PROBLEMS INVOLVED IN UNDERSTANDING ORDERS OF NUCLEOPHILIC REACTIVITY

Calvin D. Ritchie

Department of Chemistry, State University of New York at Buffalo,
Buffalo, New York 14214, USA

Abstract - The N_+ relationship has been found to have considerable
generality for the correlation of rate constants of electrophile-
nucleophile combination reactions. There are, however, some serious
deviations from the relationship, particularly for thiolate anions and
for azide ion reactions. Data for a large number of reactions show an
absence of selectivity-reactivity relationships and a general absence of
observable coulombic effects. Detailed examination of the data by the
use of the N_+ relationship reveals some examples of apparent steric
effects on reactivity which, in the case of secondary amines, cause
deviations of up to ca. 1 log unit. The deviant behavior of thiolate
and azide ions do not appear to be rationalizable by any of the current
theories of nucleophilic reactivity.

INTRODUCTION

A major, perhaps predominant, proportion of the important reactions of Organic Chemistry
involve nucleophilic addition or substitution steps. Thus, the problem of understanding
nucleophilic reactivity is one of the central foci of Physical-Organic Chemistry and has a
rather long history. Important early work on this problem includes J. O. Edwards' recogni-
tion of the influence of both basicity and polarizability (1) and A. J. Parker's demon-
stration of the sometimes overwhelming importance of solvent effects (2). By the late
1960's there appeared to be a general consensus (3) that quantitative correlations of
nucleophilic reactivities were unlikely to exist.

In our opinion, one of the major stumbling blocks in much of the early work was the failure
to distinguish mechanistic types of nucleophilic reactions. Following this belief, we have
concentrated our efforts toward the study of reactions in which an electrophile-nucleophile
combination step is rate-determining. The simplest example of such reactions is a cation-
anion combination such as the reaction of tropylium ion with cyanide ion. The large major-
ity of amine reactions with cations, nucleophilic aromatic substitution reactions in protic
solvents, nucleophilic substitution reactions of very reactive esters, and Michael reactions,
are other examples.

From extensive data on such reactions, obtained principally in our laboratories, those of W.
P. Jencks, and those of J. L. Kice, we have shown (4) that rate constants can be correlated
by the simple N_+ equation:

$$\text{Log } k = \text{Log } k_o + N_+ \qquad\qquad (1)$$

in which Log k_o is a parameter characteristic of the electrophile and N_+ is a parameter
characteristic of the nucleophile. In words, the equation states that the relative re-
activities of electrophiles are independent of nucleophile and those of nucleophiles are
independent of electrophile. There is an obvious implication of the absence of specific
interactions between electrophile and nucleophile at the transition states for these react-
ions.

We have also shown that Eq. 1 applies to the addition step for the reactions of nucleophiles
with aryl acetates, N-methylimidazolium acetate, and 2,2,2-trifluoroethylthiol acetate. The
observed rate constants for these reactions, in which the combination step is not always
rate-determining, must be "corrected" to account for the relative leaving-group abilities of
nucleophiles. We found (5) that a single set of values for these leaving-group abilities
could be assigned which led to very good correlations, and which have now been shown to be
reasonably related to rate constants for dissociation of cation-amine adducts (6).

Eq. 1 and its simple extension to account for leaving-group abilities have been applied to nearly 800 rate constants involving reactions of over 30 electrophiles with ca. 80 nucleophiles. The results are shown in Fig. 1.
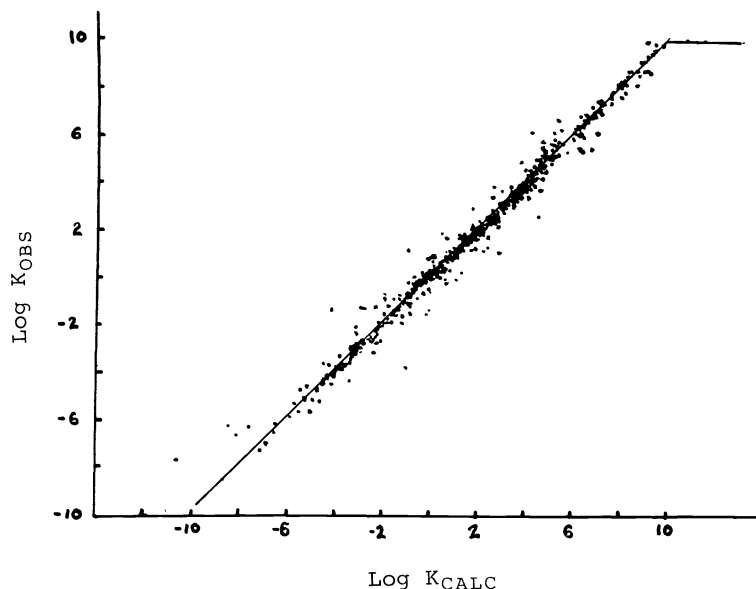

