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CATALYSIS IN NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS. A REINVESTIGATION OF THE REACTION BETWEEN 1-FLUORO-2,4-DINITROBENZENE AND *n*-BUTYLAMINE

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The reaction between 1-fluoro-2,4-dinitrobenzene and *n*-butylamine in toluene shows a two-step plot of k_{obs} values vs the initial values of the concentration of the amine. The usual base-catalysis mechanism for HF elimination from the zwitterionic intermediate hardly explains this kinetic behaviour and the kinetic effect of addition of salts (and of 2-hydroxypyridine) to the reaction mixtures at different initial values of the concentration of *n*-butylamine. In contrast, the kinetic behaviours are easily explained by the presence of substrate–amine (or catalyst) interactions on the pathway of the substitution reaction.

INTRODUCTION

Nucleophilic aromatic substitution reactions in apolar solvents with neutral nucleophiles (aliphatic and aromatic amines) show a particular kinetic behaviour, i.e. observed kinetic constant (k_{obs}, s^{-1} mol^{-1} l) increases on increasing the initial concentration of the nucleophile.

The initial addition to the reaction mixture of substances such as tertiary amines or 2-hydroxypyridine causes an increase in k_{obs} values. The usual explanation for this increase is related to the rate-limiting expulsion of HL[1] (where L is the leaving group) from the zwitterionic intermediate in the usual two-step mechanism as represented in Scheme 1, where k_2 refers to the uncatalysed process and k_3 refers to the C-catalysed step; C can be the same reacting amine or another catalyst. From Scheme 1,[1] equation (1) is obtained (on the basis of the steady-state approximation):

$$k_{obs} = \text{rate}/([\text{ArL}]\,[\text{RNH}_2]) = (k_1k_2 + k_1k_3[\text{C}])/(k_{-1} + k_2 + k_3[\text{C}]) \quad (1)$$

By assuming the condition $k_{-1} \gg k_2 + k_3[\text{C}]$, equation (1) becomes

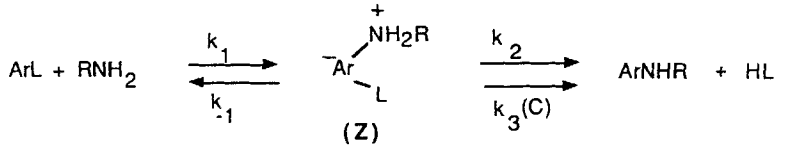
$$k_{obs} = (k_1/k_{-1})k_2 + (k_1/k_{-1})k_3[\text{C}] \quad (2)$$

When the initial concentration of C is increased, the $k_3[\text{C}]$ value increases ($k_3[\text{C}] \gg k_{-1}$), and equation (1) becomes

$$k_{obs} = k_1 \quad (3)$$

A number of examples have been reported in which k_{obs} increases linearly on increasing [C] until it reaches a maximum [equation (3)]. This interpretation of the kinetic behaviour of S_NAr reactions in apolar solvents is generally accepted. It includes the possibility that the proton abstraction from the zwitterionic intermediate (Z) is an equilibrium limiting the substitution rate.

As an alternative to this mechanism, we proposed a different explanation of the observed kinetic behaviours.[2–4] Inspection of the reaction mixtures at zero reaction time (immediately after mixing the solutions of



Scheme 1

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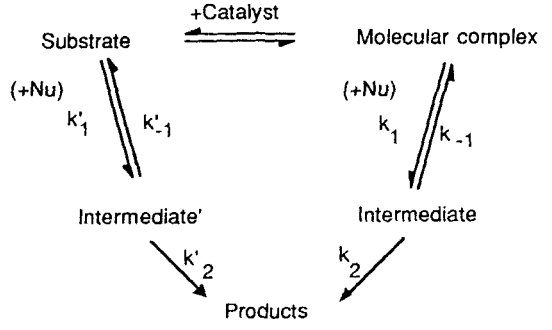
the reagents) indicates the presence of a molecular complex (substrate–nucleophile, substrate–catalyst) in a rapidly established equilibrium.[2-5] The model that we proposed suggests the probable position of the molecular complex in the substitution reaction pathway, as represented in Scheme 2. The catalyst can be the same reacting amine.

