Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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Online publication date: 29 October 2010

To cite this Article Bacchi, Alessia , Pelizzi, Giancarlo , Sheldrick, George M. , Amari, Gabriele , Delcanale, Maurizio and Redenti, Enrico(2002) 'The Molecular Structure and Crystal Organization Of Rac -terfenadine/β-cyclodextrin/tartaric Acid Multicomponent Inclusion Complex', Supramolecular Chemistry, 14: 1, 67 — 74
To link to this Article: DOI: 10.1080/10610270290006583
URL: http://dx.doi.org/10.1080/10610270290006583

Supramolecular Chemistry, 2002 Vol. 14 (1), pp. 67–74

The Molecular Structure and Crystal Organization Of *Rac*-terfenadine/β-cyclodextrin/tartaric Acid Multicomponent Inclusion Complex

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(Received 28 March 2001; Revised 16 July 2001; In final form 24 July 2001)

The crystalline ternary inclusion complex terfenadine/β-cyclodextrin/tartaric acid (TFN/βCD/TA, 2:4:1) has been prepared from a aqueous solution (terfenadine, TFN, *rac*-α-[4-(1,1-dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)-1-piperidine-butanol). The solubility of the multicomponent system in water is remarkably different from that of the single components. The crystal structure shows that the TFN guest adopts an extended conformation and that the diphenyl end of the molecule is docked in the cavity formed by the association of two independent βCD molecules through hydrogen bonds connecting their wide rims. The structure of the dimer is deformed with respect to uncomplexed βCDs, due to the shape of the guest. The two aromatic rings interact differently with the macrocycles forming the dimer, one being included perpendicular in the central cavity of one βCD, the other laying parallel to the interface between the two rims. The t-Bu- end of the guest is included in the cavity of a βCD belonging to a different dimer, entering from the side of the narrow rim. The central part of the guest is surrounded by water molecules and tartaric acid, which creates a hydrophilic microenvironment in the interstices among dimers. The enhanced solubility of the multicomponent system could be related to the hydrogen bonds between the tartaric acid and the oxygens belonging to the wide rims. The overall structural arrangement of the βCD units is driven by the shape of the TFN guest which needs a hydrophobic environment at both ends. The lipophilic interactions between TFN and βCD cavities are responsible for the relevant perturbation in the regularity of the packing of the hosts.

Keywords: Multicomponent complexes; Host–guest chemistry; Cyclodextrin; Terfenadine; Tartaric acid; X-ray crystallography

INTRODUCTION

Cyclodextrins (CDs) are a well-known family of cyclic oligosaccharides, widely used to form inclusion compounds with a variety of molecules. Complexation might improve some molecular physical and chemical properties such as stability, solubility and bioavailability [1–5]. However natural CDs are generally not very soluble in water because of the relatively strong binding of the molecules in the crystal state (consequence of a relatively high crystal lattice energy). In particular β-cyclodextrin (βCD), which consists of seven glucose units with an inner diameter of 6.5–8.0 Å, exhibits a limited aqueous solubility (1.85% at 25°C) which often hinders its successful employment as a solubilizing agent. For instance, βCD is about sevenfold less soluble than αCD and 14-fold less soluble than γCD. The most probable explanation grounds on the fact that the arrangement of its secondary hydroxyl groups is optimal for intramolecular hydrogen bond interactions so preventing adequate hydration by water molecules [6,7].

We extensively reported that the complexes of amino type drugs with βCD, in the presence of hydroxy acids like citric or tartaric, became unexpectedly soluble in water [8–11]. For instance, the solubility of the guest was enhanced by several orders of magnitude and that of βCD by more than 10 times.

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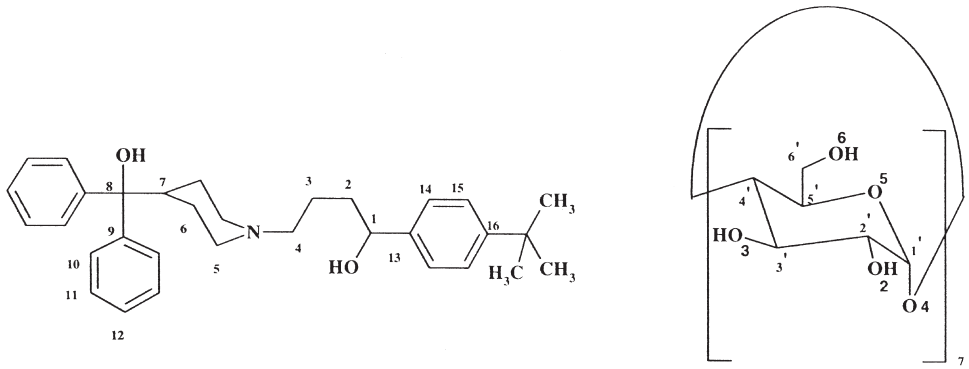
ISSN 1061-0278 print/ISSN 1029-0478 online © 2002 Taylor & Francis Ltd
DOI: 10.1080/10610270290006583



