# Catalysis of Nucleophilic Aromatic Substitution Reactions in Mixed Solvents. Part 1. Reaction of Phenyl 2,4,6-Trinitrophenyl Ether with Aniline in Benzene–Methanol Mixtures: Strong Evidence against the 'Dimer' Mechanism

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The reaction of phenyl 2,4,6-trinitrophenyl ether with aniline in benzene and benzene–methanol was studied at different amine concentrations. Addition of increasing amounts of methanol (from 0.1 to 90%) to benzene resulted in a continuous increase in rate. This trend is contrary to that expected on the basis of the dimer mechanism which predicts an initial diminution in rate followed by an increase in rate at higher methanol concentration (above 30%). In pure benzene and benzene–methanol mixtures of low methanol content, third-order kinetics with respect to the amine were observed, while at constant amine concentrations first-order kinetics with respect to methanol were observed. Addition of equivalent amounts of phenol in place of methanol at low methanol concentrations (0.1—0.4%) had no effect on the rate of reaction. These and other results herein described could not be satisfactorily explained on the basis of the dimer mechanism but are satisfactorily accommodated by a previously proposed reaction scheme involving single catalysing entities in a cyclic transition state.

In furtherance of their proposed dimer mechanism,[1-3] Nudelman and Palleros recently reported an unusual finding[4] in the reaction of 2,6-dinitroanisole with cyclohexylamine in benzene–methanol mixtures of low methanol content. This finding has aroused our curiosity in two respects. First, we would like to know whether the phenomenon observed could be satisfactorily explained in terms of the dimer mechanism and, secondly, whether it is observable generally (*i.e.* in other systems) or is peculiar to the anisoles only.

For the reaction in question, in pure benzene, Nudelman and Palleros observed a third-order dependence of the second-order rate coefficient k_A on amine concentration. This they interpreted as derived from a mechanism where the dimer of cyclohexylamine (B:B) acts as a nucleophile forming an intermediate complex SB_2 [equation (1) where S stands for substrate and P

$$S + B:B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [SB_2] \underset{k_3 B}{\overset{k_2}{\rightleftharpoons}} P \qquad (1)$$
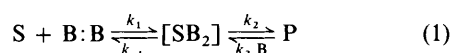
for product]. From this mechanism, the kinetic equation (2) was derived (where $K = [B:B]/[B]_o^2$), and this, on assuming $k_{-1} \gg (k_2 + k_3[B])$, simplifies to equation (3).

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

$$\frac{k_A}{[B]} = \frac{k_1 k_2 K}{k_{-1}} + \frac{k_1 k_3 K[B]}{k_{-1}} \qquad (3)$$

Addition of small amounts of methanol to the reaction mixture was found to produce a decrease in the rate which reached a minimum at nearly 30% methanol. For mixtures richer in methanol, the rate began to increase and did so sharply at higher methanol content. This effect was interpreted by Nudelman and Palleros as being due to competition between the self-association of the amine (dimer) and the amine–methanol aggregates. They contended that the amine–amine dimer concentration would diminish on addition of small amounts of methanol to a benzene solution of the amine and that ROH••• NHR₂ association depresses the nucleophilicity

of the reagent because of the reduced charge density on the nitrogen atom. They then argued that if the dimer mechanism depicted in equation (1) were operating, the above phenomenon should result in a diminution in the rate on addition of a protic solvent, methanol, to the aprotic solvent, benzene, and this they observed.

Linear profiles were achieved when $k_A/[Amine]$ was plotted against [Amine], thus giving credence to equation (3). In the plot, however, a decrease in slope with increasing methanol content was observed while a constant intercept was obtained for all additions from 4 to 30% methanol. The diminution in slope was explained, through equation (3), as being due to a continuous diminution in the self-association constant K of the amine (by competition with amine–solvent interactions) which reached a minimum at 30% methanol when the monomer was assumed to take over. We are intrigued, however, by the constancy of the intercept of that plot. By equation (3), both the intercept $\left(\dfrac{k_1 k_2}{k_{-1}} K\right)$ and the slope $\left(\dfrac{k_1 k_3}{k_{-1}} K\right)$ are influenced by the dimerization constant K. By the argument offered above, if the continuous addition of methanol continuously reduces the self-association constant K of the amine resulting in a continuous diminution of the slope, we strongly feel that the same effect should have been observed for the intercept if the dimer mechanism were operating. The intercept should have decreased in value progressively until it reaches a constant value at *ca.* 30% methanol. The gap between the intercept obtained for pure benzene (*i.e.* 0% methanol) and the constant intercept obtained for benzene–methanol mixtures is large enough for progressive decreases in intercept with addition of methanol to be noticeable. The fact that this was not observed at all casts serious doubt on the validity of equation (3) and hence on the dimer mechanism on which it is based.

