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Effects of Solvation on the Nucleophilic Reaction of Stable Carbanions with Diaryl Disulfides[1]

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Abstract: Stable carbanions react with diaryl disulfides in aqueous solution by a direct displacement (S_N2) reaction to yield an arylthiol anion and the corresponding sulfide as products. The reaction of 1,3-dicarbonyl carbanions with 5,5′-dithiobis(2-nitrobenzoic acid) is characterized by a Brønsted β_C value of 0.5. Nitroalkane carbanions react 10^2–10^4 slower than 1,3-dicarbonyl carbanions of the same p*K* and are correlated by a Brønsted β_C of 0.95. The second-order rate constants for the reaction of nitroalkane carbanions increase by factors of 10^4–10^6 as the solvent is changed from water to dimethyl sulfoxide. Smaller increases are observed in the rate constants for reaction of 2,4-pentanedione carbanion (10^2) and malonitrile carbanion ($10^{0.6}$) with the same disulfide. A linear correlation is found between log (k_{Me_2SO}/k_{HOH}) and the increase in p*K* for the carbon acid ionization on changing the solvent from water to dimethyl sulfoxide. The effect is attributed to large differences in ground-state carbanion solvation which are reduced or absent in the transition state. Parallels are drawn between the nucleophilic reaction of stable carbanions with diaryl disulfides and proton-transfer reactions of the same carbanions.

Proton-transfer reactions to and from carbon present two phenomenological anomalies. (1) Brønsted exponents (β_C or α_{CH}) observed for proton transfer to or from a series of homologous carbon acids or carbanions may not accurately reflect the extent of proton transfer in the transition state.[2,3] For reactions of nitroalkanes, Brønsted exponents outside the conventional limits (0–1.0) are observed.[4–6] This apparently anomalous behavior may be satisfactorily accounted for by realizing that for reaction centers undergoing changes in hybridization, the structure of the transition state may not be intermediate between reactants and products in all respects.[2–7] (2) Thermodynamically favorable proton transfers involving carbon acids or carbanions are frequently several orders of magnitude slower than the diffusion-controlled proton transfers between nitrogen and oxygen.[8,9] Slow proton transfers to and from carbon, in particular nitroalkanes, have been attributed to energetic barriers resulting from extensive heavy-atom reorganization required upon rehybridization of carbon,[10] desolvation of the general-acid–base catalyst,[11–13] and/or desolvation of the carbanion in the transition state.[14]

We were interested in systematically examining the nucleophilic reaction of a series of stable carbanions of differing structure with an electrophile other than a Brønsted acid to determine if the anomalous kinetic behavior is a general property of carbanion nucleophiles or if it is related to the inability of carbanions to participate in specialized interactions, notably hydrogen bonds, with strongly solvated oxygen or nitrogen proton donors. Since a disulfide electrophile should not be as extensively solvated in water as a Brønsted acid, the contribution of changes in electrophile solvation to the free energy of activation should be greatly reduced. Consequently, we have studied the kinetics of the reaction of a series of stable carbanions with 5,5′-dithiobis(2-nitrobenzoic acid), Ellman's reagent,[15] and other diaryl disulfides in aqueous solution and dimethyl sulfoxide (Me_2SO).

Experimental Section

Materials. All organic reagents were redistilled or recrystallized before use except nitromethane and 2,4-pentanedione which were Aldrich "Gold Label" (99+%). Acetoacetylethanethiol was prepared by the reaction of freshly distilled diketene with ethanethiol in the presence of triethylamine.[16] Substituted diaryl disulfides which were not commercially available were prepared by oxidation of the corresponding thiol with hydrogen peroxide in aqueous potassium hydroxide.[17]

Dimethyl sulfoxide (Me_2SO) was Aldrich "Gold Label" (>99.9%) containing less than 0.05% water as supplied. The Me_2SO was stored under dry argon and purged before each experiment by bubbling dry argon through all solutions for at least 10 min. Water was deionized and glass distilled.

Methods. Spectrophotometric measurements were made on either a Varian 634 or Gilford 222 recording spectrophotometer with the cell compartment maintained at 25.0 ± 0.1 °C. A Corning Model 130 pH meter with a Radiometer GK2321 combination electrode calibrated by the two-point method was used to measure pH. Carbon acid solutions were prepared by weight. The concentration of Ellman's reagent was determined by measuring the change in absorbance at 412 nm on the addition of excess mercaptoethanol at pH 7.5 (0.1 M potassium phosphate buffer). Under these conditions, both thiol anions of Ellman's reagent are liberated.[18] An extinction coefficient of 1.36×10^4 M^{-1} cm^{-1} was used for thionitrobenzoate anion.[15] NMR spectra were recorded on a Varian EM-360 spectrometer. Chemical shifts are reported as ppm downfield from an internal Me_4Si standard. Melting points were determined on a Fisher-Johns apparatus and are uncorrected.

Kinetics. Reactions of Ellman's reagent with carbanions in water were performed at 25.0 ± 0.10 °C maintaining ionic strength constant at 1.0 M with KCl. All solutions were prepared immediately before use. Solutions contained ethylenediaminetetraacetic acid (1×10^{-4} M) and were degassed for at least 5 min by bubbling argon into each cell.

Reactions of carbanions with Ellman's reagent were usually initiated after temperature equilibration by the addition of Ellman's reagent (7×10^{-6}–5×10^{-5} M final concentration) to a solution of the carbanion. The absorbance increase at 412 nm due to the formation of thionitrobenzoate anion was followed spectrophotometrically for 8–10 half-lives. For the slower reactions, a slow decrease in the absorbance at 412 nm was noted after completion of the reaction. This was due to a slow oxidation of the thiol anion of Ellman's reagent. In these cases, the infinity point was estimated by adding 3.1% to the absorbance change observed after 5 half-lives.

Rate constants for the reaction of acetoacetylethanethiol carbanion and malonitrile carbanion with Ellman's reagent were determined in

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buffered solution, 0.067 M (tris(hydroxymethyl)amino)methane, with Ellman's reagent in excess (0.01 M). The observed rate constants were at least tenfold greater than the rate constant for acetoacetylethanethiol hydrolysis. The observed kinetics were first order to at least 3 half-lives after correction for a slow zero-order hydrolysis or aminolysis[19] of Ellman's reagent. This correction (<10% of the total absorbance change) was made by subtracting the zero-order increase in absorbance observed in a control experiment omitting acetoacetylethanethiol or malonitrile.

