# Inclusion complexes of coumarin in cucurbiturils†

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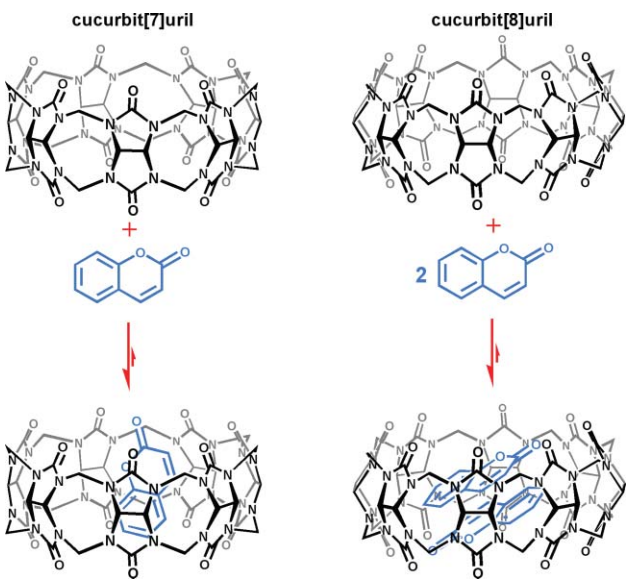
***Received 16th February 2009, Accepted 19th March 2009***
***First published as an Advance Article on the web 17th April 2009***
**DOI: 10.1039/b903057c**

Coumarin was found to form stable inclusion complexes with cucurbiturils. In the presence of cucurbit[7]uril (CB[7]), 1 : 1 inclusion complexes were observed in aqueous solution, as monitored by $^1$H NMR and UV-visible absorption spectroscopies, and further supported by *ab initio* calculations, whereas with cucurbit[8]uril (CB[8]) a solid phase 1 : 2 host : guest complex was found in a single crystal X-ray diffraction structure determination.

## Introduction

Cucurbit[*n*]urils (CB[*n*]s, $n$ = 5–8, 10), a growing family of synthetic macrocycles consisting of $n$ glycoluril units bridged by $n$ pairs of methylene groups, possess unique guest binding properties in water.[1] Indeed, their constricted hydrophobic cavity, delineated with rigid carbonyl-laced portals, renders the entry of guest molecules more difficult as compared with cyclodextrins (CDs) or calixarenes. Once complexed inside, however, it is also harder for the guest to exit. This may be one important factor responsible for the significantly better complex stabilities (higher binding constants) than those obtained when using CDs or calixarenes. However, up to the year 2000 cucurbit[*n*]uril chemistry was limited to almost a single representative, CB[6],[2] but then dramatically expanded when Kim and coworkers reported the synthesis and separation of CB[5] and higher homologues.[3] Since then, CB[7] and CB[8] have attracted a great deal of interest because of their larger cavities, opening the way for the study of aromatic-containing guest molecules. As a consequence, CB[7] and CB[8] have been intensively studied in research disciplines as diverse as catalysis,[4] separation[5] and molecular materials.[6] In addition, their inherent ring shape together with their versatile binding properties also make them particularly attractive for constructing molecular machines.[7] Conversely, having been known for much longer and studied extensively in fundamental research for several decades, cyclodextrins have already found numerous industrial applications.[8] Among them, pharmaceutical solubilization and controlled drug delivery is an important and successful example.[9] Compared with cyclodextrins, however, the use of CB[*n*]s for drug molecule encapsulation and delivery has barely been investigated. The research groups of Kim[10] and Day[11] pioneered the use of cucurbiturils to encapsulate drug molecules such as anticancer metal complexes, followed by others with organic drug molecules[12] and peptides.[13]

Coumarin is a natural product with a sweet odour found in many plants that is used in medicine directly (or sometimes as its analogues) as an anticoagulant and has also been effective in the treatment of lymphedema, among several other applications.[14] This molecule is actually quite versatile since it has also found applications as a dye for lasers and as an additive to perfumes. Recently, CB[8] has been used as a nanoreactor to photodimerize included coumarin derivatives, though the parent coumarin molecule was not mentioned,[15] the stereoselectivity of the reaction products being largely dependent on the coumarin substituents. Here we report the formation of stable 1 : 1 and 1 : 2 host : guest inclusion complexes of the parent coumarin with CB[7] and CB[8] respectively (Scheme 1). The formation of the complexes was characterized by $^1$H NMR, UV-vis absorption spectroscopy, and the binding geometry and stoichiometry were confirmed by *ab initio* molecular modelling for the CB[7] complex, and by single crystal X-ray crystallography for the CB[8] complex.




