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Structure of the 1 : 1 Complex of Hexakis(2,3,6-tri-*O*-methyl) α-Cyclodextrin with (*R*)-(-)-1,7-Dioxaspiro[5.5]undecane

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Abstract. The crystal structure of the 1 : 1 inclusion complex of hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin (TMαCD) with 1,7-dioxaspiro[5.5]undecane (spiroacetal) is orthorhombic, space group $C222_1$, with a = 24.002(2), b = 14.812(1), c = 21.792(2) Å, V = 7747.3(11) Å^3 and Z = 8. The molecular six-fold axis of TMαCD coincides with the a two-fold crystallographic axis and the guest is located at the secondary methoxy group side, disordered over two positions related by that axis. The guest model used during the refinement is that of the (*R*)-enantiomer alone because trials to either refine a 1 : 1 mixture of (*R*)- and (*S*)-enantiomers or the (*S*)-enantiomer alone failed. The crystallographic evidence of enantioselectivity towards the (*R*)-enantiomer of spiroacetal was confirmed by independent experiments and may be attributed to numerous non bonding interactions between host and guest involving non conventional H-bonds.

Key words: crystal structure; hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin; (*R*)-(-)-1,7-dioxaspiro [5.5]undecane; chiral recognition.

Supplementary Data relating to this article are deposited with the British Library as Supplementary Publication No. 822408 (17 pages)

1. Introduction

1,7-Dioxaspiro[5.5]undecane (spiroacetal), Figure 1, the primary constituent of the sex pheromone of the olive pest *Bactrocera oleae*, is a chiral molecule. The synthetic product, as well as the isolated compound from the insect, is the racemic mixture of the (*R*)- and (*S*)- enantiomers. Cyclodextrins, which are also chiral compounds, have the ability to provide inclusion complexes enriched in one of the enantiomers upon crystallization from a racemic mixture [1–3]. The enantioselectivity has generally been attributed to stronger binding of the host with

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one of the optical antipodes, due to the topology of the cavity. It is believed [1] that permethylated CDs are more suitable for enantiomeric discrimination than the unsubstituted CDs, since they posses flexible cavities distorted from the usual regular polygonal symmetry of the unsubstituted CDs and are, therefore, capable of undergoing "induced fit" during complexation. It has been shown [3] that an asymmetrically substituted β-CD selectively binds the (*S*)-enantiomer of the spiroacetal. The present study, one in a series of structures of spiroacetal in a variety of CD hosts, is an example of complete resolution of the racemic mixture of the guest by enantiospecific complexation and crystallization of the (*R*)-enantiomer only, as determined by the crystal structure described here, and independent experiments [4].

2. Experimental

2.1. PREPARATION AND CRYSTALLIZATION OF THE COMPLEX

Colorless crystals of the title complex were obtained from a 10mM aqueous solution of synthetic racemic spirocetal (1 equivalent), purchased from Vioryl S.A., and TMαCD (1 equivalent) obtained from Cyclolab, at room temperature.

2.2. DATA COLLECTION AND STRUCTURE REFINEMENT

Final lattice parameters, determined from 32 reflections with $3.0 < 2\theta < 23.0$ (°), are given in Table I along with other information of data collection and refinement. Data collection was done on a crystal sealed in a glass capillary to prevent water loss on a Syntex $P2_1$ diffractometer, upgraded by Crystal Logic, with Nb-filtered Mo Kα radiation, by the $\theta - 2\theta$ scan mode, at a scan rate of 3°/min and scan width of 2.7° (2θ) plus $\alpha_1 - \alpha_2$ divergence. One octand of data, $2\theta < 43°$, was collected. Three standard reflections monitored every 67 reflections showed a fluctuation of the intensities of less than 3%. The intensities were corrected for Lp and absorption (by Psi-scan, μ = 0.105 mm^{-1}) effects.

