Displacement Reactions. XIX.[1] The Rates and Heats of Reaction of Nucleophiles with β-Propiolactone

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Abstract: The nucleophilic constants of a thiol, mercaptoethylammonium ion, have been determined using β-propiolactone as a substrate in aqueous solution at 25°. The data are correlated with the nucleophilic properties of HO^-, H_2O, HS^-, H_2S, RS^-, and RSH. The trends are regular and good predictions can be made. The reaction of hydroxide ion with β-propiolactone is discussed. The fraction of attack at the methylene carbon has been predicted but not yet tested. The rates and heats of reaction of β-propiolactone with NO_2^-, SO_3^{2-}, ^-SCN, ^-OH, I^-, CH_3COO^-, and $S_2O_3^{2-}$ have been measured. The ΔH values are reported and discussed.

It is not too surprising that almost any material containing an electronegative atom with an unshared pair of electrons can serve as a nucleophile. Thus acetone, dioxane, and urea (all oxygen compounds) can be expected to be nucleophiles for displacement reactions on carbon. The nucleophilic properties of numerous sulfur anions are well known. Examination of the literature shows that no accurate rate data are available to assign the oxibase scale nucleophilic constants to a free thiol, RSH, compared to its anion, RS^-, in water. In continuing our study[1] on the antiradiation drug, mercaptoethylamine, we have measured the rate of reaction of the thiol form with a convenient substrate, β-propiolactone. The lactone is a very useful substrate because it is transparent in the ultraviolet, because it and its reaction products are water soluble, and because the specific rate constants are large.

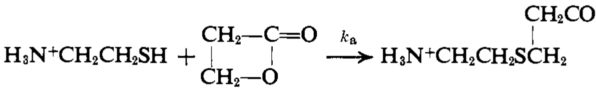
I. MEA with Propiolactone

β-Propiolactone. In an aqueous acetate buffer solution the rate of disappearance of the lactone (L) would be the sum of the rate with water, with hydroxide, with the acetate buffer anion, and with the four forms of MEA.

$$-\mathrm{d}[L]/\mathrm{d}t = k_0[H_2O][L] + k_{OH^-}[OH^-][L] + k_{AcO^-}[AcO^-][L] + k_a[H_3N^+CH_2CH_2SH][L] + k_b[H_2NCH_2CH_2SH][L] + k_c[H_3N^+CH_2CH_2S^-][L] + k_d[H_2NCH_2CH_2S^-][L] \quad (1)$$

The value of k_{H_2O} is $1.0 \times 10^{-6}\ M^{-1}\ sec^{-1}$ as reported by Bartlett.[3] Thus the magnitude of the first term with $[L] = 0.1\ M$ would be only 5×10^{-6} mol/l. sec. While the value of k_{OH^-} is large[3] ($1.2\ M^{-1}\ sec^{-1}$) in acidic media of pH 2–5, the rate of disappearance of the lactone by reaction with hydroxide is very small and of the order of 10^{-10} to 10^{-13} mol/l. sec. Using *dilute* acetate buffers, one can control the magnitude of the term $k_{AcO^-}[AcO^-][L]$ as the value[3] of k_{AcO^-} is $3.0 \times 10^{-4}\ M^{-1}\ sec^{-1}$.

Thus the kinetic system (1) can be reduced from a seven-term equation to a four-term kinetic equation by control of the concentrations. In the previous paper,[1] the *E* and *H* values of the thiolate anions, $H_3N^+CH_2CH_2S^-$ and $H_2NCH_2CH_2S^-$, were obtained. In the present paper we have used β-propiolactone as a substrate to obtain the *E* value of $H_3N^+CH_2CH_2SH$. Therefore, the reaction was studied in quite acidic media forming the sulfide (eq 2). The data are presented in Table I. The constant, k_a, was determined using a computer. The total reaction is an extremely rapid process; some of the pseudo-first-order half-times for systems in Table I are about 20 sec or so in length at the higher pH values.



$$H_3N^+CH_2CH_2SH + \begin{matrix} CH_2\text{—}C\text{=}O \\ | \qquad\quad | \\ CH_2\text{—}O \end{matrix} \xrightarrow{k_a} H_3N^+CH_2CH_2S\overset{\overset{\displaystyle CH_2COOH}{|}}{CH_2} \quad (2)$$

