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REVIEW COMMENTARY

THE 'DIMER MECHANISM' IN AROMATIC NUCLEOPHILIC SUBSTITUTION BY AMINES IN APROTIC SOLVENTS

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ABSTRACT

The mechanism of aromatic nucleophilic substitutions by amines in protic solvents is well established; on the contrary the mechanism/s of the reactions in aprotic solvents is/are still subject of controversy. The present paper describes several systems for which fourth-order kinetics (third-order in amine) were observed. A mechanism is proposed to account for this as well as other observations such as: overall negative energies of activation, quadratic dependence of k_A with non-nucleophilic tertiary bases, spectacular effects of hydrogen-bond donor (HBD) and hydrogen-bond acceptor (HBA) catalysts, etc. Other alternative mechanisms are also discussed.

INTRODUCTION

The mechanisms of chemical reactions in solution are concerned largely with the sequence in which reactants are assembled and dispersed in relation to the bond-making and -breaking steps.[1] It is now well established that molecular complexes may play a catalytic role in chemical transformations.[2–5] On the other hand, the solvent in which the reaction is carried out plays a critical role in determining reaction mechanisms by controlling the degree of aggregation of reactants and the lifetime of the different intermediates that can be formed.

Some of the most important evidence for the two-step mechanism of aromatic nucleophilic substitution (ANS) comes from studies of base catalysis of reactions involving amine nucleophiles, but the mechanism/s in non-polar, aprotic solvent is/are still unclear.[6] In spite of the several studies carried out on ANS over the last two decades special findings concerning the amine concentration kinetic law in some systems has been only recently realized.[7–9] These findings are: a) fourth-order reactions (third-order in amine) and, usually, b) over-all negative energies of activation. The present paper reports some own and literature studies where such (and other) results have been observed. The proposed mechanism that accounts for all the observations as well as some alternative proposals are discussed. Reasons why the so-called dimer nucleophile mechanism is preferred are given.

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RESULTS AND DISCUSSION

Fourth-order kinetics

The classical two-step base-catalyzed ANS by amines, B, follow a third-order kinetic law. The overall second-order rate constant, k_A, derived by standard steady-state approximation has the form of equation (1), and the plot of k_A vs. [B] is usually a straight line or exhibits a *downward* curvature.[6]

$$k_A = \frac{k_1 k_2 + k_1 \sum_i k_3^{B_i} [B_i]}{k_{-1} + k_2 + \sum_i k_3^{B_i} [B_i]} \tag{1}$$

But several ANS in aprotic solvents recently studied in our laboratory exhibit an *upward* curvature in the plot of k_A vs. [B] as is shown in Figure 1 for the reaction of 2,4-dinitroanisole

