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Solvation as the Cause for Slower Rates of Cyanide and Thiol Anion Catalyzed Proton Abstraction from Carbon Compared to Oxy Anions of the Same Basicity

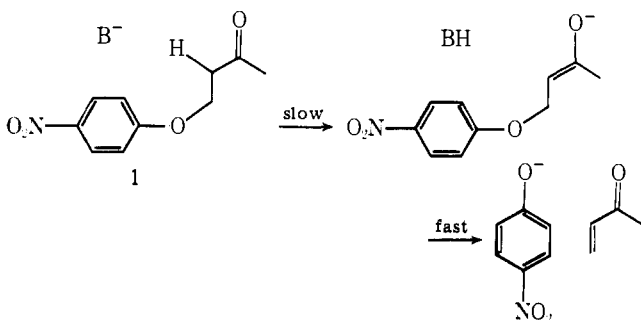
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Abstract: Rate constants have been measured for the elimination of 4-nitrophenol from **1** at 25°C in aqueous solution with $\mu = 1.0$ using cyanide ion and thiol anions (pK_a range 2.68–10.35) as catalysts. The Brønsted plot for the rate-determining proton transfer from carbon has a value of 0.59 and shows that thiol anions are much slower than moderately basic oxy anions of equivalent pK_a . Thus, even though the equilibrium constants for proton abstraction from carbon are equivalent for $\text{HOCH}_2\text{CH}_2\text{S}^-$ and phenoxide ion, the rate constant for phenoxide is approximately 30 times greater. The cyanide ion catalyzed proton abstraction, an unusual example of proton transfer between carbon atoms, exhibits a rate constant that fits on the thiol anion Brønsted line rather than the oxy anion line. These results are consistent with a previously proposed explanation for the curvature of the oxy anion Brønsted-plot. The solvation effect which enhances the rate of oxy anion catalyzed proton abstraction is predicted to be absent for thiol anions and cyanide ion and is therefore consistent with the results of this study.

Introduction

The compound 4-(4-nitrophenoxy)-2-butanone (**1**) exhibits general base catalyzed decomposition in aqueous solution to yield *p*-nitrophenol and methyl vinyl ketone.¹ The reaction involves rate-determining proton abstraction from carbon with no E2 component and **1** is therefore a very convenient substrate



for the spectrophotometric study of the enolization process. It has been previously demonstrated that the Brønsted plot for the reaction of a wide variety of oxy anion catalysts with **1** is curved, as shown in Figure 1.

We suggested that this rapid change in slope was not due to a "Hammond postulate" type of change in transition state structure in which the β value can be directly translated into the degree of bond formation in the transition state. Rather, it was argued that an effect due to solvation was responsible

for the observed behavior. As shown in Figure 2, the energy required for desolvation of an oxy anion increases with increasing basicity and tends to make the transition state more solvated. Opposing this tendency is the fact that the solvent molecules would then be left in an entropically unfavorable position. This solvation effect increases the rate of proton abstraction for moderately basic oxy anions from carbon because the favorable stabilization of the partial negative charge in the transition state is not completely offset by the unfavorable effect of leaving the solvent molecules in position.¹

If this interpretation is correct, then it should be possible to predict the behavior of bases of the same charge type but having different solvation properties. Thiol anions are less well solvated than correspondingly basic oxy anions² and thiols hydrogen bond much less readily than do oxygen analogues.³ Therefore, as is shown in Figure 2, the desolvated corner of the energy diagram is lower for thiols than for comparably basic oxy anions whereas the solvated corner is higher. It seemed reasonable to expect, therefore, that thiol anions would be slower than correspondingly basic oxy anions in abstracting a proton from carbon and that the dramatic curvature observed in the Brønsted plot for oxy anions would not be present for thiol anions.

