Catalysis in Nucleophilic Aromatic Substitution Reactions. The Presence of Molecular Complexes on the Pathway of Reactions between 1-Fluoro- and 1-Chloro-2,4-dinitrobenzene and Aliphatic Amines

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The kinetics of reactions between 1-halogeno-2,4-dinitrobenzene (halogen = F, Cl) and butylamine and piperidine were re-investigated in cyclohexane. The k_{obs} values (s^{-1} mol^{-1} dm^3) increased with increases in the initial concentration of the reacting amine. Investigation of the reaction mixtures at zero reaction time, indicated the presence of an interaction between the substrate and the amine which occurred in a rapidly established equilibrium and which preceded the substitution process. The nature of the molecular complexes observed is discussed. Present and previous data indicate that the k_{obs} increase was difficult to explain with the traditional hypothesis of proton and leaving group departure as a rate determining step. A better rationalisation of the experimental data may be obtained by involving the molecular complexes on the substitution reaction pathway.

The reactions between 1-halogeno-2,4-dinitrobenzene and aliphatic amines were extensively investigated in both polar and apolar solvents.[1,2] In polar solvents (such as dimethylsulfoxide, alcohols, *etc.*) the reactions followed a second-order kinetic law, first in both reagents, while in apolar solvents[2] (such as benzene, hexane, carbon tetrachloride, *etc.*) the experimental reaction order in amine was in the range 1–3, depending on the nature of the solvent and the nature of the amine.[3,4]

The 'anomalous' reaction order in nucleophile was explained[4] by the presence of a catalysed step for the proton and leaving group departure from the zwitterionic intermediate of the usual two-step mechanism. The catalysis may be performed by the reacting amine (autocatalysis) or by other poorly reactive substances (tertiary amine, α-pyridone, *etc.*).

$$ArL + RNHR' \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{zwitterionic intermediate} \xrightarrow[k_3(\text{catalyst})]{k_2} ArNRR' + HL$$

Scheme 1 R' = H, Alkyl; L = leaving group. Structure of the zwitterionic intermediate may be as reported in Fig. 1.

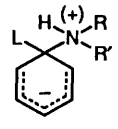
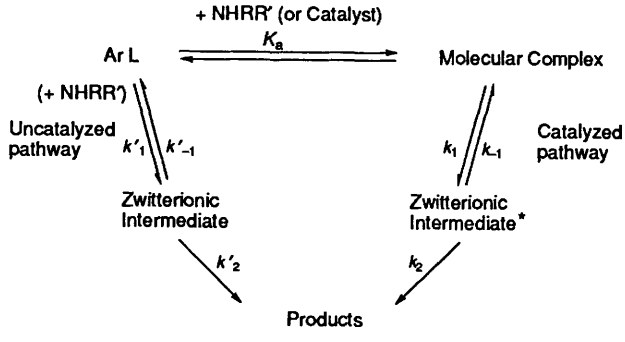


Fig. 1

When catalysis is observed, the spontaneous HL departure (k_2 of Scheme 1) becomes the rate-limiting step and the zwitterionic intermediate prefers to evolve toward the products *via* a catalysed pathway (k_3 of Scheme 1). This interpretation is generally accepted, but it does not explain some experimental data such as the kinetic results on the reaction of the aromatic amines,[5,6] ρ values calculated for the electronic effects of substituent changes in aniline on the rate of the process catalysed by the same catalyst,[7] the kinetic behaviour of the primary aliphatic amines in comparison with the kinetic behaviour of the secondary aliphatic amines[8] and anomalous temperature effects: in some cases, the substitution reaction rate was lowered by raising the temperature.[9,10]

As an alternative to this interpretation, we proposed a different reaction pathway to explain the enhancement of the reaction rate (as expressed by k_{obs}/s^{-1} mol^{-1} dm^3), by increasing the initial amount of the nucleophile. Our interpretation concerns the presence in the reaction mixtures of interactions between the substrate and the nucleophile (or the generic catalyst) with a rapidly established equilibrium, yielding a molecular complex which was investigated by ^1H NMR and UV–VIS spectroscopic methods to establish the apparent relative stability of the complexes observed. In some cases it was also possible to calculate the stability of the molecular complexes K_a with kinetic data and they agree with values obtained from direct spectroscopic observations. The proposed mechanism is reported in Scheme 2. In Scheme 2, starred



