

Binary and Ternary Complexes Containing α -Cyclodextrin and Bromonaphthalene Derivatives: A Note of Caution in Interpreting UV Absorption Spectral Data

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Ultraviolet absorption spectra, NMR spectra, and phosphorescence measurements were used to confirm that α -cyclodextrin (CD) and 2-bromo-6- β -D-glucopyranosidyl naphthalene (BGN) form only a binary complex and to characterize its properties. The binding constant for the CD·BGN complex was found to be $886 \pm 24 \text{ M}^{-1}$ and $770 \pm 110 \text{ M}^{-1}$ from NMR and UV absorbance measurements, respectively. Comparison of spectral properties revealed the CD·BGN complex to be binary and complexes containing CD and *n*-alkoxy (*n*-alkanoloxo) derivatives of 2-bromonaphthalene (N) to be of higher order, notably ternary. A red shift was observed in the UV absorption spectra of the CD₂·N complexes. The absence of a hydroxyl hydrogen atom on the naphthalene ring of N molecules made it impossible for hydrogen bond formation to a glucosidic oxygen in the CD cavity to be the cause of the red shift. The similar red shifts reported herein and for the ternary complexes of CD with 2-naphthol and 2-bromo-6-hydroxynaphthalene (BOHN) indicated that hydrogen bond formation between the hydroxyl hydrogen and glucosidic oxygen atom might not be the cause of the red shift for the latter guest molecules, as has been proposed previously. This result emphasizes the caution necessary in using UV absorption spectral data as evidence for hydrogen bond formation in molecular complexes containing CD.

Introduction

Supramolecular chemistry continues to develop, and future growth in this field will be guided by an improved understanding of intramolecular and intermolecular interactions, especially noncovalent interactions such as hydrophobic interactions and hydrogen bonding. Toward this end the best model systems of molecular complexes are those consisting of sufficiently small molecules to produce molecular complexes with reasonably defined geometries in which interactions between specific atoms can be probed. As a result, molecular complexes have been extensively studied that contain as host molecules calixarenes, crown ethers, and cyclodextrins, which are the subject of the research described herein.^{1,2}

Cyclodextrins have been among the most frequently studied molecules in supramolecular chemistry.³ They have been used in food, cosmetic, and toiletry applications,^{4–6} in drug stabilization and delivery technology,^{7,8} in pesticide formulations, by biotechnological industries,^{4,6} for analytical applications,⁹ for use as part of an optical thermometer,¹⁰ and for polyrotaxanes in which two or more cyclodextrin host molecules slide along a single long-chain guest molecule.^{11,12} Numerous attempts have been made to characterize the interactions responsible for formation and stabilization of such molecular complexes.^{13,14} Since the cyclodextrin cavity is relatively hydrophobic, it is perhaps natural to focus on van der Waals interactions, which can generally be regarded as being somewhat diffuse and having little directionality in space. Despite this general presence of hydrophobic and van der Waals forces, it has been demonstrated that hydrogen bonding between the guest molecule and hydroxyls of the cyclodextrins can also play an important role.^{15–19} For instance, chemical groups that make the smallest possible

chemical perturbation have been successively added to guest molecules.²⁰ By comparing the values of the thermodynamic quantities in the presence and absence of the additional interactions, the individual contributions of hydrogen bonds to the thermodynamic stability of the complexes have been measured. When the specific atoms involved in hydrogen bonds can be identified, specific information about the geometry of the complex can sometimes be gained. Because of the importance of such structural information it is imperative that the use of different types of experimental evidence for the existence of hydrogen bonds be thoroughly understood. Furthermore, the logical design of binary and ternary complexes of cyclodextrins depends on a knowledge of the relative importance of hydrogen bonding in stabilizing such complexes.

One type of evidence for the formation of hydrogen bonds has come from ultraviolet absorption spectroscopy. For instance, the 2 nm red shift in the UV absorption spectrum of 4-hydroxyphenethylamine (tyramine) that occurs upon formation of a 1:1 complex of tyramine and β -cyclodextrin in aqueous solution buffered at pH 6.9 has been attributed to the formation of a hydrogen bond between the tyramine hydroxyl group and β -cyclodextrin.²⁰ A new band appears at 335 nm in the absorption spectrum of 2-naphthol when it is incorporated into 1:1 and 1 guest/2 host complexes with α -cyclodextrin (CD) at a concentration of 0.0657 M.²¹ The new band is red shifted by 8 nm from the absorption band for unbound 2-naphthol in aqueous solution and has been proposed as most likely due to the formation of a hydrogen bond between the hydroxyl hydrogen of 2-naphthol and an oxygen of a glucosidic link of the cyclodextrin.²¹ Attribution of the red shift to hydrogen bond formation is based on numerous well-established studies of the effects of solvents with a range of polarity and hydrogen bond-forming ability on absorption bands of different solutes.^{22–24} The purpose of this paper is to demonstrate that a red shift in

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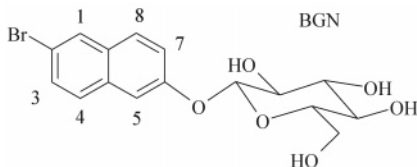
the first UV absorption band of molecules such as 2-naphthol when complexed with CD need not be caused by hydrogen bond formation in which the hydroxyl group is the hydrogen donor and that, in general, care must be taken in interpreting spectral shifts in solute (guest) molecules. In particular, it is reported that a sizable red shift occurs when ternary complexes are formed between CD and bromonaphthalene derivatives that do not possess a hydroxyl group, and alternate explanations are suggested.

