

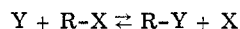
Nucleophilic Substitution. Linear Free Energy Relationships between Reactivity and Physical Properties of Leaving Groups and Substrates

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In a nucleophilic substitution, a nucleophile replaces a nucleofugic (leaving) group attached to a substrate framework. Letting Y represent the nucleophile, X the nucleofuge, and R the rest of the substrate, we can represent the process as



(For generality, the electrical charges on Y and X are omitted.) Inasmuch as the nucleofugic moiety X after being released has the properties of a nucleophile, such a process is in principle reversible, and reversibility can often be recognized in practice.

One might expect that a good nucleophile would react faster than a poor nucleophile with all substrates. Analogously a good nucleofugic group might be expected to give an increased rate of substitution, whatever substrate or nucleophile is involved. However, such a one-dimensional ranking of nucleophiles, substrates, and nucleofugic groups is not supported by actual experimental data. In fact, in order to explain the nucleophilic power of the reagents or the mobility of the leaving groups one must consider the mechanism of the particular substitution reaction as well as other factors which are the focus of attention in this Account.

Several properties of the nucleophiles (basicity, polarizability, degree of solvation, etc.) or nucleofugic groups more or less influence reactivity depending on what kind of interactions between nucleophile, nucleofuge, substrate moiety, and solvent are operating in the mechanism followed in a particular reaction. Our premise is that the detailed study of a particular nucleophilic substitution for which the mechanism is well established can enable evaluation of at least some of the interactions between nucleophiles, nucleofuges, and substrate moieties. Knowledge of those interactions can then be used as a basis for examination of reactivity in other reactions following different mechanisms. We have chosen for primary attention nucleophilic aromatic substitution involving anionic (or neutral) nucleophiles. Our treatment can be applied profitably to other kinds of bimolecular nucleophilic substitution reactions.

P. E. Todesco was born in Bologna in 1933, and studied at the University there for his degree in Industrial Chemistry. He returned to the University of Bologna, where he is Professor of Organic Chemistry, following faculty appointments at Bari and Ferrara. Dr. Todesco's research interests include free-energy correlations, reactivity studies in heterocyclic systems, and synthesis of new pesticides.

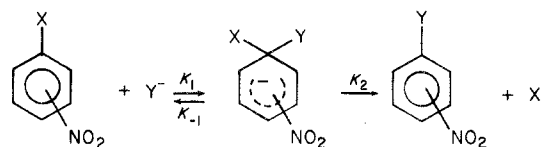
G. Bartoli also did his university studies in Bologna. In 1968 he became Assistant Professor of Organic Chemistry at the University of Bari, but in 1976 returned to Bologna, where he is now teaching mathematics for chemists. His research is concerned with various aspects of aromatic and heteroaromatic chemistry, mainly synthetic developments using metal organic reagents and mechanistic aspects.

Nucleophilic Aromatic Substitution

Nucleophilic aromatic substitution is generally observed in aromatic or heteroaromatic compounds carrying a nucleofugic group (e.g., an halogen) with activation by a strong electron-withdrawing group (e.g., a nitro group) in conjugable position with respect to the carbon carrying the nucleofugic group.

Several years ago Bunnett¹ strongly supported the hypothesis of a two-step pathway for nucleophilic aromatic substitution, using as a criterion the so-called "element effect", i.e., the variation in rate of substitution as a leaving group is varied, as well as other types of evidence.

For many reactions of this type, the rate does not depend on the carbon-nucleofugic group bond energy. The fluoro derivative is typically much more reactive than its chlorine, bromine, or iodine analogues, contrary to what would be expected on the basis of bond energies if C-X bond breaking occurred in the rate-limiting step. Consequently the following two-step mechanism, in which the rate-limiting step is generally the first one, was proposed.



The two-step mechanism is today generally accepted.²⁻⁶ It is now supported by other forms of evidence, such as the observation in some cases of base catalysis and curvilinear response of rate to base concentration in reactions with neutral nucleophiles, such as amines.⁷⁻⁹ We discuss in this Account kinetic data relative to the first step as a rate-limiting step.

The Nonexistence of Unique Scales of Nucleophilicity or Nucleofugicity

We present in Table I some kinetic data concerned with the dependence of reaction rate on nucleofugic

† This work was presented in part at the Symposium on Nucleophilic Substitution, Pocono Manor, Pa., April 1975.

(1) J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *J. Am. Chem. Soc.*, **79**, 385 (1957).

(2) F. Pietra, *Q. Rev., Chem. Soc.*, **23**, 504 (1969).

(3) J. Miller, "Aromatic Nucleophilic Substitution", Elsevier, London, 1968.

(4) C. F. Bernasconi, *MTP Int. Rev. Sci.:Org. Chem., Ser. One*, **3**, 33 (1973).

(5) D. M. Brevis, N. B. Chapmann, J. S. Paine, J. Shorther, and D. J. Wright, *J. Chem. Soc., Perkin Trans 2*, 1787 (1974).

(6) J. F. Bunnett and J. J. Randall, *J. Am. Chem. Soc.*, **80**, 6020 (1958).

(7) J. F. Bunnett and R. H. Garst, *J. Am. Chem. Soc.*, **87**, 3875 (1965).

(8) F. Pietra and D. Vitali, *J. Chem. Soc. B*, 1200 (1968).

(9) J. F. Bunnett and C. F. Bernasconi, *J. Org. Chem.*, **35**, 70 (1970).

