room temperature for 12 days and then evaporated to dryness under reduced pressure, and the ethyl benzoate present was removed by repeated evaporation with ethanol. Tlc on silica (10% ethanol in benzene) showed the presence of three uv-absorbing components in the mixture. Two minor compounds accounting for about 10% of the total product were unchanged starting material and 2′,3′,5′-tri-*O*-benzoyluridine. The third compound was isolated in a pure state by recrystallization of the hydrolysis products from boiling chloroform–ethanol (1:4) to which petroleum ether (60–80° fraction) had been added to incipient cloudiness, and the solution was allowed to cool. A flucculent white precipitate of 2′,3′,5′-tri-*O*-benzoylcytidine (IV) (as the hydrochloride) was collected and dried (0.22 g, 32% overall yield from cytidine): mp 226–227° dec; λmax (in ethanol) 230 nm (ε 29,500) and 280 (9500); λmin (in ethanol) 253 nm. *Anal.* Calcd for $C_{30}H_{25}N_3O_8\cdot HCl$: C, 60.87; H, 4.44; N, 7.10. Found: C, 60.80; H, 4.43; N, 7.11. No evidence for any glycosyl bond cleavage was obtained.

4-*N*-Acetyl-2′,3′,5′-tri-*O*-benzoylcytidine (III).—Cytidine was selectively 4-N-acylated using acetic anhydride in methanol as described by Watanabe and Fox,[2] and the product was benzoylated as follows. 4-*N*-Acetylcytidine (0.9 g) was suspended in dry pyridine (25 ml) and benzoyl chloride (2 ml) was added. The mixture was stirred at room temperature for 2 hr and then poured into 200 ml of 0.01 *N* HCl. After stirring for 1 hr, the sticky precipitate was extracted with chloroform, washed with sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and evaporated to dryness. The residue was dissolved in hot chloroform and *n*-hexane was added to give a slightly turbid solution. On standing, the product crystallized to give a mixture which was mainly the desired compound III but which contained traces of 4-*N*-benzoyl-2′,3′,5′-tri-*O*-benzoylcytidine. Recrystallization from ethanol gave the chromatographically pure product III (1.3 g, 45% overall yield from cytidine): mp 191–192°; λmax (in ethanol) 231 nm (ε 40,400) and 284 (7500), shoulder at 295 nm. *Anal.* Calcd for $C_{32}H_{27}N_3O_9$: C, 64.30; H, 4.56; N, 7.03. Found: C, 64.64; H, 4.42; N, 6.50.

Acid Hydrolysis of 4-*N*-Acetyl-2′,3′,5′-tri-*O*-benzoylcytidine (III).—III (1.3 g) was dissolved in chloroform–ethanol (3:1, 100 ml) and 1 *N* HCl (11 ml) was added. The solution was allowed to stand at room temperature for 3 days, at the end of which time the uv absorption of the solution at 300 nm had dropped to zero. The solvent was removed under reduced pressure and ethanol was added to the residue which was evaporated to dryness several times to remove the HCl. Tlc on silica (10% ethanol in benzene) showed the presence of a single uv-absorbing compound which had the same R_f as a marker of IV, prepared as described above. The product was recrystallized as described before to give 2′,3′,5′-tri-*O*-benzoylcytidine (1.1 g, 40% overall yield from cytidine) (as the hydrochloride): mp 226–227° dec; λmax (in ethanol) 230 nm (ε 29,700) and 280 (9650); λmin (in ethanol) 253 nm. *Anal.* Calcd for $C_{30}H_{25}N_3O_8\cdot HCl$: C, 60.87; H. 4.44; N, 7.10. Found: C, 60.54; H, 4.41; N, 7.10.

Registry No.—II, 27391-02-2; III, 27391-03-3; IV HCl, 20649-51-8; V HCl, 27415-59-4; VI, 27391-05-5; VII, 14630-99-0; X, 14383-43-8.

