Reaction of 2,6-Dinitroanisole with Cyclohexylamine in Toluene–Octanol Binary Solvents. Further Support for the 'Dimer Nucleophile Mechanism' in Aromatic Nucleophilic Substitution

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The reaction of 2,6-dinitroanisole with cyclohexylamine in toluene, octanol and toluene–octanol mixtures has been studied at several amine concentrations. The reactions in toluene and in octanol–toluene mixtures up to 30% octanol show a third-order kinetic dependence on [amine]. Although the reaction rates in toluene and octanol are very similar, addition of small amounts of octanol to the toluene solution diminishes the rate of reaction, reaching a minimum value at 30–50% octanol, after which the rate increases almost linearly with the octanol content. These and other results, here described, are satisfactorily explained by the previously proposed 'dimer nucleophile mechanism'. Previously reported similar observations in methanol–benzene mixtures were criticised as being due to the reversibility of the reaction. The present results confirm the previously reported mechanism and the irreversibility of the reaction under the reaction conditions.

Recent studies of aromatic nucleophilic substitutions (ANS) by amines have been characterised by unusual findings, especially when reactions were carried out in aprotic solvents.[1–6] Most of these 'abnormal' results are characterised, among other features, by a third-order dependence on [amine], and can be consistently explained by a mechanism called the 'dimer nucleophile mechanism' which has been recently reviewed.[7]

In that mechanism, the dimer of the amine, (B:B), acts as a nucleophile forming an intermediate complex, (SB_2) [eqn. (1)

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

where S stands for substrate and P for product]. From this mechanism, the kinetic eqn. (2) is derived (where $K = [B{:}B]/[B]_0^2$). Taking into account that for these systems the departure of the nucleofuge is rate determining, *i.e.* $k_{-1} \gg (k_2 + k_3[B])$, eqn. (2) simplifies to eqn. (3).

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

$$k_A = \frac{k_1k_2K[B]}{k_{-1}} + \frac{k_1k_3K[B]^2}{k_{-1}} \qquad (3)$$

When the reactions are carried out in the presence of small additions of a hydrogen bond donor (HBD) cosolvent, *e.g.* methanol, competition between the self-association of the amine (dimer, $R^1R^2NH \cdots NHR^1R^2$) and the formation of amine–methanol aggregates ('mixed aggregate' $ROH \cdots NHR^1R^2$) occurs. Formation of the mixed dimer depresses the nucleophilicity of the reagent because of the reduced charge density on the nitrogen atom, and this phenomenon results in a decrease in the rate on addition of a HBD solvent to the aprotic solvent, as was observed.[8] In contrast, additions of a HBA (hydrogen bond acceptor) cosolvent, *e.g.* dimethyl sulfoxide (DMSO), in catalytic amounts, increase the reaction rate[9] by forming a mixed aggregate, $[R^1R^2NH \cdots OS(CH_3)_2]$, which increases the nucleophilicity of the amine. DMSO has been shown to increase the nitrogen electron density of primary and secondary amines.[10]

The above interpretation of specific solvent effects on the 'dimer nucleophile mechanism' has recently been criticised, however, by Banjoko and Bayeroju[3] in a paper which they called 'strong evidence against the "dimer" mechanism'. Their contention is that the observed decrease in rate is due to a special feature in the system studied: the reaction of 2,6-dinitroanisole with cyclohexylamine in benzene.[8] According to their suggestions, this reaction would be reversible. As methanol is formed as a product arising from the nucleofuge departure, additions of small amounts of methanol to the solvent would result in a decrease in rate as expected by Le Chatelier's principle. Although this argument could be refuted by the observation of the 'dimer nucleophile' in other systems,[1,6] it was of interest to examine the effect of addition of a HBD cosolvent other than methanol, to the reaction of a substrate where the nucleofuge is methoxide. The present paper describes the study of the reaction of 2,6-dinitroanisole (DNA) with cyclohexylamine in toluene, in octanol and in binary toluene–octanol mixtures.

Results and Discussion

The reactions of DNA with cyclohexylamine in toluene and in octanol proceed straightforwardly to give the expected *N*-cyclohexyl-2,6-dinitroaniline. Since the substrate is very sensitive to solvolysis, giving rise to 2,6-dinitrophenol, special care was taken to avoid any traces of water in the reaction vessels, and no complications were detected. S_N2 demethylation is important in the reaction of this substrate with other nucleophiles[11,12] but it was not detected at all in these systems: 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 spectrophotometrically 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_ψ 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_ψ by the amine concentration.

