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*Review Commentary*

# Are weak interactions responsible for kinetic catalytic behaviour in $S_NAr$ reactions?

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ABSTRACT: In solvents of low permittivity, non-covalent interactions between nitroaromatic derivatives and amines are detected and quantitatively evaluated by common spectroscopic methods. The nature of these complexes may be discussed. Mainly, these interactions are donor–acceptor and hydrogen bonding interactions. Electron-donor solvents compete with the amine in complexing the substrate. In $S_NAr$ reactions carried out with neutral nucleophiles (amines), in poorly polar solvents (such as aliphatic and aromatic hydrocarbons, tetrahydrofuran, chloroform, carbon tetrachloride, etc.), the experimental rate constant ($k_{obs}$ in $s^{-1}\,mol^{-1}\,dm^3$) increases on increasing the initial concentration value of the amine. The intervention of the amine (or other catalysts) on the leaving group/proton departure from the zwitterionic intermediate is the more usual explanation of the autocatalytic behaviour. This mechanism conflicts with the usual nucleophugality order (in apolar solvents also the reactivity order is F > Cl) observed in $S_NAr$ reactions. An alternative interpretation of the 'anomalous' kinetic behaviour involves the presence of molecular complexes on the reaction pathway. In agreement with this hypothesis, the evaluation of the stability of complexes from kinetic data agree well with the evaluation from independent spectroscopic data. The main points supporting the presence of the molecular complex on the reaction pathway of $S_NAr$ reactions are: (*i*) the electronic effects of substituents on aniline; (*ii*) the kinetic behaviour of systems without a leaving group and NH protons; (*iii*) the effect of change of the temperature; (*iv*) the absence of self-catalysis which corresponds to the absence of complexes; and (*v*) the kinetic behaviour of neutral oxygenated nucleophiles which parallels the behaviour of amines.


KEYWORDS: $S_NAr$ reactions; kinetic catalytic behaviour; weak interactions; amines

## INTRODUCTION

Recently, weak, non-covalent interactions[1] (including hydrogen bonding interactions[2]) have assumed increased importance in both practical and theoretical aspects of chemistry. The formation of molecular complexes contributes to explaining some chemical behaviour, e.g. the effects of change of solvent[3,4] or, in general, of the medium.

The energetic level of molecules may be modified by interactions with surrounding molecules, and it may be difficult to relate molecular structure to chemical properties. This aspect is scarcely considered in most student textbooks: reacting substances are depicted as 'free' molecules. Instances of the importance of non-covalent interactions are self-assembling of molecules and the formation of supramolecular species.[5]

In electrophilic aromatic substitutions,[6] and also in electrophilic addition to C=C double bonds,[7] the first step of the reaction is the formation of an interaction (donor–acceptor-like) between the nucleophile (the substrate) and the electrophilic reagent.

In mixtures of nitro-activated substrates and amines in apolar aprotic solvents, several kinds of non-covalent complexes are observed by spectroscopic analysis of the reaction mixtures.[8] The formation of these complexes is a very fast process and it precedes the substitution reaction.

In agreement with Reichardt's observations,[3] the products of interactions may be named 'molecular complexes' (MC). This generic definition is related to the presence of different interactions which mainly involve electron donor–acceptor and hydrogen bonding interactions. Depending on the nature of the solvent used, amines may compete with solvent in complexing the substrate which is an electrophilic molecule.

The kinetic feature of the reactions between nitro-activated substrates and amines in apolar aprotic solvents is an exception to the usual second-order kinetic law ($v = k_{obs}$ [substrate] [amine]). In these solvents the experimental reaction order in amine may rise from 1 to 3: the $k_{obs}$ (in $s^{-1}\,mol^{-1}\,dm^3$) value increases on increasing the initial amount of amine, $[amine]_0$.

The purpose of this paper is to focus the presence of

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feeble interactions (solute–solvent or solute–solute) in a simple and common reacting system (the $S_NAr$ reaction with neutral nucleophiles in apolar solvents) and to examine the possibility that the observed molecular complexes are on the coordinates of the reaction and cause unusual kinetic behaviour.

