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Photochemical Reaction between β-Cyclodextrin and p-Nitroacetophenone in an Inclusion Complex in Water Solution

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Abstract : In aqueous solution and under U.V. irradiation, p-nitroacetophenone oxidizes β-cyclodextrin to give diacetylazoxybenzene. The reaction takes place in the inclusion complex

A number of examples using cyclodextrins to alter the course of chemical (and photochemical) reactions have been reported[2-5]. These utilise the general ability of cyclodextrins to form inclusion complexes in aqueous solution with a wide variety of organic molecules. There are few report on the utilisation of the same principle to cause the cyclodextrin to react : a photochemical hydrogen-abstraction by benzophenone[6a] and an intramolecular reaction in a functionnalized cyclodextrin[6b] (see also [5]).

We wish to describe a photochemical reaction[7] in the inclusion complex using the well-established hydrogen abstracting ability of triplet-state aromatic nitro group to mediate this reaction[8]. If inclusion is stereospecific, and if a single reaction occurs in the complex, selective oxidation of one of the equivalent glucose unit may be expected. In contrast, chemical modifications, in the absence of complexation, take place on several glucose units, even though the reagents may selectively attack one site of the glucose moiety[9]. Analogous photochemical reactions in the solid state between aromatic ketones included in deoxycholic acid selectively modify deoxycholic acid[10-14].

p-nitroacetophenone (PNA) (373 mg) dissolved in a solution of 2,25 g of β-cyclodextrin (βCD) (Aldrich) (MP = 298°C) in 160 ml of water was irradiated for 8 h[15] under nitrogen bubbling. 20 ml of toluene were then added to displace any product complexed by the cyclodextrin and the mixture was extracted with ether (100 ml). 270 mg of p-nitroacetophenone and 85 mg of 4,4'-diacetylazoxybenzene[16] (97 % yield based upon consumed PNA) were obtained after chromatography on silica gel (pentane/ether, 1/1). This product has also been obtained by photochemical reaction of p-nitroacetophenone in isopropanol[16]. β-cyclodextrin has been oxidized : evaporation of the remaining aqueous phase yields after recrystallisation 1,65 g of a crystalline material X[17]. Chromatography on Sephadex[19] shows this material to be a 1:1 mixture of unreacted βCD and a "oxidized fraction" containing mainly monooxidized βCD. This compound could not be obtained in pure form, probably

because the anhydrous monooxidized ketonic βCD is in equilibrium with its hydrated form and/or an internal hemiacetal[21].

The photochemical reaction (Ar = CH_3-CO-C_6H_4, $ArNO_2$ = PNA)

$$\beta CD + ArNO_2 \xrightarrow{h\nu} \text{oxidized } \beta CD + Ar\text{–}\overset{+}{N}(\overset{-}{O})\text{=N–}Ar$$

may proceed according to the following scheme : complexation and photochemical activation (a), (b) :

$$\begin{array}{lcc} \text{(a)} & \text{PNA} + / \ \backslash & \rightleftarrows \ / \text{PNA} \backslash \\ & h\nu \ \Big\uparrow\Big\downarrow & h\nu \ \Big\uparrow\Big\downarrow \\ \text{(b)} & \text{PNA}^* + / \ \backslash & \rightleftarrows \ / \text{PNA} \backslash ^* \end{array}$$

(where / \ is βCD in water solution) in competition with reactions (c) and (d) :

$$\text{(c)} \qquad \text{PNA}^* + / \ \backslash \ \rightarrow \text{products}$$

$$\text{(d)} \qquad / \text{PNA} \backslash ^* \ \rightarrow \text{products}$$

In order to distinguish between the (c) and (d) steps, other reactions have been examined under the same experimental conditions : **(i)** when the previous reaction is performed in the presence of benzene (5 ml), the starting materials are obtained without modification. This result may be attributed to a preferential complexation of benzene by βCD, shifting equilibrium (a) towards uncomplexed PNA. **(ii)** if βCD is replaced by glycerol at the same hydroxy group concentration, the starting material is again obtained without modification. This may be interpreted as evidence for a reaction proceeding along path (d) rather than (c). **(iii)** when PNA is replaced by o-nitroacetophenone (ONA) or m-nitroacetophenone (MNA) at the same concentration, no reaction is observed. Esr spectroscopy[22] shows that only PNA is complexed by βCD.

