it is a ground state triplet dication with π symmetry. The sharp singlet of its ^{13}C NMR spectrum also argues against the possibility of a π triplet ground state[4] and provides strong evidence against a pentagonal pyramidal structure.[5] The 46.2 ppm upfield ^{13}C chemical shift of the aromatic dication of **6**, relative to C_6I_6, is possibly the result of a ring current effect of the postulated 10-electron σ-delocalized Hückel aromatic system based in the cyclic array of iodine atoms in the dication of **6** $(C_6I_6)^{2+}$.

Acknowledgment. The research was partially funded by the National Science Foundation (Grant CHE-84-09404), the National Institutes of Health (Grant GM 33064), and the University of Illinous, where most of the experimental work was done. Helpful discussions with A. J. Arduengo, III and L. J. Schaad are acknowledged. We thank Dr. Michael Wasserman, Department of Physics, for his assistance in measurements of magnetic susceptibilities.

Registry No. **5**, 608-74-2; **6**, 115162-16-8; **6** (dication), 109264-72-4; **7**, 115162-13-5; **7** (radical cation), 115162-12-4; **8**, 115162-15-7; **10**, 115162-11-3; **11**, 115162-18-0; **12**, 64349-88-8; TFAT, 68602-57-3; Me_4NI, 75-58-1; C_6Cl_6, 118-74-1; C_6Br_6, 87-82-1; tetramethylammonium triflate, 25628-09-5; tetramethylammonium chloride, 75-57-0; fluorobenzene, 462-06-6; trifluoromethaneperoxysulfonic acid, 85963-78-6.

Crystal Structure of an Inclusion Complex of β-Cyclodextrin with Racemic Fenoprofen: Direct Evidence for Chiral Recognition

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Abstract: The crystal structure of the inclusion complex of β-cyclodextrin (β-CD, cycloheptaamylose) with the racemic mixture of (*RS*)-fenoprofen [FP, 2-(3-phenoxyphenyl)propionic acid] has been determined by X-ray diffraction techniques. The complex crystallizes in space group $P2_1$ with cell dimensions a = 15.277 (3) Å, b = 32.232 (7) Å, c = 15.316 (3) Å, and β = 101.18 (1)°. The complex asymmetric unit consists of a head-to-head dimer of β-CD formed by hydrogen bonding across the secondary hydroxyl faces of adjacent β-CD monomers, with one guest FP in each β-CD monomer unit. Both enantiomers of FP exist in the crystal of the complex; however, the molecular ratio of FP in the crystal is ~3:1 for the *S* and *R* isomers, respectively. The β-CD dimer contains only an *R*/*R* pair or an *S*/*S* pair of crystallographically independent FP molecules, which means that chiral resolution has occurred in the crystalline complex. As in the individual enantiomeric complexes, these crystallographically unique FP molecules exist in the β-CD dimer in a head-to-tail arrangement for the (*S*)-FP and a head-to-head arrangement for the (*R*)-FP. The carboxylic acid groups of (*S*)-FP form hydrogen bonds with primary or secondary hydroxyl oxygen atoms from β-CD molecules, whereas the carboxylic acid groups of (*R*)-FP are hydrogen-bonded to two water molecules, which exist in the same occupancy as the (*R*)-FP guest molecules.

Cyclodextrins (CD), also known as cycloamyloses, are cyclic oligosaccharides formed from starch by the action of bacteria such as *Bacillus macerans*.[1] The best characterized forms are those containing 6-8 D-glucopyranosyl units, linked by α(1→4)-glycosidic bonds to form a macrocyclic polymer. β-Cyclodextrin (β-CD), or cycloheptaamylose, which contains 7 glucose units with an inner diameter of 6.5-8.0 Å (Figure 1), is the most versatile of the cyclodextrins. The cyclodextrins have a cylindrical shape with all the secondary hydroxyl groups, i.e. O(2)-H and O(3)-H, located on the wider end and all primary hydroxyl groups, O(6)-H, on the narrower end (numbering scheme on Figure 1). All 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] The C(6)-O(6) bonds are usually directed away from the center of the cyclodextrin ring. They can, however, turn "inward", usually 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) always exist between the secondary hydroxyl groups of adjacent glucose units.

The cyclodextrins show remarkable ability to form inclusion complexes with various natural and synthetic molecules that fit inside the CD cavity.[1-3] The inclusion process is influenced mainly by the hydrophobic nature of the interaction between the guest molecules and the cavity, and also by the shape and size of the guest. The encapsulation process can change the chemical and physical properties of the guest. In particular, pharmacological properties, such as stability, solubility, bioavailability, and toxicity, can be improved, and these changes have been intensively investigated. Examples of drugs that are reported to be complexed with CD include prostaglandins, barbiturates, steroids, and nonsteroid antiinflammatory drugs (NSAID). An extensive review of cyclodextrin chemistry is given by Bender and Komiyama.[4] A review of the complexation phenomena as well as the applications of cyclodextrins in research and industry is given by Saenger.[1] Many studies of the crystal structures of CD inclusion complexes have been reported by Saenger et al., Harata et al., and Stezowski et al. (see ref 5-8 for recent examples).

Another important property of all CD's is chirality: β-CD is dextrorotatory with $[\alpha]_D$ +162°. The hydroxyl groups (the

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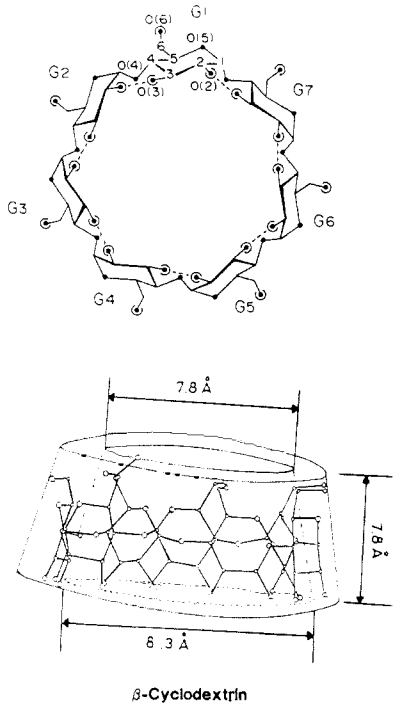

Figure 1. β-Cyclodextrin molecule and a cylindrical model to show the dimensions.

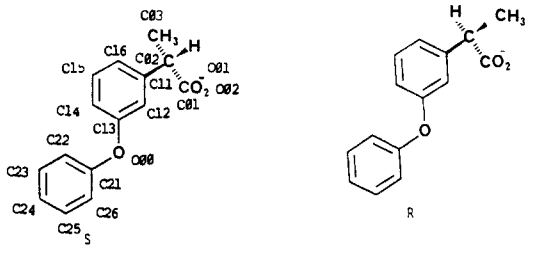

Figure 2. Fenoprofen, 2-(3-phenoxyphenyl)propionic acid.

secondary hydroxyl groups in particular) can interact stereoselectively with complexed chiral guest molecules and thus function as optical resolution phases.[9]

Fenoprofen (FP), 2-(3-phenoxyphenyl)propionic acid or α-methyl-3-phenoxybenzeneacetic acid (Figure 2), is a nonsteroidal antiinflammatory, antipyretic, analgesic drug developed at the Lilly Research Laboratories.[10,11] 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.[12] The marketed form of fenoprofen is the calcium dihydrate (Nalfon; Eli Lilly & Co.).

Fenoprofen has a chiral carbon atom, resulting in two possible 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. This reaction has been used to detect drugs that have antiinflammatory activity associated with inhibition of prostaglandin synthesis.[13] 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.[14] An X-ray crystallographic study[15] of FP showed that the absolute configurations of the active isomer is *S*.

The present study was undertaken to determine the binding of racemic FP in the cavity of β-CD. Our initial electron density maps showed that both guests exhibited a disorder that could not be immediately resolved. Therefore, elucidation of the structures of the individual *R* and *S* isomers with β-CD was undertaken. The results of these determinations[16] revealed very different packing and interaction for the two isomers. By use of the coordinates from the individual studies, solution of the disorder in the racemic structure was achieved.

Structure Determination and Refinement. Racemic fenoprofen calcium salts (FP-Ca) were obtained from Eli Lilly & Co. The solubility of the calcium salts in water is 2.5 mg/mL (pK_a 4.5). The calcium salt was added to a two-layer water–ethyl acetate system (W:EA = 1:3). The pH was adjusted to 3–3.5 with HCl. After several cycles of separation and washing with ethyl acetate, all ethyl acetate extractions were collected and combined. The concentration of FP in the ethyl acetate was measured by UV at 271 nm. The ethyl acetate was evaporated, and the acid fenoprofen thus obtained was an oil. β-CD was dissolved in water and the solution mixed with the oil in a molar ratio of 1:3 (β-CD to FP). The mixture was heated for 2 h in a water bath (50 °C), and on cooling, microprecipitates were formed. The mixture was refrigerated for 5–7 days, and good crystals in the form of parallelogram plates were obtained.