Scheme 2 provides an easy explanation of an autocatalytic kinetic behaviour or of some other catalytic phenomena in aromatic nucleophilic substitution reactions in apolar solvents and with neutral nucleophiles. From Scheme 2, the following equation can be obtained to describe the kinetic behaviour:[5]

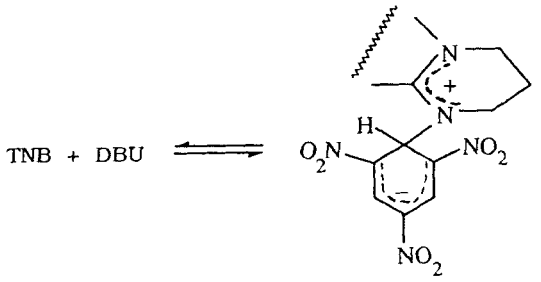
$$k_{obs}(1 + K[Nu]_0) = k_0 + kK[Nu]_0 \quad (4)$$

where k_0 is a measure of the reactivity of the free substrate [$k_0 = (k_1'/k_{-1}')k_2'$ in Scheme 2], k is a measure of the reactivity of the molecular complex between 1-fluoro-2,4-dinitrobenzene and the nucleophile (Nu) [$k = (k_1/k_{-1})\,k_2$] and K is a measure of the stability of the molecular complex.

Scheme 2 was confirmed by the autocatalytic behaviour of the reaction between 1,3,5-trinitrobenzene



Scheme 2



Scheme 3

(TNB) and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), in toluene[4,6] which affords the zwitterionic complex shown in Scheme 3. This system presents neither a leaving group nor a proton and the observed autocatalytic behaviour was explained by the presence of a substrate–nucleophile interaction.

To learn more about Scheme 2 for a very popular reaction, we report some data on a reinvestigation of the kinetic behaviour of the reaction between 1-fluoro-2,4-dinitrobenzene (FDNB) and *n*-butylamine (BU) in toluene.

RESULTS

Under all the experimental conditions reported here, the usual substitution product was obtained in almost quantitative yields, as verified by preparative runs and by absorbance values at 'infinite' reaction time. The kinetic data are reported in Table 1. The major part of the data available in the literature and those reported here were obtained under the experimental conditions $[FDNB]_0 < [amine]_0$ (where $[]_0$ are initial concentration values). Some of the data in Table 1 were obtained under the less usual experimental conditions $[FDNB]_0 > [amine]_0$, in which the catalytic effects are

Table 1. Reactions between 1-fluoro-2,4-dinitrobenzene (FDNB) and *n*-butylamine (BU) in toluene at 21 °C

Initial concentration	Parameter	Values				
$[FDNB]_0 = 4{\cdot}2 \times 10^{-5}$ mol l^{-1}	$10^3[BU]_0$(mol l^{-1})	0·762	0·914	1·22	1·48	1·87
	k_{obs}(s^{-1} mol^{-1} l)	0·172	0·171	0·175	0·175	0·179
	$10^3[BU]_0$(mol l^{-1})	2·06	2·36	3·06	4·13	5·33
	k_{obs}(s^{-1} mol^{-1} l)	0·182	0·182	0·184	0·199	0·221
	$10^3[BU]_0$(mol l^{-1})	5·36	9·90	10·7	13·4	17·9
	k_{obs}(s^{-1} mol^{-1} l)	0·220	0·272	0·273	0·282	0·307
	$10^2[BU]_0$(mol l^{-1})	2·11	2·82	4·43	6·30	9·39
	k_{obs}(s^{-1} mol^{-1} l)	0·321	0·376	0·452	0·480	0·543
	$10[BU]_0$(mol l^{-1})	1·23	1·48	1·72	2·08	4·13
	k_{obs}(s^{-1} mol^{-1} l)	0·630	0·628	0·625	0·709	1·02
	$10[BU]_0$(mol l^{-1})	6·30	7·80	9·39		
	k_{obs}(s^{-1} mol^{-1} l)	1·28	1·61	1·83		
$[BU]_0 = 4{\cdot}3 \times 10^{-5}$ ml l^{-1}	$10^3[FDNB]_0$(mol l^{-1})	0·766	1·03	1·28	2·55	
	$10k_{obs}$(s^{-1} mol^{-1} l)	1·70	1·82	1·80	1·74	

minimized in order to evaluate the second-order rate constant for the uncatalysed process.