**Scheme 1** Schematic illustration of the coumarin binding mode inside CB[7] and CB[8] forming 1 : 1 and 1 : 2 host : guest complexes respectively.

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† CCDC reference number 720730. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b903057c

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## Results and discussion

### $^1$H NMR study

In the $^1$H NMR spectra of cucurbituril host–guest complexes, the guest proton resonances show complexation-induced shifts (CIS, $\Delta\delta = \delta_{bound} - \delta_{free}$) which are very informative regarding the average location of the guest with respect to the CB[7] cavity. Large upfield shifts (negative CIS values) are normally observed for guest protons located in the shielding (central) region of the cavity, while guest protons in the shallower area experience smaller upfield shifts. In some cases positive CIS values can be observed for guest protons situated outside the cavity (or facing the carbonyl portals). As shown in Fig. 1, for coumarin in CB[7] the entire set of guest proton resonances are shifted upfield in agreement with the formation of a strong inclusion complex.

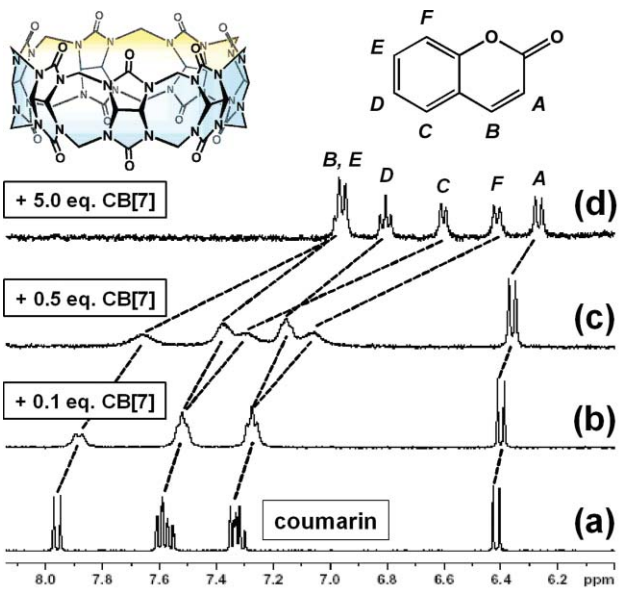


**Fig. 1** $^1$H NMR spectra of 1 mM coumarin in the absence (a) and in the presence of 0.1 (b), 0.5 (c) and 5 (d) equivalents of cucurbit[7]uril in $D_2O$. The guest proton resonances are labeled as indicated from *A* to *F*.

The relatively large CIS values for protons *B*, *C*, *D*, *E* and *F* (> −0.52 ppm) and the comparatively small CIS value for proton *A* (−0.16 ppm) suggest an inclusion geometry where the aromatic ring is preferentially located in the centre of the cavity and the more polar cyclic ester and proton *A* are further out, in the vicinity of the CB[7] carbonyl groups. Of course this would be an average situation and one should consider a fully centered aromatic inclusion and an ester centered complex with all the intermediate cases. With the quadrupolar nature of the cucurbituril cavities, the oxygen atoms of included guest coumarin may be involved in dipolar–quadrupolar interactions with the CB[7] interior. It has recently been shown by Wyman and Macartney that small polar neutral molecules such as ketones bind reasonably strongly to CB[7] ($10^3$–$10^4$ $M^{-1}$) as a result of contributions from dipole–quadrupole interactions, with oxygen atoms of the guests pointing toward the center of the cavity wall.[16] Moreover, because of the appearance of broad proton resonances upon guest encapsulation and the fact that there are no separate resonances for free and bound guest protons, the complexation–decomplexation process between coumarin and CB[7] occurs at intermediate to fast exchange rates on a timescale determined by the $^1$H NMR chemical shift splittings.

### UV-visible study

The formation of 1 : 1 inclusion complexes between coumarin and CB[7] in aqueous solution was also suggested by UV-visible absorbance measurements of coumarin titrated with various amounts of CB[7]. The gradual addition of CB[7] to a solution of coumarin results in decreases in both peaks at 277 and 312 nm (Fig. 2) in line with the inclusion of the guest into the hydrophobic host molecule.

