

mole) of methyl bromide, and 10 ml. of acetonitrile was sealed in an ampoule. After 4 days, the solid product was collected by filtration, washed with ether and petroleum ether, and air-dried. The yield of white needles was 3.3 g., m.p. 140–143°. One crystallization from propyl alcohol–ether gave 2.9 g. (36.6%) of purified product. The salt volatilized without melting when it was heated in a capillary tube at 145–147°.

Anal. Calcd. for $C_8H_{16}Br_2S$: C, 31.60; H, 5.30; Br, 52.58. Found: C, 31.34; H, 5.31; Br, 52.41.

Trimethyloxonium Trinitrobenzenesulfonate and Precursors.—The oxonium salt was prepared by the diazomethane procedure previously described.¹¹

Cyclooctene S-Methylepisulfonium 2,4,6-Trinitrobenzenesulfonate and Precursors.—The episulfonium salt was prepared from trimethyloxonium trinitrobenzenesulfonate and cyclooctene episulfide by a procedure previously described.¹¹

Elimination Reactions Using Iodine.—The reaction of *threo*-2-bromo-3-methylthiobutane with iodine will serve as a model for the various substrates as listed in Table I.

A 100-ml., three-necked flask was fitted with a glass stopper, condenser, and nitrogen inlet tube reaching nearly to the bottom. A delivery tube from the top of the condenser led to a 10-ml. calibrated ampoule immersed in a Dry Ice–isopropyl alcohol bath. The condenser was cooled with water at 10–15°, and the reaction flask was heated with an oil bath at 3–5° above the boiling point of the solvent.

To 3.66 g. (0.0200 mole) of sulfide in 20 ml. of acetone or acetonitrile, 5.1 g. (0.020 mole) of iodine was added. The mixture was heated under reflux for 5 hr. while a slow stream of nitrogen was bubbled through the train. Although less iodine was effective in bringing about quantitative desulfurization, the reaction period was longer. The volatile fraction (about 5 ml.) was distilled into a second tube kept at –75°. The distillate contained mostly butenes (yields, 1.4–1.8 ml., 75–98%). The butenes were analyzed by gas chromatography on a 15-ft. column of 25% G. E. "SF-96" silicone oil on firebrick at room temperature.

The solvent residue remaining in the reaction flask was diluted with 100 ml. of 5% aqueous sodium thiosulfate and extracted with 10 ml. of pentane. The pentane extract was analyzed for the presence of methyl disulfide by chromatography on a 10-ft. column of silicone oil on Fluoropak at 100°.

Elimination Reactions Using Sodium Iodide.—The apparatus described for the iodine-induced eliminations was employed, and the same general procedure for analysis was applied.

To a warm solution of 9.0 g. (0.060 mole) of sodium iodide in 60 ml. of acetonitrile, 3.7 g. (0.020 mole) of the β -bromosulfide

was added. A large quantity of sodium bromide precipitated immediately and the color of iodine appeared. Within 5 min. the reaction mixture was black. The mixture was heated under reflux with a slow stream of nitrogen flowing through the system. After 1 hr., a 1.0-ml. sample of the solution required 5.5 ml. of 0.10 *N* sodium thiosulfate (82% of theory) to titrate the iodine to a visual end point. After 4 hr., 5.7 ml. (84%) was required. Iodine yields varied from about 85–98% after 4 hr. Yields of butenes were 1.8–2.0 ml. (97–101%).

Methyl disulfide was detected by the extraction–chromatography procedure described before.

Elimination Reactions Using Methyl Iodide.—To 3.7 g. (0.020 mole) of the β -bromosulfide in 25 ml. of acetonitrile, 5.7 g. (0.040 mole) of methyl iodide was added, and the solution was brought to reflux temperature. The reaction mixture turned dark red within 10 min. After 3 hr., the yield of iodine, determined by thiosulfate titration, was 58%. Lower yields of iodine (30–40%) were found with acetone solvent. Yields of butenes were 0.5–1.0 ml. (28–55%).

A trace of methyl sulfide was detected in the volatile fraction. Since methyl bromide and *cis*-2-butene were not adequately separated by the chromatographic column used for butenes, the presence of methyl bromide in the butene fraction was verified by adding a small excess of bromine to volatile products and observing the disappearance of the *trans*-2-butene peak in the chromatogram. The adjacent peak (in the position corresponding to *cis*-2-butene and methyl bromide) remained strong.

Analysis by extraction–chromatography showed the presence of a small amount of methyl disulfide.

***trans*-1-Bromo-2-dimethylsulfoniocyclooctane Bromide.**—Anhydrous hydrogen bromide (1.0 g.) was passed into 10 ml. of acetonitrile containing 0.45 g. (0.0010 mole) of cyclooctane S-methylepisulfonium 2,4,6-trinitrobenzenesulfonate. After 5.5 hr. the solvent and excess hydrogen bromide were removed with a rotary evaporator and water aspirator. The residue was washed with two 10-ml. portions of pentane. Evaporation of the combined pentane washings at reduced pressure left a clear oil.

A solution of the oil in 5 ml. of acetonitrile and 2 g. of methyl bromide was placed in an ampoule and kept in the dark at room temperature. After 5 days the ampoule was opened and the white solid precipitate was isolated by filtration. After one crystallization from isopropyl alcohol, the product had a melting point of 147–148°; yield 0.11 g., 33%. A mixture melting point of the product with a sample of *trans*-1-bromo-2-dimethylsulfoniocyclooctane bromide from cyclooctene sulfide and methyl bromide¹¹ was undepressed.

The Mechanism of Dimethyl Sulfoxide Catalysis in Nucleophilic Displacement

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Kinetic data on nucleophilic aromatic substitution in several systems are reported which have bearing on the mechanism of catalysis by dimethyl sulfoxide and other dipolar aprotic solvents. Significant rate increases occur even at low dimethyl sulfoxide concentrations where desolvation of the nucleophile is not an important effect. The rate increase per mole of dimethyl sulfoxide is due to changes in ΔH^\ddagger ; changes in ΔS^\ddagger are slight. Using substituted phenoxide molecules as nucleophiles, dimethyl sulfoxide concentration has little effect on ρ of a Hammett ρ - σ plot, although striking rate increases occur. Dimethyl sulfoxide catalysis is independent of the charge the nucleophile bears. The rate increase per mole of dimethyl sulfoxide is relatively independent of nucleophile or solvent system. The mechanism of dimethyl sulfoxide catalysis is thought to involve polarization of the substrate by a random dimethyl sulfoxide molecule and rapid nucleophilic attack upon this species. The change in solvent structure is thought to allow more rapid reaction rates where hydrogen-bond acceptors are present.

The dramatic increase in rates of nucleophilic or basic attack by certain anions in aprotic solvents has been the subject of considerable interest in recent years.^{1–6}

(1) R. Fuchs, G. McCrary, and J. J. Bloomfield, *J. Am. Chem. Soc.*, **83**, 4281 (1961).

(2) D. J. Cram, B. Rickborn, C. A. Kingsbury, and P. Haberfeld, *ibid.*, **83**, 5835 (1961).

(3) (a) A. J. Parker, *Quart. Rev. (London)*, **16**, 163 (1962); (b) *J. Chem. Soc.*, 1328 (1961).

Cram and co-workers have shown that the rate of racemization of an optically active hydrocarbon using potassium *t*-butoxide is increased by a factor of 10⁶ going from *t*-butyl alcohol to 80% dimethyl sulfoxide–20% *t*-butyl alcohol. A recent review article by Parker

(4) L. Clark, *J. Phys. Chem.*, **65**, 1651 (1961).

(5) H. Zook and T. J. Russo, *J. Am. Chem. Soc.*, **82**, 1258 (1960).