Determination of the unit cell parameters and collection of the diffraction data were done on a Picker four-circle automated diffractometer at −150 °C using Mo Kα radiation. A total of 9919 reflections in the range $5° < 2\theta < 93°$ was collected, corresponding to approximately 0.9 Å resolution. The crystal, which is isomorphous with the enantiomeric FP–β-CD complexes, is monoclinic, with space group $P2_1$, and there are two complexes per asymmetric unit. The unit cell parameters are as follows: a = 15.277 (3) Å; b = 32.232 (7) Å; c = 15.316 (3) Å; β = 101.18 (1)°. The positional parameters for β-CD (except for the primary hydroxyl oxygen atoms) from an isomorphous complex[16] were used as a starting point for phase determination. The resultant difference map showed what appeared to be two guest FP molecules in a head-to-tail arrangement as was observed for the (*S*)-FP–β-CD complex and the reverse of the arrangement observed for the (*R*)-FP–β-CD complex.[16] However, only one could be identified as a specific isomer with any certainty [the (*S*)-FP], and there were minor peaks of lower electron density inside the β-CD cavity, particularly in the vicinity of the carboxylic acid groups. These could be interpreted as due to disorder of the carboxylic acid groups or due to disorder of the *R* and *S* enantiomers [i.e., not simply (*R*)-SP fully occupying one β-CD monomer and (*S*)-FP fully occupying the other]. A satisfactory solution could not be obtained at this juncture. To help decide the question of disorder of the enantiomers, determination of the crystal structures of the resolved (*R*)- and (*S*)-FPs complexed with β-CD was undertaken.

The refined coordinates of the (*R*)- and (*S*)-FPs from these structure determinations[16] were then plotted onto the difference map for the racemic complex. The coordinates of the (*S*)-FP guest corresponded exactly to major electron density peaks in the cavity of the β-CD dimer, while most of the coordinates of the (*R*)-FP corresponded to the minor peaks. This meant that in the racemic FP complex the guests are disordered, the asymmetric complex containing two crystallographically unique (*R*)-FP and two crystallographically unique (*S*)-FP molecules with occupancy factors less than 1 [the final refined occupancy factors were 0.75 for both (*S*)-FP molecules and 0.25 for both (*R*)-FP molecules].

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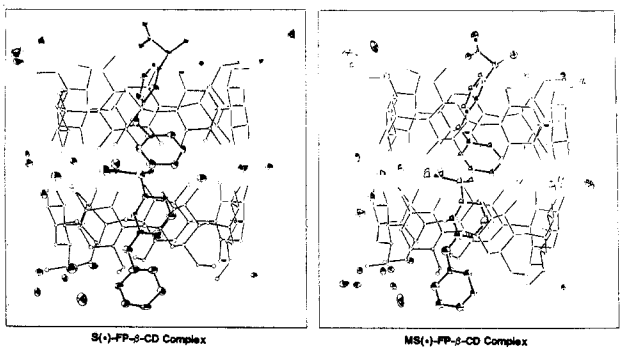

Figure 3. Comparison of the ORTEP plots of *S* vs MS structures.

The *R* and *S* isomers complex differently with the β-CD; the *S* complex is head-to-tail and the *R* complex is head-to-head as in the resolved enantiomeric complexes. The reason the guest positions could not be solved from the original difference maps was that most of the minor peaks for the (*R*)-FP overlapped with major peaks corresponding to the (*S*)-FP. The coordinates from the individual enantiomeric complexes (now designated R1, S1, and S2) were used as starting points for least-squares refinement of MR1, MS1, and MS2 (the FP enantiomers in the racemate). R2 did not quite fit MR2, and the positional parameters of MR2 were determined from a difference map by using more refined phases. Thirty water molecules were observed in the racemic complex structure. For the included guests the positional and isotropic temperature parameters were refined by using group refinement, allowing only one guest to vary and keeping the others constant in any one cycle of least-squares refinement. Anisotropic temperature parameters were used for the atoms in the β-CD. Only those reflections with $F_0 > 3\sigma$ were used in the refinement. Due to the large number of parameters, refinement was carried out in segments: one β-CD alone, guest molecules alone, or water molecules alone were refined in alternate cycles. A final cycle of structure factors using data with $F_0 > 1\sigma$ was performed [this represents a reflection percentage of 94.3 (9313)]. Calculated hydrogen atom positions were included with isotropic temperature parameters half of those of the atoms bonded to them. The final *R* value was 0.108 for all data.

Results and Discussion

Dimer Structure and Packing Scheme. The final atomic coordinates for the non-hydrogen atoms are given in Table I. The numbering scheme uses a three-digit code as follows: The first digit represents the monomer for β-CD or FP, the second represents the glucose residue of β-CD or the phenyl ring of FP (0 for ring side-chain atoms), and the third represents the atoms in the individual glucose residues or FP molecules as shown in Figures 1 and 2. Hydrogen bonds were analyzed in a distance range of 2.3–3.2 Å and angle range of 90–130°. Table II lists the hydrogen bonds involving the β-CD hydroxyl groups and the guest molecules. Hydrogen bonds involving water molecules are available as supplementary material. In contrast to other β-CD dimer complexes, only the O(3)-hydroxyl groups of the glucose residues are involved in the intermolecular hydrogen bonds that form the β-CD dimer. There are four intermolecular hydrogen bonds between O(2)-hydroxyl atoms; however, their partners are from symmetry-related units. Intramolecular hydrogen bonds always exist between O(2)- and O(3)-hydroxyl groups of adjacent residues. Intramolecular and intermolecular hydrogen bond distances are shown in Table III. Some hydrogen bonds exist between primary hydroxyl groups on neighboring CD units.

Guest Geometry and Packing. The position and conformation of the MS-FP molecules are identical with those of the (*S*)-FP molecules, as may be seen by comparison of the ORTEP plots as well as the packing schemes for both structures (Figures 3 and 4). The (*S*)- and MS-FP molecules are in a head-to-tail arrangement, in which one guest is oriented with its phenoxy group within the β-CD dimer interface and the other with the polar carboxyl group in the dimer interface and the phenoxy group protruding from the β-CD cavity. The dimer complexes are stacked in a disjointed channel throughout the crystal. This is stabilized by a parallel water channel and by hydrogen bonding via water molecules of the primary hydroxyl ends of adjacent dimer complexes. For the (*S*)-FP complex, there is also a hydrogen bond from the carboxylic acid group of the (*S*)-FP to a primary hydroxyl group of an adjacent dimer complex.

The MR-FP molecules are almost identical with those of (*R*)-FP, slight differences occurring due to the interfacing of a β-CD dimer containing a pair of *R* enantiomers with one containing a pair of *S* enantiomers (Figures 5 and 6). This situation, of course, does not occur in the individual *R* and *S* crystal structures. These differences can be seen from the computed

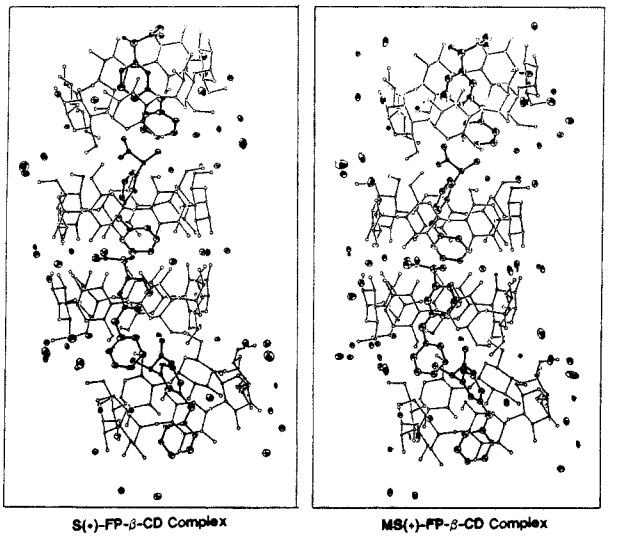

Figure 4. Comparison of the packing scheme of *S* vs MS structures.