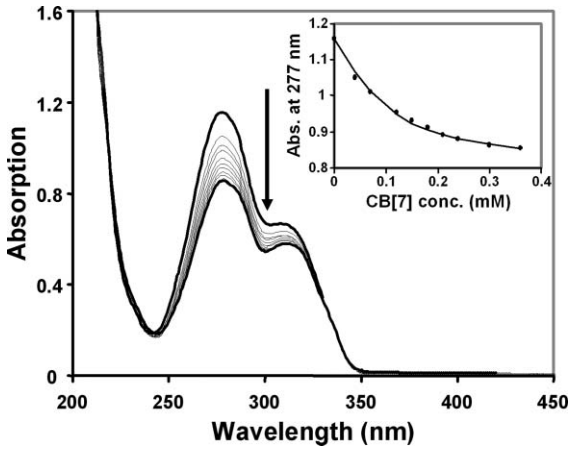


**Fig. 2** UV-visible spectra of coumarin (0.1 mM) in the presence of increasing amounts of CB[7] (from 0 to 3.6 equiv from top to bottom) in aqueous solution. Inset: dependence of the absorbance at 277 nm as a function of CB[7] concentration. The solid line represents the best fit of the data corresponding to a binding constant $K_a$ of 2.6 (±0.5)×$10^4$ $M^{-1}$.

The non-linear least squares fit (Fig. 2 inset) is in good agreement with a 1 : 1 binding stoichiometry model and provides a binding constant $K_a$ of 2.6 (±0.5)×$10^4$ $M^{-1}$. The complexation is thus fairly strong, especially considering that coumarin is neutral and the complexation driving force is mainly hydrophobic without the often seen charge-dipole forces between the guest and host molecules. The binding constant is even comparable with the values reported for the inclusion of other cationic aromatic molecules such as methylviologen ($K_a$ = 2 (±0.5)×$10^5$) in CB[7].[17]

The 1 : 1 binding stoichiometry has also been confirmed by the continuous variation method. Indeed, a Job's plot for the CB[7]–coumarin system (with [*CB[7]*]+[*coumarin*] fixed to 0.1 mM), as monitored using UV-visible spectroscopy (Fig. 3) reached a maximum at a ratio of 0.50 for [*CB[7]*]/[*CB[7]*]+[*coumarin*]. This indicates that the major species in this concentration region are 1 : 1 complexes between CB[7] and coumarin.

### *Ab initio* calculations

$^1$H NMR and optical measurements have demonstrated the formation of 1 : 1 inclusion complexes between coumarin and CB[7]. Attempts to grow single crystals to confirm the 1 : 1 complex in the solid-state were not successful. Therefore, we relied on *ab initio* calculations to further assess the existence of the 1 : 1 coumarin–CB[7] guest–host complexes and propose a detailed

 

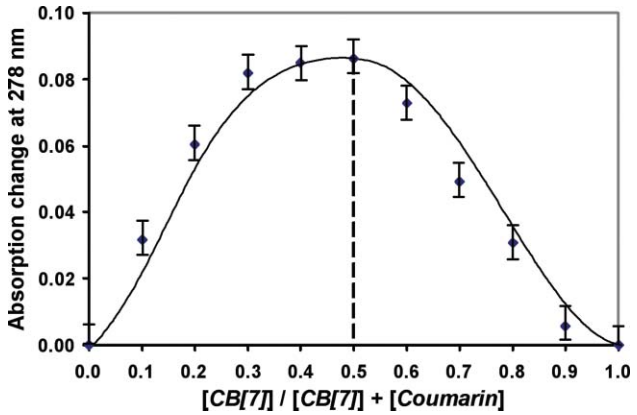


**Fig. 3** Job's plot for the 1 : 1 CB[7]–coumarin host–guest complexes from the continuous variation titration monitored at 278 nm.

geometry of the inclusion complexes. The gas-phase structure of the CB[7] host–guest complex with coumarin has been determined from *ab initio* calculations (HF method with 3–21G** basis set). As illustrated in Fig. 4, the position of coumarin inside the CB[7] cavity is consistent with the picture deduced from the experimental variations of the guest proton resonances ($\Delta\delta$ values) in the presence of CB[7]. The aromatic ring of the molecule is found included almost at the centre of the cavity, leaving the lactone part and proton *A* pushed out of the portal with access to bulk solvent (hence the small value of CIS from $^1$H NMR).