Hydrolysis of cyanoethyl acetate and diethyl malonate led to significant changes in pH during the course of an experiment, and an initial velocity method was employed. A small amount of potassium hydroxide was added to temperature-equilibrated solutions of these carbon acids, and the pH was measured immediately. Ellman's reagent was added, and the initial velocity of absorbance increase at 412 nm was recorded for 1–5% reaction. During this time there was no significant change in pH (<0.04 pH unit). The infinity point was determined by adding a known amount of 4.0 M potassium hydroxide to each cuvette to bring the pH to 12–13. Under these conditions, greater than 90% of the product formed was due to reaction of the carbanion with Ellman's reagent. The same total absorbance change was observed if the reactions with higher concentrations of carbon acid were allowed to go to completion. The first-order rate constants were obtained by dividing the initial velocity by the total absorbance change.

The reaction of nitromethane carbanion with Ellman's reagent in aqueous solution was complicated by an increase in absorbance at 412 nm due to a background reaction of nitromethane. This background reaction increased in velocity with increasing pH and prevented rate measurements with carbanion/carbon acid ratios greater than 0.4 at a total nitromethane concentration of 1.0 M. In all cases the background reaction in the absence of Ellman's reagent was zero order over the entire course of an experiment. At a total concentration of 1.0 M nitromethane, 40% base, the increase in absorbance at 412 nm was 0.023 OD/min. The zero-order increase in absorbance at 412 nm due to the background reaction was subtracted from the observed increase in absorbance after the addition of Ellman's reagent by running a parallel experiment without Ellman's reagent. The nature of this background reaction is unknown but has been noted by other investigators.[20] The background reaction did not result in the synthesis of any compound which reacted with Ellman's reagent faster than the nitromethane carbanion. Rate constants for the reaction of Ellman's reagent immediately after preparing the carbanion solution were within experimental error (±10%) of the rate constants observed after aging of the solution over the course of one kinetic measurement. The change in absorbance observed on completion of the reaction with Ellman's reagent was that expected for formation of 1 equiv of thionitrobenzoate after correction for the background increase in absorbance. This background reaction was not observed for nitroethane.

The reaction of 2,4-pentanedione with substituted diaryl disulfides in aqueous solution could not be followed by a continuous spectrophotometric procedure because of the high background absorbance of 2,4-pentanedione at wavelengths where the thiolate anion product absorbed. The reaction of 2,4-pentanedione with substituted diaryl disulfides was followed by measuring the thiophenoxide concentration with Ellman's reagent. A solution of the carbon acid in 20% (v/v) 2-propanol (0.93 mole fraction water), ionic strength 0.5 M (KCl), 25.0 °C, was made 1.5 $\times 10^{-4}$ M in diaryl disulfide by the addition of a solution of disulfide (0.01 M) in 2-propanol. At various times a 1.0-mL aliquot was withdrawn and added to a cuvette containing 2.0 mL of potassium dihydrogen phosphate which was 1.1 $\times 10^{-4}$ M in Ellman's reagent. The concentration of potassium dihydrogen phosphate was such that complete neutralization of the carbanion solution gave a ratio of dihydrogen phosphate to monohydrogen phosphate of 4.0 and a final pH of 5.9. Under these conditions, the reaction of 2,4-pentanedione with Ellman's reagent was slow compared to the reaction of the thiophenoxide. The change in absorbance at 412 nm on reaction of the thiol anion with Ellman's reagent was proportional to the concentration of thiolate anion product formed. The second-order rate constants were reproducible to within ±20% unless higher error limits are indiciated.

For reactions in Me_2SO the carbanions were generated by adding a small volume (1–10 μL) of aqueous potassium hydroxide to a temperature-equilibrated solution of the carbon acid in Me_2SO. The pK of water in Me_2SO is considerably larger than the pK of all carbon acids examined so that no significant concentration of free hydroxide or dimsyl anion was present at equilibrium.[14] The resulting carbanion solutions were 95–99.9 mol % Me_2SO. At a constant carbanion concentration, the observed first-order rate constants for the reaction of 2,4-pentanedione and nitroethane carbanions with Ellman's reagent were constant between 99.9 and 95 mol % Me_2SO. Further drying of the Me_2SO by distillation from calcium hydride had no significant effect on the rate constants for the reaction of nitroethane carbanion with Ellman's reagent between 99.9 and 95 mol % Me_2SO (based on the amount of water added).

Following generation of the carbanion, the reactions were initiated by adding a small volume (1–5 μL) of 0.01 M disulfide in Me_2SO. Disulfide concentrations were (0.3–1.0) $\times 10^{-5}$ M, and total absorbance changes were generally from 0.1 to 0.3. The observed first-order rate constants were independent of the time of preincubation of the carbon acid and potassium hydroxide for periods of preincubation of up to 10 min.

For most kinetic experiments, the concentration of carbanion was at least 20 times greater than the concentration of Ellman's reagent. For very fast reactions, where low concentrations of carbanion were employed, the dipotassium salt of Ellman's reagent[18] was utilized as the substrate to prevent neutralization of the carbanion by reaction with the carboxylic acid groups of Ellman's reagent. In these experiments, the concentration of Ellman's reagent was still seven- to tenfold less than the carbanion concentration. For reactions of diaryl disulfides in Me_2SO, the wavelengths used to monitor the formation of thiol anion are shown in Table IV. These wavelengths do not, in general, correspond to the absorption maxima of the various thiol anions in Me_2SO. Wavelengths slightly higher than the absorption maximum were used to avoid high background absorbance from the carbanion species.

Except for those experiments conducted under initial velocity conditions, first-order rate constants were evaluated from plots of ln $(A_\infty - A)$ against time where A is the observed absorbance at time t and A_∞ is the absorbance at the end of the reaction. First-order plots for reactions with half-times greater than 10 s were linear to at least 3 half-lives after correction for the slower background reactions noted previously. For some of the faster reactions in Me_2SO (half lives of 5-10 s), a significant portion of the reaction had occurred between the time of mixing and initiation of recording. In these cases, rate constants were determined from the increase in absorbance during the last half to two-thirds of the overall reaction. First-order plots were still linear for at least 2 observed half-lives. Extrapolation of the absorbance back to the time of mixing showed that the initial absorbance was zero at zero reaction time. For the faster reactions, rate constants were reproducible within ±20%.