Table I
Leaving Group Mobility in Some 1-Substituted 2,4-Dinitrobenzenes with
Oxyanion and Sulfanion Nucleophiles in MeOH at 25 °C

X	k with MeO ⁻ s ⁻¹ M ⁻¹	Rel to I = 1	k with PhS ⁻ s ⁻¹ M ⁻¹	Rel to I = 1	$k_{\text{PhS}^-}/k_{\text{MeO}^-}$
F	1.8×10^1 ^a	3100	7.8×10^2 ^c	27	43
OPh	5.1×10^{-3} ^a	0.88	2.9×10^{-1} ^a	0.01	56.9
OC ₆ H ₄ NO ₂ (<i>p</i>)	7.7×10^{-2} ^a	13.3	8.8 ^a	0.30	114
Cl	3.0×10^{-2} ^b	5.2	2.1×10^1 ^a	0.7	700
Br	2.0×10^{-2} ^b	3.4	4.4×10^1 ^a	1.5	2200
NO ₂	1.5×10^1 ^a	2590	3.9×10^4 ^a	1345	2600
SC ₆ H ₄ NO ₂ (<i>p</i>)	2.6×10^{-3} ^a	0.45	8.1 ^a	0.28	3110
I	5.8×10^{-3} ^b	1	2.9×10^1 ^a	1	5000

^a Reference 29. ^b Reference 27. ^c Reference 28.

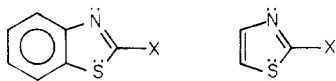
group in reactions of 1-X-2,4-dinitrobenzenes with oxyanion and sulfanion reagents. The reactivity order is not invariant; it depends on the nucleophile employed. For methoxide ion the sequence is F ~ NO₂ > OC₆H₄NO₂(*p*) > Cl > OC₆H₅ > SC₆H₄NO₂(*p*), while for the thiophenoxide ion it is NO₂ >> F > Cl > OC₆H₄NO₂ ~ SC₆H₄NO₂ > OC₆H₅. Data for thiomethoxide (not shown) are similar to those for thiophenoxide ion.

Further instances of nucleophilic reactivity dependence on the identity of the nucleofugic group, including actual inversion of relative nucleophilicity, are shown in Table II.

One observes that the thiophenoxide ion in many cases reacts much faster than methoxide ion (Table II, entries 2-4, 6-8, 16, column 6), but there are some cases in which methoxide reacts about as fast as (Table II, entries 1, 5, 11, 12, 14, 15, column 6) or faster (Table II, entries 9, 10, 13, column 6) than thiophenoxide.

In Table II it is evident not only that the reactivity of a given nucleophile depends on the nucleofugic group but that the pattern of variation varies from one substrate series to another. The only regular trend in Table II is that, with increasing polarizability of the nucleofugic group, the ratio $k_{\text{C}_6\text{H}_5\text{S}^-}/k_{\text{CH}_3\text{O}^-}$ regularly increases. This observation was originally made, with attention to some data of Table I and series a of Table II, by Bunnett¹⁰ in 1957. Bunnett attributed this trend to the intervention of London forces between entering and leaving group, a factor more important when the nucleophile and the leaving group are larger and more polarizable.

Moreover, the substrate framework also plays an important role. In fact, values of the ratios $k_{\text{PhS}^-}/k_{\text{MeO}^-}$ near or lower than unity have been observed by us in the benzothiazole^{11,12} or thiazole derivatives^{13,14}



even for larger halogens such as chloro (Table II, entries 10, 14), bromo (Table II, entries 11, 15) and iodo (Table II, entry 12). Some analogous data were subsequently obtained in quinoline systems by Illuminati.¹⁵

(10) J. F. Bunnett, *J. Am. Chem. Soc.*, **79**, 5969 (1957).

(11) P. E. Todesco and P. Vivarelli, *Boll. Sci. Fac. Chim. Ind. Bologna*, **20**, 143 (1962).

(12) A. Ricci, P. E. Todesco, and P. E. Vivarelli, *Tetrahedron Lett.*, 3703 (1964).

(13) M. Foa', A. Ricci, and P. E. Todesco, *Boll. Sci. Fac. Chim. Ind. Bologna*, **23**, 229 (1965).

(14) G. Bartoli and P. E. Todesco, unpublished results.

(15) G. Illuminati and G. Marino, *Tetrahedron Lett.*, 1055 (1963).

Table II
Comparison of Reactivity of Some Aromatic and
Heteroaromatic Halogen Derivatives towards
Thiophenoxide and Methoxide Ion

Ha- lo- gen	k with MeO ⁻ , s ⁻¹ M ⁻¹	Rel to I = 1	k with PhS ⁻ , s ⁻¹ M ⁻¹	Rel to I = 1	$k_{\text{PhS}^-}/$ k_{MeO^-}
(a) With 1-Halo-4-nitrobenzenes in MeOH at 25 °C ^{26,31}					
F	1.7×10^{-4}	1300	2.2×10^{-4}	3.5	1.3
Cl	3.8×10^{-7}	3	2.1×10^{-5}	0.3	55
Br	2.6×10^{-7}	2	5.1×10^{-5}	0.8	200
I	1.3×10^{-7}	1	6.3×10^{-5}	1	480
(b) With 2-Halo-6-nitrobenzothiazoles in MeOH at 25 °C ^{12,29}					
F	1.4×10^2	4800	1.2×10^2	124	0.9
Cl	2.7×10^{-1}	9	1.7	1.7	6
Br	1.5×10^{-1}	5	2.5	2.5	17
I	2.9×10^{-2}	1	9.7×10^{-1}	1	34
(c) With 2-Halobenzothiazoles in MeOH at 25 °C ¹²					
F	5.5×10^{-1}	8700	2.2×10^{-2}	160	0.04
Cl	5.5×10^{-4}	9	2.0×10^{-4}	1.4	0.36
Br	4.1×10^{-4}	7	4.4×10^{-4}	3	1.1
I	6.8×10^{-5}	1	1.4×10^{-4}	1	2.2
(d) With 2-Halothiazoles in MeOH at 50 °C ¹⁴					
F	1.8×10^{-2}	4500	1.2×10^{-4}	1.1	0.007
Cl	8.1×10^{-6}	2	4.5×10^{-6}	0.04	0.55
Br	1.1×10^{-5}	3	1.8×10^{-5}	0.16	1.6
I	4.0×10^{-6}	1	1.1×10^{-4}	1	27