(6) H. E. Zaugg, *ibid.*, **83**, 837 (1961); **82**, 2895 (1960).

disclosed that not only dimethyl sulfoxide (DMSO) and dimethylformamide but common aprotic solvents such as acetone and acetonitrile result in enhanced rates of nucleophilic displacement compared to protic solvents such as alcohols and water. Thus, the reaction of chloride ion and methyl iodide was increased by a factor of *ca.* 10^6 both in acetone and in acetonitrile, very similar to the rate increase observed in DMSO. Parker also showed that substances usually considered weak nucleophiles, such as fluoride ion, reacted at quite respectable rates in aprotic solvents.

Winstein, Darwish, and Holness⁷ commented on the enhanced elimination rates of 4-*t*-butylcyclohexyl toluenesulfonate with weak bases such, as chloride ion, in acetone as solvent.

Other examples of enhanced reactivity include the effect of DMSO on ester saponification.⁸ Thus, the rate increase cannot be entirely a polarity effect since DMSO gives the faster rate although its dielectric constant is less than water. Parker's results^{3b} on S_N2 displacements in various aprotic solvents show the same effect.

It is of interest to consider why a particular anion is markedly more reactive in aprotic solvents, such as DMSO, acetone, or acetonitrile, than in hydroxylic solvents such as alcohols and water.

One factor frequently mentioned as increasing the reactivity of anions is the state of solvation of that species. In pure dipolar solvents anions apparently are poorly solvated,^{3,9} and as such they are considerably more reactive than the heavily solvated species which occur in protic solvents. Thus, as Weaver and Hutchison¹⁰ have pointed out, the viewpoint perhaps should be that hydroxylic solvents diminish reactivity rather than that aprotic solvents enhance reactivity.

Several authors have demonstrated the effect of ion pairing^{10,11} or states of higher aggregation,⁶ as factors in diminishing the reactivity of a nucleophile. This factor seems to be more important in solvents such as DMSO than in aqueous systems,⁸ perhaps because anions in DMSO have a greater tendency to form ion pairs because of their unsolvated state.

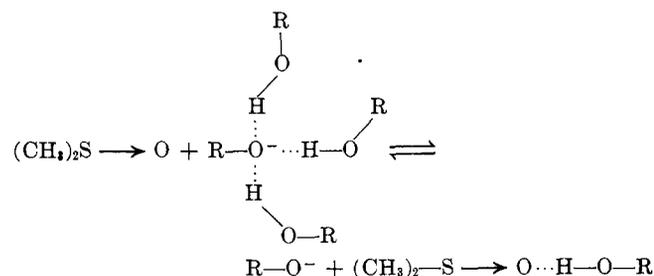
A third factor which possibly increases reactivity, pointed out by Parker,³ also by Stewart and co-workers,¹² and by Cram and co-workers,^{2,12} concerns the ability of DMSO to solvate extended charged structures such as transition states. Exactly why DMSO should be efficacious was not considered by them in detail.

Thus, reaction rates are enhanced, going to dipolar solvents from hydroxylic solvents, due to an increase in ground-state energy or a decrease in transition state energy or a combination of these effects.

It was of interest to study the effect of mixed solvents upon nucleophilic reactions. The solvent pair dimethyl sulfoxide-methanol seemed particularly attractive since their dielectric constants are similar (DMSO *ca.* 47,¹³

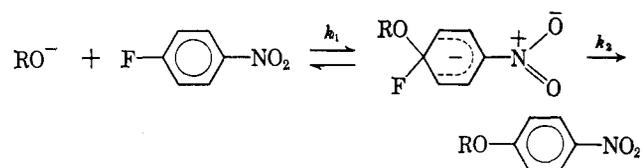
methyl alcohol *ca.* 30). Thus, polarity differences should not be a significant factor in the reactivity of a nucleophile toward the substrate.

It is well known that DMSO is a powerful hydrogen bond acceptor.¹⁴⁻¹⁶ Indeed if equal volumes of water and DMSO are mixed, the flask becomes quite hot (although the temperature change is slight when alcohols are used). Thus by progressively enriching the solvent mixture in DMSO the equilibrium between the hydrogen-bonded nucleophile (in this case alkoxide anion) and DMSO might be shifted toward the right.



The effect of enriching the solvent in DMSO, then, should be to produce a less heavily hydrogen-bonded nucleophile, which is presumably more reactive than the more heavily hydrogen-bonded species.

The systems chosen for study were 4-fluoronitrobenzene for the reactive nucleophiles and 2,4-dinitrochlorobenzene for the less reactive nucleophiles.



Nucleophilic displacement of this system was attractive because the mechanism was reasonably well understood¹⁷⁻¹⁹ and especially because the first step of the reaction (k_1) is usually rate determining and so solvation of the leaving group should not be a factor affecting the kinetics. Recently, however, Miller⁹ presented data showing that the breakup of the complex, k_2 , may approach k_1 in velocity and, in fact, may be rate determining in certain systems particularly where fluoride is the leaving group. Data from this study do not support this contention in the solvent systems studied.

Experimental

Reaction rates were determined as follows. The substrate was weighed into a dried volumetric flask. The solvent was added by pipet and the mixture was thermostatted at the correct temperature. A standardized solution was prepared and similarly thermostatted. A known volume of the base solution was added to begin the reaction. The final concentration of substrate was 0.02–0.04 *M*, while that of nucleophile was usually 0.008–0.012 *M*. The final concentrations of the runs using benzylamine were *ca.* 0.4 and 0.1 *M*, respectively. In runs using thioalkoxide and substituted phenoxides as nucleophiles, a slight molar excess of the thiol or phenol was weighed into the reaction vessel and

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(8) C. A. Kingsbury, unpublished work; also E. Tommila and M. Murto, *Acta Chem. Scand.*, **17**, 1947 (1963).

(9) (a) J. Miller, *J. Am. Chem. Soc.*, **85**, 1628 (1963); (b) J. Miller and A. J. Parker, *ibid.*, **83**, 117 (1961).

(10) W. Weaver and J. Hutchison, *ibid.*, **86**, 261 (1964).

(11) (a) E. Cavell, *J. Chem. Soc.*, 4217 (1958); (b) E. Cavell and J. Speed, *ibid.*, 1453 (1959).

(12) R. Stewart, J. P. O'Donnell, D. J. Cram, and B. Rickborn, *Tetrahedron*, **18**, 917 (1962).

(13) I. Kolthoff and T. Reddy, *Inorg. Chem.*, **1**, 189 (1962).

(14) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

(15) D. Barnard, J. Fabian, and H. Koch, *J. Chem. Soc.*, 2442 (1949).

(16) A. Allerhand and P. von R. Schleyer, *J. Am. Chem. Soc.*, **85**, 1715 (1963).

(17) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).

(18) S. D. Ross, J. Bruno, and R. C. Peterson, *J. Am. Chem. Soc.*, **85**, 3999 (1963).

(19) J. D. Reinheimer, J. T. Gerig, and J. C. Cochran, *ibid.*, **83**, 2873 (1961).

the anion formed by addition of sodium methoxide. A total of nine points were taken, each being quenched by addition to a standard acid solution. This mixture was heated to drive off volatile organic solvents and back-titrated with standard base while still warm, using brom cresol purple as indicator. Infinity titers indicated that between 85–99% reaction occurred, 96% being a common figure. In the benzylamine runs a Volhard determination was used to determine extent of reaction.²⁰

Calculations were made by the standard methods as described in Frost and Pearson.²¹ For DMSO runs, the densities of the solvent mixtures were determined and the volume change upon mixing was calculated,²² and this correction was applied to the apparent initial solution volumes before the rate constant was calculated. Reproducibility of the data between different workers using fresh reagents was *ca.* 5%. The reaction temperature of *ca.* 26° was sufficiently close to room temperature that no correction for liquid expansion was made.