The kinetic behaviour of the reactions between *n*-butylamine and FDNB in toluene is also particularly interesting if compared with published data for the same reaction.[7] The range of the initial concentration of *n*-butylamine, $[BU]_0$, used here is unusual (more than 10^3-fold). Up to about $[BU]_0 = 3 \times 10^{-3}$ mol l^{-1} (the first eight values in Table 1), k_{obs} is unchanged on increasing $[BU]_0$. This kinetic behaviour was reported by Pietra and Vitali in 1968[8] and confirmed by us for other systems,[9] but it was not satisfactorily explained. For values of $[BU]_0 > 3 \times 10^{-3}$ mol l^{-1}, k_{obs} begins to increase with increase in $[BU]_0$. This is the usual kinetic behaviour when the so-called 'base catalysis' is operative.[1] The increase in k_{obs} value relative to increasing $[BU]_0$ reaches a plateau, which was explained[1] by considering $k_{obs} = k_1$ in Scheme 1. For the data of Table 1, this plateau remains in the $[BU]_0$ range from about 0·1 to 0·2 mol l^{-1}. At higher $[BU]_0$

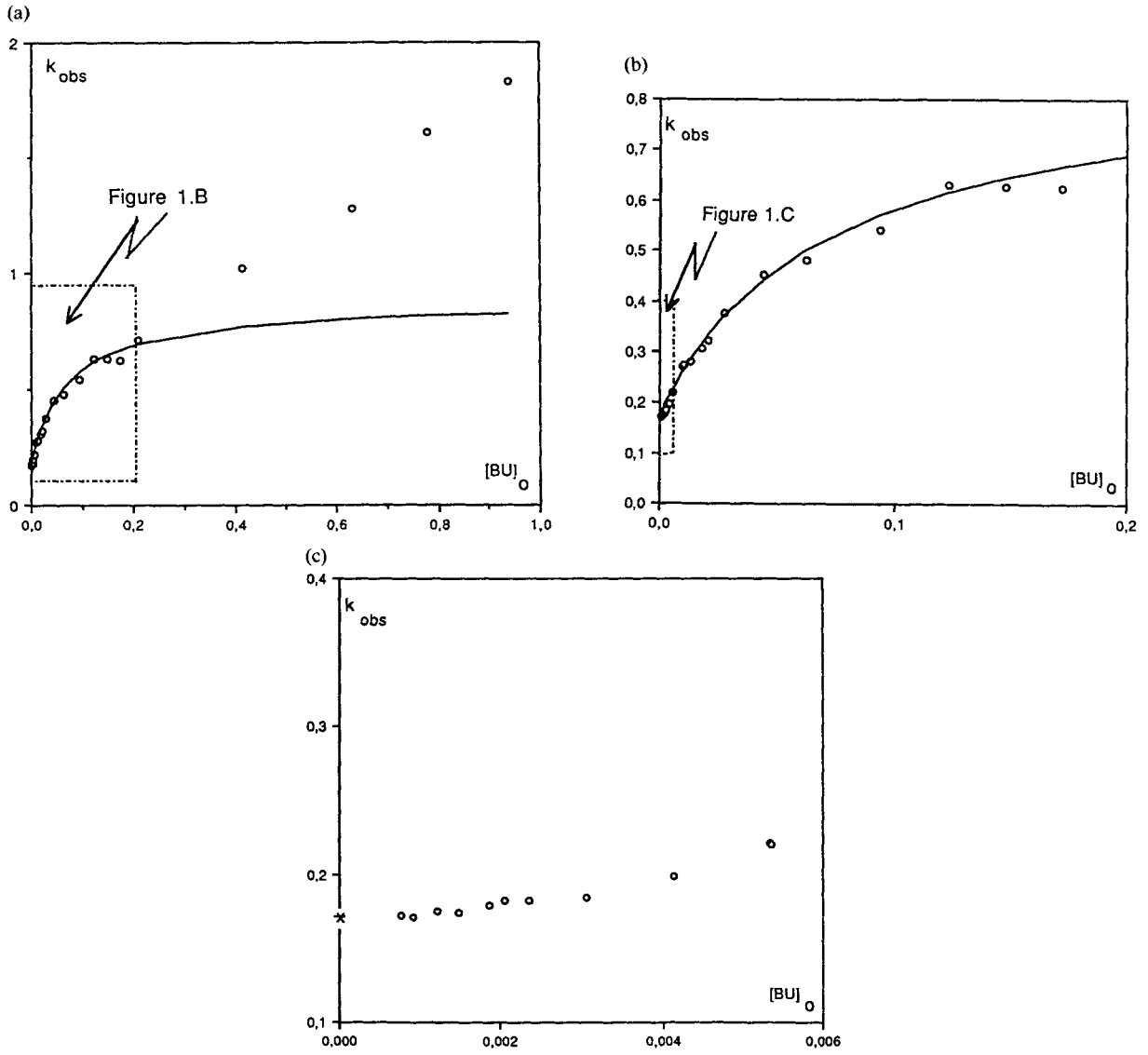


Figure 1. Reactions between FDNB and BU in toluene. (A) Overall plot. Solid line: *k* values calculated from equation (4). (B) usual plot (in the usual range of $[BU]_0$ values) to observe 'base catalysis'. Solid line: *k* values calculated from equation (4). (C) Plot for low $[BU]_0$ values. The asterisk is the k_{obs} value under the experimental conditions $[FDNB]_0 > [amine]_0$.