These data indicate that the relative reactivity of nucleophiles depends not only on interactions between entering and leaving groups, but it is also influenced by interactions with the substrate framework. It is not, therefore, possible to correlate the leaving group effect by means of a two-parameter linear free energy relationship.

This situation is strictly analogous to that of the nucleophilic order of different reagents; nucleophilic reactivity cannot be rationalized on the basis of simple two-parameter equations such as those of Swain and Scott¹⁶ or Bronsted¹⁷ or of one-parameter equations such as that of Ritchie.¹⁸ The data are more satisfactorily rationalized by a four-parameter equation such as Edwards' equation^{19,20} which considers both basicity and polarizability as factors contributing to nucleophilicity. Similar, though less specific, is the concept

(16) C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, **75**, 4231 (1963).

(17) R. F. Hudson, *Chimia*, **16**, 173 (1963).

(18) C. D. Ritchie, *Acc. Chem. Res.*, **5**, 348 (1972).

(19) J. O. Edwards, *J. Am. Chem. Soc.*, **76**, 154 (1954).

(20) J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).

of hard and soft acid and bases²¹ or symbiosis.²²

Interactions between Nucleophile, Nucleofuge, and Substrate Framework

In order to understand the leaving group sequence, we start by considering a small, low-polarizability reagent such as methoxide ion. The factors determining its reactivity are: (a) its ability to bond to a positive center which is well represented by its basicity and (b) repulsion between the negative charge on the nucleophile and the electronic clouds of the leaving group and the substrate framework in the vicinity of the site of substitution.

According to this theory, the fluoro derivative is more reactive than other halo derivatives because, owing to the small radius of fluorine, repulsion is minimized and because the positive charge at the reaction center is relatively high. When the other halogens appear as leaving groups, the repulsions can be supposed to be more important because the other halogens are larger, with the consequence that there is a larger interaction zone between the incoming nucleophile and the leaving group which, significantly, does not leave in the rate-limiting step (k_1). In this zone repulsion can operate. This provides one possible explanation for the observation that, as a nucleofugic group in reactions with methoxide ion, the nitro group is not significantly more reactive than fluorine, despite its much higher electron-withdrawing power. Then the usual sequence is $F \sim NO_2 > Cl \gtrsim Br > I$.

On the other hand, in recent years many data have been collected⁴ indicating that attack on a carbon carrying a hydrogen is more rapid than attack on a carbon carrying a chlorine or a bromine atom, which are definitely more electron withdrawing than hydrogen. These facts are well explained by taking into account the intervention of repulsion phenomena between the nucleophile and the nucleofugic group in the transition state. When the nucleophile is softer, larger, and more polarizable, it can efficiently make the new bond at a larger distance, minimizing the repulsion phenomena. In fact, highly polarizable nucleophiles can easily distort their bonding electrons forward toward the site of substitution so as to avoid bringing the rest of the molecule close enough to cause excessive repulsion.²⁰ In agreement with this concept, the nitro group is an extremely good nucleofugic group, much better than fluorine, when a more polarizable reagent such as thiophenoxide is used. Similar interpretations can be given for other leaving groups, including other halogens. In our opinion the larger reactivity of polarizable reagents with respect to the less polarizable one arises from reduced repulsion, while the same factor is ascribed by Bunnett to London dispersion forces. Both ideas are based on the same experimental evidence.

Free-Energy Correlations between Nucleophilic Reactivity and Polarizability of Leaving Halogens

The subsequent discussion is limited to the cases of halogen nucleofugic groups for a clean comparison between similar leaving groups, but the conclusion and the correlations may be extended to polyatomic nu-

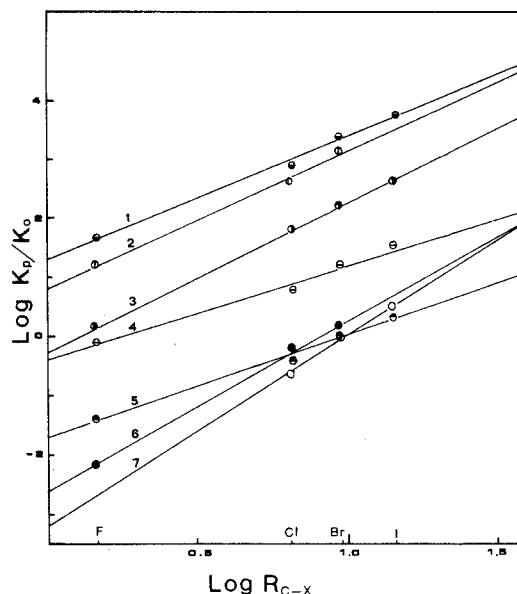


Figure 1. Plots according to eq 1 for reactions of aryl and heteroaryl halides with thiophenoxide (k_p) and methoxide (k_o) ions in methanol: (1) 2,4-dinitrohalobenzenes at 25 °C; (2) trans-*p*-nitro- β -halostyrenes at 25 °C; (3) 1-halo-4-nitrobenzenes at 25 °C; (4) 2-halo-6-nitrobenzothiazoles at 25 °C; (5) 2-halobenzothiazoles at 25 °C; (6) 2-halothiazoles at 50 °C; (7) 2-halo-6-methoxybenzothiazoles at 50 °C.

cleofugic groups, as discussed below.

