

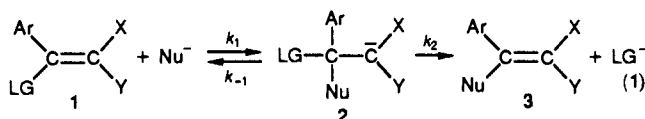
Kinetics of Reactions of Thiolate Ions with α -Nitro β -Substituted Stilbenes in 50% Me₂SO–50% Water. Observation of the Intermediate in Nucleophilic Vinyllic Substitution Reactions^{1a}

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Abstract: The kinetics of reactions of the type $\text{Ph(LG)C}=\text{CPh(NO}_2\text{)} + \text{RS}^- \rightarrow \text{Ph(RS)C}=\text{CPh(NO}_2\text{)} + \text{LG}^-$ were measured in 50% Me₂SO–50% water (v/v) at 20 °C. Results on the following leaving group/nucleophile combinations are reported: LG = I, Cl, 4-CH₃C₆H₄O, CH₃O, CH₃O₂CCH₂CH₂S, and CH₃CH₂CH₂S with RS⁻ = HOCH₂CH₂S⁻; LG = CH₃O with RS⁻ = EtS⁻, CH₃O₂CCH₂CH₂S⁻, and CH₃O₂CCH₂S⁻; LG = HOCH₂CH₂S with RS⁻ = CH₃CH₂CH₂S⁻; LG = CH₃O₂CCH₂CH₂S with RS⁻ = CH₃CH₂CH₂S⁻. Furthermore, the kinetics of reversible addition in the symmetrical systems LG = HOCH₂CH₂S with RS⁻ = HOCH₂CH₂S⁻, and LG = CH₃CH₂CH₂S with RS⁻ = CH₃CH₂CH₂S⁻, were determined. For the combinations LG = CH₃O with various RS⁻, LG = R'S with various RS⁻, and possibly LG = 4-CH₃C₆H₄O with HOCH₂CH₂S⁻, the intermediate, $\text{Ph(LG)(Nu)C}=\text{CPh(NO}_2\text{)}^-$, that is commonly postulated in nucleophilic vinyllic substitution reactions could be directly observed spectrophotometrically and the kinetics of its formation and its conversion to products were measured separately in several cases. Three conditions must be met for the intermediate to be observable by our method. (1) The equilibrium of intermediate formation from the reactants must be favorable, i.e., $K_1[\text{Nu}^-] > (\gg) 1$. (2) The conversion of the intermediate to products must be slower than its formation from reactants, i.e., $k_1[\text{Nu}^-] > (\gg) k_2$. (3) The absolute magnitude of k_2 must be low enough to allow detection of the intermediate by conventional or stopped-flow spectrophotometry. The reasons why some of the systems described in this study meet these conditions, while none of the numerous systems reported previously do, are discussed in detail.

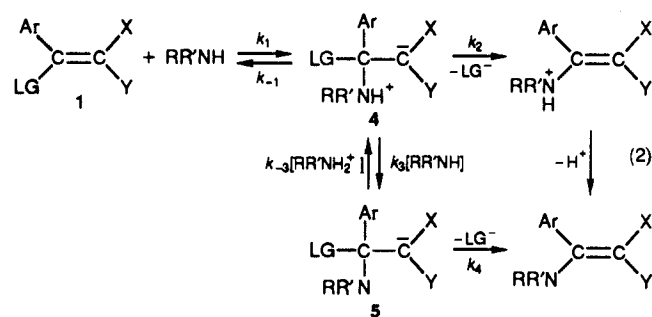
Nucleophilic vinyllic substitution reactions proceed by a multitude of mechanisms.² The most common one is the addition–elimination mechanism shown for an anionic nucleophile in eq 1. This two-step mechanism is favored by strongly electron



withdrawing groups X and/or Y. In almost all cases known, even with halogens as leaving groups, the addition–elimination mechanism is favored as long as X, Y, or both are strongly electron withdrawing.² However, with moderate or poor electron-withdrawing X and/or Y a concerted substitution process is feasible, although unequivocal evidence for it has never been presented.^{2d} In such a case, a poor leaving group may shift the mechanism toward the two-step mode.

There exist several lines of evidence that support this mechanism. Four of them are as follows. (1) Even though the intermediate **2** has not been observed directly, carbanionic adducts similar to **2**, derived from 1-like olefins without a “real” leaving group (e.g., LG = H, alkyl, aryl) have been detected under reaction conditions conducive to nucleophilic vinyllic substitution.³ Note, however, that the presence of a leaving group may change the situation by opening a concerted pathway and bypassing the intermediate **2**. (2) The rate constant ratios with LG = Br, Cl, and F are typically $k_{\text{Br}}/k_{\text{Cl}} \sim 1$ and $k_{\text{F}}/k_{\text{Cl}} \gg 1$.^{2a,d,e} Such ratios are consistent with rate-limiting nucleophilic attack without C–LG

bond cleavage, and with acceleration by electron withdrawal by the highly electronegative fluorine atom. Note, however, that a concerted mechanism for the chloro, and a two-step mechanism for the fluoro, compound may also be consistent with $k_{\text{F}}/k_{\text{Cl}} \gg 1$. (3) Partial or complete stereoconvergence has frequently been observed, i.e., starting from either the *E* or *Z* precursor, the reaction leads to both *E* and *Z* substitution products.^{2d,4} These results indicate the presence of an intermediate (**2**) whose lifetime is long enough for rotation around the C–C bond to occur before leaving group expulsion. (4) Substitution of sluggish leaving groups (LG = CN, F, RO) by amines occurs with amine catalysis, which may be attributed either to (partly) rate-limiting deprotonation of **4** in eq 2 (k_3) or to a fast proton-transfer equilibrium followed by rate-limiting loss of the leaving group (k_4).⁵ Mild catalysis has also recently been observed with NO₂ as the leaving group.^{5f}



(1) (a) A preliminary account of some of the results of this work has been published: Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 6862. (b) Santa Cruz. (c) Jerusalem.

(2) For reviews, see: (a) Rappoport, Z. *Adv. Phys. Org. Chem.* **1969**, *7*, 1. (b) Modena, G. *Acc. Chem. Res.* **1971**, *4*, 73. (c) Miller, S. I. *Tetrahedron* **1977**, *33*, 1211. (d) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7. (e) Rappoport, Z. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 309. (f) Shaiyanyan, B. A. *Usp. Khim.* **1986**, *55*, 942.

(3) For reviews, see: (a) Patai, S.; Rappoport, Z. In *The Chemistry of the Alkenes*; Patai, S., Ed.; Wiley-Interscience: New York, 1964; p 469. (b) Rappoport, Z.; Ladkani, D. *Chem. Scr.* **1974**, *5*, 124. (c) Bernasconi, C. F. *Tetrahedron* **1989**, *45*, 4017.

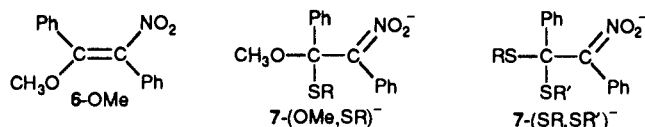
(4) (a) Rappoport, Z.; Topol, A. *J. Am. Chem. Soc.* **1980**, *102*, 406. (b) Rappoport, Z.; Avramovitch, B. *J. Org. Chem.* **1982**, *47*, 1397. (c) Rappoport, Z.; Gazit, A. *J. Org. Chem.* **1985**, *50*, 3184. (d) Rappoport, Z.; Gazit, A. *Ibid.* **1986**, *51*, 4112. (e) Rappoport, Z.; Gazit, A. *J. Am. Chem. Soc.* **1987**, *109*, 6698. (f) Rappoport, Z.; Avramovitch, B. *Ibid.* **1988**, *110*, 911. (g) Lodder, G.; van Dorp, J. W. J.; Avramovitch, B.; Rappoport, Z. *J. Org. Chem.* **1989**, *54*, 2574.

(5) (a) Rappoport, Z.; Ta-Shma, R. *J. Chem. Soc. B* **1971**, 871, 1461. (b) Rappoport, Z.; Ronen, N. *J. Chem. Soc., Perkin Trans. 2* **1972**, 955. (c) Rappoport, Z.; Peled, P. *Ibid.* **1973**, 616. (d) Rappoport, Z.; Ladkani, D. *Ibid.* **1973**, 1045. (e) Rappoport, Z.; Peled, P. *J. Am. Chem. Soc.* **1979**, *101*, 2682. (f) Rappoport, Z.; Topol, A. *J. Org. Chem.* **1989**, *54*, 5967.

The most compelling evidence for the presence of an intermediate (**2**, **4**, **5**) would of course be its direct observation during the substitution process. If the rates of its formation and decomposition to products could be measured and shown to be consistent with the overall substitution rate, this would serve as compelling evidence that it is also on the reaction coordinate. It seemed to us that the considerable body of structure–reactivity data on nucleophilic vinylic substitution^{2,5,6a} and nucleophilic addition to olefins,^{3,6b} and general structure–reactivity principles of physical organic chemistry, should be sufficient to allow the design of some systems in which the intermediate is indeed detectable. This is what we set out to do.

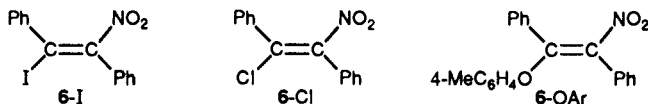
Three conditions must be met for the intermediate **2** in eq 1⁷ to be observable. (1) The equilibrium of the first step must be favorable, i.e., $K_1[\text{Nu}^-] > (\gg) 1$.⁸ (2) The conversion of the intermediate to products must be slower than its formation, i.e., $k_1[\text{Nu}^-] > (\gg) k_2$.⁸ (3) The absolute magnitude of k_2 must be low enough to allow detection of **2** by a suitable technique, e.g., by conventional UV/vis or stopped-flow spectrophotometry.

