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SOLVENT INTERACTIONS WITH β-CYCLODEXTRIN AS OBSERVED IN CRYSTAL STRUCTURES

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Nimesulide, an anti-inflammatory drug, was complexed with β cyclodextrin (βCD) in the presence of lysine in 10:10:1 molar ratio to increase its water solubility. The complexation did not take place in the crystal structure, but it exhibits two different crystal forms. The crystal structures show a difference in hydration pattern and conservation of the organic molecule 2,4 methyl pentane diol (MPD) binding site. Molecular mechanics studies carried out suggest a probable mode of binding of nimesulide with βCD.

Keywords: β cyclodextrin; solvent interactions with βCD; βCD monomer packing; nimesulide βCD complex; hydration pattern; molecular mechanics; host–guest interaction

INTRODUCTION

β Cyclodextrin (βCD) is composed of seven α-1,4 linked glucopyranose residues. βCD has a large hydrophobic cavity that can accommodate a drug molecule and that acts as a drug delivery system. The periphery of the βCD is hydrophilic in nature. The overall structure of βCD is like a truncated cone where the primary hydroxyl groups (CH_2-OH) occupy the narrow rim and the secondary hydroxyls (OH) occupy the wider rim (Scheme I).

Nimesulide (4′-nitro-2′-phenoxymethane sulfonanilide) is an acidic non-steroidal anti-inflammatory (NSAID) agent that exhibits very poor water solubility. Solution state studies clearly indicate an increase in solubility of nimesulide in the presence of lysine-treated βCD [1], hence we

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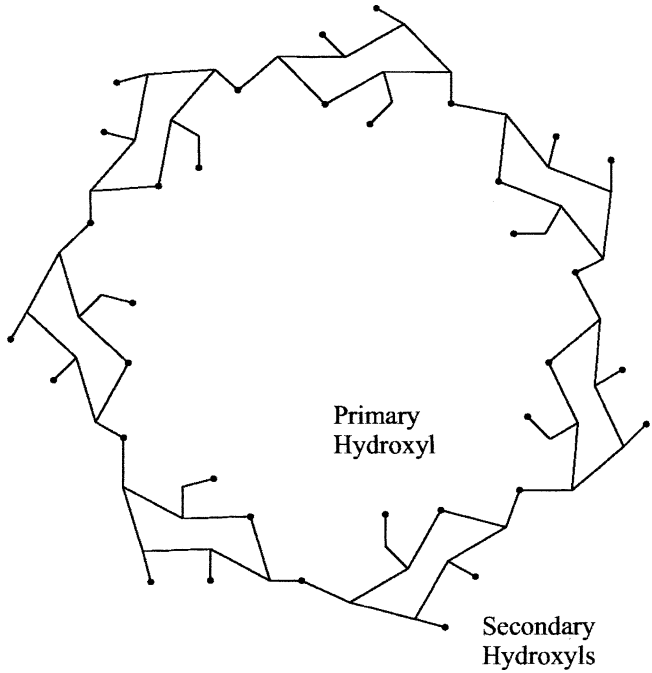


SCHEME 1 β cyclodextrin molecule showing primary and secondary hydroxyl. Oxygens are shown dots.

attempted crystallization of lysine-treated βCD with nimesulide for structure determination using slow evaporation technique.

EXPERIMENTAL PROCEDURE

Complexation was done using 10:10:1 molar ratio of lysine, nimesulide, and βCD in water, methanol mixture. Parallelopiped crystals were obtained from water within a week (Figure 1, Form **I**).

Dissolving lysine and nimesulide in hot methanol and mixing it with aqueous βCD in 10:10:1 ratio also carried out the complexation. The precipitate from the above reaction was then dissolved in 2,4 methyl pentane diol (MPD), yielding biprism-shaped crystals in four weeks (Figure 2, Form **II**). The data was collected using Enraf-Nonius CAD4 diffractometer [2], and the structures have been solved and refined using SHELXS97 and SHELXL97, respectively [3]. Form **I** could be solved after a few trials, but Form **II**'s structure was solved using Karle recycling option in SHELXS.

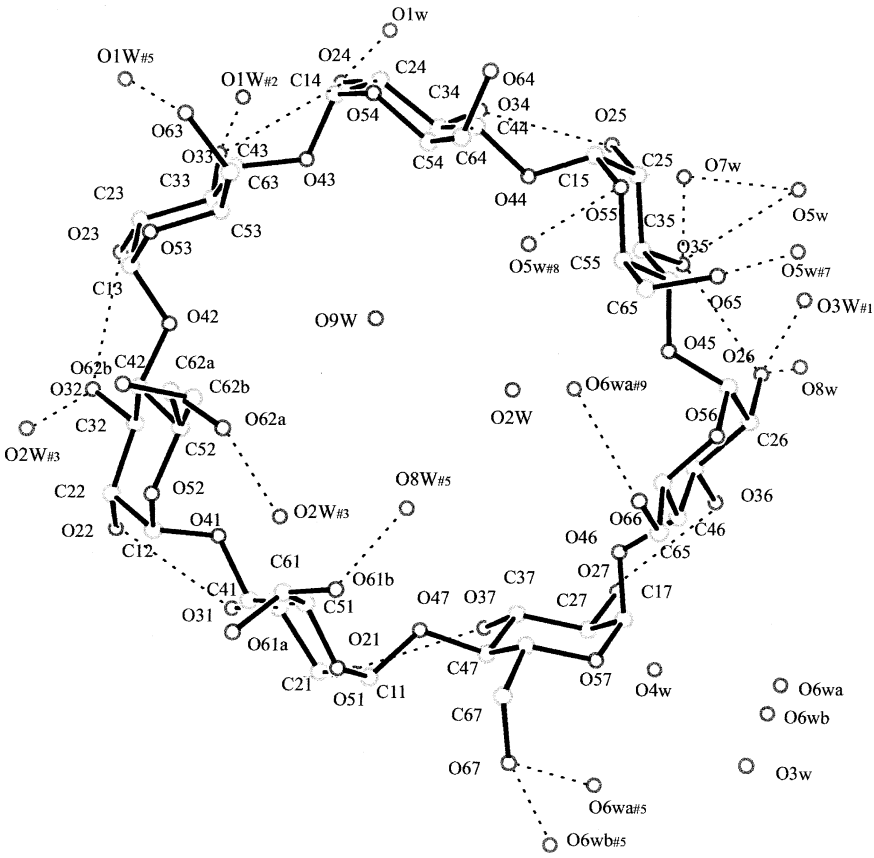


FIGURE 1 Perspective view of the βCD molecule (Form **I**) with atomic numbering scheme. Solvent interactions are shown. # indicates symmetry-related molecules (See Table IV).

