Evidence for Concerted General Acid Catalysis in an S_N2-like Transition State for the Reduction of Sulfilimines by Thiols

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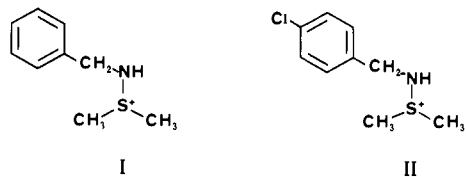
Abstract: N-(Substituted benzyl)-S,S-dimethylsulfilimmonium salts are reduced by thiol anions to give dimethyl sulfide, the benzylamine, and the reductant disulfide. With use of 3-nitro-5-thiobenzoic acid (NTBA) or 3-thiobenzoic acid (TBA) as reductant, the reaction is first order in proton activity below pH 5 and first order in both thiol anion and sulfilimine cation (aqueous solution, 25 °C, ionic strength 1.0 with KCl). The rate constants for the reduction reaction are a linear function of the concentration of buffer acids, and Brønsted α values of 0.50 and 0.63 are observed for the NTBA reduction of N-benzyl- and N-(4-chlorobenzyl)sulfilimines, respectively. The leaving group effects for these compounds are $\beta_{lg} = -1.1$ and $+0.8$ for the reductions catalyzed by difluoroacetic and acetic acids, respectively. For the reduction of the N-benzylsulfilimine by NTBA and TBA, values of β_{nuc} of 0.38 and 0.51 are observed for the proton- and acetate-catalyzed reductions, respectively. The data are consistent with a concerted mechanism in which proton transfer is further advanced than either S–N cleavage or S–S bond formation. The direction of the reaction coordinate is oriented toward the formation of a protonated tetracoordinate sulfurane addition intermediate. The thermodynamic restraints on concerted catalysis, however, require that this tetracoordinate intermediate cannot be the final product of the concerted proton transfer. It is concluded that the substitution reaction is *concerted* and follows a reaction coordinate proceeding near to, but not including, the sulfurane intermediate.

Introduction

Sulfilimines react with thiol nucleophiles in a general acid catalyzed reaction to give the sulfide, the free amine, and the reductant disulfide[1,2] (eq 1). Experimentally, the reaction is first
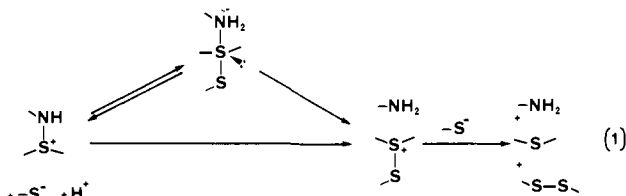
order in thiol concentration[1] and the initial product is thought to be the thiasulfonium cation. Two distinct mechanisms can be written for the overall substitution reaction, one involving stepwise addition to give a tetracoordinate sulfurane intermediate (which is observed for iodide addition[3]) and a fully concerted mechanism where the general acid would directly protonate the amine in an S_N2-like transition state. The nature and driving force for concerted general-acid catalysis in an S_N2 transition state is a matter of considerable fundamental interest since extensive coupling of the necessary vibrational modes would seem unlikely unless there were clear energetic reasons for the concerted mechanism to be favored over stepwise addition.[4] In order to approach an understanding of the nature of the S_N2 transition state, we have examined the reduction N-benzyl- (I) and N-(4-chlorobenzyl)-S,S-dimethylsulfilimmonium (II) salts by 5-nitro-3-thiobenzoic acid (NTBA) and the reduction of I and II by 3-thiobenzoic acid (TBA). We have found that the reaction is indeed an example of a general acid catalyzed S_N2 reaction.

<div align="center">

I   II

</div>

(1) Lambeth, D. O. *J. Am. Chem. Soc.* **1978**, *100*, 4808–4813.
(2) Lavine, T. F., U.S. Patent No. 2465461, Mar. 29, 1949.
(3) (a) Young, P. R.; McMahon, P. E. *J. Am. Chem. Soc.*, preceding paper in this issue. (b) Young, P. R.; Hsieh, L.-S. *J. Am. Chem. Soc.* **1978**, *100*, 7121–7122.
(4) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425–432.