Fig. 1. Observed rate constants vs those calculated by the use of Eq. 1
        for all available data.

The characteristics of Eq. 1, its generality, successes, and failures, are the topic of the present discussion.

GENERAL CHARACTERISTICS OF ELECTROPHILE-NUCLEOPHILE COMBINATION

One of the most surprising facets of Eq. 1 is that it does not accommodate any change in selectivity with reactivity of either electrophile or nucleophile. There is, of course, no selectivity when reaction rates reach diffusion control, but this is simply another example of cases in which the combination step is not rate-determining. Within this limit, selectivity is quite constant. This fact is generally illustrated in Fig. 1. Fig. 2 shows rate constants for reactions of cyanide ion plotted against those for peroxide ion with different electrophiles. The slope of the line shown is unity even though cyanide and peroxide ions differ in reactivity by more than four powers of ten. The same behavior is illustrated in Fig. 3 from the different viewpoint of comparison of reactions of two electrophiles, differing in reactivity by nearly three powers of ten, with a range of nucleophiles. The only significant deviations from the line of unit slope shown are for reactions of thiolate nucleophiles, to which we shall return later.

The general absence of selectivity-reactivity relationships in these reactions has recently been contested by Scott (7). Fig. 4 shows the data on which Scott bases his conclusions. The best least-squares line through all of the data has a slope of 0.85. Prior to our own work leading to Eq. 1, this would have been considered a surprisingly small difference from unit slope for two electrophiles differing in reactivity by more than four powers of ten. We believe, however, that even this small difference is misleading. Most importantly, the two points for reactions of water represent reactions whose mechanisms are not simple electrophile-nucleophile combination. The reactions of both cations with water are general-base catalyzed (8,9) and the catalysis is almost certainly concerted with attack (8). If these two points are removed from consideration, the line of unit slope correlates the data quite well, with sulfite ion being the only deviant nucleophile.

