

Kinetics of the Reaction of 1-Halo-2,4-dinitrobenzenes with *N*-(3-Dimethylaminopropyl)-*p*-anisidine and *N*-Isohexyl-*p*-anisidine in Benzene

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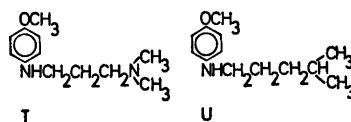
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The reactions of *N*-(3-dimethylaminopropyl)-*p*-anisidine and *N*-isohexyl-*p*-anisidine with 1-*X*-2,4-dinitrobenzene, *X* = F, Cl and Br, have been studied in benzene with and without 1,4-diazabicyclo[2.2.2]octane as a catalyst. With the first of these amines, the fluorine compound was found to react much faster than the two other halogeno compounds. With the second amine, however, fluoride ion as the leaving group gives the slowest reaction, indicating a rate-limiting second step. Intramolecular base catalysis is supposed to be operating with the diamine as nucleophile.

In an earlier paper,¹ the reaction of 2,6-dinitroanisole with a series of α,ω -diaminoalkanes, $H_2N(CH_2)_nNH_2$, $n = 2 - 5$, was kinetically studied. From the results, no definite conclusions could be drawn whether intramolecular base catalysis was operating. In dry dioxane, the reaction is entirely second-order with respect to diamine. In aqueous dioxane or methanol, the rate can be expressed as a sum of a first- and a second-order term with respect to diamine. The first-order term would indicate intramolecular base catalysis if the second step of the reaction were rate-limiting and the solvent did not act as a base. Only small rate changes were found upon varying the chain length of the diamines. It was supposed that proton transfer *via* solvent molecules takes place in the collapse of the intermediate to products.

A different system has now been studied, namely the reaction of 1-halo-2,4-dinitrobenzenes in which the halogen is fluorine, chlorine or bromine, with the amines *N*-(3-dimethyl-

aminopropyl)-*p*-anisidine and *N*-isohexyl-*p*-anisidine, designated for brevity, T and U. The reactions were studied in benzene at 25 °C, with and without 1,4-diazabicyclo[2.2.2]octane (DABCO) as a catalyst.



The choice of substituted *p*-anisidines is based on work by Bernasconi and Zollinger,² who demonstrated base catalysis in the reaction of 1-halo-2,4-dinitrobenzenes with *p*-anisidine in benzene. The diamine T is a substituted *p*-anisidine, carrying an aliphatic chain with a terminal tertiary amino group. The terminal amino group might serve as a built-in catalyst. The compound U was designed to be sterically closely similar to T.

EXPERIMENTAL

General. For spectral identification, a Varian Model A 60 and a Bruker WH 270 NMR spectrometer were used. The UV spectra were recorded on a Cary Model 15 spectrophotometer. A Perkin-Elmer Model 900 instrument was used for gas chromatography. The purity of the chemicals was also checked by TLC. Melting points were determined on a Kofler Hot Stage microscope.

Synthesis. *N*-(3-Dimethylaminopropyl)-*p*-anisidine was prepared from 3-dimethylaminopropyl chloride hydrochloride, *p*-anisidine and anhydrous sodium carbonate in toluene, fol-

lowing the directions by Wright and co-workers.³ The oily residue was distilled and the diamine was obtained in a 54 % yield, b.p. 128°C/26.7 Pa. The product was found to contain a minor amount of *p*-anisidine, which was removed in the following way. The impure product (10 g) was dissolved in 500 ml of an aqueous phosphate buffer of pH 6.5. Addition of a few drops of phosphoric acid was necessary in order to restore the pH value to 6.5. Extractions with 15 ml portions of benzene were repeated until no more *p*-anisidine could be detected in the extracts (GLC). The aqueous phase was made strongly alkaline with potassium hydroxide solution and the diamine extracted with ether. Drying over potassium carbonate and evaporation of the solvent gave an oily residue, which could be recrystallized from hexane at -20°C. Colourless crystals (5 g) of m.p. 23–24°C were obtained.

4-Methylpentanoyl chloride was prepared from 100 g (0.86 mol) of 4-methylpentanoic acid and 154.7 g (1.3 mol) of thionyl chloride. After a 3 h reflux period, the reaction mixture was distilled, yielding 105 g of product (91 % yield), b.p. 143–144°C, lit.⁴ 143.8–144.5°C.

