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Semiempirical Calculations on Cyclodextrins

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Abstract. In order to obtain information on the different reactivities of the hydroxyl groups of the glucopyranose units or the inclusion complex formation mechanism, the charge distributions and the geometrical constraints must be determined. Geometry optimizations, employing the AM1 semiempirical method, have been performed for α-D-glucopyranose, α-, β-, and γ-cyclodextrins. The data obtained were compared with X-ray diffraction data of the cyclodextrins.

Key words: α-D-Glucopyranose, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, charge distribution, AM1 molecular orbital calculation, optimized geometries.

1. Introduction

Both 'naked' and chemically modified glucopyranose oligomers and polymers represent an important group of carbohydrates with wide industrial applications. Cyclodextrins are cyclic oligomers of $\alpha(1 \rightarrow 4)$ linked glucopyranose monomers, which can incorporate small organic (and several inorganic) compounds into their cavity. The most common cyclodextrins (CDs), αCD, βCD, and γCD, consist of six, seven, or eight anhydroglucopyranose units, respectively [1]. Several X-ray diffraction studies have been carried out to reveal the geometric structures of CDs and their complexes. Theoretical investigations of these structures are scarce.

Only small molecules, such as α-D-glucopyranose (αDGlcp) or maltose and its several derivatives, have been investigated by semiempirical methods, as in [2]. The main purpose of these calculations was to find an explanation for the experimentally observed substitution patterns of glucopyranosyl oligomer derivatives. The results of these calculations cannot be transferred directly to cyclodextrins, due to the flexibility of the studied molecules. The transferability of the results obtained remained unclear because the small, free-ended molecules have essential structural differences from CDs, though the reactivity characteristic of the glucopyranose unit could be similar to glucose.

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X-ray studies of a number of crystalline complexes of cyclodextrins revealed: (a) geometrical features of the host–guest interaction; (b) the conformation of the macrocyclic ring [11]. On the basis of these data the chemical and physical properties of the inclusion complexes have been interpreted. X-ray diffraction data are also available for unsubstituted, uncomplexed α-, β-, and γ-cyclodextrin hydrates [3–5]. These studies indicate a rigid, well-defined, round-shaped molecular structure for all the cyclodextrins studied. It is well known that X-ray diffraction experiments do not yield information on the positions of the hydrogens or about possible motions of the glucopyranose units.

While in the solid phase the molecules have well-defined, rigid structures, which more or less reflect the structure in solution, the theoretical calculations are performed '*in vacuo*'. Although, in principle, solvent–solute interactions could be estimated theoretically, parametrization of these methods is still under development. The dynamic character of the molecules, particularly in solutions, permits other structural features than those present in the solid state. This also assumes that: (a) semiempirical calculations may predict conformations which are lower in energy than the conformer in the crystal; and (b) in solutions the lowest energy conformer is not necessarily the same as that calculated '*in vacuo*'. However, most hydrogen bonds, both intra- and intermolecular, can be preserved in the solid state, because of the solvent molecules intercalated into the crystal. Semiempirical calculations are focused on the intramolecular correlations, so the appropriate equilibrium between the two structural determinations is necessary to approach the real conformations in solution. In order to determine the effects of symmetry breaking molecular mechanics studies (using the MM2 and AMBER force fields) on cyclodextrins have also been done, because these changes could play an essential role in solutions or during the process of complexation [6].

In order to investigate the geometrical changes during the complexation process, it is necessary to compare the results of semiempirical calculations to structures obtained from X-ray experiments on unsubstituted, uncomplexed cyclodextrins. For the present study the AM1 semiempirical method was chosen for geometry optimizations. α-Cyclodextrin hydrates without added guest molecules exit in three crystal forms: two hexahydrates, and one with 7.25 molecules of crystal water. For the structural comparisons the latter was chosen, where a circular hydrogen bond system was found between O2–O3′. In the case of β- and γCDs only one X-ray structure is available for the unsubstituted, uncomplexed state.

The energy surface has a large number of minima which differ at most by 1–2 kcal/mole from each other due to minimal conformational differences. There is no evidence that the energy minimum obtained is the global minimum, but small geometric variations do not cause essential differences in the charge distribution. In order to obtain information about the minima found, several preliminary molecular mechanics and molecular dynamics runs were also performed. These calculations showed deep minima in the optimized geometries. In order to avoid a false mini-

mum caused by a saddle-point, normal mode analyses were also performed on the geometries obtained.

The main purpose of our calculations was to obtain a reliable charge distribution for cyclodextrins, i.e. only the main features of the obtained geometries have practical value. The semiempirical method used is available in various software packages, therefore for guest molecules it is easy to obtain a usable starting geometry and charge distribution for molecular mechanics or molecular dynamics calculations.

2. Experimental

The AM1 semiempirical molecular orbital calculations were performed on an IBM RS6000/m350 computer using the quantum chemical program MOPAC 6.0. Initial and final geometrical data were handled on an IBM AT compatible 486/DX-33 computer using MolIdea®, Version: 4β [8]. Initial structures were obtained from the appropriate X-ray coordinates [3–5], and αDGlcp was built by a former version of MolIdea®. The required computational times from X-ray data, as initial geometries, were $\sim$ 18 h, $\sim$ 50 h, $\sim$ 120 h for αCD, βCD, and γCD, respectively; and αDGlcp required several minutes. Preliminary molecular mechanics (MM2) and molecular dynamics simulations were made by HyperChem® (Release 3) on an IBM AT compatible computer.

