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TRAPPING OF A REACTION INTERMEDIATE BY CYCLODEXTRINS

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Abstract: The formation and decomposition of an intermediate is observed spectrophotometrically in the coupling reaction between *p*-nitrophenyldiazonium chloride and *N,N*-dimethylaniline in the presence of β-cyclodextrin. A kinetic analysis of this process is reported.

Cyclodextrins,[1] cyclic oligomers of glucose, have been widely used as catalysts, enzyme mimics,[2] micro-reaction vessels and stabilizers.[3] Recently, we reported[4] catalysis of an aromatic electrophillic substitution reaction by cyclodextrins and attributed this to the stabilization of the sigma complex intermediate of the reaction. We now report the trapping of an intermediate by β-cyclodextrin (1) in a similar reaction between *p*-nitrophenyl diazonium salt (2) and *N,N*-dimethylaniline (3).

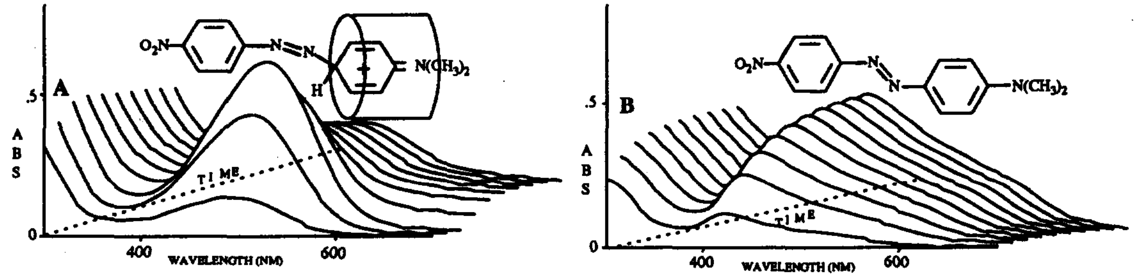

Figure 1 - Time dependent UV-Vis spectra of a reaction mixture of **2** and **3** at pH 4.0: (**A**) in the presence of **1**; (**B**) in the absence of **1**. The Z axis in this three dimensional illustration represents time. Each spectra are recorded at two minute intervals.

The time dependent UV-VIS absorption spectra of the reaction mixture[5] of **2** and **3** in the presence (**A**) and in the absence (**B**) of **1** are given in figure 1. Production and subsequent decomposition of a band at 500 nm, indicative of formation of an intermediate, is observed in the presence of **1** (Fig. 1 **A**). However, in the absence of **1**, the broad band formed with λ_{max} at 410 (due to the product) does not decompose over time (Fig. 1 **B**), suggesting that the intermediate is not observed. The products isolated at the end of both the reactions are identical and are identified to be 4-nitro-4'-*N,N*-dimethylaminoazobenzene (**4**).

The time dependent absorption spectra which represent a cross sections of figure 1 at 500 nm are given in figure 2. In the absence of **1**, the increase in the absorbance gives an excellent fit to a first order rate law (curve A in Fig. 2). In the presence of **1**, its shape is a classical[6] example of formation, followed by decomposition of an intermediate (curve B in Fig. 2). An equation for this reaction is given in scheme I; where CD is **1**, D^+ is **2**, A is **3**, A.CD is the complex of **3** and **1**, $[A.CD.D]^+$ is the observed intermediate and P is the reaction product **4**. The absorbance at 500 nm (A_{500}) at any time can be broken down into the sum of the absorbances of the intermediate, $[A.CD.D]^+$, and of the product, (P), due to catalyzed and uncatalyzed reactions as follows:

$$A_{500} = e_1[A.CD.D]^+ + e_2[P]_{cat} + e_2[P]_{uncat} \quad \text{.......} \quad \text{Eq. 1}$$

where e_1 and e_2 are extinction coefficients for the intermediate, $[A.CD.D]^+$, and the product and $[P]_{cat}$ and $[P]_{uncat}$ are the concentrations of the product due to catalyzed and uncatalyzed reactions respectively. Expressions for the concentration of the various species formed in the reaction can be derived[6] as:

$$[A.CD.D^+] = \frac{[ACD]_o\, k_1'}{k_2 - k_1'}(e^{-k_1't} - e^{-k_2t});\; [P]_{cat} = \frac{[ACD]_o}{k_2 - k_1'}\,(k_2e^{-k_1't} - k_1'\, e^{-k_2t}) + C;\; [P]_{uncat} = a(1 - e^{-k_3t}) + C \quad \text{.....} \quad \text{Eq. 2}$$

where $[ACD]_o$ is the concentration[7] of the complex at time zero, $k'_1 = k_1\,[D^+]$ and k_3 is the pseudo first order rate constant for the uncatalyzed reaction. Fits for the calculated[8] lines to the experimental data are satisfactory (similar to the solid line curve B in Fig. 2) between pHs 4.5 and 6.5. The binding constants K_a for A.CD are in the same range as those reported[9] for complexes of aromatic substrates with **1** and the transient bright red color observed in these reactions is characterized by a high extinction coefficient for the intermediate (1×10^5 to 1×10^6).

