# Elimination Reactions of β-Cyano Thioethers: Internal Return and the Lifetime of the Carbanion Intermediate[1]

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Abstract: The E1cB elimination reaction of the pentafluorothiophenol adduct of fumaronitrile (3) in water containing 8.3% Me_2SO shows strong buffer catalysis and primary deuterium isotope effects of $k_H/k_D = 4-5$. In contrast, hydrogen exchange of the methanethiol adduct of 3 shows little or no buffer catalysis. There is no incorporation of deuterium that gives an inverse solvent isotope effect in the buffer-catalyzed elimination of the thionitrobenzoate adduct of 3 in D_2O and H_2O, although thiol anion expulsion is partly rate limiting for this reaction. These observations are consistent with internal return of the abstracted proton from the protonated buffer base that is competitive with the expulsion of leaving groups with $pK_a > 4$. The primary deuterium isotope effects for elimination catalyzed by hydroxide ion are $k_H/k_D = 4.9 \pm 0.4, 4.2 \pm 0.1, 4.2 \pm 0.3$, and 3.1 ± 0.1 for the pentafluorothiophenol and thionitrobenzoate adducts of 3, the N-methyl-2-mercaptopyridinium ion adduct of acrylonitrile (1), and the pentafluorothiophenol adduct of chloroacrylonitrile (2), respectively. These isotope effects are significantly larger than values of $k_H/k_D = 2.6 \pm 0.3, 2.2 \pm 0.1$, and 2.1 ± 0.1 for buffer-catalyzed elimination from the adducts of 1 and 3. They are also larger than (1) the primary isotope effects of $k_H/k_D = 2.5 \pm 0.3, 2.3 \pm 0.2$, and 2.3 ± 0.2 for the p-nitrothiophenol adducts of 1 and 3 and the thiophenol adduct of 2 that were obtained from the biphasic kinetics for elimination of these compounds in D_2O and (2) the product discrimination isotope effects of ~3 for the addition of thiol anions to 1 and 3. These observations are consistent with the formation of an unstable carbanion intermediate that undergoes competitive reprotonation by solvent, k_{-1}, exchange of the abstracted proton with the bulk solvent, k_s, and elimination, k_2. Ratios of k_{-1}/k_s and k_{-1}/k_2 that were obtained from these results give values of $k_{-1} \sim 10^{11}$ s^{-1} and $k_2 = 10^{10}-10^{13}$ s^{-1}, assuming a value of $k_s = 10^{11}$ s^{-1}. Estimated pK_a values in aqueous solution include 26.8 for $NCCH_2CH_2SPh$, 22.0 for $NCCH(Cl)CH_2SPhNO_2$, and 23.2 for $NCCH_2CH(CN)SCH_3$.

The preceding paper describes evidence that the addition–elimination reactions of thiol adducts of acrylonitrile, 1, chloroacrylonitrile, 2, and fumaronitrile, 3, in aqueous solution proceed through a carbanion intermediate by an E1cB mechanism. Partitioning of this intermediate between reprotonation and leaving-group expulsion, and the rate-limiting step of the reaction, change with changing substituents on the leaving group and on the α-carbon atom.[2]

$$NCCH_2CH_2SR \qquad NCCH(Cl)CH_2SR$$
$$\mathbf{1} \qquad\qquad\qquad \mathbf{2}$$
$$NCCH_2CH(CN)SR$$
$$\mathbf{3}$$
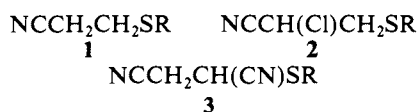
The goal of the work reported here was to obtain estimates of the lifetimes of the carbanion intermediates in aqueous solution and the rate constants for leaving-group expulsion and protonation of the carbanion in these reactions. The original plan was to generate the carbanion intermediate by addition of thiol anions to substituted acrylonitriles and search for catalysis of the protonation step by buffer acids of increasing acidity in H_2O and D_2O. It was expected that a point would be reached at which protonation by the acid would be diffusion controlled and would show no discrimination between hydrogen and deuterium. This protonation could then serve as a "clock" to estimate the lifetime of the carbanion in water, which would permit calculation of the rate constants for leaving-group expulsion from the partitioning ratios of the intermediate. This plan failed because the intermediate has such a short lifetime that protonation of the carbanion by water is faster than even diffusion-controlled protonation by buffer acids.

In this paper we describe evidence that these reactions do not proceed through a free carbanion intermediate that is diffusionally equilibrated with the bulk solvent. The magnitudes of isotope effects and buffer catalysis provide evidence for extensive internal return of the abstracted proton to the carbanion from protonated buffer bases and for significant internal return from water. The internal return is competitive with elimination of the leaving group,

as well as with diffusional equilibration of the abstracted proton and solvent protons.

We conclude that these reactions proceed through a stepwise mechanism with a short-lived carbanion intermediate. The results are consistent with the notion that olefin-forming elimination reactions proceed through a concerted E2 mechanism only when they cannot proceed through a stepwise mechanism because the carbanion has too short a lifetime to exist for several vibration frequencies.[3]

Experimental Section

Materials. Generally these were the same as described in the previous paper.[2,4] Additional synthetic methods for obtaining the deuteriated substrates are as follows.

[²H₁]Acrylonitrile. To 15 mL of acrylonitrile were added 80 mL of D_2O and 5 mL of triethylamine. This solution was stoppered and stirred for 48 h, after which hydrogen chloride was added to bring the pH of the aqueous phase to 5. The (biphasic) solution was distilled, and the (biphasic) fraction at 72–80 °C was collected. To this fraction was added magnesium sulfate, and, after filtration, the remaining liquid was distilled. A biphasic fraction at 77 °C was collected and again treated with magnesium sulfate. The remaining liquid was distilled twice more. The NMR spectrum showed no signal for protons α to the nitrile group, and it was estimated that exchange was >95% complete.

Deuteriated Adducts. The deuteriated adducts were synthesized in D_2O by using procedures similar to those described for the protium adducts.[2] Exchangeable protium in the starting materials was exchanged prior to the synthesis using a 50–100-fold molar excess of D_2O. All deuteriated adducts gave melting points that were within 0.5 °C of the values determined for the protium adducts.

In a typical procedure, 3.5 g (0.023 mol) of 4-nitrothiophenol was added to 20 mL of dry tetrahydrofuran and 10 mL of D_2O. This solution was dried by rotary evaporation under vacuum for 2 h. To the dried material was added 10 mL of dry tetrahydrofuran, 0.5 g of fused anhydrous sodium acetate, 0.5 mL of 2.9 M deuterium chloride (99% D), and 30 mL of D_2O. This was stirred to an emulsion, and 10 mL of chloroacrylonitrile was added. After 2 h the reaction mixture was extracted with ethyl acetate, and the aqueous phase was discarded. The organic phase was dried with magnesium sulfate, and the solvent was removed. The adduct was recrystallized in ethyl acetate/hexane. The NMR spectrum showed no protium in the position β to the leaving group.

(1) This research was supported in part by grants from the National Institutes of Health (GM20888 and GM07596) and the National Science Foundation (PCM8117816).
(2) Fishbein, J. C.; Jencks, W. P. *J. Am. Chem. Soc.*, previous paper in this issue.
(3) Gandler, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 1937.
(4) Abbreviations: MOPS, 3-N-morpholinopropanesulfonic acid; Tris, [tris(hydroxymethyl)amino]methane.

Table I. Rate Constants and Primary Deuterium Isotope Effects for Elimination from Substituted Acrylonitrile Adducts[a]