## NATURE OF THE INTERACTIONS BETWEEN NITRO-ACTIVATED SUBSTRATES AND AMINES

The fact that an electron-rich compound interacts with an electron-deficient substance in an electron donor–acceptor complex is not surprising.[9] Naphthalene derivatives and picric acid have long been known to afford a yellow complex[10] which crystallizes from ethanol. Interactions (donor–acceptor-like) in the reaction mixtures of nitro-activated substrates and amines were investigated also from the kinetic point of view by Ross and Kuntz.[11]

In the equilibrium in Scheme 1, $K^{MC}$ is the apparent stability constant of the complex ArL·RR′NH.

$$ArL + RR'NH \underset{}{\overset{K^{MC}}{\rightleftharpoons}} ArL{\cdot}RR'NH$$

**Scheme 1**

In many cases, the observed interactions were quantitatively evaluated by the Benesi–Hildebrand treatment.[9] Complexes with different donor to acceptor ratios (2:1, 1:1, 1:2) are known.[12]

The nature of molecular complexes may be questioned.[8] In principle, a number of interactions are possible, depending on the nature of the partners and of the medium (solvent). In some cases a particular interaction prevails over the others, or appears to prevail, depending also on the kind of measurements used to reveal it.

Nitroaromatic derivatives and aromatic amines interact mainly by a donor–acceptor interaction.[8] For mixtures of 2,4-dinitrofluorobenzene (or 2,4-dinitrochlorobenzene) and substituted anilines in benzene, UV–visible spectrophotometric data allowed an evaluation of $K^{MC}$ values (in $mol^{-1}\,dm^3$). Table 1 gives some apparent stability constants of selected complexes between dinitro aromatic derivatives and amines.

The $K^{MC}$ values of the interactions between substituted anilines and 2,4-dinitrofluorobenzene (DNFB) in benzene were independently calculated from kinetic data and from spectroscopic data obtained by inspection of reaction mixtures at zero time of reaction. $K^{MC}$ values were related to the donor ability of anilines, as indicated by the $\rho$ value (= −2.8) of the Hammett plot (log $K^{MC}$ versus $\sigma$ values).

When the solvent is an electron donor molecule (benzene, toluene), it solvates the electron acceptor molecule (the nitroaromatic derivative); consequently, the amine may compete with the solvent in complexing the substrate.

**Table 1.** Apparent stability constants of selected molecular complexes between 1-fluoro-2,4-dinitrobenzene (unless indicated otherwise) and amines or (catalysts) in poorly polar solvents

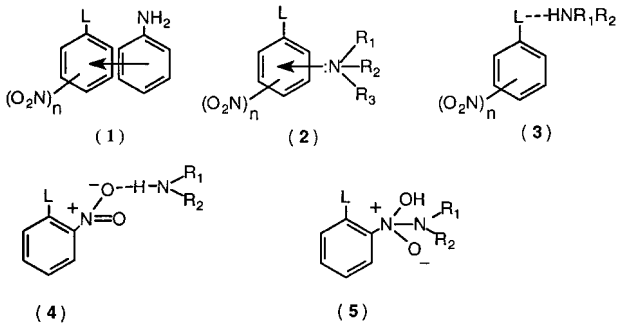
| Amine[a] | $T$ (°C) (solvent) | $K^{MC}$ [b] ($mol^{-1}\,dm^3$) | Ref. |
|---|---|---|---|
| Aniline | 40 (benzene) | 0.068 | 13 |
| Aniline | 40 (chloroform) | 0.70 | 13 |
| [$^2$H] Aniline-$d_7$ | 40 (chloroform) | 0.60[c] | 13 |
| Aniline | 40 (tetrahydrofuran) | 0.20; 0.31[d] | 14 |
| *N*-Methylaniline | 40 (tetrahydrofuran) | 1.0; 0.65[d] | 14 |
| *p*-Methylaniline | 40 (tetrahydrofuran) | 0.40; 0.31[d] | 14 |
| *p*-Methoxyaniline | 40 (tetrahydrofuran) | 1.2; 1.6[d] | 14 |
| *m*-Methylaniline | 40 (tetrahydrofuran) | 0.43; 0.16[d] | 14 |
| *m*-Methoxyaniline | 40 (tetrahydrofuran) | 0.20; 0.43[d] | 14 |
| *p*-Chloroaniline | 40 (tetrahydrofuran) | 0.46; 0.29[d] | 14 |
| DABCO[e] | 25 (benzene) | 0.31; 0.31[d] | 15 |
| Triethylamine | 40 (benzene) | 0.47 | 16 |
| 2-Pyridone | 30 (benzene) | 27[d] | 17 |
| δ-Valerolactam | 30 (benzene) | 2.1[d] | 17 |
| *n*-Butylamine | 21 (toluene) | 14[d]. | 18 |
| *n*-Butylamine | 21 (cyclohexane) | 27 | 19 |
| Piperidine | 21 (cyclohexane) | 79 | 19 |
| *n*-Butylamine[f] | 27 (hexane) | 0.39 | 20 |
| Di-*n*-butylamine[f] | 27 (hexane) | 0.20 | 20 |
| Tributylamine[f] | 27 (hexane) | 0.043 | 20 |