N-(4'-Methoxyphenyl)-4-methylpentanamide. A solution of 56.7 g (0.46 mol) of *p*-anisidine in 500 ml of dry benzene was chilled in an ice bath, and 31 g (0.23 mol) of the above acid chloride was slowly added. After a stirring period of 1.5 h, the reaction mixture was washed with dilute hydrochloric acid, water and 5 % sodium hydrogen carbonate solution. The organic layer was dried and the solvent removed *in vacuo*. Recrystallization from ligroin gave 38.9 g of the product (76 % yield), m.p. 80.5–81.5°C.

N-Isohexyl-p-anisidine was prepared from 22.1 g (0.10 mol) of the above amide by the method of Mićović and Mihailović.⁵ Lithium tetrahydroaluminate (5.7 g, 0.15 mol) was used. The amide was only slightly soluble in ether and was therefore initially placed in an extractor thimble through which the refluxing ether percolated. The reaction required 24 h for completion. Excess hydride was destroyed with a 1:1 mixture of ethanol and ether, and dilute sodium hydroxide solution was then added. The ethereal phase was separated off, dried and the solvent evaporated. The remainder was distilled on a 60 cm spinning-band column (Normag, Teflon band) and gave 19 g (92 %) of an almost colourless oil, b.p. 114°C/40 Pa.

N-(3-Dimethylaminopropyl)-2,4-dinitro-4'-methoxydiphenylamine was prepared for spectral comparison by mixing 1-chloro-2,4-dinitrobenzene and *N*-(3-dimethylaminopropyl)-*p*-anisidine in the molar proportions 1:2 in dry benzene. After three days at room temperature, the mixture was washed with water. The benzene solution was dried and the solvent removed *in vacuo*. Recrystallization of the residue from ethanol gave red crystals in 61 % yield, m.p. 75.5–76.5°C.

N-Isohexyl-2,4-dinitro-4'-methoxydiphenylamine was analogously prepared from 1-chloro-2,4-dinitrobenzene and *N*-isohexyl-*p*-anisidine. Recrystallization from 2-propanol gave orange-red crystals in 60 % yield, m.p. 83.5–84.5°C.

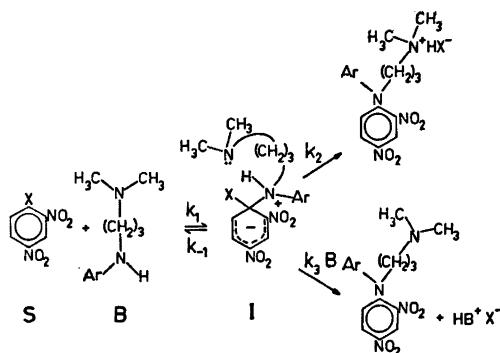
Other chemicals used in this work were of commercial origin or available from previous work in the laboratory. They were recrystallized before use, and their purity was verified by NMR, GLC and/or TLC. The benzene used as solvent in the kinetic runs was dried over Molecular Sieves 4 A and distilled through an effective column.

Kinetic procedure. For the rate measurements, the apparatus described in previous work,¹ a Beckmann Model DU spectrophotometer, equipped with a thermostated water bath in the optical path, was first used. In the course of the present work, the instrument was modified. The original null detection bridge was replaced with a digital transmission readout device. The photomultiplier current was converted into voltage in a FET operational amplifier. The voltage was read off a digital voltmeter. Furthermore, the tungsten lamp and photomultiplier were fed by suitably regulated power supplies. The long-time stability of the system was found to be superior to that of the original one.

The optical measurements were performed at a temperature of 25.00 ± 0.05°C of the thermostated water bath at the wavelength 420 nm. Care was taken to exclude oxygen and carbon dioxide from the solutions by flushing with argon.

In order to facilitate the treatment of the data, first-order conditions were chosen. The 1-halo-2,4-dinitrobenzenes had initial concentrations 1.0×10^{-3} M or, for the fluorine compound in its reaction with T, 1.0×10^{-4} M, whereas the amine concentration range was 0.010 to 0.233 M. The DABCO concentration was 0.022 M. For each kinetic run about 20 points were taken, and all runs were made in duplicate or triplicate. The absorbance infinity values, A_{∞} , were obtained by preparing solutions of the appropriate concentration from the independently synthesized reaction products. These solutions had the same content of amine and DABCO as those in the runs. The molar absorptivities are, for the terminal dimethylaminopropyl compound, 10470 and for the isohexyl compound, 9670 at 420 nm. The entire UV spectra of the synthesized products and those obtained in the kinetic runs agreed, thus identifying the reactions under study. Precipitation of amine hydrochloride was not observed during the time the reaction was followed.