Although Pearson concluded some time ago that four-parameter equations generally fail to correlate nucleophilic reactivity,²² we have had a good deal of success in rationalizing the nucleofugic group effect on the relative reactivity of two different nucleophiles by taking into account the difference of basicity and polarizability of the nucleophiles, of the substrate framework, and of the leaving groups.

We proposed¹² some years ago correlations of the type presented in eq 1. In this relationship, k_p is the rate

$$\log(k_p/k_o) = A + B \log R_{C-X} \quad (1)$$

constant for reaction of some substrate with a polarizable reagent (such as a sulfur nucleophile), k_o is the rate constant for reaction of the same substrate with a less polarizable reagent (such as an oxygen nucleophile) under the same experimental conditions, R_{C-X} is the value of the refractivity constant of the bond C-X where X is a halogen nucleofugic group, and A and B are proportionality constants.

Equation 1, which is empirical, attempts to express in a quantitative form the observation made by Bunnett¹⁰ that more polarizable reagents such as thiophenoxide are more favored than methoxide when the leaving group is more polarizable, e.g., that the ratio k_{PhS^-}/k_{MeO^-} increases with increasing leaving group polarizability.

Equation 1 successfully correlates the rates of reaction of many aromatic or heteroaromatic or activated ethylenic substrates with many nucleophiles in many solvents. In Table III some examples of the application of eq 1 are given, and some correlations are graphically shown in Figure 1. The correlations were originally found for halogens as leaving groups but are valid also for all other usual nucleofugic groups, even if polyatomic.

(21) R. G. Pearson, *J. Am. Chem. Soc.*, **85**, 3533 (1963).

(22) R. G. Pearson and J. Songstad, *J. Org. Chem.*, **32**, 2899 (1967).

Table III
A and B Parameters from Equation 1 for Nucleophilic Replacement of Halogen
from Aromatic and Heteroaromatic Systems^a

Substrate	Temp, °C	Nucleophile, N _p ^b	A	B	s ^c	r ^c	Ref
1-Halo-2,4-dinitrobenzenes	25	PhS ⁻	1.3	2.1	0.1	0.996	27-29
		MeS ⁻	1.5	1.6	0.1	0.995	27, 29
		N ₃ ⁻	-2.0	0.6	0.1	0.905	27, 29, 41, 42
		Piperidine	-0.6	0.3	0.1	0.909	1, 27, 29
		PhCH ₂ S ⁻	1.2	1.7	0.1	0.996	27, 29
		PhO ⁻	-1.57	0.1	0.1	0.625	27, 29
1-Halo-4-nitrobenzenes	25	PhS ⁻	1.3	2.4	0.1	0.999	27, 36, 37
		Piperidine	-0.1	0.2	0.1	0.859	1, 27, 36
		PhS ⁻	-0.3	2.6	0.1	0.999	29, 31
1-Halo-2-nitrobenzene 2-Halobenzothiazoles	50	MeS ⁻	0.9	2.1	0.1	0.999	29, 31
		N ₃ ⁻	-3.6	0.7	0.1	0.963	29, 31, 40
	25	PhS ⁻	-0.5	2.5	0.0	1.000	31, 33
		<i>m</i> -CH ₃ C ₆ H ₄ S ⁻	-0.4	2.6	0.0	1.000	31, 33
		<i>p</i> -CH ₃ C ₆ H ₄ S ⁻	-0.3	2.7	0.0	0.999	31, 33
		<i>m</i> -ClC ₆ H ₄ S ⁻	-1.0	2.6	0.1	0.999	31, 33
		<i>p</i> -ClC ₆ H ₄ S ⁻	-0.7	2.6	0.0	1.000	31, 33
		MeS ⁻	0.5	2.2	0.0	0.999	26, 31
		PhS ⁻	-0.3	2.5	0.1	0.999	29, 38, 39
		PhS ⁻	-1.7	1.8	0.1	0.992	12
2-Halo-6-nitrobenzothiazoles	50	MeS ⁻	0.0	1.5	0.1	0.997	12, 26
		N ₃ ⁻	-3.7	0.4	0.2	0.792	12, 29
	25	<i>p</i> -ClC ₆ H ₄ S ⁻	-3.0	3.0	0.1	0.996	12, 32
		<i>p</i> -BrC ₆ H ₄ S ⁻	-3.1	3.1	0.1	0.999	12, 32
		PhS ⁻	-0.4	1.6	0.1	0.991	12, 29
		MeS ⁻	0.5	1.5	0.1	0.999	12, 29
		N ₃ ⁻	-2.6	0.3	0.2	0.617	12, 29
		PhS ⁻	-3.3	3.3	0.1	0.989	23, 34
		PhS ⁻	-2.9	3.4	0.3	0.983	14
		PhS ⁻	0.8	2.4	0.1	0.997	35
1-Halo-4-nitrobenzenes	25 ^d	PhS ^{-d}	0.1	2.2	0.1	0.997	30

^a The solvent is CH₃OH unless otherwise indicated. ^b N_o is methoxide ion except in one case, as indicated. ^c s is the standard error and r the correlation coefficient. ^d Solvent dimethyl sulfoxide; N_o is PhO⁻.

