EFFECTS OF THE NUCLEOPHILE STRUCTURE ON THE MECHANISMS OF REACTION OF 1-CHLORO-2,4-DINITROBENZENE WITH AROMATIC AMINES IN APROTIC SOLVENTS

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Dedicated to Professor Otto Exner on the occasion of his 75th birthday.

The kinetics of reactions of 1-chloro-2,4-dinitrobenzene with aniline and several substituted aromatic amines, B, in toluene shows a quadratic dependence of the second-order rate constant, k_A, on [B], which is preserved even in the presence of increasing amounts of dimethylaniline, while the reaction with *N*-methylaniline shows a linear dependence of k_A *vs* [B]. All these results are interpreted by the "dimer nucleophile" mechanism, and confirmed by the effects of a non-nucleophilic hydrogen bond acceptor tertiary amine which show the relevance of the structure of the nucleophile and the role of mixed aggregates in defining the mechanisms of aromatic nucleophilic substitutions with amines in aprotic solvents.

Key words: Aromatic nucleophilic substitutions; Aprotic solvents; Dimer nucleophile mechanism; Amine aggregation states; Nucleophile structure; Reaction mechanism; Reaction kinetics.

The solvent in which an aromatic nucleophilic substitution (S_NAr) is carried out plays a critical role in determining the reaction mechanism by controlling the degree of aggregation of reactants and the life-time of the different intermediates that can be formed[1]. Thus, the nature of the solvent determines whether the formation or the decomposition of the zwitterionic intermediate will be the rate-determining step[2,3].

However, recent studies on S_NAr with neutral nucleophiles (aliphatic and aromatic amines) in aprotic solvents have been characterized by unusual findings, especially when the second step is rate determining[1,4,5]. These

"abnormal" results are characterized, among other features, by a third-order dependence on amine concentration, and most of them can be consistently explained by the "dimer nucleophile mechanism" which was previously described[6].

The nature and extent of solute–solvent interactions can alter the properties of the nucleophile[7]. It is well known[8,9] that amines undergo self-association giving rise to aggregates of various stoichiometries; the predominating aggregate is usually a dimer with typical formation constant of $0.1–1$ mol^{-1} dm^3. The nucleophile dimer is formed because of the known ability of primary and secondary amines to interact through hydrogen bonds. A non-nucleophilic tertiary amine could act as a hydrogen bond acceptor (HBA) toward the nucleophile, forming a mixed aggregate providing that the nucleophilic amine is less basic than the previous one. The mixed dimer would then be a better nucleophile than the pure dimer, as it was recently reported[10].

In order to search into the extent of this new mechanism, kinetic and spectrophotometric studies on the reaction of 1-chloro-2,4-dinitrobenzene with aniline and substituted anilines in an aprotic solvent such as toluene, have been carried out. The effects of the structure of the nucleophile, its self-aggregation states, and the formation of mixed aggregates on the rates of reaction are examined.

EXPERIMENTAL

Reagents and Solvents

Aniline (Fluka), *p*-toluidine (Fluka), 2,4-dimethylaniline (Fluka), *N*-methylaniline (Fluka) and *N,N*-dimethylaniline (Fluka) were kept overnight over potassium hydroxide, distilled over zinc powder and then over sodium; both distillations were carried out under nitrogen at reduced pressure; *p*-anisidine (Fluka) was purified to constant melting point by recrystallization with toluene (m.p. 56–57 °C, ref.[11] gives 57 °C). 1-Chloro-2,4-dinitrobenzene (Sigma) was crystallized twice from absolute ethanol (m.p. 52–53 °C, ref.[12] gives 52–53 °C). Toluene was kept over sodium wire for several days, and distilled twice over sodium. *N*-(2,4-dinitrophenyl)aniline (m.p. 155–156 °C, ref.[13] gives 155–156 °C) was prepared from 1-chloro-2,4-dinitrobenzene and aniline following the procedure reported for *N*-(2,4-dinitrophenyl)-2-methoxyaniline[14]. *N*-(2,4-Dinitrophenyl)-2,4-dimethylaniline (m.p. 156–157 °C), *N*-(2,4-dinitrophenyl)-*N*-methylaniline (m.p. 165–167 °C, ref.[13] gives 166–167 °C), *N*-(2,4-dinitrophenyl)-*p*-toluidine (m.p. 132–134 °C, ref.[13] gives 136–137 °C) and *N*-(2,4-dinitrophenyl)-*p*-anisidine (m.p. 133–134 °C, ref.[11] gives 133–134 °C) were prepared by the same procedure[14]. The solvents were purified as already described[15] and stored in special vessels which allow delivery without air contamination.

