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Fluorescence Enhancement of Curcumin upon Inclusion into Cucurbituril

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The effect of the macrocyclic host compounds cucurbit[*n*]urils (Qn), with $n = 5–7$, on the fluorescence of the biologically active compound curcumin has been studied. Curcumin, the main constituent of the Indian spice turmeric, is of growing interest because of its wide-ranging pharmaceutical properties. This compound forms strong 2:1 host–guest inclusion complexes with Q6 (the original cucurbituril), with an overall equilibrium constant of $(1.9 \pm 0.8) \times 10^4\,M^{-2}$. It is postulated that a Q6 host partially encapsulates each of the two phenyl groups at the ends of the curcumin molecule. The difference in magnitude of the equilibrium constants K_1 ($72 \pm 2\,M^{-1}$) and K_2 ($260 \pm 120\,M^{-1}$) for stepwise encapsulation of the two ends of the curcumin molecule indicates that encapsulation by the first Q6 significantly alters its entire electronic structure, resulting in a more favorable second encapsulation. A very large enhancement of the fluorescence of curcumin results from this complex formation, on the order of 5.0; this is a significant fraction of the polarity sensitivity factor (PSF) of 39 measured for curcumin, that is the ratio of fluorescence intensity in ethanol vs. water. Surprisingly, no such enhancement could be observed in the case of Q7, indicating that the interactions between the guest and the host cavity are not favorable in this case, contrary to expectations. Similarly, no enhancement was observed in the case of Q5, which is not unexpected, because of the extremely small size of the host cavity and portal in this case.

INTRODUCTION

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], shown in Fig. 1a, is the main constituent of the Indian spice turmeric. This yellow compound has generated much excitement in recent years as a result of research that has found that curcumin has potent antioxidant, antiinflammatory and anticarcinogenic properties [1–7]. Curcumin also has very interesting spectroscopic and photophysical properties [8–10], exhibiting solvent-dependent absorption and fluorescence spectra. In particular, its fluorescence intensity and the position of the band maximum were found to be extremely sensitive to the nature of the solvent, while its absorption maximum showed little solvent dependence, and the molar absorptivity showed a small solvent dependence [8].

Because of its polarity-sensitive fluorescence, and also its very narrow, streamlined shape, curcumin is potentially an ideal probe for investigating the host-guest inclusion complexes of the interesting macrocyclic host cucurbituril. Cucurbituril [11–14] is an organic cage compound consisting of a σ-bonded C,N framework, with two opposing portals defined by carbonyl groups. Its structure is shown in Fig. 1b. It is a very rigid cage, consisting of six glycoluril monomers joined by pairs of methylene bridges. The presence of the internal cavity, accessible by these two openings, makes this molecule interesting, as it is can serve as a host for the inclusion of smaller guest molecules. The host–guest inclusion complexes of cucurbituril in solution have been studied extensively in recent years, using NMR [15–22], X-ray crystallography [19,23,24], calorimetry [25–28] and UV–vis [16,29–31] spectroscopy.

However, there has been only one reported fluorescence study of inclusion into cucurbituril in solution [32]. This is because of the relatively small cavity and portal size for cucurbituril as compared to cyclodextrins, for example. As most fluorescent probe molecules are rather large and contain multiple or fused aromatic rings, there is a poor size match for forming inclusion complexes.

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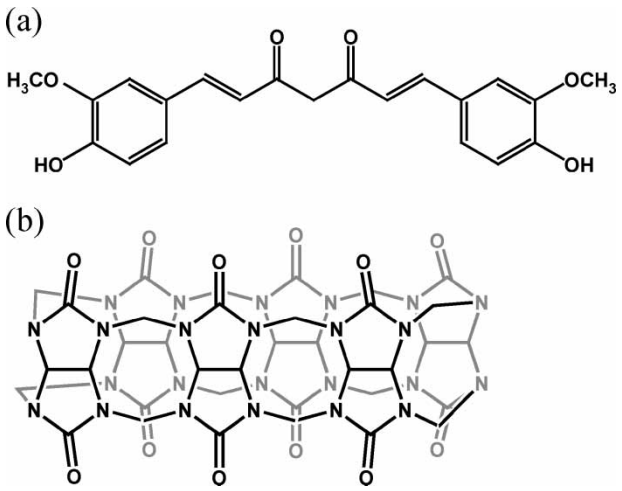

FIGURE 1 Molecular structures of (a) curcumin and (b) cucurbit[6]uril (Q6).