Crystal data and refinement statistics are given in Table I. The coordinates have been submitted to Cambridge structural database; accession numbers are CCDC* 217343 and CCDC 21742, respectively, for Forms **I** and **II**.

*CCDC, Cambridge Crystallographic Data Center. CCDC 217343 contains the supplementary crystallographic data for the structure. These data can be obtained free of charge through www.ccdc.cam.ac.uk/consts/retrieving.html from the CCDC, 12 Union Road, Cambridge CB2 IEZ, UK.

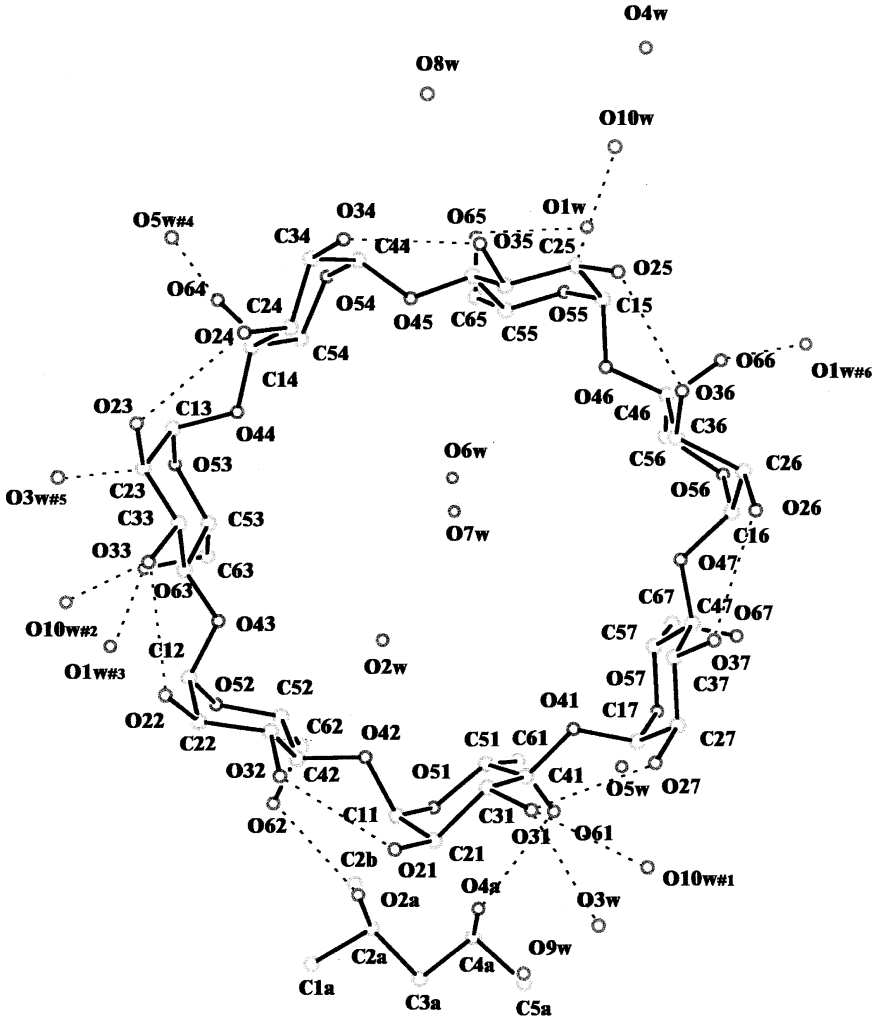


FIGURE 2 Perspective view of the βCD molecule (Form **II**) with atomic numbering scheme. Solvent interactions are shown. # indicates symmetry-related molecules (See Table V).

RESULTS AND DISCUSSION

All the pyranose rings adopt a chair conformation ($^4C_1$) in both structures. Though it has been reported that nimesulide binds to βCD in solution state [1], nimesulide–βCD complex was not formed in our case.

TABLE I Crystal Data and Structure Refinement for Forms **I** and **II**

Identification code	Form **I**	Form **II**
Empirical formula	$C_{42}H_{70}O_{35} \cdot 9H_2O$	$C_{42}H_{70}O_{35} \cdot 9H_2O$, $C_6O_2H_{14}$
Formula weight	1276.96	1367.04
Temperature	293(2) K	293(2) K
Wavelength	1.5418 Å	1.5418 Å
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1$	$C222_1$
Unit cell dimensionless	a=15.107(7) Å b=10.242(3) Å, β=110.27(3)° c=20.911(8) Å	a=19.67(1) Å b=24.05(2) Å c=32.62(4) Å
Volume	3035(2) Å^3	15428(23) Å^3
Z	2	8
Density (calculated)	1.397 Mg/m^3	1.177 Mg/m^3
Absorption coefficient	1.133 mm^{-1}	0.935 mm^{-1}
F(000)	1344	5744
Crystal size	0.45 × 0.3 × 0.3 mm^3	0.3 × 0.3 × 0.3 mm^3
Theta range for data collection	2.25–71.94°	2.90–59.90°
Index ranges	0→h→18, 0→k→12, −25→l→24	0→h→22, 0→k→26, 0→l→36
Reflections collected	8227	6157
Independent reflections	6308 [R(int)=0.0122]	6157 [R(int)=0.1551]
Completeness of theta=71.94°	99.70%	49.80% (diffracted upto θ=60° only)
Absorption correction	None	None
Refinement method	Full-matrix least-squares on F_o^2	Full-matrix-block least-squares on F_o^2
Data/restraints/parameters	6308/4/737	6157/11/713
Goodness-of-fit on F_o^2	0.992	1.226
Final R indices [I > 2σ(I)]	R1=0.0749, wR2=0.2166	R1=0.1244, wR2=0.2845
R indices (all data)	R1=0.0931, wR2=0.2427	R1=0.4016, wR2=0.3480
Absolute structure parameter	−0.1(3)	−0.1(12)
Largest diff. peak and hole	0.691 and −0.398 e.Å^{-3}	0.581 and −491 e.Å^{-3}

Crystal structure of Form **I** contains nine water molecules (Figure 1). Four primary (O63, O64, O65, O67) hydroxyls point outside the cavity and are in gauche (60°), -gauch (−60°) [O53-C53-C43-O63/O64/O65/O67 ≅ 60° & C63/C64/C65/C67-C53-C43-O63 ≅ −60°] conformation. However, O66 primary hydroxyl is in gauch(60°), trans (180°) conformation and O61, O62 primary hydroxyls assume both of the above-mentioned conformations due to disorder. The disorder is mainly driven by water molecules (O2W and O8W), which makes hydrogen bonds with O61 and O62. Water O6W also has the positional disorder with the occupancy of 0.83 (O6WA) and 0.17 (O6WB).

