Structure−Reactivity Relationships for Addition of Sulfur Nucleophiles to Electrophilic Carbon: Resonance, Polarization, and Steric/Electrostatic Effects

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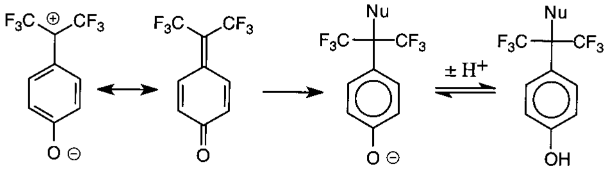
Received June 19, 2000

Abstract: Second-order rate constants k_{RS} and k_{RSH} (M^{-1} s^{-1}) for the direct addition of substituted alkanethiol anions RS^- and neutral thiols RSH and third-order rate constants $(k_{RSH})_H$ (M^{-2} s^{-1}) for acid-catalyzed addition of RSH to the simple quinone methide 4-[bis(trifluoromethyl)methylene]cyclohexa-2,5-dienone (**1**) in water are reported. Rate and equilibrium constants for the addition of Me_2S and H^+ to give **H-1-SMe$_2$$^+$** were also determined. The data for addition of RS^- to **1** are correlated by the Brønsted coefficient $\beta_{nuc} = 0.11$, which is similar to that for addition of RS^- to other highly resonance-stabilized carbocations. The rate constants for addition of RS^- to **1** are similar to those for addition of substituted alkyl alcohol ROH to the much more electrophilic 1-(4-methoxyphenyl)ethyl carbocation (**5**$^+$). The larger value of $\beta_{nuc} = 0.32$ for addition of ROH to **5**$^+$ than $\beta_{nuc} = 0.11$ for addition of RS^- to **1** shows that there are important differences in the reaction coordinate profiles for these nucleophile addition reactions, which are discussed. The transition state for addition of RSH to **1** is stabilized by electron-donating alkyl groups R ($\beta_{nuc} > 0.5$) and by substitution of an electron-donating methyl group for hydrogen at RSH. By contrast, there is relatively little destabilization of the transition state for addition of Me_2S to **1** from interactions between the developing cationic center at the bulky sulfur nucleophile and the electron-withdrawing α-CF_3 groups at **1**. The results suggest that C−S bonding interactions in the transition state for addition of Me_2S to **1** develop at a relatively long distance and that product destabilizing steric/electrostatic interactions become significant only at smaller C−S bond distances, after the transition state has been traversed on the reaction coordinate.

Introduction

Quinone methides are a class of organic compounds with considerable importance in chemistry and biology.[2] We recently reported that the simple quinone methide **1** shows a reactivity similar to other strongly resonance-stabilized carbocations and that there is exceptional scope for study of the addition of weakly nucleophilic reagents to **1**, because the nucleophile adduct **1-Nu** can be stabilized toward C−Nu bond cleavage by protonation at oxygen to give **H-1-Nu** (Scheme 1).[2a] We now report the results of studies of the addition of thiols and dimethyl sulfide to **1**, designed to probe the effects of changing nucleophile and electrophile reactivity on the structure of the transition state for carbocation−nucleophile bond formation. These studies were initiated for the following reasons:

Scheme 1



1 **1-Nu** **H-1-Nu**

(1) We are interested in understanding how the transition state for nucleophile addition changes with *extreme* changes in electrophile reactivity.[3−11] We report here that the Brønsted

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10.1021/ja0021868 CCC: $19.00

parameter $\beta_{nuc} = 0.11$ for addition of strongly nucleophilic thiol anions to the weak electrophile **1**, with rate constants $k_{Nu} \approx 3 \times 10^6$ M^{-1} s^{-1}, is significantly smaller than $\beta_{nuc} = 0.32$ for addition of weakly nucleophilic alcohols to the 1-(4-methoxyphenyl)ethyl carbocation, with rate constants $k_{Nu} \approx 1 \times 10^7$ M^{-1} s^{-1}. This striking observation of similar rate constants, but very different values of β_{nuc}, for two related carbocation−nucleophile addition reactions provides interesting insight into the nature of the reaction coordinate profiles for nucleophile addition.

(2) We were interested in obtaining the first direct comparison of the reactivities of thiol anions and sulfides toward carbocations in water. Such a comparison is difficult because thiol anions are strongly nucleophilic and undergo activation-limited addition only to relatively stable carbocations, and these carbocations do not form stable adducts with the much more weakly nucleophilic sulfides. We report here a comparison of the rate constants for addition of thiol anions (RS^-), thiols (RSH), and dimethyl sulfide (Me_2S) to the common electrophile **1** in water. The data show that the effect of substitution of Me for H at RSH on nucleophilic reactivity in water is a significant fraction of that expected for reaction in the gas phase, where the greater polarizability of the methyl group provides strong stabilization of positive charge at sulfur.[12]

Neutral nucleophiles react with **1** to form a cationic adduct that is stabilized by interactions with electron-donating substituents at the nucleophile and strongly destabilized by interactions with the strongly electron-withdrawing α-CF_3 groups. We were surprised to observe that the partial positive charge that develops at the transition state for addition of Me_2S to **1** is relatively strongly stabilized by interactions with the polarizable methyl groups at Me_2S but that there is apparently little destabilization from interaction of this charge with the strongly electron-withdrawing α-CF_3 groups at **1**. This provides direct evidence that bond formation to the sulfur nucleophile in the transition state develops at a considerable distance but that the destabilizing steric/electrostatic interactions of the bulky sulfur nucleophile and the developing positive charge with the two electron-withdrawing α-CF_3 groups becomes significant only *after* this transition state has been passed on the reaction coordinate.

Experimental Section

Materials. Inorganic salts and organic chemicals were reagent grade from commercial sources and were used without additional purification. HPLC grade methanol was used for all HPLC analyses. The water used for kinetic and product studies was distilled and then passed through a Milli-Q water purification system. The quinone methide 4-[bis(trifluoromethyl)methylene]cyclohexa-2,5-dienone (**1**) was generated from reaction of 4-$MeOC_6H_4C(CF_3)_2OTs$ in 2/1 (v/v) TFE/H_2O (TFE = trifluoroethanol), as described previously.[2a,13] Solutions of methanethiol used in kinetic studies were prepared from methanethiol gas (Aldrich). Methanethiol prepared in this way gave kinetic data that were superior to those obtained when methanethiol was prepared by neutralization of sodium methanethiolate (NaSMe, Aldrich) with $HClO_4$ (see Results).

The pH of aqueous solutions ($I = 1.0$, $NaClO_4$) was determined as described previously.[2a] The apparent pK_as of the thiols at 25 °C and $I = 1.0$ ($NaClO_4$), given by $p(K_a)_{RSH} = pH - \log([RS^-]/[RSH])$, were determined by spectrophotometric titration as described previously.[2a]

Kinetic Studies. Kinetic studies were carried out at 25 °C and $I = 1.0$ ($NaClO_4$) in water that contained 2.5% (v/v) TFE. Solution pH was maintained using the buffers described previously[2a] or with $HClO_4$. The reactions of **1** (*ca*. 1×10^{-5} M) were followed by monitoring the decrease in its absorbance at 283 nm using either the SX17.MV stopped-flow device from Applied Photophysics ($t_{1/2} < 5$ s) or by conventional UV spectrophotometry.[2a] A ≥10-fold molar excess of nucleophile over **1** was used, to ensure that the nucleophile addition reactions were pseudo-first-order. The concentrations of thiols were determined directly before and after each kinetic run using Ellman's reagent [5,5′-dithiobis-(2-nitrobenzoic acid)].[14] In cases where a small change in the concentration of thiol was observed during the kinetic analysis (≤7%) the reported value is the average of the thiol concentrations determined at the beginning and end of the run.

Observed first-order rate constants, k_{obsd} (s^{-1}), for the reactions of **1** were determined as the negative slopes of linear semilogarithmic plots of reaction progress against time (conventional UV) or from the fit of the absorbance data to a single exponential (stopped-flow) and were reproducible to ±5%. Second-order rate constants, $(k_{Nu})_{obsd}$ (M^{-1} s^{-1}), for addition of nucleophiles to **1** were determined as the slopes of linear plots of k_{obsd} against the total concentration of the nucleophile. The standard errors in these slopes were <10%, unless noted otherwise. The quoted errors for least-squares fits of data are standard deviations.

Two well-resolved phases were observed for the reactions of **1** in the presence of dimethyl sulfide that were followed by monitoring the absorbance at 283 nm as a function of time: (1) an initial fast decrease in absorbance from A_o to A_{eq} ($t_{1/2} \leq 15$ ms, stopped-flow); (2) a subsequent much slower decrease from A_{eq} to A_∞ ($t_{1/2} \geq 30$ s, conventional UV). Values of k_{obsd} (s^{-1}) for the fast and slow phases differ by at least 2000-fold and were obtained from the fit to a single exponential and the slopes of linear semilogarithmic plots of $(A_{eq} - A_\infty)$ against time, respectively.

