly acidic amines and amides involved expulsion of the amine anion (Scheme I). Further, the order with respect to the proton was slightly >1.0, suggesting that acid catalysis of the expulsion of the amine anion was occurring.[2] Since the pK_a of the intermediate amide anion in these reactions would be less than that of the solvent (water),[5] it would not be possible for the solvent to function as a proton donor in a transition state which involved proton transfer that was concerted with S–N bond cleavage;[6] for carboxylic acids, however, the pK_a change would be favorable and concerted catalysis would be "allowed". In order to define more clearly the mechanistic consequences of progressing from regions of "allowed" to "disallowed" concerted catalysis, we have examined leaving group effects and the effects of general acids on the iodide reduction of sulfilimine ylides with benzamide and benzenesulfonamide leaving groups. The data suggest that the catalysis by general acids is concerted with S–N bond cleavage and that the expected "preassociation with hydrogen bonding" mechanism[7] is of minor importance in the present system.

Scheme I

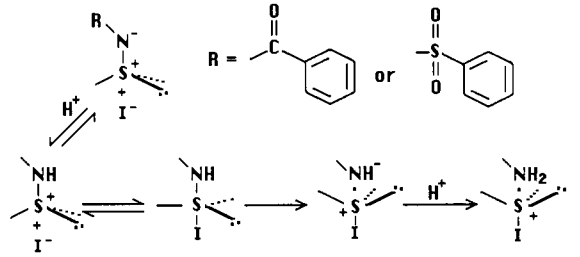

Table I. Third-Order Rate Constants for the Iodide Reduction of *N*-(Substituted)-*S*,*S*-dimethylsulfilimmonium Salts[a]

substituent	pK_a[b]	$10^3 k_{H^+}/M^{-2}\ s^{-1}$[c]	α[d]
N-benzoyl			
4-methoxy	2.30	0.090	0.15
4-methyl	2.05	0.105	
unsubstituted	1.70	0.177	
4-chloro	1.30	0.343	0.19
(k_{H^+}/k_{D^+})[e]		(0.60)	
N-sulfonyl			
4-chloro	−0.02	2.96	0.29

[a] Reactions in aqueous solution, 25 °C, ionic strength 1.0 with KCl. [b] Determined by spectrophotometric titration. [c] Third-order rate constant for the proton-catalyzed reduction by iodide anion. [d] Brønsted coefficient for the general-acid-catalyzed reduction reaction. [e] Observed solvent deuterium isotope effect on the proton-catalyzed reaction.

Experimental Section

Synthesis. *N*-(Substituted)-*S*,*S*-dimethylsulfilimmonium salts were prepared from trifluoroacetic anhydride, dimethyl sulfoxide, and the corresponding benzamide or benzenesulfonamide according to the method described by Swern et al.[8] All sulfilimines were isolated as the picrate salts and subsequently converted to the chloride by passing methanolic solutions over Dowex anionic exchange resins, as previously described.[2,3] All compounds were recrystallized from dichloromethane/ether mixtures at 4 °C and had melting points and spectra consistent with literature values. Elemental analyses were performed on all new compounds, and these were within acceptable error limits on carbon, hydrogen, and nitrogen.[9]

Kinetic Studies. All kinetic runs were performed by following the appearance of I_3^- at 353 nm on a Hitachi 100-60 UV–vis spectrophotometer equipped with an automatic cell changer and a thermostated cell compartment. Temperature was maintained at 25 °C, and the ionic strength was maintained at 1.0 with KCl. The pH of each cell was determined at the end of each run with a Corning pH meter equipped with a combined glass electrode. First-order rate constants were obtained from initial rate measurements with use of the extinction coefficient of 24 700 M^{-1} for I_3^- at 353 nm. Catalytic constants for buffer catalysis,

