ACTA CHEMICA SCANDINAVICA 23 (1969) 3361–3368

Kinetics of the Reaction of α,ω-Diaminoalkanes with 2,6-Dinitroanisole. Search for Evidence of Intramolecular Base Catalysis

INGELA PALMERTZ and BO LAMM

Department of Organic Chemistry, University of Göteborg and Chalmers Institute of Technology, Fack, S-402 20 Göteborg 5, Sweden

The reaction between 2,6-dinitroanisole and a series of α,ω-diaminoalkanes $H_2N(CH_2)_nNH_2$ ($n=2-5$) has been studied kinetically in three solvents: methanol, 60 % dioxane-40 % water, and pure dioxane. The rates were determined spectrophotometrically.

The rate expression for the reaction is a sum of a second- and a third-order term. In dioxane, however, the second-order term is missing. Both the second- and third-order rate constants (and consequently, the ratio between them) were found to be surprisingly insensitive to a variation of the number of methylene groups in the diamine, suggesting the absence of intramolecular base catalysis.

Base catalysis in nucleophilic aromatic substitution by amines has been a subject of recent controversy. In the reaction between 2,4-dinitrochlorobenzene and butylamine in methanol Ross *et al.*[1] found that the second-order rate constant was mildly augmented by the addition of bases. This observation was taken as a proof of base catalysis of the second step of the reaction on the assumption that the generally accepted two-step mechanism [2,3] is valid.

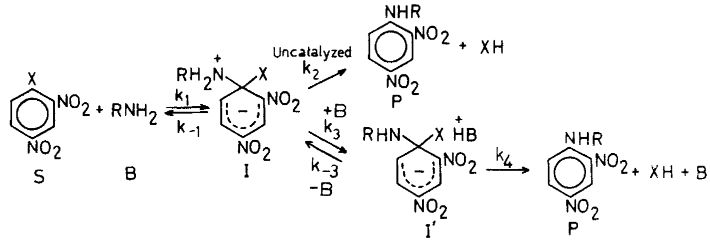

Fig. 1. Reaction scheme for nucleophilic aromatic substitution of 2,4-dinitro-1-X-benzene by a monoamine.

The interpretation offered above has been criticized by Bunnett and Garst,[4] who pointed out that with a good leaving group such as chlorine, the first step of the reaction, *i.e.*, the formation of the intermediate I (see Fig. 1), is rate-determining. Base catalysis of a subsequent step therefore cannot influence the over-all rate. A confirmation of the correctness of this kinetic behaviour was later provided by Bunnett and Bernasconi.[5] In their work, the reaction of 2,4-dinitrophenyl phenyl ether with piperidine in 10 % aqueous dioxane was studied. The observed formal second-order rate constant was found to vary with the piperidine concentration in a curvilinear fashion. At high piperidine concentrations, the formal second-order rate constant asymptotically approaches a constant value, rendering the first step rate-determining. At moderate concentrations, a curve is obtained, the slope of which increases with decreasing piperidine concentration. At still lower amine concentration, the formal second-order rate constant linearly increases with the piperidine concentration. The reaction was also found to be catalysed by other bases.

Bunnett and Garst [4] suggested that the rate accelerations observed by Ross *et al.*[1] are due to medium effects on the first step of the reaction. Bernasconi and Zollinger [6,7] have shown that nucleophilic aromatic substitution reactions with amines are subject to appreciable medium effects, particularly in non-polar media. This obviously complicates the study of base catalysis in these reactions, since it may be difficult to distinguish between medium effects and genuine catalysis.

The present investigation was undertaken with the expectation that by using a series of α,ω-diaminoalkanes as nucleophilic reagents in the reaction with some suitable aromatic compound, intramolecular base catalysis might be operative. If one amino group acts as a nucleophile, the other amino group in the same molecule might function as the catalyzing base by abstracting a proton from the "inner" amino group. The number of methylene groups between the two amino groups should determine the relative importance of this intramolecular mechanism, since rings of different size should be involved.

