Steroids 77 (2012) 1228–1232

Contents lists available at SciVerse ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Ice-like encapsulated water by two cholic acid moieties

Victor H. Soto [b], Mercedes Alvarez [a], Francisco Meijide [a], Juan V. Trillo [a], Alvaro Antelo [a], Aida Jover [a], L. Galantini [c], José Vázquez Tato [a,*]

[a] Departament of Physical Chemistry, Facultad de Ciencias, Universidad de Santiago de Compostela, Avda. Alfonso X El Sabio s/n, 27002 Lugo, Spain
[b] Department of Chemistry, University of Costa Rica, San José, Costa Rica
[c] Department of Chemistry, Sapienza University of Rome, P. le A. Moro 5, 00185 Rome, Italy

ARTICLE INFO

Article history:
Received 12 March 2012
Received in revised form 24 May 2012
Accepted 3 July 2012
Available online 21 July 2012

Keywords:
Cholic acid
Bile acids
Ice-like structure
Encapsulated water

ABSTRACT

Starting from the structure of ice (in which each water molecule is surrounded by other four water molecules forming a tetrahedron with a value of 4.51 Å for the edge O–O distance), and the knowledge that this value also corresponds to the O7–O12 distance of the skeleton of cholic acid, it is hypothesized that two steroid cholic acid moieties, with an appropriate steroid–steroid distance and a belly-to-belly orientation, could encapsulate a single water molecule between them. To check this hypothesis two succinyl derivatives of cholic acid (a monomer and the related head–head dimer in which the succinyl group is the linking bridge) were designed. The expected "ice-like" structure is found in the crystal of the dimer. There is a hydrogen bond synergy between those participating in the "ice-like" structure, and those in which the bridge is involved with the O7–H hydroxy group and the side chain of the steroid.

© 2012 Elsevier Inc. All rights reserved.

1. Introduction

After the discovery of crown ethers by Pedersen [1], several attempts have been made for encapsulating water inside a host. For instance, Newkome et al. [2] reported the first successful attempt of bound water in the center of an uncharged host molecule by hydrogen bonding. Nowadays this is a well-known phenomenon, but usually the inclusion involves water clusters rather that individual water molecules [3–6]. Encapsulated water polymers have been obtained in rigid metal complexes based on mono-N-substitued carboxylate 4,4′-bipyridine [7] and entrapped water wires have been prepared in peptide nanotubes [8]. They are also known in aquaporins which are the predominant water channel in membranes [9,10]. In general, as Braun et al. [11] have pointed out, the inclusion of water molecules affects many solid state properties, determining chemical processing.

However, the encapsulation of single water molecules is much less common. For instance, Morris et al. [12] have found that the cage inside potassium aryloxide aggregates contains a single encapsulated water molecule, giving the molecular formula $[(2\text{-}^{t}BuC_6H_4OK)_6 \supset (H_2O)\cdot(diox)4]_\infty$, and observed that encapsulation by the hexameric prism does not significantly perturb the structure of the water molecule. Garric et al. [13] have prepared aromatic oligoamides that have alternating 1,6-diaminopyridine and 1,6-pyridinedicarboxylic acid units at the center of the sequence and two 8-amino-2-quinolinecarboxylic acid units at each extremity. They adopt helically folded conformations in solution and in the solid state, the diameter of the helix being larger in the center than at each extremity forming a closed shell that may act as a capsule. Depending on the number of pyridine rings, one or two water molecules are bound within the capsules.

Here we will adopt a different strategy for encapsulating a single water molecule and for designing such a device, we will refer to the structure of ice as a starting model. In ice the intermolecular bonding consists primarily of hydrogen bonds and each H_2O is surrounded by other four water molecules forming a tetrahedron with values of 2.76 and 4.51 Å for the nearest-neighbor O–O and the edge O–O average distances, respectively [14,15]. It may be hypothesized that any other tetrahedral structure with four oxygen atoms and the indicated O–O edge distance can possibly bound a single water molecule inside it.

This distance condition is fulfilled by the two O7-H and O12-H hydroxy groups of cholic acid (Fig. 1, top left) and derivatives since the indicated value has been obtained in several crystal structures. Thus, a priori two cholic acid skeletons, with an appropriate steroid–steroid distance and a belly-to-belly orientation (see below), could encapsulate a single water molecule between them. In a crystal, this would require the formation of alternating hydrophilic/hydrophobic layers, which is not an uncommon fact in crystals of cholic acid and derivatives [16–26]. However although several cholic acid crystals including water alone or as a second guest have been obtained [21–29], none of them shows the desired structure indicated in Fig. 1 (top right). This is also the case of cholic acid derivatives with an extended hydrophobic region [30–32].