TFN βCD

SCHEME 1 General formula and conventional numbering for terfenadine (TFN) and β-cyclodextrin (βCD). In the βCD molecule, each glucose residue is numbered as shown in the scheme, and is assigned an italic suffix from 1 to 7 along the cycle, e.g. atom O2 of glucose 6 is denoted as O2*6*.

The mechanism through which the above complexes elicit their synergetic effects on the drug solubility has been extensively discussed in a recent review [12], where the drug structural requirements for solubility enhancement were also analyzed.

In order to cast more light on the role played by the hydroxy acids, a single X-ray crystal structure determination of the terfenadine/β-cyclodextrin/tartaric acid (TFN/βCD/TA) multicomponent inclusion complex was undertaken. (Scheme 1)

The study was also aimed at examining the structure of terfenadine upon complexation. Terfenadine (*rac*-α-[4-(1,1-dimethylethyl)phenyl]-4-(hydroxy-diphenylmethyl)-1-piperidine-butanol, TFN) is a selective histamine H_1 receptor antagonist, whose structural versatility is shown by the existence of three polymorphic and two pseudopolymorphic forms [13] in the solid state.

Although the binding of TFN in the cavity of βCD has been extensively studied by NMR spectroscopy in solution [14] and molecular modeling [15], the structure of its inclusion compound has never been reported.

MATERIALS AND METHODS

The following materials were used: β-cyclodextrin, water content 11% (Roquette, Lestrem, France),*rac*--terfenadine (Sibefat, Milano, Italy) and (+)-L-tartaric acid (Fluka, Buchs, Switzerland). Melting points were measured on a Buchi apparatus and are uncorrected.

^{1}H-NMR spectra were obtained at 400.13 MHz on a Bruker AMX 400 spectrometer. The chemical shifts in D_2O were measured with the sodium salt of 3-trimethylsilylpropionic acid as external reference.

Preparation of Single Crystals of the Multicomponent Complex *Rac*-terfenadine/β-cyclodextrin/tartaric Acid in the 2:4:1 Molar Ratio

1.9 g of powdered complex was dissolved in 20 ml of distilled hot water; after filtration, the solution was transferred into a 500 ml large mouthed flask which, in turn, was put into a glass crystallization vessel, freely floating over a water bath thermostated at 95°C. Small amounts of water were added to dissolve the possible precipitate. The solution was allowed to cool slowly to room temperature (15°C), left overnight, then reheated to 95°C the following day. After 4 days at room temperature, suitable single crystals for X-ray diffraction were obtained.

Mp $>$ 255°C (decomp.); ^{1}H-NMR δ, ppm: 1.36 (s, 9H; CH_3), 1.78 (m, 6H, H6, H3), 1.90 (m, 2H; H2), 2.95 (m, 2H; H7), 3.03 (m, 2H; H5ax), 3.25 (t, $^3J = 6.1$ Hz, 2H; H4), 3.4–3.7 (m, 44H; H5eq, H2′, H4′, H5′), 3.7–4.0 (m, 42H; H6′, H3′), 4.34 (s, 1H; tartaric protons), 4.76 (m, 1H; H1), 5.04 (d, $^3J = 3.7$ Hz, 14H; H1′), 7.2–7.3 (m, 4H; H14, H12), 7.3–7.4 (m, 6H; H11, H14), 7.56 (m, 4H; H10).

