J. Org. Chem. **1998,** *63,* 6266−6272

Kinetics of the Reactions of Benzylidene Meldrum's Acid with Thiolate and Alkoxide Ions in Aqueous Dimethyl Sulfoxide

Claude F. Bernasconi* and Rodney J. Ketner

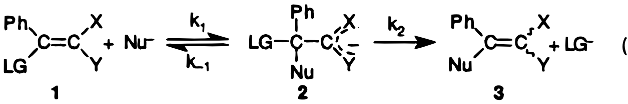
Department of Chemistry, University of California, Santa Cruz, California 95064

Received March 30, 1998

A kinetic study of the reaction of benzylidene Meldrum's acid, $PhCH{=}C(COO)_2C(CH_3)_2$ (**5-H**), with a series of thiolate and alkoxide ions in 50% DMSO−50% water (v/v) at 20 °C is reported. The reactions with RX^- (X = S or O) lead to adducts of the type $PhCH(XR)C(COO)_2C(CH_3)_2^-$ ((**5-H,XR**)$^-$), which can be viewed as a model for the intermediate of a nucleophilic vinylic substitution on substrates such as $PhC(LG){=}C(COO)_2C(CH_3)_2$ (LG = leaving group). Our measurements allowed a determination of rate and equilibrium constants for these processes with $RS^- = n\text{-}BuS^-$, $HOCH_2CH_2S^-$, $MeO_2CCH_2CH_2S^-$, and $MeO_2CCH_2S^-$ and $RO^- = OH^-$, MeO^- (only rate constant of breakdown of adduct), $HC{\equiv}CCH_2O^-$, and $CF_3CH_2O^-$. Our results show that there are major differences between the alkoxide and thiolate ions with respect to their thermodynamic and kinetic affinities to **5-H**. They arise mainly from differences in the polarizability and solvation between the sulfur and the oxygen bases. Similarities and differences between the reactions of thiolate ions with **5-H** and α-nitrostilbenes (**4-H**) are also discussed.

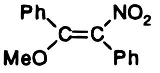
Introduction

Nucleophilic vinylic substitution (S_NV) reactions involving substrates activated by electron-withdrawing groups (X, Y) are known to proceed by the two-step mechanism shown in eq 1 (LG = nucleofuge, Nu^- = nucleophile).[1] The study of this mechanism took a new turn when reaction systems were discovered that allowed a direct determination of all rate constants (k_1, k_{-1}, and k_2) in eq 1. This discovery opened up the possibility of systematically investigating the various factors that affect each step in the mechanism, thereby greatly enhancing our understanding of structure−reactivity relationships in S_NV reactions in general. The first reaction that was shown to lead to an intermediate (**2**) stable enough to become directly detectable, a precondition to the measurement of k_{-1} and k_2, was that of β-methoxy-α-nitrostilbene, **4-OMe**, with thiolate ions in 50% DMSO−50% water.[2] Subsequent work showed that reactions of **4-OMe** with some alkoxide ions and weakly basic amines (but not strongly basic amines),[4] the reaction of **4-SR** (R = $CH_3CH_2CH_2$, $HOCH_2CH_2$, $CH_3O_2CCH_2CH_2$) with various thiolate ions,[2b] and the reaction of **4-OCH₂CF₃** with $CF_3CH_2O^-$ and $HOCH_2CH_2S^-$ [3b] allowed a similar dissection of k_1, k_{-1}, and k_2.

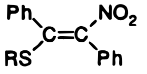


(1)

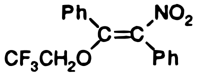
1 2 3



4-OMe

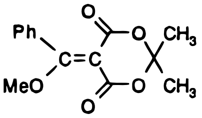


4-SR

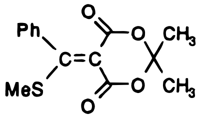


4-OCH₂CF₃

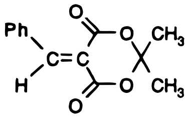
Recently, it was shown that the S_NV intermediates in the reactions of methoxybenzylidene Meldrum's acid (**5-OMe**)[5] and thiomethoxybenzylidene Meldrum's acid (**5-SMe**)[6] with thiolate and alkoxide ions also accumulate to detectable levels, thus making it possible to determine k_1, k_{-1}, and k_2 separately for these reactions. An important observation was that the presence of the methoxy and thiomethoxy groups in **5-OMe** and **5-SMe**, respectively, appear to affect the various rate constants, especially k_1 and k_{-1}, in a major way. To better understand the reasons for these large effects and to put them into more quantitative terms, it seemed imperative to have a reference point and investigate the reactions of thiolate and alkoxide ions with benzylidene Meldrum's acid, **5-H**, which does not contain a leaving group. We now report such a study.



5-OMe



5-SMe



5-H

Results

General Features. All experiments were performed in 50% DMSO−50% water (v/v) at 20 °C and conducted

---

(1) 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) Shainyan, B. A. *Usp. Khim.* **1986**, *55*, 942. (g) Rappoport, Z. *Acc. Chem. Res.* **1992**, *25*, 474.

(2) (a) Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 6862. (b) Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Rappoport, Z. *J. Am. Chem. Soc.* **1990**, *112*, 3169.

(3) (a) Bernasconi, C. F.; Schuck, D. F.; Ketner, R. J.; Weiss, M.; Rappoport, Z. *J. Am. Chem. Soc.* **1994**, *116*, 11764. (b) Bernasconi, C. F.; Schuck, D. F.; Ketner, R. J.; Eventova, I.; Rappoport, Z. *J. Am. Chem. Soc.* **1995**, *117*, 2719.

(4) (a) Bernasconi, C. F.; Leyes, A. E.; Rappoport, Z.; Eventova, I. *J. Am. Chem. Soc.* **1993**, *115*, 7513. (b) Bernasconi, C. F.; Leyes, A. E.; Eventova, I.; Rappoport, Z. *J. Am. Chem. Soc.* **1995**, *117*, 1703.

(5) Bernasconi, C. F.; Ketner, R. J.; Chen, X.; Rappoport, Z. *J. Am. Chem. Soc.* **1998**, *120*, 7461.