* Corresponding author. Tel.: +34 982824082.
E-mail address: jose.vazquez@usc.es (J.V. Tato).

0039-128X/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.steroids.2012.07.003

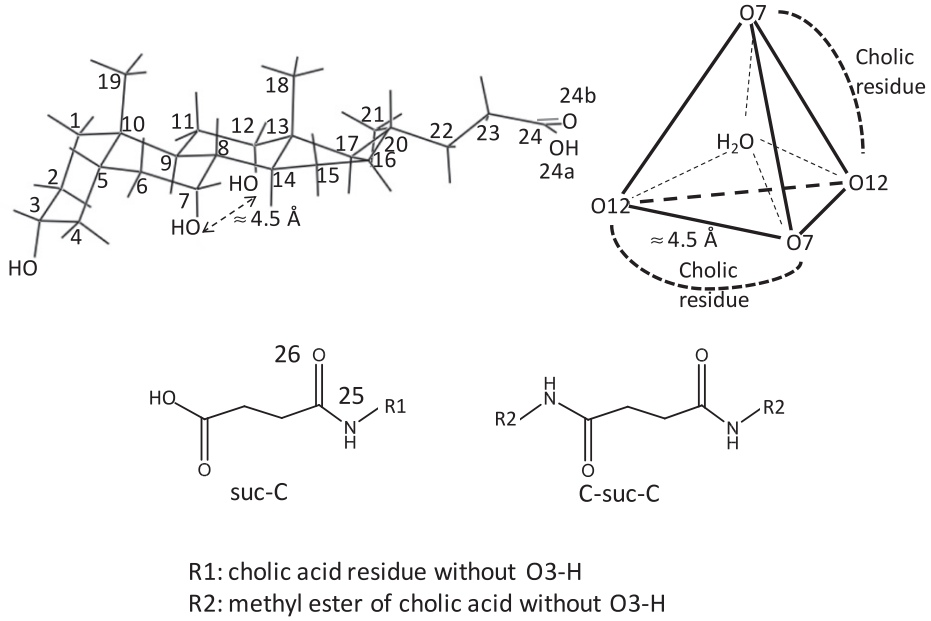

Fig. 1. Top left: Structure and atom label of cholic acid. The number of each oxygen atom is the same of the carbon atom to which is attached. Top right: Schematic belly-to-belly orientation of two cholic residues for encapsulating a H_2O molecule. Bottom: Structure of the monomer (suc-C) and the dimer (C-suc-C) derivatives of cholic acid.

The structure of cholic nucleus is well established and with the restriction of the tetrahedral structure, we can infer which relative orientation must the two steroid nuclei have in order to obtain the ideal tetrahedron. For instance, if the angle formed by a virtual line linking the two O7 and O12 hydroxy groups with the vertical plane [33] of the steroid was 90°, the formation of the ideal tetrahedron would require that the vertical planes of the two steroid nuclei were also perpendicular to each other. If this angle was 45°, then the two steroid nuclei should be parallel to each other and because of the concave surface of the α-side, the two heads would probably be in opposite directions. Since the actual angle is around 66°, an intermediate orientation of the steroid nuclei can be expected. Similar arguments may be use for predicting the distance between the two complexing steroid nuclei (see below).

It is a very well-known fact that hydrogen bonds determine in great extension the final crystal structure of bile acids [33,34]. So the reason why the crystals of cholic acid and its derivatives (see above) do not show the "ice-like" structure is probably due to other hydrogen bonds in which the carboxylate group (tail) and the O3-H hydroxy group (head) are involved. New derivatives with different or additional characteristics to those of previous compounds can be explored. For this purpose the O3-H hydroxy group and the side chain at C17 (including the carboxylic group) can be modified for finding a right derivative.

In fact some options have been explored in the literature although the purpose of the published papers was another one. For instance Miyata et al. [18,35] have shortened and lengthened the C17 side chain but although water is included in those crystals [35], the tetrahedral structure is not present. Neither the change of the carboxylic acid nor the O3-H hydroxy groups by amines [29], show the desired result.

The closest results found in the literature correspond to two hydrophobic derivatives (with the residue located at C3) [30–32,36–38] and to a cholaphane of cholic acid. One water molecule is forming hydrogen bonds with O7-H and O12-H in a crystal of an adamantyl derivative of cholic acid [30], but only one steroid molecule is involved and the water is forming only these two hydrogen bonds. The "ice-like structure" is incomplete. A similar structure was found for a *tert*-butylphenyl derivative of cholic acid [31] but now the water is forming a third hydrogen bond with the O24a-H of the carboxylic group of another steroid molecule. In a cholaphane crystal [39] five water molecules are included, two of them forming hydrogen bonds with the O7-H and O12-H hydroxy groups (belonging to the same steroid nucleus) and mutually interacting.