X-ray Diffraction Analysis

A single crystal of TFN·2βCD·0.5TA·16.5H_2O suitable for X-ray analysis was glued to a glass fiber and mounted on a Enraf-Nonius CAD4 diffractometer employing Cu Kα radiation. The instrument was equipped with a graphite monochromator. Intensities were collected at room temperature. During data collection, no intensity decay was observed. Corrections for Lorenz and polarization effects were applied. Relevant data collection and structure refinement parameters are summarized in Table III. The most common programs for small molecules and for macromolecules employing direct methods were not able to solve the phase problem. Attempts to determine acceptable phases by molecular

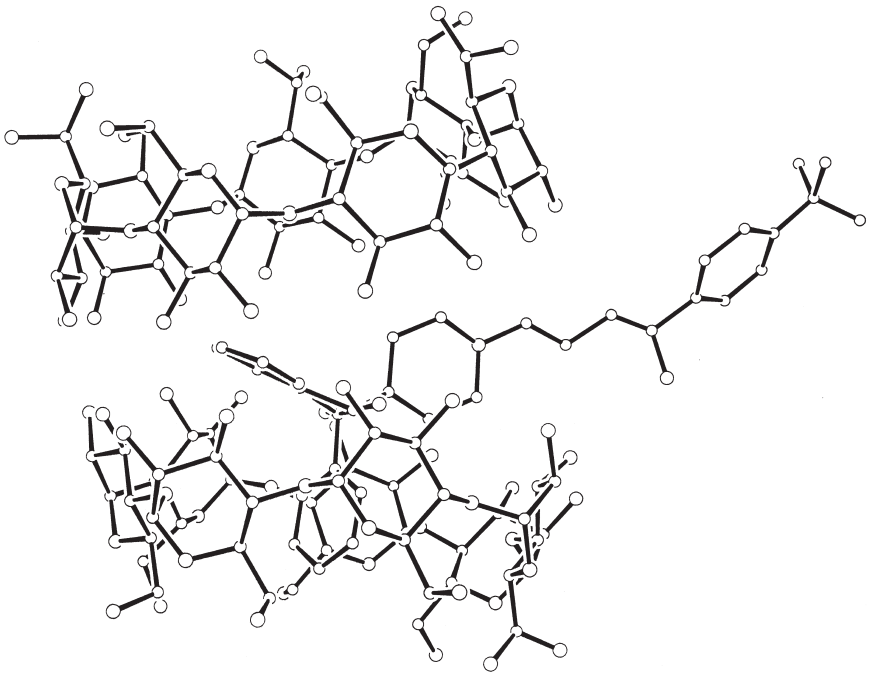


FIGURE 1 View of the βCD dimer complexed with terfenadine in the crystal of TFN·2βCD·0.5TA·16.5H_2O. Tartaric acid and water molecules are omitted. Hydrogen atoms are omitted. βCD molecules are indicated as A (below in the figure, hosting the TFN phenyl group) and B (top in the figure).

replacement were not successful. The structure was eventually solved employing SHELXD [20]. Atom co-ordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms using conjugate gradient least-squares in the initial stages, and finally full-matrix least squares on F^2 with the Shelxl97 program [21]. All hydrogen atoms were introduced in idealized positions, those belonging to tartaric acid and waters were not introduced. Density maps were examined with the package Xtalview [22]. The modeling of the half-occupied tartaric acid has been possible only by enhancing the local quality of the electron density map *via* the Squeeze procedure implemented in PLATON [23]. The improved map has been then fit by a model obtained by averaging the most frequent tartaric acid conformations occurring in the Cambridge Structural Database [24]. Some disorder is also present on the tartaric acid molecule. The final geometry was analyzed with the program PARST97 [25]. The calculations were performed on a DIGITAL Alpha255 workstation at the "Centro di Studio per la Strutturistica Diffrattometrica del C.N.R." in Parma. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-153074. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

RESULTS AND DISCUSSION

The multicomponent system TFN/βCD/tartaric acid crystallizes with the stoichiometry 1:2:0.5, and

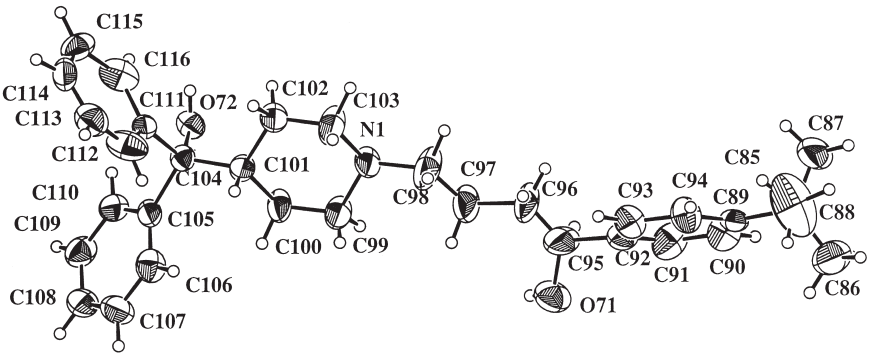


FIGURE 2 Perspective view of terfenadine structure in the crystal. Thermal ellipsoids are drawn at the 30% probability level.

