Elimination Reactions of β-Cyano Thioethers: Evidence for a Carbanion Intermediate and a Change in Rate-Limiting Step[1]

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Abstract: The addition reactions of thiol anions to form adducts with acrylonitrile (**1**), 1-chloroacrylonitrile (**2**), and fumaronitrile (**3**) and the corresponding elimination reactions were examined in aqueous solution, generally containing 8.3% Me$_2$SO at 25 °C. Deuterium exchange into the methanethiol and thiosalicylate adducts of **1** is faster than elimination. Deuterium exchange causes biphasic kinetics for elimination reactions in D$_2$O of the *p*-nitrothiophenol, but not of the pentafluorothiophenol, adducts **1** and **2**. The kinetic solvent deuterium isotope effects of $k_n^{HOH}/k_n^{DOD} = 2.0$ for addition of thiosalicylate to form **3** and 1.1–1.2 for addition of β-mercaptoethanol and thioacetic acid anions to form **1** are smaller than the product discrimination isotope effects of $k_H/k_D = 3.2$, 2.8 and 3.2 for these reactions. These differences show that the reactions proceed through a carbanion intermediate that is protonated faster than it expels basic thiol anions. These results exclude a concerted mechanism for addition–elimination with a concurrent, separate exchange reaction. The solvent kinetic deuterium isotope effect is 3.9 for the addition of thionitrobenzoate dianion to form **3**. Buffer catalysis of elimination becomes more significant with more acidic leaving groups and is larger for **3** than for **1** with a given leaving group. The results show that the rate-limiting step changes from addition–elimination of the thiol anion to proton transfer with decreasing pK_a of the thiol; the same change is favored by addition of CN to the α-position for a given thiol. The effect of the α-CN group is attributed to conjugation with the developing double bond in the transition state for elimination. The Brønsted slope is β = 0.90 for rate-limiting deprotonation of the pentafluorothiophenol adduct **3** and Brønsted-type plots against the pK_a of the leaving group have slopes of $\beta_{lg} = -0.25$ and −0.54 for predominantly rate-limiting deprotonation and leaving group expulsion, respectively.

We have been interested in the way that the mechanisms of elimination (and other) reactions are related to the lifetimes of intermediates that may be formed in these reactions.[2-5] It is clear that a reaction must follow a concerted, one-step mechanism if no intermediate can exist because the lifetime of a potential intermediate species is less than a vibration frequency, i.e. if there is no restoring force that prevents its collapse. What is not so clear is whether the converse is true—can a reaction follow a concerted mechanism when the intermediate of a stepwise mechanism can exist with a significant lifetime? Such concurrent stepwise and concerted pathways have been observed for reactions in which one of the steps involves proton transfer between electronegative atoms, which has a small barrier but can cause a large stabilization of the transition state.[6] This is less likely for reactions in which both processes have larger barriers.

It appears that cleavage of the anion of 1-phenylcyclopropanol[3] and the intramolecular addition of phenolate ion to an unactivated olefin[7] proceed by concerted mechanisms because there is no barrier to abstraction of a proton from solvent by the carbanions that are generated in these reactions, which have pK_a values in the range of ∼50–70. The elimination reactions of a number of N-(2-arylethyl)quinuclidinium ions proceed through a concerted, E2 mechanism, but the N-[2-(*p*-nitrophenyl)ethyl]quinuclidinium ion follows a stepwise, E1cB mechanism with a transition state of very similar structure, which closely resembles the carbanion intermediate.[4,8] If the carbanion formed from the other arylethyl compounds had a significant lifetime, the reaction path would also be expected to proceed through this intermediate and give a stepwise mechanism. Therefore, the observation that the mechanism is concerted rather than stepwise suggests that the carbanion must be too unstable to exist as an intermediate;[4] i.e., the concerted mechanism is *enforced* because the intermediate does not exist.

The anions of several cyanocarbon acids have been shown to have short, but significant, lifetimes in hydroxylic solvents. Malononitrile and *tert*-butylmalonitrile anions are protonated by substituted acetic acids with rate constants of ∼10^8 M^{-1} s^{-1}, and the anion of 1,4-dicyano-2-butene is protonated by phenols and secondary ammonium ions with estimated rate constants of ∼10^8 and 10^9 M^{-1} s^{-1}, respectively.[9,10] There is evidence that α-cyano carbanions are intermediates in several elimination reactions. The elimination catalyzed by ethoxide ion is slower than detritiation of the thiophenol and benzenesulfinic acid adducts by acrylonitrile by factors of 10^2–10^3, and the addition reactions of substituted thiol and benzenesulfinic acid anions to acrylonitrile in water show a dependence on thiol anion basicity but no buffer catalysis.[11,12] It was concluded that these reactions follow the E1cB(rev) mechanism, with rate-limiting expulsion or attack of the anion.

We describe here an investigation of addition–elimination reactions (eq 1) of the acrylonitrile derivatives **1-3**, with thiol anions
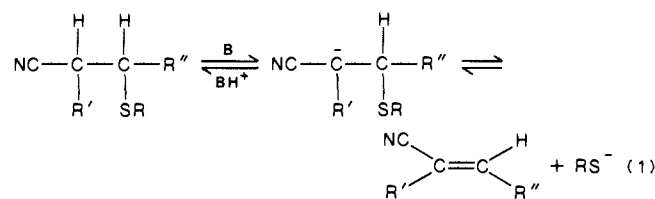
as the attacking and leaving groups. The goal was to determine the behavior and the approximate lifetime of the carbanion intermediates and to probe the possibility of a transition to a concerted mechanism or the coexistence of stepwise and concerted mechanisms. It has been suggested that stepwise and concerted mechanisms may coexist in the olefin-forming elimination reaction of a single compound,[13] but we are not aware that this has been demonstrated to occur. The results that are reported in this paper establish the E1cB mechanism, the rate-limiting step, and changes

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Table I. Proton NMR Spectral[a] Data and Melting or Boiling Points of β-Cyano Thioethers

compound	mp, °C	bp, °C	NMR spectral shifts, ppm
CH_3-$^+NC_5H_4$-$2S$-CH_2CH_2CN ($MeOSO_3^-$)	165–170.5 dec		(D_2O, DSS) 8.69 (d, 1 H), 8.38 (t, 1 H), 8.09 (d, 1 H), 7.75 (t, 1 H), 4.27 (s, 3 H), 3.73 (m, 5 H), 3.11 (t, 2 H)
$F_5PhSCH_2CH_2CN$	59–60		3.11 (t, 2 H), 2.63 (t, 2 H)
$(4\text{-}NO_2)C_6H_4SCH_2CH_2CN$	66–68		8.14 (d, 2 H), 7.47 (d, 2 H), 3.31 (t, 2 H), 2.72 (t, 3 H)
$(3\text{-}CO_2H,4\text{-}NO_2)C_6H_3SCH_2CH_2CN$	153–154.5		($[^2H_6]Me_2SO$, Me_2SO) 7.73 (d, 1 H), 7.55 (d, 2 H), 3.37 (t, 2 H), 2.90 (t, 3 H)
$C_6H_5SCH_2CH_2CN$		132 (3 mmHg)[b]	7.35 (m, 5 H), 3.11 (t, 2 H), 2.56 (t, 2 H)
$(2\text{-}CO_2H)C_6H_4SCH_2CH_2CN$	183–185		($[^2H_6]$acetone, acetone) 8.12 (d, 1 H), 7.58 (br s, 2 H), 7.41 (m, 1 H), 3.32 (t, 2 H), 2.88 (t, 2 H)
$HOCH_2CH_2SCH_2CH_2CN$		136 (1 mmHg)	3.74 (t, 2 H), 2.75 (m, 6 H)
$CH_3COSCH_2CH_2CN$		76 (2 mmHg)	3.13 (t, 2 H), 2.68 (t, 2 H), 2.40 (s, 3 H)
$F_5PhCH(Ph)CH_2CN$	100.5–102.5		7.32 (s, 5 H), 4.57 (t, 1 H), 2.98 (d, 2 H)
$F_5PhSCH(CN)CH_2CN$	81.5–82.5		3.06 (d, 2 H), 4.13 (t, 1 H)
$(4\text{-}NO_2)C_6H_4SCH(CN)CH_2CN$	111.5–113.5		8.27 (d, 2 H), 7.88 (d, 2 H), 4.16 (t, 1 H), 2.99 (m, 2 H)
$(3\text{-}CO_2H,4\text{-}NO_2)C_6H_3SCH(CN)CH_2CN$	161–163		8.09 (m, 1 H), 7.94 (d, 2 H), 4.65 (t, 1 H), 3.22 (d, 2 H)
$C_6H_5SCH(CN)CH_2CN$	52–53		7.63 (m, 2 H), 7.50 (m, 3 H), 4.0 (t, 1 H), 2.48 (d, 1 H), 2.79 (d, 1 H)
$(2\text{-}CO_2H)C_6H_4SCH(CN)CH_2CN$	160–161		($[^2H_6]$acetone, acetone) 8.11 (d, 1 H), 7.86–7.41 (m, 3 H), 5.01 (t, 1 H), 3.41 (d, 2 H)
$CH_3COSCH(CN)CH_2CN$		138–140 (2 mmHg)	4.59 (t, 1 H), 3.10 (d, 2 H), 2.48 (s, 3 H)
$CH_3SCH(CN)CH_2CN$		124 (0.75 mmHg)	3.89 (t, 1 H), 3.04 (d, 2 H), 2.40 (s, 3 H)
$F_5PhSCH(Cl)CN$		90 (0.25 mmHg)	4.54 (t, 1 H), 3.40 (d, 2 H)
$(4\text{-}NO_2)C_6H_4SCH_2CH(Cl)CN$	77.5–79		8.11 (d, 2 H), 7.55 (d, 2 H), 4.60 (t, 1 H), 3.62 (d, 2 H)

[a] Spectra in $CDCl_3$; chemical shifts relative to tetramethylsilane unless otherwise noted. [b] Reported as 104 °C at 0.5 mmHg in Marshall, D. R.; Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1914.

in the rate-limiting step with changing leaving groups and substituents on the central atoms of **1–3**; they also provide evidence against the coexistence of stepwise and concerted reaction mechanisms.

$$NCCH_2CH_2SR \qquad NCCH(Cl)CH_2SR$$
$$\mathbf{1} \qquad\qquad \mathbf{2}$$
$$NCCH_2CH(CN)SR$$
$$\mathbf{3}$$
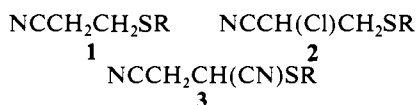
Experimental Section

Materials. Reagent grade organic chemicals were used unless otherwise specified and were normally purified by recrystallization or distillation; thiosalicylic acid was sublimed. Reagent grade inorganic chemicals were used as received. Water was distilled in glass. Deuterium oxide was 99.8% isotopically pure. Stock solutions of reagents in D_2O were prepared by first exchanging exchangeable protium from the reagents with D_2O to give <2 atom % of exchangeable protium in the stock solution.

Synthesis of Adducts. The adducts synthesized and their proton NMR spectral characteristics and melting or boiling points are summarized in Table I; the yields were >10%.