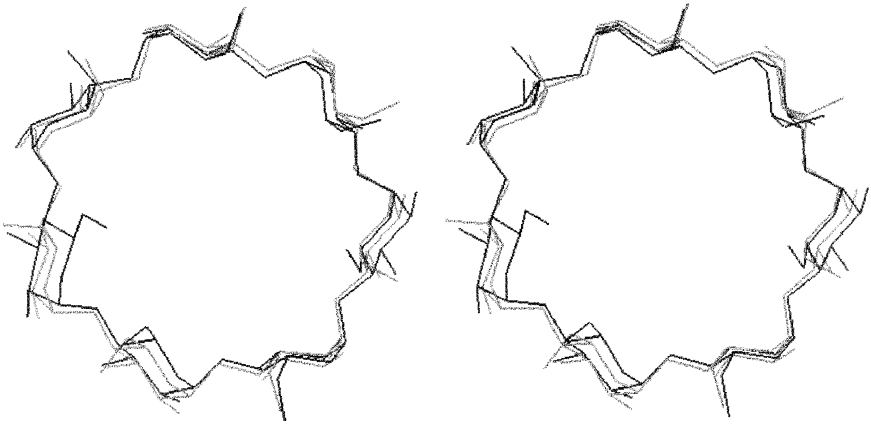


FIGURE 3 Stereo view of super position of Form **I** (dark line) and Form **II** (grey line), showing slight distortion in the conformation of Form **I**.

The crystal structure of Form **II** has nine water molecules and one MPD molecule (Figure 2). All of the primary hydroxyls are pointing outwards from the center. In this form the βCD molecules are arranged in a head-to-head fashion, forming a dimer that helps in maintaining the seven-fold symmetry of the βCD [4].

Seven-fold symmetry in Form **I** is slightly distorted (Figure 3), leading to the deviation of the oxygen atoms in the O4 plane (O41, O42, O43, O44, O45, O46 and O47) of βCD from planarity. However, in Form **II** the symmetry is maintained (Table II).

Hydration of βCD

The positions of water molecules around βCD in both of the forms have been compared with those found in similar structures (Table III) [4]. In general, the water molecules interact with both primary and secondary hydroxyls of βCD. Although this is the case for Form **II**, in Form **I** the interaction of water molecules is with secondary hydroxyls only.

In Form **I** a water network formed (O...O distances ≤ 3.11 Å) by four water molecules, namely O3W, O5W, O7W, and O9W from the primary hydroxyl to the center of the cavity (Figure 4(a)). Similar water network has been found in the crystal structure of βCD under 15% humidity conditions (POBRON[#]) and this water network is generally replaced by drug molecules (Figure 4(a)) [5]. In additon to these O3W and O9W form a network with O61 and O4A of MPD in Form **II** (Figure 4(b)).

[#]POBRON: CSD code for the crystal structure of βCD in 15% humidity condition.

TABLE II Plane Calculations for O4 Plane (O41, O42, O43, O45, O46, and O47) of Forms **I** and **II**

O4 Plane (Form **I**)
m1 = −0.15502(0.00049)
m2 = −0.72438(0.00036)
m3 = −0.67175(0.00038)
D = −3.43752(0.00514)

Atom	d	s	d/s	$(d/s)^2$
O41*	−0.1906	0.0049	−38.517	1483.536
O42*	−0.1366	0.0048	−28.741	826.028
O43*	0.1672	0.0040	42.020	1765.701
O44*	0.0392	0.0043	9.212	84.865
O45*	−0.2556	0.0044	−58.691	3444.618
O46*	0.1503	0.0050	30.180	910.858
O47*	0.2089	0.0050	42.182	1779.297

Sum$((d/s)^2)$ for starred atoms: 10294.903
χ^2 at 95% for 4 degrees of freedom: 9.49
The group of atoms deviates significantly from planarity.

O4 Plane (Form **II**)
m1 = −0.15990(0.00150)
m2 = 0.00324(0.00142)
m3 = −0.98713(0.00024)
D = −22.15653(0.01236)

Atom	d	s	d/s	$(d/s)^2$
O41*	−0.0104	0.0154	−0.675	0.455
O42*	0.0007	0.0135	0.051	0.003
O43*	0.0157	0.0135	1.169	1.366
O44*	−0.0190	0.0148	−1.279	1.636
O45*	−0.0029	0.0128	−0.225	0.051
O46*	0.0164	0.0141	1.163	1.352
O47*	−0.0054	0.0145	−0.369	0.136

Sum$((d/s)^2)$ for starred atoms: 4.998
χ^2 at 95% for 4 degrees of freedom: 9.49
The group of atoms does not deviate significantly from planarity.

Interaction of MPD with βCD

Position of the MPD molecule is conserved with respect to the earlier reported βCD–MPD complex [6]. Oxygens O2A and O4A of the MPD molecule interact with the primary hydroxyls (O62 and O61, respectively) of

TABLE III Water Molecule Comparison of Primary Hydroxyl with Related Structures and Secondary Hydroxyl with Related Structures

Hydroxyl	Water Molecules	Average[@]	Form **I** (water)	Form **II** (MPD)
Primary				
O61	W61	2.73(8)	—	2.73(3)*
O62	W62	2.76(7)	—	2.87(5)*
O63	W63	2.76(11)	—	—
O64	W64	2.75(5)	—	—
O65	W65	2.79(6)	—	2.83(7)
O66	W66	2.87(12)	—	—
O67	W67	2.75(6)	—	—
Secondary				
O21	W21	2.69(4)	—	—
O22	W22	2.76(1)	—	—
O23	W23	2.74(10)	—	—
O24	W24	2.74(6)	2.74(3)	—
O26	W26	2.84(9)	2.93(5)	—
O32	W32	2.92(10)	—	—
O34	W22	2.85(8)	—	—
O35	W21	2.86(5)	2.87(7)	—
O36	W24	2.87(8)	—	—
O25	O10W	—	—	2.65(3)
O31	O3W	—	—	2.95(4)

*Oxygen atoms of the MPD molecule.
[@] Reference [4].

the βCD through O-H...O hydrogen bonds, as found in the earlier complex (Figure 2).