In our quest to ascertain the validity of the above claim, we have investigated the effect of the addition of increasing amounts of methanol (ranging from 0.1 to 90% v/v) to the benzene medium of a reaction of another substrate, phenyl 2,4,6-trinitrophenyl ether, with a similar amine, aniline, a reaction we have carried out before in pure benzene as well as pure methanol.[5]

Table 1. Second-order rate coefficients for the reaction of phenyl 2,4,6-trinitrophenyl ether[a] with aniline in benzene–methanol at 25 °C

[Aniline]/M	Methanol (%)	$10^3 \, k_A$/l mol^{-1} s^{-1}
0.30	0	1.90
	0.1	2.46
	0.2	3.28
	0.3	3.97
	0.4	4.83
	0.5	5.73
0.25	0	1.31
	0.1	1.78
	0.2	2.35
	0.3	2.90
	0.4	3.56
	0.5	4.28
	0.6	4.84
0.20	0	0.85
	0.1	1.14
	0.15	1.41
	0.2	1.62
	0.3	2.03
	0.4	2.50
	0.5	3.03
	0.6	3.54
	0.8	5.01
	1.0	7.01
	2.0	10.90
0.15	0	0.52
	0.1	0.74
	0.2	1.02
	0.3	1.36
	0.4	1.72
	0.5	2.08
	0.6	2.39
	0.8	3.58
	1.0	4.75
	1.0[b]	4.74
0.02	2.0	1.30
	5.0	3.50
	10.0	6.20
	20.0	10.80
	30.0	14.70
	40.0	18.30
	50.0	22.50
	50.0[c]	22.00
	60.0	25.20
	70.0	26.60
	80.0	28.10
	90.0	29.10
	100.0	30.40

[a] [Substrate] 5 × 10^{-4}M. [b] Aniline hydrochloride (0.001M) also present. [c] Aniline hydrochloride (0.01M) also present.
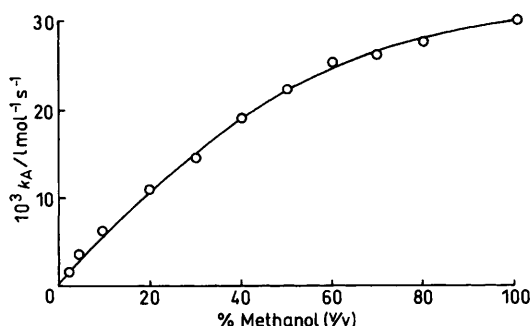
Figure 1. Plot of second-order rate coefficients k_A against % methanol for the reaction of phenyl 2,4,6-trinitrophenyl ether with aniline (0.02M) in benzene–methanol (v/v) at 25 °C

Results and Discussion

The reactions were studied spectrophotometrically at 25 °C in the presence of varying excess of the amine to ensure pseudo-first-order kinetics. The observed second-order rate coefficients k_A were calculated from the pseudo-first-order rate constants and are listed in Table 1. The reaction in the pure solvents as well as in benzene–methanol proceeded straightforwardly to give the expected 2,4,6-trinitrophenylaniline and phenol with no side-products. As expected, the reaction is slower in benzene than in methanol. Addition of increasing amounts of methanol from 0.1 to 90% showed no decrease at all in rate. Instead, the rate increased progressively as shown in Table 1 and Figure 1. Figure 1 shows that the increase in rate is nearly proportional to the methanol content of the mixed solvents from 0.1 to *ca.* 50%, but at higher percentage methanol the rate increased less rapidly than expected. A similar progressive increase in rate with methanol addition was observed by Bernasconi and Zollinger in the reaction of 2,4-dinitrofluorobenzene with piperidine in benzene.[6] If the vulnerability of amine–amine hydrogen bonding (dimer) to solvent hydrogen bonding is responsible for the decrease in rate observed by Nudelman and Palleros in the cyclohexylamine reaction, the difference in the results of their reaction and ours should have been one of degree (*i.e.* one based simply on the relative magnitude of the expected decrease in rate with methanol addition) and not of kind and this could easily have been attributable to the difference in the pK_a values or basicities of the two primary amines, cyclohexylamine and aniline. In fact, a greater initial decrease in rate is to be expected for methanol incursion on an aniline dimer than on a cyclohexylamine dimer because of the weaker hydrogen bond of the former due to the much lower pK_a of the aromatic amine. Since no decrease at all in rate was observed for the aniline reaction, it means that the dimer mechanism invoked to explain the observations of Nudelman and Palleros for the cyclohexylamine reaction is not the operating factor. We have therefore sought an alternative explanation for their results by considering the nature of the substrate involved in the reaction.