Table I. Reaction of MEA with Propiolactone

[MEA], $10^2\ M$[a]	[Lactone], $10\ M$[b]	pH[c]	μ[d]	k_a, $M^{-1}\ sec^{-1} \times 10^4$[e,f]	k_c, $M^{-1}\ sec^{-1}$[f]
1.17	2.24	2.24	0.252	6.8 ± 0.2[g]	
1.18	4.25	2.24	0.252	7.4 ± 0.2	
0.404	3.74	2.25	0.252	7.0 ± 0.1	
1.76	4.26	3.47	0.072	7.6 ± 0.2	
0.880	0.52	3.47	0.072	7.8 ± 0.3	
1.77	2.24	3.47	0.072	7.4 ± 0.3	
1.76	2.30	4.03	0.15	7.2 ± 0.6	
0.73	2.18	4.03	0.02	7.4 ± 0.5	
1.76	4.17	4.57	0.240	6.4 ± 0.7	
1.76	4.30	4.57	0.159	6.8 ± 0.8	
0.644	4.38	5.11	0.400	6.4 ± 0.3[h]	0.30[h,i]
1.17	4.29	5.11	0.400	7.2 ± 0.2[h]	0.25[h,i]

[a] Concentration of MEA·HCl added. [b] Concentration of β-propiolactone. [c] pH ± 0.02. [d] Ionic strength. [e] Computed value of k_a, see eq 1. [f] Average of several kinetic experiments. In dilute aqueous buffers with the pH near 5, eq 1 becomes rate $\approx k_a[H_3N^+CH_2CH_2SH][L] + k_c[H_3N^+CH_2CH_2S^-][L]$, since k_0 is small, $[OH^-]$ is very small, and $k_{AcO^-}[AcO^-]$ is small. See ref 3. Likewise $[H_2NCH_2CH_2S^-]$ and $[H_2NCH_2CH_2SH]$ are very small. Using the ionization constants the amount of $H_3N^+CH_2CH_2SH$ and of $H_3N^+CH_2CH_2S^-$ can be computed at each pH. Since the lactone concentration is large, the rate equation reduces to a pseudo-first-order rate expression The observed first-order constant is k_1 which equals $k_a[L] + k_c[L]$. At low pH (down to 2) the k_c term drops out as the concentration of $H_3N^+CH_2CH_2S^-$ becomes very low. [g] Estimate of the standard derivation, σ. Average rate constant of at least three kinetic experiments. [h] The $H_3N^+CH_2CH_2S^-$ concentration is starting to rise and the $t_{1/2}$ is 20 sec or less. Data recorded in a fast mixing apparatus. [i] Value of k_c estimated errors are ±10%.

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(1) Paper XVIII: R. E. Davis, S. P. Molnar, and R. Nehring, *J. Am. Chem. Soc.*, **91**, 97 (1969).

(2) (a) Taken in part from the M.S. Thesis of L. Suba, June 1964. (b) Undergraduate thesis student.

(3) P. D. Bartlett and G. Small, Jr., *J. Am. Chem. Soc.*, **72**, 4867 (1950). The value of k_{OH^-} is reported to be $1.2\ M^{-1}\ sec^{-1}$ at 25° in water. This value is below that estimated by extrapolation of the data of Long and Purchase (*ibid.*, **72**, 3267 (1950)) and of Johansson (*Chem. Zentr.*, **87**, II 558 (1916)). Presently the reaction of hydroxide is under study using fast-flow techniques.

A value of 0.25 ± 0.03 M^{-1} sec^{-1} can be estimated using these data for the rate constant with $H_3N^+CH_2CH_2S^-$.

In Figure 1, the oxibase scale plot of β-propiolactone is presented. The rate constants with iodide, bromide, chloride, thiocyanate, thiosulfate, acetate, hydroxide (top point), and water (k_0) were reported by Bartlett.[3] The data on ethyl xanthate and diethyl dithiocarbamate were reported in a previous paper.[4]

The point for $H_3N^+CH_2CH_2SH$ has been placed on the line and the E value (and H/E) computed. The point for $H_3N^+CH_2CH_2S^-$ has been placed using the rate constant obtained (data from Table I and the E and H values obtained with methyl iodide and ethyl tosylate[1]).

