Journal of Computer-Aided Molecular Design, 5 (1991) 525–543
ESCOM

J-CAMD 133

Modeling and conformation analysis of β-cyclodextrin complexes

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Received 25 June 1990
Accepted 26 April 1991

Key words Structure; Distortion, Molecular modeling; Docking; Interaction energy

SUMMARY

A series of β-cyclodextrin complexes containing various guest molecules was studied using computer-aided molecular modeling and conformation analysis techniques. The geometry of each complex was studied using crystallographic data. The positions of the glycosidic O4 atoms indicate that the β-cyclodextrin molecules are elliptically distorted. This distortion can be related to the van der Waals volume of the guest molecules. This correlation is different for aromatic and non-aromatic guest compounds. Rigid body docking experiments demonstrated that in crystal structures the guest molecule occupies a position in the cavity of nearly minimum interaction energy when there are no other molecules having interactions with the guest molecule. From the crystallographic data several rules could be deduced which seem to determine the conformation of β-cyclodextrin molecules in complexes. A procedure was developed to construct β-cyclodextrin molecules that are able to encompass guest molecules having a given van der Waals volume.

INTRODUCTION

Cyclodextrins or cycloamyloses are cyclic oligosaccharides consisting of 6, 7 or 8 1→4 linked α-D-glucopyranosyl residues. These compounds are called α-, β- and γ-cyclodextrin, respectively. The glucose units of all β-cyclodextrin molecules have the $^4C_1$ chair conformation. All glucose units are slightly tilted so that they form a hollow truncated cone. The secondary hydroxyl groups are found at the wider rim and the primary hydroxyl groups are found at the narrower rim. The hydrogen atoms attached to the carbon atoms point to the center of the molecule (see Fig. 1). As a result the molecule has a hydrophobic center and a relatively hydrophilic outer surface. Because of these properties cyclodextrins are able to bind a large number of guest molecules provided the guest molecule or part of it is small enough to fit into the cavity. For review articles on the properties of cyclodextrin complexes see Refs. 1, 2 and 3.

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0920-654X/$ 5.00

TABLE 1
GUEST MOLECULES OF THE COMPLEXES STUDIED TOGETHER WITH THEIR VAN DER WAALS VOLUME, AS CALCULATED BY CHEM-X, AND THEIR EXPERIMENTAL LOG P [5,6]

Complex	Guest molecule	v.d. Waals volume (Å^3)	Log P
1	water	18.4	−1.38
2	methanol	27.1	−0.66
3	hydrogen iodide	38.6	
4	potassium heptaiodide [a]	71.8	2.49
5	1,4-diazabicyclo[2.2.2]octane	95.1	
6	hexamethylenetetramine	109.5	−2.15
7	1-adamantanemethanol	132.4	
8+9[d]	1-adamantanecarboxylic acid	140.9	
10	benzyl alcohol	92.7	1.10
11	*p*-nitroacetanilide	125.3	
12	benzocaine	127.8	2.15
13+14[d]	acetylsalicylic acid	128.2	1.19
15+16[d]	ethyl cinnamate	143.0	2.91
17	2-bromo-5-*tert*-butylphenol	151.2	4.32[b]
18	2,5-diiodobenzoic acid	153.1	3.52[c]

[a] Van der Waals volume and log P given for I_2.
[b] Log P calculated from log P(2-bromophenol) = 2.34 and π(*tert*-butyl) = 1.98.
[c] Log P calculated from log P(2-iodobenzoic acid) = 2.40 and π(I) = 1.12.
[d] Two β-cyclodextrin complexes present in unit cell of crystal.

We carried out the present investigation to find out whether it is possible to predict the conformation and formation energy of β-cyclodextrin complexes as found in crystal structures. Eighteen crystal structures of β-cyclodextrin complexes were studied using computer-aided molecular modeling techniques. In this way we were able to gain insight into the conformation of the β-cyclodextrin molecule and to study the possible influence that the guest molecule has on the conformation of the β-cyclodextrin molecule. Since the conformation of a guest was considered rigid in this study the complex formation energy was determined only from the conformation of the matching β-cyclodextrin molecule and the position of the guest molecule in the cavity of the β-cyclodextrin molecule. We discuss a simple procedure for producing structures of β-cyclodextrin complexes that resemble those of the crystal structures.

METHODS

Crystal structures of β-cyclodextrin complexes were taken from the Cambridge Structural Database [4,5]. The guest molecules of the studied complexes together with some physical chemical properties are listed in Table 1. The van der Waals volume of the guest molecules was calculated with Chem-X [6] using a mesh value of 0.5 Å. The term P represents the partition coefficient of a compound partitioned over the phases octanol and water. Log P values can be calculated as described by Hansch and Leo [7]. The log P value of a substituted organic compound is equal to the

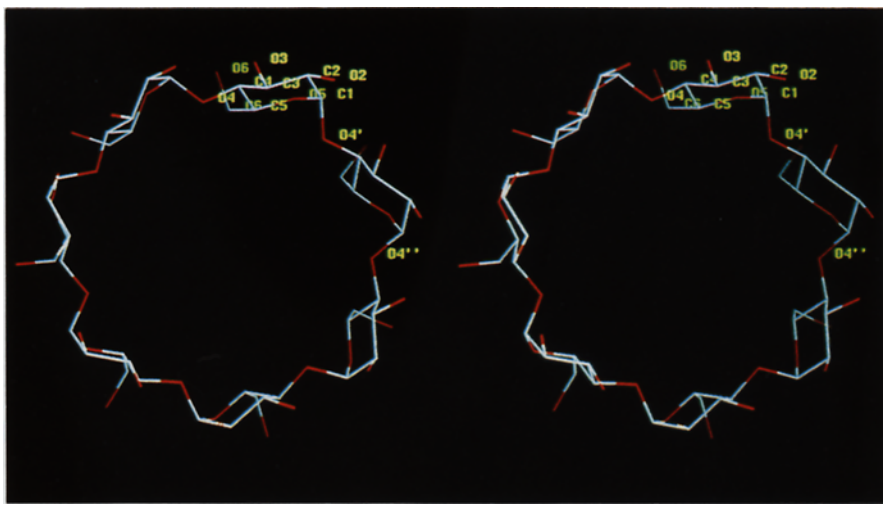

Fig. 1. Stereo view of β-cyclodextrin showing the atom numbering scheme. The narrower rim of the cavity is directed towards the reader.

log P value of the non-substituted organic compound plus a constant value (π) for the substituent.

The structure of β-cyclodextrin and the numbering scheme for one glucose unit can be seen in Fig. 1.

The geometry of the complexes was studied using Chem-X. The glucose units are arranged in what is termed in this study the macrocyclic ring conformation. The x-y plane was defined as the least-squares plane through all O4 atoms. The center of a β-cyclodextrin molecule was defined as the mean position of the 7 O4 atoms. The z-axis of a β-cyclodextrin molecule is the axis through the center of the molecule and perpendicular to the x-y plane of that same molecule. The positive z-axis points to the wider rim of the β-cyclodextrin molecule. The tilt of a glucose residue was defined as the angle between the x-y plane and the least-squares plane through the O4, C1 and C4 atoms of that residue and through the O4 atom of the next glucose residue. The center of a guest molecule is defined as the mean position of all the atoms of that molecule.