(1) Young, P. R.; Hsieh, L.-S. *J. Am. Chem. Soc.* **1978**, *100*, 7121–7122.
(2) Young, P. R.; McMahon, P. E. *J. Am. Chem. Soc.* **1985**, *107*, 7572–7577.
(3) Young, P. R.; Huang, H. C. *J. Am. Chem. Soc.*, preceding paper.
(4) Tillett, J. G. *Chem. Rev.* **1976**, *76*, 747–772. Gilchrest, T. L.; Moody, C. J. *Ibid.* **1977**, *77*, 409–435. Oae, S.; Furukawa, N. In *Sulfilimines and Related Derivatives*; ACS Monograph 179, American Chemical Society: Washington, D.C., 1983.
(5) Exner, O.; Janak, P. *Collect. Czech. Chem. Commun.* **1975**, *40*, 2510–2523.
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(9) Huang, H. C. Thesis, University of Illinois at Chicago, Chicago, IL, 1986. Analytical and spectroscopic data available on request.

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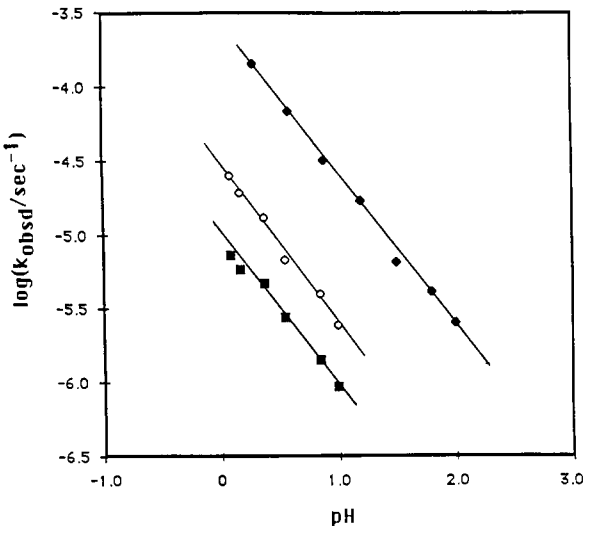

Figure 1. Plot of observed rate constants as a function of pH for the iodide reduction of *N*-(4-chlorobenzenesulfonyl)- (◆), *N*-(4-chlorobenzoyl)- (◇), and *N*-(4-methoxybenzoyl)-*S*,*S*-dimethylsulfilimine (■). Aqueous solution, 25 °C, [I⁻] = 0.1 M, ionic strength 1.0 with KCl. The lines have slopes of 1.05, 1.15, and 1.16, respectively.

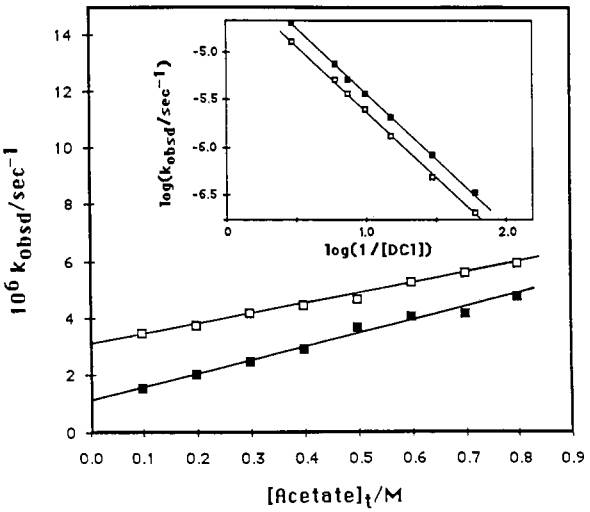

Figure 2. Plot of observed rate constants for the iodide reduction of *N*-(4-chlorobenzoyl)-*S*,*S*-dimethylsulfilimine (**1**), as a function of the concentration of acetic acid buffer, pH 1.0, in H_2O (■) and in D_2O (□). Aqueous solution, 25 °C, [I⁻] = 0.1 M, ionic strength 1.0 with KCl. Inset: Double logarithmic plot of the rate constants for the reduction of **1** as a function of added acid concentration in H_2O (□) and in D_2O (■).