Experimental Section

Kinetic Studies. N-(Substituted benzyl)-S,S-dimethylsulfilimmonium chlorides were prepared from dimethyl sulfide, N-chlorosuccinimide, and the amine as described previously.[3,5] All compounds were recrystallized from dichloromethane/ether mixtures at 4 °C and had melting points and NMR spectra consistent with literature data. All kinetic runs were performed by following the disappearance of thiol anion at either 412 (NTBA)[1] or 270 (TBA) nm with 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 immediately after each run with a Corning pH meter with a combined glass electrode. Observed first-order rate constants were obtained from semilogarithmic plots of $A_\infty - A_t$ against time. Such plots were typically linear for over 4 half-lives. Apparent constants for buffer catalysis were converted to third-order rate constants by dividing by the concentration of thiolate *anion*,[1] calculated from the observed pH and the pK_a of the thiol used. A value of 4.25 was taken for the pK_a of NTBA,[1] and the pK_a of TBA was determined by spectrophotometric titration to be 6.05 at 25 °C and at an ionic strength of 1.0 with KCl. Plots of these third-order rate constants against the fraction of the buffer in the acidic form were linear and passed through zero at 100% buffer base. Values of k_{BH} were obtained by extrapolating to 100% buffer acid. Catalytic constants for strongly acidic buffers were obtained from plots of observed rate constants against total buffer concentration at pH $\simeq4.6$.[6] Acetate buffer (50% ionized, 0.1 M) was used to maintain the pH, and the stock solution of the buffer in question was preadjusted to this pH. The apparent catalytic constants thus obtained were corrected for thiolate anion concentration, as above, and divided by the fraction of the buffer in the acidic form[6] (usually less than 1%). Although acid catalysis being observed at >99% buffer base sounds odd, it is readily apparent[6,7] that under these conditions the ratio between the apparent catalytic constant (the slope) and the observed rate constant for the proton-catalyzed reaction (the intercept) approaches its upper limit. Errors in pK_a, when they occur, are essentially balanced out since that pK_a is also used in the Brønsted correlation.[6]
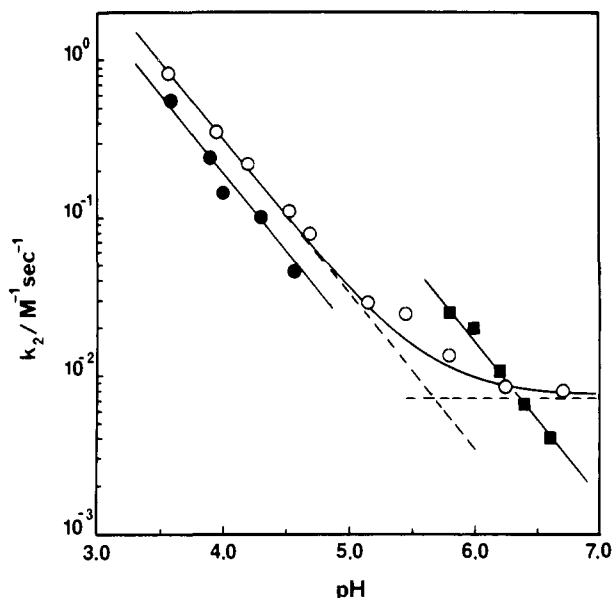
Results and Discussion

The pH dependence of the second-order rate constants for the reduction of I and II by NTBA (O and ●, respectively) and for TBA reduction of I (■) is shown in Figure 1. The data have been corrected for the ionization of the thiol reductant according to the following rate law:

$$v/[RS^-][\text{sulfilimine}] = k_H[H^+] + k_{BH}[BH] + k_s \quad (2)$$

The slopes in Figure 1 are 1.0 ± 0.01. For the NTBA reduction

(5) Dawson, A. D.; Swern, D. *J. Org. Chem.* **1977**, *42*, 592–597.
(6) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 1206–1214.
(7) Jensen, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 1476–1488.