[a] Or catalyst.
[b] Calculated from UV–visible spectrophotometric analyses, unless indicated otherwise.
[c] Calculated from $^1$H NMR spectroscopic measurements.
[d] Calculated from kinetic data.
[e] DABCO = 1,4-Diaza[2.2.2]bicyclooctane.
[f] 1,3-Dinitrobenzene.

The apparent stability constants of the DNFB–aliphatic amine complexes in cyclohexane are higher than $K^{MC}$ values of the complexes between DNFB and substituted anilines.

In some cases UV–visible spectrophotometric evaluation of $K^{MC}$ values agrees with other measurements such as $^1$H NMR measurements and kinetic determinations (see Table 1).

Some instances of particular interactions involving mixtures of halonitro derivatives and amines are illustrated in (**1**–**5**); L is the leaving group of $S_NAr$ reactions.



(1) (2) (3) (4) (5)

Aromatic amines may offer a ring–ring package (with the possibility of a $\pi$–$\pi$ charge transfer) such as that illustrated in **1**. Recently, an evaluation of the hydrogen bonding interaction between amine and aromatic fluoro derivatives, as depicted in **3**, was carried out.[21]

Species **1** and **2** are electron donor–acceptor complexes ($\pi \rightarrow \pi^*$ and n $\rightarrow \pi$, respectively), **3** and **4** are examples of proton donor–acceptor interactions and **5** is a particular complex showing covalent bonds;[22] **2** is probably the most important interaction in the case of tertiary amines, in particular cyclic amines or imines such as 1,4-diazabicyclo[2.2.2]octane (DABCO) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); non-cyclic tertiary amines (such as $Et_3N$) are less able than cyclic amines to complex electron-deficient substrates, probably because of steric hindrance.

In conclusion, the presence of several interactions in the reaction mixtures of nitro derivatives and amines is quantitatively ascertained by different techniques (see Table 1). These interactions engage not only both partners of the usual $S_NAr$ reactions, but also the solvent.

## KINETIC FEATURES OF $S_NAr$ REACTIONS: THE BASE CATALYSIS EXPLAINS THE CATALYTIC BEHAVIOUR

The two-step mechanism of aromatic nucleophilic substitution reactions was proposed by Bunnett and Zahler in 1951[23] for substrates activated by the presence of electron-withdrawing groups.

The major indication favouring the two-step mechanism of Scheme 2 (see later) is the fact that the leaving group departure occurs in a fast step. For instance, the reactivity of fluoro derivatives is higher than that of chloro derivatives.

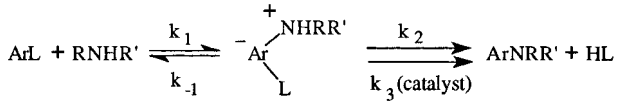
The $S_NAr$ reactions in polar solvents (such as alcohols, dimethyl sulphoxide and dimethylformamide) with anionic or neutral nucleophiles follow the usual second-order kinetic law ($n = 1$) as expressed by the equation.

$$v = k_{obs}[S][Nu]^n \qquad (1)$$

When poorly polar solvents (such as aliphatic and aromatic hydrocarbons, tetrahydrofuran, chloroform or carbon tetrachloride) are used with neutral nucleophiles (amines), the experimental reaction constant ($k_{obs}$ in $s^{-1}\,mol^{-1}\,dm^3$) increases on increasing the initial concentration of the amine ($[amine]_0$) and $n > 1$.

Major evidence for this kinetic behaviour comes from reactions involving aromatic activated fluoro derivatives.[24] The value of $n$ changes from 1 to 3 (the whole reaction order may rise to 4) depending on the nature of the solvent, and also on the nucleophile and on the substrate.