Acrylonitrile Adducts. In general the syntheses were carried out by mixing the nitrile and thiol in aqueous buffer. In a typical procedure, 10 mL of thiophenol (0.098 mol), 10 mL of acrylonitrile (0.15 mol), 10 mL of 0.5 M phosphate buffer (pH 6), and 100 mL of water were stirred under argon for 24 h. The reaction mixture was then extracted four times with 100 mL of benzene. The benzene fractions were combined and extracted four times with 50 mL of 0.5 M phosphate buffer, pH 7.0. The benzene fraction was recovered, and the solvent was removed by rotary evaporation, leaving a clear viscous liquid. The product was purified by distillation.

For the thionitrobenzoate adduct the reaction with acrylonitrile was carried out after generation of the free thiol from the disulfide with excess sodium borohydride, followed by quenching with hydrochloric acid. The addition reaction was carried out by adding a large excess of acrylonitrile and maintaining the pH at 6 with hydrochloric acid. Subsequent extraction and recrystallization from ethyl acetate/chloroform gave yellow crystals.

For the *N*-methyl-2-mercaptopyridinium ion adduct, the unmethylated thiol was prepared from 2-pyridyl disulfide with sodium borohydride, as described above. The addition reaction was carried out with excess acrylonitrile at pH 10–10.5, maintained with hydrochloric acid. When there was no further increase in pH, the solution was extracted with ethyl acetate. An NMR spectrum of the viscous orange liquid remaining after removal of the ethyl acetate showed roughly equal amounts of the N and S adducts, as judged by the integrations of the thione and pyridinium ion protons. Partial separation of the N and S adducts was achieved by suspending the product mixture in water at pH 1. Insoluble material, shown by NMR to be ~90% N adduct, was filtered, and the filtrate was brought to pH 5, whereupon insoluble material appeared. Extraction

with ethyl acetate and evaporation of the organic phase gave a viscous liquid, which contained ~20% N adduct and 80% S adduct. This material was refluxed for 2 h with 10 mL of methyl iodide in 75 mL of ethyl acetate and stirred at room temperature for 24 h to give unmethylated S adduct in solution and crystals of mostly S-methylated N adduct. After filtration, the filtrate was evaporated and then refluxed with 10 mL of dimethyl sulfate in 50 mL of ethyl acetate for several hours. The mixture was extracted with 0.1 M hydrochloric acid in water, and the aqueous phase was evaporated to give an oil. The product was crystallized from $MeOH/i$-PrOH.

Fumaronitrile Adducts. The procedures followed were generally the same as those for the acrylonitrile adducts except that the solvents were 10–50% ethanol or acetonitrile. In the case of the pentafluorothiophenol adduct, after two recrystallizations from ethyl acetate/hexane, contaminating alkene was removed by suspending the crude product in water and reacting with excess β-mercaptoethanol. The pure pentafluorothiophenol adduct was then isolated by extraction and recrystallization.

The methanethiol adduct was prepared by bubbling methanethiol into 300 mL of water containing 5 g of potassium hydroxide until the pH of the solution reached 11. Fumaronitrile, 7 g, was added, and the pH was maintained at 11 with 2 M hydrochloric acid. The reaction was complete in minutes. After extraction with 200 mL of ethyl acetate, the organic phase was evaporated, the product was distilled at 124 °C (0.75 mmHg), and 10 g of the product was suspended in 200 mL of 1.5 M ammonium chloride buffer (90% cation) for 10 min, after which 10 mL of hydrochloric acid was added. The solution was extracted with methylene chloride, the solvent was evaporated, and the product was distilled twice. The product crystallized upon refrigeration. The NMR spectrum of the final material was that expected for the pure adduct except for a small singlet at δ 2.23 ($CDCl_3$, TMS),[14] which represented <2% of the signal for the methyl protons of the methanethiol adduct.

Chloroacrylonitrile Adducts. These were prepared using the general method described for acrylonitrile adducts.

$[^2H_2]$Fumaronitrile. To 10 g of fumaronitrile in 150 mL of benzene were added 5 mL of trimethylamine, 1 mL of 10.4 M deuterium chloride in D_2O, and 25 mL of D_2O. This solution was stoppered and stirred for 48 h, after which the dark brown aqueous phase was separated from the benzene phase. The aqueous phase was extracted with 100 mL of benzene, and the two benzene fractions were combined. The benzene was removed by rotary evaporation, leaving 8 g of material that was 91% exchanged by NMR. The exchange procedure was repeated and gave product that was >97% exchanged by NMR analysis. The nitrile was recrystallized three times in ethyl acetate/hexane and gave mp 95–96 °C, identical with that of the pure fumaronitrile.

Kinetics. Kinetics of elimination and addition reactions were monitored at 25.0 ± 0.2 °C on a Zeiss PM6 spectrophotometer with a ther-

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(14) Abbreviations: DABCO, diazabicyclooctane; DTNB, 5,5'-dithiobis-(2-nitrobenzoic acid); Tris, [tris(hydroxymethyl)amino]methane; TMS, tetramethylsilane.

mostated cuvette carriage. The ionic strength was maintained at 1.0 M with potassium chloride. The solutions for elimination reactions contained 8.3% Me$_2$SO (v/v). All reactions were run in the presence of ethylenediaminetetraacetic acid, generally 10^{-4} M. For reactions that were observed for longer than 1 h, all stock solutions were bubbled under argon for 15 min, and the cuvettes were tightly stoppered under a stream of argon.

Rate constants were obtained under either pseudo-first-order or initial rate conditions by observing the appearance of the thiol anion. When both conditions were used with the same substrate, comparable rate constants agreed within experimental error. The anions and wavelengths at which the reactions were observed were as follows: pentafluorothiophenolate, 255 or 260 nm; 4-nitrothiophenolate, 410 or 412 nm; thionitrobenzoate dianion, 412 nm; thiophenolate, 263 nm; thiosalicylate dianion, 270 nm; thioacetate, 246 nm; β-mercaptoethanol anion, 240 nm; 2-mercapto-*N*-methylpyridinium zwitterion, 339 nm. Under pseudo-first-order conditions, rate constants were usually obtained from semilogarithmic plots of $A_∞ - A_t$ against time, which were linear for 3-4 half-lives, and from the relationship $k_{obsd} = 0.693/t_{1/2}$. Reactions of the less reactive fumaronitrile adducts showed a slow further change in absorbance after 10$t_{1/2}$ at >0.5 M buffer, which may represent buffer-catalyzed hydrolysis of fumaronitrile. First-order plots, linear to >3$t_{1/2}$, were obtained by using an endpoint calculated from $ΔA$ at 5$t_{1/2}$, A_5, and an approximate halftime according to $A_∞ = A_0 + 1.03(A_5 - A_0)$. Rate constants for slow elimination reactions were obtained from the rate, v, of the initial linear change in absorbance, usually from the thiol anion, of reactions that were followed to <10% completion. The rate constant k_{obsd} was obtained from $k_{obsd} = v/Δε[S]$, in which [S] is the substrate concentration and $Δε$ is the change in extinction coefficient upon reaction. The value of $Δε$ was determined in each experiment by determining the change in absorbance upon reaction to completion of a known concentration of the substrate in dilute potassium hydroxide.

Initial rate measurements with thiosalicylate and thiophenolate adducts of fumaronitrile were obtained in the presence of 2 × 10^{-4} M DTNB[14] by following the appearance of thionitrobenzoate dianion at 412 nm. The first-order rate constant for disappearance of the thiol anion products of the elimination reaction is >10^6 times larger than the first-order rate constants for elimination in the experiments, based on a second-order rate constant of 5.8 × 10^4 M^{-1} s^{-1} for the reaction of 4-fluorothiophenolate anion with DTNB.[15] The value of $Δε$ was measured after 10$t_{1/2}$ in the presence of hydroxide ion but without DTNB. The solution was neutralized, and an aliquot was added to a solution of DTNB and buffer. The extinction coefficient (13 600 ± 5% at 412 nm) was calculated from the change in absorbance by dividing by the substrate concentration. Controls in the absence of substrate showed that hydrolysis of DTNB contributed <3% to the observed initial rate.

Measurements of pH were made on an Orion Model 701A pH meter. For measurements above pH 10, a commercial standard of pH 7 and freshly filtered saturated calcium hydroxide, pH 12.45, were used.[16] On the basis of measurements of pH at known concentrations of hydroxide ion in 8.3% Me$_2$SO at 1 M ionic strength, maintained with potassium chloride, eq 2 was used to determine the concentration of hydroxide ion

$$[OH^-] = 0.73 × 10^{(pH_{obsd}-14)} \tag{2}$$

at any pH. The value of pD was obtained by adding 0.4 to the observed pH of solutions in D$_2$O. The concentration of deuteroxide ion was calculated from eq 3, which includes the ion product of deuterium oxide.[17]

$$[OD^-] = 0.73 × 10^{(pD-14.86)} \tag{3}$$

Second-order rate constants for base-catalyzed elimination reactions were obtained from the slopes of plots of k_{obsd} against buffer base concentration with ≥4 buffer concentrations. Second-order rate constants for hydroxide ion catalysis were obtained either from the slopes of plots of k_{obsd} against hydroxide ion concentration or from values of k_{obsd} extrapolated to zero buffer concentration, by using the concentration of hydroxide ion calculated from the observed pH at the lowest buffer concentration and eq 2. When both methods were used with the same compound, the rate constants agreed within ±10%.

Product Isotope Effects. Product isotope effects for addition of the anions of β-mercaptoethanol and of thioacetic, mercaptoacetic, and thiosalicylic acids to acrylonitrile or fumaronitrile were determined by product analysis. Reactions were carried out at room temperature in a glass titrating vessel covered with parafilm, with magnetic stirring. The

reaction was monitored with a Radiometer pH meter/pH stat. A stream of argon was passed through the reaction solution. Reactions were generally carried out at a pH 1.2-2 units above the pK_a of the thiol.

In a typical experiment with β-mercaptoethanol, a total of 6 mmol of acrylonitrile, in 50-μL aliquots, was added over the course of 5 min to a 0.05 M solution of thiol (>93% anion). The increase in pH was countered by the addition of an aqueous solution of thiol. When the increase in pH ceased, after the final addition of alkene, the reaction mixture was extracted three times with 100 mL of ether. The ether fractions were combined, and the solvent was removed by rotary evaporation. The residue was dried under vacuum. At the end of some experiments with mercaptoacetic acid dianion and acrylonitrile the pH was brought to 2 with hydrochloric acid before ether extraction. If the product solidified after the ether was removed, the solid was resuspended in a small amount of 0.1 M hydrochloric acid, and most of the water was removed by rotary evaporation, leaving a viscous liquid. The reactions with 0.5-1.0 M thioacetic acid were terminated before completion by extraction with ether. The pH was maintained at 5.5 with 0.56 M thioacetic acid, and acrylonitrile was added in one aliquot to give a concentration of 1 M. In the reactions with fumaronitrile or [^{2}H$_2$]fumaronitrile, the concentration of the alkene was 0.05-0.15 M.

For the reaction of thiosalicylate anion with [^{2}H$_2$]fumaronitrile, 1 mL of 0.3 M thiosalicylate monoanion was added in 10 aliquots of 0.1 mL each to 0.02 M fumaronitrile maintained at pH 7 with 0.3 M hydrochloric acid of the correct isotopic composition. At the end of the reaction concentrated hydrochloric acid was added to pH 1.5, at which point a cloudy precipitate appeared. The solution was extracted with 100 mL of ethyl acetate, and the organic phase was evaporated. To the remaining solid was added 200 μL of D$_2$O and 2 mL of acetone. This solution was dried by rotary evaporation, the above procedure was repeated, and the solid was dried under vacuum.

