Crystal Structures of Inclusion Complexes of β-Cyclodextrin with (S)-(+)- and (R)-(-)-Fenoprofen

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Abstract: The crystal structures of the inclusion complexes of β-cyclodextrin (β-CD, cycloheptaamylose) with (S)-(+)- and (R)-(-)-fenoprofen [FP, 2-(3-phenoxyphenyl)propionic acid] have been determined by X-ray diffraction techniques. The complexes crystallize in space group $P2_1$ with cell dimensions as follows. (R)-(-) complex: a = 15.259 (16) Å, b = 32.759 (44) Å, c = 15.353 (11) Å; β = 101.53 (1)°. (S)-(+) complex: a = 15.310 (3) Å, b = 32.124 (7) Å, c = 15.277 (3) Å; β = 100.76 (1)°. In the crystal the β-CD molecules exist as a head-to-head dimer by means of extensive hydrogen bonding across the secondary hydroxyl ends of two symmetry-independent β-CD molecules. One guest molecule is included in the cavity of each β-CD monomer. Although the β-CD is isomorphous in both complexes, the two independent guest molecules of the S complex pack in a parallel, or head-to-tail, arrangement while those of the R complex pack in an antiparallel, or head-to-head, manner. One of the carboxylic acid groups of the (S)-FP, which is located in the β-CD dimer interface, forms hydrogen bonds with secondary hydroxyl oxygen atoms from β-CD molecules, while the other one, which protrudes from the β-CD dimer, forms a hydrogen bond with a primary hydroxyl oxygen from a neighboring β-CD dimer. In the (R)-FP complex, both carboxylic acid groups form hydrogen bonds with water alone. These water molecules are not present in the (S)-FP complex. Fenoprofen is a nonsteroidal antiinflammatory drug. Recent studies have shown that only the (S)-(+) isomer is pharmacologically active. The different interactions between β-CD with the enantiomeric isomers of FP revealed by the crystal structures help to explain the inhibition of the enzyme cyclooxygenase by (S)-FP alone, as well as the ability of cyclodextrins to act as a racemic resolution phase.

The cyclodextrins (CD), also called cycloamyloses and Schardinger dextrins, are cyclic oligosaccharides consisting of 6–12 D-glucopyranosyl units, linked by α-(1→4)-glycosidic bonds.[1,2] β-Cyclodextrin (β-CD), or cycloheptaamylose, containing seven glucose units with an inner diameter of 6.5–8.0 Å, is one of the most chemically useful cyclodextrins. Cyclodextrins have a "round", slightly conical form with all the secondary hydroxyl, i.e., the O(2)–H and O(3)–H groups located on the wider end and all primary hydroxyl groups O(6)–H on the narrower end. The glucose units are in the $^4C_1$ chair conformation. The inner surface of the cavity is dominated by hydrogen atoms and glycosidic oxygen atoms and is thus relatively hydrophobic.[2] In the crystal structure, the C(6)–O(6) bonds are usually directed away from the center of the cyclodextrin ring,[1,2] forming hydrogen bonds with water. They can, however, turn "inward" due to hydrogen bonding between the O(6)–H group and the guest molecule. Intramolecular hydrogen bonds O(3)–H···O(2) or O(3)···H–O(2) exist between the secondary hydroxyl groups of adjacent glucose units (Figure 1).

The cyclodextrins have the ability to form inclusion compounds with a variety of molecules that fit inside the CD cavity.[1-3] The guest molecule is surrounded or encapsulated by CD in the inclusion complex and, as a result, shows advantageous changes in its chemical and physical properties. In particular, drug properties such as stability, solubility, and bioavailability, as well as toxicity, can be improved, and these changes have been intensively investigated. Examples of CD–drug complexes reported include CD with prostaglandins, barbiturates, chemotherapeutics, steroids, and nonsteroid antiinflammatory drugs (NSAID). Many studies of the crystal structures of CD complexes have been reported. The first structure of a β-CD complex was reported by Hamilton et al. in 1976.[4] Compounds containing meta-substituted phenyl rings have usually resulted in disordered crystal structures when complexed with β-CD.[5] Fenoprofen, however, is a meta-substituted phenol derivative that does not show any disorder in the β-CD complexes.

Fenoprofen (FP), *dl*-2-(3-phenoxyphenyl)propionic acid (Figure 2) (α-methyl-3-phenoxybenzeneacetic acid), is a nonsteroidal antiinflammatory, antipyretic, analgesic drug developed at the Lilly Research Laboratories.[6,7] It belongs to the group of compounds commonly referred to as the 2-arylpropionic acids. Other members of this group that have been widely studied include ibuprofen, naproxen, ketoprofen, and flurbiprofen.[8] The marketed form of fenoprofen is the calcium dihydrate (Nalfon; Eli Lilly Co.).

Fenoprofen has an asymmetric center, which allows the existence of two enantiomers, (R)-(-) and (S)-(+). Recently, the resolved R and S isomers and the RS racemate of FP were compared in vitro as inhibitors of the fatty acid cyclooxygenase system from human platelets, which is often used to detect drugs that have antiinflammatory activity associated with inhibition of prostaglandin synthesis.[9] On the basis of 50% inhibition of the system, one isomer was found to be 2 times more active than the racemate and ~35 times more active than the other isomer.[10] An X-ray crystallographic study[11] of FP showed that the absolute configuration of the active isomer is S.

This present X-ray crystal structure determination was undertaken in order to examine and compare the binding of the optical isomers of FP in the cavity of β-CD. Different interactions were anticipated. The results should be significant in the studies of the pharmacology of fenoprofen as well as in the application of cyclodextrin in chromatography.

Experimental Section

(R)- and (S)-fenoprofen calcium salts (FPCa) were obtained from the Eli Lilly Co. as white powders. The solubility of the calcium salts in water is about 2.5 mg/mL (pK_a 4.5). The FPCa's were each added to a two-layer water–ethyl acetate (EA) (1:3) system. The mixture was adjusted to pH 3–3.5 with HCl. After several cycles of separation and washing with EA, all EA portions were collected and combined. The

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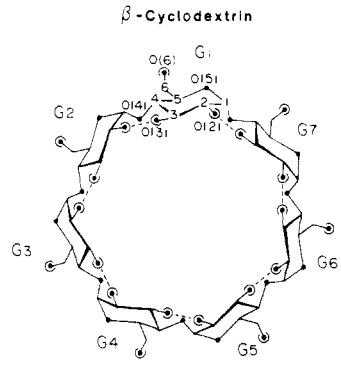

Figure 1. Numbering shceme for β-cyclodextrin.

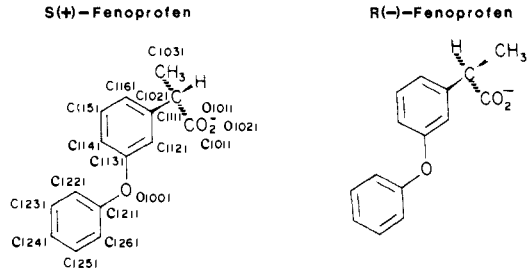

Figure 2. Numbering scheme for (*S*)-(+) and (*R*)-(−)-fenoprofen.

concentration of the FP in EA extracts was measured by UV at 271 nm. The EA was evaporated; the acid fenoprofens thus obtained were oils. β-CD was dissolved in water, and the solution was mixed with each oil in a molar ratio of 1:3 (β-CD to FP). The mixtures were heated for 2 h in a water bath (50 °C), and on cooling, microprecipitates were formed. The mixtures were refrigerated for 5–7 days, and good crystals in the form of parallelogram plates were obtained for both the *R* and *S* complexes.

Determination of the unit cell parameters and data collection were done on a Picker four-circle automated diffractometer at −130 to −135 °C using Cu Kα radiation. A total of 6571 and 6430 reflections in the range of $5° < 2\theta < 93°$ was collected for *S* and *R* complexes respectively, corresponding to approximately 1.07-Å resolution. The crystals are monoclinic with space group $P2_1$. The asymmetric unit contains two β-CD monomers and two FP molecules not related by symmetry, i.e., one complex dimer. The crystal parameters are listed in Table I.

Structure Determination and Refinement. The structures were solved with data from an isomorphous crystal of the complex of β-CD with *p*-ethylaniline, which was in turn solved by single isomorphous replacement using the β-CD–*p*-iodoaniline complex.[12] Atomic coordinates for β-CD (omitting the primary hydroxyl groups) from the β-CD–*p*-ethylaniline complex were used for the initial structure factor calculations. After several cycles of structure factor calculation followed by Fourier synthesis, the electron density map showed the primary hydroxyl groups of the CD and the two FP guest molecules, as well as the water of crystallization (25 water molecules for the (*S*)-FP and 28 for the (*R*)-FP). Refinement was carried out using a combination of difference Fourier synthesis and full-matrix and block-diagonal least-squares calculations. During refinement of the anisotropic temperature factors, the amount of CPU time needed, even on a large, fast computer like CDC Cyber 855, was enormous. The huge quantity of parameters and variables [215 and 218 non-hydrogen atoms for the (*S*)- and (*R*)-FP complexes, respectively] also exceeded the maximum core memory of the computer. The refinement was therefore carried out in a series of partial refinements: Only one β-CD or only guest or water molecules were refined in alternate cycles. The calculated hydrogen positions for the β-CD carbon atoms and guest benzene rings were added after the first cycle of anisotropic refinement. Isotropic temperature factors equal to half of the equivalent isotropic temperature factor of the bonding atom were used for the hydrogen atoms. Many hydrogen atoms were in fact observed on the later difference Fourier maps in positions expected from calculation. The parameters of the hydrogen atoms were refined during the final least-squares calculation and behaved well. During the refinement, only those reflections with $F_o > 3\sigma(F_o)$ were used. The percentage of reflections with $F_o > 3\sigma$ is 97.1% for *R* and 87.2% for *S*. In the final cycle of structure factor calculation, a cutoff of 1σ was used, which resulted in a reflection percentage of 99.3% for *R* and 96.4% for *S*. The final *R* values for reflections with $F_o > 1\sigma$ are 0.083 for *R* and 0.113 for *S* (Table I).

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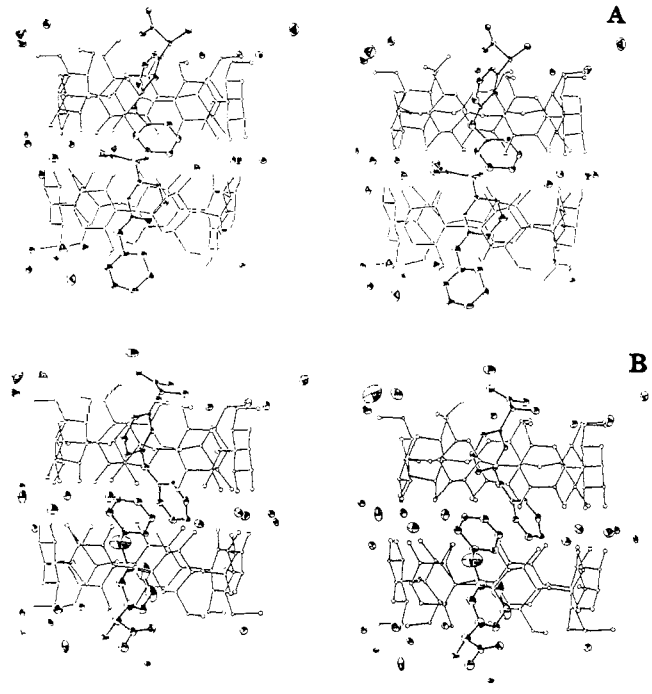

Figure 3. ORTEP plot of dimer structure: (A) β-CD–(*R*)-FP complex; (B) β-CD–(*S*)-FP complex. Atoms of guests and waters are shown with thermal motion.

Table I. Crystal Data and Refinement Results for the FP–β-CD Complexes

	(*R*)-(−)-FP–CD complex	(*S*)-(+)-FP–CD complex
mol formula	$(C_{42}H_{70}O_{35})_2 \cdot (C_{15}H_{14}O_3)_2 \cdot 26H_2O$	$(C_{42}H_{70}O_{35})_2 \cdot (C_{15}H_{14}O_3)_2 \cdot 2H_2O$
mw	3222.89	3186.87
space group	$P2_1$	$P2_1$
cell parameters		
a, Å	15.26 (2)	15.310 (3)
b, Å	32.76 (4)	32.124 (7)
c, Å	15.35 (2)	15.277 (3)
β, deg	101.5 (1)	100.76 (2)
V, Å^3	7519.63	7381.41
D_{measd}, mg/mL	1.424	1.441
Z	2	2
no. of measd reflcns[a]	6571	6430
$F_o \geq 3\sigma(F_o)$	6378 (97.1%)	5610 (87.2%)
R (3σ)	0.081	0.106
$F_o \geq 1\sigma(F_o)$	6526 (99.3%)	6196 (96.4%)
R (1σ)	0.083	0.113

[a] The reflection data were collected at a wavelength of 1.5418 Å (Cu) and temperature of −135 °C. The resolutions are 1.07 Å.

Results and Discussion

General Description. The final atomic coordinates for the non-hydrogen atoms are given in Table II. The numbering scheme uses a three-digit code as follows: The first digit represents the monomer of β-CD or FP molecule, the second represents the individual glucose residues of β-CD or the phenyl rings for FP (0 for ring side-chain atoms), and the third digit represents atoms within the glucose residue or FP molecule as shown in Figures 1 and 2. The structure analysis showed that in both complexes a head-to-head β-CD dimer is formed by means of extensive hydrogen bonding across the secondary hydroxyl ends of two adjacent β-CD monomers, with one guest being included in each of the two β-CD monomer units. For ease of discussion the symmetry-independent (*S*)-FP molecules will be called S1 and S2, the symmetry-independent (*R*)-FP molecules R1 and R2.

