

Aggregation effects in the reactions of 2,4-dinitrochlorobenzene with aniline in aprotic solvents



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The kinetics of the reaction of 2,4-dinitrochlorobenzene with aniline have been studied in toluene and in toluene-methanol binary solvents and compared with the reactions in benzene and chloroform. The reactions in aprotic solvents exhibit a rate dependence that is third-order in amine consistent with aggregates of the aniline acting as the nucleophile. Molecular complexes between the aniline and the substrate were also detected spectrophotometrically. Additionally, an inhibitory effect of toluene complexes was observed, which is similar to the previously reported effect of benzene in the reaction of the same substrate with *n*-butylamine. The reaction in the presence of pyridine shows an amine dependence which indicates formation of 'mixed aggregates' between aniline and pyridine. All the above results, as well as recently reported studies of other reactions different from S_NAr, are fully interpreted within the 'dimer nucleophile' mechanism.

There is active research at present to elucidate how the aggregation state of reactants can influence the mechanisms of organic reactions.¹ Chemists are increasingly interested not only because of the fundamental aspects of organic reactions but also because the knowledge of the influence of aggregated species can be constructively used in synthetic applications.^{2,3} The advent of techniques that enable the study of fast reactions allowed the measurement of proton affinities for strong bases^{4,5} as well as low-basicity compounds.^{6,7} These data are useful as a reference for further estimations of the specific solute-solvent interactions, specially in solvents of low permittivity.

The effect of basicity of the nucleophile on aromatic nucleophilic substitutions has recently been shown by the dependence of the rates of structurally related nucleophiles.^{8,9} Bordwell⁸ has pointed out that Brønsted plots reported in the literature for reactions in which bond formation to the nucleophile is rate-limiting have slopes β_{Nu} that range for the most part between 0.5–0.7, in particular the reactions of 2,4-dinitrochlorobenzene with amines show $\beta_{Nu} = 0.52$.

The nature and extent of solute-solvent interactions can alter tremendously the properties of the nucleophile;¹⁰ the variations are usually satisfactorily correlated by some of the several quantitative structure-activity relationships reported.^{10,11} The term quantitative structure-property relationship (QSPR) has been proposed for cases where a specific property, such as basicity, is examined.¹² It is well known^{13,14} that amines undergo autoassociation in aprotic media giving rise to aggregates of various stoichiometries; the dominating aggregate is usually a dimer with typical formation constants of 0.1–1.0 dm³ mol⁻¹.

On the other hand, it is now well established that molecular complexes may play a catalytic role in chemical transformations,^{15,16} and their influence in S_NAr reactions with amines is the subject of intense current research.¹⁷ Although some authors argue that these complexes are not real intermediates on the reaction path,¹⁸ increasing evidence is being accumulated regarding their role in substitution reactions.¹⁹

The present work described kinetic and spectrophotometric studies on the reaction of 2,4-dinitrochlorobenzene with aro-

matic amines (as nucleophile and/or as catalysts) in aromatic solvents, as well as in binary mixtures with protic solvents. The effects of aggregation of the nucleophile, formation of molecular complexes, mixed aggregates and solvent effects are examined.

Experimental

Reagents and solvents

N-(2,4-Dinitrophenyl)aniline (mp 155–156 °C, lit., 155–156 °C²⁰) was prepared from 2,4-dinitrochlorobenzene (mp 52–53 °C) and aniline following the procedure reported for the *N*-(2,4-dinitrophenyl)-2-methoxyaniline.²¹ Aniline (Fluka) was kept overnight over potassium hydroxide, distilled over zinc powder and then over sodium; both distillations were carried out under nitrogen at reduced pressure. Toluene was kept over sodium wire for several days, and distilled twice over sodium. Methanol²² and pyridine²¹ were purified by the methods already described. Solvents were stored in special vessels which allow delivery without air contamination.

