pentane–CH_2Cl_2 (1:1) as eluent. The compounds isolated in order of increasing R_f values were **24** (30 mg), **25** (70 mg), **8** (20 mg), and 2-phenyl-2-norbornene (20 mg). For **25**: mp 80–81 °C; ^1H NMR δ 4.20 (d, J = 2.1 Hz, 1 H), 3.75 (s, 3 H), 2.78 (m, 1 H), 2.40 (m, 1 H), 2.20 (d, J = 10.7 Hz, 1 H), 1.75 (m, 2 H), 1.20 (m, 3 H); ^{13}C NMR 171.98 (s), 83.90 (s), 68.88 (d), 52.88 (q), 44.04 (d), 41.66 (d), 34.19 (t), 26.70 (t), 25.08 (t) ppm; IR (neat) 2950, 1720, 1420, 1250, 1218, 1010, 760 cm^{-1}; mass spectrum for $C_9H_{12}O_2S_3$, calcd 247.9999, obsd 247.9988. Yield of **25** based on recovered **8** was 68%.

Reaction of 26 with 8. A solution of **8** (130 mg, 0.49 mmol) and **26** (80 mg, 0.53 mmol) in benzene (1 mL) was heated in a sealed tube at 100 °C for 12 h. The benzene was removed under reduced pressure, and the crude material was chromatographed over silica gel with pentane–ether (9:1) as eluent. The compounds isolated in order of increasing R_f were **26** (20 mg), **27**, and **28** as a mixture (45 mg, 40% based on recovered **8**), **8** (20 mg), and 2-phenyl-2-norbornene (40 mg). The mixture of **27** and **28** was separated by a second chromatography over silica gel with pentane–CH_2Cl_2 (1:1) as eluent to give **28** (R_f 0.31, 20 mg) and **27** (R_f 0.51, 20 mg). For **28**: ^1H NMR δ 7.20 (d, J = 3.1 Hz, 1 H), 4.10 (AB q, J_1 = 18.1 Hz, J_2 = 1.9 Hz, 2 H), 3.78 (s, 3 H), 3.30 (m, 1 H), 3.08 (m, 1 H), 2.60 (d, J = 9.8 Hz), 1.85 (d, J = 9.8 Hz, 1 H); ^{13}C NMR 164.00, 149.22, 145.00, 69.80, 69.42, 57.80, 47.93, 46.67, 43.14 ppm; IR (neat) 2925, 1700, 1585, 1420, 1260, 1150, 1080, 760 cm^{-1}; mass spectrum for $C_9H_{10}O_2S_3$, calcd 245.9844, obsd 245.9850. For **27**: ^1H NMR δ 6.45 (m, 1 H), 6.35 (m, 1 H), 4.55 (d, J = 2.3 Hz, 1 H), 3.75 (s, 3 H), 3.20 (m, 1 H), 2.85 (m, 1 H), 2.65 (d, J = 9.8 Hz, 1 H), 1.85 (d, J = 9.8 Hz, 1 H); ^{13}C NMR 172.03, 139.81, 137.66, 86.09, 72.24, 52.81, 48.43, 46.32, 44.66 ppm; IR (neat) 2945, 1720, 1420, 1030, 700 cm^{-1}; mass spectrum for $C_9H_{10}O_2S_3$, calcd 245.9843, obsd 245.9842.

Competitive Trithiane Transfer. (i) A solution of **8** (70 mg, 0.26 mmol), norbornene (30 mg, 0.32 mmol), and norbornadiene (30 mg, 0.33 mmol) in 0.6 mL of benzene-d_6 was heated in a sealed tube at 101 °C for 6 h. After cooling, the contents of the tube were analyzed by ^1H NMR. The relative amounts of **3** and **21** were determined by integrating the doublets at δ 3.20 (for **3**) and δ 3.40 (for **21**). The ratio **3**:**21** = 1.35. (ii) In a similar experiment 57.3 mg (0.22 mmol) of **8**, 21.7 mg (0.23 mmol) of norbornene, and 32.7 mg (0.23 mmol) of benzonorbornadiene was heated in 0.3 mL of benzene-d_6 for 6.5 h, and the contents were analyzed by ^1H NMR. Since the absorption of the bridgehead protons of **29** and H_2, H_6 of **3** overlap in benzene-d_6, the benzene was removed under reduced pressure and the oil redissolved in $CDCl_3$. The relative amounts of **3** and **29** were determined by integrating the doublets at δ 3.60 (for **3**) and δ 3.98 (for **29**). The ratio of **3**:**29** = 1.56. (iii) In a similar experiment 51.8 mg (0.19 mmol) of **8**, 18.2 mg (0.19 mmol) of norbornene, and 21.7 mg (0.2 mmol) of 2-methyl-2-norbornene were heated for 6.5 h. Analysis of the mixture by ^1H NMR indicated **3** and unreacted **8**.

9 as a Transfer Reagent. A mixture of **9** (60 mg, 0.21 mmol) and norbornene (30 mg, 0.32 mmol) in 1 mL of benzene was heated in a sealed tube at 100 °C for 12 h. The dark oil obtained after removal of unreacted norbornene and benzene under reduced pressure was chromatographed over silica gel with pentane–ether (65:35) as eluent to give a mixture of **5** and **6** (20 mg), 2-phenyl-2-norbornene (20 mg), and 20 mg of a viscous yellow oil that could not be characterized. The ratio **5**:**6** as determined by ^1H NMR was 2.7.

10 as a Transfer Reagent. An identical experiment as described above was carried out with **10** (40 mg) and norbornene (20 mg). After heating, the unreacted norbornene and benzene was removed under reduced pressure. ^1H NMR analysis of the oil showed **5**, **6**, and 2-phenyl-2-norbornene. The ratio **5**:**6** was 2.4.

Acknowledgment. We are indebted to the Welch Foundation for financial support, Professor Shigeru Oae for helpful discussions, and Professor William H. Watson for carrying out the X-ray analysis on **4**.

Registry No. **3**, 23657-27-4; **4**, 116376-52-4; **5**, 116376-53-5; **6**, 116497-38-2; **7**, 116497-40-6; **8**, 109909-04-8; **9**, 116376-54-6; **10**, 116497-39-3; **17**, 23657-28-5; **18**, 116376-55-7; **19**, 116376-56-8; **20**, 116497-41-7; **21**, 109958-15-8; **24**, 701-15-5; **25**, 116376-57-9; **26**, 3604-36-2; **27**, 116376-58-0; **28**, 116376-59-1; 2-phenyl-2-norbornene, 4237-08-5.

Supplementary Material Available: Experimental details and data for S_3-transfer kinetics (4 pages). Ordering information is given on any current masthead page.

High Intrinsic Rate Constant and Large Imbalances in the Thiolate Ion Addition to Substituted α-Nitrostilbenes[1]

Claude F. Bernasconi* and Robert B. Killion, Jr.

Contribution from the Thimann Laboratories of the University of California, Santa Cruz, California 95064.
Received April 14, 1988

Abstract: The kinetics of the reversible addition of alkyl thiolate ions (RS^- with R = Et, $HOCH_2CH_2$, $CH_3OCOCH_2CH_2$, and CH_3OCOCH_2) to α-nitrostilbene and of $HOCH_2CH_2S^-$ to α-nitrostilbene substituted in the α-phenyl ring (Z = 4-CH_3, H, 4-Br, 3-NO_2, and 4-NO_2) have been measured in 50% Me_2SO–50% water at 20 °C. Brønsted β values (β_{nuc}, β_{lg}, β_{eq}), Hammett ρ values ($\rho(k_1)$, $\rho(k_{-1})$, $\rho(K_1)$), and the intrinsic rate constant ($k_0 = k$ when $K = 1$) have been determined and compared with the corresponding parameters for piperidine and morpholine addition to the same substrates reported previously. For a given pK_a of the nucleophile, thiolate ion addition is thermodynamically and kinetically much more favorable than amine addition, presumably because of soft–soft type interactions both in the adduct and in the transition state. The fact that the *intrinsic* rate for thiolate ion addition is also much higher than for amine addition implies that the soft–soft interactions in the transition state have progressed more than bond formation. The structure–reactivity coefficients indicate a strongly imbalanced transition state in which development of resonance and solvation at the α-nitro group lags behind carbon–sulfur bond formation. Rate constants for carbon protonation of the $HOCH_2CH_2S^-$ adducts of the substituted α-nitrostilbenes by acetic acid were also determined. They are correlated by a *positive* Hammett ρ value of 0.33, indicating that electron-withdrawing substituents enhance the rate. This unusual substituent dependence is reminiscent of the nitroalkane anomaly reported for phenylnitroalkanes.

