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CATALYSIS OF INTERMEDIATE FORMATION IN NUCLEOPHILIC AROMATIC SUBSTITUTION

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Abstract—The rates of reaction of 2,4-dinitrochlorobenzene and n-butylamine in chloroform have been studied as a function of the initial concentration of the amine and as a function of varied concentrations of an added salt, benzyltriethylammonium nitrate. It is proposed that base catalysis in this reaction, which involves a good leaving group and does not attain a limiting rate at high concentrations of the catalyst, is due to the presence of a hydrogen bond from the amine nucleophile to a suitable acceptor in the transition state for intermediate formation.

THE observed cases of base catalysis in nucleophilic aromatic substitution have been divided by Bunnett[1] into two broad categories. Since all of the data can be accommodated empirically by Eq. (1).

$$k_2^* = k' + k''[\mathrm{B}], \tag{1}$$

in which k_2^* is the experimental second-order rate constant, k' is the rate constant for the uncatalyzed reaction, k'' is the rate constant for the catalyzed reaction and B is the base, the distinction was made in terms of the ratio, k''/k'. The first category was for systems showing strong catalysis, with k''/k' frequently greater than 50 l.mole^{-1}. The second category included those reactions which could still be fitted by Eq. (1) but for which the ratios, k''/k', were significantly lower than 50 l.mole^{-1} and more commonly 5 l.mole^{-1} or lower.

These two categories of base catalysis may also be distinguished in terms of the character of the leaving group. In reactions strongly accelerated by base the leaving group is generally a poor one, whereas reactions only mildly catalyzed by base usually involve a good leaving group. The character of a leaving group may be classified semi-quantitatively in terms of the pK_A of its conjugate acid in water, with the larger pK_A values corresponding to the poorer leaving groups. Since fluorides occupy a pivotal position in nucleophilic aromatic substitution and can show either strong or weak base catalysis depending on the nature of the nucleophile and the remaining substituents on the substrate, it is convenient, for the present purpose, to classify all leaving groups whose conjugate acids have pK_A's significantly greater than 3, the approximate pK_A of hydrofluoric acid, as poor leaving groups and all leaving groups whose conjugate acids have pK_A's appreciably lower than 3 as good leaving groups.

Two additional characteristics distinguish the strongly base catalyzed reactions. At a high concentration of the catalyst the experimental second-order rate constant, k_2^*, approaches a limiting value. Plots of k_2^* vs [B]o are curvilinear, rising rapidly at low [B]o and flattening out to a nearly constant value of k_2^* at high [B]o. Equally important, there is at least a qualitative relationship between the base strength of the catalyst and its effectiveness in accelerating the reaction. Thus hydroxide ion is a more effective catalyst than acetate ion, which is, in turn, a more effective catalyst than an amine such as aniline.

In contrast the mildly catalyzed reactions show no sign of approaching a limiting rate with increasing concentrations of the base. Plots of k_2^* vs $[B]o$ are linear and show no signs of curvature at high $[B]o$. Moreover, there is little or no relationship between the base strength of the catalyst and its ability to increase the reaction rate. In general any compound capable of serving as an acceptor in H-bonding will accelerate the rate, and amines, hydroxide ion, acetate ion and nitro compounds all appear to be almost equally effective catalysts.[2]

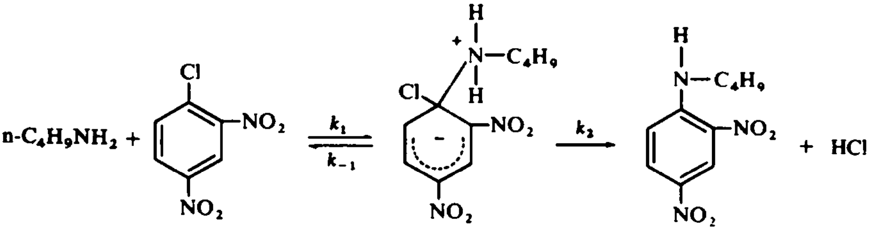
Typical examples of strongly catalyzed reactions are the base catalyzed reactions of secondary amines with *p*-nitrophenyl phosphate[3] and of ethers of 2,4-dinitrophenol with piperidine.[1, 4, 5] In these reactions a limiting rate is attained at high concentrations of the catalyst. This is interpreted as involving a change in the rate-determining step, which in turn requires that there be an intermediate in the reaction pathway. Such observations constitute the most convincing evidence for an addition intermediate in nucleophilic aromatic substitution, and it is generally agreed that the observed rate accelerations are due to catalysis of intermediate decomposition to product.

