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Complex Formation of Nitrobenzoic Acids and Some Naphthalene Derivatives with β-Cyclodextrin

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Abstract. Host–guest complexation of benzoic acid, its nitro-derivatives, 1- and 2-naphthols and 1- and 2-naphthylamines with β-cyclodextrin have been investigated by a spectrophotometric method. Formation constants for both the conjugate acid and base forms have been determined. Only in the case of 4-nitrobenzoic acid, is a more stable complex formed with the ionic species, compared with the undissociated one, supporting the assumption that resonance charge delocalisation and London dispersion interactions are responsible for their stability. With naphthalene derivatives, the 2-isomers give more stable complexes indicating deeper penetration into the cyclodextrin cavity.

Key words. β-cyclodextrin, formation constants, nitrobenzoic acids, naphthols and naphthylamines.

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides with internal cavities capable of forming inclusion complexes with hydrophobic organic and organometallic guest molecules in aqueous solutions [1–3]. These host–guest complexes have proved to be excellent model systems [4–6] for studying the nature of noncovalent bonding forces in aqueous media. They have provided valuable insights into the hydrophobic effect and London dispersion forces [7–9] and are good models for understanding the specificity of enzyme–substrate interactions [10]. Physical aspects of complexation by cyclodextrins have been extensively reported [4–9, 11]. Inclusion complexes of cyclodextrins are also found to modify the intramolecular photoreactions of guest molecules [11–14] by imposing constraints on the conformations and on the mobility of reactive intermediates.

The acid–base equilibria of several organic compounds are found to be shifted [15] in the presence of cyclodextrins. The shift is regarded as a measure of complex formation, when the stability constants related to the conjugate acid and base forms are different. Generally, cyclodextrins have been found to preferentially associate with the neutral forms of several aliphatic and aromatic carboxylic acids [16] and with the ionized form of 4-substituted phenols [17–20]. In a recent work [9], the interactions of phenol, aniline and their nitroderivatives with β-CD have been studied and the complex formation constants have been determined for both the conjugate acid and base forms. 4-Nitrophenol is the only case where a more stable complex is formed with the ionic species than with the undissociated one, supporting the concept that resonance charge delocalization and London dispersion interactions [9, 19] are important factors influencing the stability of the complexes.

Here we report the results of our investigation on complex formation of 2-, 3- and 4-nitro- and 3,5-dinitrobenzoic acids and their anions with β-cyclodextrin.

Formation constants of 1- and 2-naphthol and 1- and 2-naphthylamine complexes are also reported. The results are discussed in terms of the binding forces.

2. Experimental

β-Cyclodextrin (Aldrich) was used after recrystallisation from water. Benzoic acids were recrystallised from alcohol-water mixture. 1- and 2-naphthols (Sisco, reagent grade), 1-naphthylamine (Loba-chemie) and 2-naphthylamine (Merck) were used after distillation under reduced pressure and recrystallisation from an alcohol–water mixture. Their melting points were consistent with reported values. Buffers of different composition were chosen to be as simple as possible, and analytical grade buffer materials were used.

The formation of complexes between nitrobenzoic acids, naphthols, naphthylamines and their anions with β-CD has been investigated spectrophotometrically [21] using a Pye Unicam PU8800 UV-visible spectrophotometer at 23°C. The spectrophotometric method was based on the fact that protonation equilibria are shifted in the presence of CD and the spectra of the ionized and neutral forms are significantly different while complex formation causes only minor variations (Figure 1). Measurements were carried out at three or four different wavelengths selected