The reactions with acrylonitrile in 99.8% D$_2$O and some other reactions were carried out in the presence of buffer by the same general method, but without the pH stat. The concentration of alkene used was 1 M in the reactions with acrylonitrile and 0.05 M with fumaronitrile. For the reactions with β-mercaptoethanol, the thiol was added last. When acrylonitrile was added last, different results were obtained at high concentrations of salt or buffer, which were attributed to poor mixing. For the reaction of β-mercaptoethanol in the presence of ethylenediamine dication buffer and the reaction of thioacetic acid in the presence of DABCO dication buffer, the reactions were terminated after 1 h by extraction with two 100-mL portions of ether. The ether extracts were combined and extracted with three 25-mL portions of 0.5 M potassium phosphate buffer, pH 6, or three 25-mL portions of 0.5 M potassium carbonate buffer, pH 10, in the reactions of thioacetic acid and β-mercaptoethanol, respectively. The reactions of β-mercaptoethanol with acrylonitrile in the presence of ammonia or DABCO monocation buffers were carried out for 10$t_{1/2}$ (≤1 h).

Analysis of Product Isotope Effects. Product isotope effects for the reactions with acrylonitrile were determined by deuterium NMR with a 270-MHz Fourier transform spectrometer equipped with a deuterium probe operating at 41.448 MHz. Each reaction was run in 99.8% D$_2$O and in mixed HOL/DOL solvent, and the deuterium at the β-position of equal volumes of the products from the two solvents was analyzed. Integration of the signals was generally performed after Fourier transform of data collected from 4-10 scans and repeated three times for each sample. The product ratio, PH/PD, for the reaction in mixed solvent was calculated from the average number of integration units, D, for the deuterium peak of the product formed from the reaction in the isotopically mixed solvent, and F, for products formed in D$_2$O, according to eq 4. The product isotope effect was obtained from eq 5, in which

$$PH/PD = (F - D)/D \tag{4}$$

HOL/DOL represents the molar ratio of the two isotopes. The con-

$$\text{product isotope effect} = (PH/PD)/(HOL/DOL) \tag{5}$$

centrations of the mercaptoacetic acid from the two solvents were determined by integration of the NMR signal of the methylene protons adjacent to the carboxyl group of the product. The concentrations of product varied in these experiments because of contaminating water and unreacted thiol in the material isolated by ether extraction. Analysis by proton NMR showed <5% variation between the total product concentrations of the two samples isolated from experiments with β-mercaptoethanol and thioacetic acid.

Product isotope effects for reactions with [^{2}H$_2$]fumaronitrile were determined by proton NMR, measured with a modified 90-MHz Bruker instrument. For each determination the integration values of the signals of the product methylene proton β to the leaving group, H, and an internal standard proton, I, were measured. The methyl proton singlet of the thioacetic acid adduct ($δ$ 2.5, [^{2}H$_6$]Me$_2$SO) and the aryl proton

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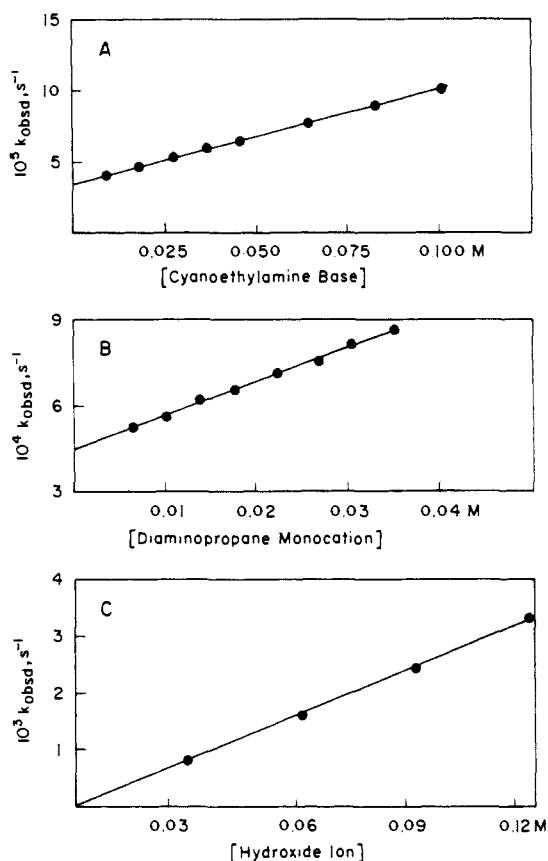
Figure 1. The dependence of k_{obsd} on the concentration of base catalyst for elimination reactions at 25 °C, μ = 1 M (KCl), 8.3% DMSO (v/v). (A) Catalysis by cyanoethylamine, BH^+/B = 9, of elimination from the pentafluorothiophenol adduct of fumaronitrile. (B) Catalysis by diaminopropane monocation, BH^{2+}/BH^+ = 9, of elimination from the pentafluorothiophenol adduct of fumaronitrile. (C) Catalysis by hydroxide ion of elimination from the thionitrobenzoate adduct of acrylonitrile.

doublet, ortho to the carboxyl group of the thiosalicylate adduct (δ 8.1, $[^2H_6]$acetone), were used as standards. A control in each experiment, in which the addition was carried out in H_2O, showed the expected ratio of integrations for the β and the standard protons. The product ratios, PH/DH, and product isotope effects were calculated from eq 6 and 5, respectively. The value of I for the thioacetic acid adduct was divided by three to normalize the integration of the methyl group to that for a single proton.

$$PH/PD = H/(I - H) \qquad (6)$$

Proton Exchange. Rate constants for proton exchange in D_2O were measured by using 90-MHz Fourier transform proton NMR spectroscopy. The temperature was measured by a thermocouple at the probe, which was calibrated with methanol.[18]

The following procedure was used to obtain rate constants for exchange of the methylene protons β to the sulfur atom in the methanethiol adduct of fumaronitrile. A 5-mm NMR tube containing 0.5 mL of a solution of $[^2H_5]$methylamine buffer (90% acid/10% base) and potassium chloride in D_2O and a flask containing 0.16 M methanethiol adduct and 16.6% $[^2H_6]Me_2SO$ (v/v) in D_2O were equilibrated at 25 °C. The reaction was started by adding 0.5 mL of the solution containing the adduct to the solution in the NMR tube. The tube was capped, shaken vigorously, and placed in the NMR. The final reaction conditions were 1 M ionic strength, maintained with potassium chloride, and 8.3% Me_2SO (v/v). Spectra were collected over 35 s. A spectrum was recorded after the Fourier transform of five sweeps, each sweep followed by a 3-s rest. The signals representing the methylene protons β to the sulfur atom and the methyl protons α to the sulfur atom, which were used as a nonexchanging internal standard, were integrated. The first-order rate constant for exchange was obtained from a semilogarithmic plot against time of $\beta_t/0.67M_t$, in which β_t and M_t are the values for integration of the methylene and the methyl protons, respectively, at time

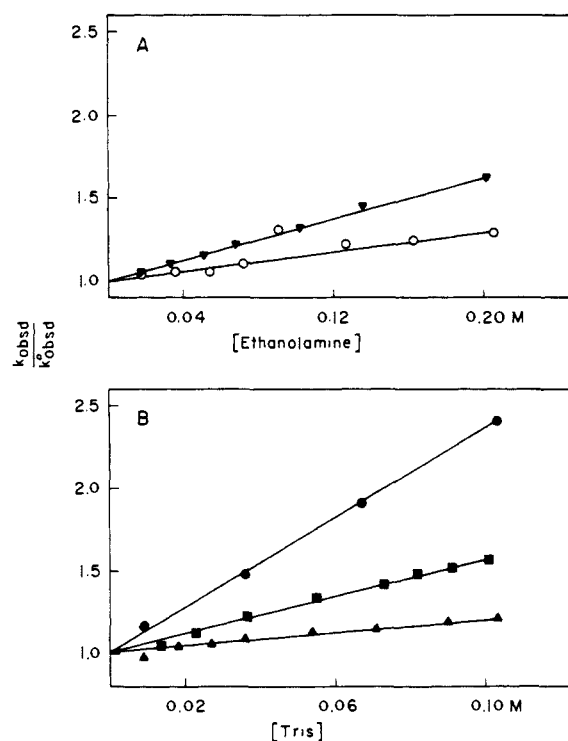(18) Van Geet, A. L. *Anal. Chem.* **1968**, *40*, 2227.

Figure 2. Comparison of the amounts of buffer catalysis of elimination observed for different leaving groups at 25 °C, μ = 1 M, 8.3% Me_2SO. The value of k_{obsd}/k^0_{obsd} is k_{obsd} at a given buffer concentration divided by k_{obsd} extrapolated to zero buffer concentration. (A) Catalysis by ethanolamine buffer (BH^+/B = 4) of elimination from the acrylonitrile adducts of N-methyl-2-mercaptopyridinium zwitterion (▼) and pentafluorothiophenolate (O). (B) Catalysis by Tris buffer (BH^+/B = 9) of elimination from fumaronitrile adducts of pentafluorothiophenolate (●), thionitrobenzoate (■) and thiophenolate (▲).

t. The exchange reaction was followed for $>2t_{1/2}$ with 12–16 time points. The rate constant for exchange of protons β to the leaving group of the thiosalicylate adduct of acrylonitrile, catalyzed by deuteroxide ion, was determined similarly. The methylene group α to the sulfur atom was used as an internal standard. The rate constants were obtained from semilogarithmic plots of the ratio β_t/α_t, in which β_t and α_t are the number of integration units of the exchanging proton and the internal standard, respectively, at time t. The exchange reaction was followed for $1-2t_{1/2}$ with 12–15 time points.

Results

Kinetics of Elimination. The kinetics of reactions at 25 °C and ionic strength 1 M, maintained with potassium chloride, in 8.3% Me_2SO in water (v/v) were followed spectrophotometrically under pseudo-first-order and initial rate conditions. The reactions obey the rate law described by eq 7. The rate constants for catalysis

$$k_{obsd} = k_{OH}[OH^-] + k_B[B] \qquad (7)$$

of elimination by buffer bases and hydroxide ion were determined as described in the Experimental Section. Typical data are shown in Figure 1A–C. A summary of the rate constants is contained in Table II.

The amounts of buffer catalysis vary with substitution at C_α and C_β and with leaving-group pK_a. The most catalysis, for a given buffer, was observed with the pentafluorothiophenol adduct of fumaronitrile, which typically showed 80–200% increases in k_{obsd} at the highest buffer concentrations (Figure 2B). Figure 2, parts A and B, show that there is a decrease in the amount of catalysis with increasing pK_a of the leaving group for both the acrylonitrile (1) and fumaronitrile (3) adducts. There is little buffer catalysis with the pentafluorothiophenol adduct of acrylonitrile (Figure 2A) or chloroacrylonitrile.