Figure 1. Dependence of pH of the observed second-order rate constants for the reduction of N-benzyl-S,S-dimethylsulfilimmonium chloride by 3-nitro-5-thiobenzoic acid (●) and 3-thiobenzoic acid (■) and for the reduction of N-(4-chlorobenzyl)-S,S-dimethylsulfilimmonium chloride by 3-nitro-5-thiobenzoic acid (O). Aqueous solution, 25 °C, ionic strength 1.0 with KCl.

Table I. Catalytic Constants for Buffer Catalysis of the Reduction of N-(Substituted benzyl)-S,S-dimethylsulfilimines by Thiophenolate Anions[a]

| buffer	pK_a[b]	$k_{BH}/M^{-2} s^{-1}$[c]
N-Benzyl-*S*,*S*-dimethylsulfilimmonium Chloride		
reduction by 3-nitro-5-thiobenzoic acid		
dihydrogen phosphate	6.80	0.620
acetic acid	4.65	3.72
formic acid	3.56	12.95
chloroacetic acid	2.70	31.88
dichloroacetic acid	1.29	199.6
difluoroacetic acid	1.24	211.1
trifluoroacetic acid	0.25	601
H_3O^+	−1.74	3400
reduction by 3-thiobenzoic acid		
acetic acid	4.65	31.7
H_3O^+	−1.74	16500
N-(4-Chlorobenzyl)-*S*,*S*-dimethylsulfilimmonium Chloride		
reduction by 3-nitro-5-thiobenzoic acid		
cacodylic acid	6.27	0.295
acetic acid	4.65	2.50
formic acid	3.56	9.05
chloroacetic acid	2.70	81.0
dichloroacetic acid	1.29	351
difluoroacetic acid	1.24	382
trifluoroacetic acid	0.25	1790
H_3O^+	−1.74	2200

[a] Aqueous solution, 25 °C, ionic strength, 1.0 with KCl. [b] From Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 1228–1235. [c] Catalytic constant for catalysis by the buffer acid.

of I upward curvature is apparent at pH ≥5, and the smooth curve has been drawn for a change to zero slope with an apparent uncatalyzed rate constant $k_s = 7 \times 10^{-3}$ M^{-1} s^{-1}. Third-order rate constants for the proton-catalyzed pathways are collected in Table I.

The observed rate constants for the reduction reaction are systematically increased by the presence of buffer acids. Plots of observed first-order rate constants for the NTBA reduction of I as a function of the concentration of acetate buffers at constant pH for four buffer ratios are shown in Figure 2. Correcting these, and comparable data for other buffers, for the protonation of the thiol anion[1] according to eq 2 and replotting as a function of buffer ratio gives the catalytic constants listed in Table I.
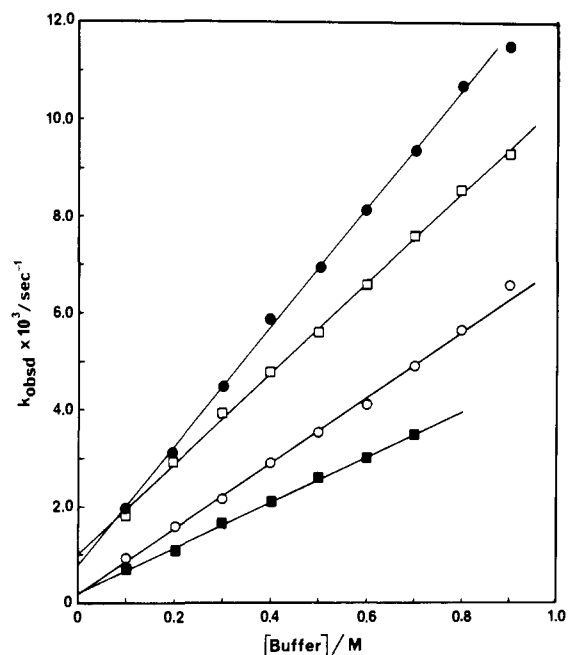
Figure 2. Plot of observed first-order rate constants for the reduction of N-benzyl-S,S-dimethylsulfilimmonium chloride by 3-nitro-5-thiobenzoic acid as a function of the concentration of acetic acid buffers at the following buffer ratios (all as percent acetate anion): (■) 88%; (O) 80%; (□) 30%; (●) 50%. Aqueous solution, 25 °C, ionic strength 1.0 with KCl.
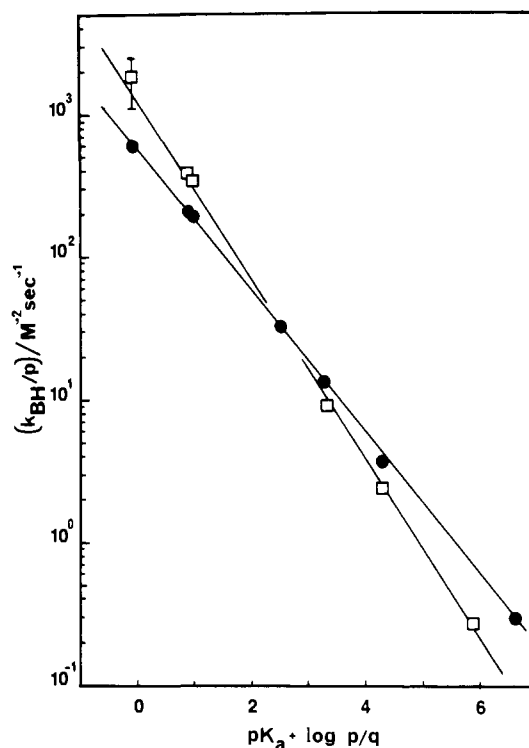
Figure 3. Brønsted plot for buffer catalysis of the reduction of N-benzyl-S,S-dimethylsulfilimmonium chloride (●) and of N-(4-chlorobenzyl)-S,S-dimethylsulfilimmonium chloride (□) by 3-nitro-5-thiobenzoic acid. See the table for the buffers used. Aqueous solution, 25 °C, ionic strength 1.0 with KCl.