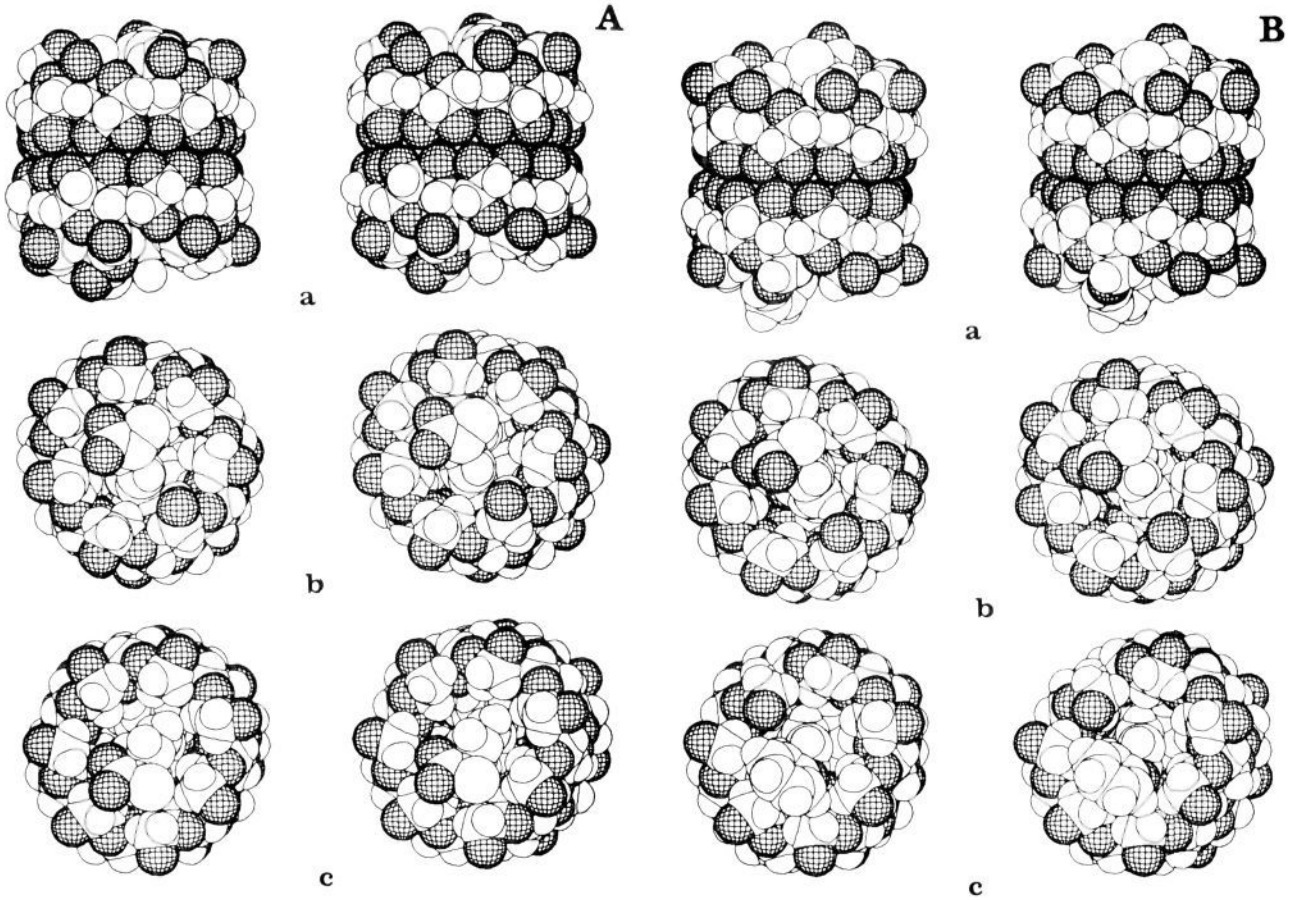

Figure 4. Stereoview of the space-filling model: (A) β-CD–(*R*)-FP complex; (B) β-CD–(*S*)-FP complex. Key: (a) viewed from side; (b) viewed from top; (c) viewed from bottom.

Figures 3 and 4 show ORTEP plots and space-filling plots of these dimer structures. The bond lengths and angles for the β-CD and FP molecules are within expected values. They are available as supplementary material. All D-glucosyl residues are in $^4C_1$ conformation. In the *R* complex, all primary hydroxyl groups point away from the cavity and are in the gauche–gauche orientation except one, O(126), which points in toward the cavity and is in the gauche–trans orientation; in the *S* complex, there are two primary hydroxyl groups, O(126) and O(276), one for each β-CD monomer, which point in toward the cavity. This is to facilitate hydrogen bonding to the guest or water in the primary end of the β-CD.

The β-CD Macrocycles. The formation of the β-CD dimer results in an overall more rigid complex structure than in the case of monomeric complexes. For example, motion of the glucose residues about the glucosidic bonds is restricted. Calculation of radial distances from the center of gravity of the β-CD molecule to each of the sevenfold related atoms of any type shows remarkable uniformity in the case of a spherical guest such as adamantane derivatives.[13] One might expect some tendency toward ellipticity of the β-CD due to the planar benzene rings of the FP, but in fact, the radii show only slightly greater internal deviation than for the adamantane complexes. The average values of the $O(4)_n$–$O(4)_{n+1}$ distances (see Table III) are 4.38 Å (σ 0.06) and 4.37 Å (σ 0.12) for the *S* complex and 4.37 Å (σ 0.06) and 4.36 Å (σ 0.14) for the *R* complex. These agree with a value of 4.367 ± 0.065 Å averaged over several dimer complexes.[13] The average $O(4)_n$–$O(4)_{n+1}$–$O(4)_{n+2}$ angles (Table III) are 128.5° (σ 2.5) and 128.6° (σ 4.2) for the *R* and 128.6° (σ 3.7) and 128.5° (σ 5.3) for the *S* complex. The value is 128.6° for an ideal heptagon.

The glucosidic angles C(4)–O(4)–C(1)′ have average values of 118.0° (±2.9) and 118.0° (±2.3) for the *S* complex and 117.4° (±2.6) and 117.8° (±1.2) for the *R* complex. These are in agreement with a value of 117.4 ± 1.0° averaged over eight independent β-CD structure determinations.[13] These data show that the β-CD molecule (in particular the dimer form) is very consistent as far as the central circle of O(4), C(1), C(4) atoms are concerned.

Packing Scheme. No hydrogen positions were determined experimentally. Hydrogen bonding was analyzed in a distance range of 2.3–3.2 Å and an angle range of 90–130°. Tables IV and V list the hydrogen bonds for both complexes. Figure 5 illustrates the hydrogen-bond network stabilizing the complexes. Several structural features are apparent. The intermolecular hydrogen bonds that form the β-CD dimer involve only O(3) hydroxyl groups (Table VI), in contrast to previous crystalline complexes where both O(2) and O(3) hydroxyl groups have taken part in dimer formation.[5,13] The contact distances in the postulated hydrogen-bonding pair O(123)–O(253) in both complexes are considerably longer than all others. The O(2) hydroxyl groups do form four intermolecular hydrogen bonds; however, their partners are not from the same CD dimer but from other symmetry-related units. The number of hydrogen bonds forming the CD dimer appears to vary with included guest.[5,13] Within each β-CD molecule, intramolecular hydrogen bonding always exists between O(3) and O(2) hydroxyl groups of adjacent glucose residues. The intramolecular hydrogen-bond lengths are listed in Table VII. They are more varied in length for the *S* complex. This is due to interaction of (*S*)-FP with the secondary hydroxyl groups of CD, as will be discussed later. The carbonyl oxygen and hydroxyl oxygen in the carboxylic acid group can be differentiated on the basis of bond length (Table VIII). Thus, for both (*R*)- and (*S*)-FP, O(101G) and O(201G) are carbonyl oxygen atoms, while O(102G) and O(202G) are hydroxyl oxygen

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Table II. Fractional Coordinates ($\times 10^4$) and Isotropic Temperature Factors ($\times 10^2$) of the Non-Hydrogen Atoms of the (*R*)-(−)- and (*S*)-(+)-FP-β-CD Complexes[a]

	(*R*)-(−)-FP-β-CD complex				(*S*)-(+)-FP-β-CD complex			
atom	*x*	*y*	*z*	*U*	*x*	*y*	*z*	*U*
				CD 1				
C(111)	−3562 (6)	5711 (3)	1702 (6)	1.53	−3546 (12)	5735 (7)	1632 (12)	2.97
C(112)	−4125 (7)	5383 (3)	1145 (7)	2.68	−4107 (12)	5406 (6)	1040 (13)	2.80
C(113)	−4004 (7)	5408 (3)	185 (7)	2.02	−4010 (13)	5422 (7)	103 (11)	3.09
C(114)	−4300 (7)	5831 (4)	−183 (8)	2.83	−4281 (12)	5851 (6)	−248 (11)	1.88
C(115)	−3786 (8)	6163 (4)	422 (8)	2.95	−3756 (12)	6188 (6)	349 (12)	2.41
C(116)	−4091 (7)	6585 (3)	204 (7)	2.41	−4150 (15)	6615 (7)	66 (13)	4.12
O(112)	−3924 (5)	4997 (2)	1504 (5)	2.89	−3886 (8)	5010 (4)	1482 (8)	2.33
O(113)	−4552 (5)	5099 (2)	−323 (5)	2.58	−4567 (8)	5107 (4)	−394 (8)	2.23
O(114)	−4124 (4)	5865 (2)	−1058 (4)	1.74	−4162 (9)	5881 (4)	−1143 (8)	3.19
O(115)	−3808 (5)	6105 (2)	1338 (5)	2.47	−3808 (9)	6134 (4)	1236 (8)	3.10
O(116)	−4967 (5)	6641 (2)	340 (5)	3.17	−5016 (9)	6656 (4)	223 (7)	3.13
C(121)	−4838 (7)	6019 (3)	−1760 (7)	2.74	−4813 (11)	6030 (6)	−1786 (10)	1.57
C(122)	−5044 (8)	5698 (4)	−2451 (9)	2.96	−5045 (10)	5679 (5)	−2576 (10)	0.76
C(123)	−4240 (9)	5634 (4)	−2892 (8)	2.87	−4242 (14)	5627 (6)	−2974 (14)	3.33
C(124)	−3918 (8)	6034 (3)	−3221 (7)	2.29	−3909 (11)	6020 (6)	−3319 (13)	2.26
C(125)	−3762 (8)	6345 (4)	−2462 (8)	3.42	−3793 (11)	6344 (5)	−2585 (13)	2.10
C(126)	−3594 (9)	6784 (4)	−2799 (9)	3.31	−3618 (14)	6790 (6)	−2918 (13)	3.46
O(122)	−5308 (5)	5327 (2)	−2091 (5)	3.08	−5295 (9)	5312 (4)	−2182 (8)	3.01
O(123)	−4432 (6)	5333 (2)	−3559 (5)	3.11	−4408 (8)	5326 (4)	−3638 (9)	2.93
O(124)	−3074 (5)	5963 (3)	−3471 (4)	2.71	−3091 (8)	5958 (4)	−3549 (7)	1.86
O(125)	−4570 (5)	6385 (2)	−2076 (5)	2.60	−4587 (8)	6390 (4)	−2192 (8)	2.72
O(126)	−3249 (6)	7039 (3)	−2051 (6)	4.18	−3288 (10)	7066 (4)	−2172 (8)	3.12
C(131)	−2996 (7)	6032 (3)	−4377 (6)	2.12	−2954 (13)	6033 (6)	−4435 (13)	3.19
C(132)	−2671 (8)	5644 (4)	−4694 (7)	3.60	−2606 (13)	5639 (6)	−4777 (14)	3.68
C(133)	−1732 (8)	5534 (3)	−4167 (7)	2.80	−1724 (12)	5532 (6)	−4178 (12)	2.32
C(134)	−1125 (8)	5892 (4)	−4215 (7)	2.69	−1097 (13)	5904 (6)	−4278 (12)	2.81
C(135)	−1463 (7)	6286 (3)	−3911 (8)	2.69	−1434 (11)	6310 (5)	−3900 (11)	1.49
C(136)	−923 (10)	6652 (4)	−4112 (8)	4.51	−904 (13)	6660 (6)	−4106 (17)	4.04
O(132)	−3267 (5)	5319 (2)	−4696 (5)	3.56	−3245 (8)	5317 (4)	−4816 (8)	2.69
O(133)	−1453 (6)	5170 (2)	−4526 (5)	3.54	−1375 (9)	5133 (4)	−4427 (10)	3.79
O(134)	−283 (5)	5793 (2)	−3614 (5)	2.86	−241 (8)	5798 (4)	−3637 (8)	2.55
O(135)	−2384 (5)	6362 (2)	−4400 (5)	2.95	−2357 (9)	6363 (4)	−4477 (9)	4.07
O(136)	−922 (7)	6674 (3)	−5038 (7)	5.80	−873 (10)	6693 (4)	−5007 (10)	4.15
C(141)	529 (7)	5829 (3)	−3921 (7)	2.63	525 (11)	5871 (6)	−3988 (13)	2.02
C(142)	994 (9)	5447 (4)	−3887 (8)	3.83	994 (11)	5445 (5)	−3936 (12)	1.72
C(143)	1278 (8)	5301 (4)	−2884 (7)	2.73	1299 (13)	5329 (6)	−3006 (12)	2.74
C(144)	1862 (8)	5647 (3)	−2410 (8)	2.47	1883 (13)	5656 (6)	−2482 (15)	3.33
C(145)	1359 (11)	6044 (4)	−2513 (9)	4.93	1363 (12)	6065 (6)	−2556 (13)	3.08
C(146)	1940 (10)	6408 (4)	−2115 (10)	4.18	2004 (17)	6434 (7)	−2098 (15)	5.00
O(142)	435 (5)	5137 (2)	−4362 (5)	3.21	466 (9)	5172 (4)	−4439 (9)	3.13
O(143)	1783 (5)	4934 (2)	−2846 (5)	3.40	1787 (7)	4929 (4)	−2922 (8)	2.35
O(144)	2103 (5)	5551 (2)	−1480 (5)	2.56	2105 (7)	5541 (4)	−1571 (8)	2.19
O(145)	1086 (6)	6151 (2)	−3420 (5)	3.70	1047 (8)	6171 (4)	−3500 (8)	2.89
O(146)	2773 (7)	6437 (3)	−2378 (8)	5.91	2761 (10)	6465 (5)	−2480 (10)	4.61
C(151)	3045 (6)	5536 (3)	−1092 (7)	1.91	3014 (13)	5540 (7)	−1142 (15)	4.27
C(152)	3236 (8)	5113 (3)	−687 (9)	3.72	3195 (11)	5111 (5)	−730 (10)	1.22
C(153)	2705 (7)	5046 (3)	72 (7)	2.28	2689 (11)	5064 (6)	27 (13)	2.29
C(154)	2950 (8)	5401 (4)	724 (7)	2.67	2923 (12)	5431 (5)	640 (12)	1.96
C(155)	2810 (7)	5822 (4)	305 (9)	3.70	2858 (11)	5846 (6)	252 (13)	2.45
C(156)	3160 (7)	6169 (3)	886 (8)	2.42	3220 (12)	6189 (6)	795 (12)	2.90
O(152)	3021 (5)	4808 (2)	−1318 (6)	3.30	2963 (8)	4781 (3)	−1360 (8)	2.06
O(153)	2982 (5)	4684 (3)	529 (6)	3.26	2966 (8)	4688 (4)	507 (8)	2.60
O(154)	2343 (5)	5354 (2)	1344 (5)	3.12	2363 (7)	5405 (4)	1300 (7)	2.18
O(155)	3260 (4)	5838 (2)	−444 (5)	2.35	3274 (8)	5860 (4)	−537 (8)	2.32
O(156)	4095 (5)	6106 (3)	1314 (5)	3.17	4129 (8)	6132 (4)	1197 (8)	3.09
C(161)	2716 (8)	5367 (3)	2257 (8)	2.87	2724 (12)	5415 (7)	2242 (13)	3.24
C(162)	2384 (7)	4972 (4)	2674 (8)	2.55	2453 (12)	5007 (6)	2651 (13)	2.54
C(163)	1400 (7)	4996 (3)	2553 (7)	1.80	1454 (11)	5020 (6)	2562 (13)	2.14
C(164)	1151 (7)	5375 (3)	2974 (7)	1.35	1135 (12)	5417 (6)	2937 (14)	2.92
C(165)	1523 (8)	5748 (4)	2601 (8)	3.06	1518 (15)	5806 (6)	2539 (14)	3.64
C(166)	1368 (9)	6148 (4)	3047 (9)	4.14	1406 (15)	6194 (7)	3065 (13)	4.28
O(162)	2690 (5)	4621 (3)	2279 (5)	3.14	2739 (9)	4649 (4)	2284 (10)	4.40
O(163)	1114 (5)	4639 (2)	2999 (6)	3.11	1119 (8)	4665 (4)	2968 (8)	2.95
O(164)	179 (5)	5428 (3)	2790 (5)	2.97	173 (7)	5461 (4)	2721 (7)	1.80
O(165)	2466 (5)	5710 (2)	2694 (5)	3.24	2458 (8)	5767 (4)	2667 (10)	3.94
O(166)	1756 (6)	6127 (3)	3980 (6)	4.91	1728 (9)	6180 (5)	3988 (9)	4.22
C(171)	−262 (8)	5452 (4)	3498 (8)	3.11	−294 (12)	5487 (6)	3435 (12)	2.38
C(172)	−955 (7)	5113 (4)	3406 (8)	3.08	−968 (12)	5137 (6)	3319 (14)	2.80
C(173)	−1638 (8)	5165 (4)	2556 (7)	2.59	−1625 (11)	5172 (6)	2470 (11)	2.32
C(174)	−2075 (8)	5572 (3)	2560 (7)	2.25	−2078 (12)	5582 (6)	2462 (12)	2.02
C(175)	−1382 (7)	5907 (4)	2671 (7)	3.33	−1358 (12)	5955 (6)	2577 (11)	2.41
C(176)	−1789 (8)	6332 (4)	2807 (7)	2.45	−1820 (11)	6358 (5)	2769 (12)	1.73
O(172)	−498 (5)	4722 (2)	3459 (5)	2.76	−530 (9)	4728 (4)	3399 (9)	3.50