Scheme 2

'zwitterionic intermediate*' is assumed to differ from the usual zwitterionic intermediate in the presence of a further molecule of amine (or of catalyst). Two main reaction pathways are possible: the reaction between the 'free' substrate and the amine (uncatalysed pathway) and the reaction of the molecular complex (substrate–catalyst) with the nucleophile (catalysed pathway). Both reaction pathways include the attack of the nucleophile (k_1 or k'_1) in the rate determining step. As a consequence, the experimental kinetic orders in amine depend on the presence of molecular complexes which may have different stoichiometric values (1:1 or 1:2, substrate:nucleophile).[11] Catalytic behaviour[12] only appears with $k'_1 > k_1$ (the molecular complex is more reactive than the substrate), but with $k'_1 < k_1$ negative catalysis may be observed.[1,13] These conditions strongly depend on the nature of the solvent.[4] When apolar solvents are used $k'_1 > k_1$ and the k_{obs} values are increased with increases in the $[amine]_0$ value, where $[\ ]_0$ indicates the initial amount of the nucleophile or of the catalyst.

In polar solvents $k'_1 < k_1$ and k_{obs} decreases (or is unaffected) by increases in the $[amine]_0$ value.

Recently[14] we re-investigated the reactions between butylamine and 1-fluoro-2,4-dinitrobenzene in toluene. A large $[amine]_0$ range was used and this revealed a two step plot of k_{obs} (s^{-1} mol^{-1} dm^3) *vs.* $[amine]_0$ values. The kinetic behaviour observed and the effect on the reaction rate of the addition of 2-hydroxypyridine or of salts were explained by the presence of interactions between substrate and catalyst (or nucleophile) on the substitution reaction pathway as reported by Scheme 2. Unfortunately, in the solvent (toluene) used inspection of the reaction mixtures at zero reaction time did not reveal the presence of substrate–amine interactions. This inspection was performed in the wavelength region of the solvent absorbance, as in the previously reported cases of aromatic amines (or tertiary aliphatic amines). The UV–VIS spectrophotometric measurements[15] indicate the presence of interactions between aliphatic amines and poorly reactive nitro-derivatives at λ near to 300 nm (at this wavelength the toluence absorbance is strong). Now we are reconsidering the kinetic behaviour of the reactions between 1-fluoro-2,4-dinitrobenzene (FDNB) or 1-chloro-2,4-dinitrobenzene (CDNB) and butylamine (BU) or piperidine (PI) in an apolar solvent (cyclohexane), suitable for the inspection of the reaction mixtures (at zero reaction time) in the UV region of the spectrum.

Results

All the reactions reported here provided, in almost quantitative yields, the usual substitution products, as demonstrated by preparative runs and by absorbance values of the reaction mixtures at 'infinite' reaction times (see Experimental section). Tables 1, 2, 3 and 4 present the kinetic data obtained with butylamine and piperidine. Most of the runs were performed under the experimental conditions $[nucleophile]_0 > [substrate]_0$ under pseudo-monomolecular conditions and the first-order law was followed up to a high conversion percentage. To minimise the catalysis effects, some data were obtained under the experimental conditions $[substrate]_0 > [nucleophile]_0$. Under these experimental conditions, the k_{obs} values are unaffected by changes in the initial concentration of the reagent (the substrate) used in excess, at least in the concentration range used here. Under normal experimental conditions of $[substrate]_0 < [nucleophile]_0$, when piperidine is the nucleophile, the k_{obs} value increases linearly with increases in the $[piperidine]_0$ value. For the butylamine reactions, at low $[amine]_0$ values, there is a first range of $[amine]_0$ values at which k_{obs} is unaffected by the enhancement of $[amine]_0$ values. The multi-step plot, previously observed for the reactions of FDNB and butylamine in toluene, is not observed in cyclohexane. It is interesting to observe that the kinetic behaviour of the chloro derivative parallels that of the fluoro derivative.

Due to the high speed of the reactions investigated, inspection of the reaction mixtures at zero reaction time could not be performed with traditional equipment, but it required the use of a stopped-flow apparatus with a fast wavelength scanner (see Experimental section). The reaction mixtures at zero reaction time showed absorbances (in the UV–VIS spectrum) beyond those of the starting materials and those of the substitution reaction products. The standard equations were used with the absorbance values to evaluate the apparent constant (K_a) of the substrate–amine complex stability. K_a values are reported in Table 5, together with some relevant parameters. In every case the stoichiometry 1:1 (substrate–nucleophile) was assumed. No extra-absorbance values were obtained for the system CDNB–butylamine.