Experimental Section

Model for Complex Formation and Methods of Data Analysis. Previous ultraviolet absorption results for 2-bromo-6-hydroxynaphthalene (BOHN) in solutions containing a range of initial CD concentrations ($[CD]_0$) have been successfully interpreted by assuming the formation of binary and ternary complexes.^{25,26} The same assumption is made herein for some of the complexes, and the binding equilibria are represented in the following equation, in which N refers to a bromonaphthalene derivative guest molecule, and K_1 and K_2 denote the binding constants for the binary and ternary complexes, respectively.



Crucial to the work reported herein is the need to know the spectral features associated with binary and ternary complexes. For this purpose the properties of the binary complex formed between 2-bromo-6- β -D-glucopyranosidynaphthalene (BGN) and CD were characterized by several studies, including UV absorption and NMR spectroscopy.



When only a binary complex is formed via the first equilibrium in eq 1, the total absorbance equals the sum of the N and $CD \cdot N$ absorbances and is given by eq 2, where l is the cuvette path length, ϵ_0 and ϵ_1 are the molar absorptivities of N and $CD \cdot N$, respectively, and $[CD \cdot N]$ is given by eq 3.

$$\frac{A}{l} = \epsilon_0([N]_0 - [CD \cdot N]) + \epsilon_1[CD \cdot N] \quad (2)$$

$$[CD \cdot N] = \frac{1}{2} \left([N]_0 + [CD]_0 + \frac{1}{K_1} - \sqrt{([N]_0 + [CD]_0 + \frac{1}{K_1})^2 - 4[N]_0[CD]_0} \right) \quad (3)$$

The value of ϵ_0 was obtained from measurements of the absorbance at 331 nm versus guest concentration in solutions containing no CD. Values ϵ_1 and K_1 were obtained by fitting to eq 2 absorbance values recorded at 331 nm as a function of $[CD]_0$ by using the Levenburg–Marquardt nonlinear regression program available with Mathematica software.²⁷

When both binary and ternary complexes are formed, and as in the experiments described herein, the condition is satisfied that $[CD]_0 \gg [N]_0$, then eq 4 can be used to fit experimental data.^{26,28} ϵ_2 is the molar absorptivity of the ternary complex. A unique value of ϵ_0 is obtained

$$\frac{A}{l} = \frac{[N]_0(\epsilon_0 + \epsilon_1 K_1 [CD]_0 + \epsilon_2 K_1 K_2 [CD]_0^2)}{(1 + K_1 [CD]_0 + K_1 K_2 [CD]_0^2)} \quad (4)$$

from a Beer–Lambert plot for a solution containing only the guest molecule, and a unique value of ϵ_2 is obtained by extrapolation of the absorbance to infinite $[CD]_0$. These values of ϵ_0 and ϵ_2 are used in fitting absorbance versus $[CD]_0$ data to eq 4 which yields a nonunique set of ϵ_1 , K_1 , and K_2 values.

In NMR spectra the peak(s) for each of the naphthalene ring protons in BGN were assigned on the basis of the similarity between the NMR spectra for BGN and BOHN.²⁸ A standard method was used to measure the binding constant for formation of the binary complex of BGN and CD.²⁹ The chemical shift for each ring proton is represented as the linear combination of the chemical shifts for BGN in the bound and unbound states, each term weighted by its mole fraction. The chemical shift difference, $\Delta\delta$, which is defined as the difference between the observed chemical shift at each CD concentration and the chemical shift when $[CD] = 0$, is given by eq 5 in which $\Delta\delta_\infty$ is the chemical shift difference extrapolated to infinite CD concentration.

$$\Delta\delta = \frac{\Delta\delta_\infty [CD \cdot N]}{[N]_0} \quad (5)$$

The values of K_1 and $\Delta\delta_\infty$ are determined by using a nonlinear regression routine to fit the experimental values for $\Delta\delta$ to eq 5, in which $[CD \cdot N]$ is given by eq 3.

Chemicals and Sample Preparation. Water was deionized with a Barnstead EASY pure water purification system and typically had a resistivity of 18 megohms cm or higher.