(6) Bernasconi, C. F.; Ketner, R. J.; Chen, X.; Rappoport, Z. To be published.

S0022-3263(98)00574-X CCC: $15.00

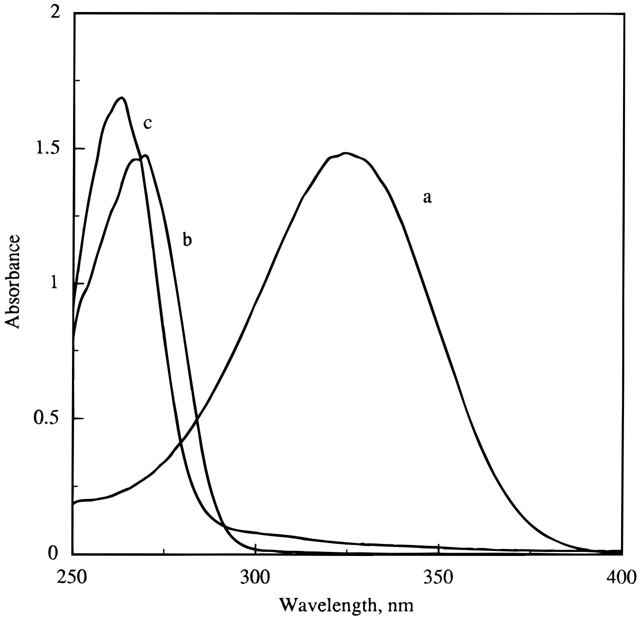
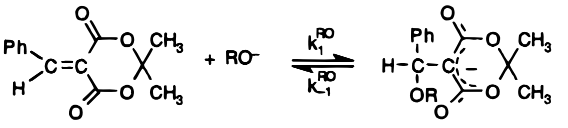


Figure 1. Absorption spectra in 50% DMSO−50% water: (a) **5-H** in 0.001 M HCl; (b) **5-(H,SMe)**$^-$; (c) **5-(H,OMe)**$^-$. **[5-H]$_o$** = 10^{-4} M in all cases.

under pseudo-first-order conditions with **5-H** as the minor component.

Reactions of 5-H with Alkoxide Ions and OH$^-$. These reactions can be represented by eq 2; the alkoxide ions used in this study are $CF_3CH_2O^-$, $HC{\equiv}CCH_2O^-$, and MeO^- (k_{-1}^{RO} only). There is a large difference in the UV spectra between **5-H** and **5-(H,OR)**$^-$ (Figure 1), which makes it easy to measure rate and equilibrium constants spectrophotometrically. The equilibrium of eq 2 strongly favors the adduct in all cases. For example, the pseudo-acidity constant of **5-H** (**5-H** + $H_2O \rightleftarrows$ **5-(H,OH)**$^-$ + H^+) was determined in acetate buffers to yield a pK_a of 5.83, which corresponds to an equilibrium constant for OH^- addition, $K_1^{OH} = k_1^{OH}/k_{-1}^{OH}$, of 1.15×10^{10} M^{-1}.



5-H **5-(H,OR)$^-$** (2)

The rate constants for nucleophilic addition, k_1^{RO}, are quite high; they were determined by stopped-flow spectrometry from the slopes of plots of k_{obsd} vs $[RO^-]$ according to eq 3. For $RO^- = OH^-$, k_{obsd} was measured

$$k_{obsd} = k_1^{RO}[RO^-] + k_{-1}^{RO} \tag{3}$$

in KOH solutions ranging from 0.0045 to 0.1 M. Under these conditions, $k_{-1}^{RO} = k_{-1}^{OH}$ in eq 3 is negligibly small and could not be determined from these experiments. However, on the basis of $k_1^{OH} = 1.80 \times 10^3$ M^{-1} s^{-1} and $K_1^{OH} = 1.15 \times 10^{10}$ M^{-1}, k_{-1}^{OH} can be calculated to be 1.57×10^{-7} s^{-1}.

For $RO^- = CF_3CH_2O^-$ and $HC{\equiv}CCH_2O^-$, k_{obsd} was obtained in buffers prepared from the corresponding alcohols at pH values around 13.1−13.4 for $CF_3CH_2O^-$ and 13.4−14.0 for $HC{\equiv}CCH_2O^-$, respectively. A small correction was applied to k_{obsd} to account for the competing reaction with OH^-, eq 4. For the reaction with

$$k_{obsd}^{corr} = k_{obsd} - k_1^{OH}[OH^-] = k_1^{RO}[RO^-] \tag{4}$$

$CF_3CH_2O^-$, a correction was also applied to the concentrations of $CF_3CH_2O^-$, due to the self-association equilibrium (eq 5, $K_{assoc} = 1.8$ M^{-1}).[3a]

$$CF_3CH_2O^- + CF_3CH_2OH \overset{K_{assoc}}{\rightleftharpoons} CF_3CH_2O^-{\bullet}HOCH_2CF_3 \tag{5}$$

The k_{-1}^{RO} values for the alkoxide ion reactions were determined from experiments in which the respective adduct was first generated in strongly basic solution and then placed into triethylamine buffers at pH 10.5. In these experiments, the alkoxide ion concentration used to generate **5-(H,OR)**$^-$ was quite low, just sufficient to favor formation of **5-(H,OR)**$^-$ over that of **5-(H,OH)**$^-$; in the case of **5-(H,OMe)**$^-$, the adduct was formed in a methanolic MeO^- solution, again using a minimal amount of KOMe. Under these conditions, the remaining alkoxide ion concentration in the pH 10.5 triethylamine buffers was very small. This allowed conversion of **5-(H,OR)**$^-$ to **5-(H,OH)**$^-$ to occur according to eq 6 with $k_1^{H_2O}$ + $k_1^{OH}[OH^-] \gg k_1^{RO}[RO^-]$ (for a determination of $k_1^{H_2O}$ for the water reaction, see below) as well as $k_1^{H_2O} + k_1^{OH}[OH^-] \gg k_{-1}^{RO}$, i.e., **5-H** is a steady-state intermediate and k_{obsd} should be given by k_{-1}^{RO}.