The interaction energies at various locations of the guest molecule in the β-cyclodextrin cavity were analysed using the 'calculate conformation utility' in Chem-X. The energies were calculated as van der Waals interaction energies using all terms over a range of 50 Å, so as to include all interactions. The guest molecule is moved, in steps of 0.25 Å, over a vector parallel to the z-axis of the matching β-cyclodextrin molecule from 10 Å below to 10 Å above the x-y plane. At the same time it is rotated in steps of 15° around the z-axis. In this way an isoenergy contour map can be obtained, the x-axis of which shows the angle over which the guest has been rotated and the y-axis of which shows the distance over which it has been translated. Points with equal energy are connected by lines.

Rigid body docking experiments were carried out using the 'minimize utility' of Chem-X. Docking was continued until the interaction energy was at its minimum. Two different starting positions for the guest molecule were used: the position that was found in the crystal structure (in-

ternal position) and a position where the center of the guest molecule was located on the positive z-axis 5 Å away from the center of the β-cyclodextrin molecule (external position).

The energies of the constructed complexes and of complexes similar to those found in crystal structures were minimized using the MM2 force field in MacroModel [9]. Only 20–30 iterations were carried out for each complex. The energies of the complex, of the empty β-cyclodextrin molecule and of the guest molecule were calculated after optimization. The complex formation energy was obtained by subtracting the last two energies from the first energy.

RESULTS AND DISCUSSION

Table 1 shows the β-cyclodextrin complexes that were obtained from the Cambridge Structural Database. In some cases (complexes 4, 8, 11, 13 and 15) two complexes were present in the unit cell. In these cases the two β-cyclodextrin molecules were found to be positioned in such a way that hydrogen bonds could form between the secondary hydroxyl groups of the two cyclodextrin molecules.

In the case of the acetylsalicylic acid β-cyclodextrin complex (complexes 13 and 14) the salicylic acid molecule between the two complexes was not taken into account. In the case of the potassium heptaiodide β-cyclodextrin complex (complex 4) the two I_2 units are positioned in the cavities of two β-cyclodextrin molecules whereas the I^-_3 unit is positioned between the two complexes. Therefore the I_3^- unit was not studied. In the case of the water-β-cyclodextrin complex it was assumed that 4 water molecules were fully in the cavity. Since the locations and the number of the water molecules varied considerably in the crystal structures, these molecules were not taken into account in the energy calculations.

Conformation of β-cyclodextrin in β-cyclodextrin complexes

We studied the following items to gain insight into the macrocyclic ring conformation: the glycosidic angle (C1-O4′-C4′), the distance between the oxygen atoms of the secondary hydroxyl groups of neighbouring glucose units, the position of the O4 atoms and the tilt of the glucose units.

In the β-cyclodextrin complexes the glycosidic angle varies between 111.2 and 126.2°. The mean glycosidic angle over 84 values is 117.8°. The distance between the O2 and O3′ atoms of neighbouring glucose units varies between 2.69 and 3.32 Å. Because the mean distance over 84 values is 2.83 Å, hydrogen bonds can almost always form between these two oxygen atoms.

Analysis of the arrangement of the O4 atoms led us to hypothesize that the O4 atoms are positioned approximately on an ellipse. If this is true, then the distance (R) from the center to any point on that ellipse is a function of the angle (φ) between the long axis of the ellipse and the line through the center and that particular point. An ellipse which does not differ much from a circle can be approximated by Eq. 1.

$$R = a + b\cos(2\varphi + c) \tag{1}$$

The length of the long axis is 2 times a + b and the length of the short axis is 2 times a − b. Variable b is a measure of the distortion of a β-cyclodextrin molecule. When b equals zero the above equation describes a circle with a radius determined by variable a. Because the orientation of the long axis was not known a third variable c was introduced.

TABLE 2
VARIABLES a AND b OF EQ 1 AND CORRELATION COEFFICIENT r

Complex	a (Å)	b (Å)	r
1	5.030	0.158	0.967
2	5.026	0.228	0 976
3	5.031	0 201	0.896
4	5.084	0.162	0.998
5	5.002	0.112	0.931
6	5.045	0.081	0.784
7	5.025	0.032	0.691
8	5.022	0.181	0.966
9	5 039	0.066	0.977
10	5.004	0.294	0.989
11	4.994	0.160	0.993
12	5.036	0 149	0.949
13	5.014	0.141	0.992
14	5.016	0.152	0.980
15	5.035	0.151	0.977
16	5.036	0.116	0.978
17	5 045	0.079	0.963
18	5.079	0.040	0.655

To eliminate possible errors caused by the fact that the O4 atoms are not lying in the x-y plane they were projected onto this plane. R is then the distance between each projected O4 atom and the center of the β-cyclodextrin molecule which lies in the x-y plane. The angle φ is the angle between the line through a projected O4 atom and the center of the β-cyclodextrin molecule, and the line through this center and any other projected O4 atom.

For each β-cyclodextrin molecule studied the variables a and b of Eq. 1 as well as the correlation coefficient are listed in Table 2. From the correlation coefficient in this table it can be seen that Eq. 1 can be used successfully to measure the distortion of almost all β-cyclodextrin molecules studied.

The long axis of the ellipse coincides approximately with an axis through one of the O4 atoms. The variable a of Eq. 1 has a mean value of 5.031 ($\pm$0.023) Å. When the variable b is plotted against the van der Waals volume of the guest, two groups of guest molecules can be distinguished (see Fig. 2). The first group consists of small or spherical molecules (complexes 1–9), and the second group consists of substituted benzene compounds (complexes 10–18). In both groups the variable b gives a good correlation with the van der Waals volume of the guest. The equation for the spherical molecules is

$$b = -1.6(\pm 0.4)10^{-3}\,\text{volume} + 0.26 \qquad (2)$$
$$n = 8,\ r^2 = 0.953,\ s = 0.016,\ F = 120.41,\ F_{1,6,0.005} = 18.63$$

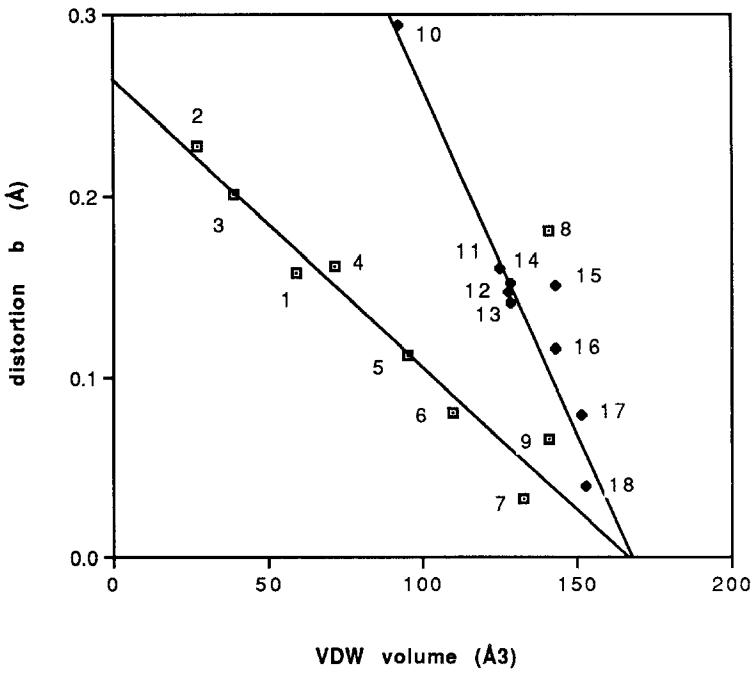

Fig. 2. The distortion of the β-cyclodextrin molecule (variable b of Eq. 1) plotted against the van der Waals volume of the guest molecule. □, spherical molecules; ◆, substituted aromatic compounds.