This kinetic behaviour was explained (in particular, when aliphatic amines are considered, where $n = 2$) by




(6) (2)

R' H, alkyl; R = alkyl, aryl.

**Scheme 2**

the action of a second molecule of amine on the zwitterionic intermediate **6** (see Scheme 2) to promote the HL departure.[25]

This explanation of the kinetic data (usually reported as 'base catalysis') is considered a convincing indication of the existence of the two-step mechanism. SBGA (specific base–general acid) is a frequent mechanism of the catalysed pathway proposed by Bernasconi[25] (see Scheme 2). The two reaction pathways may be in competition in affording the reaction products, as shown in Scheme 2.

Equation (3) is derived from Scheme 2:

$$k_{obs} = k + k_B[amine]_0 \qquad (3)$$

where $k = (k_1/k_{-1})k_2$ is the spontaneous transformation of the zwitterionic intermediate into the products of the substitution reaction; $k_B = (k_1/k_{-1})k_3$ refers to the reaction pathway with the intervention of the catalyst.[26]

Base catalysis in $S_NAr$ reactions in apolar solvents is a well constructed theory which starts from two main points:[23,25]

(i) The two-step mechanism: usually the formation of the $\sigma$ complex is rate-limiting, as reported by Fig. 1(A). HL departure is a fast step ($k_2$ in Scheme 2).
(ii) The departure of HL (in particular HF in apolar solvents) may be a difficult process. The decomposition of the intermediate is rate-limiting of the uncatalysed pathway, as depicted in Fig. 1(B). As a consequence, the HL departure prefers a different easier pathway, which is the base-catalysed pathway.

Some considerations on the second point are illustrated in the next section.

### Relative reactivity of fluoro and chloro derivatives in apolar solvents

The peculiarity of the two-step mechanism of the $S_NAr$ reaction in polar solvents is the leaving group departure in a fast step and the reactivity order $F \gg Cl$ was observed for $(k_1/k_{-1})k_2 = k$ values of Eqn (3).

Reactions carried out in apolar aprotic solvents show the reactivity order $F > Cl$ (see Table 2) for simple nucleophilic attack (the bond breaking occurs in a fast step). An explanation of the fast departure of the fluoride ion is the hydrogen-bonding interaction with protic

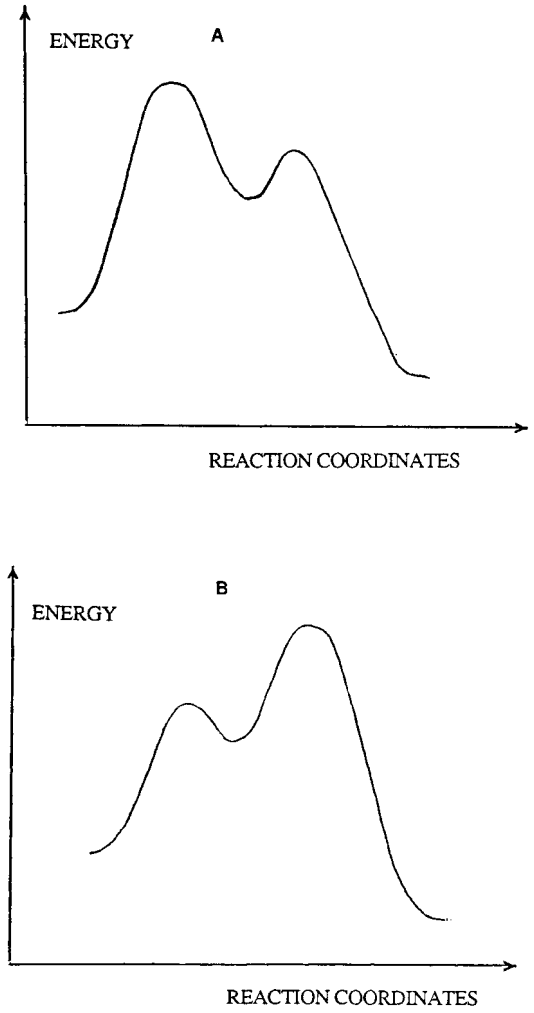



**Figure 1.** Energy diagram for $S_NAr$ reaction: (**A**) fast leaving group departure; (**B**) difficult leaving group departure; a different reaction pathway may take place

amines. Consequently, the fluoride ion hardly involves another protic molecule to have catalysis on its departure.