Recently, the synthesis of other cucurbituril homologues has been reported [33,34], with differing numbers of glycoluril monomer units in the macrocycles. These have been named cucurbit[*n*]-urils, where *n* is the number of glycoluril units, and abbreviated as Qn [34]. The original cucurbituril is thus cucurbit[6]uril, or Q6. These homologues are of great interest, as they represent chemically similar hosts to cucurbituril, but with widely varying cavity and portal sizes, as well as aqueous and organic solubilities. A number of studies of the inclusion complexes of these homologues, particularly Q7 and Q8, have also been reported; these have been recently reviewed [35]. As in the case of Q6 itself, few of these have involved fluorescence studies [36,37]. Recently, Isaacs and colleagues [38] reported the synthesis of fluorescent Qn analogs; these are interesting because of the potential use of this intrinsic fluorescence to study inclusion of non-fluorescent guests.

In this paper we report studies on the effect of the host molecules Q5, Q6 and Q7 on the fluorescence of curcumin. We show that Q6 forms very strong 2:1 host–guest complexes with curcumin, resulting in a very significant enhancement of the curcumin fluorescence.

RESULTS AND DISCUSSION

Polarity Sensitivity of Curcumin

Although the significant polarity sensitivity of the fluorescence of curcumin has been described previously, the degree of this polarity sensitivity compared to other polarity-sensitive fluorescence probes has not been reported. To perform this comparison, we previously developed a quantitative measure of the polarity sensitivity of fluorescent probes, based on the relative fluorescence of the probe in ethanol as compared to aqueous solution. [39] We have since named this quantity the polarity sensitivity factor, or PSF. The numerical value of the PSF for a given probe is determined by taking the ratio of the integrated fluorescence spectrum in ethanol and water (measured using the same excitation wavelength), and correcting for the difference in absorbance between the two solutions:

$$\mathrm{PSF} = \frac{\delta I_F(\nu)\mathrm{d}\nu,\ \text{ethanol}}{\delta I_F(\nu)\mathrm{d}\nu,\ \text{water}} \times \frac{A_{\text{water}}}{A_{\text{ethanol}}} \qquad (1)$$

This provides a convenient scale of polarity sensitivity that can be used to compare different fluorescent probes.

Five trials were conducted, yielding an average PSF value of 39 ± 2. These trials involved various concentrations of curcumin, with absorbances in the range of 0.10 to 0.54 (roughly the range of absorbance appropriate for fluorescence measurements); this indicates that this PSF value is not concentration dependent, at least in the fivefold range of concentrations used. Thus a fluorescence enhancement of a factor of approximately 40 can be expected when curcumin moves from an aqueous environment into an environment with a polarity similar to ethanol. For comparison, the PSF values for 1-anilino-8-naphthalenesulfonic acid (1,8-ANS) and 2-anilino-6-naphthalenesulfonic acid (2,6-ANS), two commonly used polarity-sensitive fluorescence probes, were found to be 197 and 120, respectively [39]. Thus curcumin exhibits significant polarity sensitivity as measured by the PSF, although it is significantly lower than that of the widely used ANS polarity-sensitive probes.

Fluorescence Enhancement

The fluorescence spectrum of curcumin in aqueous 0.2 M Na_2SO_4 solution in the absence and presence of various amounts of Q6 is shown in Fig. 2. As can

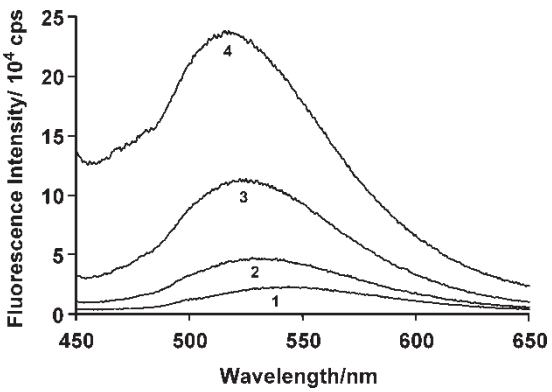

FIGURE 2 Fluorescence spectra of curcumin in the presence of various amounts of Q6: **1**, 0 mM; **2**, 2.5 mM; **3**, 10 mM; **4**, 40 mM.

