Rationalization of the effects of hydrogen bond donor solvent and nucleofugicity of fluoride ion on nucleophilic aromatic substitution reactions in non-polar aprotic solvent: reaction of 2,4-dinitrofluorobenzene with cyclohexylamine in toluene and toluene-alkanol mixtures

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Abstract
The kinetics of the reaction of 2,4-dinitrofluorobenzene with cyclohexylamine were studied at different concentrations in toluene and toluene-alkanol mixtures. The reaction was not base-catalysed in toluene. Addition of small amounts of hydrogen-bond donor solvent, alkanol (ranging from methanol to hexanol) to the toluene medium of the reactions produced a different effect in comparison to uncatalysed reactions — slight increase in rate of reaction. The results are rationalized in terms of the effect of amine-solvent interaction on the nucleophilicity of the amine in addition to some other factors operating through cyclic transition states leading to products. It is also attributed to the peculiar nature of fluoride ion as a leaving group.

Keywords: Aprotic solvents, Nucleophilic aromatic substitution, Nucleofugicity, Base catalysis, Toluene-alkanol mixtures, Hydrogen bond donor solvent.

Introduction
The general mechanism for aromatic bimolecular nucleophilic substitution reactions in all solvents when either primary or secondary amines are the nucleophiles [1] is given in Scheme 1 (where X is the nucleofugal group and Y the electron withdrawing group. Application of the steady state hypothesis to Scheme 1 gives Eq. 1,

$$k_A = \frac{k_1(k_3 + k_6[B])}{k_1 + k_2 + k_6[B]}$$

(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 [2, 3] or non-polar aprotic [4, 5, 6] solvents or whether the reaction is catalyzed by one or two amine molecules, or an entirely different catalytic entity.

Scheme 1. General mechanism for bimolecular $S_NAr$

The leaving group capability (nucleofugicity) has been recognised to increase with decreasing pKa of the conjugate acid of the leaving group [7, 8]. The correlations are quite good when leaving groups with the same heteroatom involved in bond breaking are compared.

Fluoride ion is always a much poorer leaving group than chloride ion and consequently, these reactions are associated with a smaller $k_2/k_1$ ratio depending on the solvent medium. The reaction of 2,4-dinitrofluorobenzene (1) with cyclohexylamine (CHA) in toluene and toluene-alkanol mixtures have been studied in order to have a more general view of the effects of hydrogen bond donor solvent on $S_NAr$ reactions in non-polar aprotic solvent.

2,4-dinitrofluorobenzene 1

Materials and Methods
Analar grade of alkanols viz; methanol, ethanol, propanol, butanol, pentanol, hexanol; cyclohexylamine and 2,4-dinitrofluorobenzene were purchased from Sigma-Aldrich, Germany and used without further purification. Toluene was kept over anhydrous calcium chloride for 48 h and then heated under reflux with sodium wire for 1 h and then distilled (bp 112 °C).
The product of the reaction studied was prepared by standard method. N-(2,4-Dinitrophenyl)cyclohexylamine, mp 157 °C, λ\text{max} (C₆H₅CH₃) 355nm

**Kinetic procedure.** The rates of formation of the product of the reaction were determined spectrophotometrically. The reactions were carried out at 30 °C. For reactions in mixed solvents, the alkanol content (v/v) refers to its final volume in the reaction mixture. Optical densities were recorded at the absorption maximum wavelength (λ\text{max}) of the product. 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-Dinitrophenyl)cyclohexylamine obtained as a product of the reaction. The reactions were carried out with the concentration of amine in equimolar quantity of the parent concentration and pseudo 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%.

**Results and Discussion**

The results were studied spectrophotometrically at 30 °C with the concentration of amine in equimolar quantity, and pseudo-first order kinetics were observed. 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 toluene-alkanol mixtures, gave the expected products of substitution of fluoro in >95% yield.