Table II (Continued)

	(*R*)-(−)-FP-β-CD complex				(*S*)-(+)-FP-β-CD complex			
atom	*x*	*y*	*z*	*U*	*x*	*y*	*z*	*U*
O(173)	−2277 (5)	4834 (2)	2499 (6)	3.45	−2270 (8)	4832 (4)	2378 (9)	3.25
O(174)	−2671 (5)	5625 (2)	1718 (4)	2.51	−2635 (8)	5646 (4)	1639 (8)	3.12
O(175)	−706 (5)	5844 (2)	3496 (5)	2.95	−750 (8)	5872 (4)	3405 (7)	2.43
O(176)	−2224 (5)	6332 (2)	3565 (5)	3.72	−2248 (8)	6346 (4)	3523 (8)	2.48
				CD 2				
C(211)	−199 (7)	3159 (3)	2916 (8)	2.66	−215 (14)	3173 (6)	2787 (13)	2.38
C(212)	512 (7)	3498 (4)	3123 (9)	3.50	444 (12)	3512 (7)	2999 (13)	2.50
C(213)	915 (6)	3550 (3)	2299 (6)	1.76	884 (12)	3545 (6)	2201 (13)	2.76
C(214)	1296 (6)	3148 (3)	2040 (6)	2.00	1282 (13)	3138 (6)	1945 (15)	3.20
C(215)	604 (7)	2825 (3)	1898 (7)	2.40	589 (15)	2820 (7)	1905 (17)	3.11
C(216)	969 (10)	2408 (4)	1754 (11)	5.99	980 (15)	2366 (6)	1833 (15)	3.94
O(212)	117 (4)	3853 (2)	3362 (4)	2.19	98 (10)	3888 (4)	3231 (10)	3.77
O(213)	1624 (5)	3854 (2)	2485 (5)	3.66	1594 (7)	3866 (4)	2391 (8)	2.13
O(214)	1550 (4)	3220 (2)	1185 (5)	2.85	1549 (10)	3187 (4)	1113 (8)	3.15
O(215)	182 (4)	2795 (2)	2679 (5)	2.80	138 (7)	2776 (4)	2634 (8)	1.79
O(216)	1736 (6)	2312 (3)	2501 (6)	5.17	1678 (10)	2302 (4)	2531 (9)	3.44
C(221)	2426 (6)	3142 (3)	1107 (7)	2.91	2450 (12)	3102 (7)	1087 (13)	2.04
C(222)	2821 (7)	3530 (4)	739 (8)	3.32	2805 (13)	3499 (6)	672 (15)	3.56
C(223)	2259 (8)	3627 (4)	−161 (9)	4.00	2310 (12)	3646 (6)	−212 (13)	2.63
C(224)	2280 (7)	3281 (4)	−766 (7)	2.85	2200 (11)	3247 (6)	−809 (12)	2.62
C(225)	1969 (7)	2880 (3)	−410 (8)	2.36	1962 (14)	2862 (7)	−496 (21)	4.93
C(226)	2110 (6)	2513 (4)	−911 (7)	2.90	2195 (18)	2484 (7)	1007 (15)	3.89
O(222)	2861 (5)	3852 (2)	1384 (5)	3.29	2885 (10)	3807 (4)	1357 (9)	4.11
O(223)	2609 (5)	3990 (2)	−474 (5)	3.44	2612 (8)	3970 (4)	−521 (8)	2.01
O(224)	1650 (4)	3382 (2)	−1575 (4)	2.51	1650 (9)	3383 (4)	−1621 (8)	2.97
O(225)	2463 (5)	2813 (2)	494 (5)	2.77	2441 (7)	2776 (4)	424 (8)	1.46
O(226)	3023 (5)	2488 (2)	−1055 (5)	4.06	3082 (9)	2489 (4)	−1151 (8)	2.00
C(231)	1942 (7)	3317 (4)	−2370 (8)	3.30	1909 (17)	3313 (8)	−2407 (17)	5.52
C(232)	1925 (8)	3720 (3)	−2858 (7)	2.91	1911 (13)	3696 (7)	−2955 (14)	2.87
C(233)	909 (8)	3855 (4)	−3174 (8)	3.63	897 (14)	3851 (6)	−3251 (15)	3.45
C(234)	421 (8)	3511 (3)	−3716 (7)	2.81	402 (14)	3500 (6)	−3777 (12)	2.34
C(235)	496 (8)	3125 (3)	−3207 (8)	3.33	449 (18)	3094 (7)	−3220 (17)	4.16
C(236)	55 (9)	2768 (4)	−3710 (9)	4.27	−36 (18)	2753 (8)	−3664 (23)	6.22
O(232)	2419 (5)	4017 (2)	−2329 (5)	3.47	2413 (8)	4014 (4)	−2423 (8)	3.02
O(233)	867 (5)	4232 (2)	−3689 (5)	3.09	903 (8)	4224 (4)	−3786 (8)	1.85
O(234)	−525 (5)	3628 (2)	−4022 (5)	3.04	−510 (8)	3632 (4)	−4085 (8)	1.80
O(235)	1427 (4)	3016 (2)	−2891 (5)	2.81	1339 (9)	2977 (4)	−2934 (9)	2.37
O(236)	390 (6)	2716 (3)	−4541 (6)	5.38	248 (17)	2667 (6)	−4512 (15)	10.42
C(241)	−864 (8)	3621 (4)	−4961 (7)	2.69	−833 (12)	3635 (6)	−4995 (14)	3.83
C(242)	−1290 (9)	4039 (4)	−5203 (7)	3.49	−1259 (13)	4049 (7)	−5301 (14)	3.15
C(243)	−2037 (7)	4097 (4)	−4740 (7)	2.73	−2058 (12)	4093 (6)	−4832 (12)	2.60
C(244)	−2697 (7)	3754 (3)	−4946 (7)	2.42	−2685 (13)	3753 (8)	−5050 (12)	3.27
C(245)	−2250 (7)	3346 (3)	−4766 (7)	2.47	−2213 (12)	3325 (6)	−4855 (12)	2.12
C(246)	−2846 (8)	2975 (4)	−5105 (7)	3.08	−2734 (13)	2931 (6)	−5140 (15)	3.57
O(242)	−655 (5)	4369 (2)	−4996 (5)	3.68	−606 (9)	4384 (4)	−5059 (9)	2.72
O(243)	−2495 (5)	4479 (2)	−4985 (5)	3.23	−2527 (8)	4466 (4)	−5155 (9)	2.59
O(244)	−3345 (5)	3791 (2)	−4374 (5)	3.53	−3321 (9)	3786 (4)	−4482 (8)	2.86
O(245)	−1485 (5)	3313 (2)	−5198 (5)	3.17	−1444 (8)	3299 (4)	−5233 (8)	2.84
O(246)	−3191 (6)	3016 (3)	−6071 (6)	4.97	−3074 (10)	2941 (5)	−6097 (10)	3.92
C(251)	−4260 (7)	3806 (4)	−4756 (7)	2.83	−4252 (14)	3789 (7)	−4818 (13)	3.75
C(252)	−4640 (7)	4192 (4)	−4388 (7)	2.88	−4647 (14)	4144 (6)	−4556 (15)	3.51
C(253)	−4522 (8)	4147 (3)	−3403 (7)	2.82	−4566 (12)	4145 (6)	−3487 (12)	1.49
C(254)	−4981 (7)	3775 (3)	−3145 (7)	2.80	−4975 (13)	3740 (6)	−3236 (13)	2.56
C(255)	−4636 (8)	3398 (3)	−3602 (7)	2.81	−4512 (10)	3363 (5)	−3627 (10)	0.63
C(256)	−5116 (10)	3017 (4)	−3433 (10)	5.39	−4926 (15)	2945 (9)	−3424 (14)	3.35
O(252)	−4266 (5)	4555 (2)	−4687 (5)	3.19	−4336 (9)	4529 (4)	−4822 (8)	3.39
O(253)	−4973 (5)	4515 (2)	−3078 (5)	3.14	−5042 (9)	4489 (4)	−3232 (8)	2.12
O(254)	−4757 (4)	3726 (2)	−2232 (5)	2.46	−4749 (7)	3696 (4)	−2295 (8)	1.87
O(255)	−4704 (5)	3457 (3)	−4501 (5)	3.99	−4623 (10)	3401 (4)	−4568 (9)	4.50
O(256)	−6053 (6)	3064 (3)	−3751 (6)	5.17	−5778 (13)	2927 (5)	−3815 (11)	7.72
C(261)	−5462 (7)	3684 (3)	−1738 (8)	2.85	−5495 (14)	3670 (6)	−1838 (11)	2.24
C(262)	−5408 (7)	4000 (3)	−1068 (7)	2.54	−5385 (14)	3998 (6)	−1150 (11)	2.16
C(263)	−4520 (8)	3967 (4)	−409 (9)	3.67	−4604 (14)	3995 (6)	−522 (12)	1.91
C(264)	−4569 (7)	3553 (4)	35 (7)	2.68	−4523 (13)	3548 (7)	−19 (17)	4.96
C(265)	−4651 (7)	3213 (4)	−677 (7)	3.19	−4681 (12)	3217 (5)	−796 (11)	1.09
C(266)	−4792 (7)	2801 (3)	−285 (7)	2.53	−4804 (13)	2790 (7)	−355 (15)	2.95
O(262)	−5489 (5)	4410 (2)	−1476 (5)	3.01	−5492 (8)	4410 (3)	−1578 (9)	2.39
O(263)	−4438 (5)	4281 (2)	278 (5)	3.28	−4469 (8)	4297 (4)	177 (8)	1.95
O(264)	−3664 (4)	3496 (2)	638 (5)	2.73	−3677 (7)	3509 (4)	517 (8)	1.90
O(265)	−5442 (4)	3295 (2)	−1349 (5)	2.68	−5480 (8)	3274 (4)	−1448 (8)	2.22
O(266)	−5546 (5)	2797 (3)	148 (5)	3.23	−5534 (7)	2776 (4)	150 (8)	1.98
C(271)	−3651 (8)	3404 (4)	1517 (9)	4.01	−3648 (11)	3371 (6)	1405 (13)	2.10
C(272)	−3135 (7)	3741 (3)	2103 (7)	2.09	−3179 (14)	3689 (6)	2019 (11)	2.31
C(273)	−2158 (7)	3729 (3)	2007 (7)	2.74	−2167 (14)	3734 (6)	1910 (13)	2.67
C(274)	−1801 (7)	3306 (3)	2249 (7)	2.10	−1833 (13)	3282 (5)	2148 (12)	1.60