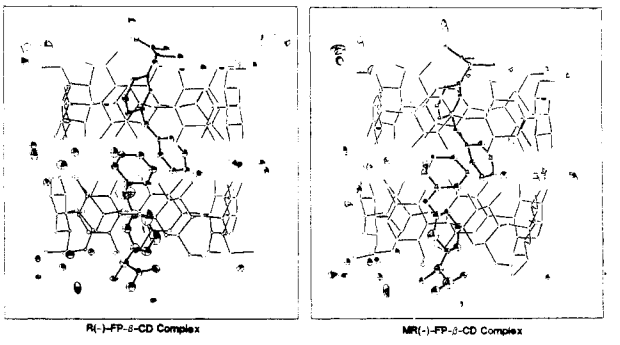

Figure 5. Comparison of the ORTEP plots of *R* vs MR structures.

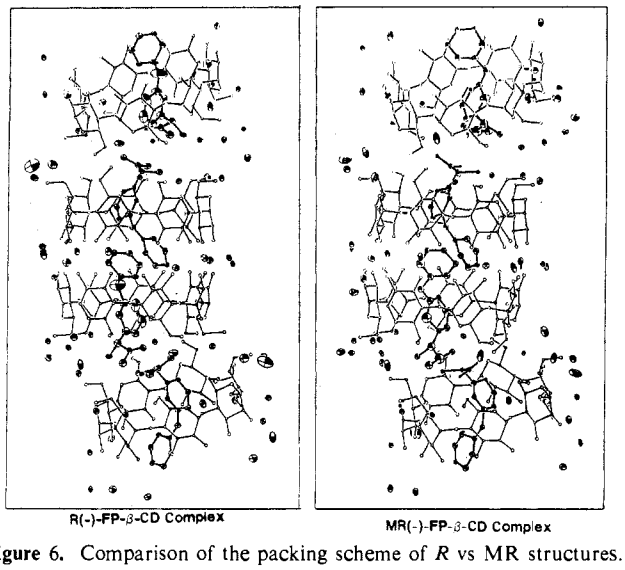

Figure 6. Comparison of the packing scheme of *R* vs MR structures.

Table I. Fractional Coordinates ($\times 10^4$) and Isotropic Thermal Parameters ($\times 10^2$) of the Non-Hydrogen Atoms of the (*RS*)-FP–β-CD Complex

CD1					CD2				
atom	*x*	*y*	*z*	*U*	atom	*x*	*y*	*z*	*U*
C(111)	−3595 (8)	5734 (4)	1638 (8)	2.3	C(211)	−232 (8)	3164 (4)	2829 (9)	2.2
C(112)	−4177 (8)	5410 (4)	1100 (8)	2.2	C(212)	461 (7)	3500 (5)	3021 (9)	2.9
C(113)	−4035 (7)	5419 (4)	114 (8)	1.9	C(213)	896 (8)	3558 (4)	2196 (7)	2.0
C(114)	−4338 (7)	5865 (3)	−253 (7)	1.4	C(214)	1266 (9)	3155 (4)	1969 (9)	3.0
C(115)	−3776 (9)	6185 (4)	319 (8)	2.7	C(215)	590 (10)	2801 (4)	1862 (10)	3.0
C(116)	−4134 (9)	6618 (4)	111 (8)	2.1	C(216)	1025 (11)	2372 (5)	1763 (11)	4.6
O(112)	−3930 (6)	4999 (3)	1457 (6)	3.1	O(212)	97 (5)	3878 (3)	3266 (5)	2.1
O(113)	−4569 (6)	5112 (3)	−374 (6)	2.6	O(213)	1583 (5)	3873 (3)	2375 (6)	2.5
O(114)	−4123 (5)	5870 (3)	−1125 (5)	1.9	O(214)	1542 (5)	3201 (3)	1128 (5)	2.4
O(115)	−3822 (5)	6133 (3)	1281 (5)	2.2	O(215)	176 (6)	2784 (3)	2642 (6)	3.0
O(116)	−5019 (6)	6662 (3)	247 (6)	3.1	O(216)	1743 (6)	2299 (3)	2508 (7)	3.9
C(121)	−4848 (8)	6023 (4)	−1795 (8)	2.1	C(221)	2431 (8)	3112 (4)	1059 (9)	2.7
C(122)	−5016 (8)	5695 (4)	−2530 (8)	2.0	C(222)	2834 (9)	3499 (4)	712 (8)	2.9
C(123)	−4236 (8)	5620 (4)	−2939 (8)	2.3	C(223)	2233 (9)	3622 (4)	−191 (9)	2.9
C(124)	−3918 (8)	6033 (4)	−3282 (8)	2.1	C(224)	2254 (8)	3256 (4)	−824 (9)	2.4
C(125)	−3794 (8)	6341 (4)	−2549 (8)	2.1	C(225)	1983 (9)	2853 (4)	−487 (9)	2.9
C(126)	−3599 (10)	6788 (4)	−2866 (8)	2.8	C(226)	2169 (8)	2496 (4)	−1024 (10)	2.6
O(122)	−5300 (6)	5314 (3)	−2169 (6)	2.3	O(222)	2863 (5)	3830 (3)	1331 (6)	2.7
O(123)	−4428 (6)	5327 (3)	−3635 (6)	2.5	O(223)	2601 (6)	3981 (3)	−519 (6)	3.3
O(124)	−3073 (5)	5966 (2)	−3546 (5)	1.8	O(224)	1645 (5)	3364 (3)	−1626 (6)	2.4
O(125)	−4587 (5)	6395 (2)	−2158 (6)	2.0	O(225)	2463 (6)	2785 (3)	440 (5)	2.4
O(126)	−3305 (6)	7054 (3)	−2129 (7)	3.5	O(226)	3050 (6)	2486 (3)	−1124 (6)	3.0
C(131)	−2992 (9)	6050 (5)	−4428 (8)	3.0	C(231)	191 (8)	3292 (4)	−2422 (8)	2.2
C(132)	−2637 (10)	5650 (4)	−4769 (8)	2.7	C(232)	1881 (8)	3705 (4)	−2976 (9)	2.5
C(133)	−1748 (10)	5541 (4)	−4204 (8)	3.0	C(233)	924 (8)	3844 (5)	−3234 (9)	3.0
C(134)	−1095 (9)	5898 (4)	−4240 (9)	2.7	C(234)	396 (9)	3491 (4)	−3783 (8)	2.6
C(135)	−1476 (9)	6285 (4)	−3988 (9)	2.6	C(235)	449 (10)	3104 (4)	−3220 (10)	3.2
C(136)	−913 (10)	6666 (5)	−4123 (11)	4.0	C(236)	−11 (15)	2752 (6)	−3767 (18)	7.4
O(132)	−3270 (6)	5319 (3)	−4781 (6)	3.3	O(232)	2408 (6)	4023 (3)	−2426 (6)	3.1
O(133)	−1417 (6)	5151 (3)	−4535 (6)	2.9	O(233)	894 (6)	4222 (3)	−3743 (6)	3.2
O(134)	−283 (6)	5797 (3)	−3677 (6)	2.6	O(234)	−497 (5)	3620 (3)	−4078 (5)	2.0
O(135)	−2363 (6)	6365 (3)	−4429 (6)	2.9	O(235)	1375 (6)	2987 (3)	−2958 (6)	3.2
O(136)	−908 (7)	6692 (4)	−5048 (9)	5.0	O(236)	336 (12)	2695 (5)	−4585 (14)	9.6
C(141)	521 (9)	5849 (4)	−4019 (8)	2.8	C(241)	−835 (8)	3611 (4)	−5006 (7)	2.1
C(142)	1020 (8)	5454 (3)	−3943 (7)	1.8	C(242)	−1253 (9)	4038 (4)	−5271 (7)	2.4
C(143)	1278 (8)	5316 (4)	−2977 (8)	2.2	C(243)	−2056 (9)	4097 (3)	−4824 (8)	2.4