In this paper, we have explored another option based on the linking of a hydrophilic and flexible residue at C3. For this purpose, two succinyl derivatives of cholic acid were obtained and recrystallized. The first one (suc-C), a monomer, was previously studied because of its biological properties [40,41] and the second one is the related head–head dimer in which the succinyl group is the linking bridge. Since it was not possible to obtain good crystals for the dimer in its acid form, we tested its methyl ester derivative (C-suc-C, Fig. 1).

2. Experimental

2.1. Synthesis of the 3-amide-succinyl derivative of cholic acid (suc-C)

The methyl ester of 3β-aminocholic acid is obtained from 3β-amino-cholic acid (the synthesis of this amine derivative from commercial cholic acid has been described elsewhere) [42,43]. Succinic anhydride (1.5 g, 15 millimol) is added to a solution of the methyl ester derivative (6.15 g, 15 millimol) dissolved in a mixture of THF (85 mL) and triethlamine (17 mL). The reaction was maintained for 4 h at room temperature. The reaction mixture was added to 200 mL of HCl (1 M) in water and the solute extracted with ethyl acetate. The organic phase was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The compound is purified in a silica gel column using 3:2 ethyl acetate/methanol as eluent and dried in a vacuum oven. Yield: 82%.

2.2. Synthesis of C-suc-C

The compound is obtained by the reaction between succinic dichloride and the methyl ester of 3β-amino-cholic acid. To synthesize the succinic dichloride, succinic acid (0.24 g, 2 millimol)

Table 1
Crystal data for the four epimers studied.

Empirical formula	$C_{28}H_{45}NO_7 \cdot H_2O$	$C_{56}H_{90}N_2O_{11}$
Formula weight	525.67	943.28
Temperature (K)	293 (2)	100 (2)
Wavelength (Å)	0.71069	0.71073
Crystal system	Monoclínic	Monoclinic
Space group	C_2	P 21
a (Å)	29.420 (5)	10.612 (4)
b (Å)	7.848 (5)	22.603 (9)
c (Å)	13.434 (5)	10.982 (4)
α (°)	90.000 (5)	90
β (°)	91.940 (5)	96.966 (7)
γ (°)	90.000 (5)	90
Cell volume	3100 (2)	2614.73 (18)
Z, crystal density (g/cc)	4; 1.126	2; 1.198
Absorption coefficient (mm^{-1})	0.081	0.082
F(000)	1144	1032
Crystal size (mm^3)	0.41 × 0.14 × 0.09	0.68 × 0.38 × 0.19
Theta range for data collection	1.39–20.81°	1.80–25.68°
Index ranges	−29 = < *h* = <29 0 = < *k* = <7 0 = < *l* = <13	−12 = < *h* = <12 −27 = < *k* = <12 0 = < *l* = <13
Data/restraints/parameters	1781/3/350	9918/27/622
Max. and min. transmission	1 and 0.795537	0.9846 and 0.9463
Goodness of fit on F^2	1.065	1.059
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0488, wR_2 = 0.1361	R_1 = 0.0516, wR_2 = 0.1187
R indices (all data)	R_1 = 0.0726, wR_2 = 0.1489	R_1 = 0.0726, wR_2 = 0.1269
Largest diff. peak and hole/ e Å^3	0.16 and −0.188 e Å-3	0.255 and −0.245
Absolute structure parameter	4 (3)	−0.8 (9)

in $SOCl_2$ (20 mL) is refluxed during 45 min under a $CaCl_2$ trap and concentrated under vacuum. The product is used without further purification. The methyl ester of 3β-aminocholic acid (1.89 g, 4.5 millimol) and dried triethylamine (0.72 mL, 4.5 millimol) were dissolved in dried $CHCl_3$ (50 mL). The mixture is cooled to 0 °C and succinic dichloride (0.31 g, 2 mM) in $CHCl_3$ (5 mL) was added dropwise. The reaction mixture is stirred for 12 h. The precipitated is washed with $CHCl_3$ and the solid is filtered off. The organic phase is washed with water (2 × 20 mL) and NaOH (10%) in water (2 × 15 mL) and again with water (20 mL). The solution is dried with $MgSO_4$ and the compound is purified in a silica gel column using 9:1 ethyl acetate/methanol as eluent.