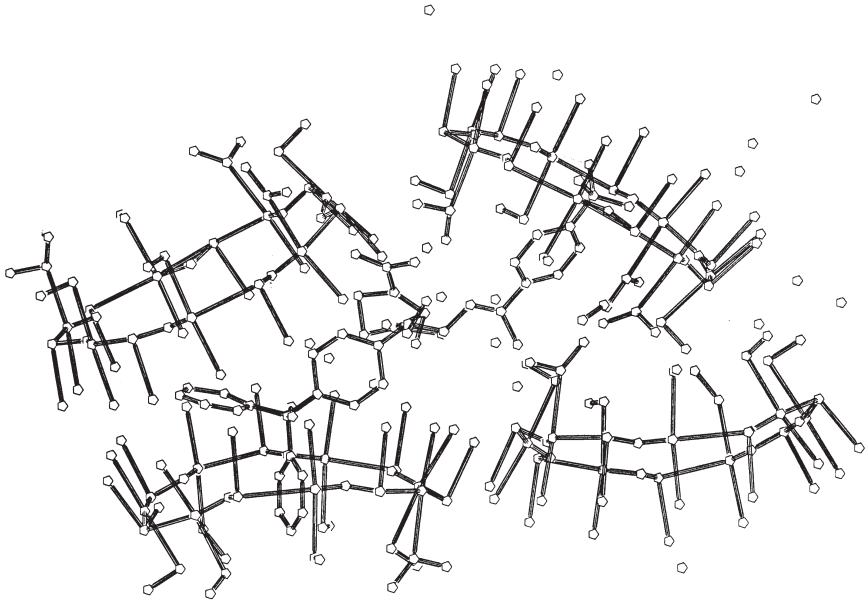


FIGURE 3 Inclusion of terfenadine in the crystal structure of TFN·2βCD·0.5TA·16.5H_2O. βCD molecules are represented schematically.

the crystal structure includes 16.5 water molecules, 10 of which are located inside the cavity with full occupancy. In the discussion of crystallographic results we have followed the conventional numbering [16] shown in Scheme 1 for βCD, and the labeling shown in Fig. 2 for TFN.

Two independent βCD molecules (indicated with A and B) are present associated to one TFN guest (Fig. 1). One and three O6*n* hydroxyls of the narrow rim are disordered on pairs of alternative orientations on the first (A) and the second (B) independent βCD molecules, respectively. The reciprocal orientation of βCD A and B, and the deformation of the macrocycle if compared with the conformation typical of uncomplexed βCD, can be described through the heptagonal rings defined by the O4*n* atoms bridging the seven glucopyranose units (average values for uncomplexed βCD: r.m.s. deviation from planarity=0.18 Å, radius of the O4*n* heptagon=5.04 Å, values ranging between 4.86 and 5.18 Å, O4$n\cdots$O4$_{n+1}$ distance=4.31 Å, ranging between 4.20 and 4.50 Å) [17]. The guest molecule, whose molecular structure is in Fig. 2, interacts differently with the two macrocyclic hosts and this causes different degrees of deformation in the βCD rings (Fig. 3): ring B, which hosts the t-Bu group, has a shape slightly elongated compared to the one observed for hydrated βCD (r.m.s. deviation from planarity of the O4*n* ring: 0.18 Å, maximum deviation 0.28 Å, radius of the O4*n* heptagon=4.96(35) Å, range=4.68–5.40 Å, O4$n\cdots$O4$_{n+1}$ distance=4.37(15) Å, range=4.20–4.62 Å). Ring A hosts a phenyl group oriented perpendicularly with respect to the O4*n* plane, and its shape is more regular and similar to the uncomplexed βCD, apart from a larger deviation from planarity of the O4*n* heptagon (r.m.s. deviation from planarity of the O4*n* ring: 0.30 Å, maximum deviation 0.37 Å, radius of the O4*n* heptagon=4.99(16) Å, range=4.77–5.17 Å, O4$n\cdots$O4$_{n+1}$ distance=4.35(9) Å, range=4.23–4.46 Å).