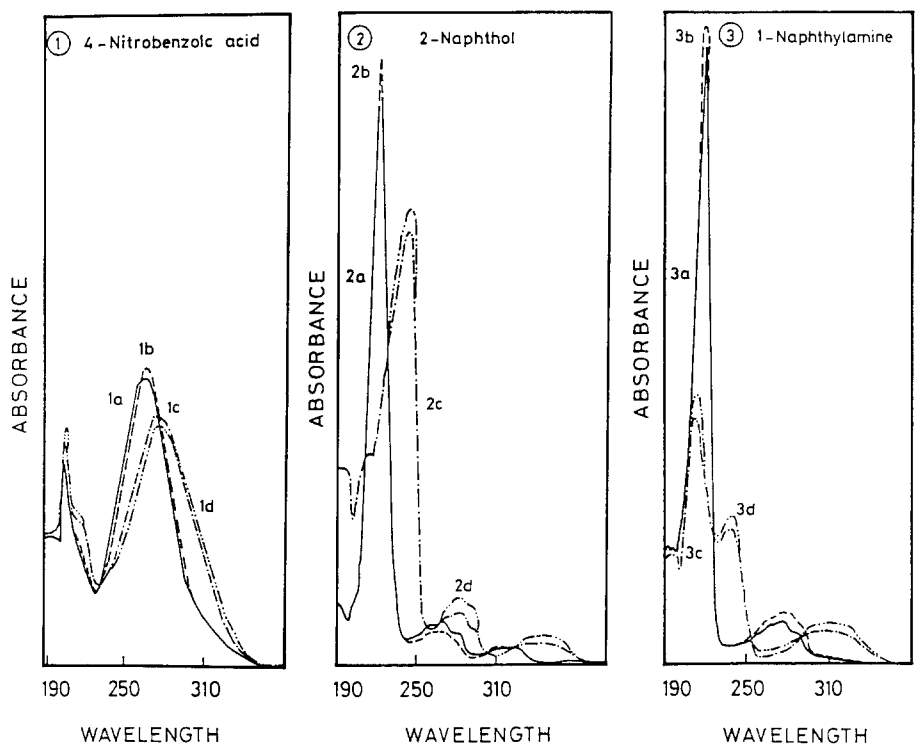


Fig. 1. UV–visible spectra of (1) 4-nitrobenzoic acid: (a) pH 1.0, (b) pH 1.0 + CD, (c) pH 7.0 and (d) pH 7.0 + CD; (2) 2-naphthol: (a) pH 7.0, (b) pH 7.0 + CD, (c) pH 10.51 and (d) pH 10.51 + CD; and (3) 1-naphthylamine: (a) pH 2.0, (b) pH 2.0 + CD, (c) pH 7.0 and (d) pH 7.0 + CD.

according to the absorption maxima of the acidic and basic forms of the free guests in solutions of different pH depending on the pK_a value of the given guest molecule.

Absorbance spectra were recorded for solutions containing varying amounts of β-CD stock solution and a constant amount of the guest. The concentration of β-CD was changed from zero to 6×10^{-3} mol dm^{-3}. A plot of $a_0 b_0/\Delta OD$ vs. $(a_0 + b_0)$ was linear with the slope and intercept being equal to $1/\Delta\varepsilon$ and $K_d/\Delta\varepsilon$, respectively (a_0 and b_0 are the concentrations of β-CD and the guest, respectively). The values of K_d were obtained from these linear plots on the basis of the Benesi–Hildebrand method [21]. The experimental conditions are reported in Table I.

3. Results and Discussion

The relationship between protonation and complex formation equilibria is represented in Equation (1), where HA denotes the protonated form (or) free acid and A denotes the unprotonated species or the ionic form (charges being omitted).

$$\begin{array}{ccc} HA + CD & \underset{\longleftarrow}{\overset{K_a}{\longrightarrow}} & A + H^+ + CD \\ \uparrow\downarrow K_{HA} & & \uparrow\downarrow K_A \\ CA{-}HA & \underset{\longleftarrow}{\overset{K}{\longrightarrow}} & CD{-}A + H^+ \end{array} \qquad (1)$$

Table I. Experimental conditions at 23°C

Guest compound[a] (pK_a)	Concentration range of host (mol dm^{-3})	pH	Wavelength (nm)
Benzoic acid (4.20)	$0-4 \times 10^{-3}$	2.2,[b] 7.0[c] 10.18[d]	265, 198
2-Nitrobenzoic acid (2.17)	$0-4 \times 10^{-3}$	1.0,[b] 7.0 10.18	265, 203
3-Nitrobenzoic acid (3.46)	$0-4.9 \times 10^{-3}$	1.0, 7.0 10.18	265, 212 198
4-Nitrobenzoic acid (3.44)	$0-4.9 \times 10^{-3}$	1.0, 7.0 10.18	272, 202 196
3,5-dinitrobenzoic acid (2.80)	$0-4.9 \times 10^{-3}$	1.0, 7.0 10.18	237, 206 195
1-Naphthol (9.39)	$0-6 \times 10^{-3}$	7.0, 10.51[d]	319, 288 226, 209
2-Naphthol (9.63)	$0-4 \times 10^{-3}$	7.0, 10.51	282, 270 232, 222
1-Naphthylamine (3.92)	$0-4 \times 10^{-3}$	2.0,[b] 7.0	275, 209
2-Naphthylamine (4.16)	$0-4 \times 10^{-3}$	2.0, 7.0	325, 280 270, 222

[a]Concentration of guest = 1×10^{-5} M. pK_a values are from Ref. 25. pH values are maintained by the following buffers.
[b]HCl and KCl.
[c]Sodium dihydrogen phosphate and disodium hydrogen phosphate.
[d]NH_3 and NH_4Cl.

It is assumed that at pH values well above pK_a (in the case of acids and naphthols) and below pK_a (with naphthylamines) ionization/protonation will be complete. The formation constants of the β-CD complexes of benzoic acid, 2-, 3-, 4-nitro- and 3,5-dinitrobenzoic acids along with those of 1- and 2-naphthols, 1- and 2-naphthylamines in their ionized and unionized forms are summarized in Table II. The 3-isomer yields complexes of comparable stability in both anionic and neutral forms. The results show that only in the case of the 4-nitrobenzoate anion is a more stable complex formed than with the undissociated acid. With all other guests the formation constants obtained for the ionized species are smaller. The observed results agree well with the formation constants reported earlier [22] for benzoic acid (1397 and 751 $dm^3\,mol^{-1}$ at 15°C and 25°C respectively). Yorozu *et al.* [23] reported that the β-naphthol/β-CD complex is characterised by a formation constant of 625 $dm^3\,mol^{-1}$ at pH 6.2.