If the 'anomalous' kinetic features are explained by Scheme 2 (i.e. by the presence of base catalysis), then the second maximum is higher than the first [Fig. 1(B)], in contradiction with the reactivity order F > Cl; therefore, we need an explanation alternative to base catalysis.

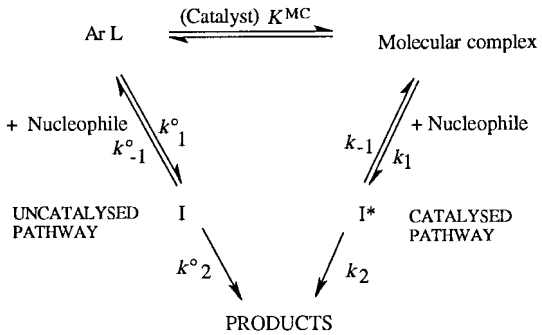
## AN ALTERNATIVE EXPLANATION TO BASE CATALYSIS

Several years ago, a study of reactions between 2,4-dinitrofluorobenzene (DNFB) and substituted anilines was started.[13]

In previous literature data, a strong effect of change of substituent in aniline[27,28] was reported, together with the fact that the experimental reaction order [Eqn (4)] in substituted aniline was 3.[29] This value can hardly be explained by the model of Scheme 2, which involves a reaction order in amine of 2.

$$v = k_{obs}[S][\text{aniline}]_0^{\,3} \qquad (4)$$

Scheme 3 reports a pathway, alternative to the model of Scheme 2, more general in explaining the data,[19] and involving the formation of the observed molecular complexes.




**Scheme 3**

**Table 2.** Relative reactivity (for the uncatalysed process) of activated aromatic fluoro and chloro derivatives towards amines in poorly polar solvents

| Substrate[a] | Nucleophile | $T$(°C) (solvent) | $(k_F/k_{Cl})$[b] | Ref. |
|---|---|---|---|---|
| 1-X-2,4-dinitrobenzene | *n*-Butylamine | 25 (benzene) | 400 | 30 |
| 1-X-2,4-dinitrobenzene | *sec*-Butylamine | 25 (benzene) | 1800 | 30 |
| 1-X-2,4-dinitrobenzene | *tert*-Butylamine | 25 (benzene) | 1000 | 30 |
| 1-X-2,4-dinitrobenzene | Aniline | 40 (benzene) | 300 | 31 |
| 1-X-2,4-dinitrobenzene | Aniline | 40 (chloroform) | 122 | 31 |
| 2-X-6-nitrobenzothiazole | Piperidine | 25 (benzene) | 76 | 13 |
| 2-X-6-nitrobenzothiazole | *n*-Butylamine | 25 (benzene) | 219 | 31 |
| 1-X-2,4,6-trinitrobenzene | α-pyridone | 45 (chlorobenzene) | 1000 | 32 |
| 1-X-2-nitrobenzene | Piperidine | (toluene)[c] | >100 | 33 |

[a] X = F, Cl.
[b] $k_X$ (in $s^{-1}\,mol^{-1}\,dm^3$) = $(k_1/k_{-1})k_2$.
[c] 1-Fluoro-2-nitrobenzene and piperidine at 25 °C (toluene), $k_{obs}$ ($s^{-1}\,mol^{-1}\,dm^3$) = $2.9 \times 10^{-4}$;[33] 1-chloro-2-nitrobenzene and piperidine at 45 °C (benzene), $k_{obs}$ ($s^{-1}\,mol^{-1}\,dm^3$) = $3.6 \times 10^{-6}$.[34]

From Scheme 3, Eqn (5) may be obtained,[11] where $k^0 = (k^0_1/k^0_{-1})k^0_2$ is a measure of the reactivity of the uncomplexed substrate, $K^{MC}$ is the apparent stability of the complex (the stoichiometry of the formation of the molecular complex is assumed to be 1:1) and $k^{MC} = (k_1/k_{-1})k_2$ is a measure of the reactivity of the substrate complexed with the amine.

$$k_{obs}(1 + K^{MC}[\text{amine}]_0) = k^0 + K^{MC}k^{MC}[\text{amine}]_0 \quad (5)$$

In Scheme 3, two main reaction pathways are involved: the reaction of the 'free' substrate and the amine (uncatalysed pathway) and the reaction of the substrate complexed by the catalyst (catalysed pathway). As a consequence, the experimental kinetic order in amine depends on the presence of molecular complexes, which may be of different stoichiometry (1:1 or 1:2, substrate:nucleophile[12]). Catalysis on HL departure may be overimposed on both pathways of Scheme 3.