substrate[b]	catalyst (pK_a)[c]	buffer ratio, BH$^+$/B	buffer concn, M	$10^3 k_B^{H,d,e}$ M^{-1} s^{-1}	$10^3 k_B^{D,e}$ M^{-1} s^{-1}	$k_{OH}^{H,d,e}$ M^{-1} s^{-1}	$k_{OH}^{D,e}$ M^{-1} s^{-1}	$k_B^H/ k_B^{D/}$	$k_{OH}^H/ k_{OH}^{D/}$
CH$_3^+$NC$_5$H$_4$-2-S-CH$_2$CL$_2$CN (MeOSO$_3^-$)	propylamine[g] (10.89)	9	0.1–1.0	0.92	0.43	2.7	0.66	2.1	4.1
		2.3	0.08–0.3	1.10[h]	0.52[h]	2.20	0.54	2.1	4.1
	ethanolamine (9.76)	2.3	0.08–0.63	0.095	0.048	2.7	0.70	2.0	3.9
	HO$^-$[g]		0.006–0.024			2.9	0.66		4.4
F$_5$PhSCH$_2$CL(Cl)CN	ethanolamine	9	0.09–1.0	24	16	1360	460	1.5	3.0
	ethylenediamine (H$^+$) (7.42)	9	0.11–0.34	<0.085[i]	<0.23[i]	1380	430		3.2
F$_5$PhSCL(CN)CL$_2$CN	2'-OH, 1,3-diaminopropane (H$^+$) (8.40)	9	0.09–0.35	2.1	0.94	370	75	2.3	4.9
		5.7	0.06–0.35	2.5	1.0	350	75	2.5	4.7
	ethylenediamine (H$^+$)	4	0.09–0.36	0.35	0.13	350	82	2.7	4.3
	ethanolamine	20	0.14–0.96	22	8.2	370	77	2.7	4.8
	cyanoethylamine (8.17)	9	0.09–1.0	0.67	0.31	320	57	2.2	5.6
	1,3-diaminopropane (H$^+$) (9.24)	5.7	0.06–0.35	12.2	4.4	370	78	2.8	4.8
		9	0.07–0.35	15.8	5.3	380	77	3.0	4.9
	Tris[j] (8.37)	5.7	0.09–1.0	1.24	0.48	400	86	2.6	4.7
		9	0.09–1.0	1.07	0.41	360	71	2.6	5.1
	MOPS[j] (7.31)	0.11	0.11–1.0	k	k	370	71		5.1
(4-NO$_2$,3-CO$_2^-$) PhSCL(CN)CL$_2$CN	ethanolamine[g]	4	0.08–1.0	4.4	2.1	160	38	2.1	4.2
	1,3-diaminopropane (H$^+$)	9	0.07–0.35	2.6	1.2	152	37	2.2	4.1

[a] In water, 25 °C, 1 M ionic strength maintained with potassium chloride, 8.3% Me$_2$SO (v/v). [b] The letter L represents protium or deuterium. For a given substrate, all of the L sites were either H or D. [c] See Table 11 of the previous paper for references.[2] [d] From Table 11 of the preceding paper.[2] [e] ±5%. [f] ±10%. [g] Good first-order kinetics were observed for more than 4 half-times of reaction. [h] Less than an 18% increase in k_{obsd} was observed at the highest buffer concentration. [i] Less than a 30% increase in k_{obsd} was observed at the highest buffer concentration. [j] Reference 4. [k] A 15% decrease in k_{obsd} was observed at the highest buffer concentration.
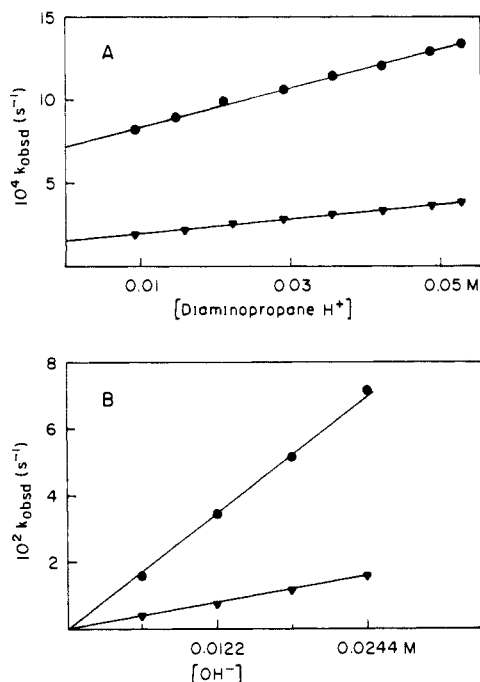

Figure 1. Dependence of k_{obsd} for elimination on catalyst concentration at 25 °C, μ = 1 M (KCl), 8.3% Me$_2$SO (v/v) in water. (A) Catalysis by 1,3-diaminopropane monocation (BH^{2+}/BH$^+$ = 5.7) of elimination from the β-protium (●) and deuterium (▼) pentafluorothiophenol adducts of fumaronitrile. (B) Catalysis by hydroxide ion of elimination from the β-protium (●) and deuterium (▼) N-methyl-2-thiopyridinium adducts of acrylonitrile.

A mass spectrum of this compound indicated that the adduct was >99% deuteriated. Proton NMR analysis of the other adducts indicated that they were >97% deuteriated in the position β to the leaving group.

Methods. Kinetics of elimination were followed at 25 °C, 1 M ionic strength (KCl) and 8.3% DMSO (v/v) with a Zeiss PM6 spectrophotometer, and proton exchange in D$_2$O was followed by proton NMR, as described previously.[2]

Results

Buffer Catalysis and Primary Isotope Effects. Rate constants and primary deuterium isotope effects for base-catalyzed elimination were determined spectrophotometrically by using the same reagents and alternating cuvettes in the same cell compartment
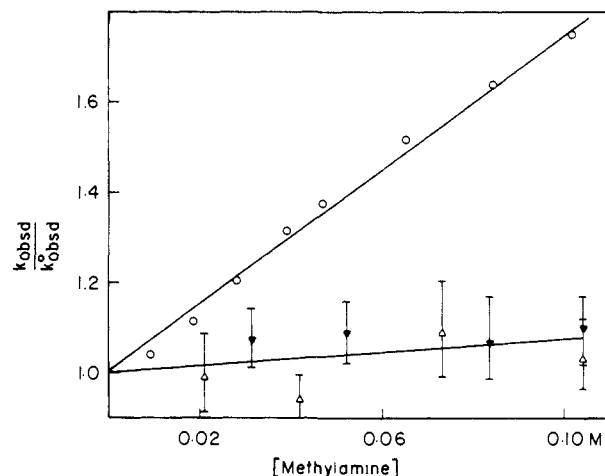

Figure 2. Comparison of catalysis by methylamine of elimination from the pentafluorothiophenol adduct of fumaronitrile in water at 25 °C (○) with catalysis by [^{2}H$_5$]methylamine of β proton exchange of the methanethiol adduct of fumaronitrile in D$_2$O at 23.8 °C in two different experiments (△ and ▼), in 8.3% Me$_2$SO (v/v), ionic strength 1 M (KCl). The value of k_{obsd} at zero buffer concentration, k_{obsd}^0, was obtained from the least-squares line for the points at all buffer concentrations. The buffer ratios were BL$^+$/B = 9.

for the protium and deuterium adducts. Figure 1 shows typical data for elimination from pentafluorothiophenol adducts of fumaronitrile catalyzed by 1,3-diaminopropane monocation (Figure 1A) and from N-methyl-2-mercaptopyridinium adducts of acrylonitrile catalyzed by hydroxide ion (Figure 1B). Rate constants were obtained from initial rates, except for some experiments with acrylonitrile and chloroacrylonitrile in which they were obtained from pseudo-first-order rate constants. The first-order plots were linear for >4$t_{1/2}$, unless noted otherwise, and were shown to give isotope effects that agree within <10% with those determined by initial rate measurements in several cases.

Figure 2 shows catalysis by methylamine of elimination from the pentafluorothiophenol adduct of fumaronitrile and proton exchange from the methanethiol adduct of fumaronitrile in the presence of [^{2}H$_5$]methylamine buffers in D$_2$O. There is a 75% increase in the rate of the elimination reaction in the presence of 0.1 M methylamine but little or no catalysis of exchange under the same conditions. There is at least twice as much catalysis of elimination as there is of exchange, estimated from the max-

Table II. Summary of Experiments in Which Biphasic First-Order Kinetics of Elimination Were Observed[a]

substrate	solvent	buffer (base form)	buffer concn, M	$10^4 k_{obsi}$[b] s⁻¹	$10^4 k_{obsf}$[c] s⁻¹	k_{obsi}/k_{obsf}	$10^4 k_{obsx}$[d] s⁻¹	k_{OLi}[e] M⁻¹ s⁻¹	k_{OLf}[e] M⁻¹ s⁻¹	k_x[e] M⁻¹ s⁻¹
(4-NO₂)PhSCH₂CH(Cl)CN	D₂O	1,3-diaminopropane (D⁺)	0.09	3.9	1.71	2.3	9.4			
			0.18	4.0	1.81	2.2	10.4	380[f]	174[f]	960[f]
			0.27	4.0	1.72	2.3	9.2			
			0.36	3.9	1.80	2.2	9.7			
		(BD²⁺/B⁺ = 5.6)								
(4-NO₂)PhSCH₂CD(Cl)CN	H₂O	1,3-diaminopropane (H⁺)	0.11	0.83[g]	2.1	0.40	2.8	71	188[f,h]	240[f,h]
			0.18	0.83[g]	2.26	0.36	2.7			
			0.26	0.83[g]	2.31	0.36	2.8			
			0.35	0.85[g]	2.31	0.37	2.9			
		(BH²⁺/B⁺ = 5.6)								
(4-NO₂)PhSCH₂CH₂CN	D₂O	⁻OD	0.01	5.2	2.3	2.3	7.2	0.049	0.021	0.075
			0.02	9.8	3.7	2.7	12.4			
			0.03	14.5	6.7	2.2	21.7			
			0.04	20	7.8	2.6	25.6			
PhSCH₂CH₂CN	D₂O	⁻OD	0.031	2.6	1.25	2.1	4.4	0.0082	0.0034	0.0152
			0.047	3.8	1.56	2.4	5.8			
			0.062	5.2	2.2	2.4	9.2			
			0.078	6.8	2.8	2.4	12.2			

[a] 25 °C, 1 M ionic strength with KCl, 8.3% Me₂SO (v/v). [b] ±5%. From initial rate measurements. [c] Based on the final linear phase. [d] See text. [e] ±10% unless otherwise indicated. [f] The value of k_{obsd} extrapolated to zero buffer concentration divided by the calculated lyoxide ion concentration. [g] From plots of A vs time, less than 3% reaction. [h] ±15%.

imum errors of the rate constants (Figure 2).