Table II (Continued)

	(*R*)-(−)-FP-β-CD complex				(*S*)-(+)-FP-β-CD complex			
atom	*x*	*y*	*z*	*U*	*x*	*y*	*z*	*U*
C(275)	−2347 (9)	2981 (4)	1747 (9)	4.10	−2320 (12)	2990 (6)	1521 (13)	2.17
C(276)	−2065 (10)	2547 (5)	2047 (14)	7.50	−2031 (16)	2536 (7)	1569 (16)	3.92
O(272)	−3554 (5)	4111 (3)	1908 (5)	3.60	−3592 (8)	4103 (5)	1819 (9)	3.39
O(273)	−1663 (4)	4024 (2)	2598 (4)	2.56	−1720 (8)	4016 (4)	2534 (9)	2.51
O(274)	−876 (4)	3294 (2)	2145 (4)	2.57	−881 (8)	3302 (4)	2045 (8)	1.57
O(275)	−3266 (5)	3015 (2)	1772 (6)	3.51	−3224 (8)	2973 (4)	1577 (9)	2.44
O(276)	−2157 (7)	2541 (3)	3124 (6)	6.29	−2496 (9)	2282 (5)	876 (10)	3.88
				Water				
O(001W)	2620 (9)	7201 (5)	−235 (12)	11.16				
O(002W)	−4318 (10)	6957 (5)	4948 (9)	9.46	−4378 (25)	7096 (12)	4914 (20)	17.44
O(003W)	−6070 (6)	6912 (3)	−1184 (7)	5.00	−6035 (8)	6936 (4)	−1342 (9)	3.44
O(004W)	2687 (15)	6863 (7)	−3884 (13)	14.74	2509 (18)	7051 (8)	−3815 (14)	10.08
O(005W)	3990 (21)	6800 (12)	−4694 (29)	28.37	4081 (32)	6756 (16)	−4565 (27)	20.89
O(006W)	851 (19)	6714 (8)	−5302 (15)	11.82	934 (15)	6828 (6)	−5240 (14)	9.87
O(007W)	−3985 (6)	6501 (4)	3516 (6)	6.10	−3996 (8)	6627 (5)	6490 (10)	5.28
O(008W)	3580 (8)	6044 (4)	4404 (8)	7.24	3612 (12)	6071 (6)	4342 (10)	6.04
O(009W)	4653 (7)	5941 (3)	3100 (7)	5.56	4705 (11)	6026 (5)	2999 (9)	5.82
O(010W)	−4092 (8)	5324 (3)	−6368 (7)	6.46	−4136 (11)	5367 (5)	−6466 (8)	5.03
O(011W)	−5962 (8)	5227 (4)	−4983 (8)	6.86	−5942 (12)	5250 (5)	−5052 (10)	5.16
O(012W)	−6680 (9)	5188 (6)	−3463 (9)	8.56	−6614 (14)	5149 (8)	−3537 (15)	9.04
O(013W)	1699 (12)	4721 (6)	−5123 (12)	14.30	1659 (13)	4730 (6)	−5187 (12)	8.05
O(014W)	−5412 (7)	4657 (4)	1844 (8)	7.39	−5398 (10)	4660 (7)	1725 (13)	5.65
O(015W)	−5689 (7)	4635 (4)	−6278 (8)	5.65	−5702 (11)	4650 (6)	−6340 (11)	7.10
O(016W)	−3855 (6)	4481 (3)	3439 (6)	5.33	−3923 (11)	4482 (5)	3310 (10)	5.82
O(017W)	3129 (10)	4342 (5)	−3667 (11)	11.06	3080 (12)	4294 (7)	−3863 (15)	8.88
O(018W)	3157 (9)	3981 (4)	3910 (10)	9.62	3188 (12)	3696 (5)	3837 (11)	7.59
O(019W)	1520 (16)	3937 (8)	4746 (16)	4.76				
O(020W)	4584 (7)	3789 (4)	2392 (9)	7.35	4525 (13)	3777 (6)	2309 (14)	8.30
O(021W)	−6335 (11)	3149 (5)	−5725 (11)	10.53	−6284 (22)	3156 (9)	−5791 (18)	13.20
O(022W)	−4982 (7)	3034 (4)	−6843 (8)	4.81	−4840 (10)	3052 (5)	−6800 (11)	6.16
O(023W)	−7347 (10)	2521 (7)	−5767 (8)	11.35	−7533 (18)	2614 (8)	−5843 (16)	14.76
O(024W)	3254 (6)	2479 (3)	−2785 (6)	4.80	3307 (11)	2413 (5)	−2836 (12)	6.53
O(025W)	−5249 (6)	2446 (3)	1753 (7)	5.68	−5275 (8)	2473 (4)	1809 (9)	3.50
O(026W)	−573 (8)	2342 (3)	−5959 (9)	3.70	−630 (30)	2335 (11)	−6076 (25)	7.16
O(027W)	1961 (7)	2321 (3)	−4326 (7)	5.35	1888 (11)	2353 (6)	−4343 (10)	5.70
O(028W)	−5286 (7)	−1963 (3)	−2138 (7)	3.56				
				Guests[b]				
O(101G)	1348 (6)	6636 (3)	861 (8)	6.04	676 (9)	7300 (5)	−1 (9)	4.78
O(102G)	917 (6)	6963 (3)	−442 (6)	6.77	1630 (9)	6789 (4)	−88 (9)	4.70
C(101G)	757 (9)	6732 (4)	226 (9)	4.71	922 (13)	6956 (8)	207 (14)	3.86
C(103G)	−418 (9)	6583 (4)	1078 (10)	6.00	125 (20)	6894 (8)	1520 (16)	6.14
C(102G)	−221 (8)	6643 (4)	185 (7)	4.74	513 (12)	6644 (7)	774 (11)	8.58
C(111G)	−431 (8)	6261 (4)	−388 (7)	3.55	−184 (15)	6412 (7)	138 (14)	6.81
C(112G)	97 (7)	5906 (4)	−198 (7)	3.56	−83 (14)	6043 (8)	−122 (17)	5.83
C(113G)	−124 (8)	5567 (4)	−705 (9)	4.67	−695 (14)	5831 (7)	−778 (14)	4.75
C(114G)	−823 (8)	5552 (4)	−1439 (8)	4.61	−1431 (17)	6025 (8)	−1047 (18)	3.20
C(115G)	−1354 (9)	5900 (5)	−1608 (9)	5.64	−1664 (22)	6422 (9)	−817 (18)	3.17
C(116G)	−1174 (9)	6256 (4)	−1108 (8)	4.65	−1012 (21)	6590 (8)	−202 (20)	6.64
O(100G)	427 (5)	5213 (2)	−500 (6)	5.51	−451 (14)	5460 (7)	−1178 (13)	3.37
C(121G)	92 (7)	4898 (3)	−60 (7)	3.39	−186 (18)	5109 (7)	−615 (15)	6.61
C(122G)	545 (8)	4528 (4)	40 (8)	4.97	377 (18)	4841 (8)	−982 (14)	6.90
C(123G)	226 (8)	4208 (4)	446 (9)	5.55	647 (17)	4493 (11)	−526 (23)	6.68
C(124G)	−533 (8)	4266 (4)	834 (8)	4.45	558 (20)	4427 (10)	427 (21)	8.90
C(125G)	−971 (8)	4627 (5)	764 (8)	5.90	−50 (20)	4747 (10)	705 (18)	6.28
C(126G)	−678 (8)	4951 (4)	303 (8)	4.32	−387 (17)	5090 (9)	234 (17)	6.70
C(201G)	−3267 (11)	2430 (6)	−2214 (12)	7.30	2041 (21)	4649 (8)	−2550 (21)	5.83
C(203G)	−2165 (12)	2267 (4)	−3092 (10)	7.28	−2818 (15)	4609 (7)	−1316 (14)	5.56
O(201G)	−3345 (8)	2471 (4)	−1479 (9)	10.60	−2710 (14)	4719 (6)	−3161 (14)	8.48
O(202G)	−3896 (9)	2185 (4)	−2761 (9)	9.12	−1211 (11)	4651 (5)	−2815 (10)	6.94
C(202G)	−2579 (10)	2598 (6)	−2638 (13)	8.43	−1945 (14)	4513 (10)	−1577 (23)	7.22
C(211G)	−1904 (14)	2838 (8)	−1999 (17)	10.07	−1779 (14)	4049 (7)	−1471 (14)	4.33
C(212G)	−1838 (13)	3254 (7)	−2230 (13)	9.32	−1997 (15)	3731 (8)	2058 (14)	5.05
C(213G)	−1211 (24)	3499 (8)	−1777 (26)	13.61	−1682 (19)	3344 (7)	−1854 (16)	5.78
C(214G)	−613 (23)	3331 (21)	−994 (33)	19.19	−1200 (28)	3225 (13)	−1048 (41)	13.33
C(215G)	−745 (25)	2902 (20)	−842 (25)	17.70	−1044 (26)	3547 (11)	−363 (25)	11.07
C(216G)	−1304 (19)	2700 (6)	−1386 (21)	9.36	−1370 (15)	3932 (6)	−581 (14)	4.64
O(200G)	−1026 (27)	3924 (11)	−1958 (33)	31.36	−1877 (11)	3052 (6)	−2496 (14)	8.25
C(221G)	−1712 (19)	4188 (5)	−1929 (12)	10.95	−2383 (17)	2675 (8)	−2443 (23)	8.45
C(222G)	−1968 (13)	4567 (6)	−2508 (11)	8.30	−2443 (19)	2401 (9)	−3164 (18)	7.32
C(223G)	−2515 (9)	4846 (4)	−2270 (9)	5.43	−2971 (18)	2071 (9)	−3094 (22)	7.38
C(224G)	−2882 (9)	4809 (5)	−1546 (11)	6.59	−3467 (12)	1986 (8)	−2410 (24)	9.20
C(225G)	−2701 (9)	4477 (5)	−1033 (10)	6.11	−3329 (19)	2251 (10)	−1663 (18)	7.52
C(226G)	−2150 (10)	4166 (4)	−1208 (9)	6.25	−2813 (20)	2650 (8)	−1780 (21)	7.80

[a] Atom names start with atomic name followed by three digits. For atoms in CD: (i) CD molecule, (ii) glucosyl residue, (iii) atom position in each glucose. For atoms in guests: (i) FP molecule, (ii) phenyl ring unit (0 for side chain), (iii) atom position. Extension: G stands for guest, W for water. [b] I.e., (*R*)-fenoprofen in the (*R*)-(−)-FP-β-CD complex and (*S*)-fenoprofen in the (*S*)-(+)-FP-β-CD complex.