Reactions in Toluene and in Octanol.—Table 1 shows the k_A

Table 1 Reaction of 2,6-dinitroanisole (DNA) with cyclohexylamine (CHA) in toluene and octanol. Second-order rate coefficients and activation parameters

Solvent	[CHA]/mol dm^{-3}	T/°C	k_A/10^{-4} dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$-\Delta S^{\ddagger}_{25°C}$/J K^{-1} s^{-1}
Toluene[a]	0.264	35	2.53		
	0.285	45	2.99	7.7	289
	0.285	60	3.43		
Octanol[b]	0.264	35	2.36		
	0.264	50	3.35	24.2	270
	0.293	60	5.2		

[a] [DNA] = 1.94 × 10^{-4} mol dm^{-3}. [b] [DNA] = 1.85 × 10^{-4} mol dm^{-3}.

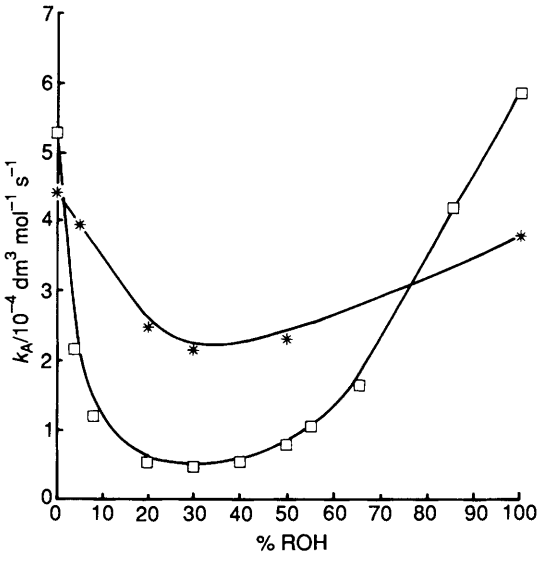

Fig. 1 Overall second-order rate coefficients, k_A, for the reaction of 2,6-dinitroanisole with cyclohexylamine in binary solvents: □, benzene–methanol; *, toluene–octanol

values for the reaction of DNA with cyclohexylamine in toluene and in octanol at three temperatures. It can be observed that at 35 °C the reaction is slightly faster in toluene than in octanol, whereas at the other temperatures the reverse is observed. These results show, once more, the difficulties of studying related reaction rates at a single temperature.

Table 1 also shows the activation parameters. A very low enthalpy of activation is observed for the reactions in toluene. Amine aggregations are known to be affected by temperature[13,14] in the opposite way to ANS rates, so that very low or even overall negative enthalpies of activation are observed where a pre-equilibrium, such as (2B $\rightleftharpoons$ B:B), exists.[7]

The reaction in octanol shows a higher enthalpy of activation and similar entropy of activation. In this respect, ANS in octanol exhibits a markedly different behaviour than is observed in more polar alcohols, *e.g.* ethanol or methanol. On passing from benzene or toluene to these polar protic solvents a sharp increase in the entropy of activation is usually observed, consistent with a highly ordered initial state (*e.g.* the enthalpy and entropy of activation of 2,4-DNA with cyclohexylamine change from 9.4 and 291 in benzene to 55.4 and 145 in methanol, respectively).[15] The lower values observed in octanol are consistent with the weaker hydrogen-bonding properties of this alcohol.

Reactions in Toluene–Octanol Mixtures.—Dependence on the octanol content. We have previously reported that the reaction of DNA with cyclohexylamine shows an almost negligible classical solvent effect, since it exhibits almost the same rate in benzene as in methanol, *e.g.* 10^{-4} k_A at 45 °C and [B] = 0.4 mol dm^{-3} are 5.27 (in benzene) and 5.82 (in methanol) dm^3 mol^{-1} s^{-1}. However, a spectacular effect was observed 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 [Fig. 1(*a*)]. We interpreted the huge decrease in rate as a result of competition between auto-association of the amine and formation of the amine–methanol aggregates, where the polar solvent acts as proton donor (ROH ••• NH_2R), thereby decreasing the nucleophilicity of the amine.