Ancillary spectrophotometric measurements

UV-VIS spectra of the substrate, the product, and different mixtures of both compounds with aniline at several concentrations were recorded in a Shimadzu spectrophotometer. UV spectra of control solutions of the substitution product in toluene containing different amounts of aniline were recorded, and the extinction coefficients determined at $\lambda = 450$ nm where the reagents are transparent under these conditions. All the solutions were found to obey Beer's law.

Kinetic procedures

Kinetic runs were performed by the methods previously reported,²³ following the appearance of the reaction product at $\lambda = 450$ nm. In all cases pseudo-first-order kinetics were observed. Pseudo-first-order rate coefficients, k_v , were obtained by the least-squares method as the slope of the correlation $\ln(A_\infty - A_t)/A_\infty$ against time, where A_∞ is the optical density of the reaction mixture measured at 'infinity' (more than ten half-lives); the second-order rate coefficients, k_A , were obtained by dividing k_v by the amine concentrations. Rate coefficients were reproducible to $\pm 2\%$. No corrections for expansion coefficients were applied to the concentration values.

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Table 1 Reaction of 2,4-dinitrochlorobenzene, DNCIB,^a with aniline, B, in toluene at 40 °C. Pseudo-first- (k_p), second- (k_A) and third- ($k_A/[B]$) order rate coefficients

[B]/M	$k_p/10^{-6}$ s^{-1}	$k_A/10^{-6}$ $dm^3 mol^{-1} s^{-1}$	$(k_A/[B])/10^{-6}$ $dm^6 mol^{-2} s^{-1}$
0.504	0.150	0.30	0.481
1.01	0.489	0.485	0.588
1.50	1.71	1.14	0.759
2.01	3.29	1.64	0.813
2.47	5.33	2.16	0.874
3.01	9.16	3.05	1.01

^a [DNCIB] = 2.5×10^{-3} M.

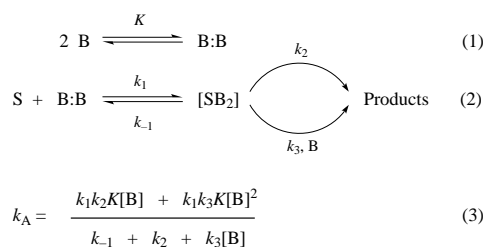
Results and discussion

Rate dependence with aniline concentration

The rate of reaction of 2,4-dinitrochlorobenzene, DNCIB, with aniline in toluene was determined at aniline concentrations 0.5–3.0 M. Formation of *N*-(2,4-dinitrophenyl)aniline was quantitative and pseudo-first-order kinetics were observed throughout the work; the pseudo-first-order rate coefficients are given in Table 1. The second-order rate coefficients, k_A , were found to increase rapidly with aniline concentration, [B], as shown in Table 1; the plot of k_A vs. [B] (Fig. 1) shows a quadratic dependence. If the quotient $k_A/[B]$ is plotted against [B], (not shown) a straight line is obtained, consistent with it being third-order in the amine term in the kinetic law, as had been previously observed for other aromatic nucleophilic substitutions with amines in aprotic solvents.²⁴

This result is striking, since most of the S_NAr for which a rate dependence that is third-order in amine had previously been reported were reactions in which the decomposition of the zwitterionic intermediate was rate determining.^{17,25,26} The reactions of 2,4-dinitrochlorobenzene with amines show a $\beta_{Nu} = 0.52$,²⁷ consistent with bond formation to the nucleophile being rate limiting and an almost symmetric position of the transition state along the reaction coordinate.⁸ On the other hand, a recent study of reactions of DNCIB with a series of nucleophiles that spans a reactivity range of almost 10^7 shows a satisfactory correlation (slope 0.95 ± 0.13) with the N_u values.⁹ This last correlation includes neutral as well as anionic nucleophiles, for which doubtless the first step is rate limiting.

The present results can be interpreted in terms of the 'dimer nucleophile' mechanism in which a dimeric aggregate of the amine is considered to attack the substrate in the first step²⁸ [eqns. (1–3)]. In this mechanism, attack by the monomer of the



nucleophile is not excluded, but the dimer is more reactive because of its higher donicity.

