The Reaction of 2,4-Dinitrofluorobenzene with Aniline, Cyclohexylamine, and 1,2-Diaminocyclohexanes in Aprotic Solvents. A New Approach to the 'Dimer Mechanism'

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The reaction of 2,4-dinitrofluorobenzene (DNF) with aniline in toluene and in chloroform at 35 °C shows a third-order kinetic dependence on [amine]. In hydrogen-bond acceptor (HBA) solvents, an important rate increase, and a second-order dependence on [amine], are observed. Finally, the reaction shows a second-order dependence on non-nucleophilic tertiary amines. All these results are fully consistent with the previously proposed 'dimer nucleophile mechanism.'

Another approach towards confirming the mechanism was designed: a system where an 'intramolecular dimer nucleophile' is possible. The reactions of DNF with cyclohexylamine, and with *cis*- and *trans*-1,2-diaminocyclohexane, were studied in toluene, and also in toluene–methanol mixtures in some cases. The kinetic order observed, as well as the enhanced reactivity of the *cis* isomer and the solvent effects are new evidence in favour of the 'dimer nucleophile' mechanism. The results cannot be explained by other, alternative mechanisms.

Amines in aprotic media are known to self-aggregate through intermolecular hydrogen bonding;[1–3] the structure of the aggregates has been studied in some cases and found to be that of non-cyclic oligomers.[2] Aggregates play an important role in determining reactivity and their catalytic role in chemical transformations is now well established.[1,4–7] Aromatic nucleophilic substitutions (ANS) by amines in aprotic solvents are very sensitive to hydrogen-bonding interactions.[1,6–8] We have studied a relatively large number of systems where the second step is rate determining, and have found in several of them a rate law with a third-order dependence on amine (B) and some other peculiar features, which could be interpreted as an indication that an amine aggregate (the dimer B:B) was reacting without previous dissociation,[7] [equation (1), where S and P stand for substrate and products, respectively].

$$\mathrm{S} + \mathrm{B{:}B} \xrightleftharpoons[k_{-1}]{k_1} [\mathrm{SBB}] \underset{k_3\mathrm{B}}{\overset{k_2}{\rightrightarrows}} \mathrm{P} \qquad (1)$$

To strengthen the point, a nucleophile was chosen in which intramolecular N–H • • • N hydrogen bonding could exist. With such a reagent, the reaction with the intramolecularly H-bonded nucleophiles should be faster than with the non-H-bonded molecule; and, furthermore, a third-order rate dependence in amine should not be observed for systems (substrate and solvent) where this kinetic behaviour *has* been found in ANS with related amines.[7] The present paper describes the reactions of 2,4-dinitrofluorobenzene (DNF) with cyclohexylamine and with *cis*- and *trans*-1,2-diaminocyclohexanes in toluene. Since some arguments against the dimer mechanism have been put forward in connection with ANS with aromatic amines,[9] the reactions of the same substrate with aniline in toluene and chloroform have been studied, and will be described first.

Table 1. Reaction of 2,4-dinitrofluorobenzene (DNF) with aniline in toluene and in chloroform at 35 °C.[a]

Toluene		Chloroform	
[B]/mol dm^{-3}	k_A/10^{-6} dm^3 mol^{-1} s^{-1}	[B]/mol dm^{-3}	k_A/10^{-6} dm^3 mol^{-1} s^{-1}
0.100	1.32	0.104	2.63
0.200	3.43	0.203	4.98
0.300	5.81	0.311	7.2
0.400	8.22	0.404	11.0
0.501	11.0	0.599	21.0
0.700	16.0	0.712	29.0

[a] [DNF] 1.73 × 10^{-4} mol dm^{-3}; error in k_A < %.

Results and Discussion

The reactions of DNF with aniline, cyclohexylamine, *trans*-1,2-diaminocyclohexane, and a mixture of *cis*- and *trans*-1,2-diaminocyclohexane in the aprotic solvents studied proceed straightforwardly to give the expected *N*-substituted-2,4-dinitroaniline. Complications arising from solvolysis, giving rise to 2,4-dinitrophenol produced by traces of water in the systems,[10–12] were carefully avoided. A quantitative yield of the substitution product was obtained in all the reactions under study.