There are two main possibilities: (1) the complexes are on the reaction pathway or (2) they are a non-productive (a 'cul-de-sac') equilibrium.[35] Kinetic law itself cannot discriminate between (1) and (2). When the rate of the reaction of the uncomplexed substrate is known (as in a number of instances of reactions[19] discussed here) it is possible to indicate that the catalysis is a positive catalysis.[35] For example, when the reactions are carried out under experimental conditions qualified to minimize the formation of complexes, such as when $[\text{nucleophile}]_0 < [\text{substrate}]_0$ or within a range of $[\text{nucleophile}]_0$ values in which no catalysis is observed,[18] the $k^0$ ($= k_{obs}$) value means the reactivity of the 'free' substrate (i.e. complexed by the solvent only).

Positive catalytic behaviour appears when $k_1 > k^0_1$ (the molecular complex is more reactive than the free substrate), but when $k_1 < k^0_1$ negative catalysis may be observed.[11] These possibilities strongly depend on the nature of the solvent.[13,16] When apolar solvents are used and $k_1 > k^0_1$, the $k_{obs}$ values are increased on increasing the $[\text{amine}]_0$ value. In polar solvents $k_1 < k^0_1$ and $k_{obs}$ decreases (or it is unaffected) by increasing the $[\text{amine}]_0$ value. Obviously, when $k_1 = k^0_1$, no catalysis can be observed.

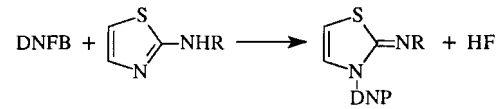
In solvents of high donicity (as expressed by the 'donicity number'[4]), such as tetrahydrofuran, the reaction order in the reacting aromatic amine may be decreased from 3 (in benzene) to 2 (in tetrahydrofuran).[16] The presence of substances of high donicity and low polarity decreases the order of reaction in the reacting amine. This is the case of the triethylamine[16] added to the reaction mixtures between 2,4-dinitrofluorobenzene and substituted anilines. Triethylamine added in a range of concentrations in which its action as catalyst is low but its complexing ability is high reduces the reaction order in the reacting amine to 1 and the overall reaction order becomes 2 (first in both reactants). The desolvating mechanism[36] starts from the competition between the neutral nucleophile and the solvent (or other added substances) in complexing the substrate.

It is important to emphasize that in a number of cases, the $K^{MC}$ values calculated from UV–visible spectroscopic data agree with those calculated from kinetic measurements by Eqn (5) (see Table 1).

The following section are worthy of consideration in supporting the pathways of Scheme 3.

## Absence of self-catalysis corresponds to the absence of complex

The absence of self-catalysis in the reactions between DNFB and 2-thiazoleamine derivatives[17] in benzene (Scheme 4) is unexpected considering that the properties (nucleophilic power, p$K_a$ values) of these heterocyclic amines are close to the properties of amines known to exhibit self-catalysis.




R = H, Bu$^s$, Ph

DNP = 2,4-dinitrophenyl

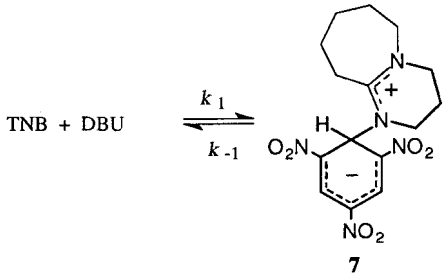
**Scheme 4**

Absence of self-catalysis was explained by the absence (in the reaction mixtures) of detectable amounts of complexes between DNFB and 2-thiazoleamine derivatives. On the other hand, the reactions of Scheme 4 are strongly catalysed by catalysts able to complex DNFB (DABCO, 2-pyridone, $\delta$-valerolactam; see Table 1).

## Systems without leaving group and NH protons

The reaction between 1,3,5-trinitrobenzene (TNB) and DBU produces, in dimethyl sulphoxide,[37] a $\sigma$-like complex as shown in Scheme 5.

