transition state for normal reaction   transition state for abnormal reaction

the one on carbon is nearer than the other two to the substituent group and, to a first approximation, only the interaction between this charge and the substituent group need be considered.

On the other hand, two of the three charges on the transition state for the normal reactions (those on oxygen and carbon) are almost exactly equidistant from the substituent group and are nearer than the charge on nitrogen. To a first approximation, therefore, only the interactions between the substituent group and these two charges need be considered. Since the three charges must add up to zero, the positive charge on carbon must be smaller than the negative charge on oxygen. Consequently, an electron-withdrawing group will stabilize the negative charge on oxygen more than it will de-stabilize the positive charge on carbon and the reaction will have a positive ρ. The same conclusion can be reached from a consideration of the structure of the epoxide itself, where a substituent group, since it is almost exactly equidistant from both ends of the $O-CH_2$ bond, will have no effect

on the ease of breaking of this bond. The only remaining effect of the substituent will be on the ease of approach of the nucleophile and this will necessarily result in a positive ρ.

The unusual situation of a nucleophilic displacement reaction, in which bond breaking is dominant, having a positive ρ should also occur in reactions involving the attack of a nucleophile at the primary carbon atom of monosubstituted ethyleneimines and ethylene sulfides and in certain ring-opening reactions of larger-ring compounds.

In view of the limited accuracy, the variations in the Arrhenius parameters and the heats and entropies of activation are not large enough to justify any detailed comment. The energies of activation all fall within the range 13.6 ± 2.9 kcal. mole^{-1} and the values of $\log_{10} A$ within the range 5.1 ± 1.8, except for the abnormal reaction of the m-chloro compound and the values of E and $\log_{10} A$ for this reaction are among the least accurate of all the values. The low values of the entropy of activation are what would be expected for a reaction in which two neutral molecules form a charged transition state in a hydrogen-bonding solvent and the general similarity of energies and entropies of activation for both the normal and the abnormal reactions supports the conclusion that both reactions take place by similar mechanisms, in spite of the reversal of sign of ρ.

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Mechanisms of Nucleophilic Displacement in Aqueous Dimethyl Sulfoxide Solutions

BY RICHARD FUCHS, GLORIA E. McCRARY[1] AND JORDAN J. BLOOMFIELD

Sodium thiosulfate and α-chlorotoluene react in dimethyl sulfoxide (DMSO)–acetonitrile–water mixtures predominantly by a "normal" mechanism in which DMSO acts only as a solvent. Studies of substituent effects, salt effects, activation energies and the stereochemistry of the 2-bromoöctane-thiocyanate reaction all support this mechanism. Evidence is presented for a second mechanism in which DMSO slowly reacts with α-chlorotoluene to give a highly reactive intermediate which is rapidly attacked by thiosulfate. The over-all reaction is first order in α-chlorotoluene and thiosulfate; the rate increases markedly with increasing DMSO concentration in the solvent mixture.

The remarkable acceleration of a variety of reactions by the solvent dimethyl sulfoxide (DMSO) has been reported during the last few years. Thus, the elimination reaction of arylsulfonate esters to give olefins,[2] base-catalyzed proton abstraction from carbon,[3] the alkylation of sodiomalonic esters with alkyl halides,[4] the displacement of halide by cyanide, azide, thiocyanate and halide ions,[5] and the thiosulfate-α-chlorotoluene reaction[6]

(1) Based on the M.S. Thesis of Gloria E. McCrary, The University of Texas, June, 1961.

(2) H. R. Nace, J. Am. Chem. Soc., 81, 5428 (1959).

(3) D. J. Cram, B. Rickborn and G. R. Knox, ibid., 82, 6412 (1960).

(4) H. E. Zaugg, B. W. Horrom and S. Borgwardt, ibid., 82, 2895, 2903 (1960).

(5) L. Friedman and H. Shechter, J. Org. Chem., 25, 877 (1960);

are reported qualitatively or quantitatively to react at greatly enhanced rates when DMSO is a component of the solvent. The last three of these reactions are bimolecular, nucleophilic displacements on carbon—a type which appears to be widely, but not universally, speeded by DMSO.

