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Rate Controlling Role of the Aprotic Solvents in the Aromatic Nucleophilic Substitution Reaction and the Possible Intervention of a Substrate-Nucleophile Complex as an Intermediate of the Reaction#

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S_NAr reactions of 1,2,3,5-tetranitrobenzene or 2,4,6-trinitrofluorobenzene with aromatic amines were studied in aprotic solvents by means of stopped-flow kinetic measurements. Base catalysis and negative activation enthalpy were observed in nonpolar solvents, which were ascribed to an intermediate encounter complex.

The aromatic nucleophilic substitution reaction is one of the most widely studied of the organic unit reactions.[1] However, not many studies were undertaken of the rate-controlling role of the reaction medium and of the role of the solute-solute interactions that may affect the rate of the reaction.

In this communication, the authors report reactions of 1,2,3,5-tetranitrobenzene ($PicNO_2$) or 2,4,6-trinitrofluorobenzene (PicF) with 2,4-dimethoxyaniline (DMA) or N,N-dimethyl-p-phenylenediamine in an aprotic solvent as studied by means of stopped-flow kinetic measurements.[2] The course of the substitution reaction was followed by monitoring the absorption of the final product, substituted diphenylamines, at 380-400 nm under pseudo-first-order conditions.

As is shown in Table 1, reactions were fairly rapid. In solvent acetonitrile, the reaction was first order with respect to the aromatic amine. The addition of aliphatic tertiary amines gave no effect upon the rate of the substitution reaction. Aliphatic primary and secondary amines produced abortive 1,3-Meisenheimer complex which was vindicated by the development of a visible absorption at 480-530 nm. These findings are in good agreement with the prevailing view of the S_NAr reaction with the rate-limiting addition of the nucleophile to the substrate.

However, a "base catalysis" was observed in solvent cyclohexane and in other nonpolar solvents. As is shown in Fig. 1, the order of the reaction of $PicNO_2$ with DMA was higher than unity and close to second-order at the lower concentration of this aromatic amine. The substitution reaction was also catalyzed by aliphatic amines, with essentially no sign of the accumulation of the 1,3-Meisenheimer complex at the catalyst amine concentration utilized.

This paper is dedicated to the late Professor Ryozo Goto, Kyoto University.

The aromatic amine was almost as effective as aliphatic amines in catalyzing this S_NAr reaction, although it is much weaker a base than the aliphatic amines.

Table 1. Reaction of PicX and Y,Z-$C_6H_3NH_2$ at 298 K

X	Y,Z	Solvent	k_2 / $M^{-1}s^{-1}$	$\Delta H^{\ddagger}$ / kJ mol^{-1}
Cl	2,4-$(OCH_3)_2$	cyclohexane	14.6	
F	2,4-$(OCH_3)_2$	cyclohexane	27000	-29.3
NO_2	2,4-$(OCH_3)_2$	acetonitrile	15000	2.1
NO_2	2,4-$(OCH_3)_2$	cyclohexane	434000[a]	-38.1
NO_2	2-H,4-$N(CH_3)_2$	cyclohexane	1454000[b]	
NO_2	2,4-$(OCH_3)_2$	benzene	2000	
NO_2	2,4-$(OCH_3)_2$	mesitylene	593	

a) $k_B\ k_2$[Catalyst], k_B = 1.736 x 10^8 , [DABCO] = 2.5 x 10^{-3} M
b) $k_B\ k_2$[Catalyst], k_B = 5.815 x 10^8 , [Piperidine] = 2.5 x 10^{-3} M , 293 K
Note: k_B(Tributylamine) = 2.06 x 10^7 , k_B(Dimethoxyaniline) = 5.50 x 10^7
k_B(Propylamine) = 4.37 x 10^8 , k_B(DBU) = 1.26 x 10^6

The second-order dependency of the rate on the concentration of the aromatic amine decreased to a fractional dependency at the higher concentration of the amine (Fig. 2). Such an operation of a saturation kinetics implies the intervention of a substrate-nucleophile complex in this S_NAr reaction.