The data in the table can be analyzed to yield several interactive structure–reactivity parameters.[8] The most direct is the Brønsted analysis shown in Figure 3 in which the constants for buffer catalysis are plotted against the pK_a of the buffer acid. The slopes
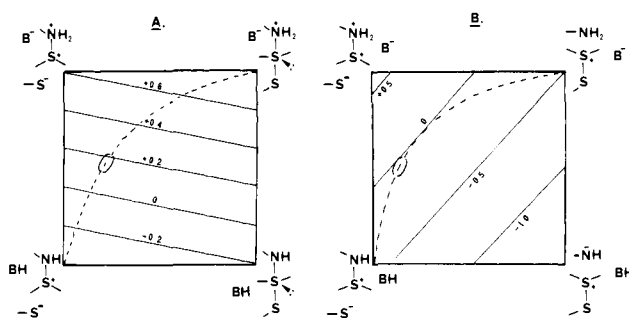
(8) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948–7960.

of these plots are 0.50 and 0.63 for the catalysis of the reduction of I and II, respectively, by NTBA. The data are well described by the linear correlation, the major negative deviations being for catalysis by the solvated proton (not shown). A similar negative deviation for proton catalysis has also been observed for the general catalyzed iodide reduction of sulfilimines,[3] and this systematic deviation has been attributed to a simple electrostatic effect between the cationic acid and sulfilimine. The relationship between the observed Brønsted α and the pK_a of the leaving group is given by the Cordes coefficient[8] $p_{xy} = \partial\alpha/-\partial pK_a(\text{lg}) = 0.54$. This is equivalent to the quantity $\partial\beta_{\text{lg}}/\partial pK_a(\text{BH})$ and values of β_{lg} of -1.1 and $+0.8$ are calculated for the reductions catalyzed by difluoroacetic and acetic acids, respectively. This value of p_{xy} (0.54) is remarkably large relative to the value of about 0.07 observed by Gravitz and Jencks[9] for the general acid catalyzed expulsion of alcohols from phthalimidium addition compounds and values of 0.022[10] and 0.026[11] for nucleophile expulsion from additon intermediates in carbonyl reactions. The observed value of p_{xy} is far too large to have arisen from electrostatic effects not coupled to bonding changes (Hine has estimated this to be about $p_{xy} = 0.024$[12]) and strongly suggests a direct coupling between S–N bond lengthening and proton donation from the general acid. It is unlikely, however, that the magnitude of the p_{xy} coefficient accurately reflects the degree of this coupling. In order to generate such a large change in transition-state structure with such a small perturbation in the pK_a of the leaving group (9.38 for I to 9.14 for II), the potential energy surface for the proton transfer would have to be very "flat" with small barriers for the S–N and B–H motions. In a case such as this, the direct p_x coefficient $\partial\alpha/\partial pK_a(\text{BH})$ would be expected to be quite significant and the Brønsted plots in Figure 3 would show noticeable curvature.[8] It is most probable that the large apparent value of p_{xy} is associated with a substituent effect on the formation of the preassociation complex between the sulfilimine, the general acid, and the thiolate anion. These preassociation substituent effects can be quite large, based on the estimated value of $\rho_{\text{preequil}} > 1$ in the reaction between benzyl bromides and thiolate anions in methanol.[13]