Determination of p*K*. The pK of acetoacetylethanethiol was determined spectrophotometrically at 25 °C, ionic strength 1.0 M (KCl), 10% (v/v) methanol in a series of 0.067 M (tris(hydroxymethyl)amino)methane buffers, pH 8.46–9.34. The pK was calculated from the absorbance of a 3.3 $\times 10^{-5}$ M solution of acetoacetylethanethiol at 303 nm and the measured pH using the relationship $pK = pH + \log (A_b - A)/(A - A_a)$ where A is the absorbance at 303 nm at a given pH, A_b is the absorbance at a pH at least 3 pH units above the pK, and A_a is the absorbance at a pH at least 3 pH units below the pK. The pK's of other carbon acids were obtained by measuring the pH of solutions of known concentrations of carbon acid and its conjugate base for at least 5 different acid/base ratios.

Stoichiometry. The $\Delta\epsilon$ for reacion of excess 2,4-pentanedione with Ellman's reagent was found to be 1.93×10^4 M^{-1} cm^{-1} at 412 nm from the absorbance change observed on reaction of a known quantity of Ellman's reagent with excess 2,4-pentanedione (50% base). The same $\Delta\epsilon$ was observed when Ellman's reagent was in excess. The observed $\Delta\epsilon$ can be completely accounted for by the absorbance of the monosulfide product of the reaction ($\epsilon_{412} = 5.3 \times 10^3$ M^{-1} cm^{-1}, pH 8.0) and 1 equiv of Ellman's anion ($\epsilon = 1.36 \times 10^4$ M^{-1} cm^{-1}).[15] The observed absorbance changes for the reaction of all carbanions with all diaryl disulfides in water and Me_2SO were never greater than 30% larger than could be accounted for by the absorbance of the thiol anion product alone.

Product Identification. Ellman's reagent (0.4 g, 0.01 mol) was added in approximately 0.05-g portions with stirring to a solution of 1.0 g (0.01 mol) of 2,4-pentanedione in 10 mL of 0.5 M KOH. The pH of this solution was approximately 9. After addition of Ellman's reagent, the solution was stirred for at least 2 min. The pH was lowered to 5.5 with 12 M hydrochloric acid, and the solution was extracted three times with 15–20 mL of chloroform to remove the excess 2,4-pentanedione. The pH of the aqueous layer was lowered to 0.5 with 12 M hydrochloric acid, and the solution was extracted three times with 20 mL of chloroform. The chloroform layer was dried over molecular sieves and filtered, and the chloroform was evaporated under reduced pressure leaving a yellow oil. The oil was dissolved in chloroform/methanol and applied to two preparative silica gel plates and developed with chloroform/acetic acid (95:5, v/v). Two major bands were detected. The slower moving band was bright yellow in color and exhibited the same mobility as thionitrobenzoate. The fast moving band was removed from the plate, and the product was extracted into methanol. The methanol was removed under reduced pressure and finally under high vacuum to leave 0.22 g of a dark yellow solid. This yellow solid was found to be a solvate of the reaction

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Table I. Second-Order Rate Constants for the Reaction of Various Carbanions with Ellman's Reagent in Aqueous Solution (Ionic Strength = 1.0 M (KCl), 25.0 °C)

carbon acid	pK_a	pH	[carbon acid]/M	no. of points	k_c/M^{-1} s^{-1}
$EtOCOCH_2CO_2Et$	13.3[a]	7.85–8.59[b,c]	0.042	6	310
$EtOCOCH_2COCH_3$	10.7[a]	8.00–10.48[d]	0.1–0.2	9	10
CH_3COCH_2COSEt	9.14[e]	8.33–9.20[b,f]	g	5	3.5 ± 1
$CH_3COCH_2COCH_3$	8.73[e]	7.98–9.91	0.004–0.25	12	1.03
$(CH_3CO)_3CH$	6.15[e]	7.92[d]	0.06–0.24	4	0.10
$NCCH_2CO_2Et$	11.7[h]	6.53–8.24[d]	0.05	5	470
$NCCH_2CN$	11.25[h]	8.76–9.28[b]	g	7	670 ± 70
HCN	9.06[e]	8.35–9.91	0.0067	8	23
NO_2CH_3	10.08[e]	9.03–9.97	1.0	5	0.012 ± 0.002
$NO_2CH_2CH_3$	8.60[e]	8.60	0.1–0.9	17	$(7 \pm 2) \times 10^{-4}$
$NO_2CH(CH_3)_2$	7.57[e]	8.53	0.2–1.0	5	$\leq 4 \times 10^{-5}$

[a] Reference 8. [b] 0.067 M (tris(hydroxymethyl)amino)methane buffer. [c] 4% (v/v) methanol. [d] 0.05 M potassium ethylphosphonate buffer at pH 8.5. [e] This study. [f] 12% (v/v) methanol. [g] Ellman's reagent in excess at 1×10^{-3} M. [h] Reference 22.

product and the acetic acid used for development of the thin-layer plate. The solvate was dissolved in water and extracted ten times with 20 mL of petroleum ether (bp 40–60 °C). The pH was lowered to 4.0 with dilute hydrochloric acid and the aqueous layer extracted three times with 10 mL of chloroform. The pH was then lowered to 0.5 with 12 M hydrochloric acid, and the aqueous layer was extracted four times with 15 mL of chloroform. The chloroform layer was dried over molecular sieves and filtered. The chloroform was evaporated under reduced pressure, leaving a light yellow solid which was recrystallized three times from benzene/petroleum ether to yield 0.1 g of a light yellow solid with mp 156–158 °C.

NMR (acetone-d_6): δ 13.0–18.0 (v br, 1 H), 10.0–12.0 (v br, 1 H), 7.95 (d, J = 8 Hz, 1 H), 7.50 (s, 1 H), 7.42 (d, J = 8 Hz, 1 H), 2.33 (s, 6 H).