As a starting point for the kinetic treatment of the reaction, the scheme given in Fig. 1, which is valid for a monoamine acting both as a nucleophilic reagent and as a base will be analyzed. The modifications caused by the incorporation of a second amino group in the nucleophilic reagent will then be discussed.

Using the symbols in Fig. 1, the following equations are obtained:

$$\mathrm{d[I]/d}t = k_1[\mathrm{S}][\mathrm{B}] + k_{-3}[\mathrm{I'}][\mathrm{HB^+}] - k_{-1}[\mathrm{I}] - k_2[\mathrm{I}] - k_3[\mathrm{B}][\mathrm{I}] \quad (1)$$

$$\mathrm{d[I']/d}t = k_3[\mathrm{B}][\mathrm{I}] - k_{-3}[\mathrm{I'}][\mathrm{HB^+}] - k_4[\mathrm{I'}][\mathrm{HB^+}] \quad (2)$$

$$\mathrm{d[P]/d}t = k_2[\mathrm{I}] + k_4[\mathrm{I'}][\mathrm{HB^+}] \quad (3)$$

The intermediates I and I′ are both assumed to be present in very small amounts, so that the steady-state approximation is applicable to both eqns. (1) and (2). From eqn. (2)

$$[\mathrm{I'}] = \frac{k_3[\mathrm{B}]}{(k_{-3} + k_4)[\mathrm{HB^+}]}[\mathrm{I}] \quad (4)$$

is first obtained.

The introduction of this value of [I′] into eqn. (1) gives

$$[\mathrm{I}] = \frac{k_1[\mathrm{S}][\mathrm{B}]}{k_{-1} + k_2 + k_3k_4[\mathrm{B}]/(k_{-3} + k_4)} \tag{5}$$

Insertion in eqn. (3) gives the final expression

$$\frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} = \frac{k_1[\mathrm{S}][\mathrm{B}](k_2 + k_3k_4[\mathrm{B}]/(k_{-3} + k_4)}{k_{-1} + k_2 + k_3k_4[\mathrm{B}]/(k_{-3} + k_4)} \tag{6}$$

If the leaving group X is a good one, or if the concentration of B is sufficiently large, the inequality $k_{-1} \ll k_2 + k_3k_4[\mathrm{B}]/(k_{-3} + k_4)$ holds. Eqn. (6) then becomes

$$\mathrm{d}[\mathrm{P}]/\mathrm{d}t = k_1[\mathrm{S}][\mathrm{B}] \tag{7}$$

and no base catalysis is observed.

Strictly, when X is a good leaving group, the decomposition of I′ to P does not require assistance by HB^+ as indicated in Fig. 1. Eqns. (2) and (3) must therefore be modified and the final expression for d[P]/dt becomes

$$\frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} = \frac{k_1[\mathrm{S}][\mathrm{B}](k_2 + k_3k_4^*[\mathrm{B}]/(k_{-3}[\mathrm{HB}^+] + k_4^*)}{k_{-1} + k_2 + k_3k_4^*[\mathrm{B}]/(k_{-3}[\mathrm{HB}^+] + k_4^*)} \tag{8}$$

where k_4^* is the rate constant for the step I′ to P without assistance by HB^+.

With the approximation $k_{-1} \ll k_2 + k_3k_4^*[\mathrm{B}]/(k_{-3}[\mathrm{HB}^+] + k_4^*)$ eqn. (7) still holds. This would have been obvious even without deducing eqn. (8), since the absence of HB^+ in the step I′ to P lends support to the validity of the above inequality. The conversion of I′ to P can proceed in a unimolecular fashion when X is a good leaving group.