solvent deuterium isotope effects, and isotope effects on the general-catalyzed reaction were obtained as described in the preceding paper.[3]

The pK_a values of the sulfilimines used in this study were determined by spectrophotometric titration[10] at 255–275 nm with perchloric acid solutions in the concentration range 10^{-3}–2 M; pK_a values were determined by standard replots.[11]

Results and Discussion

Rate constants for the iodide reduction of *N*-(substituted)-*S*,*S*-dimethylsulfilimines derived from benzamides and benzenesulfonamides are strictly first order with respect to iodide in the pH range 0.2–5. The order with respect to proton is slightly >1.0 (Figure 1) and varies in the range 1.05–1.22. The greater than first-order dependence on proton concentration is a result of the fact that sulfilimines derived from strongly acidic amines exist as ylides[4,10] at neutral pH and the predominate reaction that is observed in solution is the reduction of the protonated ylide species.[7] The pK_as of the sulfilimine ylides used in this work were determined by spectrophotometric titration and are listed in Table I along with the third-order rate constants for the solvent-catalyzed reduction of the protonated ylides, calculated from proton activities and iodide concentrations (typically 0.1 M), as described in the preceding paper.[3] The solvent deuterium isotope effect for the reduction of the protonated ylide derived from *p*-chlorobenzamide is k_H/k_D = 0.6 (Figure 2, inset). This observed effect is the product of the isotope effects on the equilibrium protonation of the ylide and the true solvent isotope effect on the rate-limiting step. Taking the observed isotope effect of K_H/K_D = 0.63 for the first ionization of phosphoric acid[12] (pK_a = 2.1) to be an approximation for the isotope effect on the protonation of the ylide derived from *p*-chlorobenzamide (pK_a = 2.05), there is virtually *no* isotope effect on the solvent-catalyzed reduction reaction (k_H/k_D = 1.0), suggesting that diffusion steps may be rate limiting.[13]

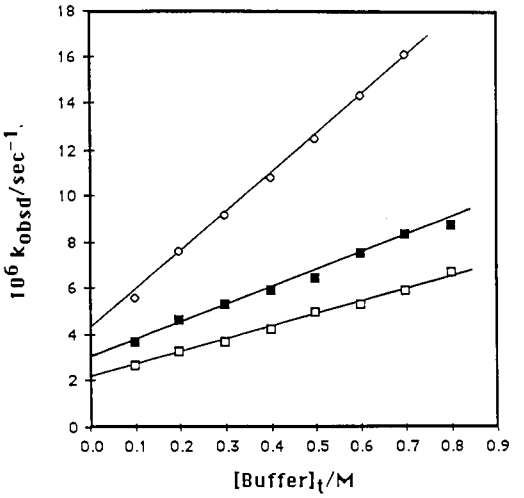

Figure 3. Plot of observed rate constants as a function of buffer concentration for the iodide reduction of *N*-(4-chlorobenzoyl)-*S*,*S*-dimethylsulfilimine for the following buffers: dichloroacetic acid (◇), glycolic acid (■), and acetic acid (□). Aqueous solution, 25 °C, [I⁻] = 0.1 M, ionic strength 1.0 with KCl.

Table II. Catalytic Constants for Buffer Catalysis of the Iodide Reduction of *N*-(Substituted)-*S*,*S*-dimethylsulfilimmonium Salts[a]

	pK_a[b]	$10^5 k_{BH}/M^{-2}\ s^{-1}$[c]	
substituted benzamides		*p*-OCH_3	*p*-Cl
buffer			
acetic acid	4.60	0.36	0.57
(k_{BH}/k_{BD})[d]			(1.31)
glycolic acid	3.82	0.44	0.76
chloroacetic acid	2.70	0.53	1.32
(k_{BH}/k_{BD}[d])			(1.33)
dichloroacetic acid	1.29	1.06	2.55
trifluoroacetic acid	0.23	1.83	3.33
p-chlorobenzenesulfonamide			
buffer			
acetic acid	4.60	1.25	
chloroacetic acid	2.70	4.72	
betain	1.84	7.40	
dichloroacetic acid	1.29	6.45	