$$\textbf{5-(H,OR)}^- \underset{k_1^{RO}[RO^-]}{\overset{k_{-1}^{RO}}{\rightleftharpoons}} \textbf{5-H} \xrightarrow{k_1^{H_2O} + k_1^{OH}[OH^-]} \textbf{5-(H,OH)}^- \tag{6}$$

As to measuring the rate of eq 6, even though the spectra of **5-(H,OR)**$^-$ and **5-(H,OH)**$^-$ are quite similar, they are not identical, and the somewhat higher absorbance of **5-(H,OR)**$^-$ at 260 nm was exploited for the determination of k_{-1}^{RO} with R = CF_3CH_2 and $HC{\equiv}CCH_2$. In the case of R = CH_3, substantially larger absorbance changes were observed, leading to an *increase* in absorbance at 260 nm during the reaction. The reason for this different behavior is that the k_{-1}^{RO} step with R = CH_3 is much slower than with R = CF_3CH_2 and $HC{\equiv}CCH_2$ and, in fact, slower than the decomposition of **5-(H,OH)**$^-$ to benzaldehyde and Meldrum's acid anion. Hence, the absorbance changes observed in this case refer to the conversion of **5-(H,OR)**$^-$ to these latter decomposition products.

A test for general acid catalysis of alkoxide ion departure by Et_3NH^+ revealed that for R = CF_3CH_2 and $HC{\equiv}CCH_2$, k_{obsd} was, within experimental error, independent of $[Et_3NH^+]$ at concentrations up to 0.08 M. With R = CH_3, a small dependence according to eq 7 was observed with $k_{-1}^{RO} = (2.35 \pm 0.22) \times 10^{-6}$ s^{-1} and $k_{-1}^{RO,BH} = (3.6 \pm 0.6) \times 10^{-5}$ M^{-1} s^{-1}.

$$k_{obsd} = k_{-1}^{RO} + k_{-1}^{RO,BH}[Et_3NH^+] \tag{7}$$

A summary of all the rate and equilibrium constants of the reactions of **5-H** with OH^- and alkoxide ions is provided in Table 1. Included in the table are K_1^{RO} values obtained as k_1^{RO}/k_{-1}^{RO} and also K_1^{ROH} values referring to eq 8, calculated as $K_1^{RO}{\cdot}K_a^{ROH}$, with K_a^{ROH} being

Table 1. Rate and Equilibrium Constants for the Reactions of 5-H with Alkoxide Ions, Alcohols, Thiolate Ions, and Thiols in 50% DMSO−50% Water at 20 °C, $\mu = 0.5$ M (KCl)

Nu^-	pK_a^{RXH}	k_1^{RX} ($M^{-1}\ s^{-1}$)	k_{-1}^{RX} (s^{-1})	K_1^{RX} (M^{-1})	K_1^{RXH} [b]
OH^- [a]	15.47	7.45×10^2	3.73×10^{-6}	2.00×10^8	3.75×10^{-6} [c]
OH^-	17.33[d]	$(1.80 \pm 0.02) \times 10^3$	$(1.57 \pm 0.08) \times 10^{-7}$	$(1.15 \pm 0.05) \times 10^{10}$	$(1.48 \pm 0.10) \times 10^{-6}$ [c,e]
MeO^-	17.2[f]		$(2.35 \pm 0.22) \times 10^{-6}$		
$HC{\equiv}CCH_2O^-$	15.2[g]	$(3.93) \pm 0.12) \times 10^4$	$(4.71 \pm 0.56) \times 10^{-4}$	$(8.34 \pm 1.24) \times 10^7$	$(5.26 \pm 0.78) \times 10^{-8}$
$CF_3CH_2O^-$	14.0[h]	$(2.06 \pm 0.08) \times 10^4$	$(3.25 \pm 0.54) \times 10^{-3}$	$(6.43 \pm 1.31) \times 10^6$	$(6.43 \pm 1.31) \times 10^{-8}$
n-BuS^-	11.40	$(2.48 \pm 0.06) \times 10^7$	$(4.25 \pm 0.20) \times 10^{-5}$	$(5.89 \pm 0.13) \times 10^{11}$	2.34 ± 0.05
$HOCH_2CH_2S^-$	10.56	$(1.44 \pm 0.13) \times 10^7$	$(2.68 \pm 0.33) \times 10^{-4}$	$(5.38 \pm 0.17) \times 10^{10}$	1.48 ± 0.05
$MeO_2CCH_2CH_2S^-$	10.40	$(1.50 \pm 0.03) \times 10^7$	$(3.21 \pm 0.10) \times 10^{-4}$	$(4.68 \pm 0.05) \times 10^{10}$	1.86 ± 0.02
$MeO_2CCH_2S^-$	8.83	$(8.82 \pm 0.06) \times 10^6$	$(3.35 \pm 0.18) \times 10^{-3}$	$(2.63 \pm 0.11) \times 10^9$	3.14 ± 0.16

[a] In water at 25 °C, ref 16. [b] From $K_1^{RX} \cdot K_a^{RXH}$. [c] In units of M. [d] Based on $pK_w = 15.89$, ref 42. [e] Determined spectrophotometrically. [f] pK_a^{RXH} estimated as discussed in ref 3a. [g] pK_a^{RXH} estimated as discussed in ref 5. [h] Reference 3a.