The Oxibase Scale Parameters. The substrate, β-propiolactone, has only a slight sensitivity to the basicity of the nucleophile. In quantitative terms, the β is 0.069. The oxibase equation

$$\log (k/k_0) = \alpha E + \beta H \tag{3}$$

$$\log (k/k_0) = 2.00E + 0.069H \tag{4}$$

requires a knowledge of the H of the ammonium ethylthiol cation with

$$H_3N^+CH_2CH_2SH + H^+ \overset{K}{\rightleftharpoons} H_3N^+CH_2CH_2SH_2^+ \tag{5}$$

$$H \equiv pK_a + 1.74 \tag{6}$$

protonation on the thiol group. The value of K in eq 5 has not been reported but for the present investigation it can be estimated from the pK_a of ethyl thiol (pK_a =

$$CH_3CH_2SH + H^+ \rightleftharpoons CH_3CH_2S^+H_2 \tag{7}$$

-6.7_2). The value of -6.7_2 is the average of three literature values reported[5] as −6.68, −6.70, and −6.80. The presence of the ammonium group in the β position ought to increase the pK_a of the thiol by about 2 or 3 pK units. This estimate is based on the effect of the ammonium group of the pK_a of thiolate anions: $CH_3CH_2S^-$, $pK = 10.65$; $H_3N^+CH_2CH_2S^-$, $pK = 8.35$; $\Delta pK = 2.3$. Thus

$$pK_{a(5)} \approx -9 \text{ to } -10 \tag{8}$$

$$H \approx -7.3 \text{ to } -8.3 \approx -8 \tag{9}$$

the H value of $H_3N^+CH_2CH_2SH$ is probably about −8. This value of H might be in error by ±2 or ±3. While the estimate of H is in error this error would cause an error in E of only a few per cent because the α value of the lactone is so large. An error in H of two pK units would effect the rate constant, k, by 1.3-fold. Using the average value of $k_{H_3N^+CH_2CH_2SH}$ to be 7.2×10^{-4} M^{-1} sec^{-1}, the E value of the ammonium thiol is 1.68 ± 0.06 V. Using an error of three pK_a units, E = 1.68 ± 0.10 V. The E values are compared in Table II. The uncertainty in H is reflected in the uncertainty in the E value of the ammonium thiol.

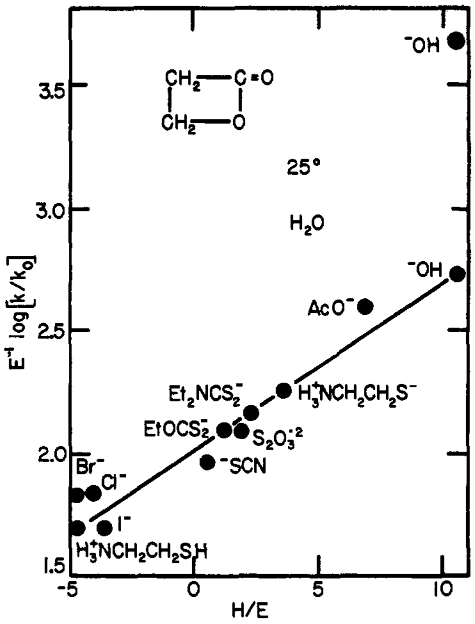

Figure 1. Oxibase scale plot of the E^{-1} log (k/k_0) *vs.* H/E for numerous nucleophiles. Both points for hydroxide ion have been placed on the graph. See the text for a discussion of hydroxide ion.

Table II. E Values of MEA in Water at 25°

Form	E, V[a]
$H_2NCH_2CH_2S^-$	3.08 ± 0.04[b]
$H_3N^+CH_2CH_2S^-$	2.84 ± 0.04[b]
$H_3N^+CH_2CH_2SH$	1.68 ± 0.06[c]

[a] $E = \epsilon^0 + 2.60$ V.

$$2RS^- \overset{\epsilon^0}{\rightleftharpoons} RSSR + 2e^-$$

$$2RSH \overset{\epsilon^{0\prime}}{\rightleftharpoons} \underset{HH}{RSSR}^{2+} + 2e^-$$

[b] Paper XV; ref 1. [c] This study assuming an error in H of ±2 pK_a units.