Although the physical meaning of the leaving group effect for the general catalyzed reaction may not be immediately clear due to the preassociation effect cited above, the trends are unambiguous. For strong acids β_{lg} is negative, and for weak acids it is positive. The cross-over point with a β of zero occurs at about the pK_a of chloroacetic acid for the pair of compounds examined in the figure.

The effect of changing the pK_a of the reductant thiol from 4.25 (NTBA) to 6.05 (TBA) on the second-order rate constant for the reduction reaction is to increase the rate constant for the proton-catalyzed reaction by about fivefold. These data can be combined to generate a β_{nuc} of about 0.38 for the proton-catalyzed reaction. For the reduction catalyzed by acetic acid, the change in third-order rate constant is larger (8.5-fold) and the β_{nuc} is about 0.51. These data are comparable in magnitude and direction to the β values calculated from the data reported by Lambeth[1] for the proton and acetic acid catalyzed reduction of dehydromethionine by NTBA and 5-nitro-2-thiopyridine. A direct comparison is not warranted, however, since the latter thiol has considerable α-thione character.

Given the values for the Brønsted α, β_{nuc}, and $\beta_{\text{lg}} \simeq 0$ for a general acid of pK_a 2.3, the position of the transition state and the direction of the reaction coordinate motion can be estimated. For this purpose, we will use a "reaction cube" (Scheme I) as previously described[3] for the iodide reduction of sulfilimines. Briefly, the cubic geometry is required by the simple fact that at least three modes of coupled motion are possible in the general

(9) Gravitz, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 507–515.

(10) Funderburk, L. H.; Aldwin, L.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 5444–5459.

(11) Gilbert, H. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7931–7947.

(12) Hine, J. *J. Am. Chem. Soc.* **1972**, *94*, 5766.

(13) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 3288–3294. It is argued that the observed Hammett ρ values for this reaction result from a substituent effect on the formation of an encounter complex, rather than a "failure" of simple reactivity-selectivity predictions.

Figure 4. Potential energy surfaces (contours omitted) for the reduction of sulfilimines by thiol anions. (A) Reaction surface for the formation of a tetracoordinate sulfurane intermediate. (B) Reaction surface depicting a concerted displacement reaction. In both surfaces the grid represents estimated values of β_{lg} and the dashed line represents the projection of the reaction coordinate in the plane of observation. The projection of the transition state is shown by the curved brackets.