Only limited data exist for the rates of proton abstraction from carbon by thiol anions. The rates of proton abstraction from acetylacetone by several thiol anions having a pK_a range of less than two units have been reported.⁴ These data suggest that thiol anions are less effective than oxy anions of the same

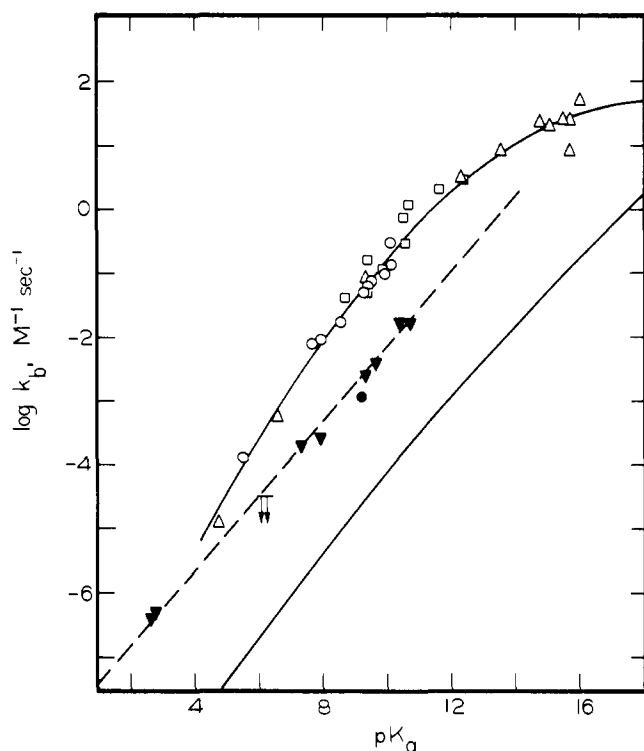


Figure 1. A plot of the logarithms of rate constants for the reaction of **1** with a variety of oxy anions (Δ , \square , \circ) and with cyanide (\bullet) and thiol anions (\blacktriangledown) vs. pK_a values. The curved line through the oxy anion points was computed as previously described¹ and the dashed line through the thiol anions is the least-squares slope of 0.587. The solid line below the data was added for comparison and shows the degree of curvature expected if the intrinsic barrier, ΔG^\ddagger_0 , in the Marcus expression is 10 kcal.

basicity. It is not possible to get an accurate β value from these data, however, because of the narrow pK_a range and the fact that some of the thiols used are charged. In addition, the possibility exists that some of the ketone being studied is tied up as the hemithioacetal at high concentrations of thiol giving an apparent rate constant for enolization that is smaller than the real value.

We have therefore undertaken a study of the rate of enolization of **1** catalyzed by thiol anions having a broad range of pK_a values. Because cyanide ion is of the same charge type and would also not benefit from the solvation effect, it was expected that the rate constant for this catalyst might be comparable to those for thiol anions rather than for oxy anions.

Experimental Section

4-(4-Nitrophenoxy)-2-butanone (1). In a modification of the previously described synthesis,¹ 18.1 g (0.134 mol) of 4-nitrophenol was dissolved in 30 g (0.4 mol) of methyl vinyl ketone and 2.0 g of sodium 4-nitrophenoxide was added. The mixture was stirred for 96 h during which time the process of the reaction was monitored by NMR.¹ The reaction mixture was poured into 150 mL of ether, precipitated sodium *p*-nitrophenoxide was removed by filtration, and the resulting solution was washed with 3×100 mL of pH 6.2 phosphate buffer. After the ether layer was dried over magnesium sulfate and filtered, it was cooled in a dry ice-acetone bath to yield crude **1**. This material was recrystallized from ether to give 10.3 g (0.05 mol, 37%) of pure **1**, mp 69.5–70 °C.