Rate constants and primary deuterium isotope effects for these and other elimination reactions are summarized in Table I.

Elimination Concurrent with Exchange. Figure 3A shows nonlinear first-order kinetics for elimination of the *p*-nitrothiophenol adduct of chloroacrylonitrile in D₂O, which arises from deuterium exchange into the adduct. When exchange is complete the reaction is first order. Similar results were obtained for the thiophenol and *p*-nitrothiophenol adducts of acrylonitrile; linear first-order kinetics were observed for both reactions in H₂O (not shown).

Three rate constants were obtained from these data. (1) The first-order rate constant for the final phase of the reaction, k_{obsf}, was obtained directly from the first-order plot. (2) The pseudo-first-order rate constant for elimination of the protium adduct in D₂O, k_{obsi}, was obtained from initial rate plots of absorbance against time (Figure 3B; note the different time scales of Figure 3A,B). Alternatively, k_{obsi} was determined by the method of More O'Ferrall and Slae;[5] rate constants obtained by the two methods generally differed by <10%. (3) The pseudo-first-order rate constant for disappearance of starting material by elimination and exchange, k_{obsx} (More O'Ferrall's k_x)[5] was obtained from first-order plots of $(A_\infty - A_t) - A_{e_t}$ against time (or $A_{e_t} - (A_\infty - A_t)$ against time for experiments in H₂O), in which A_{e_t} is the absorbance at time *t* extrapolated from the final first-order phase of the reaction. Such plots, illustrated in Figure 3C, were linear for $\geq 3t_{1/2}$. Exchange during the initial period in which k_{obsi} was determined, calculated from k_x, gives <5% error in the value of k_{obsi}; the error is <10% for experiments with acrylonitrile adducts.

The results are summarized in Table II. The primary deuterium isotope effect for the *p*-nitrothiophenol adduct of chloroacrylonitrile is $k_H/k_D = k_{obsi}/k_{obsf} = 2.3$. Similar experiments with the thiophenol and 4-nitrothiophenol adducts of acrylonitrile gave very similar isotope effects of $k_H/k_D = 2.4$–2.5.

The absence of a significant effect of increasing 1,3-diaminopropane buffer concentration up to 0.35 M on k_{obsx}, the rate constant for proton exchange with the *p*-nitrothiophenol adduct of chloroacrylonitrile (Table II), confirms the conclusion that there is little or no buffer catalysis of proton exchange.

Elimination of the deuteriated *p*-nitrothiophenol adduct of chloroacrylonitrile in H₂O gives an initial slow reaction, followed by first-order elimination when exchange is complete (not shown). The rate constants for this reaction were obtained by essentially the same procedure and are shown in Table II. The value of k_{obsf} is less accurate than the other rate constants because it was obtained from the final 8% of reaction. The primary deuterium

(5) More O'Ferrall, R. A.; Slae, S. *J. Chem. Soc. B* **1970**, 260.
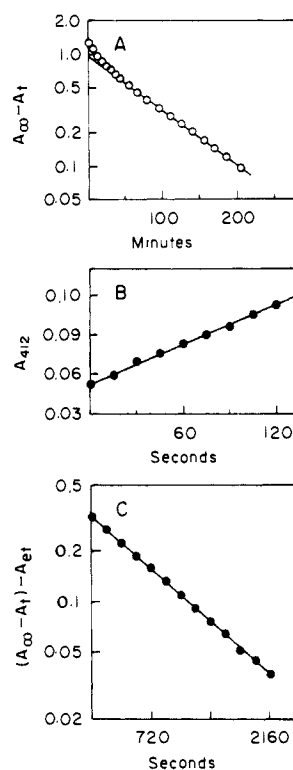
Figure 3. The elimination in D₂O of the protium adduct of chloroacrylonitrile and *p*-nitrothiophenol at 25 °C, $\mu = 1$ M (KCl), 8.3% Me₂SO (v/v). (A) Nonlinear first-order plot of $(A_\infty - A_t)$. The line is drawn through points in the late phase and is extrapolated to zero time. (B) The initial rate of the first 5% of elimination followed at 412 nm. (C) First-order plot derived from the nonlinear portion of the first-order plot in Figure 3A. The value $(A_\infty - A_t) - A_{e_t}$ is the value at time *t* of $(A_\infty - A_t)$ minus the value of *A* at time *t*, A_{e_t}, for the extrapolated line in A.

isotope effect of $k_H/k_D = k_{obsf}/k_{obsi} = 1/0.37 = 2.7$ is slightly, but probably not significantly, larger than the value of $k_H/k_D = 2.3$ for the reaction of the protium adduct in D₂O; the fact, that it is not smaller shows that there is no error that arises from incomplete incorporation of deuterium into the substrate.

Absence of an Inverse Solvent Isotope Effect on Buffer-Catalyzed Elimination. Figure 4 shows rate constants for elimination of the thionitrobenzoate adduct of fumaronitrile in H₂O and in D₂O catalyzed by increasing concentrations of tris buffer in the range 0.1–1.0 M. The line has a slope of 0.94. This shows that there

Figure 4. Catalysis by Tris base of elimination from the thionitrobenzoate ion adduct of fumaronitrile in D_2O compared with H_2O. The closed circles represent increasing concentrations of Tris buffer, BH^+/B = 9, in the range 0.1 to 1.0 M. The solid, least-squares line has a slope of 0.94.

is no inverse deuterium isotope effect for the buffer-catalyzed reaction, which would give a slope of >1.0. A similar experiment with the thiosalicylate adduct gave a slope of 0.98.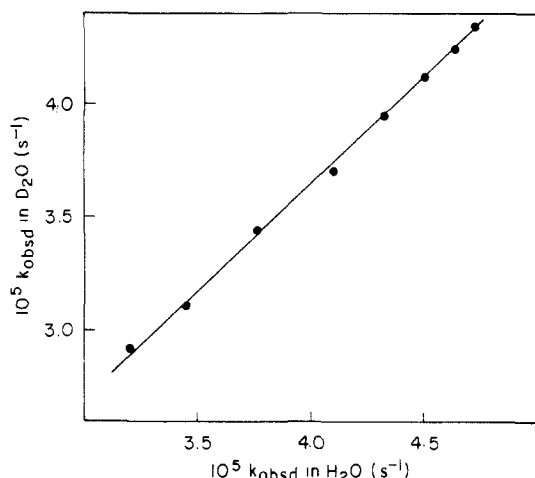 However, there is less catalysis of this reaction, and an upper limit of k_{DOD}/k_{HOH} < 1.3 was estimated from the data. Analysis of the solvent deuterium isotope effect for the lyoxide ion catalyzed reaction is complex and was not attempted.

Discussion

Evidence described in the preceding paper shows that the elimination reactions of 1–3 proceed through a carbanion intermediate by an E1cB mechanism, with a change from rate-limiting proton removal to rate-limiting leaving-group expulsion as the pK_a of the leaving thiol increases.[2] The data presented in this paper are consistent with this conclusion. Table I and Figure 1 show that the elimination reactions of the β-cyano thioethers with the least basic leaving groups are characterized by large primary isotope effects on the hydroxide ion catalyzed reaction and smaller, but significant, primary isotope effects on the buffer-catalyzed reactions. With more basic leaving groups, reactions carried out with the protium adducts in D_2O exhibit nonlinear first-order kinetics for elimination because proton exchange is concurrent with elimination. The rate constants that describe the biphasic reaction are summarized in Table II.