Table IV
Comparison between Experimental and Calculated R_{C-X} Values of Polyatomic Nucleofugic Groups^{a-c}

Substrate	N _p	Temp, °C	R _{C-X} exptl	R _{C-X} calcd	Ref
X = NO ₂					
1-X-2,4-dinitrobenzenes	N ₃ ⁻	100	6.5		3
1-X-4-nitrobenzenes	PhS ⁻	50	6.8		23
2-X-6-methoxybenzothiazoles	PhS ⁻	50	7.3		29
2-X-benzothiazoles	PhS ⁻	25	6.9		23
Mean value 6.9				7.3	
X = SO ₂ C ₆ H ₅					
2-X-benzothiazoles	PhS ⁻	25	8.9		23
2-X-6-methoxybenzothiazoles	PhS ⁻	50	9.3		23
Mean value 9.1				9.6	
X = OC ₆ H ₅					
1-X-4-nitrobenzenes	PhS ⁻	50	2.6 ^d		29
1-X-2,4-dinitrobenzenes	PhS ⁻	25	2.5 ^d		29
	MeS ⁻	25	2.7 ^e and 3.1 ^d		44
Mean value 2.8				3.3	
X = SC ₆ H ₄ NO ₂ (<i>p</i>)					
1-X-2,4-dinitrobenzenes	PhS ⁻	25	10.7	10.	29, 44

^a R_{C-X}(experimental) is from extrapolation from plots according to eq 1 based on halogen nucleofugic groups; see Table III and Figure 1. ^b Calculated as follows: R_{C-NO₂} = R_{C-N} + R_{N=O} + R_{N⁺O⁻}; R_{C-SO₂Ph} = R_{C-S} + 2R_{S⁺O⁻} + R_{C_{Ar}-S}; R_{C-OPh} = R_{C-O} + R_{C_{Ar}-O}; R_{C-SPh} = R_{C-S} + R_{C_{Ar}-S}. (For values of bond refractivity, see Table V). ^c N_o is methoxide ion in all cases. ^d X = *p*-nitrophenoxy. ^e X = phenoxy.

Leaving Groups Other than Halogens

For more complex nucleofugic groups such as the nitro group or the benzenesulfonyl group, one can assume that they conform to linear correlations and from the observed rate ratios (e.g., log (k_{PhS}/k_{MeO})) deduce an "experimental" value of R_{C-X}. The resulting

values for a particular nucleofugic group are almost the same regardless of the substrate framework to which it is attached. Experimental values so obtained are reported in Table IV.²³

(23) Some preliminary results are reported by G. Bartoli, A. Latrofa, and P. E. Todesco, *Boll. Sci. Fac. Chim. Ind. Bologna*, 27, 79 (1969).

Table V
Bond Refractions (cm^3) by Le Fevre²⁴

Bond	R_D^b	Bond	R_D^b
C-H	1.68	C _{Ar} -O	1.83
C-F ^a	1.48	C-S	4.61
C-Cl	6.51	C _{Ar} -S	5.35
C-Br	9.39	C _{Ar} -C _{Ar}	2.69
C-I	14.61	C _{Ar} -N	2.44 ^c
C-N	1.57	N=O	4.00
C=N	3.78	N ⁺ -O ⁻	1.78
(C-O) _{ethers}	1.54	S ⁺ -O ⁻	-0.20

^a For C_{Ar}-halogens the values are: F, 1.43; Cl, 6.62; Br, 9.19; I, 14.61. ^b For Na D light. ^c For ArNO₂.

It is convenient to examine the empirical values of R_{C-X} obtained for polyatomic nucleofugic groups such as NO₂, OPh, and SO₂Ph. One can for comparison calculate such values by simple addition of refractivity constants for all the bonds connecting other atoms with the first atom of the leaving group (e.g., with the sulfur atom of the benzenesulfonyl group). The values so calculated (Table IV) agree remarkably well with those obtained from kinetic data, as described above.

The more remote bonds and atoms are not counted because they are not involved in the repulsion phenomenon that is, in our opinion, responsible for the polarizability effect.

We list in Table V the R_D values used for the calculations. They are the values proposed by Le Fevre²⁴ for C-X aliphatic and aromatic bonds. Since the geometry in the transition state closely approximates to a tetrahedral structure, it is unlikely that a considerable conjugative effect can be operative between the nucleofugic group and the carbon at the point of substitution. Therefore aliphatic refractivity values were used for the bond between the site of substitution and the first atom of the leaving group.

For the halogens, Le Fevre's data show little or no difference between R_{C-X} values toward aliphatic and aromatic carbon.

In Table IV experimental values for R_{C-X} are listed so as to enable comparison.

Solvent Effect and Polarizability of Leaving Groups

Let us consider a series of reactions of one nucleophile in two or more solvents with a set of substrates differing only in the nucleofugic group.²⁵ It turns out that the data can be correlated by means of eq 2.

$$\log(k_{\text{sol}1}/k_{\text{sol}2}) = C + D \log R_{C-X} \quad (2)$$

Some examples of the application of eq 2 are reported in Table VI. This relationship is valid both for aromatic and aliphatic substrates.