A careful look at the reaction [equation (4)] shows that apart from the N-(2,6-dinitrophenyl)cyclohexylamine monitored in the reaction, methanol is also a product. If the reaction proceeds ordinarily, small additions of methanol to the benzene medium should only increase the polarity of the medium and hence the rate of reaction, but if, on the other hand, the reaction is a reversible one, then one would expect by Le Chatelier's principle that the reverse reaction would be enhanced while the forward reaction is retarded on addition of small amounts of methanol at equilibrium. Since a retarding effect was observed in that reaction, our explanation is that the reaction is a reversible one and should be so written. The fact that a similar reaction of 2,4-dinitroanisole with piperidine in methanol[7] had been shown by Bunnett and Garst to be reversible strengthens our contention in this regard. With this in mind, we have investigated the reaction of phenyl 2,4,6-trinitrophenyl ether with aniline in benzene for reversibility by adding small amounts of phenol. The results (Table 2) show that at low phenol concentration (equivalent to 0.1—0.4% methanol addition) there was no effect on the rate. It can therefore be inferred from the three nucleophilic aromatic substitutions discussed above that the reactions of amines with substrates having methoxy nucleofuges are likely to be reversible while those with phenoxy nucleofuges are not likely to be.

The increase in rate for methanol concentrations >30% observed by Nudelman and Palleros is due to the fact that the methanol concentration has reached a fairly large value where its effect on the reverse reaction had reached its maximum and further additions could only be manifested by an increase in the polarity of the medium, a situation which would progressively increase the rate of the forward reaction. The contention by
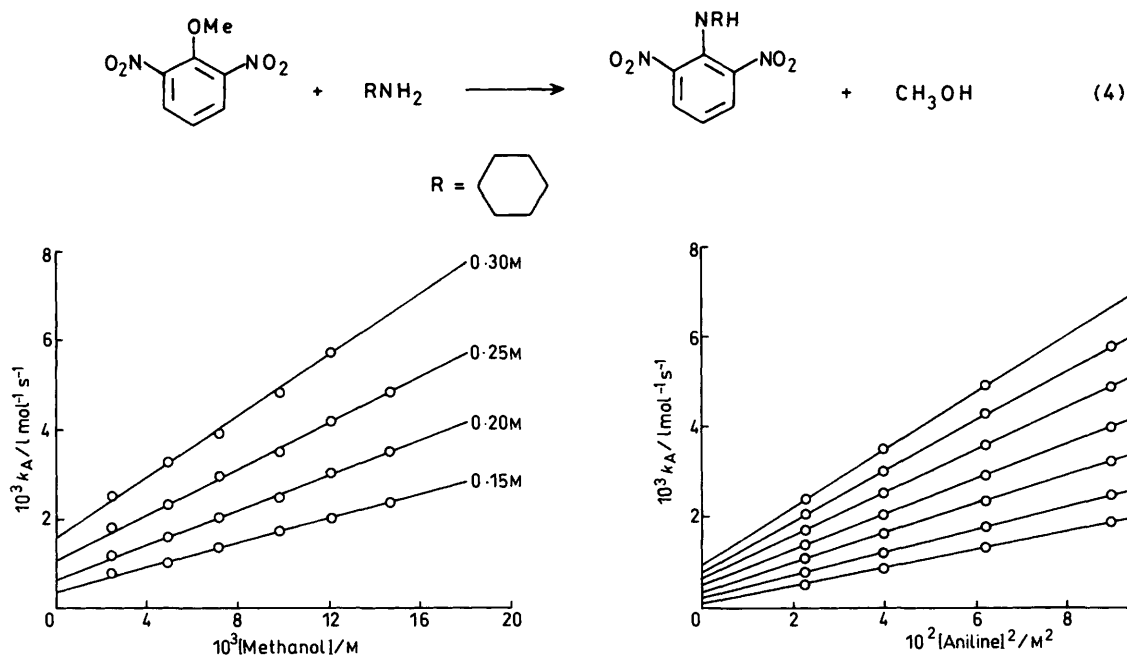
(4)