Scheme I
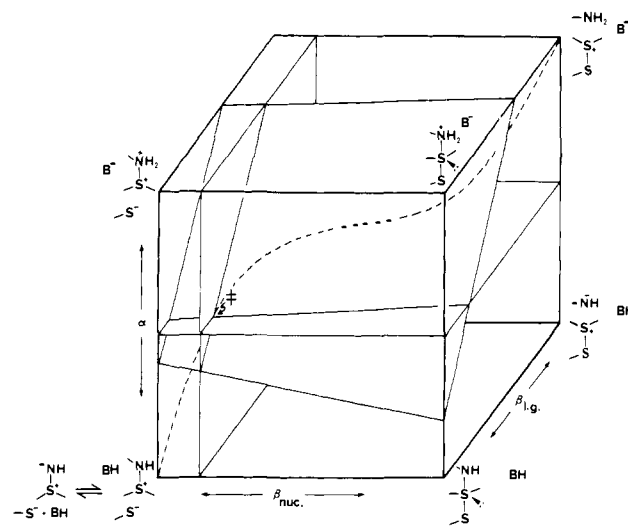
acid catalyzed reaction. In Scheme I, these are represented by the three Brønsted coefficients given above. For a given Brønsted parameter, a plane can be drawn intersecting the cube. The value of that parameter (for example $\alpha = 0.5$) is constant anywhere on the surface of the plane. In Scheme I, simple orthogonal planes are shown for $\alpha = 0.5$ and $\beta_{\text{nuc}} \simeq 0.4$. The plane describing β_{lg} is not simple since apparent changes in the leaving group effect are associated with both intermediate sulfurane formation and actual cleavage of the S–N bond.[3] The assignments of β_{lg} at the vertices of the cube are approximated by using the method described in ref 3, and these same (approximate) values are used in the present case. The plane shown is for $\beta_{\text{lg}} = 0$ and represents the reaction catalyzed by a general acid of pK_a approximately 2.3 (the intersection in Figure 3). The transition state, then, is given by the simple intersection of the three planes.

The data support a transition state that is slightly on the interior of the reaction cube, suggesting a large amount of proton transfer coupled to small and approximately equal changes in S–N and S–S bond lengths. This raises the interesting possibility that the entire reaction may be very highly coupled, that is, that the developing S–S bond order may be described as $(1 - x)$, where x represents the remaining S–N bond order. The question is, simply, whether the reaction coordinate is best described as diagonal along the "front face" of the cube in the scheme or along the plane including starting materials and final products.

These two possibilities are shown in Figure 4, and the estimated position of the transition state in each projection is shown in curved brackets. The grid for each figure corresponds to the values of β_{lg} as viewed from that projection. Two simple exercises allow the direction of the reaction coordinate to be diagnosed: first, lowering the pK_a of the leaving group will destabilize the top edge

of the surface in A resulting in Hammond movement toward the top of the figure and anti-Hammond movement toward the neutral sulfurane intermediate.[8] Of these, the Hammond movement will dominate since the reaction coordinate has a larger vertical component.[8] The resultant will be net movement toward the protonated sulfurane intermediate. This will lead to an *increase* in the Brønsted α value with a decrease in the pK_a of the leaving group. This prediction is consistent with the change in Brønsted α shown in Figure 3. In Figure 4B, lowering the pK_a of the leaving group will have the largest effect on the upper-left and lower-right corners of the diagram.[8] The transition-state motion will be away from the dicationic sulfilimine and toward the nitrogen anion. The net resultant will be anti-Hammond movement toward the lower right with a *decrease* in the Brønsted α as the pK_a of the leaving group decreases. This prediction is contrary to the observed fact.

The second parameter to examine on the surfaces in Figure 4 is the effect of lowering the pK_a of the catalyzing acid. In A, this will result in the raising of the energy of the bottom edge. Coupled movements parallel and perpendicular to the reaction coordinate are predicted with parallel movement again dominating. The resultant is movement toward starting materials with a *decrease* in both β_{lg} and β_{nuc} as the acid strength is increased. Both of these are consistent with the observed data. In Figure 4B, the effect of acid strength will be greatest on the ionic intermediates in the upper-left and lower-right corners. This is because high-energy intermediates tend to dominate changes in potential energy surfaces for S_N2 reactions.[14] This phenomena is most often observed as the dominant anti-Hammond movement in S_N2 and E2 reactions involving benzyl carbons.[15] The effect of the anti-Hammond movement in B is to move the transition state toward the dicationic intermediate with a resulting *increase* in β_{lg} coupled to a decrease in β_{nuc}. The predicted increase in the leaving group effect is inconsistent with the observed facts.