Ancillary Spectrophotometric Measurements

UV-VIS spectra of the substrate and products, of various mixtures of both compounds with aniline and with substituted anilines at several amine concentrations were recorded in a Shimadzu spectrophotometer. UV spectra of control solutions of the substitution products in toluene containing various amounts of the amines were recorded, and the absorption coefficients determined at λ = 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[12] following the appearance of the reaction product at λ = 450 nm. In all cases pseudo-first-order kinetics were observed. Pseudo-first-order rate constants, k_ψ, were obtained by the least-squares method as the slope of the dependence [ln $(A_\infty - A_t)/A_\infty$] against time, where A_∞ is the absorbance of the reaction mixture measured at "infinity" (more than ten half-lives); the second-order rate constants, k_A, were obtained by dividing k_ψ by the amine concentrations. The rate constants were reproducible to ±2%. No corrections for expansion were applied to the concentration values.

RESULTS AND DISCUSSION

Effect of the Nucleophile Structure

The rates of the reactions of 1-chloro-2,4-dinitrobenzene, DNClB, with aniline, *p*-methylaniline, *p*-anisidine, 2,4-dimethylaniline and *N*-methylaniline in toluene at 40 °C were determined at amine concentrations ranging from 0.25 to 3.0 mol dm^{-3}. In all the reactions studied, quantitative formation of the *N*-(2,4-dinitrophenyl)aniline was observed and pseudo-first-order conditions were used throughout this work. The determined pseudo-first- and second-order rate constants are given in Table I. The second-order rate constants, k_A, were found to increase rapidly with amine concentration, [B]; the plots of k_A *vs* [B] (Fig. 1) show a quadratic dependence for the reactions of the primary anilines. If the quotient k_A/[B] is plotted against [B] (not shown), a straight line is obtained, consistent with a third-order kinetic law, with respect to the amine, as it has been previously observed for other aromatic nucleophilic substitutions with amines in aprotic solvents[1,14,16]. On the other hand, the reaction of 2,4-DNClB with *N*-methylaniline shows a strictly linear dependence of k_A *vs* [B] (not shown).

The classic two-step base-catalyzed S_NAr with amines, B, follows a third-order kinetic law. The overall second-order rate constant, k_A, derived by standard steady-state approximation has the form of Eq. (*1*)

$$k_A = \frac{k_1 k_2 + k_1 k_3^B [B]}{k_{-1} + k_2 + k_3^B [B]} \quad , \tag{1}$$

which came from the addition–elimination mechanism depicted in Eq. (*2*) for neutral nucleophiles (amines, alcohols, water) and nitro-activated aromatic substrates[1,2].
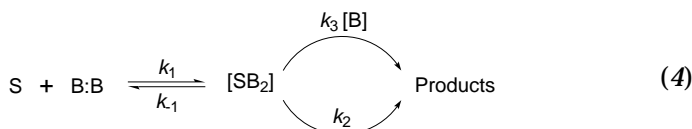
$$S + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [SB] \xrightarrow{\overset{k_3[B]}{}}_{k_2} \text{Products} \tag{2}$$
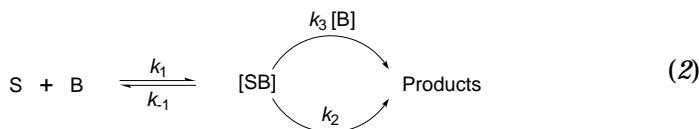
Equation (*1*) predicts a straight line for the plot of k_A *vs* [B] or a downward curvature. But several $S_N Ar$ reactions with amines in aprotic solvents studied in the last years exhibit an *upward* curvature, this kinetic behaviour being interpreted by the mechanism shown in Eqs (*3*) and (*4*) where a *dimer* (B:B) of the nucleophile attacks the substrate, S, forming the intermediate, SB_2, a third molecule of amine assisting the decomposition step. The transi-

