PERKIN 2

Chemical insight from crystallographic disorder-structural studies of supramolecular photochemical systems. Part 2.[1] The β-cyclodextrin–4,7-dimethylcoumarin inclusion complex: a new β-cyclodextrin dimer packing type, unanticipated photoproduct formation, and an examination of guest influence on β-CD dimer packing

Tom J. Brett,[a,b] Jennifer M. Alexander[a] and John J. Stezowski *[a,b]

[a] *Department of Chemistry, University of Nebraska-Lincoln, Lincoln, Nebraska 68588-0304, USA. E-mail: jstezowski1@unl.edu*
[b] *Center for Materials Research and Analysis, University of Nebraska-Lincoln, Lincoln, Nebraska 68588-0113, USA*

Received (in Gainesville, FL) 23rd July 1999, Accepted 10th March 2000

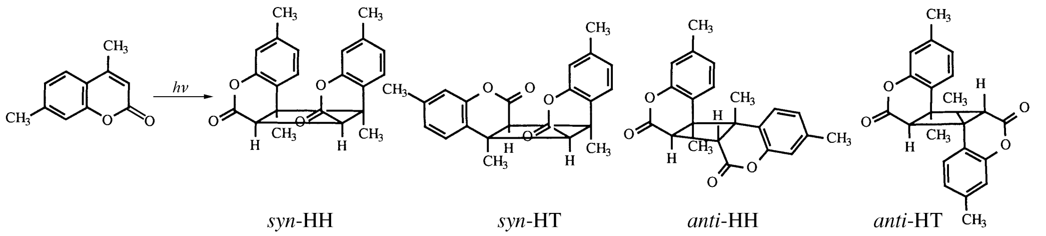
As part of an ongoing structural study of supramolecular photochemical β-cyclodextrin(β-CD)–coumarin derivatives systems the crystal structure of the β-CD–4,7-dimethylcoumarin complex has been determined at 13 K and complemented with *ab initio* molecular orbital calculations on selected guest coumarin molecules. The 4,7-dimethylcoumarin molecules form a crystalline 2:2 host–guest (H–G) complex with β-CD that is appropriately described as a "reaction nano-vessel" in which the inter-molecular interactions of import to the outcome of the reaction are confined to a single β-CD dimer host. Structure determination of the isolated photoproduct showed the product formed is the *anti*-HT photodimer. Production of this dimer is only possible with much rearrangement of the guests. This appears to occur because of a preferential spatial fit of this product to the β-CD dimer cavity. The crystal structure reveals a new β-CD dimer packing pattern, designated *tetrad* type, with reduced reaction tube intermolecular interactions among guest molecules. Tetrad packing is characterized in comparison with the previously reported β-CD dimer packing types. Guest influence on packing of β-CD dimers is examined in β-CD inclusion complexes with different derivatized coumarins. To probe basic molecular properties giving rise to inter-molecular interactions influencing crystal packing, *ab initio* molecular orbital calculations for the guest coumarin molecules were carried out to examine electrostatic interactions.

Introduction

Solid-state photochemical reactions are attractive from the synthetic chemist's viewpoint in that they typically display more selective product distributions than their solution-phase counterparts and from a "green chemistry" viewpoint, because they are carried out in the absence of solvents. Not surprisingly, study in the field of solid-state reactions has been rigorous in an effort to determine the mechanistic and controlling factors that produce given reaction outcomes. Several important contributions to understanding the factors controlling reactions in crystals have been reported.[2] Most such studies have focused on reactions carried out in neat crystals, however co-crystallizing or "host" media have been used to produce reaction outcomes not observed in neat crystals.[3] The result is expanding the arsenal of the solid-state photo-chemist.

β-Cyclodextrin (β-CD), a cyclic oligomer made of seven D-glucose units, provides an example of a naturally occurring chiral host system in which the outcome of photochemical reactions can be modified.[4] Photodimerization of coumarin and coumarin derivatives in supramolecular β-CD complexes presents a particularly interesting example system. Upon photolysis, coumarin and its derivatives can give four structural isomers (Scheme 1), the product ratio of which in solution is strongly influenced by the solvent polarity and the multiplicity of the excited state involved.[5] Photodimerizations of coumarins in neat and co-crystals have generally been found to proceed topochemically.[6,7]

The dimerization of coumarins is also of practical significance. Specific stereoisomers, illustrated in Scheme 1, have been found to undergo facile lactone ring-opening reactions with various nucleophiles. These photodimers and this reaction have been used in the preparation of optically active polyamides,[8] in the preparation of chiral stationary phases for resolution of enantiomers[9] and in the analytical determination of the enantiomeric excess of chiral amines or alcohols.[10] Stereoselective



Scheme 1 Possible [2 + 2] photodimers produced in 4,7-dimethylcoumarin photodimerization.

photodimerizations have also been employed as key steps in the synthesis of natural products;[11] hence the study of controlled photodimerizations is of general interest. A study of the photodimerization of coumarin and coumarin derivatives in crystalline powders of β-CD complexes has been reported,[12] however these complexes have not been subjected to detailed structural studies. Detailed structural studies of such important supramolecular host–guest systems at the molecular level are much less common than comparative studies on neat crystals.

A recent report from this laboratory presented an explanation of the 64% yield for the photolysis of coumarin in the supramolecular β-cyclodextrin–coumarin complex.[1] Extending this study to other coumarin complexes, we have determined the structure of the β-CD–4,7-dimethylcoumarin complex for a crystal at 13 K. An unexpected packing mechanism for the complex was found prompting *ab initio* theoretical calculations for a series of coumarin derivatives to probe the influence of guest molecules on crystal packing of the supramolecular coumarin inclusion complexes.

Past studies of solid-state photochemical reactions have stressed not only the importance of topological effects on the outcome of reactions,[13–15] but also the influence of the surrounding crystalline environment.[16] In the supramolecular systems studied here, the β-CD provides not only a photochemically inert environment in which photodimerizations of included molecules take place, but one that is non-constraining[17] with respect to conformation of the included molecules and, to a large extent, an environment that provides considerable freedom for the operation of varied intermolecular interactions, as well.

