Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron 60 (2004) 4645–4654

ELSEVIER

Tetrahedron

Rationalization of the conflicting effects of hydrogen bond donor solvent on nucleophilic aromatic substitution reactions in non-polar aprotic solvent: reactions of phenyl 2,4,6-trinitrophenyl ether with primary and secondary amines in benzene–methanol mixtures

Olayinka Banjoko* and Ibitola A. Babatunde

Department of Chemistry, University of Lagos, Akoka-Yaba, Lagos, Nigeria

Received 10 October 2003; revised 22 March 2004; accepted 25 March 2004

Abstract—The kinetics of the reactions of phenyl 2,4,6-trinitrophenyl ether with piperidine and cyclohexylamine respectively were studied at different amine concentrations in benzene. The reaction of cyclohexylamine was not base-catalysed while that of piperidine was catalysed by one molecule of the nucleophilic amine. Addition of small amounts of hydrogen-bond donor solvent, methanol to the benzene medium of the reactions produced different effects—rate diminution followed by rate increase in one and continuous rate diminution in the other. These effects are compared with that of aniline (previously studied) in which a continuous rate increase was observed. The results are rationalized in terms of the effect of amine-solvent interaction on the nucleophilicity of the amines in addition to some other factors operating through cyclic transition states leading to products. It is evident from the rationalization that the idea of 'dimer nucleophile' in nucleophilic aromatic substitution reactions is erroneous.

1. Introduction

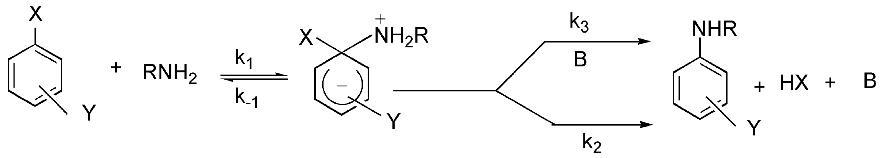
The general mechanism for aromatic bimolecular nucleophilic substitution reactions in all solvents when either primary or secondary amines are the nucleophiles[1,2] is given in Scheme 1.

Application of the steady state hypothesis to Scheme 1 gives Eq. 1,

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

where k_A is the observed second-order rate constant and B is either a second molecule of the nucleophile or an added base acting as the catalyst. Specific modifications of the above scheme and equation have, however, been made depending on whether the reaction is taking place in protic, dipolar aprotic[3,4] or non-polar aprotic[5–8] solvents or whether the reaction is catalysed by one or two amine molecules, or an entirely different catalytic entity.

In a previous paper,[9] we subjected to test the claim by Nuldelman and Palleros[10] that the vulnerability of amine–amine hydrogen bonding (dimer) is the factor responsible for the diminishing-rate effect observed on the addition of small amounts of methanol to the reaction of cyclohexylamine with 2,6-dintroanisole in benzene. We found that the addition of small amounts of methanol to the reaction of another primary amine, aniline with another substrate, phenyl 2,4,6-trinitrophenyl ether (**1**) in the same solvent showed no such behaviour, the rate of reaction



Scheme 1.

Keywords: Aprotic solvent; Aromatic substitution reaction; Benzene–methanol mixtures.

* Corresponding author. Tel.: +234-5454891x1710; fax: +234-4932669; e-mail address: yinkabanjoko@yahoo.com

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.03.079

increasing progressively in this case with increasing amounts of methanol. From this, we inferred that the diminution in rate observed by Nuldelman and Palleros could not have been due to the effect of the incursion of methanol on the supposed 'dimerization of the amine'. For, if this were so, the effect should have been more pronounced with the weaker aromatic amine, aniline. We then suggested an alternative interpretation that could explain their results.

In order to have a more general view of the phenomenon in dispute, we decided to examine the reactions of some other amines—primary and secondary, under the same conditions by adding small amounts of methanol to the benzene solutions of their reactions. We have studied the reactions of **1** with piperidine and cyclohexylamine in benzene.

2. Results and discussion

The reactions were studied spectrophotometrically at 29 °C in the presence of varying excesses of the respective amine over the substrate to ensure first-order kinetics. The observed second-order rate constants, k_A were calculated from the first-order rate constants. The reactions in pure solvent, as well as in benzene–methanol mixtures, proceeded straightforwardly to give the expected 2,4,6-trinitrophenylamine and phenol with no side-products.

The effects of methanol addition to the benzene medium of the reactions studied are in Table 1.

The reactions fall into two categories:

(i) Reactions in which addition of small amounts of methanol to the benzene medium diminishes the rate.
   (a) For the base-catalysed reaction of **1** with piperidine, the rate diminution reached a minimum at about 40–50% methanol after which the rate increased almost linearly with the methanol content.
   (b) For the uncatalysed reaction of the same substrate with cylohexylamine, the rate diminution continued to 100% methanol.

(ii) Reaction in which addition of small amounts of methanol to the benzene medium increases the rate continuously.

This was observed in the base-catalysed reaction of the substrate with aniline in benzene.[9]

2.1. Effects of methanol additions

The reaction of **1** with piperidine was observed to be first-order in the substrate and second-order in the amine. The effects of addition of small amounts of methanol to the benzene medium of the reaction at constant amine concentrations are shown in Table 2.

The observed effects of methanol addition on the reactions in the present investigation and also of the previous ones in the literature must be satisfactorily accommodated by a sound reaction mechanism. The effects could be due to the interaction of methanol with (i) the non-polar aprotic solvent or (ii) the substrate or (iii) intermediates on the reaction pathway or (iv) the nucleophile:

(i) Addition of methanol to non-polar aprotic solvent should increase the dielectric constant of the medium thereby increasing the rate of S_NAr reactions due to the extra stabilization of the intermediate first formed from the reaction of the nucleophile with the substrate.