Mildly catalyzed reactions, with $k''/k' < 5$, are most commonly encountered in the reactions of halo-2,4-dinitrobenzenes with amines.[2] Modest but very definite rate accelerations are observed with added bases and with added H-bond acceptors, but a limiting rate is not attained at a high concentration of the added catalyst. The solvent effects on these reactions are large, with the rates, in general, paralleling the polarity of the solvents as indicated by their dielectric constants.[6] For the reaction of *p*-nitrofluorobenzene and piperidine at 50° the rate in DMSO ($\varepsilon = 48{\cdot}5$) is more than four orders of magnitude faster than the rate in dibutylether ($\varepsilon = 3{\cdot}06$). However, the rate constant in acetone ($\varepsilon = 20{\cdot}9$) is almost three times larger than that in methanol ($\varepsilon = 32{\cdot}6$), probably because acetone is a better acceptor for H-bonding than the alcohol. The two most effective solvents are the dipolar, aprotic solvents, DMF and DMSO, where base catalysis is not observed. These two solvents are the most polar ones studied and, at the same time, the most efficient acceptors for H-bond formation.

Both the above solvent effects and the observed relationships between catalytic efficiency and base strength of the catalyst in these moderately catalyzed reactions suggest that this catalysis may have its origin in the presence of a H-bond from the amino-hydrogen of the nucleophile to a suitable acceptor. If this is, indeed, the case, it is not surprising that the efficiency of a catalyst is relatively insensitive to its strength as a base. H-bonds are, in general, weak bonds, and in the gamut of H-bonds the N—H···O bonds and the N—H···N bonds are amongst the weakest, with bond energies as low as 1·3–2·0 kcal.mole^{-1}.[7, 8]

Also pertinent is the question of whether this H-bonding occurs in the transition state for intermediate formation or in the transition state for intermediate decomposition. For the reaction of 2,4-dinitrochlorobenzene and n-butylamine, with which we shall be concerned, the usual formulation is shown on opposite page.

For this reaction the intermediate, I, has carbon, at the seat of substitution bonded to nitrogen from the amine nucleophile and to the leaving group, chloride ion. Whether this intermediate reverts to starting materials or goes on to products will depend on



the relative ease of breaking the bond to the amine nitrogen or the bond to the leaving group. Since chloride ion is a good leaving group, it is most certain that the transformation of intermediate to product will be very much favored over its reversion to starting materials, i.e. $k_2 \gg k_{-1}$. If there is to be base catalysis in this system, it is more plausible to have it occur in the step in which the intermediate is formed rather than in the step in which the intermediate is converted to product.

The above possibility has been suggested by Kirby and Jencks[3] but has not received detailed consideration. The present work has reexamined and expanded previous results[9] on the reaction of 2,4-dinitrochlorobenzene and n-butylamine in chloroform with this hypothesis in mind. Chloroform was chosen as the solvent, since it is a poor acceptor for H-bonding although a suitable donor.

As previously noted,[9] although individual runs follow the bimolecular rate law, the observed bimolecular rate constants for a series of measurements at constant initial chloride concentration (~0·05 M) and varying initial amine concentrations are strongly dependent on the initial amine concentration, with the rate increasing regularly as the amine concentration increases. These results are shown in Table 1.