Taking Scheme 1, using the steady state approximation and

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

$[BU]_0/10^{-2}$ mol dm^{-3} [a]	$k_{obs}/10^{-1}$ dm^3 mol^{-1} s^{-1}
0.0614	0.124
0.0818	0.126
0.102	0.149
0.205	0.255
0.307	0.351
0.409	0.438
0.614	0.601
0.818	0.781
1.09	0.924
1.25	1.09
1.49	1.26
1.74	1.48
2.05	1.63
2.49	1.94
3.07	2.62
3.49	2.85
4.09	3.54
4.98	4.33
6.14	5.43
8.18	6.95
$[FDNB]_0/10^{-3}$ mol dm^{-3} [b]	$k_{obs}/10^{-2}$ dm^3 mol^{-1} s^{-1}
0.920	1.33
1.23	1.39
1.84	1.40
$[FDNB]_0/10^{-3}$ mol dm^{-3} [c]	$k_{obs}/10^{-2}$ dm^3 mol^{-1} s^{-1}
1.36	1.35
2.29	1.33

[a] $[FDNB]_0 = 6.8 \times 10^{-5}$ mol dm^{-3}. [b] $[BU]_0 = 1.0 \times 10^{-4}$ mol dm^{-3}. [c] $[BU]_0 = 6.1 \times 10^{-5}$ mol dm^{-3}.

Table 2 Reactions between 1-chloro-2,4-dinitrobenzene (8×10^{-5} mol dm^{-3}) and butylamine (BU) in cyclohexane at 21 °C

$[BU]/10^{-1}$ mol dm^{-3}	$k_{obs}/10^{-4}$ dm^3 mol^{-1} s^{-1}
0.0138	1.55
0.0482	1.66
0.117	1.55
0.234	1.70
0.468	2.53
1.12	5.74
1.50	8.01
1.87	9.81
2.81	15.3
3.75	20.9
5.05	30.2
5.97	35.2
7.01	42.1
8.47	47.8
9.19	53.3
9.60	53.7
10.4	56.8
11.3	63.1
$[CDNB]_0/10^{-3}$ mol dm^{-3} [a]	$k_{obs}/10^{-4}$ dm^3 mol^{-1} s^{-1}
5.7	1.72
14.5	1.85

[a] $[BU]_0 = 7.4 \times 10^{-5}$ mol dm^{-3}.

assuming $k_{-1} \gg k_2$, k_3 [amine]$_0$, eqn. (1) is obtained; where

$$k_{obs} = A + B \times [amine]_0 \quad (1)$$

Table 3 Reaction between 1-fluoro-2,4-dinitrobenzene (FDNB) and piperidine (PI) in cyclohexane at 21 °C

$[PI]_0/10^{-3}$ mol dm^{-3} [a]	k_{obs}/dm^3 mol^{-1} s^{-1}
0.832	0.222
1.25	0.307
1.66	0.391
2.50	0.571
3.33	0.742
4.16	0.891
5.82	1.20
7.49	1.44
8.32	1.72
$[FDNB]_0/10^{-2}$ mol dm^{-3} [b]	$k_{obs}/10^{-1}$ dm^3 mol^{-1} s^{-1}
0.328	0.100
0.574	0.105
0.821	0.103
1.23	0.100

[a] $[FDNB]_0 = 6.6 \times 10^{-5}$ mol dm^{-3}. [b] $[PI]_0 = 6.7 \times 10^{-5}$ mol dm^{-3}.

Table 4 Reaction between 1-chloro-2,4-dinitrobenzene (CDNB) and piperidine (PI) in cyclohexane at 21 °C

$[PI]_0/10^{-1}$ mol dm^{-3} [a]	$k_{obs}/10^{-2}$ dm^3 mol^{-1} s^{-1}
0.250	3.05
0.416	3.42
0.583	3.63
0.832	3.98
1.08	4.39
1.25	4.66
1.57	5.40
2.07	5.57
2.37	6.39
2.82	6.44
3.01	6.58
3.16	6.69
3.51	7.00
3.93	7.10
$[CDNB]_0/10^{-2}$ mol dm^{-3} [b]	$k_{obs}/10^{-2}$ dm^3 mol^{-1} s^{-1}
0.382	3.10
0.975	3.30
1.21	3.11
1.60	3.31

[a] $[CDNB]_0 = 7.3 \times 10^{-5}$ mol dm^{-3}. [b] $[PI]_0 = 7.0 \times 10^{-5}$ mol dm^{-3}.