A second quite surprising facet of the applicability of Eq. 1 is that coulombic effects between electrophile and nucleophile appear to be quite negligable. This point is particularly well illustrated in Fig. 5 comparing the reactions of cyanide ion with those of hydrazine with both cationic and neutral electrophiles. In general, Eq. 1 applies to reactions of cationic and neutral electrophiles with anionic, neutral, and even cationic (i.e., monoprotonated diamines) nucleophiles. This fact is particularly surprising in view of the
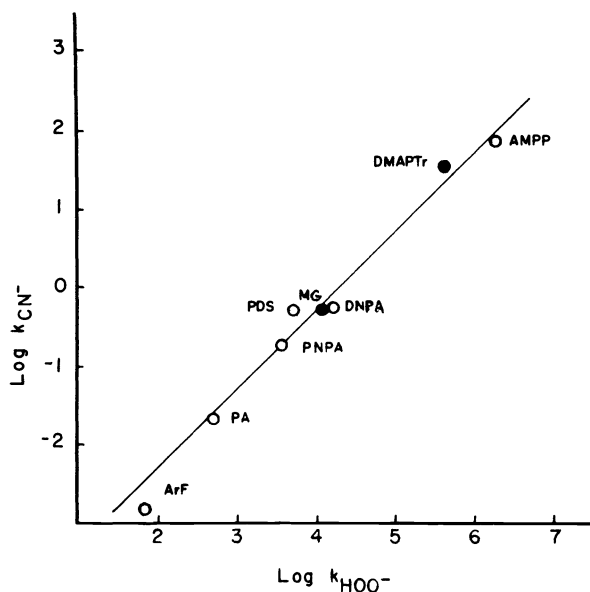
Fig. 2. Logarithmic plot of rate constants for reactions of electro-
philes with cyanide ion vs. those with peroxide ion. (See list
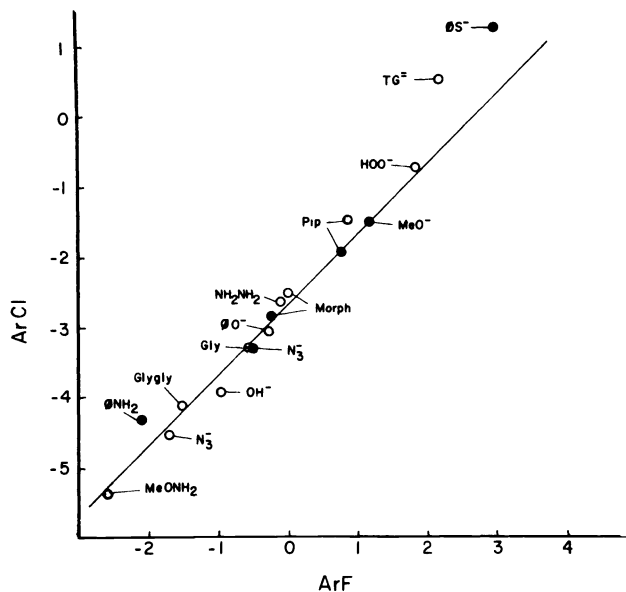of abbreviations and symbols at end of paper).

Fig. 3. Logarithmic plot of rate constants for reactions of nucleophiles
with 2,4-dinitrofluorobenzene vs. those with 2,4-dinitrochloro-
benzene. (See list of abbreviations and symbols at end of paper).

evidence which we shall present below indicating that steric effects can cause significant
deviations from Eq. 1. Thus, it appears that "long-range" coulombic interactions are absent,
while "short-range" steric interactions are present at the transition states for these
reactions.

Before leaving the general characterics of these reactions, we would like to emphasize
one of our recent experimental finding which modifies some of our earlier discussions of
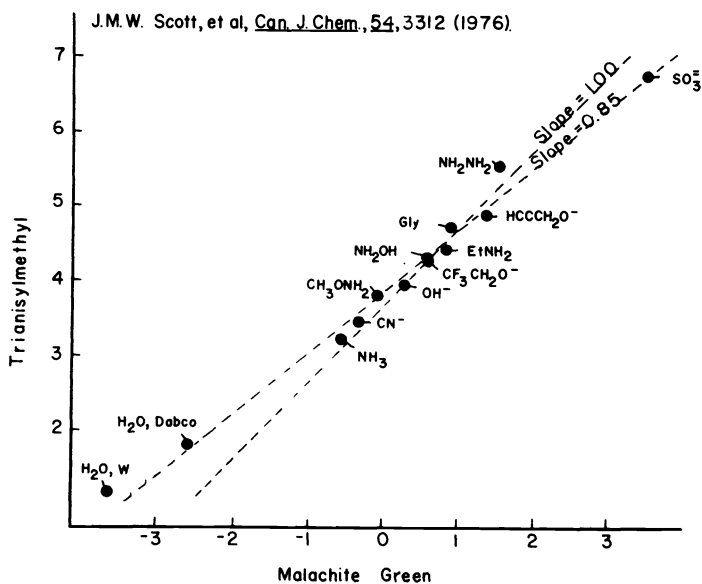
Fig. 4. Logarithmic plot of rate constants for reactions of nucleophiles
         with Malachite Green vs. those with tri-p-anisylmethyl cation.
         (See list of abbreviations and symbols at end of paper).
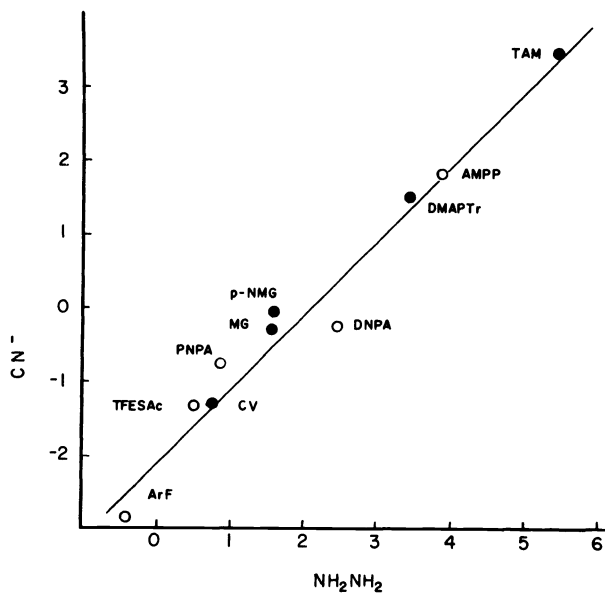