2-Bromo-6- β -D-glucopyranosidynaphthalene (BGN) and 2-bromo-6-methoxynaphthalene (BMN) were obtained from Sigma-Aldrich. α -cyclodextrin (CD) samples were obtained from Sigma-Aldrich and as a generous gift from Cerestar USA, Inc. of Indianapolis (lot no. G 8071–2). 2-Bromo-6-ethoxynaphthalene (BEN), 2-bromo-6-*n*-butoxynaphthalene (BBN), and 2-bromo-6-*n*-pentoxynaphthalene (BPn) were obtained from Key Organics. The D_2O solvent used in NMR experiments had a stated atom purity of 99.9% and was obtained from Sigma-Aldrich. Other purchased chemicals were of the highest purity and were used without further purification. 2-Bromo-6-(3-hydroxypropoxy)naphthalene (BPOHN) was synthesized using a modified Williamson ether synthesis,³⁰ and the structure was confirmed by NMR spectral analysis.

For all absorption spectroscopy experiments with BGN, a 1.2×10^{-4} M solution was prepared in water solvent. A 0.10 M CD stock solution was prepared by dissolving a weighed amount of CD in the BGN solution. Samples with constant BGN concentration and different CD concentrations were prepared by serial dilution of the stock solution with different volumes of the 1.2×10^{-4} M BGN solution. Solutions containing 0.2×10^{-4} M BPOHN and different CD concentrations were prepared similarly using water solvent. Absorption spectra were also recorded of solutions containing 0.2×10^{-4} M BPOHN and CD concentrations of zero and 0.075 M in a 3.7% methanol solvent (v/v).

Because of their low solubility in water, absorption spectra of BMN and BEN were recorded using methanol/water solvents containing 3.7% methanol (v/v) and 6.7% methanol (v/v), respectively. Solubilization of BBN required a higher concentration of methanol. However, the wavelength of the first peak in the UV absorption spectrum of BBN, λ_A , was found to decrease

linearly with decreasing methanol concentration and was estimated by extrapolation to zero methanol (334.7 nm).

To obtain absorption spectra of molecular complexes, solutions of BMN, BEN, BBN, and BPEN were prepared by sonicating or stirring solid guest samples into aqueous 0.10 M α -cyclodextrin solution until the solution first became cloudy, at which point the solution was filtered through a Millex 0.22 μ m filter. Light absorption by the guest molecules in these solutions was generally greater than 0.02, indicating the presence of roughly similar amounts of complexed guest molecules as in solutions containing the more water soluble BPOHN guest. To obtain plots of ultraviolet absorption vs CD concentration for solutions containing BMN and BEN, a similar procedure was used, except that the solvent included 3.7% methanol and 6.7% methanol for BMN and BEN, respectively. Samples at different CD concentrations were prepared by serial dilution of the stock solution with solutions containing BMN in 3.7% methanol and BEN in 6.7% methanol.

Phosphorescence intensity measurements were made on aqueous solutions, all of which contained 0.075 M CD and sufficient guest molecule to produce the same absorbance of 0.095. BMN, BPOHN, and BGN were used as the guest molecules.

The BGN concentration was 1.2×10^{-4} M, and the CD concentration ranged from 0 to 0.075 M for the NMR spectroscopy experiments.

Instrumentation and Theoretical Calculations. A Cary Bio-100 UV/visible spectrophotometer was used to record absorption spectra. UV absorbance was plotted versus $[CD]_0$ for solutions of BGN and BPOHN at the wavelength of the first spectral peak, 331 and 343 nm, respectively. Samples were contained in 1.0 cm cuvettes thermostated to within 0.1 $^{\circ}$ C in a metal housing, through which water flowed from a temperature-regulated circulating water bath.

Phosphorescence spectra were recorded with a SPEX Fluoromax-3 spectrophotometer at room temperature. The relative quantum yields of phosphorescence for different CD complexes were determined by using an excitation wavelength of 313.3 nm and measuring the phosphorescence intensity at 515.0 nm, the wavelength of maximum phosphorescence intensity. For both absorption and phosphorescence measurements, each sample was contained in a 1-cm² quartz cuvette that was stoppered by a Teflon plug fitted into a ground-glass opening.

NMR spectra were recorded at ambient temperature with a JEOL Eclipse 400 MHz FT-NMR spectrometer. Adequate signal was achieved by collecting and averaging approximately 2000 transients per sample. Chemical shifts were expressed in ppm relative to the external standard 3-(trimethylsilyl)-1-propionic-2,2,3,3-*d*₄ acid in D₂O. The stated uncertainties for all experimentally determined K_1 and K_2 values are standard deviations.

Molecular mechanics computations were implemented using the Amber 99 force field with HyperChem Professional 7.5 software on the Microsoft Windows XP platform. The structure of CD was obtained from reported neutron diffraction crystallography results and optimized in vacuo in the force field.³¹ A binary complex structure was produced by placing the optimized CD near the optimized guest in a large number (~ 200) of initial orientations and allowing the system to find an energy-minimized structure by following the path of steepest descent (Polak–Ribiere minimization algorithm).³² This led to the discovery of ~ 30 different conformers (local energy minima in conformational space), and the conformer of lowest energy was assumed to be the minimum-energy binary structure. The lowest energy conformer for each guest molecule involved