$A = (k_1/k_{-1})k_2$ refers to the uncatalysed process, $B = (k_1/k_{-1})k_3$, is a measure of the auto-catalysed process. Eqn. (2) may be obtained from Scheme 2; where $k_0 = (k'_1/k'_{-1})k_2$ is a

$$k_{obs}\{1 + K[amine]_0\} = k_0 + Kk[amine]_0 \quad (2)$$

measure of the reactivity of the free substrate and k is a measure of the reactivity of the substrate complex with the amine. K is the stability constant of the molecular complex. Data dissection (by both equations) is reported by Table 6. For the FDNB–BU system the k_{obs} values at high $[BU]_0$ values are no longer linear [eqn. (2)] probably due to the overlapping effect of a second molecular complex (or a simple medium effect). For the CDNB–butylamine system, the approximate evaluations of the molecular complex and k value (reported in Table 6) stability were obtained from eqn. (3), a modification of eqn. (2). For the

$$1/(k_{obs} - k_0) = 1/(k - k_0) + K[BU]_0/(k - k_0) \quad (3)$$

butylamine reactions, A values were lower than k_0 values (see Table 6) because the plot of k_{obs} *vs.* $[amine]_0$ was an apparent straight line only for small $[amine]_0$ value ranges (in these cases the slope was tangential to the curve).

Discussion

Molecular Complexes.—The data in this study agree with previous findings on the presence in the reaction mixtures of substrate and nucleophile 'molecular complexes', as a result of a rapidly established equilibrium which precedes the substitution reaction. Several points can be made on the nature of the molecular substrate–amine complex. Probably different kinds of interactions are present in the reaction mixtures of halogenonitrobenzenes and amines (or catalysts) in poor polar solvents. Interactions involving aliphatic amines are different from aromatic amine interactions. For aromatic amines the main interaction may be a donor–acceptor interaction, as shown by UV–VIS spectrophotometric data. In toluene the donor capacity of anilines was indicated by the ρ value (-2.8 ± 0.3)[5] which was calculated in the Hammett plot of apparent constant complex stability between FDNB and substituted anilines against σ values. For the same reaction a donor–acceptor interaction was confirmed by ^{1}H NMR measurements.[5] In apolar solvents, the hydrogen bond was shown to be the main interaction between halogeno nitrobenzenes and 2-hydroxypyridine (a catalyst for S_NAr reactions in apolar solvents[16]). The absorbance observed for the molecular complex of aliphatic amines and FDNB appears in the UV region (λ from 280 to 330 nm) of the spectrum, while aromatic

Table 5 Apparent constant of stability of molecular complexes between 1-fluoro-2,4-dinitrobenzene (1-chloro-2,4-dinitrobenzene) and butylamine (BU) or piperidine (PI) in cyclohexane at 21 °C

[Substrate] mol dm^{-3}	[Amine] mol dm^{-3}	λ/nm	ε	K_a/mol^{-1} dm^3 [a]	n [b]	R [c]
FDNB (0.0038)	BU (0.01–0.09)	290	370 ± 30	27 ± 3	12	0.997
FDNB (0.0043)	BU (0.02–0.04)	420	540 ± 160	4.5 ± 1	10	0.998
FDNB (0.0023)	PI (0.03–0.07)	290	187 ± 10	79 ± 10	13	0.995
CDNB (0.0027)	PI (0.03–0.07)	320	270 ± 60	3.4 ± 1	10	0.999

[a] Errors are estimated from standard deviations. [b] Number of points. [c] Correlation coefficient.