(ii) Complex formation between the substrate and added methanol could be a probable factor. Observations have shown, however, that a particular substrate in a non-polar aprotic medium could display rate

Table 1. Effects of methanol additions to the benzene medium of the reactions studied

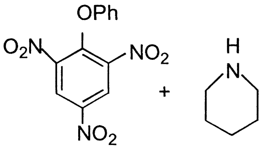
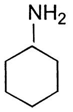
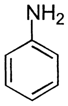
Type of reaction	Base catalysis	Effect of methanol additions
 1	Catalysed	Initial rate decrease reaching a minimum value then followed by rate increase
1 + 	Not catalysed	Continuous rate decrease
1 + 	Catalysed	Continuous rate increase[9]

Table 2. Second-order rate constants, k_A for the reaction of **1** with piperidine in benzene and benzene–methanol mixtures at 29 °C. [Substrate]=5×10^{-5} mol dm^{-3}

10^3[Pip]/mol dm^{-3}	% MeOH (v/v)	$10k_A$/dm^3 mol^{-1} s^{-1}	10^3[Pip]/mol dm^{-3}	% MeOH (v/v)	$10k_A$/dm^3 mol^{-1} s^{-1}	10^3[Pip]/mol dm^{-3}	% MeOH (v/v)	$10k_A$/dm^3 mol^{-1} s^{-1}
1.0	0	2.06	2.0	50	0.34	4.0	10	0.80
1.0	1	1.12	2.0	60	0.41	4.0	15	0.72
1.0	2	0.83	2.0	75	0.71	4.0	20	0.67
1.0	3	0.58	2.0	90	1.39	4.0	30	0.64
1.0	5	0.36	2.0	100	2.00	4.0	40	0.60
1.0	10	0.21	3.0	0	5.90	4.0	50	0.64
2.0	0	3.97	3.0	1	3.60	4.0	60	0.71
2.0	1	2.35	3.0	2	2.23	4.0	75	1.05
2.0	2	1.45	3.0	3	1.55	4.0	90	1.85
2.0	3	1.04	3.0	5	1.08	4.0	100	2.98
2.0	5	0.68	3.0	10	6.30	5.0	0	9.60
2.0	10	0.41	4.0	0	7.60	5.0	1	5.54
2.0	15	0.35	4.0	1	4.63	5.0	2	3.70
2.0	20	0.33	4.0	2	2.90	5.0	3	2.60
2.0	30	0.32	4.0	3	2.08	5.0	5	1.70
2.0	40	0.32	4.0	5	1.34	5.0	10	1.01

diminution in its reaction with one amine and a continuous rate increase in its reaction with another amine both in the presence of small amounts of methanol. For example, adding methanol to the benzene medium of the reaction of **1** with piperidine (present study) produced a rate diminution while the same addition of methanol produced a continuous rate increase for the reaction of the same substrate with aniline in our previous study.[9]

Also the reaction of 2,4-dinitrofluorobenzene with piperidine by Bernasconi and Zollinger[11] in benzene displayed a rate increase with added methanol while the reaction of the same substrate produced the opposite effect in its reaction with *cis* and *trans*-1,2-diaminocyclohexylamine[12] on the addition of methanol. It can therefore be reasonably assumed that a methanol-substrate interaction is not responsible for the observed diminution in rate in each case.

(iii) Interaction of added methanol with any zwitterionic intermediate formed as in Scheme 1 would assist the simultaneous extraction of a proton and expulsion of the leaving group through hydrogen bonding in the transition state thus leading to an increase in the rate of reaction.

(iv) The formation of aggregates via hydrogen-bonding between amines and hydrogen-bond donor solvent, methanol has been widely studied.[13–15] The methanol molecule acts as a proton donor to the amine resulting in the formation of an aggregate as shown in Scheme 2.

$$\mathrm{ROH} + \mathrm{RNH_2} \rightleftharpoons \mathrm{ROH}\text{---}\mathrm{NH_2R}$$

Scheme 2.

The nitrogen atom, having thus used its lone pair of electrons partially for hydrogen-bond formation becomes less nucleophilic compared with the free amine. The amine–methanol aggregate of reduced nucleophilicity can either react with the substrate in the first step of the S_NA_r reaction or be the catalysing entity in the decomposition of the zwitterionic intermediate complex in the second step. The first assumption is obviously more likely, since an uncatalysed reaction in the present study as well as the one reported in literature[11] displayed rate diminution on addition of methanol to the non-polar aprotic medium. The methanol–amine aggregate would slow down the reaction due to its reduced nucleophilicity. It is therefore proposed that the amine–methanol aggregate reacts with the substrate in the first step of the two-step S_NA_r reaction leading to reduced k_1.

2.2. Causes of rate increase and rate diminution

There are only a few cases of rate increase in S_NA_r reactions on addition of methanol to non-polar aprotic solvent. One is our previous study of the reaction of **1** with aniline in benzene[9] and the other is the reaction of 2,4-dinitrofluorobenzene with piperidine by Bernasconi and Zollinger[11] also in benzene.

The common features in these two reactions are:

(a) Base-catalysis with high catalytic effectiveness. This is evident in the base-catalysed reaction of 2,4-dinitrofluorobenzene with piperidine[11] for which the catalytic effectiveness, k_3/k_2=1230 dm^3 mol^{-1} and the base-catalysed reaction of **1** with aniline[7] for which k_3/k_2=1414 dm^6 mol^{-2}.