HPLC Analysis. The products of the reaction of **1** in the presence of dimethyl sulfide (**H-1-OH** and **H-1-SMe)** were separated by HPLC and detected by their absorbance at 268 nm, as described previously.[2a] Ratios of product yields were calculated using eq 1, where A_1 and A_2, and ϵ_1 and ϵ_2, are the HPLC peak areas and extinction coefficients at 268 nm (λ_{max} for **H-1-OH**) for P_1 and P_2, respectively. A value of $\epsilon_{\mathbf{H-1-SMe}}/\epsilon_{\mathbf{H-1-OH}} = 1.1$ for the adduct of MeSH to **1** was determined from the ratios of the HPLC peak areas in experiments in which a fixed concentration of **1** was converted quantitatively into **H-1-OH** by addition of water or **H-1-SMe** by direct addition of MeSH.

$$[P]_1/[P]_2 = (A_1/A_2)(\epsilon_2/\epsilon_1) \qquad (1)$$

Determination of Equilibrium Constants. Ratios of the concentrations of **H-1-SMe$_2^+$** and **1** at chemical equilibrium were determined at 25 °C and $I = 1.0$ ($NaClO_4$) in water that contained 2.5% (v/v) TFE from data obtained from experiments conducted as follows: (1) A solution of **1** in 2/1 (v/v) TFE/H_2O was diluted 100-fold with rapid stirring into a sealed spectrophotometric cell that contained 1.0 M $HClO_4$, to give a final concentration of 2×10^{-5} M **1**. (2) The absorbance at 283 nm, A_{t1}, was recorded 20 s after mixing (t_1). (3) At time t_2 (ca. 25 s), a measured volume of a solution of Me_2S in TFE was added with stirring. This generates an equilibrium mixture of **1** and **H-1-SMe$_2^+$** essentially instantaneously. (4) The absorbance of this mixture at 283 nm, A_{t3}, was recorded at t_3 (ca. 30 s). (5) The reaction was followed until there was complete decay of **1** and the final absorbance A_∞ was recorded. The ratio of [**H-1-SMe$_2^+$**]$_{eq}$ and [**1**]$_{eq}$ at chemical equilibrium was calculated from eq 2, where the following holds: (1) A_o is the calculated absorbance due to the quinone methide *before* the addition of Me_2S at time t_2. This was determined from A_{t1} using eq 3 to make a small 5−10% correction for the decrease in absorbance due to addition of solvent to **1** with a rate constant k_1 during the time that Me_2S was prepared for mixing with **1** ($t_2 - t_1$). The value of k_1 was determined by monitoring the entire time course

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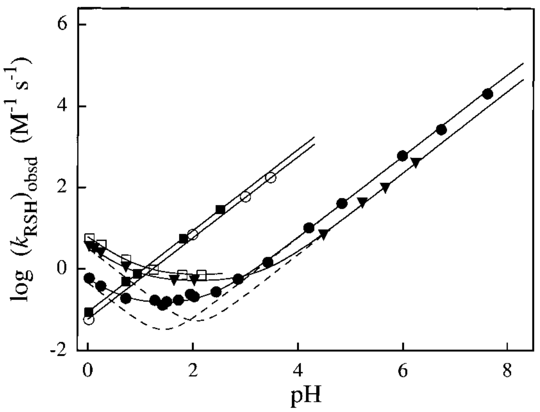


Figure 1. pH−rate profiles of the observed second-order rate constants $(k_{RSH})_{obsd}$ $(M^{-1}\ s^{-1})$ for the addition of thiols to the quinone methide **1** in water at 25 °C and $I = 1.0$ ($NaClO_4$). The solid lines show the fits of the data to eq 5, and the dashed lines show the fits of the data for mercaptoethanol and propanethiol to eq 5 with $k_{RSH} = 0$ (see text). Key: (■) data for trifluoroethanethiol; (○) data for methyl mercaptoacetate; (●) data for mercaptoethanol; (□) data for methanethiol; (▼) data for propanethiol.

for the decay of **1** under the same reaction conditions, but without the addition of Me_2S.

$$\frac{[\mathbf{H\text{-}1\text{-}SMe_2}^+]_{eq}}{[\mathbf{1}]_{eq}} = \frac{A_o - A_{eq}}{A_{eq}} \tag{2}$$

$$A_o = A_{t1} e^{-k1(t2-t1)} \tag{3}$$

$$A_{eq} = \frac{A_{t3} - A_{sulfide}}{e^{-k2(t3-t2)}} \tag{4}$$

(2) A_{eq} is the calculated absorbance due to **1** in the equilibrium mixture of **1** and **H-1-SMe$_2$$^+$**. This was determined from A_{t3} using eq 4, where $A_{sulfide}$ is the absorbance of a solution that contains only Me_2S. This correction is necessary because there is a small decrease in absorbance (≤5%) between the time that equilibrium is established by mixing Me_2S and **1** (t_2) and the time that the absorbance due to the "equilibrium" concentration of **1** was actually determined (t_3). This is due to the irreversible reaction of **1** in the equilibrium mixture of **1** and **H-1-SMe$_2$$^+$**, with a rate constant k_2 that was determined by monitoring the entire time course for decay of the equilibrium mixture of **1** and **H-1-SMe$_2$$^+$**. The absorbance of **H-1-OH** at 283 nm is negligible ($A_\infty \approx A_{sulfide}$), and it is assumed that the nucleophile adducts **H-1-SMe$_2$$^+$** and **H-1-OH** have identical extinction coefficients at 283 nm,[2a,7] so that the absorbance of **H-1-SMe$_2$$^+$** is also negligible.

Results

Reactions of Solvent. A value of $k_o = 6.4 \times 10^{-4}\ s^{-1}$ has been reported for spontaneous addition of solvent water to **1** at 25 °C and $I = 1.0$ ($NaClO_4$),[2a] and a value of $k_H = 2.1 \times 10^{-2}\ M^{-1}\ s^{-1}$ under the same conditions was determined in this work for specific acid-catalyzed addition of water to **1**, as the slope of a plot of the observed rate constants for reaction of **1** against $[H^+]$.

Reactions of Thiols. Figure 1 shows pH−rate profiles for the observed second-order rate constants $(k_{RSH})_{obsd}$ $(M^{-1}\ s^{-1})$ for the reaction of several thiols with **1** in water at 25 °C and $I = 1.0$ ($NaClO_4$). The linear regions of these profiles have slopes of 1.0 ($pH \ll p(K_a)_{RSH}$), and the observed reaction is due essentially entirely to addition of the thiol anion RS^- to **1**, k_{RS} ($M^{-1}\ s^{-1}$, Scheme 2). The averages of the values of $k_{RS} = (k_{RSH})_{obsd}/f_{RS}$ determined at several pH values, where f_{RS} is the fraction of the thiol present in the reactive thiol anion form, are reported in Table 1.

Scheme 2

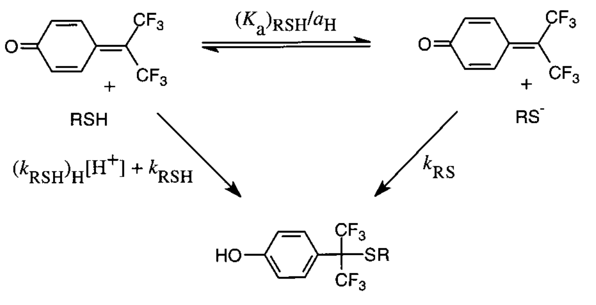


Table 1. Second-Order Rate Constants for Addition of Thiol Anions RS^- and Neutral Thiols RSH and Third-Order Rate Constants for Specific-Acid-Catalyzed Addition of RSH to the Quinone Methide **1** in Water[a]

nucleophile	$p(K_a)_{RSH}$[b]	k_{RS}[c,d] $(M^{-1}\ s^{-1})$	k_{RSH}[d,e] $(M^{-1}\ s^{-1})$	$(k_{RSH})_H$[d,f] $(M^{-2}\ s^{-1})$
$CH_3CH_2CH_2SH$	10.3	$(4.6 \pm 0.4) \times 10^6$	0.47 ± 0.1	3.2 ± 0.1
CH_3SH	10.2[g]		0.68 ± 0.03	5.1 ± 0.2
$HOCH_2CH_2SH$	9.7	$(3.0 \pm 0.5) \times 10^6$	0.12 ± 0.02	0.46 ± 0.02
MeO_2CCH_2SH	7.8	$(3.7 \pm 0.9) \times 10^6$	<0.03[h]	
CF_3CH_2SH	7.2	$(1.4 \pm 0.1) \times 10^6$	<0.05[h]	

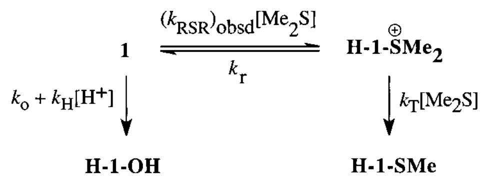
[a] At 25 °C and $I = 1.0$ ($NaClO_4$). [b] Apparent pK_a of the thiol at 25 °C. [c] Second-order rate constant for addition of RS^- to **1**. The errors show the range of the values calculated for reactions at different pH. [d] The rate constants were determined as described in the text by analysis of the data from Figure 1. [e] Second-order rate constant for uncatalyzed addition of RSH to **1**. The errors show the range of values of k_{RSH} from Figure S1. [f] Third-order rate constant for specific-acid-catalyzed addition of RSH to **1** determined as the slope of a plot of observed second-order rate constants against $[H^+]$. The errors show the standard deviation of this slope. [g] Estimated with the assumption that the difference in the pK_as of methyl mercaptoacetate (7.8, this table) and MeSH is the same as the 2.4 unit difference in the pK_as of ethyl mercaptoacetate and MeSH determined at 25 °C and unspecified ionic strength.[43] [h] Upper limit, estimated as described in the text.

The addition of the thiol anion RS^- is the only detectable pathway for the reactions of methyl mercaptoacetate (MeO_2CCH_2SH) and trifluoroethanethiol (CF_3CH_2SH) with **1** at low pH in solutions containing up to 1.0 M $HClO_4$ (Figure 1). The solid lines in Figure 1 show the fits of the data for the reactions of these nucleophiles to eq 5, derived for Scheme 2, calculated from the values of k_{RS} (Table 1) and $(k_{RSH})_H = k_{RSH} = 0$. Upper limits of $k_{RSH} < 0.03\ M^{-1}\ s^{-1}$ and $< 0.05\ M^{-1}\ s^{-1}$ (Table 1) were estimated for the uncatalyzed addition of MeO_2CCH_2SH and CF_3CH_2SH, respectively, to **1**, with the assumption that a 0.2 log unit positive deviation of $\log(k_{RSH})_{obsd}$ from the fits shown in Figure 1 could have been detected for reactions of these thiols in the presence of 1.0 M $HClO_4$.

$$(k_{RSH})_{obsd} = (k_{RSH})_H[H^+] + k_{RSH} + k_{RS}\left[\frac{(K_a)_{RSH}}{a_H + (K_a)_{RSH}}\right] \tag{5}$$

The observed rate constants $(k_{RSH})_{obsd}$ $(M^{-1}\ s^{-1})$ for the reactions of basic thiols with **1** increase with increasing $[H^+]$ (Figure 1) due to acid-catalyzed reactions of these nucleophiles. Third-order rate constants $(k_{RSH})_H$ $(M^{-2}\ s^{-1})$ for the acid-catalyzed addition of RSH to **1** (Table 1) were calculated as the slopes of linear plots of $[(k_{RSH})_{obsd} - k_{RS}f_{RS}]$ against $[H^+]$ (Figure S1A of the Supporting Information), according to eq 5. The dashed lines in Figure 1 correspond to values of $(k_{RSH})_{obsd}$

Scheme 3



for the reactions of propanethiol (PrSH) and mercaptoethanol ($HOCH_2CH_2SH$) that were calculated from the values of k_{RS} and $(k_{RSH})_H$ (Table 1) and $k_{RSH} = 0$ using eq 5. The differences between the experimental values of $(k_{RSH})_{obsd}$ for these nucleophiles and those defined by the corresponding dashed line are independent of $[H^+]$ (Figure S1B of the Supporting Information) and are equal to the rate constant for uncatalyzed addition of the neutral thiol to **1**, k_{RSH} (M^{-1} s^{-1}, Table 1). The solid lines through the data for the reactions of PrSH and $HOCH_2CH_2SH$ in Figure 1 show the fits of the data to eq 5, calculated from the values of k_{RS}, $(k_{RSH})_H$, and k_{RSH} (Table 1).