In eqn. (3), $K = [B:B]/[B_0]^2$ stands for the amine auto-association constant, which is known to be low^{12–16} and justifies application of the rate law given by eqn. (3) to the mechanism suggested. Apart from the observed kinetics, third-order in amines, the 'dimer nucleophile' mechanism was confirmed by several other features such as: (a) 'abnormal' solvent effects; (b) effects of HBD (hydrogen-bond donor) and HBA (hydrogen-bond acceptor) co-solvents;^{22,24} (c) conformational effects of *cis*- and *trans*-diaminocyclohexylamines;²⁹ (d) effects of HBD and HBA additives forming mixed aggregates;²⁸ (e) calculation

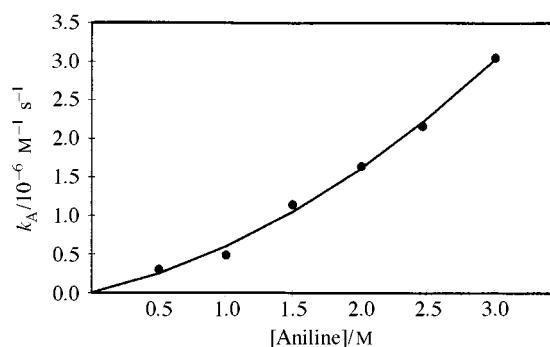
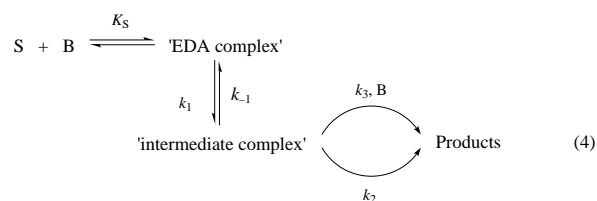


Fig. 1 Overall second-order rate coefficients, k_A , for the reaction of 2,4-dinitrochlorobenzene with aniline in toluene at 40 °C, as a function of [aniline]

of the partial reaction rate constants by the 'inversion' plot,²⁵ etc.

Molecular complexes

Formation of molecular complexes between anilines and nitro compounds has long been known.³⁰ Silber and co-workers^{19,31} have thoroughly studied the formation of electron-donor-acceptor (EDA) complexes between nitroaromatic compounds and aliphatic amines, and their role in S_NAr reactions. The proposed reaction scheme is shown by eqn. (4).



For $K_S[B] \gg 1$ and $(k_2 + k_3[B]) \ll k_{-1}$ the whole kinetic equation can be simplified to eqn. (5), which shows that a linear

$$k_A = \frac{k_1 k_2 K_S}{k_{-1}} + \frac{k_1 k_3 K_S [B]}{k_{-1}} \quad (5)$$

response between k_A and [B] is expected for base-catalysed reactions.

The reactions of 1,2-dinitrobenzene with aliphatic primary amines were fully examined; the formation of EDA complexes between reactants was not kinetically distinguishable, although their presence was detected spectrophotometrically by a non-zero optical density at zero time.³¹ Nevertheless, in any case, Silber and co-workers¹⁹ assume that the formation of EDA complexes might be responsible for a rate dependence that is third-order in amine; the EDA complex (if formed) evolves to the intermediate complex without requiring an additional amine molecule.

Aniline being a better donor than aliphatic amines, it was of interest to examine the possibility of formation of EDA complexes in the present case. Fig. 2 shows the plot of the absorbance at 450 nm extrapolated to $t = 0$ for reactions carried out at several aniline concentrations up to 3 M. In spite of the fact that the substrate is almost transparent at this wavelength, a non-negligible absorbance was observed that increases with [aniline], indicating likely formation of a complex between the substrate and aniline. Evidence for the formation of a complex between the product and aniline was thoroughly sought but was not found.