In all cases the rate dependence on amine concentration was studied and the reactions were carried out under pseudo-first-order conditions. All runs afforded linear plots of ln ($A_\infty - A_t$) *versus* time; *k*-values were taken from the slope calculated by the least-squares method (r > 0.999), and the specific second-order rate coefficients, k_A, were obtained by dividing *k* by the amine concentration.

Reaction of DNF with Aniline.—Table 1 shows the k_A-values for the reaction of DNF with aniline and in chloroform at 35 °C for several amine concentrations. In both solvents a nearly sevenfold increase in [amine] produces more than a tenfold increase in k_A.

When k_A is plotted against [B] an upward curvature is observed (Figure 1) while plots of k_A/[B] (not shown) are linear for the reactions in both solvents. This behaviour indicates a third-order rate dependence on amine, consistent with equation (2) (where $K = [\mathrm{B{:}B}]/[\mathrm{B}]^2$ stands for the amine auto-association constant).

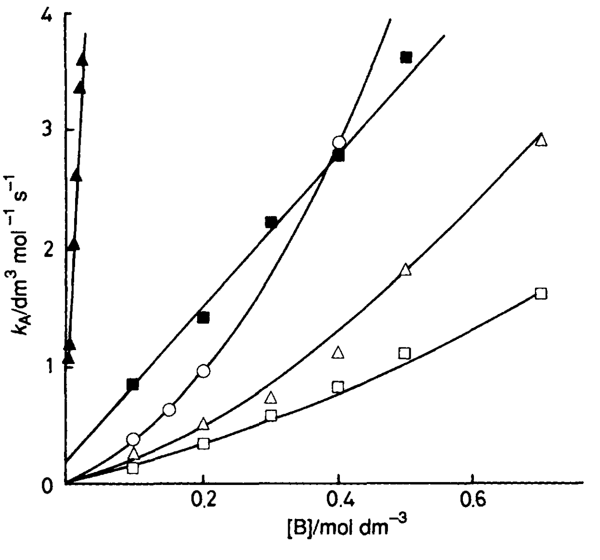

Figure 1. Reaction rates, k_A(f), of DNF with aniline in ▲ acetonitrile (× 10^4); ■ ethyl acetate (× 10^4); △ chloroform (× 10^7) and □ toluene (× 10^7) as a function of [aniline]; ○ in toluene (5 × 10^4) as a function of [pyridine].

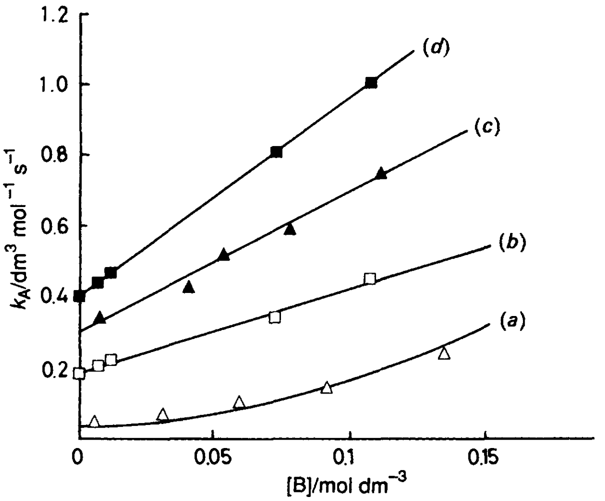

Figure 2. Reaction rates of DNF in toluene with: (*a*), cyclohexylamine; (*b*), *trans*-1,2-diaminocyclohexane (DACH); (*c*), *cis*- and *trans*-DACH; and (*d*), *cis*-DACH, as a function of [amine]. For A, [amine] = 2[B].

$$k_A = \frac{k_1k_2K[\mathrm{B}] + k_1k_3K[\mathrm{B}]^2}{k_{-1} + k_2 + k_3[\mathrm{B}]} \qquad (2)$$

Since in the reactions of amines with DNF the second step is rate determining, the inequality $k_{-1} \gg (k_2 + k_3[\mathrm{B}])$ holds, and equation (2) can be further simplified to equation (3) which accounts for the linear dependence of k_A/[B] *vs.* [B].

$$\frac{k_A}{[\mathrm{B}]} = \frac{k_1k_2K}{k_{-1}} + \frac{k_1k_3K[\mathrm{B}]}{k_{-1}} \qquad (3)$$