3. Results and Discussion

3.1. General and electronic properties

Visualization of the optimized structures of the molecules suggested that glucopyranose units are in the $^4C_1$ conformation in all cyclodextrins investigated, as indicated in Figure 1. The optimized structures are similar to the initial ones, though more puckered macrocycles were obtained in the case of α- and βCDs.

The charge and energy results of the AM1 calculations are provided in Tables I and II. Incorporation of the glucopyranosyl unit results in an increase of the absolute value of the heat of formation from αCD to βCD and from βCD to γCD. The charge distribution in cyclodextrins is practically the same as in 'free' glucose. The small differences could be explained by the exchange of the hydrogens of glucose to carbon in the macrocyclic ring. Small differences in the charge distribution do not explain the relatively high dipole moment of αCD, suggesting larger steric differences between αCD and the other two cyclodextrins than between βCD and γCD. Graphical comparison of the optimized structures confirmed this idea: αCD seems to have the least symmetric macrocycle among the studied cyclodextrins (see later). The slightly less negative charge on O4, where the largest variance was obtained compared to glucose, could also be explained by the exchange of the O4

TABLE I.

TABLE I

Formatted MOPAC output of AM1 calculations

	α-D-Glucopyranose				α-cyclodextrin				β-cyclodextrin				γ-cyclodextrin			
Final heat of formation	−304.12 Kcal				−1409.99 Kcal				−1652.67 Kcal				−1894.71 Kcal			
Total energy	−2858.51 eV				−15057.09 eV				−17566.94 eV				−20076.76 eV			
Electronic energy	−14349.34 eV				−196918.14 eV				−249574.78 eV				−296930.13 eV			
Core–core repulsion	11490.83 eV				181861.05 eV				232007.84 eV				276853.36 eV			
Ionization potential	10.91 eV				10.30 eV				10.33 eV				10.40 eV			
No. of filled levels	36				192				224				256			
Molecular weight	180.16				972.85				1134.99				1297.14			
SCF calculations	92				815				1020				1333			
Dipole	*X*				*Y*				*Z*				Total			
	αDGlcp	αCD	βCD	γCD	αDGlcp	αCD	βCD	γCD	αDGlcp	αCD	βCD	γCD	αDGlcp	αCD	βCD	γCD
Point Chg.	0.65	−2.53	2.18	0.64	−0.80	−3.24	−0.27	−0.13	1.01	1.09	1.80	−2.43	1.44	4.27	2.84	2.52
Hybrid	−0.47	0.19	−2.19	−1.18	−1.04	−2.88	−1.71	−2.75	−0.29	−3.68	−1.31	2.84	1.17	4.68	3.06	4.13
Sum	0.18	−2.34	0.00	−0.54	−1.83	−6.13	−1.97	−2.88	0.72	−2.59	0.49	0.41	1.98	7.06	2.03	2.96

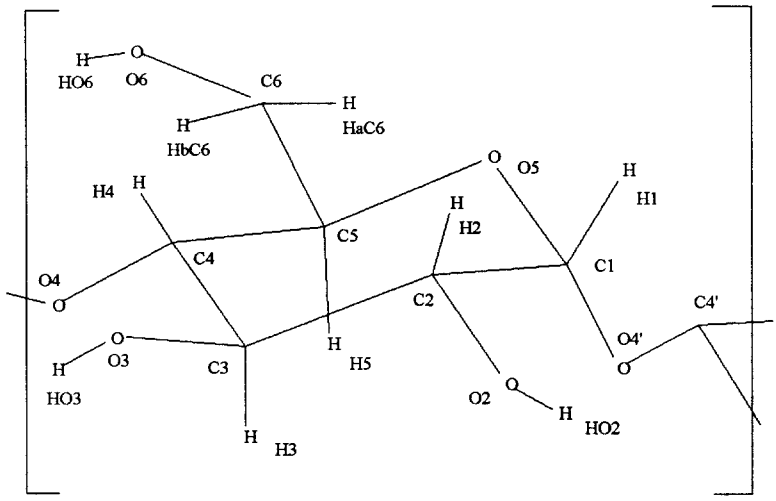

Fig. 1. Chemical structure and numbering of atoms in the glucopyranosyl residues.