be seen, significant enhancement of curcumin fluorescence is observed in the presence of Q6. Figure 2 also shows an increased baseline at the low wavelength end obtained upon Q6 addition. The calculation of F/F_o from these spectra was thus corrected using Q6 blanks, as described in the experimental section. It should be noted that although this introduces an additional source of error into the results, this same correction procedure using Qn blanks was also performed in two previous published studies of Qn inclusion complexes, namely 2,6-ANS in Q6 [32] and 1,8- and 2,6-ANS in Q7 [37]. The maximum F/F_o obtained was a factor of 5.11 measured at a Q6 concentration of 40 mM. This is significantly lower than the PSF of 39 for curcumin, indicating that the curcumin is experiencing a lower polarity environment than that in free aqueous solution, but one still higher than that of ethanol solution. A significant blue shift of the curcumin fluorescence spectrum was also observed upon addition of Q6, with a maximum shift of 20 nm, from 540 nm in the absence of Q6 to 520 nm in the presence of 40 mM Q6. This observed enhancement and spectral blue-shift is consistent with the highly polarity-sensitive nature reported for curcumin fluorescence [8,9].

The significant observed fluorescence enhancement of curcumin in the presence of Q6 suggests the formation of host–guest inclusion complexes, presumably involving the incorporation of Q6 hosts on one or both phenyl ends of the long curcumin molecule. In such a complex, the curcumin guest experiences a lower local polarity than that experienced as a free solute in the aqueous solution; this would result in the observed increase in fluorescence. By measuring the dependence of the observed fluorescence enhancement on the Q6 concentration, the type of association, as well as the association constant(s), can be determined for this host–guest system.

No such enhancement or blue shift of curcumin fluorescence was observed upon addition of either Q5 or Q7. (It should be noted that Q8 is not soluble in this aqueous system.) In the case of Q5, this is presumably due to the very small size of the host cavity and particularly the portal. The portal diameter is 2.4 Å [33], much smaller than the size of a substituted phenyl group. The lack of enhancement in the case of Q7 is much more surprising and interesting. Previous work in our group [32,37] using the fluorescent probe 2,6-ANS showed that both Q6 and Q7 formed 1:1 complexes with this probe, presumably via the anilino group, with association constants of $52 \pm 10\,M^{-1}$ [32] and $600 \pm 150\,M^{-1}$ [37], respectively. Thus, Q7 formed significantly stronger complexes with 2,6-ANS than did Q6. Given the similarities of the anilino group of 2,6-ANS and the substituted phenyl groups at both ends of curcumin, a stronger inclusion complex was also expected for curcumin with Q7 as compared to Q6, based on size and fit considerations. Indeed, the portal diameter of 5.4 Å for Q7 [33] would seem to be much better matched to the size of the substituted phenyl ends of curcumin than is that of 4.0 Å in the case of Q6 [13]. This lack of observed enhancement of curcumin by Q7 was not a result of a problem with the Q7 sample used, as this same sample was tested using 2,6-ANS as guest, and reproduced the reported enhancement [37]. Furthermore, it is unlikely that host-guest inclusion of curcumin into Q7, at one or both ends, could in fact be occurring without a resultant measurable effect on the fluorescence. Thus it must be concluded that inclusion of curcumin into Q7 does not occur. There is some precedence for this preference of dye molecules for Q6 over other larger hosts: phenol blue, another linear guest molecule with terminal phenyl groups (in this case *p*-substituted), forms a much more stable complex with Q6 than it does with β-cyclodextrin, which has a cavity size similar to that of Q7 [12]. There are also many other reports of very specific differences in the inclusion of a particular guest into different hosts, including the case of the dye acridine red, which showed fluorescence enhancement by β-cyclodextrin but decreased fluorescence in the presence of calix[6]arenesulfonate [40]. In the current case, this observed binding of curcumin by Q6 but not by Q7 must be the result of specific, but at this point unknown, host–guest interactions that are favorable with the Q6 but not with the Q7 cavity.