In terms of the oxibase scale, the low nucleophilicity of the thiol compared with the thiolate anion resides in the free energy difference between the disulfide and the diprotonated form of the disulfide (eq 10 and 11).

$$\begin{array}{cccr} 2RS^- & \rightleftharpoons & RSSR + 2e^- & (10) \\ \updownarrow & & \updownarrow & \\ 2RSH & \rightleftharpoons & \underset{HH}{RSSR}^{2+} + 2e^- & (11) \end{array}$$

Oxibase scale parameters[6] are now known for several anions and their forms. For example, the difference between the E value of hydroxide ion and the E value of water is 1.65 V (eq 12 and 13). The E difference

$$2HO^- \overset{E\,=\,1.65}{\rightleftharpoons} HOOH + 2e^- \tag{12}$$

$$2H_2O \overset{E\,=\,0}{\rightleftharpoons} H_2OOH_2^{2+} + 2e^- \tag{13}$$

$$\Delta E = 1.65 \text{ V}$$

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[4] Paper XI: R. E. Davis, H. Nakshbendi, and A. Ohno, *J. Org. Chem.*, 31, 2702 (1966).

[5] E. M. Arnett, *Progr. Phys. Org. Chem.*, 1, 223 (1963).

[6] R. E. Davis in "Survey of Progress in Chemistry," Vol. 2, A. Scott, Ed., Academic Press, New York, N. Y., 1964, pp 189–238.

of the thiolate–thiol (Table II) is 1.40 V, or less by 0.25 V than the difference of the oxygen compounds.

$$2RS^- \underset{}{\overset{E\ =\ 3.08}{\rightleftharpoons}} RSSR + 2e^- \qquad (14)$$

$$2RSH \underset{}{\overset{E\ =\ 1.68}{\rightleftharpoons}} RSSRH_2{}^{2+} + 2e^- \qquad (15)$$

$$\Delta E = 1.40\ \mathrm{V}$$

The H Values. Another interesting comparison can be made by comparing the pK_a (H = pK_a + 1.74) of several conjugate nucleophiles.

	H_2O	HO^-	
	$E = 0$	$E = 1.65$	$\Delta E = 1.65$
	$H = 0$	$H = 17.65$	$\Delta H = 17.6$
typical R	RSH	RS^-	
	$E = 1.6$	$E = 3$	$\Delta E = 1.4$
	$H = -5$	$H = 12$	$\Delta H = 17$
	H_2S	HS^-	
	$E = 1.2$	$E = 2.60$	$\Delta E = 1.4$
	$H = -7$	$H = 8.70$	$\Delta H = 16$

While the changes in ΔE and ΔH are only approximately constant, these changes can be used to guess E and H values for the other pairs, X^- and HX. At least the trend of ΔE and ΔH within the oxygen and sulfur family is regular and predictable.

Thiols as Nucleophiles. It must be stated that while the E value of a thiol as MEA is about 1.7 V and therefore as strong a carbon nucleophile as bromide ion (E = 1.51), the thiols are poor competitors with their own anions (eq 16 and 17). As a general rule the thiolate

$$RSH + AX \xrightarrow{k_1} RSA + H^+ + X^- \qquad (16)$$

$$RS^- + AX \xrightarrow{k_2} RSA + X^- \qquad (17)$$

anion will be at least several thousand times more reactive with many typical substrates of moderate α values. Thus only in very acidic solution can the ionization of the thiol be supressed so that only the kinetic term of the thiol is observed. This probably accounts for the paucity of kinetic data on the thiols. Secondly thiols are not very water soluble except as in MEA with ammonium salt formation. Low concentrations of thiol means that the thiol of E = 1.7 has a hard time even competing with the water molecules present at 55.5 M since the log (55.5) is 1.7.

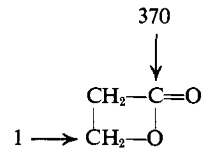
Alkyl-Oxygen Cleavage of the β-Propiolactone Ring by Hydroxide Ions. A plot of E^{-1} log (k/k_0) *vs.* H/E for the rate data is presented in Figure 1. All but one of these anions cleave the methylene carbon–oxygen bond and the data of all nucleophiles fit the straight line. However, hydroxide ion with its extreme basicity attacks the carbonyl carbon with acyl-oxygen cleavage.