Because the amounts of catalysis were typically small, buffer concentrations of up to 1 M (0.35 M for dicationic amines) were generally used. Despite the fact that the ionic strength was kept constant at 1 M with KCl, there was usually a decrease in the
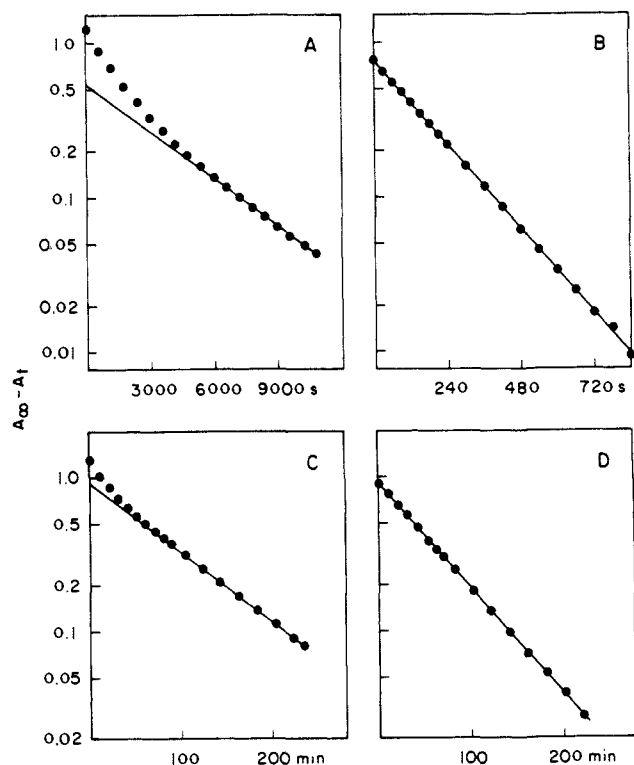
Figure 3. First-order plots for the elimination reactions of protium adducts in D_2O at 25 °C, μ = 1 M (KCl), 8.3% DMSO (v/v). (A) Thiophenol adduct of acrylonitrile, 0.047 M KOD. (B) Pentafluorothiophenol adduct of acrylonitrile, 0.020 M KOD. (C) *p*-Nitrothiophenol adduct of chloroacrylonitrile, 0.093 M, diaminopropane dication buffer, BH^{2+}/BH^+ = 9. (D) Pentafluorothiophenol adduct of chloroacrylonitrile, 0.093 M Tris buffer, BH^+/B = 9.

Figure 4. Dependence of k_{obsd} on alkene concentration for the addition of thiosalicylate dianion to fumaronitrile at 25 °C, μ = 1 M (KCl), 0.15 M bicarbonate buffer, 50% dianion in H_2O (●) and D_2O (○).

observed pH of 0.05–0.12 unit between the lowest and highest buffer concentrations. No correction was made for the decrease; there is evidence that under similar conditions it may not represent a true change in pH.[19]

The reactions of the chloroacrylonitrile adducts gave no evidence for elimination of chloride ion. The yield of thiol anion was 97% of theoretical for the *p*-nitrothiophenol adduct in the presence of diaminopropane monocation buffer (Table II, log ϵ = 4.15 for the thiol anion[20]). The changes in absorbance at 255 nm were the same within ±5% for elimination of F_5PhS^- (log ϵ = 4.11) from the fumaronitrile, acrylonitrile, and chloroacrylonitrile adducts, which also indicates that there is no significant elimination of chloride ion from the chloroacrylonitrile compound (the alkenes do not absorb significantly at 255 nm).

An upper limit of k_{OH} < 0.5 M^{-1} s^{-1} and no detectable catalysis by 0.08–1.0 M Tris buffer (30% base) were observed for elimination from the methanethiol adduct of fumaronitrile by initial rate measurements, after correction for a rapid initial reaction that was attributed to a contaminant (<2%, presumably from the imidate) and for hydrolysis of the DTNB that was used to monitor the release of methanethiol.

The elimination reactions generally followed first-order kinetics for >4 half-times in water (Figure 3B,D), but in D_2O the *p*-nitrothiophenol adducts of acrylonitrile and chloroacrylonitrile gave linear first-order kinetics only after an induction period (Figure 3A,C); similar behavior was observed for the thiophenol adduct of acrylonitrile (not shown). This behavior suggests initial exchange of deuterium into the adduct, followed by a slower reaction of the deuteriated compound.[21]

Linear first-order kinetics were observed for the thionitrobenzoate adduct of fumaronitrile and the pentafluorothiophenol adducts of fumaronitrile, acrylonitrile, and (at <0.1 M buffer)
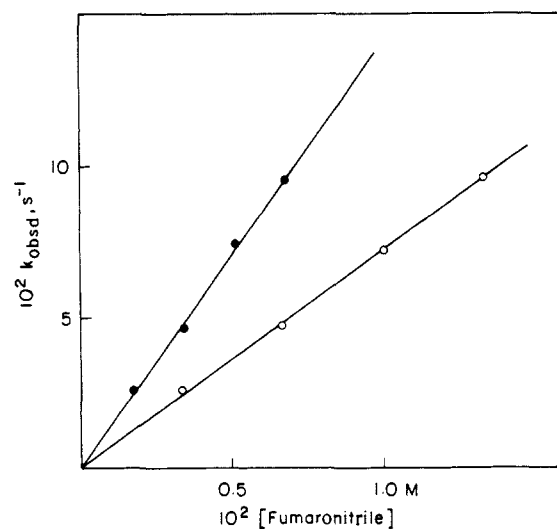
chloroacrylonitrile in both H_2O and D_2O. However, nonlinear kinetics were observed for the pentafluorothiophenol adduct of chloroacrylonitrile in H_2O and the corresponding deuteriated compound in D_2O at >0.1 M buffer; the reason for this was not determined.

Solvent deuterium isotope effects for elimination of the protium compounds catalyzed by lyoxide ion, k^H_{OD}/k^H_{OH}, are as follows: thionitrobenzoate adduct of fumaronitrile, 1.8; pentafluorothiophenol adducts of acrylonitrile, chloroacrylonitrile, and fumaronitrile, 1.7, 1.7, and 1.6, respectively; thiosalicylate adduct of fumaronitrile, 2.5. Except for the pentafluorothiophenol adduct of fumaronitrile, all of these values were obtained from parallel experiments in H_2O and D_2O on the same day (Table II).

Kinetics of Addition. The addition reactions were carried out under pseudo-first-order conditions with an excess of alkene at 25 °C and ionic strength 1 M, maintained with potassium chloride. For the addition of thionitrobenzoate dianion and thiosalicylate dianion to fumaronitrile, the solutions contained 8.3% Me_2SO (v/v). Rate constants were obtained either at a single alkene concentration, from the intercept at zero buffer concentration of plots of k_{obsd} against buffer concentration, or from the slopes of plots of k_{obsd} against alkene concentration, as shown in Figure 4 for reactions of fumaronitrile in H_2O and D_2O. Rate constants were usually measured at pH values at which the thiol was fully ionized; if not, they were corrected for the degree of ionization of the thiol. Rate constants obtained at different pH values agreed well except for the reaction of thiosalicylate dianion with fumaronitrile, which varied over ±10%. The results are summarized in Table III.

Parallel reactions in H_2O and D_2O were used to determine solvent deuterium isotope effects on the rate constants for addition, $k_n^{H_2O}/k_n^{D_2O}$ (Table III). For reactions in which the thiol was only partly neutralized, the correction for the proportion of thiol anion was obtained from the observed pD, the pK_a, and the solvent isotope effect for ionization of the thiol, calculated from the equation of Jencks and Salvesen.[22] The solvent isotope effects derived from these reactions are in good agreement with those obtained from reactions at values of pH and pD at which the thiol is completely ionized.

β-Proton Exchange. The rate constants, k_{obsd}, for exchange in D_2O (8.3% Me_2SO-d_6) of protons β to the leaving group were determined for the thiosalicylate adduct of acrylonitrile and the methanethiol adduct of fumaronitrile. Exchange was followed at 23.8 ± 1 °C by NMR for 1–2.5 half-lives. A typical first-order plot, for exchange of the methanethiol adduct of fumaronitrile, is shown in Figure 5. The term $I_\beta/0.67$ on the ordinate of Figure

(19) Stahl, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 4196.
(20) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451.
(21) More O'Ferrall, R. A.; Slae, S. *J. Chem. Soc. B* **1970**, 260.

(22) Jencks, W. P.; Salvesen, K. *J. Am. Chem. Soc.* **1971**, *93*, 4433.

Table II. Rate Constants for Elimination Reactions of β-Cyano Thioethers[a]