The kinetics and mechanism of amine and oxyanion addition to activated olefins have received a great deal of attention in recent years,[1,2] and much has been learned about structure–reactivity relationships in these reactions as well as carbanion-forming processes in general.[3]

In contrast, much fewer reports about reactions of thiols or thiolate ions at C=C double bonds have appeared. An early series of rate and equilibrium studies involved the reaction of 1-butanethiol with benzylidene-1,3-indandiones, benzylideneacetyl-

---

(1) This is part 23 in the series *Nucleophilic Addition to Olefins*. Part 22: Bernasconi, C. F.; Bunnell, R. D. *J. Org. Chem.* **1988**, *53*, 2001.

(2) Parts 1–21 in this series.

(3) Reviews: (a) Bernasconi, C. F. *Pure Appl. Chem.* **1982**, *54*, 2335. (b) Bernasconi, C. F. In *Nucleophilicity*; Harris, J. M., McManus, S. P., Eds.; Advances in Chemistry 215; American Chemical Society: Washington, DC 1987; p 137.

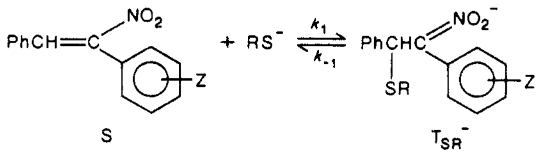
0002-7863/88/1510-7506$01.50/0

Table I. Rate and Equilibrium Constants for Addition of $HOCH_2CH_2S^-$ to Substituted α-Nitrostilbenes and for Protonation of T_{RS}^- by Acetic Acid in 50% Me_2SO–50% Water, μ = 0.5 M (KCl) at 20 °C

	4-Me	H	4-Br	3-NO_2	4-NO_2
σ	−0.17	0	0.23	0.71	0.78
k_1, $M^{-1}\ s^{-1}$	$(3.72 \pm 0.20) \times 10^4$	$(5.81 \pm 0.06) \times 10^4$	$(1.21 \pm 0.03) \times 10^5$	$(2.69 \pm 0.50) \times 10^5$	$(3.21 \pm 0.70) \times 10^5$
k_{-1}, s^{-1}	$(7.43 \pm 0.24) \times 10^{-3}$	$(7.02 \pm 0.22) \times 10^{-3}$	$(5.83 \pm 0.20) \times 10^{-3}$	$(6.43 \pm 0.14) \times 10^{-3}$	$(4.67 \pm 0.20) \times 10^{-3}$
$K_1 = k_1/k_{-1}$, M^{-1}	$(5.01 \pm 0.31) \times 10^6$	$(8.28 \pm 0.27) \times 10^6$	$(2.08 \pm 0.09) \times 10^7$	$(4.18 \pm 0.78) \times 10^7$	$(6.84 \pm 1.52) \times 10^7$
k_p^{BH}, $M^{-1}\ s^{-1}$	$(4.07 \pm 0.17) \times 10^{-1}$	$(4.59 \pm 0.14) \times 10^{-1}$	$(5.88 \pm 0.14) \times 10^{-1}$	$(7.91 \pm 0.50) \times 10^{-1}$	$(5.57 \pm 0.40) \times 10^{-1}$

acetonates, benzylidenemalononitriles, β-nitrostyrenes, and some other activated alkenes in 20% ethanol–80% water.[4] At about the same time, Friedman et al.[5] examined relative nucleophilic reactivities of thiolate ions and amines in reactions with various α,β-unsaturated compounds such as acrylonitrile and methylacrylate in water. For comparable pK_a values of the nucleophile, they found the thiolate ions to be approximately 150–300-fold more reactive than primary amines. Similar findings have recently been reported for nucleophilic addition to 2-furylethylenes.[6] A limited rate and equilibrium study of thiol addition to an α,β-unsaturated imine derived from cephalosporin has also been reported.[7]

In this paper we present the results of an investigation of the reaction of substituted α-nitrostilbenes (Z = 4-CH_3, H, 4-Br, 3-NO_2, 4-NO_2) with alkyl thiolate ions (eq 1) in 50% Me_2SO–50% water. Our study focuses on two major points. One is the determination of the intrinsic rate constant of the reaction ($k_0 = k_1 = k_{-1}$ when $K_1 = 1$) and its comparison with that of amine nucleophiles. The other is the determination of structure–reactivity coefficients ($\beta_{nuc}^n = d \log k_1 / d \log K_1$ by varying R and $\alpha_{nuc}^n = d \log k_1 / d \log K_1$ by varying Z) and the degree of transition-state imbalance ($I = \alpha_{nuc}^n - \beta_{nuc}^n$), again in comparison with that of other nucleophiles. To the best of our knowledge, this study is the first of its kind to provide data that allow such comparisons. We also report rate constants for carbon protonation of T_{SR}^- by acetic acid which are correlated with a negative Brønsted β value, which is reminiscent of results with other phenylnitroalkanes.[8]

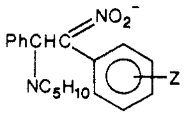


(1)

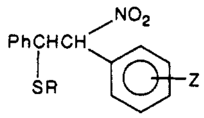
Results

General Features. The reactions of the anions of ethanethiol, 2-mercaptoethanol, methyl 3-mercaptopropionate, and methyl mercaptoacetate with substituted α-nitrostilbenes (Z = 4-Me, H, 4-Br, 3-NO_2, 4-NO_2) were studied in 50% Me_2SO–50% water (v/v), μ = 0.5 M (KCl) at 20 °C. The stereochemistry of all the stilbenes was shown previously to be *E*.[9]

The adducts, T_{SR}^- (see eq 1), were identified by their UV spectra which were quite similar to those of the corresponding amine adducts (T_A^-).[9] Supporting evidence arises from the fact that the protonated thiol adduct, T_{SR}^0, which was synthesized and isolated (see Experimental Section) for the Z = H/R = $HOCH_2CH_2$ system, is reversibly interconverted into T_{SR}^- with base. The spectra of T_{SR}^- generated by addition of the thiolate ion to the olefin and of T_{SR}^- generated by deprotonation of T_{SR}^0 were the same except that below 270 nm the former spectrum contained a contribution from the thiolate ion. Figure 1 shows the spectra of the olefin, T_{SR}^-, and T_{SR}^0 for the Z = H/R = $HOCH_2CH_2$ system.



T_A^-



T_{SR}^0

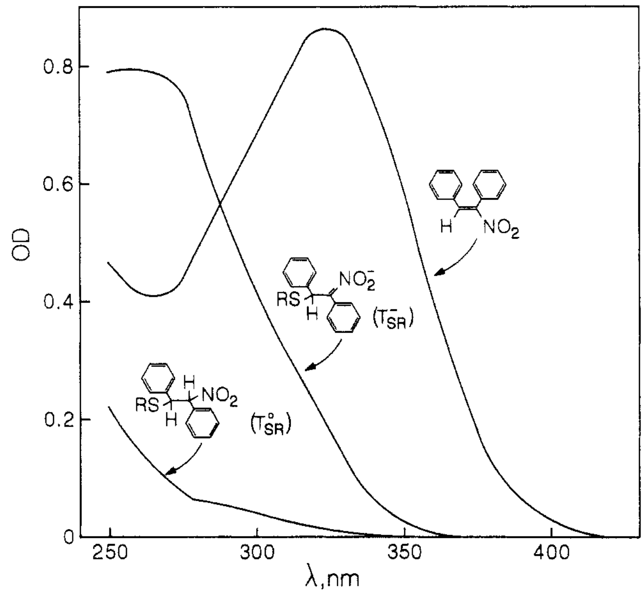


Figure 1. UV/vis spectra of α-nitrostilbene and of T_{SR}^- and T_{SR}^0 derived from α-nitrostilbene and 2-mercaptoethanol. The concentration is 8.33×10^{-5} M for all species.