It appeared to us that β -methoxy- α -nitrostilbene (**6-OMe**)⁹ would be an excellent choice as substrate for several reasons. (a)



The combination (X, Y) = (Ph, NO₂) is one of the best with respect to inductive and resonance stabilization of the carbanionic intermediate, particularly in a hydroxylic solvent.^{3c} This implies a high K_1 value as well as a relatively low k_2 . (b) Nitronate ion forming/consuming reactions have low *intrinsic* rate constants (k when $K = 1$);^{6b,10} this further depresses k_2 compared to a system in which **2** may be of similar *thermodynamic* stability but which is characterized by high intrinsic rate constants [e.g., (X, Y) = (CN, CN)]. This feature is again particularly pronounced in hydroxylic solvents. Even though a low intrinsic rate constant may depress k_1 by an amount similar to k_2 , thereby leaving the important k_1/k_2 ratio relatively unaffected, the reduction in the *absolute value* of k_2 may become crucial if this value is too high for condition 3 to be met. (c) Methoxide ion is a very poor nucleofuge,¹¹ which should render k_2 very small.

As will be described in this paper, the intermediate **2** = **7-(OMe, SR)⁻**¹² is indeed observed in the reaction of **6-OMe** with several alkylthiolate ions in 50% Me₂SO–50% water (v/v). Other intermediates that could be observed include **7-(SR, SR')⁻** with various combinations of R and R'. In contrast, the reactions of HOCH₂CH₂S⁻ with **6-I** and **6-Cl** lead to substitution without the accumulation of an intermediate, while the results of the reaction of **6-OAr** with the same nucleophile are somewhat ambiguous.



Results

General Features. All kinetic experiments were run under pseudo-first-order conditions, with the nucleophile in excess over

(6) (a) Rappoport, Z. In *Nucleophilicity*; Harris, J. M., McManus, S. P., Eds.; Advances in Chemistry 215; American Chemical Society: Washington, DC, 1987; p 399. (b) Bernasconi, C. F. *Ibid.* p 115.

(7) The conditions for **4** and **5** to be observable (eq 2) will be described in a future paper.

(8) It is assumed that $[\text{Nu}^-]_0 \gg [1]_0$.

(9) Reactants of the type Ph(LG)C=CPh(NO₂) and products of the type Ph(Nu)C=CPh(NO₂) will all be designated as **6-LG** and **6-Nu**, respectively. They are shown as the *E* isomers although we have no definite proof of this, except for **6-I**, where both isomers are known. In some cases (see text) the compound may be a mixture of the *E* and *Z* isomers.

(10) (a) Bernasconi, C. F. *Tetrahedron* **1985**, *41*, 3219. (b) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301.

(11) (a) Stirling, C. J. M. *Acc. Chem. Res.* **1979**, *12*, 198. (b) Terrier, F. *Chem. Rev.* **1982**, *82*, 77.

(12) Intermediates of structure Ph(LG)(Nu)C=CPh(NO₂)⁻ will all be designated as **7-(LG, Nu)⁻** in this paper.

Table I. Reaction of Ph(MeO)C=CPh(NO₂) with HOCH₂CH₂S⁻ in 50% Me₂SO–50% Water at 20 °C.^a Kinetics of Breakdown of the Intermediate

[HOCH ₂ CH ₂ S] _{tot} , M	[HOCH ₂ CH ₂ S ⁻], M	k_{obsd} , s ⁻¹	$k_{\text{obsd}}(\text{corr})^e$, s ⁻¹
Spectrophotometric Determination ^b			
0.5	0.05 ^c	9.6×10^{-6}	9.6×10^{-6}
HPLC Determination			
0.0318	8.91×10^{-4d}	2.34×10^{-5}	1.76×10^{-5}
0.0424	1.19×10^{-3d}	2.09×10^{-5}	1.64×10^{-5}
0.0530	1.49×10^{-3d}	1.98×10^{-5}	1.62×10^{-5}

^a $\mu = 0.5$ M (KCl). ^b By initial rate method; see text. ^c pH 9.60. ^d pH 9.00. ^e See eq 9, with $K_1 = 7.65 \times 10^3$ M⁻¹, $k_{\text{H}_2\text{O}} + k_{\text{OH}^-\text{OH}^-} \approx k_{\text{H}_2\text{O}} = 2.37 \times 10^{-5}$ s⁻¹ (ref 15).

Table II. Unsymmetrical Reactions of RS⁻ with Ph(R'S)C=CPh(NO₂) in 50% Me₂SO–50% Water at 20 °C^a

pH	[RSH] _{tot} , M	[RS ⁻], M	$k_{\text{obsd}}(\text{fast})$, s ⁻¹	$k_{\text{obsd}}(\text{slow})$, s ⁻¹
CH ₃ CH ₂ CH ₂ S ⁻ + 6-SCH₂CH₂OH ^{b,c}				
12.70	0.106	0.100	2.96	0.350
	0.149	0.141	3.47	0.341
	0.158	0.150	3.84	0.348
	0.199	0.189	4.34	0.339
	0.211	0.200	4.73	0.354
	0.249	0.236	5.26	0.353
CH ₃ CH ₂ CH ₂ S ⁻ + 6-SCH₂CH₂CO₂CH₃ ^{b,d}				
12.66	0.122	0.115	3.96	0.371
	0.180	0.170	5.39	0.370
	0.244	0.230	7.00	0.375
HOCH ₂ CH ₂ S ⁻ + 6-SCH₂CH₂CO₂CH₃ ^{b,d}				
10.54	0.30	0.15	2.26	0.260
	0.40	0.20	2.67	0.282
	0.50	0.25	3.13	0.287
HOCH ₂ CH ₂ S ⁻ + 6-SCH₂CH₂CH₃ ^{b,d}				
10.54	0.020	0.010	0.482	
	0.050	0.025	0.546	
	0.125	0.0625	0.747	
	0.200	0.100	0.908	
	0.250	0.125	1.08	
	0.300	0.150	1.17	
	0.376	0.188	1.39	
	0.500	0.25	1.65	

^a $\mu = 0.5$ M (KCl). ^b [Substrate]₀ = (0.5–1.2) $\times 10^{-4}$ M. ^c $\lambda = 360$ nm. ^d $\lambda = 365$ nm.

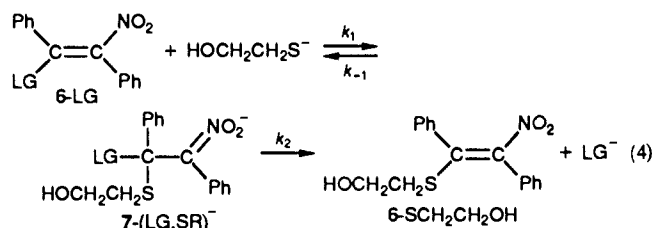
the substrate. The reaction conditions were 50% Me₂SO–50% water (v/v), 20 °C, and constant ionic strength of 0.5 M maintained with KCl.

Reaction of HOCH₂CH₂S⁻ with Ph(Cl)C=CPh(NO₂) and Ph(I)C=CPh(NO₂). The reaction of (*E*)-Ph(Cl)C=CPh(NO₂) (**6-Cl**) with HOCH₂CH₂S⁻ leads directly to the substitution product Ph(HOCH₂CH₂S)C=CPh(NO₂) (**6-SCH₂CH₂OH**), without any observable accumulation of an intermediate. There is a clean isobestic point at 300 nm, which also shows that there is no *cis*–*trans* isomerization of the starting material during the substitution. Rates were measured as a function of nucleophile concentration in the range of 10⁻³–10⁻² M by monitoring product formation at 360 nm. The results obtained at pH 10.54 are summarized in Table S1 of the supplementary material¹³ (five rate constants). Similar results, with [HOCH₂CH₂S⁻] = 5 $\times 10^{-3}$ to 2.5 $\times 10^{-2}$ M, were obtained with (*E*)-Ph(I)C=CPh(NO₂) (**6-I**); they are also reported in Table S1¹³ (five rate constants).

In both reactions there is direct proportionality between the observed pseudo-first-order rate constant and thiolate ion concentration. This is interpreted in terms of eq 3, which is the

$$k_{\text{obsd}} = \frac{k_1 k_2}{k_{-1} + k_2} [\text{HOCH}_2\text{CH}_2\text{S}^-] \quad (3)$$

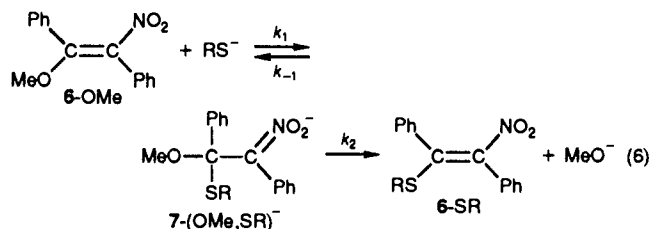
(13) See paragraph concerning supplementary material at the end of this paper.



steady-state expression for eq 4. It is reasonable to expect that Cl and I are much better nucleofuges than a thiolate, and hence, $k_2 \gg k_{-1}$ so that eq 3 reduces to eq 5. The k_1 values are collected in Table III.

$$k_{\text{obsd}} = k_1[\text{HOCH}_2\text{CH}_2\text{S}^-] \quad (5)$$

Reaction of Ph(MeO)C=CPh(NO₂) with Various Alkyl Thiolate Ions. When a solution of 6-MeO is mixed with a solution of an alkylthiolate ion (CH₃CH₂S⁻, HOCH₂CH₂S⁻, CH₃O₂CC-H₂CH₂S⁻, CH₃O₂CCH₂S⁻), a rapid reaction is observed, which leads to an intermediate whose absorption spectrum is distinctly different from that of 6-OMe or 6-SR. This is shown in Figure 1 for RS⁻ = HOCH₂CH₂S⁻. The similarity of this spectrum to that of a typical thiolate ion adduct of α -nitrostilbene, which is included in Figure 1,¹⁴ and the fact that the intermediate slowly converts to 6-SR, constitute strong evidence that the intermediate has the structure 7-(OMe,SR)⁻.