The structure was solved by direct methods using SHELXS-86 [5]. All host atoms belonging to the asymmetric unit, i.e. half of the TMαCD molecule, were located. The refinement proceeded with SHELXL-93 [6] based on F^2 of all reflections. Three water molecules were located by a difference electron density map. The $\Delta\rho$ maps revealed also the position of the guest, a strong symmetric electron density around the 2-fold crystallographic axis along the 6-fold axis of TMαCD, having the shape of the guest molecule. Since the spiroacetal molecule lacks a 2-fold axis along its length, it must be disordered. At the beginning of the refinement it was assumed that both (*R*)- and (*S*)-enantiomers were present in the crystal. Therefore, it was attempted to fit the models of both enantiomers into the guest electron density on a Silicon Graphics workstation using the program "O" [7]. The models of the spiroacetal enantiomers were taken from the structure of the (*S*)-enantiomer with a modified βCD [3]. However, refinement of the occupancies

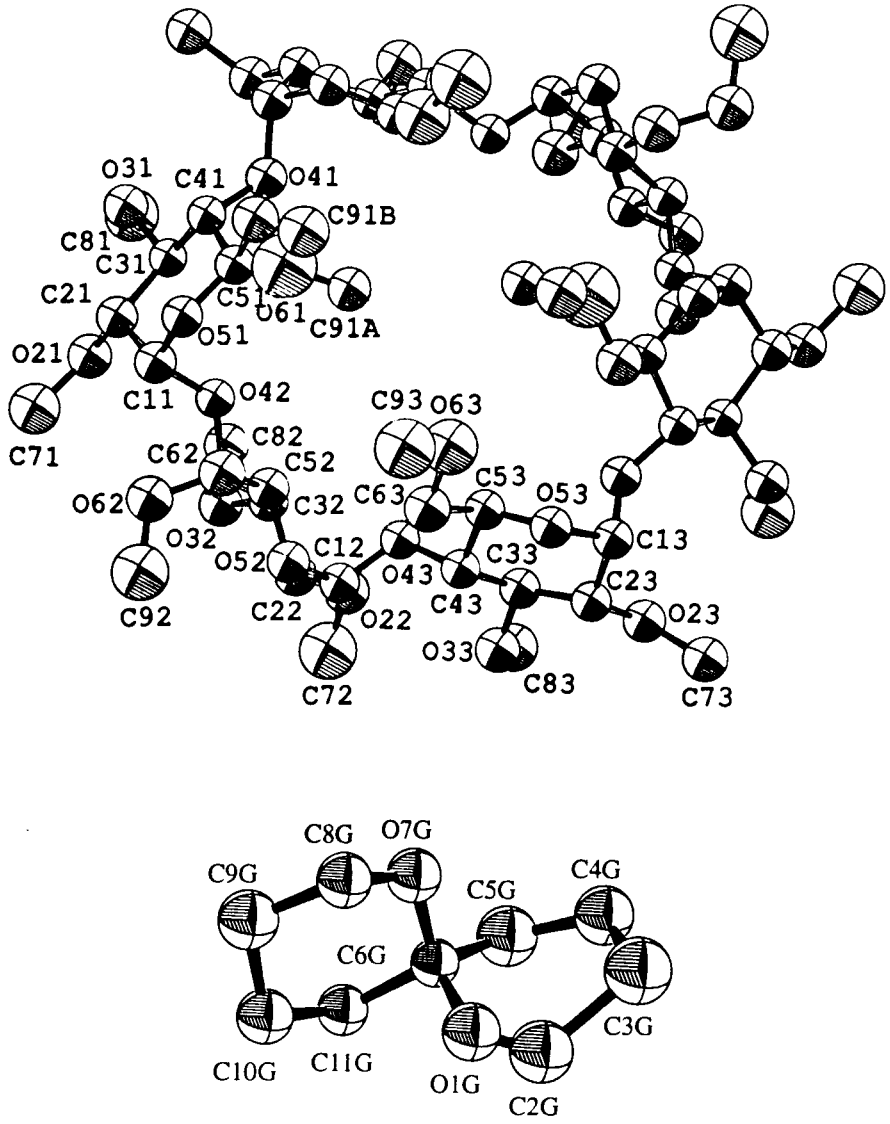

Figure 1. An ORTEP diagram of the TMαCD/spiroacetal 1 : 1 complex, with the numbering scheme of the host and guest molecules.