(b) Susceptibility to hydrogen bonding. It is noteworthy that since a continuous rate increase is only observed for strongly base-catalysed reactions on the addition of methanol to their non-polar aprotic medium, it implies that the factor responsible for this observation comes into play in the second step of the S_NA_r reaction, that is,

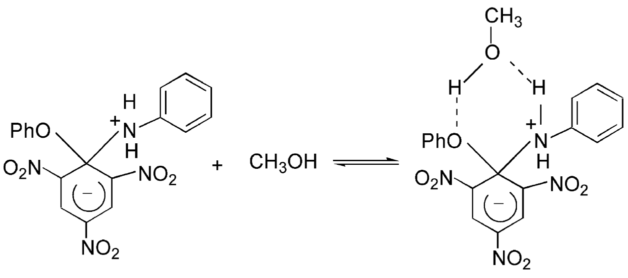


Figure 1.

the decomposition of the zwitterionic intermediate which sometimes involves catalysis.

A close scrutiny of the zwitterionic intermediates involved in the above two reactions reveals a high probability of strong hydrogen bonding in the cyclic transition state involving methanol and either a strong conjugate acid of a weak base (aniline) in the reaction of aniline with **1** (Fig. 1) on the one hand or methanol and a strong hydrogen-bond forming atom (fluorine) as a leaving group in the reaction of 2,4-dinitrofluorobenzene with piperidine (Fig. 2) on the other. Electrophilic catalysis of fluoride ion departure through hydrogen bonding has been demonstrated by Pietra and Fava[16] in the reaction of 1-fluoro-2,4-dinitrobenzene with piperidine in benzene where they observed catalysis by methanol but no catalysis by added triethylamine.

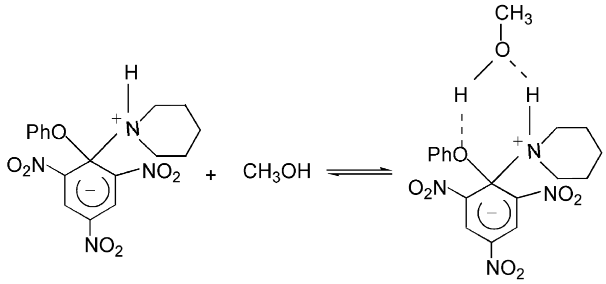


Figure 2.

From the above observations, it is clear that the addition of small amounts of methanol to the non-polar aprotic medium of S_NA_r reactions would produce two effects—(a) decrease in rate due to the reduced necleophilicity of the amine in the formed amine–methanol aggregate and (b) methanol catalysis through hydrogen-bonding.

For S_NA_r reactions in which the first step is rate determining (Scheme 1), $k_2+k_3[\mathrm{B}]\gg k_{-1}$ in Eq. 1, giving $k_A=k_1$ and thus, only effect (a) will be observed on addition of methanol because of the reduced nucleophilicity of the attacking amine–methanol aggregate which will be reflected in the reduced value of k_1.

For reactions in which the second step is rate determining, $k_{-1}\gg k_2+k_3[\mathrm{B}]$, thus Eq. 1 becomes Eq. 2

$$k_A=\frac{k_1k_2}{k_{-1}}+\frac{k_1k_3[B]}{k_{-1}} \tag{2}$$

and the above two opposing effects (a) and (b) will be in operation because

(i) the first step leading to the formation of the zwitterionic intermediate will be influenced by the reduced nucleophilicity of the resulting nucleophile which is now the amine–methanol aggregate thus causing diminution in rate and

(ii) the second step of the reaction which is the catalytic step is influenced by amine and methanol molecules respectively catalysing through hydrogen-bonding, thus causing an increase in rate.

The observed overall rate would depend on which of the two effects—(i) and (ii) predominates. For reactions in which (i) predominates over (ii), Class A, the observed overall effect is rate diminution and for reactions in which (ii) predominates over (i), Class B, the observed overall effect is rate increase on addition of small amounts of methanol to the aprotic medium.

Thus, the reaction of **1** with piperidine in benzene in the present study and the reaction of 2,6-dinitroanisole with cyclohexylamine in benzene studied by Nudelman and Palleros[10] belong to Class A, while the reaction of **1** with aniline in our previous study[9] belongs to Class B.

It is now clear, therefore, that the explanation given above for Class A reactions is the reason for the rate diminution observed by Nudelman and Palleros in the reaction of 2,6-dinitroanisole with cyclohexylamine in benzene–methanol medium and not our previously suggested explanation of possible reversibility of the reaction.[9,17]

2.3. Mechanism of the base-catalysed reaction

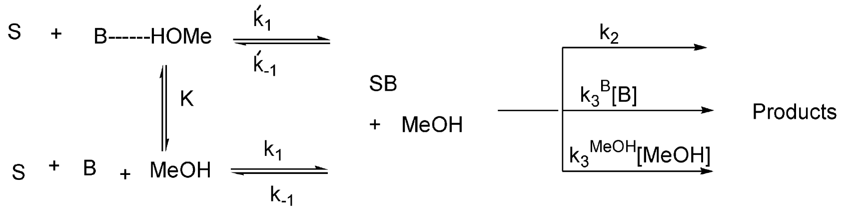
S_NA_r reactions in non-polar aprotic solvents on addition of small amounts of methanol can generally be assumed to involve the attack of the amine–methanol aggregate as well as the free amine on the substrate to produce the zwitterionic intermediate. Since amine–methanol aggregate formation via hydrogen bonding is likely to be a very rapid equilibrium process, three possible routes for conversion of the zwitterionic intermediate to products are proposed.

In Scheme 3, S stands for the substrate, B for the nucleophilic base, B···HOMe for the amine–methanol aggregate, SB for the zwitterionic intermediate, k_3^{B} and k_3^{MeOH} for the catalytic rate constants for the conversion of the intermediate into products by the base and methanol, respectively.