The kinetics of intermediate formation and conversion to products were measured separately. At the thiolate ion concentrations used ($\sim 2 \times 10^{-5}$ to $\sim 4 \times 10^{-3}$ M), the former occurs on a time scale of seconds, the latter has a half-life of several hours. Rates of reversible formation of 7-(OMe,SR)⁻ were determined in a stopped-flow apparatus by monitoring the loss of 6-OMe at 340 nm. The experiments were conducted in DABCO or triethylamine buffers; k_{obsd} values are summarized in Table S2 of the supplementary material¹³ (32 rate constants); they obey eq 7 as shown in Figure 2 for two representative examples. Rate and equilibrium constants are reported in Table III.

$$k_{\text{obsd}} = k_1[\text{RS}^-] + k_{-1} \quad (7)$$

The slow rate of conversion of 7-(OMe,SR)⁻ to 6-SR caused some problems in obtaining good kinetics for this reaction, which we attribute to slow oxidation of the thiol or thiolate ion. Despite our attempts to rigorously exclude oxygen, this oxidation could not be completely suppressed and led to the buildup of small amounts of absorbing products at high thiolate ion concentrations. The problem was the least serious with RS⁻ = HOCH₂CH₂S⁻ and hence we focused our efforts on this reaction. The best and most reproducible results were obtained at pH ~ 9.6 with [HOCH₂C-H₂S⁻] = 0.05 M. By spectrophotometrically monitoring the first 10% of the reaction, a k_2 value of 9.6×10^{-6} s⁻¹ (Table I) was obtained; repetitive HPLC analysis of the reaction mixture confirmed that 6-SR was the only product formed within this time period.

Runs conducted at lower thiolate ion concentrations reduced the interference from oxidation but suffered from a different problem. In these experiments the equilibrium of the first step does not favor 7-(OMe,SR)⁻ over 6-OMe as much as at higher thiolate concentrations, leaving a high enough equilibrium concentration of 6-OMe for hydrolysis of 6-OMe to 8 to compete with

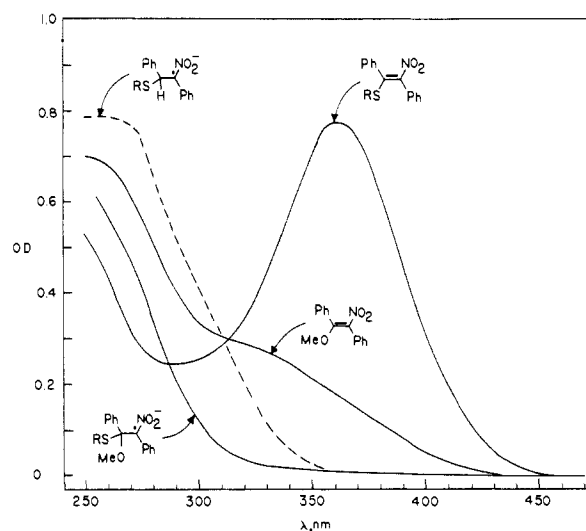


Figure 1. Absorption spectra of 6-OMe, 7-(OMe,SCH₂CH₂OH)⁻, 7-(H,SCH₂CH₂OH)⁻, and 6-SCH₂CH₂OH in 50% Me₂SO-50% water at 20 °C. [6-OMe] = [6-SCH₂CH₂OH] = 8.33×10^{-5} M. 7-(OMe,SCH₂CH₂OH)⁻ was generated from 8.33×10^{-5} M 6-OMe by adding 0.5 M HOCH₂CH₂SH in a DABCO buffer at pH 9.0; 7-(H,SCH₂CH₂OH)⁻ was generated in an analogous way from 6-H.

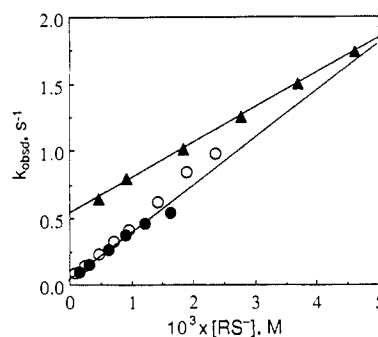
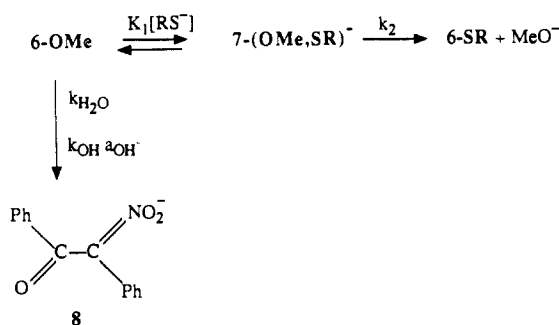


Figure 2. Reaction of 6-OMe with HOCH₂CH₂S⁻ (O, pH 10.51; ●, pH 9.00) and CH₃O₂CCH₂S⁻ (▲). Plots according to eq 7.

Scheme I



the k_2 process; i.e., Scheme I prevails. Hence, k_{obsd} is given by eq 8.

$$k_{\text{obsd}} = \frac{K_1[\text{RS}^-]}{1 + K_1[\text{RS}^-]} k_2 + \frac{1}{1 + K_1[\text{RS}^-]} (k_{\text{H}_2\text{O}} + k_{\text{OH}^+ \text{OH}^-}) \quad (8)$$

Since K_1 (Table III), $k_{\text{H}_2\text{O}}$,¹⁵ and k_{OH^+} ¹⁵ are known, eq 8 can be rearranged to

$$k_{\text{obsd}}(\text{CORR}) = k_{\text{obsd}} - \frac{1}{1 + K_1[\text{RS}^-]} (k_{\text{H}_2\text{O}} + k_{\text{OH}^+ \text{OH}^-}) = \frac{K_1[\text{RS}^-]}{1 + K_1[\text{RS}^-]} k_2 \quad (9)$$

Results at [HOCH₂CH₂S⁻] = 8.91×10^{-4} , 1.19×10^{-3} , and 1.49

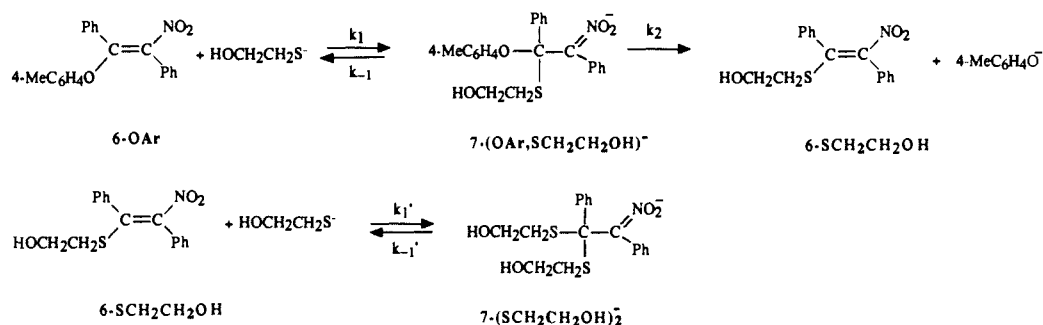
(14) Bernasconi, C. F.; Killion, R. B., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 7506.

(15) $k_{\text{H}_2\text{O}} = 2.37 \times 10^{-5}$ s⁻¹, $k_{\text{OH}^+} = 0.69$ M⁻¹ s⁻¹; Bernasconi, C. F.; Killion, R. B., Jr.; Rappoport, Z., to be published.

Table III. Summary of Rate and Equilibrium Constants for the Reaction of Nucleophiles with Ph(LG)C=CPh(NO₂) in 50% Me₂SO–50% Water at 20 °C, μ = 0.5 M (KCl)