Comparison of eq 1 and 2 shows that the same nucleophile in two different solvents behaves like two different nucleophiles, at least insofar as transition-state interactions with the nucleofugic groups are concerned. It is remarkable that the nucleofugic group should affect relative nucleophilic reactivity in different solvents. The interaction mechanism must be especially subtle for aromatic nucleophilic substitutions inasmuch as the bond to the nucleofugic group is not disturbed in the

first step—usually the rate-limiting step—of the two-step S_NAr mechanism. The nucleofugic group must interact with solvent molecules associated with the nucleophile in the transition state so as to affect the extent or the energy of solvation.

In the transition states of the one-step S_N2 reactions at saturated carbon, the nucleofugic halogen or other group has a partial negative charge, and a pronounced sensitivity to solvent change is not unexpected. In fact, in Table VI one can observe that the slopes of the correlations relative to aromatic substrates are positive (entries 1-7; column 6) while the slopes for the aliphatic substrates are high and negative (entries 8-10; column 6). Some caution must be used in evaluating these different trends because the solvent used as reference is dimethylformamide (DMF) in one case and dimethyl sulfoxide (Me₂SO) in the other. Moreover, a large difference in sensitivity to solvent changes is clearly observed in the two different mechanisms. This possibly can be used as a criterion to determine whether a substitution reaction proceeds via an adduct (S_NAr mechanism) or synchronously (S_N2 mechanism).

The application of eq 1 and 2 is very broad, since several hundred experimental rate data have been correlated successfully by this kind of equation. In some cases, when data reported in the literature were found not to correlate with the equations, a reexamination of experimental behavior²⁶ revealed mistakes. This confirms the widespread usefulness of eq 1 and 2.

Separation of Basicity and Polarizability Effects

From a theoretical point of view, eq 1 is not fully valid because the two parameters *A* and *B* do not sufficiently separate the two principal factors determining nucleophilic reactivity, i.e., basicity and polarizability. Actually, *A* contains both the different sensitivity of nucleophiles to basicity and the sensitivity of the substrate to polarizability factors which do not depend on the leaving group. *B* refers only to the sensitivity of leaving groups to polarizability factors. For these reasons we have elaborated a treatment which separates the basicity and polarizability factors, leading to eq 3,

$$\log(k_p/k_o) = A' + B' \log [(R_{\text{substrate}} + R_{C-X})/R_{\text{H}_3\text{O}^+}] \quad (3)$$

in which $A' = \alpha \Delta pK_a$ (from the Bronsted equation; it is presumed that changing the nucleofuge does not greatly change α), ΔpK_a is the difference in the pK_a values of the two nucleophiles considered, $R_{\text{substrate}}$ is the contribution of the substrate to the polarizability, R_{C-X} is the contribution of the C-X bond as previously defined, and $R_{\text{H}_3\text{O}^+}$ is the contribution to the polarizability of factors due to interaction between the nucleophile and protonated water, as expressed by basicity.

$R_{\text{substrate}}$ can be obtained from experimental data by iterative calculations, using several nucleophiles with the same substrate, and optimizing the results to achieve a good linear Bronsted fit to the equation $A' = \alpha \Delta pK_a$ (see Figure 2).

All the previously reported data which obey eq 1 and 2 can also be fitted by eq 3, even when the nucleofuge is a polyatomic group. Some examples are reported in

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Table VI
C and D Parameters from Equation 2 for Nucleophilic Replacement of Halogen
from Alkyl and Aryl Halides in Two Different Solvents

Substrate	Temp, °C	Nucleophile	Solvent 1	Solvent 2	C	D	Ref
1-Halo-4-nitrobenzenes	50	Piperidine	DMF	Me ₂ SO	-0.5	+0.04	46
	50	Piperidine	CH ₃ CN	Me ₂ SO	-1.4	0.4	46
	50	Piperidine	PhCN	Me ₂ SO	-1.9	0.7	46
	50	Piperidine	MeCOEt	Me ₂ SO	-2.2	0.9	46
	50	Piperidine	MeCOOEt	Me ₂ SO	-3.0	1.1	46
	50	Piperidine	EtOH	Me ₂ SO	-2.1	0.1	46, 47
CH ₃ X	25	PhS ⁻	MeOH	Me ₂ SO	-3.8	0.05	25
	25	N ₃ ⁽⁻⁾	MeOH	DMF	-0.13	-3.9	48
	25	N ₃ ⁽⁻⁾	HCONH ₂	DMF	1.6	-4.5	48
	25	SCN ⁻	MeOH	DMF	0.3	-2.1	48

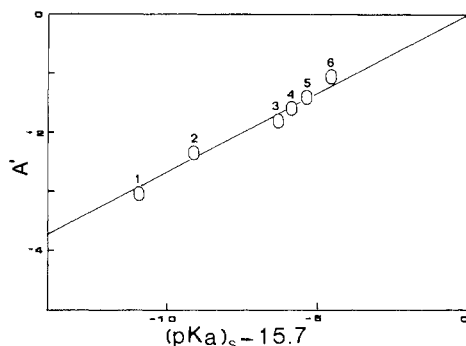


Figure 2. Reactions of 2,4-dinitro-1-halobenzenes toward nucleophiles: Bronsted plot of A' parameters (eq 3) vs. differences in pK_a values between the polarizable nucleophile (N_p) and methoxide ion as a less polarizable nucleophile (N_o) ($pK_a = 15.7$) data from Table VII; N_p is (1) N_3^- ($pK_a = 4.7$); (2) $C_6H_5S^-$ (6.5); (3) $C_6H_5CH_2S^-$ (9.4); (4) $C_6H_5O^-$ (9.9); (5) CH_3S^- (10.3); (6) piperidine (11.2).