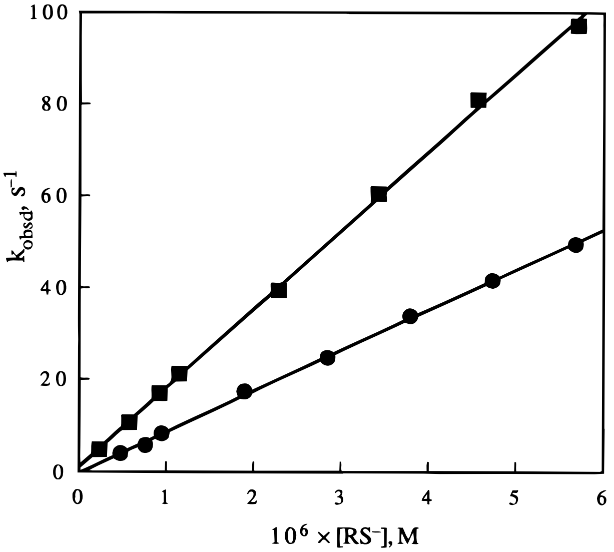
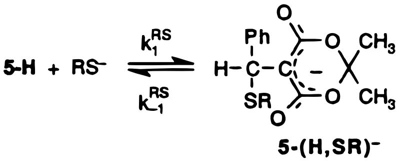


Figure 2. Reactions of **5-H** with thiolate ions. Representative plots of k_{obsd} vs thiolate ion concentration according to eq 10. ■, R = $HOCH_2CH_2$; ●, MeO_2CCH_2.

the acidity constant of ROH.

$$\mathbf{5\text{-}H} + ROH \xrightleftharpoons{K_1^{ROH}} \mathbf{5\text{-}(H,OR)^-} + H^+ \qquad (8)$$

Reactions of 5-H with Thiolate Ions. These reactions can be described by eq 9.



(9)

5-(H,SR)⁻

Four thiolate ions were studied: n-BuS^-, $HOCH_2CH_2S^-$, $MeO_2CCH_2CH_2S^-$, and $MeO_2CCH_2S^-$. The rate constants for nucleophilic addition are all very high (k_1^{RS} from 8.8×10^6 to 2.5×10^7 $M^{-1}\ s^{-1}$). Hence, the rates were measured in N-methylmorpholine buffers at pH 7.40 or acetate buffers at pH 5.97. These pH values are considerably below the pK_a of the thiols (8.83−11.40) so that the free thiolate ion concentrations could be kept below 10^{-5} M to bring k_{obsd} into a range measurable by the stopped-flow technique; at the same time, the thiol concentrations were high enough ($>5 \times 10^{-4}$ M) to ensure pseudo-first-order conditions.

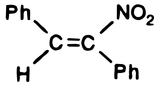
Plots of k_{obsd} vs thiolate ion concentration (Figure 2) conform to eq 10, although the intercepts are too small to yield reliable k_{-1}^{RS} values. Better k_{-1}^{RS} values were

$$k_{obsd} = k_1^{RS}[RS^-] + k_{-1}^{RS} \qquad (10)$$

obtained as $k_{-1}^{RS} = k_1^{RS}/K_1^{RS}$, with K_1^{RS} being the equilibrium constant. K_1^{RS} was determined spectrophotometrically in chloroacetate buffers in a pH range from 3.2 to 4.6, as described in the Experimental Section; this pH range is low enough that competing formation of **5-(H,OH)⁻** is insignificant. The k_1^{RS}, k_{-1}^{RS}, and K_1^{RS} values are summarized in Table 1, along with K_1^{RSH} obtained as $K_1^{RS} \cdot K_a^{RSH}$.

Discussion

Equilibrium Constants for Nucleophilic Addition. Meldrum's acid, with a pK_a^{CH} in water at 25 °C of 4.83[7] and in 50% DMSO−50% water at 20 °C of 4.70[8] is a very strong carbon acid, reflecting the unusually strong electron-withdrawing properties of the cyclic diester moiety.[9] It is therefore not surprising that the equilibrium constants of alkoxide and thiolate ion addition to **5-H** are all very high, ranging from 6.4×10^6 M^{-1} for the reaction with $CF_3CH_2O^-$ to 5.9×10^{11} M^{-1} for the reaction with n-BuS^- (Table 1). In the reaction of α-nitrostilbene (**4-H**) with nucleophiles, the corresponding equilibrium constants are significantly lower, as one would expect on the basis of the higher pK_a^{CH} of phenylnitromethane ($pK_a^{CH} = 7.93$).[12] For example, K_1^{RS} for addition of $HOCH_2CH_2S^-$ to **4-H** is 8.16×10^6 M^{-1},[14] while K_1^{RS} for addition of the same thiolate ion to **5-H** is 5.38×10^{10} M^{-1}. This yields a K_1^{RS}(**5-H**)/K_1^{RS} (**4-H**) ratio of 6.62×10^3. Or, K_1^{OH} for OH^- addition to **4-H** is 2.34×10^6 M^{-1},[15] while K_1^{OH} for **5-H** is 1.15×10^{10} M^{-1}, which



4-H

---

[7] Eigen, M.; Ilgenfritz, G.; Kruse, W. *Chem. Ber.* **1965**, *98*, 1623.

[8] Bernasconi, C. F.; Oliphant, N. Unpublished results.

[9] The cyclic nature of the diester undoubtedly contributes to the high acidity due to better π-overlap and hence more effective charge delocalization in the anion. However, theoretical studies have suggested that the main factor responsible for the high acidity is that the ester moieties are forced into an E (or anti) conformation, which leads to unfavorable dipole interactions that are released upon formation of the anion.[10,11]

[10] (a) Wang, X.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 1870. (b) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1988**, *110*, 1872.

[11] See also: Arnett, E. M.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 809.

[12] pK_a in 50% DMSO−50% water at 20 °C.[13]

[13] Bernasconi, C. F.; Kliner, D. A. V.; Mullin, A. S.; Ni, J. X. *J. Org. Chem.* **1988**, *53*, 3342.

leads to a K_1^{OH}(**5-H**)/K_1^{OH} (**4-H**) ratio of 4.91 × 10^3. These ratios are indeed quite comparable to the K_a^{CH} (Meldrum's acid)/K_a^{CH} ($PhCH_2NO_2$) ratio of 1.70 × 10^3, demonstrating the strong correlation between the equilibrium constants of nucleophilic addition and the acidity of the carbon acid from which the alkene is derived.