Thiols used in these experiments were purchased or synthesized and then purified as previously described.^{1,5} The course of the reaction of **1** with most thiols and cyanide was monitored by measurement of the absorbance of *p*-nitrophenoxide as described previously.¹ The initial rates for pentafluorothiophenol and tetrafluorothiophenol were determined by sealing samples of **1** with the thiol in aqueous solution at pH 5 in ampules and incubating them at 25 °C. In order to determine the concentration of *p*-nitrophenol that had been produced at any given time, an ampule was opened and an aliquot was mixed with

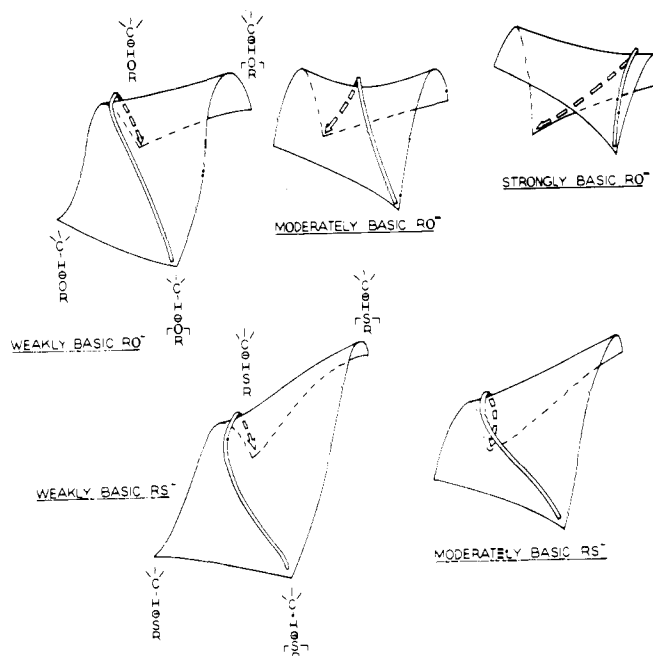


Figure 2. A family of three energy surfaces for oxy anion catalysts which reflect the greater energy required to desolvate RO^- as the basicity increases. The energy required for the construction of the solvation shell around ROH is not so great that enhancement of rate by solvation is prevented. There are lower energies of desolvation for RS^- compared to equally basic RO^- . Also, the energy required for the solvate RSH is greater than that for ROH. These effects combine to prevent the solvation effect from enhancing the rate of thiol anion catalyzed proton abstraction from carbon.

0.02 M phosphate buffer at pH 7.07 and the absorbance at 400 nm rapidly measured.

In order to prevent oxidation or volatilization of thiols, the aqueous solutions were prepared in flasks sealed with septa, using freshly boiled, doubly distilled water that had been flushed with argon. It was found that a substantial amount of oxidation occurred if reagent grade hydrochloric acid was used to adjust the pH of the solutions, and fresh hydrochloric acid solutions for this purpose were therefore prepared from hydrogen chloride gas generated with sodium chloride and sulfuric acid. The concentrations of stock solutions of thiols were checked several times during the course of experiments using Ellman's reagent.⁶

Results

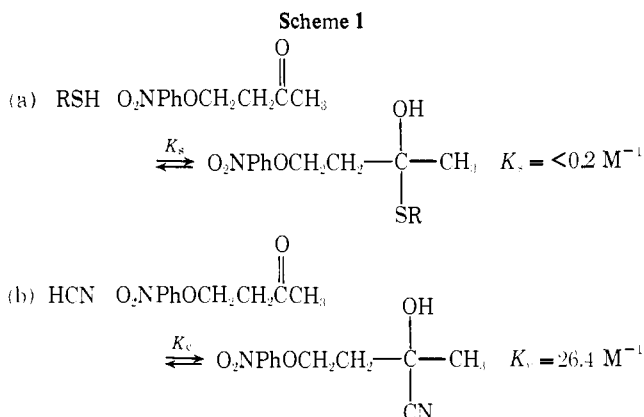
The rate of production of *p*-nitrophenoxide from **1** followed the rate law $v = k_{OH}[OH^-] + k_b[RS^-]$ in the presence of a number of thiols which varied in pK_a from 2.68 to 10.35. As shown in Figure 3, plots of the observed rate constants vs. the concentration of $HOCH_2CH_2S^-$ have slopes that are independent of pH. The rate constants for all of the thiol anions measured are listed in Table I, and the logarithms of these rate constants are plotted vs. thiol pK_a values in Figure 1. For the high pK_a aromatic thiol anions only upper limits could be obtained for k_b . If the pH was raised in order to allow a greater concentration of thiol to become soluble, then the background rate became too large. At lower pH values, the insolubility of the un-ionized thiol present became the limiting factor.