TABLE II. Calculated atomic charges (averaged)[a]

	αDGlcp	αCD	βCD	γCD
O1 (Glucose)	–0.37			
C1	0.12	0.14(2)	0.12(0)	0.13(0)
C2	–0.01	0.02(4)	–0.03(1)	–0.03(1)
O2	–0.32	–0.33(1)	–0.32(0)	–0.33(0)
C3	–0.04	0.00(1)	–0.02(2)	–0.01(1)
O3	–0.33	–0.34(1)	–0.34(0)	–0.33(2)
C4	0.01	0.00(2)	0.02(0)	0.02(0)
O4	–0.34	–0.30(0)	–0.30(0)	–0.30(0)
C5	–0.01	–0.02(0)	–0.02(1)	–0.02(0)
O5	–0.29	–0.29(1)	–0.28(1)	–0.28(1)
C6	0.00	–0.03(0)	–0.02(1)	–0.02(0)
O6	–0.33	–0.33(0)	–0.33(0)	–0.32(2)
HC1	0.12	0.14(0)	0.15(1)	0.15(1)
HC2	0.14	0.11(1)	0.13(1)	0.13(0)
HO2	0.22	0.23(1)	0.23(1)	0.23(0)
HC3	0.11	0.11(0)	0.11(1)	0.11(0)
HO3	0.22	0.23(1)	0.22(0)	0.23(0)
HC4	0.10	0.12(1)	0.12(1)	0.11(0)
HC5	0.12	0.12(0)	0.12(1)	0.12(1)
HaC6	0.07	0.09(1)	0.08(1)	0.09(0)
HbC6	0.12	0.13(1)	0.12(1)	0.12(1)
HO6	0.22	0.21(0)	0.22(0)	0.22(0)

[a] Standard deviations are given in parentheses and apply to the last digit.

hydrogen to carbon. Other differences in the charge distribution are too small to be considered significant.

3.2. GLUCOPYRANOSE CONFORMATION

3.2.1. Bond lengths

It is evident that the calculated results show smaller deviations from the means than the crystallographic data. Mean distances from both the calculation results and X-ray structures are presented in Table III. In almost all cases the bond lengths in the macrocycle were not significantly longer than in glucose. Significant differences were obtained only for C1–O4′ (C1–O1) and C4–O4. Both bond lengths were calculated to be longer than in glucose.

The mean values of the C–C and C–O bond distances showed significantly smaller standard deviations (STD) than X-ray data. The C–O and C–C distances greatly depend on the chemical structure. In particular, the C5–O5 and C4–O4 mean bond lengths of about 1.43 Å showed large variation from the overall mean C–O distance (1.419 Å). The overall mean C–O distances in cyclodextrins were larger than in glucose (1.415 Å) but the difference is not significant because of the large STDs. Other C–O distances were below the overall mean value. It is surprising that the shortest bond is C6–O6. This bond length is considerably shorter, about 0.02–0.03 Å, than the experimental values, where the hydroxylic C–O bonds have almost equal lengths. This might be explained by experimental errors, as indicated in [3]. The length of the shortest C–O bond is 0.005 Å longer than the standard value. [10] The C–C distances show smaller variations, and they are about 0.01–0.02 Å longer than the experimental values, which in turn, are close to the standard (1.523 Å).

The smaller difference in comparison with glucose and the STD of the mean value of C1–C4 interatomic distances of the AM1 calculation (2.89 Å in glucose, and 2.90 Å in CDs, and 0.005–0.007 Å, resp.) suggest that the pyranose ring presents similar conformations both in all CDs and glucose, while the corresponding values in the X-ray data show more distorted and less equivalent pyranose rings.

3.2.2. Bond angles

The optimized bond angles of the pyranose ring conformation (angles between the ring-constituting atoms, except C2–C1–O5) are similar to those of glucose within acceptable experimental error, as demonstrated in Table IV. The corresponding parameter in the X-ray derived data showed larger deviations indicating a more distorted structure in the solid state. The smaller C2–C1–O5 angles in both the computed and the measured structures (about 110° in CDs and 114.2° in glucose) indicate a small asymmetric longitudinal expansion on the glycosidic side, while the opposite side of the six-membered ring remains almost unchanged.

TABLE III. Bond lengths and selected interatomic distances (Å) of calculated and X-ray structures of cyclodextrins[a]

	AM1				X-ray		
Atom 1–Atom2	αDGlcp[b]	αCD	βCD	γCD	αCD	βCD	γCD
C1–O4′ 1.409	1.415(3)	1.417(2)	1.420(2)	1.416(12)	1.419(9)	1.421(17)	
C1–O5	1.411	1.412(4)	1.410(3)	1.410(1)	1.418(8)	1.414(10)	1.406(13)
C1–C2	1.539	1.541(2)	1.539(3)	1.539(2)	1.533(11)	1.524(13)	1.525(11)
C2–C3	1.535	1.534(1)	1.535(1)	1.536(1)	1.510(9)	1.527(6)	1.527(14)
C2–O2	1.411	1.414(2)	1.411(2)	1.409(1)	1.430(9)	1.439(8)	1.425(12)
C3–C4	1.536	1.540(1)	1.540(1)	1.540(2)	1.522(10)	1.485(45)	1.555(59)
C3–O3	1.418	1.417(1)	1.419(1)	1.418(0)	1.440(3)	1.439(7)	1.436(11)
C4–C5	1.537	1.537(1)	1.539(2)	1.539(2)	1.535(8)	1.536(15)	1.526(19)
C4–O4	1.417	1.431(3)	1.430(2)	1.428(2)	1.441(8)	1.453(31)	1.440(8)
C5–C6	1.534	1.534(2)	1.536(4)	1.534(1)	1.516(11)	1.527(18)	1.512(19)
C5–O5	1.431	1.432(1)	1.432(1)	1.434(1)	1.445(7)	1.450(12)	1.458(13)
C6–O6	1.409	1.411(1)	1.410(2)	1.409(1)	1.440(12)	1.392(38)	1.431(33)
Average C–C[c] (1.523)	1.536(2)	1.538(2)	1.538(1)	1.538(2)	1.518(17)	1.530(13)	
Average C–O[c] (1.402)	1.415(6)	1.419(7)	1.419(7)	1.418(8)	1.433(10)	1.429(18)	1.431(21)
Interatomic distances							
C1–C4	2.890	2.902(5)	2.902(7)	2.899(7)	2.878(10)	2.852(38)	2.888(26)
C1–C4′		2.371(76)	2.416(14)	2.409(5)	2.454(12)	2.467(45)	2.436(13)
O2–O3	2.932	2.870(27)	2.899(27)	2.880(14)	2.910(30)	2.895(19)	2.887(26)
O2–O3′		3.213 (166)	3.318 (343)	3.015(24)	2.981(66)	2.858(47)	2.823(43)
O4–O4′	4.513	4.23 (101)	4.127 (221)	4.392(50)	4.235(33)	4.378(75)	4.501(53)
O5–O6	3.574	2.94 (151)	3.182 (201)	3.279 (281)	2.870(82)	2.823(42)	2.828(43)
O4–O6	2.931	3.780 (177)	3.705 (392)	3.521 (511)	3.645 (109)	3.853 (291)	3.847 (293)
O4′–O5	2.263	2.248(3)	2.255(26)	2.239(17)	2.335(6)	2.331(4)	2.328(10)