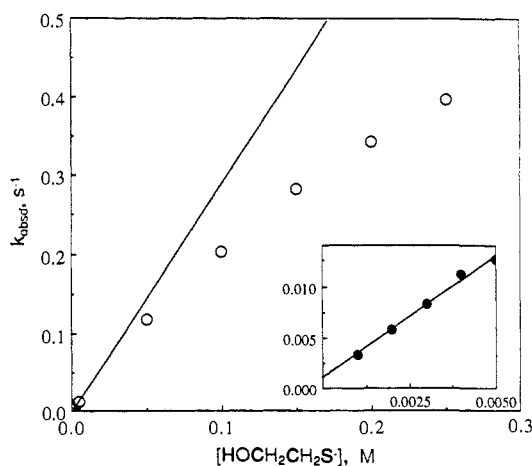
no.	LG (pK _a ^{LG})	Nu ⁻ (pK _a ^{Nu})	k ₁ (k ₁ [']), M ⁻¹ s ⁻¹	k ₋₁ (k ₋₁ [']), s ⁻¹	K ₁ = k ₁ /k ₋₁ (K ₁ ['] = k ₁ ['] /k ₋₁ [']), M ⁻¹	k ₂ , s ⁻¹
1	1 (<<0)	HOCH ₂ CH ₂ S ⁻ (10.56)	7.78 ± 0.20			
2	Cl (<<0)	HOCH ₂ CH ₂ S ⁻ (10.56)	37.8 ± 1.00			
3	4-CH ₃ C ₆ H ₄ O (11.6) ^a	HOCH ₂ CH ₂ S ⁻ (10.56)	≥2.39 ± 0.06 ^d			
4	CH ₃ O (~17.2) ^b	CH ₃ CH ₂ S ⁻ (11.26)	(4.21 ± 0.20) × 10 ²	(7.85 ± 1.73) × 10 ⁻³	(5.36 ± 1.21) × 10 ⁴	
5	CH ₃ O (~17.2) ^b	HOCH ₂ CH ₂ S ⁻ (10.56)	(3.90 ± 0.19) × 10 ²	(5.10 ± 1.00) × 10 ⁻²	(7.65 ± 1.55) × 10 ³	(9.6 ± 1.5) × 10 ⁻⁶
6	CH ₃ O (~17.2) ^b	CH ₃ O ₂ CCH ₂ CH ₂ S ⁻ (10.40)	(3.60 ± 0.16) × 10 ²	(8.99 ± 1.90) × 10 ⁻²	(4.00 ± 0.90) × 10 ³	
7	CH ₃ O (~17.2) ^b	CH ₃ O ₂ CCH ₂ S ⁻ (8.83)	(2.60 ± 0.10) × 10 ²	(5.38 ± 0.10) × 10 ⁻¹	(4.83 ± 0.12) × 10 ²	
8	HOCH ₂ CH ₂ S (10.56)	HOCH ₂ CH ₂ S ⁻ (10.56)	6.42 ± 0.08	0.504 ± 0.010	12.7 ± 0.5	
9	CH ₃ CH ₂ CH ₂ S (11.44) ^c	CH ₃ CH ₂ CH ₂ S ⁻ (11.44) ^c	11.5 ± 0.1	0.131 ± 0.007	87.8 ± 5.5	
10	HOCH ₂ CH ₂ S (10.56)	CH ₃ CH ₂ CH ₂ S ⁻ (11.44) ^c	17.7 ± 1.7	est 0.045	est 3.9 × 10 ²	~0.35 ± 0.05
11	CH ₃ O ₂ CCH ₂ CH ₂ S (10.40)	CH ₃ CH ₂ CH ₂ S ⁻ (11.44) ^c	26.4 ± 2.6	est 0.04	est 6.60 × 10 ²	~0.37 ± 0.05
12	CH ₃ O ₂ CCH ₂ CH ₂ S (10.40)	HOCH ₂ CH ₂ S ⁻ (10.56)	9.20 ± 0.90	est 0.20	est 46	~0.28 ± 0.05
13	CH ₃ CH ₂ CH ₂ S (11.44)	HOCH ₂ CH ₂ S ⁻ (10.56)	~4.74 ± 0.50	~0.45 ± 0.10	9.48 ± 2.0	
14	H ^e	CH ₃ CH ₂ S (11.26)	6.68 × 10 ⁴	3.49 × 10 ⁻³	1.91 × 10 ⁷	
15	H ^e	HOCH ₂ CH ₂ S ⁻ (10.56)	5.81 × 10 ⁴	7.02 × 10 ⁻³	8.16 × 10 ⁶	
16	H ^e	CH ₃ O ₂ CCH ₂ CH ₂ S ⁻ (10.40)	4.82 × 10 ⁴	9.47 × 10 ⁻³	5.09 × 10 ⁶	
17	H ^e	CH ₃ O ₂ CCH ₂ S ⁻ (8.83)	2.85 × 10 ⁴	1.37 × 10 ⁻¹	2.08 × 10 ⁵	

^aBased on the pK_a of phenol in 50% Me₂SO–50% water (11.35, ref 53) and the fact that in water the pK_a of 4-CH₃C₆H₄OH is 0.27 unit higher than the pK_a of phenol: Chen, D. T. Y.; Laidler, K. J. *Trans. Faraday Soc.* **1962**, *58*, 480. ^bBased on pK_a = 15.5 in water (Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1959**, *81*, 1050; **1960**, *82*, 795) and addition of 1.7 units in 50% Me₂SO–50% water, the same as the increase in pK_w of water (ref 53). ^cBased on pK_a = 11.26 for CH₃CH₂SH and addition of 0.18 unit, the difference in pK_a between CH₃CH₂SH and CH₃CH₂CH₂SH in water, ref 27a. ^dIf k₂ >> k₋₁ number given corresponds to k₁; if k₂ <<< k₋₁ number given corresponds to k₁k₂/(k₋₁ + k₂); see text. ^eReference 14.

Scheme II

× 10⁻³ M obtained by following the rate of appearance of **6-SR** by HPLC analysis are summarized in Table I. They yield a k₂ value of ~1.65 × 10⁻⁵ s⁻¹, in fair agreement with the spectrophotometric value of 9.6 × 10⁻⁶ s⁻¹ obtained at 0.05 M thiolate concentration.

Reaction of HOCH₂CH₂S⁻ with Ph(4-MeC₆H₄O)C=CPh(NO₂). Since the conditions for the detection of the intermediate are so amply met in the reaction of HOCH₂CH₂S⁻ with **6-OMe** (K₁ = 7.65 × 10³ M⁻¹, k₁ = 3.90 × 10² s⁻¹, k₂ = 9.6 × 10⁻⁶ s⁻¹), it seemed reasonable to expect that the intermediate might also be detectable in the reaction of HOCH₂CH₂S⁻ with **6-OAr**, despite the expected higher nucleofugality of the aryloxy leaving group. Hence the reaction was studied over a wide range of thiolate ion concentrations, from 10⁻³ to 0.25 M. However, at high concentrations, reaction of the product **6-SCH₂CH₂OH** with HOCH₂CH₂S⁻ to form the symmetrical adduct **7-(SCH₂CH₂OH)₂⁻** (Scheme II) introduced a complication that made the detection of possibly small levels of **7-(OAr,SCH₂CH₂OH)⁻** difficult. At low thiolate ion concentrations (<5 × 10⁻³ M) the equilibrium for the formation of **7-(SCH₂CH₂OH)₂⁻** is unfavorable (K₁['] = k₁[']/k₋₁['] = 12.7 M⁻¹; see below) and hence no significant amounts of **7-(SCH₂CH₂OH)₂⁻** are formed. The kinetics is strictly pseudo first order [λ = 360 nm, formation of **6-(SCH₂CH₂OH)**] and k_{obsd} shows a linear dependence on thiolate ion concentration [Figure 3 and Table S3 of the supplementary material¹³ (10 rate constants)]. As elaborated upon in the Discussion, for this reaction

**Figure 3.** Reaction of **6-OAr** with HOCH₂CH₂S⁻.

it is not clear whether k₂ >> k₋₁ and thus k_{obsd}/[HOCH₂CH₂S⁻] = k₁ (eq 5) or whether k₂ ≤ (<<) k₋₁, and hence, k_{obsd}/[HOCH₂CH₂S⁻] = k₁k₂/(k₋₁ + k₂) (eq 3) or k_{obsd}/[HOCH₂CH₂S⁻] = k₁k₂/k₋₁ (for k₂ << k₋₁).

At high thiolate concentrations the kinetics at 360 nm is strongly biphasic and no interpretable rate constants were obtained. This

to the first two systems, the second process manifested itself as an increase in absorbance at 360 nm because the postequilibrium $[6\text{-SR} \rightleftharpoons 7\text{-(SR)}_2^-]$ with $\text{RS}^- = \text{HOCH}_2\text{CH}_2\text{S}^-$ ($K_1' = 12.7 \text{ M}^{-1}$) does not lie as strongly on the side of 7-(SR)_2^- as with $\text{RS}^- = \text{CH}_3\text{CH}_2\text{CH}_2\text{S}^-$ ($K_1' = 87.8 \text{ M}^{-1}$).

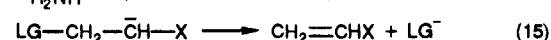
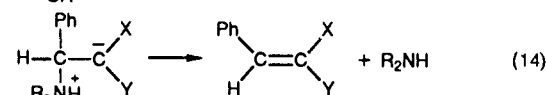
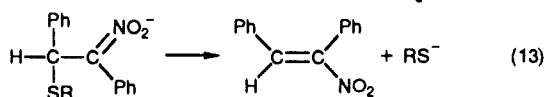
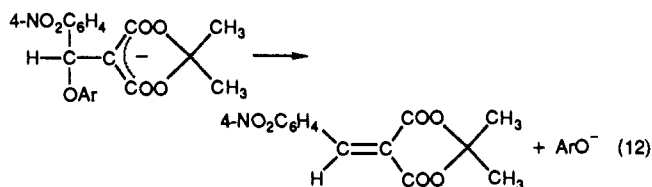
The system with $\text{R}'\text{S} = \text{CH}_3\text{CH}_2\text{CH}_2\text{S}$ and $\text{RS}^- = \text{HOCH}_2\text{CH}_2\text{S}^-$ is different from the three combinations discussed above in that the reversal of the first step (k_{-1}) must be significantly faster than the k_2 step, if the k_{-1}' values in eq 10 can be used as a guide (see above). This implies that a plot of k_{obsd} (fast process) vs $[\text{RS}^-]$ should not only provide k_1 from the slope, but also an approximate value for k_{-1} from the intercept, according to eq 7. The results are summarized in Table II and Figure 5; they afford $k_1 = 4.74 \text{ M}^{-1} \text{ s}^{-1}$, and $k_{-1} \sim 0.5 \text{ s}^{-1}$. The second process was associated with such a small change in OD that a kinetic determination was impractical.