Another approximation can be made when X is a poor leaving group, provided also that the concentration of B is not too high. Under these conditions, $k_{-1} \gg k_2 + k_3k_4[\mathrm{B}]/(k_{-3} + k_4)$. Then eqn. (6) simplifies to

$$\frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} = \frac{k_1}{k_{-1}}[\mathrm{S}][\mathrm{B}]\left(k_2 + \frac{k_3k_4}{k_{-3} + k_4}[\mathrm{B}]\right) \tag{9}$$

Under these conditions, base catalysis will be observed.

Inspection of eqn. (9) reveals that the rate expression is a sum of a second- and a third-order term. The experimental rate constants for these terms will be denoted k_2' and k_3' in the following treatment. Eqn. (9) will thus be written

$$\mathrm{d}[\mathrm{P}]/\mathrm{d}t = k_2'[\mathrm{S}][\mathrm{B}] + k_3'[\mathrm{S}][\mathrm{B}]^2 \tag{10}$$

From the work of Bunnett and his co-authors [5,8] and of Bernasconi and Zollinger [6,7] it is apparent that when eqn. (10) holds, $k_3'[\mathrm{B}]$ is generally larger than k_2'. In non-polar solvents the term involving k_3' becomes the dominant one.

As stated above, the main purpose of the present investigation was to use a series of α,ω-diaminoalkanes as nucleophiles, thereby providing a mechanism for intramolecular base catalysis. The intermediate I would have the structure shown in Fig. 2, in which the substrate, 2,6-dinitroanisole, is the one actually chosen for study. If the role of the catalyzing base B of steps

3 and 4 in Fig. 1 could be played by the "outer" amino group, one would expect the ratio of the experimental rate constants, k_2'/k_3', to be relatively high and, most important, to be a function of the ring-size (Fig. 2), the highest values being reached with five- and six-membered rings. It should be noted that if an intramolecular mechanism is operative, k_2' would include both the uncatalyzed path governed by k_2 in Fig. 1 and, to a variable extent, the base catalyzed path governed by k_3, k_{-3}, and k_4 in the same scheme.

The following points were considered in the choice of a suitable aromatic substrate. First, remembering the discussion above, if base catalysis is to be observed at all a poor leaving group must be chosen. The methoxy group fulfills this requirement and was the one selected. Second, steric factors may be of importance. With a substrate having bulky *ortho* substituents, the rate of the second step, in which the bond to the entering nucleophile becomes coplanar with the aromatic ring, should be more decreased than that of the reversal of the first step, if the entering nucleophile has larger steric requirements than the group being displaced. Two *ortho* nitro groups were therefore decided on instead of the more commonly used 2,4-dinitro system. Third, the substrate should react with the diamines at conveniently measurable rates. This condition can be fulfilled by introducing if necessary, a suitable *para* substituent, but in the present case 2,6-dinitroanisole itself was found to react at rates which could be followed by electron spectroscopy.

EXPERIMENTAL

Materials. 1,4-Dioxane (Fisher Scientific Company) was further purified by refluxing with calcium hydride under nitrogen, and was distilled shortly before use and stored over Molecular Sieves of type 4 A. B.p. 101.1 – 101.3°C.

A batch of 60 % dioxane-40 % water, sufficiently large for all runs, was prepared by mixing three volumes of dioxane with two volumes of water.

Methanol (Fluka UV-grade) was further dried with Molecular Sieves of type 4 A.

2,6-Dinitroanisole was available in the laboratory. It was recrystallized three times from methanol. The purity was controlled by NMR and by GLC. M.p. 118 – 119°C.

All diamines used were commercial products (Fluka puriss. grade). They were refluxed with calcium hydride for about 6 h, then distilled under nitrogen and stored over Molecular Sieves of type 4 A.

Kinetic procedure. The kinetic measurements were performed at 25.00 ± 0.05°C at the wave-length 420 mμ in 1 cm cells in a Beckman DU Spectrophotometer, equipped with a thermostated water bath in the beam path. Runs were made at five different amine concentrations in each of the following solvents: methanol, 60 % dioxane-40 % water, and pure dioxane. The amine concentration was within the range 0.05 – 0.60 mole l^{-1}.