β-CD's commonly crystallize as face-to-face dimers when including moderate-to-large size molecules. Such β-CD dimers have been observed to pack in different fashions to produce varying patterns throughout the crystal. Upwards of 50 different examples of β-CD dimeric crystal structures are deposited in the Cambridge Crystallographic Data Centre (CCDC); their packing types have been analysed.[18] The β-CD dimeric structures have been grouped in four packing types. An important feature of these different packing types is that they present different environments for intermolecular interactions at the primary ends of the β-CD dimer. Because these different interactions can influence the overall outcome of the photochemical reaction of the included guest, it is of importance to understand the factors that control the packing arrangement of β-CD dimers in crystals. For example, channel type packing in β-CD–coumarin crystals produces a "reaction nano-tube" which has a profound effect on the overall reaction outcome.[1]

This paper examines three facets of our study of supramolecular photochemical β-CD complexes with various coumarins: the crystal structure and solid-state photoreactivity of one of the complexes (the β-CD–4,7-dimethylcoumarin complex), a system which exhibits a new form of β-CD dimer packing; an analysis of guest influence on β-CD dimer packing by considering complexes of β-CD with various substituted coumarins; and the influence of the dimer packing on the nature of the nano-reaction vessel in the photochemical process.

Experimental

Synthesis

4,7-Dimethylcoumarin was synthesized *via* the Pechmann condensation of ethyl acetoacetate with *m*-cresol using 75% H_2SO_4 as the condensing agent.[19] TLC, GC-MS, and ^1H NMR analysis indicated that only one product was formed. All other coumarins were purchased from Aldrich and recrystallized once before using.

Preparation and crystallization of β-CD inclusion complexes

In a typical inclusion complex preparation, about 180 mg of the solid guest compound were suspended in 40 ml of a saturated aqueous solution of β-CD. The mole ratio of guest : β-CD was in slight excess of 3 : 2. This solution was heated until either the guest coumarin melted or dissolved, at which point the coumarin would interact and complex with the β-CD in the aqueous phase. Cooling of this solution produced an aqueous solution saturated in the inclusion complex. Slow evaporation of the water at room temperature from the filtered aqueous solution typically produced crystals after 2–3 weeks.

Crystallographic studies of the β-CD inclusion complexes

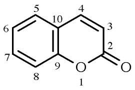
For structure determination of the β-CD–4,7-dimethylcoumarin complex, a colorless crystal of dimensions 0.5 × 0.5 × 0.1 mm was encased in a thin layer of Vaseline Petroleum Jelly and mounted on the end of a long glass capillary. The crystal was then flash frozen at 13 K and maintained at that temperature using a custom-built He cryostat from Oxford Cryosystems. Diffraction data were collected by the oscillation method using a Bruker AXS molybdenum-target rotating anode X-ray source and an 18 cm MARResearch imaging plate detector. The program MARXDS[20] was used for indexing and integration of the data set. In all, 16934 reflections (6956 unique, $R_{int} = 0.0365$) were recorded to a resolution of 0.90 Å. The overall completeness of the data set was 94.9%. The phase problem was solved by molecular replacement with a β-CD monomer search fragment using the program XPS in the SHELXTL5.0 program package (Bruker AXS, Madison, WI, USA). Waters of hydration and guest 4,7-dimethylcoumarin sites were located in difference electron density maps ($F_o - F_c$). Analysis of these maps revealed two separate sites for each coumarin molecule. The population of each site was required (by crystallographic symmetry) to be 50%. Least-squares refinement on F^2 of 1039 parameters was carried out using SHELXL97[21] and converged to a final $R_1 = 0.0811$, $wR_2 = 0.2041$, and GOF = 1.107 for 6697 reflections with $F_o > 4\sigma(F_o)$. For the β-CD and waters, all non-hydrogen atoms were treated anisotropically. 4,7-Dimethylcoumarin molecules were refined subject to geometric restraints with restrained refinement of anisotropic displacement parameters. Hydrogens on carbon atoms were generated geometrically and were fixed in a riding model. A final difference electron density map showed no distinct features with $\rho_{max} = 0.929$ and $\rho_{min} = -0.641$ e Å^{-3}. Crystal data and refinement details are summarized in Table 1. CCDC reference number 188/240. See http://www.rsc.org/suppdata/p2/a9/a906041c/ for crystallographic files in .cif format.

A summary of cell parameters and space group information for β-CD complexes with various derivatized coumarins is given in Table 2. The parameters, determined by different methods described below, are summarized here. For the β-CD–coumarin and β-CD–6-methylcoumarin complexes, data were collected on an automated Siemens P4 diffractometer with a Mo sealed tube source. Unit cell parameters were obtained by the least-squares treatment of 18 and 24 reflections in the ranges of $25 \geq 2\theta \geq 15$ and $20 \geq 2\theta \geq 19.8°$ for the β-CD–coumarin and β-CD–6-methylcoumarin complexes, respectively. For the β-CD–7-methylcoumarin and β-CD–7-methoxycoumarin complexes, data were collected by the oscillation method using a Cu rotating anode X-ray source and an 18 cm MARResearch imaging plate. Cell parameters were refined against the positions of 78 and 66 indexed reflections for the β-CD–7-methylcoumarin and β-CD–7-methoxycoumarin complexes, respectively. For the β-CD–7-hydroxy-4-methylcoumarin and β-CD–7-hydroxycoumarin complexes, full hemisphere data sets were collected by the oscillation method using a Mo-target rotating anode source and an 18 cm MARResearch imaging plate. Cell parameters were refined against the positions of 18563 and 4935 indexed reflections for the β-CD–7-hydroxy-4-methylcoumarin and β-CD–7-hydroxycoumarin

Table 1 Crystal data and structure refinement statistics

	β-CD–4,7-dimethylcoumarin complex	*anti*-HT 4,7-dimethylcoumarin photodimer
Empirical formula	$(C_{42}H_{70}O_{35})(C_{11}H_{10}O_2)(H_2O)_{17}$	$C_{22}H_{20}O_2$
Formula weight	1615.44	348.3
T/K	13.0(1)	293(2)
Crystal system	Monoclinic	Monoclinic
Space group	$C2$	$P2_1/c$
a/Å	19.513(4)	9.733
b/Å	24.024(5)	15.587
c/Å	16.414(3)	5.722
β/°	104.49(3)	99.184(2)
V/Å^3	7450(3)	856.9
Z	4	2
D_c/g cm^{-3}	1.440	1.350
Reflections (unique)	16934 (6956, R_{int} = 0.0365)	3423 (946, R_{int} = 0.0546)
Goodness-of-fit on F^2	1.107	1.665
$R1$, $wR2$ [$F_o > 4\sigma(F_o)$]	0.0811, 0.2041	0.0870, 0.2233

Table 2 Crystal data for β-cyclodextrin inclusion complexes with substituted coumarins



Coumarin substituents	Space group	a/Å	b/Å	c/Å	α/°	β/°	γ/°	Temp. of measurements/K
None	$C2$	19.322(2)	24.641(3)	16.050(2)		108.756(8)		293(2)
6-Methyl	$C2$	19.210(3)	24.600(3)	15.726(2)		109.462(9)		293(2)
7-Methyl	$C2$	19.348(3)	24.582(4)	15.784(1)		109.843(9)		293(2)
7-Methoxy	$C2$	20.058(2)	24.441(6)	15.662(1)		109.843(9)		293(2)
4,7-Dimethyl	$C2$	19.513(4)	24.024(5)	16.414(1)		104.49(3)		13.0(1)
7-Hydroxy-4-methyl	$P1$	18.01(6)	15.53(6)	15.37(6)	103.35(6)	113.22(6)	99.47(6)	293(2)
7-Hydroxy	$P1$	18.16(6)	15.55(6)	15.46(6)	103.23(6)	113.21(6)	99.22(6)	293(2)

complexes, respectively. The MARXDS software was used for treatment of all oscillation method data.