For the reaction with OH^-, a K_1^{OH} value had been determined previously in water at 25 °C ($K_1^{OH} = 2.0 \times 10^8\ M^{-1}$);[16] the value in 50% DMSO−50% water at 20 °C is 1.15 × 10^{10} M^{-1}, reflecting the enhanced basicity of OH^- in the DMSO-containing solvent.[17]

Turning to a comparison between sulfur and oxygen nucleophiles, we note that the equilibrium constants for thiolate ion addition are significantly larger than for alkoxide or hydroxide ion addition, despite the much lower proton basicities of the thiolate ions. When the differences in the proton basicities are being corrected for by comparing K_1^{RSH} (**5-H** + RSH $\rightleftharpoons$ **5-(H,SR)**$^-$ + H^+) with K_1^{ROH} (eq 8) instead of K_1^{RS} with K_1^{RO}, this greater affinity of the sulfur bases manifests itself much more dramatically. The K_1^{RSH} values are in the range from 1.5 to 3.9, while the K_1^{ROH} values are all around (5−6) × 10^{-8} (Table 1);[20] thus, the K_1^{RSH}/K_1^{ROH} ratios range from 2.5 × 10^7 to 7.8 × 10^7. These results are similar to earlier findings for the reactions of β-nitrostilbene, **4-H**, with the same bases. For example, $K_1^{RS} = 8.16 \times 10^6\ M^{-1}$ and $K_1^{RSH} = 2.24 \times 10^{-4}$ for the reactions with $HOCH_2CH_2S^-$ and $HOCH_2CH_2SH$, respectively,[14] while $K_1^{RO} = 3.02 \times 10^2\ M^{-1}$ and $K_1^{ROH} = 3.02 \times 10^{-12}$ for the reactions with $CF_3CH_2O^-$ and CF_3CH_2OH, respectively.[21] This leads to $K_1^{RSH}/K_1^{ROH} = 7.4 \times 10^7$. These K_1^{RSH}/K_1^{ROH} values for **5-H** and **4-H** are also quite comparable to the corresponding ratios for the relative affinity of thiols and alcohols toward the methyl cation[22] or the relative affinity of thiols and water toward a variety of carbocations.[23]

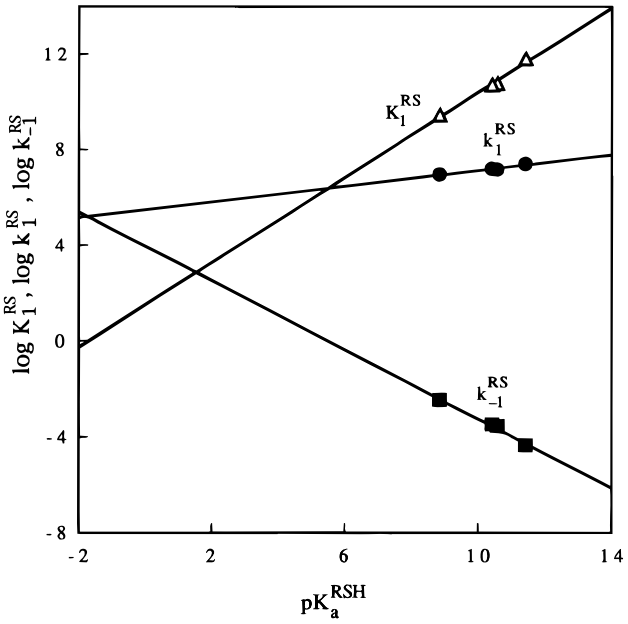


Figure 3. Brønsted plots for the reaction of **5-H** with thiolate ions.

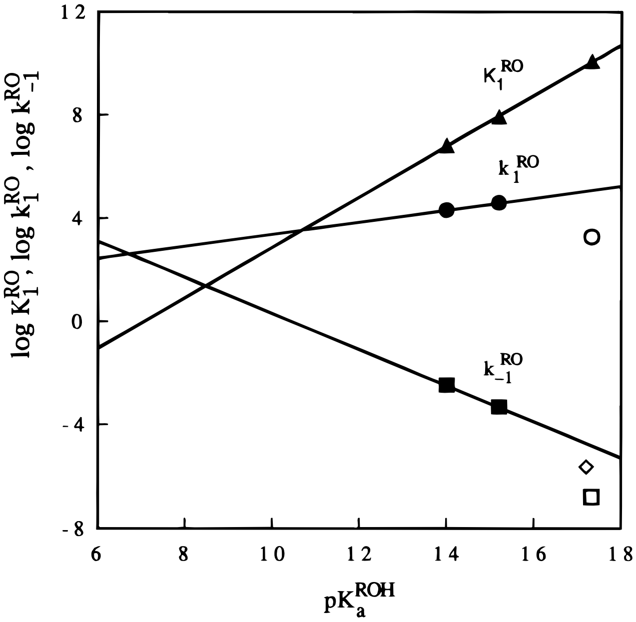


Figure 4. Brønsted plots for the reaction of **5-H** with alkoxide ions: ○ and □, OH^-; ◇, MeO^-.

The reasons for the higher carbon basicity of sulfur bases compared to oxygen bases is commonly attributed to the stronger polarizability or "softness" of the sulfur compounds;[24,25] i.e., in the reaction of sulfur bases with soft electrophiles there is a favorable soft−soft interaction, while in the reactions with alkoxide ions there is a less favorable hard−soft interaction. An additional factor that is particularly important in aqueous media is the much weaker solvation of thiolate compared to alkoxide ions.[26]

Rate Constants for Nucleophilic Addition: Brønsted Plots. Figures 3 and 4 show Brønsted plots for the reaction of **5-H** with thiolate ions and alkoxide ions, respectively. Excellent linear correlations are obtained for the four thiolate ion reactions. For the alkoxide ion reactions, the set of data is more limited for two reasons.

---

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

(15) Bernasconi, C. F.; Fassberg, J. *J. Am. Chem. Soc.* **1994**, *116*, 514.

(16) Bernasconi, C. F.; Leonarduzzi, G. D. *J. Am. Chem. Soc.* **1980**, *102*, 1361.