C(144)	1864 (7)	5655 (4)	−2467 (8)	1.8	C(244)	−2712 (9)	3747 (4)	−5028 (8)	2.4
C(145)	1330 (8)	6070 (4)	−2586 (8)	2.3	C(245)	−2235 (10)	3324 (4)	−4850 (7)	2.8
C(146)	1959 (9)	6432 (4)	−2168 (9)	2.7	C(246)	−2811 (11)	2953 (5)	−5178 (11)	4.7
O(142)	454 (6)	5141 (3)	−4456 (6)	2.7	O(242)	−664 (6)	4372 (3)	−5059 (5)	2.6
O(143)	1765 (6)	4931 (2)	−2925 (5)	2.2	O(243)	−2528 (6)	4473 (3)	−5115 (5)	2.6
O(144)	2086 (5)	5557 (2)	−1559 (5)	1.9	O(244)	−3353 (6)	3798 (3)	−4449 (6)	3.0
O(145)	1066 (6)	6166 (3)	−3509 (6)	2.8	O(245)	−1458 (6)	3296 (3)	−5247 (5)	2.4
O(146)	2734 (7)	6466 (3)	−2463 (7)	4.0	O(246)	−3100 (8)	2956 (4)	−6114 (7)	5.2
C(151)	3005 (7)	5541 (4)	−1162 (8)	2.1	C(251)	−4246 (10)	3782 (5)	−4847 (10)	3.5
C(152)	3185 (9)	5102 (5)	−733 (10)	3.3	C(252)	−4668 (8)	4171 (4)	−4493 (8)	2.1
C(153)	2674 (9)	5068 (4)	4 (8)	2.3	C(253)	−4565 (10)	4137 (4)	−3515 (9)	2.9
C(154)	2920 (8)	5426 (4)	672 (8)	2.5	C(254)	−4960 (8)	3741 (4)	−3246 (7)	2.1
C(155)	2820 (7)	5849 (4)	199 (8)	2.5	C(255)	−4556 (9)	3370 (4)	−3618 (7)	2.6
C(156)	3169 (8)	6198 (4)	805 (8)	2.1	C(256)	−4973 (13)	2995 (5)	−3461 (10)	5.1
O(152)	2977 (5)	4799 (2)	−1379 (5)	1.9	O(252)	−4324 (6)	4529 (3)	−4776 (6)	3.0
O(153)	2942 (7)	4698 (3)	476 (6)	3.2	O(253)	−5007 (6)	4499 (3)	−3205 (6)	3.1
O(154)	2344 (5)	5389 (3)	1277 (5)	2.2	O(254)	−4755 (5)	3719 (3)	−2277 (5)	2.0
O(155)	3238 (5)	5859 (2)	−553 (5)	2.0	O(255)	−4657 (7)	3410 (3)	−4582 (6)	3.7
O(156)	4085 (5)	6127 (3)	1201 (6)	2.4	O(256)	−5881 (12)	2967 (5)	−3782 (8)	8.4
C(161)	2700 (8)	5402 (5)	2216 (8)	2.6	C(261)	−5473 (8)	3670 (5)	−1827 (9)	3.1
C(162)	2400 (9)	5021 (4)	2629 (10)	3.2	C(262)	−5435 (8)	4017 (4)	−1166 (8)	2.5
C(163)	1394 (9)	5008 (4)	2538 (7)	2.5	C(263)	−4560 (9)	3991 (4)	−451 (10)	3.1
C(164)	1122 (8)	5403 (5)	2919 (8)	3.0	C(264)	−4523 (7)	3549 (3)	−47 (8)	1.4
C(165)	1491 (8)	5793 (4)	2543 (8)	2.5	C(265)	−4663 (8)	3224 (4)	−742 (8)	2.1
C(166)	1376 (10)	6191 (5)	3046 (11)	4.2	C(266)	−4834 (10)	2781 (4)	−341 (8)	2.7
O(162)	2686 (6)	4633 (3)	2199 (6)	3.1	O(262)	−5501 (5)	4416 (3)	−1552 (6)	2.6
O(163)	1106 (6)	4656 (3)	2921 (6)	3.3	O(263)	−4511 (6)	4286 (3)	206 (6)	3.0
O(164)	161 (5)	5446 (2)	2710 (5)	1.9	O(264)	−3690 (5)	3499 (3)	530 (5)	2.1
O(165)	2431 (5)	5755 (3)	2625 (5)	2.4	O(265)	−5485 (5)	3273 (3)	−1421 (5)	2.2
O(166)	1730 (8)	6150 (4)	3972 (7)	5.0	O(266)	−5538 (6)	2793 (3)	113 (6)	2.3
C(171)	−300 (8)	5468 (4)	3426 (7)	2.1	C(271)	−3665 (7)	3379 (4)	1462 (7)	1.6
C(172)	−978 (9)	5121 (4)	3345 (7)	2.2	C(272)	−3183 (8)	3703 (5)	2008 (9)	3.0
C(173)	−1668 (7)	5162 (4)	2486 (7)	1.2	C(273)	−2180 (8)	3721 (4)	1956 (8)	2.2
C(174)	−2101 (8)	5574 (5)	2481 (7)	2.5	C(274)	−1809 (9)	3298 (4)	2177 (8)	2.6
C(175)	−1437 (8)	5928 (4)	2628 (8)	2.3	C(275)	−2325 (8)	2988 (4)	1513 (10)	2.9
C(176)	−1827 (8)	6344 (5)	2768 (8)	2.7	C(276)	−2024 (10)	2529 (5)	1676 (11)	3.9
O(172)	−520 (5)	4728 (3)	3392 (6)	2.5	O(272)	−3602 (6)	4101 (3)	1855 (5)	2.5
O(173)	−2291 (6)	4826 (3)	2428 (6)	2.8	O(273)	−1697 (6)	4010 (3)	2555 (6)	3.2
O(174)	−2682 (5)	5644 (3)	1627 (5)	2.1	O(274)	−896 (5)	3291 (3)	2085 (5)	1.9
O(175)	−737 (5)	5855 (3)	3420 (5)	1.8	O(275)	−3260 (6)	2981 (3)	1575 (7)	3.4
O(176)	−2248 (6)	6352 (3)	3510 (6)	2.9	O(276*S*)	−2471 (8)	2275 (3)	881 (8)	4.9
					O(276*R*)	−2169 (7)	2568 (3)	3098 (6)	36.8