Data for the colorless prismatic crystals of the two compounds were collected on a Bruker Smart-CCD-1000. Molecular graphics were from Mercury (http://www.ccdc.cam.ac.uk/prods/mercury). A summary of the crystal data and experimental details are listed in Table 1. Cif files are available as electronic supporting material. CCDC 867498 and 867499 contain the supplementary crystallographic data for suc-C and C-suc-C crystals. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

3. Results and discussion

The monomer suc-C was recrystallized from ethyl acetate/water. The crystal belongs to the monoclinic system, spatial group C2, and includes water in the structure with a 1:1 stoichiometry. The packing shows a layer structure and a closer inspection reveals that the place where, according to our expectations, the water should be located, is occupied by the carbonyl (C = O26) of the amide group at C3 (Fig. 2) of another steroid. The lengths of the hydrogen bonds involving water are within standard values of

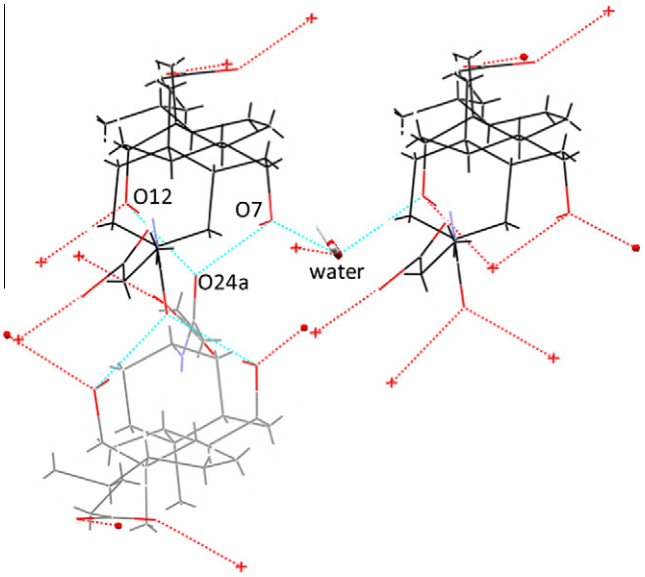

Fig. 2. Molecular packing and main hydrogen bonds in the suc-C crystal.

2.891 Å (with O7) and 2.798 Å (with O12), and an almost perfect tetrahedral O–O–O angle (107°) is also found. The water molecule is forming hydrogen bonds with O7 and O12 hydroxy groups but belonging to two different molecules. It is to say, the water molecule is in a "wrong" place as it is not located under the steroid nucleus (Fig. 2). It is forming three hydrogen bonds with three different steroid molecules, the distances being 2.740 Å (O7, first molecule), 2.721 Å (O12, second molecule), and 2.616 Å (O24a, third molecule).

The C-suc-C crystal belongs to the monoclinic system, spatial group $P2_1$, and includes water in the structure with a 1:1 stoichiometry. Fig. 3 shows the molecular packing along the *c* crystallographic axis. The packing evidences the formation of bilayers with alternating hydrophobic–hydrophylic regions. The thickness of the bilayer (11.302 Å) is half the value of the *b* crystallographic axis. The two steroid molecules in the dimer (their geometry parameters being almost identical but with some small differences in lengths and angles) are disposed in an anti-parallel way (Fig. 3), the angle between the horizontal planes [33] of the two steroid nuclei in the dimer being only 1.4° (i.e., they are almost parallel). Furthermore, these planes are also almost parallel to the bilayer plane since values of 4.5 or 5.5° (depending on the steroid nucleus of the dimer) are obtained.

The most remarkable result for the purposes of this paper is that water accommodates in the hydrophilic region of the bilayer establishing hydrogen bonds with the hydroxy groups O7 and O12 of two steroid residues (located at opposite sides of the bilayer) belonging to two dimers. These four oxygen atoms form a distorted tetrahedral structure with a water molecule in its center (Fig. 4), i.e., water is encapsulated in an ice-like structure. The main edge length values, corresponding to distances between the hydroxy groups of the steroids, are 4.52 ± 0.03 Å (O7–O12), 4.012 Å (O7–O7) and 4.549 Å (O12–O12). The first one can be considered as an imposed length as the two hydroxy groups belong to the same steroid residue (Fig. 1, top right) but the other two distances are the result of the formation of the ice-like encapsulated water, fixing the steroid distance as well (see below). The average tetrahedral angle is 110 ± 12°.

The average hydrogen bond lengths are 2.70 ± 0.06 Å and 2.94 ± 0.01 Å for O7···H–OH (water being the donor) and H_2O···H–O12 (water being the acceptor), respectively. All these values favorably compare with those mentioned above for water in ice.