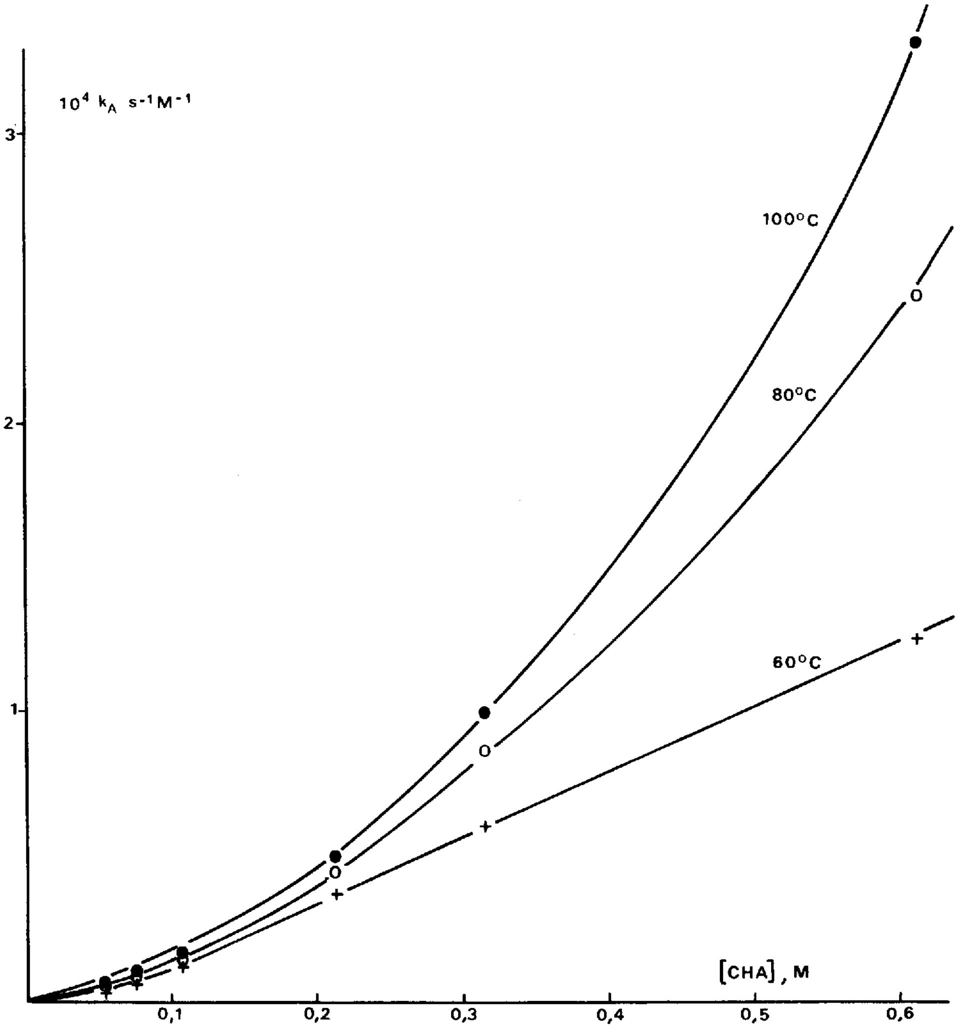

Figure 1. Reaction of 2,4-dinitroanisole with cyclohexylamine in benzene

with cyclohexylamine in benzene. If $k_A/[B]$ is plotted vs. [B] straight lines (not shown) are obtained for the reactions at 80 and 100 °C and a *downward* curvature for the reactions at 60 °C. A new kinetic law is obeyed showing third-order in amine, equation (2).

$$k_{obs} = k\,[B]^2 + k'\,[B]^3 \tag{2}$$

This kinetic behaviour was interpreted[9–11] by the mechanism shown in equation (3) where a *dimer* (B:B) of the nucleophile attacks the substrate, S, forming the intermediate, SB_2, and a third molecule of amine assists the decomposition step, equation (3). Both transition states in equation (3) are highly zwitterionic and the extra amine molecules should help to stabilize the developing charges in the non-polar solvents. (The participation of the nucleophile as an amine aggregate is suggested by further evidence, see below).

$$S + B{:}B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [SB_2] \underset{k_3B}{\overset{k_2}{\rightarrow}} P \tag{3}$$

The derived expression for k_A is equation (4).

$$k_A = \frac{k_1\,k_2\,K\,[B] + k_1\,k_3\,K\,[B]^2}{k_{-1} + k_2 + k_3\,[B]} \tag{4}$$

Where $K = [B{:}B]/[B]_o^2$ stands for the amine auto-association constant. Usually, in the reactions of amines with poor nucleofugues the second step is rate determining, the inequality $k_{-1} > (k_2 + k_3\,[B])$ holds, and equation (4) can be further simplified to equation (5) which predicts a linear dependence of $k_A/[B]$ vs. [B].

$$\frac{k_A}{[B]} = \frac{k_1\,k_2\,K}{k_{-1}} + \frac{k_1\,k_3\,K}{k_{-1}}\,[B] \tag{5}$$

If $k_{-1} \approx (k_2 + k_3\,[B])$, at high [B] equation (4) may be transformed into equation (6), which is responsible for the plateau observed in some cases. (Figure 2).

$$\frac{k_A}{[B]} = k_1\,K \tag{6}$$

The first report of this mechanism was published in 1981 for the reactions of 2,4- and 2,6-dinitroanisole with butylamine in benzene,[9] and afterwards several other systems were studied some of which are shown in Table 1. The dimer mechanism does not preclude attack by the free amine which is simultaneously operating and a whole kinetic treatment which involves the classical (monomer) and the new (dimer) mechanism was subsequently reported.[10]

It seemed hard to believe that ANS has been so thoroughly studied and this peculiar kinetic behaviour had never been observed before. A careful search into the literature[12–19] revealed some 'anomalous' results (not plotted) ambiguously ascribed by the authors to 'unspecific solvent effects'. The plots of some of those results in Figure 3 as well as other systems gathered in Table 2 show that all those ANS exhibit a fourth-order kinetic law.

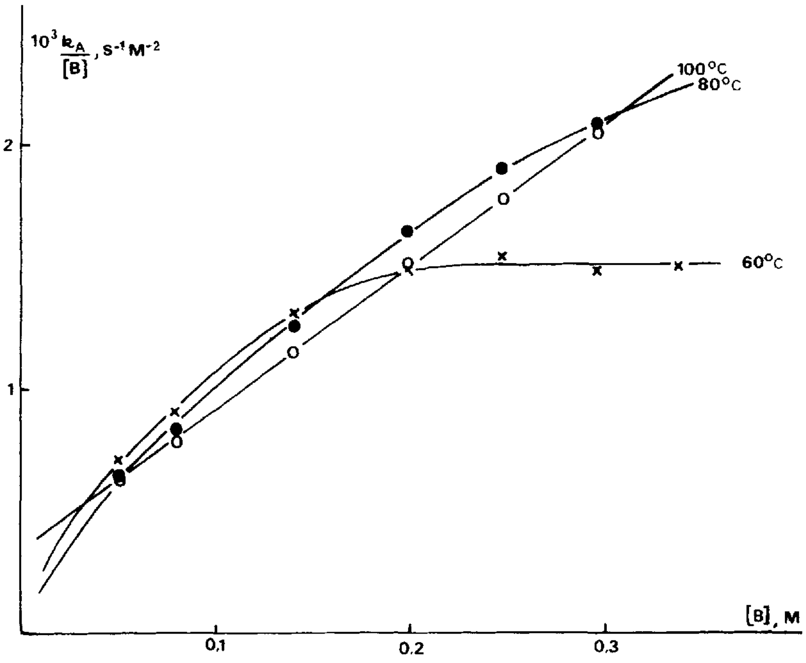

Figure 2. Reaction of 2,4-dinitroanisole with butylamine in benezene

Table 1. Aromatic nucleophilic substitution in non-polar aprotic solvents. Third-order in amine kinetic law