Table I (Continued)

guest MR					guest MS				
atom	x	y	z	U	atom	x	y	z	U
O(101R)	1335 (0)	6638 (0)	748 (0)	0.7	O(101S)	669 (0)	7293 (0)	3 (0)	7.1
O(102R)	857 (0)	6961 (0)	−552 (0)	2.3	O(102S)	1614 (0)	6780 (0)	−101 (0)	5.5
C(101R)	724 (0)	6734 (0)	131 (0)	4.2	C(101S)	909 (0)	6947 (0)	199 (0)	3.1
C(103R)	−407 (0)	6592 (0)	1040 (0)	2.2	C(103S)	110 (0)	6878 (0)	1510 (0)	7.7
C(102R)	−249 (0)	6648 (0)	131 (0)	3.0	C(102S)	493 (0)	6632 (0)	756 (0)	6.0
C(111R)	−485 (0)	6264 (0)	−432 (0)	5.4	C(111S)	−208 (0)	6407 (0)	112 (0)	6.7
C(112R)	42 (0)	5908 (0)	−256 (0)	4.3	C(112S)	−114 (0)	6039 (0)	−161 (0)	6.5
C(113R)	−201 (0)	5568 (0)	−753 (0)	5.4	C(113S)	−730 (0)	5833 (0)	−824 (0)	6.9
C(114R)	−925 (0)	5552 (0)	−1463 (0)	4.6	C(114S)	−1463 (0)	6032 (0)	−1087 (0)	7.0
C(115R)	−1454 (0)	5901 (0)	−1617 (0)	5.3	C(115S)	−1687 (0)	6428 (0)	−843 (0)	7.1
C(116R)	−1250 (0)	6259 (0)	−1126 (0)	1.9	C(116S)	−1033 (0)	6590 (0)	−222 (0)	6.8
O(100R)	349 (0)	5213 (0)	−564 (0)	4.6	O(100S)	−493 (0)	5465 (0)	−1237 (0)	10.7
C(121R)	32 (0)	4901 (0)	−102 (0)	4.3	C(121S)	−235 (0)	5109 (0)	−686 (0)	7.3
C(122R)	481 (0)	4529 (0)	−13 (0)	0.4	C(122S)	323 (0)	4842 (0)	−1063 (0)	6.0
C(123R)	178 (0)	4212 (0)	413 (0)	7.3	C(123S)	586 (0)	4490 (0)	−618 (0)	7.2
C(124R)	−558 (0)	4274 (0)	834 (0)	3.7	C(124S)	495 (0)	4418 (0)	333 (0)	6.5
C(125R)	−991 (0)	4636 (0)	776 (0)	6.2	C(125S)	−106 (0)	4738 (0)	621 (0)	9.6
C(126R)	−715 (0)	4958 (0)	295 (0)	6.9	C(126S)	−437 (0)	5085 (0)	162 (0)	8.0
O(201R)	−3292 (0)	2428 (0)	−1461 (0)	10.9	O(201S)	−2741 (0)	4717 (0)	−3148 (0)	14.8
O(202R)	−3908 (0)	2194 (0)	−2875 (0)	5.5	O(202S)	−1241 (0)	4652 (0)	−2850 (0)	10.3
C(201R)	−3219 (0)	2273 (0)	−2139 (0)	18.4	C(201S)	−2057 (0)	4646 (0)	−2557 (0)	4.3
C(203R)	−2097 (0)	2266 (0)	−3028 (0)	5.6	C(203S)	−2787 (0)	4600 (0)	−1290 (0)	7.9
C(202R)	−2472 (0)	2521 (0)	−2340 (0)	12.1	C(202S)	−1928 (0)	4508 (0)	−1583 (0)	11.1
C(211R)	−1805 (0)	2830 (0)	−1754 (0)	4.5	C(211S)	−1754 (0)	4044 (0)	−1487 (0)	10.7
C(212R)	−1857 (0)	3190 (0)	−2340 (0)	18.8	C(212S)	−1987 (0)	3728 (0)	−2075 (0)	10.6
C(213R)	−1486 (0)	3572 (0)	−2011 (0)	8.5	C(213S)	−1663 (0)	3341 (0)	−1886 (0)	11.5
C(214R)	−658 (0)	3551 (0)	−1374 (0)	5.7	C(214S)	−1156 (0)	3220 (0)	−1092 (0)	11.7
C(215R)	−518 (0)	3197 (0)	−879 (0)	8.8	C(215S)	−983 (0)	3540 (0)	−404 (0)	22.9
C(216R)	−1043 (0)	2822 (0)	−1146 (0)	8.3	C(216S)	−1318 (0)	3926 (0)	−608 (0)	10.5
O(200R)	−1754 (0)	3904 (0)	−2493 (0)	7.7	O(200S)	−1875 (0)	3050 (0)	−2529 (0)	11.0
C(221R)	−1992 (0)	4210 (0)	−2010 (0)	7.1	C(221S)	−2372 (0)	2671 (0)	−2464 (0)	6.6
C(222R)	−2014 (0)	4549 (0)	−2474 (0)	13.8	C(222S)	−2452 (0)	2399 (0)	−3190 (0)	9.7
C(223R)	−2432 (0)	4909 (0)	−2180 (0)	4.4	C(223S)	−2970 (0	2068 (0)	−3108 (0)	10.1
C(224R)	−2704 (0)	4897 (0)	−1368 (0)	5.2	C(224S)	−3440 (0)	1979 (0)	−2404 (0)	8.2
C(225R)	−2662 (0)	4545 (0)	−789 (0)	5.3	C(225S)	−3281 (0)	2242 (0)	−1655 (0)	5.8
C(226R)	−2348 (0)	4238 (0)	−1228 (0)	7.3	C(226S)	−2777 (0)	2643 (0)	−1783 (0)	8.3
water					water				
atom	x	y	z	U	atom	x	y	z	U
O(001W)	2707 (50)	7227 (31)	−121 (47)	15.3	O(016W)	−3920 (6)	4500 (3)	3346 (5)	3.9
O(002W)	−4424 (16)	7038 (8)	−5087 (14)	15.4	O(017W)	3098 (10)	4291 (5)	−3857 (10)	7.6
O(003W)	−6061 (5)	6928 (3)	−1291 (6)	3.9	O(018W)	3144 (11)	3948 (6)	3821 (10)	8.5
O(004W)	2551 (14)	7017 (9)	−3885 (13)	12.1	O(019W)	1477 (27)	3923 (18)	4734 (28)	6.7
O(005W)	4061 (34)	6743 (10)	−4621 (29)	22.6	O(020W)	4545 (7)	3769 (4)	2363 (9)	6.8
O(006W)	846 (12)	6792 (5)	−5282 (9)	9.3	O(021WA)	−6266 (15)	3155 (6)	−5843 (13)	6.4
O(007W)	−3992 (7)	6599 (4)	3487 (8)	6.5	O(021WB)	−5801 (13)	2761 (8)	−5686 (14)	4.4
O(008W)	3571 (7)	6053 (4)	4345 (6)	5.3	O(022W)	−4864 (6)	3044 (3)	−6849 (6)	4.9
O(009W)	4661 (6)	6016 (3)	3020 (5)	4.6	O(023W)	−7429 (18)	2605 (8)	−5795 (10)	15.3
O(010W)	−4145 (7)	5367 (3)	−6467 (6)	5.2	O(024W)	3284 (7)	2415 (3)	−2845 (7)	5.1
O(011W)	−5953 (7)	5242 (4)	−5055 (7)	6.2	O(025W)	−5242 (5)	2454 (3)	1765 (5)	2.9
O(012W)	−6661 (9)	5170 (5)	−3521 (8)	7.9	O(026W)	−624 (11)	2348 (6)	−6054 (14)	5.5
O(013W)	1631 (8)	4737 (5)	−5169 (7)	6.0	O(027W)	1900 (7)	2360 (4)	−4346 (7)	5.0
O(014WA)	−5439 (16)	4664 (10)	1911 (14)	6.5	O(028W)	−5270 (28)	2014 (11)	−2073 (19)	4.1
O(014WB)	−5401 (18)	4602 (11)	1530 (23)	9.8	O(029W)	2874 (29)	3526 (10)	−4932 (21)	13.6
O(015W)	−5723 (7)	4651 (4)	−6326 (7)	7.1	O(030W)	−2153 (19)	2537 (9)	−6950 (21)	9.7

superpositions in Figure 7. The dihedral angles also show these differences (Table V). The *R* enantiomers are in a head-to-head arrangement with both propionic acid groups pointing to the primary hydroxyl face of the β-CD. *The occupancy ratio is 1:3 for the MR-FP guests with respect to the MS-FP guests* (Table IV). Thus, the binding affinities of MR- and MS-FPs for β-CD are different, and these crystal structures (together with those for the individual enantiomeric complexes) provide information on the requirements necessary for chiral resolution by β-CD.

Chiral Recognition by β-CD. β-CD is composed of D-glucose and, thus, is an optically active compound that might be expected to show stereoselectivity when inclusion complexes with enantiomeric isomers are formed.[19] CD, especially β-CD, has been applied as a powerful optical resolution phase, and a number of racemic materials[20–22] have been resolved by complexation with β-CD where β-CD is applied in TLC, HPLC, and other chromatographic techniques. Armstrong[9,23,24] recently summarized the requirements for chiral recognition and stereoselective binding by β-CD. These requirements are as follows:

(a) An inclusion complex must be formed.

(b) There must be a "tight fit" of the included moiety within β-CD. For chiral interaction, a compound needs at least one aromatic ring, and biphenyl or naphthalene are better in size for enantioselectivity.

(c) The chiral center of the guest or a substituent of the chiral center (e.g., a carboxylic acid group) must be able to form at least one strong interaction with the hydroxyl groups at the CD cavity entrance.

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Table II. Hydrogen Bonds Involving the CD and FP Oxygen Atoms of the (*RS*)-FP-β-CD Complex[a]