The βCD cavity is hydrophobic in nature. The MPD molecule does not penetrate into the cavity, as it contains two branched oxygen atoms. However, solvents such as diethanolamine (HO-CH_2-CH_2-NH-CH_2-CH_2-OH) [7], Methyl 1,5 pentane diol (HO-CH_2-CH_2-CH_2-CH_2-CH_2-OH) [7], and But-2-yne-1, 4 diol (HO-CH_2-C$\equiv$C-CH_2-OH) [8] penetrate the cavity, forming a host–guest complex. From the present study we suggest that the hydrophobic threshold chain length of four carbons ($\sim$4.2 Å) may be required to participate in host–guest interactions.

Packing of βCD Molecule

Form **I** has a lesser number of C-H...O interactions (19) compared to Form **II** (37), which has a dimer packing. In Form **I**, with monomer packing all primary and secondary hydroxyls are utilized in strong O-H...O–type inter- and intramolecular hydrogen bonds. In Form **II** the secondary hydroxyls are involved in dimerization. Hence the additional C-H. . .O hydrogen bonds

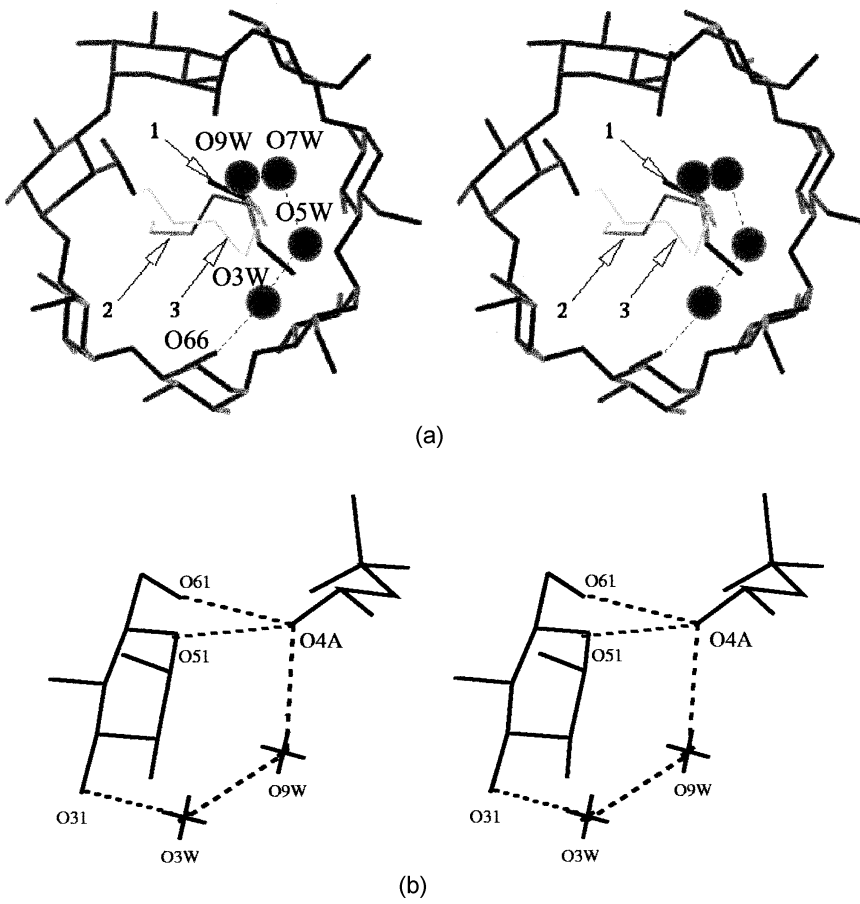


FIGURE 4 (a) Stereo view showing the replacement of water molecules by the drugs (1) But-2-yne-1,4 diol, (2) Methyl 1,5 pentane diol, and (3) Di ethanolamine. (b) Stereo view of network formed by two water molecules and one oxygen atom of MPD connecting the primary and secondary hydroxyls of *β*CD in Form **II**.

may be compensating for the missing O-H. . .O interactions interactions in crystal packing of Form **II** [9,10] (Tables IV and V).

The monomers are packed in herringbone fashion in Form **I** (Figure 5), while Form **II** exists as dimer and adopts a screw channel (SC) packing mode. In SC mode the adjacent dimers are related by the two-fold screw axis (Figure 6). Database analysis for the dimerized packing of *β*CD molecules has been done by D Mentzafos *et al.* [4]. Similar analysis on monomer packing of the *β*CD molecules and the driving force to adopt the monomer packing is of interest.

TABLE IV Hydrogen Bonds for Form **I** (Å and °)