Substrate, S	Amine, B	[B]	Solvent	Temp., °C	Ref.
2,4-dinitroanisole	cyclohexylamine	0·06–0·51	cyclohexane	60; 80; 100[c]	10
		0·05–0·61	benzene	60; 80; 100[c]	10
	n-butylamine	0·05–0·34	benzene	60; 80; 100[c]	9
2,6-dinitroanisole	cyclohexylamine	0·03–0·46	benzene	27; 35; 45	10
		0·03–1·25	cyclohexane	35; 45; 55	10
		0·10–0·50	benzene:MeOH[a]	45	30
		0·30–0·70	toluene	35	33
		0·10–0·70	toluene–DMSO[b]	35	33
	n-butylamine	0·01–0·17	benzene	27; 35; 45	47
2,4-dinitrofluorobenzene	*o*-anisidine	0·01–0·82	benzene	35; 50; 60	24
	o-anisidine-pyridine	0·10–0·82 0·00–0·06	benzene	60	24
p-fluoronitrobenzene	*n*-propylamine	0·1 –1·5	toluene	60; 80; 100	11
3,5-dinitro-2-methoxypyridine	cyclohexylamine	0·01–0·10	toluene	35	46
3,5-dinitro-2-methoxypiridine	benzylamine	0·02–0·12	toluene	35	46

[a] Up to 30% MeOH;
[b] Up to 2% DMSO;
[c] Overall negative activation energies were observed.

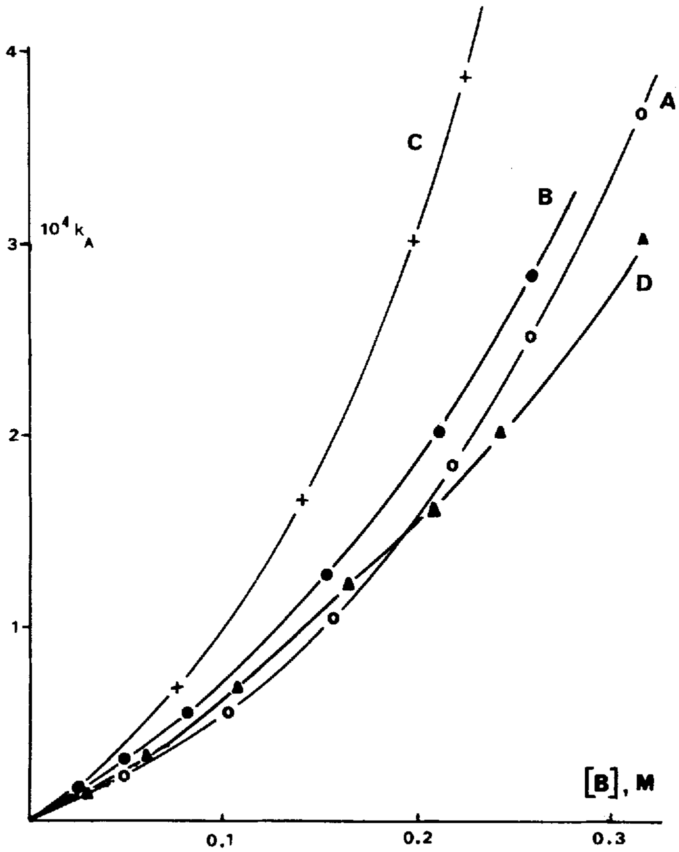

Figure 3. Reaction of 2,4-dinitrofluorobenzene with *p*-anisidine in benzene (A). Reaction of 2,6-dinitroanisole with cyclohexylamine in benzene (B). Reaction of 2,6-dinitroanisole with butylamine in benzene (C). Reaction of 2-methoxy-3-nitrothiophene with piperidine in benzene (D). Data from Refs. 35, 10, 49 and 15, respectively

Table 2. Literature 'anomalous' aromatic nucleophilic substitutions[a]