The equation for the substituted benzene compounds is

$$b = -3.8(\pm 0.7)10^{-3}\,\text{volume} + 0.64 \qquad (3)$$
$$n = 8,\ r^2 = 0.971,\ s = 0.014,\ F = 201.96,\ F_{1,6,0.005} = 18.63$$

In the complexes with 1-adamantanecarboxylic acid and ethyl cinnamate one of the two β-cyclodextrin molecules in the unit cell has a larger distortion than expected. Therefore these outliers were not included in Eqs. 2 and 3.

The smaller the van der Waals volume of the guest molecule, the more pronounced the ellipse. Benzene derivatives with the same van der Waals volume as spherical molecules give rise to a more pronounced ellipse than do spherical molecules. A possible explanation is that benzene derivatives are positioned in the cavity in such a way that the plane of the benzene ring coincides approximately with the plane defined by the long axis of the ellipse and the z-axis. From Fig. 2 the following theory can be deduced. When a guest molecule enters the empty cavity of a β-cyclodextrin molecule the β-cyclodextrin will seek to adopt a conformation which fits best round the guest molecule. The larger the volume of this guest the longer the short axis of the ellipse will have to be. As a result the long axis will become shorter. In the case of very large guest molecules the β-cyclodextrin will adopt a circular conformation.

Since the O4 atoms of a β-cyclodextrin molecule do not form an equilateral heptagon the O4-O4′ distance of each glucose unit is different. Therefore additional data are needed to describe the positions of the O4 atoms on the ellipse. When the angle between the line through C1 and O4 and

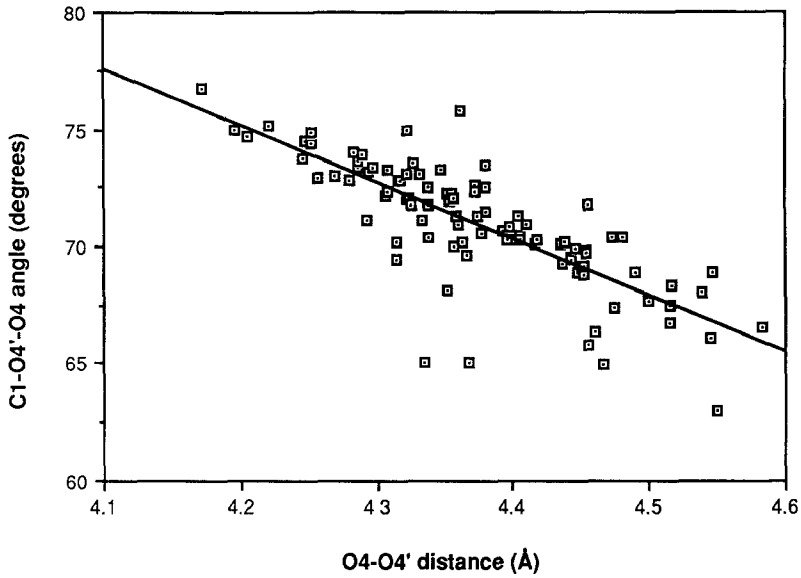

Fig. 3. The C1-O4'-O4 angle vs. the distance between O4 and O4' of 14 β-cyclodextrin molecules.

the line through O4 and O4' is plotted against the distance between O4 and O4' a linear correlation is observed (see Fig. 3). The same holds for the angle between the line through C4 and O4 and the line through O4 and O4' (see Fig. 4). The glucose units which show the largest deviation from these equations have an absolute torsion angle between C1, O4, O4' and C4 atoms which is larger than 5°. Similar correlations have been found in the case of α-cyclodextrin molecules [10].

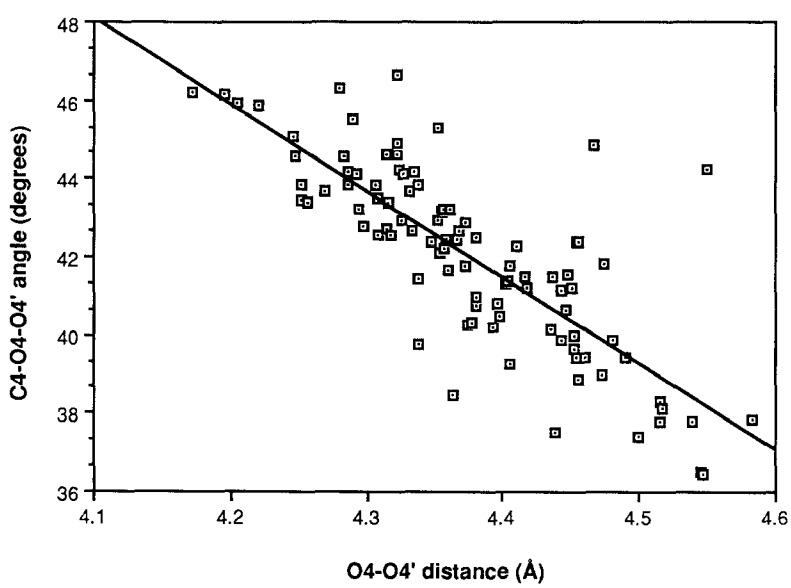

Fig. 4. The C4-O4-O4' angle vs. the distance between O4 and O4' of 14 β-cyclodextrin molecules.