Table 6 Data dissection calculated from eqns. (1) and (2) for the reactions between 1-fluoro-(chloro)-2,4-dinitrobenzene and butylamine (BU) {or piperidine, (PI)} in cyclohexane at 21 °C

Substrate	Amine	k_0[a]/dm^3 mol^{-1} s^{-1}	k[b]/dm^3 mol^{-1} s^{-1}	n[c]	R[d]	A[e]/dm^3 mol^{-1} s^{-1}	B[f]/dm^6 mol^{-2} s^{-1}	K_a[g]/dm^3 mol^{-1}
FDNB	PI	1.02×10^{-1}	4.3 ± 0.2	9	0.995	(7.8 ± 2) × 10^{-2}	192 ± 5	79
CDNB	0 PI	3.20×10^{-2}	(1.1 ± 0.1) × 10^{-1}	14	0.999	(3.1 ± 0.1) × 10^{-2}	(1.1 ± 0.1) × 10^{-1}	3.4
FDNB	BU	1.36×10^{-2}	(4.6 ± 0.1) × 10^{-1}	14	0.997	(3.3 ± 2) × 10^{-3}	8.5 ± 0.1	27
CDNB	BU	1.59×10^{-4}	(7.3 ± 2) × 10^{-2}[h]	8	0.998	(5.1 ± 4) × 10^{-5}	(5.6 ± 0.1) × 10^{-3}	(8.2 ± 2) × 10^{-2}[h]
FCNB[i]	BU[i]	1.72×10^{-1}	8.7×10^{-1}					14

[a] Values for the uncatalysed process (see the text). [b] Values calculated from eqn. (2). [c] Number of points. [d] Coefficient of correlation. [e,f] Intercept and slope respectively of plot of k_{obs} *vs.* [amine]$_0$ [see eqn. (2)]. [g] Values from Table 5. [h] Values from eqn. (3). [i] Values in toluene from ref. 6.

amines–FDNB systems show a maximum absorbance between 400 to 450 nm. Aliphatic amines interact with FDNB or CDNB according to a mechanism that is different from that of aromatic amines. For the FDNB–butylamine system alone, an extra-absorbance was also detected at 420 nm (see Table 5), as expected for charge-transfer complexes. Recently an n–π donor–acceptor interaction was reported for interactions between nitroaromatic compounds and aliphatic amines.[15] In our study, the fact that the fluoro derivative is more prone to interact with amines than the chloro derivatives (see Table 5) confirms the possibility that the hydrogen bond is an important interaction, probably additional to the donor–acceptor interaction.

The substrate, in apolar solvent, is surrounded not only by solvent, but also by more polar molecules (nucleophile or catalyst) which may support[17] incipient charge separation on the pathway towards the zwitterionic intermediate after the nucleophile attack on the reaction centre (k_1 is increased by presence of polar sustances and k_{-1} is decreased).

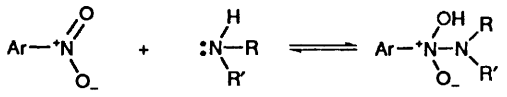
The stability of the FDNB–benzene interaction, measured by ^{1}H NMR spectral data,[5] was low, but when benzene was the solvent and present in high amounts it competes with amines to complex the substrate.[4,5,18] Interactions between cyclohexane and dinitro-derivatives are relatively unimportant, as shown by the higher K_a value in cyclohexane than K_a in toluene (see Table 6). K_a values are higher for the aliphatic amines than for the aromatic amines. This trend confirms the greater electron donating power of aliphatic amines as compared with the electron donating power of anilines. On the basis of donor power, K_a values were higher for the secondary amine (piperidine) than for the primary amine (butylamine). Consequently, nitrogen electron donating power is an important parameter for establishing the stability of molecular complexes with electron accepting centres. The discharged centre of the substrate involved in the interaction may be hard to establish. The ratios K_a^F/K_a^{Cl} (which are 24 and 300 for piperidine and butylamine respectively) confirm that previously reported for the FDNB (or CDNB) mixtures and aniline in toluene (K_a^F/K_a^{Cl} was 10 at 40 °C)[5] and may also be explained by the ability of the fluorine atom (with respect to the chlorine) to make hydrogen bonds, as illustrated in Scheme 3. This conclusion

Scheme 3

agrees with the fact that the interaction of 1,3-dinitrobenzene (DNB) and butylamine in hexane (K_a = 0.36 mol^{-1} dm^3)[15] is lower than K_a values of Table 5: the presence of the halogen strongly stabilises the molecular complex probably with a hydrogen bond (see Scheme 3).

Several years ago, a possible interaction between amines and nitro-derivatives was proposed:[19] the amino nitrogen interacts with the nitrogen of the nitro group, as illustrated in Scheme 4.