Photochemical studies

Crystals of the β-CD–4,7-dimethylcoumarin inclusion complex prepared as described above were put into Pyrex test tubes, which were sealed and flushed with N_2, and then irradiated with a Hanovia 450W medium pressure Hg arc lamp for 7 days. Care was taken to make sure the crystals did not dehydrate. The photolysed crystals were then dissolved in water, and methylene chloride was used to extract the photoproduct. Thin layer chromotography (EtOAc–Hexane) showed formation of only one photoproduct. This was verified by GC-MS. This photodimer was then isolated by silica gel column chromatography and crystallized from chloroform. The crystals obtained were thin needles and diffracted X-rays weakly, however data of reasonable quality to determine the structure of the unknown photoproduct were obtained. Diffraction data were collected at room temperature in the same manner as described above for the β-CD–4,7-dimethylcoumarin complex. In all, 3423 reflections (946 unique, R_{int} = 0.0546) were recorded to a resolution of 0.95 Å. The overall completeness of the data set was 90.7%. The phase problem was solved by direct methods with the program SHELXS97.[21] The crystal structure revealed the identity of the photoproduct to be the *anti*-HT dimer. Hydrogens on carbon atoms were generated geometrically and fixed in a riding model. All non-hydrogen atoms were refined with anisotropic displacement parameters. Crystal data and refinement details are summarized in Table 1.

Quantum-chemical calculations

To gain a better understanding of how the nature of the guest has influence on the different β-CD dimeric packing types, the electrostatic properties of the derivatized coumarin guests were analysed. Density functional theory (B3LYP) geometry optimizations of each of the molecules were carried out employing the split-valence 6-31++G(d,p) basis set using the Gaussian98 program.[22] Then single-point Hartree–Fock calculations using the same basis set were performed on the optimized structures and electrostatic potential-derived charges determined using the Merz–Kollman–Singh method (MK).[23,24]

Results and discussion

Structure of the β-CD–4,7-dimethylcoumarin complex

The β-CD–4,7-dimethylcoumarin complex crystallizes as a face-to-face β-CD dimer containing two 4,7-dimethylcoumarin molecules (Fig. 1). The β-CD dimer has twofold crystallographic symmetry with the 4,7-dimethylcoumarin molecules disordered over two sites. The occupancy of each site is crystallographically required to be 50%, as the replicate of one site packs with the other. Therefore, throughout the analysis of this structure, when referring to the pair of guest molecules which pack together, only one pair will be addressed since the two pairs are crystallographically identical. The guest molecules pack in an aromatic face-to-face fashion within the β-CD dimer cavity with the carbonyl ends of the molecules pointing into the dimer center. This leaves the 7-methyl substituents of the guest molecules pointing out the primary ends of the β-CD dimer.

The conformation of the β-CD molecule at the primary hydroxy end presents a unique feature. Of the seven primary hydroxys, five take on the most commonly observed −*gauche* conformation,[25] with the C6–O6 bond pointing away from the

Table 3 Close electrostatic interactions in the interdimer region (including possible hydrogen bonds)

Atoms	Distance/Å	Angle/°
O6(G1) · · · O6(G2)^{I}	2.726(8)	C6(G1)–O6(G1) · · · O6(G1)^{I} 100.5(4)
O6(G2) · · · O6(G2)^{I}	2.708(7)	C6(G2)–O6(G2) · · · O6(G2)^{I} 120.4(4)
O6(G1) · · · O(10)	2.813(8)	C6(G1)–O6(G1) · · · O(10) 109.1(5)
O(20) · · · O(13)^{I}	2.73(1)	
O(20) · · · O(19)^{II}	2.79(1)	
C12(25) · · · O(20)	3.13(1)	C7(25)–C12(25) · · · O(20) 150.5(4)
C12(25) · · · O(19)^{II}	2.89(1)	C7(25)–C12(25) · · · O(19)^{II} 149.4(5)
C12(25) · · · O(13)^{I}	3.82(1)	C7(25)–C12(25) · · · O(13)^{I} 120.8(4)
C12(25) · · · O6(G2)^{I}	3.54(1)	C7(25)–C12(25) · · · O6(G2)^{I} 109.0(3)
C12(26) · · · O(20)	3.50(1)	C7(26)–C12(26) · · · O(20) 131.2(3)
C12(26) · · · O(19)^{II}	3.89(1)	C7(26)–C12(26) · · · O(19)^{II} 99.2(2)
C12(26) · · · O(13)^{I}	3.280(9)	C7(26)–C12(26) · · · O(13)^{I} 173.3(4)
C12(26) · · · O6(G2)^{I}	3.64(1)	C7(26)–C12(26) · · · O6(G2)^{I} 100.7(2)

I = $-x + 1, y, -z + 2$; II = $-x + 3/2, y - 1/2, -z + 2$.

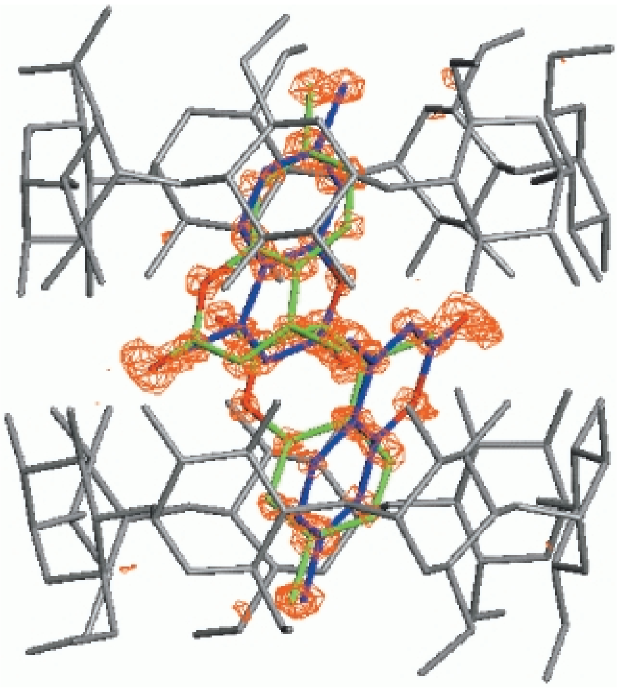


Fig. 1 Crystal structure of the β-CD–4,7-dimethylcoumarin complex at 13 K. Hydrogens and water oxygens have been omitted for clarity. The β-CD dimer contains two disordered pairs of guest molecules, each with an occupancy of 50%. The individual pairs are color-coded with the carbon atoms green or blue for the respective pairs. Oxygen atoms in all of the guest molecules are red. The difference electron density map ($F_o - F_c$) which the guest molecules were fit to is shown in orange.