The length of the TNF guest is approximately 20 Å, as the central aliphatic chain presents an extended conformation, with torsion angles of 31(1), 180(1), 158(1), 180(1), 51(1)° around the bonds belonging to the section from N1 to C92. The piperidinic ring has a chair geometry, with total puckering amplitude QT=0.31(1) Å^2 and spherical polar angle $\theta 2 = 5(1)°$ [18]. The molecule is included in the crystal in the racemic form, and the two enantiomers occupy statistically the same position in the packing, with the exception of the orientation of the hydroxyl group O72 belonging to the hydroxy-diphenyl terminus of the molecule, which, in the two enantiomers, indicated with (1) and (2), points in opposite directions with respect to the average molecular plane, making contacts with two water molecules (O72(1)$\cdots$O14w = 2.80(1) Å, 115(1)° and O72(2)$\cdots$O11w$(3/2 - x, -y, 1/2 + z)$ = 2.99(2) Å, 112(1)°). Another water molecule is hydrogen bonded to O71 (O71$\cdots$O4w = 2.798(8) Å, 155(1)°).

The association of the components in the crystal packing is of particular interest in view of elucidating the significant enhancement of the complex solubility with respect to that of the single compounds. The two lipophilic ends of the TNF molecule are both included in the hosting βCD cavities. The arrangement of the inclusion pattern is depicted in Fig. 3. The hydroxy-diphenyl terminus of TFN is inserted in a cage formed by the association of two independent βCD, which face each other

TABLE I Relevant hydrogen bonds (D···A < 3.2 Å and D–H···A > 110°) involving atoms of the wide rim of β-cyclodextrins A and B. Suffixes "w" and "T" refer to water molecules and tartaric acid, respectively (equivalent positions: (*1*) $-x+5/2, -y, +z+1/2$; (*2*) $x+1/2, -y+1/2, -z-1$; (*3*) $-x+5/2, -y, +z-1/2$; (*4*) $x, +y, +z-1$; (*5*) $x+1/2, -y+1/2, -z$; (*6*) $x, +y, +z+1$)

Donor···acceptor (Å)	*Donor–H···acceptor* (°)
O32(A)···O21(B) 2.824(5)	O32(A)–H···O21(B) 112.7(3)
O32(A)···O31(B) 3.014(5)	O32(A)–H···O31(B) 166.0(3)
O23(A)···O37(B) 2.739(5)	O23(A)–H···O37(B) 119.5(3)
O33(A)···O24(A) 2.889(6)	O33(A)–H···O24(A) 174.8(3)
O34(A)···O25(A) 2.869(6)	O34(A)–H···O25(A) 152.9(3)
O25(A)···O4w 2.796(6)	O25(A)–H···O4w 162.3(3)
O35(A)···O26(A) 2.851(6)	O35(A)–H···O26(A) 171.8(3)
O26(A)···O6T 2.87(2)	O26(A)–H···O6T 155.6(6)
O36(A)···O7w 2.94(1)	O36(A)–H···O7w 118.6(4)
O37(A)···O21(A) 2.976(4)	O37(A)–H···O21(A) 168.8(2)
O21(B)···O37(B) 2.858(6)	O21(B)–H···O37(B) 153.9(3)
O31(B)···O32(A) 3.014(5)	O31(B)–H···O32(A) 123.8(2)
O33(B)···O24(B) 2.843(5)	O33(B)–H···O24(B) 170.2(3)
O24(B)···O14w 3.16(1)	O24(B)–H···O14w 117.7(3)
O34(B)···O9T 3.11(3)	O34(B)–H···O9T 133.4(7)
O25(B)···O15w 2.83(1)	O25(B)–H···O15w 169.8(4)
O35(B)···O26(B) 2.768(9)	O35(B)–H···O26(B) 163.2(4)
O26(B)···O35(B) 2.768(9)	O26(B)–H···O35(B) 122.5(5)
O36(B)···O27(B) 2.982(7)	O36(B)–H···O27(B) 134.2(4)
O27(B)···O36(B) 2.982(7)	O27(B)–H···O36(B) 168.6(3)
O37(B)···O21(B) 2.858(6)	O37(B)–H···O21(B) 167.0(3)
O21(A)···O22(A) (*1*) 2.962(5)	O21(A)–H···O22(A) (*1*) 146.8(2)
O31(A)···O2w (*2*) 3.166(5)	O31(A)–H···O2w (*2*) 136.6(2)
O24(A)···O5w (*2*) 3.15(1)	O24(A)–H···O5w (*2*) 133.9(4)
O22(A)···O21(A) (*3*) 2.962(5)	O22(A)–H···O21(A) (*3*) 137.0(2)
O24(A)···O7w (*4*) 2.87(1)	O24(A)–H···O7w (*4*) 147.6(4)
O36(A)···O10w (*5*) 2.95(6)	O36(A)–H···O10w (*5*) 132(2)
O27(A)···O27(B) (*6*) 2.778(5)	O27(A)–H···O27(B) (*6*) 173.1(3)