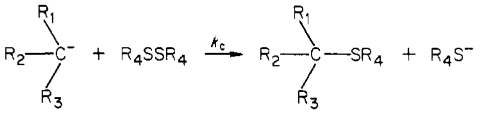
UV (pH 8.0, 0.1 M potassium phosphate buffer): λ_{max} 371 nm (ϵ 1.1×10^4 M^{-1} cm^{-1}), λ_{max} = 289 (1.5×10^4), λ_{min} = 289 (8.1×10^3).

Anal. Calcd for $C_{12}H_{11}NSO_6$: C, 48.48; H, 3.73; N, 4.71; S, 10.78. Found: C, 48.27; H, 3.81; N, 4.95; S, 10.52.

Thin-layer chromatography on silica gel developed with chloroform/acetic acid, 95:5 (v/v), of reaction mixtures of excess 2,4-pentanedione carbanion (50% base) and Ellman's reagent in Me_2SO showed only two spots which were of identical R_f to thionitrobenzoate, and the monosulfide product was isolated and characterized for the same reaction in aqueous solution.

Results

The reaction of stable carbanions with diaryl disulfides in aqueous solution, pH 7–11 at 25.0 °C, μ = 1.0 M (KCl) proceeds with the formation of 1 equiv of arylthiol anion and the corresponding sulfide (eq 1).[21] The product of the reaction of 2,4-



$$R_1R_2R_3C^- + R_4SSR_4 \xrightarrow{k_c} R_1R_2R_3C{-}SR_4 + R_4S^- \quad (1)$$

pentanedione carbanion with 5,5′-dithiobis(2-nitrobenzoic acid) (Ellman's reagent) was isolated from preparative scale experiments and identified as the enol of 3-thio-(3-carboxy-4-nitrophenyl)-2,4-pentanedione ($R_1 = R_2 = CH_3CO$, R_3 = H, $R_4 = C_7H_9NO_2$).

The kinetics of the reaction of stable carbanions with Ellman's reagent in aqueous solution is described by the rate law in eq 2.

$$v = k_c[\text{disulfide}][\text{carbanion}] \quad (2)$$

The apparent second-order rate constant based on the concentration of total carbon acid species (carbon acid plus carbanion) increases with pH below the pK of the carbon acid and becomes pH independent above the pK (Figure 1). Second-order rate constants for the reaction of various stable carbanions with Ellman's reagent in aqueous solution are given in Table I. Uncertainties in the values of k_c are ±10% unless higher error limits are indicated.

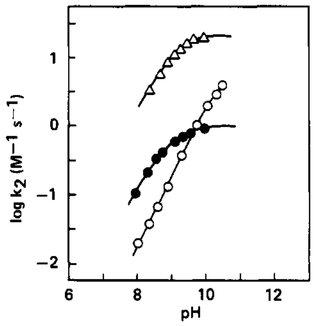


Figure 1. Dependence of the second-order rate constant (based on total carbon acid concentration) on pH for the reaction of carbon acids with Ellman's reagent in aqueous solution at 25.0 °C, μ = 1.0 M (KCl): (●) 2,4-pentanedione; (○) ethyl acetoacetate; (△) hydrogen cyanide. Solid lines are calculated from the pK and k_c values in Table I.

Table II. Second-Order Rate Constants for the Reaction of 2,4-Pentanedione Anion and Cyanide Anion with Symmetrical Disubstituted Diaryl Disulfides (X-Ph-SS-Ph-X) in Aqueous 2-Propanol at 25.0 °C

	k_c/M^{-1} s^{-1}	
substituent	pentanedione anion[a]	cyanide anion[b]
H	0.0022	0.47
p-chloro	0.011	6.0
3,4-dichloro		50
3-carboxy-4-nitro	0.3	20
p-nitro	1.1	160

[a] 93 mol % water. [b] 90 mol % water.

Second-order rate constants for the reaction of 2,4-pentanedione carbanion and cyanide anion with symmetrically disubstituted diaryl disulfides in aqueous 2-propanol at 25.0 °C are shown in Table II. The rate constants in Table II are not of high precision (±20–50%) because of the experimental difficulties introduced by the low solubility of the disulfides in predominantly aqueous solution. The reaction of nitroalkane carbanions with disulfides other than Ellman's reagent and *p*-nitrophenyl disulfide are sufficiently slow that interference from thiol anion oxidation and carbanion side-reactions precludes rate measurements in aqueous solution.

As the solvent is gradually changed from water to Me_2SO, the second-order rate constants for the reaction of 2,4-pentanedione and nitroethane carbanions with Ellman's reagent increase by factors of approximately 10^2 and 10^5, respectively (Figure 2). The observed rate constants do not change significantly (<10%) between 99.9 and 95.0 mol % Me_2SO (99.9 and 98.8 wt %). For the reaction of nitroethane carbanion with Ellman's reagent, distillation of the Me_2SO from calcium hydride has no effect on

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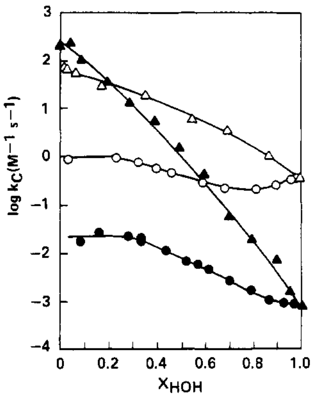

Figure 2. The effect of changing mole fraction water on the second-order rate constants for the reaction of 2,4-pentanedione and nitroethane carbanions with Ellman's reagent at 25.0 °C: (○) 2,4-pentanedione in water/2-propanol mixtures; (△) 2,4-pentanedione in water/Me_2SO mixtures; (●) nitroethane carbanion in water/2-propanol mixtures; (▲) nitroethane carbanion in water/Me_2SO mixtures.