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.[16]

Nevertheless, so-called 'strong evidence' against the 'dimer' mechanism has recently been put forward by Banjoko and Bayeroju.[3] Since they did not observe a similar behaviour in the reaction of phenyl 2,4,6-trinitrophenyl ether with aniline in benzene–methanol they contended that the retarding effect observed in the reaction of DNA with cyclohexylamine is the result of the reaction being reversible. Since methanol is one of the products, they argued that by operation of Le Chatelier's principle, the reversed reaction should be enhanced while the forward reaction is retarded on additions of small amounts of methanol at equilibrium. This argument, obviously, does not take into account the rising portion of the curve, and the fact that the reaction produces quantitatively *N*-(2,6-dinitrophenyl)-cyclohexylamine even in pure methanol. Moreover, the authors suggest that all the reactions of amines with substrates having methoxy nucleofuges are likely to be reversible.

To add new experimental evidence for the argument of competition between self- and mixed-aggregates we studied the reaction in toluene–octanol mixtures at the same base concentration used in the studies in toluene–methanol, *i.e.* [B] = 0.4 mol dm^{-3}. Octanol was chosen as a co-solvent on the following grounds: (*a*) it would not compete with the product, methanol, in case of a reversible reaction; (*b*) its dipolarity (π^* = 0.37) is between that of toluene (π^* = 0.49) and methanol (π^* = 0.60);[17] (*c*) its hydrogen bond donor ability (α = 0.62)[17] is greater than that of toluene or cyclohexylamine (α = 0 for both)[18] but smaller than that of methanol (α = 0.93).[17]

Taking into account the above properties of octanol, a continuous increase in rate on addition of increasing amounts of octanol to toluene would be expected on the basis of Banjoko and Bayeroju's arguments. On the contrary, a decrease in rate is observed on small additions of octanol [Fig. 1(*b*)] up to nearly 30% of octanol where the minimum of the curve is reached; then it begins to increase up to the given value in pure octanol. As expected, on the basis of a special effect of a medium hydrogen bond donor co-solvent, the reaction in the toluene–octanol system exhibits a similar, although smaller, dependence on the protic solvent content, to that observed in the toluene–methanol system.

Table 2 Reaction of 2,6-dinitroanisole (DNA) with cyclohexylamine (CHA) in toluene–octanol binary solvents, at 35 °C[a]

% Octanol	[CHA]/mol dm^{-3}	$k_A/10^{-4}$ dm^3 mol^{-1} s^{-1}	k_A/[CHA]/ 10^{-4} dm^6 mol^{-2} s^{-1}	k_1k_3K/k_{-1}/ 10^{-4} dm^9 mol^{-3} s^{-1}	k_1k_2K/k_{-1}/ 10^{-4} dm^6 mol^{-2} s^{-1}
0	0.109	0.67	6.14		
	0.188	1.27	6.84		
	0.264	2.53	9.58	24 ± 2	3.1 ± 0.5
	0.376	4.39	11.78		
	0.470	6.76	14.51		
5	0.096	0.38	3.98		
	0.223	1.28	5.76		
	0.260	1.77	6.81	15 ± 1	2.6 ± 0.4
	0.415	3.93	9.48		
	0.518	5.28	10.19		
10	0.264	1.29	4.89		
15	0.264	1.08	4.10		
20	0.109	0.45	4.17		
	0.218	1.13	5.19		
	0.393	2.46	6.26	8 ± 1	3.3 ± 0.2
	0.492	3.66	7.44		
30	0.096	0.30	3.07		
	0.223	0.85	3.79		
	0.415	2.13	5.13	8 ± 1	2.2 ± 0.2
	0.518	3.28	6.34		
50	0.264	1.05	3.98		
	0.415	2.05	4.94	9 ± 1	1.3 ± 0.2
	0.518	3.35	6.45		
100	0.109	0.92	9.20		
	0.194	1.61	8.30		
	0.260	2.37	9.11	8 ± 1	6.8 ± 0.2
	0.388	3.76	9.69		
	0.485	5.36	11.05		
	0.530	5.90	11.13		

[a] [DNA] = 2.0 × 10^{-4} mol dm^{-3}.

