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Naphthalene Complexation by β-Cyclodextrin: Influence of Added Short Chain Branched and Linear Alcohols

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Abstract. Naphthalene forms 1 : 1 complexes with β-cyclodextrin (β-CD) in water. The binding constant is 377 $\pm$ 35 M^{-1}. Addition of linear or branched alcohols causes a reduction in the apparent strength of naphthalene binding (K_{app}) compared to the value in the absence of additives. For example, 1% 1-pentanol reduces K_{app} to 184 $\pm$ 31 M^{-1}. Branching does not alter K_{app} much for a given number of carbon atoms, e.g., it is 113 $\pm$ 9 $M^{-1}$for 2-pentanol and 116 $\pm$ 8 M^{-1} for 3-pentanol. The exception to this is tert-butanol for which K_{app} is 577 $\pm$ 40 M^{-1}. The variation in K_{app} as a function of [1-pentanol] yields values for the individual equilibrium constants contributing to K_{app}. This reveals that a ternary complex forms involving naphthalene, the CD and 1-pentanol. The constant for formation of the ternary complex is 99 $\pm$ 29 M^{-2}. NaI quenching of naphthalene fluorescence indicates that the CD cavity partially protects the naphthalene excited state from this water phase quencher. Interestingly, the Stern–Volmer constant is lower in the presence of 1-pentanol than in its absence, although there should be more unbound (and therefore more NaI accessible) naphthalene in the former system than in the latter. These apparently contradictory results are discussed in terms of ternary complex formation.

Key words: β-cyclodextrin, naphthalenes, alcohols, ternary complexes

1. Introduction

Control of both thermochemical [1–3] and photochemical [4–7] reactivity by cyclodextrins (CD) is well established. For example, CD-complexed reagents can exhibit photochemistry which is quite different from that observed in homogeneous solution [4–8]. Recently there has also been a lot of interest in using CDs as drug delivery media [9–13]. CDs are valuable in this context because they increase the aqueous solubility, stability and bioavailability of drugs [9–13]. CDs can also be applied as chiral discriminating compounds for chromatography [14–16] and enzymatic studies [17] as well as in analytical chemistry [16, 18, 19] and photophysics [4, 6, 20–25]. In nearly all of these applications a critical factor is

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the strength of complexation as reflected by the binding constant for inclusion of the hydrophobic "guest" molecule in the cavity of the water soluble CD "host". A number of factors influence complexation. These include the "goodness of fit" of guest to host, the hydrophobic effect, the presence of hydroxyl groups at both CD cavity entrances and flexibility of the CD framework [1, 26, 27]. Of these, the goodness of fit (i.e., size and shape matching between the guest and the CD cavity) and the hydrophobic effect appear to be most significant [1].

Recently the impact of adding a third component on CD host:guest binding has attracted attention. Studies of "third-party effects" have examined inter- and intramolecular excimer formation within CD cavities [28, 29], alteration of quenching of guest fluorescence by quenchers that might also be CD complexed [30–33], variation in chemical behavior with surfactants as the third component [34–38] and the influence of amino acids on pyrene binding [39]. Addition of small amounts of water soluble polymers to CD-drug solutions has been shown to improve drug solubility and bioavailablity relative to simple CD-drug formulations [40, 41]. In the latter context understanding the role of additives is crucial as drug formulations invariably contain excipients such as buffer salts, anti-microbial agents etc.

Alcohols have also been studied as "third parties" for a variety of CD:guest systems [18, 42–48]. The behavior of CD:guest systems has been probed by both steady-state [19, 22, 25, 32, 33, 43, 44, 46, 47] and time-resolved fluorescence [23, 25, 49] techniques. By far the largest portion of these studies have made use of polyaromatic hydrocarbons (PAHs), especially pyrene derivatives, as guests. PAHs are strongly fluorescent and bind to the CD because of their hydrophobicity [50]. Addition of alcohols can increase the extent of binding by formation of ternary CD : PAH : alcohol complexes [18, 42, 43, 46]. Similar results have been found for binding of the more water soluble α-(naphthyloxy)-acetic acid with γ-CD [50], although ternary complexes do not play a role in the β-CD:2-naphthol:alcohol systems [25]. From these studies a picture of the binding in ternary CD:PAH:alcohol complexes has been emerging. The size and geometry of the alcohol seem to be important factors [18, 42] as is its ability to alter the hydrophobicity of the CD cavity [43]. The presence of the primary and secondary hydroxyl groups of the CD are also essential for formation of ternary alcohol complexes [43], the stoichiometry of which depends on the specific guest, type of CD and type of alcohol [42, 43].

Naphthalene (NAP) is also a very convenient fluorophore for studying CD:PAH interactions. NAP binding to CDs has been studied previously [34, 51–53], as has the influence of certain alcohols on these complexes. Benzyl alcohol has been judged to form ternary complexes with β-CD and NAP based on quenching of NAP fluorescence by NaI [52]. Cyclopentanol also induces ternary complex formation as judged by solubility studies, although this system precipitates at [CD] $>$ 1 mM [53]. These seem to be the only articles addressing the impact of alcohols on complexation of unsubstituted NAP by CDs.