TABLE I
Reactions of 1-chloro-2,4-dinitrobenzene, DNClB, with substituted anilines in toluene at 40 °C[a]

[Aniline], mol dm^{-3}	0.50	1.00	2.00	2.98	
$10^6 k\psi$, s^{-1}	0.32	1.20	5.20	14.0	
$10^6 k_A$, s^{-1} mol^{-1} dm^3	0.64	1.20	2.60	4.70	
[4-Methylaniline], mol dm^{-3}	0.50	1.00	2.00	3.00	
$10^6 k\psi$, s^{-1}	0.16	0.73	4.28	17.20	
$10^6 k_A$, s^{-1} mol^{-1} dm^3	0.32	0.73	2.14	5.73	
[4-Methoxyaniline], mol dm^{-3}	0.25	0.50	0.75	1.00	
$10^6 k\psi$, s^{-1}	1.05	4.32	11.68	27.63	
$10^6 k_A$, s^{-1} mol^{-1} dm^3	4.20	8.64	15.57	27.63	
[2,4-Dimethylaniline], mol dm^{-3}	0.520	1.01	1.51	1.99	2.50
$10^6 k\psi$, s^{-1}	0.054	0.179	0.431	0.794	1.526
$10^6 k_A$, s^{-1} mol^{-1} dm^3	0.104	0.177	0.286	0.399	0.610
[*N*-methylaniline], mol dm^{-3}	0.498	1.01	1.51	2.01	2.51
$10^6 k\psi$, s^{-1}	0.035	0.111	0.234	0.382	0.59
$10^6 k_A$, s^{-1} mol^{-1} dm^3	0.070	0.110	0.155	0.190	0.235

[a] [DNClB] = $2.00 \cdot 10^{-4}$ mol dm^{-3}, [b] [DNClB] = $5.12 \cdot 10^{-4}$ mol dm^{-3}.

tion states in Eq. (*4*) are highly zwitterionic and the extra amine molecule should help to stabilize the developing charge in the nonpolar solvents. The kinetic law is given by Eq. (*5*) where $K = [B:B]/[B]_0^2$ stands for the amine self-association constant.

$$2\ B\ \underset{}{\overset{K}{\rightleftharpoons}}\ B:B \qquad (3)$$

$$S\ +\ B:B\ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}\ [SB_2]\ \overset{k_3[B]}{\underset{k_2}{\longrightarrow}}\ Products \qquad (4)$$

$$k_A = \frac{k_1 k_2 K[B] + k_1 k_3 K[B]^2}{k_{-1} + k_2 + k_3[B]} \qquad (5)$$

The present results can be interpreted in terms of "dimer nucleophile" mechanism in which a dimeric aggregate of the amine, (B:B) is considered to attack the substrate in the first step[17] (Eqs (*3*)–(*5*)).The dimer mechanism does not preclude attack by free amine which is simultaneously operating. A whole kinetic treatment which involves the classic (monomer) and the new (dimer) mechanism was subsequently reported[6].
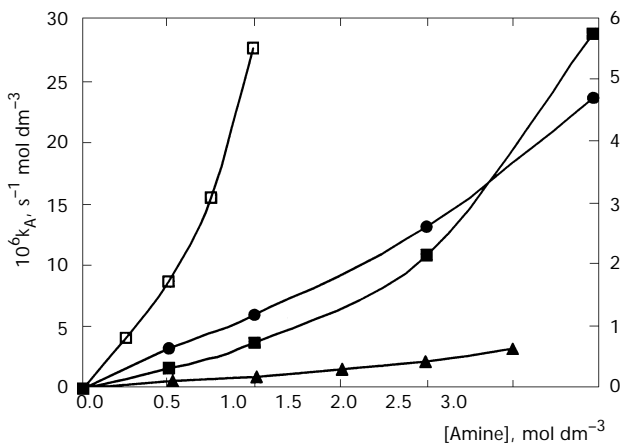