The reaction of DNF with aniline in toluene had been studied previously by Chapman and co-workers,[13] who observed a non-linear behaviour in the plot of k_A *vs.* [B]. They stated that 'medium effects are superimposed on base catalysis' and that 'self-association of aniline is a possible complication'.[7,13]

The Dimroth–Reichardt solvent polarity parameters E_T (as well as their new scale)[14] were found to be a convenient model for the solvent interaction in ANS with amines 'free of complications'.[15] The E_T-values are 33.9 and 39.1 kcal mol^{-1}* for toluene and chloroform, respectively,[14] and the observed rate increase is consistent with these values. Acetonitrile (E_T 46.0 kcal mol^{-1}) is a well known hydrogen-bond acceptor solvent (Kamlet–Taft–Abraham HBA parameters $\beta = 0.31$).[16] If the 'dimer' proposal is valid, then since association with the abundant solvent should prevent self-association of the amine, the dependence of k_A on [B] should no longer be parabolic. The reaction has been studied by Hirst and co-workers[17] and the results are plotted in Figure 1. An important increase in rate is observed which cannot be explained by bulk solvent polarity alone, and a linear dependence of k_A *vs.* [B] is also shown. The reaction in the slightly weaker HBA ethyl acetate (β 0.45)[16] also exhibits a linear dependence on [B] (Figure 1), and the reaction is faster than in chloroform in spite of the smaller E_T value (38.1) for the ester. These results are explicable within the 'dimer nucleophile' mechanism: a sort of 'mixed dimer' is formed between aniline and the HBA solvents, which increases the nucleophilicity of the amine nitrogen in the complex, when compared with the self-associated aniline molecule.

Finally, an interesting result is observed on the addition of a non-nucleophilic base to the reaction mixture in toluene; this result cannot be interpreted by other mechanistic proposals. Addition of a tertiary amine, B′, such as triethylamine or pyridine, considerably enhances the rate, and k_A varies in **curvilinear** way with [B′] (Figure 1). Analysis of the kinetic data shows that in both cases the rate varies as a linear function of [B′]^2. This peculiar kinetic behaviour is easily explained within the 'dimer nucleophile' mechanism. A 'mixed dimer' between the HBA tertiary amine and aniline is formed: this 'mixed dimer' is a better nucleophile than aniline (monomer or dimer) alone, thereby the rate increases but, furthermore, since both amines are more basic than aniline, a second molecule of tertiary amine is involved in the catalytic decomposition of the zwitterionic intermediate. This explains the quadratic dependence of k_A with the tertiary base B′. This kinetic behaviour, that naturally fits into the dimer mechanism, cannot be explained by the mechanism of Banjoko *et al.*[9]

Reaction of DNF with Cyclohexylamines.—Table 2 shows the second-order rate coefficients for the reaction of DNF with cyclohexylamine, *cis*- and *trans*-1,2-diaminocyclohexane, and a mixture of both isomers, in toluene at 5 °C. Although the rate–concentration curvature is relatively slight, it can be observed in Figure 2(*a*) that the dependence of k_A on [cyclohexylamine] is curvilinear. {A straight line followed by a plateau is observed in the plot (not shown) of k_A/[B] *vs.* [B], as predicted by the dimer mechanism for reactions at high [B].}[7]

Figure 2(*b*) shows the important increase in rate observed with *trans*-1,2-diaminocyclohexane, and the linear dependence of k_A on [B]: it is known that diaxial interactions in this type of amine prevent self-association,[2] and the kinetic behaviour is then that usually found in the classical base-catalysed rate-determining decomposition of the zwitterionic intermediate. However, the interesting result, expected within the dimer nucleophile mechanism, is the more than twofold increase in rate with the *cis*-isomer, in spite of enhanced steric hindrance. Intramolecular hydrogen bonding between both amino groups in the *cis*-configuration increases the nucleophilicity of the hydrogen-bond donor amine, thereby increasing the rate. We believe this result is an additional piece of evidence, obtained from a new approach, in favour of the importance of self-association of a nucleophile in determining its nucleophilicity.

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* 1 cal = 4.185 J.