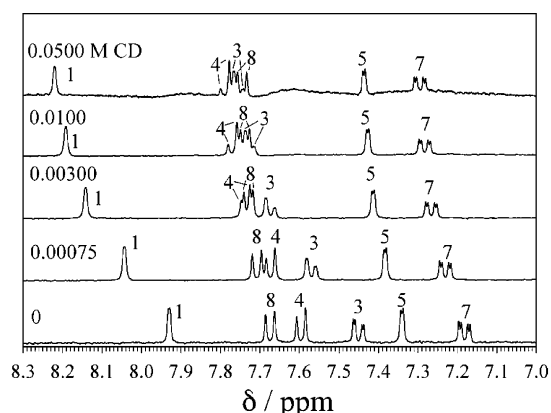


Figure 1. ^1H NMR spectra of BGN in D₂O containing different CD concentrations given at the left-hand side of the spectra. Numbers near the signal peaks represent proton positions in BGN. $[\text{BGN}]_0 = 1.2 \times 10^{-4}$ M for all samples.

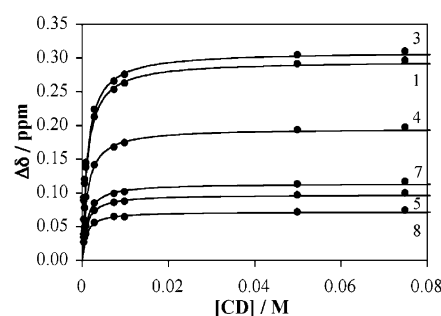


Figure 2. Plots of observed $\Delta\delta$ values for all naphthalene ring protons of BGN (denoted by numbers above the curves) versus the α -cyclodextrin concentration. The solid curves are the best fits of the $\Delta\delta$ values to eq 5.

partial inclusion of the naphthalene moiety into the cyclodextrin cavity in such a way that the long symmetry axis of the naphthalene moiety was within roughly $\pm 20^{\circ}$ of being parallel to the symmetry axis of the CD. Conformations where opposite ends of the naphthalene moiety were placed in the CD cavity were similar in energy, differing by typically less than 5%.

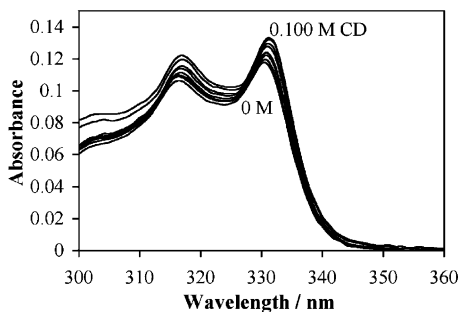
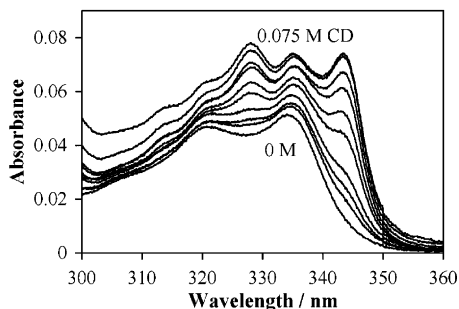
The structures of ternary CD complexes were then found by placing a second optimized host structure near the minimum-energy binary structure and following the same procedure as above. Both head-to-head and head-to-tail conformations of the CDs were considered, and it was found that head-to-head conformations generally had significantly lower energy, probably owing to improved hydrogen-bonding interactions between CD molecules.

Results

Figure 1 shows the FT NMR spectra for solutions containing the same amount of BGN and different initial CD concentrations. Figure 2 contains plots of the chemical shift differences for the six naphthalene ring protons in BGN versus $[CD]_0$. The curves are the nonlinear least-squares fits of the data to eq 5. The values of K_1 obtained from the six curves in Figure 2 had a standard deviation of 13% from the mean value. However, the best value of K_1 ($886 \pm 24 \text{ M}^{-1}$) was taken to be that for H-1 because the corresponding peak has a large chemical shift difference and remains isolated at all values of $[CD]_0$ so that its measured value does not require deconvolution from overlapping peaks. The uncertainties in K_1 values determined from the plots for H-3, H-4, and H-8 are larger because of the overlap between the chemical shifts for these protons at higher $[CD]_0$.

TABLE 1: Chemical Shifts and Chemical Shift Differences of Protons 5, 7, and 8 for BGN and BOHN When Bound and Unbound to CD in 0.010 M CD