Table VII and shown graphically in Figure 3.

Now the intercept (A') is clearly relevant. It is a Bronsted term and expresses the reactivity that would be expected if the polarizability factors were not operating, or when those for the two nucleophiles were the same and canceled.

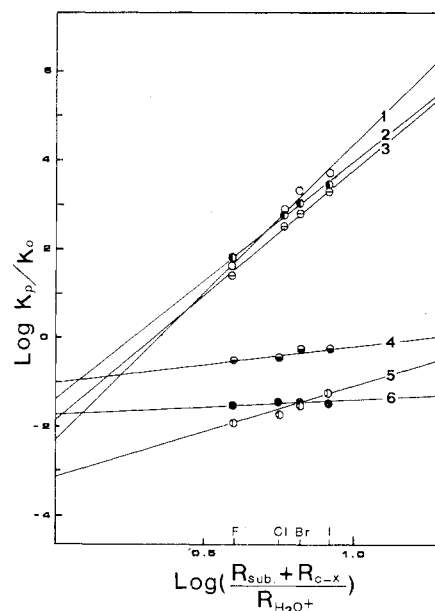


Figure 3. Plots according to eq 3 for reactions of 2,4-dinitrohalobenzenes with nucleophiles at 25 °C in methanol. The more polarizable nucleophiles N_p are: (1) $C_6H_5S^-$; (2) CH_3S^- ; (3) $C_6H_5CH_2S^-$; (4) piperidine; (5) N_3^- ; (6) $C_6H_5O^-$. The less polarizable nucleophile is always the methoxide ion.

The B' values are connected with the difference of polarizability of the two nucleophiles chosen, as shown in Table VII. In fact the observed order of B' values is in the sequence expected on the basis of the polarizability of the atoms which carry the nucleophilic attack and the bond connected with them. Moreover, the B' values for a fixed pair of nucleophiles also depend on the kind of substrate used. In our opinion this dependence can be related to different geometries of the attack on a five-membered or six-membered ring and to the different degree of new bond formation in different substrates.

Evaluation of $R_{\text{substrate}}$

In accordance with the prior assumption that only bonds and atoms close to the reaction site are responsible for the interactions which are expressed by the polarizability, one can calculate $R_{\text{substrate}}$ values as listed in Table VII; they agree rather well with the values arising from the experimental data. Thus all

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Table VII
A', B', α , (R_{sub})_{exp}, and (R_{sub})_{calcd} Parameters from Equation 3 for Nucleophilic Replacement of Halogen from Aryl and Heteroaryl Halides^a

	N _p	A'	B'	s	α	(R_{sub}) _{exptl} ^b cm ³	(R_{sub}) _{calcd} ^c cm ³
1-Halo-2,4-dinitrobenzenes	C ₆ H ₄ S ⁻	-2.2	6.6	0.15			
	C ₆ H ₃ CH ₂ S ⁻	-1.8	5.6	0.1			
	CH ₃ S ⁻	-1.4	5.3	0.1	0.26	10.5	9.49 ^d
	N ₃ (⁻)	-3.1	2.1	0.1			
	Piperidine	-1.0	0.8	0.1			
1-Halo-4-nitrobenzenes	C ₆ H ₄ O ⁻	-1.6	0.1	0.1			
	C ₆ H ₃ S ⁻	-4.3	7.9	0.2	0.44	10	8.73
	CH ₃ S ⁻	-2.4	6.5	0.2			
	N ₃ (⁻)	-4.8	2.3	0.1			
	C ₆ H ₃ S ⁻	-3.9	5.2	0.1	0.40	8	8.82
2-Halobenzothiazoles	CH ₃ S ⁻	-2.1	4.7	0.1			
	N ₃ (⁻)	-4.3	1.1	0.1			
	C ₆ H ₃ S ⁻	-2.4	4.7	0.1	0.27	8	8.82
2-Halo-6-nitrobenzothiazoles	CH ₃ S ⁻	-1.5	4.5	0.1			
	N ₃ (⁻)	-3.0	0.9	0.15			

^aN_p are the more polarizable nucleophiles, N_o is always MeO⁻, and s is the standard error for a linear plot of log k_p/k_o vs. log [($R_{\text{sub}} + R_{\text{C-X}}/R_{\text{H}_3\text{O}^+}$)]¹. Reference as in Table III. ^bThe experimental error is ± 1 cm³. $R_{\text{H}_3\text{O}^+} = 3.04$ cm³ (ref 24). ^dFor these calculation, refractivity values were computed by the method described in the text for the following bond: C(1)-C(2), C(1)-C(6), C(2)-N, C(6)-H.

parameters of eq 3 can be calculated a priori and correlate well with the experimental data.