Alcohols and surfactants can be viewed as comparable additives in that both consist of alkyl chains terminating in polar groups. This points to an interesting dis-

crepancy in the literature concerning CD-NAP-alcohol interactions. While benzyl alcohol and cyclopentanol enhance CD-NAP binding [52, 53], the linear sodium n-alkyl sulfates, below the critical micelle concentration, are effective in causing re-distribution of NAP from the CD environment into the water phase [34]. This point, combined with the fact that the impact of linear alcohols on CD-NAP binding has not been reported, was the motivation behind the present study. In the present contribution the influence of added short chain linear and branched alcohols on the binding of NAP to β-CD is reported. This is part of an ongoing study of the influence of alcohols on the CD binding of NAP derivatives [25].

2. Experimental

NAP (Aldrich) of scintillation grade, was used as received as was sodium iodide (NaI, Merck). β-Cyclodextrin (β-CD, Aldrich) was recrystallized twice from water. All alcohols (Aldrich, Merck, Rathburn) were of spectroscopic or HPLC grade and used without additional purification. Water was conductivity grade (Lab-Ion L2 System).

Samples for fluorescence analysis were prepared as follows. A saturated solution of NAP in water was stirred overnight and then filtered. The filtered solution was ca. 0.2 mM in NAP based on its absorption spectrum. This solution was diluted with water to yield an approximately 5 μM aqueous NAP stock which was used to prepare all subsequent solutions. A 10 mM β-CD stock was prepared by weighing an appropriate mass of β-CD into a volumetric flask and diluting it with the 5 μM NAP stock. This was subsequently diluted with the 5 μM NAP stock to obtain solutions with a constant NAP concentration but the desired variable concentration of CD. If an alcohol was to be added, the neat alcohol was injected via a Hamilton microlitre syringe directly into 10 mL of the β-CD:NAP solution. The CD samples were stirred overnight to obtain equilibrium. Quencher stock solutions in water were prepared just before use by dissolving an appropriate mass of NaI in the appropriate β-CD/5 μM NAP/alcohol solution. Quenching experiments were performed by injecting small aliquots of quencher stock into 2 mL samples of β-CD:NAP solutions, with or without alcohol, immediately prior to measurement. Exposure to light was kept to a minimum during all sample preparation and handling. All samples were air saturated.

Steady-state fluorescence measurements were carried out at 20 $\pm$ 1 °C with a Perkin–Elmer LS-50B instrument. Instrument control, data collection and preliminary data processing were carried out by a micro-computer interfaced to the fluorimeter. Samples for fluorescence measurements were contained in 1×1 cm^2 standard (Hellma) quartz cuvettes. The spectra were recorded with excitation at 280 nm. Spectra were scanned between 300 and 500 nm. The band pass was typically 2 nm. The emission spectra were uncorrected. Fluorescence intensities were determined by integrating the emission spectra between 300 and 450 nm. Absorption spectra were recorded with a Lambda 40 UV-VIS spectrophotometer. The

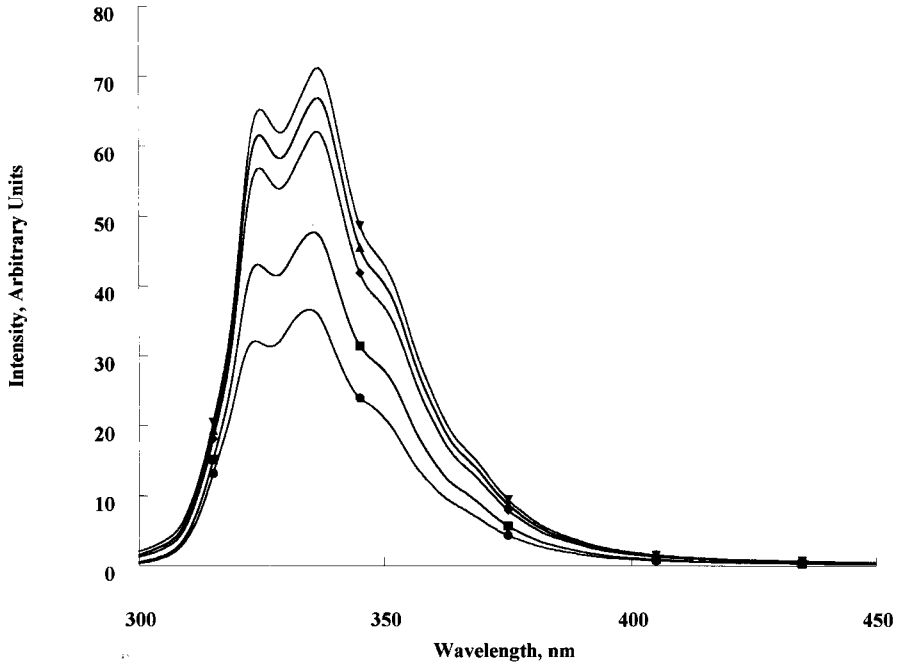

Figure 1. Naphthalene fluorescence spectra recorded in water at different concentrations of β-CD. Excitation at 280 nm. [Naphthalene] = 5 μM. [CD], from bottom to top, 0, 1, 5, 8 and 10 mM.

calculations of the association constants were performed within the Kaleidagraph (Abelbeck) framework.