[a] Reactions in aqueous solution, 25 °C, ionic strength 1.0 with KCl. [b] From: Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry and Molecular Biology*; Fasman, G. D., Ed.; CRC Press, Inc.: Cleveland, OH, 1975; or, Sayer, J. M.; Peskin, M.; Jencks, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 4277–4287. [c] Third-order rate constant for general-acid-catalyzed reduction by iodide anion. [d] Observed solvent deuterium isotope effect on the general-acid-catalyzed reaction.

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(13) Schowen, R. L. *Prog. Phy. Org. Chem.* **1972**, *9*, 275–332.

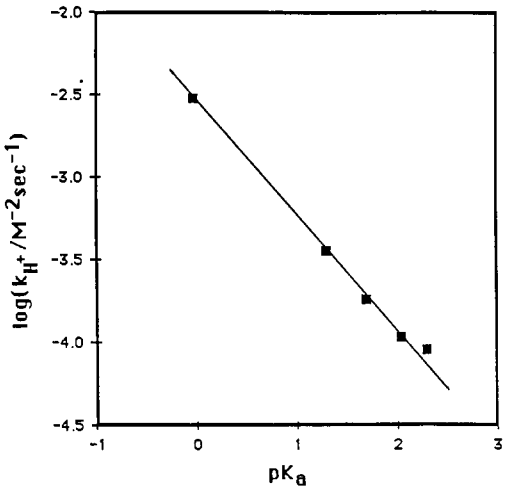


Figure 4. Plot of the logarithm of the third-order rate constant for the iodide reduction of *N*-(substituted)-*S*,*S*-dimethylsulfilimines as a function of sulfilimine pK_a for the following N substituents: 4-chlorobenzenesulfonyl, 4-chlorobenzoyl, benzoyl, 4-methylbenzoyl, and 4-methoxybenzoyl. Aqueous solution, 25 °C, [I^-] = 0.1 M, ionic strength 1.0 with KCl. The line has a slope of −0.67.

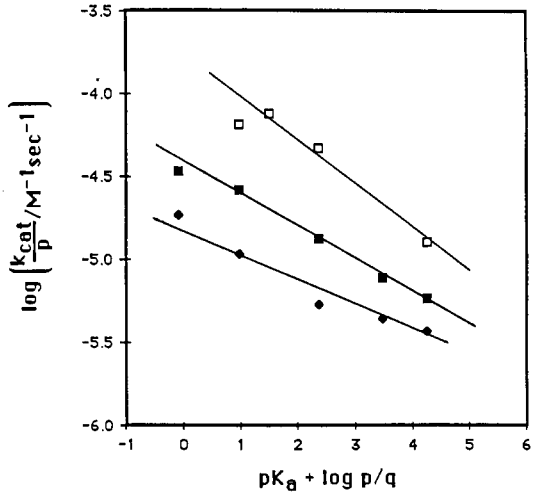


Figure 5. Brønsted plots for the general-acid-catalyzed iodide reduction of *N*-(substituted)-*S*,*S*-dimethylsulfilimines for the following N substituents: 4-chlorobenzenesulfonyl (□), 4-chlorobenzoyl (■), and 4-smethoxybenzoyl (◆). Aqueous solution, 25 °C, [I^-] = 0.1 M, ionic strength 1.0 with KCl. The slopes are 0.29, 0.19, and 0.15, respectively.

Rate constants for the reduction of sulfilimines derived from benzamides and benzenesulfonamides were dependent upon the concentration of buffer acid (Figure 3). Catalytic constants for the general-acid-catalyzed reaction are collected in Table II. The generalized rate law for the reduction of the compounds investigated is shown below in eq 1. As before,[3] the dissociation constant for the formation of the sulfilimine ylide is K_a; k_H and k_{BH} represent the constants for proton and general catalysis, respectively. For the compounds investigated in this work, $K_a \geq [H^+]$, making the reaction slightly greater than first order in proton activity (Figure 1).