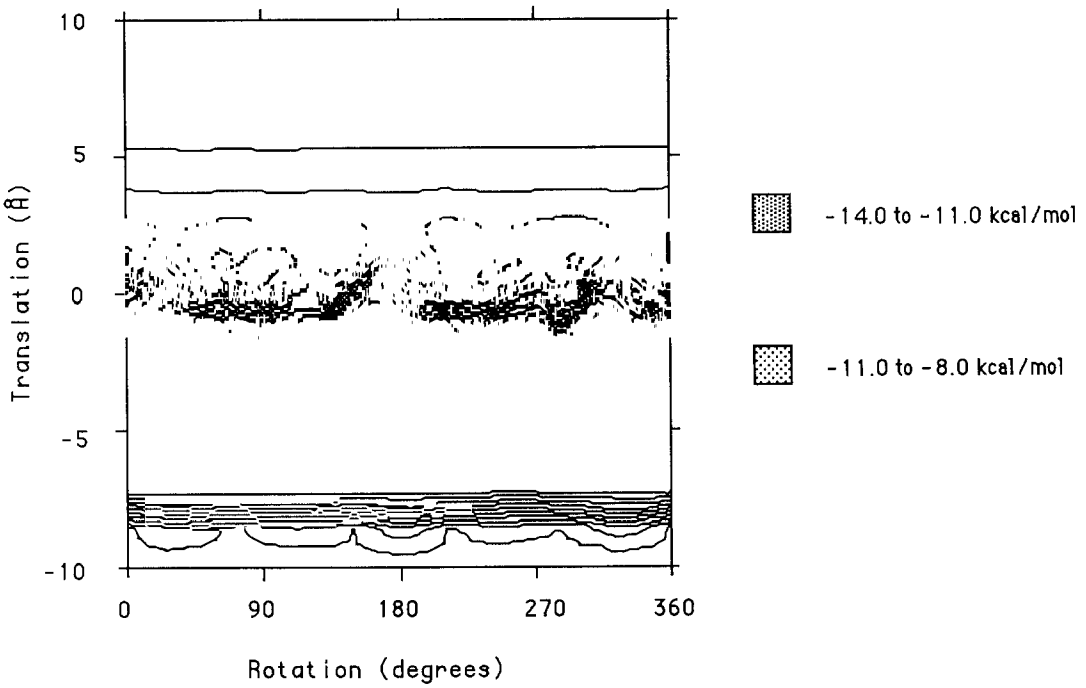

Fig. 5. Isoenergy contour map for translation and rotation of acetylsalicylic acid in the cavity of β-cyclodextrin (complex 13 in Table 1). Fifteen contours are drawn at intervals of 12.6 kJ (3.0 kcal) starting with the lowest interaction energy (−71.1 kJ). The areas corresponding to the lower interaction energies have been shaded.

In order to describe the conformation of a β-cyclodextrin molecule one needs other data besides the positions of the O4 atoms. The major degree of freedom left is the tilt of each glucose unit. The tilt of the glucose units determines to what depth a guest molecule can enter the cavity. The mean tilt of 98 glucose units is 10.3 (±5.5)°.

Energy calculations

Contour maps were generated for complexes 4, 5, 6, 7, 8, 10, 12, 13 and 15. A typical example can be seen in Fig. 5. Since all maps are different this seems to be a good way to characterize a given β-cyclodextrin complex. The contour maps were similar in the following respects. When the guest is moved down into the cavity the van der Waals interaction energy slowly decreases until the guest is fully in the cavity. Depending on the guest molecule one or more minima in the interaction energy can be observed. When the guest molecule is moved further down the energy increases dramatically due to overlap of the β-cyclodextrin with the guest molecule. Only after the guest molecule has left the cavity does the interaction energy decrease again. This is in agreement with the study of Menger and Sherrod [11]. In contrast, we found no significant energy barrier hindering the guest molecule from entering the cavity of the β-cyclodextrin molecule, whereas such a barrier has been reported in other studies [12, 13].

The contour map of the ethyl cinnamate-β-cyclodextrin complex is different. Ethyl cinnamate

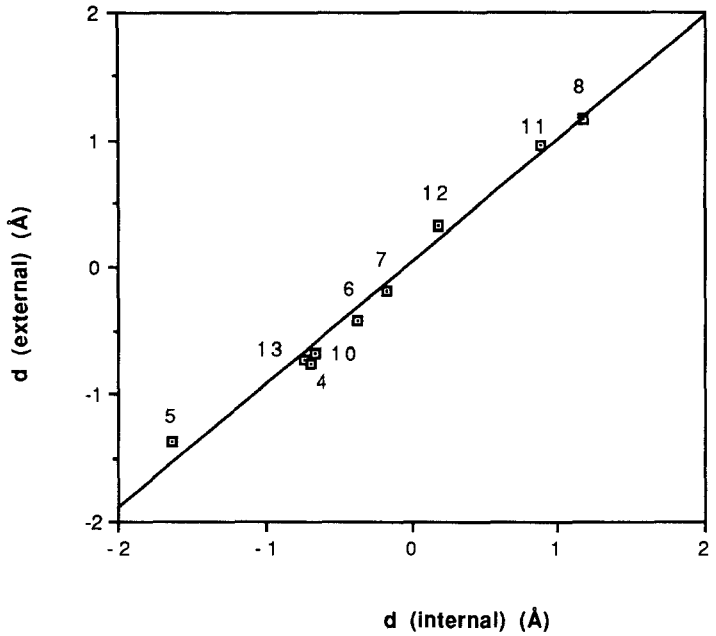

Fig. 6. The depth of the guest in the cavity after docking from the external position [d(external)] compared to the depth of the guest in the cavity in the crystal structure after docking from the internal position [d(internal)]. The external position is the position where the center of the guest molecule is located on the positive z-axis 5 Å away from the center of the β-cyclodextrin molecule. The internal position is the position of the guest molecule such as found in the crystal structure.

is the only guest molecule studied which protrudes from both sides of the β-cyclodextrin molecule. This guest molecule cannot leave or enter the cavity without changing its conformation.

Since we found that there was no energy barrier hindering entry to the cavity, rigid body docking experiments were carried out with complexes 4, 5, 6, 7, 8, 10, 11, 12 and 13. The position of the guest molecule, after it has been docked from the external location, correlates well with its position after it has been docked from its internal location (see Fig. 6).

The equation for the depth in the cavity is

$$\begin{aligned} &d(\text{external}) = 0.97(\pm 0.05)d(\text{internal}) + 0.03 \\ &n = 9,\ r^2 = 0.984,\ s = 0.114,\ F = 435.65 \end{aligned} \tag{4}$$

where d(external) is the distance from the center of the guest molecule to the x-y plane after it has been docked from a location on the positive z-axis 5 Å away from the center of the β-cyclodextrin molecule; d(internal) is the distance from the center of the guest molecule to the x-y plane after it has been docked from its location as indicated by the crystal structure.

The van der Waals energies after docking from both locations are also comparable (see Fig. 7). The equation for the van der Waals interaction energy is

$$\begin{aligned} &E(\text{external}) = 1.00(\pm 0.02)E(\text{internal}) + 0.47 \\ &n = 9,\ r^2 = 0.997,\ s = 1.223,\ F = 2204.90 \end{aligned} \tag{5}$$

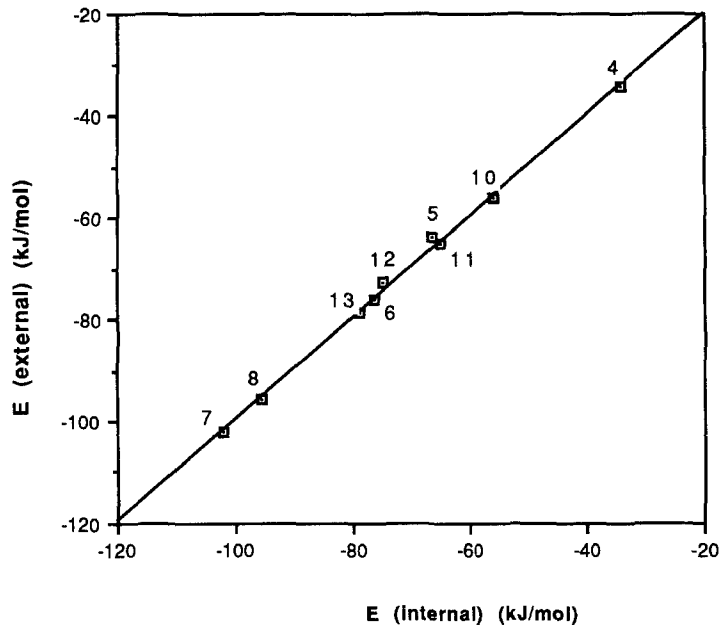

Fig. 7. The interaction energy of the complex after docking from the external position [E(external)] compared to the interaction energy of the complex obtained after docking from the internal position [E(internal)]. The external position is the position where the center of the guest molecule is located on the positive z-axis 5 Å away from the center of the β-cyclodextrin molecule. The internal position is the position of the guest molecule such as found in the crystal structure.