Since the amine may exist in free or hydrogen-bonded forms as given by Eq. 3,

$$\mathrm{B}+\mathrm{MeOH}\overset{K}{\rightleftharpoons}\mathrm{B}\cdots\mathrm{HOMe} \tag{3}$$

the stoichiometric measured concentration, $\mathrm{B}_{\mathrm{Stoich}}$ will be



Scheme 3.

related to the free base $[\mathrm{B}]_{\mathrm{Free}}$ by Eq. 4.

$$[\mathrm{B}\cdots\mathrm{HOMe}] + [\mathrm{B}]_{\mathrm{Free}} = [\mathrm{B}]_{\mathrm{Stoich}} \tag{4}$$

From Eqs. 3 and 4, the unmeasurable quantities $[\mathrm{B}\cdots\mathrm{HOMe}]$ and $[\mathrm{B}]_{\mathrm{Free}}$ are derived in terms of the measurable quantity $[\mathrm{B}]_{\mathrm{Stoich}}$.

Application of the steady-state hypothesis to Scheme 3 in terms of the stoichiometric base concentration leads to Eq. 5

$$k_{\mathrm{A}} = \frac{\left(\dfrac{k_1' K[\mathrm{MeOH}]}{1+K[\mathrm{MeOH}]} + \dfrac{k_1}{1+K[\mathrm{MeOH}]}\right)\left(k_2 + \dfrac{k_3^{\mathrm{B}}[\mathrm{B}]}{1+K[\mathrm{MeOH}]} + k_3^{\mathrm{MeOH}}[\mathrm{MeOH}]\right)}{k_{-1} + k_{-1}'[\mathrm{MeOH}] + k_2 + \dfrac{k_3^{\mathrm{B}}[\mathrm{B}]}{1+K[\mathrm{MeOH}]} + k_3^{\mathrm{MeOH}}[\mathrm{MeOH}]} \tag{5}$$

where [B] is the total (stoichiometric) base concentration and K is the association constant for amine–methanol aggregate formation.

For the base-catalysed reaction, when the second step is rate determining, Eq. 6 holds and Eq. 5 becomes Eq. 7.

$$k_{-1} + k_{-1}'[\mathrm{MeOH}] \gg k_2 + \frac{k_3^{\mathrm{B}}[\mathrm{B}]}{1+K[\mathrm{MeOH}]} + k_3^{\mathrm{MeOH}}[\mathrm{MeOH}] \tag{6}$$

$$k_{\mathrm{A}} = \frac{\left(\dfrac{k_1' K[\mathrm{MeOH}] + k_1}{1+K[\mathrm{MeOH}]}\right)\left(k_2 + \dfrac{k_3^{\mathrm{B}}[\mathrm{B}]}{1+K[\mathrm{MeOH}]} + k_3^{\mathrm{MeOH}}[\mathrm{MeOH}]\right)}{k_{-1} + k_{-1}'[\mathrm{MeOH}]} \tag{7}$$

On the assumption that hydrogen bonding with methanol substantially reduces the nucleophilicity of the amine, $k_1 \gg k_1'$, and Eq. 7 then reduces to Eq. 8 which can also be expressed in the form of Eq. 9.

$$k_{\mathrm{A}} = \frac{k_1}{1+K[\mathrm{MeOH}]} \times \left(k_2 + \frac{k_3^{\mathrm{B}}[\mathrm{B}]}{1+K[\mathrm{MeOH}]} + k_3^{\mathrm{MeOH}}[\mathrm{MeOH}]\right) \tag{8}$$

$$k_{\mathrm{A}} = \frac{k_1 k_2}{k_{-1}(1+K[\mathrm{MeOH}])} + \frac{k_1 k_3^{\mathrm{B}}[\mathrm{B}]}{k_{-1}(1+K[\mathrm{MeOH}]^2)} + \frac{k_1 k_3^{\mathrm{MeOH}}[\mathrm{MeOH}]}{k_{-1}(1+K[\mathrm{MeOH}])} \tag{9}$$

At constant methanol concentration, this equation reduces to Eq. 10

$$k_{\mathrm{A}} = k' + k''[\mathrm{B}] \tag{10}$$

where k' and k'' are defined by Eqs. 11 and 12, respectively.

$$k' = \frac{k_1 k_2}{k_{-1}(1+K[\mathrm{MeOH}])} + \frac{k_1 k_3^{\mathrm{MeOH}}[\mathrm{MeOH}]}{k_{-1}(1+K[\mathrm{MeOH}])} \tag{11}$$

$$k'' = \frac{k_1 k_3^{\mathrm{B}}[\mathrm{B}]}{k_{-1}(1+K[\mathrm{MeOH}]^2)} \tag{12}$$

For the reaction of **1** with piperidine, which is catalysed by one amine molecule in benzene, as well as in benzene–methanol mixtures at low methanol concentration, Eq. 9 applies.

The plot of k_{A} against [amine] for the reaction gave straight lines giving credence to Eq. 10. The values of the intercepts and slopes are listed in Table 3.

The table shows that the intercepts obtained on addition of methanol are all within the proximity of the origin and are, within experimental error, equal to zero. In this reaction, the overall effect of methanol addition is rate diminution. This is because the conjugate acid of the strong base, piperidine (p*K*a=11.06) is not sufficiently acidic to promote strong hydrogen-bonding with methanol in the cyclic transition state involving the zwitterionic intermediate. The resulting small value of methanol catalytic rate constant, k_3^{MeOH} for the decomposition of the zwitterionic intermediate into products is thus not comparable with the rate diminishing effect of the reduced nucleophilicity of the amine–methanol aggregate.

It is important to note that addition of small amounts of methanol to the reactions of **1** with piperidine (present study) and with aniline (previous study[9]) is expected to produce similar effects of rate diminution in both reactions due to the reduced nucleophilicity of the amine–methanol aggregate. However, the former reaction shows the expected rate decrease while on the contrary the latter reaction shows a continuous rate increase.[9] This is due to the strong methanol catalysis k_3^{MeOH} which comes into play (through a cyclic transition state—Figure 1) in the latter.