In toluene, the kinetic data showed autocatalytic behaviour which obviously cannot be related to the abstraction of proton or of leaving group, because both

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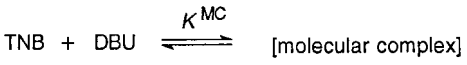
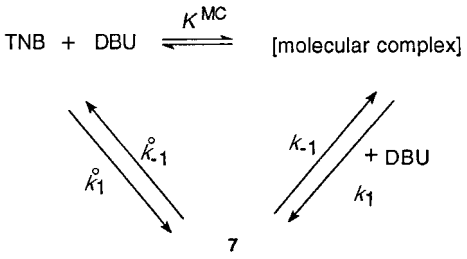
**Scheme 5**




**Scheme 6**




**Scheme 7**

are absent. An equilibrium between TNB and DBU (preceding the nucleophilic attack) was observed[38] (Scheme 6).

The presence of the molecular complex (donor–acceptor-like) in an equilibrium preceding the formation of the zwitterionic complex is the most reasonable explanation of the observed catalytic behaviour (see Scheme 7), which cannot be explained by the 'base catalysis' mechanism. Similar behaviour was observed with DABCO and quinuclidine.[39]

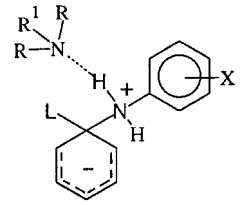
## Electronic effects of substituents on the catalysed pathway: change of substituents on the aniline

In 1972, Kavàlek *et al.*[28] reported an unusual $\rho$ value (calculated by the Hammett plot) of $-6.5$ for the catalysed step of the reactions between substituted anilines and 2,4-dinitrofluorobenzene. In fact, the data for the reactions between 2,4-dinitrofluorobenzene and substituted anilines in benzene analysed by Eqn (3) affords a $\rho$ value [in the plot of $\log k_B = (k_1/k_{-1})k_3$ versus $\sigma$ values] $= -6.4$,[13] which cannot be explained by a solvent effect, by self-association of amines or by HF abstraction from the zwitterionic intermediate **6**. The data analysis by Eqn (5) affords a $\rho$ value of $-3.6$ for the attack of the nucleophile on the complexed substrate. This value is usual when the nucleophilic attack is the rate-limiting step. For example, $\rho = -4.0$ was calculated[40] for reactions between 2,4-dinitrofluorobenzene and substituted anilines in 99.8% ethanol.

In Scheme 3 there are two steps enhanced by the electron-donating substituents on the aniline: the formation of the molecular complex ($\rho = -2.8$) and the attack of the nitrogen atom of the aniline on the carbon bearing the leaving group ($\rho = -3.6$) The formation of the products by the catalysed pathway for the overall electronic effect is the sum ($\rho = -6.4$) of the two effects on the separate steps. In THF, the $\rho$ value for the reactivity of the DNFB–aniline molecular complex and anilines is $-4.0$.[14]

The effect of the change of the substituent on the aniline related to the pathway catalysed by other unreactive amines such as *N*,*N*-dimethylaniline,[26] DABCO[15] and triethylamine[16] clearly matches the conclusion that the molecular complexes are on the reaction pathway of the substitution. In particular, for reactions between 2,4-dinitrofluorobenzene and substituted anilines when the catalyst (unchanged for all substituted anilines) is *N*,*N*-dimethylaniline, the effect of the substituents on the rate of the catalysed pathway is evaluated by a $\rho$ value of $-4.9$. This value clearly indicates that in the pathway catalysed by *N*,*N*-dimethylaniline the nucleophilic power of the reacting substituted aniline is important,[13] as required by Scheme 3.

In contrast, when the transition state of the catalysed step is represented by **8**, a high (negative) $\rho$ value hardly agrees with a pathway including a rate-determining step involving $H^+$ abstraction from the substituted zwitterionic intermediates by the same (unreacting) base. In this case the $\rho$ value should be positive (or zero).




$NR^1R_2$ = triethylamine, DABCO, N,N-dimethylaniline

**8**

## Effects of changes of temperature

Generally, the effects of temperature increase on $S_NAr$ reactions in polar solvents produces an increase in the $k_{obs}$ value in agreement with the Arrhenius law. The effect of a change in temperature on the uncatalysed pathway is different from that on the catalysed pathway.[31] In some cases, in apolar solvents, a temperature increase produces a decrease in $k_{obs}$ v.[36,41,42]

Also for the reaction in Scheme 5, the $k_{obs}$ values decrease with increase in temperature.[38] This anomalous behaviour strongly supports the presence of a pre-association on the reaction pathway towards the formation of the zwitterionic complex. The association between the substrate and the nucleophile (equilibrium of Scheme 6) is depressed on increasing the temperature, as usual in association processes with non-covalent bonds.