An alternative interpretation for the 'more than two' order in amine observed in this reaction was the formation of a molecular complex substrate-amine, which would not be on the reaction coordinate to products (Scheme 1).²⁰ A similar mechanism was then proposed to explain the third-order dependence

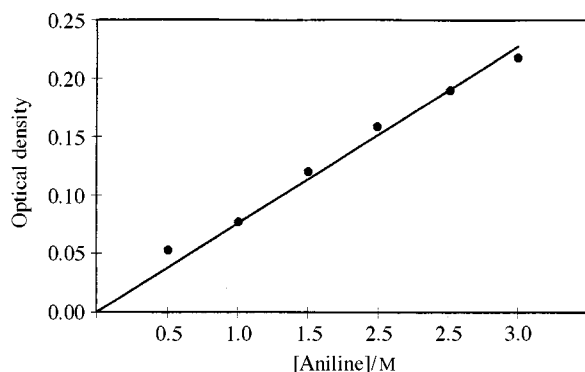
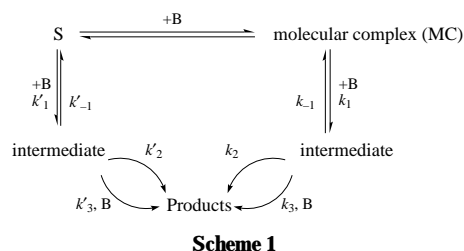


Fig. 2 Optical densities at 450 nm of the reaction mixtures of 2,4-dinitrochlorobenzene with aniline in toluene at 40 °C, extrapolated to $t=0$, as a function of [aniline]



on amine observed for systems where the decomposition of the intermediate is rate determining.¹⁸

The mechanism shown in (Scheme 1) is essentially the same as that in eqn. (4), but the major conflict of this mechanism is the requirement of an additional molecule of amine, associated with the assumption that the molecular complex cannot evolve to the intermediate.

Solvent effects

In S_NAr involving amines as the nucleophile, numerous recent studies have afforded evidence for the importance of the nature of the solvent in determining whether the formation or the decomposition of the zwitterionic intermediate will be the rate-determining step and it is known that a change in solvent may cause a change in the rate-determining step.¹⁷ In the reactions of DNCIB with amines it was previously observed that the rates were higher in benzene than in methanol; the increase in rate was ascribed to the 'built-in solvation' effect due to the interaction between the *o*-nitro group and the amine hydrogen, in the zwitterionic complex.³² It was further reported that addition of small amounts of ethanol to benzene causes a huge decrease in the rates of reaction of *o*-nitro substituted halobenzenes with piperidine.¹⁷

In a thorough examination of the solvent effects in the reactions of DNCIB with piperidine the rate dependence with amine concentration was studied in twelve aprotic solvents^{33a} as well as in ten protic solvents.³² It was found that the reaction does not exhibit base catalysis in any of the solvents studied; that is, addition of piperidine is rate limiting in all the cases.³³ Moreover, the rates in aprotic solvents were well correlated with the Dimroth-Reichardt $E_T(30)$ values.¹⁰ The observation of a satisfactory correlation between reactivity and the E_T parameter in HBA aprotic solvents was interpreted as an indication of the strong intramolecular hydrogen bonding in the intermediate complex.^{33a} On the other hand, and in spite of increased polarity, the reactivity in hydroxylic solvents is slower than in any of the aprotic solvents studied and no correlation was observed with E_T values.^{33b}

It was then of interest to examine the effect of adding small amounts of methanol, in the reactions of DNCIB with aniline. Table 2 gives the observed second-order rate coefficients for the reactions of DNCIB with aniline in methanol-toluene

Table 2 Reaction of 2,4-dinitrochlorobenzene, DNCIB, with aniline, B, in methanol-toluene binary solvents at 40 °C.^a Second-order reaction rate coefficients, k_A ($10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$).

x (MeOH)	(%) Methanol (v/v)	$E_T(30)/\text{kcal mol}^{-1b}$	$k_A/10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
0.00	0	33.9	0.052
0.05	2	33.9	0.113
0.22	10	47.9	1.09
0.40	20	49.4	1.58
0.64	40	51.2	1.86
0.80	60	52.8	2.85
0.91	80	53.1	3.04
1.00	100	55.5	3.11

^a [DNCIB] = 5×10^{-4} M; [B] = 2 M. ^b P. M. E. Mancini, A. Terenzani, M. G. Gasparri and L. R. Vottero, *J. Phys. Org. Chem.*, 1995, **8**, 617. 1 cal = 4.184 J.