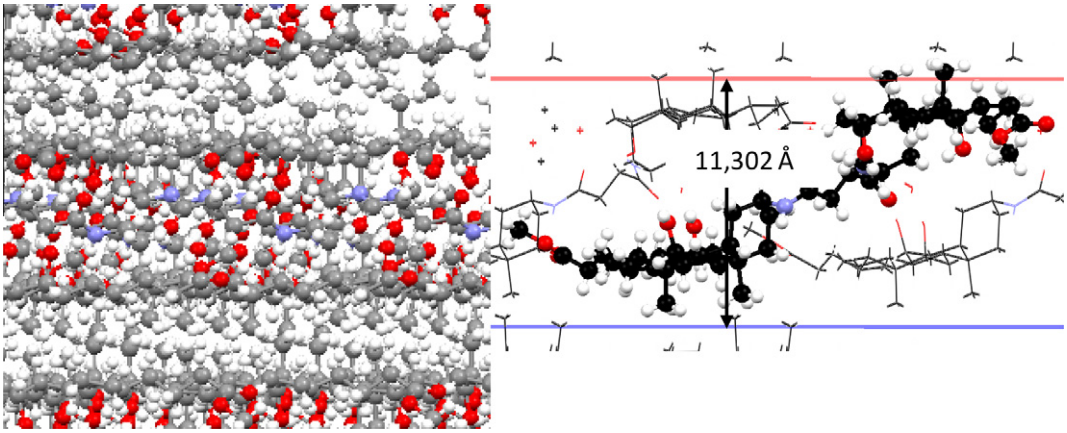

Fig. 3. Left: Bilayer structure in the C-suc-C crystal (view along the *c* crystallographic axis). Right: Detail of the dimer located in opposite sides of the bilayer with the linking bridge crossing the hydrophilic layer.

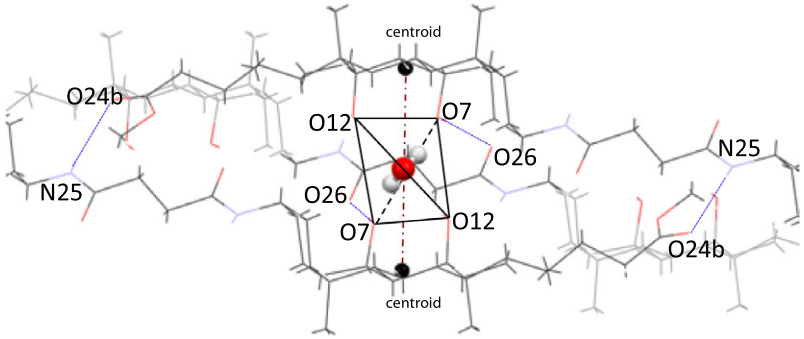

Fig. 4. Hydrogen bonds of (i) the central water molecule with two steroid residues belonging to two dimers, (ii) bridge of a third steroid dimer [located behind the previous two dimers] forming a clamp, and (iii) N25–H···O24b which mutually link each C24 carboxylic end of the one cholic residue with the nitrogen atom of the more distant amide group of the bridge of the other cholic moiety. Location of the two centroids of the steroid residues participating in the formation of the "ice" tetrahedron.

It is interesting to notice that water being donor only towards O7 and acceptor only towards O12 guarantees the existence of only one kind of hydrogen bond for each hydroxy group. This would not be the case if water was simultaneously donor and acceptor towards both hydroxy groups. This is a clear difference with what is observed in the crystals of the adamantyl [30] and *tert*-butylphenyl [31] derivatives of cholic acid, where water is simultaneously donor towards O7 and O12 and the ice-like structure is incomplete.

Another remarkable result in this structure is that each moiety of the dimer is located in opposite sides of the bilayer with the linking bridge crossing the hydrophilic layer (Fig. 3). The oxygen atoms of the two amide groups of the bridge act as a clamp since they establish hydrogen bonds with the two O7-H hydroxy groups (O7-H···O26, 2.655–2.672 Å) which participate in the formation of the tetrahedron. The bridge belongs to a third molecule. Those hydrogen bonds together with the O7-water-O7 mentioned above form a cycle (Fig. 4). The clamp helps in fixing the distance between the two steroid nuclei which encapsulate the water molecule. The two centroids of the C1/C5–C17 carbon atoms of the steroid skeleton are on the same vertical line crossing the oxygen atom of water (Fig. 4), the distance between them being 6.580 Å.