The pK_a values of the thiols (Table II) were determined potentiometrically in 50% Me_2SO–50% water at the same ionic strength and temperature as the kinetic experiments. They are all approximately 0.9 pK_a unit higher than the corresponding values in water at 25 °C, μ = 1.0 M (NaCl),[10] except for methyl 3-mercaptopropionate whose pK_a is 1.07 units higher than in water.

Kinetics of Adduct Formation. Because of the high reactivity of the thiolate ions, and also because alkaline solutions of thiolate ions are not very stable, the rates of adduct formation were determined in dilute *N*-methylmorpholine buffers of around pH 7.5. At this pH, the thiol/thiolate ion equilibrium favors the thiol. This assures relatively low thiolate ion concentrations and rates in a convenient time range, even under the pseudo-first-order conditions used throughout this study. The reactions were monitored in a stopped-flow spectrophotometer at or near λ_{max} of the substrate. Excellent first-order kinetics were observed in all cases.

The observed pseudo-first-order rate constant for equilibrium approach of reaction 1 is given by

$$k_{obsd} = k_1[RS^-] + k_{-1} = k_1 \frac{K_a^{RSH}}{K_a^{RSH} + a_{H^+}}[RSH]_0 + k_{-1} \qquad (2)$$

with K_a^{RSH} being the acid dissociation constant of the thiol. The k_{obsd} values for the reaction of mercaptoethanol thiolate anion with S (Z = 4-Me, H, 4-Br, 3-NO_2, 4-NO_2) are summarized in Table S1[11] (42 rate constants) while k_{obsd} for the reaction of S (Z = H)

---

[4] (a) Lough, C. E.; Currie, D. J.; Holmes, H. L. *Can. J. Chem.* **1968**, *46*, 771. (b) Pritchard, R. B.; Lough, C. E.; Currie, D. J.; Holmes, H. L. *Ibid.* **1968**, *46*, 775.

[5] Friedman, M.; Cavins, J. F.; Wall, J. S. *J. Am. Chem. Soc.* **1965**, *87*, 3672.

[6] Rosenberg, M.; Balaz, S.; Sturdik, E.; Kucher, A. *Collect. Czech. Chem. Commun.* **1987**, *52*, 425.

[7] Buckwell, S.; Page, M. I.; Longridge, J. L. *J. Chem. Soc., Chem. Commun.* **1986**, 1039.

[8] Bordwell, F. G.; Boyle, W. J., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 3907.

[9] Bernasconi, C. F.; Renfrow, R. A. *J. Org. Chem.* **1987**, *52*, 3035.

[10] Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451.

[11] See paragraph at the end of this paper regarding supplementary material.

Table II. Rate and Equilibrium Constants for the Addition of Various Thiolate Ions to α-Nitrostilbene and for the Protonation of T_{SR}^- by Acetic Acid in 50% Me_2SO–50% Water, μ = 0.5 M (KCl) at 20 °C

	$CH_3CH_2S^-$	$HOCH_2CH_2S^-$	$CH_3OCOCH_2CH_2S^-$	$CH_3OCOCH_2S^-$
pK_a^{RSH}	11.26	10.54	10.40	8.83
k_1, $M^{-1}\ s^{-1}$	$(6.68 \pm 0.25) \times 10^4$	$(5.81 \pm 0.06) \times 10^4$	$(4.82 \pm 0.13) \times 10^4$	$(2.85 \pm 0.06) \times 10^4$
k_{-1}, s^{-1}	$(3.49 \pm 0.07) \times 10^{-3}$	$(7.02 \pm 0.22) \times 10^{-3}$	$(9.47 \pm 0.17) \times 10^{-3}$	$(1.37 \pm 0.06) \times 10^{-1}$
$K_1 = k_1/k_{-1}$, M^{-1}	$(1.91 \pm 0.08) \times 10^7$	$(8.16 \pm 0.27) \times 10^6$	$(5.09 \pm 0.17) \times 10^6$	$(2.08 \pm 0.10) \times 10^5$
k_p^{BH}, $M^{-1}\ s^{-1}$	$(3.92 \pm 0.05) \times 10^{-1}$	$(4.70 \pm 0.14) \times 10^{-1}$	$(2.81 \pm 0.14) \times 10^{-1}$	

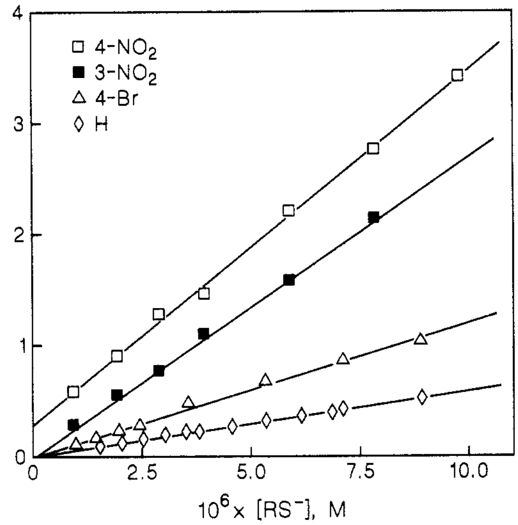


Figure 2. Representative plots of k_{obsd} vs $[RS^-]$ for the reaction of substituted α-nitrostilbenes with $HOCH_2CH_2S^-$.

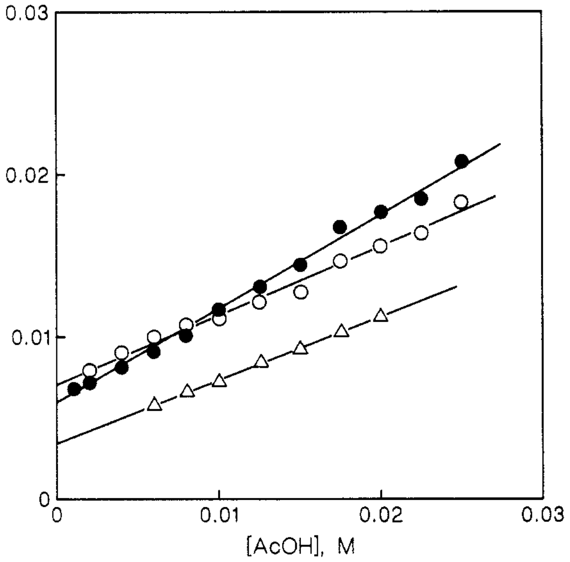


Figure 3. Representative plots of k_{obsd} vs [AcOH] in pH-jump experiments: ○, $HOCH_2CH_2S^-$/4-CH_3; ●, $HOCH_2CH_2S^-$/4-Br; △, EtS^-/H.

with the other thiolate ions are summarized in Table S2[11] (16 rate constants). Figure 2 shows representative plots of k_{obsd} vs $[RS^-]$.