Fig. 5. Logarithmic plot of rate constants for reactions of cyanide ion
         vs those for hydrazine illustrating the absence of significant
         coulombic effects. (See list of abbreviations and symbols at
         end of paper).

solvent dependencies of electrophilic reactivity.

In our earliest work (10), we noted that the relative reactivities of cations show a remark-
able solvent independence, although, as expected from Parker's work (2) the relative reactiv-
ities of nucleophiles are strongly solvent dependent. Hopkins (11) has verified our sugges-
tion that the solvent independence of relative electrophilic reactivity does not arise from
the nearly trivial possibility that the free energies of transfer of the cations studied are

all the same.

Our more recent studies of reactions of arylhalides (12) and of acrylophenone derivatives demonstrate a significant solvent dependence of relative reactivities of electrophiles in general. For example, the Log k_o values of DMAPTr (p-dimethylaminophenyltropylium ion) and 2,4-dinitrofluorobenzene differ by 4.2 units in water and by 4.9 units in methanol solutions. From rather limited data for the reactions of nucleophiles with β-methoxyacrylophenone, it appears that the Log k_o value, relative to that for DMAPTr, changes by slightly more than one unit on going from water to methanol.

It is clear, then, that both Log k_o and N_+ values are solvent dependent. At the present time, we do not have enough data on these dependencies to draw conclusions, but it may be worth remarking that there is no apparent relationship with free energies of transfer of the reactants involved.

DEVIATIONS FROM EQ. 1

As can be seen in Fig. 1, there are some reactions which show rather large deviations from the N_+ relationship. Any patterns of deviations, however, are very difficult to detect. This probably results, at least partly, from the averaging process used in setting Log k_o and N_+ values, which tends to smooth out patterns and thereby cloud interpretation.

In order to resolve this problem, we have begun to rely on direct comparisons of reactivities, such as those shown in Figs. 2-5, to reveal any regularities in the deviations. Plots of reactions of one nucleophile vs. those of another with a range of electrophiles are found to be very precise when the two nucleophiles are of the same type (for example, both primary amines), but are somewhat less precise when dissimilar nucleophiles are compared. There are, however, four dissimilar nucleophiles which give remarkably precise plots when compared in this manner. These are cyanide ion, peroxide ion, hydrazine and methoxylamine.

As judged by current theories of nucleophilicity, this is a strange collection of nucleophiles to show such concordant behavior. For example, cyanide ion is classified (3) as a "soft" nucleophile, while the other three are "hard" and "α-effect" nucleophiles. Semicarbazide and phenylhydrazine, both "α-effect" nucleophiles, show behavior more like ordinary primary amines than like hydrazine and methoxylamine. The only obvious similarity of the four nucleophiles is their small size, and presumable resulting minimal steric requirements in the combination reactions. We believe, therefore, that comparison of reactions of other nucleophiles with these four are most likely to reveal steric, and perhaps other, effects in the electrophile-nucleophile combination reactions.