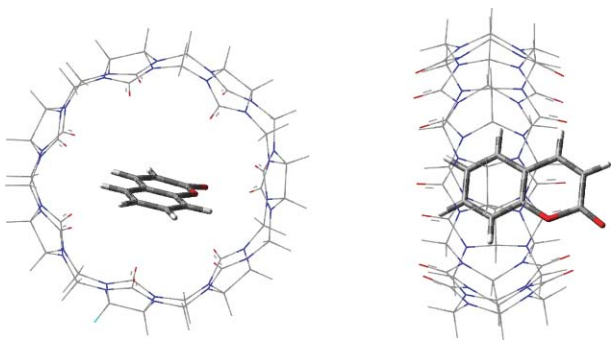

**Fig. 4** *Ab initio* calculations of the 1 : 1 CB[7]–coumarin host–guest complex (HF/3–21G** basis set).

It is noteworthy that the location of protons *B*, *C*, *D*, *E* and *F* are all in positions to interact with the CB[7] cavity in agreement with the observed relatively large values of the corresponding CIS once the guest is encapsulated in the cavity, as deduced from the $^1$H NMR spectra.

### Single crystal X-ray diffraction

The mixing of coumarin with CB[8] in water quickly resulted in cloudy solutions or precipitates even at really low concentrations (*i.e.* 20 μM) for which CB[8] and coumarin are individually soluble. This means that the suspected coumarin–CB[8] complexes have a very low water solubility (likely in the μM range or below) therefore precluding characterization by solution NMR. UV and photoluminescent (PL) spectroscopies show the formation of coumarin–CB[8] inclusion complexes. This was finally ascertained by single crystal X-ray diffraction.§ Heating coumarin (2.2 mg) and CB[8] (10 mg of the $H_2SO_4$, $H_2O$ solvate crystals) in water (5 mL) provided a clear solution and slow cooling to room temperature resulted in the complex crystallizing. X-Ray quality crystals were collected and analyzed thus providing the structure shown in Fig. 5.

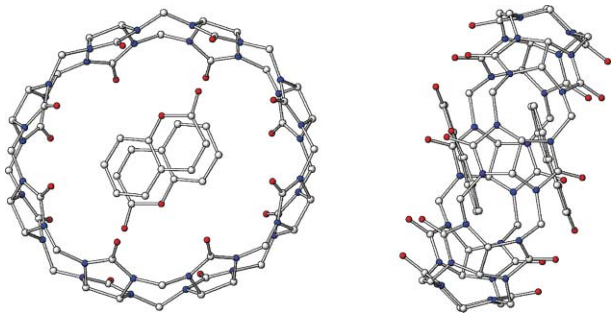

**Fig. 5** Crystal structure of the 1 : 2 CB[8]–coumarin host–guest complexes (only one orientation of the dimer inside the cavity is displayed and hydrogen atoms are omitted for clarity).[18]

The structure shows two coumarins included in a CB[8] cavity which is distorted from ideal $D_{8h}$ symmetry (longer intramolecular O–O distance between facing carbonyl oxygens of one rim = 10.47 Å *versus* corresponding smaller distance = 9.45 Å). This probably arises from the accommodation of the two planar, elongated guests inside the cavity. The coumarin molecules show typical carbon–carbon (1.39 Å for the benzenes) and carbon–oxygen distances (1.20–1.22 Å for the double bonds and 1.35–1.42 Å for the single bonds) and are not remarkable. The disordered guests are facing each other and display π–π interactions (the distance between the flat included guests is 3.73 Å) despite a slight offset between the six-membered rings (~1.2 Å) and a tilted orientation of the dimer planes of 32.0° with respect to the equatorial plane of the cavity. Interestingly, most of the reported CB[8] crystal structures show only one guest included in the cavity. However, there are a few examples of included homo[4c,19,20] and heteroguest pairs.[21] The host–guest inclusion compound crystallizes in the $I4_1/a$ space group and is isostructural with that of the water solvate of CB[8] which has only water in the cavity.[3] Remarkably, this means that the presence of 2 coumarins as guests does not perturb the natural crystallization of CB[8]. The deep inclusion of the two facing guests (that do not protrude significantly from the carbonyl rims) inside the CB[8] cavity allows for the C=O oxygen atoms to hydrogen bond normally with others cucurbiturils (multiple CH···O close contacts).[6a,6e] Only one other instance of a CB[8] complex crystallizing in the same space group has been reported, namely the 1 : 1 bis(ethylenediamine)-diaqua-copper(II) complex included inside CB[8],[22] but to our knowledge the coumarin complex is the first observation of a ternary complex of CB[8] isotructural to the CB[8] water solvate phase.