Using the scale parameters for HO^- of E = 1.65 and H = 17.48, one can compute the k_{OH^-} for attack *on the methylene carbon* (eq 18–20). Since the observed rate is 1.2 M^{-1} sec^{-1}, the attack on the C=O group occurs 370 times faster than attack on the β-CH_2 group.

$$\log (k'/k_0) = \alpha E + \beta H \qquad (18)$$

$$\log (k'/k_0) = 2.00(1.65) + 0.069(17.48) \qquad (19)$$

$$k'_{OH^-} = 3.2 \times 10^{-3}\ M^{-1}\ \mathrm{sec}^{-1} \qquad (20)$$



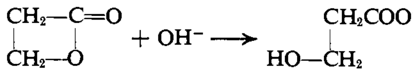
Relative rates with OH^-

It would require extremely accurate ^{18}O data to determine a fraction per cent of ^{18}O from hydroxide ion in the ω-alcohol group in the product. In Figure 1 the two hydroxide points are placed on the graph. Experiments using ^{18}O are in progress to test this prediction of the oxibase scale.[7]

II. Rates and ΔH's of Reaction with β-Propiolactone

Few thermodynamic parameters have been measured on displacement reactions of interest to the physical-organic chemist. Using the calorimeter previously discussed,[8] the total amount of heat, ΔH at constant pressure, and the rate of heat production have been measured for numerous nucleophiles in aqueous solution. The data are presented in Table III.

There is a general trend in $-\Delta H$ values and the rate constant. The fastest rate constant in Table III is that of hydroxide ion. Its value is



about a factor of 2 slower than that reported[3] but until the stopped flow studies are finished, the difference is probably due to the difference in ionic strength and the experimental errors of the calorimetric method and the titrametric method.[3]

Thiosulfate gives a ΔH of −25.8 kcal/mol. The rate constant of 8.1 × 10^{-2} M^{-1} sec^{-1} differs a bit from the value reported,[3] but the ionic strengths in the thermochemical experiments are much larger to insure fast reaction with the lactone. In separate titrametric experiments using iodine solutions to analyze for the thiosulfate, the rate constant was 7.8 × 10^{-2} M^{-1} sec^{-1} using the same concentrations as in the thermochemical reaction.

The rate constant of acetate is about the limit in rate that the submarine calorimeter can measure with an error (σ) of less than 2%.

Thiocyanate ion reacts smoothly to produce the β-thiocyanopropionate. The value of ΔH is the lowest value in Table III, reflecting the weakness of carbon–sulfur bonds. However, the ease of the formation of the carbon–sulfur bond is reflected by the rate constant.

Iodide ion produces a small amount of heat (ΔH = −15.7 kcal/mol) but the rate constant is large; k_{I^-} is 4.40 × 10^{-3} M^{-1} sec^{-1} which compares[3] with a value of 3.0 × 10^{-3} M^{-1} sec^{-1}. However, the value measured using the ultraviolet absorption of I^- was 4.5 × 10^{-3} M^{-1} sec^{-1}.

Conclusion

The aqueous solution chemistry of β-propiolactone can be adequately treated using the oxibase scale. The ability to predict rate ratios lends it to quantitative tests.

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[7] The ratio of 370 to 1 depends upon the value given to k_{OH^-}, see ref 3.

[8] R. E. Davis and J. Carter, *Tetrahedron*, **22**, 495 (1966).