A simple E1cB mechanism is described in eq 1 (B = buffer base or hydroxide ion), in which diffusional steps are assumed to be fast relative to expulsion of the leaving group and proton transfer to the carbanion intermediate from buffer acid or water. Experimental results are described in this paper that are inconsistent with the mechanism of eq 1.

$$B + HC-C-SR \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} BH^+ + {>}C^- - C-SR \xrightarrow{k_2}$$

$$ {>}C{=}C{<} + RS^- \quad (1)$$
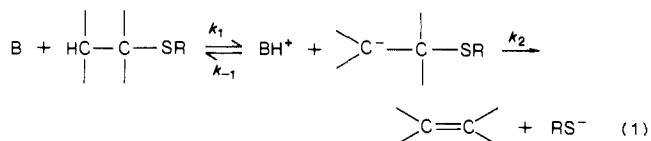
All of the results are consistent with the mechanism of Scheme 1 (or Scheme II, which is described later). According to this scheme, the carbanion intermediate can undergo elimination or reprotonation with the rate constants k_2 and k_{-1}, respectively, but must exchange the abstracted proton for a hydron from the bulk solvent, with the rate constant k_s, in order to undergo exchange.

Internal Return from Buffer Acids. The large amount of catalysis by buffer of elimination from the pentafluorothiophenol adduct of fumaronitrile (Figure 2) shows that proton transfer to the buffer base is largely rate limiting in this E1cB reaction with a good leaving group. Figure 2 also shows that there is little or no buffer catalysis of proton exchange from the methanethiol
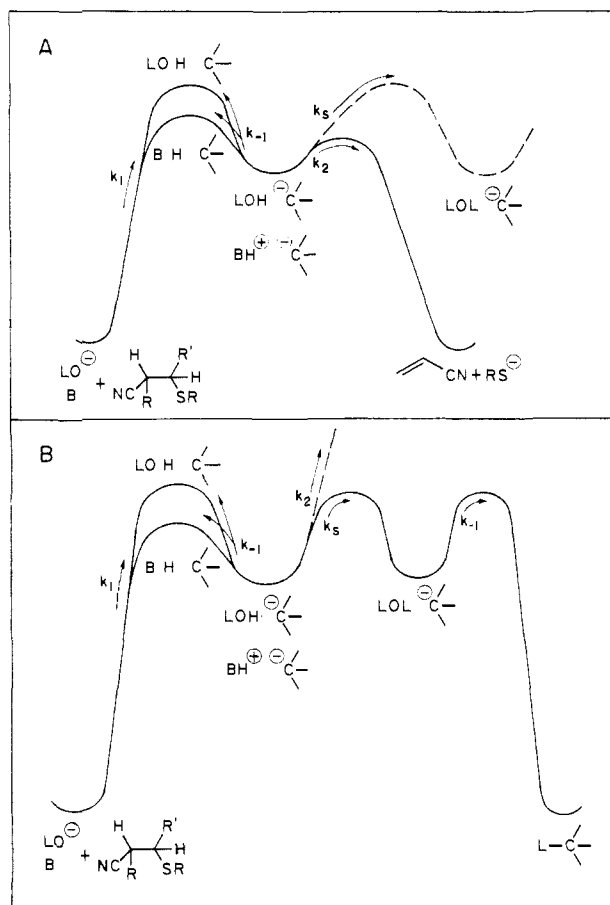
Figure 5. Free energy diagrams illustrating the relative energies of hydroxide ion and buffer catalyzed pathways. (A) Catalysis of elimination. The rate-limiting step is k_1, and the amount of catalysis expected is indicated by the difference in barrier height between the k_{1B} and k_{1OH} step. (B) Catalysis of exchange. The k_s step is partly rate-limiting for both buffer and hydroxide ion catalysis of exchange, so that the amount of catalysis expected is less than the difference in barrier height between the k_{1B} and k_{1OH} step.

Scheme I
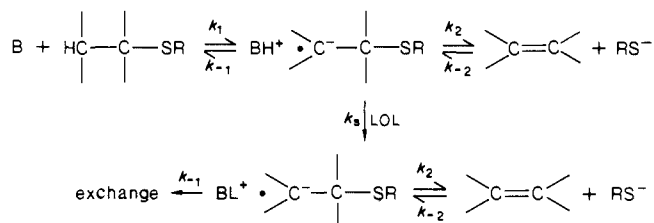
adduct of fumaronitrile. This result means that proton transfer does not provide the major contribution to the rate-limiting step for proton exchange. This result is expected if diffusional separation of the protonated base catalyst from the carbanion (k_s in Scheme I) is largely rate limiting for proton exchange, as explained below. Additional evidence for this conclusion is the absence of detectable buffer catalysis of proton exchange in the k_{obsx} step for the biphasic elimination reactions of protium adducts in D_2O (Figure 4 and Table II).

The absence of buffer catalysis of proton exchange is inconsistent with the simple E1cB mechanism of eq 1, because this mechanism requires at least as much buffer catalysis of exchange as of elimination, depending on the extent to which k_1 is rate limiting for elimination.

The results are consistent with the mechanism of Scheme I, as illustrated by the Gibbs energy diagrams of Figure 5. Buffer catalysis is observed for elimination with a good leaving group because k_2 is fast and proton removal, k_1, is largely rate limiting (Figure 5A). Buffer catalysis of exchange decreases or disappears

when the equilibration of the proton with the bulk solvent, k_s, becomes rate limiting (Figure 5B). This occurs because re-protonation by the conjugate acid of the buffer is faster than by water (k_{-1}), but k_s is similar for BH^+ and water. When this is the case most of the exchange reaction will proceed with catalysis by lyoxide ion. The proton is completely transferred to the base in the transition state for the k_s step, with $\beta = 1.0$, and catalysis by buffers becomes weak or insignificant when $\beta = 1.0$.

The smaller primary deuterium isotope effects for buffer-catalyzed elimination, generally in the range of $k_H/k_D = 2.0$–3.0, compared with values in the range $k_H/k_D = 4.0$–5.0 for catalysis of elimination by hydroxide ion (Table I), are also consistent with significant reprotonation of the carbanion by BL^+ in the k_{-1} step. This reprotonation is faster for BH^+ than for BD^+ and makes proton removal less rate limiting. The large isotope effects for catalysis by hydroxide ion show that there is a significant kinetic barrier for proton transfer between HO^- and a simple CN-acti-vated carbon acid, and suggest that internal return from HOH does not compete effectively with elimination of these good leaving groups.

Finally, a simple E1cB mechanism (eq 1) would show an inverse solvent deuterium isotope effect on the initial rate of elimination when leaving group expulsion is partly rate limiting. This arises from the primary deuterium isotope effect on k_{-1} for the back reaction in D_2O, which results in an increase of the steady-state concentration of the carbanion and of k_{obsd}.[6,7] Three experimental results[2] show that leaving-group expulsion, k_2, becomes signifi-cantly rate limiting for elimination reactions of fumaronitrile adducts as the pK_a of the leaving thiol increases: (1) There is a marked decrease in buffer catalysis for elimination of thiol anions more basic than pentafluorothiophenolate from fumaronitrile adducts. (2) The kinetic solvent isotope effect decreases with increasing pK_a of the thiol in the addition reaction, which suggests that the proton-transfer step becomes less rate limiting. (3) The kinetic solvent isotope effect of $k_{HOH}/k_{DOD} = 2.0$ is smaller than the product discrimination isotope effect of $k_H/k_D = 3.2$ for the addition of thiosalicylate anion to fumaronitrile.

Therefore, an inverse solvent deuterium isotope effect should be observed[6,7] for buffer catalysis of elimination from the thio-nitrobenzoate and thiosalicylate adducts of fumaronitrile by a simple E1cB mechanism. The absence of such an inverse solvent isotope effect for elimination of these adducts (Figure 4, Results) shows that these reactions do not proceed according to the E1cB mechanism of eq 1. However, it is consistent with the mechanism of Scheme I, in which equilibration of the carbanion–BH^+ in-termediate with D_2O is slow relative to k_{-1} and k_2 so that there is no deuterium isotope effect on k_{-1}.

Internal Return from Solvent. Almost all of the primary deu-terium isotope effects in Table I for catalysis of elimination by hydroxide ion are in the range $k_H/k_D = 4$–5; the value of k_H/k_D ~ 3 for the pentafluorothiophenol adduct of chloroacrylonitrile is consistent with the conclusion that leaving-group expulsion is partly rate limiting in this reaction. Comparison of these isotope effects with the product discrimination isotope effects of k_H/k_D ~ 3 for the thiol addition reactions in the reverse direction[2] shows that the primary deuterium isotope effect is not fully expressed in the product-determining transition state for carbanion pro-tonation. Furthermore, comparison of the kinetic isotope effects of $k_H/k_D = 4$–5 with the isotope effects of $k_{obsi}/k_{obsf} = 2.3 \pm 0.3$ for the biphasic elimination reactions in D_2O of protium adducts of thiophenol and p-nitrothiophenol with acrylonitrile and of p-nitrothiophenol with chloroacrylonitrile (Table II, Figure 3) shows that the primary deuterium isotope effect is not fully ex-pressed in these rate-constant ratios.