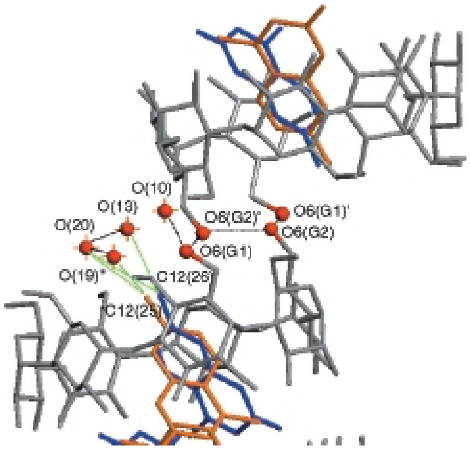


Fig. 2 Close electrostatic interactions (including possible hydrogen bonds) in the interdimer region. All cyclodextrin atoms are colored grey except for the primary hydroxy oxygens (red) involved in interdimer hydrogen bonds. Water oxygens are red also. The two 4,7-dimethylcoumarin molecules are blue and orange respectively. Possible hydrogen bonds are designated with dashed lines. Close C–H · · · O contacts with C · · · O ≤ 3.50 Å are shown with green lines. See Table 3 for geometric information. Hydrogens have been omitted for clarity.

cavity. The other two primary hydroxys, of G1 and G2,† are +*gauche* conformers, with the C6–O6 bond pointing in toward the cavity. A perusal of the Cambridge Structural Database (CSD) shows this (two adjacent +*gauche* conformers in a β-CD dimeric structure) to be a feature unique to this complex.‡ As a result, these hydroxys are involved in a network of interdimer hydrogen bonds (see Fig. 2 and Table 3) that produces a packing pattern for the β-CD dimers that has not been reported before. Because the distinguishing feature of this packing type is the presence of the interdimer hydrogen bonding interaction of four primary hydroxys, we designate this new packing type as *tetrad* type packing. The tetrad packing type is described in more detail below.

While this interdimer hydrogen bonding interaction definitely adds stability to this type of packing, the reason for its formation is unclear. As described above, the guest 4,7-dimethylcoumarin molecules are arranged with their 7-methyl ends oriented towards the primary ends of the dimer. However, the 7-methyl group is enclosed well within the β-CD dimer cavity; that is, it does not protrude past the primary hydroxys. From an intuitive viewpoint, one would expect this structure to pack in a channel, in order to maximize hydrophobic interactions between guests in adjacent β-CD dimer cavities and minimize contact with waters of crystallization. A possible explanation for the formation of this packing type is discussed below.

Analysis of the structure at the interdimer interface reveals a handful of intermolecular interactions, from strong hydrogen bond interactions to weaker electrostatic C–H · · · O interactions. C–H · · · O hydrogen bonding has been observed to be prominent in organic crystals in general[26] and in cyclodextrin inclusion complexes as well.[27–30] A significant observation has been that the strength of the C–H · · · O interaction (gauged by the C · · · O separation distance) is dependent on the acidity of the donor carbon.[31] A methyl carbon, in general, would not be expected to be very acidic. However, the 7-methyl carbon of the guest molecule should be a bit more acidic in nature due to its attachment to the electron-withdrawing aromatic ring. This

---

† Atom naming throughout is as follows. For the cyclodextrins, A*n*(G*m*), where element symbol A, atom number *n* of glucose residue *m*. For the guest 4,7-dimethylcoumarin molecules, atom names are shown in Fig. 3, and followed in the text by a residue number, either (25) or (26). Water oxygens are simply O followed by a residue number in parentheses.

‡ It should be noted that of the 57 dimeric β-CD structures deposited in the CSD (version 5.16; October, 1998), only 22 have coordinates deposited. Therefore, only those structures could be examined.

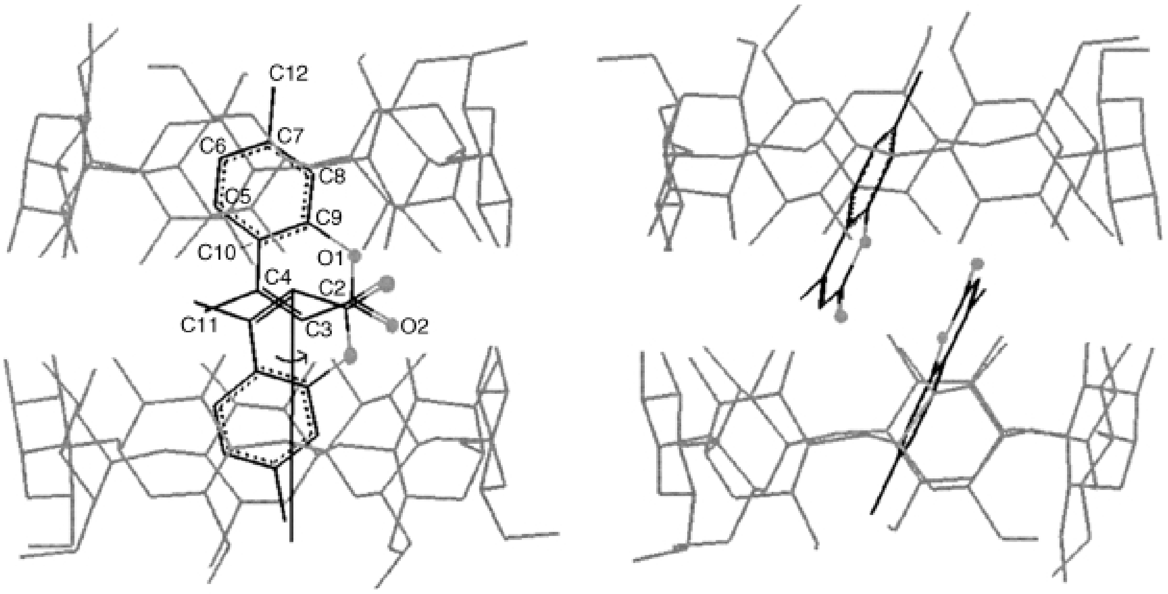


Fig. 3 Two views of the arrangement of the pair of 4,7-dimethylcoumarin molecules in the β-CD dimer cavity. β-CD is shown as grey lines. Guest 4,7-dimethylcoumarin molecules are shown as black lines with grey filled circles for the oxygen atoms. Atom naming is shown for the 4,7-dimethylcoumarin molecule. Hydrogens are omitted for clarity. The axis around which the proposed guest flip occurs is shown in the picture on the right. See text for details.