A possibility that must be considered is that, for the diamine T, the terminal dimethylamino group may initially attack the 1-halo-2,4-dinitrobenzene, forming a quaternary ammonium compound, which may then rearrange to the final product. No evidence was found for this,



Scheme 1. Scheme for the reaction of 1-X-2,4-dinitrobenzene with *N*-(3-dimethylaminopropyl)-*p*-anisidine.

however, neither by following the reaction with UV nor with NMR.

The tertiary amine DABCO, used as a catalyst in the present study might also react with the 1-halo-2,4-dinitrobenzene. However, solutions with these two compounds present in the same concentrations as in the kinetic runs, showed no spectral changes even after standing for several days at room temperature.

Treatment of data. From the kinetic runs, absorbance values A or, after modification of the spectrophotometer, transmittance values T were obtained. The function $\ln(A_\infty - A)$ or $\ln \log(T/T_\infty)$ was plotted against time and the slope was calculated by the least-squares method. All calculations were made on an Olivetti Programma 101 electronic desk-top computer or on a Compucorp 425 Scientist computer. The standard deviation in each separate run, typically 1–2 %, equals the deviations between the different runs.

RESULTS AND DISCUSSION

A kinetic scheme for activated nucleophilic aromatic substitution with a diamine is shown in Scheme 1. Two routes have been drawn for the conversion of the intermediate to product. One involves intramolecular proton transfer from the “inner” to the “outer” nitrogen atom, whereas in the other, intermolecular proton transfer to another base takes place. Whether departure of the leaving group is concerted with this proton transfer or occurs in a separate step is hard to tell. A careful kinetic analysis by Ross⁶ shows that other possibilities lead to the same dependence of the observed rate upon the concentrations of nucleophile and base. For example, in one mechanism, a rapid equilibrium

between two intermediates involving proton transfer is established, followed by a slow, acid-catalyzed loss of the leaving group. Another possibility is a rate-limiting proton transfer from the first intermediate I to the base, forming a second, anionic intermediate, followed by a rapid loss of the leaving group.⁷

From Scheme 1 we obtain, using the steady state approximation, the following expression

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

Tables 1–3. First- and second-order rate constants in the reactions of 1-X-2,4-dinitrobenzene, X = F, Cl and Br, with *N*-(3-dimethylaminopropyl)-*p*-anisidine (T). Substrate concentration 1.0×10^{-4} M for X = F and 1.0×10^{-3} M for X = Cl and Br.

Table 1.

[Amine]/M	$k_{\text{obs}}/10^{-4} \text{ s}^{-1}$	$k_A/10^{-2} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
X = F, [DABCO] = 0 M		
0.010	5.44	5.44
0.020	11.28	5.64
0.025	14.30	5.72
0.035	21.18	6.05
X = F, [DABCO] = 0.022 M		
0.010	5.35	5.35
0.020	11.01	5.50
0.025	14.01	5.60
0.035	19.83	5.67

Table 2.

[Amine]/M	$k_{\text{obs}}/10^{-6} \text{ s}^{-1}$	$k_A/10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
X = Cl, [DABCO] = 0 M		
0.050	3.23	6.47
0.075	4.99	6.66
0.100	6.84	6.84
0.125	8.60	6.88
0.150	10.43	6.95
X = Cl, [DABCO] = 0.022 M		
0.050	3.21	6.42
0.075	4.98	6.65
0.100	6.74	6.74
0.125	8.56	6.85
0.150	10.34	6.89

Table 3.

[Amine]/M	$k_{\text{obs}}/10^{-6} \text{ s}^{-1}$	$k_{\text{A}}/10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
X = Br, [DABCO] = 0 M		
0.050	7.50	15.01
0.075	11.33	15.11
0.100	15.47	15.47
0.150	23.75	15.83
0.200	32.01	16.01
X = Br, [DABCO] = 0.022 M		
0.050	7.61	15.23
0.075	11.56	15.42
0.100	15.44	15.44
0.150	23.86	15.91
0.200	32.29	16.14

where k_{A} , the effective second-order rate constant, is related to the experimentally obtained first-order rate constants, k_{obs} , through $k_{\text{A}} = k_{\text{obs}}/[B]$. If bases different from B are kinetically effective in step 3, the $k_3[B]$ term in eqn. (1) should be replaced by sum of the type $\sum_i k_{3,i}[B_i]$.