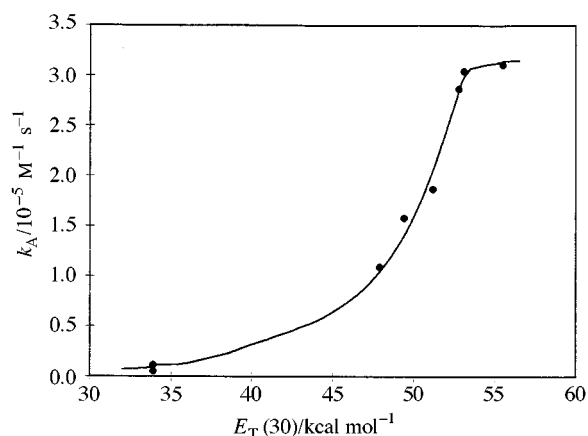


Fig. 3 Solvent effects on the second-order rate coefficients, k_A , for the reaction of 2,4-dinitrochlorobenzene with 2 M aniline in toluene-methanol as a function of $E_T(30)$ values (see ref. 34)

binary solvents from small additions of methanol up to pure methanol. An 'inverse' solvent effect is found for this reaction: an increase in rate is observed instead of the expected decrease. The plot of k_A vs. MeOH (%) (not shown) is a curve; the increase in rate is greater for small contents of the hydroxylic solvent, and then asymptotically decreases.

The E_T values for several binary solvents have been recently reported;³⁴ Fig. 3 shows the plot of k_A vs. E_T values for the mixed solvents. It is evident that no correlation exists between the rates and the parameter which is considered to be a good measure of the polarity of the medium; therefore the observed effect cannot be due to a non-specific bulk solvent effect.

Taking into account the increasing effect of small additions of methanol, a specific effect must be involved instead. It is proposed that the aromatic solvent forms complexes with the substrate; these complexes would be less reactive than the 'free' reactants and should 'decompose' before reaction; addition of small amounts of methanol would interfere with the complexes, and an increase in rate is expected. To confirm this assumption, the effect of addition of a non-protic aliphatic co-solvent, like hexane, was examined: the rate of the reaction increases with small additions of hexane to toluene, and the same was observed for the reactions of DNCIB with substituted anilines.³⁵ A similar inhibitory effect by benzene was reported in the reactions of the same substrate with butylamine and the rates increased with the addition of small amounts of hexane to the benzene.¹⁹ Within the frame of the 'dimer nucleophile' mechanism it is easily understood that the reactant-toluene complexes should be less reactive; the effect of methanol on the complexes is expected to be greater than on the aniline-aniline aggregates, due to their smaller concentrations and the weaker interactions in those complexes. It can be observed in Table 2 that the effect of methanol becomes almost negligible for

Table 3 Reaction of 2,4-dinitrochlorobenzene, DNCIB^a with aniline in the presence of pyridine in toluene at 40 °C. Second-order rate coefficients, k_A ($10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$).

[Pyridine] /M	[Aniline]		
	0.5 M	1 M	2 M
0.0	0.0240	0.0470	0.101
0.1	0.0622	0.0820	0.132
0.2	0.0569	0.0945	0.182
0.3	0.0725	0.129	0.228
0.5			0.284

^a [DNCIB] = $5 \times 10^{-4} \text{ M}$.

