fining attention to groups having E_s values in the limited range from 0 to −2.

Registry No. CH_3COOEt, 141-78-6; CH_3CH_2COOEt, 105-37-3; $CH_3CH_2CH_2COOEt$, 105-54-4; $(CH_3)_2CHCOOEt$, 97-62-1; $(CH_3)_2CHCH_2COOEt$, 108-64-5; $CH_3CH_2CH(CH_3)COOEt$, 7452-79-1; $(CH_3)_3CCOOEt$, 3938-95-2; CH_3OCH_2COOEt, 3938-96-3; $C_6H_5CH_2COOEt$, 701-97-3; FCH_2COOEt, 459-72-3; $F_2CHCOOEt$, 454-31-9; $F_3CCOOEt$, 383-63-1; $ClCH_2COOEt$, 105-39-5; $Cl_2CHCOOEt$, 535-15-9; $Cl_3CCOOEt$, 515-84-4; $BrCH_2COOEt$, 105-36-2; $Br_2CHCOOEt$, 617-33-4; ICH_2COOEt, 623-48-3; $NCCH_2COOEt$, 105-56-6; $CH_3CH(OH)COOCH_3$, 547-64-8; $CH_3CH(OH)COOCH_2CH_3$, 97-64-3; $CH_3CH(OH)COOCH_2CH_2CH_3$, 616-09-1; $CH_3CH(OH)COOCH_2CH_2CH_2CH_3$, 138-22-7; $CH_3CH(OH)COOCH_2CH(CH_3)_2$, 585-24-0; $CH_3CH(OH)COOCH(CH_3)CH_2CH_3$, 18449-60-0; $CH_3CH(OH)COOC(CH_3)_3$, 59854-10-3; $CH_3CH(OH)COOCH_2CH_2OCH_3$, 75066-30-7; $CH_3CH(OH)COOCH_2CH_2Cl$, 75066-31-8; $CH_3COOCH_2CF_3$, 406-95-1; $CH_3COOCH(CH_3)CF_3$, 400-37-3; $CH_3COOCH_2OCH_3$, 4382-76-7; $CH_3COOCH_2OCH_2CH_3$, 32665-19-3; $CH_3COOCH_2CH_2OCH_3$, 110-49-6; $CH_3COOCH_2CH_2OCH_2CH_3$, 111-15-9; $CH_3COOCH_2C_6H_5$, 140-11-4; $CH_3COOCH(CH_3)_2$, 108-21-4; $CH_3COOCH_2CH(CH_3)_2$, 110-19-0; $CH_3COOC(CH_3)_3$, 540-88-5.

Effects of Alkyl Groups on Rates of S_N2 Reactions

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Rates of S_N2 reactions are subject to steric effects that can be measured quantitatively providing that bonding effects are held constant and that polar effects are either negligible or else computed. It is shown for the first time that steric effects in the nucleophile can be correlated by the Taft equation $\log k = a + \rho_s E_s$.

S_N2 substitution reactions provide especially interesting examples for observation of steric effects.[1-3] The S_N2 halide exchange was an early target of theoretical computations of steric effects,[2-4] and recent studies have been successful with exchange[5] and with S_N2 ring closure of bromo amines.[6] In order to provide a proper foundation for more extensive experimental work aimed at evaluating steric effects, one finds it necessary to examine the ways in which substituent groups can influence the rates of S_N2 reactions. It is also of interest to ascertain whether certain S_N2 reactions can be correlated by linear free-energy relationships such as the Taft equation (eq 1).[7]

$$\log k = a + \rho_s E_s + \rho_I \sigma_I \tag{1}$$

It is generally considered that substituents influence rates of reactions by four principal effects: steric, polar, resonance, and solvation.[1,7] Steric, polar, and solvation effects operate through space while resonance effects operate through bonds.[8] We present arguments elsewhere that through-bond effects can usefully be referred to as bonding effects in order to include the considerable variety of known effects.[8] These include hyperconjugation, the stabilization attendant on chain branching, and the differences between formic esters and acetic esters. Any substantial change in the bonding pattern at a reaction center may have a significant effect on rates that is distinct from polar, steric, or solvation effects.