Substrate, S	Amine, B	[B]	Solvent	Temp., °C	Ref.
2,4-dinitrofluorobenzene	*p*-anisidine	0·05 –0·29	benzene	25	12
	aniline	0·05 –0·30	toluene	40	13
	morpholine	0·002–0·20	benzene	25	12
2,3-dinitronaphtalene	piperidine	0·02 –3·0	benzene	22; 50; 60	46
2-methoxy-3-nitrotiophene	piperidine	0·10 –2·04	benzene	20	15
2-phenoxy-1,3,5-triazine	piperidine	0·03 –0·330	iso-octane	23; 71	16
1-fluoro-4-nitronaphtalene	*n*-butylamine	0·03 –0·30	benzene	25	17
1-fluoro-4,5-dinitronaphtalene	*n*-butylamine	0·01 –0·24	benzene	25	15
2-nitrophenyl-2,4,6-trinitrophenylether	aniline	0·02 –0·08	benzene	5, 15, 25, 35	18
3-nitrophenylether	aniline	0·18 –0·25	benzene	5, 15, 25, 35	18
4-nitrophenylether	aniline	0·18 –0·25	benzene	5, 15, 25, 35	18
bis-2,4-dinitrophenylether	morpholine	0·10 –0·60	benzene	30	7
phenyl-2,4,6-trinitrophenylether	aniline	0·03 –0·06	benzene	15; 25; 30	14

[a] Treatment of the reported data shows third-order in amine kinetic laws.

Amine aggregates

The third-order in amine kinetic law is observed only in aprotic solvents: the zwitterionic transition states involved in these reactions are species that demand stabilization of the developing charges which cannot be provided by the bulk solvent.

It is now well known[4,20–22] that amines may undergo auto-association in aprotic media giving rise to aggregates of various stoichiometry, the dominating aggregate being a dimer with typical formation constant $K \sim 0{\cdot}1\ \text{M}^{-1}$ (value for cyclohexylamine in cyclohexane). The structure of the aggregates has been studied in some cases and found to be non-cyclic oligomers.[21]

As can be deduced from Figure 2 an overall negative energy of activation is observed in the reaction of 2,4-dinitroanisole with *n*-butylamine in benzene, the same is observed in other reactions in Table 1 and 2. Amine aggregations are known[20,23] to be affected by temperature inversely that ANS rates, then, overall negative energies of activation can be observed in reactions where a pre-equilibrium, such as ($2\ \text{B} \overset{K}{\rightleftarrows} \text{B:B}$), exists.

Mixed dimer

The dimer of the nucleophile 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 a nucleophilic amine providing that this one is less basic than the previous one. This mixed dimer would then be a better nucleophile than the pure dimer. Aromatic amines were chosen to test this hypothesis.

The reactions of 2,4-dinitrofluorobenzene with *p*- and *o*-anisidine in benzene show a quadratic dependence of k_A with [B] which can be explained by the dimer nucleophile.[24] Self-association of *o*- and *p*-anisidine has been proven by several methods,[25,26] as has the formation of mixed dimers with pyridine.[27] Addition of pyridine to the reaction media increases the rate of reaction for all the *o*-anisidine concentrations studied, and preserves the quadratic dependence of k_A with [B]. k_A is linearly related to the pyridine, R_3N, concentration. Formation of the mixed dimer, $R_3N \ldots H_2NAr$, which competes with the pure dimer, is thought to be responsible for the rate increase. The whole analytical expression for k_A is shown in a condensed way in equation (7).

$$k_A = k_a\,[B] + k_b\,[B]^2 + k_c\,[B]\,[R_3N] + k_d\,[R_3N] \qquad (7)$$

The different *k*'s were evaluated from several runs at constant [B] and variable $[R_3N]$ and vice versa.[24] The values are $0{\cdot}152 \pm 0{\cdot}06\ \text{s}^{-1}\ \text{M}^{-2}$; $0{\cdot}780 \pm 0{\cdot}09\ \text{s}^{-1}\ \text{M}^{-3}$; $9{\cdot}23 \pm 0{\cdot}09\ \text{s}^{-1}\ \text{M}^{-3}$ and $13{\cdot}5 \pm 0{\cdot}1\ \text{s}^{-1}\ \text{M}^{-2}$, respectively.

An additional test was performed: if equation (7) holds the slope of k_A vs. [B] at the origin is a measure of $k_a + k_c\,[R_3N]$ which can be evaluated from the experimental data and found to be $4{\cdot}4 \times 10^{-5}\ \text{s}^{-1}\ \text{M}^{-2}$ ($k_c\,[R_3N] = 4{\cdot}1\ \text{s}^{-1}\ \text{M}^{-1}$). Some experiments were run in the range [B] = 0·025–0·1 M at 60 °C in the presence of $[R_3N]$ 0·037 and 0·063 M. At these low values of [B] the points for k_A vs. [B] tend toward a straight line of slope $5{\cdot}9 \times 10^{-5}\ \text{s}^{-1}\ \text{M}^{-2}$ and intercept $3{\cdot}8 \times 10^{-5}\ \text{s}^{-1}\ \text{M}^{-1}$ ($[R_3N] = 0{\cdot}037\ \text{M}$). The satisfactory agreement between both sets of data obtained by different procedures allows the conclusion that equation (7) holds in the whole range of [B] studied, i.e. 0·025–1 M.