In the present work an effort has been made to study the mechanism or mechanisms of the α-chlorotoluene–thiosulfate reaction in aqueous DMSO by a consideration of the kinetics, and by a comparison of the activation energy, substituent effect and ionic strength effect with those in other solvent mixtures of similar dielectric constant.[6]

R. A. Smiley and C. Arnold, ibid., 25, 257 (1960); J. Miller and A. J. Parker, J. Am. Chem. Soc., 83, 117 (1961).

(6) R. Fuchs and Alex Nisbet, ibid., 81, 2371 (1959).

A stereochemical study of the optically active 2-bromooctane–thiocyanate reaction in DMSO has been made.

Results

Order.—Rates of reaction of the α-chlorotoluene–thiosulfate reaction were measured in solvent mixtures containing 40% (by volume) water and 60% of DMSO + acetonitrile. Water is a necessary solvent component for thiosulfate solubility. The choice of acetonitrile was dictated by the desirability of having a low rate in the absence of DMSO, and of minimizing changes in dielectric constant as DMSO concentration is increased at the expense of acetonitrile. A plot of the rate constant (Table I) vs. the square of DMSO concentration (expressed as volume %) is essentially linear from 3% to a concentration of about 40% DMSO. The intercept of the plot at 0% DMSO is somewhat greater than the rate in 60% acetonitrile–40% water. Further increases in DMSO concentration (50 or 60%) increase the rate even more strongly.

TABLE I

RATES OF THE α-CHLOROTOLUENE–THIOSULFATE REACTION IN DMSO–ACETONITRILE–40% WATER AT 30°

% DMSO[a]	Dielectric constant[b]	k[c]	% DMSO[a]	Dielectric constant[b]	k[c]
0	52.3	2.97 (2.88)[d]	25	60.9	17.7
3	53.9	3.98	30	62.5	24.0
5[e]	54.4	4.50	35	63.8	32.8
8	55.8	5.42	40	65.5	41.5
10	56.4	6.60	50	68.5	73.0
20	59.5	12.9	60	72	(13.3 at 0°)[d]

[a] Percentage by volume. [b] Measured with a Sargent Oscillometer at 25°. [c] Average of two or more determinations; second-order rate constants (l. mole^{-1} sec.$^{-1}$) × 10^3, at 30.00 ± 0.02; at time of mixing ($S_2O_3^-$) = 0.04 M, (RCl) = 0.025 M, buffer (KOAc) = 0.008 M. [d] Ref. 6. [e] 4.36 in 5% tetramethylene sulfoxide.

Activation Energy.—From rate measurements at 10°, 20° and 30° (Table II), the Arrhenius activation energy of the thiosulfate–α-chlorotoluene reaction in 25% DMSO is 16.5 kcal. mole^{-1}

TABLE II

RATES OF THE α-CHLOROTOLUENE–THIOSULFATE REACTION IN 25% DMSO–35% ACETONITRILE–40% WATER AT VARIOUS CONCENTRATIONS AND TEMPERATURES

($S_2O_3^-$)[a]	Temp., °C.[b]	k[c]	($S_2O_3^-$)[a]	Temp., °C.[b]	k[c]
0.04	30	17.7	0.02	30	18.8
	20	7.26	.008	30	24.0
	10	2.77	.004	30	27.0
0.08	30	14.2[d]			

[a] Concentration in moles per liter; (RCl) = 0.625 ($S_2O_3^-$); buffer, (KOAc) = 0.20 ($S_2O_3^-$). [b] Stated temperatures ±0.02°. [c] Second-order rate constants (l. mole^{-1} sec.$^{-1}$) × 10^3; average of two or more determinations. [d] With (RCl) = 0.0125 M, k = 14.9.

TABLE III

RATES OF REACTION OF p-SUBSTITUTED-α-CHLOROTOLUENES WITH THIOSULFATE IN 30% DMSO AT 30°

Substituent	p-NO$_2$	p-Cl	p-H	p-i-C$_3$H$_7$
k[a]	49.4	31.6	24.0	33.7

[a] Table I, footnote c.