D-H...A	d(H...A)	d(D...A)	<(DHA)
Intramolecular O-H...O hydrogen bond			
O(33)-H(33)...O(43)	2.58	2.85(1)	100.6
O(33)-H(33)...O(24)	2.31	2.89(1)	128.0
O(27)-H(27)...O(37)	2.57	2.88(1)	103.8
O(63)-H(63)...O(53)	2.43	2.76(1)	104.8
O(64)-H(64)...O(54)	2.51	2.83(1)	103.9
O(37)-H(37)...O(47)	2.50	2.79	102.7
O(37)-H(37)...O(21)	2.15	2.88(1)	147.7
O(34)-H(34a)...O(44)	2.51	2.82(1)	104.3
O(34)-H(34a)...O(25)	2.13	2.81(1)	140.3
O(25)-H(25)...O(35)	2.52	2.84(1)	104.4
O(32)-H(32)...O(22)	2.58	2.90(1)	104.8
O(31)-H(31a)...O(41)	2.55	2.84(1)	102.0
O(31)-H(31a)...O(22)	2.28	2.97(1)	141.7
O(35)-H(35)...O(45)	2.51	2.83(1)	103.9
O(35)-H(35)...O(26)	2.15	2.78(1)	133.3
O(36)-H(36)...O(26)	2.52	2.85(1)	105.5
O(24)-H(24a)...O(34)	2.57	2.89(1)	104.6
O(22)-H(22a)...O(41)	2.41	2.76(1)	106.4
O(22)-H(22a)...O(31)	2.26	2.97(1)	144.9
O(62a)-H(62C)...O(52)	2.58	2.82(1)	98.8
O(24)-H(24a)...O(1w)	1.97	2.74(1)	155.2
O(26)-H(26)...O(3w)#1	2.01	2.80(1)	163.5
O(33)-H(33)...O(1w)#2	2.36	2.81(1)	115.5
O(32)-H(32)...O(2w)#3	2.06	2.81(1)	150.8
O(23)-H(23)...O(37)#3	2.12	2.73(1)	131.5
O(62b)-H(62f)...O(31)#3	2.39	3.04(2)	137.0
O(36)-H(36)...O(61b)#4	2.02	2.62(2)	129.8
O(27)-H(27)...O(61a)#4	2.23	2.92(1)	143.3
O(67)-H(67)...O(6wb)#5	2.07	2.76(3)	142.8
O(63)-H(63)...O(1w)#5	2.22	3.04(1)	174.9
O(62a)-H(62C)...O(2w)#5	2.02	2.81(2)	160.9
O(61a)-H(61a)...O(27)#5	2.17	2.92(1)	152.7
O(61b)-H(61b)...O(8w)#5	2.52	3.16(5)	135.4
O(67)-H(67)...O(6wa)#5	2.03	2.85(1)	172.7
O(65)-H(65)...O(5w)#7	1.96	2.76(1)	166.6
O(64)-H(64)...O(67)#8	2.25	2.84(1)	129.0
O(66)-H(66)...O(6wa)#9	2.19	3.00(1)	169.4
C-H...O Hydrogen bonds			
C(54)-H(54)...O(43)	2.49	2.82(1)	99.8
C(55)-H(55)...O(44)	2.48	2.83(1)	100.4
C(43)-H(43)...O(63)	2.53	2.93(1)	104.2
C(52)-H(52)...O(41)	2.51	2.78(1)	95.8
C(33)-H(33a)...O(42)	2.59	2.88(1)	97.5
C(51)-H(51)...O(47)	2.42	2.81(1)	103.2

(*Continued*)

TABLE IV (*Continued*)

D-H...A	d(H...A)	d(D...A)	<(DHA)
C(47)-H(47)...O(67)	2.47	2.87(1)	104.0
C(37)-H(37a)...O(46)	2.55	2.85(1)	97.6
C(56)-H(56)...O(45)	2.49	2.79(1)	96.9
C(36)-H(36a)...O(45)	2.51	2.83(1)	98.7
C(63)-H(63b)...O(54)	2.55	3.38(1)	143.0
C(67)-H(67b)...O(51)	2.56	3.38(1)	142.5
C(62a)-H(62a)...O(53)	2.54	3.38(2)	145.2
C(62b)-H(62e)...O(42)	2.86	3.08(2)	93.8
C(63)-H(63a)...O(34)#5	2.53	3.35(1)	142.0
C(63)-H(63a)...O(25)#5	2.57	3.44(1)	149.9
C(47)-H(47)...O(54)#6	2.55	3.51	165.1
C(14)-H(14)...O(21)#8	2.52	3.49(1)	170.9

Symmetry transformations used to generate equivalent atoms: #1 −x+1, y−1/2, −z+1; #2 −x+2, y+1/2, −z; #3 −x+1, y+1/2,−z; #4 x, y−1, z; #5 x, y+1, z; #6 x−1,y, z; #7 −x+2, y+1/2, −z+1; #8 x+1,y, z; #9 −x+1, y+1/2,−z+1.

Monomer Packing Analysis of βCD Molecule

We have retrieved eleven monomer packing crystal structures of *β*CD from the 1998 release of Cambridge Structural Database (CSD) [11,12]. The CSD code for the data are BISTAY [13], DEBGOG [14], DIRVOP [15], KUFHOI [16], KUTKOZ [17], PIJGIY & PIJGOE [18], POBRON [5], YIYSII & YIYSOO [19], and ZIGZIY [20] (Table VIII). All of the above molecules are packed in herring bone fashion except KUFHOI. The KUFHOI is crystallized with eight pyridine and three water molecules. The pyridine rings not only participate in the host–guest interaction but also have interstitial interaction with *β*CD, which induces a cross-stacking style of packing (Figure 7(a)).

Most of the monomers, except primary hydroxyl-modified *β*CD, crystallize in $P2_1$ space group, whereas dimers crystallize in C2, $C222_1$, $P2_1$, and P1 space groups [4]. The primary hydroxyl-modified *β*CD-DEZMOK[#] [21] crystallizes in $P2_12_12_1$ space group and has an extended herringbone style of packing (Figure 7(b)). In addition to the primary hydroxyls, if the secondary hydroxyls are modified then they also form dimers. Dimer packing has head-to-head arrangement, while monomer packing induces head-to-tail interactions. Dimers in $P2_1$ space group adopt screw channel packing, while monomers adopt a herringbone-type packing[4]. It has been observed that if a guest molecule is a linear chain consisiting of seven

[#]CSD code for the crystal structure of primary hydroxyl-modified *β*CD.