The rate constant for the reaction of phenoxide ion was measured in the presence of up to 0.23 M $HOCH_2CH_2SH$ and was found to be identical with the phenoxide ion rate measured in the absence of the thiol. An analogous experiment was done in which the phenoxide ion rate constant was measured in the presence of 0.42 and 0.50 M cyanide at pH 9.6. The rate constant for phenoxide decreased with increasing cyanide concentration as indicated in Table I. The rate of production of *p*-nitrophenoxide from **1** decreased with increasing concentration of cyanide at pH 9.6 as shown in Figure 3.

Table I. Second-Order Rate Constants for the Reaction of Thiol Anions and Cyanide Ion with **1** in Aqueous Solution at 25 °C, $\mu = 1.0$

catalyst	pK_a	total catalyst concn, M	pH	$k_b, M^{-1} s^{-1} (r^2)$
EtSH	10.35 ^a	0.008 65–0.0396	10.60	1.64×10^{-2} (0.966)
HOCH ₂ CH ₂ CH ₂ SH	10.19 ^b	0.0138–0.0637	7.10	1.70×10^{-2} (0.927)
HOCH ₂ CH ₂ SH	9.61 ^a	0.009 02–0.0420	7.42	3.79×10^{-3} (0.989)
		0.0275–0.005 95	7.98	3.85×10^{-3} (0.991)
MeOCOCH ₂ CH ₂ SH	9.33 ^a	0.008 18–0.0385	9.08	2.39×10^{-3} (0.953)
MeOCOCH ₂ SH	7.91 ^a	0.0134–0.0633	7.53	2.59×10^{-4} (0.991)
CF ₃ CH ₂ SH	7.30 ^a	0.008 23–0.0376	7.67	1.98×10^{-4} (0.999)
4-FC ₆ H ₄ SH	6.20 ^b	0.008 23–0.0391	8.09	$<3 \times 10^{-5e}$
4-AcNHC ₆ H ₄ SH	6.08 ^a	0.006 01–0.0280	7.73	$<3 \times 10^{-5e}$
2,3,5,6-F ₄ C ₆ HSH	2.75 ^a	0.0422–0.195	5.56	4.91×10^{-7} (0.986)
F ₅ C ₆ SH	2.68 ^a	0.0342–0.156	5.42	3.99×10^{-7} (0.894)
HCN	9.21 ^c	0.183–0.915	9.66	1.08×10^{-3} (0.959)
C ₆ H ₅ OH ^{d,f,g}	9.86 ^a	0.253–0.421	9.47	9.19×10^{-2} (0.999)
		0.030–0.150	9.33	9.29×10^{-2} (0.997)
C ₆ H ₅ OH + 0.139 M HOCH ₂ CH ₂ SH ^f		0.030–0.150	9.33	9.16×10^{-2} (0.999)
C ₆ H ₅ OH + 0.232 M HOCH ₂ CH ₂ SH ^f		0.030–0.150	9.33	9.26×10^{-2} (0.999)
C ₆ H ₅ OH + 0.124 M HCN ^g		0.042–0.211	9.59	2.14×10^{-2} (0.987)
C ₆ H ₅ OH + 0.149 M HCN ^g		0.042–0.168	9.59	1.89×10^{-2} (0.989)

^a Reference 5. ^b Reference 7. ^c Reference 8. ^d The phenoxide ion rate constant found in this study was about 20% smaller than the previously reported value.¹ ^e Owing to solubility problems only upper limits for these rate constants were obtainable. ^f No measurable hemithioacetal formation. ^g Consistent with an equilibrium constant for cyanohydrin formation of $26.4 M^{-1}$.