(17) It is noteworthy that the increase in K_1^{OH} in 50% DMSO is mostly the result of a much lower k_{-1}^{OH}[k_{-1}^{OH} (50% DMSO)/k_{-1}^{OH}(H_2O) = 4.2 × 10^{-2}], while there is only little enhancement in k_1^{OH}[k_1^{OH}(50% DMSO)/k_1^{OH}(H_2O) = 2.42]. It is unclear whether these findings imply a strongly reactant-like transition state[18,19] because the lower temperature in 50% DMSO is a contributing factor in rendering k_1^{OH}(50% DMSO)/k_1^{OH}(H_2O) just slightly larger than unity and k_{-1}^{OH} (50% DMSO)/k_{-1}^{OH}(H_2O) $\ll$ 1.

(18) (a) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 554. (b) Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*, Wiley: New York, 1963; p 156.

(19) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511.

(20) To conform to the definition of K_1^{ROH} with the alcohols, $K_1^{H_2O}$ for water addition has to be divided by the water concentration (27.75 M), which yields 5.33 × 10^{-8}.

(21) Bernasconi, C. F.; Ketner, R. J. To be published.

(22) (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-Interscience: New York, 1975; p 226.

(23) Ritchie, C. D.; Gandler, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7318.

(24) (a) Kallen, R. G.; Jencks, W. P. *J. Biol. Chem.* **1966**, *241*, 5864. (b) Lienhard, G. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1966**, *88*, 3982. (c) Sander, E. G.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 6154.

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

(26) (a) Parker, A. J. *J. Chem. Rev.* **1969**, *69*, 1. (b) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1982**, *47*, 3224. (c) Taft, R. W. *Prog. Phys. Org. Chem.* **1983**, *14*, 247.

Table 2. Brønsted Coefficients and Intrinsic Rate Constants for the Reactions of 5-H with Thiolate and Alkoxide Ions

parameter	RS^-	RO^-
$\mathbf{5\text{-}H} + RX^- \underset{k_{-1}^{RX}}{\overset{k_1^{RX}}{\rightleftharpoons}} \mathbf{5\text{-}(H,XR)}^-$		
$\dfrac{d \log k_1^{RX}}{dpK_a^{RXH}} = \beta_{nuc}$	0.17 ± 0.03	ca. 0.23[a]
$\dfrac{d \log k_{-1}^{RX}}{dpK_a^{RXH}} = \beta_{1g}$	-0.72 ± 0.06	ca. −0.81
$\dfrac{d \log K_1^{RX}}{dpK_a^{RXH}} = \beta_{eq}$	0.89 ± 0.08	ca. 1.03[a]
$\dfrac{d \log k_1^{RX}}{d \log K_1^{RX}} = \beta_{nuc}^{n}$ [b]	0.19 ± 0.01	ca. 0.25
$\dfrac{d \log k_{-1}^{RX}}{d \log K_1^{RX}} = \beta_{1g}^{n}$ [b]	-0.81 ± 0.01	ca. −0.78
$\log k_o^{RX}$ [c]	5.15 ± 0.14	ca. 2.60

[a] Based on $CF_3CH_2O^-$ and $HC{\equiv}CCH_2O^-$ only; if CH_3O^- is included, $\beta_{lg} = -1.04 \pm 0.09$. [b] β_{nuc}^{n} and β_{lg}^{n} are normalized Brønsted coefficients; they can also be obtained as β_{nuc}/β_{eq} and β_{lg}/β_{eq}, respectively, but this method introduces a larger error. [c] $k_o^{RX} = k_1^{RX} = k_{-1}^{RX}$ when $K_1^{RX} = 1$; $\log k_o^{RX}$ obtained from plot of $\log k_1^{RX}$ vs $\log K_1^{RX}$ by extrapolation to $\log K_1^{RX} = 0$.

(1) For $RO^- = MeO^-$ only k_{-1}^{RO} is available. (2) Because of the unusually strong solvation of OH^-, the rate constants for the OH^- reaction show the typical negative deviations from the Brønsted plots of k_1^{OH} and k_{-1}^{RO};[27] i.e., OH^- is not really a member of the RO^- family.

Table 2 summarizes the Brønsted coefficients obtained from the Brønsted plots; because of the limited data for the alkoxide ion reactions, these parameters should be considered as only approximate. The table includes $\log k_o^{RX}$ values for the intrinsic rate constant defined as $k_o^{RX} = k_1^{RX} = k_{-1}^{RX}$ when $K_1^{RX} = 1$.

The low β_{nuc} (β_{nuc}^{n}) values, which imply transition states with little bond formation,[28] are consistent with previous findings. In particular, β_{nuc} (β_{nuc}^{n}) for thiolate ion addition to a variety of electrophilic alkenes,[14,31] activated vinylic substrates,[2] and other electrophiles[23,32,33] is generally quite low. A number of representative cases are summarized in Table 3; for additional examples, see ref 23.

Table 3. Representative β_{nuc}, β_{eq}, and β_{nuc}^{n} Values for the Addition of Thiolate Ions to Electrophiles

	β_{nuc}	β_{eq}	β_{nuc}^{n}
5-H[a,b]	0.17	0.89	0.19
5-OMe[a,c]	0.17	0.76	0.22
4-H[a,d]	0.16	0.84	0.19
4-OMe[a,e]	0.09	0.80	0.11
$PhCH{=}CHNO_2$[a,f]	0.11	0.50	0.22
$CH_3CH{=}O$[g,h]	ca. 0.20		
$CH_3C(O)OAr$[g,i]	0.27		
carbocations[g,j]	0−0.2		

[a] In 50% DMSO−50% water at 20 °C. [b] This work. [c] Reference 5. [d] Reference 14. [e] Reference 2b. [f] Reference 31. [g] In water at 25 °C. [h] Reference 32. [i] Reference 33. [j] Reference 23.