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Nucleophilicities toward *n*-Propyl Tosylate in Dimethyl Sulfoxide

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An important contribution to the understanding of solvent effects on reaction rates has been the recent calculation of solvent activity coefficients[1,2] (${}^O\gamma^S_{\ddagger}$) and enthalpies of transfer[3] ($\Delta\Delta H_{ts}$) of transition states. ${}^O\gamma^S_{\ddagger}$ for SN2 reactions can be calculated[1] from the rates in the two solvents of interest (O and S)

$$\log k^S/k^O = \log {}^O\gamma^S{}_{Y^-} + \log {}^O\gamma^S{}_{RX} - \log {}^O\gamma^S{}_{\ddagger}$$

provided that the solvent activity coefficients for the transfer of each reactant from solvent S to the reference solvent O have been measured. Parker[1] has found that, in the transfer from methanol to dipolar aprotic solvents, the rate increase may be assisted or resisted by the change in transition state solvation.

The purposes of the present study are (1) to establish the relative reactivities of a series of nucleophiles toward *n*-propyl tosylate under sufficiently similar experimental conditions to permit comparisons, and (2) to estimate ${}^O\gamma^S{}_{YRX\ddagger}$ values for the reactions where possible. Attention has been given to the small anions hydroxide, methoxide, and fluoride, for which few rate data are available under comparable conditions.

Experimental Section

The nucleophile sources were tetrabutylammonium thiosulfate, hydroxide, fluoride, chloride, bromide, and iodide, sodium methoxide, phenoxide, and thiocyanate, and *N*-methylaniline. The substrate was *n*-propyl tosylate in all reactions except that with fluoride, where *n*-hexyl tosylate was used. Nucleophile concentrations were about 0.03 *M*, and the tosylate was about 0.015 *M*, except in the case of fluoride, and the chloride rate at −4.5°, in which concentrations were 0.45 *M* in the nucleophile and 0.25 *M* in the substrate (to facilitate gas chromatographic determination of hexyl fluoride). Rate measurements were made at −4.5, 20, 30, or 40°. The solvent in each case was dimethyl sulfoxide containing no more than 0.05% water, except that the rates at −4.5° were measured in 45% DMSO–55% tetramethylene sulfoxide (v/v).

The reaction rates were followed by potentiometric titration of aliquots (*vs.* standard iodine, sulfuric acid, or silver nitrate solutions). In the fluoride reaction the appearance of hexyl fluoride was followed by gas chromatography (DC 710 on Chromosorb W).

Tetrabutylammonium thiosulfate (mp 60.1°) and tetrabutylammonium fluoride (mp 58°) were prepared from the bromide by anion exchange. The other nucleophile sources are commercially available.

The rates of reaction of the chloride ion were measured under each condition of temperature, substrate, concentration, and solvent. The slightly inexact assumption has been made that other nucleophiles are affected by these experimental differences to the same extent as is the chloride reaction, and corrections have been made on this basis. The rates of the bromide runs with Bu_4NBr and KBr are, within experimental error, the same. The effect of cation variation is insignificant with this anion, and this is probably true also for the majority of the other nucleophiles. With the small anions, OH^-, F^-, and CH_3O^-, appreciable differences in rate would be anticipated as a function of the cation, due to ion-pair association of the salts in nonaqueous media. It is extremely difficult to obtain Bu_4NF free from water and $NaOCH_3$ free from methanol. The low melting point of Bu_4NF (58°) suggests that the sample is a hydrate, probably with 3–5 molecules of water. Solvation of the anions by hydroxylic solvents should decrease nucleophilic reactivity. Our rates should be considered only as establishing for OH^-, F^-, and CH_3O^- the *lower limit* of the reactivity which would be observed at infinite dilution in the absence of water or methanol. The rates of reaction with chloride in DMSO and in 45% DMSO–55% tetramethylene sulfoxide are substantially the same. In the hydroxide reaction with *n*-propyl tosylate, 48% of the product (by gc) is 1-propanol, and the remainder is the E2 product propylene. The rate of substitution by hydroxide was taken as 0.48 × the overall rate of disappearance of hydroxide as de-

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(1) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).

(2) M. H. Abraham, *Chem. Commun.*, 1307 (1969).

(3) P. Haberfield, L. Clayman, and J. S. Cooper, *J. Amer. Chem. Soc.*, **91**, 787 (1969).

termined by potentiometric titration of aliquots. The methoxide solution after completion of the reaction contained methyl propyl ether (74%) and methanol (26%). Neither propylene nor 1-propanol was present, which indicates that the methanol detected by gc was present in the original sodium methoxide. Had methanol been formed by methoxide hydrolysis, the hydroxide ion also produced would have yielded 1-propanol with propyl tosylate.