[a] Standard deviations are given in parentheses and apply to the last digit(s).

[b] C1–O4′ corresponds to C1–O1 in case of αDGlcp.

[c] Standard value [10] is given in parenthesis.

The overall means of the C–C–C bond angles are close to the standard value, but slightly higher. The average C–C–O bond angles are closer to the tetrahedral value than the C–C–C angles but they have a larger deviation from the tetrahedral value not only in the X-ray but also in the computed structures. It is interesting

TABLE IV. Bond angles (in degrees)[a]

Atom 1– Atom 2– Atom3	AM1				X-ray		
	αDGlcp[b]	αCD	βCD	γCD	αCD	βCD	γCD
C4′–O4′–C1		116.3(3)	116.1(12)	115.7(4)	118.4(5)	118.3(11)	116.8(6)
O4′–C1–O5	106.7	105.4(2)	104.8(12)	104.6(13)	111.0(8)	110.8(6)	111.0(13)
O4′–C1–C2	107.7	109.1(8)	109.1(14)	109.6(19)	107.6(4)	108.1(6)	108.7(11)
C1–C2–C3	110.7	110.0(5)	110.0(7)	110.3(3)	110.2(7)	110.0(10)	110.7(14)
C1–C2–O2	111.3	108.8(16)	112.1(5)	112.4(2)	108.1(15)	109.4(10)	110.3(9)
C1–O5–C5	115.2	115.4(4)	115.5(8)	115.5(4)	114.0(4)	114.0(5)	114.5(10)
C2–C3–C4	109.7	110.0(5)	111.4(9)	109.7(5)	111.0(8)	109.1(9)	109.8(11)
C2–C1–O5	114.2	111.1(9)	110.8(10)	112.0(7)	109.2(1)	110.2(7)	110.9(9)
O2–C2–C3	110.4	110.5(17)	109.6(6)	110.3(5)	110.6(11)	110.9(5)	110.5(10)
C2–C3–O3	111.1	107.7(15)	110.7(4)	110.7(6)	109.0(7)	109.8(6)	109.4(14)
C3–C4–C5	109.0	111.0(12)	111.2(19)	109.0(5)	112.0(4)	111.6(24)	109.7(8)
C3–C4–O4	110.9	105.2(11)	105.7(24)	106.8(10)	106.0(9)	106.9(8)	106.6(4)
O3–C3–C48	106.7	109.6(20)	106.7(3)	107.5(3)	108.8(9)	110.0(9)	109.4(14)
C4–C5–C6	111.8	112.3(10)	112.3(6)	112.8(12)	113.3(1)	114.0(23)	114.1(14)
C4–C5–O5	110.0	111.2(11)	112.0(21)	110.4(7)	109.2(8)	108.1(19)	107.5(10)
O4–C4–C5	107.0	108.4(8)	107.5(7)	108.6(7)	108.1(9)	108.0(19)	109.7(14)
O5–C5–C6	106.0	104.9(6)	104.5(10)	104.5(8)	106.1(9)	105.5(6)	105.8(13)
C5–C6–O6	110.7	111.9(5)	111.9(10)	111.9(8)	112.5(11)	110.8(14)	110.3(20)
O4–O4′–O4″		119.7(46)	123.4(61)	132.1(25)	119.9(16)	128.3(20)	134.9(11)
(theoretical[c])		120.0	128.6	135	120.0	128.6	135
Average C–C–C[d] (109.5)	110.3(9)	110.9(11)	111.1(13)	110.4(12)	111.6(11)	111.4(20)	111.1(19)
Average C–C–O[d] (107.7)	109.6(20)	108.9(23)	109.2(25)	109.5(28)	108.6(16)	108.8(17)	109.0(18)
Average C–O–C[d] (106.8)	115.2	115.8(5)	115.8(10)	115.6(4)	116.2(22)	116.1(22)	115.6(13)
Average O–C–O[d] (97.0)	106.7	105.4(2)	104.8(12)	104.6(13)	111.0(8)	110.8(6)	111.0(13)

[a] Standard deviations are given in parentheses and apply to the last digit(s).