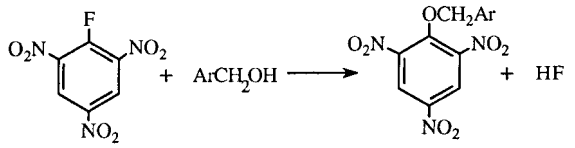
Both rates of formation of **7** are increased on increasing the temperature as required in $S_NAr$ reactions

and all the kinetic features agree with the mechanism of Scheme 7. The effect of temperature depends on the relative importance of the two reaction pathways (uncatalysed and catalysed). An increase in temperature shifts the real reaction pathway towards the uncatalysed mechanism because $K^{MC}$ is depressed by enhancement of the temperature.

Other authors[43] explain the anomalous effect of the temperature by self-association of protic amines. Obviously, self-association of DBU cannot explain the kinetic features of the equilibrium reactions in Scheme 5.

## Reactivity of neutral oxygen nucleophiles

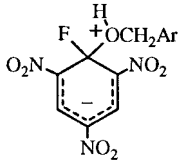
Recently, the reactions between 2,4,6-trinitrobenzene and methanol or substituted benzyl alcohols in carbon tetrachloride (Scheme 8) have shown kinetic behaviour similar to that of amines.[44]




**9**

**Scheme 8**

$k_{obs}$ increases on increasing the $[ArCH_2OH]_0$ values. Inspection (by a UV–visible spectrophotometric method) of the reaction mixtures at zero reaction time reveals the presence of an interaction (donor–acceptor-like) between $ArCH_2OH$ and **9**. This kinetic behaviour cannot be explained by HF abstraction from the zwitterionic intermediate **10** because the $pK_a$ values of oxonium ions are much higher than those of ammonium derivatives and the alcohol is in large excess.




**10**

This kinetic behaviour may be explained by a mechanism similar to Scheme 3 for neutral nitrogen nucleophiles.

## CONCLUSIONS

The reaction pathway of Scheme 3 concerns a simple mechanism which explains some important data difficult to explain by other mechanisms and is based on the presence of interactions actually observed and measured in the reaction mixtures.

Recently, a charge-transfer (CT) complex between 1,3,5-trinitrobenzene and indole-3-carboxylate was isolated.[45] This complex (in DMSO) spontaneously affords $\sigma$-adducts. A problem is to state whether $\sigma$-adducts are obtained directly from the CT complex or from the dissociated compounds of the CT complex.

A central subject of discussion is why the molecular complex may be considered more reactive than the 'free' substrate. In polar solvents, the association of an electrophile (the nitroaromatic substrate) with a nucleophile appears decreasing the positive charge of electrophile towards further attack of another molecule of the nucleophile. Consequently, the complex formation depresses the concentration of the 'free' substrate and the $k_{obs}$ value may decrease on increasing the $[nucleophile]_0$ value, as observed in polar solvents by Ross and Kuntz.[11]

In contrast, in apolar solvents, the reaction starts from neutral reagents towards a transition state in which charge separation is high. If the molecules of apolar solvents are replaced by polar molecules surrounding the substrate, the rate of nucleophilic attack ($k_1$) is enhanced and $k_{-1}$ is depressed.[46] Accordingly, when the $S_NAr$ reactions may be conceived as having a neutral transition state,[33] no increase in $k_{obs}$ values to increasing the $[amine]_0$ values were observed

In principle, in a mechanistic discussion of reactions, the exclusion of a particular mechanism may be unreasonable because different reaction pathways may be active in affording the products of reaction. One reaction pathway (in competition with others) may be the 'most populated' under particular experimental conditions, which depresses other possible reaction pathways (and vice versa).

However, the nucleophugality order $F \gg Cl$ scarcely agrees with the usual explanation of catalytic kinetic behaviour. In contrast, $F \gg Cl$ is the general nucleophugality order required by Scheme 3.

In conclusion, there are clear indications that the answer to the title question is positive. Probably more attention should be paid to the non-covalent interactions of the reagents in the reaction mixtures as an important step to rationalize also other chemical behaviours.

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