It thus may be concluded that an inclusion complex between βCD and PNA is necessary for the photochemical reaction to take place.

As a consequence, a high percentage of unreacted βCD at the end of the reaction seems unavoidable, unless one could design a photoreagent with a very high affinity for βCD in aqueous solution. Furthermore, since conversion of PNA to diacetyl azoxybenzene requires three electrons per PNA, while oxidation of an alcool to a

ketone requires only two, the exact mechanism is probably a series of dark and/or photochemical reactions following step (d) and involving intermediate radicals and nitroso and hydroxylamine derivatives[23].

This raises the question of selectivity in the oxidation of βCD : isolation of the "oxidized βCD" in a pure form should be necessary for a definite answer. Although this is not the case, the following facts suggest that the major constituent of this fraction is βCD monooxidized at C_3 : by acetylation of crude X, an enediol diacetate is detected by ^{13}C NMR[24]. Using a standard procedure[25],a 90 mg sample of the "oxidized βCD" fraction has been converted to a mixture of alditol acetates (120 mg) consisting of 89 % glucitol acetate and 11 % allitol acetate. Monooxidation of βCD at C_3 position should give glucitol and allitol acetates in 86:14 ratio, while monooxidation at C_2 would have given mannitol (instead of allitol) acetate.

CONCLUSION :

It has been shown that a photochemical reaction between PNA and βCD, analogous to a photoaffinity reaction[26] takes place in the inclusion complex in water solution.

To make this reaction of preparative value, further work should be necessary in order to increase the affinity of receptor molecule for the photoreagent and to improve the isolation of the selectively monooxidized βCD.

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17. Crude X : mp 285°C, I.R. absorption at 1730 cm^{-1}, ^{13}C NMR : βCD spectrum[18] with an extra peak at δ = 209 ppm (relative to TMS). Both spectra indicate the presence of a carbonyl group. Mass spectroscopy (F.A.B.) : 1135 (βCD+H^+), 1133 and a weak peak at 1131 (βCD minus 2 hydrogens and 4 hydrogens).
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19. By chromatography on a G15 Sephadex column (70 cm length, 2 cm diameter) of X (500 mg) with water as an eluant, two fractions A and B were obtained :
• First eluted A (245 mg) has mp = 210°C, I.R. (KBr) $\nu_{C=O}$ at 1730 cm^{-1} and mass spectra (F.A.B.) m/z at 1151, 1133 and other peaks at 989, 973, 971 and 1007, 991, 989. The molecular peaks are consistent with an hydrated form (M_2 + H^+) = 1151, M_2 = M_1 + H_2O, of oxidized βCD (M_1 + H^+) = 1133 and fragments have lost one glucose unit (162), one oxidized glucose unit (160) or one hydrated oxidized glucose unit (178). 989 = M_2 + H^+ - 162 ; 973 = M_2 + H^+ - 178 or M_1 + H^+ - 160 ; 971 = M_1 + H^+ - 162[20]. The other molecular peaks are consistent with molecules 1007 = M_2 + H^+ - 162 + 18 ; 991 = M_2 + H^+ - 178 + 18 or M_1 + H^+ - 160 + 18 ; 989 = M_1 + H^+ - 162 + 18. These molecules are not seen in the mass spectra of crude X ; they are apparently formed by hydrolysis during evaporation of water after chromatography, since if this was not the case, they should have been eluted last.
• Second eluted B (255 mg) is unreacted βCD. M.S. m/z = 1135.
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24. Treatment of X (350 mg) for 8 days with acetic anhydride (30 ml) in pyridine (60 ml)at 20°C yields a product (500 mg) whose ^{13}C NMR spectrum shows the characteristic peaks of βCD peracetate[18a] and 4 extra peaks at δ = 131 ppm and 135 ppm (relative to TMS) (ethylinic ^{13}C) and at 167 ppm and 167,2 ppm (carbonyl ^{13}C of acetate).
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