The greater stability of the inclusion complex of the 4-nitrobenzoate anion in relation to that of the 4-nitrobenzoic acid may be interpreted in terms of dipolar interactions, London dispersion forces and also due to the enhanced mesomeric interaction (observed in the 4-isomer) between the carboxylate anion and the nitro group which increases the electron density and polarizability of the aryl ring thereby increasing the complex stability. A similar trend is observed in the case of nitrophenols [9] also, with the 4-isomer being the only case where a more stable complex is formed with the ionic species than with the undissociated ones. An enhanced mesomeric interaction as given below is possible only with the 2- and

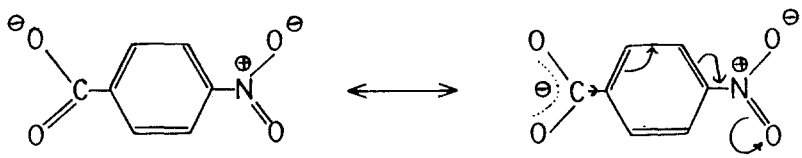


Table II. Formation constants of the β-cyclodextrin complexes

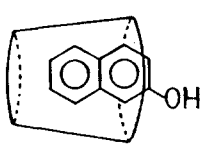
Guest compound	Unionized form (Protonated) $K_{HA}/dm^3\,mol^{-1}$	Ionized form (Unprotonated) $K_A/dm^3\,mol^{-1}$	pK^a
Benzoic acid	1380	174	5.10
2-Nitrobenzoic acid	1200	594	2.48
3-Nitrobenzoic acid	1190	1080	3.50
4-Nitrobenzoic acid	220	1470	2.62
3,5-Dinitrobenzoic acid	4170	1250	3.32
1-Naphthol	124	43	9.85
2-Naphthol	556	71	10.5
1-Naphthylamine	198	2290	2.86
2-Naphthylamine	226	6430	2.71

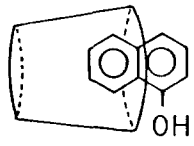
[a] pK values are obtained from K, the acid dissociation constant of the inclusion complex of the protonated guest, CD–HA using the relation $K_a/K = K_{HA}/K_A$ (Equation 1).

4-isomers thereby eliminating the 3-isomer or the unsubstituted acid. However, steric hindrance will lead to deviation from coplanarity and therefore this type of mesomeric interaction will be very much reduced in the 2-isomer. Indeed a higher formation constant is observed for the unionized form. It is to be noted here that absence of such delocalisation in cases other than the *para*-isomer leads to stronger hydration of the charged species which acts as an impediment to complexation.

With dinitrobenzoic acid, it is interesting to note that the complex is much more stable than that of the mononitrobenzoic acids. This may be attributed to hydrogen bonding between the hydroxyl groups of CD and the two nitro groups, with the carboxyl side penetrating into the cyclodextrin cavity. The contribution of hydrogen bonding towards stabilising CD complexes had also been reported by Eftink and Harrison [20] and also by Harata [24]. According to the latter, in the case of hydroxybenzoic acids and nitrophenols, the 3-isomer had a larger negative enthalpy for complex formation than the 4-isomer. In the α-CD cavity, the fit of the guest is tighter and the van der Waals' interactions are relatively stronger but there is little possibility of hydrogen bonding between the hydroxyl groups of CD and that of nitrophenol, especially in the case of the 4-isomer. With β-CD, where the cavity is larger and the fit not so tight, van der Waals' forces will be weaker and hence hydrogen bonding may contribute to the interaction and the 3-isomer offers better prospects for hydrogen bonding.

With the naphthalene systems (Table II) the complexes of the ionized species are also much less stable than those of the unionized species with the hydrophobic cyclodextrin cavity favouring the uncharged molecule in all four cases. It is interesting to note that the stability constant of the complex of 1-naphthol agrees with that of phenol (129 $dm^3\,mol^{-1}$) reported earlier [9]. In both naphthols and naphthylamines, the 2-isomers form more stable complexes than the 1-isomers and this may be ascribed to deeper penetration of the 2-isomers into the cyclodextrin cavity as it does not experience any hindrance from the hydroxyl group unlike the 1-isomers as shown below.





The larger size of the naphthylamines compared to the naphthols and the aniline/phenol systems may be attributed to an increased polarizability in naphthylamines which will increase the complex stability.

The acid dissociation constant (K) of the inclusion complex of the protonated guest (CD–HA) is obtained from the relation $K_a/K = K_{HA}/K_A$ (Equation 1). The corresponding pK values reported in Table II reflect the effect of the inclusion process on the acid-base equilibrium of the guest. It is interesting to note that only in 4-nitrobenzoic acid CD complexation increases the acid strength of the guest. With naphthylamines, complexation results in reduced basicity.

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