An interaction between the nitro group and sp^2 nitrogen[10]



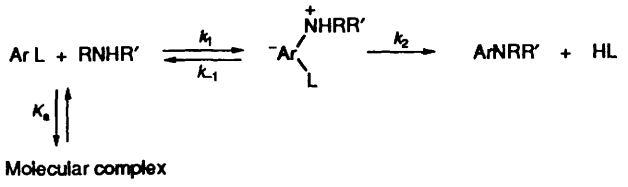
Scheme 4

was recently confirmed by X-ray diffraction[20] of 2-*N*-(2,4,6-trinitrophenyl)pyridineamine and of other related compounds. In this case there is an attraction between the nitrogens 'aza' and nitro which is twisted from the phenyl ring plane.

Kinetics and Mechanism.—The k_{obs} values reported in Tables 1, 2, 3, 4 provide the value of the constant for the uncatalysed process [$A = (k_1/k_{-1})k_2$ in eqn. (1) from Scheme 1 and $k_0 = (k'_1/k'_{-1})k_2$ in eqn. (2), from Scheme 2]. For the reactions of butylamine, when [substrate]$_0$ < [BU]$_0$, the k_{obs} value at low [BU]$_0$ values was unchanged by increases in the [BU]$_0$ values. This k_{obs} value agrees with k_{obs} values obtained under the [substrate]$_0$ > [BU]$_0$ experimental conditions. For the concentration range used here, the k_{obs} obtained under both experimental conditions were a measure of a second-order process, as the uncatalysed process requires. For butylamine, the ratio k_0^F/k_0^{Cl} is 86. The uncatalysed process for piperidine may be evaluated from data obtained under the [substrate]$_0$ > [PI]$_0$ experimental conditions. In these cases k_0 values are very near to A values. The traditional explanation of k_{obs} increase with an increase in [nucleophile]$_0$ or [catalyst] is based on the idea that the spontaneous departure of fluoride ion (in apolar solvents) from the zwitterionic intermediate is a difficult process ($k_{-1} \gg k_2$ in Scheme 1), or it is more difficult than from the anionic intermediate. The experimental data reported here and most data reported in literature are in contrast with this hypothesis because the most frequent trend for the uncatalysed process of the leaving group departure is F > Cl. Consequently, the strength of the bond between the leaving group and the reaction centre is unimportant, as stated by J. F. Bunnett[1] with regard to the two step mechanism in S_NAr reactions in apolar solvents: the leaving group departure is also a fast process in apolar solvents. The high nucleofugicity of fluorine in spite of the statement that it is a poor leaving group (because its departure needs catalysis), was explained by the presence of hydrogen bonds which may be responsible for the apparently high nucleofugicity of fluorine[3] (with respect to the other halogens). The presence of the hydrogen bond is important in polar protic solvents.[21] In aprotic solvent the hydrogen bond between substrate and nucleophile (or catalyst) is one of the hypotheses proposed by us to explain anomalous kinetic behaviour (Scheme 2) on the basis of the interaction ('molecular complex') between fluoro derivative and amines (or catalysts). But the hydrogen bond cannot be applied to the uncatalysed process, as shown by present (and previous) k_2 values which clearly measure a simple second-order process because they are obtained under both [FDNB]$_0$ > [nucleophile]$_0$ and [FDNB]$_0$ < [nucleophile]$_0$ experimental conditions and K values (see Table 6) are not high enough to be

included in the kinetic constant. In addition, if the reactivity order F > Cl for the second-order process is the result of a catalysis with a protic nucleophile, (RNH_2) or with conjugated acid (RNH_3^+), further catalysis on a fluoro-derivative is pointless because the second catalyst (or nucleophile) molecule may be hard to access the fluorine atom. The major catalytic effects should be observed for chloro-derivatives which are less involved than fluoro-derivatives in the first hydrogen bond. On the contrary, the usual experimental data indicate that fluoro derivatives are even more prone to show catalytic behaviour than other halogeno derivatives. The reason why fluorine is a better leaving group than chlorine remains a matter of opinion. The experimental results indicate that fluorine is a better leaving group than chlorine, in this study as well as in literature.