Values of the solvent activity coefficient differences between methanol and DMSO (${}^{M}\gamma^{D}{}_{Y^-}$) for anions have been published.[1] Values of ${}^{M}\gamma^{D}{}_{PrOTs}$ and the rates of reaction of *n*-propyl tosylate with nucleophilies in methanol are not available but have been estimated from Parker's data[1] for methyl tosylate. The uncertainties of these estimates are probably no greater than that for the anions (±0.3 log units[1]). Log ${}^{M}\gamma^{D}$ was estimated in the following way: $\log {}^{M}\gamma^{DMF}{}_{MeOTs} = -0.6$; $\log {}^{M}\gamma^{DMF}{}_{MeCl} - \log {}^{M}\gamma^{DMF}{}_{t\text{-BuCl}} = +0.2$, and $\log {}^{M}\gamma^{DMF}{}_{MeBr} - \log {}^{M}\gamma^{DMF}{}_{n\text{-BuBr}} = +0.2$; $\log {}^{DMF}\gamma^{D} =$ 0.0 to +0.2 (MeI, *n*-BuBr, *t*-BuCl). We have therefore made corrections of +0.2 for the larger alkyl group of *n*-PrOTs, and +0.1 for the DMF to DMSO transfer, to give an estimated value of $\log {}^{M}\gamma^{D}{}_{PrOTs} = -0.3$.

From our unpublished rate data for the reactions of MeOTs with Cl⁻, Br⁻, and I⁻ in aqueous DMSO (70, 80, and 85% DMSO by volume), we have estimated $\log k_{MeOTs} - \log k_{PrOTs} = 1.4$ (a comparison of values[1] for MeX and *n*-BuX with five nucleophiles in MeOH affords an average value of 1.1). Transfer values for some of the anions in Table I, or appropriate rates in methanol, are not available; these have been omitted from Table II.

TABLE I

RATES OF TOSYLATE DISPLACEMENT IN DMSO

Nucleophile	Tosylate	Temp, °C	$10^5 k_{obsd}$ l. mol⁻¹ sec⁻¹	Corrections[a]	Est $10^5 k_2$ PrOTs, 25°
$S_2O_3^{2-}$	Pr	20	5.60×10^4	t_1	9.4×10^4
OH^-	Pr	20	3.67×10^4	t_1, p_1	2.9×10^4
CH_3O^-	Pr	20	1.63×10^4	t_1	2.7×10^4
F^-	Hex	−4.5	7.34×10^2	t_2, s[b]	2.0×10^4
$C_6H_5O^-$	Pr	20	1.57×10^3	t_1	2.6×10^3
N_3^-	Pr	30	3.89×10^2	t_4	2.7×10^2
Cl^-	Pr	20	5.68×10		
	Pr	30	1.37×10^2	t_4	9.5×10
	Pr	40	3.54×10^2		
	Hex	20	4.64×10		
	Hex	−4.5	3.54	*b*	
	Pr	60	3.03×10^3	*b*	
	Pr	60	2.90×10^3		
Br^-	Pr	30	5.26×10	t_4	4.1×10
	Pr	50	4.88×10^2	(Bu_4NBr)	
	Pr	50	4.78×10^2	(KBr)	
I^-	Pr	40	4.33×10	t_3	1.2×10
SCN^-	Pr	40	1.26×10	t_3	3.4
C_6H_5NHMe	Pr	40	1.20×10	t_3	3.2

[a] Temperature: t_1, $k_{25}/k_{20} = 1.67$; t_2, $k_{25}/k_{-4.5} = 22.0$; t_3, $k_{25}/k_{40} = 0.268$; t_4, $k_{25}/k_{30} = 0.692$; k_{25}, obtained from Arrhenius plot for PrOTs with chloride ion. Product (fraction of total rate leaing to expected substitution product): p_1, $k_S/(k_T + k_E) = 0.48$. Substrate(s), $k_{Pr}/k_{Hex} = 1.22$. [b] At higher concentration in 45% DMSO–55% tetramethylene sulfoxide (v/v) (see text). All rates are the average of two or more determinations.