Figure 2. Plots of second-order rate coefficients k_A against methanol concentrations at constant aniline concentrations for the reaction of phenyl 2,4,6-trinitrophenyl ether with aniline in benzene–methanol at 25 °C

Figure 3. Plots of second-order rate coefficients k_A against the squares of aniline concentrations at constant methanol concentrations for the reaction of phenyl 2,4,6-trinitrophenyl ether with aniline in benzene–methanol at 25 °C

Table 2. Effect of addition of phenol to the reaction of phenyl 2,4,6-trinitrophenyl ether[a] with aniline[b] in benzene at 25 °C

10^3 [Phenol]/M	$10^4 \, k_A$/l mol^{-1} s^{-1}
0	8.45
2.25	8.45
5.0	8.50
7.5	8.45
10.0	8.45

[a] [Substrate] 5×10^{-4}M. [b] [Aniline] 0.2M.

Table 3. Values of intercepts and slopes of the plot of k_A versus [methanol] at constant amine concentrations for the reaction of phenyl 2,4,6-trinitrophenyl ether with aniline in benzene–methanol at 25 °C

[Aniline]/M	$10^4 \, k'_{Me}$/l mol^{-1} s^{-1}	$10^2 \, k''_{Me}$/l^3 mol^{-3} s^{-1}	r^a
0.15	3.85	13.61	0.9994
0.20	6.56	19.24	0.9995
0.25	11.32	25.08	0.9995
0.30	16.47	32.80	0.9997

[a] Correlation coefficient.

Nudelman and Palleros that the increase is due to a new and effective base, the methoxide ion (CH$_3$O$^-$) produced in the medium by the solvolysis of the amine, was not confirmed by us in our own reaction as shown by the constant value of k_A (Table 1) for amine concentration with or without aniline hydrochloride, a salt whose principal effect is to repress the reversible solvolysis leading to the formation of the methoxide ion.[7] Since the medium is predominantly aprotic, solvolysis is probably repressed. Catalysis by methoxide ion could, however,

be peculiar to the reversible anisole reactions in a sufficiently polar medium as the addition of aniline hydrochloride also has no effect on the rate of the reaction of phenyl 3,5-dinitropyridine ether with aniline in methanol.[8]

Our results show that the reaction of aniline with phenyl 2,4,6-trinitrophenyl ether in benzene is catalysed by the base, aniline, as well as the added methanol. As previously shown[5,9] the reaction is third-order with respect to the amine.* A plot of the observed second-order rate coefficients k_A at constant amine concentration against methanol concentrations is linear (Figure 2) at low methanol concentrations (0—0.6%), showing that the reaction is first order with respect to methanol. The plot, however, tends to curve upwards at higher methanol concentrations. The equation for the linear plot is given by (5)

$$k_A = k_o + k''_A \, [\text{Aniline}]^2 + k''_{Me} \, [\text{MeOH}] \qquad (5)$$

where k_o, k''_A, and k''_{Me} represent the composite rate coefficients for the uncatalysed, the aniline-catalysed, and the methanol-catalysed reactions respectively. When no methanol is added to the medium, equation (5) becomes (6). At constant amine
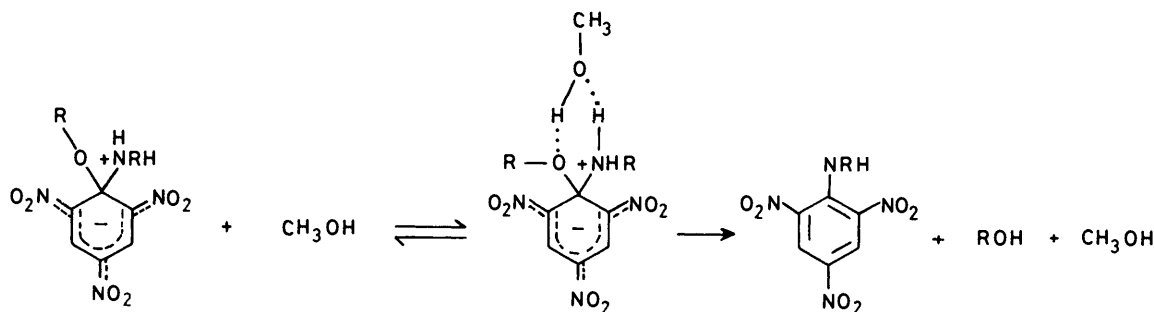
$$k_A = k_o + k''_{An} \, [\text{Aniline}]^2 \qquad (6)$$

concentration, the second term in equation (5) becomes constant and the equation can then be written as (7a) (where the combined constant k' is given by $k' = k_o + k''_{An} \, [\text{Aniline}]^2$).