Table 3. Values of intercepts and slopes of the plots of k_{A} against [piperidine] at constant methanol concentrations for the reaction of **1** with piperidine in benzene–methanol at 29 °C

% Methanol	$10^2 k'/\mathrm{dm}^3\ \mathrm{mol}^{-1}\ \mathrm{s}^{-1}$	$k''/\mathrm{dm}^6\ \mathrm{mol}^{-1}\ \mathrm{s}^{-1}$	r
0	2.13±0.78	187.10±2.35	0.9998
1	1.12±1.44	111.434±4.34	0.9982
2	0.65±0.65	71.90±1.66	0.9990
3	0.46±0.25	50.80±0.76	0.9997
5	0.30±0.35	33.40±1.05	0.9980
10	0.15±0.15	19.90±0.40	0.9990

This is more than enough to compensate for the reduced nucleophilicity of the amine–methanol aggregate because the conjugate acid of the weak base, aniline (p*K*a=4.61) is sufficiently acidic to promote strong hydrogen-bonding with methanol in the cyclic transition state involving the zwitterionic intermediate, hence the rate increase.

The aniline reaction with **1** in benzene and benzene–methanol mixtures is catalysed by two amine molecules and so the corresponding rate Eqs. 8 and 9 involving the free amine and the amine–methanol aggregate would have $[B]^2$ terms instead of [B].

2.4. Effect of temperature

The observations from the study of S_NAr reactions in a non polar aprotic solvent on addition of small amounts of a hydrogen-bond donor solvent, methanol, to the reaction medium have brought into focus the difference in the mechanisms of these reactions in non-polar aprotic and polar protic solvents. The common feature in some of these studies is the parabolic curve sometimes obtained in a plot of the second-order rate constants, k_A against % methanol for some of the base-catalysed reactions (Fig. 3) as observed by us in the present investigation as well as by Nudelman and Palleros.[10,17]

On the left side of these curves, a region in which the medium is predominantly non-polar aprotic is an effect symbolic of a mechanism different from that on the right side which is predominantly polar protic. This is because an increase in the percentage of methanol results in rate diminution on the left while it is rate increase on the right side of the curves. The reaction represented by the left side of the plot (say 3–40% methanol content) was subjected to temperature variation ranging from 15 to 35 °C. It was observed that the rate of the reaction decreased slightly with increasing temperature (Table 4), thus resulting in a small negative activation energy of −1.20 kJ mol^{-1}.

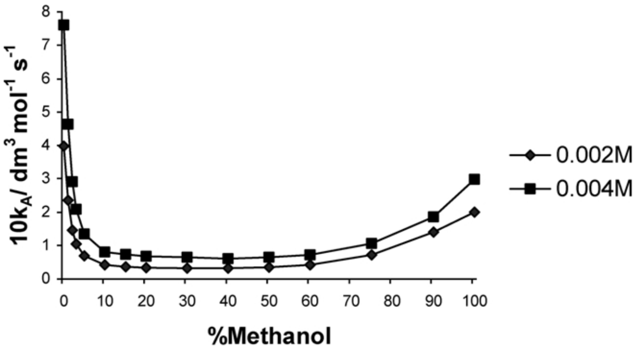


Figure 3. Plots of second-order rate constants k_A against % methanol at constant piperidine concentrations for the reaction of phenyl 2,4,6-trinitrophenyl ether with piperidine in benzene–methanol mixtures at 29 °C.

Similar negative temperature effects have been observed by E. F. Caldin et al.[18] in the reaction of 2,4-dinitrophenol with tri-*n*-octylamine in chlorobenzene and by Banjoko and Ezeani[7] in the reaction of **1** with some substituted anilines in benzene.

The observation in each case has been attributed to hydrogen-bond formation in the transition state as the strength of hydrogen-bonding is known to decrease with increasing temperature.

At the right side of the plot, however, a region where the addition of methanol has considerably increased to make the medium polar (say 60–75% methanol), increase in temperature from 15 to 35 °C led to an increase in rate (Table 4). This thus resulted in a positive activation energy of 3.20 kJ mol^{-1}. This change from negative activation energy to positive activation energy is clearly indicative of a change in mechanism of the reaction in the medium. It could be rightly inferred, therefore, that the reaction represented by the right hand side of the curve does not involve hydrogen-bonding in the transition state. Since the medium is polar in this section, it could now support ionic charges, hence the Specific Base-General Acid (SB-GA) or proton transfer mechanism can be assumed to be operating in this now polar protic medium. Evidence in recent times, however, is in support of a proton transfer mechanism over the widely accepted SB-GA mechanism in polar protic and dipolar aprotic solvents[19,20] when the leaving group is fairly good.

The above observation of a change in mechanism as the medium changes from a non-polar aprotic to a polar protic is a strong support for the cyclic transition state mechanism in non polar aprotic medium. The mechanism thus differs remarkably in this respect from the hetero/homoconjugate mechanism,[21] which does not differentiate between mechanisms in the two media.

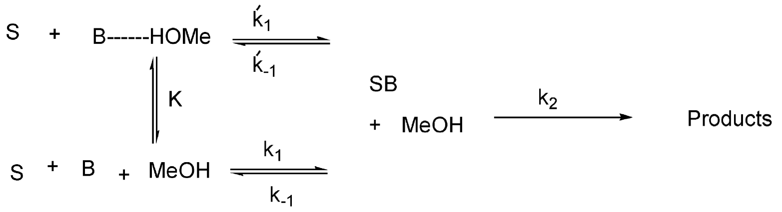
2.5. Mechanism of the uncatalysed reaction

For a reaction that is not base-catalysed and occurs in the presence of small amounts of methanol in non-polar aprotic solvent, Scheme 4 applies.