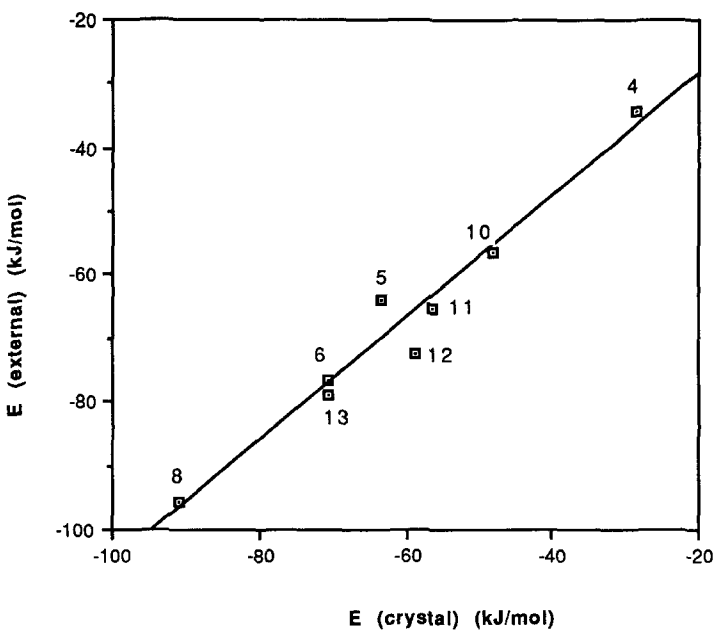

Fig. 8. The interaction energy of the complex after docking from the external position [E(external)] compared to the interaction energy of the complex as found in the crystal structure [E(crystal)]. The external position is the position where the center of the guest molecule is located on the positive z-axis 5 Å away from the center of the β-cyclodextrin molecule.

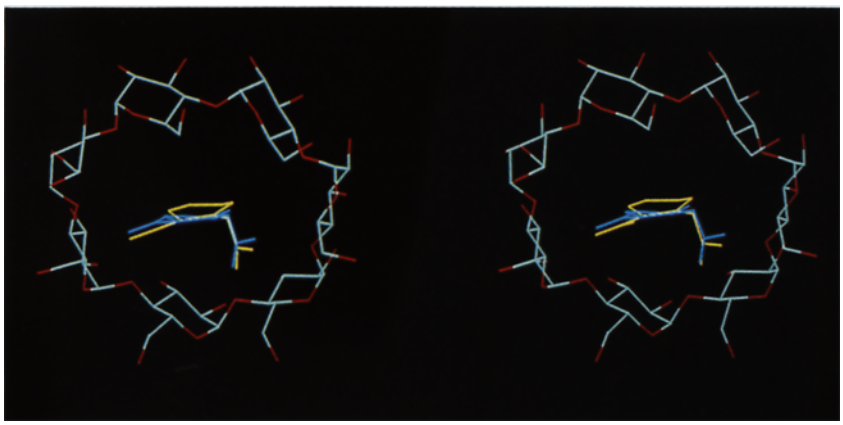

Fig. 9. Stereo view of the complex of β-cyclodextrin with acetylsalicylic acid showing the position of the guest compound in the crystal structure in yellow and the position that was found after docking in blue.

E(external) is the van der Waals interaction energy in kJ after the guest molecule has been docked from a location on the positive z-axis 5 Å away from the center of the β-cyclodextrin molecule. E(internal) is the van der Waals interaction energy in kJ after the guest molecule has been docked from its location as found in the crystal structure.

It can be concluded that docking a guest molecule from the external location enables one to find the location of a guest molecule in the cavity when no crystal structures of the complex are available.

The van der Waals interaction energy of the complex as found in crystal structures correlates well with the van der Waals interaction energy of the complex obtained when the guest has been docked into the cavity of the β-cyclodextrin from the external location (see Fig. 8).

The position of the guest after docking from the external position is very similar to the position of the guest in crystal structures, with two major exceptions: 1-adamantanemethanol and potassium heptaiodide. The crystal structure of the 1-adamantane–methanol complex shows that 3 water molecules are trapped between the two β-cyclodextrin complexes in the unit cell. The 1-adamantanemethanol molecule is therefore forced out of the cavity [14]. Since these water molecules were not taken into account in the docking process the guest molecule could be placed in an energeti-

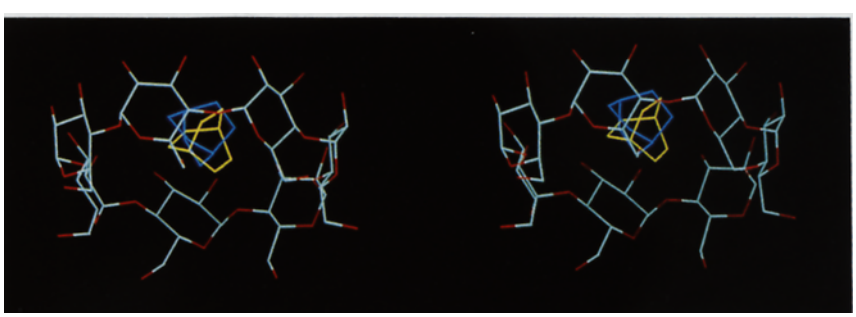

Fig. 10. Stereo view of the complex of β-cyclodextrin with diazabicyclooctane showing the position of the guest compound in the crystal structure in yellow and the position that was found after docking in blue.

TABLE 3
r.m.s. DIFFERENCES FOR NON-HYDROGEN ATOMS, BETWEEN POSITION OF THE GUEST AFTER DOCKING AND THE POSITION OF THE GUEST IN CRYSTAL STRUCTURES

Complex	r.m.s
5	1.66
6	1.52
8	1.43
10	1.62
11	0.97
12	1.49
13	0.56

cally more favourable position deeper in the cavity. In the crystal structure of the potassium heptaiodide–β-cyclodextrin complex the I_2 unit is located deeper in the cavity than in the structure obtained after docking the I_2 unit from the external position in the cavity. The reason is that π-bonding occurs between the I_2 and I_3^- units [15]. The r.m.s. differences between the non-hydrogen atoms of the remaining guest molecules range from 0.56 to 1.66 (Table 3). To illustrate the differences in position, stereo views of the acetylsalicylic acid complex (r.m.s. 0.56) and the diazabicyclooctane complex (r.m.s. 1.66) are given in Figs. 9 and 10. The larger r.m.s. value for the latter complex is partly caused by a rotation of the guest around the z-axis. This rotation, however, is not very significant due to the spheric nature of diazabicyclooctane.