Discussion

The reaction rate of phenoxide ion with **1** is unaffected by addition of HSCH₂CH₂OH in concentrations comparable to those used in the other experiments in this study. This indicates that hemithioacetal formation, shown in Scheme Ia, does not diminish substantially the concentration of **1** available for reaction. The data require a value for K_s of less than $0.25 M^{-1}$. This is similar to the upper limit of $<0.2 M^{-1}$ reported for the equilibrium constant for addition of CH₃OCH₂CH₂SH to acetone.⁹

An increase in cyanide concentration actually decreases the observed rate for the reaction of **1**, as shown in Figure 3. The phenoxide ion catalyzed rate decreases dramatically upon addition of HCN, as shown in Table I. If it is assumed that the rate of elimination of 4-nitrophenol from the cyanohydrin is negligible, then the ratio of rates of reaction of **1** with PhO⁻ in the presence and absence of HCN gives a direct measure of the ratio of ketone to cyanohydrin. An equilibrium constant of $26.4 M^{-1}$ was computed using these data, and this is similar to the value of $32.8 M^{-1}$ found for the addition of HCN to methyl ethyl ketone.¹⁰ The equilibrium constant was used to correct k_{obsd} values for cyanide-catalyzed proton abstraction as shown in Figure 3.

Thiol anions define a Brønsted line with a slope of 0.59 which shows no apparent curvature. The rates for oxy anions are 30–50 times greater than those of anions of the same pK_a value in the range of $pK_a = 7$ –10. This means that even though the equilibrium constants are identical for these two reactions of

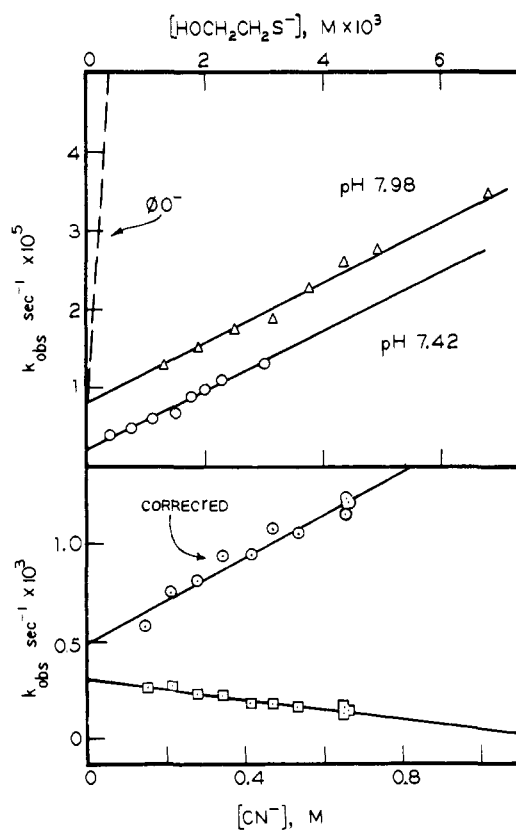


Figure 3. In the top figure are shown the values of k_{obsd} measured for various concentrations of HOCH₂CH₂S⁻. The value of the slopes at pH 7.98 ($3.85 \times 10^{-3} M^{-1} s^{-1}$) and 7.42 ($3.79 \times 10^{-3} M^{-1} s^{-1}$) are identical within experimental error indicating dependence only on the concentration of the ionized thiol. For comparison is shown the slope measured for phenoxide ion which is much larger even though phenoxide ion and HOCH₂CH₂S⁻ are equally basic. In the bottom figure is shown a plot of k_{obsd} values (\square) vs. concentration of cyanide ion which has a negative slope of $-2.57 \times 10^{-4} M^{-1} s^{-1}$ (0.962). Using a value of $K_c = 26.4 M^{-1}$ for the equilibrium constant for cyanohydrin formation, corrected values of k_{obsd} (\circ) were obtained which give a slope of $1.09 \times 10^{-3} M^{-1} s^{-1}$ (0.954).

the same charge type, there is a considerably lower barrier for the oxy anions. There is also a substantial difference in the β value for thiol anions (0.59) and the β value for the oxy anions

having the same range of basicity (0.75¹). The gradually curving solid line in Figure 1 was computed using a value of $\Delta G^\ddagger_0 = 10$ kcal in the Marcus expression for proton transfer.^{1,11-13} This degree of curvature is approximately the amount expected for a "Hammond postulate" type of change in transition state structure, judging from isotope effect^{14,15} and other¹⁶ data. The thiol anion data are more similar to this curve than are the oxy anion data both in β value and in degree of curvature.