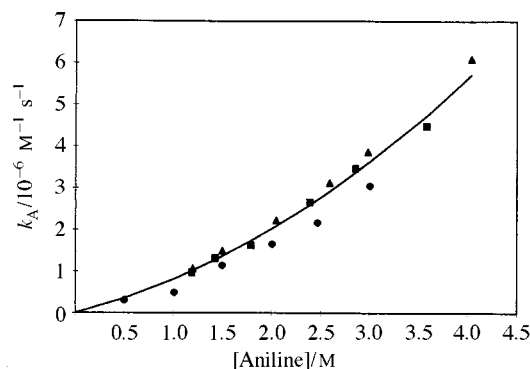


Fig. 4 Reaction of 2,4-dinitrochlorobenzene with aniline at 40 °C. Second-order rate coefficients, k_A , plotted as a function of [aniline]; in ● toluene, ■ benzene, ▲ chloroform. [2,4-DNCIB] = $2.5 \times 10^{-3} \text{ M}$

methanol contents >60%. For small contents of methanol the release of the inhibitory effect of toluene overcomes the effect expected for a HBD solvent on the aniline dimer; as previously reported for MeOH >20% the third-order dependence on amine no longer holds.²²

The solvent effect on the amine concentration dependence was then examined in other aprotic solvents. Fig. 4 shows the plot of k_A vs. [aniline] in toluene, benzene²⁰ and chloroform.²⁰ It can be observed that in the three solvents the behaviour is parabolic; a similar solvent effect was observed in the reactions of aniline with 2,4-dinitrofluorobenzene, where also the 'dimer nucleophile' mechanism was fully confirmed.²⁹ On the other hand, the observed lack of sensitivity to a change in the aprotic solvent (Fig. 4) justifies the analysis of the effect of [aniline] in Fig. 1 purely as a matter of the composition of the activated complex.

Effect of a HBA additive

Overwhelming evidence of the participation of mixed aggregates between the amine nucleophile and HBA additives on the rates of S_NAr has been accumulated in recent years.^{17,19,36} The enhancement effect of the HBA additives is intrinsically involved in the 'dimer nucleophile' mechanism,¹⁷ and it is also interpreted by the mono-hetero-conjugate mechanism developed by Hirst.²⁶ In fact, both mechanisms can be considered as part of the same spectrum.

The influence of pyridine was studied by measuring the rate dependence with the aniline concentration at various fixed [pyridine]; the second-order rate coefficients are given in Table 3. It can be observed in Fig. 5 that the quadratic dependence of k_A on [aniline] holds at every fixed [pyridine], even in the presence of [pyridine] as high as 0.5 M. On the other hand, when the reactions were carried out in the presence of fixed amounts of aniline, the observed second-order rate coefficients were proportional to [pyridine]. Fig. 6 shows the linear dependence of k_A with [pyridine] at fixed [aniline].

Within the frame of the 'dimer nucleophile' mechanism, these results are interpreted as an indication of the formation of mixed aggregates between aniline and pyridine; Scheme 2

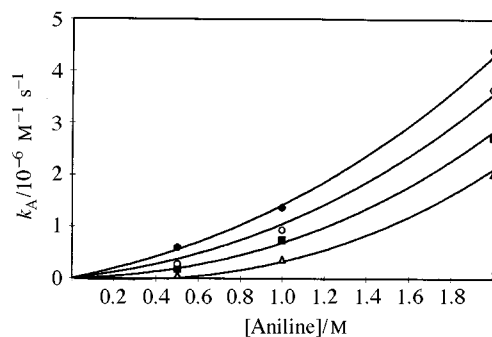


Fig. 5 Overall second-order rate coefficient, k_A , for the reaction of 2,4-dinitrochlorobenzene with aniline in presence of constant [pyridine] in toluene at 40 °C, as a function of [aniline]. △ [pyridine] = 0; ■ 0.1 M pyridine; ○ 0.2 M pyridine; ● 0.3 M pyridine