would create more polar C–H bonds in this methyl group. Indeed, strong $C–H\cdots O$ interactions are observed for the 7-methyl groups for each guest molecule (see Fig. 2 and Table 3). For each, quite short $C\cdots O$ distances are observed in interactions with water molecules. For C12(25), close contacts are with O(19) and O(20), while C12(26) interacts most strongly with O(13) and O(20). These waters are all within strong hydrogen bonding contacts of each other (as can be seen in Fig. 2 and Table 3). With this "hydration shell" surrounding the 7-methyl end of the guest molecule, channel type (CH type) packing would not be possible. In addition, this "shell" looks to be weakly hydrogen bonded to one of the +*gauche* conformer hydroxys [$O6(G1)\cdots O(19)^{II} = 3.281(9)$ Å ($II = -x + 3/2, y - \frac{1}{2}, -z + 2$)]. This produces an environment in which the individual reaction cavities are well-separated with no opportunity for interaction between molecules in separate cavities, very unlike the "reaction nano-tube" observed in the β-CD–coumarin complex.[1]

Photochemistry of the β-CD–4,7-dimethylcoumarin complex

Examination of the orientation of the guest 4,7-dimethylcoumarin molecules within the β-CD dimer reveals that the reactive double bonds are not ideally placed to photodimerize (Fig. 3). According to topochemical stipulations,[13–15] the reactive double bonds which undergo dimerization should lie within 4.2 Å of each other and should be parallel to each other. The reactive centers have reasonable separation distances [$C3(25)\cdots C4(26)^{III} = 3.91(1)$ Å, and $C4(25)\cdots C3(26)^{III} = 3.95(1)$ Å ($III = -x + 1, y, -z + 1$)], however, the double bonds are nearly perpendicular to each other, with the angle being 80.6(5)°. Given this fact, rotation about an axis connecting the centers of the reactive double bonds could produce favorable orientations to provide two different products (depending on the direction of rotation), either *syn*-HT or anti-HH. Neither product is observed. Instead, X-ray crystallographic analysis of the recrystallized photoproduct shows it to be the *anti*-HT photodimer (Fig. 4). The occurrence of this photoproduct can be explained in terms of a preferential fit of the product in the reaction cavity. Using computer modeling, it can be seen that the observed *anti*-HT photodimer fits well in the β-CD dimer cavity. Models built of the possible *syn*-HT and *anti*-HH photodimers do not fit as well or at all. In other words, the shape of the observed photoproduct fits the shape of the cavity it is formed within. It should be noted that in the previous photochemical studies on crystalline powder β-CD–coumarin complexes[12] the observed photoproduct for the 4,7-dimethylcoumarin complex was reported to be the *anti*-HH dimer. The reason for the discrepancy with our results could be because of the difference in the samples used (carefully grown crystals *versus* crystalline powders) or due to an incorrect identification in the previous report. In that report the products were characterized by NMR spectroscopy and there was some admitted discrepancy in the identity of the 4,7-dimethylcoumarin photodimer from β-CD complexes.

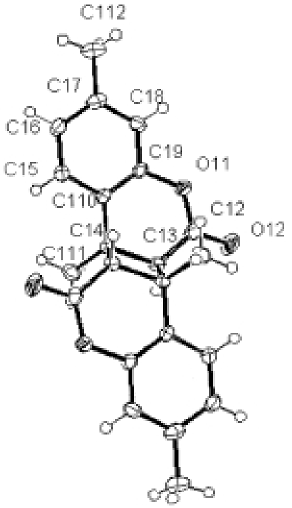


Fig. 4 Structure of the *anti*-HT 4,7-dimethylcoumarin photodimer produced by the photoreaction carried out in the β-CD complex. Only atom labels for the crystallographically unique half of the molecule are shown.

The next question is then how do the molecules reorient in the cavity to produce the observed product? A 180° flip of one of the molecules (Fig. 3) about an axis connecting C3 to C12 would provide a favorable orientation to produce the observed photoproduct. Due to lack of space, this could not occur readily with the molecules packed as they are in the crystal structure. However, with modest libration of the molecules in the general direction of the long axis of the β-CD dimer, the suggested flipping event could occur. Given the fact that the

Table 4 Average unit cells for different β-CD dimer packing types

Number in group	a/Å	b/Å	c/Å	α/°	β/°	γ/°	Vol. per dimer/Å^3 [a]	Hydration [b]
Space group $P1$ (packing type IM)								
16 [c]	18.010	15.404	15.443	102.985	113.349	99.304	3679	24
Space group $P2_1$ (packing type SC)								
6 [d]	15.342	32.526	15.347		102.189		3742	28
Space group $C2$ (packing type CH)								
12 [e]	19.231	24.561	15.831		109.37		3528	17
Space group $C222_1$ (packing type CB)								
5 [f]	19.292	24.142	32.666				3803	18
Space group $C2$ (packing type TETRAD)								
1	19.513	24.024	16.414		104.49		3725	34

[a] Unit cell volume divided by number of β-CD dimers per unit cell. [b] Average number of waters per β-CD dimer. [c] CCDC Refcodes used: BCDIPH10, BCDMPH, BCDNPR10, BIDMOQ, BOGCAB, CDEXPR, CEDMUT, CIGXOF, CIGXOF10, DOCVUM, DOCVUM01, DOCVUM02, DOCVUM03, HEGXUM, TEJHAR. [d] CCDC Refcodes used: CDETAN, CIVBUE, DUTLIN10, GETPAW, GETPEA, NIZGUY. [e] CCDC Refcodes used: BIHJEH, COCMIQ, DEVTED, DEVTIH, HAMBZB, HPAMIB, HPAMIB10, KOGLIB, TEMCIX, VIJXAN, VIJXAN10, ZUZXOH. [f] CCDC Refcodes used: DEVTUT, DEVTON, FASXUS, GIPFEQ, KOFJEU.

7-methyl ends of the molecules sit on the edge of a large water channel, it is possible that such a libration and flipping motion could occur. It should be noted that at such a low temperature (13 K) this motion is probably "frozen out". A determination of the structure at room temperature might well reveal much more disorder in the guest molecules.