Discussion

Detection of the Intermediate in Nucleophilic Vinylic Substitution. The most significant result of this study is that intermediates of the type **2** in the nucleophilic vinylic substitution reaction of eq 1 have been observed for the first time. They are 7-(OMe,SR)^- in eq 6 and 7-(SR,SR')^- in Scheme III.

7-(OMe,SR)^- is actually remarkably stable, both thermodynamically (with respect to reactants) and kinetically (with respect to product formation). For example, with $\text{CH}_3\text{CH}_2\text{S}^-$ as the nucleophile, the equilibrium constant for intermediate formation, K_1 , is $5.36 \times 10^4 \text{ M}^{-1}$, and even with the much less basic $\text{CH}_3\text{O}_2\text{CCH}_2\text{S}^-$, K_1 is still $4.83 \times 10^2 \text{ M}^{-1}$. The rate constant for the conversion of $7\text{-(OMe,SCH}_2\text{CH}_2\text{OH)}^-$ to products, k_2 , is $9.6 \times 10^{-6} \text{ s}^{-1}$, which is many orders of magnitude slower than its rate of formation, even at relatively low thiolate ion concentrations (e.g., $k_1[\text{HOCH}_2\text{CH}_2\text{S}^-] = 0.39 \text{ s}^{-1}$ at $[\text{HOCH}_2\text{CH}_2\text{S}^-] = 10^{-3} \text{ M}$). It thus appears that when the three factors enumerated in the introduction, i.e., strong stabilization of the carbanion by (X, Y) = (Ph, NO_2), low intrinsic rate constant for nitronate ion forming/consuming reactions, and low nucleofugality of methoxide, are combined with the strong nucleophilicity of thiolate ions,^{3b,c5f,6a} the necessary conditions for the intermediate to be observable ($K_1[\text{Nu}^-] \gg 1$ and $k_1[\text{Nu}^-] \gg k_2$) are amply met.

On the basis of the results obtained with **6-OMe**, it seemed that in the reaction of **6-OAr** with $\text{HOCH}_2\text{CH}_2\text{S}^-$ one might also be able to observe the intermediate. If the change in the leaving group from CH_3O to $4\text{-MeC}_6\text{H}_4\text{O}$ only affected k_2 , but not k_1 and K_1 , it is almost certain that the relationship $k_1[\text{HOCH}_2\text{CH}_2\text{S}^-] \gg k_2$ would still hold. Even if β_{1g} were as large as -1.0 , k_2 would only become $\sim 3.8 \text{ s}^{-1}$ based on $\text{p}K_a(\text{CH}_3\text{OH}) - \text{p}K_a(4\text{-MeC}_6\text{H}_4\text{OH}) \approx 5.6$. With $k_1 = 3.90 \times 10^2$ we would have $k_1[\text{HOCH}_2\text{CH}_2\text{S}^-]/k_2 \geq 10$ at $[\text{HOCH}_2\text{CH}_2\text{S}^-] \geq 0.098 \text{ M}$. It is likely that β_{1g} in our system would be less negative than -1.0 . For example, β_{1g} for reaction 12 is -0.63 ,¹⁸ β_{1g} for reaction 13



is -0.68 ,¹⁴ β_{1g} for reactions of the type of eq 14 ranges from -0.50

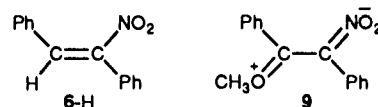
to -0.84 ,^{3c} while the $k(\text{C}_6\text{H}_5\text{O})/k(\text{CH}_3\text{O})$ ratios of ~ 80 and 631 for reactions 15^{11a} with $\text{X} = \text{CN}$ and $\text{X} = \text{PhSO}_2$, respectively, correspond to $\beta_{1g} \approx -0.34$ and $\beta_{1g} \approx -0.50$, respectively, based on the $\text{p}K_a(\text{LG})$ values in Table III. This would imply a $k_2 \ll 3.8 \text{ s}^{-1}$ for the reaction of **6-OAr** with $\text{HOCH}_2\text{CH}_2\text{S}^-$ and a $k_1[\text{HOCH}_2\text{CH}_2\text{S}^-]/k_2 \gg 10$ at $[\text{HOCH}_2\text{CH}_2\text{S}^-] \ll 0.1 \text{ M}$.

The evidence for the observation of the intermediate is discussed under Results. The slightly biphasic kinetic plots and the curvilinear dependence of k_{obsd} on $[\text{HOCH}_2\text{CH}_2\text{S}^-]$ in Figure 2 are suggestive for some accumulation of the intermediate, but we do not consider these findings to constitute compelling evidence. Even if there is some accumulation, the $k_1[\text{HOCH}_2\text{CH}_2\text{S}^-]/k_2$ ratio and/or $K_1[\text{HOCH}_2\text{CH}_2\text{S}^-]$ are (is) much smaller than the above calculations imply. It is most likely that the difficulty in detecting the intermediate is mainly a steric effect owing to the bulkiness of the $4\text{-CH}_3\text{C}_6\text{H}_4\text{O}$ group. This steric effect, which can be clearly seen with space-filling molecular models, probably reduces k_1 and enhances k_{-1} and k_2 , which results in lower K_1 and k_1/k_2 values.

In the reactions where the leaving group is a thiolate (Scheme III), the intermediate 7-(SR,SR')^- was observable for all combinations of R and R' studied, i.e., $\text{RS}^- = \text{Nu}^- = \text{CH}_3\text{CH}_2\text{CH}_2\text{S}^-$ with $\text{R}'\text{S} = \text{LG} = \text{HOCH}_2\text{CH}_2\text{S}$ and $\text{CH}_3\text{O}_2\text{CCH}_2\text{CH}_2\text{S}$, and $\text{RS}^- = \text{Nu}^- = \text{HOCH}_2\text{CH}_2\text{S}^-$ with $\text{R}'\text{S} = \text{LG} = \text{CH}_3\text{CH}_2\text{CH}_2\text{S}$ and $\text{CH}_3\text{O}_2\text{CCH}_2\text{CH}_2\text{S}$. However, inspection of Table III reveals that k_1 and K_1 are considerably smaller and k_2 is considerably larger than in the reactions of thiolate ions with **6-OMe**, making $K_1[\text{RS}^-]$ and $k_1[\text{RS}^-]/k_2$ much less favorable and, hence, requiring much higher thiolate ion concentrations for the intermediates to accumulate. For example, with $\text{Nu}^- = \text{CH}_3\text{CH}_2\text{CH}_2\text{S}^-$ and $\text{LG} = \text{HOCH}_2\text{CH}_2\text{S}$ a nucleophile concentration of 0.2 M is necessary to make $k_1[\text{RS}^-]/k_2 \approx 10$, while with $\text{Nu}^- = \text{HOCH}_2\text{CH}_2\text{S}^-$ and $\text{LG} = \text{CH}_3\text{O}_2\text{CCH}_2\text{CH}_2\text{S}$, $k_1[\text{RS}^-]/k_2$ is ~ 6.6 at $0.2 \text{ M HOCH}_2\text{CH}_2\text{S}^-$.

Structure-Reactivity Relationships. The dependence on structure of the rate and equilibrium constants summarized in Table III is the result of a delicate interplay of a variety of factors. A prominent factor mentioned previously is steric crowding in the intermediate, which reduces k_1 and K_1 and enhances k_2 . One manifestation of the steric effect is the low k_1 values for **6-Cl** ($37.8 \text{ M}^{-1} \text{ s}^{-1}$) and **6-I** ($7.78 \text{ M}^{-1} \text{ s}^{-1}$), compared to the reaction of the same nucleophile with **6-OMe** ($3.90 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$), and also the fact that $k_1(\text{Cl})/k_1(\text{I}) = 4.86$; if electronic factors were dominant, **6-Cl** should be more reactive than **6-OMe**.¹⁹ As discussed earlier, the reduced reactivity of **6-OAr** compared to **6-OMe** can also be traced, at least in part, to a steric effect.

The finding that $k_1 = 3.9 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ for the reaction of $\text{HOCH}_2\text{CH}_2\text{S}^-$ with **6-OMe** is 149-fold lower than for the reaction with $\text{PhCH}=\text{CPh}(\text{NO}_2)$ (**6-H**) ($5.18 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$) and $K_1 =$



$7.65 \times 10^3 \text{ M}^{-1}$ is 1.07×10^3 fold lower ($K_1 = 8.16 \times 10^6 \text{ M}^{-1}$) may again, in part, be due to a steric effect. However, resonance stabilization of **6-OMe** (**9**) is likely to be a major contributor to the lowering of k_1 and K_1 . This notion is supported by a comparison of the intrinsic rate constants ($k_0 = k_1 = k_{-1}$ when $K_1 = 1$)²¹ for thiolate ion addition to **6-OMe** and **6-H**. A $\log k_0 = 2.16$

(19) The stronger electron-withdrawing inductive effect of Cl is reflected in the σ_1 values, which are 0.48 for Cl and 0.34 for OMe.²⁰

(20) Exner, O. In *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum: New York, 1978; p 439.

(21) As pointed out by a reviewer, this definition of k_0 creates a problem of units because k_1 is in units of $\text{M}^{-1} \text{ s}^{-1}$ and k_{-1} in s^{-1} . A possible solution to the problem was suggested by Hine,²² but his solution suffers from the disadvantage of having to assume the same equilibrium constant for encounter complex formation between nucleophile and electrophile in all reactions. When relative k_0 values are compared, little numerical difference exists between our and Hine's definition.

(22) Hine, J. *J. Am. Chem. Soc.* **1971**, *93*, 3701.

(18) Bernasconi, C. F.; Leonarduzzi, G. D. *J. Am. Chem. Soc.* **1982**, *104*, 5133.