CD1				CD2			
angle	sym code[b]	dist, Å	angle, deg	angle	sym code[b]	dist, Å	angle, deg
C(112)-O(112)···O(173)		2.71	123	C(212)-O(212)···O(273)		2.78	116
C(112)-O(112)···O(014WA)		2.76	106	C(212)-O(212)···O(019W)		2.77	89
C(112)-O(112)···O(014WB)		2.61	107	C(213)-O(213)···O(163)		2.80	118
C(113)-O(113)···O(122)		2.84	116	C(213)-O(213)···O(222)		2.76	115
C(113)-O(113)···O(263)		2.80	121	C(213)-O(213)···O(018W)		2.93	131
C(116)-O(116)···O(003W)		2.71	109	C(211)-O(215)···O(026W)	4	2.90	91
C(116)-O(116)···O(156)	8	2.79	127	C(216)-O(216)···O(126)	12	2.68	117
C(116)-O(116)···O(028W)	14	2.97	102	C(222)-O(222)···O(213)		2.76	119
C(122)-O(122)···O(113)		2.84	118	C(222)-O(222)···O(020W)		2.75	111
C(122)-O(122)···O(012W)		2.68	96	C(223)-O(223)···O(153)		2.76	122
C(123)-O(123)···O(132)		2.72	115	C(223)-O(223)···O(232)		2.88	115
C(123)-O(123)···O(253)		2.93	118	C(226)-O(226)···O(266)	2	2.76	124
C(123)-O(123)···O(011W)		2.88	131	C(226)-O(226)···O(024W)		2.74	115
C(126)-O(126)···O(216)	10	2.68	100	C(232)-O(232)···O(223)		2.88	119
C(126)-O(126)···O(025W)	14	2.72	108	C(232)-O(232)···O(017W)		2.75	91
C(132)-O(132)···O(123)		2.72	120	C(233)-O(233)···O(143)		2.81	119
C(132)-O(132)···O(010W)		2.67	100	C(233)-O(233)···O(242)		2.85	117
C(133)-O(133)···O(142)		2.84	114	C(233)-O(233)···O(019W)	6	2.82	100
C(133)-O(133)···O(243)		2.80	123	C(236)-O(236)···O(026W)		2.68	123
C(133)-O(133)···O(202S)		3.01	98	C(236)-O(236)···O(027W)		2.58	114
C(136)-O(136)···O(176)	6	2.92	126	C(242)-O(242)···O(233)		2.85	116
C(136)-O(136)···O(006W)		2.79	109	C(242)-O(242)···O(172)	6	2.68	106
C(136)-O(136)···O(027W)	11	2.69	106	C(243)-O(243)···O(133)		2.80	109
C(142)-O(142)···O(133)		2.84	120	C(243)-O(243)···O(252)		2.89	116
C(142)-O(142)···O(013W)		2.62	101	C(243)-O(243)···O(016W)	6	2.85	122
C(143)-O(143)···O(152)		2.74	116	C(243)-O(243)···O(201S)		3.19	93
C(143)-O(143)···O(233)		2.81	119	C(246)-O(246)···O(276R)	6	2.65	108
C(143)-O(143)···O(012W)	2	2.84	102	C(246)-O(246)···O(022W)		2.73	121
C(146)-O(146)···O(004W)		2.78	111	C(246)-O(246)···O(030W)		2.51	115
C(146)-O(146)···O(003W)	2	2.75	110	C(252)-O(252)···O(243)		2.89	115
C(152)-O(152)···O(143)		2.74	122	C(252)-O(252)···O(015W)		2.90	94
C(152)-O(152)···O(262)	2	2.69	108	C(253)-O(253)···O(123)		2.93	118
C(153)-O(153)···O(162)		2.75	118	C(253)-O(253)···O(262)		2.79	116
C(153)-O(153)···O(223)		2.76	115	C(253)-O(253)···O(017W)	8	2.95	101
C(153)-O(153)···O(014WA)	2	2.97	122	C(256)-O(256)···O(021WA)		3.16	109
C(153)-O(153)···O(14WB)	2	2.74	123	C(256)-O(256)···O(021WB)		3.02	98
C(156)-O(156)···O(116)	2	2.79	103	C(256)-O(256)···O(024W)	8	2.75	113
C(156)-O(156)···O(009W)		2.78	123	C(262)-O(262)···O(253)		2.79	117
C(162)-O(162)···O(153)		2.75	117	C(262)-O(262)···O(152)	8	2.69	112
C(162)-O(162)···O(014WA)	2	2.98	114	C(263)-O(263)···O(113)		2.80	115
C(162)-O(162)···O(014WB)	2	3.28	121	C(263)-O(263)···O(272)		2.70	119
C(163)-O(163)···O(172)		2.73	115	C(266)-O(266)···O(226)	8	2.76	103
C(163)-O(163)···O(213)		2.80	119	C(266)-O(266)···O(025W)		2.71	118
C(163)-O(163)···O(013W)	4	2.89	108	C(272)-O(272)···O(263)		2.70	119
C(166)-O(166)···O(008W)		2.78	113	C(272)-O(272)···O(016W)		2.74	115
C(166)-O(166)···O(006W)	4	2.83	102	C(273)-O(273)···O(173)		2.78	117
C(172)-O(172)···O(163)		2.73	121	C(273)-O(273)···O(212)		2.78	120
C(172)-O(172)···O(242)	4	2.68	107	C(276)-O(276S)···O(102S)	12	2.51	122
C(173)-O(173)···O(112)		2.71	114	C(276)-O(276S)···O(003W)	16	2.69	108
C(173)-O(173)···O(273)		2.78	120	C(276)-O(276R)···O(246)	4	2.65	132
C(176)-O(176)···O(136)	4	2.92	105	C(276)-O(276R)···O(026W)	4	3.03	98
C(176)-O(176)···O(007W)		2.77	126	C(276)-O(276R)···O(004W)	12	2.31	124

MS				MR			
angle	sym code[b]	dist, Å	angle, deg	angle	sym code[b]	dist, Å	angle, deg
C(101S)-O(102S)···O(276S)	10	2.51	115	C(101R)-O(102R)···O(001W)		2.90	106
C(201S)-O(202S)···O(133)		3.01	110	C(201R)-O(202R)···O(028W)		2.68	101
C(201S)-O(201S)···O(243)		3.19	114				

[a] Standard deviation range: for distances, 0.01-0.03 Å; for torsion angles, 0.2-1.2°. [b] 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, $-x-1, y-{}^1/_2, -z-1$.

(d) The unidirectional 2- or 3-hydroxyl groups at the secondary hydroxyl face of the β-CD are particularly important for chiral recognition.

In the context of the crystal structures of the complexes of (*R*)-, (*S*)-, MR-, and MS-FPs with β-CD, it is apparent that (*S*)-FP can fulfill all these requirements: (*R*)-FP fulfills all except conditions c and d. The (*S*)-FP guest can form important hydrogen bonds to β-CD at the primary and secondary hydroxyl ends in a manner that (*R*)-FP cannot (Figure 8). This results from the steric considerations imposed on the fenoprofen enantiomers on complexation with the β-CD.

For ease of discussion, the phenyl ring containing the propionic acid group will be called ring 1 and the other phenyl ring, ring 2. Uncomplexed FP molecules have possible freedom of rotation about the O(0G)-C(13G) and O(0G)-C(21G) bonds for the phenyl rings and about the C(11G)-C(2G) and C(2G)-C(3G) 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 2-fold rotation of the phenyl rings, which has no effect as far as ring 2 is concerned

Table III.

bond	dist	bond	dist
(a) Intermolecular Hydrogen Bonding across the CD Secondary Hydroxyl Interface (Å)			
O(113)–O(263)	2.80 (1)	O(152)–O(262)(65501)	2.69 (1)
O(123)–O(253)	2.93 (1)		
O(133)–O(243)	2.80 (1)	O(172)–O(242)(55601)	2.68 (1)
O(143)–O(233)	2.81 (1)		
O(153)–O(223)	2.76 (1)		
O(163)–O(213)	2.80 (1)		
O(173)–O(273)	2.78 (1)		
mean	2.81 (1)	mean	2.69 (1)
σ	0.05	σ	0.01

bond	CD1	CD2
(b) Intramolecular O(2)–O(3) Hydrogen Bonding within Each β-CD Unit (Å)		
O(13)–O(22)	2.84 (2)	2.76 (2)
O(23)–O(32)	2.72 (2)	2.88 (1)
O(33)–O(42)	2.84 (1)	2.85 (2)
O(43)–O(52)	2.74 (2)	2.89 (1)
O(53)–O(62)	2.75 (1)	2.79 (2)
O(63)–O(72)	2.73 (1)	2.70 (2)
O(73)–O(12)	2.71 (2)	2.78 (2)
mean	2.76 (2)	2.81 (2)
σ	0.05	0.07

Table IV. Occupancy of Guest Molecules in the Racemic FP Complex

FP atoms	MR1	MR2	MS1	MS2
O(01)	0.29	0.15	0.68	0.68
O(02)	0.32	0.23	0.68	0.70
C(01)	0.24	0.22	0.72	0.72
C(02)	0.22	0.27	0.76	0.76
C(03)	0.29	0.24	0.72	0.72
C(11)	0.23	0.28	0.66	0.67
C(12)	0.28	0.18	0.72	0.66
C(13)	0.26	0.24	0.71	0.70
C(14)	0.26	0.25	0.77	0.81
C(15)	0.24	0.26	0.68	0.62
C(16)	0.25	0.19	0.70	0.68
O(00)	0.26	0.21	0.74	0.75
C(21)	0.25	0.26	0.81	0.69
C(22)	0.23	0.22	0.73	0.86
C(23)	0.19	0.26	0.81	0.86
C(24)	0.24	0.26	0.71	0.80
C(25)	0.22	0.29	0.76	0.68
C(26)	0.29	0.20	0.81	0.73
mean	0.25	0.23	0.73	0.73
σ	0.03	0.04	0.05	0.07

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(2G) 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 inherent steric