Application of the steady-state hypothesis to Scheme 4, working in terms of the stoichiometric base concentration,

Table 4. Second-order rate constants for the reaction of **1** with piperidine at constant amine concentration [4×10^{-3} M] in benzene–methanol mixtures at varying temperatures

3% Methanol					60% Methanol				
Temperature (°C)	15	20	25	35	Temperature (°C)	15	20	25	35
$10k_A$/dm^3 mol^{-1} s^{-1}	2.14	2.12	2.10	2.07	$10\ k_A$/dm^3 mol^{-1} s^{-1}	0.66	0.68	0.70	0.73
40% Methanol					75% Methanol				
Temperature (°C)	15	20	25	35	Temperature (°C)	15	20	25	35
$10k_A$/dm^3 mol^{-1} s^{-1}	0.57	0.59	0.61	0.63	$10\ k_A$/dm^3 mol^{-1} s^{-1}	0.94	0.96	0.99	1.05



Scheme 4.

gives the observed overall second-order rate constant, k_A as

$$k_A = \frac{k_2\left(\frac{k_1}{1+K[\text{MeOH}]} + \frac{k_1' K[\text{MeOH}]}{1+K[\text{MeOH}]}\right)}{k_{-1}+k_{-1}'[\text{MeOH}]+k_2}$$

Since the reaction is not base-catalysed, the first step is rate determining and inequality Eq. 13 holds.

$$k_2 \gg k_{-1}+k_{-1}'[\text{MeOH}] \qquad (13)$$

$$\therefore k_A = \frac{k_1}{1+K[\text{MeOH}]} + \frac{k_1' K[\text{MeOH}]}{1+K[\text{MeOH}]} \qquad (14)$$

The reaction of **1** with cyclohexylamine in benzene is not base-catalysed and so conforms with Scheme 4 and Eq. 14 derived from it. When no methanol is added to the reaction medium, Eq. 14 reduces to

$$k_A = k_1 \qquad (15)$$

Table 5 shows the constancy of the second-order rate constant, k_A with [cyclohexylamine] when the reaction is carried out in benzene without methanol, thus giving credence to Eq. 9. Addition of small amounts of methanol to the benzene medium of the reaction showed a sharp decrease in k_A [Table 6] from the initial value of 12.84 dm^3 mol^{-1} s^{-1} in pure benzene to 1.88 dm^3 mol^{-1} s^{-1} in benzene–10% methanol after which the decrease became gradual.

Table 5. Second-order rate constants, k_A for the reaction of phenyl 2,4,6-trinitrophenyl ether with cyclohexylamine (CHA) in benzene at 29 °C

10^4[CHA]/mol dm^{-3}	2.5	3.0	3.5	4.0
k_A/dm^3 mol^{-1} s^{-1}	12.83	12.85	12.83	12.84

The experimental data in Table 6 indicate that up to 10% methanol (2.5 mol dm^{-3}), values may be accommodated by the expression for k_A given by Eq. 8. With k_1= 12.84 dm^3 mol^{-1} s^{-1}, k_1' ca. 1.5 dm^3 mol^{-1} s^{-1} and K ca. 7 dm^3 mol^{-1}. At higher methanol concentrations, however, values of rate and equilibrium constants will be expected to be affected by medium effects and so these values will change.

Unlike in the base catalysed reactions, the diminution in rate continued at higher methanol content, reaching a minimum value at 100% methanol (Fig. 4).

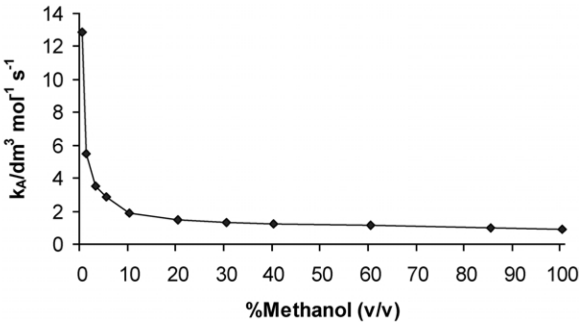


Figure 4. Plot of second-order rate constants, k_A against % methanol at constant cyclohexylamine concentration for the reaction of phenyl 2,4,6-trinitrophenyl ether with cyclohexylamine in benzene–methanol mixtures at 29 °C.

It is worth noting that the value of the second-order rate constant, k_A, in 100% methanol (0.92 dm^3 mol^{-1} s^{-1}) is much less than that in 100% benzene (12.84 dm^3 mol^{-1} s^{-1}). This is because the first step of the uncatalysed reaction involves the amine–methanol aggregate of reduced nucleophilicity in the former, while in the latter, it involves the free amine molecule with unreduced nucleophilicity.

2.6. Effect of temperature

As the above observation is an unusual one, we felt it worthwhile to investigate the effect of temperature on the reaction. Temperature probe ranging from 15 to 35 °C was therefore, carried out. The rate of the reaction at low methanol content (3% methanol) as well as that at high methanol content (60% methanol) increased appreciably with increase in temperature (Table 7), thus resulting in positive activation energies of 30.49 and 32.11 kJ mol^{-1}, respectively.

The facts to be considered in explaining the above observations are:

(i) diminution in rate on addition of methanol at both low and high methanol contents,
(ii) increase in rate with increase in temperature also at both low and high methanol contents.