Association Constants

Figure 3 shows a plot of F/F_o versus [Q6]; the inset shows the double reciprocal plot of $1/(F/F_o - 1)$ versus 1/[Q6]. If the observed enhancement was a result of simple 1:1 host–guest inclusion, then

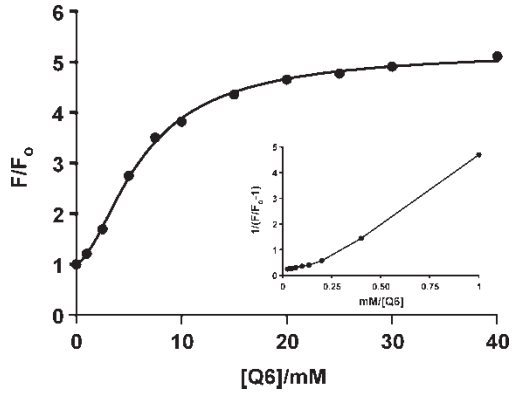

FIGURE 3 The fluorescence enhancement, F/F_o, of curcumin as a function of Q6 concentration. The solid line shows the line of best fit of the data to Eq. (6). The inset shows the nonlinear double reciprocal plot, indicating the formation of higher-order complexes.

the reciprocal plot would be linear [41]. The inset clearly shows a nonlinear double reciprocal plot, indicating the formation of higher-order complexes. Considering the elongated, symmetrical shape of curcumin, 2:1 host:guest complexation in which each curcumin guest is complexed by a Q6 host at each end of the molecule, as illustrated in Fig. 4 (curcumin shown in its enol form; see below), would seem most likely. This complexation can be described by the following stepwise mechanism, involving the initial formation of the 1:1 host:guest complex Q6:curcumin, followed by addition of a second host to give the 2:1 host:guest complex $Q6_2$:curcumin:

$$\text{Q6} + \text{curcumin} \rightleftharpoons \text{Q6 : curcumin} \quad (2)$$

$$\text{Q6} + \text{Q6 : curcumin} \rightleftharpoons \text{Q6}_2 \text{ : curcumin} \quad (3)$$

These two equilibria are described by the equilibrium constants K_1 and K_2:

$$K_1 = [\text{Q6 : curcumin}]/([\text{Q6}][\text{curcumin}]) \quad (4)$$

$$K_2 = [\text{Q6}_2 \text{ : curcumin}]/([\text{Q6}][\text{Q6 : curcumin}]) \quad (5)$$

with the overall equilibrium constant K for 2:1 complexation equal to the product K_1K_2. The dependence of F/F_o on [Q6] for this complexation mechanism is given by [42]:

$$F/F_o = \frac{1 + F_1/F_o\, K_1[\text{Q6}]_o + F_2/F_o K_1K_2[\text{Q6}]_o^2}{1 + K_1[\text{Q6}]_o + K_1K_2[\text{Q6}]_o^2} \quad (6)$$

where F_1/F_o and F_2/F_o are the fluorescence enhancement of the 1:1 and 2:1 complexes, respectively, relative to unbound guest. The solid line in Fig. 3 shows the excellent fit of the experimental data to Eq. (6) using nonlinear least squares; this provides strong support for the formation of 2:1 complexes. The best fit for the data shown in Fig. 3 was obtained with the fit parameters $F_1/F_o = 2.3$, $K_1 = 72\,\text{M}^{-1}$, $F_2/F_o = 5.3$, and $K_2 = 396\,\text{M}^{-1}$. This gives an overall equilibrium constant for 2:1 complex formation of $2.9 \times 10^4\,\text{M}^{-2}$. Fits of the data to equations based on 1:1 [41] and 2:2 complexation [43] were also attempted; these fits were very poor in both cases, supporting our assertion that 2:1 complexes are being formed.

A total of four trials were performed (including that shown in Fig. 3), yielding the following average values and standard deviations: $F_1/F_o = 3.3 \pm 0.8$, $K_1 = 72 \pm 2\,\text{M}^{-1}$, $F_2/F_o = 5.4 \pm 0.4$, and $K_2 = 260 \pm 120\,\text{M}^{-1}$, with an average overall equilibrium constant for 2:1 complex formation of $1.9 \pm 0.8 \times 10^4\,\text{M}^{-2}$. The observation of $K_2 > K_1$ indicates that the second Q6 goes on more readily than the first Q6, or more precisely that there is a better affinity between the Q6 cavity and the curcumin phenyl group when there is already a Q6 complexed to the other phenyl group. This indicates that complexation by the first Q6 significantly alters the electronic structure of the curcumin molecule. It is also interesting to note the stepwise enhancement obtained, with a similar increase in fluorescence of a factor of 2.5 to 3 with each of the two Q6 encapsulations, indicating a similar reduction in local polarity with each encapsulation.