It can be concluded that in crystal structures the guest molecule occupies a position in the cavity of nearly minimum interaction energy when there are no other molecules having interactions with the guest molecule.

Construction of β-cyclodextrin complexes

With the previously discussed set of data about β-cyclodextrin molecules it is possible to describe their macrocyclic ring conformation. If one also knows how the distortion of the β-cyclodextrin molecule is related to the van der Waals volume of the guest molecule it is possible to construct a β-cyclodextrin molecule which has a conformation that is similar to the conformation as found in the corresponding crystal structure. We decided to construct the β-cyclodextrin molecules with glucose units as found in the crystal structures of β-cyclodextrin molecules. A set of 87 different glucose units was used. Since one O4 atom is positioned on the long axis of the ellipse, this axis is an axis of symmetry with regard to the positions of the O4 atoms. Therefore a set of not more than 4 different glucose units positioned as shown in Fig. 11 allows one to construct β-

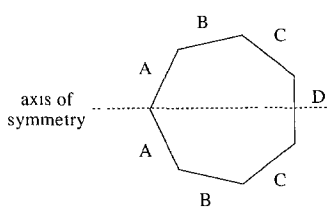

Fig. 11. The sequence of the 4 different glucose units used to construct a β-cyclodextrin molecule.

cyclodextrin molecules with various conformations such as are found in crystal structures. This set of 4 glucose units can be selected on the basis of the following observations.

(1) The O4 atoms are located on an ellipse. The dimensions of this ellipse are calculated from the van der Waals volume of the guest.

(2) There is a relationship between the O4-O4′ distance and the angle between the C1, O4′ and O4 atoms and the angle between the C4, O4 and O4′ atoms of a glucose unit.

(3) Each glycosidic angle has to be as close as possible to 117.8°.

(4) Each glucose unit has a tilt of 10.3°.

If the position of one glucose unit is known, the position of the adjacent glucose units can be calculated. The primary hydroxyl groups are automatically set in the gauche-gauche conformation. Hydrogen atoms are added in a consistent way such that hydrogen bonds can form between the secondary hydroxyl groups of neighbouring glucose units.

A program was written for the construction of such a β-cyclodextrin molecule using as input the van der Waals volume of the guest molecule. In addition one has to specify whether the guest compound is aromatic or nonaromatic. The resulting molecule will be referred to as a constructed β-cyclodextrin molecule.

β-Cyclodextrin molecules were constructed for the guest molecules in complexes 5, 6, 7, 8, 10, 12 and 13. Two methods were used to place the guest molecule in the cavity. Firstly, the constructed β-cyclodextrin molecule was fitted at the same position as the β-cyclodextrin in the crystal structure, using the positions of the O4 atoms. Secondly, the guest molecule with the same conformation as found in the crystal structure, was docked into the cavity of the constructed β-cyclodextrin molecule from the external position. Unlike the first method this method can be applied when the position of the guest molecule in the cavity is unknown.

As far as their energy is concerned, the constructed β-cyclodextrin molecules have several deficiencies: the positions of the hydrogen atoms and the tilts of the glucose units are not perfect. Therefore, the complexes were optimized using the MM2 force field in MacroModel. Since the purpose of this optimization was to eliminate the major deficiencies and not to obtain a complex with a minimum energy, only 20–30 iterations were performed.

The complex formation energies of the optimized, constructed complexes in which the guest has the same position as in the crystal structure correlate well to the complex formation energies of the β-cyclodextrin complexes in crystal structures after these complexes have been optimized (see Fig. 12). The following relation was found:

$$\begin{aligned} &E(\text{constructed}) = 1.26(\pm 0.18)E(\text{crystal}) + 20.10 \\ &n = 8,\ r^2 = 0.979,\ s = 1.600,\ F = 285.29,\ F_{1,6,0\,005} = 18.63 \end{aligned} \tag{6}$$

E(constructed) is the complex formation energy in kJ after optimization of the complex of the constructed β-cyclodextrin molecule in which the guest molecule occupies the same position as in the crystal structure. E(crystal) is the complex formation energy in kJ after optimization of the crystal structure.

We made contour maps to see whether the interaction energies at various locations of the guest in the cavity of the constructed β-cyclodextrin complex corresponded to the interaction energies of the complex as observed in crystal structures (see Fig. 13). These maps were compared with contour maps of the optimized crystal structures (see Fig. 14).

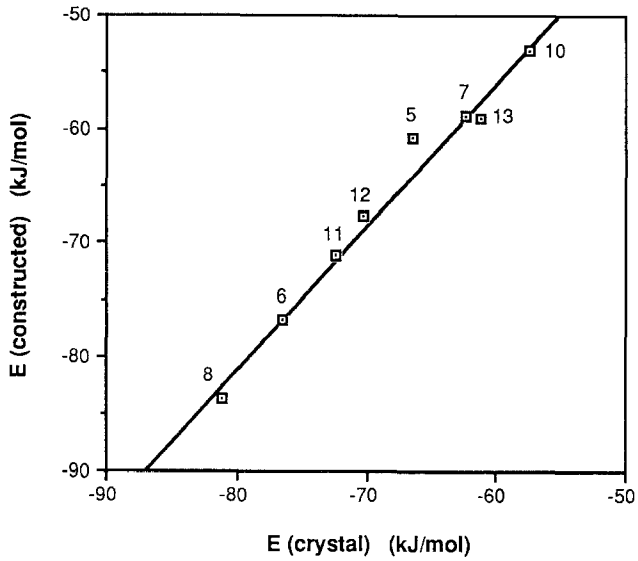

Fig. 12. The interaction energies of constructed and optimized β-cyclodextrin complexes in which the guest occupies the same position in the cavity as in the crystal structure [E(constructed)] compared to the interaction energy after optimization of the complex as present in the crystal structure [E(crystal)].