Comparison between Equation 3 and the Edwards Equation

The validity of eq 3 is clearly connected with that of concepts which are expressed by Edwards in his equation (eq 4) in which $P_N (= \log R_N/R_{\text{H}_2\text{O}})$ is the $\log (k_N/k_{\text{H}_2\text{O}}) = DP_N + EH_N$ (4)

polarizability of a nucleophile relative to water, H_N is the basicity of the nucleophile, and D and E , respectively, express the sensitivity of the substrate to polarizability and basicity effects. Writing eq 4 for two different nucleophiles p and o, reacting with the same substrate, and subtracting one equation from the other, one obtains

$$\log (k_p/k_o) = E[(pK_a)_p - (pK_a)_o] + D \log (R_p/R_o) \quad (5)$$

Comparing (5) with (3), admitting that $E = \alpha$, and naming $\log ((R_S + R_{\text{C-X}})/R_{\text{H}_3\text{O}^+}) = P_{\text{substrate-X}}$, one gets

$$D \log (R_p/R_o) = B' P_{\text{substrate-X}} \quad (6)$$

or

$$D:P_{\text{substrate-X}} = B':\log (R_p/R_o) \quad (7)$$

This means that Edwards' D parameter is related to our polarizability of substrate to the same extent that our parameter B' is related to the difference in polarizability of two nucleophiles as measured by Edwards.

According to Edwards, in order to evaluate the polarizability of a nucleophile it is necessary to consider overall polarizability of the nucleophile as measured by the molar refractivity constant at λ_∞ , related to the corresponding constant of water, i.e., $P_N = \log (MR_\infty)_N/(MR_\infty)_{\text{H}_2\text{O}}$.

Moreover, our work indicates that the polarizability which significantly affects reactivity is that of atoms or bonds close to the site of substitution in the transition state, in the substrate, in the leaving group, and in the nucleophile. In terms of this concept the reason for Pearson's²² statement that four-parameter equations fail is understandable. If overall polarizability of the molecule (or any other physical parameter related to the whole molecule) is employed to evaluate the polarizability of different nucleophiles, our equations would not be expected to work properly.

Our results suggest that, if the polarizability of the nucleophile is correctly evaluated, taking into account only the atoms and bonds of the nucleophile close to the site of the reaction in the transition state, Edwards' equation can be successfully employed in cases usually considered to resist correlation.

Comparison between Equation 3 and Other Simpler Equations, and with the HSAB Concept

Equation 3 is general; in cases in which more simple equations (such as the Bronsted, Swain, or Ritchie equations) can accommodate the experimental results, one of the values A' or B' is negligible, or both change in a concerted manner, balancing the respective effects.

Equations 1 and 2, which were originally empirical, now have, as expressed in eq 3, a theoretical basis. The

HSAB concept simply affirms that soft or hard nucleophiles react better respectively at soft or hard centers, but this qualitative point of view cannot fully explain nucleophilic reactivity because it is difficult to recognize the relative degree of softness or hardness of the nucleophiles or the reaction center and this fact has sometimes led to incorrect predictions.

The intervention of London dispersion forces, proposed by Bunnett, can be reconciled with the validity of eq 1, 2, and 3 and with our interpretation. We consider that the increase of reactivity for polarizable reagents with respect to less polarizable ones is due to the attenuation of strong repulsion forces between entering group, nucleofuge, and substrate framework. Following Bunnett's idea, this attenuation would be attributed to London forces. The relevance of repulsion phenomena with low polarizability reagents is revealed by the nucleofuge reactivity order observed in this case, as well as the modification of this order observed with more polarizable reagents.

Summary of Concepts Arising from Equation 3

Equation 3 allows some concepts to be established which can be summarized thus:

(a) The primary driving force of reaction is bond formation between the nucleophile and the (somewhat) positively charged atom which is the site of nucleophilic attack. In order to evaluate this factor one can use the basicity (interaction between nucleophile and a simple positive charge such as a proton).

(b) Repulsions between nucleophile and nucleofuge and between nucleophile and substrate framework make the nucleophilic attack more difficult, modifying the nucleophilic order with respect to basicity order, especially with small nucleophiles of low polarizability. To evaluate this effect it is convenient to observe the difference of reactivity between a more polarizable

reagent and a less polarizable one (such as methoxide or OH^-), taken as a reference nucleophile.

This difference depends on the polarizability of the nucleofuge and the substrate framework.

(c) In evaluating the polarizability of substrate, nucleophile, and nucleofuge one must consider only the polarizability of atoms and bonds close to the reaction site, as expressed by the respective refractivity constants.

(d) These concepts are valid not only for $\text{S}_{\text{N}}\text{Ar}$ reactions but also for all bimolecular substitution reactions which have interactions between entering reagent, leaving group, and substrate in the rate limiting step ($\text{S}_{\text{N}}\text{Eth}$; $\text{S}_{\text{N}}2$; substitution at metal complexes, etc.).

Concluding Remarks

We have demonstrated that differences in reactivity, expressed by rate constants for the attack of nucleophiles at aromatic sites in $\text{S}_{\text{N}}\text{Ar}$ reactions, as the polarizability of nucleophile is varied, depend linearly on the polarizability of the nucleofuge for a fixed substrate framework, obeying eq 1 for several nucleofuges, substrate frameworks, nucleophiles, and solvents. For the same aromatic system in two different solvents, eq 2 is valid. As a further development, eq 3 is also proposed which separates the contribution of basicity and polarizability of nucleophile, nucleofuge, and substrate framework. Equation 3 is comprehensive of the Bronsted equation and simplifies to it for cases in which polarizability effects are not relevant. All the parameters in eq 3 can be easily calculated *a priori*. Employment of the proposed equations is easy. They can be used for prevision of data and as a criterion for evaluating what kind of mechanism is operating in reactions under investigation.

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