Although the significant fluorescence blue shift and enhancement strongly indicate that inclusion of curcumin into Q6 is occurring, and the nonlinear double reciprocal plot and excellent fit of the enhancement data indicate a 2:1 host:guest stoichiometry, the fluorescence data do not indicate the geometry of the inclusion complex, that is how the curcumin is included into the two Q6 host cavities. In our previous study of the inclusion of 2,6-ANS by Q7 [37], we were able to use ^{1}H NMR to deduce the mode of inclusion of the guest into the host by determining which protons on the guest were significantly shifted in the NMR spectrum in the presence of the host (in this case phenyl insertion was confirmed). Unfortunately, this is not possible in the case of curcumin because of its extremely low solubility in aqueous solution. Thus, a number of possible structures for this 2:1 inclusion complex are shown in Fig. 4; all of these involve encapsulation of the two phenyl ends of the curcumin guest by two Q6 hosts, but they differ in the degree and orientation of this inclusion. We propose these configurations based on the strong effect of inclusion on the curcumin fluorescence, which indicates some degree of inclusion of the aromatic rings, and the match in size between the Q6 portal and the phenyl group. Although these are cartoon representations only, they do indicate the relative sizes of the Q6 host opening and the width of the phenyl ring, based on a Q6 portal of 4.0 Å and a C_2–C_5 distance of 2.794 Å (based on that for benzene; this neglects the effects of the C–H bonds).

The proposed configuration depicted in Fig. 4a involves complete inclusion of the phenyl groups into the Q6 cavity. Such complete inclusion of a phenyl or related group into Q6 has been reported before, for example in the cases of pyridinyl groups [44], phenyl groups on organic dyes [30], aromatic amines [45], anilino groups [32] and polyviologens [46]. In fact, two of these reports describe rotaxanes of Q6, in which Q6 is able to thread over these phenyl-sized groups [44,46]. On the other hand, the benzoyl group has been reported to act as a stopper for Q6 rotaxanes, indicating that Q6 cannot thread over that group [47]. More importantly, Mock reports that while *p*-$CH_3C_6H_4CH_2NH_3^+$ forms a complex with Q6, its *o*- and *m*-isomers do not [13]. Thus, the presence of the 3,4-substitution of methoxy and hydroxyl groups, both in terms of their steric bulk and the fact that inclusion is prevented along