Figure 1 includes rate constants $(k_{RSH})_{obsd}$ (M^{-1} s^{-1}) for addition of MeSH to **1** at pH ≤ 2.2; these reactions were cleanly first-order in [**1**]. At pH > 2.2 biphasic kinetics were observed; these deviations from first-order kinetics were more severe and occurred at lower pH for reactions in the presence MeSH that was prepared from NaSMe rather than gaseous MeSH. This suggests that these deviations from first-order kinetics are due to a basic contaminant that is present at higher levels in solutions of MeSH prepared from commercial NaSMe.

The third-order rate constant $(k_{RSH})_H$ (M^{-2} s^{-1}) for acid-catalyzed addition of MeSH to **1** (Table 1) was determined as the slope of the linear plot of $(k_{RSH})_{obsd}$ against $[H^+]$ (inset, Figure S1A). The rate constant k_{RSH} (M^{-1} s^{-1}, Table 1) for the uncatalyzed addition of MeSH to **1** was calculated as the average of the values of $\{(k_{RSH})_{obsd} - (k_{RSH})_H[H^+]\}$ determined for reactions at four different pH values between 0.8 and 2.2 (inset, Figure S1B). The observation that the difference $\{(k_{RSH})_{obsd} - (k_{RSH})_H[H^+]\}$ is constant (±10%) over this pH range shows that the contribution of reaction of the thiol anion ($k_{RS}f_{RS}$) to $(k_{RSH})_{obsd}$ (Scheme 2) is small for reactions of MeSH at pH ≤ 2.2.

Reactions of Sulfides. The reactions of **1** with dimethyl sulfide in acidic solution in water at 25 °C and $I = 1.0$ ($NaClO_4$) exhibit two very well resolved kinetic phases. There is an initial rapid ($t_{1/2} \leq 15$ ms) 10−60% decrease in the absorbance of **1** at 283 nm, followed by a much slower ($t_{1/2} \geq 30$ s) decrease in absorbance. First-order rate constants, k_{obsd} (s^{-1}), for the fast and slow reactions of **1** were determined as described in the Experimental Section. The fast reaction corresponds to the approach to an equilibrium mixture of **1** and the dimethyl sulfide adduct $\mathbf{H\text{-}1\text{-}SMe_2}^+$. Values of $[\mathbf{H\text{-}1\text{-}SMe_2}^+]_{eq}/[\mathbf{1}]_{eq}$ at chemical equilibrium were determined as described in the Experimental Section. Figure S2 of the Supporting Information shows the linear plot of $[\mathbf{H\text{-}1\text{-}SMe_2}^+]_{eq}/[\mathbf{1}]_{eq}$ against $[Me_2S]$ for reactions at $[HClO_4] = 1.0$ M according to eq 6 derived for Scheme 3; the slope gives the overall equilibrium constant $K_{RSR} = (60 \pm 0.7)$ M^{-2} for addition of Me_2S and H^+ to **1** to form $\mathbf{H\text{-}1\text{-}SMe_2}^+$.

$$\frac{[\mathbf{H\text{-}1\text{-}SMe_2}^+]_{eq}}{[\mathbf{1}]_{eq}} = [H^+][Me_2S]K_{RSR} \qquad (6)$$

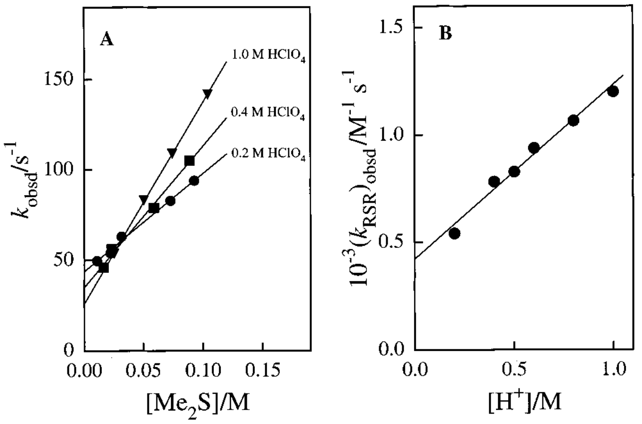


Figure 2. (A) Dependence of k_{obsd} (s^{-1}) for the fast reversible addition of Me_2S to **1** on the concentration of Me_2S in the presence of different fixed concentrations of $HClO_4$ in water at 25 °C and $I = 1.0$ ($NaClO_4$). The slopes of these plots give the observed second-order rate constants $(k_{RSR})_{obsd}$ (M^{-1} s^{-1}) for addition of Me_2S to **1**. (B) Dependence of $(k_{RSR})_{obsd}$ (M^{-1} s^{-1}) for the addition of Me_2S to **1** on the concentration of hydrogen ion in water at 25 °C and $I = 1.0$ ($NaClO_4$). The slope of this plot gives $(k_{RSR})_H = 800$ M^{-2} s^{-1}, and the intercept gives $k_{RSR} = 430$ M^{-1} s^{-1} for the acid-catalyzed and uncatalyzed addition of Me_2S to **1**, respectively.

(a) Fast Reaction of 1 in the Presence of Dimethyl Sulfide. The rate constants k_{obsd} (s^{-1}) for the fast approach of the mixture of **1** to chemical equilibrium with $\mathbf{H\text{-}1\text{-}SMe_2}^+$ (Scheme 3) are equal to the sum of the rate constants for reaction in the forward and reverse directions (eq 7). Figure 2A shows the dependence of k_{obsd} (s^{-1}) for approach to equilibrium for the reactions of **1** on the concentration of dimethyl sulfide in the presence of fixed concentrations of $HClO_4$. The slopes of these linear correlations give $(k_{RSR})_{obsd}$ (M^{-1} s^{-1}) for formation of $\mathbf{H\text{-}1\text{-}SMe_2}^+$ in the forward direction, and the intercepts give k_r (s^{-1}) for the reverse cleavage reaction (Scheme 3 and eq 7). Figure 2B shows the dependence of $(k_{RSR})_{obsd}$ (M^{-1} s^{-1}) on $[H^+]$ according to eq 8; the increases in $(k_{RSR})_{obsd}$ with increasing $[H^+]$ represent acid catalysis of the addition of dimethyl sulfide to **1**. The slope and intercept of this plot give $(k_{RSR})_H = 800 \pm 60$ M^{-2} s^{-1} and $k_{RSR} = 430 \pm 40$ M^{-1} s^{-1} for specific-acid-catalyzed and uncatalyzed addition of Me_2S to **1**, respectively.

$$k_{obsd} = k_r + (k_{RSR})_{obsd}[Me_2S] \qquad (7)$$

$$(k_{RSR})_{obsd} = k_{RSR} + (k_{RSR})_H[H^+] \qquad (8)$$

$$k_r = \frac{(k_{RSR})_{obsd}}{K_{RSR}[H^+]} \qquad (9)$$

Rate constants k_r (s^{-1}) for cleavage of $\mathbf{H\text{-}1\text{-}SMe_2}^+$ to give **1**, Me_2S, and H^+ were determined by two methods: (1) (□, Figure 3) Values of k_r were determined by extrapolation of the values of k_{obsd} for approach to chemical equilibrium to $[Me_2S] = 0$ (Figure 2A). (2) (●, Figure 3) Values of k_r were calculated from the values of $(k_{RSR})_{obsd}$ determined from the slopes of the plots in Figure 2A and the overall equilibrium constant $K_{RSR} = 60$ M^{-2} using eq 9. There is fair to good agreement between the values of k_r determined by these two methods. However, there is a larger uncertainty in the values of k_r determined by extrapolation to $[Me_2S] = 0$ for reactions in the presence of high $[H^+]$ (Figure 2A). This is reflected in the relatively large differences in the values of k_r obtained by extrapolation of different sets of experimental data (Figure 3, □). By contrast, there is much better reproducibility of the values of k_r determined by the second method.

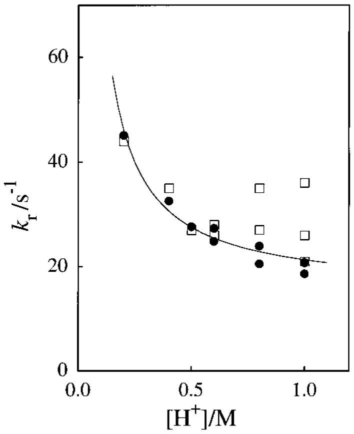


Figure 3. Dependence of the first-order rate constant k_r (s^{-1}) for the breakdown of **H-1-SMe₂**$^+$ to give **1**, Me_2S, and H^+ on the concentration of hydronium ion in water at 25 °C and $I = 1.0$ ($NaClO_4$). Key: (□) values of k_r determined as the intercepts of plots such as those in Figure 2A; (●) values of k_r determined from the slopes of plots such as those in Figure 2A, according to eq 9 (see text). The solid line shows the fit of the data (●) to eq 10 (see text).