TABLE V Hydrogen Bonds for Form **II** (Å and °)

D-H...A	d(H...A)	d(D...A)	<(DHA)
O(37)-H(37)...O(26)	2.12	2.82(2)	144.3
O(27)-H(27A)...O(31)	1.99	2.72(2)	148.6
O(24)-H(24A)...O(23)	2.31	2.94(2)	134.8
O(23)-H(23A)...O(24)	2.18	2.94(2)	155.3
O(22)-H(22)...O(33)	2.06	2.80(1)	150.0
O(61)-H(61)...O(4A)	1.96	2.77(2)	171.0
O(65)-H(65)...O(1W)	2.10	2.81(2)	144.8
O(31)-H(31A)...O(3W)	2.19	3.00(3)	171.9
O(21)-H(21)...O(35)#1	2.65	3.29(2)	135.0
O(31)-H(31A)...O(10W)#1	2.65	3.19(3)	124.7
O(32)-H(32A)...O(24)#1	1.96	2.77(2)	170.8
O(33)-H(33)...O(10W)#2	2.55	2.88(3)	105.4
O(34)-H(34)...O(32)#1	2.46	3.05(2)	129.7
O(64)-H(64)...O(5W)#4	2.36	2.75(3)	109.9
O(64)-H(64)...O(67)#5	2.78	3.09(3)	104.2
O(25)-H(25)...O(31)#1	2.48	3.20(2)	145.8
O(25)-H(25)...O(27)#1	2.59	3.05(1)	117.4
O(35)-H(35)...O(31)#1	2.13	2.94(2)	170.4
O(26)-H(26)...O(37)#1	2.34	3.09(2)	151.6
O(36)-H(36)...O(37)#1	1.98	2.79(2)	168.3
O(66)-H(66)...O(1W)#6	2.30	2.81(2)	120.8
O(67)-H(67)...O(64)#7	2.48	3.09(3)	131.6
O(63)-H(63)...O(1W)#3	2.15	2.79(2)	135.5
C-H...O Hydrogen bonds			
C(51)-H(51)...O(42)	2.41	2.76(3)	100.2
C(31)-H(31)...O(42)	2.57	2.90(3)	99.5
C(61)-H(61B)...O(41)	2.87	3.07(3)	92.7
C(41)-H(41)...O(61)	2.53	2.90(3)	102.3
C(32)-H(32)...O(43)	2.61	2.88(3)	96.1
C(42)-H(42)...O(62)	2.64	3.00(3)	101.6
C(62)-H(62B)...O(51)	2.68	3.47(3)	138.3
C(62)-H(62B)...O(42)	2.72	3.02(3)	98.6
C(52)-H(52)...O(43)	2.51	2.80(3)	96.5
C(53)-H(53)...O(44)	2.56	2.89(3)	99.7
C(63)-H(63B)...O(43)	2.68	2.99(3)	99.2
C(33)-H(33A)...O(44)	2.38	2.77(3)	103.0
C(54)-H(54)...O(45)	2.71	2.93(3)	93.2
C(14)-H(14)...O(64)	2.71	3.06(4)	101.9
C(24)-H(24)...O(45)	2.42	2.81(2)	102.9
C(64)-H(64B)...O(53)	2.61	3.46(4)	145.8
C(45)-H(45)...O(65)	2.55	2.88(3)	99.4
C(25)-H(25A)...O(10W)	2.82	3.24(3)	106.4
C(65)-H(65B)...O(54)	2.72	3.48(3)	135.5
C(65)-H(65B)...O(45)	2.67	2.96(3)	98.1

(*Continued*)

TABLE V (*Continued*)

D-H...A	d(H...A)	d(D...A)	<(DHA)
C(55)-H(55)...O(46)	2.50	2.84(3)	99.8
C(56)-H(56)...O(47)	2.65	2.91(3)	95.4
C(66)-H(66B)...O(55)	2.65	3.45(3)	140.2
C(66)-H(66B)...O(46)	2.84	3.06(4)	93.9
C(46)-H(46)...O(66)	2.53	2.90(3)	102.2
C(36)-H(36A)...O(47)	2.44	2.83(3)	103.3
C(47)-H(47)...O(67)	2.48	2.84(3)	101.0
C(37)-H(37A)...O(41)	2.53	2.85(3)	98.7
C(57)-H(57)...O(41)	2.36	2.73(3)	101.0
C(67)-H(67B)...O(47)	2.81	3.04(3)	93.7
C(12)-H(12)...O(25)#2	2.52	3.31(2)	137.7
C(22)-H(22A)...O(36)#2	2.45	3.39(3)	159.5
C(23)-H(23)...O(3W)#5	2.90	3.28(3)	104.7
C(17)-H(17)...O(23)#7	2.59	3.45(3)	146.9
C(27)-H(27)...O(24)#7	2.43	3.37(3)	161.2

Symmetry transformations used to generate equivalent atoms: #1 −x+1, y,−z+3/2; #2 x−1/2,y+1/2,z; #3 x−1/2,−y+1/2,−z+1; #4 x+1/2,−y+1/2,−z+1; #5 x+1/2,y+1/2,z; #6 x,−y,−z+1; #7 x−1/2,y−1/2,z.

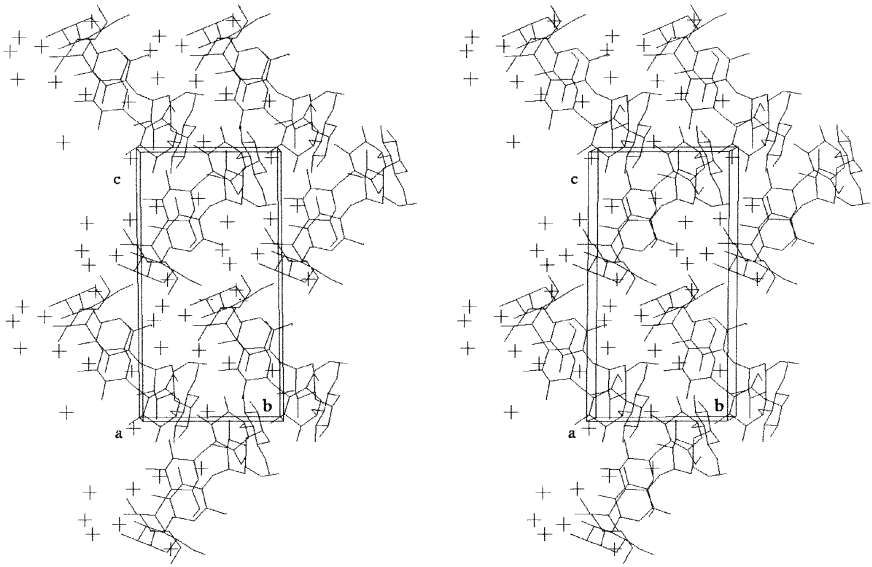


FIGURE 5 Stereo view of the herringbone-type packing of Form **I** in bc plane; +, water molecules.