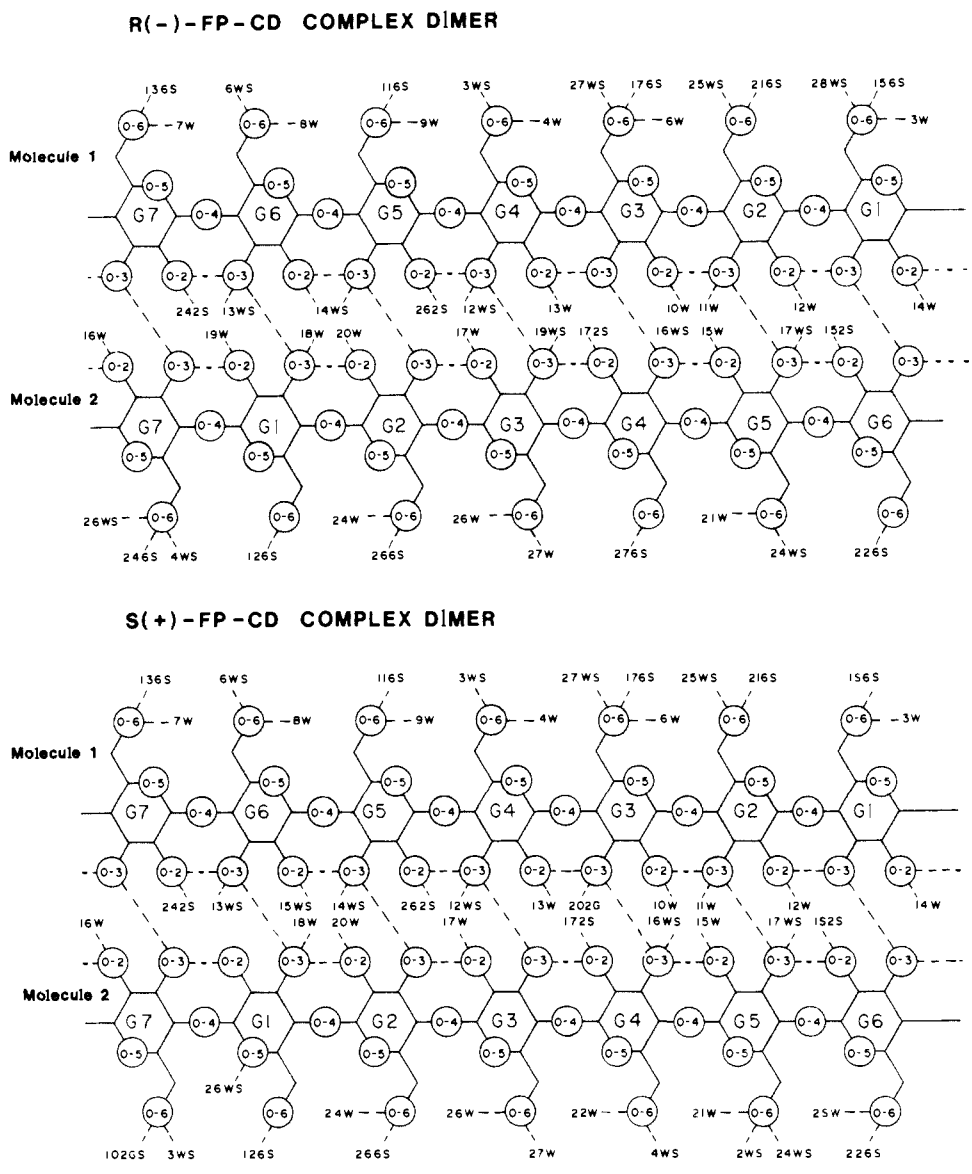

Figure 5. Hydrogen-bonding network scheme of (*R*)- and (*S*)-FP-β-CD dimers along with the crystalline water molecules. The dotted lines show the hydrogen bonding. Extension: W for water; G for guest; S for atoms from symmetrical related position.

Table III

	(*R*)-FP-CD1	(*S*)-FP-CD1	(*R*)-FP-CD2	(*S*)-FP-CD2
(a) $O(4)_n$–$O(4)_{n+1}$ Distances (Å) of the β-CD Molecules				
O(14)–O(24)	4.30 (2)	4.33 (2)	4.25 (1)	4.30 (2)
O(24)–O(34)	4.42 (1)	4.34 (2)	4.59 (3)	4.56 (3)
O(34)–O(44)	4.39 (3)	4.46 (3)	4.26 (1)	4.26 (2)
O(44)–O(54)	4.35 (1)	4.33 (2)	4.33 (2)	4.28 (2)
O(54)–O(64)	4.32 (2)	4.34 (2)	4.35 (2)	4.45 (2)
O(64)–O(74)	4.35 (2)	4.38 (2)	4.53 (2)	4.47 (3)
O(74)–O(14)	4.46 (2)	4.46 (3)	4.24 (2)	4.26 (2)
mean	4.37 (2)	4.38 (2)	4.36 (2)	4.37 (2)
σ	0.06	0.06	0.14	0.12
(b) $O(4)_{n-1}$–$O(4)_n$–$O(4)_{n+1}$ Angles (deg) of the β-CD Molecules				
O(74)–O(14)–O(24)	126.9 (2)	129.2 (4)	120.8 (2)	122.6 (4)
O(14)–O(24)–O(34)	123.7 (2)	124.6 (3)	132.7 (2)	132.1 (4)
O(24)–O(34)–O(44)	132.8 (2)	130.2 (4)	133.6 (2)	132.6 (4)
O(34)–O(44)–O(54)	130.6 (2)	131.0 (4)	121.6 (2)	123.1 (3)
O(44)–O(54)–O(64)	124.7 (2)	125.7 (3)	128.3 (2)	128.5 (3)
O(54)–O(64)–O(74)	128.2 (2)	128.0 (3)	132.5 (2)	131.8 (4)
O(64)–O(74)–O(14)	133.0 (2)	130.6 (4)	130.1 (2)	129.3 (4)
mean	128.6 (2)	128.5 (4)	128.5 (2)	128.6 (4)
σ	3.7	2.5	5.3	4.2

atoms. In the *R* complex, both protruding carboxylic acid groups (i.e., for molecules R1 and R2) interact with water molecules via the hydroxyl oxygen atoms, i.e., O(102G)–O(001W) and O-(202G)–O(028W), and these two water molecules do not exist in the S complex. In the S complex, the hydroxyl oxygen O(102G) of the carboxylic acid group that protrudes (on S1) interacts with a primary hydroxyl oxygen O(276) of the next symmetry-related CD dimer, whereas the carboxylic acid group that is enclosed in the dimer interface (on S2) interacts again by means of the hydroxyl oxygen with the secondary hydroxyl group O(133) of a β-CD.

Comparison of the ORTEP packing schemes in Figure 6 shows differences in the relationship of a CD dimer with the neighboring dimers above and below. As mentioned previously, in the *R* complex both carboxylic acid groups interact with water molecules, while in the *S* complex there is no water involved and the carboxylic acid group that protrudes forms a hydrogen bond to a primary hydroxyl group on the neighboring β-CD ring. Both situations result in the fit of adjacent symmetry-related CD dimers, which stack to form a disjointed channel throughout the crystal. This channel is stabilized by hydrogen bonds to a parallel water channel. The distance apart of the complex dimers at the primary hydroxyl junction is slightly greater for the (*R*)-FP structure due to the presence of extra water molecules that hydrogen bond to the carboxylic acid group of the (*R*)-FP.

In contrast to the strong and direct hydrogen bonds across the secondary hydroxyl ends of the β-CD monomers, the primary ends are farther apart and are mostly connected via hydrogen-bonded water molecules. The *R* and *S* complexes have 25 water molecules

Table IV. Hydrogen Bonds Involving the CD and FP Oxygen Atoms

	(*R*)-(−)-FP-β-CD complex[a]				(*S*)-(+)-FP-β-CD complex[b]		
	sym code[c]	dist, Å	angle, deg		sym code[c]	dist, Å	angle, deg
C(112)–O(112)···O(173)		2.72	120	C(112)–O(112)···O(173)		2.66	123
C(112)–O(112)···O(014W)		2.67	109	C(112)–O(112)···O(014W)		2.66	108
C(113)–O(113)···O(122)		2.83	114	C(113)–O(113)···O(122)		2.83	115
C(113)–O(113)···O(263)		2.83	120	C(113)–O(113)···O(263)		2.74	120
C(116)–O(116)···O(003W)		2.74	111	C(116)–O(116)···O(156)	8	2.74	127
C(116)–O(116)···O(156)	8	2.87	126	C(116)–O(116)···O(003W)		2.75	106
C(116)–O(116)···O(028W)	14	2.91	104	C(122)–O(122)···O(113)		2.83	121
C(122)–O(122)···O(113)		2.83	120	C(122)–O(122)···O(012W)		2.66	93
C(122)–O(122)···O(012W)		2.69	94	C(123)–O(123)···O(132)		2.76	115
C(123)–O(123)···O(132)		2.73	114	C(123)–O(123)···O(253)		2.96	120
C(123)–O(123)···O(253)		2.94	119	C(123)–O(123)···O(011W)		2.89	128
C(123)–O(123)···O(011W)		2.88	131	C(126)–O(126)···O(216)	10	2.73	102
C(126)–O(126)···O(216)	10	2.69	100	C(126)–O(126)···O(025W)	14	2.70	106
C(126)–O(126)···O(025W)	14	2.77	103	C(132)–O(132)···O(123)		2.76	119
C(132)–O(132)···O(123)		2.73	119	C(132)–O(132)···O(010W)		2.67	103
C(132)–O(132)···O(010W)		2.62	100	C(133)–O(133)···O(142)		2.82	112
C(133)–O(133)···O(142)		2.84	112	C(133)–O(133)···O(243)		2.86	122
C(133)–O(133)···O(243)		2.78	126	C(133)–O(133)···O(202G)		2.88	103
C(136)–O(136)···O(176)	6	2.85	126	C(136)–O(136)···O(176)	6	2.99	124
C(136)–O(136)···O(006W)		2.82	110	C(136)–O(136)···O(006W)		2.89	110
C(136)–O(136)···O(027W)	11	2.71	106	C(136)–O(136)···O(027W)	11	2.71	107
C(142)–O(142)···O(133)		2.84	121	C(142)–O(142)···O(133)		2.82	122
C(142)–O(142)···O(013W)		2.80	100	C(142)–O(142)···O(013W)		2.72	102
C(143)–O(143)···O(152)		2.73	116	C(143)–O(143)···O(152)		2.75	118
C(143)–O(143)···O(233)		2.86	117	C(143)–O(143)···O(233)		2.83	118
C(143)–O(143)···O(012W)	2	2.83	102	C(143)–O(143)···O(012W)	2	2.87	102
C(146)–O(146)···O(004W)		2.68	113	C(146)–O(146)···O(004W)		2.75	110
C(146)–O(146)···O(003W)	2	2.76	110	C(146)–O(146)···O(003W)	2	2.74	107
C(152)–O(152)···O(143)		2.73	121	C(152)–O(152)···O(143)		2.75	120
C(152)–O(152)···O(262)	2	2.67	109	C(152)–O(152)···O(262)	2	2.72	107
C(153)–O(153)···O(162)		2.82	117	C(153)–O(153)···O(162)		2.80	117
C(153)–O(153)···O(223)		2.74	114	C(153)–O(153)···O(223)		2.79	114
C(153)–O(153)···O(014W)	2	2.85	121	C(153)–O(153)···O(014W)	2	2.83	120
C(156)–O(156)···O(116)	2	2.87	103	C(156)–O(156)···O(116)	2	2.74	102
C(156)–O(156)···O(009W)		2.76	124	C(156)–O(156)···O(009W)		2.75	123
C(162)–O(162)···O(153)		2.82	118	C(162)–O(162)···O(153)		2.80	117
C(162)–O(162)···O(014W)	2	3.10	117	C(162)–O(162)···O(015W)	1	2.87	89
C(163)–O(163)···O(172)		2.70	114	C(163)–O(163)···O(172)		2.73	118
C(163)–O(163)···O(213)		2.84	118	C(163)–O(163)···O(213)		2.85	118
C(163)–O(163)···O(013W)	4	2.85	110	C(163)–O(163)···O(013W)	4	2.79	108
C(166)–O(166)···O(008W)		2.74	116	C(166)–O(166)···O(008W)		2.85	110
C(166)–O(166)···O(006W)	4	2.73	103	C(166)–O(166)···O(006W)	4	2.78	107
C(172)–O(172)···O(163)		2.70	122	C(172)–O(172)···O(163)		2.73	118
C(172)–O(172)···O(242)	4	2.69	107	C(172)–O(172)···O(242)	4	2.62	111
C(173)–O(173)···O(112)		2.72	115	C(173)–O(173)···O(112)		2.66	116
C(173)–O(173)···O(273)		2.81	119	C(173)–O(173)···O(273)		2.75	121
C(176)–O(176)···O(136)	4	2.85	104	C(176)–O(176)···O(136)	4	2.99	103
C(176)–O(176)···O(007W)		2.73	126	C(176)–O(176)···O(007W)		2.82	124
C(212)–O(212)···O(273)		2.79	119	C(212)–O(212)···O(273)		2.82	115
C(212)–O(212)···O(019W)		2.71	89	C(213)–O(213)···O(163)		2.85	118
C(213)–O(213)···O(163)		2.84	116	C(213)–O(213)···O(222)		2.76	115
C(213)–O(213)···O(222)		2.77	117	C(213)–O(213)···O(018W)		2.99	133
C(213)–O(213)···O(018W)		2.89	135	C(211)–O(215)···O(026W)	4	2.85	96
C(216)–O(216)···O(126)	12	2.69	117	C(216)–O(216)···O(126)	12	2.73	119
C(222)–O(222)···O(213)		2.77	119	C(222)–O(222)···O(213)		2.76	120
C(222)–O(222)···O(020W)		2.78	103	C(222)–O(222)···O(020W)		2.66	109
C(223)–O(223)···O(153)		2.74	123	C(223)–O(223)···O(153)		2.79	121
C(223)–O(223)···O(232)		2.81	113	C(223)–O(223)···O(232)		2.87	116
C(226)–O(226)···O(266)	2	2.75	122	C(226)–O(226)···O(266)	2	2.78	121
C(226)–O(226)···O(024W)		2.75	117	C(226)–O(226)···O(024W)		2.67	117
C(232)–O(232)···O(223)		2.81	120	C(232)–O(232)···O(223)		2.87	119
C(232)–O(232)···O(017W)		2.72	95	C(232)–O(232)···O(017W)		2.74	91
C(233)–O(233)···O(143)		2.86	118	C(233)–O(233)···O(143)		2.83	117
C(233)–O(233)···O(242)		2.79	118	C(233)–O(233)···O(242)		2.77	117
C(233)–O(233)···O(019W)	6	2.94	100	C(236)–O(236)···O(026W)		2.73	132
C(236)–O(236)···O(026W)		2.67	122	C(236)–O(236)···O(027W)		2.67	114
C(236)–O(236)···O(027W)		2.69	114	C(242)–O(242)···O(233)		2.77	119
C(242)–O(242)···O(233)		2.79	118	C(242)–O(242)···O(172)	6	2.62	103
C(242)–O(242)···O(172)	6	2.69	108	C(243)–O(243)···O(133)		2.86	105
C(243)–O(243)···O(133)		2.78	115	C(243)–O(243)···O(252)		2.91	115
C(243)–O(243)···O(252)		2.84	117	C(243)–O(243)···O(016W)	6	2.86	123
C(243)–O(243)···O(016W)	6	2.86	117	C(246)–O(246)···O(022W)		2.74	123
C(246)–O(246)···O(276)	6	2.68	107	C(246)–O(246)···O(004W)	13	3.00	88
C(252)–O(252)···O(243)		2.84	115	C(252)–O(252)···O(243)		2.91	112
C(252)–O(252)···O(015W)		2.94	94	C(252)–O(252)···O(015W)		2.84	97