Since the reaction is not base catalysed, the first step of the

Table 6. Second-order rate constants for the reaction of **1** with cyclohexylamine (CHA) in benzene–methanol mixtures.at constant cyclohexylamine concentration (0.02 mol^{-1}) at 29 °C [Substrate]=2.5×10^{-5} mol dm^{-3}

% Methanol (v/v)	0	1	3	5	10	20	30	40	60	85	100
k_A (dm^3 mol^{-1} s^{-1})	12.84	5.48	3.51	2.84	1.88	1.50	1.32	1.25	1.14	0.99	0.92

Table 7. Effect of Temperature on the reaction of phenyl-2,4,6-trinitrophenyl ether with cyclohexylamine at constant cyclohexylamine concentration [2.5×10^{-4} M] in benzene–methanol mixtures

3% Methanol					60% Methanol				
Temperature (°C)	15	20	25	35	Temperature (°C)	15	20	25	35
k_A/dm^3 $^{-1}$ s^{-1}	2.04	2.51	3.02	3.76	k_A/dm^3 mol^{-1} s^{-1}	0.61	0.82	1.06	1.52

reaction involving the amine–methanol aggregate of reduced nucleophilicity (as well as that involving the remaining free amine molecules) is rate-determining. It is therefore reasonable to assume that any factor that represses the amine–methanol aggregate formation will lead to an increase in rate while a factor that promotes it will result in rate diminution. Hydrogen-bonds are known to be weakened with an increase in temperature, hence an increase in rate with an increase in temperature is expected at both low and high methanol contents as was indeed observed for the reaction with 3 and 60% methanol content. On the other hand, an increase in methanol content that promotes amine–methanol aggregate formation (of reduced nucleophilicity) should produce rate diminution. The rapid diminution in rate at low methanol content can thus be attributed to the rapid involvement of amine molecules in amine–methanol aggregate formation with the little available methanol molecules and so the concentration of these aggregates increases with additional small amounts of methanol. At reasonably high methanol content, most amine molecules are in the aggregate forms. Further addition of methanol will only result in little increase in their concentration, thus resulting in less rapid diminution in rate, hence the tailing off of the curve (Fig. 4) which reaches a minimum at 100% methanol.

2.7. Deductions

There is no doubt that the factor responsible for the diminution in rate on addition of small amounts of methanol to an S_NA_r reaction in an aprotic solvent of low relative permitivity is the reduced nucleophilicity of the resulting nucleophilic entity. How this comes about, however, is not without some controversy. While from the explanation given earlier, we strongly feel that the reduced nucleophilicity results from the interaction of the amine with the added methanol to form an amine–methanol aggregate, Nudelman and Palleros maintain[10,12,17] that it results from the incursion of the added methanol on the supposed 'amine–amine dimer' thus forming the same amine–methanol aggregate which they termed 'mixed dimer'. It is the contention of these authors that amines exist in aprotic solvents largely as dimers and that it is the dimer that is the nuclophile in S_NA_r reactions. We, on the other hand, believe that in dilute amine solutions as is generally the case in S_NA_r reactions, amines exist largely as free molecules and that it is the free amine molecule that is the nucleophile in S_NA_r reactions. Our contention is buttressed by the fact that the formation constant for aliphatic amine dimers is in the range 0.02–0.1.[21,22a,b] In concentrated amine solutions, however, self-aggregation is likely to occur.

The above two differing views will no doubt result in different interpretations of similar experimental observations. It is remarkable that while the first view is of general applicability, the second one is not. It is difficult, for example, to comprehend how the dimer mechanism would explain the first-order dependence of k_A on the concentration of amines in S_NA_r reactions.

If the dimer, claimed to be the effective nucleophile, reacts with the substrate in the first step of S_NA_r reactions, then, every reaction of the amine should display at least second order dependence of the rate constant k_A on amine concentration, but this is not always the case. For example, the reaction of *n*-butylamine with 2,4,6-trinitrophenyl ether[23] in benzene and that of cyclohexylamine with 2,4-dinitrochlorobenzene,[24] also in benzene, are first order in the amines. The base-catalysed reaction of 2,6-dinitroanisole with cyclohexylamine in toluene[10]which is third-order in amine was explained on the basis of the dimer mechanism but the reaction of the same amine in benzene with 2,4-dinitrochlorobenzene[24] and with **1** (present study, Table 5) are first order in amine. The observation of first-order dependence of k_A on amine concentration in a number of S_NA_r reactions[23–25] in non-polar aprotic solvents shows that the 'dimer nucleophile' mechanism is not of general applicability.

The other notable instance in which the dimer mechanism had been found to be inapplicable is in the base-catalysed reaction of dinitrofluorobenzene with piperidine in benzene by Bernasconi and Zollinger[11] in which added ethanol caused an increase in rate. Nudelman and Mentserrat also carried out the same reaction and made similar observations[12] of rate increase on the addition of ethanol, instead of the rate decrease they expected on the basis of the dimer mechanism. To explain this anomaly, the authors attributed the rate increase to lack of self-association or dimerization of piperidine in benzene, an assertion that is inconsistent with their stand on the dimerization of amines generally. No reason was given for this inconsistency. The authors, however, asserted that the rate increase with small additions of a protic solvent was expected on the basis of hydrogen-bonding assistance to the nucleofuge departure. The above observation, which could not be explained by the dimer mechanism is easily explained on the basis of the cyclic transition state mechanism. This has been extensively dealt with in the section under which S_NA_r reactions exhibiting rate increase on addition of methanol are classified as Class B while those exhibiting rate decrease are classified as Class A. In the second step of the reaction in question, methanol catalysis involving hydrogen-bonding between methanol and the zwitterionic intermediate in the cyclic transition state (Fig. 2), more than compensates for the effect of reduced nucleophilicity of the amine–methanol aggregate operating in the first step of the reaction, hence the rate increase.

3. Conclusion

Addition of hydrogen-bond donor (hbd) solvent to S_NAr reactions involving a substrate and an amine in a non-polar aprotic solvent results in the formation of amine-solvent aggregates of reduced nucleophilicity. The effect should normally result in diminution in rate of reaction but could instead result in an increase in rate if the nature of the zwitterionic intermediate first formed between the substrate and the amine is such that could promote strong hydrogen-bonding between it and the hbd solvent in the cyclic transition state thus leading to its catalytic decomposition into products.