of the (*R*)- and (*S*)- enantiomers resulted in occupation factors of 0.5 and 0.0, respectively. A trial to refine the (*S*)-enantiomer alone also failed. Therefore, it was assumed that only the TMαCD/(*R*)-spiroacetal was present in the crystal. This assumption was verified experimentally [4] by extracting the guest from the complex. A solution of the recovered liquid had an optical rotation of $[\alpha]_D^{21} = -115$ (c = 0.172 in *n*-pentane), Lit $[\alpha]_D^{21} = -121$ (c = 1.84, *n*-pentane) [8]. Moreover, chiral gas chromatography and ^{13}C NMR spectroscopy in the presence of αCD,

Table I. Crystal data for the permethylated α-Cyclodextrin (*R*)-(-)-1,7-dioxaspiro[5,5]undecane 1 : 1 complex

Formula	$C_{27}H_{48}O_{15}\cdot(C_9H_{16}O_2)_{0.5}\cdot(H_2O)_{2.7}$
M.W.	739.43
lattice type	orthorhombic
space group	$C222_1$
T(K)	293(2)
Cell dimensions	
a (Å)	24.002(2)
b (Å)	14.8120(10)
c (Å)	21.792(2)
V (Å^3)	7747.3(11)
Z	8
d_{calc} (gcm^{-3})	1.268
Crystal dimensions (mm)	$0.7 \times 0.2 \times 0.2$
2θ range (°)	3.0–43.0
Index range	$h = 0 \rightarrow 24$; $k = 0 \rightarrow 15$; $l = -22 \rightarrow 0$
No of reflections (all)	2450
No of reflections (obs) with $F_0 \geq 4\sigma$ (F_0)	1540
No of refined parameters	244
R (obs)	0.0832 (based on F's)
R (all data)	0.1544 (based on F's)
wR (obs)	0.2032 (based on F^2's)
wR (all)	0.3078 (based on F^2's)
Weigh. scheme	$w = 1/[\sigma^2(F_0^2) + (0.0973P)^2 + 61.5537P]$ where $P = (F_0^2 + 2F_c^2)/3'$
$(\Delta/\sigma)_{max}$	−0.051
$\Delta\rho_{max}$	0.344 eÅ^{-3}
$\Delta\rho_{min}$	−0.345 eÅ^{-3}

each gave a single peak for the extracted spiroacetal, whereas the racemic molecule gave two peaks in each of the methods. Thus refinement continued with only the R enantiomer of the guest and converged to R = 0.0832 for observed reflections and R = 0.1544 for all reflections. Towards the end of the refinement the coordinates of the (*R*)-spiroacetal molecule were refined by one least squares cycle. Additional cycles destroyed molecular geometry and further refinement of the atomic coordinates of the guest was abandoned. Calculated coordinates were used for hydrogen atoms linked to the TMαCD carbon atoms (C—H distances 0.96 Å for the primary, 0.97 Å for the secondary and 0.98 Å for the tertiary H-atoms) and their thermal parameters were set equal to 1.2 of the isotropic thermal parameter of the corresponding C

Table II. Fractional atomic coordinates and isotropic displacement parameters ($Å^2$) for non-H atoms