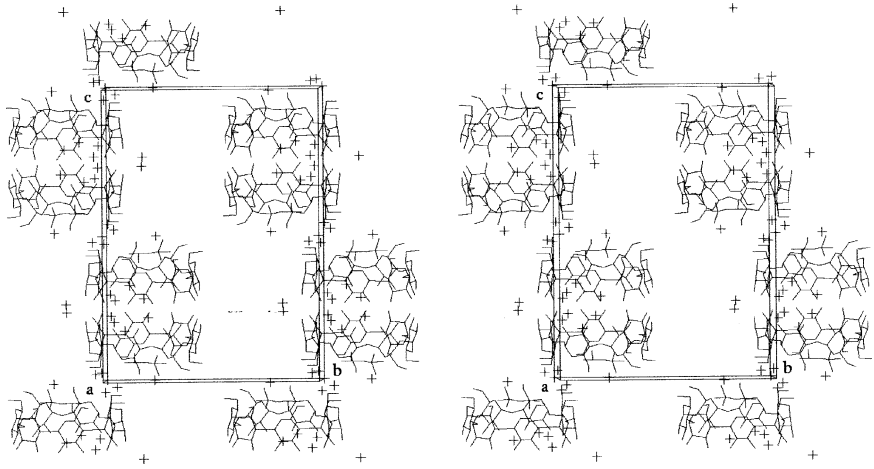


FIGURE 6 Stereo view of SC packing of Form **II** in bc plane; +, water molecules.

or more atoms then βCD dimerization is induced or else it may adopt a monomer packing. In a few cases βCD dimerizes without a drug molecule, suggesting that host–guest interaction may not be necessary for dimerization.

From our observation we suggest that the dimerization may not require any additional hydrophobic element, as a single MPD molecule has induced the βCD to undergo the dimerization without any host–guest interaction.

TABLE VI CSD Codes and the βCD Crystal Structures Used in Monomer Packing Analysis with References

CSD codes	Name of the compound	Reference
BISTAY	βCD 1,4-diazabicyclo(2.2.2)octane clathrate tridecahydrate	13
DEBGOG	βCD benzyl alcohol clathrate pentahydrate	14
DIRVOP	βCD hexamethylenetetramine clathrate hexahydrate	15
KUFHOI	βCD octakis(pdidine) clathrate trihydrate	16
KUTKOZ	βCD 1,4-butanediol hydrate heptasaccharide	17
PIJGIY	βCD ethylene glycol octahydrate heptasaccharide	18
PIJGOE	βCD glycerol hydrate	18
POBRON	βCD hydrate	5
YIYSII &	βCD diethanolamine hydrate heptasaccharide	19
YIYSOO	βCD 1,5-pentanediol hydrate heptasaccharide	19
ZIGZIY	βCD but-2-yne-1,4-diol heptahyrate clathrate	20

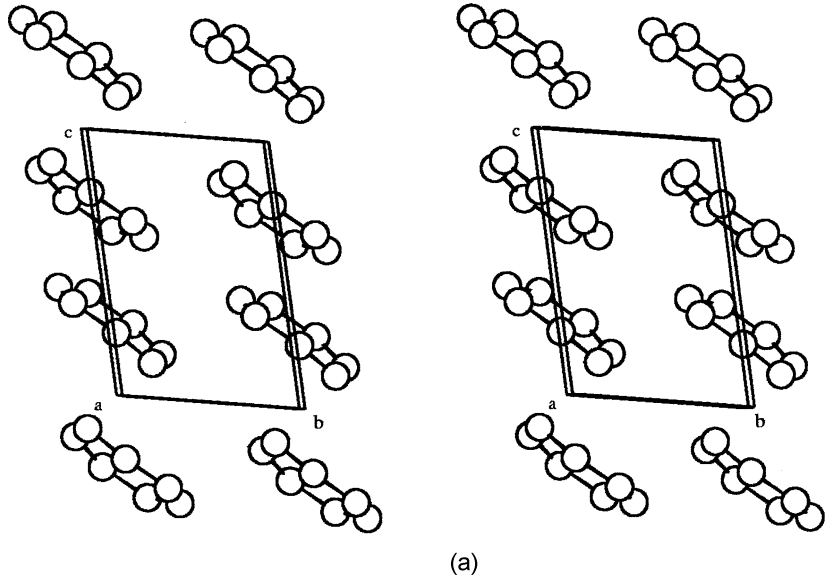


FIGURE 7 (a) Stereo view of the cross-stacking-type monomer packing in modified βCD (KUFHOI). For calirity, virtual bond connecting (O4) oxygen atoms in βCD along are shown. (b) Stereo view of the extended herringbone-type monomer packing in modified βCD (DEZMOK). For clarity, virtual bond connecting (O4) oxygen atoms in βCD alone are shown.

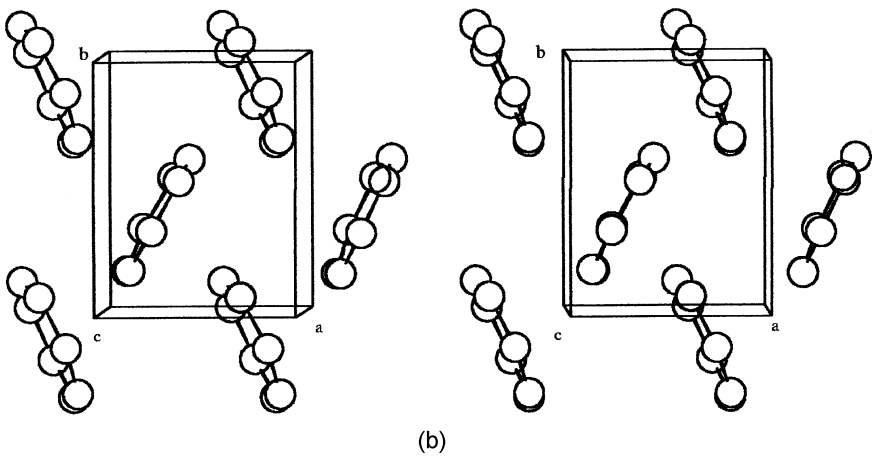


FIGURE 7 Continued.