The solvents were purified as follows. Methanol (Mallinckrodt anhydrous) was refluxed over KOCH₃ for 24 hr., then slowly distilled through a 24-cm. Podbielniak column, a center cut being taken. Dimethyl sulfoxide (Crown-Zellerbach) was purified by passing twice through a column of Linde 4A Molecular Sieve and distillation at reduced pressure from a small quantity of sieve. The center cut was taken, and stored over Molecular Sieve. Another procedure involving heating for *ca.* 16 hr. over calcium hydride and distillation as before yielded DMSO of comparable quality. No claims are made as to dryness, however. Rates were similar in both solvents. Absolute ethyl alcohol (Gold Shield), isopropyl alcohol (Mallinckrodt spectrophotometric grade), and *t*-butyl alcohol (Eastman White Label), were all refluxed over their respective alkoxides and slowly distilled through a 24-cm. Podbielniak, large ends being discarded. Reagent grade acetone (Mallinckrodt) was simply distilled as before since attempts to purify it usually caused a slight amount of condensation. Dioxane (Baker and Adamson) was purified by Fieser's procedure.²³ More conveniently dioxane was purified by distillation from LiAlH₄. Reaction rates were very similar using dioxane purified by either procedure. The reagents *p*-fluoronitrobenzene (Aldrich) and benzyl mercaptan (Eastman White Label) were distilled at reduced pressure, large end cuts being discarded; phenol (Mallinckrodt) and cresol (Eastman) were similarly distilled. Benzylamine (Eastman) was distilled from zinc dust. The following reagents were purified by crystallization: 2,4-dinitrochlorobenzene (Eastman), m.p. 51.5–52.0°; 4-bromophenol (Eastman), m.p. 63.5–64.8°; 4-methoxyphenol (Eastman), m.p. 53.0–54.2°. Mallinckrodt photograde hydroquinone, m.p. 172–174°, was used without purification.

Product studies were run in selected instances. *p*-Cresol, 0.120 g., was mixed with 2,4-dinitrochlorobenzene, 0.200 g., dissolved in 25.0 ml. of DMSO and 25.0 ml. of CH₃OH which was 0.024 *N* in KOCH₃. After about 5 half-lives of reaction, the reaction mixture was worked up yielding 0.129 g. (4.7×10^{-4} moles) of 2,4-dinitro-4-methyldiphenyl ether, m.p. 91.5–92.5°, 79% yield, lit.²⁴ m.p. 93°. This material was identical with the product resulting from reaction in pure methyl alcohol as solvent.

A similar product study with 4-bromophenoxide with 2,4-dinitrochlorobenzene in 50% DMSO–50% CH₃OH yielded a product identical with that in 100% methyl alcohol, m.p. 135.5–136.2°, lit.²⁵ m.p. 136–137.5°.

A similar product study was run with 0.140 g. of benzyl mercaptan on 4-fluoronitrobenzene, 0.160 g., in a solution 0.024 *N* in KOCH₃. The product benzyl *p*-nitrophenyl sulfide, m.p. 121.9–122.9°, 0.241 g. (82% yield), was isolated (identical yield in CH₃OH and 50% CH₃OH–50% DMSO), lit.²⁶ m.p. 123°.

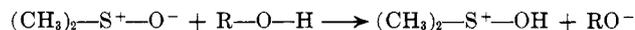
A similar study on 1.90 g. of 4-fluoronitrobenzene with a two-fold molar excess of potassium isopropoxide in 50% isopropyl alcohol–50% dimethyl sulfoxide at room temperature yielded 1.85 g. of isopropyl *p*-nitrophenyl ether (89% yield), which was

distilled over a short-pass still at 108–111° (2 mm.). The n.m.r. spectrum showed the expected resonance absorptions.

Discussion and Results

The rather large effect of DMSO on the rates of nucleophilic aromatic substitution might be due to a direct chemical effect or general solvent effect. These possibilities will be discussed in turn.

Direct Chemical Effects.—The direct chemical effect might assume two forms. One possible form concerns the basicity of DMSO with respect to the solvent.

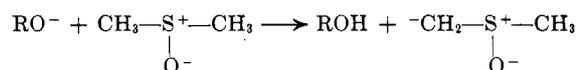


The effect of this equilibrium is to generate a nucleophilic species, which, if it were in the vicinity of the substrate, could lead to a very fast reaction, since the nucleophile generated in such a manner may well be relatively more reactive than the more heavily solvent-encumbered alkoxide originally added to the reaction mixture. Similar acid–base interaction with water has been reported for amine oxides.²⁷



Product studies on certain selected reactions render the above possibility unlikely. Thus, with C₆H₅CH₂—S—K⁺ as the added nucleophile and 4-fluoronitrobenzene as the substrate in methyl alcohol–dimethyl sulfoxide mixtures, the above effect should yield 4-methoxynitrobenzene as product. In fact, the product expected from normal nucleophilic attack of the added nucleophile was isolated. Similarly the reaction of 4-cresol and 4-bromophenol with 2,4-dinitrochlorobenzene yielded the respective ethers as the only isolable product in basic methyl alcohol–dimethyl sulfoxide mixtures.

Another possibility involves participation of DMSO in an acid–base reaction yielding the DMSO anion.²⁸



The *pK_a* of DMSO²⁹ is *ca.* 37 compared with *ca.* 17 for weakly acidic alcohols such as isopropyl alcohol and *t*-butyl alcohol. However, the reaction of potassium isopropoxide with 2,4-dinitrochlorobenzene in 50% dimethyl sulfoxide–50% isopropyl alcohol yielded the isopropyl 2,4-dinitrophenyl ether as the only isolable product. Thus the minute concentration of DMSO anion is not kinetically significant. In general the DMSO solvent effects on potassium isopropoxide are very similar to other alkoxides (*vide infra*). There is no evidence, either kinetic or *via* product analysis, for the incursion of a second nucleophilic species.

General Solvent Effects.—Table I gives a typical set of experimental data in which the nucleophile is methoxide and the substrates are 4-fluoronitrobenzene and 2,4-dinitrochlorobenzene. It is seen that at very low concentrations of DMSO, substantial rate increases are observed. In 80% CH₃OH–20% DMSO the methyl alcohol is 19.6 *M*. There is sufficient alcohol present to form a hydrogen bond with DMSO and to completely solvate the 0.01 *N* methoxide as well; yet the

(20) H. Diehl and G. F. Smith, "Quantitative Analysis," John Wiley and Sons, Inc., New York, N. Y., 1952, p. 330.

(21) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1961, p. 15.

(22) F. Daniels, J. Matthews, and J. Williams, "Experimental Physical Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1949, p. 100.

(23) L. F. Fieser, "Experiments in Organic Chemistry," 3rd. Ed., D. C. Heath and Co., Boston, Mass., 1955, p. 284.

(24) N. Cook, *J. Am. Chem. Soc.*, **32**, 1289 (1910).

(25) L. Raiford and J. Colbert, *ibid.*, **48**, 2660 (1926).

(26) W. Waldron and E. Reid, *ibid.*, **45**, 2402 (1923).

(27) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1962, p. 513.

(28) E. J. Corey and M. Chaykorsky, *J. Am. Chem. Soc.*, **84**, 867 (1962).

(29) E. C. Steiner and J. Gilbert, *ibid.*, **85**, 3054 (1963).