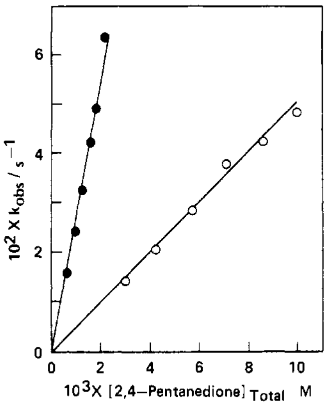

Figure 3. The dependence of the observed pseudo-first-order rate constant for the reaction of 2,4-pentanedione with Ellman's reagent in Me_2SO at 25.0 °C, on the concentration of 2,4-pentanedione at a [carbanion]/[carbon acid] of 1.0 (●) and 0.11 (○).

the observed rate constant for the reaction between 99.9 and 95 mol % Me_2SO (based on the amount of water added). The observed first-order rate constant for reaction with Ellman's reagent shows a linear dependence on the total concentration of carbon acid species at different ratios of carbon acid to carbanion, consistent with the rate law of eq 2. Typical results are shown in Figure 3. The intercepts of the plots shown in Figure 3 are not significantly different from zero, indicating that there is no appreciable "solvent" reaction—either disulfide hydrolysis by trace amounts of water or reaction of Ellman's reagent with low concentrations of dimsyl anion. Second-order rate constants for the reaction of various carbanions with Ellman's reagent in 95 to 99.9 mol % Me_2SO at 25.0 °C are shown in Table III. Rate constants for the reaction of 2,4-pentanedione and nitroethane carbanions with disubstituted diaryl disulfides in Me_2SO are given in Table IV.

Discussion

Nucleophilic substitution at divalent sulfur could proceed by a concerted (S_N2) mechanism or by an addition–elmination mechanism involving the formation of a valence expanded, tricoordinate sulfur intermediate.[25,26] Several lines of evidence point to a concerted mechanism for the reaction of carbanions with diaryl disulfides.

Table III. Second-Order Rate Constants for the Reaction of Carbanions with Ellman's Reagent in Dimethyl Sulfoxide Solution at 25 °C

carbon acid	pK_{Me_2SO}	[carbanion]/M	no. of points	k_{Me_2SO}/ $M^{-1} s^{-1}$
CH_3COCH_2-$COCH_3$	13.4[a]	(0.3–1.1) × 10^{-3}	12	60
CH_3COCH_2-CO_2Et		(1.5–8.0) × 10^{-4}	5	124
CH_3NO_2	17.2[b]	(1.5–4.8) × 10^{-4}	5	340
$CH_3CH_2NO_2$	16.7[b]	(1.4–4.8) × 10^{-4}	6	230
$(CH_3)_2$-$CHNO_2$	16.9[b]	(0.4–1.6) × 10^{-3}	5	61
$NCCH_2CN$	11.1[b]	(0.6–1.6) × 10^{-4}	5	3000
HCN	12.9[a]	3 × 10^{-4}		>2000

[a] Reference 23. [b] Reference 24.

Table IV. Second-Order Rate Constants for the Reaction of 2,4-Pentanedione and Nitroethane Carbanions with Disubstituted Diaryl Disulfides (X–Ph–SS–Ph–X) in Dimethyl Sulfoxide at 25.0 °C

substituents (X)	[carbanion]/M	no. of points	$k_c/M^{-1} s^{-1}$	wave-length/ nm
A. Reaction with 2,4-Pentanedione Carbanion				
H	(8.2–40) × 10^{-4}	5	5.4	330
p-chloro	(8.1–41) × 10^{-4}	5	1.7 × 10^2	330
3,4-dichloro	(3.3–8.3) × 10^{-5}	6	(7 ± 3) × 10^3	315
p-nitro	(8.3–21) × 10^{-6}	6	1.2 × 10^4	480
p-nitro-3-carboxy	(3.0–11.0) × 10^{-4}	12	53	480
B. Reaction with Nitroethane Carbanion				
H	(1.6–8.0) × 10^{-4}	5	72	310
p-chloro	(3.3–16) × 10^{-5}	5	1.2 × 10^3	310
3,4-dichloro	(2.0–3.3) × 10^{-5}	3	(1.0 ± 0.3) × 10^4	310
p-nitro	2 × 10^{-5}	1	>4 × 10^4	480
p-nitro-3-carboxy	(1.4–4.8) × 10^{-4}	6	230	480

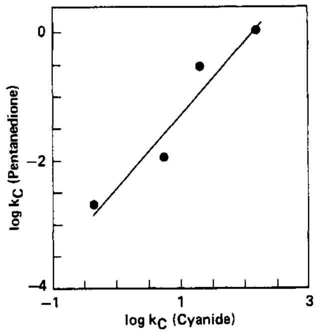

Figure 4. Correlation of the logarithm of the second-order rate constants for the reaction of 2,4-pentanedione anion and disubstituted diaryl disulfides with the logarithm of the second-order rate constant for the reaction of cyanide anion and the same disulfides in aqueous solution at 25.0 °C. The line is drawn with slope of 1.1, correlation coefficient of 0.96. Experimental points and conditions are as shown in Table II.

Electron-withdrawing substituents in the disulfide accelerate the reactions of 2,4-pentanedione carbanion and cyanide in the same way (Table II, Figure 4), suggesting a similar development of negative charge on sulfur in the transition states for the two reactions. Harper and co-workers[27] have reported a ρ of +1.97 for the leaving thiophenoxide and +1.70 for the central sulfur in the reaction of unsymmetrically substituted diaryl disulfides with cyanide in 60% aqueous *tert*-butyl alcohol. Comparison with a ρ of +2.56 for the equilibrium ionization of benzenethiols[27] indicates a significant development of negative charge on both sulfur atoms in the transition state with the extent of sulfur–sulfur bond breaking possibly lagging behind carbon–sulfur bond formation.[27]

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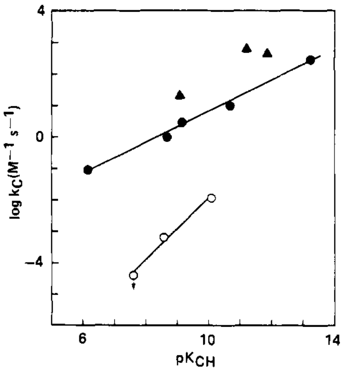


Figure 5. Logarithm of the second-order rate constant for reaction of various carbanions with Ellman's reagent in aqueous solution as a function of carbon acid p*K* at 25.0 °C, μ = 1.0 M (KCl): (●) 1,3-dicarbonyl compounds; (○) nitroalkanes; (▲) cyanocarbons. The line correlating 1,3-dicarbonyl compounds is drawn with a slope (β_c) of 0.49. The line correlating nitroalkanes is drawn with a slope (β_c) of 0.95.