FIG. 1
Overall second-order rate constants, k_A, for the reaction of 1-chloro-2,4-dinitrobenzene with: □ 4-methoxyaniline, ● aniline, ■ 4-methylaniline and ▲ 2,4-dimethylaniline in toluene at 40 °C, as a function of amone molar concentration

There is evidence that a higher basicity of the amines supports their dimerization, the dimer being more reactive because of its higher donicity[18–20]. When 4-methoxyaniline is used as nucleophile, a greater second-order rate constant and a greater curvature in the plot of k_A *vs* [B], (Fig. 1), were observed. In order to evaluate the magnitude of the curvature, the experimental values were fitted to a second-degree polynomial function. The quadratic coefficients and standard deviations (SD) for all nucleophiles are shown in Table II. These data indicate that the quadratic coefficients, except for *N*-methylaniline, are significantly different from zero.

When 2,4-dimethylaniline is used, the second-order rate constants are considerably smaller than for aniline at any concentration, in spite of its expected greater nucleophilicity; the quadratic coefficient is also much less relevant than for the other anilines. These results are consistent with the "dimer nucleophile" mechanism and can be easily explained by decreased dimerization due to the steric hindrance produced by the methyl group at the *ortho* position.

For the reaction of DNClB with *N*-methylaniline in toluene, the plot of k_A *vs* [*N*-methylaniline] (not shown) shows a clear linear dependence with a zero intercept, which can be properly described by Eqs (*1*) and *2*, where the spontaneous decomposition of the zwitterionic intermediate is negligible. This kinetic behaviour different from that observed with the other nucleophiles (Table I), is consistent with what could be expected for the *N*-alkylanilines, considering that they undergo less self-association than aniline. For this reason the attack by the "dimer nucleophile" is not relevant. Con-

TABLE II
Quadratic coefficient of the polynomial equation for the reaction of DNClB with aniline and substituted anilines in toluene at 40 °C[a]

Nucleophile	Quadratic coefficient	*SD*
Aniline	0.2302	0.0572
4-Methylaniline	0.7043	0.1383
4-Methoxyaniline	19.714	4.6299
2,4-Dimethylaniline[b]	0.0141	0.0041
N-Methylaniline[b]	–0.0218	0.0126

[a] [DNClB] = $2.00 \cdot 10^{-4}$ mol dm^{-3}, [b] [DNClB] = $5.12 \cdot 10^{-4}$ mol dm^{-3}.

sistent with this interpretation, the reaction with *N*-methylanilines are slower than with aniline, in spite of their increased basicity, $pK_b = 9.21$ and $pK_b = 9.40$, respectively[21].