TABLE I
EFFECT OF DIMETHYL SULFOXIDE CONCENTRATION ON
NUCLEOPHILIC DISPLACEMENT

Solvent (CH ₃ OH-DMSO), % DMSO (v./v.)	k_{obsd} , l. mole ⁻¹ sec. ⁻¹	Relative rate, $k_{\text{ox}} = k_{\text{obsd}}/k_0$
25.4°		
CH ₃ O ⁻ Na ⁺ + FC ₆ H ₄ NO ₂ → CH ₃ OC ₆ H ₄ NO ₂ + NaF		
0	$k_0 = 1.78 \pm 0.03 \times 10^{-4}$	1
20	$7.63 \pm 0.07 \times 10^{-4}$	4.29
40	$4.22 \pm 0.02 \times 10^{-2}$	23.7
60	$3.04 \pm 0.03 \times 10^{-2}$	171
70	$9.86 \pm 0.34 \times 10^{-2}$	554
80	$3.77 \pm 0.11 \times 10^{-1}$	2120
25.6°		
CH ₃ O ⁻ Na ⁺ + ClC ₆ H ₄ (NO ₂) ₂ → CH ₃ OC ₆ H ₄ (NO ₂) ₂ + NaCl		
0	$k_0 = 7.44 \pm 0.05 \times 10^{-2}$	1
20	$1.19 \pm 0.02 \times 10^{-2}$	4.87
40	$5.26 \pm 0.12 \times 10^{-1}$	21.6

Incidentally, Miller's prediction⁹ that the lack of solvation of the leaving group will slow step 2 of the displacement is probably correct, at least in concentrated DMSO solutions. The n.m.r. spectrum of 2,4-dinitrochlorobenzene in 100% DMSO with piperidine showed two superimposed ABX patterns, one considerably upfield from the other. The pattern occurring at higher field is tentatively ascribed to the Meisenheimer complex.³¹ The chemical shifts in δ -units from TMS are shown in the illustration. The negative charge in

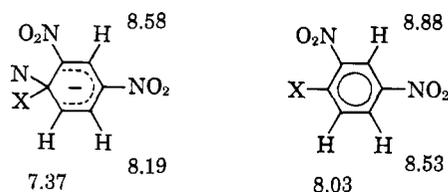


TABLE II
EFFECT OF DIMETHYL SULFOXIDE CONCENTRATION ON NUCLEOPHILIC DISPLACEMENT

CH ₃ OH-DMSO, % DMSO (v./v.)	Temp., °C.	k_{obsd} , l. mole ⁻¹ sec. ⁻¹	Relative rate, k_{obsd}/k_0	ΔH^* , kcal/mole	ΔS^* , e.u.
C ₆ H ₅ CH ₂ S ⁻ K ⁺ + FC ₆ H ₄ NO ₂ → C ₆ H ₅ CH ₂ SC ₆ H ₄ NO ₂					
0	25.9	$1.07 \pm 0.02 \times 10^{-3}$	1.00		
	40.1	$5.30 \pm 0.06 \times 10^{-3}$		19.4	-7.5
20	25.9	$6.14 \pm 0.08 \times 10^{-3}$	5.72		
	40.1	$2.53 \pm 0.08 \times 10^{-2}$		18.0	-8.5
40	25.9	$3.82 \pm 0.03 \times 10^{-2}$	35.7		
	40.1	$1.41 \pm 0.03 \times 10^{-1}$		16.6	-9.9
60	25.9	$2.85 \pm 0.04 \times 10^{-1}$	266		
C ₆ H ₅ CH ₂ NH ₂ + ClC ₆ H ₃ (NO ₂) ₂ → C ₆ H ₅ CH ₂ NHC ₆ H ₃ (NO ₂) ₂					
0	25.6	$k_0 = 3.99 \pm 0.04 \times 10^{-4}$	1.00		
10					
20	25.6	$1.08 \pm 0.06 \times 10^{-3}$	2.71		
30					
40					
50	25.1	$4.54 \pm 0.15 \times 10^{-3}$	11.4		
60					
70	25.1	$1.36 \pm 0.03 \times 10^{-2}$	34.1		
80					
90	25.6	$2.91 \pm 0.10 \times 10^{-2}$	72.9		

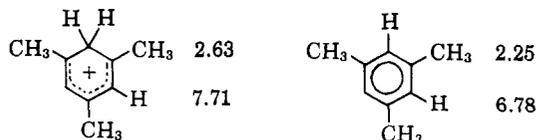
relative reaction rate is considerably greater than in 100% CH₃OH.

It is also seen that the rate increase is relatively independent of substrate. Thus the relative rates k_{obsd}/k_0 for the substrate 2,4-dinitrochlorobenzene are 21.6 between 0 and 40% DMSO while they are 23.7 for 4-fluoronitrobenzene for the same solvents. These results allow extrapolation of solvent effects from substrate to substrate to be done with some confidence.

Since the transition state for the reaction of 4-fluoronitrobenzene probably occurs farther along the reaction coordinate³⁰ than the corresponding transition state for attack on 2,4-dinitrochlorobenzene, the former might have been expected to be more sensitive to solvent effects. However, this effect is very slight as the relative rate ratios show.

The difference in solvent effects for the leaving groups fluoride and chloride is likewise very slight. Thus, differential solvation effects of the leaving group are of little importance whether or not the detachment of the fluoride is rate determining. Parker^{3b} noticed similar effects in the study of SN₂ displacements.

the aromatic ring shields the protons *ca.* 0.7–0.3 p.p.m. compared to the neutral substrate. Interruption of ring current also contributes to the shielding. Surprisingly, the shielding effect in this case is less dramatic than the deshielding effect observed in the π -complex,³² *ca.* 0.93 p.p.m. In the latter case the deshielding effect due to the presence of the positive charge is opposed by the interruption of the ring current. It is possible that π -overlap between the 2- and 6-positions allows ring current to persist in both complexes. However, fast



equilibrium between substrate and complex probably perturbs the true chemical shift in both cases.

Table II shows the effect of DMSO concentration on rates of nucleophilic displacement using sodium benzyl

(31) J. Meisenheimer, *Ann. Chem. Liebigs*, **323**, 205 (1902).

(32) The author's measurement in 96% H₂SO₄, but first reported by C. MacLean and E. Mackor, *Mol. Phys.*, **4**, 241 (1961).

(30) G. F. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

thioalkoxide and benzylamine as nucleophiles. Compared to sodium methoxide, the thioalkoxide anion shows a slightly larger rate increase per increment of DMSO. On the other hand benzylamine is much less sensitive to DMSO concentration.

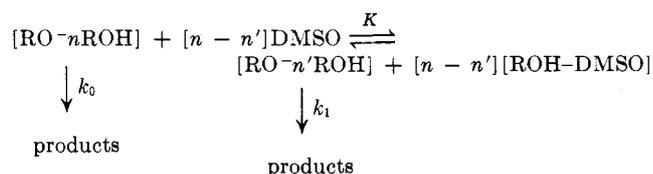
Table II also lists activation parameters for reaction at three different DMSO concentrations. The increase in rate observed with increasing DMSO concentrations is associated with a decrease in activation enthalpy, and is slightly opposed by a decrease in entropy. These changes in activation parameters result from a more shallow rate increase per increment of DMSO at higher temperatures compared to lower temperatures.

Other Alkoxides as Nucleophiles.—Table III shows the kinetic data for nucleophilic attack of potassium isopropoxide in isopropyl alcohol and ethoxide in absolute ethyl alcohol. Once again as the solvent alcohol is replaced by DMSO, a strong rate increase is observed, even at low DMSO concentrations.