Suitable absorbance values were obtained when the concentration of the aromatic substrate was about 10^{-4} mole l^{-1}. Thus, even in the most dilute amine solutions, a sufficiently large excess of amine was present to ensure pseudo-monomolecular kinetic conditions. This was verified by varying the initial concentration of the aromatic substrate in the kinetic runs, which turned out to have no influence on the observed reaction rate.

The solutions in the 1 cm cells were prepared in the following way. A solution of the diamine in the particular solvent studied was pipetted into four cells, which were placed in the thermostat. When thermal equilibrium had been attained, 12, 15, and 18 μl, respectively, of a stock solution of 2,6-dinitroanisole in the proper solvent was added to three of the cells. The fourth one was used as the optical blank. Zero time was recorded at the moment of addition. Absorbance values were determined at regular intervals. Around 20 measurements were made for each cell.

The base concentrations were determined by potentiometric titration (Radiometer Titrigraph Type TTT 1c) with standard hydrochloric acid.

Identification of the reaction product. In a previous communication,[9] the reaction product obtained from 2,6-dinitroanisole and ethylenediamine has been studied by NMR spectroscopy and then identified as *N*-(2,6-dinitrophenyl)-ethylenediamine. Since the electron spectra of the reaction products when higher diamines were used were almost superimposable on that of *N*-(2,6-dinitrophenyl)-ethylenediamine, the reaction products are considered to be properly identified.

Treatment of data. From the kinetic measurements values of A_t, *i.e.* the absorbance A at time t were obtained. These data were treated according to the method of Guggenheim.[10]

This method is applicable to a first-order reaction in cases where the final reading, in our case the absorbance at infinite time, A_∞, is unknown. The values of $A_{t+\Delta}$, *i.e.* the absorbance at the time $t+\Delta$, where Δ must be at least three half-lives, were estimated from the plot of A *vs.* time t. When the values of $\ln(A_t - A_{t+\Delta})$ were plotted *vs.* time t, straight lines were obtained.

All calculations by the least-squares method were made on an Olivetti Programma 101 electronic desk-top computer.

RESULTS

The rate expression that can be expected to be valid is the one given in eqn. (10). Since the kinetic runs have been carried out under pseudo-monomolecular conditions, using a large excess of amine, the first-order rate con-

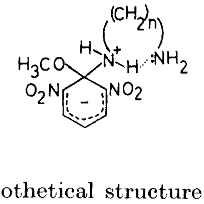

Fig. 2. Hypothetical structure of the first intermediate formed in the reaction between 2,6-dinitroanisole and an α,ω-diaminoalkane.

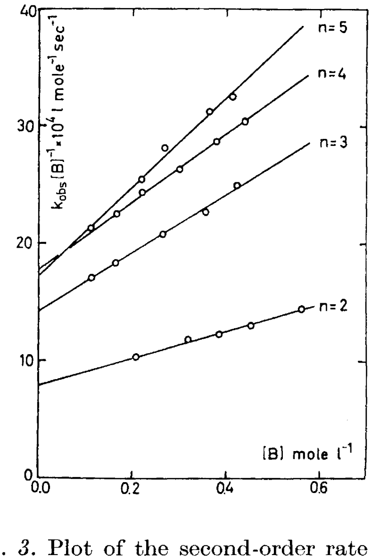

Fig. 3. Plot of the second-order rate constant *vs.* amine concentration for the reaction of $H_2N(CH_2)_nNH_2$ with 2,6-dinitroanisole in methanol.

Each point is the average value of two or three measurements.

stants k_{obs}, obtained as averages from two or three different runs, are related to the constants of eqn. (10) by the equation

$$k_{obs} = k_2'[B] + k_3'[B]^2 \qquad (11)$$

A convenient graphic representation is obtained if $k_{obs}/[B]$ is plotted *vs.* [B]. Such plots are given in Figs. 3—5. From an inspection of these plots, it is seen that straight lines are obtained. This shows that the approximation leading to eqn. (10) is justified, *i.e.*, the forward reactions of the intermediate illustrated in Fig. 2 are rate-determining.