In the reaction of 2,4-dinitrofluorobenzene with morpholine, M, in benzene[12] the dependence of k_A on $[R_3N]$ departs from the line (upward curvature), and this was considered to be a medium effect due to the relatively high $[R_3N]$ used (up to 0·5 M). Nevertheless, if data are treated as if a 1:1 complex between morpholine and pyridine is formed, an empirical equation can be formulated, equation (8), for the overall-rate second-order coefficient which contains a term in $[R_3N]^2$.

$$k_A = k_o + k_M\,[M] + k_{R_3N}\,[R_3N] + k_{M:R_3N}\,[R_3N]^2 \tag{8}$$

The plot of $k_A/[R_3N]$ vs. $[R_3N]$ gives a straight line which demonstrates the validity of equation (8) and the existence of a non-negligible term in $[R_3N]^2$ for this case.

Similar mixed dimers between the nucleophile and a tertiary amine have been recently proposed for some ester aminolysis in aprotic media.[28]

Specific solvent effects

Interactions between alcohols and amines are known to be stronger than among amines themselves and it has been demonstrated that nitrogen-to-nitrogen proton transfers are intrinsically slower than nitrogen-to-oxygen proton transfers.[29] It was therefore of critical importance to determine the effect of the addition of defined amounts of a protic solvent to the reaction media.

A special system where classical solvent effects should be negligible was chosen to test this effect. The k_A of the reaction of 2,6-dinitroanisole with cyclohexylamine at 45 °C and $[B] =$ 0·4 M has the following values: 5·27 (in benzene) and 5·82 (in methanol) $\times 10^{-4}\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$. If no special effects were operating the reaction rate should increase slightly and steadily on additions of methanol to benzene in the reaction media; an increase in rate by additions of methanol should be expected since the zwitterionic transition states should be stabilized by the more polar solvent. However, a spectacular effect was observed[30] for small additions of methanol: the reaction rate decreases abruptly on small additions of methanol to benzene, reaches a minimum at nearly 25% of methanol and then begins to increase up to the given value in pure methanol (Figure 4).

The huge decrease in rate is the result of competition between auto-association of the amine and the amine–methanol aggregates, where the hydroxylic solvent acts as proton donor: $ROH \ldots NH_2R$, thereby *decreasing* the nucleophilicity of the amine. Higher oligomers with more than one ROH molecule are also possible. In spite of the rate decrease, the third-order in amine rate dependence is observed up to 25% methanol: 75% benzene; linearization of the amine profiles ($k_A/[B]$ vs. $[B]$) shows decreasing slopes for 0–25% methanol. The continuous diminution of the slope with increasing methanol percentage shows the continuous diminution in the auto-association constant of the amine, K, to be practically nil at 25% methanol. For higher methanol content in the mixed solvent the classical mechanism is observed.

Hydrogen-bond acceptor catalyst

If the above interpretation is correct, addition of a HBA cosolvent, e.g. dimethyl sulphoxide (DMSO), (β value = 0·76)[31] in catalytic amounts should *increase* the reaction rate by forming a mixed aggregate $RNH_2 \ldots OS(CH_3)_2$, B:DMSO, equation (9), where the amine acts now as a HBD and therefore increases its nucleophilicity. DMSO has been shown to increase the nitrogen electron density of primary and secondary amines.[32]

$$\mathrm{S} + [\mathrm{B{:}DMSO}] \rightleftarrows [\mathrm{SB{:}DMSO}] \underset{\mathrm{B}}{\rightrightarrows} \mathrm{P} \tag{9}$$

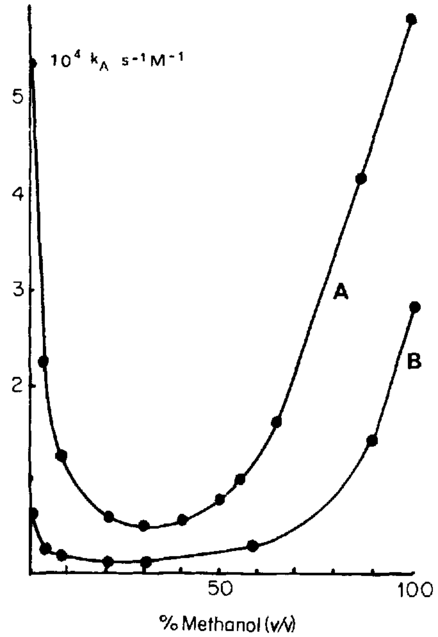

Figure 4. Reaction of 2,6-dinitroanisole with cyclohexylamine in benzene–methanol mixtures. [Cyclohexylamine] A: 0·400 and B: 0·400 M

The reaction rate of 2,6-dinitroanisole with cyclohexylamine in toluene increases rapidly with small additions of DMSO up to 0·5% then the increase with [DMSO] is slower. Studies[33] of the amine concentration rate dependence show that the reactions are strictly third-order in amine for DMSO < 2%. For DMSO contents > 10% the reactions show the classical behaviour usually found in base catalysed ANS.