3. Results and Discussion

The fluorescence intensity of NAP in aqueous solution is sensitive to added β-CD, as shown in Figure 1. Under our experimental conditions (ca. 5 μM NAP) no excimer emission is observed indicating that there are no instances of doubly occupied β-CD cavities.

When the integrated intensity values are plotted as a function of [β-CD] a typical binding isotherm [54, 55] is observed (Figure 2). According to the literature [34, 51–53] the β-CD:NAP complex is a so-called 1 : 1 complex formed via the equilibrium process

$$\text{NAP} + \beta\text{-CD} \rightleftarrows \beta\text{-CD:NAP}, \tag{1}$$

which has the binding constant defined by

$$K_1 = \frac{[\beta\text{-CD:NAP}]}{[\text{NAP}][\beta\text{-CD}]}. \tag{2}$$

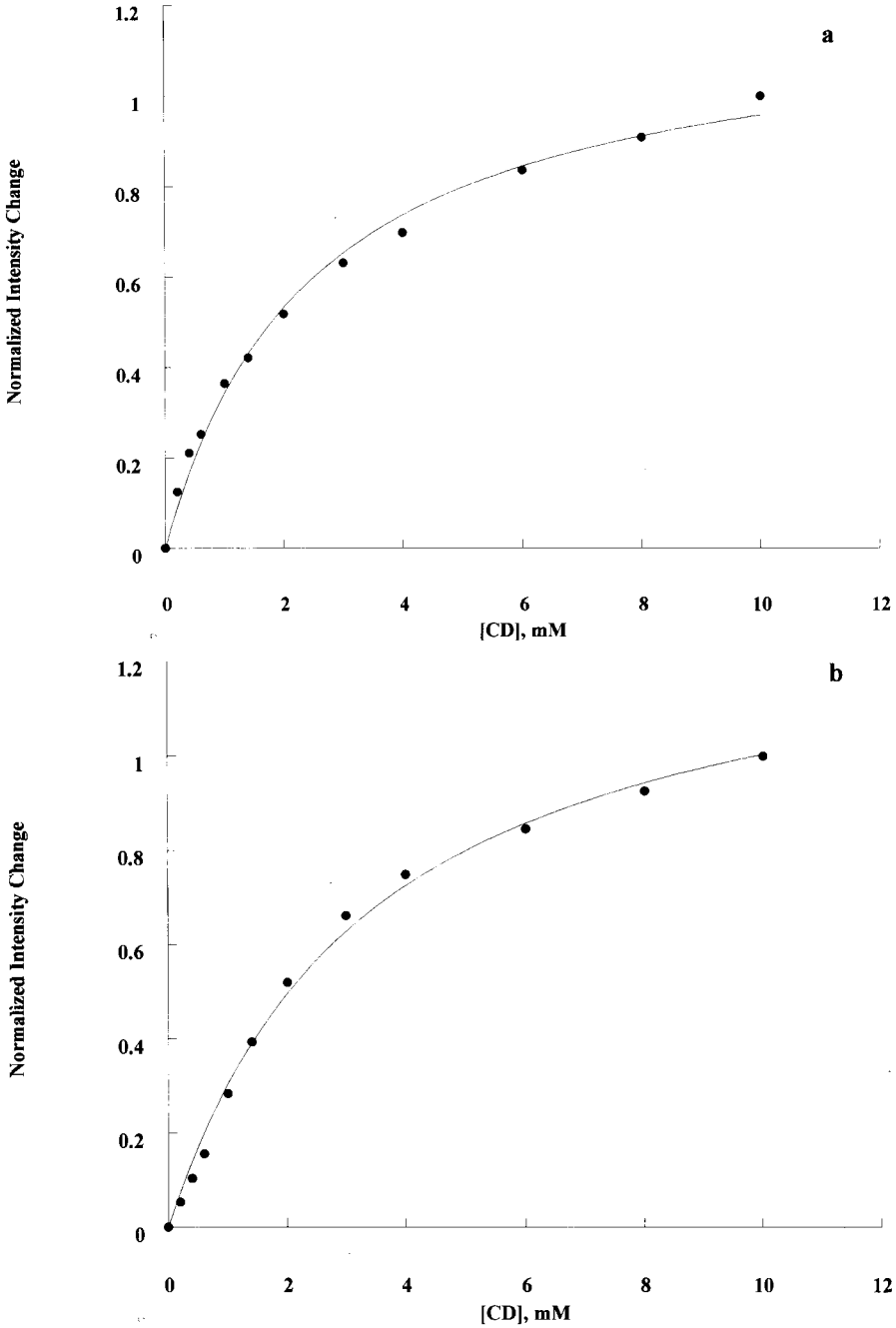

Figure 2. Binding isotherms for naphthalene complexation with β-CD in the absence (a) and presence (b) of 100 mM propanol. The solid lines represent fits of Equation (7) to the data points.