As a consequence of the presence in the reaction mixtures of molecular complexes, and by considering the HL departure a fast step of the substitution reaction, the usual Scheme 1 becomes Scheme 5, where the formation of the molecular complex is a non-productive equilibrium. Scheme 5 is a particular case of the Scheme 2: when $k_1 \ll k'_1$, Scheme 2 becomes Scheme 5.



Scheme 5

As an alternative to Scheme 1, Scheme 2 proposes a model to explain present and previous data without internal contradictions. Scheme 2 reports two main reaction pathways: on the left the attack of the nucleophile on the 'free' substrate (*i.e.* interacting only with the solvent), the uncatalysed pathway, while the pathway on the right concerns the reactivity of the substrate complexed by the catalyst (or by the nucleophile). Obviously, the detection of the presence in the reaction mixtures of a complex (or of several different molecular complexes) does not put it on the substitution reaction pathway. In principle, both Schemes 2 and 5 are reasonable models to explain the observed kinetic features.

When the kinetic behaviour cannot be studied in the absence of the molecular complex and the reactivity of the 'free' reagents is unknown, it has been clearly stated that kinetic law by itself cannot indicate whether the complexes observed are on the reaction pathway or are a nonproductive *cul-de-sac*.[12] But if the rate of the free reagents is known (and this is the case), the kinetic behaviour reported is a positive catalysis as compared with the 'normal' rate of reaction. On the contrary, when the formation of the molecular complex is a non-productive process (see Scheme 5), the k_{obs} values are depressed by increasing the $[amine]_0$ value.[12,13] Consequently, the formation of the complex cannot be a *cul-de-sac* which lowers the rate of product formation by reducing the substrate concentration.

This conclusion is strongly supported by previous information other than the kinetic law. Major points which support the Scheme 2 may be summarised as follows.

(i) Electronic effects of change of substituents in the nucleophile:[5,6] ρ values calculated for catalysed pathway (such as k_3 of Scheme 1) indicate that the rate determining step of the catalysed pathway (also when the same catalyst was used) is the attack of the nucleophile, as Scheme 2 requires.

(ii) Effects of changes of temperature.[9,10] In some cases the increase of the temperature produces a decrease of the k_{obs} value. The usual activation parameters agree with the presence of an association equilibrium.

(iii) Systems without leaving group and protons,[10] such as the formation of zwitterionic σ-complex, between 1,3,5-trinitrobenzene and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), show autocatalytic behaviour. The presence of a molecular complex (between the substrate and the nucleophile) which precedes the attack of the nucleophile is responsible of the observed kinetic features.

(iv) Solvent donor capacity and addition of substances poorly able to make substitution reactions, but capable of complexing FDNB, strongly affect the value of the experimental reaction order in nucleophile.[4]

(v) Amines unable to complex FDNB[22] are unable to show self-catalysis, but their reactions are catalysed by usual catalysts.

These arguments strongly support the hypothesis that the observed molecular complexes may be responsible for the increase in k_{obs} values with increasing $[amine]_0$ values (or the concentration of the catalyst) as illustrated by Scheme 2. Scheme 2 explains the catalysis in S_NAr as an alternative to the traditional view which involves the departure of leaving group in a rate-determining step (Scheme 1).

The kinetic behaviour of the reaction between FDNB and butylamine in cyclohexane differs from that previously observed in toluene.[14] In toluene the k_{obs} value reaches a maximum value in which k_{obs} does not change by increasing $[amine]_0$ value. In cyclohexane this 'saturation' plateau was not observed. For higher ranges of $[amine]_0$ values, above this plateau we reported another increase of k_{obs} value on increasing $[amine]_0$ value. Tentatively, the behaviour observed in toluene may be explained by the presence of a further molecular complex. Even if a full comparison of the kinetic behaviour observed in the two considered solvents is difficult, probably cyclohexane does not show kinetic saturation because the second molecular complex takes place at $[amine]_0$ values lower than that in toluene (cyclohexane does not compete with amines in complexing FDNB). A feeble support of this idea is the interaction FDNB–butyalmine (at λ = 420 nm, see Table 5) which takes place at high amine concentrations and which was not observed in toluene. Obviously, the presence of different medium effects may be a reasonable explanation of the observed differences.