Atom	Occupancy	x	y	z	U_{iso}
C(11)	1	0.3120(5)	0.7196(9)	0.6933(6)	0.057(3)
C(21)	1	0.3431(6)	0.6834(8)	0.7479(6)	0.058(4)
C(31)	1	0.3553(5)	0.5827(8)	0.7402(6)	0.051(3)
C(41)	1	0.3043(5)	0.5298(8)	0.7211(6)	0.053(3)
C(51)	1	0.2706(5)	0.5774(9)	0.6711(6)	0.056(3)
O(51)	1	0.2622(4)	0.6709(6)	0.6855(4)	0.064(3)
O(41)	1	0.3250(3)	0.4438(6)	0.6970(4)	0.057(2)
O(21)	1	0.3940(4)	0.7267(6)	0.7594(4)	0.067(3)
C(71)	1	0.3891(8)	0.8200(11)	0.7736(8)	0.088(5)
O(31)	1	0.3758(4)	0.5451(6)	0.7958(4)	0.071(3)
C(81)	1	0.4338(7)	0.5327(14)	0.7963(10)	0.105(6)
C(61)	1	0.2139(6)	0.5367(11)	0.6649(8)	0.085(5)
O(61)	1	0.1834(6)	0.5768(10)	0.6173(7)	0.129(5)
C(91A)	0.63	0.2000(16)	0.553(3)	0.562(2)	0.141(13)
C(91B)	0.37	0.130(3)	0.542(4)	0.601(3)	0.13(2)
C(12)	1	0.3033(5)	0.3639(9)	0.7209(7)	0.058(4)
C(22)	1	0.3495(6)	0.2944(9)	0.7266(6)	0.059(4)
C(32)	1	0.3756(5)	0.2759(9)	0.6642(6)	0.054(3)
C(42)	1	0.3315(5)	0.2466(9)	0.6192(6)	0.057(3)
C(52)	1	0.2799(5)	0.3078(10)	0.6203(6)	0.058(4)
O(52)	1	0.2622(4)	0.3247(6)	0.6813(4)	0.059(2)
O(42)	1	0.3556(3)	0.2476(5)	0.5584(4)	0.056(2)
O(22)	1	0.3942(4)	0.3221(6)	0.7662(4)	0.064(2)
C(72)	1	0.3811(6)	0.3122(11)	0.8290(7)	0.075(4)
O(32)	1	0.4163(4)	0.2063(7)	0.6675(4)	0.072(3)
C(82)	1	0.4722(7)	0.2365(12)	0.6679(9)	0.088(5)
C(62)	1	0.2303(6)	0.2616(11)	0.5889(8)	0.074(4)
O(62)	1	0.1894(6)	0.3261(9)	0.5832(6)	0.106(4)
C(92)	1	0.1386(10)	0.2825(18)	0.5604(12)	0.139(8)
C(13)	1	0.3635(5)	0.1645(10)	0.5296(6)	0.060(4)
C(23)	1	0.4138(5)	0.1652(10)	0.4871(6)	0.062(4)
C(33)	1	0.4070(5)	0.2267(9)	0.43287(12)	0.130(7)
C(43)	1	0.3519(5)	0.2117(9)	0.3995(6)	0.054(3)
C(53)	1	0.3035(5)	0.2054(9)	0.4452(6)	0.056(3)
O(53)	1	0.3155(4)	0.1410(6)	0.4925(4)	0.064(3)
O(43)	1	0.3463(3)	0.2884(6)	0.3597(4)	0.056(2)
O(23)	1	0.4613(4)	0.1917(7)	0.5213(4)	0.074(3)
C(73)	1	0.5019(10)	0.1302(15)	0.5287(12)	0.130(7)
O(33)	1	0.4524(4)	0.2075(6)	0.3918(4)	0.069(3)

Table II. Continued

Atom	Occupancy	x	y	z	U_{iso}
C(83)	1	0.4793(7)	0.2845(11)	0.3650(7)	0.075(4)
C(63)	1	0.2484(6)	0.1761(10)	0.4164(7)	0.068(4)
O(63)	1	0.2540(4)	0.1052(7)	0.3742(5)	0.077(3)
C(93)	1	0.2553(10)	0.0168(14)	0.3994(11)	0.116(7)
O(W32)	1	0.1007(12)	0.5432(18)	0.7812(14)	0.267(12)
O(W33)	1	0.4843(10)	0.0392(15)	0.3529(12)	0.230(10)
O(W61)	1	0.0766(12)	0.539(20)	0.6689(15)	0.291(14)
O(1G)	0.50	0.5021	0.5649	0.5280	0.098(7)
C(2G)	0.50	0.5391	0.5970	0.4870	0.11(3)
C(3G)	0.50	0.5954	0.5482	0.4871	0.137(15)
C(4G)	0.50	0.5934	0.4447	0.4767	0.100(11)
C(5G)	0.50	0.5406	0.4143	0.5176	0.11(3)
C(6G)	0.50	0.4902	0.4709	0.5127	0.067(8)
O(7G)	0.50	0.4662	0.4659	0.4524	0.086(6)
C(8G)	0.50	0.4163	0.5192	0.4414	0.089(10)
C(9G)	0.50	0.3734	0.4884	0.4865	0.103(11)
C(10G)	0.50	0.3924	0.4970	0.5516	0.088(10)
C(11G)	0.50	0.4467	0.4421	0.5591	0.075(8)