TABLE III

Solvent ROH-DMSO, % DMSO (v./v.)	k_{obsd} , l. mole ⁻¹ sec. ⁻¹	Relative rate, k_{obsd}/k_0
25.8°		
$\text{C}_2\text{H}_5\text{O}^-\text{Na}^+ + \text{FC}_6\text{H}_4\text{NO}_2 \longrightarrow \text{C}_2\text{H}_5\text{OC}_6\text{H}_4\text{NO}_2$		
0	$k_0 = 1.01 \pm 0.02 \times 10^{-3}$	1.00
20	$3.39 \pm 0.03 \times 10^{-3}$	3.36
40	$2.15 \pm 0.07 \times 10^{-2}$	21.3
50	$4.08 \pm 0.11 \times 10^{-2}$	40.3
60	$1.20 \pm 0.03 \times 10^{-1}$	119
80	$9.18 \pm 0.08 \times 10^{-1}$	908
25.6°		
$(\text{CH}_3)_2\text{CHO}^-\text{K}^+ + \text{FC}_6\text{H}_4\text{NO}_2 \longrightarrow (\text{CH}_3)_2\text{CHOC}_6\text{H}_4\text{NO}_2$		
0	$k_0 = 5.42 \pm 0.06 \times 10^{-4}$	1.00
10	$2.54 \pm 0.10 \times 10^{-3}$	4.68
20	$6.40 \pm 0.10 \times 10^{-3}$	11.9
40	$4.21 \pm 0.14 \times 10^{-2}$	77.8
50	$8.60 \pm 0.16 \times 10^{-2}$	159
60	$2.06 \pm 0.03 \times 10^{-1}$	380
70	$5.24 \pm 0.08 \times 10^{-1}$	967

If DMSO is able to promote nucleophilic attack by removal of hydroxylic species hydrogen bonded to the anion, an equilibrium relationship should exist between the hydrogen-bonded anion and DMSO.



In the above relationship n is the number of hydrogen-bonding molecules associated with the alkoxide RO^- ; the quantity $n - n'$ is the number of hydrogen-bonding molecules lost by interaction with DMSO. The kinetic equation then should be

$$-\frac{d[S]}{dt} = k_{\text{obsd}}[S][\text{RO}^{-\text{stoi}}] = \frac{k_0[\text{RO}^{-n}\text{ROH}][S] + k_1[\text{RO}^{-n'}\text{ROH}][S]}{K[\text{RO}^{-n}\text{ROH}] + [\text{DMSO}]^{n-n'}}$$

where S is substrate, $[\text{RO}^{-\text{stoi}}]$ is the total amount of added alkoxide, and k_0 is the rate constant in 100% ROH. Applying the equilibrium conditions

$$k_{\text{obsd}}[\text{RO}^{-\text{stoi}}] = k_0[\text{RO}^{-n}\text{ROH}] + \frac{k_1}{K}[\text{RO}^{-n'}\text{ROH}] \frac{[\text{DMSO}]^{n-n'}}{[\text{DMSO-ROH}]^{n-n'}}$$

At fairly low DMSO concentrations $[\text{RO}^{-\text{stoi}}]$ will be close to $[\text{RO}^{-n}\text{ROH}]$, and the following relationship can be derived.

$$[k_{\text{obsd}} - k_0] = \frac{k_1}{[K]^{n-n'}} [\text{ROH}]^{n-n'}$$

$$\log [k_{\text{obsd}} - k_0] = [n - n'] \log [\text{ROH}] + \text{constant}$$

However, no plot of $\log [k_{\text{obsd}} - k_0]$ vs. $\log [\text{ROH}]$ is a straight line. Ignoring the lack of linearity and taking the initial slope for the data in Table I, where the anion is methoxide, $n - n' = 8.2$. This is a completely unrealistic figure for the number of hydrogen-bonding molecules lost by interaction of the anion with DMSO. Most anions are considered to have not more than three or four solvation molecules in the primary shell.³³ Many similar mathematical approaches can be made depending upon the assumptions made, but none treat the data satisfactorily. It is concluded that the DMSO systems in this study do not obey equilibrium relationships. Hence, removal of hydrogen-bonding molecules from the anion by direct chemical equilibrium means is unlikely.

If one or more molecules of DMSO are directly involved in the transition state by direct chemical interaction, obeying equilibrium laws, the following relationship can be derived.

$$\log [k_{\text{obsd}} - k_0] = [n - n'] \log [\text{DMSO}] + \text{constant}$$

A log-log plot again is not linear indicating that the interaction of DMSO with the transition state is non-specific.

On the other hand, an excellent linear plot of $\log [k_{\text{obsd}} - k_0]$ vs. $[\text{DMSO}]$ is possible for the data in Table I, II, and III. This indicates that the following mathematical relationship is obeyed.

$$\log [k_{\text{obsd}} - k_0] = r[\text{DMSO}] + v$$

The constant r is a measure of the sensitivity of a given system to DMSO catalysis. A typical plot for three solvent systems is shown in Fig. 1. Table IV lists the r -values for the several systems studied.

TABLE IV
SENSITIVITY TO DIMETHYL SULFOXIDE CATALYSIS

Anion	Substrate	Solvent-DMSO	r
$\text{CH}_3\text{O}^-\text{Na}^+$	$\text{FC}_6\text{H}_4\text{NO}_2$	CH_3OH	0.277
$\text{C}_2\text{H}_5\text{O}^-\text{Na}^+$	$\text{FC}_6\text{H}_4\text{NO}_2$	$\text{C}_2\text{H}_5\text{OH}$	0.270
$(\text{CH}_3)_2\text{CHO}^-\text{K}^+$	$\text{FC}_6\text{H}_4\text{NO}_2$	$(\text{CH}_3)_2\text{CHOH}$	0.267
$\text{C}_6\text{H}_5\text{CH}_2\text{S}^-\text{K}^+$	$\text{FC}_6\text{H}_4\text{NO}_2$	CH_3OH	0.282
$\text{C}_6\text{H}_5\text{O}^-\text{K}^+$	$\text{ClC}_6\text{H}_3(\text{NO}_2)_2$	CH_3OH	0.238
$\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$	$\text{ClC}_6\text{H}_3(\text{NO}_2)_2$	CH_3OH	0.178

The r -values decrease somewhat for weak nucleophiles and increase somewhat for strong nucleophiles.

However, for four of the six systems studied, r is surprisingly constant, *ca.* 0.275, even though the character of the anion and of the solvent varies considerably. From these results it would seem that the DMSO catalysis is relatively nondependent on the system involved. The sterically hindered anion, potassium isopropoxide, has almost the same sensitivity to DMSO concentration as sodium methoxide.

Solvent Polarity Effects.—The data in Tables I and II have bearing upon the well-known theory of solvent

(33) R. W. Gurney, "Ionic Processes in Solution," McGraw-Hill Book Co., Inc., New York, N. Y., 1953, p. 87.

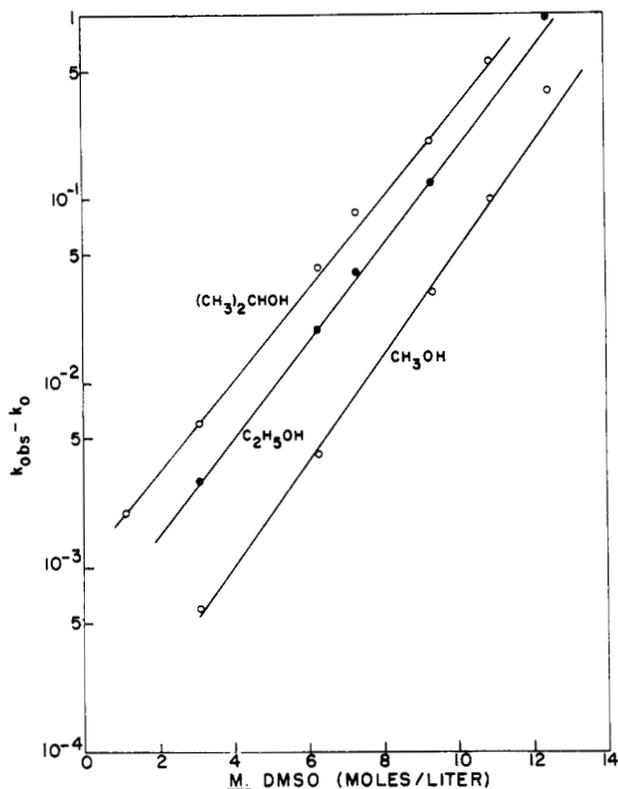


Fig. 1.—Effect of DMSO concentration on nucleophilic displacement in DMSO-ROH mixtures: upper line, potassium isopropoxide in isopropyl alcohol on 4-fluoronitrobenzene at 25.6°; middle line, sodium ethoxide in ethyl alcohol at 25.6°; lower line, sodium methoxide in methyl alcohol at 25.4°.

polarity effects as formulated by Ingold.³⁴ The theory states that reactions in which existing charge is dispersed should experience a rate decrease going to more polar solvents. Conversely, reactions in which charge is generated in the transition state should undergo a strong rate increase, under the same conditions.