TABLE 1. RATES OF REACTION OF 2,4-DINITROCHLOROBENZENE AND n-BUTYLAMINE IN CHLOROFORM AT 24·8 ± 0·1°

2,4-Dinitrochlorobenzene, mole l^{-1}	n-Butylamine mole l^{-1}	$k_2 \times 10^4$ l $mole^{-1}$ sec^{-1}
0·05165	0·1038	2·47
0·05141	0·1866	3·25
0·05111	0·1985	3·07
0·05061	0·4961	4·37
0·05168	0·8018	6·22
0·05108	0·9997	7·45
0·05196	1·009	7·20
0·04908	1·201	8·78
0·04908	1·499	10·6

In these experiments the initial chloride concentration has been held roughly constant at 0·05 M and the amine concentrations have been varied from 0·1 M to 1·5 M. Over this range of initial amine concentrations the observed rate constants vary more than 4-fold. At the highest amine concentration, 1·499 M, more than 7% of the solution volume is made up of amine, and at any significantly higher amine concentrations it might seriously be questioned that one was still making measurements in chloroform as the medium.

Nevertheless, for all the data in Table 1 a plot of k_2 vs the initial amine concentration is linear, well within experimental error. This is shown in Fig. 1, where the method of least squares was used to determine the best straight line through the experimental points. These data can be fitted with Eqn (1), with k' equal to 1·87 × 10^{-4} l.mole^{-1} sec^{-1} and k'' equal to 5·63 × 10^4 l.^{2} mole^{-2} sec^{-1}.

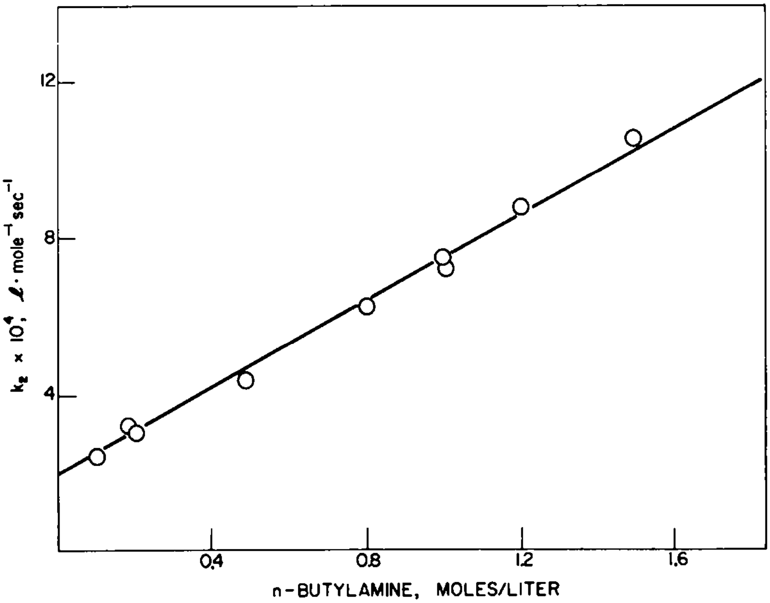


Fig. 1 Plot of k_2 vs. the initial amine concentrations for the reaction of 0·05 M. 2,4-dinitrochlorobenzene and n-butyamine in chloroform at 24·8 ± 0·1°.

The rates were also measured in the presence of added benzyltriethylammonium nitrate, and these results are collected in Table 2. One series of measurements was made at constant initial amine concentration, constant initial chloride and variable

Table 2. Effect of added benzyltriethylammonium nitrate on the rates of reaction of 2,4-dinitrochlorobenzene and n-butylamine in chloroform at 24·8 ± 0·1°

2,4-Dinitrochlorobenzene, mole l^{-1}	n-Butylamine mole l^{-1}	Benzyltriethylammonium nitrate, mole l^{-1}	$k_2 \times 10^4$ l. mole^{-1} sec^{-1}
0·05111	0·1985	0	3·07
0·05000	0·2009	0·0495	6·85
0·04972	0·1987	0·0804	9·67
0·05030	0·2003	0·9069	10·6
0·04965	0·1990	0·1608	14·5
0·05014	0·1970	0·2123	19·8
0·04961	0·2012	0·3395	27·8
0·04944	0·1996	0·0502	6·93
0·05158	0·3984	0·0502	8·35
0·04982	0·6018	0·0502	10·4
0·05018	0·8029	0·0502	11·8

initial salt concentrations. In the second series of measurements the initial chloride and salt concentrations were constant and the initial amine concentrations were varied.