Table 2. Reaction of 2,4-dinitrofluorobenzene (DNF) with cyclohexylamine, and with 1,2-diaminocyclohexane (DACH) in toluene at 5 °C.[a]

Cyclohexylamine		1,2-DACH			*cis*- and *trans*-1,2-DACH	
			k_A/dm^3 mol^{-1} s^{-1}			
[B]/mol dm^{-3}	k_A/dm^3 mol^{-1} s^{-1}	[B]/mol dm^3	*trans*	*cis*	[B]/mol dm^{-3}	k_A/dm^3 mol^{-1} s^{-1}
0.0234	0.044	0.000 218	0.181	0.399	0.007 56	0.338
0.127	0.067	0.007 33	0.206	0.440	0.0407	0.425
0.236	0.102	0.0118	0.223	0.466	0.0535	0.516
0.365	0.142	0.0719	0.342	0.810	0.0774	0.590
0.539	0.239	0.107	0.451	1.01	0.111	0.749

[a] [DNF] 2.05 × 10^{-6} mol dm^{-3}; error in k_A <2%.

Table 3. Reaction of 2,4-dinitrofluorobenzene (DNF) with *cis*- and *trans*-1,2-diaminocyclohexane (DACH) in toluene–methanol mixtures at 5 °C,[a] and with piperidine in benzene–ethanol mixtures.

cis- and *trans*-1,2-DACH		Piperidine[b]	
MeOH (% v/v)	k_A/dm^3 mol^{-1} s^{-1}	EtOH (% v/v)	k_A/dm^3 mol^{-1} s^{-1}
0	0.481	0	1.44
3	0.0591	2	6.52
6	0.0355	4	7.68
10	0.0283	8	8.58
20	0.0248	20	8.70
30	0.0229	40	8.80
40	0.0226	100	10.3
50	0.0211		
70	0.0352		
100	0.0434		

[a] [DNF] 6.08 × 10^{-5} mol dm^{-3}; [DACH] 0.0802 mol dm^{-3} (49% *cis*, 51% *trans*); error in k_A <2%. [b] Ref. 19.

Table 4. Reaction of 2,4-dinitrofluorobenzene with 1,2-diaminocyclohexanes in toluene at 5 °C, with rate coefficients quotient.

	1,2-DACH	*cis*-1,2-DACH	*cis*/*trans*
k_1k_3/k_{-1}	2.4	5.7	65
k_1k_2/k_{-1}	0.19	0.40	2.1
k_3/k_2	12.9	14.3	1.1
k_1	0.413	2.08	5.0

The effect of addition of small amounts of a hydrogen-bond donor solvent in the reaction of DNF with *cis*- and *trans*-1,2-diaminocyclohexane was studied in toluene–methanol mixtures (Table 3). The rate behaviour is compared with that shown in the reaction of DNF with piperidine in benzene–ethanol mixtures. It is known that the reaction of DNF with piperidine in benzene is base catalysed: $k_3/k_2 = 1\,230$,[8b] and no self-association of the nucleophile in benzene is observed.[18] When small amounts of ethanol are added an important **increase** in rate is observed, after which the rate remains almost constant (Table 3).[19] The increase in rate with small additions of a protic solvent was expected on the basis of hydrogen-bonding assistance to the nucleofuge departure. On other hand, an important **decrease** in the rate of reaction with the *cis*- and *trans*-1,2-diaminocyclohexane mixture was observed on addition of small amounts of methanol. The rate decreases up to 50% toluene–50% methanol and then a twofold increase in rate takes place on going to pure methanol. The sharp decrease in rate is interpreted as partially due to the rupture of the intramolecular hydrogen-bonding between both *cis*-amino groups, by competition with external hydrogen bonding with the good hydrogen-bond donor (HBD) methanol (α 0.93).[16]

Further Treatment of Kinetic Results.—The reactions of both 1,2-diaminocyclohexanes with DNF exhibit a conventional base-catalysed rate-determining second step, the kinetic law being given by equation (4). Since fluoride is a poor nucleofuge,

$$k_A = \frac{k_1(k_2 + k_3[\mathrm{B}])}{k_{-1} + k_2 + k_3[\mathrm{B}]} \qquad (4)$$

the inequality $k_{-1} \gg (k_2 + k_3[\mathrm{B}])$ holds, and equation (4) can be further simplifed to equation (5).

$$k_A = \frac{k_1k_2}{k_{-1}} + \frac{k_1k_3}{k_{-1}}[\mathrm{B}] \qquad (5)$$

Table 4 shows the intercept and the slope of equation (5) for the reactions with 1,2-diaminocyclohexanes. The k_3/k_2 quotients for both nucleophiles are almost equal; the more than twofold increase in rate observed for the *cis*-isomer should then be due to a similar increase in k_1 or a decrease in k_{-1}. It is reasonable to expect that k_{-1} would be similar for the two amines (or even bigger for the *cis*-isomer due to the greater steric effects); then the increase in rate observed with the *cis*-1,2-diaminocyclohexane should be due to an increase in k_1. The k_1-values were calculated in both cases by standard procedures[8a] and Table 4 shows that the value is five times greater for the *cis*-isomer. This enhanced rate in the first step is fully consistent with the proposal of an 'intramolecularly self-associated' nucleophile.