If our interest is to measure steric effects, the objective will be either to maintain the other effects constant or else to find ways to evaluate them. Solvation is a major factor in S_N2 reactions.[1,9] The expectation is that when two sufficiently similar reactions are compared, the differential solvation effect will be small. A partial test is to compare relative rates in more than one solvent.

It is important to recognize bonding effects, and it is necessary to estimate the probable importance of polar effects. The discussion is organized as follows. (1) An example of bonding effects is evaluated. (2) Other examples of substituent effects in the substrate RBr are presented. (3) Polar effects in substrate RBr are evaluated. (4) Examples are presented of the application of the Taft equation to the correlation of S_N2 rates.

The example of bonding effects involves successive alkyl substitution at the electrophilic center as in the α series: MeBr, EtBr, *i*-PrBr, and *t*-BuBr. The rate of bromide exchange, for example, diminishes along this series.[2,3,10,11] Streitwieser suggested that this reflected a differential effect, a "resonance" acceleration with increasing alkyl substitution, and a dominating steric retardation.[1] Now that the steric effect has been estimated quantitatively,[5] it is possible to estimate the bonding effect at this saturated center. The data are summarized in Table I. The predicted increase in steric hindrance in the series is large, amounting to some 13 powers of ten from MeBr to *t*-BuBr. The S_N2 rate for bromide exchange of *t*-BuBr has not been measured; the reported rate constant for exchange is too large by a factor of about 50 because it pertains to an elimination–readdition process.[11]

The theoretical rates of exchange should be in the correct relative order, but the number of available examples for testing the theoretical calculations is small. Therefore, the numbers in the column labeled "bonding effects" must be considered approximations. In any event it is clear that direct replacement of hydrogen by methyl at the electrophilic carbon atom has a large effect on the rate. Just how the effect should be partitioned into polar and bonding effects is subject to discussion and perhaps to experimental study. If our interest is to evaluate steric effects, then the

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Table I. Estimation of the α-Methyl Bonding Effect

	ΔΔSE[a]	k(rel)[b] from ΔΔSE	k(rel)[c] from "bonding effect"	k(rel)[d] obsd (Br^- + RBr)	k(rel)[e] obsd (Cl^- + RBr)	k(rel)[f] obsd (I^- + RBr)	k(rel)[g] obsd (Cl^- + RI)
CH_3Br	−6.20	1	1	1	1	1	1
CH_3CH_2Br	0	2.8×10^{-5}	320	1.2×10^{-2}	1.6×10^{-2}	6.0×10^{-2}	9.3×10^{-2}
$(CH_3)_2CHBr$	4.61	1.1×10^{-8}	320 × 125	1.3×10^{-4}	3.3×10^{-4}	4.5×10^{-5}	2.9×10^{-3}
$(CH_3)_3CBr$	11.77	6.1×10^{-14}	320 × 125 × 50[h]	3.8×10^{-5},[i] 1×10^{-7}[j]	3.3×10^{-5}[i]		

[a] For the reaction Br^- + RBr (Table II of ref 5). [b] Assuming ΔΔSE = ΔΔG; calculated for 25 °C. [c] $k_{obsd}/k_{\Delta\Delta SE}$ (approximately). Factors shown are for successive α-methyl substitution. [d] RBr + LiBr (acetone) [Table I (k_{obsd} from ref 5) and ref 10]. [e] RBr + LiCl (acetone).[5,30] [f] RBr + LiI (acetone).[5,31] [g] RI + LiCl (acetone).[5,32] [h] Hypothetical, based on ln 50 = ln 125 − (ln 320 − ln 125). [i] This rate is for E2 elimination plus readdition of HBr; the S_N2 rate is lower by a factor of 10–100. [j] $6.1 \times 10^{-14} \times 320 \times 125 \times 50$.