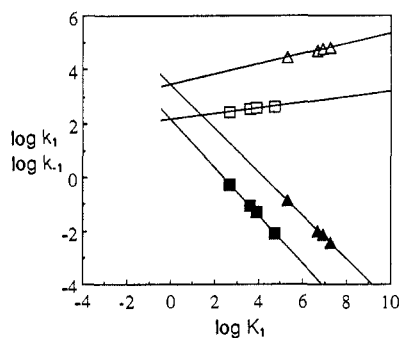
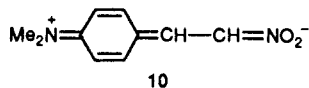


Figure 6. Plots of $\log k_1$ and $\log k_{-1}$ vs $\log K_1$ for the addition of thiolate ions to 6-Ome (\square , \blacksquare) and 6-H (Δ , \blacktriangle), respectively. The points of intersection of the lines for $\log k_1$ and $\log k_{-1}$ at $\log K_1 = 0$ correspond to $\log k_0$; see Discussion.

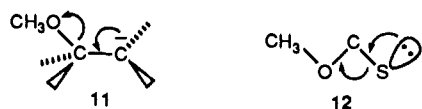
for 6-Ome is obtained by extrapolating a plot of $\log k_1$ or $\log k_{-1}$ vs $\log K_1$ to $\log K_1 = 0$ (Figure 6). This compares with $\log k_0 = 3.43$ for 6-H.¹⁴ Resonance effects typically lead to a lower k_0 because their development (in a product) generally lags behind bond formation, or their loss (in a reactant) is ahead of bond formation.¹⁰ Thus, the decrease from $\log k_0 = 3.43$ (LG = H) to $\log k_0 = 2.16$ (LG = CH₃O) is consistent with a resonance effect as shown in 9.

A reviewer has suggested that inasmuch as charge is already delocalized by resonance in the starting material (9), this could lead to an increase rather than a decrease in k_0 . Such a phenomenon has indeed been observed in the addition of piperidine to β -nitrostyrenes, where k_0 for the *p*-dimethylamino derivative is higher than for the parent β -nitrostyrene,²³ presumably because the negative charge is already partially delocalized into the nitro group of the substrate (10). As discussed elsewhere,^{3c,23} there



is a delicate balance between the k_0 increasing effect of this kind of resonance and its k_0 decreasing effect; in the present case (9) the net result of the two effects appears to be a decrease of k_0 .

It is interesting to note that in the absence of steric and resonance effects the addition intermediate derived from 6-Ome may actually be thermodynamically somewhat more stable (relative to the reactants) than that derived from 6-H, owing to two factors. The first is hyperconjugative stabilization^{4f,24} by the CH₃O group (11); the second is an anomeric effect^{25,26} caused by having an



oxygen and a sulfur attached to the same carbon (12). It is difficult to assess, without detailed calculation, whether these factors would lead to a significant increase in the stabilization of the adduct derived from 6-Ome, but if they do, this implies that the steric and resonance effects may be even larger than the differences in k_1 and K_1 suggest.

When both the nucleophile and the leaving group are thiolates, k_1 and K_1 are substantially smaller than for LG = MeO. For example, for the symmetrical adduct 7-(SCH₂CH₂OH)₂⁻, $K_1 =$

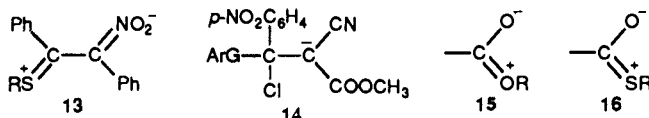
Table IV. Brønsted β Values and $\log k_0$ for the Addition of Thiolate Ions to Ph(MeO)C=CPh(NO₂) and PhCH=CPh(NO₂) in 50% Me₂SO-50% Water at 20 °C

parameter	Ph(MeO)C=CPh(NO ₂) (6-Ome)	PhCH=CPh(NO ₂) ^a (6-H)
$\beta_{\text{nuc}} = \text{dlog } k_1 / \text{dp}K_a^{\text{RSH}}$	0.09 ± 0.01	0.16 ± 0.02
$\beta_{\text{lg}} = \text{dlog } k_{-1} / \text{dp}K_a^{\text{RSH}}$	-0.71 ± 0.14	-0.68 ± 0.06
$\beta_{\text{eq}} = \text{dlog } K_1 / \text{dp}K_a^{\text{RSH}}$	0.80 ± 0.13	0.84 ± 0.07
$\beta_{\text{nuc}}^{\text{p}} = \beta_{\text{nuc}} / \beta_{\text{eq}} = \text{dlog } k_1 / \text{dlog } K_1$	0.11 ± 0.02	0.19 ± 0.03
$\beta_{\text{lg}}^{\text{p}} = \beta_{\text{lg}} / \beta_{\text{eq}} = \text{dlog } k_{-1} / \text{dlog } K_1$	-0.89 ± 0.02	-0.81 ± 0.10
$\log k_0$	2.16 ± 0.09	3.43 ± 0.10

^aReference 14.

12.7 M⁻¹ is 602-fold lower than K_1 for HOCH₂CH₂S⁻ addition to 6-Ome, while $k_1 = 6.42$ M⁻¹ s⁻¹ is reduced 61-fold. Again it appears that steric crowding in the adduct is mainly responsible for these reductions. Another factor that would tend to reduce K_1 and k_1 for nucleophilic addition to 6-SR compared to 6-Ome is the anomeric stabilization of the adduct, which should be weaker with LG = RS compared to LG = MeO.^{26a}

The steric and anomeric effects are probably somewhat counteracted by a stronger resonance stabilization of 6-Ome (9) compared to 6-SR (13). That the π overlap with oxygen may



be stronger than with sulfur can be deduced from the observation that Cl⁻ departure from 14 (G = O) appears to be faster than from 14 (G = S).^{4b} In the breakdown of tetrahedral intermediates, the "push" exerted by RO groups is also generally stronger than that exerted by RS groups,²⁷ suggesting that the resonance structure 15 in an ester is more significant than 16 in a thiol ester. This is in agreement with ab initio calculations,²⁸ although it has recently been claimed that the push exerted by ArS is stronger than that exerted by an ArO group of comparable basicity.²⁹ In conclusion, if the resonance stabilization of 6-SR (13) is weaker than that of 6-Ome (9),³⁰ this would enhance k_1 and K_1 for 6-SR.

Turning to the product-forming step, the k_2 values for RS departure are [(3-4) × 10⁴]-fold higher than the k_2 for the CH₃O departure. In the absence of more data it is difficult to assess how much of this difference may be attributed to the lower basicity of the thiolate leaving groups (see pK_a values in Table III), to the greater steric strain in 7-(SR,SR')⁻, to a smaller anomeric effect in 7-(SR,SR')⁻, and to a higher intrinsic rate for thiolate vs alkoxide ion departure.¹⁴ It should be noted, though, that the [(3-4) × 10⁴]-fold acceleration in k_2 actually underestimates the combined influence of these factors. This is because thiolate ions have stronger carbon basicities than oxyanions of the same pK_a,^{31,32} and hence, for a given pK_a of the leaving group, and in the absence of steric and anomeric effects, the stability of 7-(SR,SR')⁻ relative

(27) (a) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451. (b) Jensen, J. L.; Jencks, W. P. *Ibid.* **1979**, *101*, 1476. (c) Santry, L. J.; McClelland, R. A. *Ibid.* **1983**, *105*, 3167.

(28) (a) Hayes, D. M.; Kenyon, G. L.; Kollman, P. A. *J. Am. Chem. Soc.* **1978**, *100*, 4331. (b) Santry, L. J.; Poirier, R. A.; McClelland, R. A.; Cszimadia, I. G. *Theor. Chim. Acta* **1984**, *65*, 139.

(29) Castro, E. A.; Ureta, C. *J. Org. Chem.* **1989**, *54*, 2153.

(30) Since MeO⁻ is considerably more basic than RS⁻, the arguments of ref 29 probably do not apply.

(31) (a) Hine, J.; Welmar, R. D., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 3387. (b) Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley: New York, 1975; p 225. (c) Sander, E. G.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 6154.

(32) (a) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827. (b) Pearson, R. G. *Surv. Prog. Chem.* **1969**, *5*, 1.

(23) Bernasconi, C. F.; Renfrow, R. A.; Tla, P. R. *J. Am. Chem. Soc.* **1986**, *108*, 4541.

(24) (a) Apeloig, Y.; Rappoport, Z. *J. Am. Chem. Soc.* **1979**, *101*, 5095. (b) Apeloig, Y.; Karni, M.; Rappoport, Z. *Ibid.* **1983**, *105*, 2784. (c) Rappoport, Z.; Avramovitch, B.; Karni, M.; Apeloig, Y. *Isr. J. Chem.*, in press.

(25) (a) Kirby, A. G. *The Anomeric Effect and Related Stereoelectronic Effects of Oxygen*; Springer Verlag: Berlin, 1983. (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983.

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to products should be higher than that of 7-(OMe,SR)⁻ toward MeO loss. This factor would reduce k_2 for the breakdown of 7-(SR,SR')⁻.