$$k_A = k'_{Me} + k''_{Me} \, [\text{MeOH}] \qquad (7a)$$

The plot of k_A against methanol concentrations at constant amine concentrations is shown in Figure 2. The values of the intercepts k'_{Me} and the slopes k''_{Me} are listed in Table 3.

When the methanol concentration in equation (5) is kept constant while the aniline concentration is varied, equation (7b), analogous to (7a), becomes applicable. Figure 3 shows a plot of k_A against the square of the aniline concentration at
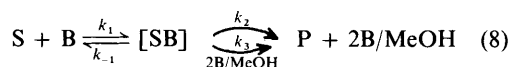
* A plot (not shown) of k_A versus [Aniline] at low methanol content (0—0.6%) gave upward curvatures, indicating kinetics of order higher than two with respect to the amine.

Scheme.

Table 4. Values of intercepts and slopes of the plot of k_A versus [aniline]^2 at constant methanol concentrations for the reactions of phenyl 2,4,6-trinitrophenyl ether with aniline in benzene–methanol at 25 °C

Methanol (%)	$10^4\ k'_{An}/l\ mol^{-1}\ s^{-1}$	$10^2\ k''_{An}/l^3\ mol^{-3}\ s^{-1}$	r
0	0.38	2.06	0.9997
0.1	1.43	2.58	0.9993
0.2	2.71	3.34	0.9999
0.3	4.88	3.87	0.9999
0.4	6.69	4.62	0.9999
0.5	8.68	5.42	0.9999
0.6	10.45	6.10	0.9995

constant methanol concentrations. The intercepts k'_{An} and slopes k''_{An} are listed in Table 4.

$$k_A = k'_{An} + k''_{An}\ [\text{Aniline}] \qquad (7b)$$

The reaction can be represented by equation (8) where S

$$S + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [SB] \underset{2B/MeOH}{\overset{k_2}{\underset{k_3}{\rightleftharpoons}}} P + 2B/MeOH \qquad (8)$$

stands for the substrate, B the amine, SB the intermediate complex, and P the product. From this mechanism, the kinetic expression (9) for the amine and methanol-catalysed reactions in benzene–methanol can be derived using the steady-state hypothesis. Since base catalysis was observed in these reactions, it means that the second step is rate-determining, thus the inequality $k_{-1} \gg (k_2 + k_3^B\ [\text{B}]^2 + k_3^{Me}\ [\text{MeOH}])$ holds, and equation (9) can be simplified to (10). This equation fits the

$$k_A = \frac{k_1 k_2 + k_1 k_3^B\ [\text{B}]^2 + k_1 k_3^{Me}\ [\text{MeOH}]}{k_{-1} + k_2 + k_3^B\ [\text{B}]^2 + k_3^{Me}\ [\text{MeOH}]} \qquad (9)$$

$$k_A = \frac{k_1 k_2}{k_{-1}} + \frac{k_1 k_3^B\ [\text{B}]^2}{k_{-1}} + \frac{k_1 k_3^{Me}\ [\text{MeOH}]}{k_{-1}} \qquad (10)$$

observed results and is in fact the same as the empirical equation (5) (obtained above) which shows third-order dependence on the amine concentration for the rate of the reaction in benzene–methanol mixtures of low methanol content (Figure 3) as well as first-order dependence on the methanol concentration at constant amine concentrations (Figure 2). From the two identical equations, the intercept and slopes are given by $k_o = k_1 k_2/k_{-1}$, $k''_{An} = k_1 k_3^B/k_{-1}$, and $k''_{Me} = k_1 k_3^{Me}/k_{-1}$.