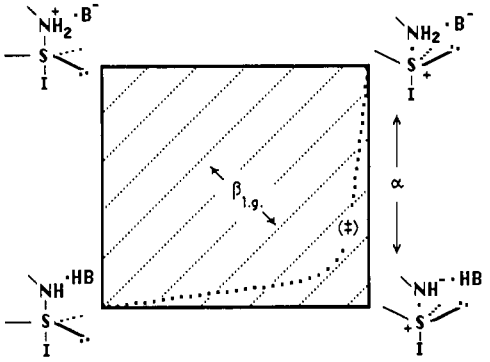
$$k_{obsd} = \{(k_H[H^+] + k_{BH}[BH])[H^+][I^-]\}/(K_a + [H^+]) \quad (1)$$

The dependence of the third-order rate constant for the solvent-catalyzed reduction reaction on the pK_a of the leaving group is shown in Figure 4; the slope of this plot gives $\beta_{l.g.} = -0.67$. As described previously,[2] this observed β value is actually a composite of the values for the protonation of the ylide ($\beta_H = 0.92$)[10] and for the approach to the rate-limiting transition state (β_k) by the expression $\beta_{obsd} = (\beta_H + \beta_k)$. The actual leaving group effect for the solvent-catalyzed reduction reaction, β_k, is therefore about −1.6. This indicates a great deal of negative charge has accumulated on the nitrogen in the leaving group and that the rate-limiting step involves the reaction of an essentially fully formed nitrogen anion. The pK_as of these nitrogen anions are somewhat less than the pK_a of the solvent, based on the reported pK_a values[5] of 10.1 and 14.5 for benzenesulfonamide and benzamide, respectively, making the solvent impotent (via the libido rule)[6] as a catalyst for proton transfer in a concerted mechanism.

General-Acid-Catalyzed Reduction. As the concentration of buffer acid is increased at constant pH, the observed rate constants for the iodide reduction of sulfilimines derived from benzamides and sulfonamides increase linearly (Figure 3). The catalytic constants for the buffers examined are collected in Table II and representative data appear plotted in the Brønsted plots in Figure 5. The slopes of these plots, the Brønsted α values (Table II), decrease as the pK_a of the amine leaving group decreases. This change is shown numerically by the term $p_{xy} = (\partial\alpha/\partial\text{-p}K_a^{l.g.}) \approx 0.05$,[14] similar in magnitude but opposite in sign to that observed for the iodide reduction of sulfilimines derived from more basic amines[3] where $(\partial\alpha/\partial\text{-p}K_a^{l.g.}) \approx -0.06$. As is evident from the Brønsted plots in Figure 5, the predicted structure/reactivity cross correlation,[14] $(\partial\beta_{l.g.}/\partial pK_a^{HA}) = (\partial\alpha/\partial\text{-p}K_a^{l.g.})$, is also observed.

For the sulfilimine derived from *p*-chlorobenzamide, the solvent deuterium isotope effect on the general-acid-catalyzed reaction is normal (Figure 2) and is independent of the pK_a of the catalyzing acid (Table II; $k_{BH}/k_{BD} = 1.31$ and 1.33 for acetic and chloroacetic acids, respectively). This result differs from that observed with the more basic amine leaving groups where the isotope effect increased with increasing acid strength.[3] The small value of this effect in the present case suggests that the transition state is very early with respect to proton transfer.[13]