In systems containing alcohols the following two equilibria must also be considered

$$\text{ROH} + \beta\text{-CD} \leftrightarrows \beta\text{-CD:ROH}, \tag{3}$$

$$\text{ROH} + \beta\text{-CD:NAP} \leftrightarrows \beta\text{-CD:NAP:ROH}. \tag{4}$$

We can combine these two equilibria with that of Equation (1) into the general process

$$\text{ROH} + \beta\text{-CD} + \text{NAP} \leftrightarrows (\text{NAP})_{\text{bound}} \tag{5}$$

for which we can write an apparent binding constant

$$K_{\text{app}} = \frac{[\text{NAP}]_{\text{bound}}}{[\text{NAP}][\beta\text{-CD}]} \tag{6}$$

under conditions of excess alcohol. The treatment for extracting the value of K_{app} from the binding isotherm has been described previously [25, 47, 56]. Essentially the binding isotherm data are fitted by the model

$$\Delta I = K_{\text{app}} \left(\frac{\Delta i [\text{NAP}]_0 [\beta - \text{CD}]}{1 + K_{\text{app}} [\beta - \text{CD}]} \right). \tag{7}$$

The integrated emission intensities were treated according to this equation. ΔI refers to the difference between the fluorescence intensity at [β-CD] and that in the absence of β-CD. $[\text{NAP}]_0$ was held constant in all the measurements at 5 μM, and Δi reflects the maximum value of ΔI. Figure 2 shows non-linear regression fits of Equation (7) to the binding isotherm data for the aqueous system. Similar plots were obtained for the other aqueous systems examined. The K_{app} values obtained are shown in Table I. In principle it is also possible to use changes in the absorption spectrum of NAP to follow the binding process. In practice, at the low [NAP] used here, the weakness of the absorbance makes such an approach fraught with error and the fluorescence method is to be preferred.

In the absence of added alcohol the value of K_{app} obtained corresponds to K_1, the binding constant for the reaction described in Equation (1). The K_1 value we obtained for the β-CD:NAP system is somewhat lower than had been reported previously [34, 51]. However we note that the value of K_1 measured using the 1 : 1 complex model (Equation (7)) seems to depend on the concentration of NAP used (Table II). This trend may reflect the formation of higher-order complexes at higher [NAP] making the assumption of a purely 1 : 1 model invalid at higher naphthalene concentrations. The good fit of Equation (7) to our data makes us confident, however, that higher-order complexes make at most a minor contribution in our systems under our experimental conditions (5 μM NAP).

Table I. Values of K_{app} for binding of 5 μM naphthalene with β-CD in the presence of various linear and branched alcohols. The values are obtained by fitting the binding isotherms to Equation (7)

Alcohol	K_{app} (M^{-1})
None	377 ± 35[a]
Propanol	350 ± 16
1-Butanol	290 ± 25
1-Pentanol	184 ± 31[b]
2-Butanol	306 ± 32
2-Pentanol	113 ± 9
3-Pentanol	116 ± 8
tert-Butanol	577 ± 40[b]

[a] Average of 9 individual determinations.
[b] Average of 3 individual determinations.

Table II. Values of K_{app} for naphthalene binding to β-CD at different total naphthalene concentrations in the absence of alcohols

[Naphthalene] (μM)	K_{app} (M^{-1})
5	377 ± 35
17	665
50	736

The K_{app} data in Table I for the linear alcohols follow the same trend as that observed for the influence of linear alcohols on the binding of the more water soluble 2-naphthol [25] and for the influence of sodium *n*-alkyl sulfate surfactants on NAP binding to β-CD [34]. That is, the apparent binding of NAP to β-CD decreases systematically as the chain length of the linear alcohol increases. This is in marked contrast to the influence of linear alcohols on pyrene binding to β- and γ-CD. This larger PAH binds more tightly to these CDs in the presence of alcohols [18, 42, 43, 46]. These effects have been attributed to the relative size of guest, alcohol and cavity. The most favorable configuration for linear alcohols is with the tail located within the CD cavity and the hydroxyl group at the CD/water boundary [57]. With some guests this increases the hydrophobicity of the cavity by displacing included water and results in a better "fit", thus resulting in stronger complexation. Alcohol inclusion can also cause displacement from the CD in the case of other types of guests. This might happen if the available space in the cavity is insufficient for both the guest and the alcohol [18]. The conclusion seems to be

Table III. Values of K_{app} for binding of 5 μM naphthalene with β-CD in the presence of various concentrations of 1-pentanol

[1-Pentanol] (mM)	K_{app} (M^{-1})
0	377 ± 35
5	353 ± 19
10	284 ± 17
18	261 ± 32
55	185 ± 32
92	158 ± 19

that the detailed impact of alcohols on CD binding of a particular guest is intimately related to the relative sizes of the CD cavity, the alcohol and the guest [42, 44, 45]. In the β-CD:NAP system linear alcohols clearly cause displacement.

Simple branching of the alcohols (e.g., 2- and 3-pentanol vs. 1-pentanol) does not seem to change this generalization (Table I). However, the more highly branched tert-butanol enhances the β-CD:NAP binding significantly. Benzyl alcohol also improves β-CD:NAP binding [52]. An explanation consistent with the literature on CD:PAH:alcohol systems is that, in both these cases, these alcohols are able to fill space in the CD cavity left unoccupied by NAP alone. This explanation has been put forward previously [18] for the effect of large, bulky alcohols on pyrene binding to β-CD. However, since the space of the CD cavity is limited it seems unlikely that both tert-butanol and NAP are *included* in the cavity of one CD at the same time. A more likely arrangement might be a "capping" of one end of the cavity by the alcohol.