Table III. Selected torsion angles (°)

	n = 1	n = 2	n = 3	Site
C(1n)-C(2n)-O(2n)-C(7n)	62.4(15)	78.6(14)	114.7(17)	
C(3n)-C(2n)-O(2n)-C(7n)	−174.1(12)	−159.8(11)	−120.7(16)	
C(2n)-C(3n)-O(3n)-C(8n)	−101.7(15)	−101.9(14)	−136.7(12)	
C(4n)-C(3n)-O(3n)-C(8n)	134.7(13)	137.1(13)	101.4(13)	
C(4n)-C(5n)-C(6n)-O(6n)	−177.2(13)	−170.4(12)	42.6(17)	
O(5n)-C(5n)-C(6n)-O(6n)	61.5(17)	69.2(15)	−79.7(14)	
O(5n)-C(6n)-O(6n)-C(9n)	74(3)	−173.1(15)	83.8(19)	A
	175(3)			B

atom. The coordinates of some H-atoms of the water molecules found by $\Delta\rho$ maps, were kept constant during the refinement. Isotropic thermal parameters were used for all atoms, the small number of observations did not allow the use of anisotropic refinement. Twelve reflections exhibiting poor agreement or being negative were given zero weight during the final refinement cycles.

Table IV. Distances between host and guest molecular atoms less than 4.0 Å

Atoms		sc*	Distance	Atoms		sc*	Distance
O(1G)	O(33)	i	3.98	O(1G)	C(83)	i	3.27
C(2G)	O(23)	i	3.65	C(2G)	C(83)	i	3.97
C(2G)	C(92)	iii	3.98	C(3G)	C(92)	iii	3.96
C(4G)	O(31)	ii	4.01	C(4G)	C(81)	ii	4.00
C(4G)	C(92)	iv	3.63	C(5G)	O(23)		3.81
O(7G)	C(33)		3.84	O(7G)	C(83)		3.31
C(8G)	O(41)	i	3.77	C(8G)	C(32)	i	3.93
C(8G)	O(42)	i	3.75	C(9G)	O(42)		3.92
C(10G)	O(41)		3.64	C(10G)	O(42)		3.80
C(10G)	O(43)	i	3.88	C(11G)	C(32)		3.77
C(11G)	O(42)		3.62	C(11G)	C(82)		3.91

* sc = symmetry code: i = x, $1 - y$, $1 - z$; ii = $1 - x$, $1 - y$, $-0.5 + z$; iii = $0.5 + x$, $0.5 + y$, z; iv = $0.5 + x$, $0.5 - y$, $1 - z$.

3. Results and Discussion

The numbering scheme of the host and guest molecules is given in Figure 1, C(mn) and O(mn) denoting the mth atom within the nth glucosidic residue. Fractional atomic coordinates and isotropic displacement parameters (Å^2) are given in Table II. The TMαCD six-fold axis coincides with the two-fold crystal axis. Therefore, only three glucose units have independent symmetry. All glucose residues have the $^4C_1$ chair conformation. The O(4n)-O(4(n + 1)) distances between adjacent glycosidic O(4n) atoms, range between 4.19 and 4.38 Å and the angles O(4(n − 1))-O(4n)-O(4(n+1)) vary between 114.6 and 126.8°. The tilt angles, defined as the dihedral angles between the O(4n) optimum plane and the planes through the atoms O(4n), C(1n), C(4n) and O(4(n + 1)) of each residue are all positive and vary from 8.0 to 34.8°, indicating a very uneven tilting of the glucopyranose rings. The deviations of the glycosidic O(4) atoms from their optimum plane range between 0.015 and 0.471 Å, significantly greater than that observed in the other TMαCD structures (maximum value, 0.271 Å, in the (*S*)-mandelic acid/TMαCD complex, where the macrocycle is governed by a pseudo two-fold axis [9]).