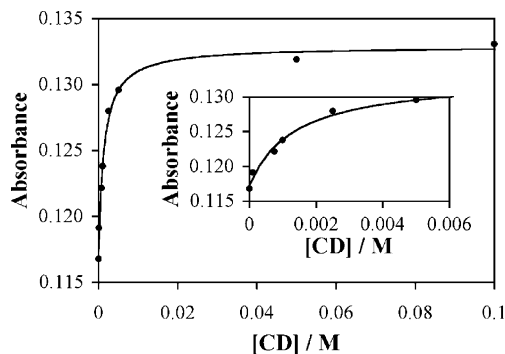
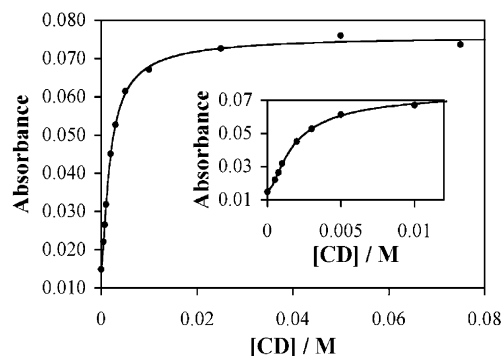
molecule(s)	δ_5 (ppm)	$\Delta\delta_5$ (ppm)	δ_7 (ppm)	$\Delta\delta_7$ (ppm)	δ_8 (ppm)	$\Delta\delta_8$ (ppm)
BOHN ^a	7.26		7.22		7.82	
BOHN/CD ^a	7.73	0.47	7.46	0.240	8.07	0.25
BGN	7.340		7.182		7.674	
BGN/CD	7.427	0.087	7.283	0.101	7.738	0.064

^a Data are from ref 28.**Figure 3.** Absorption spectra of BGN in aqueous solutions at 25.0 °C containing different α -cyclodextrin molarities of 0, 1.0×10^{-4} , 7.5×10^{-4} , 0.0010, 0.0025, 0.0050, 0.050, and 0.10. The absorbance was observed to increase monotonically between 0 and 0.100 M CD. $[\text{BGN}]_0 = 1.2 \times 10^{-4}$ M.**Figure 4.** Absorption spectra of BPOHN in aqueous solutions at 25.0 °C containing different α -cyclodextrin molarities of 0, 5.0×10^{-4} , 7.5×10^{-4} , 0.0010, 0.0020, 0.0030, 0.0050, 0.010, 0.025, and 0.10. The absorbance increased monotonically between 0 and 0.100 M CD. $[\text{BPOHN}]_0 = 2 \times 10^{-5}$ M.

and the uncertainties in K_1 values determined from the plots for H-5 and H-7 are relatively large because of their small chemical shift differences over the range of $[\text{CD}]_0$. It is significant that all of the plots in Figure 2 are hyperbolic and approach an asymptotic maximum rather than pass through a maximum value and/or show sigmoidicity, as has been reported for some of the naphthalene protons of BOHN in complexes with CD.²⁸

Table 1 compares the chemical shift differences for protons 5, 7, and 8 in the BGN/CD and BOHN/CD complexes for 0.010 M CD solutions and shows that the $\Delta\delta$ values for these protons are much smaller in BGN than in BOHN.²⁸ This result is consistent with the occurrence of weaker interactions between a CD molecule and protons 5, 7, and 8 of BGN than of BOHN. Proper comparison of $\Delta\delta$ values for two guest molecules is dependent on the relative concentrations of bound and unbound guest molecules. However, for $[\text{CD}]_0 = 0.010$ M it is expected that most of the BGN and BOHN is bound to CD.

Figures 3 and 4 show the absorption spectra for BGN and BPOHN, respectively, in the wavelength range 300–360 nm for different $[\text{CD}]_0$ s. The former spectra show very little red shift, and the latter show a large red shift. Although not shown

**Figure 5.** Absorbance of BGN at 331.0 nm as a function of the α -cyclodextrin concentration. The solid curve is the best fit of the data to eq 2 for which $K_1 = 770 \pm 110 \text{ M}^{-1}$. The inset emphasizes the hyperbolic shape of the plot at low concentrations. $[\text{BGN}]_0 = 1.2 \times 10^{-4}$ M.**Figure 6.** Absorbance of BPOHN at 343.0 nm as a function of the α -cyclodextrin concentration. The solid curve is the best fit of the data to eq 4. The inset emphasizes the sigmoidicity of the plot at low concentrations. $[\text{BPOHN}]_0 = 2 \times 10^{-5}$ M.

here, the absorption spectra for BMN, BEN, BBN, and BPeN display the same new red-shifted peak and five-peak profile upon complexation with CD. The same spectral change has been reported for formation of ternary complexes between BOHN and 2-naphthol and CD.^{21,25} Thus, the 8–9 nm red shift apparently is observed only when the substituent at the 6 position of the naphthalene ring is sufficiently small to permit encapsulation of the 6-position end of the naphthalene by a second CD molecule (vide infra).

Figures 5 and 6 compare plots of absorbance at λ_A for BGN and BPOHN, at 331 and 343 nm, respectively, versus $[\text{CD}]_0$. The curves through the plots in Figures 5 and 6 are the best fits to eqs 2 and 4, respectively. The plot for BGN is a simple hyperbola, whereas the plot for BPOHN shows subtle but significant sigmoidicity at low $[\text{CD}]_0$. Similar sigmoidicity is observed in the corresponding plot for BOHN.^{25,26} Although the spectra are not shown here, a similar sigmoidicity has also been observed in plots of absorbance versus $[\text{CD}]_0$ for BMN and BEN. For BGN the measured value of ϵ_0 equals $980 \pm 40 \text{ M}^{-1} \text{ cm}^{-1}$, and the values of ϵ_1 and K_1 obtained from the fitted curve in Figure 5 equal $1100 \pm 40 \text{ M}^{-1} \text{ cm}^{-1}$ and $770 \pm 110 \text{ M}^{-1}$, respectively. The reliability of the fitted K_1 value is noted from the fact that the values of K_1 obtained from UV absorbance and NMR data are in agreement. Also, when all three terms ϵ_0 , ϵ_1 , and K_1 are obtained by fitting to eq 2, the fitted value of ϵ_0 is within the uncertainty range of the experimental value.