Such comparisons are most conveniently carried out by assigning Log k_o values to electrophiles based only on reactions with cyanide ion, peroxide ion, hydrazine and methoxylamine. This procedure leads to more extensive comparisons than would be possible in the direct plots of one nucleophile vs. another because we do not have data for any one of these nucleophiles reacting with all of the electrophiles studied.

For the remainder of the present discussion, we shall use Log k_o values which are based on the reactions only of cyanide ion, peroxide ion, hydrazine and methoxylamine.

Steric effects are the most reasonable source of behavior of piperidine shown in Fig. 6. The line shown in the figure is of unit slope passing through the points for those electrophiles which we believe to be least sterically hindered. The points for reactions of triarylmethyl cations and for esters fall significantly below this line. There is abundant evidence that steric effects on the equilibrium formation of triarylmethyl cation - secondary amine adducts are much greater than the kinetic effects shown here. For example, Malachite Green derivatives give no observable reaction with secondary amines although the reactions with primary amines of even lower basicity give fairly large equilibrium constants (13).

The reactions of primary amines show much closer adherance to Eq. 1 than do those of secondary amines. As shown in Fig. 7 for the particular case of trifluoroethylamine, however, there are some detectable steric effects in the reactions of these nucleophiles. The deviations of the points for the triarylmethyl cations and esters are smaller than those shown in Fig. 6, but the pattern of deviations is the same.

A different pattern of behavior is shown by hydroxide and alkoxide ions. As shown in Fig. 8 for reactions of hydroxide ion, there is an excellent correlation for all electrophiles except the triarylmethyl cations. The same pattern, but with the deviations of the triarylmethyl cation reactions being greater, is shown by alkoxide ions as illustrated for the case of 2,2,2-trifluoroethoxide ion in Fig. 9.
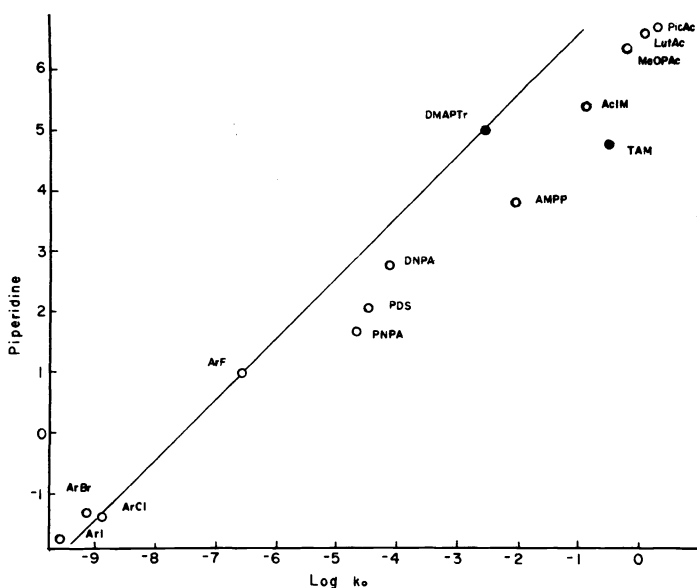
Fig. 6. Logarithms of rate constants for reactions of piperidine plotted
vs. Log k_o values illustrating probable steric effects. (See
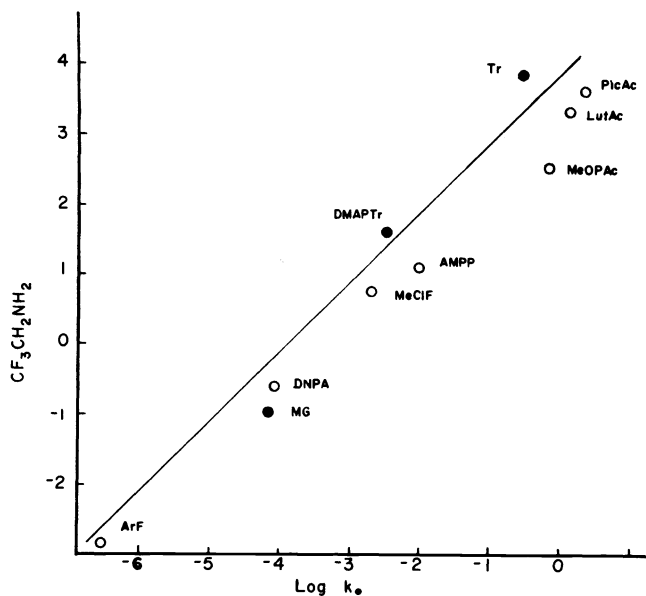list of abbreviations and symbols at end of paper).