Factors other than simply relative size may play a role in determining the strength of guest binding in a given system. To gain additional insight into the β-CD:NAP system we determined the value of K_{app} at various concentrations of 1-pentanol (Table III, Figure 3). These measurements allow estimation of the three equilibrium constants K_1, K_2 and K_3 (Equations (1), (3) and (4), respectively). The relation between K_{app} and these three equilibrium constants is given by [47]

$$K_{app} = \frac{K_1 + K_2 K_3[\mathrm{ROH}]}{1 + K_2[\mathrm{ROH}]}. \tag{8}$$

K_1 is the equilibrium constant for binding of NAP to β-CD in the absence of alcohols and can be determined independently. We prefer, however, to use it as a variable which provides an internal check of the reliability of the fit.

Figure 3 shows K_{app} values for the β-CD:NAP system as a function of the 1-pentanol concentration. The data were fitted by Equation (8) and yielded an

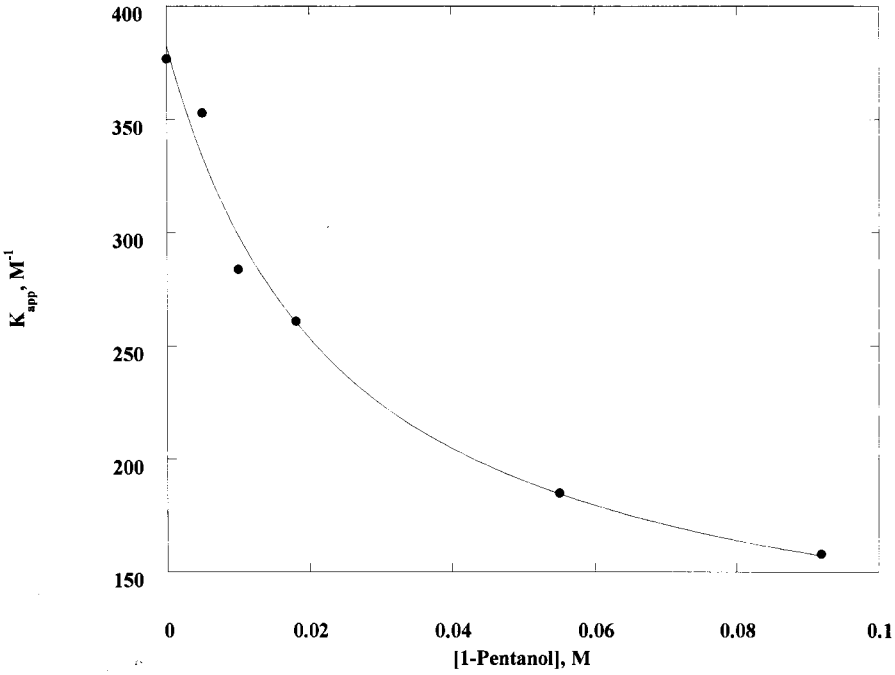

Figure 3. Variation in K_{app} for the β-CD:naphthalene system as a function of 1-pentanol concentration. The solid line represents a fit of Equation 8 to the data points.

excellent correlation. The equilibrium constants obtained from the fit were $K_1 = 383 \pm 14\ M^{-1}$, $K_2 = 42 \pm 14\ M^{-1}$ and $K_3 = 99 \pm 29\ M^{-2}$.

The K_1 value closely matches that obtained by fitting the variation in NAP fluorescence intensity in the absence of alcohol to Equation (7). The value of K_2, corresponding to the binding constant for the association of pentanol with β-CD, is in good agreement with the literature value of 63 M^{-1} [58]. This gives us confidence that our model and fitting procedure are reliable.

The results of our modeling procedures support the view that the β-CD:NAP system forms ternary complexes in the presence of linear alcohols. By contrast, the β-CD complexes of 2-naphthol do not [25]. 2-Naphthol and NAP are similar in size but nonetheless exhibit quite different complex stoichiometries in CD/alcohol solutions. Clearly it is insufficient to attribute additive effects on binding to steric issues alone at least in some cases.

Water soluble fluorescence quenchers have also been used to gain insight into the relative distribution of a guest between the aqueous and CD environments [25, 30, 52] NaI is a good choice of fluorescence quencher in this context. Iodide salts are often used to quench excited singlet states [4, 59] and NaI has at most a very weak association ($K = 18\ M^{-1}$) with the β-CD cavity [60].