The hydrogen bond network in the crystal is completed by the formation of N25–H···O24b hydrogen bonds (2.958–2.982 Å) which mutually link each end of one cholic residue with the nitrogen atom of the more distant amide group of the bridge of the other cholic moiety. These interactions are possible because of a fully favorable geometry of the dimer since the C17–O24b (side chain) length (6.117 Å) is close to the C3–N25 (succinyl bridge) length (6.930 Å), together with the verticality of the two centroids.

The "ice-like" network, the clamp and the N25–H···O24b bonds undoubtedly lead the whole structure towards the minimum free energy. To the stabilization of the bilayers also contribute the hydrophobic interactions between the β faces of the steroids (with a β interdigitation of C18 and C19 methyl groups). This synergy suggests that the whole structure will only be favored by a right choice of the geometry of the bridge which must also carry hydrogen binding groups.

The suitability of the previous structure to specifically trap a H_2O molecule is supported by the fact that water was not the major component of the solvent [methanol/ethyl acetate] used for the recrystallization. The major components are not included guests in the crystal, so the minor component (water, approx. 0.3%) is in fact extracted from the bulk solvent.

This also suggests that other packings for inclusion of specific molecules can be designed by varying the bridge or by using other pair of hydroxyl groups of the steroid nucleus. Since the O3–O7 and O3–O12 distances (5.0 and 5.7 Å, respectively) are larger than the O7–O12 used here, bile acids with those α-hydroxy groups can also be used for the inclusion of molecules with appropriate geometries through hydrogen bonds interactions. Since bile acid crystals are useful for the enantioresolution of different compounds (see [32] and references therein) such an ability can advantageously be used for developing new resolving systems. Attaching appropriate groups on these sites of the steroid nucleus is an additional option already found in the literature. Resolution of enantiomers [32],

or recognition of ions [44–48] and molecules [39,49–51] by modified bile acids are nice published examples.

Acknowledgment

The authors thank the Ministerio de Ciencia y Tecnología, Spain [Projects MAT2007-61721 and MAT2010-19440] for financial support. J. V. Trillo also thanks for a scholarship. We thank Sapienza Università di Roma [Project C26A08SZ38] for financial support.