Fig. 7. Logarithms of rate constants for reactions of 2,2,2-trifluoro-
ethylamine vs. Log k_o values. (See list of abbreviations and
symbols at end of paper).

If steric effects are responsible for the behaviors shown in Figs. 8 and 9, it would seem
that solvation of the ions is important. Moreover, since the esters, which show apparent
steric effects for reactions of amines, do not show any significant effects for the alkox-
ide ion reactions, one would be forced to consider interactions of solvation shells of
electrophile and nucleophile. At this point, however, such suggestions are pure speculation.
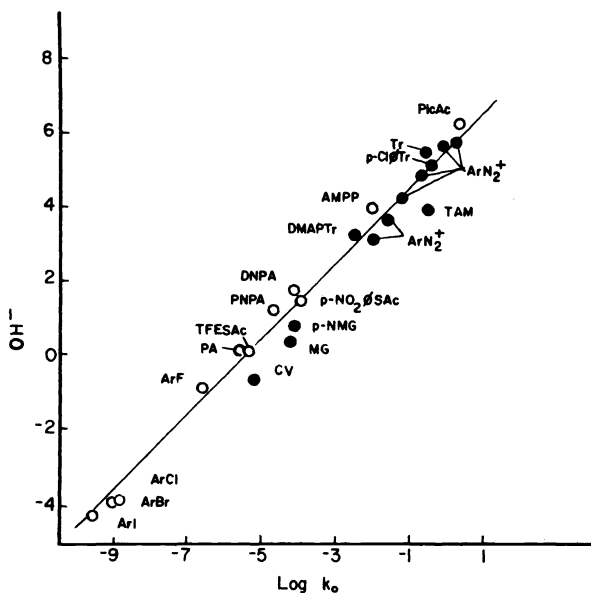
Fig. 8. Logarithms of rate constants for reactions of hydroxide ion vs.
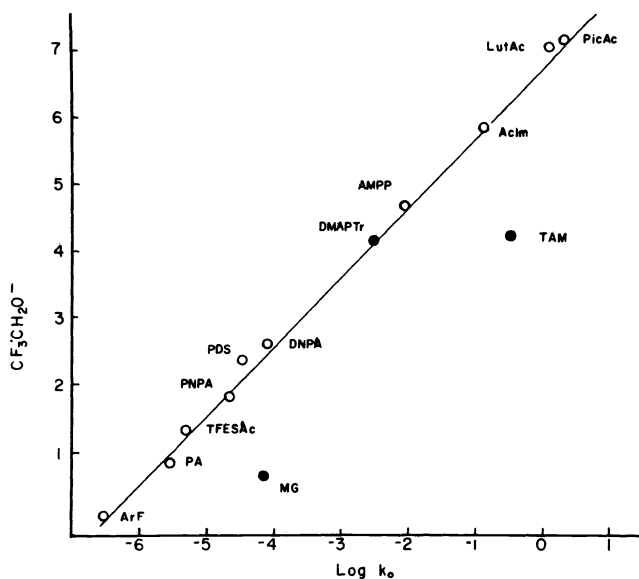Log k_o values. (See list of abbreviations and symbols at end
of paper.

Fig. 9. Logarithms of rate constants for reactions of 2,2,2-trifluoro-
ethoxide ion vs Log k_o values. (See list of abbreviations and
symbols at end of paper).