Literature reports indicate that secondary aliphatic amines are more prone to catalytic effects than primary amines. Some explanations have been offered for this trend[8,23] which may be easily rationalised by Scheme 2; it is known that piperidine is a better nucleophile than butylamine (*e.g.* reactivity in polar solvents,[24] *i.e.* in the absence of catalytic effects). Both pathways in Scheme 2 involve the nucleophilic power of amine in the rate limiting steps. The trend $k_{piperidine} > k_{butylamine}$ is reinforced by the fact that there is a higher amount of molecular complex between the substrate and the piperidine than between the substrate and butylamine ($K_{piperidine} > K_{butylamine}$ for both fluoro and chloro derivatives). Consequently, data dissection by eqn. (2) explains why the secondary aliphatic amines are more prone to present catalytic behaviour than primary amines.

The k_0 and k values for butylamine are slightly higher in toluene than in cyclohexane. The ratio $k_0^{toluene}/k_0^{cyclohexane}$ = 13 probably arises from a moderate medium effect, which is reduced ($k^{toluene}/k^{cyclohexane}$ = 1.9) when the reactivity of the substrate complexed by the amine is considered.

In conclusion, the possibility of observing increases in k_{obs} values with increasing $[amine]_0$ values depends on the kK value [eqn. (2)] as compared with the k_0 value. When the K value is low and the k value is not very different from the k_0 value, $k_{obs} = k'_1/k'_{-1})k'_2$ and no auto-catalysis is observed.[22] When the k value is equal to k_0 no kinetic catalysis is observed even if the K value is large. Positive catalysis is observed when appreciable amounts of molecular complexes are present in the reaction mixtures and $k > k_0$, while when $k < k_0$, negative catalytic behaviour is expected.[13]

Table 7 Absorbances extrapolated to zero reaction time for the reaction of 1-fluoro-2,4-dinitrobenzene and butylamine in cyclohexane at 21 °C

$[BU]_0/10^{-2}$ mol dm^{-3} [a]	A
1.02	0.286
1.52	0.390
1.81	0.440
2.00	0.520
2.17	0.505
3.12	0.640
4.43	0.680
5.12	0.785
6.50	0.815
7.85	0.890
8.65	0.960
9.75	1.03

[a] $[FDNB]_0 = 3.8 \times 10^{-3}$ mol dm^{-3}; $\lambda = 290$ nm.

Experimental

Materials.—1-Fluoro-2,4-dinitrobenzene, 1-chloro-2,4-dinitrobenzene (C. Erba), butylamine and piperidine (Fluka) were commercial samples purified by the usual procedures.[25] Cyclohexane was purified by distillation from sodium and stored under nitrogen.[26]

Kinetics.—Kinetic runs were performed by following the appearance of the reaction product at $\lambda = 330$ or 350 nm, as appropriate, with a Perkin-Elmer (mod. Lambda 5) spectrophotometer and with a stopped flow apparatus Hi-Tech Scientific SF 51. k_{obs} reproducibility was ± 3%. The value of the absorbance at 'infinite' reaction time is consistent with the value obtained from authentic samples. *N*-Butyl-2,4-dinitroaniline, m.p. 89–90 °C,[27] $\varepsilon = 1.55 \times 10^4$ dm^3 mol^{-1} cm^{-1} at $\lambda_{max} = 350$ nm; *N*-piperidyl-2,4-dinitrobenzene, m.p. 119–120 °C,[27] $\varepsilon = 1.60 \times 10^4$ dm^3 mol^{-1} cm^{-1} at $\lambda_{max} = 330$ nm.

k_{obs} values for experimental conditions $[FDNB]_0 > [amine]_0$ were calculated as initial rate. In these cases, when butylamine is used, k_{obs} value is independent of the $[BU]_0$ value (see Table 1) at least in the concentration range used, as expected when the second-order law is followed.

Determination of Apparent Stability Constant of Molecular Complexes.—The UV–VIS spectrophotometric method used has been described by Ross and Kuntz.[13] Since the reactions considered are very fast, the inspection of the reaction mixtures at zero reaction time was performed with a stopped-flow apparatus equipped with a SpectraScan (Hi-Tech Scientific) instrument and a fast data acquisition set. Table 7 reports an instance of absorbance values obtained. Applying the analytical data in the usual Benesi–Hildebrand equation,[28] or (as appropriate) the Ross–Labes equation,[11] by the assumption that 1:1 complexes are formed, it was possible to assess the K_a values reported in Table 5.

Up to now, all attempts to obtain further evidence of the presence of molecular substrate–amine complexes by IR spectroscopy have failed.

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