Table II shows that a moderate rate increase is observed when benzylamine is the nucleophile, which fits the Ingold theory. Yet with methoxide and benzyl thioalkoxide as nucleophiles, a much stronger rate increase is observed, going from methyl alcohol (dielectric constant *ca.* 30³⁵) to methyl alcohol-dimethyl sulfoxide mixtures (DMSO dielectric constant *ca.* 46¹³). Unless methyl alcohol-dimethyl sulfoxide mixtures have an abnormally low dielectric constant, the latter observation violates Ingold's theory.

A diametrically opposite situation results in ester saponification.⁸ In this case, replacement of water by DMSO results in a rate increase.

On the other hand, replacement of water by alcohols produces a rate decrease, although the Ingold theory predicts the opposite effect. This rate decrease has been ascribed to the transition state being more polar than the reagents rather than less polar.³⁶ However, it is not clear how attack of a hydroxide anion upon an ester molecule can result in anything but dispersal of charge.

At any rate, it is clear that the type of solvent is more important than its polar character as estimated by

(34) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 345.

(35) "International Critical Tables," Vol. 6, E. Washburn, Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1929, p. 32.

(36) M. Bender, *Chem. Rev.*, **60**, 53 (1960).

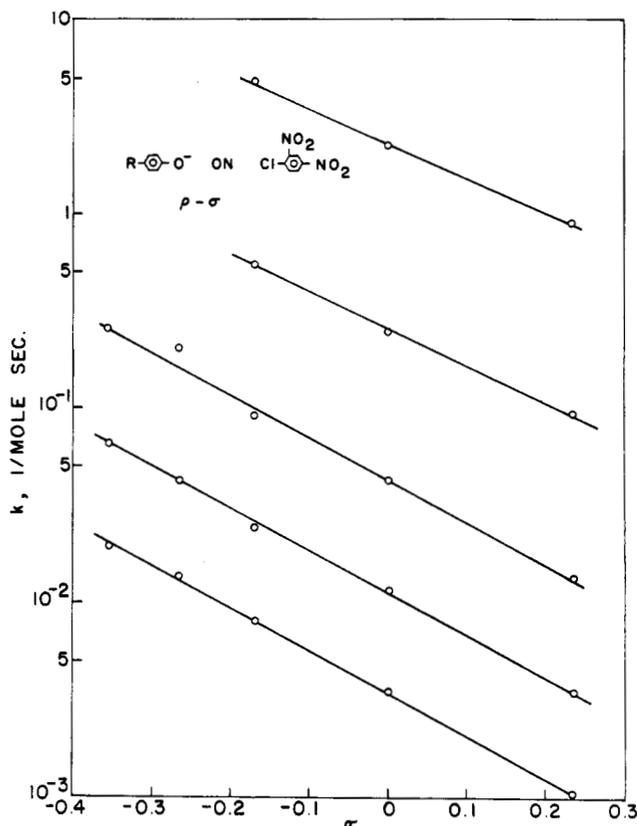


Fig. 2.—Hammett plot using substituents hydroxy, methoxy, methyl, hydrogen, and bromo (in order); solvents (top to bottom), 80% DMSO, 60% DMSO, 40% DMSO, 20% DMSO, and 0% DMSO (100% CH₃OH); temperature, 25.9°.

the usual criteria, *e.g.*, dielectric constant. The Ingold theory is probably good for small changes in solvent, *i.e.*, methanol to ethanol or DMSO to sulfolane, but not for gross changes in type of solvent, *i.e.*, from methanol to DMSO. A more accurate definition of "polarity" is needed to account for all solvents. It is of interest to note that Tommila has found that solvolysis of benzyl halides occurs at a lower rate going from water to water-dimethyl sulfoxide mixtures.³⁷

Solvent Effect on ρ - σ Relations.—The reaction studied was the attack of substituted phenoxide anions upon 2,4-dinitrochlorobenzene in methyl alcohol-dimethyl sulfoxide mixtures.³⁸ The results are shown in Fig. 2. It is seen that in methyl alcohol-dimethyl sulfoxide mixtures of 0, 20, and 40% DMSO, the slope remains quite constant at *ca.* -2.16. A quite sharp break occurs in the vicinity of 60% DMSO (although the data are less complete); ρ increases to -1.88 at 60% DMSO and -1.80 at 80% DMSO. It is interesting to note that this is the region of solvent composition in which the DMSO concentration overtakes and becomes larger than the methyl alcohol concentration.

Although ρ does not change significantly in solutions of less than 60% DMSO, the individual reaction rates once again increase dramatically. Thus going from 0-40% DMSO results in a rate increase of *ca.* 13 for each nucleophile studied.

The *p*-hydroxy substituent (*i.e.*, a hydroquinone monoanion) seems to exert only an electronic effect on the reaction rates at various DMSO concentrations.

(37) E. Tommila and O. Virtanen, *Suomen Kemistilehti*, **34B**, 139 (1961).

(38) J. Miller and A. J. Parker, *Australian J. Chem.*, **9**, 312 (1956).

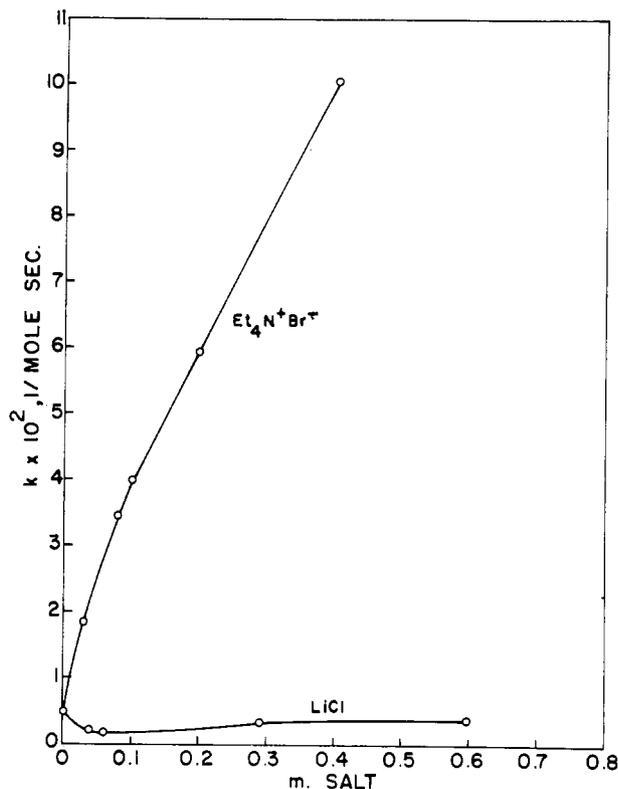


Fig. 3.—Effect of added salt, benzyl thioalkoxide, on 4-fluoronitrobenzene at 25.9°, in 80% dioxane–20% methyl alcohol.

An *o*-hydroxy substituent (*i.e.*, catechol monoanion) exhibits quite different behavior at Table V shows.