In general, greater uncertainty accompanies values of K_1 and K_2 obtained from fitting of data to eq 4 for a ternary complex because it is not possible to obtain a unique set of values for ϵ_1 , K_1 , and K_2 . Moreover, the fitted values of K_1 and K_2 depend on the fitted value of ϵ_1 . For BPOHN the values of ϵ_0 and ϵ_2

TABLE 2: Wavelength, λ_A , of the First Peak in the UV Absorption Spectrum of Guest Molecules and the Red Shifts Caused by Complexation with CD

guest (solvent) ^a	λ_A (nm) ^b	λ_A (complex) (nm) ^{b,c}	red shift (nm)
BGN (water)	330.5	331.3	0.8
BMN (3.7% v/v methanol)	334.3	343.8	9.5
BEN (6.7% v/v methanol)	334.4	343.0	8.6
BPOHN (3.7% v/v methanol)	334.3	343.1	8.8
BPOHN (water)	334.2	343.3	9.1
BBN (methanol)	336.9		
BBN (75% v/v methanol)	336.4		
BBN (50% v/v methanol)	335.8		
BBN (water, extrapolated)	334.7 ^d	343.8	9.1
BPeN	334.4 ^e	343.6	9.2
2-naphthol ^f	327	335	8
BOHN ^g	336.5	345	8.5

^a Solvent used only for the unbound guest molecule. ^b Uncertainty is estimated to be ± 0.4 nm. ^c The solvent was water for all complexes. ^d 334.7 nm was obtained by extrapolating the plot of λ_A versus the % volume methanol to zero % methanol. ^e Insolubility of BPeN prevented experimental determination of λ_A , and the value is assumed to be the same as for BEN. ^f Spectral data were taken from ref 21. ^g Spectral data were taken from ref 28.

obtained from absorbance measurements are 830 ± 60 M⁻¹ cm⁻¹ and 4300 ± 500 M⁻¹ cm⁻¹, respectively, and the values of ϵ_1 , K_1 , and K_2 (and corresponding statistical uncertainties) obtained by fitting data to eq 4 are 1800 ± 200 M⁻¹ cm⁻¹, 830 ± 90 M⁻¹, and 300 ± 60 M⁻¹, respectively. Although the stated statistical uncertainties are relatively small, the actual uncertainties are believed to be larger but are not determinable because this is a nonunique set of ϵ_1 , K_1 , and K_2 values. Because of the lower solubility of BMN, BEN, BBN and BPeN, unique values of ϵ_0 have not been obtained, preventing determination of reliable values of K_1 and K_2 for these guest molecules.

Table 2 gives for the bromonaphthalene derivatives the values of the experimentally observed wavelength of the first UV absorption peak for the uncomplexed, λ_A , and complexed guest molecules, λ_A (complex). Table 2 shows that within experimental uncertainty λ_A has the same value for BPOHN in both water and 3.7% methanol solution and for BMN in 3.7% methanol and BEN in 6.7% methanol, and these values are ≤ 0.4 nm smaller than the value for BBN that is obtained by extrapolation to zero percent methanol. These similarities make reasonable the assumption that the λ_A values are approximately the same as for BPeN, which is assumed to equal 334.4 nm.

The shift in the first ultraviolet absorbance peak caused by complexation with CD is also given in Table 2. The red shift of 0.8 nm in the case of BGN is about an order of magnitude smaller than the red shifts for 2-naphthol, BOHN, BMN, BEN, BPOHN, BBN, and BPeN that are all very similar and in the range 8–9.5 nm.

The relative quantum yields of phosphorescence for the molecular complexes of BMN, BPOHN, and BGN with CD were found to be 6.05, 4.96, and <1.0 , respectively. The relative quantum yield for the BGN complex is an upper limit because of its uncertainty caused by the spectral overlap of the red edge of the fluorescence spectrum with the indistinguishably weak phosphorescence peak.