We performed a series of experiments in which we used NaI to quench the fluorescence of NAP in the presence of varying [CD] either in the absence or

Table IV. Stern–Volmer constants for iodide quenching of naphthalene in the presence of β-CD with/without 93 mM 1-pentanol

[β-CD] (mM)	[Pentanol] = 0 mM K_{SV}, (M^{-1})	[Pentanol] = 93 mM K_{SV}, (M^{-1})
0	207.0	210.0
0.5	175.8	165.2
1.1	169	112.5
2.0	140	55.2
6.2	96	14.0
10.1	110	8.8

presence of 1-pentanol. Stern-Volmer plots (I_0/I_q vs. [NaI]) were measured up to 0.1 M NaI. Over the entire range of added NaI different types of behavior were observed. For example, in the absence of CD a noticeable upward curvature was detected without pentanol (Figure 4a). The exact same behavior was observed with pentanol in the absence of CD (data not shown). This can be attributed to the well known contribution of static quenching at high quencher concentrations [61, p. 268]. When no alcohol is present the Stern–Volmer plots at higher [CD] are linear (e.g., [CD] = 7 mM, Figure 4a) but they curve downward when 93 mM 1-pentanol is present (e.g., [CD] = 6 mM, Figure 4b). The latter effect suggests two different populations of NAP, one of which is not readily quenched. Because of the complex nature of the Stern–Volmer plots over this wide range of [NaI] we have focused our attention on quenching at 20 mM NaI or less. Under these conditions the plots are linear (Figure 5) in all cases and the resulting Stern–Volmer constants, K_{SV}, are presented in Table IV.

Based on the value of K_1 (*vide supra*) we can estimate that significant fractions of NAP are only complexed at [CD] $>$ 2 mM (43% complexation at 2.0 mM, 79% at 10.1 mM). Figure 5a shows that CD complexation of NAP reduces K_{SV}. As the [CD] increases, and the NAP is more completely complexed, the trend is towards lower K_{SV}. This indicates that the CD protects the NAP excited singlet from aqueous phase quenchers as reported previously for other aromatic compounds [25, 30, 51, 52, 62].

The situation when 1-pentanol is present (Table IV, Figure 5b) is more complex. K_{SV} is strongly suppressed, even at quite low [CD]. That is, the CD appears to protect NAP more effectively from the quencher when 1-pentanol is present than when there is no alcohol in the solution. This seems to contradict the data of Table I which show that K_{app} is reduced by the presence of 1-pentanol. That is, for a given β-CD concentration we would have expected to see higher values of K_{SV} in the presence of 1-pentanol than in its absence as there should be less bound NAP in