In most cases the intercepts were indistinguishable from zero, indicating $k_1[RS^-] \gg k_{-1}$. Even in the reaction of S (Z = 4-NO_2) with $HOCH_2CH_2S^-$ (Figure 2), which shows a measurable intercept, the intercept cannot be attributed to k_{-1} (see below) but probably represents competing hydrolysis of the substrate. The k_1 values are summarized in Tables I and II.

pH-Jump Experiments. In order to evaluate k_{-1}, k_{obsd} was measured by approaching the equilibrium from the T_{SR}^- side. T_{SR}^- was generated in the presence of 0.1 M thiol and 0.1 M triethylamine in acetonitrile and diluted into 0.01 M KOH in 50% Me_2SO–50% water, as detailed in the Experimental Section. The concentration of T_{SR}^- in the acetonitrile solution was such that only very small volumes of acetonitrile solution had to be used (<1 mL for 100 mL of 50% Me_2SO–50% water). The 50% Me_2SO–50% water solution of T_{SR}^- was then mixed with an acetic acid buffer in the stopped-flow apparatus ("pH-jump") to give a final pH of 5.78 and final nominal concentrations of $[RSH]_0$ = 5×10^{-5} M and $[S]_0$ = 2.5×10^{-5} M.

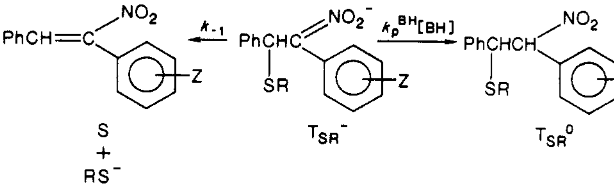
Table III. Brønsted β Values and log k_0 for the Addition of Thiolate Ions and the Piperidine/Morpholine Pair to α-Nitrostilbene in 50% Me_2SO–50% Water, μ = 0.5 M (KCl) at 20 °C

Parameter	RS^-	pip/mor[a]
$\beta_{nuc} = d \log k_1/d\ pK_a^{RSH}$	0.16 ± 0.02	0.34
$\beta_{lg} = d \log k_{-1}/d\ pK_a^{RSH}$	-0.68 ± 0.06	-0.58
$\beta_{eq} = d \log K_1/d\ pK_a^{RSH}$	0.84 ± 0.07	0.93
$\beta_{nuc}^n = \beta_{nuc}/\beta_{eq}$[b]	0.19 ± 0.03	0.37
$\beta_{lg}^n = \beta_{lg}/\beta_{eq}$[b]	-0.81 ± 0.10	-0.63
log k_0[c]	3.43 ± 0.10	1.42

[a] Reference 9, $\beta_{nuc} = d \log k_1/pK_a^{R_2NH^+}$, etc. [b] Equivalent to d log k_1/d log K_1 and d log k_{-1}/d log K_1, respectively. [c] log k_0 obtained from log k_1 vs log K_1, extrapolated to log K_1 = 0.

The reaction, which was monitored at or near λ_{max} of the olefin, showed an increase in absorption (formation of olefin) which was first order, although the infinity line had a slight downward slope (more on this below). The k_{obsd} values are summarized in Table S3 (45 rate constants)[11] for the adducts of 2-mercaptoethanol thiol anion with the substituted α-nitrostilbenes and in Table S4 (24 rate constants)[11] for the adducts of the other thiolate ions with α-nitrostilbene.

In most cases k_{obsd} increased with increasing buffer concentration while at the same time the change in absorption ("amplitude") decreased. Figure 3 shows representative plots of k_{obsd} vs [AcOH]. These observations are consistent with a competition between breakdown of T_{SR}^- into S and protonation of T_{SR}^- to form T_{SR}^0, as shown in eq 3. k_{obsd} is given by eq 4.



(3)

$$k_{obsd} = k_{-1} + k_p^{BH}[BH] \qquad (4)$$

The reduced amplitude is due to the fact that increasing amounts of T_{SR}^0, which does not significantly absorb at λ_{max} of S, are being formed at the expense of S.

The k_{-1} and k_p^{BH} values are summarized in Tables I and II. The only system for which no k_p^{BH} could be determined is S (Z = H/R = $CH_3OOCCH_2S^-$). This is because the ratio k_{-1}/k_p^{BH} which increases with decreasing pK_a of RSH, is so large for this system that $k_{-1} \gg k_p^{BH}[BH]$ and k_{obsd} is independent of [AcOH].

The sloping infinity lines of the kinetic plots were not investigated further. They presumably represent a slow equilibration between S and T_{RS}^0 since the kinetic ratio $[S]/[T_{RS}^0] = k_{-1}/k_p^{BH}[B]$ is unlikely to be equal to the thermodynamic ratio.

Discussion

Rate and equilibrium constants for eq 1 are summarized in Table I ($HOCH_2CH_2S^-$ with various substrates) and Table II (α-nitrostilbene with various RS^-). The tables also include k_p^{BH} values for the protonation of T_{SR}^- by acetic acid (eq 3).

Dependence on Thiolate Ion. Brønsted type plots of log k_1, log k_{-1}, and log K_1 vs pK_a^{RSH} for the reaction of thiolate ions with α-nitrostilbene (Z = H) are shown in Figure 4. The various

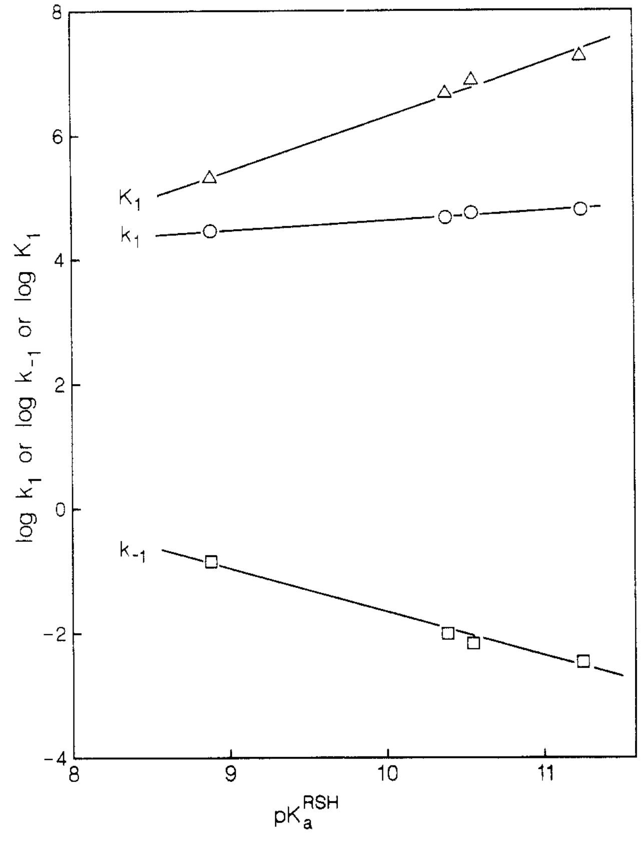


Figure 4. Brønsted plots of k_1, k_{-1}, and K_1 for the addition of various thiolate ions to α-nitrostilbene.

structure–reactivity parameters (β values derived from the slopes of these plots) are summarized in Table III, along with log k_0 for the intrinsic rate constant ($k_0 = k_1 = k_{-1}$ when $K_1 = 1$). The table also lists the corresponding parameters for the reaction of α-nitrostilbene with piperidine and morpholine under the same conditions.

In comparing β_{nuc} (or $\beta_{nuc}{}^n$) for thiolate ion and amine addition, we note that these parameters are much smaller for the thiolate ions (0.16 (0.19)) than for the amines (0.34 (0.37)). The reason for this difference is unclear. Examples are known where β_{nuc} for both amine and thiolate ion addition to an electrophilic carbon are about the same, while other cases have been reported where β_{nuc} for thiolate ion addition is much smaller than for amine addition. Some representative examples are summarized in Table IV. No clear pattern emerges from Table IV. Even the electrophile most closely related to α-nitrostilbene, acrylonitrile, shows very different behavior (both β_{nuc} values about the same) from that found in the present work.

According to traditional views,[12,13] our results suggest that sulfur–carbon bond formation (or probably better: charge transfer from the nucleophile to the electrophile) has made much less progress at the transition state than nitrogen–carbon bond formation in the amine reactions. However the use of β_{nuc} or $\beta_{nuc}{}^n$ as a measure of transition-state structure has recently been questioned,[14-17] and hence we shall refrain from drawing quantitative conclusions regarding the degree of bond formation in the two reactions, a point to which we shall return at the end of this paper.