Table IV (Continued)

	(*R*)-(−)-FP-β-CD complex[a]				(*S*)-(+)-FP-β-CD complex[b]		
	sym code[c]	dist, Å	angle, deg		sym code[c]	dist, Å	angle, deg
C(253)-O(253)···O(123)		2.94	118	C(253)-O(253)···O(123)		2.96	116
C(253)-O(253)···O(262)		2.75	115	C(253)-O(253)···O(262)		2.75	114
C(253)-O(253)···O(017W)	8	2.91	103	C(253)-O(253)···O(017W)	8	2.92	105
C(256)-O(256)···O(021W)		2.99	107	C(256)-O(256)···O(021W)		3.06	119
C(256)-O(256)···O(024W)	8	2.76	102	C(256)-O(256)···O(024W)	8	2.78	109
C(262)-O(262)···O(253)		2.75	119	C(256)-O(256)···O(002W)	16	3.19	96
C(262)-O(262)···O(152)	8	2.67	114	C(262)-O(262)···O(253)		2.75	118
C(263)-O(263)···O(113)		2.83	116	C(262)-O(262)···O(152)	8	2.72	111
C(263)-O(263)···O(272)		2.65	119	C(263)-O(263)···O(113)		2.74	114
C(266)-O(266)···O(226)	8	2.75	107	C(263)-O(263)···O(272)		2.69	121
C(272)-O(272)···O(263)		2.65	121	C(266)-O(266)···O(226)	8	2.78	101
C(272)-O(272)···O(016W)		2.76	110	C(266)-O(266)···O(025W)		2.67	121
C(273)-O(273)···O(173)		2.81	118	C(272)-O(272)···O(263)		2.69	121
C(273)-O(273)···O(212)		2.79	118	C(272)-O(272)···O(016W)		2.71	112
C(276)-O(276)···O(246)	4	2.68	128	C(273)-O(273)···O(173)		2.75	117
C(276)-O(276)···O(026W)	4	2.62	106	C(273)-O(273)···O(212)		2.82	119
C(276)-O(276)···O(004W)	12	2.71	121	C(276)-O(276)···O(102G)	12	2.51	119
C(101G)-O(102G)···O(001W)		2.67	113	C(276)-O(276)···O(003W)	16	2.72	111
C(201G)-O(202G)···O(028W)		2.60	117	C(101G)-O(102G)···O(276)	10	2.51	116
				C(201G)-O(202G)···O(133)		2.88	108

[a] Standard deviation range: for distance, 0.01–0.03 Å; for angle, 0.2–1.2°. [b] Standard deviation range: for distance, 0.01–0.04 Å; for angle, 0.3–1.3°. [c] Symmetry codes and corresponding operations: 1, 65601, $x+1, y, z+1$; 2, 65501, $x+1, y, z$; 3, 65401, $x+1, y, z-1$; 4, 55601, $x, y, z+1$; 5, 55501, x, y, z; 6, 55401, $x, y, z-1$; 7, 45601, $x-1, y, z+1$; 8, 45501, $x-1, y, z$; 9, 45401, $x-1, y, z-1$; 10, 55502, $-x, y+{}^1/_2, -z$; 11, 55402, $-x, y+{}^1/_2, -z-1$; 12, 54502, $-x, y-{}^1/_2, -z$; 13, 54402, $-x, y-{}^1/_2, -z-1$; 14, 45502, $-x-1, y+{}^1/_2, -z$; 15, 45402, $-x-1, y+{}^1/_2, -z-1$; 16, 44502, $-x-1, y-{}^1/_2, -z$; 17, 44402, $-x-1, y-{}^1/_2, -z-1$.

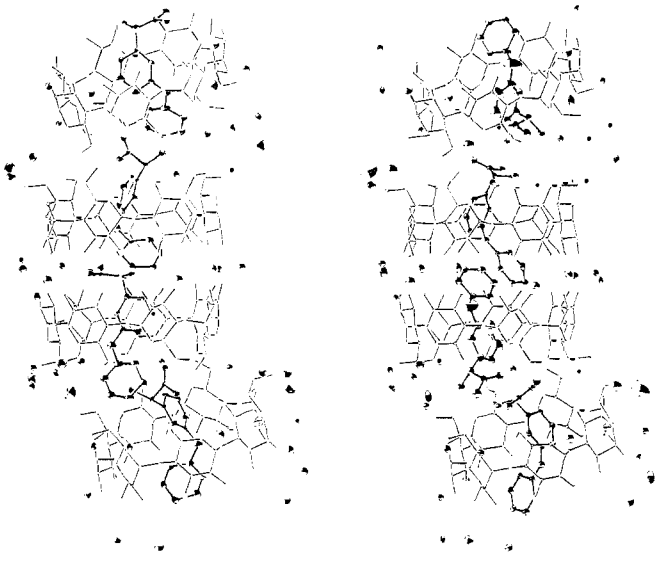

Figure 6. ORTEP packing schemes of (*S*)-FP-β-CD (left) and (*R*)-FP-β-CD (right) complexes.

in common. The *R* complex has three additional unique water molecules, two of which are hydrogen bonded to the guest carboxylic acid groups (one to R1 and one to R2).

Guest Geometry and Packing. The most interesting result of the crystal structure determinations is the different mode of inclusion of the two enantiomers within the CD dimer cavity (Figures 3 and 4). In the *R* complex, R1 and R2 are in an antiparallel or head-to-head arrangement; that is, both guests are oriented in the β-CD cavities with their phenoxy groups pointing toward the secondary hydroxyl end of the CD and the propionic acid group protruding into the water matrix. In contrast, in the *S* complex, S1 and S2 are in a parallel or head-to-tail arrangement, where one guest (S2) is oriented with its phenoxy group within the CD dimer interface and the other (S1) with its polar carboxylic acid group in the CD dimer interface opposing the phenoxy group of the first. The phenoxy group of S1 protrudes from the CD cavity.

The arrangement of the *S* dimer is unexpected. The CD cavity is relatively hydrophobic, and the expected packing of the FP would have been head-to-head, with the more hydrophobic parts of the molecules in the hydrophobic cavity of the CD dimer. Recent studies on a complex of (±)-flurbiprofen with β-CD[14,15] showed no difference in orientation of the *R* and *S* guests in the β-CD cavity. Crystallization of the racemic flurbiprofen with β-CD resulted in the *R* isomer in one half of the β-CD dimer and *S* in the other. The structures of the separate *R* and *S* complexes showed the same orientation for the guests as was found in the racemate complex. All have the expected head-to-head arrangement of the FP in the β-CD dimer.

The difference in packing of the FP molecules in the β-CD cavity is presumably due to the influence of the *R* versus *S* configuration of the *m*-propionic acid group. For ease of discussion, the phenyl ring containing the propionic acid substituent in each FP molecule will be called ring 1 and the other phenyl ring, ring 2. The atom numbering for the FP molecules is shown in Figures 1 and 2. The FP molecules have possible freedom of rotation about the O(00G)–C(13G) and O(00G)–C(21G) bonds for the phenyl rings and about the C(11G)–C(02G), C(02G)–C(01G), and C(02G)–C(03G) bonds for the propionic acid group. The possible interplanar angles for the phenyl rings are restricted to a small range of values in the region of 60–90°. There can of course be a twofold rotation of the phenyl rings, which has no effect as far as ring 2 is concerned but will change the position of the propionic acid group by 180° in ring 1.

The possible conformations for the propionic acid group are limited to those where the hydrogen atom on chiral carbon C(02G) is near the plane of the phenyl ring 1 and the methyl and carboxylic acid groups are staggered with respect to this plane. The approach of the methyl group to the plane is sterically hindered, as is the too close approach of the carboxylic acid group. The carboxylic acid group can certainly move closer than the methyl group if the oxygen atoms of the carboxylic acid group rotate out of the plane of the phenyl ring. Keeping these steric restrictions in mind, the observed conformations for the propionic acid group (diagrammed in Figure 7 relative to ring 1) can be discussed. The propionic acid groups of S1, R1, and R2 show the expected stable conformation, with the methyl groups and carboxylic acid groups staggered with respect to the plane of ring 1 and the hydrogen lying in the plane. Interchanging the methyl and carboxylic acid groups, which changes *R* to *S*, as in R1 to S1 in the figure, *changes the direction in which the carboxylic acid group points* and ne-

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Table V. Hydrogen Bonds Involving Water Molecules