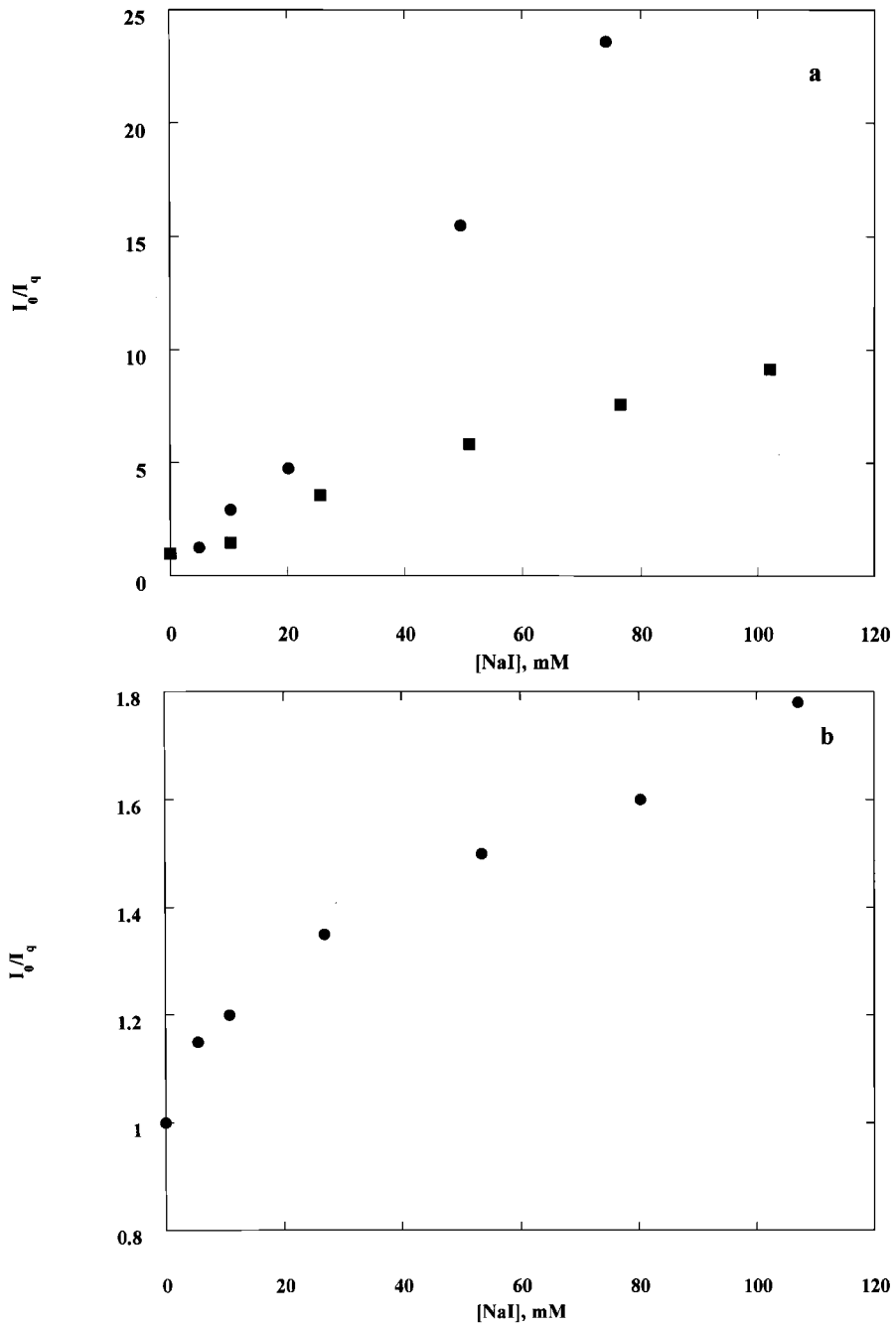

Figure 4. Quenching of naphthalene fluorescence by NaI over a wide iodide concentration range. (a) no alcohol, 0 mM (circles) and 7 mM CD; (b) 93 mM 1-pentanol, 6 mM CD.

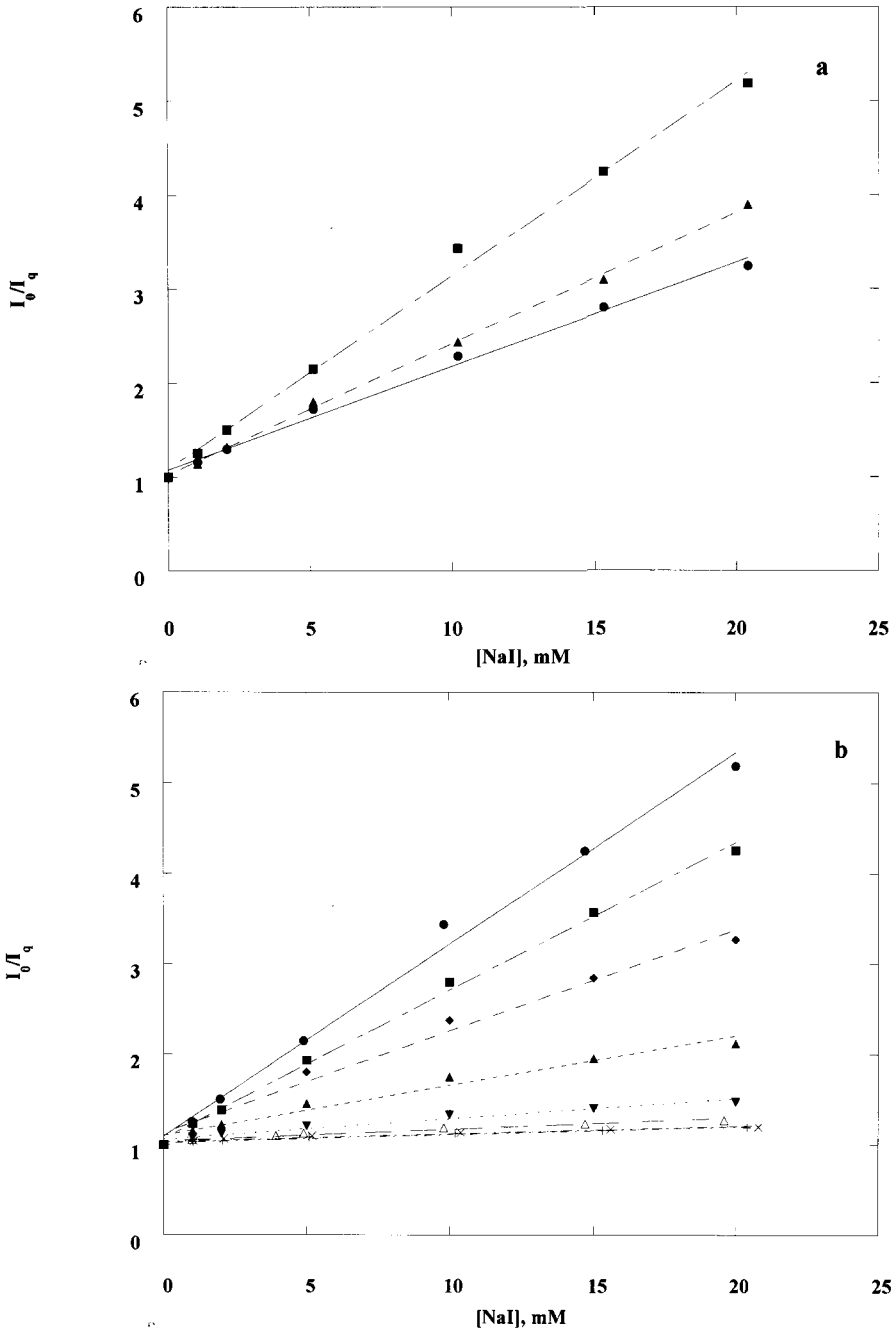

Figure 5. Stern–Volmer plots for NaI quenching of naphthalene fluorescence at various concentrations of β-CD (a) in the absence ([CD] is ■ = 0 mM, ▲ = 2.0 mM, ● = 10 mM) and (b) the presence ([CD] is ● = 0 mM, ■ = 0.5 mM, ♦ = 1.1 mM, ▲ = 2.0 mM, ▼ = 6.2 mM, △ = 8.0 mM, × = 10.1 mM) of 93 mM 1-pentanol.

the former case. Such was the situation with the 2-naphthol/β-CD/alcohol system we studied earlier [25].