Figure 7 shows the minimum potential energy structure obtained from molecular mechanics calculations for the ternary complex containing BMN as the guest. The view is directly into the CD cavity from the methyl end. The methyl group has been removed to allow the alkoxy oxygen (dark sphere) to be seen. The hydrogen atoms of the two CD molecules are shown as the small, dark-shaded spheres, which decrease somewhat

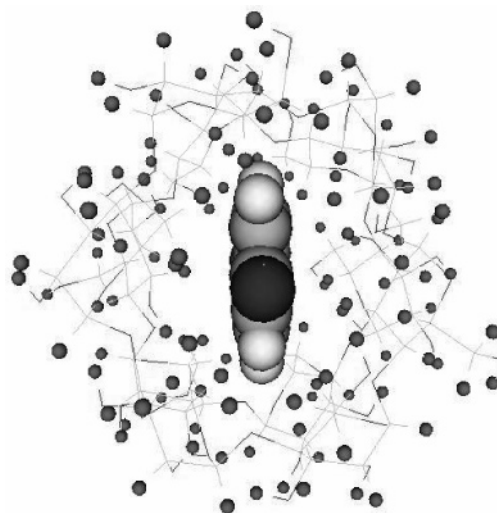


Figure 7. Minimum potential energy structure for a complex of BMN and two CD molecules. The larger openings of the two CD molecules, containing the secondary hydrogens, face each other, and the view is into the smaller opening. The methyl group has been deleted from the image, and the methoxy oxygen is the dark sphere facing toward the viewer. The hydrogen atoms of the CD guest molecules are shown as small shaded circles. The diameter of the glucosidic hydrogens decreases somewhat with increasing depth into the cavity. The closest distance between atomic centers for the methoxy oxygen and glucosidic hydrogens is 3.91 Å.

in diameter the further they are located from the opening of the cavity closest to the reader.

Discussion

Binary and Ternary Complexes. It is expected that BGN will form only a binary complex with CD for two reasons. The maximum width of the guest glucopyranose substituent of >8 Å exceeds the diameter of ~ 5.7 Å for the larger opening of CD,^{33,34} and the glucose units of CD are not sufficiently flexible to permit insertion of the glucopyranose unit.³⁵ Thus, at most, only shallow entry of the bulky glucopyranose substituent is sterically possible. Second, because of the hydrophilicity of the glucopyranose substituent, it is expected to be thermodynamically destabilized if it is encapsulated by the hydrophobic core of a second CD host molecule.

The conclusion that only a binary complex is formed by BGN is supported by several lines of evidence. First, the plots of $\Delta\delta$ and UV absorbance versus $[CD]_0$ in Figures 2 and 5 are purely hyperbolic at low concentrations. If a ternary complex were formed in which the second CD molecule interacted with the naphthalene chromophore, then the corresponding equations for absorbance and $\Delta\delta$ would contain dependencies on $[CD]_0^2$ terms, which should be manifest as sigmoidicity in the plots at low concentrations.²⁸ Second, as is seen in Figures 1 and 2, the shift in δ for H-5, H-7, and H-8 is notably less than for H-1, H-3, and H-4 as $[CD]_0$ increases. This is in contrast to the large shift in δ for H-5, H-7, and H-8 in BOHN when complexed to CD, which has been attributed to the encapsulation of the hydroxyl end of the BOHN molecule by a second CD molecule after the brominated end is encapsulated by the first CD.²⁸ Moreover, in Table 1 the small $\Delta\delta$ values for H-5, H-7, and H-8 in the BGN complex relative to the corresponding $\Delta\delta$ values in BOHN indicate that any interactions between the naphthalene protons of BGN and the cavity of a second CD molecule are weak or absent. Third, a fit of the data in Figure 5 to eq 4 yielded a value of K_2 of approximately zero. Fourth, the absorption spectrum in Figure 3 does not reveal the

formation of the red-shifted peak, which is apparent in Figure 4 for BPOHN and in the absorption spectra for BMN, BEN, BBN, BPEN, and 2-naphthol. Since the red-shifted peak is believed to be due to the interactions of the 6-substituent end of the naphthalene ring and/or atom(s) of the 6-substituent with a second CD molecule, its absence in Figure 3 indicates that if a second CD molecule does bind to the guest molecule, it encapsulates the glucopyranose ring to such a limited extent that it does not interact much with the naphthalene ring in BGN. The small red shift also indicates that the alkoxy oxygen atom of bound BGN remains sufficiently exposed to the water solvent to produce little change in its microenvironment upon binding to CD. Fifth, the relative phosphorescence quantum yields for CD complexes with BMN and BPOHN were several times larger than the signal for the CD/BGN complex. This result indicates that the naphthalene ring of BGN in its triplet electronic state is less well protected from solvent quenching than is the case for BMN and BPOHN. It is assumed that the geometries of the complexes are similar for guest molecules in the ground and triplet states. Sixth, the binding constants obtained by fitting both UV absorbance data and NMR data to eqs 2 and 5 corresponding to a model in which only a binary complex is formed are in good agreement.

Points 4 and 5 give support for the formation of ternary complexes of CD with the alkoxy- and alkanolxy-substituted bromonaphthalene derivatives. Furthermore, the sigmoidicity of the plot in Figure 6 and similar plots for BMN and BEN (figures not shown) supports formation of a ternary complex by these guest molecules. The red shift of ≥ 8 nm in the UV absorption spectrum was not observed for the BGN/CD complex, which was convincingly shown to be a binary complex. However, since a similar red shift was observed for all of the guest molecules in Table 2, and since a similar five-peak profile (as in Figure 4) was observed for the ternary complexes of BMN, BEN, BPOHN, BBN, and BPEN, the red shift is taken to be a "signature" feature for their ternary complexes. The values of ϵ_0 , ϵ_1 , ϵ_2 , K_1 , and K_2 for BPOHN are somewhat larger than but in the same range as the corresponding values for BNOH ($500 \text{ M}^{-1} \text{ cm}^{-1}$, $930 \text{ M}^{-1} \text{ cm}^{-1}$, $2730 \text{ M}^{-1} \text{ cm}^{-1}$, 560 M^{-1} , and 530 M^{-1} , respectively)²⁵ and are consistent with formation of a ternary complex involving BPOHN.