References

[1] Pedersen CJ. Cyclic polyethers and their complexes with metal salts. J Am Chem Soc 1967;89:7017–36.
[2] Newkome GR, Taylor HCR, Fronczek FR, Delord TJ, Kohli DK, Voegtle F. Encircling of water by crown compounds. J Am Chem Soc 1981;103:7376–8.
[3] Garcia-Rates M, Miro P, Poblet JM, Bo C, Avalos JB. Dynamics of encapsulated water inside Mo132 cavities. J Phys Chem B 2011;115:5980–92.
[4] Sun D, Xu H-R, Yang C-F, Wei Z-H, Zhang N, Huang R-B, Zheng L-S. Encapsulated diverse water aggregates in two Ag[I]/4,4′-bipyridine/dicarboxylate hosts: 1D water tape and chain. Crystal Growth Des 2010;10:4642–9.
[5] Li Y, Jiang L, Feng X-L, Lu T-B. Anion dependent water clusters encapsulated inside a cryptand cavity. Crystal Growth Des 2008;8:3689–94.
[6] Wang Y, Okamura T-a, Sun W-Y, Ueyama N. Large [H2O]56[OH]6 and [H2O]20 clusters inside a nanometer-sized M6L8 cage constructed by five-coordinated copper[II] and flexible carboxamide-containing tripodal ligand. Crystal Growth Des 2008;8:802–4.
[7] Phillips AD, Fei Z, Ang WH, Scopelliti R, Dyson PJ. A crystallographic story of snakes and ladders: encapsulated water polymers and rigid metal complexes based on mono-*N*-substituted carboxylate 4,4′-bipyridine. Crystal Growth Des 2009;9:1966–78.
[8] Raghavender US, Kantharaju, Aravinda S, Shamala N, Balaram P. Hydrophobic peptide channels and encapsulated water wires. J Am Chem Soc 2010;132:1075–86.
[9] Fujiyoshi Y, Mitsuoka K, De Groot BL, Philippsen A, Grubmuller H, Agre P, Engel A. Structure and function of water channels. Curr Opin Struct Biol 2002;12:509–15.
[10] Ho JD, Yeh R, Sandstrom A, Chorny I, Harries WEC, Robbins RA, et al. Crystal structure of human aquaporin 4 at 18 Å and its mechanism of conductance. Proc Natl Acad Sci USA 2009;106:7437–42.
[11] Braun DE, Tocher DA, Price SL, Griesser UJ. The complexity of hydration of phloroglucinol: a comprehensive structural and thermodynamic characterization. J Phys Chem B 2012;116:3961–72.
[12] Morris JJ, Noll BC, Schultz AJ, Piccoli PMB, Henderson KW. X-ray and neutron diffraction studies of water-encapsulated inside potassium aryloxide aggregates: complementary host-guest stabilization of mono- and dihydrated cages. Inorg Chem 2007;46:10473–5.
[13] Garric J, Léger J-M, Huc I. Encapsulation of small polar guests in molecular apple peels. Chem Eur J 2007;13:8454–62.
[14] Bergmann U, Di Cicco A, Wernet P, Principi E, Glatzel P, Nilsson A. Nearest-neighbor oxygen distances in liquid water and ice observed by X-ray Raman based extended X-ray absorption fine structure. J Chem Phys 2007;127:174504/1-174504/5.
[15] Fletcher NH. The chemical physics of ice. Cambridge University Press, 1970.
[16] Yoswathananont N, Chirachanchai S, Tashiro K, Nakano K, Sada K, Miyata M. A novel host framework of cholic acid inclusion crystals by slide and flip of the layers. Cryst Eng Comm 2001:1–4.
[17] Yoswathananont N, Sadaand K, Miyata M. Inclusion compounds of cholic acid with large aliphatic alcohols. Mol Cryst Liq Cryst 2002;389:47–51.
[18] Kato K, Sugahara M, Tohnai N, Sada K, Miyata M. Systematic structural study of asymmetric supramolecular assembly by a series of bile acid derivatives with different side-chain lengths. Crystal Growth Des 2004;4:263–72.
[19] Miragaya J, Jover A, Fraga F, Meijide F, Vázquez Tato J. Influence of the solvent ability to form hydrogen bonds in the crystal structure of [3,5,7,12]-3[[norbornyl-2-acetyl]-amino]-7,12-dihydroxycholan-24-oic acid [a norbornyl derivative of cholic acid. Steroids 2009;74:735–41.
[20] Sada K, Sugahara M, Kato K, Miyata M. Controlled expansion of a molecular cavity in a steroid host compound. J Am Chem Soc 2001;123:4386–92.
[21] Lessinger L. Cholic acid monohydrate, $C_{24}H_{40}O_5{\cdot}H_2O$. Cryst Struct Commun 1982;11:1787–92.
[22] Caira MR, Nassimbeni LR, Scott JL. Crystal structure and multiphase decomposition of a novel cholic acid inclusion compound with mixed guests. J Chem Soc Perkin Trans 2, 1994:1403–5.
[23] Shibakami M, Tamura M, Sekiya A. Topological and nontopological rearrangement in crystal lattice of cholic acid inclusion complex induced by guest exchange. J Am Chem Soc 1995;117:4499–505.
[24] Dastidar P. Crystal structure of the inclusion complex of cholic acid with 4-aminopyridine: a novel supramolecular architecture of cholic acid. Cryst Eng Commun 2000:8.
[25] Hishikawa Y, Watanabe R, Sada K, Miyata M. Molecular arrangements in chiral sheets of *N*-alkylcholamides bilayered crystals. Chirality 1998;10:600–18.
[26] Yoswathananont N, Kita H, Tohnai N, Sada K, Miyata M. A novel three-component pseudo-polymorphism in the cholamide inclusion crystals promoted by the combination of organic guest and water. Chem Lett 2002:1234–5.