[b] O4′ corresponds to O1 in case of αDGlcp.

[c] Counted as angle of an ideal polygon, $180° - 360°/n$, n = number of glucose units.

[d] Standard value [10] is given in parentheses.

that among the computed bond angles the overall means of the C–O–C angles have the smallest differences to those in glucose. The variations of computed and

experimental values are relatively small. However, differences between those and the standard values are quite high (8.4–9.8°).

The largest differences between the computed and experimental values were observed in the case of the O–C–O angles. The computed values were essentially identical in both cases, but interestingly the experimental values have smaller deviations. These differences varied from about 8° (computed) to about 14° (experimental).

3.3. MACROCYCLIC RING CONFORMATION

The macrocyclic ring conformations can be described in three different ways: (a) using certain interatomic distances; (b) using several bond angles; and (c) employing characteristic, torsion angles.

3.3.1. Interatomic distances

Since interatomic distances between the adjacent glucopyranosyl units are indicative of the shape of the macrocyclic ring, their STDs must be higher than for the bond lengths and interatomic distances in the same glucose. The deviations generally give more information on the macrocyclic structure than the absolute value itself. The only two exceptions are the O2–O3 and O2–O3′ distances. Smaller values were obtained for cyclodextrins (both experimental and computed cases) than for glucose. A possible explanation could be that macrocycle formation makes the glucopyranose rings more planar, causing a small, about 0.02–0.06 Å, shortening of the O2–O3 distances. Circular hydrogen bonding systems were assumed in the case of α- and βCDs [3,4], and only two hydrogen bonds were assumed in γCD [5]. While the interatomic distances (with small deviations) in the experimentally obtained structures permit this explanation, there seem to be no reasons to conclude that circular hydrogen bond formation leads to the lowest energy structure, as demonstrated in Figure 2. It can be seen that some 'extra' hydrogen bonds may be also formed. In solutions the intramolecular hydrogen bonds can change resulting in a structure having lower energy. The large variations of this parameter in computed cases suggest that in aqueous solutions intermolecular hydrogen bonds may be more important than intramolecular hydrogen bonds.

Large deviations of C1–C4′ and O4–O4′ may give information about the asymmetric character of the round shape. Higher deviations in the O4–O4′ distances (as in cases of computed α- and βCDs) could be derived from the offset of one or several glycosidic oxygens from the plane fixed between the averaged position of these oxygens. Deformation of that plane requires the inward twisting of the pyranosyl plane from the cylindrical shape. Another consequence of the mentioned torsion in the interatomic distances is the large deviations in the O5–O6 and O6–O6′ distances, but the latter depends on other factors, as well. The overall mean of the O6–O6′ distances and their large deviations, particularly in the case of β- and