substrate	catalyst base[b] (pK_a)	buffer ratio (BH$^+$/B)	buffer concn range, M	$10^3 k_B$, M^{-1} s^{-1}	k_{OL}, M^{-1} s^{-1}	av^c $10^4 k_B$, M^{-1} s^{-1}	av^d k_{OH}, M^{-1} s^{-1}
F$_5$PhSCH$_2$CH$_2$CN	HO$^-$		0.08–0.2		0.18		0.18
	quinuclidine (11.45)[e]	1	0.052–0.55	<0.3[f]	0.19		
	ethanolamine (9.76)[g]	9	0.09–1.0	<0.004[f]	0.18		
		4	0.09–1.0	<0.003[f]	0.17		
	(D$_2$O)			<0.003[f]	0.28[h]		
	HO$^-$		0.02–0.08		0.17[h]		
	(D$_2$O)[e]				0.28[h]		
	quinuclidine (D$_2$O)	0.43	0.043–0.30	<0.1[f]	0.30		
(4-NO$_2$)PhSCH$_2$CH$_2$CN	HO$^-$		0.01–0.04		0.023		0.023
	HO^{-i}		0.11–0.40		0.026		
(3-CO$_2^-$,4-NO$_2$)PhSCH$_2$CH$_2$CN	HO$^-$		0.03–0.12		0.027		0.029
	piperidine (11.42)[j]		0.19–0.96	<0.04[f]	0.031		
PhSCH$_2$CH$_2$CN	HO$^-$		0.1–0.4		0.0027		0.0032[k]
	HO$^-$		0.1–0.4		0.0037		
	HO$^-$		0.2–0.08		0.0032		
(2-CO$_2^-$)PhSCH$_2$CH$_2$CN	HO^{-l}		0.02–0.067		0.0014		0.0012[k]
	HO^{-l}		0.01–0.036		0.0010[m]		
HOCH$_2$CH$_2$SCH$_2$CH$_2$CN[n]	HO$^-$		0.025–0.082		4.4 × 10^{-5}		4.4 × 10^{-5}
CH$_3$-$^+$NC$_5$H$_4$-2S-CH$_2$CH$_2$CN (MeOSO$_3^-$)	HO$^-$		0.006–0.024		2.9		2.69
	methylamine (10.88)[o]	9	0.10–1.0	0.90	3.0	9.0	
	propylamine (10.89)[j]	9	0.09–1.0	0.92	2.7	9.6	
		2.3	0.08–0.3	1.10	2.20		
		9	0.09–1.0	0.86	3.0		
	ethanolamine (9.76)[g]	4	0.08–1.0	0.105	2.6	1.0	
		2.3	0.08–0.63	0.095	2.7		
	diaminopropane (H$^+$) (9.24)[p]	9	0.09–0.35	0.050	2.7	0.50	
	cyanoethylamine (8.17)[q]	4	0.08–1.0	0.0030	2.5	0.03	
	Tris (8.37)[p]	4	0.09–1.0	0.0084	2.5	0.084	
	ethylenediamine (H$^+$) (7.42)[j]	4	0.08–0.36	0.00150	2.6	0.0140	
		4	0.08–0.36	0.0013	2.9		
(4-NO$_2$)PhSCH$_2$CH(Cl)CN	diaminopropane (H$^+$)	9	0.09–0.27		166		153
F$_5$PhSCH$_2$CH(Cl)CN	piperidine	20	0.01–0.10	1360	1410		1385
	diaminopropane (H$^+$)	9	0.09–0.35	<8[f]	1340		
	ethanolamine	9	0.09–1.0	24	1360		
	ethylenediamine (H$^+$)	9	0.11–0.34	<0.09[f]	1380		
	Tris (D$_2$O)[r]	20	0.14–1.0	<0.4[f]	1460		
				<0.2[f]	2400		
		4	0.08, 1.0	<0.5[f]	1370		
	(D$_2$O)[r]			<0.6[f]	2300		
		9	0.09, 1.0	<0.4[f]	1371		
	(D$_2$O)[r]			<0.4[f]	2400		
	(D$_2$O)[r]	9	0.09, 1.0	<0.6[f]	2400		
	ethanolamine (D$_2$O)[r,s]	9	0.09, 1.0	8.3	770		
F$_5$PhSCH(Ph)CH$_2$CN[t]	ethanolamine	9	0.10–1.0	0.076	1.19	0.76	1.19
F$_5$PhSCH(CN)CH$_2$CN	(2'-OH)-1,3-diaminopropane (H$^+$)	9	0.09–0.35	2.13	370	24	360
		5.7	0.06–0.35	2.5	350		
		5.7	0.087–0.34	2.5	400		
	ethylenediamine (H$^+$)	4	0.09–0.36	0.35	350	3.3	
		9	0.09–0.35	0.33	360		
		9	0.09–0.35	0.33	320		
		4	0.095–0.38	0.30	340		
	ethanolamine	20	0.14–0.96	22	370	230	
		9	0.09–1.0	20	360		
		1.5	0.07–1.0	24	360		
		9	0.09–1.0	23	370		
		4	0.09–1.0	25	310		
		1	0.13–0.94	24	360		
	cyanoethylamine	9	0.09–1.0	0.67	320	6.5	
		4	0.09–1.0	0.65	360		
		9	0.09–1.0	0.63	330		
	1,3-diaminopropane (H$^+$)	9	0.06–0.35	12.2	390	134[k]	
		5.7	0.06–0.35	12.2	370		
		9	0.07–0.35	15.8	380		
	(D$_2$O)	3	0.048–0.32	12.0	600[h]		
	(D$_2$O)	9	0.10–0.35	11.0	590[h]		
	serine methyl ester (7.28)[u]	4	0.09–1.0	0.145	340	1.45	
	propylamine	9	0.09–1.0	200	340	2000	
	Tris	5.7	0.09–1.0	1.34	400	11.0	
		4	0.09–1.0	1.0	430		
		9	0.09–1.0	1.07	360		
	methylamine	20	0.14–1.0	220	370	2150	
		9	0.09–1.0	210	420		
	v	20	0.14–1.0	180	310		

Table II (Continued)

substrate	catalyst base[b] (pK_a)	buffer ratio (BH+/B)	buffer concn range, M	$10^3 k_B$, M⁻¹ s⁻¹	k_{OL}, M⁻¹ s⁻¹	av[c] $10^4 k_B$, M⁻¹ s⁻¹	av[d] k_{OH}, M⁻¹ s⁻¹
	(D₂O)	20	0.12–1.0	210	700		
	MOPS⁻¹ (7.31)[p]	0.11	0.11–1.0	w	360		
	ammonia (9.51)[j]	20	0.16–1.0	0.57	400	5.7	
	hydrazine (8.20)[j]	9	0.08–0.35	0.77	350	7.7	
	piperazine (H⁺) (6.01)[j]	4	0.05–0.35	0.0115	360	0.115	
	morpholine (8.89)[j]	20	0.12–1.0	0.33	350	3.28	
(4-NO₂,3-CO₂⁻)PhSCH(CN)CH₂CN	piperidine	9	0.09–1.0	250	159	2500[x]	156
	ethanolamine	9	0.05–1.0	4.6	145	45	
		4	0.08–1.0	4.4	160		
	(2'-OH)-1,3-diaminopropane (H⁺) (8.40)[p]	9	0.05–0.35	0.54	160		
	ethylenediamine (H⁺)	9	0.05–0.34	0.074	153	0.74	
	morpholine	20	0.1–1.0	0.65	171	6.5[x]	
	1,3-diaminopropane (H⁺)	9	0.07–0.35	2.6	152	28	
		9	0.07–0.35	3.0	163		
	Tris	4	0.05–0.81	0.20	152	1.9[x]	
		9	0.14–1.0	0.18	146		
	(D₂O)			0.18	260		
(4-NO₂)PhSCH(CN)CH₂CN	ethanolamine	4	0.08–1.0	4.4	164	44	164
PhSCH(CN)CH₂CN	3'-OH-quinuclidine (10.02)[e]	0.43	0.03–0.23	f	35		36
	ethanolamine	1	0.03–0.14	f	40		
	Tris	9	0.09–1.0	f	34		
(2-CO₂⁻)-PhSCH(CN)CH₂CN	3'-OH-quinuclidine	1	0.013–0.25	f	21		21
	Tris[z]	9	0.09–1.0	f	22		
	Tris[z]	9	0.09–1.0	f	21		
	(D₂O)[z]			f	52		

[a] In water with 8.3% Me₂SO (v/v) (unless otherwise stated), 1 M ionic strength maintained with potassium chloride, 25 °C. [b] Runs in D₂O are denoted by "(D₂O)". Parallel runs, with the same catalyst species in D₂O and H₂O, are listed in pairs. [c] Average value for all runs involving the same catalyst ± 10% unless otherwise stated. [d] Average value for all experiments involving the same substrate ± 10% unless otherwise stated. [e] Reference 28. [f] Less than a 33% increase in k_{obsd} at highest buffer concentration based on the minimum value of k_{obsd} extrapolated to zero buffer concentration. [g] Page, M. I.; Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 8818. [h] Good first-order kinetics to more than 4 half-lives. [i] Solutions were 6% by volume Me₂SO. [j] Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622. [k] ±15%. [l] Based on initial rates obtained by quenching aliquots as a function of time and reacting with DTNB. [m] ±30%. [n] 0% Me₂SO. [o] Jencks, W. P.; Gilchrist, M., unpublished. [p] Based on the average value calculated from the observed pH at known buffer ratio. [q] Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436. [r] Linear first-order kinetics to more than 4 half-lives for runs at lowest buffer concentration. Nonlinear first-order kinetics at high buffer concentration (see text). Reported rate constants based on the first half-life. [s] Substrate contains one deuterium atom in the position β to the leaving group. [t] Based on initial rates with 5-cm path length cuvettes. [u] Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 572. [v] 23 °C. The value of k_{OL} was calculated based on a pH measurement at 25 °C. [w] There was a 15% decrease in k_{obsd} at the highest buffer concentration. [x] ±20%. [y] 2.44 M ionic strength at highest buffer concentration. [z] Under initial rate conditions with DTNB in the reaction mixture (see text).
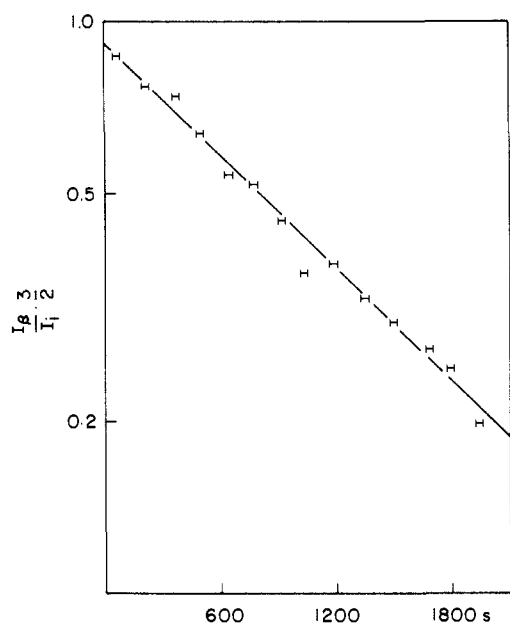

Figure 5. First-order plot for exchange of the β protons of the methanethiol adduct of fumaronitrile in D₂O at 23.8 °C, μ = 1 M (KCl), 8.3% [²H₆]Me₂SO (v/v), [²H₅]methylamine buffer, BD⁺/B = 9. The values of $I_β$ and I_i are the integrations of the β protons and the internal standard methyl protons, respectively.

5 is the number of integration units for the two β protons normalized by ²/₃ the number of integration units for nonexchanging methyl protons. The intercept at zero time is <1.0 because of a proton signal from contaminating ¹H in the [²H₃]methylamine buffer that overlaps the methyl proton signal from the methanethiol adduct.

A value of $k_{OD_{ex}}$ = 20 ± 3 M⁻¹ s⁻¹ for the methanethiol adduct of fumaronitrile was obtained from the observed pD and measurements of k_{ex} at eight buffer concentrations by extrapolation to zero buffer concentration (here and elsewhere the range refers to ±1 SD). A value of $k_{OD_{ex}}$ = 0.0065 ± 0.0005 M⁻¹ s⁻¹ for the thiosalicylate adduct of acrylonitrile was obtained from measurements at three concentrations of OD⁻. A limit of <1.7 × 10⁻⁷ s⁻¹ for pH-independent exchange was calculated from <3% observed exchange after 50 h at 25 °C.

Product Isotope Effects. Deuterium isotope effects for the addition reaction were determined by reaction in H₂O–D₂O mixtures and analysis of protium or deuterium in the β position of the isolated products by NMR. The reactions with acrylonitrile were anayzed by deuterium NMR by comparison with product formed in 99.8% D₂O, as described in the Experimental Section. Most reactions with fumaronitrile were analyzed by proton NMR after addition to [²H₂]fumaronitrile. The product isotope effects for reactions in the absence of buffer are shown in Table IV.