Yet another pattern of deviations from Eq. 1 is shown by the reactions of thiolate ions.
Unfortunately, the studies of ester reactions by Jencks (14) and of other reactions by
ourselves (6, 12) do not include a common thiolate nucleophile. The use of the Brønsted
relationships reported by Jencks, however, leads to what should be fairly reliable estimates
of rate constants for the reactions of thioglycollate ion with the esters. These estimates

for ester reactions and measured data for other reactions are used in the construction of
Fig. 10. It is virtually inconceivable that the estimates for the ester rate constants are
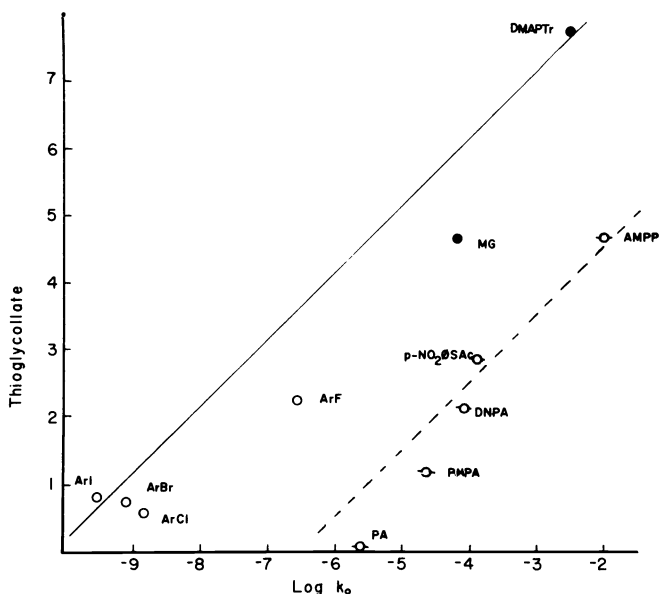

Fig. 10. Logarithms of rate constants for reactions of thioglycollate
          ion vs. Log k_o values. (See list of abbreviations and symbols
          at end of paper).

in error by the three powers of ten separating the points for these reactions from the line
shown in Fig. 10.

The behavior of sulfur nucleophiles has been discussed by Edwards and Pearson (15), Pearson
(3), Bunnett (16), and more recently, Todesco (17) in terms of polarizability interactions.
Such interactions do not provide a very satisfying rationalization of the present data.
Even the more flexible "hard-soft" concept (3) would have to be severely bent to accommodate
the results. For example, cyanide ion has been assigned a polarizability similar to that of
thiolates (1) and is classed (3) as a "soft" nucleophile along with the thiolates. Since
the Log k_o values used here are based largely on the reactions of cyanide ion, it is apparent
that thiolates and cyanide ion behave in completely different ways.

It is interesting to note that 2,4-dinitroiodobenzene, but not 2,4-dinitrofluorobenzene,
behaves "normally" relative to DMAPTr in the reactions of thioglycollate ion. As shown in
Figure 11, the same is true for reactions of thiophenoxide ion in methanol solution. We
have no explanation for the behavior of the thiolate ion nucleophiles, but believe that this
data requires a revision of current theories.

A quite unique pattern of deviations from Eq. 1 is shown by azide ion reactions. Although
our data are not as extensive as one would like, the available information shown in Fig. 12
presents an interesting pattern. In this case, it appears that there is a distinction
between reaction with a cationic and with a formally neutral electrophilic center. No other
nucleophile which we have studied shows this type of behavior. Again, we have no explanation.

          CONCLUSION

The heavy emphasis in the above discussion on deviations from the N_+ relationship should not
cause one to lose sight of the fact clearly shown in Fig. 1 that Eq. 1 is amazingly general
and far more precise than any other existing correlation of the data. We belive that the N_+
and Log k_o parameters form a meaningful data base which must be accommodated by any future
theory of nuccleophilic reactivity. Work on such a theory is clearly necessary since current
theories are unable to accommodate either Eq. 1 or the deviations from it.