These observations, along with the fact that cyanide ion fits well with the thiol anion data rather than with the oxy anion data, support the solvation effect argument used to explain Brønsted plot curvature for the oxy anions.¹ According to this argument, oxy anions can benefit from a solvation shell in the transition state because the charge stabilization is great enough to offset the unfavorable effect of leaving solvent molecules in position after proton transfer. Cyanide and thiol anions would benefit less from such charge stabilization and would, in addition, have to pay a larger energetic price for the construction of the solvation shell. It is therefore reasonable that the rate constants for these catalysts are smaller and that the β value measured more closely reflects the degree of proton transfer in the transition state.

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Solvolysis of Cyclopentyl *p*-Bromobenzenesulfonate in Aqueous Hexafluoroisopropyl Alcohol. Deuterium Rate Effects, Stereochemistry of Substitution and Elimination, and Reaction Mechanism

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Abstract: In 90% hexafluoroisopropyl alcohol–10% water cyclopentyl *p*-bromobenzenesulfonate solvolyzes at 25 °C with a half-life of 26 min. The yield of cyclopentene is 80% and syn elimination is favored over anti by a factor of about 4. The α -*d* rate effect is large (1.23), indicating that the intimate ion pair is reversibly formed and that nucleophilic attack to give cyclopentanol is not rate determining or partially rate determining. The cis- β -*d* rate effect (1.35) is larger than the trans- β -*d* effect (1.22). The β -*d*₄ rate effect (2.86) is large and greater than the square of the product of the cis- β -*d* and the trans- β -*d* rate effects (2.71). It is concluded that the reaction mechanism involves reversible formation of the intimate ion pair which further reacts mainly by two irreversible, competitive processes: (1) removal of the cis- β proton by the leaving group to give cyclopentene and (2) conversion to the solvent-separated ion pair. The solvent-separated ion pair gives cyclopentanol and possibly some additional cyclopentene. These results are briefly compared with results published earlier for the solvolysis of cyclopentyl *p*-bromobenzenesulfonate in ethanol–water, dioxane–water, and trifluoroethanol–water solvents.

Introduction

In earlier papers¹⁻⁴ α - and β -deuterium rate effects,^{1,2} product distributions,^{1,2} and the stereochemistry of elimination³ and substitution⁴ in the solvolysis of cyclopentyl *p*-bromobenzenesulfonate (I) in various solvents have been reported. It was concluded that in 70–100% ethanol–water (E–W) solvents both elimination and substitution products were predominantly derived by rate-determining solvent attack on the reversibly formed intimate ion pair, A. The evidence also strongly suggests that in 70% 2,2,2-trifluoroethanol–water (70 TFE–W) elimination and substitution take place after the rate-determining step, most probably from the solvent-separated ion pair (B), the formation of which via rate constant k_2 is rate determining. However, in 97 TFE–W the evidence

strongly supports the incursion of still another reaction, rate-determining syn elimination of the β proton in the intimate ion pair by the leaving group;⁴ this process competes with rate-determining formation of the solvent-separated ion pair, which in turn leads to additional elimination and substitution (k_{6e} and k_{6s}).⁴ In 80% dioxane–water (80 D–W)² it appears that rate-determining product formation at the intimate ion pair stage competes with rate-determining formation of the solvent-separated ion pair, and products are formed by solvent attack on both ion pairs.

It appeared to us to be of interest to examine the solvolysis of I in a solvent even less nucleophilic than TFE to establish more firmly, if possible, the occurrence of rate-determining syn elimination by the leaving group at the intimate ion pair