Table II. RCH_2Br and C_6H_5SNa in CH_3OH at 20 °C

R	σ_I	−log k[a]	R	σ_I	−log k[a]
CH_3	0[b]	2.408	FCH_2	0.18[c]	3.305
CH_3CH_2	0	2.592	$ClCH_2$	0.16[c]	3.251
$CH_3CH_2CH_2$	0	2.570	$BrCH_2$	0.17[c]	3.302

[a] Reference 23; k values in units of $M^{-1} s^{-1}$. [b] Reference 8. [c] Reference 33, Table 10.4.

Table III. Halogen Exchange. $XArCH_2CH_2Cl$ and KI in Acetone at 75 °C[a]

X	σ[b]	−log k[c]	X	σ[b]	−log k[c]
H	0	3.690	p-Cl	0.24	3.339
p-MeO	−0.12	3.539	p-F	0.15	3.366
p-I	0.28	3.410	p-NO_2	0.81	2.981
p-Br	0.26	3.344			

[a] Reference 25. [b] Reference 33, Table 10.1. [c] $\log k = -3.540 + 0.685\sigma$; $s = 0.09$; $r^2 = 0.927$; k values in units of $M^{-1} h^{-1}$.

Table IV. 4-Substituted Bicyclo[2.2.2]octyl-1-methyl p-Toluenesulfonates and C_6H_5SNa in Ethanol at 75 °C

X	σ_I	−log k[a,b]	X	σ_I	−log k[a,b]
H	0	3.658	COOEt	0.30[e]	3.476
Me	0[c]	3.627	Cl	0.46[e]	3.389
$HOCH_2$	0.07[d]	3.590	Br	0.44[e]	3.355

[a] Reference 24; k values in units of $M^{-1} s^{-1}$. [b] $\log k = -3.630 + 0.558\sigma_I$; $s = 0.027$; $r^2 = 0.964$. [c] Reference 8. [d] O. Exner, "Correlation Analysis in Chemistry", N. B. Chapman and J. Shorter, Eds., Pelnum Press, 1978, p 439, Table 10.1. [e] S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1 (1973).

Table V. Reaction of RNH_2 with 2,4-Dinitrochlorobenzene in Ethanol at 25 °C[a]

run	R	$-E_s(RCH_2)$[b]	log k_{obsd}	log k_{obsd} − log k_{calcd}
1	Me	0.07	−2.500	−0.010
4	Bu	0.41	−3.022	0.064
5	i-Bu	(0.43)	−3.168	−0.048
3	Pr	0.39	−3.018	−0.033
2	Et	0.36	−3.036	−0.038
6	i-Pr	0.93	−4.000	−0.004
7	sec-Bu	(0.96)	−4.041	0.008
8	t-Bu	1.74	−5.420	−0.005

[a] Values of k in units of $M^{-1} s^{-1}$; $\log k = 2.367 - 1.752E_s$; $s = 0.04$; $r^2 = 0.9983$. [b] E_s values in parentheses are interpolated.

reaction series of primary halides must be considered separately from the series of secondary halides until data are available to permit a quantitative estimate of the bonding effects.

The other exchange reactions raise interesting questions. The difference between Br^- + RBr and Cl^- + RI and other types of exchange has both steric components and bond-effect components. Likewise in the Menschutkin S_N2 substitution, in which an amine displaces a halide, the differences between ammonia and primary, secondary, and tertiary amines involve a bonding-effect component along with a polar and a steric component. In order to focus on steric effects, one must be careful to minimize such complications by treating appropriate families of compounds. In the past the importance of sorting out the bonding effect has not been recognized.[2-4]

At least four other recognizable types of substituent effects control the reaction rates of an S_N2 substrate such as RBr. These are (a) the effect of α heteroatoms,[1] (b) the effect of adjacent carbonyl or cyano groups as in phenacyl halides,[1,12-14] (c) the effect of allylic and benzylic substitution,[1,15-22] and (d) remote polar effects.[1,23-25]

In the development of reactions for the determination of steric effects on rates the first three complications would generally be avoided. But the question of polar effects is of importance; these cannot be avoided entirely, particularly in S_N2 cyclization reactions where polar substituents must be present.