through the O2*n*–O3*n* wide rim. The dimensions of the cavity formed by the dimeric association of the two βCDs are not sufficient to accommodate the large guest, which therefore extends out of the cage, pulling apart the facing rims on one side of the dimer. The average planes of the O4*n* heptagons are tilted and form a dihedral angle of 24°. In fact the hydrogen bonding interactions between the O2*n* and O3*n* atoms of the two halves of the dimer are localized only in the region of contact between glycosidic rings 2–3 for A and 7–1 for B, where the two molecules are closest to each other (Table I). It is shown by data in Table I that on the opposite side of the interfacial region, *i.e.* the region of glycosidic rings 5–6 for A and 4–5 for B, hydroxyl groups O2–H and O3–H make contacts mainly with water molecules and tartaric acid; the presence of bifurcated hydrogen bonds breaks the pattern of O2···O3 intramolecular hydrogen bonds characteristic of the wide rim of uncomplexed βCDs. βCD A also interacts with two adjacent dimers at (i = $5/2-x, -y, 1/2+z$) and (ii = $x, y, z+1$), respectively, by means of interactions O21(A)···O22(A)(i) and O27(A)···O27(B)(ii).

The narrow rims of βCD A and B are on the outer region of the dimer. Hydroxyls O5 and O6 on the narrow rims are mainly involved in hydrogen bonds with water molecules, and in some intramolecular O6···O5 interactions (Table II). Some O6 groups are also involved in four inter-dimer interactions: O61(B)···O35(B)(x+1/2, $1/2-y$, $-z-1$), O61(A)···O61(B)–O51(B)($5/2-x$, $-y$,z+1/2), O63(A)···O66(A)–O67(A)(x,y,$z-1$) and O64(B)–O65(B)···O64(A)–O67(A) ($2-x$, y+1/2, $-z-1/2$).

The two terminal phenyl groups interact differently with the cavity inside the cage: one aromatic ring (*a*, C105–C111) is fully enclosed in the lipophilic cavity inside βCD(A), with C105 and C106 at 1.0 Å from the geometric center of the O4*n*(A) heptagon. The aromatic plane is almost perpendicular (83°) to the plane defined by the seven O4*n*(A), and the shortest contacts between the aromatic ring (*a*) and the macrocycle (A) involve βCD atoms belonging to the inner surface of the cavity: O4*6*···C110 3.725(9), C51···C109 4.065(8), C5*6*···C109 4.055(9), C5*6*···C110 4.086(9) Å. The second phenyl (*b*, C111–C116) lies in the interface between βCDs A and B, and is stacked between the O4*n* planes (dihedral angles of 18 and 41° for A and B, respectively). The shortest contacts involving the second aromatic group (*b*) are with atoms of the two βCD wider rims: O3*1*(A)···C114 = 3.587(8), O3*7*(A)···C116 = 3.751(9), C3*1*(A)···C115 = 3.730(8), O3*1*(B)···C114 = 3.627(9) Å. The other end of TFN consists of a p(*t*-Bu)-Ph- group. This is hosted by a third βCD(B′), at $x-1/2, -y+1/2, -z-1$. It enters the cavity through the rear narrow rim lined by O6*n*s and C85 is placed at only 0.14 Å from the center of the O4*n* heptagon. The shortest contacts formed in this lipophilic inclusion are C86···O44(B′) = 3.36(1), C86···O47(B′) = 3.57(1) Å. The *t*-Bu terminus is also in close contact (C87···C113(b′) = 3.66(1), C88···C115(b′) = 3.67(1)) with the second phenyl group of a different TFN

