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Crystal structure of head-to-head dimers of cholic and deoxycholic acid derivatives with different symmetric bridges

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ABSTRACT

The crystal structure of three head-to-head dimers (having two cholic acid or deoxycholic acid units) linked at carbon atoms C3 by aromatic or alkyl bridges is studied. An internal coordinates system is necessary for describing the relative orientation in the space of the two bile acid residues. Five angles (three torsion and two common ones) are necessary for defining the relative position of both steroid residues in space. Carbon atoms C3 (which always carries a α-hydroxy group in natural bile acids), and C10 and C13 (which always carry β-methyl groups) of each steroid residue are suitable for this purpose. Furthermore, the distance between each C3 carbon atoms of both steroid residues will allow one to locate the steroids in space. The three dimers selected provide a large range of values for these angles. The packing, hydrogen bond network, and location of guest in the three crystals are discussed.

1. Introduction

Bile acids are at the focus of intensive research. These compounds are interesting because of their biological function, their therapeutic applications, and, in recent years, their extensive use in supramolecular chemistry, materials chemistry and nanotechnology [1–7]. Bile salts exhibit a facial amphiphilicity derived from the existence of a hydrophilic side (α-face, concave lower side) and a hydrophobic side (β-face, convex upper side). The side chain with a carboxylic group or an amide group also contributes to the hydrophilicity of the compound. As a consequence, they are good surfactants and form aggregates in water as long as the concentration is above a critical concentration [8,9].

During the last years the number of published papers related to the synthesis and the study of the physicochemical and biological properties of new bile salts derivatives has grown enormously. For the purposes of this paper we shall briefly mention dimer derivatives. The concept of linking two bile acid moieties was first reported by McKenna et al. [10] and Dias et al. have reviewed the subject of early papers [11,12]. Depending on the respective orientation of the backbone steroid, there are three main types of junction: head (position 3) to tail (position 24) [13,14], head to head [15,16] and tail to tail [17], but the formation of dimers is not confined to the conjugation of the former positions [18–21]. Different methodologies for their synthesis have been published [12,17,22–25].

The cmc of natural bile salts can be significantly lowered by forming *gemini* surfactants [17] or by the presence of bile acid dimers [26]. Some dimers form twisted ribbons [27], other are organogelators [28], or are able to solubilize a hydrophilic dye in a nonpolar solvent [29]. Other authors have used dimers for the formation of copolymers [30] (for which potential applications in the biomedical and pharmaceutical fields have been published [31]), biochemical insecticides [32], as precursors for the formation of cyclic tetramers and hexamers [33], and poly(choloyl)-based amphiphiles [34]. Steroid-capped porphyrins have also been obtained [35,36] as well as other cyclic oligomers [5,12,21,37–43]. Potential precursors for the design of bile acid derived receptors have been obtained [44].

Molecular umbrellas [45–47], with two cholic acid moieties have been designed. They selectively transport different species (including ATP) across a phospholipid bilayer [48–50]. Molecular cleft devices based on bile acid dimers have been designed [51], while other have been used for the synthesis of foldamers [52]. Head to head dimers have been used to develop new cholate-based ion channels that can be gated "open" or "closed" by the addition or removal of palladium(II) [53]. Recognition for different compounds is also a common subject [36], in which cholaphanes [40,54,55] offer enough space for binding high variety of substrates

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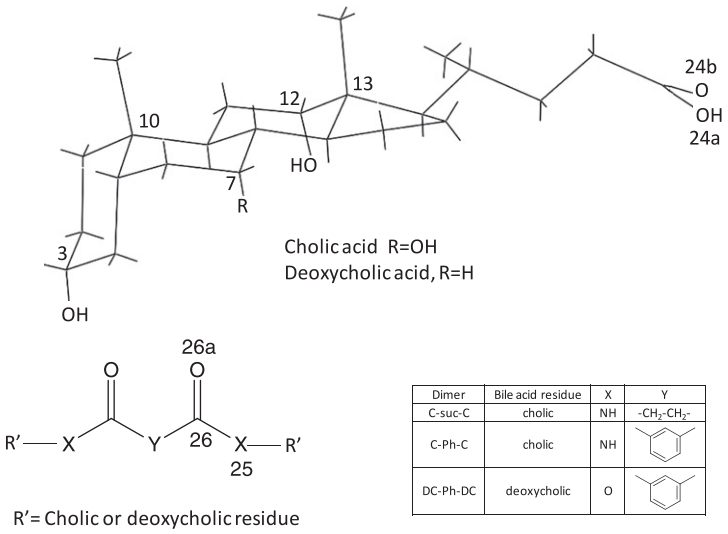