If $k_{-1} \gg k_2 + k_3[B]$, then eqn. (1) reduces to

$$k_{\text{A}} = \frac{k_1 k_2}{k_{-1}} + \frac{k_1 k_3}{k_{-1}} [B] \quad (2)$$

and the reaction could be sensitive to base catalysis provided that $k_3[B]$ is not too small compared to k_2 .

If $k_{-1} \ll k_2 + k_3[B]$, we obtain $k_{\text{A}} = k_1$, and the reaction is of first order with respect to the base concentration.

If $k_{-1} \approx k_2 + k_3[B]$, a curvilinear dependence of k_{A} on the base concentration is observed.⁸

An important feature of the rate constants obtained in this work (Tables 1–6), is that those for the fluorine compound are somewhat lower than those for the chlorine and bromine compounds in the reaction with U, whereas in the reaction with T, the order of reactivity is $F \gg \text{Br} > \text{Cl}$.

It is known from many kinetic studies that the choice of fluoride ion instead of a heavier halogen as the leaving group produces dramatic rate differences. An analysis of the factors causing these differences has been given in a book by Miller.⁹ In reactions with amines, one generally finds the reactivity order $F \gg \text{Cl} \approx \text{Br}$,

Tables 4–6. First- and second-order rate constants in the reactions of 1-X-2,4-dinitrobenzene, X = F, Cl and Br, with *N*-isohexyl-*p*-anisidine (U). Substrate concentration 1.0×10^{-3} M.

Table 4.

[Amine]/M	[DABCO]/M	$k_{\text{obs}}/10^{-7} \text{ s}^{-1}$	$k_{\text{A}}/10^{-6} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
X = F			
0.200	0	0.80	0.4
0.200	0.022	5.17	2.6

Table 5.

[Amine]/M	$k_{\text{obs}}/10^{-7} \text{ s}^{-1}$	$k_{\text{A}}/10^{-6} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
X = Cl, [DABCO] = 0 M		
0.100	1.13	1.13
0.150	1.69	1.13
0.175	2.00	1.14
0.200	2.33	1.17
0.225	2.70	1.20
X = Cl, [DABCO] = 0.022 M		
0.100	1.12	1.12
0.150	1.75	1.16
0.175	2.03	1.16
0.200	2.40	1.20
0.225	2.79	1.24

Table 6.

[Amine]/M	$k_{\text{obs}}/10^{-7} \text{ s}^{-1}$	$k_{\text{A}}/10^{-6} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
X = Br, [DABCO] = 0 M		
0.100	4.19	4.19
0.117	4.99	4.27
0.150	6.58	4.39
0.200	9.01	4.51
0.225	10.37	4.61
X = Br, [DABCO] = 0.022 M		
0.100	5.58	5.58
0.117	6.45	5.51
0.150	8.28	5.52
0.200	11.05	5.53
0.233	13.02	5.59

indicating a rate-limiting first step. There are, however, also cases in which $F < Cl < Br$, for example, in the reactions of 1-halo-2,4-dinitrobenzenes with *N*-methylaniline in nitrobenzene solution.¹⁰ When the *N*-methylaniline reaction was performed in ethanol,¹¹ the F/Cl ratio was found to be 1. With potassium acetate also present, the F/Cl ratio increased. Base catalysis is thus more important for the fluorine compound. The effect of the base is to increase the $k_3[B]$ term in the kinetic expression of eqn. (1). Bernasconi and Zollinger² studied the reactions of 1-fluoro- and 1-chloro-2,4-dinitrobenzene with *p*-anisidine in benzene solution. The ratio of the rate constants for the F and the Cl reaction, at the same *p*-anisidine concentration, 0.2 M, in the absence of the catalyst DABCO is close to 100.

Rossi and Rossi¹² have measured the rates for the reactions of the same two dinitro compounds with aniline in acetone at 50°C. They found an F/Cl ratio of 9.7 at 0.1 M base concentration.