These two differences provide evidence that proton transfer is not the only step that controls isotope discrimination in the addition direction or the observed isotope effect in the biphasic elimination reactions. These results are expected if equilibration of the transferred proton with the solvent, k_s in Scheme I, is competitive

Scheme II
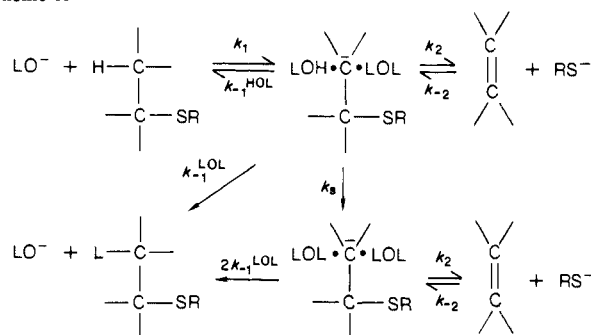
with reprotonation, k_{-1}. The differences are consistent and are larger than experimental error. The most accurate values for the product isotope effects are $k_H/k_D = 2.8 \pm 0.3$ for addition of the anion of β-mercaptoethanol to acrylonitrile and 3.2 ± 0.2 for addition of thiosalicylate dianion to fumaronitrile.

The differences are larger than can be accounted for by sec-ondary α or β deuterium isotope effects. Secondary α deuterium isotope effects (at the position β to the leaving group) are ≤ 1.2, and almost all of the observed isotope effect of $k_H/k_D = 1.51$ for the ionization of malononitrile in water, a closely related reaction, can be accounted for by the fractionation factor $1/l = 1/0.69 = 1.45$ for the formation of LOH_2^+; the β value for proton transfer to weak bases is 0.98 in this reaction.[8-10] The hydrogen atom adjacent to the leaving group in fumaronitrile adducts is not expected to contribute significantly to the difference in isotope effects because reported β deuterium isotope effects for carbanion formation are smaller than α isotope effects and are commonly in the range of $k_H/k_D = 1.01$–1.03 per hydron.[5,11] The contri-bution from a change in fractionation factor upon transfer to hydroxide ion is expected to be small because the fractionation factor of the carbon acid is estimated to be 1.0 ± 0.1.[12]

The biphasic kinetics for elimination of protium adducts in D_2O arise from elimination from the protium adduct that is competitive with exchange to give the deuterium adduct in the initial phase, followed by elimination from the deuterium adduct in the second phase. Both the initial and final phases are corrected by the same factor for partitioning between elimination and reprotonation of the carbanion according to eq 2 and 3, which are derived for E1cB

$$k_{obsi} = k_1^H[OD^-]/(k_{-1}^{DOD}/k_2 + 1) \qquad (2)$$

$$k_{obsf} = k_1^D[OD^-]/(k_{-1}^{DOD}/k_2 + 1) \qquad (3)$$

elimination with diffusionally equilibrated protons according to the mechanism of eq 1.[5] The primary deuterium isotope effect for the proton-transfer step is given by the ratio of the initial and final rate constants, $k_1^H/k_1^D = k_{obsi}/k_{obsf}$, according to this mechanism. However, the values of $k_1^H/k_1^D = 2.3 \pm 0.3$ for elimination reactions of the thiophenol and p-nitrothiophenol

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(10) Subramanian, R.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 7887.
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(12) The equilibrium isotope effect is expected to be between 0.9 and 1.1. The number 1.1 is based on the calculated fractionation factor of 0.86 for acetonitrile and an expected increase in this factor by 10% due to replacement of one hydrogen by a carbon. The numbers have been normalized to a solvent fractionation factor of 1.0 by using a fractionation factor of 0.63 for acetylene (Buddenbaum, W. E.; Shiner, V. J. In *Isotope Effects on Enzyme Catalyzed Reactions*; Cleland, W. W., O'Leary, M. H., Northrop, D. B., Eds.; University Park: Baltimore, 1977; p 1). The number 0.90 is based on the approximate fractionation factor of 1/1.2 determined by Bergmann for PhCH$_2$CLMeCN corrected by a factor of 1/1.1 for replacement of the methyl group by a hydrogen (Bergman, N. A. *Acta Chem. Scand.* **1971**, *25*, 1517, and Cleland, W. W. In *Methods in Enzymology*; Purich, D. L., eds., Academic: New York, 1980; Vol. 64, p 104.

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Table III. Rate Constant Ratios for Schemes I and II[a]

		k_{-1}^{HOL}/k_2[b,c]		
	k_{-1}^{HO}/k_s[b]	PhSCH$_2$-CH$_2$CN	(4-NO$_2$)-PhSCH$_2$-CH$_2$CN	(4-NO$_2$)-PhSCH$_2$-CH(Cl)CN
Scheme I	1.5 (1.1–2.1)	12 (7–16)	5 (4–9)	10 (7–11)
Scheme II	4 (1.4–4.4)	14 (7–18)	5 (4–8)	9 (7–12)

[a] The ratios were used for the calculated lines in Figure 6 for reactions in D$_2$O; the values in parentheses are ranges (see text). [b] Rate constants for Schemes I and II. [c] For Scheme II the values of k_{-1}/k_2 for reactions in D$_2$O, obtained as described in the text, were multiplied by 2.0 in order to account for the two k_{-1}^{HOH} steps in water.

adducts of acrylonitrile and the *p*-nitrothiophenol adduct of chloroacrylonitrile are significantly smaller than the directly determined primary isotope effects of k_H/k_D in the range 4–5 for elimination from acrylonitrile and fumaronitrile adducts (Table I). Again, the difference may be accounted for by internal return without fast proton exchange with the bulk solvent, according to the mechanism of Scheme I. When proton exchange with the bulk solvent is not fast, the back reaction in the initial phase will be faster because it sometimes involves H instead of D, so that k_{obsi} and the observed isotope effect will be decreased. Furthermore, internal return will decrease k_{obsi} more than k_{obsf} because of the deuterium isotope effect on k_{-1}.

Models and Rate Constants for Reactions of the Carbanion. Scheme I, with B = LO$^-$, and Scheme II describe models in which the carbanion intermediate can be reprotonated by only one or by either of two water molecules, respectively. A planar, resonance-stabilized carbanion could presumably react with either of two water molecules (Scheme II) and an sp^3 hybridized carbanion with a single molecule (Scheme I), but the structure of cyanocarbon anions is still not certain. The large effect of the CN group on the pK_a of carbon acids and on σ^- provides evidence for resonance delocalization,[13,14] while photoelectron spectra and molecular orbital calculations suggest that the carbanions are nearly planar with small barriers for inversion.[15] In principle, the models could be distinguished by the dependence of isotope discrimination on the isotope composition of the solvent, from the difference between values of k_{obsi}/k_{obsf} and k_{obsf}/k_{obsi} for biphasic reactions of protium and deuterium substrates in D$_2$O and H$_2$O, respectively, and by stereochemistry,[16] but we do not have sufficient data to make the distinction.

Ratios of the rate constants for reprotonation, k_{-1}, and for solvent equilibration, k_s, that are consistent with the experimental data are shown in Table III for the mechanisms of Schemes I and II. The ratios were calculated by using the equations in the Appendix (supplementary material) and the following isotope effects: a primary isotope effect of k_H/k_D = 4.5–5.3, a value of k_{obsi}/k_{obsf} ≤ 2.7, and a product isotope effect of ≥2.5 that was taken from the experimental ratio of 2.8 ± 0.3 for the addition of β-mercaptoethanol anion to acrylonitrile at a solvent isotope composition of H/D = 1 and k_{-1}^{HOL}/k_2 = 10.[2]