Experimental

Reagents and Solvents.—DNF was distilled at reduced pressure under nitrogen, b.p. 119 °C at 2 mmHg. Aniline was distilled over zinc powder, the distillate was dried over potassium hydroxide and then twice distilled over sodium strings at reduced pressure, b.p. 61 °C at 5 mmHg. It was kept in a desiccator protected from light, at 10–15 °C. *trans*-1,2-Diaminocyclohexane was distilled (×3) over sodium strings, b.p. 161 °C at 30 mmHg. The Aldrich commercial mixture of 50% *cis*- and 50% *trans*-1,2-diaminocyclohexane was distilled (×3) over sodium strings, b.p. 119.0 °C (20 mmHg). The exact composition of the mixture in the distillate (*cis*:*trans* 0.49:0.51) was determined by ^{1}H NMR spectroscopy, measuring the amine protons signals [chemical shifts (in $CDCl_3$): δ 2.80 and 2.20 for the *cis*- and *trans*-isomer, respectively]. *N*-(2,4-Dinitrophenyl)aniline was prepared from DNF and aniline as previously described,[20] m.p. 157 °C (lit.,[20] 157 °C); λ_{max}(toluene) 349 nm (ε 13 380); λ_{max}($CHCl_3$) 347 nm (ε 15 980). 1-Amino-2-(2,4-dinitrophenylamino)cyclohexane was prepared by the reaction of *trans*-1,2-diaminocyclohexane (1.185 g) and DNF (0.718 g) in toluene at 70 °C for 2 h. The product was crystallized from methanol–water (1:1), to yield crystals, m.p. 164 °C; $\delta_H(CDCl_3)$ 9.2 (1 H), 8.25 (2 H), 7.1 (1 H), 3.35 (1 H), 2.85 (1 H), 2.15 (1 H), 1.85 (3 H), and 1.35 (6 H); δ_C 148.4, 129.9, 127.1, 124.4, 121.8, and 114.6; *m/z* (rel. ab.) 280 (M^+), 262 (1.7), 245 (5.5), 190 (15), 170 (79), 114 (85), and 56 (100); λ_{max}(toluene) 400 nm (ε 3 970). Toluene was purified, and anhydrous methanol prepared, as previously described.[21] Chloroform was shaken several times with half its volume of water, and was distilled at atmospheric pressure, b.p. 61.5–62.0 °C. It was then dried with P_2O_5 and distilled at atmospheric pressure (this procedure was repeated twice), b.p. 61.5–62.0 °C. The solvents were stored in special vessels which allow delivery without contamination by air.

Kinetic Procedure.—The kinetics were studied spectrophotometrically by the procedure previously described;[19] optical densities were recorded at the absorption maximum wavelength of each product. In all cases, the absorption spectrum of the reaction mixture at 'infinite time' corresponded within 2% with the 'theoretical' value calculated from application of Beer's law to solutions of the product independently prepared in the desired solvent. The reactions with aniline were carried out in sealed ampoules (under nitrogen) and the absorbances were measured in a Gilford mod. 250 spectrophotometer. The reactions with cyclohexylamines were followed directly in the thermostatted cell of the spectrophotometer: a stock solution (5 mm^3) of DNF was syringed into a thermostatted solution (*ca.* 2.7 cm^3) of the amine. Some reactions were also followed using a diode array Hewlett Packard spectrophotometer. For reactions in mixed solvents the methanol content (v/v) refers to its final volume in the reaction mixture. All the kinetics were carried out at least in duplicate and they agreed to within $< \pm 2\%$. The reported second-order rate coefficients, k_A, were calculated by the least-squares method as previously described.[21] The k_1 values were calculated as the intercept of a plot of $1/k_A$ *vs.* $1/[B]$.[8a]

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