$$\begin{aligned} AH^+ &\overset{K_H}{\rightleftharpoons} A + H^+ \\ A + CD &\overset{K_a}{\rightleftharpoons} A.CD \\ A.CD + D^+ &\xrightarrow{k_1} [A.CD.D^+] \\ [A.CD.D^+] &\xrightarrow[k_2]{} CD + P \end{aligned}$$

Scheme 1

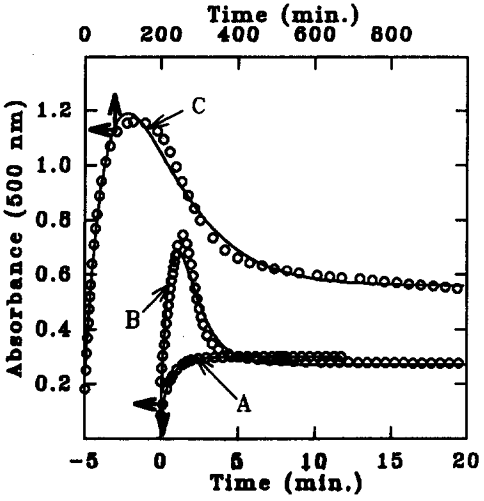

Figure 2 - Time dependent absorbance for the reaction at pH 5.5: **A** - in the absence of **1**; **B**- in the presence of **1** ; **C** - in the presence of heptakis-2,6-dimethylcyclodextrin (**5**) at pH 3.7. Circles are experimental points and the line is calculated using equations 1 and 2.

Table I: Physical constants for the reaction between **2** and **3**.

pH	k'_1 [a]	k_2 [a]	e_1 [a] $\times 10^{-5}$	K_a [a] $\times 10^{-2}$	k_3 [b]
6.5	1.4	1.4	9.1	0.85	3.1
6.0	1.0	1.1	1.1	1.2	2.4
5.5	1.2	1.0	1.4	0.65	1.4
5.3	1.3	1.3	1.5	0.67	1.3
5.15	0.88	0.99	1.7	0.86	0.91
5.0	0.85	0.75	1.6	0.89	0.67
4.8	1.0	1.0	2.0	0.74	0.49
4.5	0.63	0.55	2.2	1.1	0.27
3.7	0.01[c]	0.01[c]	8.3[c]	2.1[c]	0.02

[a] in the presence of **1**, computed using equation 1 and 2.
[b] in the absence of 1 determined using first order rate law.
[c] in the presence of **5** instead of **1**

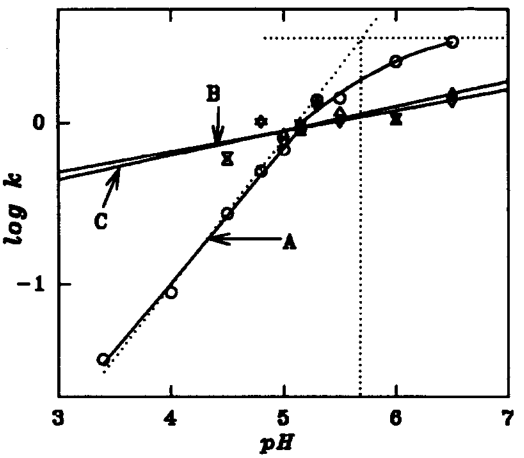

Figure 3 - *pH* profile for the reaction between 2 and 3: (○) A - uncatalyzed reaction; (△) B and (▽) C - k'_1 and k_2 respectively for the catalyzed reaction calculated using equations 1 and 2.

Coupling reactions of aryldiazonium ions with aromatic compounds in polar media proceed by formation of a σ-complex followed by proton transfer to a base or the solvent.[10] The relative magnitudes of k_1 and k_2 determine the rate limiting steps in this reaction.[11] The rate determining step changes from k_1 to k_2 in going from water to acetonitrile or nitromethane for the coupling of 4-toluenediazonium ion with *N,N*-dimethylaniline.[12] The rate limiting step in the reaction between 2 and 3 in aqueous solutions in the absence of 1 is k_1 because the proton transfer from the sigma complex to water is fast.[13] However, in the presence of 1 the sigma complex may not be accessible to the aqueous solvent depending on its orientation within the cavity of cyclodextrin. Hence, the second step (k_2) is decelerated, becomes partially rate determining, and gives rise to the time dependent absorption spectra observed in these reactions. This suggestion is supported by the pH-rate profile shown in figure 3. The reaction in the absence of 1 shows a normal rate profile for a reaction with a kinetic pK_a of the substrate of 5.7 which is close to the reported[14] pK_a (5.15) for 3 (curve A in Fig. 3). The rate constants, k_1 and k_2 in the presence of cyclodextrin seems to be relatively insensitive to changes in pH suggesting that the reacting species are not influenced by and may not be accessible to the surrounding solvent. When heptakis-2,6-dimethylcyclodextrin[15] (5) is used instead of 1, the rates of formation and decomposition of the intermediate become ten fold lower (curve C in Fig. 2, Table I). This further indicates that accessibility (hindered by the methyl groups of 5) of the reacting species to the solvent system plays an important role in these reactions.