Effect of HBA Additive

Abundant evidence of the effect of mixed aggregates of the amine nucleophile and HBA additives on the rates of S_NNAr has been accumulated in recent years[1,22,23]. The enhancement effect of the HBA additives is intrinsically involved in the "dimer nucleophile" mechanism[1], and it is also interpreted by the mono–hetero-conjugate mechanism developed by Hirst[23,24].
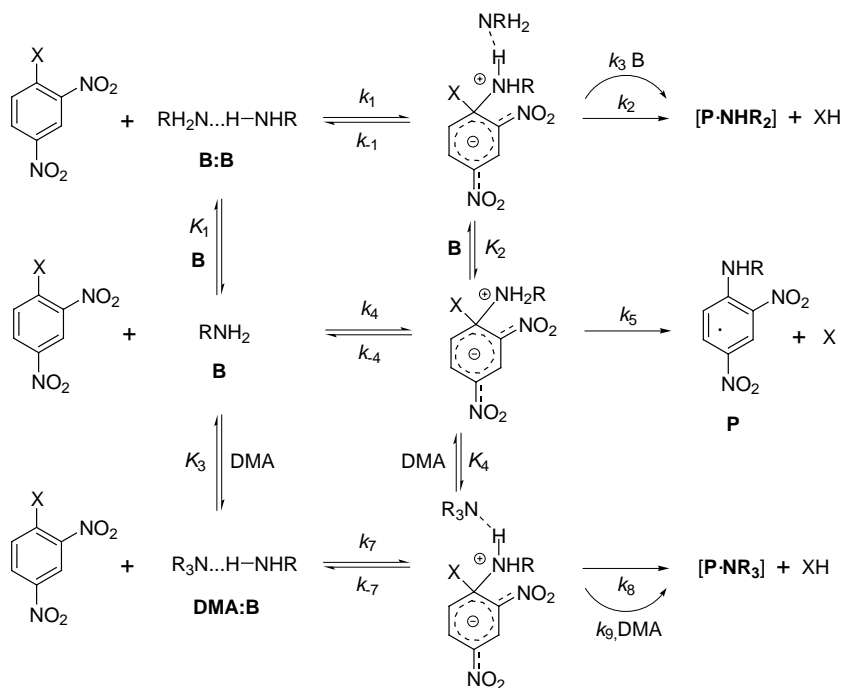
The influence of *N,N*-dimethylaniline, DMA, a good HBA, was studied by measuring the rate dependence with the aniline concentration at various fixed [DMA] values; the second-order rate constants are given in Table III. Addition of DMA to the reaction mixture increases the reaction rate at all the aniline concentrations studied, and the quadratic dependence of k_A with [B] (Fig. 2), is preserved even in the presence of [DMA] as high as 0.8 mol dm^{-3}. The plots of k_A *vs* [DMA] at fixed [aniline] (not shown) are linear with no zero intercepts, and the slope is almost 2 for the reaction with 2 M aniline. Formation of the mixed dimer, $Ph(CH_3)_2N\cdots H_2NPh$, which competes with the pure dimer, is thought to be responsible for the rate increase. Scheme 1 shows the overall reaction picture which involves the monomer, the dimer and the mixed aggregate mechanisms. An aggre-

TABLE III
Second-order rate constants, $10^6\ k_A$, s^{-1} mol^{-1} dm^3, in the reaction of 1-chloro-2,4-dinitrobenzene, DNClB[a], with aniline, B, in the presence of *N,N*-dimethylaniline, DMA, in toluene at 40 °C

[DMA], mol dm^{-3}	[Aniline], mol dm^{-3}		
	0.50	1.00	2.00
0.100	0.178	0.397	0.789
0.200	0.206	0.461	0.921
0.300	0.228	0.513	1.078
0.505	0.260	0.646	1.40
0.804	0.316	0.834	1.93

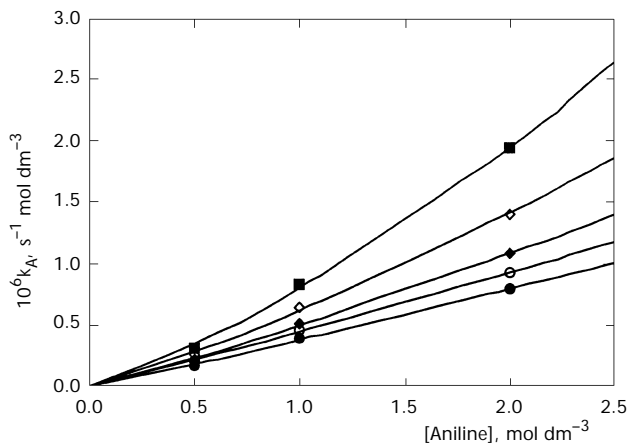[a] [DNClB] = $5.12 \cdot 10^{-4}$ mol dm^{-3}.