The data in Figure 3 shows that there are two pathways, with different dependencies on [H^+], for the cleavage of **H-1-SMe₂**$^+$ in water. These correspond to the microscopic reverse of the pathways for formation of this adduct. The reverse of the acid-catalyzed addition of Me_2S to **1** is the uncatalyzed cleavage of **H-1-SMe₂**$^+$ to give **1**, H^+, and Me_2S, with a rate constant $k_{solv}{}^{H}$ (s^{-1}) (eq 10). The reverse of the uncatalyzed addition of Me_2S to **1** is specific-base-catalyzed cleavage of **H-1-SMe₂**$^+$ through the intermediate phenoxide anion **1-SMe₂**$^+$, with an apparent rate constant of $k_{solv}'/[H^+]$ (s^{-1}). The solid line in Figure 3 shows the nonlinear least-squares fit of the experimental data determined using the second method (see above) and averaging the points at high acid concentrations to eq 10, which gave $k_{solv}{}^{H} = 15.2 \pm 1.1$ s^{-1} and $k_{solv}' = 6.2 \pm 0.4$ M s^{-1}, respectively, for the uncatalyzed and specific-base-catalyzed cleavage of **H-1-SMe₂**$^+$. We have used the data for the second method (Figure 3, ●) because the precision of these data is better than those determined by the first method (Figure 3, □).

$$k_r = k_{solv}'/[H^+] + k_{solv}{}^{H} \tag{10}$$

(b) Slow Reaction of 1 in the Presence of Dimethyl Sulfide. Figure 4A shows the dependence of k_{obsd} (s^{-1}) for the *slow* irreversible reaction of the rapidly equilibrating mixture of **1** and **H-1-SMe₂**$^+$ on the concentration of dimethyl sulfide in the presence of different fixed concentrations of $HClO_4$. The decrease in k_{obsd} with increasing [Me_2S] reflects the decrease in the fraction of substrate present as **1**, which is the form that undergoes irreversible addition solvent water to give **H-1-OH**. The value of $[\mathbf{1}]_{eq}$ will approach zero at high [Me_2S], where its conversion to **H-1-SMe₂**$^+$ is essentially quantitative. By contrast, k_{obsd} for the slow reaction of **1** in the presence of high [Me_2S] does not approach zero (Figure 4A). This shows that there is an additional pathway for the direct conversion of **H-1-SMe₂**$^+$ to a stable product.

HPLC product analysis showed that the reaction of Me_2S with **H-1-SMe₂**$^+$ gives **H-1-SMe** and, we presume, Me_3S^+. Figure 4B shows the effect of increasing [Me_2S] on the product ratio [**H-1-SMe**]/[**H-1-OH**] for the reactions of **1** in water in the presence of 1.0 M $HClO_4$; the inset shows the linear dependence of this product ratio on $[Me_2S]^2$, according to eq 11 derived for Scheme 3. The second-order rate constant $k_T = 7.4 \times 10^{-3}$ M^{-1} s^{-1} for methyl group transfer from **H-1-SMe₂**$^+$ to Me_2S (Scheme 3) was calculated from the slope of the plot in the inset to Figure 4B using eq 11 with $K_{RSR} = 60$ M^{-2}, $k_o = 6.4 \times 10^{-4}$ s^{-1}, and $k_H = 2.1 \times 10^{-2}$ M^{-1} s^{-1}. The solid lines in Figure 4B show the fit of the product data to eq 11, calculated using these rate and equilibrium constants. The solid lines in Figure 4A show the fit of the kinetic data for these reactions to eq 12 using these same rate and equilibrium constants. The good quality of these fits provides strong evidence that Scheme 3 accounts for all of the kinetically significant pathways for the reactions of **1** and **H-1-SMe₂**$^+$.

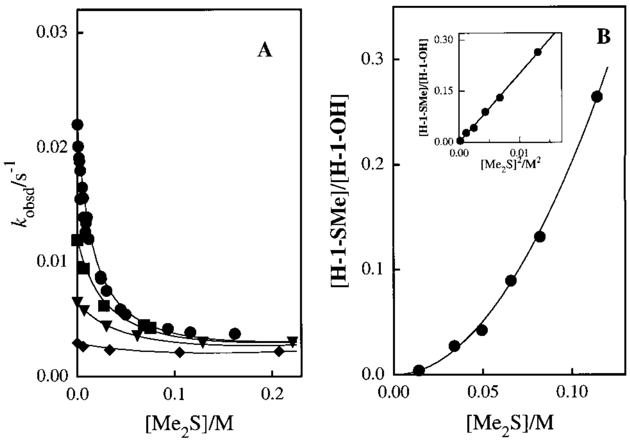


Figure 4. (A) Dependence of k_{obsd} (s^{-1}) for the slow irreversible reaction of an equilibrium mixture of **1** and **H-1-SMe₂**$^+$ on the concentration of Me_2S in the presence of different fixed concentrations of $HClO_4$ in water at 25 °C and $I = 1.0$ ($NaClO_4$). Key: (●) [$HClO_4$] = 1.0 M; (■) [$HClO_4$] = 0.5 M; (▼) [$HClO_4$] = 0.25 M; (◆) [$HClO_4$] = 0.1 M. (B) Dependence of the product ratio [**H-1-SMe**]/[**H-1-OH**] for the reaction of **1** on [Me_2S] and on $[Me_2S]^2$ (inset) in the presence of 1.0 M $HClO_4$ in water at 25 °C and $I = 1.0$ ($NaClO_4$). The solid lines show the fit of the data to eq 11 derived for Scheme 3.

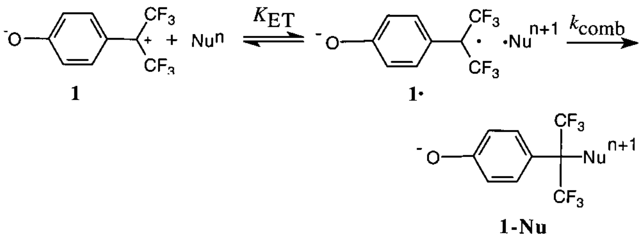
$$\frac{[\textbf{H-1-SMe}]}{[\textbf{H-1-OH}]} = \left(\frac{k_T K_{RSR}[H^+]}{k_o + k_H[H^+]}\right)[Me_2S]^2 \tag{11}$$

$$k_{obsd} = \frac{k_o + k_H[H^+] + k_T K_{RSR}[H^+][Me_2S]^2}{1 + K_{RSR}[H^+][Me_2S]} \tag{12}$$

Discussion

Reaction Mechanisms. The reactions of the quinone methide **1** in the presence of substituted alkanethiols are cleanly first-order with respect to [**1**] for at least 3 halftimes, except for reactions in the presence of methanethiol at pH > 2.2, for which biphasic kinetics were observed. The deviations from first-order kinetics were more severe and occurred at lower pH when solutions of MeSH were prepared from commercial sodium methanethiolate than when prepared from commercial gaseous methanethiol. This suggests that they may be due to a contaminant present at different levels in these different preparations that ionizes to a more reactive form at higher pH. We were not able to identify this putative contaminant(s) or determine the origin of these complex kinetics. However, only a single product was observed for the reactions of **1** with MeSH. Furthermore, propanethiol, which has a pK_a similar to that of MeSH, undergoes clean pseudo-first-order reactions with **1** at pH 0−6, and the second-order rate constants $(k_{RSH})_{obsd}$ (M^{-1} s^{-1}) determined for the reactions of PrSH and MeSH with **1** at pH < 2.2 are similar (Table 1). This provides good evidence

Scheme 4

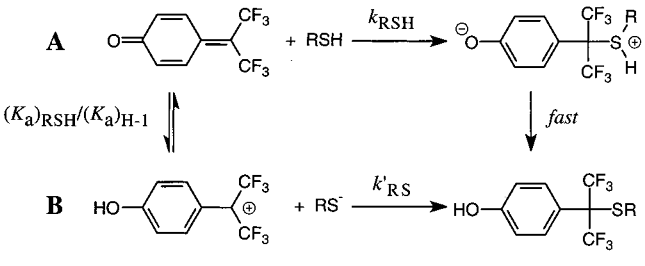


that the observed first-order rate constants k_{obsd} (s^{-1}) that we were able to determine for the reaction of **1** in the presence of MeSH are those for the nucleophilic addition of this thiol to **1**.

(a) The SET Problem. We expect nucleophile addition to **1** to proceed by classical *direct addition* observed for other benzylic carbocations rather than with stepwise electron transfer followed by collapse of radical intermediates to products (Scheme 4) for the following reasons: (1) We have no evidence that the mechanism for addition of nucleophiles to **1** is different from the mechanism for nucleophile addition to related benzylic carbocations. (2) The difference in activation barriers for addition of different nucleophiles to **1** according to Scheme 4 will be approximately equal to the difference in the barriers for unfavorable electron transfer from these nucleophiles to **1** ($\Delta\Delta G_{ET}$, Scheme 4), and the barrier for favorable radical combination should be largely independent of the radical. Therefore, the observation that the difference in the activation barriers for addition for dimethyl sulfide and propanethiol anion to **1** ($\Delta\Delta G^{\ddagger} = 5.6$ kcal/mol)[15a] is less than one-third of $\Delta\Delta G_{ET} = 20$ kcal/mol (Scheme 4) for electron transfer to **1** calculated from the difference in the standard reduction potentials for dimethyl sulfide radical cation (1.61 V) and propanethiol radical (0.74 V) in water[15b] shows that both nucleophiles cannot react by a common electron-transfer pathway. (3) The relatively low reduction potential of propanethiol radical favors the formation of this radical from the propanethiol anion (Scheme 4). However, the low activation barriers for nucleophile addition of thiolate ions to **1** (Table 1) requires a small positive value for ΔG_{ET} ($\Delta G_{ET} \leq \Delta G^{\ddagger}$) for Scheme 4 to be kinetically viable, and there is good evidence that the observed barrier to addition of $CH_3CH_2CH_2S^-$ ($\Delta G^{\ddagger} \approx 8.3$ kcal/mol)[16a] is smaller than ΔG_{ET} for electron transfer from the thiol anion to **1**.[16b]

(b) pH−Rate Profiles. The pH−rate profiles (Figure 1) show that there are three pathways for the nucleophilic addition of thiols to **1**: (1) specific base-catalyzed addition of the neutral thiol, which corresponds to direct nucleophilic addition of the thiol anion; (2) formal nucleophilic addition of the neutral thiol; (3) specific-acid-catalyzed nucleophilic addition of the neutral thiol. All three pathways are kinetically significant for addition of the strongly basic thiols PrSH and $HOCH_2CH_2SH$ to **1**. However, the dominant pathway for addition of the weakly basic thiols MeO_2CCH_2SH and CF_3CH_2SH remains the addition of the thiol anion in solutions containing up to 1.0 M $HClO_4$ (Figure 1). While the mechanisms for the specific-acid- and specific-base-catalyzed addition of thiols to **1** are unambiguous, there are two kinetically equivalent pathways, with identical stoichiometry, for the pH-independent formal addition of neutral thiols to **1**: (1) direct nucleophilic addition of RSH through transition state **2** (Scheme 5A; Chart 1); (2) specific acid catalysis of nucleophilic addition of RS^- through transition state **3** (Scheme 5B).