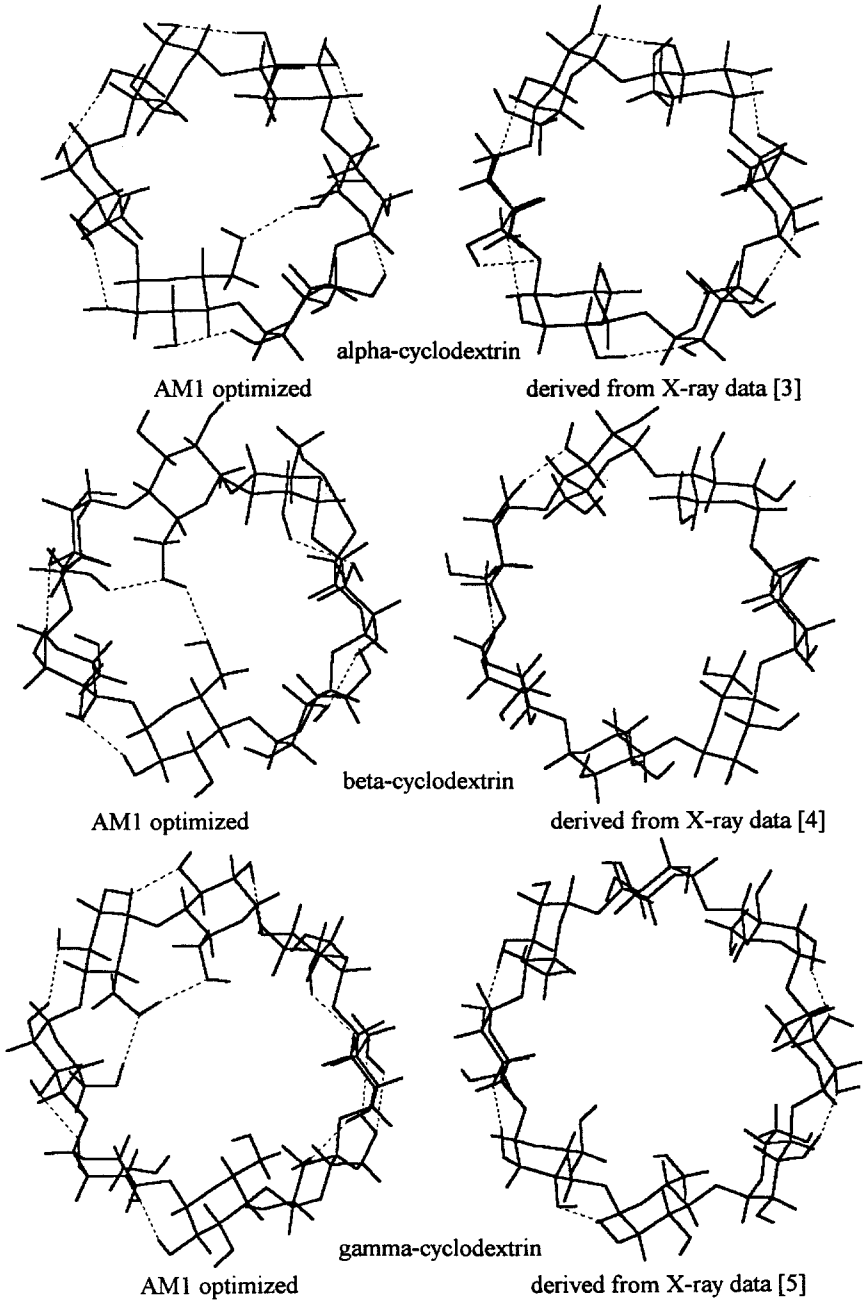

Fig. 2. Wire model plot of cyclodextrins (from the secondary hydroxyls). Dotted lines indicate the hydrogen bonds.

γCDs, more particularly in case of βCD suggest that hydrogen bonds may also exist between primary sites of glucose units.

3.3.2. Bond angles

The angles of the glycosidic oxygen between three adjacent glucose units give information on the deformation in the longitudinal direction of the glucopyranosyl planes. In ideal cases the O4–O4′–O4″ angle must correspond to angles of a hexagon (120°), heptagon (128.6°), and octagon (135°) for α-, β-, and γCD, respectively. The values presented in Table IV show that in the crystals these angles are close to the ideal values in both cases, but in the computed structures only αCD approaches that value. In the β- and γ-cyclodextrins the O4–O4′–O4″ angles are smaller (and have large STD) than expected geometrically. This indicates that the macrocycle is more flexible in the 'gas phase' than in the solid phase, where the water molecules stretch out the molecule.

3.3.3. Torsion angles

The commonly used parameter for the description of the shape deformation of CDs is the torsion angle between four adjacent glycosidic oxygens. The overall mean is almost the expected 0°, but the standard deviations indicate large differences between the individual values of O4–O4′–O4″–O4‴. In most cases the *lege artis* averaging cannot be performed and values must be grouped. Similar results were obtained in cases when the torsion angles were determined between different glucosyl moieties. Torsion angles, with only a few exceptions, showed good agreement with the corresponding values of glucose, as indicated in Table V. The largest variations were obtained in the following cases: C1–O5–C5–C6, O5–C5–C6–O6, and C4–C5–C6–O6.

Comparing the calculated geometries with the statistical evaluation of cyclodextrin structures [12] one can conclude that the main torsion angles show large deviations from the statistical mean. The O5–C5–C6–O6 angles of the computed structures are far from the crystalline ones particularly in case of α- and βCDs and only several angles approximate those values ($-61.9°$ and 70.1°, respectively). An explanation would be the intramolecular hydrogen bonds which stabilize the inside twist of several glucopyranose units. The lowest energy conformer of glucose (*trans-gauche*) is a typical theoretical optimum. While in solution the other two conformers (*gauche-gauche* and *gauche-trans*) [13] are present, the intramolecular hydrogen bond between the primary OH and O4 gives the lowest energy state *in vacuo*.

The overall mean of the C4′–O4′–C1–O5 torsion angles are slightly different in the computed structures from the crystalline ones. In the crystalline state these angles are practically the same in both CDs but the computed values showed an increasing trend with increasing size of the macrocycle. A similar tendency was

TABLE V. Torsion angles (in degrees)[a]