Table IV. β_{nuc} Values for the Addition of Thiolate Ions and Amines to Electrophilic Centers

electrophile	RS^-	RNH_2
$PhCH{=}C(NO_2)Ph$	0.16^a	0.34^b (pip./mor.)
$CH_2{=}CHCN$	0.45^c	0.43^c
$CH_3CO(O)Ar$	0.27^d $(0.40)^e$	0.2 ± 0.2^f
CH_3COCl		0.25^g
$CH_3CH{=}O$	0.1^h	
carbocations	$\approx 0^i$	$0.4\text{–}0.5^{j,k}$ $(0.27\ \text{pip./mor.})^l$
$PhCOCH{=}CHOMe$		0.4^m

[a] This work. [b] Reference 9. [c] Reference 20. [d] Reference 10. [e] Brembilla, A.; Roizard, D.; Schoenleber, J.; Lochon, P. *Can. J. Chem.* **1984**, *62*, 2330. [f] Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018. [g] Palling, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 4868. [h] Lienhard, G. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1966**, *88*, 3982. [i] Ritchie, C. D.; Gandler, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7318. [j] Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 3248. [k] Ritchie, C. D.; Virtanen, P. O. *J. Am. Chem. Soc.* **1973**, *95*, 1882. [l] Ritchie, C. D.; Minasz, R. J.; Kamego, A. A.; Sawada, M. *J. Am. Chem. Soc.* **1977**, *99*, 3747. [m] Ritchie, C. D.; Kawasaki, A. *J. Org. Chem.* **1981**, *46*, 4704.

A comparison of thermodynamic and kinetic reactivity between thiolate ions and amines is interesting. For a given pK_a of the nucleophile, the equilibrium constant for thiolate ion addition is [(4–5) × 10^5]-fold higher than for amine addition. For example, $K_1 = 1.91 \times 10^7$ M^{-1} for $CH_3CH_2S^-$ (p$K_a{}^{RSH}$ = 11.26) while K_1 = 45 M^{-1} for piperidine (p$K_a{}^{R_2NH^+}$ = 11.02), or $K_1 = 2.08 \times 10^5$ M^{-1} for $CH_3OCOCH_2S^-$ (p$K_a{}^{RHS}$ = 8.83) while K_1 = 0.34 M^{-1} for morpholine (p$K_a{}^{R_2NH_2{}^+}$ = 8.72). These results are consistent with the well-known fact that sulfur bases have stronger carbon basicities than nitrogen or oxygen bases.[18-20] Within the framework of hard–soft acid–base interactions[20] this can be understood as the soft (polarizable) alkene having a stronger affinity to the soft sulfur bases than to the hard nitrogen or oxygen bases.

The *rate* constants are also much higher for thiolate ion addition: $k_1 = 6.68 \times 10^4$ M^{-1} s^{-1} for $CH_3CH_2S^-$ vs 1.17×10^2 M^{-1} s^{-1} for the comparably basic piperidine, or $k_1 = 2.85 \times 10^4$ M^{-1} s^{-1} for $CH_3OCOCH_2S^-$ vs 17.6 M^{-1} s^{-1} for the comparably basic morpholine. The k_{RS^-}/k_{R_2NH} ratios of 5.71×10^2 ($CH_3CH_2S^-$/pip.) and 1.62×10^3 ($CH_3OCOCH_2S^-$/mor.) are remarkably similar to the k_{RS^-}/k_{RNH_2} ratios (at constant pK_a) reported for nucleophilic addition to acrylonitrile (2.75×10^2), to methyl acrylate (1.45×10^2), and to acrylamide (1.78×10^2) in aqueous solution.[5] Part of the rate enhancement for the thiolate ions over the amines may be attributed to the larger equilibrium constants, but most of it comes from a higher intrinsic rate constant for thiolate ion addition (log k_0 = 3.43, from a plot of log k_1 vs log K_1, not shown) compared to amine addition (log k_0 = 1.43).[21]

There are two possible ways to understand the enhanced intrinsic rate constant for the sulfur nucleophiles. One is that there exists, in the transition state, a stabilizing mode of interaction that has no counterpart in the adduct or which is weaker in the adduct than in the transition state. The second, more likely, possibility is that there is only one stabilizing mode both in the adduct and in the transition state, namely the soft–soft interaction referred to above. However, its development along the reaction coordinate is not linear with bond formation, but has made more progress than bond formation at the transition state.

---

(12) (a) Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*; Wiley: New York, 1963; pp 128–170. (b) Leffler, J. E. *Science (Washington, D.C.)* **1953**, *117*, 340. (c) Kresge, A. J. In *Proton Transfer Reactions*; Caldin, E. F., Gold, V., Eds.; Wiley: New York, 1975; p 179.

(13) For a recent review, see: Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511.

(14) Pross, A. *J. Org. Chem.* **1984**, *49*, 1811.

(15) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 4737; **1986**, *108*, 7300.

(16) Johnson, C. D. *Tetrahedron* **1980**, *36*, 3461.

(17) Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348.

(18) Sander, E. G.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 6154.

(19) (a) Hine, J.; Weimar, 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.

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

(21) For two reactions whose $\beta_{nuc}{}^n$ values are not the same, the comparison of log k_0 values becomes somewhat imprecise. For example, if log k_0 for the thiolate reaction were calculated from a curved hypothetical Brønsted plot with a slope near log K_1 = 0 being the same as for the amine reactions, the difference in log k_0 between the two reactions[22] would be ~1.4–1.5 instead of 2.0 log units. This would not change the qualitative result that log k_0 for sulfur addition is substantially higher than for nitrogen addition.

(22) See, e.g., Bernasconi, C. F.; Panda, M. *J. Org. Chem.* **1987**, *52*, 3042, for justification of such a procedure.

Table V. Hammett ρ Values for the Addition of 2-Mercaptoethanol Thiolate Ion to Substituted α-Nitrostilbenes (k_1, k_{-1}, K_1) and for Protonation of T_{RS}^- by Acetic Acid (k_p^{BH}) in 50% Me$_2$SO–50% Water, μ = 0.5 M (KCl) at 20 °C

parameter	value
$\rho(k_1)$	0.96 ± 0.07
$\rho(k_{-1})$	−0.15 ± 0.08
$\rho(K_1)$	1.10 ± 0.11
$\alpha_{nuc}^n = \rho(k_1)/\rho(K_1)$	0.87 ± 0.15
$\rho(k_p^{BH})$	0.33 ± 0.03[a]

[a] 4-NO$_2$ substituent omitted from correlation; see text.

This second situation would constitute an example of the operation of the principle of nonperfect synchronization (PNS),[3,23] where a product stabilizing factor develops ahead of bond formation, thereby increasing the intrinsic rate constant. This is interesting because it contrasts with most other common product-stabilizing factors (e.g., resonance, solvation, intramolecular hydrogen bonding) whose development typically lags behind bond formation, thereby lowering k_0.[3,23]

How can we understand these contrasting patterns? A common characteristic of the latter product-stabilizing factors is that they are "created" by the reaction; i.e., they would not exist in the absence of bond formation (e.g., between a base and a proton in the proton transfer reaction that leads to a resonance-stabilized carbanion). In other words, at best these factors could conceivably develop synchronously with bond formation, but not possibly ahead of it. In reality their development lags behind bond formation; the reasons for these lags, which are somewhat different for each factor, have been discussed elsewhere.[24] In contrast, soft–soft interactions are rooted in the polarizability of the interacting molecules and may not require a substantially developed bond for them to exist. It is therefore not unreasonable that they could develop faster than bond formation.[29]

Dependence of k_1, k_{-1}, and K_1 on Substituent. Hammett plots of log k_1, log k_{-1}, and log K_1 vs σ for the reaction of 2-mercaptoethanol anion with substituted α-nitrostilbenes are shown in Figure 5. The ρ values are listed in Table V. Just as for piperidine and morpholine addition,[9] the 4-nitro compound correlates with the standard σ rather than σ^-. This indicates that π overlap between the α-phenyl ring and the carbanionic center is sterically hindered.[9]