Scheme 5



Reaction of PrSH, MeSH, and $HOCH_2CH_2SH$ through pathway B in Scheme 5 is unlikely because these thiols are weakly acidic and **1** is very weakly basic, so that the product of the concentrations of **H-1** and RS^- in water should be very small. This mechanism can be effectively eliminated by application of eq 13, which relates k_{RSH} for the *formal* uncatalyzed addition of bulk thiol to **1** to k_{RS}' for addition of RS^- to the protonated quinone methide **H-1** in a stepwise mechanism (Scheme 5). Substitution of the values of $k_{RSH} = 0.12$ M^{-1} s^{-1} for addition of $HOCH_2CH_2SH$ to **1** (Table 1), $(K_a)_{RSH} = 10^{-9.7}$ (Table 1), and $(K_a)_{H-1} = 10^{8.1}$ ($pK_a = -8.1$)[13b] into eq 13 gives $k_{RS}' \approx 10^{17}$ M^{-1} s^{-1} for addition of RS^- to **H-1** (Scheme 5B). This rate constant, which is required if reaction with preequilibrium proton transfer to **1** is to account for the observed value of $k_{RSH} = 0.12$ M^{-1} s^{-1}, is 10^7-fold larger than the limiting value of $k_{RS}' \leq 10^{10}$ M^{-1} s^{-1} for addition of RS^- to **H-1**, which is the rate constant for diffusion-controlled bimolecular carbocation−nucleophile combination.[17] Therefore, even diffusion-controlled addition of $HOCH_2CH_2S^-$ to **H-1** is *far too slow* to account for the observed values of k_{RSH} for addition of PrSH, MeSH, and $HOCH_2CH_2SH$ to **1** (Table 1). We conclude that the pH-independent reaction of these thiols (Figure 1) corresponds to direct nucleophilic addition of the neutral thiol to **1** through transition state **2**.

$$k_{RSH} = \left(\frac{(K_a)_{RSH}}{(K_a)_{H-1}}\right)k_{RS}' \qquad (13)$$

Brønsted Parameters. The uncatalyzed and specific-acid-catalyzed pathways for the addition of strongly basic, but not

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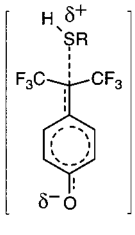
[15] (a) Calculated from the ratio of the second-order rate constants for addition of propanethiolate ($k_{RS} = 4.6 \times 10^6$ M^{-1} s^{-1}, Table 1) and dimethyl sulfide ($k_{RSR} = 430$ M^{-1} s^{-1}) to **1**. (b) Pearson, R. G. *J. Org. Chem.* **1987**, *52*, 2131−2136. (c) Itoh, T.; Tosiyuki, W.; Iwatsuki, S. *J. Polym. Sci., Part A: Polym. Chem.* **1996**, *34*, 963−969

[16] (a) Estimated using the Eyring equation [$\Delta G^{\ddagger} = 17.4 - 1.36(\log k_{RS})$] and $k_{RS} = 4.6 \times 10^6$ M^{-1} s^{-1} from Table 1. (b) The value of ΔG_{ET} can be calculated from eq 14 (Scheme 4),

$$\Delta G_{ET} = \Delta G_{RS} - \Delta G_{comb} \qquad (14)$$

where ΔG_{RS} is the overall equilibrium constant for addition of the thiol anion to **1**. A value of $\Delta G_{RS} \approx -20$ kcal/mol for addition of propanethiolate ion has been estimated from the following: (a) the value of $K_{RS} = 8 \times 10^2$ M^{-1} for addition of propanethiolate ion to the tris(4-(dimethylamino)phenyl)methyl carbocation;[19a] (b) a 10^{16}-fold larger value of $K_{RS} = 8 \times 10^{18}$ M^{-1} for addition of propanethiolate ion to the triphenylmethyl carbocation, estimated from the 16 unit difference in the values of pK_R for these two carbocations [(a) Mathivanan, N.; McClelland, R. A.; Steenken, S. *J. Am. Chem. Soc.* **1990**, *112*, 8454−8457. (b) Reference 19a] and by assuming the same difference in the values of K_{RS}. The 4×10^6-fold *smaller* value of $K_{RS} = 3.2 \times 10^{13}$ M^{-1} for addition of propanethiolate ion to **1** estimated by assuming that the difference in K_{RS} or addition of RS^- to **1** and the triphenylmethyl carbocation is the same as determined for addition of bromide ion.[2a] Combining the requirement of $\Delta G_{ET} \leq 8$ kcal/mol for the viability of Scheme 4 and $\Delta G_{RS} \approx -20$ gives $\Delta G_{comb} \leq -30$ kcal/mol (eq 14). By comparison the bond dissociation energy (BDE) for the benzylic C−S bond of benzylmethyl thioether ($-\Delta G_{comb}$) is 61 kcal/mol (McMillen, D. F.; Golden D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 483−532). The effect of the 4-O^- group on this BDE will be smaller than the 17 kcal/mol effect of the 4-O^- group on the BDE of the −OH bond of phenol (Bordwell, F. G.; Cheng, J. P. *J. Am. Chem. Soc.* **1991**, *113*,1736−1743) because of the smaller electronegativity of carbon compared to oxygen; the α-CF_3 substituents are not expected to have a large effect on this BDE, because of the small value of −0.01 for the radical substituent constant $\sigma_{JJ}^{\bullet}$ (Jiang, X.-K. *Acc. Chem. Res.* **1997**, *30*, 283−289).

Chart 1



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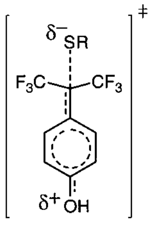

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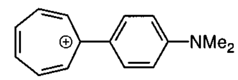

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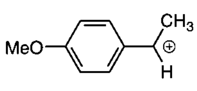

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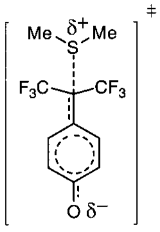

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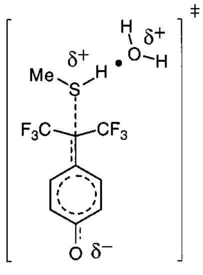

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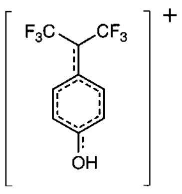
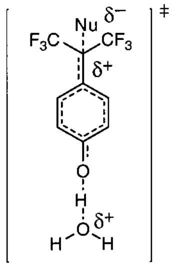


H-1



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weakly basic, neutral thiols to **1** are kinetically significant at low pH (Figure 1). This shows that there is a sharper decrease with decreasing thiol basicity in k_{RSH} and $(k_{RSH})_H$ for addition of neutral thiols than in k_{RS} for addition of thiolate anions to **1**. This is manifested in the smaller Brønsted parameter of $\beta_{nuc} = 0.11$ for addition of thiol anions (k_{RS}) than $\beta_{nuc} > 0.5$ for the uncatalyzed addition of neutral thiols to **1** (k_{RSH}) (Figure 5A).[18]

The identical values of $\beta_{nuc} = 0.11$ for addition of thiol anions to **1** and to the strongly resonance-stabilized 4-(dimethylamino)-phenyltropylium ion (**4**; Chart 1)[19a] provide further evidence supporting the conclusion that the chemical reactivity of **1** is similar to that of other strongly resonance-stabilized carbocations.[2a] These small values of β_{nuc} are consistent with an early reactant-like transition state for nucleophilic addition of thiol anions to these electrophiles.

The relatively weak resonance stabilization of the 1-(4-methoxyphenyl)ethyl carbocation ($\mathbf{5}^+$; Chart 1) results in a lifetime of this carbocation in water that is ca. 10^{11}-fold shorter than that of **1**,[20a] so that the addition of thiol anions to $\mathbf{5}^+$ should be diffusion-controlled and independent of the pK_a of the nucleophile.[20] It is interesting to compare structure−reactivity parameters for nucleophile addition to the stable electrophile **1** and the highly reactive electrophile $\mathbf{5}^+$ for a case where the difference in the intrinsic reactivity of these electrophiles is equalized by the choice of reagents of different intrinsic nucleophilic reactivity, so that the two electrophiles undergo addition with similar activation barriers. The greater electrophilic reactivity of $\mathbf{5}^+$ than of **1** is balanced by the weaker nucleophilicity of alcohols than of thiol anions, so that nucleophilic addition occurs with similar second-order rate constants of $k_{RS} \approx 3 \times 10^6$ M^{-1} s^{-1} for addition of RS$^-$ to **1** (Table 1) and $k_{ROH} \approx 1 \times 10^7$ M^{-1} s^{-1} for addition of ROH to $\mathbf{5}^+$.[20b] These reactions, which have similar activation barriers $\Delta G^{\ddagger}$, are characterized by very different Brønsted coefficients of $\beta_{nuc} = 0.11$ for addition of thiol anions to **1** (Figure 5A) and $\beta_{nuc} = 0.32$ for addition of alkyl alcohols to $\mathbf{5}^+$.[20b] The difference in these values of β_{nuc} is not due simply to the larger thermodynamic driving force for addition of RS$^-$ to **1** than for addition of ROH to $\mathbf{5}^+$.[22] This is because no large changes in β_{nuc} are observed with changing thermodynamic driving force for addition of thiol anions to strongly resonance-stabilized carbocations.[19a]