The coupled structure–reactivity data given above are consistent with a reaction coordinate oriented largely across the front face of the cube in the scheme. The *overall* reaction, however, *cannot be stepwise* with the protonated sulfurane as a distinct intermediate since the pK_a of this sulfurane is estimated to be about 2 ± 1.[16] With acetic acid as the general acid the pK_a change for the formation of the sulfurane intermediate is *unfavorable*, hence concerted catalysis of sulfurane formation by acetate is not expected.[17] The first "intermediate", therefore, must be the final product, and the overall reaction is, indeed, an example of a *general catalyzed S_N2 reaction*. The dashed line in the scheme represents a suggested reaction coordinate, proceeding largely in the face of the cube, "missing" the intermediate, and then proceeding toward products. This somewhat circuitous route allows a minimum of coupled motions in the rate-limiting transition state, probably allowing the fully concerted transition state to be observed. There are other reports of general catalyzed S_N2 reactions[18] although they seem to be most often associated with ring-closure reactions, and the Brønsted α values usually reflect a fairly early transition state. In his original study of the thiol reduction of dehydromethionine, the concerted reaction was favored by Lambeth,[1] although insufficient data were available to distinguish the stepwise and concerted reactions. The ability of sulfonium compounds to expand their valence states and exist as sulfuranes no doubt contributes to the relative ease of the concerted reaction, and the sulfonium oxidation state would seem to be a useful system for investigating transitions from stepwise to concerted addition reactions.

(14) Young, P. R.; Ruekberg, B. P. *J. Am. Chem. Soc.*, submitted.
(15) McLennan, D. J.; Wong, R. J. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1373–1380. Schmid, P.; Bourns, A. N. *Can. J. Chem.* **1975**, *53*, 3513–3525. Harris, J. M.; Shafer, S. G.; Morratt, J. R.; Becker, A. R. *J. Am. Chem. Soc.* **1979**, *101*, 3295–3300. Westaway, K. C.; Ali, S. F. *Can. J. Chem.* **1979**, *57*, 1354–1367.

(16) The pK_as for N-protonation of sulfilimines and sulfuranes derived from them are estimated to be about 16 and 7 units, respectively, below the pK_a of the parent amine. See ref 3a.
(17) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705–718.
(18) Cromartie, T. H.; Swain, C. G. *J. Am. Chem. Soc.* **1975**, *97*, 232–237. Knipe, J. O.; Vasquez, P. J.; Coward, J. K. *Ibid.* **1982**, *104*, 3202–3209 and references cited therein. Thibblin. A.; Jencks, W. P. *Ibid.* **1979**, *101*, 4963–4973.

Experimental Search for the Silanone-to-Silylene Rearrangement

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Abstract: Pyrolysis of 1,3,5,7-tetramethyl-1,3,5,7-tetrakis(trimethylsilyl)cyclotetrasiloxane in the presence of 1,3-butadiene affords the silacyclopentene product from trapping of silylene, $Me_3SiOSiMe$. Although this result is consistent with isomerization of silanone, $Me_3Si(Me)Si{=}O$, to the silylene by a 1,2-silyl shift, an alternative route to the silylene cannot be ruled out. No evidence for the reverse reaction, isomerization of $Me_3SiOSiMe$ to the silanone, could be found, although this silylene apparently decomposes to silanones.

Silanones, the silicon analogues of ketones, have frequently been postulated[1] as transient intermediates in a variety of organosilicon reactions since 1952 when Adrianov[2] proposed their involvement in the thermal redistribution of poly(dimethylsiloxanes). Most recently, the silicon–oxygen double bond has been subjected to the scrutiny of theoretical studies[3] which reveal moderate thermodynamic stability, with the C=O bond of formaldehyde being 20 kcal/mol stronger than the Si=O bond of $H_2Si{=}O$.[4] How-

(1) For a general review of π-bonding silicon, see: Gusel'nikov, L. E.; Nametkin, N. S. *Chem. Rev.* **1979**, *79*, 529.
(2) Andrianov, K. A.; Sokolov, N. N. *Dokl. Akad. Nauk SSSR* **1952**, *82*, 909.

(3) Kudo, T.; Nagasse, S. *J. Phys. Chem.* **1984**, *88*, 2833 and references therein.
(4) Gordon, M. S.; George, C. *J. Am. Chem. Soc.* **1984**, *106*, 609. These authors report a difference of only about 10 kcal/mol.