Table 2. Reactions between 1-fluoro-2,4-dinitrobenzene ($4 \cdot 1 \times 10^{-5}$ mol l^{-1}) and *n*-butylamine (BU) in the presence of tetradodecylammonium bromide (TDAB), tetrabutylammonium trifluoromethansulphonate (TFMS) and 2-hydroxypyridine (PI) in toluene at 21 °C

$[BU]_0$(mol l^{-1})	Parameter	Values					
$1 \cdot 22 \times 10^{-3}$	10^4[TDAB] (mol l^{-1})	–	1·01	1·41	2·22	3·02	4·28
	k_{obs}(s^{-1} mol^{-1} l)	0·175	0·280	0·301	0·391	0·439	0·508
$1 \cdot 23 \times 10^{-1}$	10^4[TDAB] (mol l^{-1})	–	1·22	2·68	3·88		
	k_{obs}(s^{-1} mol^{-1} l)	0·634	0·696	0·754	0·787		
$1 \cdot 23 \times 10^{-3}$	10^3[TFMS] (mol l^{-1})	–	1·03	1·72	2·75	4·13	5·16
	k_{obs}(s^{-1} mol^{-1} l)	0·175	0·280	0·332	0·352	0·411	0·439
$1 \cdot 26 \times 10^{-1}$	10^3[TFMS] (mol l^{-1})	–	2·01	3·69	5·03	5·67	
	k_{obs}(s^{-1} mol^{-1} l)	0·634	0·675	0·740	0·778	0·800	
$1 \cdot 48 \times 10^{-3}$	10^2[PI] (mol l^{-1})	–	1·16	2·55	4·35	6·11	
	k_{obs}(s^{-1} mol^{-1} l)	0·175	0·210	0·272	0·322	0·330	
$1 \cdot 28 \times 10^{-1}$	10^2[PI] (mol l^{-1})	–	1·03	2·00	5·00		
	k_{obs}(s^{-1} mol^{-1} l)	0·634	0·644	0·641	0·650		

concentrations k_{obs} begins to rise again. This effect has rarely been reported, probably because the concentration range generally used in the case of aliphatic amines is lower than that reported here (with these $[BU]_0$ values a stopped-flow technique must be used).

The kinetic behaviour (data in Table 1) is represented by a plot of k_{obs} versus $[BU]_0$ in Figure 1.

We have previously reported evidence for the presence of interactions between nitro-derivatives and aromatic amines,[2,3,10] tertiary aliphatic amines[3,4,11] or other catalysts.[11-13] We have also tried to obtain evidence for the presence of molecular complexes in the reaction mixtures of *n*-butylamine and FDNB.

The present reaction is too fast to allow a spectrophotometric inspection of the reaction mixtures at zero reaction time with the usual techniques previously employed. However, inspection of the reaction mixtures with a stopped-flow apparatus using Spectrascan equipment did not reveal the presence of absorbances (in UV and visible region) different from those of the starting materials. Some evidence for interactions between aliphatic amines and poorly reactive nitro-derivatives has been observed[14] by UV spectrophotometry at *ca* 300 cm^{-1}. Under our experimental conditions, this region of the UV–visible spectrum is unavailable because of the absorbance of the solvent (toluene).

Probably interactions between substituted anilines (or tertiary aliphatic amines) and nitro-derivatives (which were previously observed in the visible region of spectrum[2-4]), in poorly polar solvents, are different from interactions between nitro derivatives and aliphatic (primary or secondary) amines.

Table 2 reports the effect on the rate of the reactions between FDNB and BU of some 'inert' substances (unable to perform the substitution process), viz. 2-hydroxypyridine (PI), tetradodecylammonium bromide (TDAB) and tetrabutlyammonium trifluromethansulphonate (TFMS).