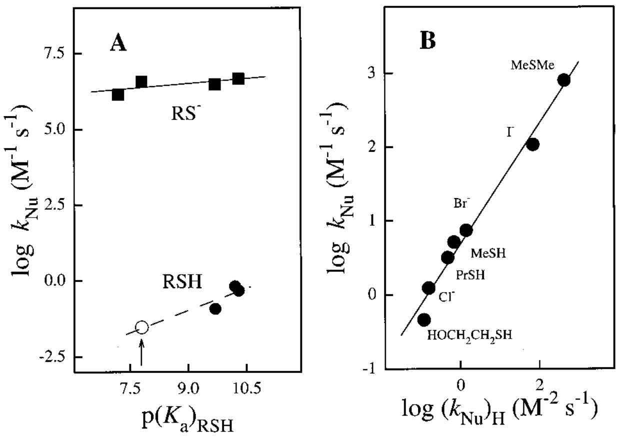

Figure 5. (A) Brønsted correlations for nucleophilic addition of thiols to the quinone methide **1** in water at 25 °C and $I = 1.0$ (NaClO$_4$). Key: (■) experimental values of log k_{RS} (M^{-1} s^{-1}) for addition of thiolate anions RS$^-$ to **1** with the slope of the least-squares line through the data giving $\beta_{nuc} = 0.11$; (●) experimental values of log k_{RSH} (M^{-1} s^{-1}) for uncatalyzed addition of neutral thiols to **1**; (○) upper limit on k_{RSH} for uncatalyzed addition of methyl mercaptoacetate to **1**, estimated as described in the text with the dashed line as the least-squares fit of the data including this upper limit, which gives $\beta_{nuc} > 0.5$ (dashed line). (B) Linear logarithmic correlation between k_{Nu} (M^{-1} s^{-1}) for uncatalyzed addition of nucleophiles to **1** and $(k_{Nu})_H$ (M^{-2} s^{-1}) for specific-acid-catalyzed addition of these nucleophiles. The slope of this correlation is 0.82 (solid line).

There is a requirement that cleavage of a hydrogen bond between solvent and the nucleophile, with equilibrium constant K_{desol}, precedes chemical bond formation to the nucleophile. A logarithmic correlation with slope β_{desol} (<0) is expected to exist between values of K_{desol} and nucleophile pK_a,[48] so that observed values of β_{nuc} will reflect the sum of β_{desol} for nucleophile desolvation and β_{chem} for chemical bond formation.[49] The smaller observed value of β_{nuc} for addition of thiol anions

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(17) McClelland, R. A.; Kanagasabapathy, V. M.; Steenken, S. *J. Am. Chem. Soc.* **1988**, *110*, 6913−6914. McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1991**, *113*, 1009−1014. McClelland, R. A.; Cozens, F. L.; Steenken, S.; Amyes, T. L.; Richard, J. P. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1717−1722.

(18) The lower limit of $\beta_{nuc} > 0.5$ for addition of neutral thiols to **1** was determined as the slope of the lower correlation from Figure 5A, which includes the upper limit on k_{RSH} for addition of MeO$_2$CCH$_2$SH to **1** (Table 1).

(19) (a) Ritchie, C. D.; Gandler, J. *J. Am. Chem. Soc.* **1979**, *101*, 7318−7323. (b) Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348−354. (c) Ritchie, C. D. *Can. J. Chem.* **1986**, *64*, 2239−2250.

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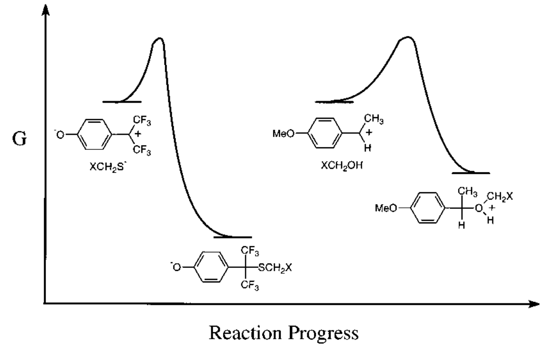

Figure 6. Hypothetical free energy reaction coordinate profiles for the addition of substituted thiol anions to the quinone methide **1** and of substituted alcohols to the 1-(4-methoxyphenyl)ethyl carbocation ($\mathbf{5}^+$). This figure emphasizes the following features of these reaction coordinate profiles: (1) the larger thermodynamic driving force and the more "reactant-like" transition state for reaction of **1**; (2) the similar activation barriers for the reactions of **1** and $\mathbf{5}^+$.

compared to alcohols might reflect the larger negative value of β_{desol} for desolvation of thiol anions. However, there is evidence that hydrogen bonds to thiol anions are weak and involve relatively little formal proton transfer to the thiol anion,[50] so that $\beta_{\text{desolv}} \approx 0$ should not be substantially more negative than for alcohols.

The values of β_{nuc} for nucleophile addition reactions provide a measure of the *change* in charge at the nucleophilic reagent which occurs on proceeding from the reaction ground to transition state.[21] The difference in the values of β_{nuc} for addition of alcohols to $\mathbf{5}^+$ ($\beta_{\text{nuc}} = 0.32$) and of thiol anions to **1** ($\beta_{\text{nuc}} = 0.11$) shows that these reactions proceed through transition states in which there is a larger *change* in charge at the alcohol compared to thiolate anion nucleophile, which is consistent with a *greater* degree of bonding to the former nucleophile at the transition state. Since these two nucleophile addition reactions proceed over nearly the same activation barriers (see above), the change in energy associated with formation of a small fractional bond at the transition state for addition of the thiol anion must be essentially the same as that associated with formation of the larger fractional bond at the transition state for addition of the oxygen nucleophile. This has been represented on free energy profiles as a relatively steep gradient (curvature) for the approach to the transition state for addition of thiol anions to **1** and a more shallow gradient for the approach to the transition state for nucleophile addition to $\mathbf{5}^+$ (Figure 6).

These *complex* structure–reactivity effects provide further evidence that the value of β_{nuc} for carbocation–nucleophile combination is sensitive to the *curvature* of the reaction coordinate on the approach to the transition state and that there is a systematic increase in the *steepness* of this approach with increasing resonance delocalization of electron density to the reactive cationic center.[2a,3,5,7,23–25] Thus, the shallow curvature for the reaction profile for nucleophile addition to $\mathbf{5}^+$ has been proposed to result in large changes in the position of the reaction transition state as measured by β_{nuc} with changing thermodynamic driving force for nucleophile,[7,20b] while the much steeper curvature for nucleophile addition to relatively stable electrophiles which follow the Ritchie N_+ scale[19b,c] has been proposed to result in essentially constant nucleophilic selectivity (e.g. β_{nuc}) for changing electrophile reactivity.[3,7]

The protonation of RS^- results in an increase from $\beta_{\text{nuc}} = 0.11$ for addition of RS^- to **1** to $\beta_{\text{nuc}} > 0.5$ for addition of neutral RSH to **1** (Figure 5A).[18] This change in β_{nuc} is due partly or entirely to the more positive value of $\Delta G°$ for formation of the protonated thiol adduct $\mathbf{1\text{-}S(H)R}^+$, the initial product of addition of neutral RSH to **1**, than for formation of **1-SR**, and the resulting Hammond-type shift to a more productlike transition state for the addition of neutral RSH.[26,27] In fact, the direct addition of neutral thiols to **1** to form protonated thioethers $\mathbf{1\text{-}S(H)R}^+$ is probably endothermic ($K_{\text{Nu}} < 1$). This is because $K_{\text{Nu}} = k_{\text{RSR}}/k_{\text{solv}} = 3 \times 10^{-7}$ M^{-1} has been determined as the equilibrium constant for addition of the neutral sulfide Me_2S to **1** to form the sulfonium ion $\mathbf{1\text{-}SMe_2}^+$ (this work, see below), and the *ca.* 600-fold smaller rate constant for addition of MeSH to **1** than for addition of Me_2S (this work) is consistent with an even smaller equilibrium carbon basicity for the neutral thiol MeSH.

Nucleophilic Addition of Sulfides. Nucleophilic addition of MeSH to **1** was monitored by conventional UV spectrophotometry, but the much faster reversible addition of Me_2S to **1** could be followed only by using stopped-flow techniques (see Experimental Section). This simple experimental observation provides *prima facie* evidence that the nucleophilic reactivity of sulfide RSR toward **1** is much greater than that of the corresponding thiol RSH. The reversible nucleophilic additions of bromide and iodide ion to **1** have also been studied in dilute acids using conventional UV spectrophotometry.[2a,13b] These nucleophiles react by the same pathways observed for the addition of Me_2S,[2a,13b] but by comparison, the addition of Me_2S to **1** is thermodynamically much more unfavorable and can be detected only for reactions in the presence of high concentrations (0.1–1.0 M) of acid, which serve to protonate the phenoxide anion $\mathbf{1\text{-}SMe_2}^+$ (Scheme 6).