From the data underlying Figs. 3—5, the values k_2' and k_3' were calculated by the least-squares method. The results are given in Table 1. It should be observed that the base concentration [B] represents the molar concentration. Since there are two amino groups in each molecule B, the rate constants need proper statistical corrections if comparisons with rate data for monoamines in similar reactions are to be made.

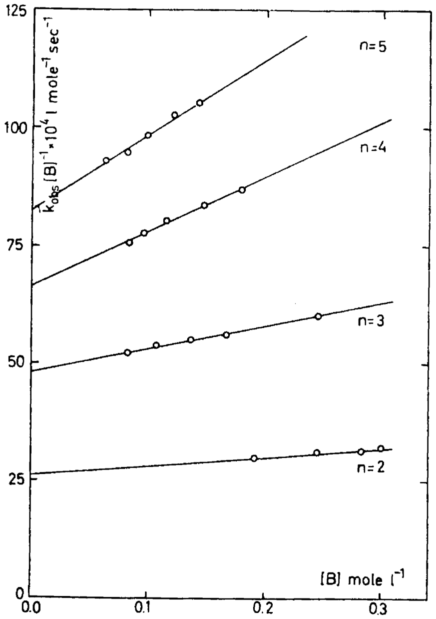

Fig. 4. Plot of the second-order rate constant *vs.* amine concentration for the reaction of $H_2N(CH_2)_nNH_2$ with 2,6-dinitroanisole in 60 % dioxane-40 % water.
Each point is the average value of two or three measurements.

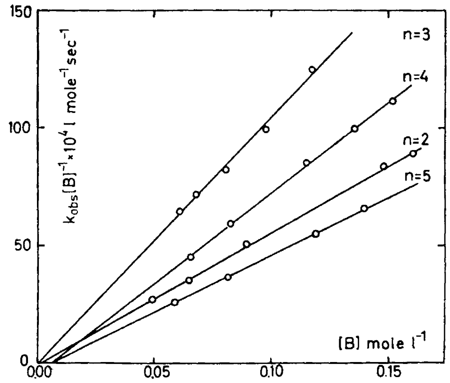

Fig. 5. Plot of the second-order rate constant *vs.* amine concentration for the reaction of $H_2N(CH_2)_nNH_2$ with 2,6-dinitroanisole in dioxane.
Each point is the average value of two or three measurements.

DISCUSSION

It is quite apparent from the data presented in Table 1 that no evidence for intramolecular catalysis has been found in this work. The data for pure dioxane, an aprotic solvent, are particularly decisive, since here the second-order term is completely absent. (The negative values in Table 1 are, within the error, equal to zero). In the solvents methanol and 60 % dioxane-40 % water, no dramatic changes of the ratio k_2'/k_3' are observed. The most straightforward interpretation is that in dioxane, intramolecular catalysis is completely absent. In the two other media, which are protic, there is even less reason to believe that direct intramolecular catalysis as suggested in Fig. 2 occurs. The second-order terms can be explained by including solvent molecules as proton transfer agents in the collapse of the intermediate in the forward direction. Quite analogous results have been obtained with monoamines by other workers.[5-8]

Table 1. Second- and third-order rate constants in the reaction of polymethylenediamines with 2,6-dinitroanisole.