The large differences observed in the reactivity of nitroalkane, 1,3-dicarbonyl, and cyanocarbon carbanions with Ellman's reagent (Figure 5) suggest that the carbon–sulfur bond is not fully formed in the transition state. If carbon–sulfur bond formation was complete, the effect of carbanion structure on the rate constants for the reaction should be similar to that observed for equilibrium iodination of the same carbanions. A plot (not shown) of the logarithm of the equilibrium constants for the iodination of a variety of carbanions[28] against the carbon acid p*K* is reasonably linear with no large deviations (<10-fold) between classes of carbanions.

The effects of disulfide and carbanion structure on reactivity support a transition-state structure in which there is a significant amount of negative charge developed on both the central and leaving sulfur with incomplete formation of the carbon–sulfur bond. These observations are most consistent with a concerted (S_N2) mechanism for the reaction.

A plot of the logarithm of the second-order rate constants for the reaction of stable carbanions with Ellman's reagent in aqueous solution against the carbon acid p*K* in water is shown in Figure 5. The rate constants for 1,3-dicarbonyl carbanions fall on a single line with a slope (β_C) of 0.5. Nitroalkane carbanions are correlated by a separate line which lies 2–4 orders of magnitude below the line established by 1,3-dicarbonyl carbanions and exhibits a β_C of 0.95. Cyanide and cyanocarbon carbanions deviate significantly above the line established by 1,3-dicarbonyl carbanions.

The structure-reactivity correlations observed for the reaction of stable carbanions with disulfides in aqueous solution are similar in many respects to those observed for proton-transfer reactions involving the same carbanions. For both reactions, cyanocarbon carbanions react significantly faster than 1,3-dicarbonyl carbanions of the same p*K* which in turn react much faster than nitroalkane carbanions of the same p*K*.[8] For both reactions, the observed value of β_C is significantly larger for nitroalkane carbanions than for 1,3-dicarbonyl carbanions.[2,4-7]

Proton transfers from a single oxygen or nitrogen acid to a homologous series of 1,3-dicarbonyl or nitroalkane carbanions are characterized by values of β_C which are generally quite different from the α_{AH} values observed for proton transfer from a series of oxygen or nitrogen acids to a single carbanion.[2,3] For nitroalkanes, values of β_C outside the conventional limits of zero to one are observed. In general, β_C does not seem to be a good indication of the extent of bond formation to carbon in the transition state.[4-6] The discrepancy between β_C and the true extent of bond formation to carbon in the transition state has been rationalized by Kresge[2] and Bordwell[4-6] as reflecting a transition state in which the amount of negative charge on carbon is greater than in the ground-state carbanion. With respect to charge development on carbon, the transition state does not possess a structure intermediate between substrate (delocalized carbanion) and product (carbon acid). This effect should apply generally to reactions in which stabilization of the ground state is predominantly through resonance interactions which are diminished or absent in the transition state. As a result, the slopes of Brønsted correlations where the carbanion structure is varied, including the reaction with disulfides, cannot be taken as indicative of the extent of carbon–electrophile bond formation in the transition state.

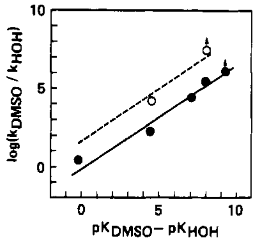
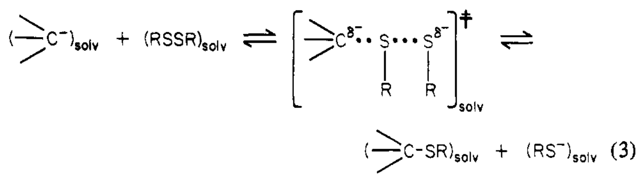


Figure 6. A plot of the logarithm of the ratio of the second-order rate constants for the reaction of carbanions with diaryl disulfides in Me_2SO and water against the difference in carbon acid p*K* in the two solvents. The solid line for the reaction of carbanions with Ellman's reagent is drawn with a slope of 0.61, correlation coefficient of 0.95. The dashed line indicates the reaction with *p*-nitrophenyl disulfide.

Solvent Effects. As the solvent is changed from water to Me_2SO, the second-order rate constants for the reaction of nitroalkane carbanions with Ellman's reagent increase by factors of 10^4–10^6. Smaller rate increases are observed for the reactions of 1,3-dicarbonyl carbanions (10^2) and cyanocarbon carbanions ($10^{0.6}$) (Figure 6). The rate increases are not due to the decreased dielectric constant of the medium—much smaller rate increases are observed on changing the solvent from water to 2-propanol (Figure 2). The observed rate increases, which are strongly dependent on carbanion structure, must result from differences in the relative solvation of the carbanion or disulfide in the transition state compared to the ground state.

For reaction 3, transfer from water to Me_2SO will result in a



(3)

large rate acceleration only if the ground state undergoes more substantial desolvation than the transition state.[29]

The *relative* extent of ground-state carbanion desolvation on transfer from water to Me_2SO may be estimated by comparing the change in p*K* of the carbon acid on transfer from water to Me_2SO.[30] Although differences in carbon acid solvation may contribute to differences in Δp*K* (pK_{Me_2SO} − pK_{HOH}), the major contribution will arise from differences in carbanion solvation.[30,31] For the ionization of nitroethane, the p*K* increases 8.1 units on changing the solvent from water to Me_2SO. Smaller Δp*K* values are observed for 2,4-pentanedione (+4.7 units) and malonitrile (−0.1 unit).[23,24] The large Δp*K* of 8.1 for nitroethane compared to a Δp*K* of −0.1 for malonitrile indicates that the nitroethane carbanion is more strongly solvated in water than the malonitrile carbanion.

A plot of the logarithm of the rate acceleration, log (k_{Me_2SO}/k_{HOH}), against the Δp*K* on changing the solvent from water to Me_2SO is shown in Figure 6.[30] Although the points are somewhat scattered, it is obvious that the reaction of malonitrile carbanion with Ellman's reagent exhibits only a small increase in rate on changing solvent and also exhibits a small value of Δp*K*.