Hydrogen Bonding. From extensive experimental and theoretical evidence, it is generally assumed that hydrogen bonding can cause a spectral shift in the absorption spectrum to either longer or shorter wavelength.^{22–24} Formation of a hydrogen bond in which the guest molecule is a proton donor or acceptor causes a red shift or blue shift, respectively. Hence, the following was proposed for the complex formed between CD and 2-naphthol: "The large bathochromic shift observed for the 1:2 complex indicates that in this case 2-naphthol forms strong hydrogen bonds, most likely to an oxygen of the glucosidic link of the cyclodextrin, but renders hydrogen bonds, where the substrate (2-naphthol) is the proton acceptor, unlikely."²¹

Since BMN, BEN, BBN, and BPEN lack a hydroxylic hydrogen, it is clear that if the red shift is due to hydrogen bond formation, it need not be formed between a hydroxylic hydrogen and glucosidic oxygen atoms, as has been proposed for 2-naphthol.²¹ Furthermore, since the hydroxyl group in BPOHN is separated from the naphthalene ring by three methylene groups, any hydrogen bond involving the hydroxyl hydrogen would have to be formed with an oxygen atom of CD that is different from that involved in hydrogen bonding to the hydroxyl hydrogen of 2-naphthol. These results do not rule out the interpretation in ref 21 applied specifically to 2-naphthol.

Nevertheless, the similar magnitude of the red shift for BMN, BEN, BBN, BPEN, and 2-naphthol suggests the applicability of the same explanation for all of these guest molecules. Since in the $\text{CD}_2\cdot\text{BOHN}$ complex a CD must encapsulate both ends or at least the hydroxyl end of the naphthalene ring to produce a red shift like that indicated in Table 2,²⁸ these results strongly suggest that the CD molecules encapsulate deeply both ends of the naphthalene ring in all of the guest molecules in Table 2 except BGN.

Hydrogen bond formation involving BMN, BEN, BBN, and BPEN can occur only if the alkoxy oxygen atom is a hydrogen acceptor. Therefore, the only reasonable explanations for the red shift produced in these molecules, on the basis of refs 22–24, must include consideration of solvation effects on the oxygen atom before incorporation of the guest into the CD cavity. For instance, a relatively strong hydrogen bond between the alkoxy oxygen atom and a water molecule should increase the energy gap between ground and first excited electronic states. So if such a hydrogen bond is replaced by a weaker hydrogen bond to a hydroxyl hydrogen atom of one of the glucose units of CD, then a red shift could be produced in the absorption spectrum. Similarly, a red shift might be observed if two hydrogen bonds between the alkoxy oxygen and more than one water molecule were replaced by just a single hydrogen bond to a hydroxyl hydrogen atom of glucose in the CD complex. However, the same red shift could occur even if no such hydrogen bond exists in the encapsulated guest molecule, as long as the hydrophobic interior of the CD produces an interaction that is weaker than the hydrogen bond(s) between the alkoxy oxygen atom and water molecules in bulk solvent. Thus, although the observed red shift in Table 2 does not prove the existence of hydrogen bonds in the complex, the similar value for the red shift does suggest that the microenvironment produced within the CD cavity and therefore the relative geometries of CD and guest molecules are similar in all of the ternary complexes describe herein. The evidence presented herein that the red shift can occur without the existence of a hydrogen bond to a glucosidic oxygen of the CD and extension of the above comments to the purported hydrogen bond in ref 21 shows that (1) the same explanation, which does not invoke formation of a hydrogen bond to the proton of a hydroxyl group on the guest molecule, may account for the results reported herein and in ref 21 and (2) caution must be exercised when invoking hydrogen bond formation to explain shifts in ultraviolet absorption spectra for guest/CD complexes.

The results of molecular mechanics calculations give some insight regarding the cause of the observed red shift. In the energy minimized structure of the $\text{CD}_2\cdot\text{BMN}$ complex shown in Figure 7 the closest distance between the centers of the alkoxy oxygen and a hydroxyl hydrogen of a glucose is 3.91 \AA , which is larger than is typically required for hydrogen bonding. Similar theoretical structures were obtained for ternary complexes containing all of the guest molecules in Table 2. Thus, the theoretically calculated structures are consistent with an interpretation that the observed spectral red shift is due to the replacement of hydrogen bond(s) to solvent water molecules with more general van der Waals interactions within the CD cavity. Although the theoretical calculations do not involve consideration of the solvent molecules, they are meaningful since the same energy minimized structures are expected because water molecules are likely not present in the small available volume of the CD cavity when a guest molecule is present.

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