Comparing Tables 1 and 2 it is apparent that the added salt accelerates the reaction rate far more than does an equivalent concentration of excess amine. The product in the presence of the salt is still N-n-butyl-2,4-dinitroaniline, which can be isolated in quantitative yield. In the absence of the salt a 15-fold increase in the initial amine concentration (from 0·1 M to 1·5 M) raises the measured rate constant by a factor of four, but at a salt concentration of 0·34 M the measured second-order rate constant is nine times larger than with the salt absent.

The data in Table 2 for the experiments at variable initial salt concentrations might be looked upon as a neutral salt effect, and, in fact, a plot of log k_2 vs the square root of the ionic strength, $\mu^{\frac{1}{2}}$, is linear. However, the reactants, in this case, are neutral molecules, not ions, in the low dielectric constant solvent, chloroform, ionic species would be largely associated, and the Bronsted–Bjerrum theory of salt effects,[10, 11] which is valid only for dilute solution reactions between ions at small μ (below 0·01 M for 1 : 1 electrolytes), does not properly apply.

Since this is a reaction in which neutral molecules react to give a dipolar or ionic transition state, some rate acceleration from the added neutral salt is to be expected,[12] since the added salt will increase the polarity or effective dielectric constant of the medium. Some of the rate increases in Table 2 are attributable to this cause, but it is doubtful that they are all thus explained. The data in Table 2 at constant initial chloride and initial salt concentrations and variable initial amine concentrations

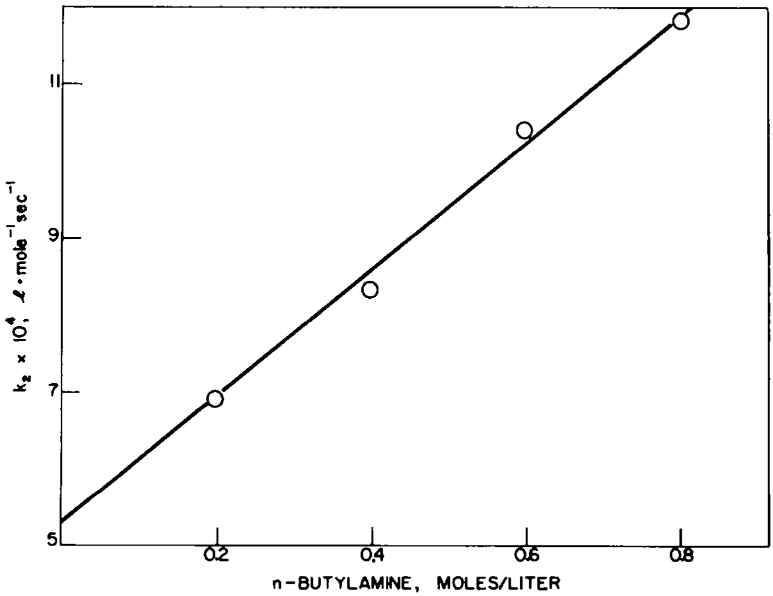


FIG. 2 Plot of k_2 vs. the initial amine concentrations for the reaction of 0·05 M. 2,4-dinitrochlorobenzene and n-butylamine in the presence of 0·05 M. benzyltriethylammonium nitrate in chloroform at 24·8 ± 0·1°

afford some insight into this aspect of the problem. By plotting k_2 vs the initial amine concentrations, as shown in Fig. 2, one can obtain k' and k'', with the new values corresponding to a salt concentration or μ of 0·05 M. The values obtained are $5{\cdot}30 \times 10^{-4}$ l.mole^{-1} sec^{-1} for k' and $8{\cdot}27 \times 10^{-4}$ l.^{2}mole^{-2} sec^{-1} for k''. In the absence of the salt k' was $1{\cdot}87 \times 10^{-4}$ l.mole^{-1} sec^{-1} and k'' was $5{\cdot}63 \times 10^{-4}$ l.^{2}mole^{-2} sec^{-1}. Thus the addition of 0·05 M benzyltriethylammonium nitrate increases k'' by 47% and k' by more than 180%.