We emphasize the fact that the N_+ relationship is not a theory but rather a systematization
of experimental facts. As illustrated in the above discussion, we believe that the systemati-
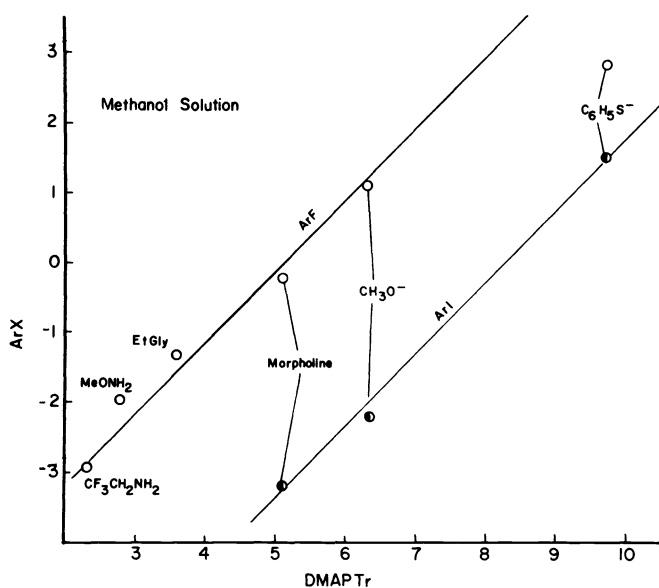
Fig. 11. Logarithmic plot of rate constants for reactions of p-dimethyl-
aminophenyltropylium ion vs those of 2,4-dinitrofluoro- and
iodo-benzene in methanol solutions.
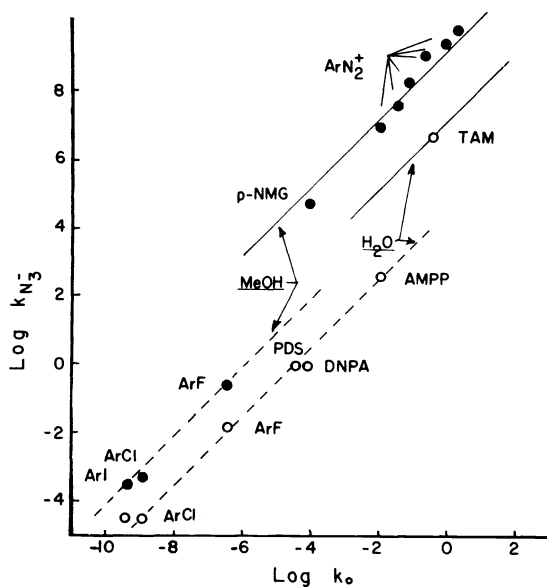(See list of abbreviations and symbols at end of paper).

Fig. 12. Lorarithms of rate constants for reactions of azide ion vs.
Log k_o values for both water and methanol solutions.
(See list of abbreviations and symbols at end of paper).

tization allows, for the first time, a directed approach to the evaluation of various
effects on the rates of electrophile-nucleophile combination reactions.

Abbreviations and Symbols used in Figures

AcIm	:	N-Methylacetylimidazolium ion
AMPP	:	N-Acetoxy, 4-methoxypyridinium ion
ArBr	:	2,4-dinitrobromobenzene
ArCl	:	2,4-dinitrochlorobenzene
ArF	:	2,4-dinitrofluorobenzene
ArI	:	2,4-dinitroiodobenzene
ArN$_2^+$	:	m-, and p-substituted Benzenediazonium ions
CV	:	Crystal Violet (tris-[p-dimethylaminophenyl]methyl cation)
p-ClØTr	:	p-Chlorophenyltropylium ion
DMAPTr	:	p-Dimethylaminophenyltropylium ion
DNPA	:	2,4-dinitrophenyl acetate
EtGly	:	Glycine Ethyl ester
Gly	:	Glycinate ion
Glygly	:	Glycylglycinate ion
LutAc	:	2,4-Lutidinium acetate
MeClF	:	Methyl chloroformate
MG	:	Malachite Green (bis-[p-dimethylaminophenyl]phenylmethyl cation)
Morph	:	Morpholine
p-NMG	:	p-Nitro Malachite Green (bis-[p-dimethylaminophenyl], p-nitrophenyl-methyl cation)
PDS	:	Phenyl, α-disulfone
PicAc	:	4-Picolinium acetate
Pip	:	Piperidine
PNPA	:	p-Nitrophenyl acetate
TAM	:	Tri-p-anisylmethyl cation
TFESAc	:	2,2,2-trifluoroethylthiol acetate
TG$^=$	:	Thioglycollate di-anion

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