TABLE V

RELATIVE RATES OF DISPLACEMENT BY SUBSTITUTED PHENOLS

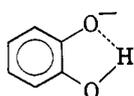
Solvent DMSO-CH ₃ OH, % DMSO (v./v.)	Relative rates ^a		
	Catechol	Hydroquinone	Phenol
0	1.82	5.60	1.00
20	3.01	17.1	3.30
40	6.42	74.6	12.4
60	49.1		71.7
80	147		651

^a Temperature, 25.9°.

The data show that the hydroquinone anion is more reactive than phenoxide by approximately a factor of 6 throughout the solvent range studied. The anion of catechol, on the other hand, was more reactive than phenoxide at the outset, but steadily lost ground, as DMSO concentration increased.

The reactivity of catechol monoanion may be due to a steric effect. If the *o*-hydroxy group is hydrogen bonded to a DMSO molecule, the nucleophilic reactivity of the neighboring anion may well be reduced, compared to phenoxide. It is noteworthy that the difference in reactivity is much more striking at high DMSO concentrations.

In 100% methyl alcohol the lower reactivity of catechol monoanion compared with that of hydroquinone monoanion may be due to a strong intramolecular hydrogen bond in the former case.



Other Solvent Systems.—Tables VI and VII record the rates of nucleophilic attack of thioalkoxide and alkoxide anions on fluoronitrobenzene in several solvent systems whose constant component was methyl alcohol. It is seen that almost all solvents, whether hydroxylic or nonhydroxylic, produce an initial rate increase. As the concentration of methyl alcohol becomes low and the concentration of the other solvent becomes high, a rate decrease is observed. This behavior is tentatively ascribed to ion-pair formation, since the rate decrease is much more marked for low dielectric constant solvents. Ion pairing seems to be much more important for methoxide than the benzyl thioalkoxide.

TABLE VI

EFFECT OF SOLVENT ON NUCLEOPHILIC DISPLACEMENT, SULFUR NUCLEOPHILES

$$\text{C}_6\text{H}_5\text{CH}_2\text{S}^-\text{K}^+ + \text{FC}_6\text{H}_4\text{NO}_2 \xrightarrow{25.92^\circ} \text{C}_6\text{H}_5\text{CH}_2\text{S}-\text{C}_6\text{H}_4\text{NO}_2$$

CH ₃ OH-S mixtures, % CH ₃ OH (v./v.)	<i>k</i> _{obsd} × 10 ²			
	S = isopropyl alcohol	S = <i>t</i> -butyl alcohol	S = dioxane	S = benzene
100	1.16	1.16	1.16	1.16
90		1.55	1.62	1.35
80	1.91	2.29		1.41
70		2.94	3.12	
60	3.62	3.35		
50			5.05	
40	7.10	10.8	4.95	1.39
30		21.3		
20		45.0	5.46	0.81
10	30.5	62.6		
0	62.3	62.8		

TABLE VII

EFFECT OF SOLVENT ON NUCLEOPHILIC DISPLACEMENT, OXYGEN NUCLEOPHILES

$$\text{CH}_3\text{O}^-\text{K}^+ + \text{FC}_6\text{H}_4\text{NO}_2 \xrightarrow{25.92^\circ} \text{CH}_3\text{O}-\text{C}_6\text{H}_4\text{NO}_2$$

CH ₃ OH-S mixtures, % CH ₃ OH (v./v.)	<i>k</i> _{obsd} × 10 ²		
	S = isopropyl alcohol	S = <i>t</i> -butyl alcohol	S = acetone
100	1.78	1.78	1.78
90			
80		3.08	
70	3.42		7.02
60		5.00	
50	8.30		15.4
40		11.4	
30	12.9		
20	20.3	37.6	39.0
10	27.9	56.2	516
0	9.55	22.6	

The data in Tables VI and VII compared with that in I and II show solvent effect on rate to be roughly DMSO > acetone > *t*-butyl alcohol > isopropyl alcohol > dioxane > benzene. Thus, strongly dipolar solvents (which are also strong hydrogen-bond acceptors) produce the fastest rates of nucleophilic attack. However, other solvents which are poor hydrogen-bond donors, but reasonably good hydrogen-bond acceptors,³⁹ compared to methyl alcohol, likewise produce modest rate increases.

An interesting comparison is possible with the data in Table III and Table VII. The anion methoxide is a considerably stronger nucleophile than isopropoxide by

(39) L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952).

a factor of *ca.* 18, in a common solvent (isopropyl alcohol). The nucleophilic activity clearly does not parallel the basicity of these species.⁴⁰

Salt Effects.—In one sense, the ion pair of an inorganic salt should resemble a dipolar DMSO molecule since both are characterized by a degree of charge separation. It was of interest to see if salts would produce the same rate increase as DMSO. Figure 3 shows the effects of tetraethylammonium bromide and lithium chloride on the reaction of benzyl thioalkoxide on 4-fluoronitrobenzene in 80% dioxane–20% methyl alcohol. This solvent was chosen to ensure a large concentration of ion pairs. Unfortunately, the results are inconclusive since the ammonium salt does indeed produce a strong rate increase, but the lithium salt shows little effect. These results are in contrast to those of Reinheimer and co-workers¹⁹ who found that lithium salts produced a marked rate decrease in 100% methyl alcohol, while potassium salts produced rate increases.

It is well known that lithium salts have a greater tendency to form ion pairs than ammonium salts.⁴¹ Thus, formation of ion aggregates with the nucleophile may have reduced the activity of this species in the lithium chloride solutions, resulting in slow rates.

Mechanism of DMSO Catalysis.—With respect to the data at hand (Parker,³ Cram,² and this work), the following observations are worthy of note.

(1) Rate increases occur even at low DMSO concentrations. No sharp change is noted as DMSO passes from the minor to the major solvent species.

(2) The rate increases per increment of DMSO is due to a change in ΔH^* ; ΔS^* accounts for only a minor rate change.

(3) DMSO catalysis results in little effect on ρ of a ρ - σ plot.

(4) The effect of DMSO is independent of the charge character of the reaction³; *i.e.*, a rate increase is observed if either a negatively charged or a neutral nucleophile is used, or if the substrate is neutral or positively charged.

(5) Many other solvents produce modest rate increases. Relative rate increases are roughly proportional to the dipole moment of the solvent. In mixed solvents the capacity of one member to accept hydrogen bonds may be a factor.

(6) The sensitivity of the system to DMSO catalysis (r -values) are roughly constant under widely varying conditions of alcoholic solvent and of nucleophile.

With the exception of the catechol monoanion data (Table V), the above observations are inconsistent with a mechanism involving removal of hydrogen-bonding molecules from the nucleophile. The fact that strong rate increases are observed in solvent mixtures where there is sufficient methyl alcohol present to hydrogen bond to both DMSO and the nucleophile shows that some other factor than the state of solvation or of hydrogen bonding must be influencing the reaction rates.

Moving from solvent mixtures in which DMSO is the minor component to mixtures where DMSO predominates results in only a moderate increase. If the anion were poorly solvated at high DMSO concentrations, a much larger rate increase might have been expected.

The fact that oxygen anions and sulfur anions show almost the same sensitivity to DMSO concentration also argues against any mechanism in which DMSO alters the state of solvation of the ground state. The difference in solvation energies for oxygen and sulfur anions may be as high as 15 kcal.^{9a} The smaller, more heavily solvated oxygen anion might be expected to be much more sensitive to DMSO concentration than the weakly solvated sulfur analog, but little difference in behavior is observed.