Brønsted Relations. β_{nuc} , β_{lg} , and β_{eq} for the reaction of 6-OMe with four thiolate ions, obtained from plots (not shown) of $\log k_1$, $\log k_{-1}$, and $\log K_1$, respectively, vs $\text{p}K_{\text{a}}^{\text{RSH}}$, are summarized in Table IV. As can be seen from the standard deviations of the β values, the scatter in the Brønsted plots is minor. Plots of $\log k_1$ and $\log k_{-1}$ vs $\log K_1$ (Figure 6), which yield the normalized β values ($\beta_{\text{nuc}}^{\text{n}}$, $\beta_{\text{lg}}^{\text{n}}$), are of even better quality. These normalized β values are also included in Table IV, as are the corresponding Brønsted β values for the reaction of 6-H with the same thiolate ions.¹⁴

β_{nuc} and $\beta_{\text{nuc}}^{\text{n}}$ are quite small, suggesting that charge transfer from the nucleophile to the substrate, and with it C-S bond formation, has probably made little progress at the transition state.³³ This is true for both substrates. The fact that β_{nuc} and $\beta_{\text{nuc}}^{\text{n}}$ for 6-OMe are even smaller than for 6-H is difficult to interpret: a simplistic application of the reactivity-selectivity principle^{34a,36} (RSP) would have predicted that β_{nuc} ($\beta_{\text{nuc}}^{\text{n}}$) for 6-OMe should be *higher* rather than lower. However, since the two substrates differ so strongly with respect to steric, resonance, and anomeric effects, the transition-state should probably not be expected to conform to the predictions of the RSP.

When the leaving group is a thiolate (6-SR), β_{nuc} appears to be significantly larger than when it is methoxide. From two-point Brønsted plots ($\text{Nu}^- = \text{CH}_3\text{CH}_2\text{CH}_2\text{S}^-$ and $\text{HOCH}_2\text{CH}_2\text{S}^-$) one calculates $\beta_{\text{nuc}} = 0.44 \pm 0.05$ for $\text{LG} = \text{CH}_3\text{CH}_2\text{CH}_2\text{S}$, $\beta_{\text{nuc}} = 0.50 \pm 0.05$ for $\text{LG} = \text{HOCH}_2\text{CH}_2\text{S}$, and $\beta_{\text{nuc}} = 0.52 \pm 0.09$ for $\text{LG} = \text{CH}_3\text{O}_2\text{CCH}_2\text{CH}_2\text{S}$. Within experimental error, these β_{nuc} values are all the same but much larger than for thiolate ion addition to either 6-OMe or 6-H. In this case the larger β_{nuc} values could be rationalized by the RSP, but again in view of the diversity of factors that are responsible for the reduced reactivity of 6-OMe, there is probably no particular physical insight to be gained from this apparent adherence to the RSP.

Inspection of Table III shows that the $\text{p}K_{\text{a}}$ of the thiolate leaving group also affects k_1 for a given nucleophile. For example, with $\text{Nu}^- = \text{CH}_3\text{CH}_2\text{CH}_2\text{S}^-$, k_1 increases from 11.5 to 17.7 to 26.4 $\text{M}^{-1} \text{s}^{-1}$ when LG is changed from $\text{CH}_3\text{CH}_2\text{CH}_2\text{S}$ to $\text{HOCH}_2\text{CH}_2\text{S}$ to $\text{CH}_3\text{O}_2\text{CCH}_2\text{CH}_2\text{S}$. In a similar way, with $\text{Nu}^- = \text{HOCH}_2\text{CH}_2\text{S}^-$, k_1 increases from 4.74 to 6.42 to 9.20 for the same changes in LG. This effect of the leaving group on k_1 , which corresponds to an average $\beta_{\text{lg}}(k_1) = \text{dlog } k_1/\text{dp}K_{\text{lg}} = -0.27 \pm 0.11$, may reflect a decreasing contribution of the resonance form 13 as the basicity of LG decreases, resulting in a destabilization of the olefin, and/or simply an inductive effect (stabilization of the intermediate and transition state by a more electron withdrawing LG). These electronic effects also lead to a decrease in k_{-1} with decreasing basicity of LG, as shown by comparing entries 8 and 13 in Table III. Since $k_{-1} = 0.504 \text{ s}^{-1}$ for entry 8 is favored by a statistical factor of 2 over entry 13, the statistically corrected k_{-1} for the loss of $\text{HOCH}_2\text{CH}_2\text{S}^-$ from 7-($\text{SCH}_2\text{CH}_2\text{OH}$)₂⁻ (0.252 s^{-1}) is seen to be significantly lower than k_{-1} for the loss of $\text{HOCH}_2\text{CH}_2\text{S}^-$ from 7-($\text{SCH}_2\text{CH}_2\text{OH}, \text{SCH}_2\text{CH}_2\text{CH}_3$)⁻ ($\sim 0.45 \text{ s}^{-1}$, entry 13), corresponding to a $\beta_{\text{lg}}(k_{-1}) = \text{dlog } k_{-1}/\text{dp}K_{\text{lg}} = 0.29$.

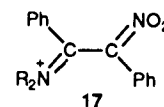
By taking the leaving group effect on k_{-1} into account, we have estimated k_{-1} and, hence, K_1 values for entries 10–12. For example, $k_{-1} \approx 0.045 \text{ s}^{-1}$ for entry 10 was arrived at by first dividing k_{-1} of entry 9 (0.131) by the statistical factor of 2 and then by

another factor of 1.45, which is the estimated correction for the change from $\text{LG} = \text{CH}_3\text{CH}_2\text{CH}_2\text{S}$ to $\text{HOCH}_2\text{CH}_2\text{S}$; k_{-1} for entries 11 and 12 were estimated by using similar reasoning.

As one would expect, k_2 is affected by electronic effects in a way similar to k_{-1} . For example, the k_2 value of 0.35 s^{-1} for the expulsion of $\text{HOCH}_2\text{CH}_2\text{S}^-$ from 7-($\text{SCH}_2\text{CH}_2\text{OH}, \text{SCH}_2\text{CH}_2\text{CH}_3$)⁻ (entry 10) can be understood as follows. In the absence of electronic effects, k_2 should be equal to $0.5k_{-1} = 0.252 \text{ s}^{-1}$ for the breakdown of 7-($\text{SCH}_2\text{CH}_2\text{OH}$)₂⁻ (entry 8). The enhanced value of 0.35 s^{-1} must therefore reflect the larger product resonance effect in 6- $\text{SCH}_2\text{CH}_2\text{CH}_3$ compared to 6- $\text{SCH}_2\text{CH}_2\text{OH}$ and/or the reduced inductive stabilization of 7-($\text{SCH}_2\text{CH}_2\text{OH}, \text{SCH}_2\text{CH}_2\text{CH}_3$)⁻ compared to 7-($\text{SCH}_2\text{CH}_2\text{OH}$)₂⁻. A similar conclusion is reached by comparing k_2 for entries 11 and 12. Incidentally, k_2 in entry 10 and k_{-1} in entry 13 refer to the same process, i.e., loss of $\text{HOCH}_2\text{CH}_2\text{S}^-$ from 7-($\text{SCH}_2\text{CH}_2\text{OH}, \text{SCH}_2\text{CH}_2\text{CH}_3$)⁻; it is rewarding that, within experimental error, they have the same value.

Comparison with Other Systems and Concluding Remarks. Why are 7-(OMe,SR)⁻ and 7-(SR',SR')⁻ the first intermediates reported to accumulate to detectable levels during a nucleophilic vinylic substitution? As we have seen, in the case of 7-(OMe,SR)⁻, all the factors known to make $K_1[\text{Nu}^-] \gg 1$ and $k_1[\text{Nu}^-]/k_2 \gg 1$, and to lead to a low absolute value of k_2 , are simultaneously present: (a) RS^- is a powerful nucleophile (high k_1 and K_1); (b) (X, Y) = (Ph, NO_2) is an excellent stabilizer of negative charge (high k_1 and K_1 , low k_2); (c) the intrinsic rate of carbanion forming/consuming reactions is low with (X, Y) = (Ph, NO_2) (low k_2); (d) CH_3O is a very poor leaving group (low k_2). Replacement of CH_3O for RS as leaving group still leads to detectable intermediates, but only under conditions of high nucleophile concentrations. When other factors become less than optimal, the intermediate is no longer detectable. For example, for the change in leaving group from CH_3O to 4-MeC₆H₄O, the lowering of k_1 and K_1 (mainly steric effect) and the increase in k_2 (mainly $\text{p}K_{\text{a}}$ and steric effect) are already sufficient to render the intermediate spectrophotometrically undetectable, or perhaps just marginally detectable. With much better leaving groups such as Cl or I there is no expectation to even approach the conditions necessary for detection, mainly due to very high k_2 values. The same is true for the reaction of 4-ClC₆H₄S⁻ with 6-Cl or 6-I in ethanol and methanol.^{5f}

The change of nucleophile from RS^- to pyrrolidine or piperidine is also sufficient to render the intermediate undetectable by spectrophotometry, even when all the other features (b–d) are preserved.³⁷ This appears to be the consequence of a strongly reduced k_1 , due to the lower nucleophilicity of amines and greater steric congestion in the adducts, probably in combination with an enhanced k_2 , due to the same steric hindrance, coupled with a stronger resonance stabilization of the product (17).



In the numerous other examples of nucleophilic vinylic substitution studied to date there are typically at least two of the factors missing that would be conducive to detection of the intermediate. (1) The substrates have (X, Y) that are less effective stabilizers of negative charge (especially in the nonaqueous solvents commonly used), and/or lead to higher intrinsic rates than (Ph, NO_2), such as (COOR)₂,^{4d,e,38} (COOR, CHO),^{4d} (CN, COOR),^{4b,f} (Ph, CHO),^{4c} (Ph, CN),³⁹ (CN)₂,^{5a,c,e,38,40} (H, NO_2),⁴¹ and C₆H₄(CO)₂.^{5d} The $\text{p}K_{\text{a}}$ values of the carbon acids CH_2XY ,^{42,43} or

(33) This is the traditional interpretation of β_{nuc} or $\beta_{\text{nuc}}^{\text{n}}$.³⁴ However, the use of β_{nuc} or $\beta_{\text{nuc}}^{\text{n}}$ as measures of transition-state structure has been questioned.³⁵

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the equilibrium constants for nucleophilic addition to $\text{PhCH}=\text{CXY}^{3c}$ may be used as approximate guides to the stabilizing effect of (X, Y), while the intrinsic rate constants for nucleophilic addition to $\text{PhCH}=\text{CXY}^{3c,6b,10b}$ may serve as a relative measure of the intrinsic rate constant of the k_2 step for a given leaving group. Except for 1,3-indanedione [(X, Y) = $\text{C}_6\text{H}_4(\text{CO})_2$] whose pK_a is 7.00,⁴⁴ all the other CH_2XY are much less acidic than phenylnitromethane [(X, Y) = (Ph, NO_2)], whose aqueous pK_a is 6.88.⁴⁵ However, the intrinsic rate constant for OH^- addition to benzylidene-1,3-indanedione⁴⁶ is $\sim 10^5$ fold higher than for OH^- addition to α -nitrostilbene,⁴⁷ implying a higher k_2 value when (X, Y) = $\text{C}_6\text{H}_4(\text{CO})_2$.