The product isotope effects for addition to acrylonitrile are k_H/k_D = 3.1 ± 0.8. The variation in different determinations, which is largest for the thioacetate reactions, probably arises from the determination of product concentrations by proton NMR. Product isolation was easier for the β-mercaptoethanol adduct, which gave reproducible values of k_H/k_D = 2.8 ± 0.3 in 12 determinations at a solvent isotope ratio of H/D = 1.0. The isotope effects are very similar for addition to fumaronitrile. The data

Table III. Rate Constants for Addition Reactions to Acrylonitrile and Fumaronitrile[a]

nucleophile	electrophile	buffer acid	solvent	buffer ratio HA/A⁻	electrophile, M	buffer, M	$10^4 k_{obsd}$, s⁻¹	k_n[b] M⁻¹ s⁻¹	$k_n^{H_2O}/k_n^{D_2O}$
CH_3COS^-	CH_2CHCN	methoxyacetic acid	H_2O[c]	4	0.41	0.044	0.38	$2.6 \times 10^{-4\ d}$	
						0.088	0.36		
						0.132	0.37		
						0.176	0.36		
		methoxyacetic acid	H_2O[c]	0.25	0.16	0.26	0.34		
					0.28		0.55	$2.4 \times 10^{-4\ d}$	
					0.41		0.87		
					0.53		1.12		
									1.2
			D_2O[c]	0.25	0.16	0.24	0.30		
					0.28		0.49	$2.0 \times 10^{-4\ f}$	
					0.41		0.71		
					0.53		0.96		
$HOCH_2CH_2S^-$	NCCHCHCN	trifluoroethanol	H_2O[c]	9	0.0010	0.10	13.1		
					0.0015		20	1.4	
					0.0020		28		
					0.0025		35		
		trifluoroethanol	H_2O[c]	9	0.0013	0.10	18.0	1.51	
					0.0026		37		1.1
			D_2O[c]	9	0.0013	0.10	18.1	1.46	
					0.0026		37		
		trifluoroethanol	H_2O[c]	9	0.0013	0.3	17.0		
					0.0020		26.0	1.5	
					0.0028		40		
					0.0036		50		1.1
			D_2O[c]	9	0.0013	0.3	18.0		
					0.0020		27	1.4	
					0.0028		41		
					0.0036		50		
$(3\text{-}CO_2^-, 4\text{-}NO_2)C_6H_3S^-$	NCCHCHCN	piperazine dication	H_2O[e]	20	0.07	0.055	5.2		
						0.11	5.4	$1.0 \times 10^{-3\ d}$	
						0.22	5.6		
						0.34	5.8		
									3.8
			D_2O[e]	20	0.07	0.055	1.7		
						0.11	2.0	$2.7 \times 10^{-4\ f}$	
						0.22	2.4		
						0.34	2.6		
$(3\text{-}CO_2^-, 4\text{-}NO_2)C_6H_3S^-$	NCCHCHCN	ethylenediamine dication	H_2O[e]	20	0.082	0.144	8.4		
						0.21	8.7	9.5×10^{-3}	
						0.27	9.0		
						0.33	9.2		4.0
			D_2O[e]	20	0.082	0.144	2.7		
						0.21	3.1	2.4×10^{-3}	
						0.27	3.4		
						0.33	3.7		
$(2\text{-}CO_2^-)C_6H_4S^-$	NCCHCHCN	Tris cation	H_2O[e]	1.5	0.0029	0.072	210		
					0.0039		270		
					0.0049		360		
					0.0059		400	11.8[d]	
					0.0069		480		
					0.0078		560		
					0.0088		620		
					0.0098		720		
		Tris cation	H_2O[e]	1	0.0059	0.20	470		
					0.0078		610	11.1[d]	
					0.0098		790		1.9
			D_2O[e]	1	0.0039		190		
					0.0059		280	5.9[f]	
					0.0079		380		
					0.0098		480		
$(2\text{-}CO_2^-)C_6H_4S^-$	NCCHCHCN	potassium bicarbonate	H_2O[e]	1	0.0017	0.152	250		
					0.0034		460		
					0.0051		740		
					0.0068		960	14.2	
					0.0033		500		
					0.0050		770		
					0.0067		960		
					0.0083		1270		2.0
			D_2O[e]	1	0.0033		260		
					0.0067		470		
					0.010		720	7.0	
					0.013		970		
					0.010		750		
					0.015		1160		
					0.020		1370		

[a] 25 °C, 1 M ionic strength (KCl). [b] ±10%. [c] No added Me₂SO. [d] Calculated for the thiol anion. [e] 8.3% Me₂SO (v/v). [f] Calculated for the thiol anion by using the pK_a for the thiol in D₂O.[22]

Table IV. Product Isotope Effects (PIE) for Addition Reactions in the Absence of Buffers[a]

nucleophile	electrophile	²H NMR chemical shift rel to solvent deuterons (solvent)[b]	¹H NMR chemical shift rel to TMS (solvent)	H/D ratio of water	apparent pH	no. of spectra integrated	H/D ratio of product	PIE[c]	av of PIE determined at one solvent H/D ratio
⁻O₂CCH₂S⁻	CH₂CHCN	−1.93 (D₂O)		0.1	11.6	1	0.37	3.3[d]	
				0.45	11.6	1	1.37	3.1[e]	
				0.92	11.6	1	2.14	2.3[f]	
CH₃COS⁻	CH₂CHCN	+0.55 ([²H₆]Me₂SO)		0.12	7.7	4	0.31	2.6[g]	
				0.43	7.7	3	1.0	2.4[g]	2.7
				0.42	7.2 ± 0.8	3	1.27	3.0	
				0.98	7.2 ± 0.8	3	3.7	3.9[f]	3.6
				1.0	7.7	3	3.4	3.4	
HOCH₂CH₂S⁻	CH₂CHCN	−1.82 (D₂O) +0.33 (Me₂SO)		0.12	11.2	4	0.35	2.9[f]	
				0.43	11.2	4	1.47	3.4	
				1.0	11.2	4	3.6	3.6	2.8
				1.0	11.3	4	2.5	2.5	
				1.0	11.5	6	3.2	3.2	
				1.0	11.6	5	3.0	3.0	
				1.0	11.7	4	2.7	2.7	
				1.0	11.2	6	3.0	3.0	
				1.0	11.2	4	2.6	2.6	
				1.0	11.2	1	2.5	2.5	
				1.0	7.0[h]	5	2.7	2.7	
				1.0	8.5[h]	6	2.8	2.8	
				1.0	7.0[h,i]	4	2.7	2.7	
				1.0	8.5[h,i]	2	2.7	2.7	
CH₃COS⁻	NCCHCHCN		3.06 (CDCl₃)	1.0	5.8	1	2.8	2.8	
CH₃COS⁻	NCCDCDCN		3.06 (CDCl₃)	0.25	5.5	1	0.75	3.0	3.2
				0.25	5.5	1	0.85	3.4	
				0.43	5.5	1	1.27	3.0[g]	
				0.43	1.6[j]	1	1.41	3.3[g]	3.2
				0.43	5.5	1	1.39	3.2	
				0.43	5.5[k]	1	1.48	3.4[g]	
(2-CO₂⁻)C₆H₄S⁻	NCCDCDCN		3.22 ([²H₆]acetone)	0.43	7.0	10	1.39	3.2	
				0.43	7.0	10	1.40	3.3	3.2
				0.43	7.0	10	1.27	3.0	

[a] Reactions were carried out at room temperature. [b] A minus sign means the signal is upfield relative to solvent deuterons, a plus sign means the signal is downfield relative to solvent deuterons. [c] ±10% based on mean and standard deviation of multiple integrations or the maximum estimated error in a single determination unless otherwise noted. [d] ±30%. [e] ±25%. [f] ±20%. [g] ±15%. [h] Thiol added last. The reaction mix was extracted twice with 100 mL of ether; the ether phase was extracted twice with 25 mL of 0.5 M potassium carbonate buffer, pH 10. [i] 3 M KCl. [j] 5% thiol anion.

Table V. Product Isotope Effects (PIE) for Addition in the Presence of Buffers[a]

nucleophile	electrophile	buffer acid (%)	H/D ratio of water	buffer acid, M	apparent pH	no. of spectra integrated	H/D ratio of product	PIE[b]
HOCH₂CH₂S⁻	CH₂CHCN	ethylenediamine dication, (95)	1.0[c]	0	11.2	6	3.0	3.0
				0.11	6.3	3	3.5	3.5
				0.23		3	3.4	3.4
				0.35		4	2.9	2.9
				0.47		4	3.0	3.0
HOCH₂CH₂S⁻	CH₂CHCN	DABCO monocation (95)	1.0	0	11.7	4	2.7	2.7
				0.21	7.6	4	2.7	2.7
				0.42	7.1	4	2.5	2.5
				0.7	7.2	4	2.9	2.9
HOCH₂CH₂S⁻	CH₂CHCN	ammonium (95)	1.0	0	11.5	6	3.1	3.1[d]
				1.26	8.0	4	3.2	3.2[d]
CH₃COS⁻	CH₂CHCN	DABCO dication (95)	1.0	0	5.8	4	2.2	2.2
				1.2		4	2.2	2.2
				2.2		4	2.0	2.0[d]
CH₃COS⁻	NCCDCDCN	DABCO dication (95)	0.43	0	5.5	1	1.39	3.2[e]
				0.5	2.0	1	1.40	3.3[e]
				1.0	1.6	1	1.31	3.0[d]

[a] Reactions were carried out at room temperature. The pH was controlled with a pH-stat in unbuffered solutions. Ionic strength was not held constant. [b] ±10% based mean and standard deviation of multiple integrations or the maximum estimated error in a single determination. [c] 99.8% D₂O reaction run at pH 11.5. [d] ±20%. [e] ±15%.

are more accurate for these reactions because of the use of an internal standard for NMR analysis of the proton signal. The agreement of the results in the pH range 7.0–11.6 for mercaptoethanol and acrylonitrile and the pH range 1.6–5.5 for thioacetate and fumaronitrile shows that base-catalyzed hydron exchange does not affect the observed product ratios. Furthermore, no deuterium incorporation into the mercaptoacetic acid adduct of acrylonitrile was observed by deuterium NMR after 10 min

in D₂O at pD 12.2. Added buffers gave no significant effect on the product isotope effects (Table V).

Discussion

Proof That a Carbanion Intermediate Is Formed on the Reaction Pathway. The observed second-order rate constants for exchange of the protons β to the leaving group catalyzed by OD⁻ in D₂O are 20 M⁻¹ s⁻¹ for the methanethiol adduct of fumaronitrile, **3**,

and 6.5×10^{-3} M^{-1} s^{-1} for the thiosalicylate adduct of acrylonitrile, **1**. These rate constants are larger than those for elimination catalyzed by hydroxide ion, by factors of >40 and 5, respectively. The differences are much larger than the factor of ~2 that could arise from the difference in the basicity of OD^- in D_2O compared with OH^- in H_2O. Still larger factors have been observed for the thiophenol adduct of acrylonitrile in the presence of ethoxide ion.[23]

Proton exchange that is faster than elimination is also demonstrated by the nonlinear first-order kinetics for elimination of the thiophenol adduct of acrylonitrile and the *p*-nitrothiophenol adduct of chloroacrylonitrile in D_2O, shown in Figure 3, parts A and C, respectively. Elimination of the β-protium adduct proceeds rapidly in the initial phase with concurrent exchange of deuterium, followed by slower elimination of the deuterium-containing adduct after exchange has occurred. Elimination is faster than exchange for the pentafluorothiophenol adducts, which contain a better leaving group and show strictly first-order kinetics for elimination with larger rate constants (Figure 3, parts B and D). Nonlinear first-order kinetics in E1cB(rev) reactions under similar conditions have been observed previously and were analyzed in detail by More O'Ferrall and Slae.[21]

Concurrent exchange and elimination are consistent with an elimination reaction that proceeds through a stepwise E1cB mechanism (eq 8, k_1, k_{-1}, and k_2); however, they could also arise from separate but concurrent exchange and concerted elimination reactions (eq 8, k_1, k_{-1}, and k_c).[13,21]

$$(8)$$
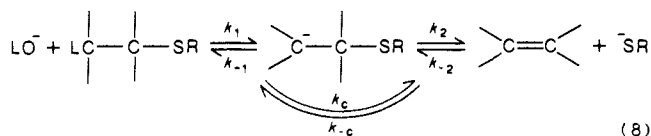
The observed difference between the small solvent kinetic isotope effects and larger solvent discrimination isotope effects for thiol anion addition to the alkene demonstrates that the reaction occurs in two steps, through a carbanion intermediate, with different isotope effects for the addition and the protonation steps, k_{-2} and k_{-1} in eq 8. The small kinetic isotope effects of $k_n^{HOH}/k_n^{DOD} = 2.0$ for the addition of thiosalicylate anion to give **3** and 1.1–1.2 for addition of β-mercaptoethanol and thioacetic acid anions to give **1** (Table III) show that the addition step to form the carbanion is largely or entirely rate-limiting. The product discrimination isotope effects of $k_H/k_D = 3.2, 2.8,$ and 3.1 ± 0.6, respectively, in these reactions (Table IV) show that there is a significant isotope effect for proton transfer to the carbanion in a subsequent step. These results are consistent with an E1cB mechanism that involves initial thiol addition (k_{-2}, eq 8), which has little or no isotope effect, followed by protonation of a carbanion intermediate, which has a sufficient lifetime to discriminate between solvent protium and deuterium (k_{-1}). The solvent kinetic isotope effect of 2.0 for the addition of thiosalicylate dianion to fumaronitrile indicates that the addition and protonation steps are both partly rate-limiting ($k_{-1} \sim k_2$, eq 8). The corresponding elimination reactions must also proceed through the same carbanion intermediate in a stepwise, E1cB mechanism (k_1 and k_2, eq 8), according to the principle of microscopic reversibility. A concerted addition reaction (k_{-c}, eq 8) is expected to show similar or identical kinetic and product isotope effects, depending on the magnitude of secondary solvent isotope effects.