angle[c]	length, Å		angle, deg	angle[c]	length, Å		angle, deg
				(*R*)-(−)-FP-β-CD Complex[a]			
O(003W)(2)···O(001W)···O(102G)	2.86	2.67	127	O(018W)(9)···O(015W)···O(252)	2.83	2.94	103
O(005W)(7)···O(002W)···O(007W)	2.79	2.79	112	O(016W)(6)···O(015W)···O(011W)	2.96	2.88	119
O(023W)(14)···O(002W)···O(007W)	3.19	2.79	111	O(010W)(4)···O(016W)···O(272)	2.81	2.76	125
O(146)(8)···O(003W)···O(116)	2.76	2.74	126	O(015W)(4)···O(016W)···O(243) (4)	2.96	2.86	115
O(025W)(14)···O(003W)···O(001W) (8)	2.93	2.86	123	O(253)(2)···O(017W)···O(232)	2.91	2.72	111
O(005W)···O(004W)···O(146)	2.56	2.68	118	O(012W)(2)···O(017W)···O(232)	2.80	2.72	111
O(276)(10)···O(004W)···O(006W)	2.71	3.22	97	O(015W)(1)···O(018W)···O(213)	2.83	2.89	117
O(008W)(6)···O(005W)···O(004W)	2.85	2.56	101	O(021W)(1)···O(018W)···O(019W)	2.86	3.03	95
O(008W)(6)···O(005W)···O(002W) (3)	2.85	2.79	101	O(018W)···O(019W)···O(212)	3.03	2.71	105
O(004W)···O(006W)···O(136)	3.22	2.82	130	O(233)(4)···O(019W)···O(212)	2.94	2.71	109
O(166)(6)···O(006W)···O(136)	2.73	2.82	127	O(022W)(1)···O(020W)···O(222)	2.76	2.78	115
O(028W)(14)···O(007W)···O(176)	2.66	2.73	113	O(018W)(9)···O(021W)···O(256)	2.86	2.99	105
O(009W)(8)···O(007W)···O(002W)	2.75	2.79	107	O(022W)···O(021W)···O(023W)	2.56	2.56	112
O(011W)(1)···O(008W)···O(166)	2.88	2.74	110	O(020W)(9)···O(022W)···O(246)	2.76	2.75	110
O(005W)(4)···O(008W)···O(009W)	2.85	2.85	110	O(025W)(6)···O(022W)···O(021W)	2.86	2.96	121
O(007W)(2)···O(009W)···O(156)	2.75	2.76	100	O(027W)(8)···O(023W)···O(021W)	2.72	2.56	120
O(010W)(1)···O(009W)···O(008W)	2.79	2.85	110	O(002W)(16)···O(023W)···O(021W)	3.19	2.56	92
O(016W)(6)···O(010W)···O(132)	2.81	2.62	93	O(027W)···O(024W)···O(226)	2.81	2.75	128
O(009W)(9)···O(010W)···O(132)	2.79	2.62	117	O(256)(2)···O(024W)···O(028W) (2)	2.76	2.82	104
O(015W)···O(011W)···O(213)	2.87	2.88	114	O(22W)(4)···O(25W)···O(266)	2.86	2.67	112
O(008W)(9)···O(011W)···O(012W)	2.88	2.77	102	O(003W)(16)···O(025W)···O(126) (16)	2.93	2.77	114
O(011W)···O(012W)···O(122)	2.77	2.69	106	O(276)(6)···O(026W)···O(236)	2.62	2.67	128
O(143)(8)···O(012W)···O(122)	2.86	2.69	111	O(024W)···O(027W)···O(236)	2.81	2.69	118
O(017W)(8)···O(012W)···O(122)	2.80	2.69	108	O(136)(13)···O(027W)···O(023W) (2)	2.71	2.72	101
O(163)(6)···O(013W)···O(142)	2.85	2.80	111	O(024W)(8)···O(028W)···O(202G)	2.82	2.60	110
O(153)(8)···O(014W)···O(112)	2.85	2.67	120	O(116)(14)···O(028W)···O(007W) (14)	2.91	2.66	120
O(162)(8)···O(014W)···O(016W)	NO	3.10	115				
				(*S*)-(+)-FP-β-CD Complex[b]			
O(007W)···O(002W)···O(005W) (7)	2.80	2.84	108	O(153)(8)···O(014W)···O(112)	2.83	2.66	126
O(256)(14)···O(002W)···O(005W) (7)	3.19	2.84	128	O(018W)(9)···O(015W)···O(252)	2.81	2.84	100
O(276)(14)···O(003W)···O(116)	2.72	2.75	106	O(018W)(9)···O(015W)···O(016W) (6)	2.81	2.92	118
O(025W)(14)···O(003W)···O(146) (8)	2.84	2.74	127	O(011W)···O(015W)···O(162) (9)	2.83	2.87	108
O(026W)(11)···O(004W)···O(146)	2.99	2.75	105	O(243)(4)···O(016W)···O(272)	2.86	2.71	117
O(005W)···O(004W)···O(006W)	3.01	3.02	104	O(010W)(4)···O(016W)···O(272)	2.89	2.71	126
O(246)(11)···O(004W)···O(006W)	3.00	3.02	113	O(015W)(4)···O(016W)···O(272)	2.92	2.71	124
O(008W)(6)···O(005W)···O(004W)	2.78	3.01	110	O(253)(2)···O(017W)···O(232)	2.92	2.74	107
O(008W)(6)···O(005W)···O(002W) (3)	2.78	2.84	106	O(012W)(2)···O(017W)···O(232)	2.81	2.74	105
O(166)(6)···O(006W)···O(136)	2.78	2.89	116	O(015W)(1)···O(018W)···O(213)	2.81	2.99	116
O(004W)···O(006W)···O(136)	3.02	2.89	127	O(021W)(1)···O(018W)···O(213)	2.76	2.99	102
O(002W)···O(007W)···O(176)	2.90	2.82	120	O(022W)(1)···O(020W)···O(222)	2.78	2.66	120
O(009W)(8)···O(007W)···O(176)	2.77	2.82	114	O(022W)···O(021W)···O(256)	2.94	3.06	114
O(011W)(1)···O(008W)···O(166)	2.83	2.85	110	O(018W)(9)···O(021W)···O(023W)	2.76	2.58	116
O(005W)(4)···O(008W)···O(009W)	2.78	2.88	110	O(020W)(9)···O(022W)···O(246)	2.78	2.74	122
O(007W)(2)···O(009W)···O(156)	2.77	2.75	105	O(025W)(6)···O(022W)···O(021W)	2.81	2.94	112
O(010W)(1)···O(009W)···O(008W)	2.79	2.88	105	O(027W)(8)···O(023W)···O(021W)	2.74	2.58	122
O(016W)(6)···O(010W)···O(132)	2.89	2.64	90	O(027W)···O(024W)···O(226)	2.86	2.67	125
O(009W)(9)···O(010W)···O(132)	2.79	2.64	121	O(256)(2)···O(024W)···O(226)	2.78	2.67	129
O(015W)···O(011W)···O(123)	2.83	2.89	113	O(022W)(4)···O(025W)···O(266)	2.67	2.67	117
O(008W)(9)···O(011W)···O(012W)	2.83	2.72	106	O(003W)(16)···O(025W)···O(126) (16)	2.84	2.70	113
O(011W)···O(012W)···O(122)	2.72	2.66	107	O(215)(6)···O(026W)···O(236)	2.85	2.73	102
O(143)(8)···O(012W)···O(122)	2.87	2.66	111	O(004W)(13)···O(026W)···O(236)	2.99	2.73	119
O(017W)(8)···O(012W)···O(122)	2.81	2.66	114	O(024W)···O(027W)···O(236)	2.86	2.67	128
O(163)(6)···O(013W)···O(142)	2.79	2.73	112	O(023W)(2)···O(027W)···O(136) (13)	2.74	2.71	101

[a] Standard deviation range: for distance, 0.01–0.04 Å; for angle, 0.4–1.6°. [b] Standard deviation range: for distance, 0.02–0.06 Å; for angle, 0.5–1.7°. [c] The number in parentheses after the atom name is the symmetry code (see Table IV).

Table VI. Intermolecular Hydrogen Bonding (Å) between Secondary Hydroxyl Groups

bond	(*R*)-FP-CD	(*S*)-FP-CD	bond	(*R*)-FP-CD	(*S*)-FP-CD
O(113)–O(263)	2.83 (1)	2.74 (2)	O(152)–O(262) (65501)	2.67 (1)	2.72 (2)
O(123)–O(253)	2.94 (1)	2.96 (2)			
O(133)–O(243)	2.78 (1)	2.86 (2)	O(172)–O(242) (55601)	2.69 (1)	2.62 (2)
O(143)–O(233)	2.86 (1)	2.83 (2)			
O(153)–O(223)	2.74 (1)	2.79 (2)	O(262)–O(152) (45501)	2.67 41)	2.72 (2)
O(163)–O(213)	2.84 (1)	2.85 (2)			
O(173)–O(273)	2.81 (1)	2.75 (2)	O(242)–O(172) (55401)	2.69 (1)	2.62 (2)
mean	2.83 (1)	2.83 (2)		2.68 (1)	2.67 (2)
σ	0.06	0.08		0.01	0.06

cessitates movement of the methyl and carboxylic acid groups to more favorable positions, mainly in order to point the carboxylic acid group to a suitable environment for hydrogen bonding. This results in a change in the direction in which the hydrogen atom points and to changes in orientation of the phenyl rings, all of these having to maintain compatibility with the restrictions imposed by the CD cavity. Co-incidence of the carboxylic acid group in the (*R*)- and (*S*)-FP *cannot be achieved by sterically possible*

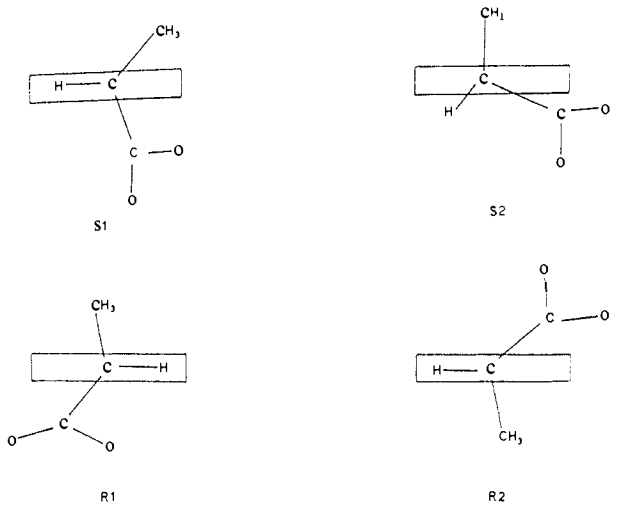

Figure 7. Schematic conformation of the propionic acid group is all four independent FP guest molecules.

Table VII. Intramolecular Hydrogen Bonding (Å) between the Secondary Hydroxyl Groups within the Same β-CD Unit

bond	(*R*)-FP-CD1	(*R*)-FP-CD2	(*S*)-FP-CD1	(*S*)-FP-CD2
O(13)-O(22)	2.83 (2)	2.77 (2)	2.83 (2)	2.76 (2)
O(23)-O(32)	2.73 (2)	2.81 (1)	2.76 (2)	2.87 (2)
O(33)-O(42)	2.84 (1)	2.79 (2)	2.82 (2)	2.83 (2)
O(43)-O(52)	2.73 (2)	2.84 (1)	2.75 (2)	2.91 (2)
O(53)-O(62)	2.82 (1)	2.75 (1)	2.80 (2)	2.75 (2)
O(63)-O(72)	2.70 (1)	2.65 (1)	2.73 (2)	2.69 (2)
O(73)-O(12)	2.72 (2)	2.79 (1)	2.66 (2)	2.82 (2)
mean	2.77 (2)	2.77 (1)	2.76 (2)	2.80 (2)
σ	0.06	0.06	0.06	0.08

rotations. On going from R2 to S2 by interchanging the methyl and carboxylic acid groups, finding suitable hydrogen-bonding acceptors is more difficult since the S2 FP molecule is oriented differently inside the CD cavity, i.e., the carboxylic acid group is up in the dimer interface at the secondary hydroxyl face of the CD. This forces the propionic acid group into a less favorable orientation, with the carboxylic acid group closer to the plane of ring 1 and the methyl group perpendicular to the plane of ring 1.

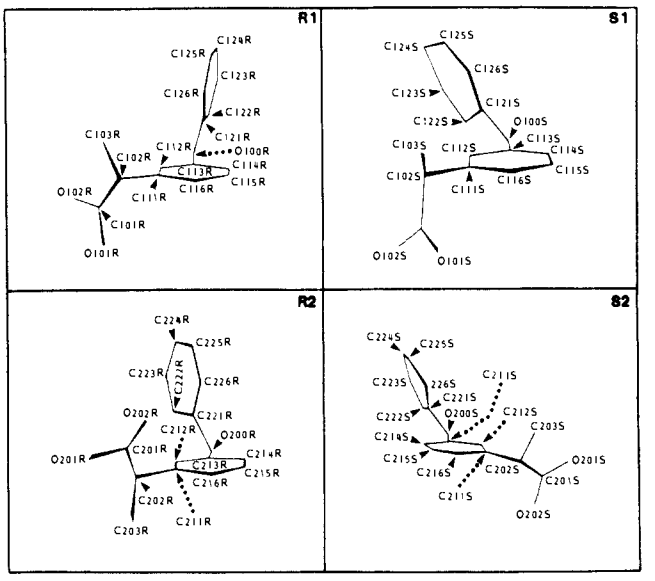

Figure 8. Observed conformational relationship of the propionic acid group and the phenoxy group with respect to benzene ring 1 in all four independent FP guest molecules.

This leads to the important question of why the S2 molecule packs with its tail toward S1 rather than its head, as for the (*R*)-FP. Consider first molecules R1 and S1, which have an overall similar position in the complexes. They differ by a rotation of phenyl ring 2 (90°) about the C(13G)-O(000G) bond (Figure 8) and the direction in which the hydrogen of the propionic acid group points, as discussed above (Figure 7). Ignoring the rotation of ring 2 for the present, the packing, inside a CD monomer, of ring 1 with a meta substituent in the *R* configuration restricts the carboxylic acid group to hydrogen bonding with water, since the steric considerations discussed above force it to sit centrally in the CD cavity but pointed down to the exterior of the primary hydroxyl face of the CD, i.e., in an unfavorable orientation for hydrogen bonding to primary hydroxyl groups on either the encapsulating CD or a neighboring CD. The same steric considerations allow the meta substituent in the *S* configuration to orient

Table VIII. Bond Lengths (Å) and Angles (deg) of the FP Guests in the (*R*)- and (*S*)-FP-β-CD Complexes

	(*R*)-FP complex		(*S*)-FP complex			(*R*)-FP complex		(*S*)-FP complex	
bond	FP 1	FP 2	FP 1	FP 2	bond	FP 1	FP 2	FP 1	FP 2
C(01)-O(01)	1.23 (2)	1.17 (2)	1.19 (3)	1.27 (4)	C(16)-C(11)	1.42 (2)	1.26 (4)	1.40 (4)	1.44 (3)
C(01)-O(02)	1.33 (2)	1.40 (2)	1.36 (3)	1.40 (4)	C(13)-O(00)	1.43 (1)	1.46 (5)	1.42 (3)	1.35 (3)
C(01)-C(02)	1.51 (2)	1.45 (3)	1.53 (3)	1.53 (5)	C(21)-O(00)	1.39 (1)	1.37 (5)	1.43 (3)	1.45 (3)
C(02)-C(03)	1.47 (2)	1.49 (3)	1.60 (3)	1.50 (4)	C(21)-C(22)	1.39 (2)	1.53 (3)	1.41 (4)	1.40 (4)
C(02)-C(11)	1.53 (2)	1.50 (3)	1.50 (3)	1.52 (4)	C(22)-C(23)	1.36 (2)	1.34 (2)	1.34 (4)	1.35 (4)
C(11)-C(12)	1.41 (2)	1.42 (3)	1.27 (4)	1.36 (3)	C(23)-C(24)	1.42 (2)	1.35 (2)	1.45 (5)	1.43 (5)
C(12)-C(13)	1.36 (2)	1.33 (4)	1.41 (3)	1.35 (4)	C(24)-C(25)	1.35 (2)	1.34 (2)	1.45 (5)	1.41 (4)
C(13)-C(14)	1.39 (2)	1.46 (6)	1.29 (3)	1.37 (6)	C(25)-C(26)	1.40 (2)	1.38 (2)	1.36 (4)	1.46 (4)
C(14)-C(15)	1.39 (2)	1.45 (9)	1.39 (4)	1.46 (6)	C(26)-C(21)	1.41 (2)	1.40 (3)	1.39 (4)	1.31 (5)
C(15)-C(16)	1.39 (2)	1.26 (5)	1.35 (4)	1.35 (4)					