We consider three examples of polar effects; the data are presented in Tables II–IV. The reaction of C_6H_5SNa with XCH_2CH_2Br was shown to be substitution.[23] Assuming that steric effects are constant, $\rho_I = -4.5$. Holtz and Stock also established that substitution was the reaction observed on reaction of C_6H_5SNa with 4-substituted bicyclo[2.2.2]octyl-1-methyl p-toluenesulfonates.[24] For this reaction $\rho_I = +0.56$. In the third example, halide exchange of KI with $XArCH_2CH_2Cl$, the mechanism was not established;[25] $\rho = 0.69$.

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Table VI. Menschutkin Reaction:[a] RNH_2 and Allyl Bromide in Benzene at 100 °C[b]

R	$-E_s(RCH_2)$[c]	$-\log k_{obsd}$	$\log k_{obsd} - \log k_{calcd}$
Me	0.07	2.081	0.100
Et	0.36	2.419	−0.005
Pr	0.39	2.422	0.016
i-Pr	0.93	2.900	−0.026
sec-Bu	(0.96)	2.907	−0.009
i-Bu	(0.43)	2.559	−0.088
t-Bu	1.74	3.503	0.023
$EtCMe_2$	(1.80)	3.569	0.006

[a] N. Menschutkin, *Z. Phys. Chem. (Wiesbaden)*, 17, 193 (1895); *Ber. Dtsch. Chem. Ges.* 30, 2775 (1897). [b] Values of k originally in units of M^{-1} min^{-1}; $\log k = -2.124 + 0.806E_s$; $s = 0.06$; $r^2 = 0.988$. [c] E_s values in parentheses are interpolated.

The apparent inconsistency of the sign of the ρ value may simply be a coulombic consequence. The transition state has a negative charge distributed over the atoms at the trigonal-bipyramidal center. In the XCH_2CH_2Br molecule the negative atom X of the dipole C–X becomes directed toward the nucleophile and the nucleofuge.

Of consequence is the magnitude of the polar effect. We can get an estimate by comparing $X \cdots CH_2Br$ with $X \cdots COOEt$. In the aliphatic system, alkaline hydrolysis of XCH_2COOEt has a ρ_I of about 12–15;[7,8] by comparison the polar effect in XCH_2CH_2Br of 4.5 is about 30% as large. In the bicyclooctyl system the ester has $\rho^* = 0.98$, equivalent to $\rho_I = 6.1$,[1,8] and the S_N2 reaction shows a sensitivity about 10% as great. For the β-arylethyl chloride, the ester $ArCH_2COOEt$ has $\rho = 0.82$, and the ρ value for the assumed substitution is 85% as large.

Clearly the polar effects of substituent groups may have a significant effect. However, in the particular example of alkyl substituents, polar effects are expected to be negligible, as they are in acyl-transfer reactions.[8]

The last topic is application of the Taft equation to S_N2 reactions. Some years ago Hall[26] attempted to correlate the nucleophilic reactivity of aliphatic amines through use of the polar term of the Taft equation (eq 1). The lack of success with alkyl groups is understandable since polar effects of alkyl groups are effectively zero.[8] In Table V the reactions of primary amines with 2,4-dinitrochlorobenzene in ethanol are correlated with eq 2 which is the steric term

$$\log k = a + \rho_s E_s \qquad (2)$$

of eq 1; we assume that polar effects are zero. The large value of ρ_s is unusual. We believe that this is the first instance of correlating alkylamine reactions; Taft correlated rate constants for a number of reactions of 2-alkylpyridines using E_s(alkyl) but did not treat alkylamines.[7] We adopted the substitution that is effective for the alkoxyl component of esters and represented $E_s(RNH_2)$ by $E_s(RCH_2)$[8,27,28] (see Figure 1).