Atom1–Atom2–Atom3–Atom4		AM1			X-ray		
	αDGlcp	αCD	βCD	γCD	αCD	βCD	γCD
O4–O4′–O4″–O4‴		12.9(21) –1.0 –6.9(8) –11.0	56.0 20.1 0.5 –8.7(17) –22.9 –35.4	50.6(48) –5.3 –15.3(27) –32.3	4.0(14) –7.8(14)	11.5 2.0 –3.9(16) –11.9	8.7(13) 2.9(12) –5.8(6)
overall mean of O4–O4′–O4″–O4‴		0.0(86)	0.1(218)	0.3(251)	0.1(52)	0.2(70)	0.0(58)
C4′–O4′–		–137.2(54)	–131.7(86) –160.7 –75.7	140.5(19) –91.4(17) –115.8 –138.8(7)	–131.3(43)	–128.7(52)	–131.8(19)
C4′–O4′–C1–O5		103.6(52)	167.1 118.9(16) 101.7(23) 79.1	149.0(24) 125.1 100.0(10)	109.2(46)	117.2(29) 108.0(27) 102.5	118.9(44) 105.7(15)
overall mean of C4′–O4′–C1–O5		103.6(52)	112.7(190)	115.4(192)	109.2(46)	109.8(47)	109.0(49)
C5′–C4′–O4′–C1		–128.8 –117.6(15) –94.2(9)	–149.0(33) –106.1(4) –89.9 –76.2	–124.0(26) –105.3(13)	–123.2(22) –109.7(20) –91.2	–123.4(23) –110.0(21) –95.4	–125.2(20) –110.7(5) –102.4(22)
overall mean of C5′–C4′–O4′–C1		108.2(112)	–117.9(226)	–120.9(119)	–111.6(86)	–111.8(73)	–114.2(85)
C1–C2–C3–C4	–51.1	–53.0(24)	–52.1(26)	–54.1(12)	–52.6(14)	–54.8(16)	–52.6(31)
C2–C3–C4–C5	57.3	53.0(36)	49.6(48)	56.0(12)	50.3(13)	55.9(18)	56.7(21)
C3–C4–C5–O5	–59.6	–53.9(49)	–39.7(33) –56.7(31)	–56.4(25)	–51.9(14)	–56.8(25)	–59.1(28)
C4–C5–O5–C1	57.8	56.8(24)	54.7(60)	57.6(18)	59.8(11)	59.5(27)	62.4(26)
C5–O5–C1–C2	–52.6	–56.2(22)	–57.7(22)	–55.7(11)	–63.1(17)	–60.5(11)	–59.1(25)
O5–C1–C2–C3	48.3	54.1(25)	55.2(43)	52.9(17)	57.9(10)	56.5(21)	52.9(32)
O4′–C1–C2–O2	53.1	60.7(30)	62.3(38)	60.7(30)	58.5(14)	57.3(16)	53.4(23)
O2–C2–C3–O3	67.4	67.3(26)	66.1(23)	62.8(15)	68.1(24)	63.6(17)	64.8(18)
O3–C3–C4–O4	–65.5	–73.0(31)	–73.4(55)	–66.6(15)	–72.1(24)	–66.0(18)	–64.5(16)
O4–C4–C5–C6	62.8	75.6(43)	88.4(45) 70.3(52)	70.6(22)	73.8(20)	66.9(44)	66.9(35)
C3–C4–C5–C6	–177.9	–169.5(38)	–166.7(84)	–173.5(26)	–169.9(15)	–173.7(34)	–174.7(21)
C1–O5–C5–C6	179.0	177.0(9) –179.4	–177.2(18) 167.8(13)	–178.1(7) 177.0(3)	–177.8(12)	–174.5(27) 178.8(4)	–174.7(26) 178.7
O5–C5–C6–O6	154.0	96.1 75.4 –61.9(52) –100.5	118.3(21) 92.9 70.1(73) –93.3 –164.8	108.9(101) 64.0(52) –174.2(23)	–66.1(63)	–64.0(35) 68.7(27)	–61.2(22) 72.8(3)
C4–C5–C6–O6	–86.1	59.1(53) 23.5 –154.9(108)	28.1 –41.1 –118.2(3) –162.4(108)	178.5 130.2 –53.6(21) –145.2(178)	44.5(32) 54.8(4) 62.3(23)	58.7(81) –172.9(24) 74.8	57.9(34) –170.8(26)

[a] In most cases values given in parentheses represent the mean differences between the highest and lowest values, and the mean value, and they should be applied to the last digit(s).