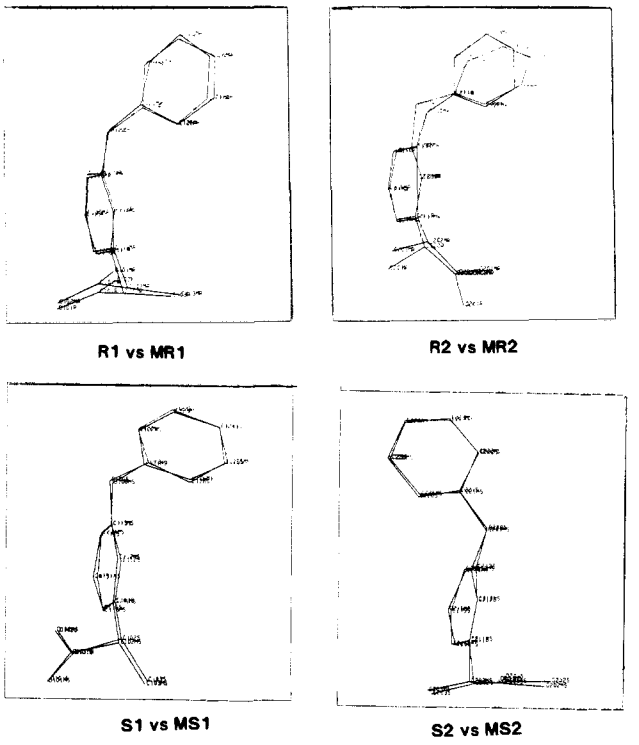

Figure 7. Molecular fitting of the fenoprofen molecules from the racemic and individual enantiomeric complexes.

restrictions in mind, the conformations observed for the four independent FP molecules, MS1, MS2, MR1, and MR2 in the crystalline β-CD complex can be discussed.

MR1 and MS1 show the expected stable conformation with the methyl and carboxylic groups staggered with respect to the plane of ring 1 and with the hydrogen atom lying in the plane. They also occupy essentially the same position inside the β-CD and are both oriented, as might be expected, with their propionic acid groups at the primary hydroxyl end of the β-CD and phenyl rings 2 in the relatively hydrophobic dimer interface. If the methyl and carboxylic acid groups are interchanged on MS1, which is equivalent to converting MS1 to the *R* enantiomer, the direction in which the carboxylic acid group points is altered considerably. It now points down in a direction roughly parallel to the 7-fold axis of the β-CD instead of roughly perpendicular to it. *It is impossible to achieve coincidence of the carboxylic acid groups by any sterically allowed rotations.* This, together with the restrictions imposed by the tight fit of the phenoxyphenyl moiety in the β-CD cavity, results in the *R* enantiomer being unable to hydrogen bond to the primary hydroxyl atoms of the β-CD as is the case for MS1. Instead, the carboxylic acid group of the *R* enantiomer hydrogen bonds to water, and in the process, slight changes occur both in the orientation of the phenyl rings and in the direction in which the hydrogen atom of the propionic acid group points, resulting in the conformation observed for MR1.

Formation of a hydrogen bond from the carboxylic acid group of MS1 to a primary hydroxyl group on a neighboring β-CD molecule pulls MS1 further down into the primary end of the encapsulating CD than MR1 (0.63 Å). This results in ring 2 of MS1 being further away from the secondary hydroxyl face of the

Table V. Dihedral Angles (deg) around the Phenoxy Oxygen and the Chiral Carbon in the FP Molecules

torsion group	S1	MS1	S2	MS2	R1	MR1	R2	MR2
C(12)–C(13)–O(00)–C(21)	61	61	−118	−119	104	104	62	131
C(14)–C(13)–O(00)–C(21)	−128	−127	60	60	−79	−80	−119	−71
C(22)–C(21)–O(00)–C(13)	−155	−155	−175	−175	171	171	−145	163
C(26)–C(21)–O(00)–C(13)	17	17	12	12	−11	−11	47	−29
C(01)–C(02)–C(11)–C(12)	104	104	−26	−26	52	52	−120	−130
C(01)–C(02)–C(11)–C(16)	−77	−77	158	159	−129	−130	73	83
C(03)–C(02)–C(11)–C(12)	−137	−137	90	91	−70	−70	115	83
C(03)–C(02)–C(11)–C(16)	42	42	−85	−85	109	109	−51	−63

Table VI. Interplanar Angles (deg) between the Planes of the Two Phenyl Rings in the FP Molecules

S1	MS1	S2	MS2	R1	MR1	R2	MR2
69.7	69.7	65.2	64.9	83.0	83.0	84.6	76.9

CD than MR1 (0.37 Å). The center of mass of ring 1 is moved laterally 0.7 Å with respect to that of MR1 and in the case of ring 2 by 0.9 Å. 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 MR1 and MR2 but not for MS1 and MS2.

The MS dimer, however, finds an energetically more favorable situation by inversion of MS2 in the CD cavity, resulting in stabilization due to hydrogen bonding between the carboxylic acid group of MS2 and the secondary hydroxyl groups of the CD at the dimer interface. If MR2 were inverted in the same manner, steric restrictions such as those for MR1 would result in the carboxylic acid group pointing down the CD cavity rather than toward the side. This would prohibit hydrogen bonding to a secondary hydroxyl group of CD. In addition, the propionic acid group of MS2 orients so that the methyl group faces ring 2 of MS1 in a methyl/phenyl close-packing arrangement.

The carboxylic acid group of MR2, being unable to hydrogen bond to the primary hydroxyl groups of β-CD for the same reasons stated for MR1, again uses water to satisfy its hydration requirements. *These water molecules involved in hydrogen bonding to the carboxylic acid groups of MR1 and MR2 are found to have the same occupancy as the MR molecules (Table VII). In the individual (R)- and (S)-FP complexes, they are present in the R complex and absent in the S complex.*[16]

The bulky phenoxyphenyl moieties of the guests provide a tight fit inside the CD cavity and can only supply small movements to facilitate the hydrogen bonding of the propionic acid groups. It is, however, significant that the dihedral angles between the planes of the phenyl rings are different and distinct for the *R* and *S* enantiomers (Table VI). The extra flexibility of the phenoxyphenyl group versus a biphenyl group is probably a significant factor in the ability of the *S* enantiomer to make the important hydrogen bond to the secondary hydroxyl groups of the β-CD (requirement d above). Recent X-ray crystallographic studies[17,18] on a complex of (±)-flurbiprofen–β-CD showed a head-to-head arrangement in which the *R* enantiomer is enclosed in half of the β-CD dimer and the *S* in the other, with full occupancy of both isomers (i.e., no chiral separation). The flurbiprofen has a substituted biphenyl ring system rather than the phenoxyphenyl ring system of fenoprofen. The biphenyl moiety packs with its long axis parallel to the 7-fold axis of the CD. The tight fit in the cavity prohibits much lateral movement of the biphenyl moiety and results in the propionic acid substituent being too far from the secondary hydroxyl groups of the CD to form a hydrogen bond. Both (*R*)- and (*S*)-flurbiprofen form hydrogen bonds with the more flexible primary hydroxyl groups of β-CD, and therefore, the most important condition for chiral resolution is the formation

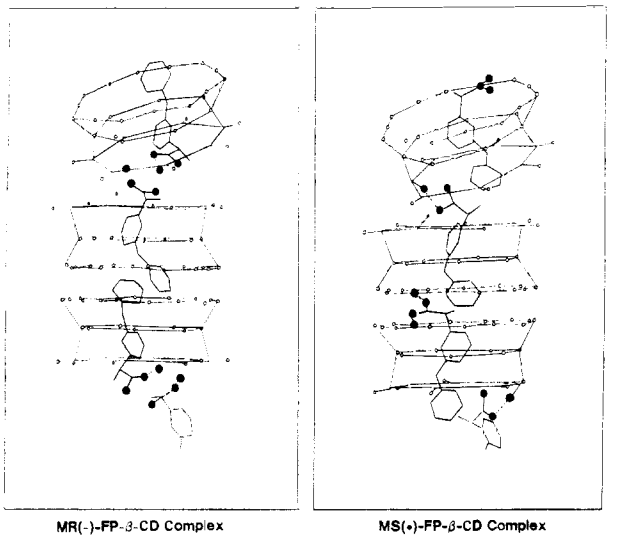

Figure 8. Hydrogen-bonding scheme for guest carboxylic acid groups.

of the hydrogen bond to the unidirectional secondary hydroxyl groups of β-CD, as Armstrong stated in condition d above. (*R*)- and (*S*)-flurbiprofen have a head-to-head packing arrangement similar to MR- and (*R*)-FP.