Characterization of the tetrad packing type

As mentioned in the introduction, β-CD dimers have been observed to crystallize in four different packing types[18] classified as: channel type (CH), intermediate type (IM), chess-board (CB), and screw-channel (SC). All four are very similar in that they consist of close packed β-CD dimer layers. The relative placement of the close packed layers leads to different stacking of the β-CD dimers. The SC type differs from the others in that there is a significant tilt angle between the planes of the close packed layers. In all the other packing types the layer-planes are essentially parallel. In the CH structures the β-CD dimers stack parallel to the c axis nearly directly one on top of the other with only a slight shift, creating β-CD dimer channels. In IM structures the shift is significant and puts the sevenfold axis of a dimer near the rim of a dimer below. The result is a nearly cage-like environment for the guest molecules. In this arrangement there is moderate opportunity for interaction between guests in adjacent dimer cavities, but interactions with waters of crystallization and adjacent β-CD dimer primary hydroxys are possible. In the CB structures the shift is even greater, such that the crystal takes on the appearance of a three-dimensional chess-board, with "squares" of water channels and β-CD dimers alternating throughout. The guest molecules in CB packed complexes are fully exposed at the primary ends to interactions with waters of crystallization. These packing types can be characterized by their unit cell and space group parameters. Averages are shown for β-CD dimeric structures found in the CSD in Table 4.

The crystal structure of the β-CD–4,7-dimethylcoumarin complex displays a new form of dimer packing (designated as the tetrad, TT, type). In the TT type the β-CD dimer layers are even more offset than in the IM type. These differences can be seen in Fig. 5 and can be evaluated quantitatively. The relative displacement of adjacent β-CD dimer centroids projected onto the same plane are 2.395(2) Å, 6.273(7) Å, and 6.865(6) Å for the CH, IM, and TT packing types, respectively. Further, the angles between a line connecting the β-CD dimer centroids of adjacent dimers and a plane defined by the O4 atoms of a β-CD are 8.68(4), 20.11(4), and 24.33(3)° for the CH, IM, and TT packing types, respectively.

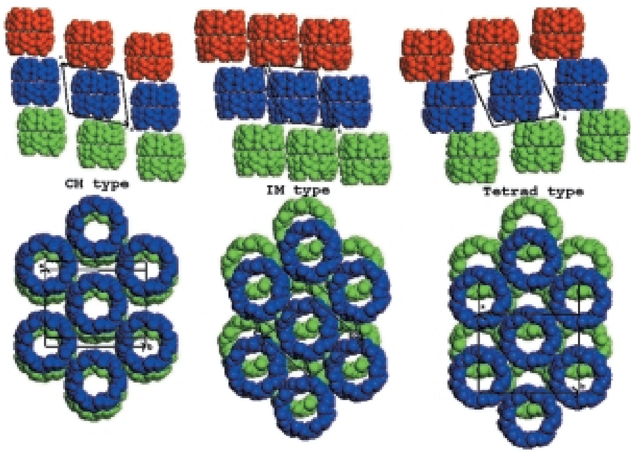


Fig. 5 View of the stacking of β-CD dimers (top) and down the center of the β-CD dimer for the CH, IM, and tetrad packing types, respectively. β-CD molecules are shown represented by space-filling models. Hydrogens and primary hydroxys have been omitted for clarity.

The TT packing type displays a larger volume per β-CD dimer than do the CH and IM types (Table 4) due at least in part to its unusually high degree of hydration. As can be seen in Table 4, the average number of water molecules per β-CD dimer ranges from 17 to 28 for the four previously established packing types; the averages for the CH and IM types are 17 and 24, respectively. The crystal structure of β-CD–4,7-dimethylcoumarin contains 34 water molecules per β-CD dimer. This is the highest degree of hydration that has been observed for a β-CD crystal structure.

Guest influence on β-CD dimer packing types

Because these different packing types allow for different environments at the primary ends of the β-CD dimer, it is important to understand the factors that control the packing arrangement of β-CD dimers in crystals. As can be seen in the tabulation of our measurements of cell parameters and space group assignments for β-CD complexes with various coumarins (Table 2), most crystallize in two different packing types. β-CD complexes with coumarin,[1] 6-methylcoumarin, 7-methylcoumarin, and 7-methoxycoumarin pack in CH modes. The complexes with 7-hydroxy-4-methylcoumarin and 7-hydroxycoumarin both exhibit IM packing. The complex reported here with 4,7-dimethylcoumarin displays the new TT type.

As described above, the guest 4,7-dimethylcoumarin molecules pack in the β-CD dimer in a face-to-face manner, with the long dimension of the molecules roughly parallel with the long dimension of the β-CD dimer. Preliminary analysis of other β-CD complexes with substituted coumarins for which full single-crystal X-ray diffraction data have been obtained shows this to be the preferred mode of inclusion of the guest coumarins in 2 : 2 host–guest (H–G) complexes.[32] This leaves the 6,7-position end of the coumarin molecules extending to the primary ends of the β-CD dimer. The nature of the protruding moieties would appear to affect the packing type produced.

In the only other previous systematic study of guest influence on β-CD dimer packing, such effects were used to explain the differences in packing in β-CD inclusion complexes with *para*-disubstituted benzenes. Complexes with 4-*tert*-butyltoluene,[33] 4-*tert*-butylbenzoic acid[34] and 4-*tert*-butylbenzyl alcohol[18] were observed to pack in CH, IM, and CB types, respectively, as one of the *para* substituents on the guest molecule was varied from a methyl group, to a carboxylic acid, to a hydroxy group. The 4-*tert*-butyltoluene complex displayed CH packing in order to maximize hydrophobic interactions between guests in adjacent dimer cavities. The 4-*tert*-butylbenzoic acid complex packed in IM type to allow for intermolecular hydrogen bonding between carboxylic acid groups on molecules in adjacent dimers. The 4-*tert*-butylbenzyl alcohol complex packed in CB type to allow for hydrogen bonding interactions with surrounding water molecules exterior to the cavity and with a primary hydroxy group on an adjacent dimer. The conclusion of that study was that it was the polar groups of the guest molecules which seem to determine the packing mode of the β-CD dimers.

In our study, groups at the 6- and 7-position of the coumarin are varied from either non-polar methyl and methoxy groups to polar hydroxyl groups. In the case of the 7-hydroxycoumarin and 7-hydroxy-4-methylcoumarin complexes, IM type packing is observed, which should allow for the hydroxy groups to maximize polar interactions with surrounding waters and adjacent primary hydroxys. The coumarin, 6-methylcoumarin, 7-methylcoumarin, and 7-methoxycoumarin complexes all exhibit CH type packing, which should allow for maximum hydrophobic interaction between guests in adjacent dimers.

Based on these arguments, the observation of the TT form in the β-CD–4,7-dimethylcoumarin complex is quite unexpected. As mentioned earlier, the extending 7-methyl groups are involved in several significant C–H···O electrostatic interactions, which create a "hydration shell" around this group and prevent the possibility of CH type packing. While an interesting observation, intuitively, one would not expect this to be the case.