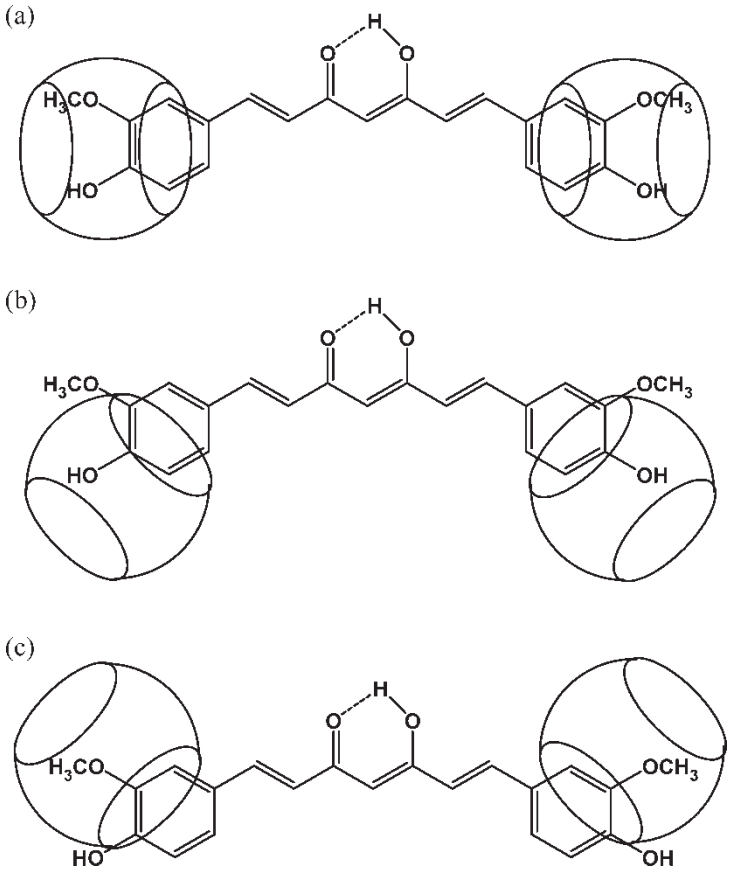

FIGURE 4 A pictorial representation of some possible models for the 2:1 Q6:curcumin inclusion complexes, with curcumin in its enol form: (a) full inclusion of the phenyl ends; (b) partial inclusion of the phenyl ends, with the hydroxyl group inside the cavity; (c) partial inclusion of the phenyl ends, with the methoxy group inside the cavity.

the narrower phenyl dimension from C_3 to C_5, makes it unlikely that complete insertion as shown in Fig. 4a is occurring. It is much more likely that only partial insertion is occurring. Two such possible 2:1 complexes are also shown in Fig. 4, involving inclusion aligned along either the hydroxyl (Fig. 4b) or methoxy (Fig. 4c) groups, with only partial inclusion of the aromatic ring. Such partial inclusion of the phenyl group could still have a significant effect on the electronic structure of the curcumin molecule, resulting in the observed fluorescence blue shift and enhancement. Of these two partial inclusion structures, that shown in Fig. 4c, with the inclusion of the $-OCH_3$ group, is the more likely, because of the better size match of the larger methoxy group with the Q6 cavity as compared to the hydroxyl group. This is consistent with previous reports for the inclusion of alkyl ammonium ions, which show an increasing binding affinity up to *n*-butylamine [13].

The observation of a significant difference in the magnitude of K_1 and K_2 is consistent with the expectation that curcumin, like other β-diketones, exists primarily in the enol form shown in Fig. 4, rather than the β-diketone form shown in Fig. 1. In the enol form, an intramolecular hydrogen bond forms between the enolic hydrogen and the second ketone group, and through resonance coupling between the two equivalent enols (i.e. enolification of either of the two ketone groups) the molecule becomes completely conjugated along its entire length. Thus, the two chromophores at the ends of the molecule are expected to be linked by this extended π-electron conjugation, and not act independently of one another; this expectation has been strongly supported by spectroscopic evidence [8–10]. Inclusion (full or partial) of one end into a host with a local polarity different from bulk solution would thus be expected to significantly alter the electronic structure of the entire molecule, including the opposite chromophore. (By contrast, in the diketone form, the two chromophores are isolated electronically from each other, and inclusion of one end would not be expected to significantly affect inclusion at the other end.) The significant increase in the magnitude of K_2 observed indicates that inclusion of one phenyl group does significantly alter the electronic structure of the opposite phenyl group, in such a way that makes its subsequent inclusion more favorable than that of the first group.

A few spectroscopic studies on the inclusion or binding of curcumin have been reported previously,

including its binding to micelles [10], bovine serum albumin [48] and β-cyclodextrin [49,50]. Of these, the only comparable host–guest inclusion reported is that with β-cyclodextrin. In that case, 2:1 host–guest complexes were also observed. An overall equilibrium constant of $5.53 \times 10^5\,M^{-2}$ was reported [49], which is over an order of magnitude larger than that obtained with Q6. This indicates that there is a better size match between the substituted phenyl ends of curcumin with β-cyclodextrin than with Q6, and is also indicative of the better electrostatic interactions with β-cyclodextrin, which preferentially binds neutral guests, as opposed to Q6, which prefers cationic guests. The better size match is undoubtedly a result of the truncated cone shape of β-cyclodextrin, which provides unrestricted access to the cavity, with a large rim diameter of 7.8 Å [51]. This result would also lead one to expect Q7, with its larger portal (still smaller than the opening of β-cyclodextrin), to be a better host for curcumin than Q6, contrary to the observed results discussed above. These absorption-based studies did not measure K_1 and K_2 separately, just the overall K, so it is not known whether the second cyclodextrin was complexed more strongly than the first, as was observed in the case of Q6.