The relative nucleophilicities of anions toward alkyl tosylates are reasonably consistent among protonic solvents, and among aprotic solvents, but not between the two groups. The orders of decreasing nucleophilicity follow: EtOTs in H₂O,[4] $S_2O_3^{2-} > N_3^- > OH^- > SCN^1 \sim I^-$; MeOTs in MeOH,[1] $N_3^- > I^- > SCN^- > Br^- > Cl^-$; MeOTs in DMF,[1] $N_3^- \sim Cl^- > I^- > SCN$; PrOTs in DMSO (Table I), $S_2O_3^{2-} > OH^- \sim CH_3O^- \sim F^- > C_6H_5O^- > N_3^- > Cl^- > Br^- > I^- > SCN^-$. In both aprotic solvents the now familiar order of halide reactivity is observed. In DMSO azide ion is distinctly more nucleophilic than chloride. Thiosulfate is most nucleophilic in water and in DMSO. However, if OH⁻, CH₃O⁻, and F⁻ were free of hydroxylic solvation and ion association in DMSO, it is probable that these anions would be more reactive than thiosulfate. There is a tendency for the small basic anions to be highly nucleophilic in DMSO, whereas strong hydrogen bonding greatly decreases the relative reactivity of these ions in protonic solvents. Larger more polarizable anions undergo relatively small changes in solvation in the transfer from aprotic to protic solvents.[1,5] The slightly increased solvation of propyl tosylate and the decreased solvation of the transition states in DMSO (relative to methanol) both have a rate decreasing effect. But the more important factor (in this system) of anion desolvation leads to the observed rate increases, which are most striking for small nucleophiles.

TABLE II

SN2 REACTIONS OF ANIONS AND *n*-PROPYL TOSYLATE AT 25° IN METHANOL AND DIMETHYL SULFOXIDE

Nu^-	Log $k^{D}{}_{PrOTs}$[a]	Log k^D/k^M[b]	Log ${}^{M}\gamma^{D}{}_{PrOTs}$	Log ${}^{M}\gamma^{D}{}_{Y^-}$	Log ${}^{M}\gamma^{D}{}_{\ddagger}$[c]	MeOTs,[d] Log ${}^{M}\gamma^{DMF}{}_{\ddagger}$
N_3^-	−2.6	2.1	−0.3	3.5	1.1	2.3
Cl^-	−3.0	3.5	−0.3	5.5	1.7	2.1
Br^-	−3.4	2.6	−0.3	3.6	0.7	1.2
I^-	−3.9	0.9	−0.3	1.3	0.1	0.6
SCN^-	−4.5	0.8	−0.3	1.4	0.3	1.3

[a] Rate of reaction of *n*-PrOTs in DMSO at 25° with indicated nucelophile. [b] Relative rates in DMSO *vs.* MeOH. [c] Change in solvent activity coefficient of the SN2 transition state upon transfer from MeOH to DMSO. [d] Change in γ for the transition state of the $CH_3OTs + Nu^-$ reaction upon transfer from MeOH to dimethylformamide (ref 1).

Registry No.—*n*-Propyl tosylate, 599-91-7.

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(4) R. E. Davis, R. Nehring, W. J. Blume, and C. O. Chuang, *J. Amer. Chem. Soc.*, **91**, 91 (1969).

(5) R. Fuchs, J. L. Bear, and R. F. Rodewald, *ibid.*, **91**, 5797 (1969).

Neighboring-Group Participation in Free-Radical Reactions of Halohydrins and Hydroxy Sulfides[1]

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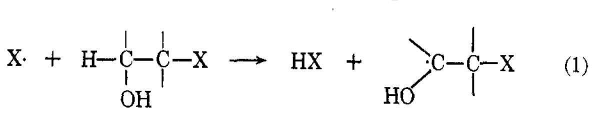
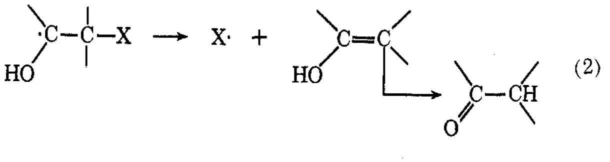
Peroxide-induced decomposition reactions of β-hydroxy sulfides (I) yielding mercaptans and ketones proceed by the free-radical chain sequence 1 and 2.[2]



I, X=RS
II, X=Cl
III, X=Br



Bromohydrins (II) and chlorohydrins (III), as expected, decompose by a similar chain sequence (see Experimental Section) since halogen atoms are both good hydrogen atom abstractors and undergo β elimi-

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(2) E. S. Huyser and R. M. Kellogg, *J. Org. Chem.*, **31**, 3366 (1966).