SCHEME 1

FIG. 2

Overall second-order rate constants, k_A, for the reaction of 1-chloro-2,4-dinitrobenzene with aniline in the presence of *N,N*-dimethylaniline, DMA, in toluene at 40 °C. [DMA] in mol dm^{-3}: ● 0.1, ○ 0.2, ◆ 0.3, ◇ 0.5, ■ 0.8

gate between the product, **P**, and the amine, depicted as [**P·NHR₂**], is shown in the scheme, since we have recently reported kinetic and spectroscopic evidence of the formation of such type of aggregates[12]. In the present case, the formation of a molecular complex between **P** and DMA, [**P·NR₃**], was also detected by the procedure already described[12], the slope of plot of the "excess" of the absorbance of the product in the presence of different amounts of DMA being 0.049 (r^2 = 0.9951).

The whole analytical expression for k_A is shown in a condensed way in Eq. (6), where B and DMA stand for aniline and *N,N*-dimethylaniline, respectively.

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

Several reactions were carried out to test Eq. (6); the four constants could be determined which are given in Eq. (7). The negative parameters in Eq. (7) are negligible and meaningless, for this reason, by putting the restriction $k_b = k_d = 0$, Eq. (7) was simplified to Eq. (8), which shows that the rate constant for the mixed-aggregate is more than twice that of the monomer.

$$k_A = 0.336 [B] - 0.017 [B]^2 + 0.957 [B] [DMA] - 0.0296 [DMA] \qquad (7)$$

$$k_A = 0.307 [B] + 0.76 [B] [DMA] \qquad (8)$$

Table IV gives the observed k_A for different [aniline] and [DMA] as well as the k_A's calculated from Eqs (7) and (8). These results shows that Eqs (7) and (8) hold in the whole concentrations range studied. As shown in Table IV, the second-order rate constants given by Eq. (8) agree satisfactorily with the experimental k_A.

Conclusions

The present results confirm that association of amines in aprotic solvents plays an important role in defining the mechanisms of aromatic nucleophilic substitutions in aprotic solvents. The nucleophile structure is crucial: primary aromatic amines are prone to react by the "dimer

nucleophile" mechanism, while secondary amines can react in the monomeric state. Steric effects in the substituted aniline near the reaction centre cause a decrease in the dimer rate constant while mixed-aggregation of the nucleophile with H-bond acceptor, a non-nucleophilic amine, shows a considerable increase in the rate, consistently with what can be expected within the "dimer nucleophile" mechanism framework.

TABLE IV
Experimental and calculated second-order rate constants, $10^6 \; k_A$, s^{-1} mol^{-1} dm^3, in the reaction of 2,4-dinitrobenzene, DNClB[a], with aniline in the presence of *N,N*-dimethylaniline, DMA, in toluene at 40 °C[a]

[Aniline] mol dm^{-3}	[DMA] mol dm^{-3}	$10^6 k_A$		
		(exp)	(calc)[b]	(calc)[b,c]
0.5	0.100	0.178	0.182	0.191
	0.200	0.206	0.200	0.229
	0.300	0.228	0.219	0.267
	0.505	0.260	0.256	0,.345
	0.812	0.316	0.312	0.462
1.0	0.105	0.393	0.389	0.387
	0.200	0.461	0.452	0.459
	0.300	0.513	0.518	0.535
	0.520	0.646	0.663	0.702
	0.789	0.834	0.841	0.907
2.0	0.100	0.789	0.767	0.766
	0.200	0.921	0.929	0.918
	0.300	1.078	1.091	1.070
	0.505	1.400	1.423	1.381
	0.804	1.930	1.907	1.836

[a] [DNClB] = $5.12 \cdot 10^{-4}$ mol dm^{-3}. [b] Calculated from Eq. (*6*). [c] Calculated with restriction: $k_b = k_d = 0$.

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