In order to gain more insight into how the electrostatic structure of the coumarin molecule is varied within the different substituted coumarins studied here, *ab initio* molecular orbital calculations were performed to obtain electrostatic charges. To obtain suitably reliable results, polarization and diffuse functions were included for all atoms, including hydrogens. Electrostatic potential derived partial charges were determined according to the Merz–Kollman–Singh scheme. The results are shown in Fig. 6.

The calculation for the series of molecules examined gives rise to some interesting observations. The biggest fluctuations in charges occur at atoms in the 6 and 7 positions. This is, of course, where most of the substitutions are taking place. An interesting observation can be made in comparing the charge distributions in 7-methylcoumarin, 7-hydroxy-4-methylcoumarin, and 4,7-dimethylcoumarin. The calculations show these molecules to be quite similar in their charge distributions and, therefore, electrostatically similar. As mentioned earlier, the preferred mode of inclusion for the guest coumarins leaves the 6,7-position end of the molecules extending to the primary ends of the β-CD dimer. Comparing the 7-hydroxy-4-methylcoumarin and 4,7-dimethylcoumarin molecules, they are similar in polarity and electrostatic appearance in this area. Both should interact electrostatically with surrounding water molecules in similar ways. The major difference is in the directional favoritism of the hydroxy group. The hydroxy group will more favorably interact with water in a specific geometric manner in order to optimize hydrogen bond interactions with surrounding water. The methyl group, on the other hand, has a polar and positively electrostatic appearance and will interact with water in a less directional manner, more akin to a charge–charge interaction. It appears that the more ordered water structure in the β-CD–7-hydroxy-4-methylcoumarin complex leads to the IM packing type, whereas the less ordered, but nonetheless significant, interaction in the β-CD–4,7-dimethylcoumarin complex leads to the TT packing type.

The question then becomes, "why is the TT packing type not observed for the β-CD–7-methylcoumarin complex?" As can be seen in Fig. 6, the charge distributions in the 7-methylcoumarin and 4,7-dimethylcoumarin molecules are nearly identical in the 6 and 7 carbon region and for the 7-methyl group. The major difference in the two molecules is their size. The 4-methyl group in the 4,7-dimethylcoumarin molecule acts to take up space and provide a tighter spatial fit to the β-CD dimer cavity. Due to the fact that it is a bit larger, the two included molecules would not be able to wobble around as much as the 7-methylcoumarin molecules would. Therefore, the "hydration shell" which forms around the 7-methyl group in the 4,7-dimethylcoumarin complex and prevents the CH type packing would be unlikely to form in the β-CD–7-methylcoumarin complex because of its looser fit within the cavity.

We suggest that the determinants of β-CD dimer packing types in the derivatized coumarin complexes appear to be a complex mix of charge distribution and "tightness of fit" in the extended β-CD dimer torus. Favorable hydrophilic interactions with surrounding water molecules seem to preclude the formation of the CH type. If the group exposed to water can interact strongly with it, such as a hydroxy or amine group, then the CH type will not form. If the exposed group interacts with water in a purely electrostatic fashion, then the spatial fit of the guest to the cavity becomes important. If the guest does not provide a tight spatial fit, the weak (but significant) interactions with water will be destabilized and the CH type will form. If the guest provides a tight enough fit to the cavity, the lessened degree of motion will stabilize ordering of a hydration shell that will prevent the CH type and form some other type.

Conclusions

The results presented here provide support for the argument that detailed structural studies are essential to understanding the chemical processes occurring in these complex supramolecular systems. The observation of a new type of β-CD dimer packing was quite unexpected and is even more spectacular given the fact that many other β-CD inclusion complexes with very similar molecules do not exhibit it. The distinctive feature of this packing type is a series of inter-dimer hydrogen bonds between four primary hydroxyl groups, hence the name given to this type as tetrad. This type of packing creates a unique reaction environment in the solid state. The individual reaction cavities are separated sufficiently enough to prevent interaction between molecules in separate cavities. The β-CD dimer acts as a boundary within which the environment is non-constraining. The dimer packing observed produces an environment at the primary ends of the dimer, which can be considered as spongy, and to allow libration in a direction out of the cavity for the included molecules. This libration allows flipping of the molecules to produce the observed *anti*-HT photodimer, the product which provides the best spatial fit to the cavity. This observation, along with our previous observation of a "reaction