It is unlikely that the kinetic solvent isotope effects of $k_n^{HOH}/k_n^{DOD} = 1.1$–1.2 represent cancellation of secondary solvent isotope effects on thiol anion addition and a primary isotope effect on protonation in a concerted reaction. Although there is evidence[22] for significant destabilization of RS^- in D_2O compared with H_2O, this solvent effect is small compared with the solvent isotope effects of ~3 for protonation, especially for the weakly basic anion of thioacetic acid. Furthermore, the similar values of the kinetic solvent isotope effect of $k_n^{HOH}/k_n^{DOD} = 3.8$–4.0 for the rate of addition of thionitrobenzoate dianion to fumaronitrile,

with rate-limiting protonation (Table III), and the primary kinetic isotope effect of $k_{OH}^H/k_{OH}^D = 4.2$ for elimination of the thionitrobenzoate adduct of fumaronitrile catalyzed by hydroxide ion, the same reaction in the reverse direction,[24] show that there is not a large secondary solvent deuterium isotope effect for the addition of this thiol anion.

Change in Rate-Limiting Step. Effect of the Leaving Group. A decrease in the pK_a of the leaving group is expected to facilitate leaving-group departure more than proton removal from the β-carbon atom. This will decrease the k_{-1}/k_2 ratio and tend to cause a change in the rate-limiting step from leaving-group departure to proton removal in a stepwise E1cB reaction mechanism; in the addition direction it can cause a change in the rate-limiting step from nucleophilic attack to protonation of the carbanion intermediate. Three different experimental consequences of this change in rate-limiting step with changing pK_a of the thiol were observed in these reactions.

(1) The change in rate-limiting step is apparent in the linear and biphasic first-order elimination reactions in D_2O of the chloroacrylonitrile and acrylonitrile adducts with different leaving groups, shown in Figure 3. The biphasic kinetics with thiophenol and *p*-nitrothiophenol leaving groups ($pK_a = 6.4$ and 4.5, Figure 3A,C) shows that leaving-group expulsion is partly rate-limiting so that deuterium exchanges into the reactant and the rate decreases, as noted above. The increase in leaving ability of the pentafluorothiophenolate anion ($pK_a = 2.7$) decreases the k_{-1}/k_2 ratio sufficiently to suppress exchange and give linear first-order kinetics in both systems (Figure 3, parts B and D).

(2) The increase in the solvent kinetic isotope effect from $k_n^{HOH}/k_n^{DOD} = 2.0$ to 3.9 in the addition reaction with fumaronitrile, as the nucleophile is changed from thiosalicylate dianion ($pK_a = 8.0$) to thionitrobenzoate dianion ($pK_a = 4.5$), suggests that protonation is more rate-limiting with the less basic nucleophile, which gives a smaller k_{-1}/k_2 ratio. The intrinsic isotope effect is not expected to differ significantly for the carbanion intermediates in these two reactions. However, for addition to acrylonitrile there is no significant solvent kinetic isotope effect for the addition of the anions of either mercaptoethanol ($pK = 9.6$) or thioacetic acid ($pK = 3.2$)[22] (Table III). This shows that the change in rate-limiting step occurs with more basic nucleophiles for the fumaronitrile than for the acrylonitrile reactions.

(3) The increase in the extent to which proton transfer is rate limiting causes an increase in the effect of buffers on the observed rate constants. Figure 2A shows that in the acrylonitrile series there is roughly twice as much buffer catalysis with the *N*-methyl-2-mercaptopyridinium ion leaving group ($pK_a \sim -1$) as with the pentafluorothiophenolate leaving group ($pK_a = 2.7$). In the fumaronitrile series (Figure 2B) there is a progressive increase in the importance of catalysis with the thiophenolate, thionitrobenzoate, and pentafluorothiophenolate leaving groups ($pK_a = 6.4, 4.5,$ and 2.7), respectively. Again, the proton transfer becomes kinetically significant with less basic leaving groups for the fumaronitrile compared with the acrylonitrile reactions.

The Nature of the Carbanion Intermediate and the Transition States for Its Reactions. The Brønsted plot in Figure 6, for general base catalysis of the elimination of the pentafluorothiophenol adduct of fumaronitrile, shows a slope of β = 0.90 for catalysis by primary amines (circles) and negative deviations for catalysis by hydroxide ion and ammonia. This large slope indicates a large amount of proton transfer in a transition state that closely resembles the carbanion intermediate. Similar values have been observed for base catalysis of carbanion formation from other cyanocarbon acids, including β = 0.93 and 0.94 for 1,4-dicyano-2-butene catalyzed by amines and phenolate ions[25] and β = 0.98 for *tert*-butylmalononitrile catalyzed by substituted acetates.[9]

The secondary lyoxide ion isotope effects of $k^H_{OD}/k^H_{OH} = 1.6$–1.8 for elimination reactions in which proton abstraction is

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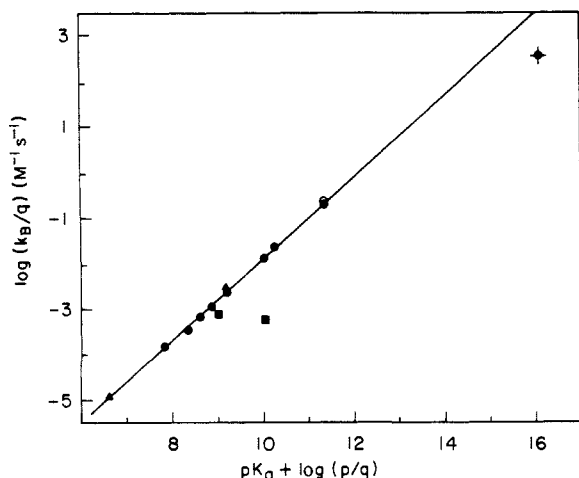(25) Walters, E. A.; Long, F. A. *J. Am. Chem. Soc.* **1969**, *91*, 3733.

Elimination Reactions of β-Cyano Thioethers

J. Am. Chem. Soc., Vol. 110, No. 15, 1988 5085

Figure 6. Statistically corrected Brønsted plot for catalysis of elimination from the pentafluorothiophenol adduct of fumaronitrile by different bases: (-●-), hydroxide ion; (●), primary amines; (▲), secondary amines; (■), hydrazine and ammonia. The solid line of slope 0.90 was calculated by least squares from the rate constants for primary amine catalysts.

largely rate-limiting (Results) correspond to β = 0.6 according to the relationship k_{OD}/k_{OH} = $(2.4)^{\beta}$.[26] The difference between this value and the observed Brønsted slope of β = 0.9 means either that this relationship underestimates β or that the negative deviation of hydroxide ion from the Brønsted plot reflects curvature of the Brønsted correlation, with a decrease in β for basic catalysts; similar deviations have been observed in other systems.[26] The larger isotope effect of k^{H}_{OD}/k^{H}_{OH} = 2.5 for elimination from the thiosalicylate adduct of fumaronitrile can be accounted for, in part, by the fact that leaving group departure is partly rate-limiting for this compound, with complete transfer of the proton to OL⁻ in the transition state for this step.

The Brønsted-type plot of log k against the pK_a of the leaving group for elimination reactions of fumaronitrile adducts catalyzed by hydroxide ion has a slope of β_{lg} = -0.25 for thiol anions of $pK_a \le 8$, shown by the triangles in Figure 7. This is of the magnitude expected for the development of a negative charge two atoms away from the normal site of ionization of the leaving group[27] and is close to the value observed for the deprotonation step in other E1cB(irrev) reactions, including β_{lg} = -0.18 for *N*-[2-(*p*-nitrophenyl)ethyl]quinuclidinium ions[28] and β_{lg} = -0.15 for (benzoyloxy)butan-2-ones.[29] The slightly more negative value for the fumaronitrile adducts may be accounted for by the change to partially rate-limiting leaving group expulsion with the more basic thiol anions, as noted above. A value of β_{lg} = -0.19 is obtained from the rate constants for the three most acidic leaving groups in this series.

Figure 7 shows large negative values of β_{lg} = -0.54 for the elimination reactions of acrylonitrile adducts, with leaving groups in the range pK_a = 2-10, and β_{lg} = -0.52 for two chloroacrylonitrile adducts. This shows that leaving-group expulsion is largely rate-limiting for the acrylonitrile adducts and is consistent with the conclusion that the ratio k_{-1}/k_2 is larger for the acrylonitrile and chloroacrylonitrile than for the fumaronitrile derivatives. There is a suggestion of downward curvature with decreasing pK_a in the correlation for the acrylonitrile compounds, which is expected as the leaving group becomes better and k_2 increases. The positive deviation of the rate constant for thiosalicylate expulsion may reflect an abnormally high pK_a that is caused by intramolecular hydrogen bonding.[30] These values of β_{lg} agree well
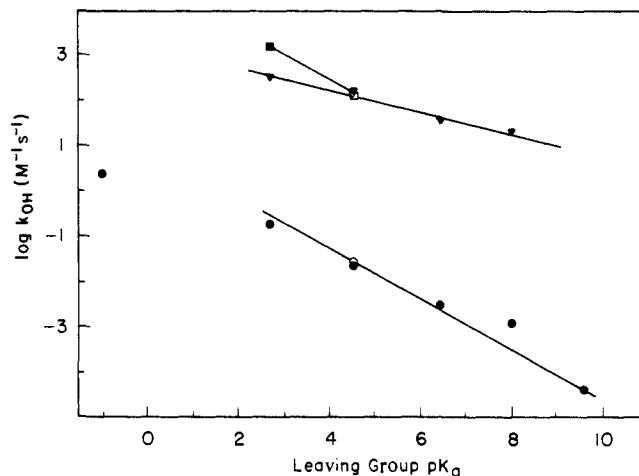

Figure 7. Dependence of the second-order rate constants for hydroxide ion catalyzed elimination on the pK_a of the leaving group for adducts of acrylonitrile (●), fumaronitrile (▼), and chloroacrylonitrile (■). The lines are calculated by least squares for the *p*-nitrothiophenolate (PNTP), thionitrobenzoate (TNB), thiophenolate, and β-mercaptoethanol anion leaving groups in the acrylonitrile series, the pentafluorothiophenolate (PF), PNTP, TNB, and thiosalicylate ion leaving groups in the fumaronitrile series, and the PF and PNTP leaving groups in the chloroacrylonitrile series. The slopes are β_{lg} = -0.54, -0.25, and -0.52, respectively.

with the value of β_{nuc} = 0.45 for the addition of substituted thiol anions to acrylonitrile, in the reverse direction.[12a]

These structure–reactivity correlations suggest that there is a considerable amount of C–S bond breaking and transfer of negative charge to the leaving group in the transition state for the k_2 step, perhaps ~50%, so that there is less charge on the β-carbon atom than in the transition state for proton transfer, which closely resembles the carbanion intermediate.