The NAP system differs from the naphthol system in that a ternary complex involving the guest, the CD and the alcohol exists in the former but not in the latter. As the alcohol concentration increases so does the importance of the ternary complex. Although the ternary complex is weaker than the 1 : 1 complex (i.e., $K_3 < K_1$) it will nonetheless dominate at higher alcohol levels. In fact, at 100 mM added pentanol the concentration of ternary complex will be about 10 times that of the 1 : 1 complex based on the K_3 value (*vide supra*). So the fluorescent species we are trying to quench in the presence of added pentanol is quite different from the species we are trying to quench in the alcohol free system.

Earlier reports have shown [45, 52] that ternary complexes are very effective at inhibiting quenching of a fluorescent guest by a primarily aqueous phase quencher. This is presumably because the alcohol partially blocks access of the quencher to the fluorophore in such aggregates. It is informative, then, to compare the impact of adding 1-pentanol on the values of K_{app} and K_{SV}. Using Equation (6) and the K_{app} values from Table III, one finds that at 10 mM β-CD the concentration of bound NAP in the absence of 1-pentanol is about 4 μM. This is reduced by a factor of 1.3 to 3.1 μM when the [1-pentanol] is 93 mM. By contrast K_{SV} = 110 M^{-1} at 10 mM CD, 0 mM 1-pentanol and is reduced by a factor of about 12 to 8.8 M^{-1} when 93 mM 1-pentanol is added. That is, addition of the alcohol does displace some naphthalene from CD complexes but the bulk (3.1 μM of a total of 5 μM or 62%) of it stays complexed even at the highest 1-pentanol concentration used.

Of that 62% of NAP which remains bound even in the presence of 1-pentanol some will be in the form of a 1 : 1 complex but some will be in the form of a ternary complex. The equilibrium expressing ternary complex formation is given in Equation (4) with the equilibrium constant K_3 = [Ternary complex]/([1 : 1 complex][1-pentanol]). The value of K_3 is about 99 M^{-2} based on our data fit. Since [1-pentanol] is in such large excess it can be treated as a constant and we obtain a ratio [Ternary complex]/[1 : 1 complex] close to 10. As indicated above, calculations based on K_{app} indicate that 3.1 μM NAP is in the bound form at 10 mM CD, 93 mM 1-pentanol. The figure is 0.4 μM bound at 0.5 mM CD, 93 mM 1-pentanol. At any given [CD], $[NAP]_{bound}$ = [1 : 1 complex] + [Ternary complex]. Combining this mass balance expression with the ratio [Ternary complex]/[1 : 1 complex] = 10, we can calculate that when $[NAP]_{bound}$ = 0.4 μM (i.e., at 0.5 mM CD), [1 : 1 complex] = 0.04 μM and [ternary complex] = 0.36 μM. When $[NAP]_{bound}$ = 3.1 μM (i.e., at 10 mM CD) [1 : 1 complex] = 0.29 μM and [ternary complex] = 2.9 μM. In other words, at high [1-pentanol] about 90% of bound NAP is in the form of a ternary complex involving the NAP, β-CD and the alcohol, even at the lowest [CD]. Thus our results can be explained by postulating that the expected increase in quenching efficiency that would accompany a relocation of NAP into the aqueous phase as 1-pentanol is added is more than offset by the greater protection offered the fluorophore in ternary complexes, the dominant form

of NAP when 1-pentanol is present. An alternative explanation, that there may be complexation between NAP and 1-pentanol, does not apply as the Stern–Volmer constant is independent of [1-pentanol] in the absence of β-CD (Table IV).

NaI quenching of NAP fluorescence was used to establish the formation of a ternary β-CD:NAP:benzyl alcohol complex [52]. No direct measurements of the influence of benzyl alcohol on the binding (K_{app}) of NAP to β-CD were reported by these authors but the quenching data supported the hypothesis that NAP binding was enhanced by benzyl alcohol. By contrast sodium n-alkyl sulfate surfactants, linear additives analogous to the linear alcohols, caused displacement of NAP from the β-CD cavity as judged by direct measurement of binding constants [34]. The current contribution sheds some light on this apparent discrepancy. Our work shows that linear alcohols can reduce K_{app} and induce formation of ternary complexes of β-CD and NAP at the same time. At high alcohol concentration (e.g., 93 mM 1-pentanol) they cause modest displacement of NAP from the CD environment (reflected in a decrease in K_{app}) but over 60% of the NAP remains bound in a relatively unquenchable ternary complex resulting in a reduced Stern–Volmer constant.

The present study shows that the behavior of β-CD and naphthalene derivatives in the presence of alcohols is complicated. With naphthalene itself both linear and non-linear alcohols can lead to formation of higher order complexes. This is in contrast to the β-CD/2-naphthol/alcohol systems in which no ternary complexes form, although the two fluorescent guests are structurally similar. This underscores the difficulties one may encounter in trying to develop commercial applications of CDs, such as drug formulations.

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