[27] Lessinger L, Low BW. Crystal structure and hydrogen-bonding system of cholic acid hemihydrate, C24H40O5.1/2H20. J Crystallogr Spectr Res 1993;23:85–99.
[28] Volkov A, Zhu H, Liu S, White MA, Coppens P. The cholic acid–methanol–water inclusion complex. Acta Crystal 1998;C54:i, IUC9800026.
[29] Meijide F, Antelo A, Alvarez M, Soto VH, Trillo JV, Jover A, Vázquez Tato J. Spontaneous formation in solid state of carbamate derivatives of bile acids. Crystal Growth Des 2011;11:356–61.
[30] Soto VH, Jover A, Galantini L, Pavel NV, Meijide F, Vázquez Tato J. New lamellar structure formed by an adamantyl derivative of cholic acid. J Phys Chem B 2006;110:13679–81.
[31] Meijide F, Trillo JV, Soto VH, Jover A, Vázquez Tato J. Additional criterion for the determination of the handedness of 21 helices in crystals of bile acids: crystal structure of a *tert*-butylphenyl derivative of cholic acid. Chirality 2011;23:940–7.
[32] Miragaya J, Jover A, Fraga F, Meijide F, Vázquez Tato J. Enantioresolution and chameleonic mimicry of 2-butanol with an adamantylacetyl derivative of cholic acid. Crystal Growth Des 2010;10:1124–9.
[33] Alvarez M, Jover A, Carrazana J, Meijide F, Soto VH, Vázquez Tato J. Crystal structure of chenodeoxycholic acid, ursodeoxycholic acid and their two 3,7- and 3,7-dihydroxy epimers. Steroids 2007;72:535–44.
[34] Jover A, Meijide F, Soto VH, Vázquez Tato J, Rodríguez Núñez E, Ton-Nu H-T, Hofmann AF. Successful prediction of the hydrogen bond network of the 3-oxo-12-hydroxy-5-cholan-24-oic acid crystal from resolution of the crystal structure of deoxycholic acid and its three 3,12-dihydroxy epimers. Steroids 2004;69:379–88.
[35] Sugahara M, Sada K, Miyata M. A robust structural motif in inclusion crystals of nor-bile acids. Chem Commun 1999:293–4.
[36] Galantini L, Leggio C, Jover A, Meijide F, Pavel NV, Soto VH, Vázquez Tato J, Di Leonardo R, Ruocco G. Kinetics of formation of supramolecular tubules of a sodium cholate derivative. Soft Matter 2009;5:3018–25.
[37] Manghisi N, Galantini L, Leggio C, Jover A, Meijide F, Pavel NV, et al. Catanionic tubules with tunable charge. Angew Chem Int Ed 2010;49:6604–7.
[38] Soto VH, Jover A, Meijide F, Vázquez Tato J, Galantini L, Pavel NV. Supramolecular structures generated by a *p-tert*-butylphenyl-amide derivative of cholic acid. From vesicles to molecular tubes. Adv Mater 2007;19:1752–6.
[39] Bhattarai KM, Davis AP, Perry JJ, Walter CJ, Menzer S, Williams DJ. A New generation of "Cholaphanes": steroid-derived macrocyclic hosts with enhanced solubility and controlled flexibility. J Org Chem 1997;62:8463–73.
[40] Herraez E, Macias RIR, Vázquez Tato J, Vicens M, Monte MJ, Marin JJG. In vitro inhibition of OATP-mediated uptake of phalloidin using bile acid derivatives. Toxicol Appl Pharm 2009;239:13–20.
[41] Herraez E, Macias RR, Vázquez Tato J, Vicens M, Monte MJ, Marin JJG. Protective effect of bile acid derivatives in phalloidin-induced rat liver toxicity. Toxicol Appl Pharm 2009;239:21–8.
[42] Anelli PL, Lattuada L, Uggeri F. One-pot Mitsunobu-Staudinger preparation of 3-aminocholan-24-oic acid esters from 3-hydroxycholan-24-oic acid esters. Synth Commun 1998;28:109–17.
[43] Ryu E-H, Ellern A, Zhao Y. High guest inclusion in 3-amino-7,12-dihydroxycholan-24-oic acid enabled by charge-assisted hydrogen bonds. Tetrahedron 2006;62:6808–13.
[44] Wilson CP, Webb SJ. Palladium[ii]-gated ion channels. Chem Commun 2008:4007–9.
[45] Bonar-Law RP, Sanders JKM. Cyclocholates: synthesis and ion binding. Tetrahedron Lett 1992;33:2071–4.
[46] Ghosh S, Choudhury AR, Guru RTN, Maitra U. Selective and unusual fluoride ion complexation by a steroidal receptor using OH···F- and CH···F-interactions: a new motif for anion coordination? Org Let 2005;7:1441–4.
[47] Virtanen E, Koivukorpi J, Tamminen J, Manttari P, Kolehmainen E. ^{1}H-, ^{13}C-, and ^{15}N NMR and ESI–TOF+ MS studies of a supramolecular complex of silver[I] and a cholaphane. J Organometal Chem 2003;668:43–50.
[48] Valkonen A, Sievaenen E, Ikonen S, Lukashev NV, Donez PA, Averin AD, Lahtinen M, Kolehmainen E. Novel lithocholaphanes: syntheses, NMR, MS, and molecular modeling studies. J Mol Struct 2007;846:65–73.
[49] Bonar-Law RP, Sanders JKM. Polyol recognition by a steroid-capped porphyrin. Enhancement and modulation of misfit guest binding by added water or methanol. J Am Chem Soc 1995;117:259–71.
[50] Chattopadhyay P, Pandey PS. Synthesis and binding ability of bile acid-based receptors for recognition of flavin analogues. Tetrahedron 2006;62:8620–4.
[51] Chattopadhyay P, Pandey PS. Bile acid-based receptors containing 2,6-bis[acylamino]pyridine for recognition of uracil derivatives. Bioorg Med Chem Lett 2007;17:1553–7.