This is the first crystal structure of a CD complex that shows an enantioselective interaction due to β-CD complexation, and our results support Armstrong's criteria for this. The inclusion complex is formed (condition a above), the fit of the phenoxyphenyl moiety inside the cavity is tight (condition b above), a hydrogen bond is formed to a primary hydroxyl group of the CD (condition c above), and most important, a hydrogen bond is formed to the unidirectional secondary hydroxyl groups of the CD (condition d above).

In order to confirm the results of the crystal structure, we measured the change of the specific rotation of the racemic FP before and after complexing with β-CD. The results obviously indicate chiral separation (Table VIII). After removal of β-CD from the precipitate a positive optical rotation was obtained, indicative of excess (*S*)-FP isomer, while the supernatant showed a negative rotation, indicative of excess (*R*)-FP isomer.

Active-Site Models for Cyclooxygenase. It has been shown that for all 2-arylpropionic acids so far studied, only the *S* isomer is an active inhibitor of cyclooxygenase activity; this is the first enzymatic activity of prostaglandin synthase, which produces prostaglandins from arachidonic acid.[12,13] This enzyme is stereoselective for the *S* conformation of 2-arylpropionic acid.

The restricted conformations for the 2-arylpropionic acid group in a tight hydrophobic pocket observed in the above crystal structures may be related to the active-site model for the cyclooxygenase/2-arylpropionic acid interaction. Several such models have been proposed.[25-27] Sallman[25] suggested that the enzyme

Table VII. Occupancy of Water Molecules in the FP–β-CD Complexes

water	M	*R*	*S*	water	M	*R*	*S*
O(01W)	0.23	1.00		O(16W)	1.00	1.00	1.00
O(02W)	1.00	1.00	1.00	O(17W)	0.82	1.00	1.00
O(03W)	1.00	1.00	1.00	O(18W)	1.00	1.00	1.00
O(04W)	0.78	1.00	1.00	O(19W)	0.23	0.45	
O(05W)	0.91	0.73	1.00	O(20W)	1.00	1.00	1.00
O(06W)	1.00	0.74	1.00	O(21WA)	0.61	1.00	1.00
O(07W)	1.00	1.00	1.00	O(21WB)	0.42		
O(08W)	1.00	1.00	0.93	O(22W)	1.00	0.86	1.00
O(09W)	1.00	1.00	1.00	O(23W)	1.00	0.94	1.00
O(10W)	1.00	1.00	1.00	O(24W)	1.00	1.00	1.00
O(11W)	1.00	0.93	0.87	O(25W)	1.00	1.00	1.00
O(12W)	1.00	0.92	1.00	O(26W)	0.58	0.69	0.51
O(13W)	0.91	1.00	1.00	O(27W)	0.89	0.93	1.00
O(14WA)	0.55	1.00	0.88	O(28W)	0.33	0.78	
O(14WB)	0.64			O(29W)	0.57		
O(15W)	1.00	0.87	1.00	O(30W)	0.49		

Table VIII. Resolution of Racemic FP (MFP) by β-CD Complexation

sample	$[\alpha]_{365}$	c, g/mL	solvent	optical purity,[a] %
CD-MFP solution	-3.03	1.32	methanol	2.35
CD-MFP precipitate	+3.01	1.99	methanol	2.33

[a] $[\alpha]_{365}$ +129.22 for (+)-(S)-FP (from Eli Lilly Laboratories).

has a cationic site that is responsible for the binding of the carboxylic acid group of arachidonic acid, and there is a hydrophobic surface and a hydrophobic pocket. The dimensions of the model active site of this enzyme are similar to those of β-cyclodextrin (Figure 1). Thus, it might be proposed that the steric restrictions imposed by fitting FP into a hydrophobic pocket in the enzyme may be similar to those experienced by the FP when fitting into the hydrophobic cavity of the β-CD. This could result in restricting the (R)-FP so that its carboxylic acid group points in the wrong direction for hydrogen bonding at the enzyme active site. Sallman also proposed that, for a biphenyl system to bind to the enzyme, the angle between the two aromatic rings should be ~70°, and this corresponds to the interplanar angles of (S)-FP in the CD complex (Table VI).

Another cyclooxygenase active-site model proposed by Sankawa et al.[27] suggests that the carboxylic acid group of NSAIDS should bind and interact with the oxygenation site on the cyclooxygenase. This model requires an S configuration. Our results indicate that when the methyl group is positioned properly for hydrophobic interaction in the case of the R isomer of FP, the carboxylic acid group is then placed in an unfavorable position for hydrogen-bonding interaction. But for the S isomer, it would sit in a favorable hydrogen-bonding position on the enzyme.

Conclusions

In the crystal of the racemic FP-β-CD complex, the (R)- and (S)-FP guest molecules adopt different packing arrangements inside the β-CD dimer: R is head-to-head and S is head-to-tail, as had been found in the individual enantiomeric complexes. The differences of the packing between (R)- and (S)-FPs are due to effects such as the interior hydrophobicity of the β-CD cavity, the steric restrictions imposed by the tight fit of the guest inside the β-CD cavity, steric restrictions on the propionic acid substituent resulting in different orientations of the carboxylic acid group, and different ways of hydrating the carboxylic acid group.

In addition, the binding affinity of (S)-FP to β-CD is approximately 3 times stronger than (R)-FP due to the strong hydrogen bonds between the acid groups of (S)-FP and the β-CD secondary hydroxyl groups, which cannot be formed with (R)-FP. In the interface between the complex dimers, the methyl/phenyl interaction is more favorable for the (S)-FP complex than is the propionic acid/propionic acid interaction for the (R)-FP complex.

These effects result in β-CD preferentially selecting the S isomer of FP in the crystal form, which is confirmed by the change in specific rotation of the racemic FP-β-CD complex after complexation. This is the first crystal structure that supports the conditions for chiral recognition and resolution proposed by Armstrong. It also suggests models for the specificity of the enzyme cyclooxygenase for the S conformation of 2-arylpropionic acids.

Acknowledgment. This work was supported by a National Institutes of Health Grant GM-24523. We are indebted Dr. Koert Gerzon, Department of Pharmacology, Indiana University School of Medicine, for his help in crystallizing the CD-FP complexes. We also thank Dr. Thakkar of Eli Lilly & Co. for providing the fenoprofens. We acknowledge Drs. Kirsten Folting and William Streib for their help in data collection.

Registry No. β-CD·FP, 115245-44-8.

Supplementary Material Available: Tables of anisotropic thermal parameters, hydrogen positional parameters, individual bond lengths, and angles for CD molecules and hydrogen bonds involving water molecules (13 pages); observed and calculated structure factors (68 pages). Ordering information is given on any current masthead page.

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Group Transfer Polymerization with Polyunsaturated Esters and Silyl Polyenolates

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Contribution No. 4352 from the Central Research and Development Department, E. I. Du Pont De Nemours and Co., Experimental Station, Wilmington, Delaware 19898.
Received June 18, 1987

Abstract: The polyunsaturated monomers, methyl pentadienoate (**1**), methyl and ethyl 2-methylpentadienoate (**2** and **3**), ethyl sorbate (**4**), ethyl muconate (**5**), and 3-(2,4-hexadien-1-ylidene)-4,5-dihydrofurone (**6**) undergo group transfer polymerization (GTP). The reaction can be initiated by silyl ketene acetals or the silyl polyenolates **10**-**15** as well as the allylic silane **16** in the presence of a variety of nucleophilic anion catalysts. When silyl ketene acetals are used to initiate GTP of **1**-**3**, **5**, and **6**, control of $\bar{M}_n$ is difficult, and polymers with $\bar{M}_n$ much higher than theory are obtained. $\bar{M}_n$ closer to theory and low polydispersity are achieved by initiation with silyl polyenolates. Regiospecific 1,4-polymerization occurs with the diene monomers, and 1,6-polymerization occurs with the triene lactone **6**. GTP of ethyl sorbate and ethyl muconate proceeds with 2:1 erythro and 2:1 meso selectivity and 3:1 trans-cis geometry of the backbone double bond. The triene lactone **6** appears to show no diastereoselectivity but high trans selectivity with respect to double-bond geometry. The unsubstituted silyl dienolates **10** and **12** and the silyl trienolate **14** show regiospecific initiation of GTP of MMA at the 2-position. The 2-methyl diene homologues **11** and **13** show regioselective initiation of GTP of MMA at the 2-position, with about 28% initiation at the 4-position.

The rapid growth of interest in regio- and stereoselective synthesis of acyclic molecules during the past decade has led to a remarkable focus upon the use of organosilicon compounds, particularly silyl enolates, in carbon-carbon bond-forming reactions. A notable result of the extension of the study of the carbon-carbon bond-forming reactions of silyl ketene acetals with

0002-7863/88/1510-5841$01.50/0