This same procedure works for the Menschutkin reaction of RNH_2 + MeBr or allyl bromide.[29] Secondary amines and tertiary amines determine their own lines and are not included because there are not enough examples. In S_N2 reactions, primary, secondary, and tertiary amines differ in bonding effects and perhaps in polar effects as well as in steric effects.[6] The ρ_s values are considerably smaller, thus suggesting a less crowded transition state for the S_N2 reaction than for displacement of the aryl halide (see Figure 1).

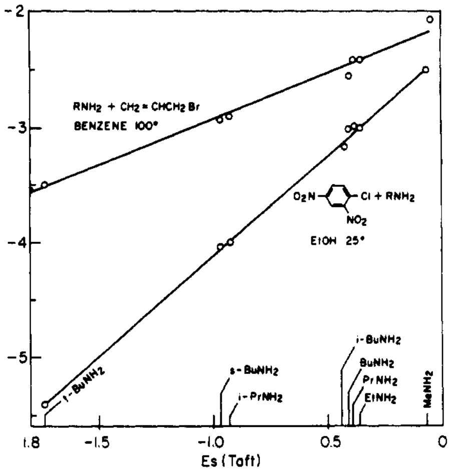

Figure 1. Correlation of reactivity of nucleophile with Taft E_s steric constants.

We conclude that S_N2 reactions provide an important tool for the study of steric effects, providing that due care is taken to avoid unwanted complications.

Registry No. Methyl bromide, 74-83-9; ethyl bromide, 74-96-4; isopropyl bromide, 75-26-3; *tert*-butyl bromide, 507-19-7; benzenethiol sodium salt, 930-69-8; propyl bromide, 106-94-5; butyl bromide, 109-65-9; 1-bromo-2-fluoroethane, 762-49-2; 1-bromo-2-chloroethane, 107-04-0; 1,2-dibromoethane, 106-93-4; 1-chloro-2-phenylethane, 622-24-2; 1-chloro-2-(*p*-methoxyphenyl)ethane, 18217-00-0; 1-chloro-2-(*p*-iodophenyl)ethane, 75067-07-1; 1-chloro-2-(*p*-bromophenyl)ethane, 23386-17-6; 1-chloro-2-(*p*-chlorophenyl)ethane, 32327-70-1; 1-chloro-2-(*p*-fluorophenyl)ethane, 332-43-4; 1-chloro-2-(*p*-nitrophenyl)ethane, 20264-95-3; bicyclo[2.2.2]octane-1-methanol *p*-toluenesulfonate, 2346-03-4; 4-methylbicyclo[2.2.2]octane-1-methanol *p*-toluenesulfonate, 2509-44-6; 1,4-dimethanolbicyclo[2.2.2]octane *p*-toluenesulfonate, 898-81-7; 4-(ethoxycarbonyl)bicyclo[2.2.2]octane-1-methanol *p*-toluenesulfonate, 2509-45-7; 4-chlorobicyclo[2.2.2]octane-1-methanol *p*-toluenesulfonate, 2346-05-6; 4-bromobicyclo[2.2.2]octane-1-methanol *p*-toluenesulfonate, 2516-15-6; 2,4-dinitrochlorobenzene, 97-00-7; methylamine, 74-89-5; butylamine, 109-73-9; isobutylamine, 78-81-9; propylamine, 107-10-8; ethylamine, 75-04-7; isopropylamine, 75-31-0; *sec*-butylamine, 13952-84-6; *tert*-butylamine, 75-64-9; allyl bromide, 106-95-6; *tert*-pentylamine, 594-39-8.

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