The interpretation of this phenomenon in the literature by a group of co-workers in the field, as being due to the formation of an 'amine–amine dimer' nucleophile is erroneous. That our contention above, is the correct position, is further buttressed by the fact that added hydrogen-bond acceptor (hba) co-solvent, which by implication (or rationalization), should increase the rate of reaction did, in fact, increase the rate. This is due to the increase in the nucleophilicity of the attacking nucleophilic amine through hydrogen-bonding between the amine and the co-solvent. The results of the reactions thus form the basis of our next publication.

4. Experimental

4.1. Materials

The preparation of phenyl 2,4,6-trinitrophenyl ether (**1**) and the purification of benzene and methanol were described previously.[26] Analar piperidine was heated under reflux with sodium wire for 4 h and then distilled. The process was repeated twice and the middle fraction distilling at 106 °C was collected and kept in a desicator, protected from light (lit.[27] bp 105–106 °C). Cyclohexylamine was purified by the same method bp 132 °C (lit.[27] 132–133 °C).

The product of each reaction studied was prepared by standard methods previously described.[28]

N-(2,4,6-Trinitrophenyl) piperidine, mp 100 °C, λ_{max} (C_6H_6) 390 nm.

N-(2,4,6-Trinitrophenyl) cyclohexylamine, mp 90–91 °C, λ_{max} (C_6H_6) 345 nm.

Kinetic procedure. The rates of formation of the products of the reactions were determined spectrophotometrically by the procedure previously described.[26] In some cases, however, the reactions were followed directly in the thermostated cell of the spectrophotometer. The reactions were carried out at 29 °C. For reactions in mixed solvents, the methanol content (v/v) refers to its final volume in the reaction mixture. Optical densities were recorded at the absorption maximum wavelength (λ_{max}) of each product. In all cases the absorption spectrum of the reaction mixture at 'infinity time' corresponded within 2% to the 'mock' infinity prepared by using the respective *N*-(2,4,6-trinitrophenyl)amine obtained as a product of the reaction. The reactions were carried out under conditions of excess of nucleophile over substrate and, in all cases, excellent first-order plots were obtained. The second-order rate constant, k_A were obtained by dividing the first-order rate constants by the amine concentration. All rate determinations were carried out at least in duplicate and the rate constants are accurate to within ±2%.

Acknowledgements

Grateful acknowledgement is made by O.B. for a grant-in-aid of research from the Central Research Committee of the University of Lagos.

References and notes

1. Bunnett, J. F. *Quart. Rev.* **1958**, *12*, 1–16.
2. Bernasconi, C. F. *M.T.P. International Reviews in Science and Organic Chemistry, Series One*; Butterworths: London, 1973; Vol. 3. pp 33–61.
3. Bunnett, J. F.; Davies, G. T. *J. Am. Chem. Soc.* **1960**, *82*, 665–674.
4. Bernasconi, C. F.; de Rossi, R. H.; Schmid, P. *J. Am. Chem. Soc.* **1977**, *4090*, 4100.
5. Capon, B.; Rees, C. W. *Annu. Rep. Prog. Chem.* **1964**, *60*, 279–284.
6. Ayediran, D.; Bamkole, T. O.; Hirst, J.; Onyido, I. *J. Chem. Soc., Perkin Trans. 2* **1977**, 597–600.
7. Banjoko, O.; Ezeani, C. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1357–1360.
8. Nudelman, N. S.; Palleros, D. *J. Org. Chem.* **1983**, *48*, 1607–1613.
9. Banjoko, O.; Bayeroju, I. A. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1853–1857.
10. Nudelman, N. S.; Palleros, D. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1277–1280.
11. Bernasconi, B.; Zollinger, H. *Helv. Chim. Acta* **1966**, 103–111.
12. Nudelman, N. S.; Montsserat, J. M. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1073–1076.
13. Kollma, P. A.; Allen, L. C. *J. Am. Chem. Soc.* **1971**, *93*, 2991–2995.
14. Bene, J. E. *J. Am. Chem. Soc.* **1973**, *95*, 5460–5465.
15. Ratkonics, F.; Salmon, T. *Acta Chim. Acad. Hung.* **1977**, *90*, 93–97.
16. Pietra, F.; Fava, A. *Tetrahedron Lett.* **1963**, 1935–1940.
17. Nudelman, N. S.; Marder, M.; Gurevich, A. *J. Chem. Soc., Perkin Trans. 2* **1993**, 229–233.
18. Caldin, E. F.; Tortschanof, K. *J. Chem. Soc., Faraday Trans. 1* **1978**, 1804–1810.
19. Chamberlin, R. A.; Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1831–1838.
20. Crampton, M. R.; Lord, S. D. *J. Chem. Soc., Perkin Trans. 2* **1997**, 369–376.
21. Hirst, J. *J. Phys. Org. Chem.* **1994**, *7*, 68–79.
22. (a) Kern, M.; Servais, B.; Abello, L.; Panneltier, G. *Bull. Soc. Chem. Fr.* **1968**, 2763–2767. (b) Wolff, H.; Gamer, G. *J. Phys. Chem.* **1972**, *76*, 871–875.
23. Banjoko, O.; Rahman, K. U. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1105–1107.

24. Nudelman, N. S.; Garrido, D. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1256–1260.
25. Pietra, F.; Del Cima, F. *Tetrahedron Lett.* **1967**, 1457–1462.
26. Banjoko, O.; Otiono, P. *J. Chem. Soc., Perkin Trans. 2* **1981**, 399–402.
27. CRC handbook of chemistry and physics, 53rd ed., **1972–1973**.
28. Banjoko, O.; Ezeani, C. *J. Chem. Soc., Perkin Trans. 2* **1986**, 531–536.