Two pathways are observed for reversible addition of Me_2S and H^+ to 1 to form $\mathbf{H\text{-}1\text{-}SMe_2}^+$ (Scheme 6): (1) There is direct uncatalyzed nucleophilic addition of Me_2S to **1** to form $\mathbf{1\text{-}SMe_2}^+$, with a rate constant $k_{\text{RSR}} = 430$ M^{-1} s^{-1}, which then undergoes rapid protonation to give $\mathbf{H\text{-}1\text{-}SMe_2}^+$. The reverse of this uncatalyzed addition is specific-base-catalyzed cleavage of $\mathbf{H\text{-}1\text{-}SMe_2}^+$ by preequilibrium deprotonation to form $\mathbf{1\text{-}SMe_2}^+$, which then undergoes rate-limiting cleavage to give **1** and Me_2S. (2) There is H_3O^+-catalyzed addition of Me_2S to **1** to form $\mathbf{H\text{-}1\text{-}SMe_2}^+$, with a rate constant $(k_{\text{RSR}})_{\text{H}} = 800$ M^{-2} s^{-1}. The

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(22) There is a greater thermodynamic driving force for addition of thiol anions to **1** to form **1-SR** than for addition of alcohols to $\mathbf{5}^+$ to form protonated oxygen ethers $\mathbf{5\text{-}O(H)R}^+$ because these reactions have very similar rate constants (see text), but the reverse heterolytic cleavage **1-SR** is much slower than cleavage of $\mathbf{5\text{-}O(H)R}^+$. For example, $k_{\text{solv}} \le 3 \times 10^{-5}$ s^{-1} can be estimated for cleavage of 1-SCH_2CF_3 (the most reactive thioether

$$\mathbf{5\text{-}OH} + \text{EtOH} + \text{H}^+ \underset{k_{\text{HOH}}}{\overset{(k_{\text{H}})_{\text{OH}}}{\rightleftharpoons}} \text{R}^+ \underset{(k_{\text{H}})_{\text{OEt}}}{\overset{k_{\text{EtOH}}}{\rightleftharpoons}} \mathbf{5\text{-}OEt} + \text{HOH} + \text{H}^+$$

$$(k_{\text{H}})_{\text{OEt}} = \left(\frac{(k_{\text{H}})_{\text{OH}}}{K_{\text{eq}}}\right)\left(\frac{k_{\text{EtOH}}}{k_{\text{HOH}}}\right) \qquad (15)$$

examined in this work) by expulsion of $CF_3CH_2S^-$, from analyses of the stability of this compound in basic solution by HPLC.[41] By comparison, $(k_{\text{H}})_{\text{OEt}} = 0.05$ M^{-1} s^{-1} for the acid-catalyzed cleavage of **5-OEt** to give $\mathbf{5}^+$ can be calculated using eq 14 with $(k_{\text{H}})_{\text{OH}} = 0.11$ M^{-1} s^{-1} for acid-catalyzed cleavage of **5-OH**,[20] $K_{\text{eq}} = 36$ as the equilibrium constant for conversion of **5-OH** to **5-OEt**,[42] and $k_{\text{EtOH}}/k_{\text{HOH}} = 16$ for partitioning of $\mathbf{5}^+$ between reaction with ethanol and water.[21] The acidity of $\mathbf{5\text{-}O(H)Et}^+$ can be estimated as $pK_a \approx -2$,[41] so that only a small fraction of **5-OEt** will be protonated at $[H^+] = 1.0$ M, and $k_{\text{solv}} \gg 0.05$ s^{-1} for cleavage of $\mathbf{5\text{-}O(H)Et}^+$ by expulsion of the neutral EtOH leaving group.

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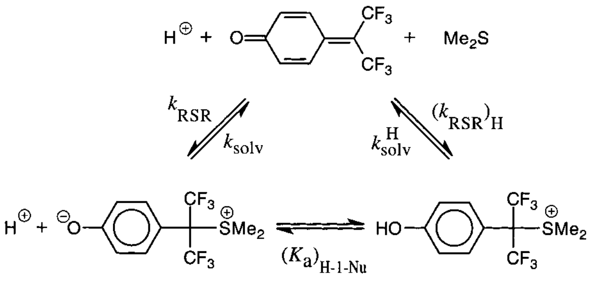
Scheme 6



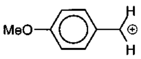
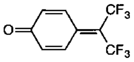
1-SMe$_2^+$ **H-1-SMe$_2^+$**

mechanism for this acid-catalyzed nucleophilic addition reaction was not investigated, but there is good evidence that the specific-acid-catalyzed addition of halide ions to **1** proceeds by a single-step concerted reaction mechanism,[13b] as shown in Scheme 6 for the reaction of Me_2S. The reverse of this acid-catalyzed addition reaction is the uncatalyzed cleavage of **H-1-SMe$_2^+$** to form **1**, Me_2S, and H^+, with a rate constant $k_{solv}{}^{H} = 15$ s^{-1} that was determined as the limiting rate constant for cleavage of **H-1-SMe$_2^+$** in the presence of high concentrations of acid (Figure 3 and Results).

The rate constant $k_{solv} = 1.4 \times 10^9$ s^{-1} for cleavage of the phenoxide anion **1-SMe$_2^+$** by expulsion of Me_2S (Scheme 6) was evaluated as follows: (a) A value of $(K_a)_{H-1-Nu} = 10^{-8.3}$ M for ionization of **H-1-SMe$_2^+$** was estimated as described in earlier work,[2a] from pK_a = 10.0 for phenol and a value of σ_{eff} = 0.79 for the "effective" Hammett substituent constant for the *p*-$C(CF_3)_2SMe_2^+$ group.[28a] (b) This acidity constant was combined with K_{RSR} = 60 M^{-2} for addition of H^+ and Me_2S to **1** (Results) using the relationship $K_{Nu} = K_{RSR}\ (K_a)_{H-1-Nu}$ to give $K_{Nu} = 3 \times 10^{-7}$ M^{-1} as the equilibrium constant for addition of Me_2S to **1** to give **1-SMe$_2^+$**. (c) The value of $k_{solv} = 1.4 \times 10^9$ s^{-1} (Table 2) for cleavage of **1-SMe$_2^+$** was calculated from $K_{Nu} = 3 \times 10^{-7}$ M^{-1} and k_{RSR} = 430 M^{-1} s^{-1} using the relationship $k_{solv} = k_{RSR}/K_{Nu}$. Essentially the same value for k_{solv} may be calculated from the relationship $k_{solv} = k_{solv}'/(K_a)_{H-1-Nu}$ using the value of k_{solv}' = 6.2 M s^{-1} obtained by analysis of the data shown in Figure 3 (see Results).

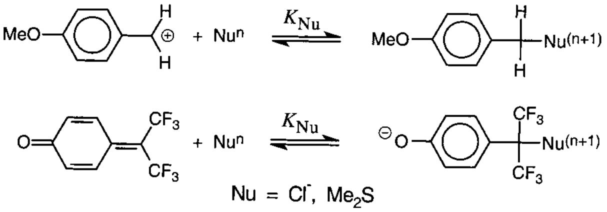
Table 2 shows a comparison of the rate and equilibrium constants for the reversible addition of Cl^- and Me_2S to the 4-methoxybenzyl carbocation and to **1** in water (Scheme 7). The larger thermodynamic driving force for addition of Me_2S than for addition of chloride ion to the 4-methoxybenzyl carbocation, $K_{MeSMe}/K_{Cl} = 1 \times 10^7$, reflects the larger carbon basicity of sulfur than of chloride ion. By contrast, the value of K_{MeSMe} for addition of Me_2S to **1** is 130-fold *smaller* than K_{Cl} for addition of Cl^-, and the ratio K_{MeSMe}/K_{Cl} for addition to **1** is 10^9-fold smaller than that for the 4-methoxybenzyl carbocation. These data show that there is a large destabilization of the cationic adduct of **1** with Me_2S relative to the neutral adduct of **1** with Cl^-, as a result of unfavorable steric and electrostatic interactions between the bulky electron-withdrawing α-CF_3 groups and the cationic sulfur at **1-SMe$_2^+$**. By comparison, a substitution of CF_3 for CH_3 at $CH_3CH_2NH_2$ results in 4.9 unit decrease in amine pK_a,[28b] which corresponds to a $10^{4.9}$-fold more favorable equilibrium constant for deprotonation of $CF_3CH_2NH_3^+$ (pK_a = 5.7) than $CH_3CH_2NH_3^+$ (pK_a = 10.6) in water.

Table 2. Rate and Equilibrium Constants for Addition of Dimethyl Sulfide and Chloride Ion to Electrophilic Carbon in Water at 25 °C (Scheme 6)

Electrophile	Nucleophile	k_{Nu} [a] (M^{-1} s^{-1})	k_{solv} [b] (s^{-1})	K_{Nu} [c] (M^{-1})	K_{MeSMe}/K_{Cl} [d]
	Cl^-	2×10^9 [e]	4 [f]	5×10^8	1×10^7
	Me_2S	5×10^9 [g]	1×10^{-6} [h]	5×10^{15}	
	Cl^- [i]	0.16	4×10^3	4×10^{-5}	0.008
	Me_2S [j]	430	1.4×10^9	3×10^{-7}	

[a] Second-order rate constant for nucleophilic addition to the electrophile. [b] First-order rate constant for reverse cleavage of the nucleophile adduct by expulsion of Me_2S or Cl^-. [c] Equilibrium constant for nucleophilic addition, calculated as $K_{Nu} = k_{Nu}/k_{solv}$. [d] Ratio of equilibrium constants for nucleophilic addition of dimethyl sulfide and chloride ion. [e] Rate constant for addition of Cl^- in 50/50 (v/v) TFE/H_2O;[44] a change in solvent to 100% H_2O results in <2-fold increase in the rate constants for addition of azide and acetate ions to **5**$^+$.[20] [f] Data from ref 45. [g] Estimated from $k_{Nu} = 1.5 \times 10^9$ M^{-1} s^{-1} for addition of propanethiol to **5**$^+$.[46] A larger diffusion-limited rate constant of $k_{Nu} = 5 \times 10^9$ M^{-1} s^{-1} is used here, because Me_2S is 640-fold more reactive than propanethiol toward **1** (Table 1) and the 4-methoxybenzyl carbocation is more electrophilic than **5**$^+$. [h] Data from ref 47. [i] Data from ref 2a. [j] Data from this work.