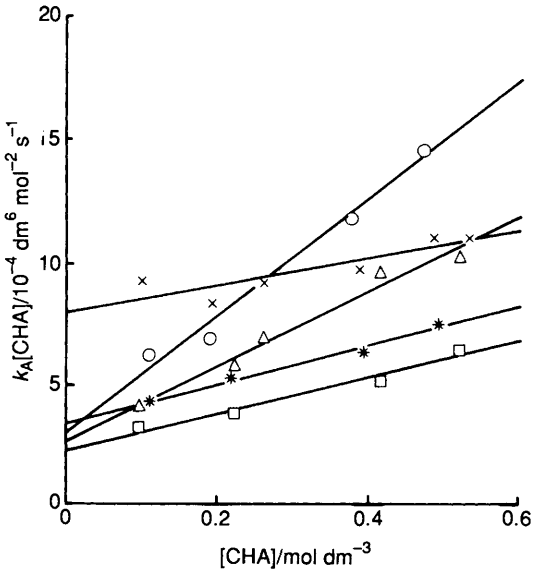

Fig. 2 Overall second-order rate coefficients over cyclohexylamine concentration, k_A/[B], for the reaction of 2,6-dinitroanisole with cyclohexylamine in: ○, toluene; and △, 5; *, 20; □, 30; ×, 100% octanol–toluene binary solvents, as a function of [B]

A complete interpretation of the process in mixed protic–aprotic solvents should also take into account the effect on the transition state or intermediate complex. In the reaction studied, addition of protic solvent should enhance the rate, owing to the increase in medium polarity, and the assistance to nucleofuge departure provided by hydrogen bonding. (In this respect, when protic solvents are present, the decomposition may be catalysed by the solvent, and k_2 in eqn. (1) may become k_2[ROH].) Nevertheless, in the present systems the retarding effect of protic solvent on the initial state (competition between self- and mixed-aggregates) is much more important than the change in medium polarity and the assistance to nucleofuge departure, especially when the ROH content is small. As the ROH content is increased the effects become balanced, and for ROH contents > 50% the classical accelerating effects of protic solvents are observed.

Dependence on the amine concentration. Table 2 gathers the second-order rate coefficients for the reactions of DNA with cyclohexylamine in toluene–octanol binary solvents at 35 °C carried out at several amine concentrations. It was observed that in pure toluene k_A exhibits a curvilinear dependence on [B]. A similar response is found in the binary solvents 5–30% octanol–toluene, the curvature being smaller on increasing the octanol content. The plot of k_A/[B] *versus* [B] (Fig. 2) in pure toluene is a straight line, which indicates the parabolic dependence of k_A on [B], consistent with eqn. (3). A similar behaviour is observed in the plot of k_A/[B] *versus* [B] for the reactions carried out in 5, 20, 30 and 50% octanol–toluene binary solvents. It can be observed in Fig. 2 that the slope decreases sharply on passing from pure toluene to 5% octanol, the decrease is smaller in 20% octanol and a small decrease is also observed in the intercepts of the plots up to 30% octanol (Table 2); then the intercept increases in pure octanol. In fact,

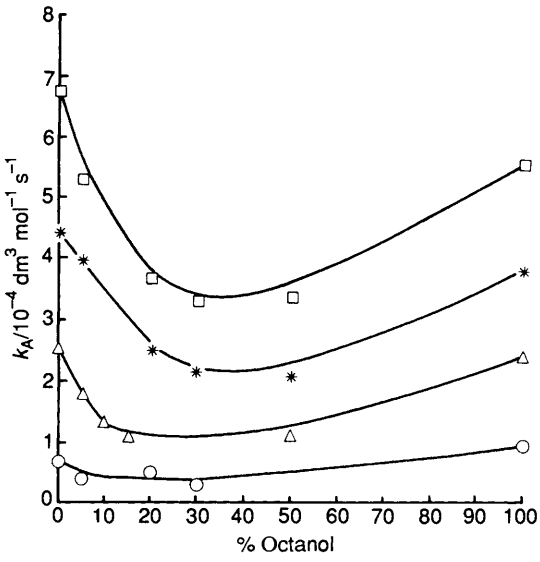

Fig. 3 Overall second-order rate coefficients, k_A, for the reaction of 2,6-dinitroanisole with cyclohexylamine at [B] = ○, 0.10; △, 0.26; *, 0.40; □,0.50 mol dm^{-3}, as a function of the octanol content

the intercept is greater than the slope in pure octanol, since in this solvent k_3 is almost negligible, consistent with the entire concept of the 'dimer' mechanism.