The kinetic data for the reaction in pure solvent at 30 °C are in Table 1.

| 10^3[CHA]/moldm⁻³ | 10⁻¹k_A(dm³/mol⁻¹s⁻¹) |
|-------------------|------------------------|
| 0.50              | 0.53                   |
| 0.75              | 0.54                   |
| 1.00              | 0.61                   |
| 1.50              | 0.63                   |
| 2.00              | 0.66                   |
| 3.00              | 0.73                   |
| 4.00              | 0.91                   |

The reactions of 1 with CHA in pure toluene gave the first-order rate constant k_{obs} with values which increased linearly with the amine concentration. Hence, values of the second-order rate constant k_A show only slight increase with increase in amine concentration as shown in Table 1 and this does not reflect base catalysis. The plot of k_A against amine concentration as shown in Figure 1 gave k_2/k_1 value of 21.14. The implication of this is that the reaction is not base catalyzed in line with Bunnett’s deduction that nucleophilic aromatic substitution with catalytic effectiveness (k_3/k_2) of less than 50 is not base catalyzed [9].

When the condition k_2 + k_3[B]≫ k_1 holds, equation (1) reduces to k_A = k_1 such that the formation of the intermediate is rate limiting. The fluoride ion is not particularly a poor leaving group in protic solvent but becomes so in non-polar aprotic solvent due to the high demand for solvation of the ion which cannot be provided by the solvent [10].

The non-observance of base-catalysis for the reaction of 1 with CHA can be partly attributed to the basicity of the amine which is a primary amine. The variation in the amine basicity affects the ratio k_2/k_1 through changes in the k_1. The smaller k_2/k_1 ratios for secondary as compared to primary amines have been attributed to steric compressions in the intermediate complex. The reversion of the intermediate complex to reactants leads to a charge neutralization, thus k_1 is expected to increase strongly in non-polar solvents [11], reducing the k_2/k_1 ratio unless a compensating effect of larger magnitude operates on k_2.
Figure 1: The plot of $k_A$ against amine concentration for the reaction of 1 with cyclohexylamine

The uncatalysed reaction of 1 with CHA in toluene can be interpreted in terms of cyclic transition state mechanism by Banjoko et al. [5, 12, 13] in which the intermediate complex proceeds to give product via a four-membered ring as shown in Scheme 2.

Scheme 2. The uncatalysed reaction of 1 with CHA showing the intermediate complex

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 3 [1] applies. Application of the steady-state hypothesis to Scheme 3, working in terms of the stoichiometric base concentration, gives the observed overall second-order rate constant, $k_A$, as shown in Eq. 2.

$$k_A = \frac{k_2(k_1 + k'_1K[MeOH])/ (1+K[MeOH])}{k_2 + k'_1[MeOH] + k_2}$$

(2)

Since the reaction is not base-catalysed, the first step is rate determining and inequality Eq. 3 holds.

$$k_2 \gg k_1 + k'_1[MeOH]$$

(3)

$$k_A = k_1 + k'_1K[MeOH]/ (1+ K[MeOH])$$

(4)

The reaction of 1 with CHA in toluene is not base-catalysed and so conforms with Scheme 3 and Eq. 4 derived from it. When no methanol is added to the reaction medium, Eq. 4 reduces to...
\[ k_A = k_1 \quad \text{(5)} \]

\[
\begin{align*}
S + B & \rightleftharpoons \text{HOMe} \quad k_1' \quad k' -1 \\
S + B + \text{MeOH} & \rightarrow \text{Products} \quad k_2 \\
S + B & \rightarrow \text{MeOH} \quad k_1 \\ & \rightarrow \text{MeOH} \quad k_1 \\
\end{align*}
\]

Scheme 3. The uncatalysed reaction of 1 with CHA

**Solvent effect**

The addition of small amounts of alkanol to toluene medium for the reaction of 1 with CHA produced slight increase in the \( k_A \) values as shown in Table 2.

Table 2. Kinetic data for the reaction of 1 with CHA in toluene-alkanol mixtures at 30 °C. [substrate]= 5 × 10^-5 M