Scheme II



With use of linear free energy parameters as rough guides to locate the transition state on the surface of a More O'Ferrell–Jencks reaction surface,[14] the transition state would appear to be in the lower right-hand quadrant of the surface shown in Scheme II. The small amount of proton transfer in the transition state, based on the Brønsted α values, and the large amount of negative charge buildup on the nitrogen, based on the large $\beta_{l.g.}$, suggests that the reaction may be following a "preassociation" style mechanism[7] which is facilitated by hydrogen bonding to the general acid. A preassociation mechanism such as this is predicted to be observed whenever the lifetime of a stepwise intermediate becomes so short that the rate constant for reversion to starting materials exceeds the rate constant for diffusion of the buffer away from the encounter complex.[7] Under these conditions, the buffer acid must be present during the formation of the stepwise intermediate and catalysis of the formation of this intermediate can then occur by hydrogen bonding to the general acid. The fact that a diffusion step (possibly diffusion apart) would seem to be rate limiting in the solvent-catalyzed reaction, based on the observed solvent deuterium isotope effect, would be consistent with this type of a mechanism where the amine anion is formed in the stepwise reaction. Hine[15] has suggested that approximate equilibrium constants for hydrogen bond formation can be calculated with eq 2. For a transition state with hydrogen bond

(14) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511–527.
(15) Author: Please give reference 15.

$$\log K_{AB} = \tau(pK_{HA} - pK_{H_2O})(pK_{H_3O^+} - pK_B) - 1.74 \quad (2)$$

stabilization, the effective pK_a of the transition state can be estimated with the expression[16]

$$(\alpha/\tau) - 1.74 = pK^{\ddagger} \quad (3)$$

The constant τ in eq 2 and 3 has been estimated to be 0.024 in methanol,[15] although the value is probably less in water.[16,17] If τ was identical in water and methanol and $pK^{\ddagger} \approx pK_a^{RNH_2}$ for a very anionic transition state, then eq 3 predicts Brønsted α values of $\approx$0.28 and 0.39 for *p*-chlorobenzenesulfonamide and *p*-chlorobenzamide leaving groups, respectively, based on the reported pK_a values of the anions.[5] The nitrogen in a transition state along the bottom edge of the reaction surface in Scheme II would have a pK_a that would increase from a very acidic value on the left (the sulfurane) to a very basic value for the amine anion. If the transition state was located along this edge, changing the leaving group from *p*-chlorobenzenesulfonamide to *p*-chlorobenzamide would destabilize the amine anion and cause a Hammond effect shift of the transition state toward the anionic intermediate,[14] increasing $pK^{\ddagger}$. Equation 3 would predict, then, that the Brønsted α from hydrogen bonding effects should increase as the leaving group takes on more electron withdrawing character. The fact that the observed Brønsted α values *decrease* with increasing electron withdrawal in the leaving group (Table II) means that the major component of the observed α value *does not arise* from hydrogen bonding effects, the reaction is *not* "preassociation, with hydrogen bonding", and that, instead, a *concerted* mechanism is most likely being followed.

For a concerted transition state in the lower right-hand quadrant, the major effect of electron-donating substituents in the leaving group is going to be to *destabilize* the amine anion and *stabilize* the protonated sulfurane in the upper left quadrant. The effect on the transition state is going to be a coupled Hammond and anti-Hammond movement *away from* (anti-Hammond) and *toward* (Hammond) the high energy amine anion intermediate.[14] Of these two effects, the largest is likely to be the Hammond movement toward the high energy intermediate since the reaction coordinate has a large vertical component in the region where the observed Brønsted coefficients appear together on the surface in Scheme II (marked as ‡). The net result in this movement will be a *decrease* in the Brønsted α value, consistent with the data in Table II. An increase in acid strength will also *destabilize* the bottom edge of the surface, causing a coupled Hammond and anti-Hammond shift of the transition state. The larger of these forces is again likely to be the Hammond effect, resulting in a movement of the transition state toward slightly larger values of $\beta_{l.g.}$ consistent with the observed value of p_{xy}.[14]