Values of the ratios k_{-1}^{HOL}/k_2 for substrates that exhibit biphasic kinetics for elimination of protium adducts in D$_2$O are included in Table III. They were obtained from k_{-1}/k_s by using the equations of More O'Ferrall and Slae,[5] which were modified to include the microscopic rate constants of Schemes I and II. The ratios in Table III were determined by solving a quadratic equation for k_{-1}^{HOL}/k_2 (combining eq S13 and S15 or S16 in the supplementary material) with the range of values of k_{-1}^{HOL}/k_s, the isotope effect for hydroxide ion catalyzed elimination of the
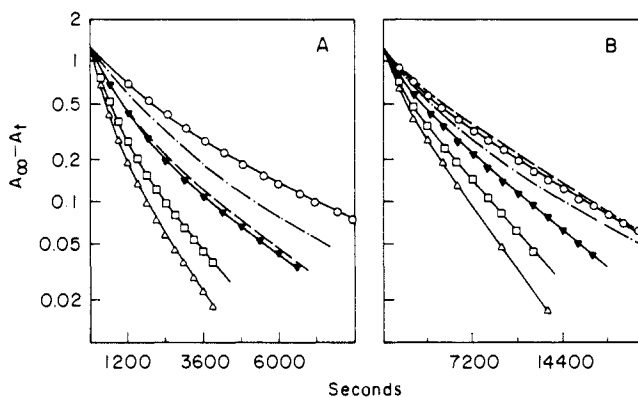
Figure 6. (A) Fit of Scheme I to the nonlinear first-order kinetics for elimination from the protium adduct of *p*-nitrothiophenol and acrylonitrile in D$_2$O at different [OD$^-$]. The solid lines were calculated for Scheme I with k_{-1}^{HOL}/k_s = 1.5, k_{-1}^{HOL}/k_2 = 5, $k_{-1}^{HOL}/k_{-1}^{DOL}$ = 4.9, k_{1OL}^H/k_{1OH}^D = 4.5. The symbols O, ▼, □, and △ are data for 0.01, 0.02, 0.03, and 0.04 M KOD, respectively. The fit to the data for 0.01 M OD$^-$ with k_{-1}^{HOL}/k_2 = 3 is shown by (–·–) and the fit for 0.02 M OD$^-$ with k_{-1}^{HOL}/k_2 = 7 is shown by (– –); other parameters were held constant. (B) Fit of Scheme II to the nonlinear first-order kinetics for elimination from the protium adduct of thiophenol and acrylonitrile. The solid lines were calculated for Scheme II with k_{-1}^{HOL}/k_s = 4, k_{-1}^{HOL}/k_2 = 14, $k_{-1}^{HOL}/k_{-1}^{DOL}$ = 4.9, and k_{1OL}^H/k_{1OL}^D = 4.5. The symbols O, ▼, □, and △ are for 0.031, 0.047, 0.062, and 0.078 M KOD, respectively. The fit to the data for 0.031 M OD$^-$ is shown by (– –) for k_{-1}^{HOL}/k_2 = 24 and by (–·–) for k_{-1}^{HOL}/k_2 = 6, keeping all other parameters constant.

pentafluorothiophenol adduct of fumaronitrile, and values of k_x and k_{obsf} (Table II). The range of solutions was further narrowed by fitting sets of parameters with the calculated value of k_{-1}^{HOL}/k_2 to the observed biphasic kinetics and varying k_1^H and k_1^D by <10% with constant k_1^H/k_1^D.

Figure 6 shows examples of the fit of calculated lines to the observed biphasic kinetics. Figure 6A,B show the fit to Schemes I and II for the *p*-nitrothiophenol and thiophenol adducts of acrylonitrile, respectively. The broken lines show the effect of varying the ratio k_{-1}/k_2, as described in the figure caption. The range of rate constant ratios in Table III reflects the use of maximum errors of the parameters for calculation; smaller ranges of k_{-1}^{HOL}/k_s = 1.2–1.6 (Scheme I) and k_{-1}^{HOL}/k_s = 1.8–4.0 (Scheme II) are obtained with a single value of k_H/k_D = 4.9 for k_1.

The values of k_{-1}^{HOL}/k_s for elimination from the pentafluorothiophenol adduct and for exchange of the methanethiol adduct of fumaronitrile are consistent with the larger catalysis by methylamine buffers of elimination than of exchange, shown in Figure 2. For the mechanism of Scheme I and k_{-1}^{HOL}/k_s = 1.5, the calculated rate increase with 0.1 M methylamine is 28% for exchange and 69% for elimination; for Scheme II and k_{-1}^{HOL}/k_s = 2.4, the increases are 25% for exchange and 69% for elimination.[17] Smaller increases for exchange are obtained with smaller association constants for ion pair formation.[18]

Table IV summarizes the ranges of k_{-1}^{HOL}/k_2 that were calculated for all of the adducts with arylthiol leaving groups. For

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(16) Fishbein, J. C. Doctoral Thesis. Brandeis University, Waltham, MA, 1985.

(17) The increases were calculated with values of k_{1B}/k_{1OH} for both the elimination and exchange reactions that were observed for catalysis of elimination of the pentafluorothiophenol adduct of fumaronitrile by methylamine (k_B) and hydroxide ion (k_{OH}), k_s = 5 × 10^9 s^{-1}, k_{-1}^{HOL}/k_s = 1.5 for Scheme I and k_{-1}^{HOL}/k_s = 2.4 for Scheme II, k_2/k_{-1}^{HOL} = 10 (which is shown later to be reasonable), for expulsion of pentafluorothiophenolate anion and k_2/k_{-1}^{HOL} = 0.02 for expulsion of methanethiolate anion, a primary isotope effect of $k_{-1}^{HOL}/k_{-1}^{DOD}$ = 5, a value of $k_{-1}^{BH^+}$ calculated from α = 0.1 (α = 1 – β = 1 – 0.9), and an association constant of 0.15 M^{-1} for the ion pair.

(18) An increase above background in the observed rate constant for exchange of 19% at 0.1 M methylamine free base (BH$^+$/B = 9) was calculated for both Schemes I and II with an association constant of 0.1 M^{-1} instead of 0.15 M^{-1}. The change in association constant also reduces the amount of catalysis of elimination if the value of k_{-1}^{HOL}/k_2 is kept constant, but an increase in this ratio to a value not outside the limits calculated later for the pentafluorothiophenol leaving group can offset this decrease. The amount of catalysis of elimination expected for this association constant is 67% for both schemes assuming k_2/k_{-1}^{HOL} = 14 for the pentafluorothiophenol leaving group.

Lifetime of the Carbanion Intermediate

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Table IV. Ranges for k_{-1}^{HOL}/k_2 in Schemes I and II

| leaving group	leaving group pK_a	k_{-1}^{HOL}/k_2 NCCH$_2$CH$_2$SR Scheme I	Scheme II	NCCH$_2$CH(CN)SR[a]	NCCH(Cl)CH$_2$SR Scheme I	Scheme II
F$_5$PhS$^-$	2.68[b]	0.3–0.8[c]	0.3–0.9[c]	0.08–0.18[d]	0.6–1.0[e]	0.6–1.3[e]
(4-NO$_2$)PhS$^-$ and (3-CO$_2^-$,4NO$_2$)PhS$^-$	4.53[b,f]	4–9[g]	4–8[g]	0.34–0.80[d]	7–11[g]	7–12[g]
PhS$^-$	6.43[b]	7–16[g]	7–18[g]	1.6–3.7[d]		
(2-CO$_2^-$)PhS$^-$	8.0[h]	8–19[c]	8–21[c]	1.9–4.4[i]		

[a] Model independent, see footnotes to each entry for method of calculation. [b] Jencks, W. P.; Salvesen, K. *J. Am. Chem. Soc.* **1971**, *93*, 4433. [c] Calculated from k_{-1}^{HOL}/k_2 for the thiophenolate ion leaving group and $\beta_{lg} = -0.35$ for k_2 (see ref 33 of the previous paper). [d] Calculated from k_{-1}^{HOL}/k_2 for the thiosalicylate dianion leaving group and $\beta_{lg} = -0.35$ for k_2 (see ref 33 of the previous paper). [e] Calculated from k_{-1}^{HOL} for the p-nitrothiophenolate ion leaving group assuming the ratio of k_{-1}^{HOL}/k_2 ratios for p-nitrothiophenolate and pentafluorothiophenolate ion leaving groups is the same as for the acrylonitrile adducts; see text. [f] Riddles, P. W.; Blakeley, R. L.; Zerner, B. *Anal. Biochem.* **1979**, *94*, 75. [g] From Table III. [h] This work, measured potentiometrically. [i] Calculated from the solvent isotope effect for addition of thiosalicylate dianion to fumaronitrile of $k_n^{H_2O}/k_n^{D_2O} = 1.8$–2.2 and an intrinsic isotope effect on k_{-1} of $k_{-1}^{HOL}/k_{-1}^{DOL} = 4.9 \pm 0.4$.

the acrylonitrile and chloroacrylonitrile adducts not listed in Table III, values of k_{-1}/k_2 were calculated by using[19] a value of β_{lg} for k_2 of –0.35, the value of k_{-1}/k_2 for the thiophenolate ion leaving group in Table III, and an assumed value of $\beta_{lg} = 0$ for k_{-1}. The range of k_{-1}^{HOL}/k_2 for the thiosalicylate ion adduct of fumaronitrile was calculated from the observed difference between the solvent isotope effect on the addition reaction of $k_n^{H_2O}/k_n^{D_2O} = 2.0 \pm 0.2$ and the range for the primary isotope effect[19] of $k_{-1}^{HOL}/k_{-1}^{DOL} = 4.5$–5.3. The ranges of k_{-1}^{HOL}/k_2 for the other arylthio adducts of fumaronitrile in Table IV were calculated from the value of k_{-1}^{HOL}/k_2 for the thiosalicylate ion adduct and the value of β_{lg} for k_2 of –0.35.[19]