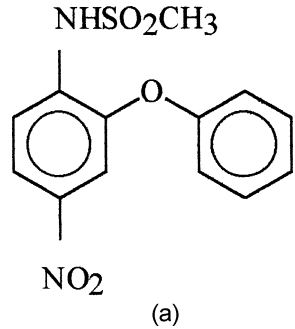
TABLE VII Groupwise Split Up of Intermolecular Energies of Nimesulide with βCD

Nimuslide groups	Interaction energy (Kcal/mole)
Methyl sulphonamide	−5.33
Phenyl ring	−11.64
Nitro phenyl	−2.06
Total	−38.03

TABLE VIII Hydrogen Bond Parameters for Nimusulide and βCD Complex

D-H...A	D...A (Å)	H...A (Å)	<D-H...A (°)
C57-H57...O5*	3.40	2.57	131
C12-H12*...O66	3.43	2.67	127
O2*...O62	3.19	—	—
O4*...O26	3.32	—	—

*Indicates the atoms of Nimusulide molecule.



(a)

FIGURE 8 (a) Chemical diagram of nimesulide. (b) Stereo view of nimesulide and βCD complex model showing the possible host–guest interactions. Numesulide (dark line) is shown superposed on Diclofenac DF (gray line). (c) Fluorescence spectrum of nimusulide-β-CD complex. Excited at 390 nm and emission tested at 430 nm. The emission maximum of complex occurs at 498 nm (Spectrum recorded using Perkin-Elmer Ls-5B Luminescence spectrometer).

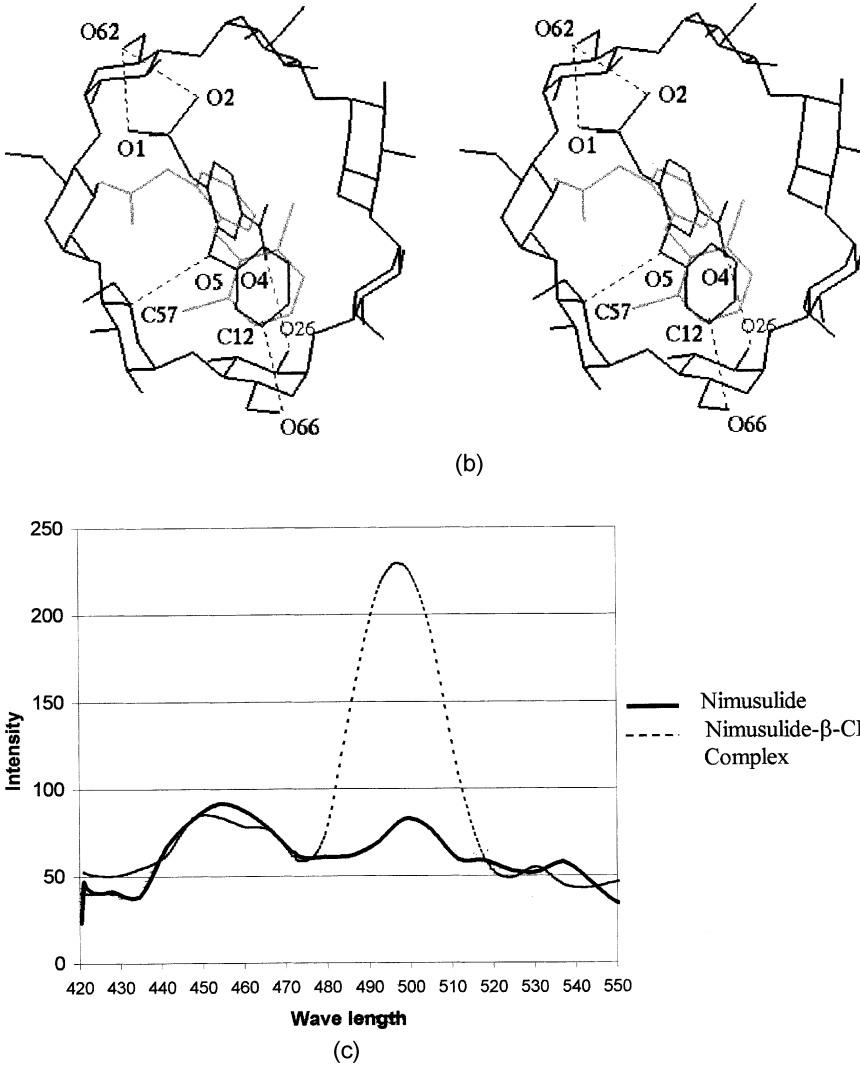


FIGURE 8 Continued.

MOLECULAR MODELING OF *β*CD WITH NIMESULIDE

It is of interest to study the probable mode of binding of nimesulide to *β*CD. In the absence of a nimesulide–*β*CD complex in the crystalline state, we carried out molecular modelling using Biosym Software [22]. Crystal structure of Diclofenac (DF) sodium undecahydrate complex of *β*CD

[23] was used as the starting model for calculations. Nimesulide [24] consists of a phenyl and a nitrophenyl ring bridged by an oxygen atom and has a methyl sulphonamide group (Figure 8(a)). The aromatic groups of nimesulide were positioned at the biphenyl portion of the DF molecule, and the energy was minimized (Figure 8(b)). The interaction energy values given in Table VII suggest that the complex is stabilized by hydrophobic interactions due to the phenyl rings. Fluoresence studies have been done using 2 ml of water containing 0.064 mg of nimusulide and 0.09 mg (10 mM) of βCD. The solution was shaken for 12 h and stabilized for 6 h, and the sample was excited at 390 nm and emission spectrum was recorded at 430 nm. The enhancement in fluorescence intensity at 498 nm shows the binding of nimesulide to hydrophobic interior of βCD (Figure 8(c)) [25].

Oxygen atom (O4) of nitro group interacts with secondary hydroxyl (O26) of βCD. Oxygen atoms of sulfonamide group (O1, O2) interact with the primary hydroxyl (O62) of βCD. Bridged oxygen of biphenyl guest makes a C-H...O–type interaction with the host (Table VIII). In crystal structure, water molecules may reinforce these and other interactions. We surmise that the nimesulide complexation with βCD is likely to be close to the one arrived at through modelling.

CONCLUSIONS

The above complexation procedures yielded different hydration patterns for βCD. Positions of the water molecules are different from previously solved crystal structures. However, position of the MPD is conserved in two related structures. Hydrophobic chain length seems to be a determining factor in host–guest complexation. The probable mode of binding of nimesulide with βCD in solution was arrived at using molecular mechanics calculations and confirmed by fluorescence studies.

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