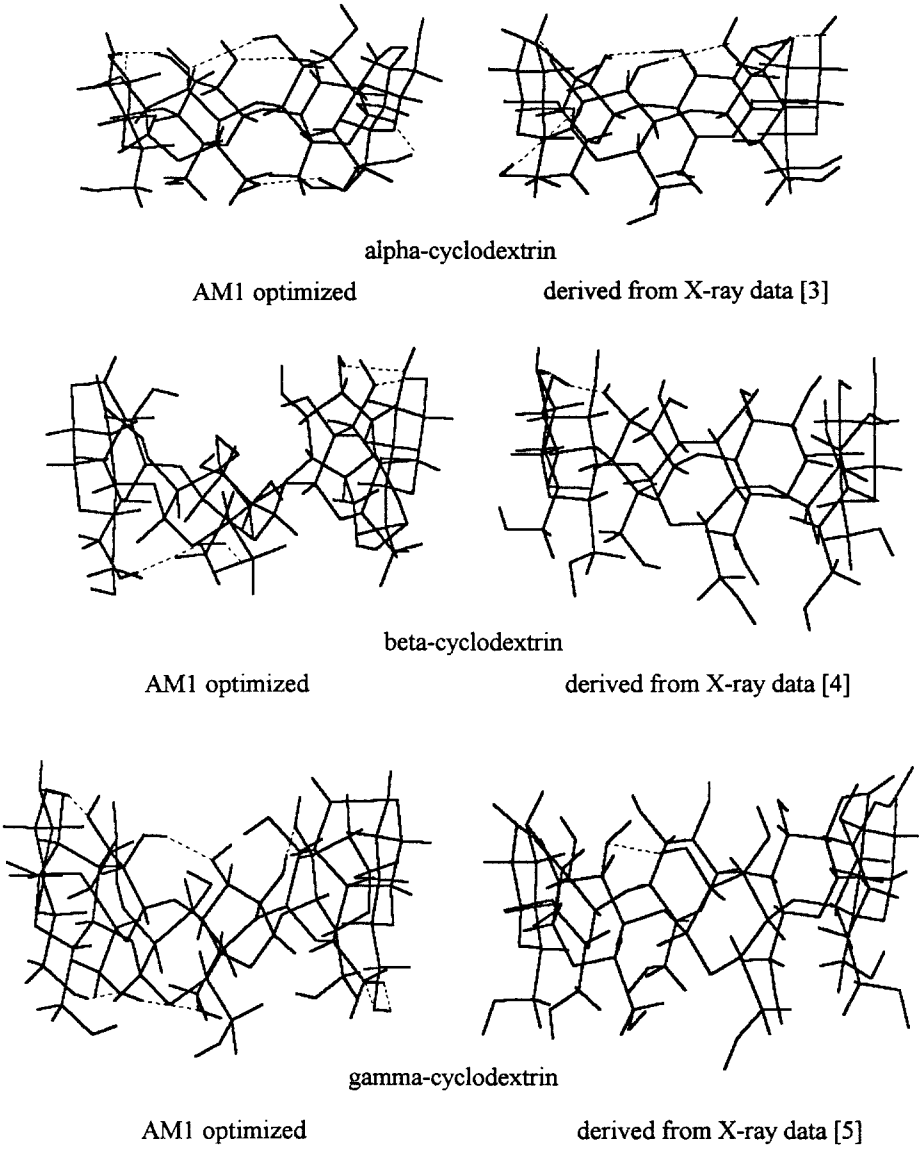

Fig. 3. Wire model plot of cyclodextrins (secondary hydroxyls up, primary hydroxyls down). Dotted lines indicate the hydrogen bonds.

also observed in the case of the C5′–C4′–O4′–C1 angles. These differences are negative in the case of αCD which indicates opposite torsion of glucopyranose units in comparison with the other CDs in the computed structures. The situation is slightly different in the case of the 'linker' oxygens (O4). While the overall means are also close to planarity the individual angles show large variations. In the

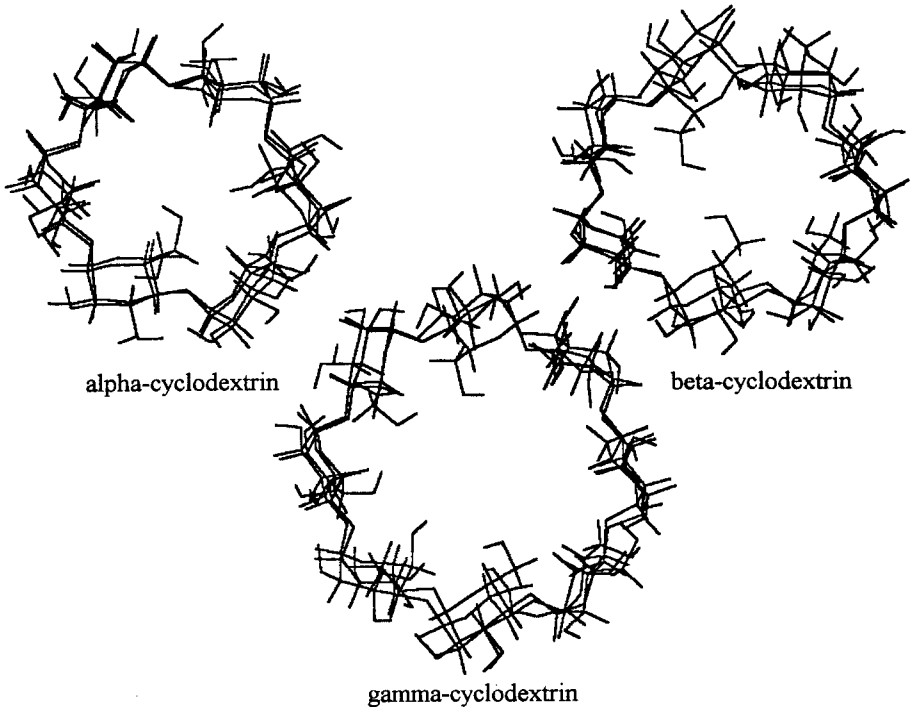

Fig. 4. Overlapped AM1 optimized and X-ray structures of cyclodextrins.

computed structures these angles show a similar increasing trend with increasing size of the macrocycle in contrast to the crystalline structures. The deviations of these angles show a larger flexibility of β- and γCD macrocycles.

4. Conclusions

The application of the AM1 semiempirical method for geometry optimization of CDs resulted in similar structures for the glucopyranosyl residues of cyclodextrins to those deduced from X-ray crystallography. Charge distributions were similar to those of glucose. The main steric parameters for the individual glucose units were close to those of glucose. However, the orientation of glucopyranosyl units in the optimized macrocycle showed marked disagreement with the solid state. The main difference was observed in the positions of the C6–O6 moieties and the presence of inward-turned glucopyranose units of α-, and particularly, βCD, as shown in Figures 2–4.

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