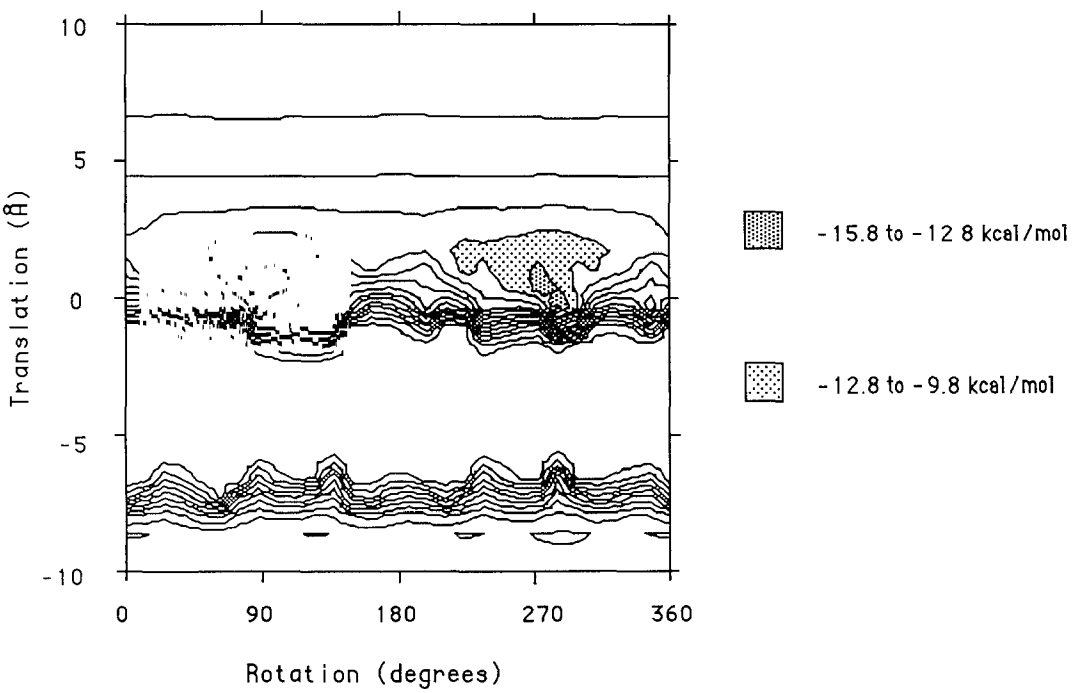

Fig. 13. Isoenergy contour map for translation and rotation of acetylsalicylic acid in the cavity of the constructed and optimized β-cyclodextrin. Fifteen contours are drawn at intervals of 12.6 kJ (3.0 kcal) starting with the lowest interaction energy (−78.7 kJ). The areas corresponding to the lower interaction energies have been shaded.

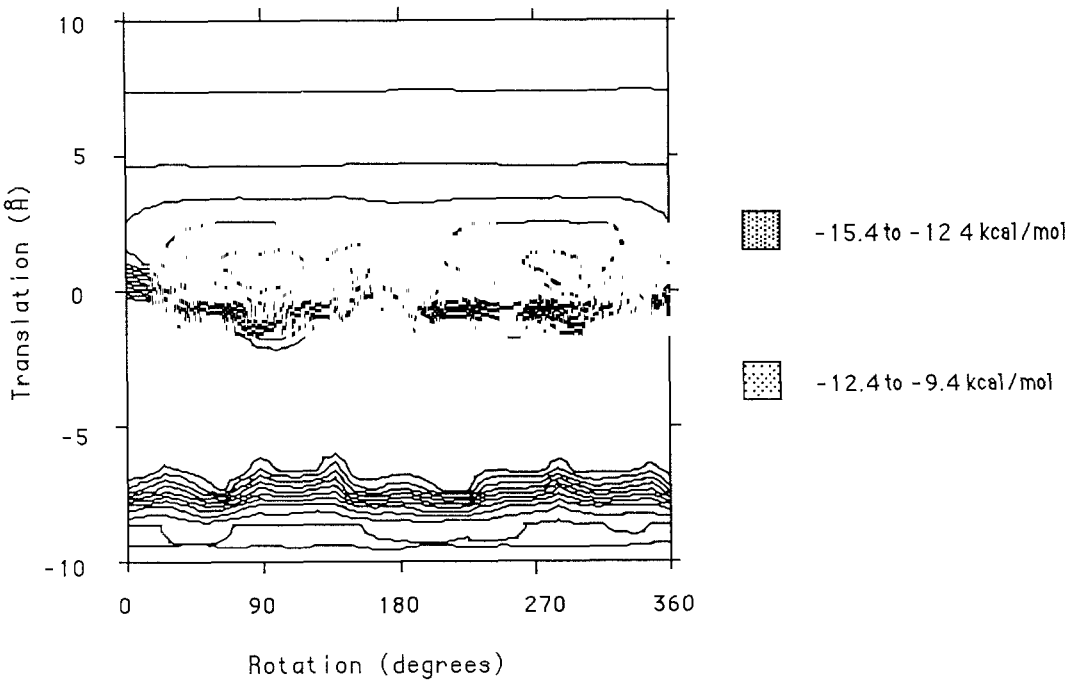

Fig. 14 Isoenergy contour map for translation and rotation of acetylsalicylic acid in the cavity of the optimized β-cyclodextrin molecule. Fifteen contours are drawn at intervals of 12.6 kJ (3.0 kcal) starting with the lowest interaction energy (−77.0 kJ). The areas corresponding to the lower interaction energies have been shaded.

In general the interaction energies at various locations of the guest molecule in the cavity are estimated accurately. In the cases of the complexes containing hexamethylenetetramine and 1,4-diazabicyclo[2.2.2]octane the highest interaction energies are much lower in the constructed complexes. In these two cases the glucose units of the β-cyclodextrin molecules have a much larger tilt than those of the constructed β-cyclodextrin molecules. Therefore as these two guest molecules are moved through the cavity they do not come into van der Waals overlap with the constructed β-cyclodextrin molecules whereas in the crystal structure they do.

It can be concluded that the constructed and optimized β-cyclodextrin molecules are a good approximation of the corresponding molecules in the crystal structure after these have been optimized.

In the case where the guest molecule is docked into the cavity of the constructed β-cyclodextrin molecule, the interaction energies of the constructed complexes after optimization correspond well to the interaction energies of the complexes obtained by optimization of the crystal structures (see Fig. 15). Only in the cases of 1-adamantanemethanol and 1-adamantane-carboxylic acid the interaction energies of the optimized constructed complexes are much lower than the interaction energies of optimized β-cyclodextrin complexes as found in the crystal structures. The equation for the interaction energy is

$$E(\text{docked}) = 0.82(\pm 0.22)E(\text{crystal}) - 8.25 \qquad (7)$$

$$n = 6,\ r^2 = 0.963,\ s = 1.291,\ F = 102.80,\ F_{1,4,0.005} = 31.33$$

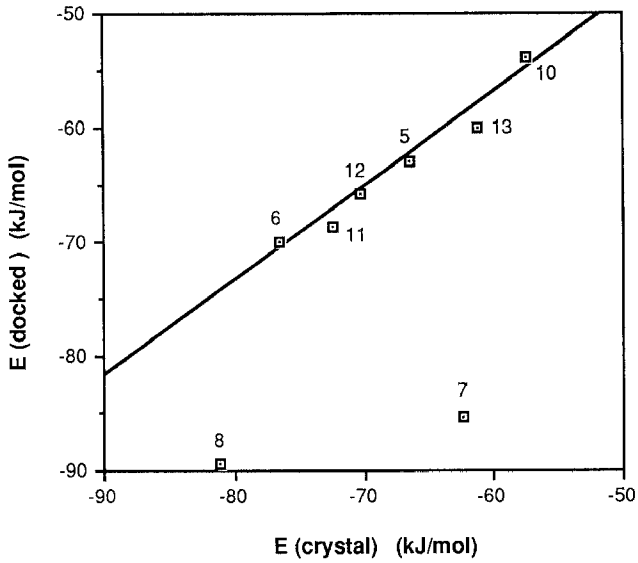

Fig. 15. The interaction energy of constructed and optimized β-cyclodextrin complexes in which the guest has been docked from the external position [E(docked)] compared to the interaction energy after optimization of the complex as present in the crystal structure [E(crystal)].