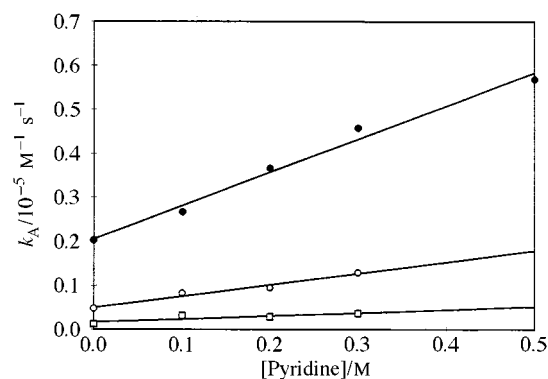


Fig. 6 Overall second-order rate coefficients, k_A , for the reaction of 2,4-dinitrochlorobenzene with aniline in the presence of pyridine in toluene at 40 °C. Influence of [pyridine] at: □ 0.5 M aniline, ○ 1 M aniline, ● 2 M aniline

shows the overall reaction picture which involves the monomer, the dimer and the mixed aggregate.

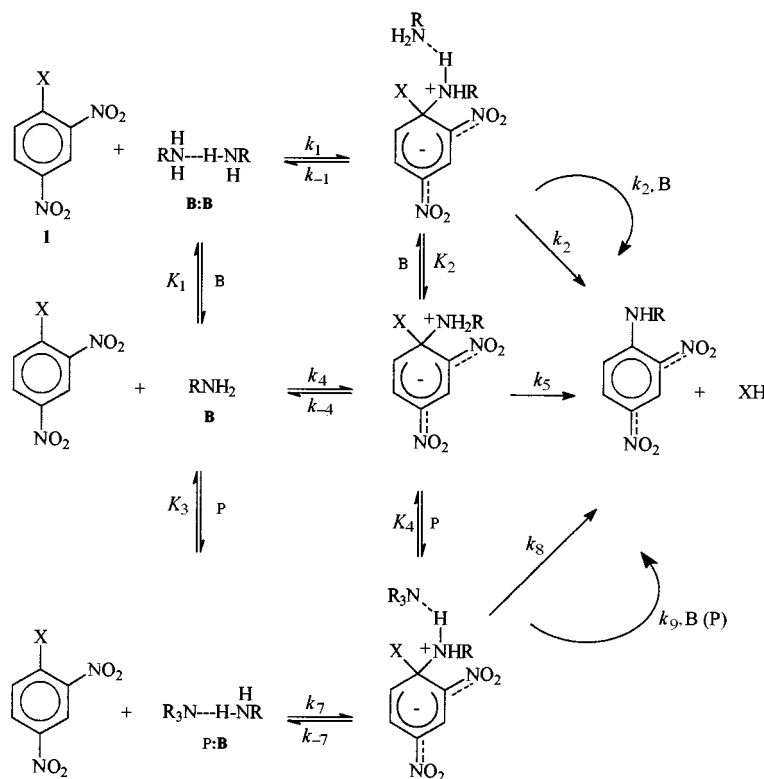
The whole kinetic expression that takes into account the various reaction pathways, as well as the simplifications that can apply to limiting situations are fully discussed in ref. 17. The general expression for k_A can be reduced to the condensed eqn. (7), where B and P stand for aniline and pyridine, respectively. Several reactions were carried out to test eqn. (6) and the four constants could be determined which are given in eqn. (7).

$$k_A = k_a[B] + k_b[B]^2 + k_c[B][P] + k_d[P] \quad (6)$$

$$k_A = 0.057[B] + 0.003[B]^2 + 0.140[B][P] + 0.09[P] \quad (7)$$

Table 4 gives the observed k_A for different [aniline] and [pyridine] as well as the k_A calculated from eqn. (7). Experiments carried out in the range [aniline] = 0.5–2.0 M, in the presence of [pyridine] from 0.1 to 0.5 M, showed that eqn. (8) holds in the whole range of concentrations studied. It can be observed that catalysis by the stronger base pyridine ($k_d = 0.090$) is more important than by aniline ($k_a = 0.057$), while reaction with the 'mixed aggregate HBA–nucleophile' (in which the nucleophile is H-bonded to a stronger base) is more important ($k_c = 0.140$) than with the self-associated nucleophile ($k_b = 0.003$), as expected on the basis of the 'dimer nucleophile' mechanism. As shown in Table 4, the second-order rate coefficients calculated by eqn. (7) agree satisfactorily with the experimental k_A .