CONCLUSIONS

Curcumin is found to form 2:1 host:guest inclusion complexes with Q6, presumably by stepwise partial encapsulation of the two chromophore ends of the molecule. A significant fluorescence enhancement of a factor of 5 accompanies this inclusion, due to the less polar local environment of the chromophores in the cavity of the Q6 hosts as compared to aqueous solution. Encapsulation of the first chromophore end by Q6 occurs with a fairly low association constant ($72 \pm 2\,M^{-1}$), but this process increases the association constant for the encapsulation by a second Q6 of the opposite end ($K_2 = 260 \pm 120\,M^{-1}$). This is a result of alteration of the electronic structure of the guest molecule upon the first encapsulation. The overall association constant for 2:1 complexation by Q6 was found to be $(1.9 \pm 0.8) \times 10^4\,M^{-2}$, significantly lower than the value of $5.53 \times 10^5\,M^{-2}$ reported for the 2:1 complexation by β-cyclodextrin. Q5 did not enhance curcumin fluorescence; this is undoubtedly a result of its very small cavity and portal diameter. Interestingly, the larger host Q7 also did not enhance curcumin fluorescence, contrary to expectations; this must be the result of specific but as yet unknown interactions between the cucurbituril host and curcumin guest, which are optimal in the case of the Q6 cavity.

EXPERIMENTAL

Materials

The following compounds were obtained from the indicated sources and used as received: curcumin (Aldrich) and sodium sulfate (Fisher). Q5, Q6 and Q7 were synthesized and purified according to the literature method [33]. The Q6 prepared was not dried before use. However, representative samples of Q6 were dried in a vacuum oven, and showed a water content of 13%; this value was used to correct the concentration of all Q6 solutions. Q5 and Q7 were vacuum dried before use, so no correction for water content was required.

Solution Preparation

The appropriate amount of the Qn of interest was weighed into a 5 mL glass vial, then dissolved by adding 3.00 mL of a 0.2 M aqueous Na_2SO_4 solution (chosen for maximum solubility of the various Qns). A 30 μL aliquot of a 1.00×10^{-3} M curcumin stock solution in methanol was then added (because of the low direct aqueous solubility of curcumin), giving a 1% methanol test solution containing 1.00×10^{-5} M curcumin and various concentrations of Q6. The solution was shaken, then immediately transferred to a fluorescence cuvette for spectroscopic measurements.

Fluorescence Spectroscopy

All absorption and fluorescence measurements were performed on solutions in 1 cm^2 quartz cuvettes, at 21 ± 1°C. The pH of these solutions ranged from 5.40 to 2.80, depending on the amount of Q6 added; this change in pH does not affect the fluorescence measurements, as the fluorescence intensity of curcumin has been shown to be unchanged over a pH range of 1.33 to 8.27 [9]. Absorption spectra were measured on a Cary 50 Bio UV–Visible spectrophotometer; the absorbance of the above-described 1.00×10^{-5} M curcumin solution was 0.20 at 425 nm. This absorbance increased only slightly upon addition of Q6, by a maximum of 15% at the highest Q6 concentration (40 mM). Fluorescence spectra were measured on a Photon Technologies International LS-100 luminescence spectrometer, with excitation and emission monochromator bandpasses set at 3 nm and an excitation wavelength of 425 nm.

Q6 was found to have a significant emission at this excitation wavelength, although much weaker than that of the curcumin solution even in the absence of host. This emission was manifested as an increased sloped baseline, with higher emission at the low wavelength end of the spectrum. This necessitated

a correction in the determination of the fluorescence enhancement of curcumin in the presence of Q6, F/F_o. This was carried out by measuring the emission spectrum of "blank" solutions, containing no curcumin, at each Q6 concentration used, and subtracting the integrated area of these spectra from those of curcumin in the presence of Q6. F/F_o was then calculated as the ratio of this corrected total fluorescence in the presence of Q6 to that of curcumin in the absence of Q6. This method of correcting the data for the emission of the Q6 host is justified by the fact that it is present at two to three orders of magnitude higher concentration than the curcumin guest, and thus only a very small fraction of the hosts are complexed at any host concentration.

Acknowledgements

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