Stereochemistry of the 2-Bromooctane–Thiocyanate Reaction in DMSO.—The reaction of optically active 2-halooctanes with thiocyanate in acetone solutions gives 2-octyl thiocyanate of the opposite configuration and sign of rotation.[7] In the present study (−)-2-bromooctane, [α]^{26}D −33.6°, and potassium thiocyanate in acetone gave (+)-2-octyl thiocyanate, [α]^{27}D +53.2.° Similarly, the same reactants in pure DMSO give (+)-2-octyl thiocyanate, [α]^{27}D +29.8°, corresponding with 78% inversion and 22% retention of configuration.

The preparation of 2-octyl thiocyanate was carried out in 10% DMSO–90% acetone, from which the bulk of the potassium bromide precipitates. The product had [α]^{27}D +54.5°. Treatment of (−)-2-bromooctane with bromide ion in DMSO resulted in complete racemization. Lithium bromide, which is soluble in acetone, also racemizes (−)-2-bromooctane in that solvent.

Kinetic Evidence for a Second Mechanism.—In separate experiments α-chlorotoluene was allowed to remain dissolved in a mixture of DMSO and acetonitrile, for two days at 30°, and for two days at 50°. Afterward, aqueous thiosulfate solution was added to bring the solvent composition to 25% DMSO, 35% acetonitrile and 40% water. During the usual 10-minute period of temperature equilibration before the first aliquot was titrated, 20% and 30% of additional reaction occurred, respectively, beyond that which normally took place without the pretreatment of α-chlorotoluene with DMSO. Within 15–20 minutes after mixing, the rate constant returned to the usual value for that solvent composition.

In separate experiments 0.04 M thiosulfate solution was made 0.005 N in acid. Whereas colloidal sulfur was formed and the iodine titer was changed in the absence of buffer, the system was unaffected by acid in the presence of potassium acetate buffer, which was also present in all kinetic experiments.

In an experiment under kinetic conditions the solvent was removed after the reaction was complete. During the isolation procedure decomposition of sodium benzylthiosulfate occurred, yielding sulfur dioxide, sodium sulfate and the theoretical yield of crude benzyl disulfide.[8]

Discussion

Participation of the DMSO in these reactions might occur by two routes: through unique solvating properties of DMSO, and by actual participation of DMSO as a reactant to give a highly reactive cationic intermediate. Evidence is presented below suggesting that both of these mechanisms may be operative. Dimethyl sulfoxide possesses a number of unusual properties. The dielectric constant (D = 45.4 at 23°) is among the highest of all solvents not containing hydrogens capable of hydrogen bonding, and is exceeded in this respect only by alkene carbonates, formamide

(7) From (+) 2-iodooctane and potassium thiocyanate in methanol there is produced (−) 2-octyl thiocyanate, [α]^{14}D −60.8. E. J. Corey and W. Wechter, J. Am. Chem. Soc., **76**, 6040 (1954).

(8) This decomposition has been reported previously by A. Purgotti, Gazz. chim. ital., **20**, 25 (1890).

and N-alkylamides among the common organic solvents. DMSO is a basic solvent by virtue of the high electron density on oxygen resulting from the rather poor p-d overlap in the S–O bond. Many inorganic salts are soluble, including the halides of the alkali metals. Less polar solvents, such as dioxane, can, in fact, be salted out of DMSO solution by the addition of lithium bromide.

The addition of DMSO to a benzene solution of an alkali metal enolate salt results[4] in a large increase in the rate of alkylation by alkyl halides, presumably due to the dissociation of the large ion aggregates present in pure benzene into more reactive ions. That this is not the only ability involved is suggested by Cram's recent work,[3] in which the substitution of DMSO for an alcohol as solvent enhances the rate of proton abstraction from carbon by a factor of many powers of ten. This rate of increase is far greater than would be expected solely from an increase in dielectric constant, and has been attributed to the inability of DMSO to hydrogen bond through its own hydrogens and, hence, to solvate anions strongly. From the resulting essentially unsolvated anion it is unnecessary that solvent molecules be stripped away in order that the transition state be attained.[9]

An additional complication appears in the explanation of the observed[6] rate enhancement of the thiosulfate–α-chlorotoluene reaction by DMSO in partially aqueous solution. In 60% DMSO–40% water mixture the mole fraction of water is nearly 0.75. Regardless of which solvent (if either) preferentially solvates the cation, there is sufficient water present to solvate the small concentration of thiosulfate anions. That the rate is, nevertheless, large, suggests that DMSO–water interaction[10] significantly reduces the concentration of "free" water available for anion solvation.