The ratio $\rho(k_1)/\rho(K_1)$ is equal to the slope of a Brønsted type plot (not shown) of log k_1 vs log K_1 and thus corresponds to a (normalized) Brønsted type parameter that we have called α_{nuc}^n.[9,23b] Its value is 0.87 for 2-mercaptoethanol anion addition. This value is quite high,[34] especially in view of the low β_{nuc}^n of 0.19, and suggests a very large imbalance,[23] $I = \alpha_{nuc}^n - \beta_{nuc}^n$ = 0.68. Imbalances, where $\alpha - \beta > 0$[34] are typical for carbanion forming reactions and are particularly large for nitronate ion forming processes.[23] They are commonly attributed to a transition state in which resonance development and concomitant solvation of the charge-bearing group lags behind bond formation (or perhaps better: lags behind charge transfer from the base or nucleophile to the electrophile). The best known case is the deprotonation of phenylnitroalkanes by amines where $I = \alpha_{CH}$[36] $- \beta_B$[36] = 1.29 − 0.55 = 0.74.[8] For the piperidine/morpholine addition to α-nitrostilbenes, $I = \alpha_{nuc}^n - \beta_{nuc}^n$ = 0.67 − 0.37 = 0.30.[9]

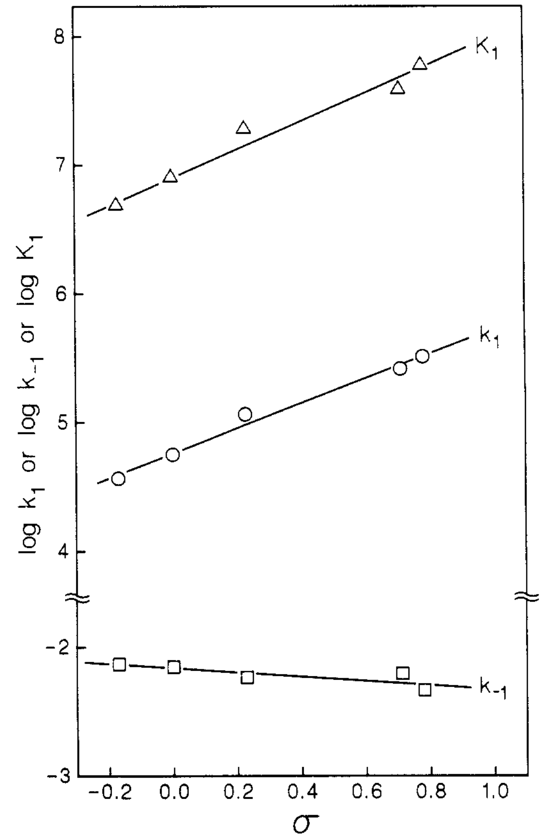


Figure 5. Hammett plots of k_1, k_{-1}, and K_1 for the addition of HOCH$_2$CH$_2$S$^-$ to substituted α-nitrostilbenes.

The reasons why the imbalance for thiolate ion addition to α-nitrostilbenes (I = 0.68) is so much larger than for amine addition (0.30), and is almost as high as for the deprotonation of phenylnitroalkanes (0.74), are not known. As elaborated upon elsewhere,[3b,9,23b] the sp^2 hybridization of the α-carbon in α-nitrostilbene should facilitate π overlap with the nitro group at the transition state. This should reduce the imbalance compared to that in proton transfer from a sp^3-hybridized carbon, as is apparently the case for amine addition to α-nitrostilbenes compared to the deprotonation of phenylnitroalkanes by the same amines.

There may be several contributing factors to the larger imbalance in the thiolate ion addition. One such factor may be related to the disproportionately large progress in the soft–soft interactions at the transition state, which we believe to be the main cause for the enhanced intrinsic rate constant. The strong polarizability of the thiolate ion would allow substantial negative charge density to develop on the α-carbon (large α_{nuc}^n) without extensive loss of the charge from the nucleophile or extensive bond formation (low β_{nuc}^n).

Another factor may be the different charge type of the nucleophiles. In the amine addition the developing positive charge on the nitrogen can influence α_{nuc}^n in two ways. In the first, the interaction of the phenyl substituent with the developing negative charge is counteracted by the positive charge. This has the effect of reducing both $\rho(K_1)$ and $\rho(k_1)$ although not by the same

---

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

(24) Resonance: see ref 23a and 25–27. Solvation: see ref 23a. Intramolecular hydrogen bonding: see ref 28.

(25) Kresge, A. J. *Can. J. Chem.* **1975**, *52*, 1897.

(26) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948.

(27) (a) Pross, A.; Shaik, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1129. (b) Pross, A. *Adv. Phys. Org. Chem.* **1985**, *21*, 99.

(28) Bernasconi, C. F.; Kanavarioti, A. *J. Am. Chem. Soc.* **1986**, *108*, 7744.

(29) Our interpretation notwithstanding, it is obvious that a firm understanding of many of the factors reponsible for nucleophilic reactivity is still elusive. For some recent papers dealing with this topic, see ref 30–33.

(30) Bordwell, F. G.; Huges, D. L. *J. Org. Chem.* **1982**, *47*, 3224; **1983**, *48*, 2206.

(31) Ritchie, C. D. *J. Am. Chem. Soc.* **1983**, *105*, 7313.

(32) Shaik, S. S. *Prog. Phys. Org. Chem.* **1985**, *15*, 197.

(33) (a) Brauman, J. I.; Dodd, J. A.; Han, C.-C. In *Nucleophilicity*; Harris, J. M., McManus, S. P., Eds.; Advances in Chemistry 215, American Chemical Society: Washington, DC, 1987; p 23. (b) Lewis, E. S.; Douglas, T. A.; McLaughlin, T. A. *Ibid.* p 35. (c) Bordwell, F. G.; Cripe, T. A.; Hughes, D. L. *Ibid.* p 137. (d) Jencks, W. P. *Ibid.*, p 155. (e) Ritchie, C. D. *Ibid.*, p 169. (f) Hoz, S. *Ibid.* p 181. (g) various other articles in the same volume.

(34) The high ρ value (2.03) reported for the addition of p-toluene thiolate ion to aryl vinyl sulfones[35] also suggest a large α_{nuc}^n.

(35) De Maria, P.; Fini, A. *J. Chem. Soc. B* **1971**, 2336.

(36) For the deprotonation of carbon acids $\alpha = \alpha_{CH}$ (change in rate with change in pK_a of the carbon acid) and $\beta = \beta_B$ (change in rate with change in pK_a of the base).

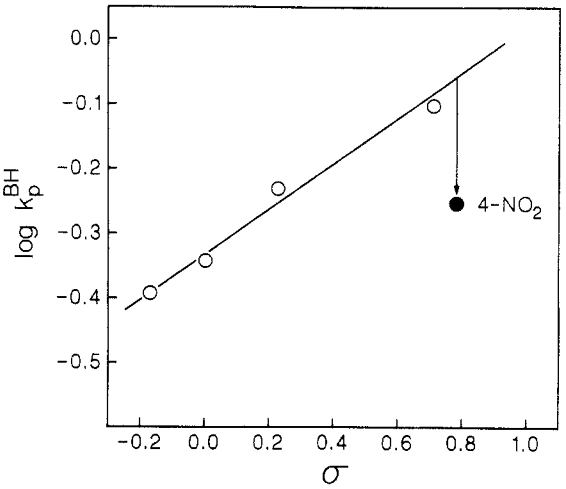


Figure 6. Hammett plot of the rate constants of protonation of T_{SR}^- (derived from $HOCH_2CH_2S^-$ and substituted α-nitrostilbenes) by acetic acid.

amount. A procedure for estimating these reductions has been proposed,[9,37] and the cited $\alpha_{nuc}{}^n = 0.67$ represents a value that has been corrected for this effect of the positive charge.