For the general-acid-catalyzed reduction reaction then, the data strongly suggest that the mechanism involves rate-limiting proton transfer which is very slightly coupled with S–N bond cleavage. The data supporting this conclusion are the following: (1) The term $p_{xy} = (\partial\beta_{l.g.}/\partial pK_a^{HA}) = (\partial\alpha/\partial pK_a^{l.g.})$ is positive; a negative value is predicted by the Hine equation[15] (eq 3) for a stepwise reaction involving a "preassociation" mechanism with catalysis by hydrogen bonding.[7] (2) The solvent deuterium isotope effect on the general-catalyzed reaction is normal and small, consistent with a small amount of proton transfer in the transition state. (3) The solvent deuterium isotope effect for the solvent-catalyzed reaction is $\approx$1.0 which, coupled with the large value of $\beta_{l.g.}$, suggests that diffusion apart of the initially formed products may be rate limiting.

Since the mechanism for the general-catalyzed reduction of sulfilimines bearing aniline and primary amine leaving groups seems to involve a concerted mechanism in which proton transfer is ahead of S–N bond cleavage[3] and the present data suggest a concerted mechanism in which proton transfer lags far behind the cleavage step, the overriding factor controlling the change from one pathway to the other must lie in the difference in the pK_a of the leaving group. If we assume that the pK_a for N-protonation of benzamide is about 17 units below the pK_a of the parent amine[18] (ammonia, $pK_a = 9.6$), then the pK_a of the sulfurane cation for this derivative will be about −14. Given this pK_a differential, the rate constant for proton transfer from H_3O^+ to the neutral sulfurane will be about 10^3 s^{-1} (based on a rate constant of about 10^{11} s^{-1} for proton transfer within an encounter complex in the favorable direction).[3] For the anilines examined in previous work,[3] the lower limit on the estimated rate constants for the proton transfer step would be about 10^6 s^{-1}. It is therefore possible that the change in mechanism simply occurs when the rate constant for the anionic pathway exceeds the microscopic rate constant for proton transfer to the neutral sulfurane rather than occurring through a systematic "anti-Hammond slide" from the upper left quadrant down to the lower right as the stability of the amine anion increases. It is also interesting to note that the amide and sulfonamide leaving groups form a more or less continuous series in spite of the fact that O-protonation[18] is far more likely in amides than in sulfonamides. This suggests that the proton transfer step in both the amide and sulfonamide derivatives is occurring directly on the nitrogen and that O-protonation is not observed. The fact that catalysis by hydrogen bonding is apparently not observed in the present system suggests that such mechanisms may be of minor importance in reactions in which pathways for concerted catalysis also exist.

Acknowledgment. This work was supported by a grant from the National Science Foundation (CHE 8511865).

Registry No. D_2, 7782-39-0; D_2O, 7789-20-0; *p*-$CH_3OC_6H_4CONHS(CH_3)_2^+$, 106358-67-2; *p*-$CH_3C_6H_4CONHS(CH_3)_2^+$, 106358-68-3; $PhCONHS(CH_3)_2^+$, 106358-69-4; *p*-$ClC_6H_4CONHS(CH_3)_2^+$, 106358-70-7; *p*-$ClC_6H_4SO_2NHS(CH_3)_2^+$, 106358-71-8; *p*-$CH_3OC_6H_4CON{=}S(CH_3)_2$, 25024-03-7; *p*-$CH_3C_6H_4CON{=}S(CH_3)_2$, 81637-87-8; $PhCON{=}S(CH_3)_2$, 19397-91-2; *p*-$ClC_6H_4CON{=}S(CH_3)_2$, 36176-95-1; *p*-$ClC_6H_4SO_2N{=}S(CH_3)_2$, 52259-84-4; betaine, 107-43-7; acetic acid, 64-19-7; glycolic acid, 79-14-1; chloroacetic acid, 79-11-8; dichloroacetic acid, 79-43-6; trifluoroacetic acid, 76-05-1.

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(17) Rothenberg, M. E.; Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1985**, *107*, 1340–1346.
(18) Fersht, A. *J. Am. Chem. Soc.* **1971**, *93*, 3504.