The reasons for the low β_{nuc} (β_{nuc}^{n}) values are not clear. For the reactions of **5-H**, **5-OMe**, **4-H**, **4-OMe**, $PhCH{=}CHNO_2$, and the carbocations, the low values might, in principle, be attributed to the fact that the equilibrium constants for nucleophilic addition are high (Hammond effect)[18,19] but this is not the case for $CH_3CH{=}O$ or $CH_3C(O)OAr$ where the equilibrium constants are much lower. It appears that, as a rule, β_{nuc} is low for thiolate ion addition to electrophiles although there are exceptions, e.g., in the reactions of thiolate ions with $CH_2{=}CHCN$[34] ($\beta_{nuc} = 0.45$) and *N*-methyl-N′-nitro-*N*-nitrosoguanidine ($\beta_{nuc} = 0.70$).[35]

Another feature to be noted is that β_{eq} for the thiolate ion reactions is generally <1, indicating that the carbon basicities of thiolate ion are not quite proportional to their proton basicities.

The database for β_{nuc} (β_{nuc}^{n}) for alkoxide ion additions is much less extensive than for thiolate ion additions. The low β_{nuc} (β_{nuc}^{n}) value for the reactions of **5-H** with alkoxide ions contrasts with the significantly larger values for alkoxide ion addition to **5-OMe** ($\beta_{nuc} = 0.51$, $\beta_{nuc}^{n} = 0.34$).[5] Whether this reflects the Hammond effect of somewhat lower equilibrium constants in the alkoxide ion reactions is unclear because of potential complications arising from the anomeric effect in the latter reactions.[5]

Intrinsic Rate Constants. The comparison between the intrinsic rate constants for thiolate (k_o^{RS}) and alkoxide ion (k_o^{RO}) addition to **5-H** is of particular interest. The $\log k_o^{RS}$ value (5.15) is seen to be more than two log units higher than $\log k_o^{RO}$ (2.86). Whether the actual difference between these $\log k_o^{RS}$ values is indeed as large as these numbers suggest or whether the rather long extrapolations required for the determination of $\log k_o$ lead to distortions in $\log k_o^{RX}$ is difficult to assess. If, for example, the plots of $\log k_1^{RX}$ vs $\log K_1^{RX}$ over a wider range than is experimentally accessible contained some Marcus curvature,[36] the numerical values of $\log k_o^{RX}$ would be reduced and possibly by different amounts for the two types of reactions.[37] In fact, a calculation of $\log k_o^{RX}$ based on the application of the Marcus equation[36] (eq 11) to the reactions of $MeO_2CCH_2S^-$ and $CF_3CH_2O^-$,

$$\Delta G^{\ddagger} = \Delta G_o^{\ddagger} + \frac{\Delta G^{\circ}}{2} + \frac{(\Delta G^{\circ})^2}{16\Delta G_o^{\ddagger}} \qquad (11)$$

respectively, yields $\log k_o^{RS} = 2.79$ and $\log k_o^{RO} = 1.52$, i.e., $\log k_o^{RS} - \log k_o^{RO} = 1.27$ instead of 2.29 based on $\log k_o^{RS}$ and $\log k_o^{RO}$ obtained from the Brønsted plots.

---

(27) (a) Kresge, A. J. *Chem. Soc. Rev.* **1979**, *2*, 475. (b) Jencks, W. P.; Brant, S. R.; Gandler, J. R.; Fendrich, G. Nakamura, C. *J. Am. Chem. Soc.* **1982**, *104*, 7045.

(28) This is the traditional view,[18b,29] although this view has been challenged[30] as well as defended.[19]

(29) Kresge, A. J. *Acc. Chem. Res.* **1975**, *8*, 354.

(30) (a) Pross, A. *J. Org. Chem.* **1984**, *49*, 1811. (b) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 4737. (c) Pross, A.; Shaik, S. S. *New J. Chem.* **1989**, *13*, 427.

(31) Bernasconi, C. F.; Schuck, D. F. *J. Org. Chem.* **1992**, *57*, 2365.

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

(33) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451.

(34) Friedman, M.; Cavins, J. F.; Wall, J. S. *J. Am. Chem. Soc.* **1965**, *87*, 3672.

(35) Santala, T.; Fishbein, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 8852.

(36) (a) Marcus, R. A. *J. Chem. Phys.* **1965**, *43*, 679. (b) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891. (c) Cohen, A. O.; Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 4249.

(37) The reaction $R'S^- + RSSR \rightarrow R'SSR + RS^-$ shows some Marcus curvature,[38] but this reaction is an S_N2-type substitution rather than an addition reaction.

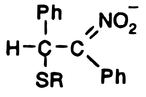
However, the β^{n}_{nuc} values calculated via eq 12 based on the $\Delta G_o^{\ddagger}$ calculated from eq 11 are much larger than the experimental β^{n}_{nuc}, which argues against using the Marcus equation.

$$\beta^{n}_{nuc} = \frac{d\Delta G^{\ddagger}}{d\Delta G^{\circ}} = \frac{1}{2} + \frac{\Delta G^{\circ}}{8\Delta G_o^{\ddagger}} \qquad (12)$$

Be that as it may, it is clear that the intrinsic rate constant for the thiolate ion reactions is substantially higher than that for the alkoxide ion reactions, irrespective of what method is used to estimate log k_o^{RX}. In other words, for a given equilibrium constant (K_1^{RX}), the rate constants for nucleophilic addition (k_1^{RX}) as well as for the reverse process (k_{-1}^{RX}) are substantially higher with RS^- than with RO^-. One important factor that contributes to this state of affairs is related to the requirement of partial desolvation of the nucleophile as it enters the transition state. This desolvation is typically more advanced than bond formation,[27,33] which, according to the principle of nonperfect synchronization (PNS),[39] results in a depression of the intrinsic rate constant. Because highly basic alkoxide ions are more strongly solvated than thiolate ions,[26,27] there is a correspondingly stronger reduction of k_o^{RO} than of k_o^{RS}, which, assuming everything else is equal, results in $k_o^{RS} > k_o^{RO}$.

A second factor that may favor the thiolate ion reactions is related to the previously discussed higher carbon basicity of thiolate ions toward **5-H** compared to that of alkoxide ions. If one assumes that in the thiolate ion reactions the soft−soft interactions run ahead of bond formation at the transition state, the stabilization of the transition state by the developing soft−soft interactions would be disproportionately strong relative to that of the adduct. According to the PNS,[39] this would translate into a higher intrinsic rate constant. The assumption that the soft−soft interactions develop ahead of bond formation is not unreasonable because these interactions are based on the polarizability of the interacting molecules and may not require a substantially developed bond for them to be effective.