DISCUSSION

The following points are worthy of consideration: (i) the first upward curvature [see Figure 1(C)] (which was reported but disregarded in previous work) is not described by a linear equation such as equation (2); (ii) the downward curvature [see Figure 1(B)] may clearly be explained by the achievement of the conditions $k_3[C] \gg k_{-1}$ to conclude $k_{obs} = k_1$, and also other saturation phenomena; (iii) equation (1) indicates that $k_{obs} = k_1$ is the maximum possible for k_{obs} values; in this way, the second upward curvature [see Figure 1(A)] cannot be assessed in Scheme 1. For these reasons, the data in Table 1 hardly agree with Scheme 1 and with related equations.

The two-step plot obtained from the data of Table 1 (see Figure 1), can easily be explained if we consider the presence of several interactions between the nucleophile and the substrate, yielding different molecular complexes with different reactivities toward the amine. Equation (4) may be rewritten[11] as the equation

$$1/(k_{obs} - k_o) = 1/(k - k_o) + 1/(k - k_o)K[BU]_0 \quad (5)$$

which can be used to interpret the data in Table 1 by introducing $k_o = 0 \cdot 17$ s^{-1} mol^{-1}, which is the value of the constant of the uncatalysed process, as tested by the reactions carried out under the experimental conditions $[FDNB]_0 > [amine]_0$ (see Table 1). Obviously, this value is higher than the value that may be calculated from the usual extrapolation of data at zero value of the initial concentration of the nucleophile by equation (2).

In the range $[BU]_0 = 5 \cdot 33 \times 10^{-3}$–$9 \cdot 38 \times 10^{-2}$ mol l^{-1}, equation (5) can be expressed algebraically by

the equation

$$1/(k_{obs} - k_0) = (1{\cdot}43 \pm 0{\cdot}3) + (0{\cdot}100 \pm 0{\cdot}004)/[BU]_0$$

(errors are standard deviations; correlation coefficient $R = 0{\cdot}994$; number of points = 11). In this way the reactivity of the molecular complex is $k = 0{\cdot}87$ s^{-1} mol^{-1} and the apparent stability of the molecular complex is $K = 14{\cdot}3$ mol^{-1} l.

The k_{obs} values calculated from equation (4) correspond closely to the experimental data [see Figures 1(A) and (B)] and the intermediate horizontal part of the plot of k_{obs} vs $[BU]_0$ represents saturation of the kinetic system.

As regards the second upward curvature [see Figure 1(A)], there are, in principle, two main possible explanations: (i) there is a further molecular complex, e.g. with stoichiometry FDNB : BU = 1 : 2, or one different from the molecular complex at low amine concentration; this is supported by considering the high $[amine]_0/[FDNB]_0$ ratio;[15] (ii) there is a medium effect, considering the high $[BU]_0$ value used here. It is difficult to discriminate between the two possibilities. However, the effect of adding inert substances (salts and 2-hydroxypyridine, see Table 2) is considerably smaller at the amine concentration corresponding to the second plateau than when the only bimolecular process is operating. In particular, the effect of the addition of 2-hydroxypyridine at $[BU]_0 = 0{\cdot}128$ mol l^{-1} is negligible and a simple medium effect is improbable. Recently, evidence for the occurrence of substrate–nucleophile interactions prior to S_NAr reactions have been reported by other workers.[16]

Table 3 reports a tentative estimation of the effect of the addition of inert substances on the equation

$$k_{obs} = A + B[X] \qquad (6)$$

where [X] is the concentration of the salt used or of 2-hydroxypyridine (PI), A represents all of the processes in the absence of the added unreactive substances and B is the sensitivity of this system to the change in the value of [X].

When $[Bu]_0$ is low (1×10^{-3} mol l^{-1}) (the first plateau of the plot in Figure 1), A represents the uncatalysed process in both Schemes 1 and 2, hence $A = (k_1/k_{-1})k_2$; A is the usual second-order rate constant for a simple bimolecular reaction according to the usual S_NAr mechanism. B is a measure of the effect of the addition of salts [or 'catalysts' (PI)] on the ratio $(k_1/k_{-1})k_2$.

When $[Bu]_0$ is in the range of the second plateau of the plot in Figure 1 (0·1 mol l^{-1}), if the mechanism reported in Scheme 1 can be considered to be operative, then $A = k_1$ and it represents the attack of the nucleophile to form the zwitterionic intermediate (Z). B in Scheme 1 is a measure of the effect of addition of salts or of a catalyst on k_1.