E(docked) is the interaction energy in kJ after a guest molecule has been docked into the constructed β-cyclodextrin cavity and the complex has been optimized.

When the location of a guest molecule is unknown, the method of docking of a guest molecule into the cavity of a constructed β-cyclodextrin and optimization of this complex can be used to obtain a complex that has an interaction energy comparable to or lower than the interaction energy obtained by using the optimized crystal structure.

Conformation of primary hydroxyl groups

The primary hydroxyl groups can occur in three different conformations, gauche-gauche, gauche-trans and trans-gauche (see Fig. 16). Up till now, only the gauche-gauche and gauche-trans conformations have been found in crystal structures of β-cyclodextrin. In the gauche-trans conformation the primary hydroxyl groups are turned towards the center of the cavity whereas in the gauche-gauche conformation they are turned away from the center of the cavity. The number of primary hydroxyl groups in gauche-trans conformation is listed in Table 4 for each β-cyclodextrine molecule investigated. When a primary hydroxyl group is statistically disordered over the gauche-gauche and gauche-trans conformations, it is counted in Table 3 as the fraction of the total number of times it occurs in the gauche-trans conformation.

It is commonly accepted that the gauche-trans conformation of the primary hydroxyl groups is more likely to occur than the gauche-gauche conformation when it is possible for a hydrogen bond to form between the guest molecule and this primary hydroxyl group [14]. In only 5 complexes all the primary hydroxyl groups are in the gauche-gauche conformation. However, only in 4 of the 18 complexes studied there was a possibility for hydrogen bonds to form between the guest molecule and the primary hydroxyl groups of the β-cyclodextrin molecule.

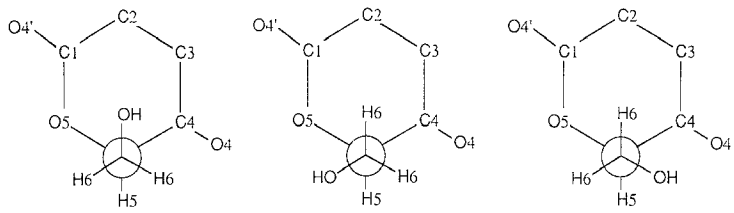

Fig. 16. The conformations of the primary hydroxyl group of glucose.

In the model described above all primary hydroxyl groups were assumed to be in the gauche-gauche conformation. To investigate the influence of the conformation of the primary hydroxyl groups on complex stability, we constructed a β-cyclodextrin molecule which had three primary hydroxyl groups in the gauche-trans conformation. This molecule was constructed so as to accommodate the guest molecule of complex 6 (hexamethylenetetraamine). Since this complex has more primary hydroxyl groups in the gauche-trans conformation than any other complex their combined influence should be the most noticeable. The contour map of this complex however, was no improvement over the contour map of the same constructed β-cyclodextrin molecule in which all primary hydroxyl groups had the gauche-gauche conformation. The reason is that a primary hydroxyl group in the gauche-trans conformation does not protrude far enough into the cavity for steric hindrance to occur. Therefore there is probably another mechanism besides steric hindrance which determines the conformation of the primary hydroxyl groups.

TABLE 4
THE NUMBER OF PRIMARY HYDROXYL GROUPS IN GAUCHE-TRANS CONFORMATION AND THE NUMBER OF HYDROGEN BONDS BETWEEN THE PRIMARY HYDROXYL GROUPS OF A β-CYCLODEXTRIN MOLECULE AND THE CORRESPONDING GUEST MOLECULE

Complex	Primary OH in gauche-trans conformation	Number of H-bonds
1	2.5	2.5
2	1	0
3	2	0
4	0	0
5	2	0
6	4	0
7	0	0
8+9	0.5	0
10	1	0
11	0	0
12	2.67	1
13+14	0.5	0
15+16	0.5	0.5
17	0	0
18	0	0

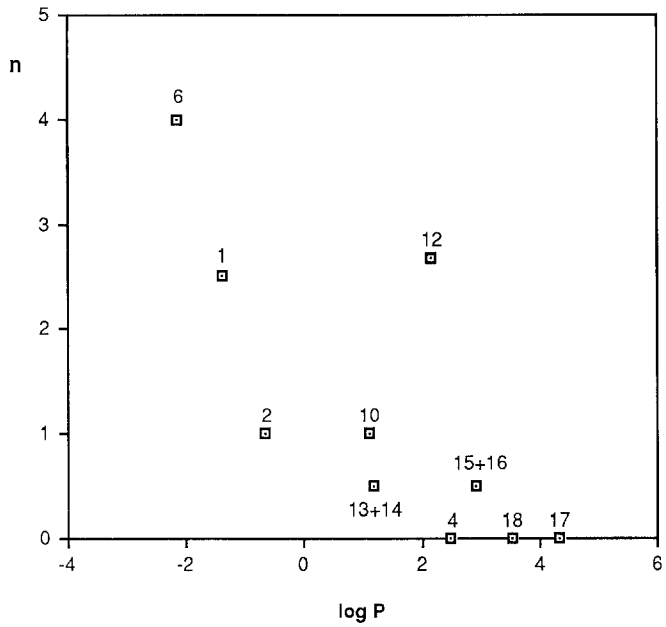

Fig. 17 The number of primary hydroxyl groups in gauche-trans conformation in β-cyclodextrin molecules (n) versus the log P of the guest molecule.

In Fig. 17 the number of primary hydroxyl groups in gauche-trans conformation is plotted against the log P of the guest molecule. β-Cyclodextrin molecules with a hydrophilic guest tend to have a higher number of primary hydroxyl groups in the gauche-trans conformation than β-cyclodextrin molecules with a hydrophobic guest. The benzocaine–β-cyclodextrin complex (complex 12) however, does not show this tendency. This is the only complex studied in which a water molecule is trapped inside the cavity. In addition the benzocaine molecule has one hydrogen bond with a primary hydroxyl group of the β-cyclodextrin molecule [16].

CONCLUSIONS

In β-cyclodextrin complexes the positions of the glycosidic O4 atoms indicate that the β-cyclodextrin molecules are elliptically distorted. This distortion correlates well with the van der Waals volume of the guest molecule, large guest molecules giving rise to less distortion than smaller guest molecules. The correlation is different for aromatic and non-aromatic compounds. Rigid body docking experiments demonstrated that in crystal structures the guest molecule occupies a position in the cavity of nearly minimum interaction energy when there are no other molecules having interactions with the guest molecule.

From the crystallographic data several rules can be deduced which seem to determine the conformation of β-cyclodextrin molecules in complexes. A simple procedure has been developed to construct β-cyclodextrin molecules which are able to encompass guest molecules that have a given van der Waals volume. After a guest has been docked into such a constructed β-cyclodextrin and the complex has been optimized, the interaction energy of this complex was calculated. In ad-

dition, we calculated the interaction energy after optimization of the same β-cyclodextrin complex as observed in the crystal structure. The fact that these two interaction energies show a good correlation indicates the usefulness of the proposed procedure for constructing β-cyclodextrin complexes.

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