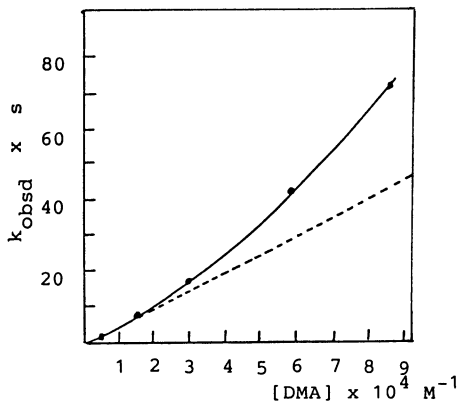


Fig. 1. Dependency of observed pseudo-first-order rate constant on the concentration of DMA in cyclohexane at 293 K.

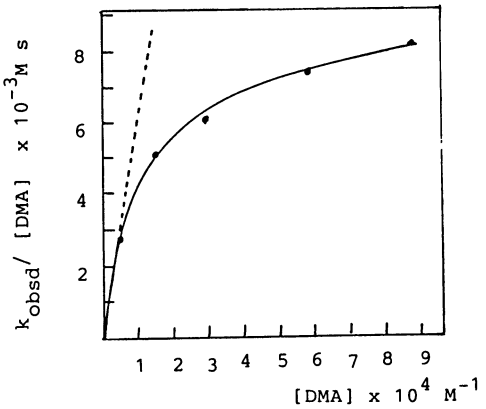


Fig. 2. Dependency of k_{obsd}/ DMA on the concentration of DMA in cyclohexane at 293 K.

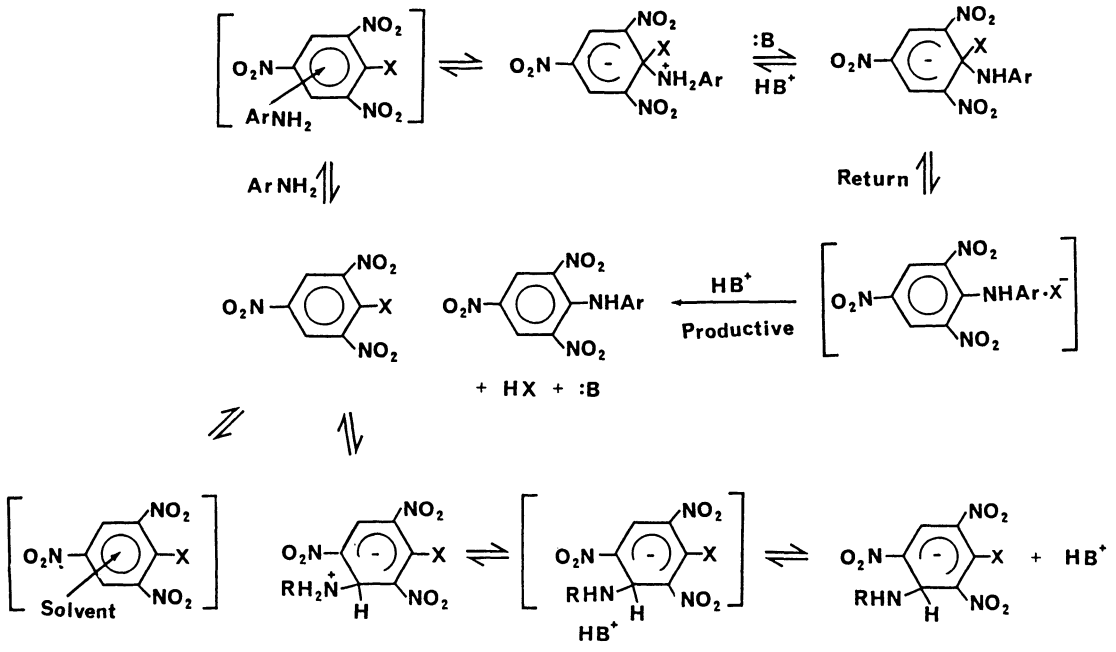
There found essentially no deuterium kinetic isotope effect when 2,4-dimethoxyaniline-N,N-d_2 was used in the presence of DABCO. This shows that none of the bond cleavage nor the bond formation involving hydrogen is rate-limiting in this multi-step reaction although the operation of a base-catalysis shows the proton-transfer process constitutes an essential part of the present instances.