Table III. Data on the Reaction of Nucleophiles with β-Propiolactone

Nucleophile	ΔH,[a] kcal/mol	Thermochemical[j] k_2, M^{-1} sec^{-1}	E_A[k]	k_2, M^{-1} sec^{-1}
OH^-[b]	-34.85 ± 0.07[i]	0.59[l]		
SO_3^{2-}[c]	-36.9 ± 0.22	8.8×10^{-2}		
$S_2O_3^{2-}$[d]	-25.78 ± 0.18	8.1×10^{-2}[m]		7.8×10^{-2}[q]
NO_2^-[e]	-24.68 ± 0.20	1.55×10^{-3}	16.6	
CH_3COO^-[f]	-24.13 ± 0.66	5.9×10^{-4}[n]		
^-SCN[g]	-22.23 ± 0.56	3.4×10^{-3}[o]	13.2	
I^-	-15.7 ± 0.47	4.40×10^{-3}[p]		4.5×10^{-3}[r]
H_2O[h]	Too slow			

[a] At 25°. [b] NaOH varied from 0.05 to 0.25 *M*. [c] Na_2SO_3 varied from 0.02 to 0.2 *M*. [d] $Na_2S_2O_3$ varied from 0.05 to 0.5 *M*. [e] $NaNO_2$ varied from 0.05 to 0.19 *M*. [f] CH_3COONa varied from 0.5 to 2.0 *M*. [g] NaSCN varied from 0.5 to 1.3 *M*. [h] An ampoule of 0.13972 g of β-propiolactone when added to a dilute phosphate buffer of pH 6.9, produced an extremely slow temperature rise. [i] ΔH in kcal/mol of β-propiolactone. Uncertainty is the Student σ. Each heat is the average of at least six experiments. [j] The rate constant was computed from the first-order rate constant of the heat rise. The Guggenheim technique was used to locate the "infinity point" for calculation of ΔH. [k] The activation energies determined from the rate constants determined at 15°, 25°, 35°, and 45°. While the ΔH's varied a bit with temperature, the calorimetric data are not accurate enough to determine $\delta \Delta H / \delta T$. [l] k_{OH^-} reported by Small, ref 3, was 1.2. [m] k reported[3] was $19. \times 10^{-2}$. [n] k reported[3] was 3.0×10^{-4}. [o] k reported[3] was 3.8×10^{-3}. [p] k reported[3] was 3.0×10^{-3}. The rate constants in ref 3 were determined by adding thiosulfate to destroy the lactone. The excess thiosulfate was then back-titrated. But since the reaction of thiosulfate with the lactone is not immediate, there are errors present in the technique. [q] This value was obtained by titrating the thiosulfate with iodine solutions. The concentrations were identical with those in the thermochemical studies. [r] Measured spectrophotometrically, this value agrees with the thermochemical result and is 30% larger than that previously reported.[3] The difference appears to be due to secondary salt effects.

Experimental Section

Materials. β-Propiolactone (Eastman) was distilled (5 mm) and the center cut collected. It was stored under nitrogen and purified by a bulb-to-bulb distillation on a high vacuum line just prior to solution for a kinetic experiment. The purification of MEA has been discussed.[1]

Buffer solutions were prepared in deionized distilled water using potassium phosphate salts (Baker AR). All solutions were degassed by bubbling with pure nitrogen gas from a gas purification train. All inorganic salts were of the highest purity (AR) available.

Kinetics. A Beckman DU spectrophotometer and a Cary Model 14 spectrophotometer with 10.0-, 1.00-, and 0.10-cm cells were used to study the rate of change of the spectra with MEA. The product of the reaction of MEA has been well characterized.

Thermochemistry. Calorimeter. A 37-gal insulated tank controlled to 25.00 ± 0.001° (checked against NBS standards) served as the constant-temperature bath for the submarine calorimeter. The calorimeter, a silvered Pyrex vacuum bottle, was 20 cm long and had a total volume of 425 ml. It had a stirring rod, a sample holder and crusher, a heating element, and a thermistor. The stirring motor was run at a very steady rate. The heater was constructed from 80 ft of no. 35 manganin wire wound noninductively around a 6-mm Pyrex rod. The wire was then painted with Glyptal and baked at 110°. The element was then placed in a slightly larger tube and the element covered with Silicone oil to serve as a heat transfer agent. A Veco 32A 24 thermistor (2070 ohms) served as the temperature-sensing element. A Sargent (SR-S-72180) recorder (1-mV full scale) served as a null-point device to record the potential.

A Sargent coulometric current source (No. 30974) with a resistance of 77.26 ± 0.01 ohms was used as a power source for the manganin heater. The current was constant to ±0.1% or better. Generally the unit was set to supply 193.0 ± 0.1 mA. Refer to ref 8 for further details.

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