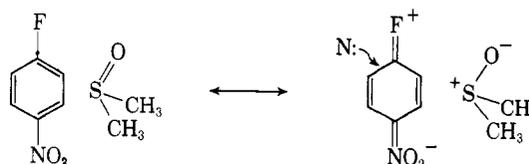
The fact that the rate increases per increment of DMSO are the consequences of changes in ΔH^* , not ΔS^* , indicates that changes in solvation of the nucleophile are not important, at least at low DMSO concentrations.⁴²

The lack of solvent effect on ρ of a Hammett ρ - σ treatment also indicates that there is little interaction between the anion and DMSO. Hydrogen bonding of solvent to the oxygen of the phenoxide nucleophile should be a function of the charge density at oxygen. Hence the state of hydrogen bonding or of solvation should be influenced by the polar character of the substituents on the aromatic ring. Removal of hydrogen-bonding solvent molecules by DMSO would be expected to produce a more effective nucleophile, particularly when an electron-donating substituent is on the aromatic ring. Hence a change in ρ in the opposite direction might have been expected.

Changes in the state of solvation of the nucleophile, although undoubtedly an important effect, apparently do not take place until the concentration of the hydroxylic species in the solvent is very low, and the concentration of DMSO is very high. Desolvation of halide anions³ going to highly concentrated DMSO solutions, may occur more easily than in the case of alkoxides.

What then is the mechanism of DMSO catalysis, at low DMSO concentrations? The presence of DMSO seems to allow the reagents to surmount the energy barrier easier than usual, irrespective of the charge type of the reagents. The effect of DMSO, then, must be to lower the energy of the transition state. Cram and co-workers² have expressed similar ideas in their studies upon DMSO catalysis, although a much more complex dependence of reaction rate upon DMSO was noted. Hyne⁴³ has commented upon selective solvation of the transition state for solvolytic reactions in mixed solvents.

One attractive interpretation involves enhanced dipolar character of the substrate upon interaction with a random DMSO molecule. Attack by the nucleophile upon the dipolar species may well be facilitated compared to an unpolarized substrate molecule.



A third possible effect is worthy of consideration. A small rate increase is observed in systems in which methyl alcohol is progressively replaced by solvents

(40) R. Pearson and F. Williams, *J. Am. Chem. Soc.*, **76**, 258 (1954).

(41) S. Winstein, S. Smith, I. Stevens, and J. S. Gall, *Tetrahedron Letters*, No. 9, 74 (1960).

(42) S. Winstein, C. Lindgren, H. Marshall, and L. L. Ingraham, *J. Am. Chem. Soc.*, **75**, 147 (1953).

(43) J. B. Hyne, R. Wills, and R. E. Wonkka, *ibid.*, **84**, 2914 (1962).

which are hydrogen-bond acceptors, but poor (or non-existent) hydrogen-bond donors. A change in solvent structure may account for part of the observed rate increase. The hydrogen-bond acceptor should break up the pseudo-polymeric structure of methyl alcohol into smaller aggregates. The solvent mixture then may be able to accommodate the electrostrictive effects associated with charge formation or charge dispersal more easily than the rigid, highly associated methyl alcohol.⁴⁴

A change in solvent structure may account for the rate increase observed upon addition of the tetraethylammonium salt, and the rate decrease observed with the

(44) J. H. Hildebrand and R. L. Scott, "The Solubility of Non-Electrolytes," Reinhold Publishing Corp., New York, N. Y., 1950, p. 172.

lithium salt. In aqueous systems ammonium salts have been classified as "order destroying" while lithium salts were termed "order producing."⁴⁵ Once again the breakup of the highly ordered solvent structure may show up in enhanced reaction rates.

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(45) See ref. 33, p. 190.

The Reaction of Phenyllithium with Some Dialkyl and 1,2-Alkylene Sulfates

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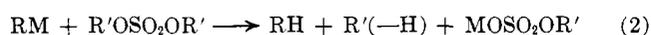
Received June 3, 1964

The reactions of phenyllithium with methyl sulfate, isopropyl sulfate, *n*-butyl sulfate, *cis*-1,2-cyclohexylene sulfate, *trans*-1,2-cyclohexylene sulfate, and *cis*-1,2-cyclopentylene sulfate have been carried out. Reaction schemes in which the phenyllithium acts as a nucleophile on carbon or sulfur in substitution reactions or as a base in elimination reactions are postulated to account for the various products. Methyl sulfate gave toluene; isopropyl sulfate gave cumene, propene, and isopropyl bromide; *n*-butyl sulfate gave *n*-butyl benzene; *cis*-1,2-cyclohexylene sulfate gave 1-phenylcyclohexanol; *trans*-1,2-cyclohexylene sulfate gave *trans*-1,2-cyclohexanediol, phenyl sulfone, benzenesulfonic acid, and *cis*- and *trans*-2-phenylcyclohexanol; and *cis*-1,2-cyclopentylene sulfate gave 1-phenylcyclopentene.

The alkylation of Grignard reagents by alkyl sulfates and the closely related alkyl esters of sulfonic acids is an old reaction which has seen extensive use.² Besides alkylation (eq. 1), several side reactions take place (eq.



2, 3, and 4). In these equations, M stands for the



magnesium and its attached groups and (X⁻) for the halide ion present in the Grignard solution. These equations were written with the assumption that the products arise *via* S_N2-like and E2-like processes.³ That is, the Grignard reagent acts both as a carbon nucleophile on carbon (eq. 1) or on sulfur (eq. 4) in substitution reactions, and as a base (eq. 2), abstracting a β-hydrogen, in an elimination reaction. The halide ion acts as a nucleophile on carbon (eq. 3). The sulfur-containing products in eq. 1 to 4 may react further in similar fashion. The extent to which any of these various reactions takes place is determined by the nature of RM, R', and X⁻.

In order to compare the reaction of phenyllithium on alkyl sulfates with the reaction of phenylmagnesium

bromide on alkyl sulfates, three alkyl sulfates were treated with excess phenyllithium. The results are tabulated in Table I. The yields show that both alkyl groups of the alkyl sulfates are replaceable by phenyllithium. The higher yields of alkylation products obtained using phenyllithium compared with phenylmagnesium bromide suggest that organolithium compounds may be superior to organomagnesium halides in synthetic applications of this type of reaction. Using a 1:1 molar ratio of phenyllithium to alkyl sulfate should increase the per cent of the phenyllithium which is alkylated above the yields reported in Table I.

TABLE I
YIELDS OF ALKYLATION PRODUCTS

R ₂ SO ₄	% C ₆ H ₅ R	
	Using C ₆ H ₅ MgBr ^a	Using C ₆ H ₅ Li
(CH ₃) ₂ SO ₄	31 ^b	61 ^c
(<i>i</i> -C ₃ H ₇) ₂ SO ₄	10 ^d	32 ^e
(<i>n</i> -C ₄ H ₉) ₂ SO ₄	16 ^f	80 ^e

^a The reactant molar ratio is 1. ^b A. Werner and F. Zilkens, *Ber.*, **36**, 2116 (1903). ^c Two moles of C₆H₅Br to 1.0 mole R₂SO₄; propene and isopropyl bromide also formed as in eq. 2 and 3. ^d L. Bert, *Compt. rend.*, **176**, 840 (1923). ^e Two and one-half moles of C₆H₅Br to 1.0 mole of R₂SO₄; yields for *c* and *e* based on alkyl sulfate and calculated assuming both R groups replaceable. ^f C. M. Suter and H. L. Gerhart, *J. Am. Chem. Soc.*, **57**, 107 (1935).

The main part of this investigation was concerned with the reaction of three cyclic sulfates, *trans*-1,2-cyclohexylene sulfate (1), *cis*-1,2-cyclohexylene sulfate (2), and *cis*-1,2-cyclopentylene sulfate (3), with phenyllithium in ethyl ether. The cyclic sulfates 1 and 2 had

(1) Based in part on the Ph.D. Thesis of K. K. Andersen submitted to the Graduate School of the University of Minnesota, May, 1959; National Science Foundation Predoctoral Fellow, 1955-1959; Department of Chemistry, University of New Hampshire, Durham, N. H.

(2) For a review see M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall Co., Inc., New York, N. Y., 1954, pp. 1277-1285.

(3) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, N. Y., 1959, Chapter 8, 12.