A diazonium salt can attack the *para*-position or the nitrogen atom of 3. The former would give a σ-complex (*C*-adduct) and, the latter, a quaternary ammonium salt (*N*-adduct). Molecular orbital calculations[16] show that the energy of π - π^* transition for the *N*-adduct is lower than that for the *C*-adduct and thus λ_{max} for the former will be at a lower wavelength than that for the latter. In an attempt to distinguish between these two possible structures for the intermediate, time dependent spectra of a mixture of 1, 2 and *N,N*-dimethyl-*p*-toluidine (6) were compared with those for a mixture of 1, 2 and *p*-*t*-butyl-*N,N*-dimethylaniline (7). Formation of bands (without decomposition) with λ_{max} at 500 nm for the

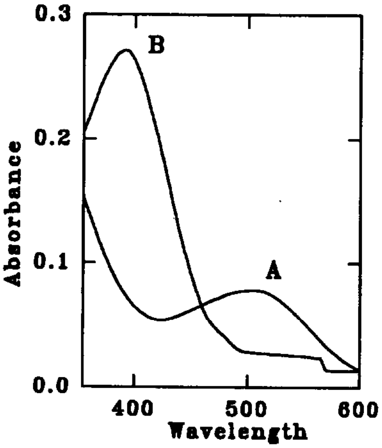

Figure 4 - Final spectra for a mixture of 1, 2 and A - *N,N*-dimethyl-*p*-toluidine; B - *p*-*t*-butyl-*N,N*-dimethylaniline at pH 4.0.

former (curve A in Fig. 4) and at 390 nm for the latter (curve B in Fig. 4) are observed. These absorption bands are not observed in the absence of β-cyclodextrin for either of the mixtures. The *ipso* attack[17] of **2** on **6** would give rise to a σ-complex. Observation of similar intermediates have been reported in aqueous bromination of phenol and *p*-cresol.[18] However, in a mixture of **2** and **7**, the electrophilic attack would be at the nitrogen atom to give the *N*-adduct because the *ipso* attack in this system would be unfavorable due to steric reasons. Thus, absorption bands with a λ_{max} at 500 nm and at λ_{max} 390 can be ascribed to the σ-complex and the *N*-adduct respectively. These observations support the view that the intermediate trapped by β-cyclodextrin in the reaction between **2** and **3**, which has an absorption band with λ_{max} at 500 nm, is the σ-complex of the electrophillic reaction.

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References

1. Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: New York, 1978.
2. D'Souza, V. T.; Bender, M. L. *Acc. Chem. Res.*, **1987**, *20*, 146.
3. Szejtli, J. *Cyclodextrin and Their Inclusion Complexes*; Academiai Kiado: Budapest, 1982.
4. Ye, H.; Rong, D.; D'Souza, V. T. *Tetrahedron Lett.*, **1991**, 5231.
5. Typical concentrations in aqueous buffer at 0°C were $[1] = 1 \times 10^{-2}$, $[2] = 5 \times 10^{-5}$ and $[3] = 3 \times 10^{-4}$. The products were compared by TLC with an authentic sample which was characterized by NMR and MS.
6. Frost, A. A.; Pearson R. G. *Kinetics and Mechanism*, 2nd ed., Wiley: New York, 1961, p 167.
7. $[ACD]_o = \{K_aK_H[CD][A]_o\}/\{(K_aK_H[CD])+(K_H+[H^+])\}$
8. The lines are calculated by Enzfitter (Elsevier-Biosoft) using experimentally determined values for $[H^+]$, e_2, k_3 and $K_H = 7.08 \times 10^{-6}$.
9. Van Etten, R. L., Sebastian, J. F., Clowes, G. A. and Bender, M. L. *J. Am. Chem. Soc.*, **1967**, *89*, 3242.
10. Carey, A. F.; Sundberg, R. J. *Advanced Organic Chemistry*; 3rd. ed. Part A, Plenum: New York, 1990; p 576.
11. Juri, P. N.; Bartsch, R. A. *J. Org. Chem.*, **1979**, *44*, 143.
12. Zollinger, H. *Acc. Chem. Res.*, **1973**, *6*, 335.
13. Zollinger, H. *Azo and Diazo Chemistry*, Interscience: New York, 1961.
14. *Handbook of Chemistry and Physics*, 70th ed., CRC press: Boca Raton, 1990, p D-161.
15. All the hydroxyl groups at the 2- and 6- position are methylated in heptakis-2,6-dimethylcyclodextrin.
16. Molecular orbital calculations were done by MINDO/3, MINDO and AM1 using the AMPAC package executed on a VAX 8600.
17. Perrin, C. L.; Skinner, G. A. *J. Am. Chem. Soc.*, **1971**, *93*, 3389.
18. Tee, O. S.; Iyengar, N. R. and Paventi, M. *J. Org. Chem.*, **1983**, *48*, 761.

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