The C(63)–O(63) bond has a *gauche-gauche* orientation pointing outside the TMαCD cavity (Table III). The two remaining methoxy groups have a *gauche-trans* orientation and point inward. As a result, the TMαCD cavity is closed at its primary methoxy group side and the free space left to the guest is small. This is a common feature of all the TMαCD structures elucidated up to now [9–12]. The C(91) methyl-group is disordered over two positions (occupancy factors of 0.63 and 0.37), Table II. At the secondary methoxy groups side, the O(3)–C(8) bonds point inwards while the O(2)–C(7) point out of the TMαCD cavity.

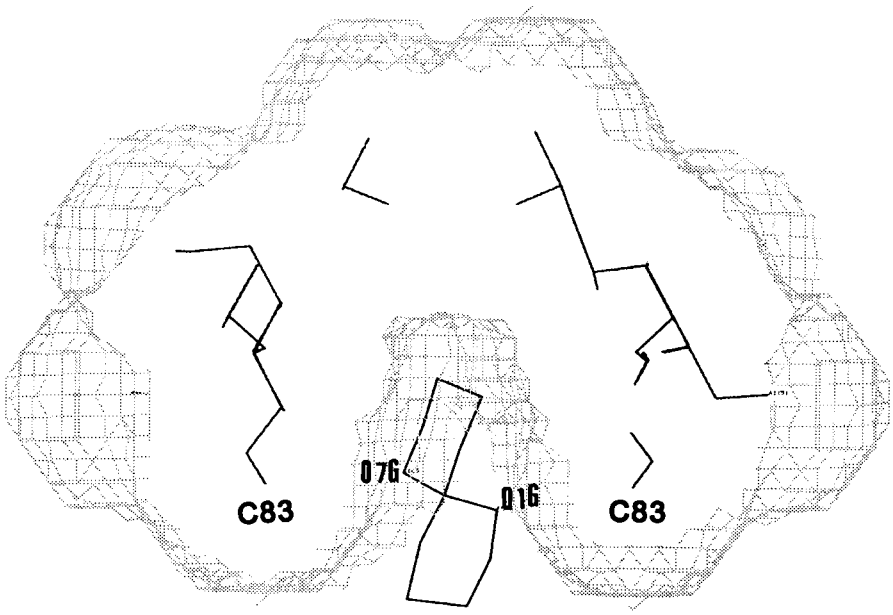

Figure 2. The fit of the spiroacetal molecule inside the host cavity.

The guest molecule resides at the secondary side of the cavity and it is only partially included. Its tetrahydropyranyl moieties are in the chair conformation. Atoms O(1G), C(2G), C(4G) and C(5G) and O(7G), C(8G), C(10G) and C(11G) lie on perfect planes forming a mutual angle of 50°. The thermal parameters of the guest atoms are similar to those of the TMαCD molecule, a rather rare feature for CD complexes, implying a tight fit of the guest molecule. Indeed, numerous van der Waals contacts are observed between the guest and host molecules. Their distances range from 3.27 to 4.01 Å, (Table IV). The shortest distances are observed between atoms O(1G) and O(7G) defining the chirality of the spiroacetal molecule, and methoxy carbon atoms C(83) and its 2-fold symmetry equivalent. They involve C—H$\cdots$O type interactions. Additional close contacts between non H-atoms of the spiroacetal molecule and ether oxygen atoms of TMαCD are also shown in Table IV. Similar close contacts are common in carbohydrate crystals [13].

The fit of spiroacetal inside the host cavity is represented in Figure 2, where the surface corresponding to the van der Waals distance increased by 1 Å for each atom has been calculated for TMαCD (H-atoms not included). The spiroacetal molecule occupies exactly the free space inside the cavity. Therefore, the enantioselectivity of TMαCD may be attributed to numerous non bonding interactions of its atoms, involving non conventional H-bonds, with (*R*)-spiroacetal. These interactions result partly from the extensive distortion of the macrocycle from the 6-fold symmetry and partly from the conformation of the primary methoxy groups that close the cavity at the primary side. Both may imply induced fit i.e. upon inclusion of the guest, the symmetrically substituted macrocycle has the flexi-