Entirely aside from its solvating ability, DMSO is potentially able to catalyze nucleophilic displacement reaction through participation as a reactant. It is well known that methyl iodide and DMSO react to give an ionic addition compound,[11]

and similar intermediates are almost certainly involved[12] in the oxidation of activated halides[13] and tosylates[14] by DMSO to give carbonyl compounds. Both S,S,S– and O,S,S–trimethylsulfoxonium salts may be formed under the appropriate conditions,[11] but it is more likely the latter which is the significant intermediate in the oxidation reaction. Regardless of which isomeric sulfoxonium salt is involved, it is reasonable to expect a greater reactivity toward nucleophilic anions than that of the original alkyl halide, both because dimethyl sulfoxide is an excellent leaving group, and because of the especially favorable energetics of cation-anion reactions. The importance of a mechanism involving displacement of halide (or other leaving group) by DMSO followed by nucleophilic displacement of DMSO on the sulfoxonium salt is dependent on the relative rates of DMSO displacement vs. direct displacement by the nucleophile on the alkyl halide. Although DMSO probably is only moderately nucleophilic, the concentration in the pure liquid is nearly 13 M, or about 20 to 1000 times the concentration of nucleophile typically present in preparative and kinetic experiments, respectively.

Different stereochemical consequences should result from the participation of DMSO as a solvent and as a reactant

$$N^- + \underset{\underset{R''(D)}{|}}{\overset{\overset{R'}{|}}{RCX}} \xrightarrow[\substack{displacement \\ (inversion)}]{direct} \underset{\underset{R(L)}{|}}{\overset{\overset{R'}{|}}{NCR''}} + X^- \quad (1)$$

$$\underset{CH_3}{\overset{CH_3}{\diagdown}}\!\!S\text{—}O^- + \underset{\underset{R''(D)}{|}}{\overset{\overset{R'}{|}}{RCX}} \xrightarrow[\text{(rate determining)}]{inversion} \quad (2)$$

$$\underset{CH_3}{\overset{CH_3}{\diagdown}}\!\!\overset{+}{S}\text{—}O\text{—}\underset{\underset{R''X^-}{|}}{\overset{\overset{R}{|}}{CR'}} \xrightarrow[\text{(rapid)}]{\substack{N^- \\ Inversion}} \underset{\underset{R''}{|}}{\overset{\overset{R}{|}}{RCN}} + \underset{R''}{\overset{R}{}}$$

(L)　　　　　　　　　　　　　　　　　(D)

CH₃SOCH₃

Direct displacement (mechanism 1) results in a product with the inverted configuration; the two inversions which occur in the two-step mechanism 2 should lead to a product with the retained configuration. There may be, however, some tendency toward racemization if the displaced anion X⁻, attacks the halide molecule with inversion.

The two mechanisms differ kinetically. In both cases there is first-order dependence on alkyl halide concentration. Reaction 1 is first order in nucleophile N⁻, but 2 is independent of N⁻ concentration, if, as proposed above, the attack of N⁻ on the trimethylsulfoxonium ion is rapid and non-rate-determining.[15] The latter could not be ob-
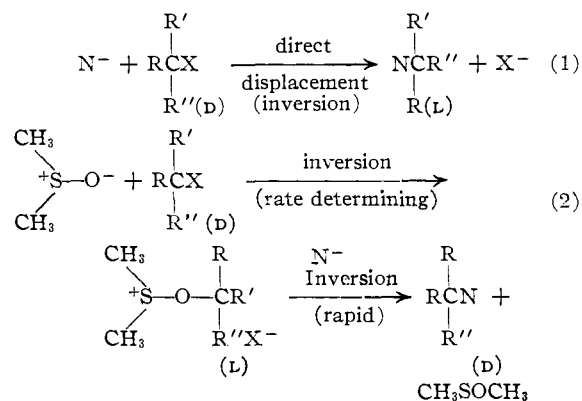
(9) Increased reactivity of anions accompanying a reduction in anion solvation has been previously reported. See, for example, S. Winstein, L. G. Savedoff, S. Smith, I. D. R. Stevens and J. S. Gall, *Tetrahedron Letters*, **9**, 24 (1960).