It is also of interest to compare the intrinsic rate constants for thiolate ion addition to **5-H** (log k_o^{RS} = 5.15) and **4-H** (log k_o^{RS} = 3.43). The lower k_o^{RS} for **4-H** reflects the fact that the adduct derived from **4-H**, **4-(H,SR)$^-$** owes a larger fraction of its stabilization to resonance than is the case for **5-(H,SR)$^-$**. As has been documented extensively,[40] for reactions that lead to resonance-stabilized products there is an inverse relationship between the intrinsic rate constant and the magnitude of the resonance effect. It is the result of a lag in the development of resonance behind bond changes, again a PNS[39] effect. The same phenomenon was observed when the intrinsic rate constants for deprotonation of Meldrum's acid by secondary alicyclic amines (log k_o = 3.90)[8] and deprotonation of phenylnitromethane by the same bases (log k_o = −0.25) were compared.[13]



4-(H,SR)$^-$

Conclusions

(1) The equilibrium constants for alkoxide and thiolate ion addition to **5-H** are very high, reflecting the strong electron-withdrawing effect of the $(COO)_2C(CH_3)_2$ moiety, which is also responsible for the high acidity of Meldrum's acid. In comparison to the alkoxide ions, the thiolate ions have a much higher affinity for **5-H**, which is best appreciated after taking the much lower proton basicity of the thiolate ions into account. This is a well-known phenomenon and is the result of the high polarizability of sulfur bases.

(2) The rate constants for nucleophilic attack on **5-H** show only a weak dependence on pK_a^{RXH}, especially for the thiolate ion reactions (small β_{nuc}). The *intrinsic* rate constant for thiolate ion addition is substantially higher than for alkoxide ion addition. This is attributed to the weaker solvation of the thiolate ions and the fact that, at the transition state, partial desolvation of the nucleophile has made more progress than bond formation. An additional factor that may contribute to this result is that the development of the soft−soft interactions between the thiolate ion and the electrophile may be more advanced at the transition state than bond formation.

(3) The intrinsic rate constant for thiolate addition to **5-H** is 50-fold larger than for addition of **4-H**, reflecting the smaller resonance effect in the stabilization of **5-(H,SR)$^-$** compared to **4-(H,SR)$^-$**.

Experimental Section

Materials. Benzylidene Meldrum's acid (**5-H**) was synthesized by the method of Schuster et al.[41] DMSO was refluxed over CaH_2 and distilled under vacuum. All organic reagents, salts, and solvents were purchased from Aldrich or Fisher Chemicals. The thiols were distilled prior to use, and β-mercaptoethanol was distilled under vacuum. 2,2,2-Trifluoroethanol, propargyl alcohol, *N*-methylmorpholine, and triethylamine were distilled and stored under nitrogen or argon. Methanol, glacial acetic acid, KCl, petroleum ether, and other solvents were used as received. Standardized solutions of HCl and KOH were prepared from Baker "Dilut-its". Millipore water was used for all experiments.

Reaction Solutions. Stock solutions of **5-H** were prepared in dry acetonitrile. After dilution with 50% DMSO−50% water, the acetonitrile content was typically 1% or less. The pH of the buffer solutions were measured in mock mixing experiments against the standards reported by Hallé et al.[42]

Spectra and Equilibrium Measurements. UV−vis spectra were obtained on a Hewlett-Packard 8452A diode array spectrophotometer. Equilibrium constants for thiolate ion addition were measured spectrophotometrically according to eq 13 with A being the absorbance where **5-(H,SR)$^-$** is partially formed, A_T- the absorbance for complete conversion to **5-(H,SR)$^-$**, and A_S the absorbance of **5-H** in the absence of

---

[38] Hupe, D. J.; Pohl, E. R. *Isr. J. Chem.* **1985**, *26*, 395.

[39] The PNS[40] states that if development of a product-stabilizing factor lags behind, or the loss of a reactant stabilizing factor is ahead of bond changes at the transition state, the intrinsic rate constant is lowered. Examples of such stabilizing factors include resonance and solvation. On the other hand, if a product-stabilizing factor develops early, or a reactant-stabilizing factor is lost late, the intrinsic rate constant is enhanced.

[40] (a) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301. (b) Bernasconi, C. F. *Acc. Chem. Res.* **1992**, *25*, 9. (c) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119.

[41] Schuster, P.; Polansky, O. E.; Wessely, F. *Monatsch. Chem.* **1964**, *95*, 53.

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

$$\log(K_1^{\mathrm{RS}}[\mathrm{RS}^-]) = \log\left(\frac{A_{\mathrm{T}^-} - A}{A - A_{\mathrm{S}}}\right) \qquad (13)$$

RS^-, respectively. Similarly, the pseudoacidity constant of **5-H** for the formation of **5-(H,OH)**$^-$ was obtained from eq 14, where A, A_{T^-}, and A_{S} have meanings similar to those in eq 13.

$$\mathrm{p}K_1^{\mathrm{H_2O}} = \mathrm{pH} + \log\left(\frac{A_{\mathrm{T}^-} - A}{A - A_{\mathrm{S}}}\right) \qquad (14)$$

Kinetic Measurements. Most kinetic determinations ($k_{\mathrm{obsd}} > 10^{-2}$ s^{-1}) were performed on an Applied Photophysics DX.17MV stopped-flow apparatus with its own nonlinear regression software. For reactions with $k_{\mathrm{obsd}} < 10^{-2}$ s^{-1}, the measurements were carried out on a Lambda 2 Perkin-Elmer spectrophotometer and analyzed using the ENZFITTER[43] nonlinear regression program.

Acknowledgment. This research was supported by Grant No. CHE-9307659 from the National Science Foundation.

JO980574A

---

(43) Program by Robin J. Leatherbarrow (Department of Chemistry, Imperial College of Science & Technology, South Kensington, London SW7 2A4, U.K.). Published and distributed by BIOSOFT, 22 Hills Road, Cambridge CB2 1JP, U.K.