Scheme 7



Transition State "Structure". It is necessary to reconcile the conflicting *picture* of the transition state for addition of thiols and sulfides to **1** that can be drawn from an analysis of the experimental data. There are two experimental observations which show that this transition state is stabilized by electron-donating substituents at the thiol nucleophile: (1) A limit of $\beta_{nuc} > 0.5$ has been set for the Brønsted parameter for nucleophilic addition of neutral thiols to **1** (Figure 5A),[18] so that the stabilization of the transition state by electron-donating groups at the thiol is more than 50% that of the protonated thiol relative to the thiol anion. (2) The rate constant k_{Nu} (M^{-1} s^{-1}) for addition of Me_2S to **1** is 630-fold larger than that for addition of MeSH. This shows that transition state **6** (Chart 1) for addition of Me_2S to **1** is stabilized by *ca.* 4 kcal/mol over transition state **7**, as a result of the second methyl group at the sulfur nucleophile. The observation that there is considerable stabilization of the transition state by electron-donating groups at sulfur is consistent with substantial C−S bond formation and concomitant positive charge development at the sulfur nucleophile. Such a productlike transition state is *expected* for the addition of dimethyl sulfide to **1**, because this reaction is strongly endothermic ($K_{Nu} = 3 \times 10^{-7}$ M^{-1}, Table 2).[27]

By contrast, there are two observations which suggest that the large steric and electrostatic destabilizations of **1-SMe$_2^+$**,

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[28] (a) The value $\sigma_{eff} = 0.40(2\sigma_{CF_3} + \sigma_{RSR}) = 0.79$ was determined using values of 0.54 and 0.90, respectively, for the Hammett substituent constants for the *p*-CF_3 and *p*-Me_2S^+ groups (ref 33, page 66) and an attenuation factor of 0.40 to account for additional carbon which separates these groups from the aryoxy anion. (b) Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry and Molecular Biology, Physical and Chemical Data*, 3rd ed.; Fasman, G. D., Ed.; CRC Press: Cleveland, OH, 1976; Vol. 1, pp 305−351.

which we propose is the major origin of 10^9-fold smaller value of K_{MeSMe}/K_{Cl} (Scheme 7) for nucleophilic addition to **1** than for addition to the 4-methoxybenzyl carbocation (Table 2), are *not* greatly expressed at the transition state for addition of Me_2S to **1**: (1) There is no evidence that dimethyl sulfide shows an abnormally low nucleophilic reactivity toward **1**. For example, $k_{Nu} = 430$ M^{-1} s^{-1} for addition of Me_2S to **1** is only 10^3-fold smaller than $k_{Nu} = 5.5 \times 10^5$ M^{-1} s^{-1} for addition of the much more nucleophilic azide ion.[2a] (2) The data in Table 2 show that Me_2S is ca. 10^6-fold *less* reactive than Cl^- as a leaving group in the solvolysis of $4\text{-}MeOC_6H_4CH_2Nu$ but ca. 10^5-fold *more* reactive than Cl^- as a leaving group in the solvolysis of **1-Nu**. This suggests that a large fraction of the destabilizing steric/electrostatic interactions between the electron-withdrawing α-CF_3 groups and the charged bulky leaving group at **1-SMe₂**$^+$ are relieved at the transition state for *cleavage* of the C−S bond, so that there is a corresponding small fractional expression of these interactions at the transition state for nucleophile addition.

These data provide evidence that nucleophilic addition of neutral sulfur nucleophiles to **1** proceeds through a transition state in which there is an *imbalance* between the relatively large expression of the effect of polar substituents at sulfur nucleophile ($\beta_{nuc} > 0.5$) but a relatively small expression of steric/electrostatic interactions with the strongly electron-withdrawing α-CF_3 groups.[29] They may be rationalized within the framework of the "*principle of nonperfect synchronization*",[30−32] by a transition state in which the product destabilizing steric/electrostatic interactions develop *late* along the reaction coordinate for addition of Me_2S to **1**, so that their effect on the rate constant for nucleophile addition is small. This results in a decrease in the Marcus intrinsic barrier for the hypothetical thermoneutral reaction, relative to that for nucleophilic additions of anions and other nucleophiles that are free of steric hindrance.[30−32] The data in Table 2 provide good evidence that there is a smaller intrinsic barrier for addition of Me_2S than for addition chloride ion to **1**. The addition of Me_2S to **1** is ca. 3 kcal/mol thermodynamically *more unfavorable* than for addition of Cl^-, yet the *absolute* rate constants for *both* formation and cleavage of **1-SMe₂**$^+$ are $>10^3$-fold larger than the corresponding rate constants for formation and cleavage of **1-Cl**. This corresponds to a 4.7 kcal/mol smaller activation barrier for the formation of **1-SMe₂**$^+$ compared to the thermodynamically favored formation of **1-Cl**.

On the basis of these results, we propose the following picture of the reaction coordinate profile for addition of neutral sulfur nucleophiles to **1**: (1) The bonding interactions between **1** and the sulfur nucleophile in the transition state develop at a relatively long distance, which minimizes steric/electrostatic interactions of the nucleophile with the α-CF_3 groups. The developing positive charge at the sulfur nucleophile shows a normal interaction with electron-donating alkyl groups that are directly attached to sulfur. (2) The steric/electrostatic interactions between the α-CF_3 groups and the incoming sulfide nucleophile develop largely *after* the transition state has been traversed on the reaction coordinate. This requires that the stabilization from C−S bond formation obtained after the transition state has been passed be greater than the destabilization from developing steric/electrostatic interactions. (3) The sulfonium ion **1-SMe₂**$^+$ is destabilized mainly by steric interactions between bonding and nonbonding electron pairs, as opposed to through space charge−dipole interactions. This is because steric interactions exhibit a $\approx(1/r^{12})$ dependence on radius, as compared with the $1/r^3$ dependence for charge−dipole interactions, and are therefore expected to develop at relatively short bond distances[33] or at a position that is "late" on the transition state for bond formation and early for bond cleavage.

The 12 kcal/mol larger proton affinity of Me_2S (197 cal/mol) than of MeSH (185 kcal/mol) in the gas phase[12] provides an upper limit for stabilization of the positive charge at sulfur in **1-SMe₂**$^+$ by interaction of charge with the polarizable methyl group. The 4 kcal/mol stabilization of transition state **6** relative to **7** by the methyl group in water is ca. 33% of this 12 kcal/mol limit. This significant fractional expression of a gas-phase substituent effect for a nucleophilic addition reaction in an aqueous solvent requires the following: (a) There is, at best, modest stabilization of the transition state **7** for addition of MeSH by hydrogen bonding of the acidic proton to solvent. This is consistent with a large body of experimental evidence that acidic protons attached to sulfur form relatively weak hydrogen bonds to solvent water.[34−38] (b) Destabilization of transition state **6** by steric/electrostatic interactions between the methyl groups of Me_2S and the CF_3 groups of **1** is relatively small (see above). These results contrast sharply with those for amines, where gas-phase stabilization of ammonium cations by polarizable methyl groups is evenly balanced by solution stabilization of the cation by hydrogen bonding between water and the acidic proton, so that methyl for hydrogen substitutions have little effect on amine basicity in water.[39]

Acid-Catalyzed Addition of Sulfides and Thiols. The third-order rate constants $(k_{Nu})_H$ for acid-catalyzed addition of neutral thiols and sulfides to **1** are given in Table 1. These termolecular reactions may follow either a stepwise mechanism in which **1** is first protonated to form **H-1** (Chart 1), which then undergoes nucleophile addition, or a concerted mechanism in which proton transfer and formation of the C−S bond occur in a single step (**8**).[13b]

Figure 5B shows that there is a linear correlation, with a slope of 0.82, between the second-order rate constants k_{Nu} for direct addition of nucleophiles to **1** and the third-order rate constants $(k_{Nu})_H$ for the corresponding specific-acid-catalyzed nucleophile addition. The near unit slope of this correlation is difficult to reconcile with a stepwise mechanism for the specific-acid-catalyzed reaction, because preequilibrium protonation of **1** to give **H-1** is expected to result in a large increase in reactivity and decrease in the nucleophilic selectivity of the electrophile.[7,13b] A less extensive correlation of data for the addition of halide ions to **1** was presented in earlier work as one piece of evidence to support a concerted reaction mechanism.[13b] The correlation in Figure 5B, which includes both halide and sulfur nucleophiles and spans a greater range of reactivity, is consistent with the conclusion that the concerted mechanism is preferred for

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specific-acid-catalyzed addition of sulfur nucleophiles to **1** but does not rigorously exclude the stepwise reaction mechanism. The slope of 0.82 for this correlation is consistent with a transition state **8** in which the bonding between the nucleophilic reagent and **1** is slightly greater than for direct nucleophile addition and where there is modest stabilization by interaction between H_3O^+ and the developing phenoxide anion. This interaction may resemble a simple hydrogen bond or involve a larger degree of proton transfer to oxygen.

Methyl Group Transfer. Dimethyl sulfide reacts rapidly with **1** in acidic solution to form an equilibrium mixture of **1** and the sulfonium ion **H-1-SMe₂**$^+$ ($K_{RSR} = 60$ M^{-2}, Scheme 3). The rate constants k_{obsd} (s^{-1}) for disappearance of **1** decrease with increasing [Me_2S], as a result of conversion of **1** to the adduct **H-1-SMe₂**$^+$. However, k_{obsd} does not approach zero for reactions in the presence of high [Me_2S] where the concentration of **1** is very low (Figure 4A). Product analyses show that the major product of the reaction of **1** in the presence of high concentrations of Me_2S is **H-1-SMe**, which we propose forms by demethylation of **H-1-SMe₂**$^+$. This slow reaction of **H-1-SMe₂**$^+$ results, effectively, in the disappearance of both **1** and **H-1-SMe₂**$^+$, because these species are in rapid equilibrium. Figure 4B shows that the yield of **H-1-SMe** depends on [Me_2S]^2, which requires that the transition state for formation of **H-1-SMe** contain two molecules of Me_2S. This provides strong evidence that **H-1-SMe** forms by methyl group transfer from **1-SMe₂**$^+$ to Me_2S rather than solvent water (k_T, Scheme 8).

The value of $k_T = 7.4 \times 10^{-3}$ M^{-1} s^{-1} (Results) determined for methyl group transfer from **H-1-SMe₂**$^+$ to Me_2S at 25 °C is larger than that for the corresponding demethylation of $4\text{-}NO_2C_6H_4CH_2SMe_2^+$, which was monitored at the much higher temperature of 78 °C.[40] Again, we attribute the high reactivity of **H-1-SMe₂**$^+$ to the weak basicity of the sulfide leaving group **H-1-SMe** and to relief of destabilizing interactions between the charged sulfur and the two α-CF_3 groups in the reaction transition state.

Acknowledgment. We acknowledge the National Institutes of Health Grant GM 39754 for its generous support of this work and Tina L. Amyes for helpful discussion.

Supporting Information Available: Figure S1, (A) dependence of [$(k_{RSH})_{obsd} - k_{RS}f_{RS}$] (M^{-1} s^{-1}) for the addition of thiols RSH to **1** on the concentration of hydronium ion and (B) rate constants for the uncatalyzed addition of neutral thiols RSH to **1** as a function of pH, and Figure S2, dependence of the ratio of the concentrations of **H-1-SMe₂**$^+$ and **1** at chemical equilibrium on the concentration of Me_2S. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0021868

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