The second mode by which the positive charge can affect $\alpha_{nuc}{}^n$ is by direct electrostatic stabilization of the negative charge, a factor not taken into account in the above correction procedure. This electrostatic stabilization should be particularly pronounced in the transition state where the negative charge is more localized on the α-carbon, and thus it should lessen the demand for transition-state stabilization by the phenyl substituent. This should have the effect of reducing $\rho(k_1)$ more than $\rho(K_1)$ and hence of reducing $\alpha_{nuc}{}^n$. For an anionic nucleophile the opposite situation prevails: In the transition state there is electrostatic repulsion,[38] which should enhance the demand for stabilization by the phenyl substituent, but no such repulsion is present in the adduct. The result is an increase in $\alpha_{nuc}{}^n$. The fact that in the deprotonation of phenylnitroalkanes by amines α_{CH} (1.29) is lower than α_{CH} for deprotonation by the negatively charged OH^- (1.54)[8] supports this contention.

Polarizability and electrostatic effects are probably not the whole story, though, since a good part of why I is so large for thiolate ion addition is that $\beta_{nuc}{}^n$ is very low, and low $\beta_{nuc}{}^n$ values tend to *decrease* imbalances.[9] The problem may lie with the assumption that $\beta_{nuc}{}^n$ is a measure of bond formation or charge transfer in the transition state. As long as nucleophiles with the same central atom are compared with each other $\beta_{nuc}{}^n$ may be an adequate *relative* measure of bond formation, but this assumption possibly breaks down when nucleophiles with different central atoms are being compared.[14-17]

Dependence of k_p^{BH} on Substituent. Figure 6 shows a Hammett plot for k_p^{BH}, the second-order rate constant for protonation by acetic acid of T_{SR}^- derived from 2-mercaptoethanol anion and substituted α-nitrostilbenes. Two features of this plot are of particular interest. The first is that the slope ($\rho(k_p^{BH}) = 0.33$) (4-NO$_2$ compound omitted from correlation) is positive, indicating that electron-withdrawing substituents accelerate the reaction. This is unusual because it implies that the less basic carbanions are protonated faster than the more basic ones, i.e., the Brønsted $\beta_C = d \log k_p^{BH}/d\, pK_a^{CH} < 0$. However, since our T_{SR}^- adducts are phenylnitromethane derivatives, this nitroalkane anomaly is actually expected and parallels the observations made by Bordwell[8] and others,[40] namely that α_C for the deprotonation of phenylnitroalkanes is >1 and β_C in the reverse direction is <0. In fact, even numerically our $\rho(k_p^{BH})$ value of 0.33 is close to $\rho = 0.24$ and 0.45 for protonation of arylnitromethane anion by morpholine and by water, respectively.[8]

The second point of interest is the negative deviation of the 4-nitro substituent from the Hammett plot. This deviation is reminiscent of a similar result reported by Keeffe et al.[41] in the deprotonation of phenylnitromethanes by benzoate ion in Me$_2$SO and of the deprotonation of various benzylic ketones in aqueous solution reported by Bunting et al.[42] It can be understood as a lowering of the intrinsic rate of the reaction caused by late development of the resonance stabilization exerted by the 4-nitro group.[23a] The effect is not very large, though, consistent with the steric hindrance to coplanarity of the phenyl group in T_{SR}^-, which reduces the resonance effect (see above).

Table II also shows k_p^{BH} in dependence of three different RS groups of the α-nitrostilbene adduct. The dependence is small and erratic. The k_p^{BH} value obtained for RS = $CH_3OCOCH_2CH_2S$ is probably less certain than the standard deviation suggests because k_{obsd} in eq 4 was dominated by k_{-1} (for RS = CH_3OCOCH_2S, k_p^{BH}/k_{-1} is so small that k_p^{BH} is not even measurable). We are therefore inclined to discount this k_p^{BH} value. The somewhat larger k_p^{BH} value for R = $HOCH_2CH_2S$ compared to that of RS = CH_3CH_2S would then again suggest that the less basic nitronate ion is protonated more rapidly than the more basic one ($\beta_C < 0$), in agreement with the effect of the phenyl substituents on k_p^{BH} discussed above.

Conclusions

1. Addition complexes between α-nitrostilbene and thiolate ions are much more stable than amine adducts derived from secondary amines of the same proton basicity. This reflects the well-known fact that the carbon basicity of sulfur bases is higher than that of nitrogen bases and can be understood within the context of soft hard acid–base interactions.

2. The rate of formation of the thiolate ion adducts are also higher than the rates of amine addition. This is in part due to the larger thermodynamic driving force and in part due to a higher intrinsic rate for thiolate ion addition. The enhanced intrinsic rate suggests that the soft–soft interaction responsible for the greater stability of the thiolate ion adduct has progressed to a greater extent than bond formation at the transition state.

3. Thiolate ion addition to α-nitrostilbenes is characterized by a $\beta_{nuc}{}^n = 0.19$, $\alpha_{nuc}{}^n = 0.87$, and an imbalance of $I = \alpha_{nuc}{}^n - \beta_{nuc}{}^n = 0.68$. The imbalance is in the usual direction for carbanion forming reactions and shows that resonance development lags behind bond formation at the transition state. The size of I is unusually large compared to I for amine addition to α-nitrostilbenes and may in part be understood by an enhanced $\alpha_{nuc}{}^n$ due to the polarizability of the thiolate ions and by differences in electrostatic effects at the transition state for the two types of nucleophiles.

4. The rate of protonation of the 2-mercaptoethanol adducts of substituted α-nitrostilbenes by acetic acid is characterized by a positive ρ value of 0.33 showing the operation of the notorious nitroalkane anomaly. The 4-nitro substituent deviates negatively from the Hammett plot, indicating a delay in the development of the resonance effect of this substituent.

Experimental Section

Materials. 4-Me-, H-, 4-Br-, 3-NO$_2$-, and 4-NO$_2$-substituted α-nitrostilbenes were available from a previous study.[9] Ethanethiol (bp 35 °C, 760 mm, Aldrich), 2-mercaptoethanol (bp 55 °C, 13 mm, Aldrich), methyl 3-mercaptopropionate (bp 54–55 °C, 14 mmHg, Aldrich), and methyl mercaptoacetate (bp 42–43°C, 10 mm, Aldrich) were distilled under vacuum and stored under nitrogen. *N*-Methylmorpholine (bp 116–117 °C, 760 mm) was refluxed over calcium hydride, distilled, and stored at 4 °C in the dark. Glacial acetic acid (Mallinckrodt, AR grade) and potassium chloride (Fisher Scientific, AR grade) were used without further purification. KOH and HCl solutions were "Dilut-it" (Baker) diluted to appropriate volumes with deionized water.

---

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

(38) These electrostatic transition state destabilizations or stabilizations, respectively, are similar to those described by Kresge.[39]

(39) Kresge, A. J.; Chiang, Y. *J. Am. Chem. Soc.* **1973**, *95*, 803.

(40) Fukuyama, M.; Flanagan, P. W. K.; Williams, F. T., Jr.; Frainer, L.; Miller, S. A.; Schechter, H. *J. Am. Chem. Soc.* **1970**, *92*, 4689.

(41) Keeffe, J. R.; Morey, J.; Palmer, C. A.; Lee, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 1295.

(42) Bunting, J. W.; Stefanidis, D. *J. Am. Chem. Soc.* **1988**, *110*, 4008.