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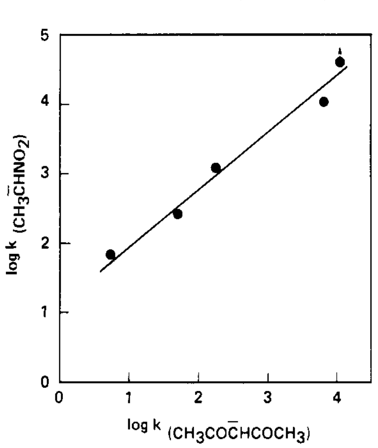

Figure 7. Correlation of the rate constant for reaction of nitroethane carbanion with substituted diaryl disulfides in Me_2SO at 25.0 °C with the rate constant for the reaction of the same disulfide with 2,4-pentanedione in Me_2SO at 25.0 °C. The line is drawn with a slope of 0.8, correlation coefficient of 0.98.

On the other hand, nitroalkane carbanions exhibit large increases in rate and large values of ΔpK. The slope of this correlation is approximately 0.6, suggesting that the transition state is less sensitive to changes in solvation than the carbanion ground state. This would imply a product-like transition state in which a considerable amount of carbanion desolvation has occurred.

The possibility must be considered that the extent of negative charge development on sulfur in the transition state is dependent on carbanion structure and related directly to ΔpK. The observed differences in rate acceleration on transfer of the reaction from water to Me_2SO could result from solvent interactions with sulfur in the transition state and be secondarily related to carbanion solvation changes. Several lines of evidence suggest that effects on the solvation of the leaving thiophenoxide are not responsible for the different rate accelerations observed for the reaction of carbanions with Ellman's reagent and other disulfides.

(1) The pK of *p*-nitrothiophenol increases by only 1.1 units on changing the solvent from water to Me_2SO.[30] This ΔpK is considerably smaller than that observed for either nitroethane or 2,4-pentanedione. Changes in thiophenoxide solvation would be expected to make a correspondingly smaller contribution to the rate effects.

(2) The extent of negative charge development on sulfur in the transition state is very similar for the reaction of 2,4-pentanedione and nitroethane carbanions in Me_2SO (Figure 7). Since the nitroethane carbanion is destabilized more than the 2,4-pentanedione carbanion on transfer to Me_2SO, any change in transition-state structure should be larger for the reaction of nitroethane carbanion than for 2,4-pentanedione carbanion. Increased ground-state destabilization in Me_2SO compared to water would be expected to result in a shift of the transition state to a more reactant-like structure (less sulfur–sulfur bond breaking) in accord with the Hammond postulate.[32,33] The direction and relative magnitude of possible carbanion-dependent shifts in the extent of sulfur–sulfur bond breaking predict that in water the transition state for the reaction of nitroethane carbanion should involve more sulfur–sulfur bond cleavage than the reaction of 2,4-pentanedione carbanion. If there is a large Hammond postulate effect (and there may not be), the increased negative charge density on sulfur for the reaction of nitroethane carbanion in water would result in increased transition-state destabilization on transfer to Me_2SO and a decrease in the relative rate acceleration. This is opposite to the effect observed and suggests that differences in solvation of the leaving thiol anion are not responsible for the observed correlation of log (k_{Me_2SO}/k_{HOH}) with ΔpK but may be responsible for the nonunit slope.

(3) The reactions of cyanide anion and 2,4-pentanedione carbanion with substituted diaryl disulfides in water show a similar development of negative charge on sulfur in the transition state (Figure 4). At least for these two carbanions, the extent of negative charge development on sulfur is independent of carbanion structure.

It might be expected that a single correlation between carbon acid pK in Me_2SO and log k_{Me_2SO} would exist for all carbanions. Examination of the data in Table III illustrates that this is not the case. In Me_2SO, nitroethane carbanion is more basic than malonitrile carbanion by approximately six powers of ten; however, the second-order rate constant for reaction of malonitrile carbanion with Ellman's reagent is a factor of 10 *larger* than that observed for the reaction of nitroethane carbanion. The continued existence of the "nitroalkane anomaly" in Me_2SO may also result from differential solvation of the various carbanion ground states in Me_2SO, which is either absent or diminished in the transition state. Relative acidities of malonitrile, 2,4-pentanedione, and nitroethane are available in water, Me_2SO, and the gas phase. In the gas phase, nitroethane is a weaker acid than malonitrile by 16 powers of ten.[31] In Me_2SO, the relative order of acid strength is the same; however, nitroethane is a weaker acid than malonitrile by only five to six powers ot ten.[24] With the assumption that the relative acidities of carbon acids in various media arise predominantly from differences in carbanion solvation,[30,31] it may be concluded that the nitroethane carbanion is more highly solvated in Me_2SO than is the malonitrile carbanion. The differences in solvation of the various carbanions in Me_2SO are more than adequate to account for the observed differences in rate constants if the extent of carbanion solvation is reduced in the transition state for the reaction in Me_2SO.

The Nitroalkane Anomaly. The thermodynamically favorable proton transfer between acetic acid and nitroethane carbanion occurs at a rate that is approximately 10^9 slower than diffusion controlled.[34] This observation stands in marked contrast to proton transfers between electronegative oxygen and nitrogen atoms which are generally diffusion controlled. Slow proton transfers to and from carbon have been attributed to the inability of carbanions and carbon acids to participate in strong hydrogen-bond interactions with Brønsted acids and bases,[11-13] energy barriers from heavy-atom reorganization around carbon,[10] and carbanion and/or Brønsted acid–base desolvation in the transition state.[12,14,35,36]

In aqueous solution, the relative rates for proton transfer from acetic acid to nitroethane,[34] 2,4-pentanedione,[9] and *tert*-butylmalonitrile[37] carbanions are 1, $10^{5.3}$, and $10^{8.1}$, respectively. This order of reactivity is similar in direction and magnitude to that observed for the reaction of nitroethane, 2,4-pentanedione, and malonitrile carbanions with Ellman's reagent (1, $10^{3.2}$, and 10^5, respectively). The slope of a plot (not shown) of the logarithm of the rate constants for proton transfer from acetic acid against the logarithm of the rate constants for reaction with Ellman's reagent is linear with a slope of approximately 1.7. This would suggest that the majority of the *difference* in proton-transfer rates to structurally different carbanions results from differences in carbanion solvation in the ground state which are reduced in the transition state. That the rate constants for proton transfer from acetic acid are a factor of 1.7 more sensitive to changes in carbanion structure than the rate constants for reaction with Ellman's reagent may reflect differences in transition-state solvation, the effect of relative hydrogen bonding ability of the carbanions with acetic acid, differences in the extent of heavy-atom rearrangement, or a combination of these factors.