Table 3. Effect of the addition of 'inert' substances (X) at different initial concentrations of *n*-butylamine[a] ($k_{obs} = A + B[X]$)

X	Parameter	Values	
PI	$[BU]_0$(mol l^{-1})	$1{\cdot}48 \times 10^{-3}$	0·128
	A(s^{-1} mol^{-1} l)	0·169 ± 0·01	–
	B(s^{-1} mol^{-2} l^2)[b]	5·0 ± 0·8	[c]
	R[d]	0·994	–
TDAB	$[BU]_0$(mol l^{-1})	$1{\cdot}22 \times 10^{-3}$	0·126
	A(s^{-1} mol^{-1} l)	0·193 ± 0·01	0·64 ± 0·008
	B(s^{-1} mol^{-2} l^2)	781 ± 56	394 ± 34
	R[d]	0·989	0·993
TFMS	$[BU]_0$(mol l^{-1})	$1{\cdot}22 \times 10^{-3}$	0·126
	A(s^{-1} mol^{-1} l)	0·21 ± 0·02	0·627 ± 0·01
	B(s^{-1} mol^{-2} l^2)	47·2 ± 7	30·0 ± 2
	R[d]	0·959	0·995

[a] Errors are standard deviations.
[b] Initial slope (see Experimental).
[c] Very small (<0·2).
[d] Correlation coefficient.

When k_{obs} (s^{-1} mol^{-1} l) does not change on increasing the initial concentration of the nucleophile [i.e. in the absence of autocalytic effects, as clearly appears in the first part of the plot of k_{obs} versus $[Bu]_0$ in Figure 1(C), where $k_{obs} = (k_1/k_{-1})k_2$], the usual mechanism of S_NAr reactions indicates that departure of the leaving group occurs in a rapid step. In this case the energy of the bond between the carbon and the leaving group is of little importance, as tested by the reactivity trend F > Cl usually observed for the uncatalysed process. Consequently, when $[BU]_0 = 1 \times 10^{-3}$, B is a measure of the effect of the medium changes on the attack of the nucleophile on the carbon bearing the leaving group.

If the data in Table 3 are explained according to the model in Scheme 1, they indicate that there are different effects of the medium changes (or of the addition of the catalyst) on the same phenomena (attack of the nucleophile on the carbon bearing the leaving group). In other words, the data in Table 3 can hardly be explained by the model in Scheme 1.

The model in Scheme 2, on the other hand, implies a 'saturation' of the equilibrium between the substrate and the nucleophile. At low amine concentration B represents the usual salt effect (or the effect of the formation of other molecular complexes with the added catalysts) on the S_NAr reactions in apolar solvents (a considerable increase in reactivity on increasing medium polarity). The B values at high amine concentrations represent the same effects on the same reaction of the substrate complexed by the nucleophile. In this case, a less relevant effect of the increase in the medium polarity is expected because immediate neighbours of the complexed substrate are clearly more polar than the

'free' substrate, which is complexed only by the poorly polar solvent. Probably the B values at higher $[BU]_0$ also include the effect of salts on the stability of the molecular complex. Usually an increase in medium polarity reduces the solute–solute interactions.

Tetraalkylammonium bromide is clearly (see Table 3) more prone to enhance the reactivity than tetraalkylammoniumm trifluoromethanesulphonate. A specific interaction between the nitro derivative and the halide is a probable explanation of this behaviour.[6]

EXPERIMENTAL

Materials. 1-Fluoro-2,4-dinitrobenzene (Carlo Erba) and *n*-butylamine (Fluka) were purified by the usual procedures.[17] Tetradodecylammonium bromide (TDAB) and tetrabutylammonium trifluromethansulphonate (TFMS) (Aldrich) were recrystallized from anhydrous tetrahydrofuran and dried by gently warming under vacuum for 5 h. Toluene was purified by distillation from sodium and stored under nitrogen.[18]

Kinetics. Kinetic runs were performed by following the appearance of the reaction product at 350 nm with a Perkin-Elmer Lambda 5 spectrophotometer and with a Hi-Tech Scientific SF 51 stopped-flow apparatus. The reproducibility of k_{obs} values was $\pm 3\%$. The value of the absorbance at 'infinite' reaction time ($\varepsilon = 1{\cdot}54 \times 10^4$ l mol^{-1} cm^{-1} at 350 nm) is consistent with the value obtained from authentic samples.

The data in Table 2 for 2-hydroxypyridine show the usual downward curvature of the plot of k_{obs} vs $[PI]_0$; the related B value reported in Table 3 is the initial slope of this plot.

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