(10) We have observed a large heat evolution upon mixing DMSO with water, which suggests, in a qualitative way, that the interaction between these two solvents exceeds the solvent-solvent interactions within the pure liquids. The conclusion that hydrogen bonding to DMSO is stronger than similar bonding to the oxygen atom of water is consistent with the proposal that DMSO is a stronger cation solvator than is water. Spectral evidence of strong hydrogen bonding to sulfoxides has been reported: M. Tamres and S. Searles, Jr., *J. Am. Chem. Soc.*, **81**, 2100 (1959). Another indication of the hydrogen bonding ability of DMSO is the high solvent power for sucrose (at least 75 g. per 100 ml.), which probably involves strong hydroxyl-DMSO hydrogen bonding. Although Kosower has reported [E. M. Kosower, *ibid.*, **80**, 3261 (1958)] complexation of DMSO with iodide anion, there is no evidence that DMSO accelerates the solvolysis of *p*-methoxyneophyl tosylate to any extent greater than that predicted for a medium of high dielectric constant which does not specifically solvate anions. [S. G. Smith, A. H. Fainberg and S. Winstein, *ibid.*, **83**, 618 (1961)].

(11) (a) S. G. Smith and S. Winstein, *Tetrahedron*, **3**, 317 (1958); (b) R. Kuhn and H. Trischmann, *Ann.*, **611**, 117 (1958); (c) R. T. Major and H. J. Hess, *J. Org. Chem.*, **23**, 1563 (1958); (d) F. A. Cotton, J. H. Fassnacht, W. D. Horrocks, Jr., and N. A. Nelson, *J. Chem. Soc.*, 4138 (1959).

(12) I. M. Hunsberger and J. M. Tien, *Chemistry & Industry*, 88 (1959).

(13) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand and W. M. Weaver, *J. Am. Chem. Soc.*, **79**, 6562 (1957).

(14) H. R. Nace and J. J. Monagle, *J. Org. Chem.*, **24**, 1792 (1959); M. M. Baizer, *ibid.*, **25**, 670 (1960); N. Kornblum, W. J. Jones and G. J. Anderson, *J. Am. Chem. Soc.*, **81**, 4113 (1959).

(15) The rate-determining step in the oxidation reaction with DMSO is by no means as certain. The halide compounds which are easily oxidized possess electron-withdrawing groups attached to the oxidizable carbon atom. They are highly reactive toward nucleophilic

served, however, unless mechanism 1 were inoperative. The order with the respect to DMSO is more difficult to predict. The alkylation of sodiomalonic esters is nearly second order in DMSO[4]; presumably two molecules are needed to solvate the alkali metal cation. This permits the dissociation of ion-agglomerates to ions as the rate-determining step under these conditions, although it is perhaps better to consider this as a solvent effect rather than a true second-order participation by DMSO. In the present case a considerable degree of dissociation of the sodium thiosulfate ion triplets and pairs exists in 60% acetonitrile–40% water (D = 52.3) in the absence of DMSO. Substitution of 60% DMSO for acetonitrile produces an estimated 70-fold rate increase, but it is unlikely that a 70-fold increase in ion-pair dissociation is probable or even physically possible.

Activation Energy.—It has been previously reported[6] that the activation energy of the α-chlorotoluene–thiosulfate reaction is increased by increases in the dielectric constant of the solvent. The value of 16.5 kcal. mole^{-1} for 25% DMSO–35% acetonitrile–40% water is (within experimental error) consistent with a "normal" mechanism of displacement in a solvent having D = 60.9 (cf. 60% butyrolactone–40% water, D = 58.5, E_a = 16.7 kcal. mole^{-1}).

Ionic Strength.—In the reaction of thiosulfate with several p-substituted and unsubstituted α-chlorotoluenes, the rate constants for a given compound have been reported[16] to increase logarithmically with the square root of the ionic strength ($\mu^{1/2}$) in both 60% dioxane and 60% acetone. The same relationship holds true in 25% DMSO (Table II), although the decrease in log k with increasing $\mu^{1/2}$ is smaller.