The plot of k_A vs. [B] in pure toluene, is curvilinear (upward curvature) and has a practically zero intercept. An analytical expression consistent with such behaviour is equation (10).

$$k_A = k_o + k_D\,[B]^2 \qquad (10)$$

On small additions of DMSO, the quadratic dependence of k_A with [B] remains, the k_D (= $2{\cdot}40 \times 10^{-3}\ \text{M}^{-3}\ \text{s}^{-1}$) is less sensitive than k_o. For runs carried out in low DMSO contents a linear correlation was found between k_o and [DMSO] equation (11):

$$k_o\,[B] = 4{\cdot}19 \times 10^{-4}\,[B] + 1{\cdot}75 \times 10^{-2}\,[DMSO]\,[B] \qquad (11)$$

These results show the catalytic effect of a HBA cosolvent. Equations (10) and (11) are valid in the whole range of [cyclohexylamine] studied (0·02–0·7 M) and in DMSO–benzene mixtures of [DMSO] < 2% (0·282 M).

$$S + B \rightleftarrows [SB] \xrightarrow[B]{B:DMSO} P \qquad (12)$$

$$S + B{:}B \rightleftarrows [SB_2] \xrightarrow[B]{DMSO} P \qquad (13)$$

Although other mechanisms, such as those depicted in equation (12) and (13), could be envisaged to explain the DMSO effect, mechanism (9) is preferred since it also explains the 'anomalous' catalytic effect of small additions of DMSO ($< 0{\cdot}2$ M) observed when the first step is rate determining (reaction of 2,4-dinitrochlorobenzene with piperidine in benzene).[34]

Further treatment of the kinetic results

Inversion of equation (4) gives expression (14) which allows some estimation of the different k's involved:

$$\frac{[\mathrm{B}]}{k_{\mathrm{A}}} = \frac{1}{k_1 K} + \frac{k_{-1}}{k_1 k_2 K + k_1 k_3 K [\mathrm{B}]} \tag{14}$$

Taking into account that the uncatalysed decomposition is slower than the base catalysed one (14) can be simplified to (15).

$$\frac{[\mathrm{B}]}{k_{\mathrm{A}}} = \frac{1}{k_1 K} + \frac{k_{-1}}{k_1 k_3 K [\mathrm{B}]} \tag{15}$$

A plot of $[\mathrm{B}]/k_{\mathrm{A}}$ vs. $[\mathrm{B}]^{-1}$ should be linear except where the conditions that allow the simplification to equation (15) are not fulfilled. Such a plot is shown in Figure 5 for the

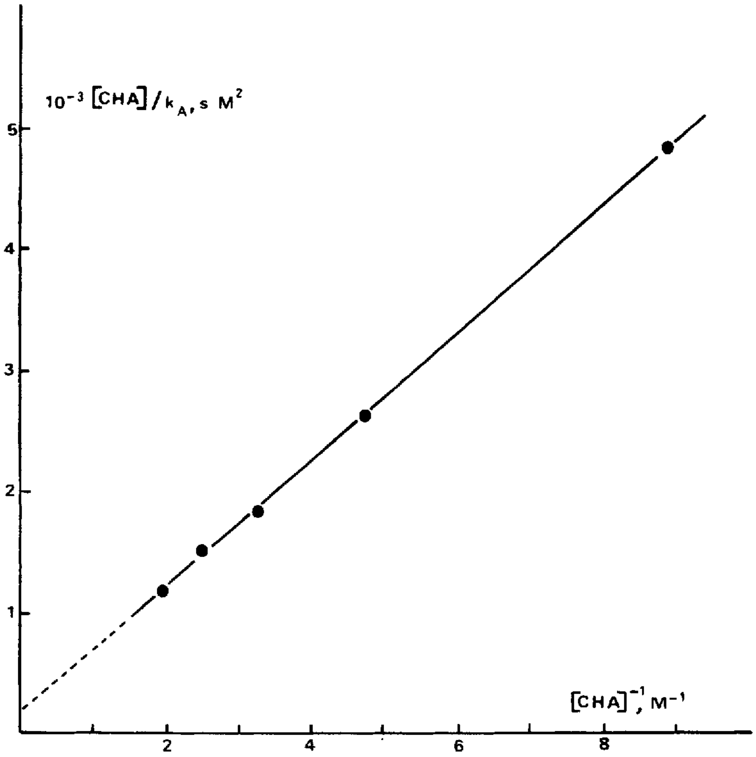

Figure 5. Inversion plot for the reaction of 2,4-dinitroanisole with cyclohexylamine in benzene

Table 3. Rate coefficients relationships for ANS of dinitroanisoles

Amine	Substrate	Solvent	Temp. °C	$10^4 \frac{k_1 k_2 K}{k_{-1}}$	$10^3 \frac{k_1 k_3 K^a}{k_{-1}}$	$10^3 \frac{k_1 k_3 K^b}{k_{-1}}$	k_3/k_2
cyclohexylamine	2,4-dinitroanisole	benzene	100	0·602	0·781		13^c
			80	<0·34	>0·86	1·26	$>37^d$
			60	<0·13	>1·00	1·81	$>140^d$
		cyclohexane	100	0	1·73		
			80	0	1·81	1·89	
			60	0	2·65	4·00	
	2,6-dinitroanisole	benzene	45	6·06	1·78		$2{\cdot}9^c$
			35	4·57	2·00		$4{\cdot}4^c$
			27	3·78	2·04		$5{\cdot}4^c$
butylamine	2,4-dinitroanisole	benzene	100	3·61	5·78		16^c
			80	<3·2	>6·8	12·9	$>40^d$
			60	<4·0	>6·6	22·7	$>57^d$
	2,6-dinitroanisole	benzene	45	19·0	9·5		$5{\cdot}0^c$
			35	15·0	10·9		$7{\cdot}3^c$
			27	13·0	12·3		$9{\cdot}5^c$