TABLE II Relevant hydrogen bonds (D···A < 3.2 Å and D–H···A > 110°) involving atoms of the narrow rim of β-cyclodextrins A and B. Suffixes "w", "TFN" and "T" refer to water molecules, terfenedine guest and tartaric acid, respectively (equivalent positions: (*1*) $-x+5/2, -y, +z+1/2$; (*2*) $x+1/2, -y+1/2, -z-1$; (*3*) $-x+3/2, -y, +z+1/2$; (*4*) $x, +y, +z-1$; (*5*) $-x+3/2, -y, +z-1/2$; (*6*) $x+1/2, -y+1/2, -z$; (*7*) $x, +y, +z+1$; (*8*) $-x+2, +y+1/2, -z-1/2$; (*9*) $x+1, +y, +z$)

Donor···*acceptor* (Å)	*Donor*–*H*···*acceptor* (°)
O64(A)2···O54(A)	O64(A)2–H···O54(A)
2.96(2)	166(2)
O61(A)···O61(B) (*1*)	O61(A)–H···O61(B) (*1*)
2.914(5)	176.3(3)
O61(B)···O35(B) (*2*)	O61(B)–H···O35(B) (*2*)
2.785(5)	170.2(3)
O65(A)···O71(TFN) (*3*)	O65(A)–H···O71(TFN) (*3*)
2.720(9)	111.7(5)
O62(A)···O8w (*3*)	O62(A)–H···O8w (*3*)
2.772(9)	157.4(4)
O66(A)···O4w (*3*)	O66(A)–H···O4w (*3*)
2.759(6)	169.1(3)
O64(A)1···O91w (*3*)	O64(A)1–H···O91w (*3*)
2.92(2)	167.0(8)
O64(A)1···O92w (*3*)	O64(A)1–H···O92w (*3*)
2.30(2)	130.5(8)
O63(A)···O66(A) (*4*)	O63(A)–H···O66(A) (*4*)
2.675(5)	157.8(3)
O64(A)2···O6T (*5*)	O64(A)2–H···O6T (*5*)
2.91(2)	131(1)
O62(B)2···O9T (*6*)	O62(B)2–H···O9T (*6*)
2.85(3)	110.2(8)
O63(B)···O201w (*6*)	O63(B)–H···O201w (*6*)
2.87(4)	144(1)
O67(A)···O63(A) (*7*)	O67(A)–H···O63(A) (*7*)
2.765(5)	152.8(3)
O65(B)···O67(A) (*8*)	O65(B)–H···O67(A) (*8*)
2.797(5)	153.9(3)
O67(B)···O6w (*9*)	O67(B)–H···O6w (*9*)
2.835(8)	140(3)

molecule (b′ at $x-1/2, -y+1/2, -z-1$), the one included in the interface region of the cage formed on the other side of βCD(B′). The solid-state inclusion pattern of the TFN molecule is consistent with the results of a solution study, which indicated the possibility that both ends of the molecule and both phenyls of the hydroxy-phenyl end were alternatively included in the βCD cavity [14].

A fourth βCD ($A' = 3/2-x, -y, z-1/2$) interacts with the TFN in the crystal, *via* hydrogen bonds between the narrow rim and the TFN O71 atom (O65 − H(A′)···O71 = 2.720(9) Å, 112(1)°), Fig. 3. The central part of the TFN molecule is thus segregated in an interstitial region among four βCDs. This region is characterized by a high concentration of crystallization water, and by the presence of tartaric acid, which occurs in a 1:2 ratio with the TFN molecule. When absent, it is replaced by disordered water. This creates a hydrophilic microenvironment in the surrounding of the central section of the guest molecule, which could be related to the larger solubility of the ternary complex compared to that of the single components. It has been suggested [11] that the formation of hydrogen bonds between TA and the oxygen atoms of βCD wide rim (Table I) is responsible for the dramatic increment of the aqueous solubility of both the host and the guest in the drug/BCD/TA multicomponent systems. TA also forms the short contact O7T···O36(B) = 3.09(4) Å (*x*,*y*,*z*+1), which can be considered as an additional hydrogen bond where TA acts as a donor. In addition, TA strongly interacts with atoms of the narrow rim of adjacent βCDs, as shown by data in Table II. In the case of O64(A) and O62(B) these interactions stabilize individual orientations of disordered groups. These findings are consistent with the aforementioned hypothesis which in the cited paper was mainly based on indirect NMR evidence and theoretical calculations.