Both in the Bernasconi and Zollinger² and the Rossi and Rossi paper,¹² a strong base catalysis by DABCO is observed with fluorine, whereas with chlorine moderate rate accelerations are observed.²

We introduce the convenient notation $k_{F,U}$ for the observed, first-order rate constant of the reaction of the fluorine compound with U, *etc.* When ratios like $k_{Cl,U}/k_{F,U}$ are calculated, the U concentration in the different kinetic runs is the same, otherwise the difference is taken into account.

First fluoride and chloride ion as leaving groups will be compared. Inspection of the data obtained in this work for the F,U- and the Cl,U-reactions shows that the $k_{F,U}/k_{Cl,U}$ ratio is 0.3, at 0.2 M amine concentration in the absence of DABCO. The rate of the Cl,U-reaction is not influenced by DABCO. Application of eqn. (1) to the Cl,U-reaction leaves us with two possibilities. Either, $k_{-1,Cl,U} \ll k_{2,Cl,U} + \sum_i k_{3,i,Cl,U}[B_i]$, *i.e.* the first step is rate-limiting, or

$k_{-1,Cl,U} \gtrsim k_{2,Cl,U} \gg \sum_i k_{3,i,Cl,U}[B_i]$ which leads to

$$k_{A,Cl,U} = \frac{k_{1,Cl,U}k_{2,Cl,U}}{k_{-1,Cl,U} + k_{2,Cl,U}}$$

We assume that the first step is rate-limiting since chloride ion is a good leaving group.

On the contrary, the F,U-reaction is catalyzed by DABCO. Due to the very slow reaction, the the F,U-reaction was measured at only one concentration of the nucleophile. From the data we can conclude that the decomposition of the intermediate I is involved in the rate-limiting step.

It is found from Tables 1–6, that $k_{Cl,T}/k_{Cl,U} = 61$ and that $k_{F,T}/k_{F,U}$ is approximately 250 000 (by linear extrapolation). Catalysis by DABCO is absent for the Cl,T-reaction. For the Cl,T-reaction, an analysis similar to the one just performed, gives the same two possibilities, *i.e.*, the first step is rate-limiting or $k_{-1,Cl,T} \gtrsim k_{2,Cl,T} \gg \sum_i k_{3,i,Cl,T}[B_i]$. The same assumption as above, that of a rate-limiting first step, will be made. Assuming that k_1 is solely rate-limiting, the factor $k_{Cl,T}/k_{Cl,U}$ reflects the increased nucleophilicity of T compared to U. Let us assume that a comparable factor, for example 100, can be applied to the k_1 's for the F,T- and the F,U-reaction. This gives

$$250\,000 = 100 \left(\frac{k_2 + \sum_i k_{3,i}[B_i]}{k_{-1} + k_2 + \sum_i k_{3,i}[B_i]} \right)_{F,T} \bigg/ \left(\frac{k_2 + \sum_i k_{3,i}[B_i]}{k_{-1} + k_2 + \sum_i k_{3,i}[B_i]} \right)_{F,U}$$

We suggest that in the F,T-reaction the first step is completely rate-limiting, in other words, $k_{-1,F,T} \ll k_{2,F,T} + \sum_i k_{3,i,F,T}[B_i]$, *e.g.*, the F,T-parenthesis equals 1. This leads to

$$\left(\frac{k_{-1} + k_2 + \sum_i k_{3,i}[B_i]}{k_2 + \sum_i k_{3,i}[B_i]} \right)_{F,U} \approx 2500$$

or $k_{-1,F,U} \approx 2500(k_{2,F,U} + \sum_i k_{3,i,F,U}[B_i])$, in other words, the second step of the reaction is rate-limiting. This reaction is also catalyzed by DABCO.

As regards the difference between chloride and bromide ion as the leaving group, our data show that the bromine compound consistently reacts faster than the chlorine compound by a factor of 2–4. In activated nucleophilic aromatic substitution, the rate constants for the chlorine and bromine compounds are often remarkably similar, and the present results

provide no exception. It is apparent, that the Br,U-reaction is weakly catalyzed by DABCO, whereas the Cl,U-reaction is not catalyzed. We can offer no explanation for this interesting difference.

To summarize, we suggest that the dramatic increase of the rate constant in going from the F,U- to the F,T-system, can be explained by intramolecular base catalysis operating with the nucleophile T.

Acknowledgement. We wish to thank Professor Lars Melander for his suggestions concerning the presentation of the kinetic data.

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Received May 13, 1975.