Solvent	Amine	$k_2' \times 10^4$ [a]	$k_3' \times 10^4$ [b]	k_2'/k_3' [c]
Methanol	1,2-diaminoethane	7.95 ± 0.29	11.5 ± 0.7	0.69 ± 0.07
	1,3-diaminopropane	14.32 ± 0.29	24.7 ± 1.0	0.58 ± 0.05
	1,4-diaminobutane	17.84 ± 0.18	28.8 ± 0.6	0.62 ± 0.02
	1,5-diaminopentane	17.36 ± 0.61	37.9 ± 2.1	0.46 ± 0.07
60 % dioxane-—40 % water	1,2-diaminoethane	26.07 ± 0.76	19.5 ± 3.0	1.34 ± 0.15
	1,3-diaminopropane	48.35 ± 0.28	48.3 ± 1.8	1.00 ± 0.04
	1,4-diaminobutane	66.44 ± 0.69	116 ± 5	0.57 ± 0.05
	1,5-diaminopentane	82.57 ± 1.00	161 ± 9	0.51 ± 0.06
Dioxane	1,2-diaminoethane	-1.0 ± 1.2	566 ± 11	
	1,3-diaminopropane	-0.8 ± 4.5	1052 ± 52	
	1,4-diaminobutane	-4.9 ± 1.4	771 ± 12	
	1,5-diaminopentane	-3.1 ± 0.5	491 ± 4	

[a] Values in l mole^{-1} sec^{-1}. Errors are standard deviations.

[b] Values in l^2 mole^{-2} sec^{-1}. Errors are standard deviations.

[c] Values in l^{-1} mole. The errors given in this column are the RMS-values of the per cent errors in k_2' and k_3'.

In an entirely different reaction, the aminolysis of phenyl acetate with different polymethylenediamines, Bruice and Willis [11] observed no intramolecular catalysis. A similar result has also been reported by Pratt and Lawlor.[12]

A situation in which bifunctional catalysis, though not intramolecular in the sense that the catalyst is incorporated in the nucleophile, does not occur has been reported by Pietra and Vitali.[13] These authors found that the rate constant for the reaction between 2,4-dinitrofluorobenzene and piperidine in benzene solution increases linearly with the concentration of monomeric α-pyridone, the catalytic coefficient having the value 3200. This catalyst contains an acidic and a basic site at a suitable distance and is thus entirely different from a diaminoalkane.

Acknowledgements. We wish to thank Professor Lars Melander for his continuous and constructive criticism. We would also like to thank Docent Arne Brändström for his kind advice on the treatment of the rate data. A grant from *Paul and Marie Berghaus' donationsfond* to one of us (I.P.) is gratefully acknowledged.

REFERENCES

1. Ross, S. D. In Cohen, S. G., Streitwieser, A., Jr. and Taft, R. W. *Progress in Physical Organic Chemistry*, Interscience, New York 1963, Vol. 1, p. 31.
2. Bunnett, J. F. and Zahler, R. E. *Chem. Revs.* **49** (1951) 273.
3. Bunnett, J. F. *Quart. Revs. London* **12** (1958) 1.
4. Bunnett, J. F. and Garst, R. H. *J. Am. Chem. Soc.* **87** (1965) 3875.
5. Bunnett, J. F. and Bernasconi, C. *J. Am. Chem. Soc.* **87** (1965) 5209.
6. Bernasconi, C. and Zollinger, H. *Tetrahedron Letters* **1965** 1083.
7. Bernasconi, C. and Zollinger, H. *Helv. Chim. Acta* **49** (1966) 103.
8. Bunnett, J. F. and Garst, R. H. *J. Am. Chem. Soc.* **87** (1965) 3879.
9. Lamm, B. *Acta Chem. Scand.* **19** (1965) 1492.
10. Frost, A. and Pearson, R. *Kinetics and Mechanism,* 2nd Ed., Wiley, New York, London 1963, p. 49.
11. Bruice, T. C. and Willis, R. G. *J. Am. Chem. Soc.* **87** (1965) 531.
12. Pratt, R. F. and Lawlor, J. M. *Chem. Commun.* **9** (1968) 522.
13. Pietra, F. and Vitali, D. *Tetrahedron Letters* **1966** 5701.

Received May 9, 1969.