Fig. 1. Structure of cholic and deoxycholic acids, and dimer derivatives studied in this paper.

by molecular recognition: fluoride [42], carbohydrates [56,57], silver [58], flavin analogues [59], uracil derivatives [60], alkali metal cations [37], etc. Cationic cholaphanes behave as "smart phase transfer agents" showing clear structure-dependent preferences in anion extraction. Their selectivity bodes well for applications in biology and medicine, where the promotion of chloride transport is relevant to potential treatments for conditions caused by absent or malfunctioning chloride channels [61]. The interaction of some dimers with specific bile acid transport system has been studied [62,63]. The number of bile acid dimers which facilitate ion-transport and generate artificial ion channels is growing continuously during the last few years [64–68]. Some dimers are anti viruses agents [69], and others exhibit antifungal and antibacterial activity [70,71]. Others show antiproliferative activity of human cancer cells [72,73] and are capable of entering live Hela cells [74]. Kramer et al. have synthesized dimers as inhibitors of bile acid resorption [75] and Burrows et al. have synthesized derivatives which binds to DNA [76,77] and evidence conformational isomerism [78].

Despite the interest in the bile acid oligomers commented on above, these compounds have not been characterized in the solid state. It must be taken into account that the knowledge of the crystal structure by X-ray resolution can be useful for the proposition of the structure of supramolecular aggregates in aqueous solutions [79–81]. It can be also useful for practical purposes of bile acids as the formation of polymers [82], the resolution of racemates [83] (and references therein), and delayed release of drugs [84]. The crystal structures of bile acid dimers can lead to new structural issues which *a priori* will be conditioned by the structural characteristics of the bridge, the bile acid moieties and by the linking of the monomers to that bridge (tail-to-tail, head-to-tail, etc.). A recently published example corresponds to the encapsulation of a single water molecule in an ice-like structure [85] by a cholic acid dimer. Apart from the last mentioned paper, as far as we know, only Bertolasi et al. [19], Bai et al. [86] and Choudhury et al. [42], and Dias et al. [87] have published crystal structures of a bile acid dimer, a cyclic bile acid dimer, and a cyclotrimer derived from deoxycholate, respectively.

Table 1
Crystal data for the dimers studied in this paper.

	C-suc-C	C-Ph-C	DC-Ph-DC
Empirical formula	$C_{54}H_{88}N_2O_{10}.H_2O$	$C_{58}H_{88}N_2O_{10}.C_4H_8O_2$	$C_{58}H_{86}O_{10}$
Formula weight	943.28	1061.41	943.27
Temperature (K)	293 (2)	120 (2)	293(2)
Wavelength (Å)	0.71073	1.5418	1.5418
Crystal system, space group	Monoclinic $P2_1$	Monoclinic $P2_1$	Monoclinic $P2_1$
a (Å)	10.612(4)	7.53260(10)	7.6225(13)
b (Å)	22.603(9)	22.6049(3)	11.2669(9)
c (Å)	10.982(4)	16.9897(2)	31.7872(26)
α (°)	90	90	90
β (°)	96.966(7)	96.7780(10)	95.319(9)
γ (°)	90	90	90
Volume (Å^3)	2614.7(18)	2872.68(6)	2718.19(56)
Z, calculated density (g/cm^3)	2, 1.198	2, 1.227	2, 1.153
Absorption coefficient (mm^{-1})	0.082	0.671	0.611
F (000)	1032	1156	1028
Crystal size (mm^3)	0.68 × 0.38 × 0.19	0.2 × 0.16 × 0.09	0.3 × 0.3 × 0.2
Theta range (data collection) (°)	1.80–25.68	2.62–72.56	1.29–26.43
Index ranges	$-12 \leqslant h \leqslant 12$	$-8 \leqslant h \leqslant 8$	$-9 \leqslant h \leqslant 9$
	$-27 \leqslant k \leqslant 27$	$-27 \leqslant k \leqslant 27$	$0 \leqslant k \leqslant 14$
	$0 \leqslant l \leqslant 13$	$0 \leqslant l \leqslant 20$	$0 \leqslant l \leqslant 39$
Data/restraints/parameters	9918/27/622	10602/1/822	5870/1/613
Goodness-of fit on F^2	1.059	1.569	1.034
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0516, wR_2 = 0.1188	R_1 = 0.0486, wR_2 = 0.1405	R_1 = 0.0491, wR_2 = 0.133
R indices (all data)	R_1 = 0.0726, wR_2 = 0.127	R_1 = 0.0499, wR_2 = 0.1417	R_1 = 0.0659, wR_2 = 0.1443