(2) The leaving groups, with few exceptions (CN^- ,^{5c,d} EtO^{5c}), are usually fairly good to excellent nucleofuges (halogens,^{4a-f,5a,c,38-41,48} TsO^- ,^{4f,38} $\text{CF}_3\text{CH}_2\text{O}^{5c}$), and/or the nucleophiles are not as powerful as thiolate ions ($\text{RR}'\text{NH}^-$,^{4a,5c,e,38,39} ArNH_2^- ,^{5a,d,38,40,41} ArO^- ,^{4c-f,48} N_3^- ,^{4a-c} SCN^- ,^{4a,24c} CH_3O^- ,^{4b,c,e} EtO^- ,³⁹ AcO^{4b}). In those cases where thiolate ions, primarily ArS^- , have been used,^{4a-f,38b,39a,48} the leaving group was invariably too nucleofugic and/or (X, Y) was too weak.

Experimental Section

Materials. $\text{Ph}(\text{I})\text{C}=\text{CPh}(\text{NO}_2)$ (**6-I**) was prepared according to Stevens and Emmons⁴⁹ and the configuration follows the assignment of Freeman and Stevens,⁵⁰ which is based on UV spectroscopy; mp 189 °C, purification procedure and spectral properties are given in ref 5f. $\text{Ph}(\text{Cl})\text{C}=\text{CPh}(\text{NO}_2)$ (**6-Cl**) was synthesized according to Iwai et al.,⁵¹ mp 144 °C, purification procedure and spectral properties are given in ref 5f. $\text{Ph}(\text{MeO})\text{C}=\text{CPh}(\text{NO}_2)$ (**6-OMe**) was prepared as described by Rappoport and Gazit.^{4c} The product was a 6:4 Z/E mixture, mp 82 °C. $\text{Ph}(4\text{-MeC}_6\text{H}_4\text{O})\text{C}=\text{CPh}(\text{NO}_2)$ (**6-OAr**) was available from a previous study.^{5f}

$\text{Ph}(\text{HOCH}_2\text{CH}_2\text{S})\text{C}=\text{CPh}(\text{NO}_2)$ (**6-SCH₂CH₂OH**). To a solution of 0.0364 g (0.140 mmol) of **6-Cl** in 5 mL of acetonitrile was added 0.098 mL (1.40 mmol) of $\text{HOCH}_2\text{CH}_2\text{SH}$, followed by 0.195 mL (1.40 mmol) of triethylamine. The solution was stirred for 1.5 h, then poured into 25 mL of dichloromethane, and washed with 3×25 mL of water. After drying the dichloromethane layer with Na_2SO_4 and evaporation under reduced pressure, a yellow oil was obtained. Recrystallization from 95% ethanol gave 0.015 g (36% yield) of yellow crystals: mp 71–72 °C; $^1\text{H NMR}$ (60 MHz, CDCl_3) δ 7.43, 7.21 (ArH), 3.62 (CH_2O , t), 2.50 (CH_2S , t), 2.11 (OH, br, exchangeable with D_2O), 1.98 (OH, exchangeable); MS, m/e = 301 (M^+).

The $^1\text{H NMR}$ analysis⁵² suggests that the product, presumably the E isomer,⁹ contains a small amount of the Z isomer. The signal representing SCH_2 at δ 2.50 appears to be two sets of triplets, a large one at δ 2.50 (J = 6 Hz) and a smaller one at δ 2.45 (J = 6 Hz). The signal representing OCH_2 at δ 3.62 appears to be a distorted quartet but is actually two sets of triplets, a large one at δ 3.62 (J = 6 Hz) and a smaller one at δ 3.52 (J = 6 Hz). The signals appearing at δ 2.11 (br,

large) and 1.98 (small) both exchange with D_2O and are attributed to the OH of the E and Z isomers, respectively.

The presence of two isomers was confirmed by HPLC analysis in 45% acetonitrile–55% water (1.5 mL/min, 40 °C, reverse phase, ODS Hypersil, 4.6×100 mm column). Two peaks with very similar, though not identical, UV spectra (λ_{max} = 360 nm) were observed, with retention times of 2.79 (major) and 3.23 min (minor), respectively.

$\text{Ph}(\text{CH}_3\text{CH}_2\text{CCH}_2\text{CH}_2\text{S})\text{C}=\text{CPh}(\text{NO}_2)$ (**6-SCH₂CH₂CH₂CH₃**). To a solution of 0.05 g (0.140 mol) of **6-I** in 5 mL of acetonitrile was added 0.127 mL (1.40 mmol) of propanethiol, followed by 0.195 mL (1.40 mmol) of triethylamine. The solution was stirred for 10 h and then worked up and recrystallized: mp 117–118 °C; $^1\text{H NMR}$ (300 MHz, CD_3CN) δ 7.20 (ArH, s), 2.17–2.22 (CH_2S , t), 1.40–1.47 ($\text{CH}_3\text{CH}_2\text{CH}_2$, sextet), 0.75–0.80 (CH_3 , t); MS m/e = 299 (M^+). The product was pure by HPLC analysis.

$\text{Ph}(\text{CH}_3\text{O}_2\text{CCH}_2\text{CH}_2\text{S})\text{C}=\text{CPh}(\text{NO}_2)$ (**6-SCH₂CH₂CO₂CH₃**). The synthetic procedure was completely analogous to that for **6-SCH₂CH₂CH₂CH₃**: mp 74–75 °C; $^1\text{H NMR}$ (300 MHz, CD_3CN) δ 7.20 (ArH, s), 3.50 (CH_3 , s), 2.39–2.45 (CH_2CH_2 , m); MS m/e = 343 (M^+). The product was pure by HPLC analysis.

Ethaneithiol (bp 35 °C (760 mmHg), Aldrich), 2-mercaptoethanol (bp 55 °C (13 mmHg), Aldrich), methyl 3-mercaptopropionate (bp 54–55 °C (14 mmHg), Aldrich), and methyl mercaptoacetate (bp 42–43 °C (10 mmHg), Aldrich) were distilled under vacuum and stored under nitrogen. DABCO (1,4-diaza[2.2.2]bicyclooctane) was purified by sublimation or recrystallization from hexane. Triethylamine was refluxed over calcium hydride, distilled, and stored in the dark at 4 °C.

Solutions. All solutions were prepared in 50% Me_2SO –50% water (v/v) with potassium chloride added as a compensating electrolyte in order to maintain a constant ionic strength of μ = 0.50 M. The solutions were purged with nitrogen or argon before adding the thiol. All pH measurements were performed on an Orion Research 611 digital pH meter calibrated for 50% Me_2SO –50% water (v/v) with buffers described by Hallé et al.⁵³

HPLC Analysis. The HPLC analyses were performed on a reverse-phase, ODS Hypersil, 4.6×100 mm column using a Hewlett-Packard 1090M instrument with diode-array detection. Typical conditions were 40 °C, 1.5 mL/min, and acetonitrile (AN)–water mixtures ranging from 45% AN–55% H_2O to 65% AN–35% H_2O .

Kinetics. The fast reactions were monitored in a Durrum-Gibson stopped-flow spectrophotometer and the slow ones in a Perkin-Elmer 559A UV/vis spectrophotometer, both thermostated and equipped with computerized data acquisition and analysis. The procedures were similar to the ones described before.¹⁴ The method of initial rates was used in measuring the kinetics of the k_2 step in the reaction of **6-OMe** with $\text{HOCH}_2\text{CH}_2\text{S}^-$. k_{obsd} was obtained according to eq 16, with c_0 being the

$$k_{\text{obsd}} = \frac{\Delta\text{OD}}{\Delta t} = \frac{1}{c_0/(\epsilon_f - 0.61\epsilon_p)} \quad (16)$$

initial concentration of $7\text{-(OMe,SCH}_2\text{CH}_2\text{OH)}^-$ and ϵ_f and ϵ_p being the extinction coefficients of $7\text{-(OMe,SCH}_2\text{CH}_2\text{OH)}^-$ and **6-SCH₂CH₂OH**, respectively; the factor 0.61 corrects for the fact that under the experimental conditions (0.05 M $\text{HOCH}_2\text{CH}_2\text{S}^-$) 39% of the product **6-SCH₂CH₂OH** is converted into $7\text{-(SCH}_2\text{CH}_2\text{OH)}_2^-$ according to eq 10. At the wavelength chosen (360 nm), ϵ_f = 0 and ϵ_p = 7.56×10^3 .

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Supplementary Material Available: Tables S1–S4 containing pseudo-first-order rate constants (k_{obsd}) for the reactions of thiolate ions with various $\text{Ph}(\text{LG})\text{C}=\text{CPh}(\text{NO}_2)$ (5 pages). Ordering information is given on any current masthead page.

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