§ Crystal structure: crystal size 0.35 × 0.25 × 0.15, $C_{66}H_{60.8}N_{32}O_{20.4}$, $M$ = 1628.67, tetragonal, space group $I4(1)/a$, $a$ = 28.364(1), $c$ = 21.862(2), $V$ = 17587(2) Å$^3$, $T$ = 100.0(1) K, $Z$ = 8, $\rho_{calc}$ = 1.230 Mg m$^{-3}$, $2\theta_{Max}$ = 46.62°, 554 parameters, 420 restrains, residual electron density max. 0.67, min. –0.49 $e$ Å$^{-3}$. Final $R$ indices ($I > 2\sigma(I)$): $R_1$ = 0.0793, w$R_2$ = 0.2292 (226081 reflections total, 6281 unique, 5390 ($I > 2\sigma(I)$).

## Conclusions

In conclusion, coumarin readily forms 1 : 1 and 2 : 1 guest–host inclusion complexes with cucurbit[7]uril and cucurbit[8]uril respectively. The discovery of such complexes may have potential applications for the delivery of coumarin and analogous drug molecules and in formulations.

## Experimental section

### Materials

Cucurbit[7]uril and cucurbit[8]uril were synthesized and characterized according to a modified literature method.[3,23] Coumarin (99%, Sigma) and all other chemicals were of the highest available purity and used as received.

### Methods

The $^1$H NMR spectra were recorded on a Bruker Avance 400 spectrometer in $D_2O$. The UV-visible spectra were acquired with a Perkin-Elmer Lambda 45 ultraviolet-visible (UV-vis) spectrometer using a 1 nm data collection interval. Photoluminescence emission spectra were collected with a Fluoromax-3 spectrometer (Jobin Yvon Horiba, Instruments SA), with a 450-Watt Xe lamp as the excitation source, an increment of data collection of 1 nm, and the slits for emission of 3 nm. The *ab initio* modeled structures of the host–guest complexes were computed by energy-minimizations using Gaussian 03 programs run on the computing facilities of the High Performance Virtual Computing Laboratory (HPVCL) at Queen's University, Kingston, Canada. The structures of the complexes were originally constructed using ChemDraw and Chem3D (ChemOffice 7.0, CambridgeSoft) programs and thereafter imported into Gaussian 03. The basis set used for the calculations was HF/3–21G**. The host–guest stability constant for the cucurbit[7]uril complexes with coumarin was determined from a UV spectrometric titration of coumarin with CB[7]. The change in the absorbance at 277 nm with [*CB[7]*] was subjected to a non-linear least squares fit to a 1 : 1 binding isotherm. Single crystal X-ray diffraction data were measured on a Bruker Apex 2 Kappa diffractometer at 100 K, using a graphite monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å). The unit cell was determined from randomly selected reflections obtained using the Bruker Apex2 automatic search, center, index, and least squares routines. Integration was carried out using the program SAINT, and an absorption correction was performed using SADABS.[24] The crystal structure was solved by direct methods and the structure was refined by full-matrix least-squares routines using the SHELXTL[25] program suite. All atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions and allowed to ride on the parent atoms. The structure has disordered water molecules and sulfate ions. Attempts were made to model this, but were unsuccessful since there were no obvious major site occupancies for the solvent molecules. PLATON/SQUEEZE[26] was used to correct the data for the presence of the disordered solvent. A potential solvent volume of 1451.9 Å$^3$ was found. 735 electrons per unit cell worth of scattering were located in the void. The modified dataset improved the $R_1$ value from 0.15 (in attempts to include the solvent) to final $R_1 = 0.079$ and w$R_2 = 0.23$ values. Estimated crystal composition is CB[8]–2 coumarins–4 $H_2SO_4$–12 $H_2O$ (based on full refinement without squeeze).


## Acknowledgements

The financial support to RW from the NRC-Nano Initiative at National Research Council of Canada is gratefully acknowledged. We thank Shihao Wang and the High Performance Virtual Computing Laboratory (HPVCL) at Queen's University, Kingston, Canada for assistance with the energy-minimization calculations of the cucurbituril complexes, and the National Research Council of Canada.


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