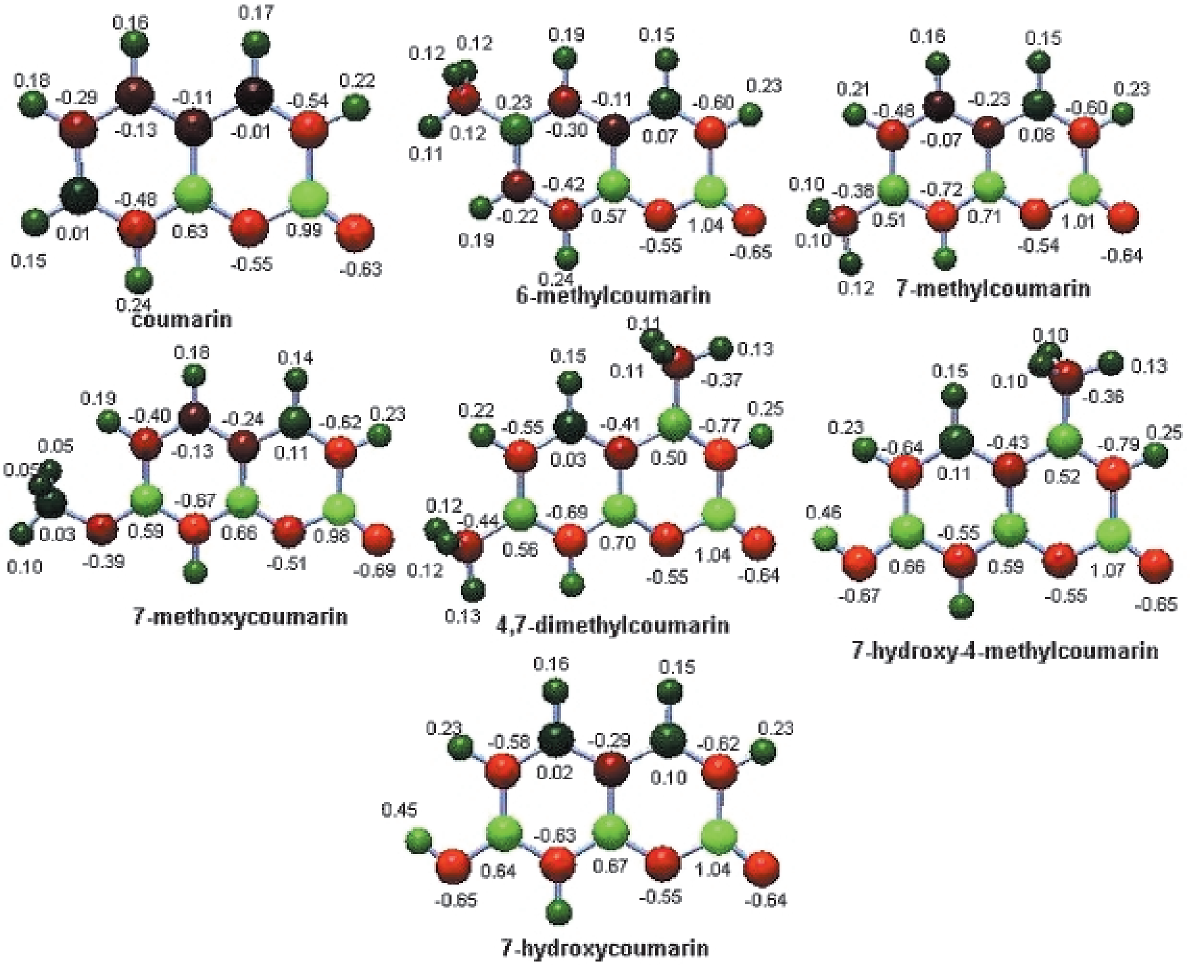


Fig. 6 Electrostatic charges for the various guest coumarin molecules derived according to the Merz–Kollman–Singh scheme from HF/6-31++G(d,p) calculations. Atoms are spectrum colored according to electrostatic potential, with the ends of the spectrum being bright red (−1.0) and bright green (+1.0).

nano-channel" in the β-CD–coumarin complex, stresses the importance of β-CD dimer packing in producing the overall reaction environment. The determinants of β-CD dimer packing types are a complex mix of intermolecular interactions and spatial fit. Determination of the crystal structure of the β-CD–7-methylcoumarin complex is expected to provide much information to either support or refute these conclusions.

Acknowledgements

Partial funding for this work was provided by the NSF (CHE-9812146). We thank Cerestar USA, Inc. (Hammond, IN) for samples of β-CD.

References

1 Part 1, T. J. Brett, J. M. Alexander, J. L. Clark, Charles R. Ross, II, G. S. Harbison and J. J. Stezowski, *Chem. Commun.*, 1999, 1275.
2 For example, see V. Ramamurthy and K. Venkatesan, *Chem. Rev.*, 1987, **87**, 433.
3 V. Ramamurthy, in *Photoprocesses of Host–Guest Complexes in the Solid State*, ed. V. Ramamurthy, VCH, New York, 1991, p. 303.
4 V. Ramamurthy, *Tetrahedron*, 1986, **42**, 5753.
5 D. O. Cowan and R. L. Drisko, *Elements of Organic Photochemistry*, Plenum Press, New York, 1976.
6 K. Gnanaguru, N. Ramasubbu, K. Venkatesan and V. Ramamurthy, *J. Org. Chem.*, 1985, **50**, 2337. It should be noted that a few examples of non-topochemical photoproduct formation have been observed for derivatized coumarins. For examples, see ref. 6 and references cited therein.
7 J. N. Moorthy and K. Venkatesan, *J. Org. Chem.*, 1991, **56**, 6957.
8 K. Saigo, *Prog. Polym. Sci.*, 1992, **17**, 35.
9 Y. Chen and M. T. Shiao, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 3423.
10 K. Saigo, K. Sekimoto, N. Yonezawa, F. Ishii and M. Hasegawa, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 1006.
11 T. Bach, *Synthesis*, 1998, 683.
12 J. N. Moorthy, K. Venkatesan and R. G. Weiss, *J. Org. Chem.*, 1992, **57**, 3292.
13 M. D. Cohen and G. M. J. Schmidt, *J. Chem. Soc.*, 1964, 1996.
14 M. D. Cohen, G. M. J. Schmidt and F. I. Sonntag, *J. Chem. Soc.*, 1964, 2000.
15 G. M. J. Schmidt, *J. Chem. Soc.*, 1964, 2014.
16 M. D. Cohen, *Angew. Chem.*, *Int. Ed. Engl.*, 1975, **14**, 386.
17 T. J. Brett, S. Liu, P. Coppens and J. J. Stezowski, *Chem. Commun.*, 1999, 551.
18 D. Mentzafos, I. M. Mavridis, G. LeBas and G. Tsoucaris, *Acta Crystallogr.*, *Sect. B*, 1991, **47**, 746.
19 S. Sethna and R. Phadke, *Org. React.* (*N.Y.*), 1953, **7**, 1.
20 W. Kabsch, *J. Appl. Crystallogr.*, 1988, **21**, 916.
21 G. Sheldrick, SHELXL97, Program for the Refinement of Crystal Structures, University of Göttingen, 1997.
22 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian98 (Revision A.3), Pittsburgh, PA, 1998.
23 B. H. Besler, J. Kenneth M. Merz and P. A. Kollman, *J. Comput. Chem.*, 1990, **11**, 431.
24 U. C. Singh and P. A. Kollman, *J. Comput. Chem.*, 1984, **5**, 129.

25 W. Saenger, *Inclusion Compounds*, ed. J. L. Atwood, J. E. D. Davies and D. D. MacNicol, Academic Press, New York, 1984.
26 G. R. Desiraju, *Acc. Chem. Res.*, 1991, **24**, 290.
27 T. Steiner and W. Saenger, *J. Am. Chem. Soc.*, 1992, **114**, 10146.
28 T. Steiner and W. Saenger, *J. Am. Chem. Soc.*, 1993, **115**, 4540.
29 T. Steiner, G. Koellner, K. Gessler and W. Saenger, *J. Chem. Soc., Chem. Commun.*, 1995, 511.
30 T. Steiner and W. Saenger, *J. Chem. Soc., Chem. Commun.*, 1995, 2087.
31 G. R. Desiraju, *Acc. Chem. Res.*, 1996, **29**, 441.
32 This lab, unpublished results. It should be noted that the mode of inclusion is quite different for coumarin, which forms a 3:2 H–G complex (see ref. 1). The rest are assumed to be 2:2 H–G complexes because of spatial contraints and analysis of other complexes.
33 I. M. Mavridis and E. Hadjoudis, *Carbohydr. Res.*, 1992, **229**, 1.
34 A. Rontoyianni, I. M. Mavridis, E. Hadjoudis and A. J. M. Duisenberg, *Carbohydr. Res.*, 1994, **252**, 19.