The conclusion that the k_s term is significant with respect to both k_{-1} and k_2 means that there is significant internal return in the elimination and exchange reactions and that part or all of the addition reaction with the olefin occurs by a stepwise preassociation mechanism, in which the acid that protonates the carbanion is present at the time addition occurs to form the carbanion. This is equivalent to rapid leaving group departure after proton abstraction, before the protonated base diffuses away, in the elimination direction. In the Bordwell nomenclature these may be described as E1cB(ip) mechanisms when k_2 is predominantly rate-limiting;[20] in IUPAC nomenclature they are described more accurately as $A_{xh}D_H*D_N$, in which the asterisk indicates that there is an intermediate with a significant lifetime, but not a long enough lifetime to allow diffusional equilibration with the solvent between proton removal ($A_{xh}D_H$) and departure of the leaving group (D_N).[21] In the reactions described here an ion pair is formed with amine catalysts, but not with anionic bases. A simple E1cB mechanism is described by $A_{xh}D_H + D_N$ in this nomenclature, in which the + sign indicates a separate step with an intermediate that is diffusionally equilibrated with solvent components, and a concerted E2 mechanism is indicated by $A_{xh}D_HD_N$, with no punctuation.

A number of carbanion-forming reactions,[22] including several elimination reactions,[23] have been proposed to occur with significant internal return according to a variety of experimental criteria. These reactions represent examples of preassociation mechanisms when the carbanion is generated in the presence of the protonating acid, as noted above.

(19) See ref 32 of the previous paper.
(20) Bordwell, F. G. *Acc. Chem. Res.* **1972**, *5*, 374.
(21) Commission on Physical-Organic Chemistry, IUPAC to be published in *Pure Appl. Chem.*
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Koch and co-workers have proposed a mechanism for dehydrohalogenation of fluorinated styrene adducts (eq 4) that involves

(4)
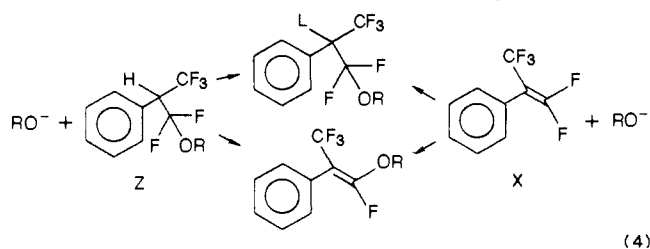
two carbanion intermediates: one a hydrogen-bonded intermediate that can undergo proton transfer or diffusional separation, and one that is not hydrogen bonded and can expel the leaving group or diffuse together with a molecule of solvent.[24] The basis for proposing the two carbanion model for the reactions of X (eq 4) is as follows. Reaction of the styrene, X, with ethoxide ion gives 85% elimination and 15% addition at –78 °C, suggesting that the rate constant for fluoride ion expulsion from the initially formed carbanion is about 5.7 times larger than the rate constant for its protonation. However, the small product isotope effects of $k_H/k_D = 1.5$ at –78 °C are interpreted as indicating internal return, and this might imply, contrary to the result above, that the rate constant for proton transfer is larger than that for fluoride ion expulsion. It is argued that the increase in the product isotope effect to $k_H/k_D = 1.86$ at 20 °C is inconsistent with an asymmetric transition state, which would be an alternative explanation of the small isotope effect. The contradiction is resolved by the two carbanion model in which the carbanion initially formed in the addition direction is not associated with a solvent molecule and partitions between fluoride ion expulsion and hydrogen-bond formation with a ratio of about 5.7 to 1. The product isotope effect represents the small amount of discrimination expected for hydrogen-bond formation. However, models involving a single carbanion intermediate, such as Scheme I or II, could account for these observations if the rate constant for rapid protonation of the carbanion, such as k_{-1} in Scheme I, increases less with increasing temperature than k_s, for diffusional equilibration of the carbanion. There is a decrease in the viscosity and an increase in the rate of dielectric relaxation of methanol of ~7-fold between –73 and 20 °C and between –43 and 30 °C, respectively.[25]

The results described here do not require more than one carbanion intermediate. They exclude the possibility that hydrogen-bond formation is rate-limiting in the addition direction because the product isotope effects of ~3 indicate that there is more discrimination than would be expected for a step involving only hydrogen bond formation.

Lifetimes. Proton Transfer. The rate constants k_{-1}^{HOL}, for protonation of the carbanion by water, and k_2, for leaving-group

(24) Koch, H. F.; Koch, J. G.; Donovan, D. B.; Toczko, A. G.; Kielbania, A. J., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 5417. Koch, H. F. *Acc. Chem. Res.* **1984**, *17*, 137.
(25) *CRC Handbook of Chemistry and Physics*; Chemical Rubber Co.: Cleveland, 1975–76; Vol. 56, p F-53. Bertolini, D.; Cassettari, M.; Salvetti, G. *J. Chem. Phys.* **1983**, *78*, 365.

expulsion, can be obtained from the rate constant ratios in Table III if k_s, for exchange with bulk solvent of the HOL adjacent to the carbanion, is known. We estimate that k_s is very fast, on the order of 10^{11} s^{-1}, which corresponds to the rate constant for dielectric relaxation of water.[26]

(1) The protonation of ammonia occurs almost entirely by proton transfer through a hydrogen-bonded water molecule, and the rate constant for exchange of this water molecule with solvent is 2.2×10^{11} s^{-1} at 25 °C.[27]

(2) Protonation of CN$^-$ by relatively strong buffer acids, on the other hand, occurs <1% through water, and reaction with the solvated proton does not occur through hydrogen-bonded water according to the Swain–Grunwald mechanism, although these reactions are essentially diffusion controlled.[28] This means that when an acid approaches CN$^-$ a water molecule escapes from the solvent-separated ion pair (k_s, eq 5) faster than proton transfer

$$\begin{array}{c} \text{BH}^+\text{·OH·}^-\text{CN} \xrightarrow{k_w} \text{B·HO·HCN} \\ \text{H} \qquad\qquad\quad \text{H} \\ \Big\downarrow k_s \\ \text{BH}^+\text{·}^-\text{CN} \xrightarrow{k_p} \text{B·HCN} \end{array} \qquad (5)$$

occurs through water (k_w), even though proton transfer is strongly favorable (eq 5). This suggests that solvating water escapes from CN$^-$ with a rate constant comparable to that for separation from ammonia or for dielectric relaxation even though it is also, presumably, hydrogen bonded to BH$^+$.

(3) The more basic carbanions of thiazolium salts show similar behavior, with no inhibition by acid that would be expected for proton exchange with solvent according to the Swain–Grunwald mechanism. Furthermore, the solvent isotope effect for proton exchange shows that the rate-limiting step is diffusional separation of H_3O^+ from the carbanion, to form a solvent-separated ion pair (k'_s, eq 6); the reaction does not occur through a mechanism

$$\begin{array}{c} \nearrow\text{C}^-\text{·HO·HOH} \\ \quad\quad \text{H} \;\; ^-\text{H} \\ \searrow\text{CH·OH} \rightleftharpoons \searrow\text{C}^-\text{·HOH} \underset{k_{-i}}{\overset{k'_s}{\rightleftarrows}} \\ \nearrow\quad\text{H} \qquad \nearrow\quad ^-\text{H} \overset{k_i}{\searrow} \\ \qquad\qquad\qquad\qquad\qquad \searrow\text{C}^-\text{·HO·HOH} \\ \qquad\qquad\qquad\qquad\qquad \nearrow\quad\; ^-\text{H}\;\; \text{H} \end{array} \qquad (6)$$

involving a proton jump to an adjacent water molecule (k_j, eq 6). This means that (a) breaking of the hydrogen bond between the strongly acidic H_3O^+ and a strongly basic carbanion (k'_s) is very fast, faster than the mechanism involving a proton jump, and (b) microscopic reversibility requires that when H_3O^+ approaches the carbanion in the diffusion-controlled reverse reaction, any water molecule that is hydrogen bonded to the carbanion is extruded from the solvent-separated ion pair (k'_s, eq 6) faster than a proton jumps to this water molecule to give protonation of the carbanion (k_{-j}).[29] Thus, if there is a water molecule hydrogen bonded to this localized carbanion, it dissociates faster than a proton can jump to it from H_3O^+. We conclude that the dissociation of water from the carbanion must be extremely fast, on the order of the dielectric relaxation rate of water, and that there is no strong hydrogen bond between the carbanion and water. The charge in the anions of cyanocarbon acids is significantly delocalized, so that the separation of a hydrogen-bonded water molecule would be expected to be at least as fast.