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Solvent effects on the reaction of carbanions with Ellman's reagent suggest a transition state in which the solvation of the carbanion is product-like. If proton transfer also occurs through a product-like transition state with respect to solvation, the prediction may be made that in the reverse direction (proton transfer from carbon acid to acetate anion), the solvent effect should be relatively independent of the structure of the carbon acid. Cox and Gibson[34] have measured the rate constants for proton transfer from 2-nitropropane, nitroethane, and 2-methyl ethylacetoacetate to acetate anion as a function of increasing mole fraction Me_2SO. Although the maximum mole fraction of Me_2SO was only 0.4 in their experiments, the observed effects on the rate constants are virtually independent of the structure of the carbon acid. In this direction, the solvent effect (a rate increase of 10^2 at 0.4 mole fraction Me_2SO) would seem to be primarily due to desolvation of acetate anion in the transition state.

The above observations are consistent with a transition-state structure for proton transfer to and from carbon in which the delocalized negative charge on the carbanion and acetate anion is less highly solvated than either the carbanion or acetate anion ground state. In the direction of proton transfer from acetic acid to a carbanion, the solvation of the carbanion would be product-like while the solvation of the acetic acid would be reactant-like. The relative differences in ground-state and transition-state solvations are more than adequate to account for the large increases in rate observed for both proton-transfer and nucleophilic reactions of carbanions on changing the medium from water to Me_2SO.

It has recently been shown that the rate constants for proton transfer from 1-arylnitromethanes to benzoate anion, and the reverse reaction, increase by approximately 10^5 on changing the medium from water to Me_2SO.[35] However, even this large rate acceleration is not enough to increase the rate constants for proton transfer to anywhere near the diffusion-controlled limit. The continued existence of slow proton transfers to and from carbon in Me_2SO could also result from changes in solvation required to reach the transition state. Carbanions are still highly solvated in Me_2SO (compared to the gas phase), the extent of solvation is dependent on carbanion structure, and solvation may be very different between the ground state and transition state.

A large portion of the nitroalkane anomaly in aqueous solution can be accounted for with a transition-state structure in which both the proton donor and acceptor are significantly desolvated in comparison to their anionic ground states. It is possible that the total nitroalkane anomaly could be accounted for by solvation phenomena; however, at the present time it is difficult to assess the contribution of hydrogen bonding between the carbanion and proton donor and the contribution of heavy-atom reorganization to the energy barrier for proton transfer to and from carbon.

Acid–Base Kinetics of Pyridine Studied with a Slow Spectrophotometric Indicator in Methanol

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Abstract: The protonation–deprotonation kinetics of pyridine in methanol has been studied by the electric field jump technique. Kinetic measurements of the electric field insensitive equilibrium $B + H^+ (k_1) \rightleftarrows BH^+ (k_{-1})$, where B denotes pyridine, were obtained by coupling the equilibrium with a field-sensitive, visibly colored indicator equilibrium. Use of the "slow" indicator 2,2′,4,4′,6,6′-hexanitrodiphenylamine allowed observation of the slower of the two relaxation times of the coupled system in a time range where measurements could be made with sufficient precision for a reliable extraction of the rate constants k_1 and k_{-1} from the data. The values obtained are $k_1 = 1.57 \pm 0.32 \times 10^{10}$ dm^3 mol^{-1} s^{-1} and $k_{-1} = 8.43 \pm 1.69 \times 10^4$ s^{-1}. The value for k_1 is within the expected limits for a diffusion-controlled reaction in this solvent. An ionic reaction radius of 3.9 Å is calculated from the protonation rate constant value, which indicates that the neutral species involved is probably a hydrogen-bonded pyridine–methanol complex rather than free pyridine. The value for k_{-1} is 1 order of magnitude greater than the constant for methyl-substituted pyridines, reflecting unsubstituted pyridine's lower basicity in methanol.

Introduction

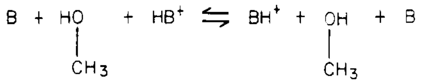
A nuclear magnetic resonance study[1] of proton exchange of ortho and para methyl-substituted pyridinium ions in methanol has revealed that the protonation rates of the bases are very fast with rate constants comparable to the values expected for a diffusion-controlled process in all cases. In this study Cocivera found no appreciable steric effect of ortho methyl substituents on the rates of protonation and deprotonation at the nitrogen atom. It is still in doubt,[2] however, whether the proton transfer involves the free amine B

$$B + CH_3OH_2^+ \rightleftharpoons BH^+ + CH_3OH \qquad (1)$$

or a hydrogen-bonded complex

$$B{\cdot}HOCH_3 + CH_3OH_2^+ \rightleftharpoons BH^+{\cdot}O(H)CH_3 + CH_3OH \qquad (2)$$

Steric effects are expected to play a significant role in reaction 1 but not in (2). On the other hand the reaction distances of 1.9–3.0 Å calculated from the NMR results are small for reaction 2 where the proton motion in the hydrogen bond is triggered by the more distant protonation of the methanol molecule. The analysis of NMR rate data is complicated by the symmetrical proton exchange[1,3]



$$B + \underset{\displaystyle CH_3}{\underset{|}{HO}} + HB^+ \rightleftharpoons BH^+ + \underset{\displaystyle CH_3}{\underset{|}{OH}} + B \qquad (3)$$

and by the large salt effects in ionic systems of high concentration.[1,2] Relaxation kinetics is free of these complications because reaction 3 does not contribute to the observed rate and the reactant concentrations are low. We describe here an electric field jump

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