In their paper against this mechanism, Banjoko and Bayeroju[3] argued that the intercepts should decrease on addition of increasing amounts of methanol to toluene, and the fact that the Figure in our previous paper (ref. 8) did not show significant changes in the range 4–30% methanol, in their opinion, 'casts serious doubt on the validity of eqn. (3) and hence on the dimer mechanism on which it is based'. The value of the intercept changes slightly in the present study, and also in the reactions in benzene–methanol mixtures: it decreases from 6.06 to 1.04 × 10^{-4} dm^6 mol^{-2} s^{-1}, on going from pure benzene to 4% methanol–benzene. But, since the changes in the intercept from 4–30% methanol are smaller than for 0–4% methanol, it is not noticeable in the Figure, although it could be calculated from the data of Table 2 in that paper (ref. 8).

Furthermore, although the intercept (k_1k_2K/k_{-1}) and the slope (k_1k_3K/k_{-1}) are equally influenced by the dimerisation constant K in eqn. (3), this does not imply that they should show the same effect on changing the solvent, as claimed by Banjoko and Bayeroju. k_2 and k_3 are not necessarily influenced to the same extent by a solvent effect and, according to the 'dimer mechanism' it could be expected that the 'base-catalysed' decomposition of the transition state SB_2, measured by k_3, should be more strongly depressed by small additions of protic solvent than the 'spontaneous' decomposition measured by k_2. Indeed, the overwhelming evidence on the classical base catalysis by amines, shows that k_3 is usually more important in aprotic than in protic solvents.[19]

As a further feature of the influence of aggregation on these reactions, Fig. 3 shows the effects of binary solvents on reactions carried out at different amine concentrations. It can be observed that at [B] = 0.1 mol dm^{-3}, the reaction is only slightly sensitive to the composition of the solvent mixture. But, on increasing the concentration of nucleophile, the rates show the changes expected on the basis of the dimer nucleophile mechanism. If regular solvent effects were operating, the changes at [B] = 0.5 mol dm^{-3} should be expected to be smaller than at [B] = 0.1 mol dm^{-3}. On the contrary, the reaction is more sensitive at higher base concentrations where aggregation becomes important.

Conclusions

In this and the previous paper[8] we have reported evidence for the existence of a 'dimer' nucleophile in ANS by amines in aprotic, low-polarity solvents. The mechanism has been proved with several substrate–nucleophile systems where departure of the nucleofuge is rate-determining. The studies involved kinetic, solvent, catalyst, steric and conformational approaches. In our opinion the existence of the dimer nucleophile mechanism is now well established.

Experimental

Materials.—Anhydrous octanol was prepared by drying over magnesium sulfate for several days and then distilled twice at reduced pressure. It was kept in special vessels to allow delivery without air contamination. Toluene[1] and cyclohexylamine[12] were purified as previously described. 2,6-Dinitroanisole (m.p. 117–118 °C) and *N*-(2,6-dinitrophenyl)cyclohexylamine (m.p. 77.5–78 °C) were prepared as already reported.[12]

Kinetic Procedures.—The reactions were studied spectrophotometrically at 434 nm in a Hewlett-Packard model 8051 with diode-array spectrophotometer. The extinction coefficients at each different amine concentration and in all the octanol–toluene binary solvents were determined by application of Beer's law. In the reactions in mixed solvents the octanol content (v/v) is referred to the final volume of the reaction mixture. In all cases pseudo-first-order kinetics were observed, the absorbances observed at 'infinity' times were those expected on the basis of a quantitative conversion to the *N*-(2,6-dinitrophenyl)cyclohexylamine. A special search for 2,6-dinitrophenol, arising from partial demethylation of DNA, usually observed in protic solvents, was carried out by careful TLC and GLC but not even traces of it were detected. The autoprotolysis constant of octanol in toluene, and even in pure octanol, is not sufficient to promote the S_N2 reaction of DNA to any extent. The reported second-order rate coefficients, k_A, were calculated by the least-squares method as previously described.[12]

Acknowledgements

We are grateful to the *Consejo Nacional de Investigaciones Cientificas y Tecnicas* (CONICET) and to the University of Buenos Aires, for financial support. MM is a grateful recipient of a fellowship from the University of Buenos Aires.

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Paper 2/03755F
Received 14*th July* 1992
Accepted 15*th October* 1992