The different kinetic and product isotope effects in the direction of thiol anion addition establish a stepwise reaction mechanism (in both directions) when the k_2 step is rate-limiting. However, the possibility must be considered that there is a change to a concerted mechanism when the k_1 step becomes rate-limiting. The small value of $-\beta_{lg}$ suggests that there is little or no cleavage of the C–S bond when k_1 is rate-limiting, but it does not exclude an uncoupled concerted mechanism in which there is little or no C–S bond cleavage in the transition state.[2] However, the appearance of a concerted reaction mechanism with good leaving groups would represent the appearance of a new reaction pathway and an additional reaction pathway should give rate constants that show positive deviations from structure–reactivity correlations for the stepwise mechanism. Figure 7 shows that there is no such positive deviation for good leaving groups in the acrylonitrile series; if anything, there is a negative deviation that may be explained by a change in rate-limiting step to proton abstraction, as described above.

Furthermore, if there were an uncoupled concerted mechanism it is likely that it would be enforced by the absence of a significant barrier for expulsion of the leaving group from the carbanion; if the rate constant for cleavage for the carbanion is > 2×10^{13} s⁻¹ the frequency for a C–S stretching vibration,[31] there is no significant restoring force that prevents C–S bond cleavage and the carbanion is not an intermediate chemical species. However, calculated upper limits for k_2 of $<10^{13}$ and $<2.6 \times 10^{12}$ s⁻¹ for the pentafluorothiophenol and thionitrobenzoate adducts of fumaronitrile, respectively, indicate that this is not the case and that the reaction does not proceed through an enforced concerted mechanism. These limits were calculated from values of $k_{-1} \le$

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(31) The C–S bond vibration frequency is between 570 and 710 cm⁻¹ for alkyl sulfides. With a value of 3 × 10¹⁰ cm/s for the speed of light, the rate constant for a single vibration is about 2 × 10¹³ s⁻¹. Sheppard, N. *Trans. Faraday Soc.* **1950**, *46*, 429.
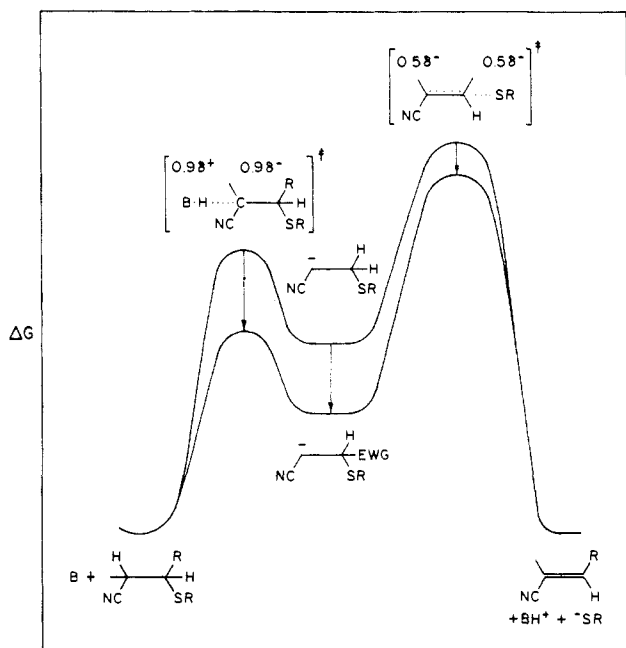
Figure 8. Predicted effects of an electron-withdrawing group (EWG) on the energies of the transition states for proton abstraction and leaving group expulsion, neglecting the effect on k_2 of conjugation with the EWG. The numbers refer to Brønsted β values of 0.90 for base catalysis and $\beta_{lg} = -0.54$ for leaving-group expulsion.

8.8×10^{11} s^{-1}, $\beta_{lg} = -0.54 - (-0.19) = -0.35$ for k_2, and k_2/k_{-1} ≤ 0.18 for the thiosalicylate leaving group; this value was obtained from the difference between the maximum solvent isotope effect on the addition reaction of $k_n^{HOH}/k_n^{DOD} = 2.2$ (Table III) and a minimum primary isotope effect for proton transfer of k^H/k^D = 4.5.[32,33]

(32) A value of $k_2/k_{-1}^{HOL} = 0.53$ was calculated from the equation k_n^{LOL} = $k_2k_{-1}^{LOL}/(k_2 + k_{-1}^{LOL})$ (see eq 8), $k_n^{HOH}/k_n^{DOD} \leq 2.2$ for the addition of thiosalicylate dianion to fumaronitrile, and a minimum isotope effect on k_{-1} of $k_{-1}^{HOL}/k_{-1}^{DOL} = 4.5$, from the minimum observed isotope effect on the elimination of the pentafluorothiophenol adduct catalyzed by hydroxide ion[24] and an equilibrium isotope effect of 1.0.[34] The value of k_2/k_{-1}^{HOL} is taken as 0.53/3 = 0.18 for a normal thiol anion leaving group of pK_a = 8. The factor of 3 is used because the thiosalicylate dianion is a better leaving group by a factor of 3 than predicted for its pK_a. A value of β_{lg} for k_2, $\beta(k_2) = -0.35$, obtained from $\beta_{lg} = \beta(k_2) + \beta(k_1)$ and the observed values of $\beta_{lg} = -0.54$ and $\beta(k_1) = -0.19$ (see text), gives $k_2/k_{-1}^{HOL} = 12.8$ for the carbanion of the pentafluorothiophenol adduct. An upper limit for k_2 was obtained from an upper limit for k_{-1}, from the calculated value of k_2/k_{-1}. An upper limit of $k_{-1} < 8.8 \times 10^{11}$ s^{-1} was obtained from a model in which there are two solvent molecules associated with the carbanion that enter the bulk solvent with the rate constant k_s.[24] According to this model, the maximum primary isotope effect of $k_{-1}^{HOL}/k_{-1}^{DOL} = 4.5$ and a minimum product isotope effect of 2.5 give $k_{-1}^{HOL}/k_s < 8.8$. A value of $k_s = 1 \times 10^{11}$ s^{-1} was obtained from the dielectric relaxation constant for water at 25 °C. This gives $k_2 < 10^{13}$ s^{-1}. The value $k_2 < 2.6 \times 10^{12}$ s^{-1} for the thionitrobenzoate leaving group was calculated by the same procedure. A similar model for the carbanion using a single hydrogen bond yields smaller values of k_2. Smaller values for the primary isotope effects also yield smaller values of k_2. Thus, while it is true that the use of the value of $k_{-1}^{HOL}/k_{-1}^{DOL} < 4.5$ assumes a stepwise mechanism for elimination of the pentafluorothiophenol adduct of fumaronitrile, the smaller primary isotope effects reported for hydrogen ion exchange of cyanocarbon acids will give smaller values of k_2.

(33) 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). 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., Ed.; Academic: New York, 1980; Vol. 64, p 104).

The conclusion that these reactions proceed through a stepwise, E1cB mechanism with a carbanion intermediate means that it is unlikely that β-carbonyl or nitro-activated compounds with similar leaving groups will undergo elimination by a concerted mechanism. The intrinsic barriers for both proton transfer and elimination–addition reactions are larger for carbonyl and nitro than for cyano-activated compounds,[34] so that it is virtually certain that there will be significant barriers for both steps of the elimination reactions of all of these compounds if there is a barrier for the corresponding cyano-activated compound.

Change in Rate-Limiting Step. Effect of α-Substituents. Compared with acrylonitrile derivatives, adducts of fumaronitrile show (1) a much smaller dependence of the rate constant for elimination on the pK_a of the leaving group (Figure 7), (2) more buffer catalysis of elimination for a given leaving group (Table II, Figure 2), and (3) larger kinetic isotope effects for the addition reaction in D$_2$O for a given pK_a of the nucleophile (Table III). These results show that the proton-transfer step is more likely to be rate-limiting for the fumaronitrile compared with the acrylonitrile reactions, because the ratio k_{-1}/k_2 is smaller for a given nucleophile or leaving group, and the change in rate-limiting step occurs with leaving groups of higher pK_a.

We had expected the opposite result, as illustrated in the energy diagram of Figure 8. The electron-withdrawing CN group will stabilize the carbanion intermediate, which is consistent with the fact that both fumaronitrile and chloroacrylonitrile derivatives ionize to the carbanion much faster than the corresponding acrylonitrile derivatives (Figure 7). The value of $\beta = 0.9$ for proton removal and the β_{lg} value of -0.5 for leaving group expulsion suggest that the transition state for protonation closely resembles the carbanion, while there is considerable transfer of charge from the carbanion to the leaving thiolate anion in the transition state for leaving group expulsion. Thus, it was expected that in the reverse direction stabilization of the carbanion by an electron-withdrawing substituent will have little effect on the barrier for protonation, but will increase the barrier for leaving group expulsion, as shown in Figure 8. This would give an increase in the k_{-1}/k_2 ratio, which is opposite to what is observed.

We conclude that the α-CN substituent specifically stabilizes the transition state for leaving-group expulsion by conjugation with the developing double bond of the fumaronitrile product and that this stabilization is large enough to overcome the expected increase in the k_{-1}/k_2 ratio from its electron-withdrawing effect. An α-phenyl substituent is known to decrease the k_{-1}/k_2 ratio and increase the observed rate constant for E1cB(rev) reactions with rate-limiting expulsion of the leaving group by factors of up to 40-fold, presumably by conjugation with the developing double bond. The α-phenyl group of the thiophenolate adduct of cinnamonitrile increases the observed rate constant 13-fold and the k_2/k_{-1} ratio by 7-fold, compared with the corresponding acrylonitrile adduct.[35]

This conclusion is consistent with the similar values of β_{lg} for chloroacrylonitrile and acrylonitrile adducts (Figure 7), although the chloroacrylonitrile and fumaronitrile derivatives show similar rate increases of $\sim 10^4$ compared with the corresponding acrylonitrile compounds. Chloride causes a large increase in acidity of the carbon acid that increases the reaction rate, but resonance stabilization from chloride is expected to be much smaller than from the cyano substituent[36] so that leaving group expulsion will not be accelerated and cause a change in rate-limiting steps.

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