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 $\mu = 0.50$ 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.[43]

Synthesis of $Ph(HOCH_2CH_2S)CHCH(Ph)(NO_2)$. To a solution of 0.345 g (1.55×10^{-3} moles) of α-nitrostilbene in 5 mL of acetonitrile were added, with stirring, 0.242 g (0.217 mL, 3.10×10^{-3} mol) of 2-mercaptoethanol and 0.433 mL (0.314 g, 3.10×10^{-3} mol) of triethylamine, whereupon a color change from pale yellow to bright yellow-orange was observed. The color change presumably corresponds to the formation of T_{SR}^-. To this solution was added 0.931 g (0.887 mL, 1.55×10^{-2} mol) of acetic acid, and the solution became colorless. The solution was poured into 25 mL of dichloromethane and washed with 3×20 mL of water. The dichloromethane layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was recrystallized from 95% ethanol to give a white solid: mp 103–105 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 7.4 (b, 10 H, Ar H), 5.78, 4.85 (AB, $J = 12$ Hz, 2 H), 3.54 (t, 2 H, $J = 6$ Hz, the OCH_2 signal was obscured by the OH signal; the triplet becomes observable when D_2O is added to exchange the OH), δ 2.30 (t, 2 H, $J = 6$ Hz, SCH_2); MS, m/e 303 (M^+).

Kinetics. All rate constants were measured in a Durrum-Gibson stopped-flow spectrophotometer with computerized data acquisition and analysis. Rate constants in the forward direction were measured by mixing a 5×10^{-5} M solution of the substrate in 0.5 M KCl, 50% Me_2SO–50% water with a solution of the thiol in a 50% Me_2SO–50% water solution buffered at pH 7.56 with N-methylmorpholine; $\mu = 0.50$ M (KCl). The thiolate concentration was calculated from the known thiol concentration, the pK_a of the thiol, and the measured pH. Pseudo-first-order conditions were maintained by keeping the thiol in excess over the substrate. The decrease in absorbance vs time was monitored at the λ_{max} of the substrate, and first-order rate constants were calculated by using a computerized data acquisition and analysis system.

Generation of Thiol Adducts and pH-Jump Experiments. A stock solution of the thiol adduct T_{SR}^- was generated in situ by preparing a solution of 0.05 M of the respective α-nitrostilbene in 0.1 M triethylamine, 0.1 M thiol, in acetonitrile. Solutions of T_{SR}^- for the pH-jump experiments were prepared by diluting 100 μL of the 0.05 M T_{SR}^- stock solution into 100 mL of 0.01 M KOH, 50% Me_2SO-50% water, $\mu = 0.50$ (KCl). The thiol adduct could be distinguished from the hydroxy adduct by their characteristic UV–vis spectra.[44] In pH-jump experiments, the solution of the T_{SR}^- adduct in 0.01 M KOH, 50% Me_2SO–50% water, $\mu = 0.50$ M (KCl), was mixed in the stopped-flow apparatus with various concentrations of acetic acid buffers to give a final pH of 5.78 and a final total thiol concentration of 5×10^{-5} M. The thiolate adducts derived from methyl mercaptoacetate and methyl-3-mercaptopropionate were unstable if kept for long periods of time, but the pH-jump experiments were successful if performed within ca. 10 min upon dilution of the 0.05 M T_{SR}^- stock solution into 0.01 M KOH.

Acknowledgment. This research was supported by Grant CHE-8617370 from the National Science Foundation.

Registry No. S (Z = 4-Me), 116467-17-5; S (Z = H), 1215-07-2; S (Z = 4-Br), 40770-84-1; S (Z = 3-NO_2), 116467-18-6; S (Z = 4-NO_2), 116467-19-7; T_{SR}^- (Z = 4-Me; R = $(CH_2)_2OH$), 116467-20-0; T_{SR}^- (Z = H; R = $(CH_2)_2OH$), 116467-21-1; T_{SR}^- (Z = 4-Br; R = $(CH_2)_2OH$), 116467-22-2; T_{SR}^- (Z = 3-NO_2; R = $(CH_2)_2OH$), 116467-23-3; T_{SR}^- (Z = 4-NO_2; R = $(CH_2)_2OH$), 116467-24-4; T_{SR}^- (Z = H; R = CH_2CH_3), 116467-25-5; T_{SR}^- (Z = H; R = $(CH_2)_2CO_2Me$), 116467-26-6; $CH_3CH_2S^-$, 20733-13-5; $HO(CH_2)_2S^-$, 57966-62-8; $CH_3OCO(CH_2)_2S^-$, 59177-13-8; $CH_3OCOCH_2S^-$, 64743-45-9; $Ph(HO(CH_2)_2S)CHCH(Ph)NO_2$, 116467-27-7; $HO(CH_2)_2SH$, 60-24-2.

Supplementary Material Available: Kinetic data, Tables S1–S4 (6 pages). Ordering information is given on any current masthead page.

---

[43] Hallé, J. C.; Gaboriaud, R.; Schaal, R. *Bull. Soc. Chim. Fr.* **1970**, 2047.

[44] Bernasconi, C. F.; Fassberg, J., unpublished results.

Intermediates in the Epoxidation of Alkenes by Cytochrome P-450 Models. 2. Use of the *trans*-2,*trans*-3-Diphenylcyclopropyl Substituent in a Search for Radical Intermediates

Angelo J. Castellino and Thomas C. Bruice*

Contribution from the Department of Chemistry, University of California at Santa Barbara, Santa Barbara, California 93106. *Received March 28, 1988*

Abstract: (Z)-1,2-Bis(*trans*-2,*trans*-3-diphenylcyclopropyl)ethene (**1-Z**) has been used to search for radical intermediates in the epoxidation reactions of cytochrome P-450 model systems. The studied systems used the following as catalysts: (*meso*-tetrakis(pentafluorophenyl)porphinato)iron(III) chloride [$(F_{20}TPP)Fe^{III}(Cl)$], (*meso*-tetrakis(2,6-dichlorophenyl)porphinato)iron(III) chloride [$(Cl_8TPP)Fe^{III}(Cl)$], and (*meso*-tetrakis(2,6-dichlorophenyl)porphinato)manganese(III) hydroxide [$(Cl_8TPP)Mn^{III}(OH)$] in CH_2Cl_2 with C_6F_5IO as oxidant. All investigated systems gave *cis*-1,2-bis(*trans*-2,*trans*-3-diphenylcyclopropyl)oxirane (**2-c**), the *cis*-epoxide corresponding to **1-Z**, in high yield (>80% based on reacted **1-Z**). Stereoisomerization products (**2-t** and **1-E**) could not be detected. The remaining reaction products were found as very nonpolar (non-oxygen containing) components and are interpreted in terms of the radical cation intermediate A which has been intercepted by a cyclopropylcarbinyl to homoallyl radical rearrangement (CPCRR). In order to discuss the mechanistic position of A (on the pathway to epoxide vs formation in a parallel reaction) the rate constant for CPCRR of the secondary (*trans*-2,*trans*-3-diphenylcyclopropyl)carbinyl radical (D) was determined. For this purpose *trans*-2,*trans*-3-diphenyldicyclopropyl ketone (**3**) was treated with the known radical reductants n-$Bu_3SnH/h\nu$ and $Li/NH_3(l)$. Product analyses showed that *trans*-2,*trans*-3-diphenyl substitution increases the CPCRR rate constant by a factor $\geq 10^3$. From this value the rate constant for CPCRR of D may be calculated as $\geq 2 \times 10^{10}$ s^{-1}. This rate constant in conjunction with the yields of very nonpolar products obtained from the cytochrome P-450 model systems would require the radical cation A, as an intermediate, to proceed to epoxide with a rate constant of $\geq 1 \times 10^{11}$ to 2×10^{11} s^{-1}. Such a rate constant is not unreasonable. No products from the neutral radical C were detected. From the preceding considerations, C, as an intermediate, is required to proceed to epoxide with a rate constant $\geq 10^{12}$ s^{-1}. Such a rate constant would argue against C as a discrete intermediate.

It has been proposed,[1] in analogy to catalase and horseradish peroxidase, that the oxidant of cytochrome P-450 is an iron oxo porphyrin π-cation radical ($(^{+\bullet}P)Fe^{IV}(O)$). The two cytochrome P-450 oxidations of principal interest to organic chemists are

0002-7863/88/1510-7512$01.50/0