[a] From equation (5).
[b] From the inverted slope of equation (15).
[c] From the quotient between the slope and the intercept of equation (5).
[d] From the quotient between the inverted slope of equation (15) and the intercept of equation (5).
[e] Cyclohexane/benzene ratio 99:1.

reaction of 2,4-dinitroanisole with cyclohexylamine in benzene. Estimations of the k_1k_3K/k_{-1} values for this and other reactions are given in the Table 3.

The reaction at 80 °C exhibits useful behaviour for evaluation of the same expression from the plot of $k_A/[B]$ vs. [B]. Indeed, at low [B] equation (5) holds the independent estimations of $k_{-1}/k_1\ k_3K$ quotient can be made. The agreement between both sets of values can be interpreted as evidence that equation (4) holds and that the simplification to equation (5) is justified.

The intercepts allow an estimation of the order of magnitude of k_1k_2K/k_{-1} and from both quotients the ratio k_3/k_2 can be reckoned (Table 3). The quotient increases with decreasing temperatures in accord with the increased association constant.

In the reaction of 2,6-dinitroanisole with cyclohexylamine and with butylamine in benzene the slopes in the curves at the origin are not nul. For the last case the rate of the reaction allows several kinetic measurements at low [B] and exact evaluation of the slope at the origin of k_A vs. [B] for a range of $[B] = 0\text{–}0{\cdot}03$ M. At 45 °C a value of $2{\cdot}2 \times 10^{-3}\ \mathrm{M}^{-2}\ \mathrm{s}^{-1}$ is obtained which agrees satisfactorily with the value $k_1k_2K/k_{-1} = 1{\cdot}9 \times 10^{-3}\ \mathrm{M}^{-2}\ \mathrm{s}^{-1}$ obtained from the intercept of the plot of $k_A/[B]$ vs. [B] constructed with the data obtained at higher [B]. Similar agreement was found for the other systems gathered in Table 3. The satisfactory concordance between the quotients obtained from both sets of data obtained under different conditions indicates that the assumptions made are correct and the whole treatment is justified.

Dimer nucleophilicity

It has been previously suggested[4,35–37] that amine dimers should be more nucleophilic than the free amine, since the formation of the hydrogen bond would increase the electronic density on the nitrogen atom which partially donates its hydrogen.

In fact, theoretical calculations by the PCILO method[38] showed that the dimers of aliphatic amines are linear, stabilized with respect to the monomer (ΔE *ca.* 4–5 kcal/mol) and the examination of the electron density shows a 0·022 electron transfer. *Ab initio* theoretical calculations[39] carried out on ammonia dimers indicate a 0·0136 electron density increase, while for the mixed-dimer $CH_3OH \ldots NH_3$ the calculations show a three times stronger interaction, and the electron transfer from nitrogen to the oxygen.[40] Recent *ab initio* calculations[41] on the hydrogen bonding ability of pyridine bases with water showed a 0·03 charge transfer from the pyridine to the water molecule and the dimers are again linear, the stabilization energy being 4·7 kcal/mol. NMR studies[42] of butylamine in benzene shows also that aggregation increases the amine nitrogen electron density.

Other reactions where amine dimers have been proposed

Although amine dimers have not been recognized before in ANS they have been proposed to be involved in other reactions. One of the earlier reports is the butylaminolysis of *p*-nitrophenolacetate in chlorobenzene,[43] among the recent ones worth mentioning the butylaminolysis of 2-hydroxy-5-nitro-α-toluene sulphonic acid sultone in acetonitrile and toluene,[44] the butylaminolysis of several nitro-substituted 4-nitrophenyl benzoates and cinnamates,[4,28] and the rearrangement of the *Z*-*p*-nitrophenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole into 4-benzoylamino-2-*p*-nitrophenyl-5-phenyl-1,2,3-triazole in benzene.[45] Curiously, in this last reaction, although the authors observed catalysis by *two* amine molecules they said that they 'have excluded the possibility that the amine behaves as a dimer because in other reactions catalysed by aliphatic secondary amines (e.g. *ANS*), this kind of dependence on amine concentration is not usually observed'. They define the effect as a 'catalysis of catalysis' term which is also used in the observed effect by two molecules of piperidine in the reaction of 1,2-dinitrobenzene in *n*-hexane.[5] Since the present results show evidence of amine dimers in ANS these last so called 'catalysis of catalysis' can also be interpreted as due to the amine aggregation.

Other more closely related reactions in which a third-order in amine rate dependence has also been found is the piperidine-cine-substitution in 2,3-dinitronaphtalene in benzene.[46] The common feature to all these reactions is that they are carried out in aprotic solvents.