The absence of a deuterium isotope effect can be rationalized in the framework of the "specific base-general acid (SB-GA) mechanism".[1b] In this SB-GA mechanism, a conjugate acid of the base catalyst is produced in a rapid equilibrium deprotonation and a slow expulsion of the leaving group is catalyzed by this conjugate acid. However, such a general acid catalysis implies the

contribution of the formation of proton-to-leaving group bond in this rate-limiting rate process and some sort of deuterium isotope effect can be expected.

One plausible explanation is that the expulsion of the leaving group itself is rate-limiting and that the direct product of this process is an ion-molecule pair that partitions into the precursor (anionic) Meisenheimer complex and the final products. General acid contributes to trap this anionic leaving group to alter the return ratio as a solvent affects the F factor of the internal return in the Winstein scheme of solvolysis.[3] In cyclohexane, the overall rate of the aromatic nucleophilic substitution reaction can easily exceed 2000 s^{-1}, which is not exceptionally fast for a unimolecular process in solution. Such a reaction can be easily masked by a rapid reversion of the rate-limiting process among the molecule-anion pair, an addition of a strongly nucleophilic anion to activated phenyl ring, provided an appropriate general acid is not available to trap the nucleophile.

Another characteristics of the S_NAr reactions observed in the present communication is the operation of a very low activation enthalpy. The apparent activation enthalpy of the reaction of $PicNO_2$ and 2,4-dimethoxyaniline was found to be 2.1 kJ mol^{-1} in acetonitrile and was -38.1 kJ mol^{-1} in cyclohexane. The reaction of PicF with 2,4-dimethoxyaniline in cyclohexane also showed a negative activation enthalpy of about -30 kJ mol^{-1}.



The observation of the negative activation enthalpy reinforced by the observation of a saturation kinetics serves as a sound evidence that a very stable chemical entity, which is formed from a substrate and a nucleophile, is intervening as a true intermediate lying on the reaction coordinate.

As there is no sign of the accumulation of an 1,1-Meisenheimer complex in the course of the reaction, one is left with the suggestion that a species which is responsible to the negative activation enthalpy is an encounter complex quite possibly of charge-transfer type between the substrate and the nucleophile.

Solvent molecules can compete with an aromatic amine to form a CT-complex with polynitro substrate. Thus as are shown in the Table 1, the reaction was very slow in benzene and even slower in mesitylene. In fact, mesitylene solution of $PicNO_2$ developed a yellow coloration that shows the formation of a CT-complex. In acetonitrile, the absence of a base-catalysis shows a rapid expulsion of a leaving anion from the anionic 1,1-Meisenheimer complex which is in an effective rapid equilibrium with the zwitterionic 1,1-Meisenheimer complex. Judging from the very fast addition of the same nucleophile to the same substrate in cyclohexane (addition stage cannot become rate-determining even in a reaction with the overall pseudo-first-order rate constant of over 2000 s^{-1}), the intrinsic rate of the addition in acetonitrile should also be very high. As the apparent activation enthalpy implies, the exothermic solvation (CT complex formation between the substrate and acetonitrile) can reduce the effective concentration of the substrate and can account for an about $1/10^7$ of the rate retardation in acetonitrile compared with the reaction in cyclohexane, where no such competing abortive equilibrium is operative.

An effective base catalysis by aliphatic primary and secondary amines in a nonpolar solvent needs comments. In a dipolar aprotic solvent such as acetonitrile, these strong nucleophiles rapidly produce 1,3-Meisehneimer complex in an abortive equilibrium involving the substrate. However, in cyclohexane and in other nonpolar solvents, this subsidiary equilibrium is essentially absent. In these solvents, zwitterionic Meisenheimer complex cannot be stabilized in an equilibrium with the available ordinary base simply because a resultant anionic Meisenheimer complex would exist essentially as an ion-pair which has an effective protonating agent in a close proximity to reproduce a zwitterionic Meisenheimer complex. This zwitterionic Meisenheimer complex has a built-in good leaving group, amine, in a form of the ammonio group, and thus brings about a very unfavorable equilibrium in nonpolar solvents.

In acetonitrile, chloride and other nucleophilic anion undergo very effective hetero-conjugation resulting in the stabilization of an anionic 1,3-Meisenheimer complex. These reactions with an aliphatic amine as a nucleophile are under study and will be reported elsewhere.

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Referenses

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