The rate constant $k_s = 10^{11}$ s^{-1} and the ratios of k_{-1}/k_s in Table III then give $k_{-1}^{\text{HOL}} = 2 \times 10^{11}$ s^{-1} for protonation of the carbanion according to Scheme I and 4×10^{11} s^{-1} for Scheme II. Since two water molecules are available in the mechanism of Scheme II, the total rate constant for protonation of the carbanion by this mechanism would be $\sim 8 \times 10^{11}$ s^{-1}.

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Table V. Ranges of Rate Constants, k_2, for Leaving-Group Expulsion from the Carbanion Intermediate

leaving group	leaving group $pK_a{}^a$	$\log k_2,{}^b$ s^{-1}		
		NCCH$_2$-CH$_2$SR	NCCH$_2$-CH(CN)SR	NCCH(Cl)-CH$_2$SR
F$_5$PhS$^-$	2.68	11.1–12.4	11.8–13.0	10.9–12.1
(4-NO$_2$)PhS$^-$ and (3-CO$_2^-$,4-NO$_2$)-PhS$^-$	4.53	10.0–11.3	11.1–12.4	9.9–11.1
PhS$^-$	6.43	9.7–11.1	10.4–11.7	
(2CO$_2^-$)PhS$^-$	8.0	9.7–11.0	10.4–11.6	

^{a}References in Table IV. ^{b}See text for method of calculation.

These large rate constants account for the observation of little or no buffer catalysis of proton exchange. Diffusional separation of the protonated base and water from the carbanion is partly rate limiting for exchange, so that β approaches 1.0 and hydroxide ion is the preferred catalyst for exchange. This shows that the intrinsic barrier for proton exchange for these cyanocarbon acids is small, although not negligible, in agreement with previous conclusions.[30] The barrier is significantly larger for proton exchange of 1,4-dicyano-2-butene, which shows significant catalysis of ^{3}H exchange by secondary amines and a Brønsted slope of $\beta = 0.93$ with a negative deviation of 10^3 for hydroxide ion; a value of $k_{-1}^{\text{HOL}} = 6 \times 10^7$ s^{-1} was estimated for protonation of the carbanion by the solvent.[31] This larger barrier is presumably a consequence of the increased resonance delocalization and structural reorganization that accompanies ionization of this acid.

Lifetimes. Leaving-Group Expulsion. Rate constants for expulsion of the leaving groups from the carbanion intermediate, k_2, were calculated from the k_{-1}^{HOL}/k_2 ratios in Tables III and IV and values of $k_{-1}^{\text{HOL}} = (1-8) \times 10^{11}$ s^{-1}. The rate constants are shown in Table V. All of the lower limits and almost all of the upper limits of k_2 are consistent with the existence of a carbanion intermediate with a short, but significant, lifetime. The upper limits of k_2 for expulsion of the best leaving groups from the carbanion of fumaronitrile adducts are near the limit of bond vibration frequencies, 2×10^{13} s^{-1} for the C–S stretching vibration.[32] Structure–reactivity correlations show no indication of increased rate constants for these leaving groups that might indicate the appearance of a new reaction mechanism, so that there is no evidence for a concerted reaction mechanism involving coupling between proton removal and leaving-group expulsion.[2]

The large rate constants are consistent with the appearance of a concerted, E2 mechanism for elimination with still better leaving groups. Stirling and co-workers have concluded that the elimination reactions of NCCH$_2$CH$_2$I and NCCH$_2$CH$_2$Br in ethanol are concerted E2 reactions because they are faster than the predicted rates of ionization.[33] Although quantitative comparisons between reactions in water and ethanol are difficult, the much larger leaving group ability of I$^-$ and Br$^-$ compared with thiol anions supports this conclusion and strongly suggests that the concerted mechanism is enforced by the absence of a significant lifetime for a carbanion intermediate in these reactions.

pK_a Values. The pK_a values of adducts that gave significant exchange were calculated from the observed rate constants,[2] the rate constant ratios in Table III for Schemes I and II, $pK_a = 15.74$ for H_2O, and the equation $k_1 = k_{OH}(k_{-1}/k_s + 1)$ from the steady-state rate expression for exchange according to eq 7. K

$$\text{HO}^- + H C \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{HO}H\text{·}^-\text{C} \underset{k_{-s}}{\overset{k_s}{\rightleftharpoons}} \text{HOH·}^-\text{C} + \text{HO}H \qquad (7)$$

$= k_1 k_s / k_{-1} k_{-s}$ was calculated with $k_{-s} = 3 \times 10^9$ M^{-1} s^{-1}, and $k_1 k_s / k_{-1}$ was corrected by a factor of $3.3 = 8/2.4$ for an 8-fold

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negative deviation of k_{OH} from the Brønsted plot of slope 1.0 for base-catalyzed proton exchange of 3,4-dimethylthiazolium ion under conditions in which diffusion-controlled separation of the products is rate-limiting and the secondary isotope effect of 2.4 for transfer of a proton to OD⁻ compared with OH⁻.[29,34] This procedure allows HO⁻ to be treated as a normal base of pK_a = 15.74; the reason for the negative deviation of hydroxide ion from the Brønsted plot is discussed elsewhere.[29]

The pK_a values are as follows: NCCH₂CH₂SPh, 26.7; NCCH₂CH₂SPhCOO⁻, 26.8; NCCH₂CH₂SPhNO₂, 25.9; NCCH(Cl)CH₂SPhNO₂, 22.0; and NCCH₂CH(CN)SCH₃, 23.2. The range of k_{-1}/k_s values (Table III) gives an uncertainty of ±0.2 unit to these pK_a values. The pK_a values of other adducts can be estimated from these values, and the pK_a of the thiol group according to ΔpK(adduct) = 0.16ΔpK(thiol) if the transmission coefficient for substituent effects is 2.5.[14]

These values may be compared with pK_a = 21 for 1,4-dicyano-2-butene, obtained in Me₂SO/water mixtures,[31] and pK_a = 20.8 and 31.3 for PhSCH₂CN and CH₃CN in Me₂SO.[35] These may be similar to the pK_a values in water, because the pK_a of malononitrile is the same in water and Me₂SO.[36] They are in the same range as an early estimate of pK_a = 25 and recent calculations of pK_a = 23.7–28.6 for acetonitrile in water.[37]

It is of interest that the β-chlorine substituent decreases the pK_a of the chloroacrylonitrile adducts by 4 units, which is a larger decrease than has been observed in a number of other systems.[38] Most of this difference appears in the rate constant k_1, for proton abstraction, which accounts for the increase in elimination rate with good leaving groups by a factor of ~10⁴ with the β-chlorine substituent,[2] there is not a large effect on the k_{-1}/k_2 ratio (Table III), and the similar amounts of internal return for the different compounds indicate that k_{-1}/k_s and k_{-1} are not very different for the chloro compound.

Partitioning of the Intermediate. The partitioning ratios k_{-1}/k_2 in Tables III and IV confirm and extend the conclusion in the previous paper[2] that the α-CN group of fumaronitrile favors

leaving-group departure compared with reprotonation of the intermediate, while a β-chloro substituent has little or no effect on the partitioning ratio of the anion of acrylonitrile adducts. The α-CN substituent increases k_2 relative to k_{-1} by a factor of 5–10, which is similar to the factors observed by Stirling and co-workers for an α-phenyl substituent in several systems, including the thiophenol adduct of acrylonitrile.[39] The effects of both the CN and Ph substituents can be attributed to stabilization of the developing double bond of the product by resonance in the transition state, although it is unexpected that the two effects would be so similar in view of the larger stabilization of an adjacent double bond by Ph compared with CN at equilibrium, by a factor of 1.8 kcal mol⁻¹.[40] It is possible that there is steric interference with the development of coplanarity and resonance with the phenyl group in the transition state.

It is surprising that the β-chloro substituent has little or no effect on the k_{-1}/k_2 ratio, although it increases the overall rate of elimination by a factor of 6000. Stabilization of the carbanion by this substituent would be expected to inhibit elimination more than reprotonation and increase k_{-1}/k_2, as described in the previous paper (see Figure 8);[2] the fact that it does not suggests that stabilization of the developing double bond by resonance with the Cl substituent[40] is sufficient to offset this effect.

It is possible that there is imbalance[41,42] (or "nonperfect synchronization")[43] between the development of charge and of resonance in the transition state. There is precedent for delayed development of resonance compared with charge in many reactions. A closely analogous example is the general base catalyzed elimination of carbinolamine ethers, which shows a large development of charge on both the nitrogen atom and the leaving group but little double-bond formation in the transition state.[41] Such imbalance may account for the relatively small effect of 5–10-fold on k_{-1}/k_2 of the α-CN substituent, compared with the factor of 280 by which it stabilizes an adjacent double bond.[40]

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