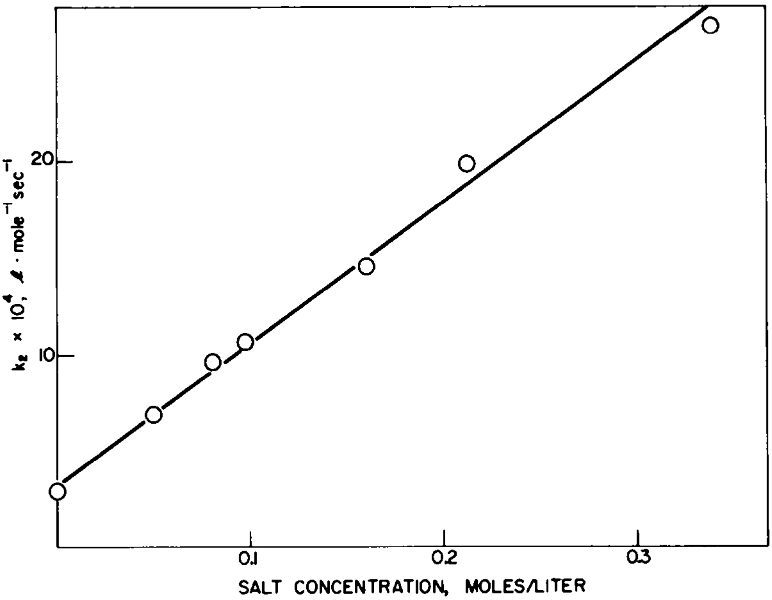


FIG. 3 Plot of k_2 vs. the concentrations of benzyltriethylammonium nitrate for the reaction of 0·05 M. 2,4-dinitrochlorobenzene and 0·2 M. n-butylamine in chloroform at 24·8 ± 0·1°.

One possible explanation for the above results is that the transition state for the uncatalyzed reaction is either more ionic or has its charges more highly separated than does the transition state for the catalyzed reaction. A consideration of possible transition state structures makes this explanation improbable, since the transition state for the catalyzed reaction would, in fact, be expected to show the greater charge separation, and this would be equally the case for both the transition states for intermediate formation and the transition states for conversion of intermediate to product.

An alternate possibility is that one of the component ions of the salt is actually involved in the rate-determining transition state and can catalyze the reaction as does the second molecule of amine. This possibility is supported by the fact that at constant initial concentrations of the substrate and the amine and variable salt concentrations, the experimental data also give a linear plot of k_2 vs the initial concentration of the salt, as shown in Fig. 3.* This hypothesis merits more detailed consideration.

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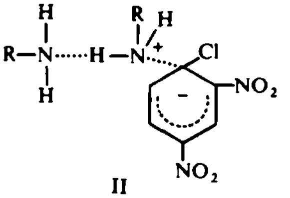
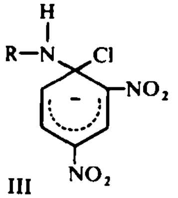
* A distinction between a fit to log k_2 vs. $\mu^{\frac{1}{2}}$ and k_2 vs. the salt concentration might be made with a bis-quaternary ammonium dinitrate. Unfortunately, the many such salts which were synthesized for this purpose all proved to be almost completely insoluble in chloroform.

For the reaction of 2,4-dinitrochlorobenzene with an amine it is highly probable, as has been noted, that the rate-determining step is intermediate formation. One possible mode of such base catalysis in this system would involve transfer of the proton in the step in which the intermediate is formed. One can conceive of a transition state such as II collapsing to the intermediate, III, and $R_3NH_3^+$.†

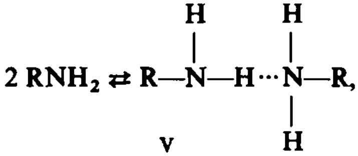


II



III

This need not necessarily involve a termolecular collision, since it may be preceded by the equilibrium,

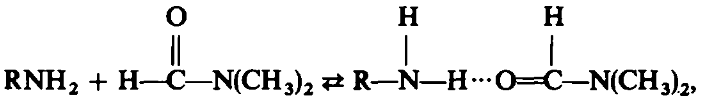


$$2\,RNH_2 \rightleftarrows R-\overset{\overset{\displaystyle H}{|}}{N}-H\cdots\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle H}{|}}{N}}-R,$$

V

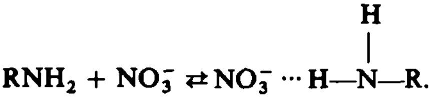
to form the H-bonded complex, V, which would be a better nucleophile than the amine itself.