| 10^-5(CHAg)/moldm^-3 | % Methanol | Ethanol | Propanol | Butanol | Pentanol | Hexanol |
|-----------------------|-----------|---------|----------|---------|----------|---------|
| 0.50                  | 0.0       | 0.053   | 0.053    | 0.053   | 0.053    | 0.053   |
| 0.4                   | 0.063     | 0.081   | 0.090    | 0.075   | 0.054    | 0.064   |
| 0.6                   | 0.054     | 0.089   | 0.098    | 0.089   | 0.059    | 0.069   |
| 1.0                   | 0.055     | 0.071   | 0.067    | 0.093   | 0.062    | 0.076   |
| 2.0                   | 0.056     | 0.094   | 0.071    | 0.088   | 0.065    | 0.071   |
| 5.0                   | 0.049     | 0.071   | 0.060    | 0.104   | 0.058    | 0.091   |
| 4.00                  | 0.0       | 0.091   | 0.091    | 0.091   | 0.091    | 0.091   |
| 0.4                   | 0.0805    | 0.083   | 0.088    | 0.080   | 0.063    | 0.079   |
| 0.6                   | 0.082     | 0.105   | 0.093    | 0.085   | 0.070    | 0.105   |
| 1.0                   | 0.0835    | 0.110   | 0.092    | 0.105   | 0.0676   | 0.092   |
| 2.0                   | 0.072     | 0.113   | 0.085    | 0.112   | 0.068    | 0.093   |
| 5.0                   | 0.058     | 0.116   | 0.084    | 0.118   | 0.061    | 0.081   |

The observed effects of alkanol addition on the reaction of 1 with CHA in toluene is contrary to some of the reactions of CHA with other substrates in non-polar aprotic solvents. [14] Nudelmann et al. [15] and Banjoko [16] observed rate diminution in the reactions of CHA with 2,6-dinitroanisole and phenyl-2,4,6-trinitrophenyl ether respectively, both in toluene in the presence of added methanol, though the reaction of the former was base-catalysed while that of the latter was not.

Banjoko et al. [13] had earlier pointed out that the effect of alkanol addition to non-polar aprotic solvent in S_NAr reactions could be due to the interaction of alkanol with (1) the non-polar aprotic solvent: Addition of alkanol 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 (2) Intermediates on the reaction pathway: Interaction of added methanol with any zwitterionic intermediate formed as in Scheme 6 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 (3) The formation of aggregates via hydrogen bonding between amines and hydrogen-bond donor solvent, methanol has been widely studied [17, 18]. The methanol molecule acts as a proton donor to the amine resulting in the formation of an aggregate of reduced nucleophilicity as shown in Scheme 4.
ROH + RNH₂ ⇌ ROH–NH₂ (4)

The reaction of 1 with CHA in this study is not base-catalysed, hence point (2) may not be applicable. The interplay of points (2) and (3) may occur in a base-catalysed reaction and the overall effect will depend on the predominant factor.

Electrophilic catalysis of fluoride ion departure through hydrogen bonding has been demonstrated by Pietra and Fava [19] in the reaction of 1 with piperidine in benzene where they observed base catalysis by methanol but no catalysis by added triethylamine. It is expected that the reaction rate in the present study be retarded by added alkanol as the reaction is not base-catalysed. The slight increase in rate in the presence of added alkanol is rather unexpected.

**Effect of temperature**

As the above observation is an unusual one, it became worthwhile to investigate the effect of temperature on the reaction. Temperature probe ranging from 25 °C to 50 °C was therefore carried out. The rate of the reaction increased appreciably with increase in temperature as shown in Table 3.

| Temperature/°C | kₐ/dm³mol⁻¹s⁻¹ |
|----------------|-----------------|
| 25             | 0.042           |
| 30             | 0.075           |
| 40             | 0.118           |
| 50             | 0.158           |

The observed positive temperature effect is like that of Banjoko et al. [1] in the uncatalyzed reaction of phenyl-2,4,6-trinitrophenyl ether with CHA in benzene-methanol mixtures, though in this reaction the addition of methanol produced remarkable decrease in rate.

Hydrogen bonds are known to be weakened with an increase in temperature, hence an increase in rate with an increase in temperature is expected on addition of ethanol for reactions that are not base catalysed.

The slight increase in the rate of the reaction of 1 with CHA on addition of alkanol to toluene can be attributed to the peculiar nature of fluoride ion as a leaving group. It is established that fluoride ion is fairly good leaving in protic solvents which provide the high solvation demand of the ion and this is lacking in non-polar aprotic solvents. The expected diminution in the rate of the reaction on addition of alkanols to toluene due to aggregate formation (Scheme 4) may have been compensated for by the enhanced solvation of fluoride ion in toluene-alkanol mixture resulting in overall slight increase in rate.

**Conclusion**

Addition of hydrogen-bond donor (hbd) solvent to SₐAr 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.

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