	(*R*)-FP complex		(*S*)-FP complex			(*R*)-FP complex		(*S*)-FP complex	
angle	FP 1	FP 2	FP 1	FP 2	angle	FP 1	FP 2	FP 1	FP 2
O(01)-C(01)-O(02)	122 (1)	117 (2)	121 (2)	116 (3)	C(16)-C(11)-C(12)	119 (1)	117 (2)	115 (2)	116 (2)
O(01)-C(01)-C(02)	114 (1)	115 (2)	128 (2)	133 (3)	C(12)-C(13)-O(00)	118 (1)	128 (3)	121 (2)	117 (2)
O(02)-C(01)-C(02)	123 (1)	128 (2)	111 (2)	111 (2)	C(14)-C(13)-O(00)	118 (1)	114 (4)	124 (2)	118 (3)
C(01)-C(02)-C(03)	112 (1)	110 (2)	109 (2)	106 (2)	C(13)-O(00)-C(21)	117 (1)	115 (3)	118 (2)	126 (2)
C(01)-C(02)-C(11)	106 (1)	112 (2)	106 (1)	111 (2)	O(00)-C(21)-C(22)	119 (1)	127 (3)	112 (2)	116 (3)
C(03)-C(02)-C(11)	111 (1)	113 (1)	113 (2)	108 (2)	O(00)-C(21)-C(26)	121 (1)	119 (2)	121 (2)	116 (3)
C(02)-C(11)-C(12)	121 (1)	115 (2)	124 (2)	131 (2)	C(21)-C(22)-C(23)	121 (1)	120 (2)	117 (2)	113 (3)
C(02)-C(11)-C(16)	120 (1)	127 (2)	121 (2)	113 (2)	C(22)-C(23)-C(24)	119 (1)	123 (1)	123 (3)	128 (3)
C(11)-C(12)-C(13)	119 (1)	122 (2)	125 (2)	120 (2)	C(23)-C(24)-C(25)	121 (1)	119 (1)	110 (2)	117 (3)
C(12)-C(13)-C(14)	124 (1)	118 (3)	115 (2)	125 (3)	C(24)-C(25)-C(26)	120 (1)	123 (1)	127 (3)	114 (3)
C(13)-C(14)-C(15)	116 (1)	114 (4)	128 (2)	116 (3)	C(25)-C(26)-C(21)	119 (1)	121 (1)	114 (3)	119 (3)
C(14)-C(15)-C(16)	123 (1)	120 (4)	111 (3)	118 (3)	C(26)-C(21)-C(22)	120 (1)	113 (2)	127 (2)	127 (3)
C(15)-C(16)-C(11)	118 (1)	127 (3)	126 (3)	123 (2)					

Table IX. Torsion Angles around the Phenoxy Oxygen and the Chiral Carbon in All Four FP Molecules

torsion group	R1	R2	S1	S2
C(12G)-C(13G)-O(00G)-C(21G)	104 (1)	62 (4)	61 (3)	-118 (3)
C(14G)-C(13G)-O(00G)-C(21G)	-79 (1)	-119 (4)	-128 (3)	60 (3)
C(22G)-C(21G)-O(00G)-C(13G)	171 (1)	-145 (4)	-155 (3)	-175 (3)
C(26G)-C(21G)-O(00G)-C(13G)	-11 (1)	47 (4)	17 (3)	12 (3)
C(01G)-C(02G)-C(11G)-C(12G)	52 (1)	-120 (2)	104 (2)	-26 (3)
C(01G)-C(02G)-C(11G)-C(16G)	-129 (1)	73 (3)	-77 (2)	158 (3)
C(03G)-C(02G)-C(11G)-C(12G)	-70 (1)	115 (2)	-137 (3)	90 (3)
C(03G)-C(02G)-C(11G)-C(16G)	109 (1)	-51 (3)	42 (3)	85 (3)

with the carboxylic acid group pointed to the side of the CD cavity so that S1 in fact hydrogen bonds to a CD primary hydroxyl group on a neighboring CD molecule (this being a stronger bond than that of the R1 to water). However, as a result of hydrogen bonding to an adjacent CD, S1 is located further down into the primary end of the encapsulating CD (0.63 Å with respect to R1). This in turn results in ring 2 of S1 being farther away from the secondary hydroxyl face of the CD than that of R1 (0.37 Å). The center of mass of ring 1 is moved laterally 0.7 Å and ring 2 by 0.9 Å with respect to that of R1. Thus, the favorable phenyl/phenyl close packing at the dimer interface for a head-to-head arrangement on formation of the complex dimer is possible for R1 and R2, but not for S1 and S2. However, the carboxylic acid group of an (*S*)-FP can also hydrogen bond to a secondary hydroxyl group of CD if the molecule is inverted in the CD cavity. In this case there is competition from the intramolecular hydrogen bonding, which stabilizes the CD ring, and intermolecular hydrogen bonding, which results in dimer formation. However, such a bond occurs for S2 and is energetically favorable so that in combination with methyl/phenyl close packing at the CD dimer interface there results a structure that is more favorable than that of the (*R*)-FP. However, the rotation of ring 2 of S1 with respect to R1, mentioned previously but temporarily ignored, results from ring 2 of S1 reorienting to maximize hydrophobic interaction with the methyl group of S2. Ring 2 of R2 similarly reorients to maximize phenyl/phenyl interaction at the dimer interface. Thus, the differences in conformation observed for the FP molecules are a result of three main packing considerations: the fit of the phenoxy phenyl moiety inside the β-CD cavity, the hydration requirements of the carboxylic acid group, and the choice of phenyl/phenyl close packing versus methyl/phenyl close packing where the FP molecules approach one another at the CD dimer interface.

A further comparison of the final FP conformations shown in Figure 8 is worthwhile. If one considers a plane through O(00G), C(13G), and C(16G) perpendicular to ring 1, in S1 and R2 the propionic acid group is on the same side of the plane as ring 2 but in R1 and R2 it is on the opposite side. This is the most obvious difference between the FP molecules. Another difference is the position of the carboxylic acid and methyl groups relative to the plane of ring 1, as was discussed above. In R1, R2, and S1 they adopt the staggered position relative to ring 1 as in Figure 7. For S2 the carboxylic acid group moves closer to the plane and the methyl group is perpendicular to the plane. These differences are reflected in the dihedral angles listed in Table IX. In addition, for three of the FPs, R1, S1, and S2, the methyl group is on the same side of ring 1 as is ring 2. This results in the hydrogen atom of C(26G) in ring 2 sitting above the plane of ring 1. For R2 the reverse is the case, and the presence of the bulkier carboxylic acid group above the plane of ring 1 causes repulsion of the C(26G) hydrogen atom and rotation of ring 2 away from the carboxylic acid group (Figure 8).

As a consequence of the steric considerations discussed above, the angles between the planes of the phenyl rings in the (*R*)- and (*S*)-FPs must be distinct and different. In the two crystallographically independent guest molecules, the *R* isomers have values of 83.0 and 84.6°, while the *S* isomers have values of 69.7 and 65.2°. The total effect of the steric and hydrogen-bonding considerations is to produce two molecules R2 and S1, which are almost superimposable on one another except for the propionic acid group and a slight difference in the interplanar angle of the phenyl rings, and in contrast two molecules R1 and S2, which appear to be related by a pseudo mirror plane (Figure 8).

The primary motivating force in determining the molecular arrangement when formation of the complex dimer occurs is the means used to satisfy the hydration requirements of the carboxylic acid group, which due to steric considerations points in a different direction in the *R* versus *S* isomer. It is significant that the water molecules involved in hydrogen bonding to the carboxylic acid groups of the (*R*)-FP are not present in the (*S*)-FP structure. The most favorable packing of the second crystallographically independent FP molecule in the other half of the β-CD dimer should be head-to-head with phenyl rings 2 of the two molecules parallel to one another in the rather hydrophobic dimer interface. This can be accomplished by the R2 FP with minor adjustments such as rotation of ring 2. For R2, some movement of ring 2 is also due to the presence of the bulky carboxylic acid group above the plane of ring 1 causing repulsion of the C(26G) hydrogen atom on ring 2.

In order for S2 to form a head-to-head arrangement, ring 2 of S2 would need to be located further up toward the secondary hydroxyl face of the β-CD. This would result in the carboxylic acid group being too far into the β-CD cavity to hydrogen bond with either a water molecule or a primary hydroxyl group. As a consequence of lack of hydration possibilities, the dimer forms with an S2 molecule in an inverted position in the CD cavity, the carboxylic acid group hydrogen bonding to a secondary hydroxyl group of the β-CD. Ring 2 of S1 and the propionic acid group of S2 reorient slightly so as to maximize the phenyl/methyl hydrophobic interaction at the CD dimer interface.

β-CD is composed of D-glucose and thus is an optically active compound, which might be expected to show stereoselectivity when inclusion complexes with enantiomeric isomers are formed.[16] A number of racemic materials[17-19] have been resolved by the complexation with β-CD. Armstrong[20,21] recently proposed that the requirements for stereoselective binding in β-CD include a phenyl ring on the guest molecule and a carboxylic acid group capable of hydrogen bonding to a secondary hydroxyl group of the β-CD. These requirements are fulfilled by (*S*)-FP. More conclusive evidence should be gained from a crystal structure of β-CD with a racemic mixture of FP. This has been crystallized and is isomorphous with the individual *R* and *S* complexes. Disorder is present, and a careful refinement is in progress. An extract of the supernatant from the crystals showed a negative optical rotation after removal of the β-CD (indicative of excess *R* isomer), while an extract of the crystals showed a positive optical rotation (indicative of excess *S* isomer).

It has been shown that for all 2-arylpropionic acids so far studied only the (*S*)-(+) isomer is an active inhibitor for the cyclooxygenase, which is the first enzyme of prostaglandin synthesis.[8,9] That means the enzyme is stereoselective for the (*S*)-(+) conformation of propionic acid. On the basis of the restricted con-

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formations observed for the propionic acid group in the above crystal structures and taking into account the modeling of the cyclooxygenase/2-arylpropionic acids interaction proposed by Sankawa et al.,[22] who concluded that the carboxylic acid group must interact with the C(15) oxygenation site on the cyclooxygenase, our results suggest that in a restricted hydrophobic pocket, such as the enzyme active site, steric considerations orient the carboxylic acid groups of the *R* and *S* isomers in different directions, so that only the *S* can interact with the C(15) oxygenation site on the enzyme.

Conclusions

(*R*)-(−)- and (*S*)-(+)-fenoprofens adopt different packing arrangements inside the β-CD dimer, the *R* being head-to-head and the *S* head-to-tail. The differences are due to the effects of formation of the complex dimer and crystal-packing effects such as the means of satisfying the hydration requirements of the carboxylic acid group. Steric restrictions on the meta-substituted propionic acid group, such as the inability of the methyl group to approach the plane of ring 1 and the restricted dihedral angles of the planes of ring 1 and ring 2, result [in the case of the (*S*)-FP] in hydrogen bonds from a guest molecule to secondary hydroxyl groups on the β-CD, which have not been previously observed in crystal structures of β-CD dimer complexes. In the case of (*R*)-FP, the less favorable hydrogen bonding of the carboxylic acid groups to water as compared with CD primary or secondary groups for the (*S*)-FP is to some extent compensated for by more favorable parallel, phenyl/phenyl packing of rings 2 in the hydrophobic CD dimer interface versus methyl/phenyl packing for the (*S*)-FP.

The difference in binding of the *R* and *S* isomers to the β-CD makes it possible that β-CD in the crystal form is stereoselective for one or the other isomer of fenoprofen but provides no evidence that the stereoselectivity also exists in solution.

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Registry No. (*R*)-(−)-FP-CD complex, 114185-91-0; (*S*)-(+)-FP-CD complex, 114185-92-1.

Supplementary Material Available: Tables of anisotropic thermal parameters, hydrogen positional parameters, and individual bond lengths and angles for CD molecules (22 pages); tables of observed and calculated structure factors (87 pages). Ordering information is given on any current masthead page.

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UV–Visible and Carbon NMR Studies of Chloroquine Binding to Urohemin I Chloride and Uroporphyrin I in Aqueous Solutions

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Abstract: Interactions of the antimalaria drug chloroquine with urohemin I and uroporphyrin I have been studied in aqueous solutions at pH 6.0 and 22 ± 1 °C with UV–visible and natural abundance carbon NMR spectroscopies. Both tetrapyrroles are water soluble and were chosen because their aggregation properties are understood and can be regulated by concentration and ionic strength. Chloroquine binding to urohemin I monomer has a stoichiometry of two urohemin molecules to one chloroquine molecule with an apparent association equilibrium constant of $(7.8 \pm 0.4) \times 10^8$ M^{-2} at pH 6.0 and a urohemin concentration of 10^{-6} M. This stoichiometry is identical with that recently reported for complexes of urohemin I with another antimalarial, quinine. In that case, the binding was found to be cooperative, whereas in this case the drug binding is noncooperative. Uroporphyrin I binds to chloroquine with 1:1 stoichiometry and an apparent equilibrium constant of $(2.8 \pm 0.2) \times 10^6$ M^{-1} at a uroporphyrin concentration 10^{-6} M. Carbon NMR spectroscopy and optical methods best describe these complexes as cofacial π–π dimers with structures different from the quinine complexes of the same tetrapyrroles.

Chloroquine and quinine (Figure 1) are perhaps the most common clinical antimalarials in use today. Their demonstrated association with the malaria pigment found in parasitized erythrocytes, which is composed of heme that is presumably released from protease degraded hemoglobin, lead to the idea that the drug's physiological efficacy involves a ferriprotoporphyrin IX–chloroquine complex.[1-5] Several studies of the ferriprotoporphyrin IX–chloroquine interaction resulted from such observations, and the dimensions of the chloroquine membrane receptor were shown to be similar to those of the heme moiety.[2,6-12]

The apparent relevance of heme–malaria drug interactions recently lead us to a study of quinine interacting with two species

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