The observed increases in the intercepts and slopes with increase in methanol content (Figures 2 and 3 and Tables 3 and 4) are easily understood in terms of the corresponding increases in the k_2, k_3^B, and k_3^{Me} values as the methanol and amine concentrations are increased. The increase in k_2 is due to the

increase in the polarity of the medium with increase in methanol content while the increases in k_3^B and k_3^{Me} are due to an increase in catalysis as the amine and methanol concentrations are increased respectively. It is noteworthy that the value of the intercept, k_o, is 3.80×10^{-5} l mol^{-1} s^{-1} (in pure benzene). Its value, however, increases progressively with increase in methanol content (Figure 3, Table 4).

It is also worth noting that the order with respect to the amine in pure methanol is two.[5] The change in order in amine from three to two thus occurs at high methanol content in the mixed solvents. The value of the catalytic effectiveness (k_3^B/k_2 or k_3^{Me}/k_2) of each catalysing entity obtainable by dividing the value of the slope by that of the intercept is $\gg 50$ in each case, clearly demonstrating according to Bunnett's postulate[10,11] that the effect being observed is indeed a catalytic and not just a medium one.

The observance of an upward curvature (not shown) at higher amine (> 0.3M) and methanol (> 0.6%) concentrations in the two plots above shows that the inequality $k_{-1} \gg (k_2 + k_3^B\ [\text{B}]^2 + k_3^{Me}\ [\text{MeOH}])$ assumed for equation (9) no longer holds at those higher amine and methanol concentrations.

Like the amine-catalysed step,[12] a cyclic mechanism is proposed for the methanol-catalysed decomposition of the intermediate complex into products (Scheme) because the medium (at low methanol content) is still predominantly non-polar aprotic and hence unlikely to stabilize highly ionic transition states[13-21] present in Bunnett's mechanism for polar protic media.[10,11,14,22,23] The methanol catalysis is a composite one involving three effects, a medium effect, electrophilic catalysis of the leaving-group departure, and base catalysis of the ammonium proton transfer from the zwitterion intermediate, the latter two occurring through hydrogen bonding to the hydrogen and oxygen atoms of the methanol respectively (Scheme).

Our proposed mechanism involving single amine[12] and methanol molecules has satisfactorily explained our present and past results as well as those of Nudelman and Palleros[4] which could not be properly explained in terms of the dimer mechanism. It is clear from our results and interpretations that the contention of Nudelman and Palleros that, in benzene–methanol mixtures of low methanol content, methanol acts as a strong hydrogen-bond donor (h.b.d.) solvent competing with the amine molecules to form aggregates cannot be sustained. It is not surprising therefore that the plot of k_A against amine concentration at 30% methanol (not shown) for the reaction of 2,6-dinitroanisole with cyclohexylamine in benzene–methanol[4] gives an upward curvature, indicating third-order kinetics in amine, while a similar plot of the same reaction at dimethyl sulphoxide > 2% in toluene–dimethyl sulphoxide[24] gives a downward curvature, indicating second-order kinetics in amine even though, in both cases, second-order kinetics in amine are proposed by the authors.

Conclusions.—Addition of increasing amounts of methanol to

the reaction of an amine with a nitro-activated substrate having a methoxy nucleofugue causes an initial decrease in the rate of reaction followed by an increase in rate at higher methanol content. No such effect is observed on addition of either methanol or phenol to a similar reaction involving a substrate having a phenoxy nucleofugue. This is because the reaction of the former (nitroanisole) is reversible while that of the latter is not. The observation is definitely not due to any effect on a supposed dimerization of the amine for if this were so, similar effects should have been obtained for the two substrate systems.

Experimental

Materials.—The preparation of phenyl 2,4,6-trinitrophenyl ether and the purification of aniline and benzene were described previously.[5,9] Anhydrous methanol was prepared by Lund and Bjerrum's method.[25] Commercial phenol (Riedel de Haen grade) was used without further purification but in an anhydrous condition.

Kinetic Procedure.—The kinetics were studied spectro-photometrically by the procedure previously described.[5] The reactions were carried out at 25 °C. For reactions in mixed solvents the methanol content (v/v) refers to its final volume in the reaction mixture. In all cases, the absorption spectrum of the reaction mixture at 'infinite time' corresponded within 2% to the 'mock infinity' prepared by using 2,4,6-trinitrophenylaniline obtained as product. The reactions were carried out under conditions of excess of nucleophile over substrate and, in all cases, excellent pseudo-first-order plots were obtained. The second-order rate coefficients k_A were obtained by dividing the pseudo-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 $\pm 2\%$.

Acknowledgements

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