The second amine molecule is not unique in being able to perform this function. A solvent molecule, e.g. DMF, would be effective,



$$RNH_2 + H-\overset{\overset{\displaystyle O}{\|}}{C}-N(CH_3)_2 \rightleftarrows R-\overset{\overset{\displaystyle H}{|}}{N}-H\cdots O{=}\overset{\overset{\displaystyle H}{|}}{C}-N(CH_3)_2,$$

as would an anion such as nitrate ion,



$$RNH_2 + NO_3^- \rightleftarrows NO_3^- \cdots H-\overset{\overset{\displaystyle H}{|}}{N}-R.$$

In fact any species capable of serving as an acceptor for hydrogen bonding could exert a catalytic effect. The intermediate formed in the catalyzed reaction would be the conjugate base of the intermediate formed in the uncatalyzed reaction. Since its

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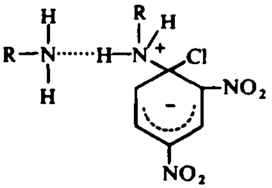
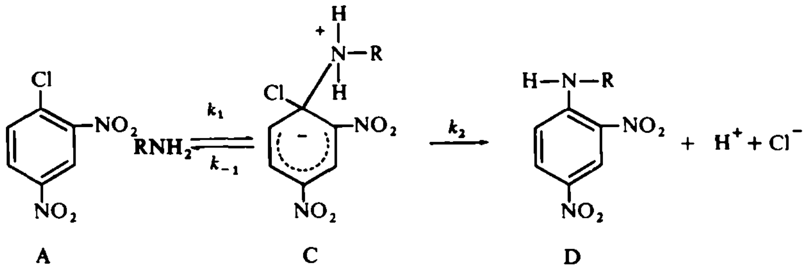
† As noted by a referee, to whom we are indebted, it is not essential that the proton be transferred in this step. An alternate catalysis mode is one in which II gives IV. This interpretation is equally consistent with the experimental data and does not significantly alter the remaining discussion.

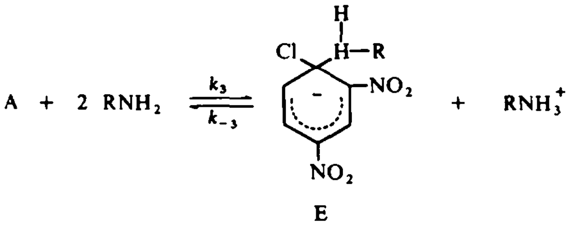


IV

proton has already been transferred, its conversion to product is no longer subject to catalysis by a base. Electrophilic catalysis to assist removal of the leaving group is possible but probably unnecessary and, in any event, would not manifest itself in the measured rates, if intermediate formation is rate-determining.

The proposed mechanism may be formulated as shown below. In this scheme B represents any species capable of serving as an acceptor in H-bonding and can be an amine molecule, an anion or even a solvent molecule.





$$A + RNH_2 + B \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} E + BH^+$$

$$E \xrightarrow{k_5} D + Cl^-$$

The desired rate is given by (2),

$$\frac{d[D]}{dt} = k_2[C] + k_5[E] \tag{2}$$

Applying the steady state approximation to both [C] and [E] one obtains (3) for the steady state concentration of C and (4) for the steady state concentration of E.

$$[C] = \frac{k_1[A][RNH_2]}{k_2 + k_{-1}} \tag{3}$$

$$[E] = \frac{k_3[A][RNH_2]^2 + k_4[A][RNH_2][B]}{k_5 + k_{-3}[RNH_3^+] + k_{-4}[BH^+]} \tag{4}$$