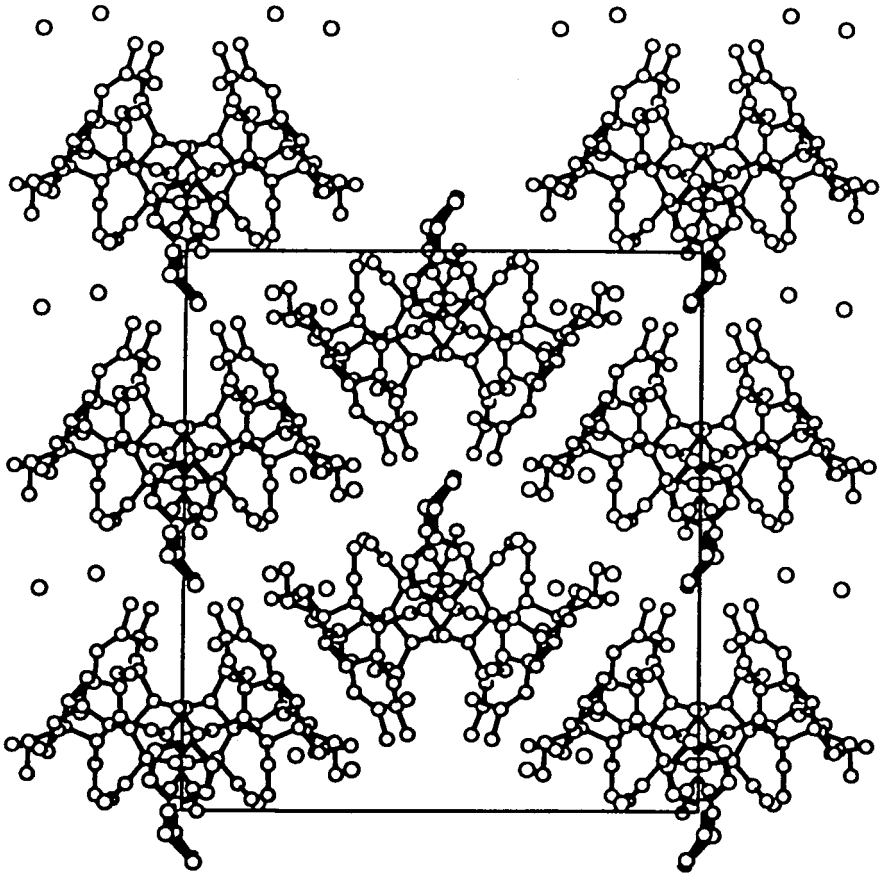

Figure 3. Molecular packing of the TMαCD/spiroacetal 1 : 1 complex. The view is along the *b* crystal axis.

bility to undergo asymmetric distortions to complement the conformation of the (*R*)-enantiomer. This is not the case in the inclusion of the (*S*)-spiroacetal to an asymmetrically substituted βCD [3] (the 2a, 2b, 2c, 2d, 2f, 3a, 3g, 6a, 6b, 6c, 6d, 6e, 6f, 6g-pentadeca-*O*-methyl-βCD).

Only three water molecules have been found in every asymmetric unit. They have thermal parameters greater than those of the guest atoms. They participate in a limited hydrogen bonding network [O(W32)···O(W33) = 2.845, O(W32)··· O(W61) = 2.516, O(W33)···O(W61) = 2.547, O(W32)···O(32) = 2.692, O(W33)···O(33) = 2.743 and O(W61)···O(61) = 2.853 Å. The angles O(Wmn)··· O(mn)—C(mn) range between 115.1 and 125.7°].

The molecular packing of the complex shown in Figure 3, does not resemble any of the known TMαCD inclusion complexes. The host molecules form layers parallel to the [*b*, *c*] plane. The TMαCD molecules related by the two-fold screw axis along the *c* direction pack head-to-tail in a kind of a chessboard mode observed

in the dimeric βCD inclusion complexes of the same space group [14]. However in this case, the shifting of the layers along the *a* axis is not regular. Two layers are shifted by a small distance, half of the height of a TMαCD molecule, forming a densely packed double-layer with a brick type pattern. Between the double layers the distance is higher because the water and the external part of the guest molecules are accommodated. The latter are isolated in cages formed partly by the host cavities and partly by the primary and secondary methoxy faces of the adjacent double layers, (Figure 3).

Acknowledgments

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