Although it has been generally accepted that base catalysis should not be expected in the S_NAr reactions with chloro-nitro compounds since chloride ion is a good nucleofuge, genuine base catalysis has previously been reported for a few reactions of DNCIB in non-polar aprotic solvents.^{19,37} For the acceleration effect observed in the reaction of DNCIB with piperidine



Scheme 2

Table 4 Reaction of 2,4-dinitrochlorobenzene, DNCIB^a with aniline in the presence of pyridine, in toluene at 40 °C. Experimental and calculated second-order rate coefficients, k_A ($10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$).

[Pyridine]/M	[Aniline]/M	k_A (exptl.)/ $10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	k_A (calc.)/ $10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
0.0	0.5	0.024	0.027
0.1	0.5	0.062	0.044
0.2	0.5	0.057	0.060
0.3	0.5	0.073	0.077
0.0	1.0	0.047	0.054
0.1	1.0	0.082	0.077
0.2	1.0	0.095	0.101
0.3	1.0	0.129	0.125
0.0	2.0	0.101	0.102
0.1	2.0	0.133	0.140
0.2	2.0	0.183	0.179
0.3	2.0	0.229	0.217
0.5	2.0	0.284	0.292

^a [DNCIB] = $5.0 \times 10^{-4} \text{ M}$.

in hexane, Silber and co-workers have proposed a mechanism in which the second molecule of amine acts as a 'bifunctional catalyst within aggregates of conveniently charged dipolar species'.¹⁹ A similar explanation, called 'catalysis of catalysis', had been offered before.³⁸ Both interpretations are based on the existence of aggregates of the nucleophile in non-polar aprotic solvents, and their involvement in the reaction coordinate; the observed results in the present work are consistent with such aggregates operating as the nucleophiles in the first step.

The alternative explanation for the greater than second-order kinetic dependence on amine of the same reaction offered by Forlani and co-workers²⁰ who assumed that the kinetic law was due to the formation of molecular complexes is conceptually conflicting. Formation of these complexes is well accepted, but its role in the mechanism is not kinetically distinguishable regarding the amine dependence. Although many authors have observed the formation of those complexes in different systems (included the present work), only Forlani and co-workers invoke them to increase the order in amine by one in the kinetic

law for S_NAr . Even in a recent re-examination of the reaction of 2,4-DNFB with *n*-butylamine in toluene, Forlani and Bosi¹⁸ explain the observed second order in amine (a classical example of base catalysis in aprotic solvents)^{17,30,39} by the formation of a similar substrate-catalyst 'molecular complex', and propose that detachment of the nucleofuge occurs in a rapid step. This is in conflict with the overwhelming evidence that decomposition of the zwitterionic intermediate is rate determining in the reactions of fluoronitrobenzenes in aprotic solvents,^{17,30,38} which has recently been confirmed by the elegant determination of a fluorine kinetic isotope effect in the reaction of 2,4-dinitrofluorobenzene with piperidine in tetrahydrofuran solution.⁴⁰

The 'amine dimer' acting without dissociation in reactions of amines in non-polar aprotic solvents, has also recently been proposed for other reactions apart from S_NAr . Thus, in the bimolecular substitution reactions of amines with: (a) hydroximoyl chlorides in benzene,⁴¹ (b) 1,1,1-trichloro-4-methoxy-pent-3-en-2-one in toluene and benzene,⁴² (c) addition to *trans*-(2-furyl)nitroethylene,⁴³ a third-order in amine kinetic law has been observed. In all these cases, the proposed reaction route is a reversible nucleophilic attack by the amine dimer followed by the base-catalysed transformation of the intermediate into the product. These results allow us to conclude that the dimer nucleophile mechanism is well established not only for S_NAr but also for other nucleophilic reactions with amines in non-polar aprotic solvents.

Acknowledgements

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