The overall packing of the βCD dimers can be described as a distorted screw-channel type, according to the classification of Mentzafos [19] for βCD dimeric complexes. The stacking of the dimers

TABLE III Crystal data and structure refinement for TFN·2βCD·0.5TA·16.5H_2O

Empirical formula	$C_{118}H_{216}NO_{90.5}$
Formula weight	3096.96
Temperature (K)	293(2)
Wavelength (Å)	1.54178
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions (Å, °)	$a = 28.227(5)$, $b = 34.018(5)$, $c = 15.256(3)$
Volume (Å^3)	14649(4)
Z, calculated density (Mg/m^3)	4, 1.404
Absorption coefficient (mm^{-1})	1.049
F(000)	6620
Crystal size (mm^3)	0.5 × 0.3 × 0.2
θ range for data collection (°)	3–70
Index ranges	$-34 \le h \le 34$, $0 \le k \le 41$, $0 \le l \le 17$
Reflections collected/unique	28889/27275 [R(int) = 0.0237]
Data/restraints/parameters	27275/107/2125
Goodness-of-fit on F^2	0.870
Final *R* indices [$I > 2\sigma(I)$]	R1 = 0.0586, wR2 = 0.1504
R indices (all data)	R1 = 0.1021, wR2 = 0.1822
Absolute structure parameter	−0.02(16)
Largest ΔF maximum/minimum (*e*/Å^3)	0.504/ − 0.264

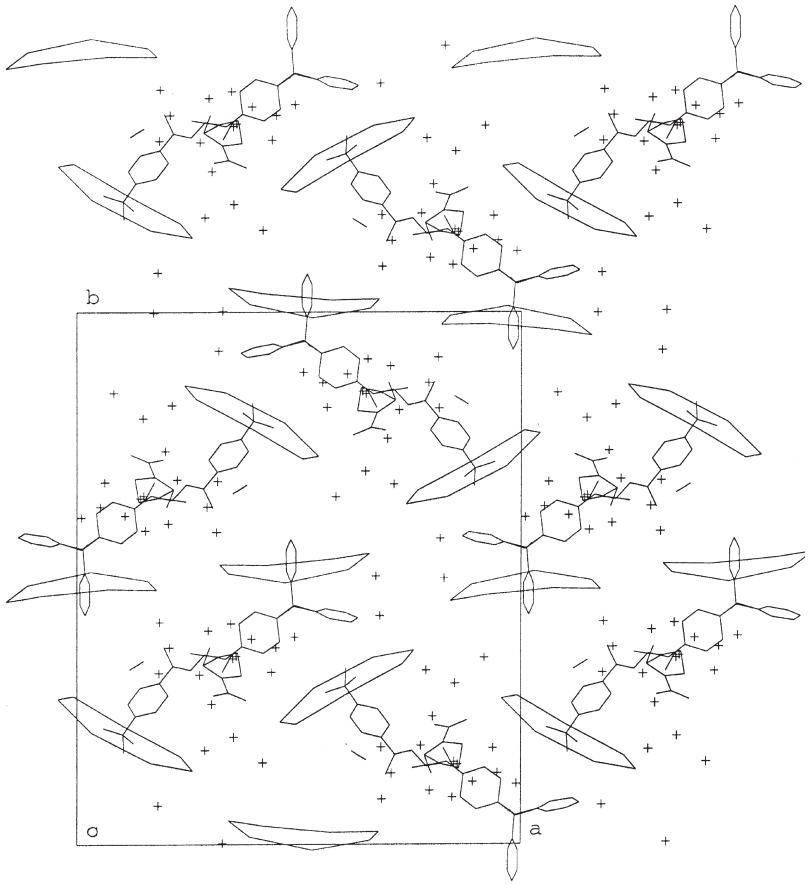


FIGURE 4 Crystal packing of the multicomponent system. βCD molecules are represented by the heptagons defined by O4*n* atoms.

occurs along the *b* direction, and the TFN molecules crosslink dimers belonging to adjacent channels (Fig. 4), by having the diphenyl head included in one dimer, and then by protruding the t-Bu tail to enter the rear of a βCD(B′) cavity belonging to a different channel. This requires a relevant tilting (38 and 65°, respectively, referred to rings O4*n*(A) and O4*n*(B)) of the B′ molecule at $x - 1/2, -y+1/2, -z - 1$, thus precluding the possibility of arranging the dimers in regular layers, as instead commonly found for βCD inclusion complexes [19].

The overall structural arrangement of the βCD units is in fact driven by the molecular conformation of the TFN guest which needs a hydrophobic environment at both ends. The lipophilic interactions between TFN and βCD cavities are therefore responsible for the relevant perturbation in the regularity of the packing of the bulky hosts.

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