Alternative mechanisms

Other alternative mechanisms have been recently proposed to explain the third-order in amine rate dependence in ANS. Hirst *et al.*[7] reported an upward curvature in the plot of k_A vs. [B] for the reactions of 2,4-dinitrophenyl-phenylether with morpholine in benzene. They explained it as due to a medium effect superposed on base catalysis by the nucleophile, but they also offered an alternative explanation that at least part of the electrophilic catalysis of the second step could be due to the homoconjugate acid $\mathrm{NuH^+Nu}$ (where Nu stands for the nucleophile). A straight line was indeed obtained when another base different from Nu was added.

Hirst's proposal, equation (16), would require that the dimer of the amine acts along with the monomer in the second step.

$$\mathrm{S + B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\mathrm{SB}] \underset{k_4\ \mathrm{B{:}B}}{\overset{k_3\ \mathrm{B}}{\rightrightarrows}} \mathrm{P} \qquad (16)$$

The derived kinetic expression for k_A is given by equation (17).

$$k_A = \frac{k_1 k_2 + k_1 k_3 K\,[\mathrm{B}] + k_1 k_4 K\,[\mathrm{B}]^2}{k_{-1} + k_2 + k_3\,[\mathrm{B}] + k_4 K\,[\mathrm{B}]^2} \qquad (17)$$

On the other hand, Banjoko and Otiono,[8] propose that two molecules of amine intervene in the decomposition of the zwitterionic intermediate to explain similar results, equation (18) and (19).

$$\mathrm{S + B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\mathrm{SB}] \underset{k_3\ 2\,\mathrm{B}}{\overset{k_2}{\rightrightarrows}} \mathrm{P} \qquad (18)$$

$$k_A = \frac{k_1 k_2 + k_1 k_3\,[\mathrm{B}]^2}{k_{-1} + k_2 + k_3\,[\mathrm{B}]} \qquad (19)$$

Equations (17) and (19) as well as equation (4) account for the quadratic dependence of k_A with [B] with a zero intercept if the uncatalysed decomposition is assumed to be negligible. But in the entire set of systems that we have studied there are some that exhibit a peculiar behaviour which allows distinction between mechanisms (3), (16) and (18); that is the plateau which is observed for some reactions in the plot of k_A/[B] vs. [B] at high [B] and relatively low temperatures (see e.g. Figure 3). For these systems equation (4) can be simplified to equation (6) which accounts for the plateau.

Hirst and Banjoko have not observed a plateau in their reactions, therefore their respective mechanisms can account satisfactorily for their results. However, only the mechanism of equation (3) is able to account for their and our observations. Furthermore, if the dimer (or two molecules) of the amine were acting in the second step, equations (16) and (18), inversion plots of $[B]/k_A$ vs. $[B]^{-1}$, equation (15), should not be linear.

Recently, Banjoko and Ezeani[19] argued against the dimer mechanism on the basis that the dimerization constant K of the amine should be extremely small according to the estimations of Bernasconi and Zollinger[35] judging by similar systems. But later[20,23] quantitative determinations of K have proved that the dimer concentration is considerable in aprotic non-polar solvents. Banjoko and Ezeani's criticism of the dimer mechanism takes into account only our first report on the quadratic dependence of k_A with [B] ignoring all the additional compelling evidence afforded afterwards.[11,24,30,33,48]

There are some additional observations that cannot be accommodated by the other mechanisms. In the recent model of the cyclic mechanism[19] one of the amine molecules is bonded at the oxygen of the phenoxide moiety, if this were the case addition of methanol should have an increasing effect on rate since methanol is a better HBD than the amine itself. Figure 4 reveals a contrary effect. Similarly, DMSO should have the opposite effect. The same can be said about the pyridine effect.

Finally, the cyclic mechanism ignores the well proven existence of aggregates in non-polar solvents, (it would require deaggregation to form each one of the three consecutive intermediates suggested) and the known conflicting problems with cyclic intermediates.

On the other hand, although more preferred, Hirst's mechanism besides the already mentioned shortcomings of equation (17) would not explain the observation of a second order term in [pyridine] mentioned above, since it is not possible to think about a pyridine dimer as a catalyst in the second step.

CONCLUSIONS

Some peculiar findings recently observed in ANS with amines, B, in aprotic solvents, namely: 1) quadratic dependence of k_A vs. [B]; 2) a plateau in the plots of $k_A/[B]$ vs. [B] at high [B]; 3) overall negative energies of activation; 4) quadratic dependence of k_A vs. [tertiary bases]; 5) spectacular effects of HBD and HBA catalysts; 6) steric effects on the base-catalysed step and 7) catalytic effect of DMSO in the first step, can be rationalized on the basis of a dimer of the amine acting in the first step simultaneously with the classical free amine attack.

Although kinetic data do not prove a mechanism they are important to eliminate mechanisms from consideration. Nevertheless, we consider that the case is not closed. This paper has the purpose of showing how widespread the occurrence of this peculiar behaviour is, as well as to discuss different explanations that were cast. Studies designed to shed more insight into the mechanism are in progress.

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