The general rate equation is given by (5)

$$d[D] = \frac{k_1k_2[A][RNH_2]}{k_2 + k_{-1}} + k_5\left(\frac{k_3[A][RNH_2]^2 + k_4[A][RNH_2][B]}{k_5 + k_{-3}[RNH_3^+] + k_{-4}[BH^+]}\right) \tag{5}$$

This mechanism is being applied only to reactions involving good leaving groups, and in these reactions the intermediates, C and E, collapse to products much more rapidly than they return to starting materials. These are, therefore, reactions in which conditions (6) and (7) are valid,

$$k_2 \gg k_{-1} \tag{6}$$

$$k_5 \gg k_{-3}[\mathrm{RNH_3^+}] + k_{-4}[\mathrm{BH^+}] \tag{7}$$

and Eqn (5) simplifies to (8),

$$\frac{\mathrm{d[D]}}{\mathrm{d}t} = k_1[\mathrm{A}][\mathrm{RNH_2}] + k_3[\mathrm{A}][\mathrm{RNH_2}]^2 + k_4[\mathrm{A}][\mathrm{RNH_2}][\mathrm{B}] \tag{8}$$

Eqn (8) can be expressed in more general form as (9),

$$\frac{\mathrm{d[D]}}{\mathrm{d}t} = [\mathrm{A}][\mathrm{RNH_2}](k_1 + \textstyle\sum_i k_i[\mathrm{B}]_i), \tag{9}$$

where B is as previously defined. The experimental second-order rate constant, k_2^*, will now be given by (10),

$$k_2^* = \frac{1}{[\mathrm{A}][\mathrm{RNH_2}]} \cdot \frac{\mathrm{d[D]}}{\mathrm{d}t} = k_1 + k_3[\mathrm{RNH_2}] + k_4[\mathrm{B}], \tag{10}$$

and again (10) can be expressed more generally as (11).

$$k_2^* = k_1 + \textstyle\sum_i k_i[\mathrm{B}]_i \tag{11}$$

Since in the present experiments the added salt serves a dual function, increasing all of the rates by augmenting the polarity of the medium and providing nitrate ion which serves as a catalyst, it is not possible to isolate all of the individual rate constants. Nevertheless, it is clear that the proposed formulation can accommodate all of the experimental data. This does not constitute proof of its correctness, but it does speak for the plausibility and even probability of this proposal.

In addition this hypothesis does no violence to and very conveniently accommodates all other experimental findings on these reactions. Bunnett's "element effect"[13] follows logically as the result of selecting all the reactions or carrying them all out under conditions such that intermediate formation is the rate-determining step. The "ortho effect",[14–17] in terms of the present hypothesis, results from the formation of a H-bond in the transition state for intermediate formation, with the *ortho* substituent acting as the acceptor and amine nucleophile serving as the donor. Finally, the small deuterium isotope effects ($k^{\mathrm{H}}/k^{\mathrm{D}}$ very close to one) observed in these reactions are in accord with Swain's "solvation rule",[18] which states that a proton being transferred from one oxygen to another or from nitrogen to oxygen or from nitrogen to nitrogen in an organic reaction, in which there are bond changes on carbon in the rate-determining step, should lie in an entirely stable potential at the transition state and not form reacting bonds nor give rise to primary hydrogen isotope effects.

EXPERIMENTAL

All of the experiment details—reagent purification, syntheses, technique for measuring the rates etc—have been described in full previously.[9]

The procedure for isolating the reaction product in the presence of added benzyltriethylammonium nitrate was the following. A solution of the salt (4·8 g), n-butylamine (1·45 g) and 2,4-dinitrochlorobenzene (1·0 g, 0·00494 mole) in $CHCl_3$ (100 ml) was left standing at room temp 4 days. The soln was taken up in benzene (400 ml) and then extracted with 3 200 ml portions water. The benzene soln was dried over anhydr $MgSO_4$. Removal of the solvents gave a quantitive yield of N-n-butyl-2,4-dinitroaniline. Crystallization from EtOH gave 0·98 g (83%) of product; m.p. 89–91°.

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