Stereochemistry of the 2-Bromoöctane–Thiocyanate Reaction.—In DMSO the second product, potassium bromide, remains dissolved, although in acetone solution, precipitation occurs. The observed 22% retention might result not only from the "abnormal" displacement with a dimethyl-2-octylsulfoxonium salt intermediate, but also from bromide exchange with the dissolved potassium bromide preceding thiocyanate displacement.

The latter was confirmed by the complete inversion in 10% DMSO–90% acetone from which potassium bromide precipitates, and by the observed racemization of (−)-2-bromoöctane by lithium bromide in DMSO and in acetone. There is no stereochemical evidence in this system which requires the invocation of a sulfoxonium salt intermediate (mechanism 2).

displacement (by DMSO), but also possess an appreciably acidic hydrogen which may be involved in the subsequent step. Thus, the substituent effect does not permit a definite decision on the rate-determining step.

(16) R. Fuchs and A. Nisbet, *J. Phys. Chem.*, **65**, 365 (1961).

The "Abnormal" Mechanism.—The rapid reaction between the α-chlorotoluene–DMSO mixture and thiosulfate is most reasonably explained as involving the dimethylbenzylsulfoxonium cation, formed by the displacement of chloride ion from α-chlorotoluene by DMSO. The alternative route for the disappearance of starting materials (the hydrolysis of α-chlorotoluene due to traces of water in the DMSO, followed by the decomposition of thiosulfate by HCl) is unlikely, for α-chlorotoluene and thiosulfate disappear in equimolar amounts, and separate experiments indicate that the acetate buffer prevents the acid-catalyzed decomposition of thiosulfate. The isolation of high yields of benzyl disulfide, the direct decomposition product of the reaction product sodium benzylthiosulfate, precludes any likelihood that a side reaction accounts for the rapid initial disappearance of α-chlorotoluene and thiosulfate. An "abnormal" mechanism of the thiosulfate–α-chlorotoluene reaction is, therefore, real, although under usual conditions it must account for only a minor fraction of the total reaction.

Experimental

Kinetic Measurements.—The procedure used was essentially that previously reported.[6] The disappearance of thiosulfate was followed by titration with 0.02 N iodine solution (Sargent–Malmstadt automatic titrator). The organic halide concentration was calculated using an infinity-time titration, but the concentration at the time of mixing was also known by weight. The thiosulfate concentration at the time of mixing was available from the volumetric dilution of thiosulfate stock solution of known concentration.

Reactions of 2-Bromoöctane with Thiocyanate.—2-Bromoöctane (0.063 mole) and potassium thiocyanate were refluxed overnight in 100 ml. of dried acetone. The organic product was dissolved in ether; the solution was filtered and the solvent was evaporated. The residue was fractionally distilled, and the fraction boiling at 130–135° (27 mm.) was collected. The optical rotation in ethyl alcohol was determined in a 1-dm. cell at 27°. Similar procedures were used in carrying out the reaction in 10% DMSO–90% acetone, and in pure DMSO. In the latter case the mixture was heated to 74° for 2 hours, and both water and ether were used in the work-up procedure. Yields in all three cases were about 50%; large tarry residues remained after the distillation of 2-octyl thiocyanate.

Product Isolation.—Acetonitrile, DMSO and 1.6 g. of α-chlorotoluene were allowed to stand for 2 days at 30°. Excess thiosulfate was added and the mixture stood for 2 more days to ensure completeness of reaction. Acetonitrile, water and DMSO were evaporated under reduced pressure at a bath temperature of 55°. The solid residue was then dried for several hours at 0.3 mm. pressure and 55°. The solid was extracted with ether, and the suspended solid (sodium sulfate) was removed by filtration. The ether was evaporated and a yellow residue of impure benzyl disulfide (1.6 g.; 100% of the theoretical yield) remained. Recrystallization from methanol afforded 0.5 g. of the disulfide (m.p. 68.4–69.4°), which did not depress the melting point of an authentic sample of benzyl disulfide.