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Inclusion of cyclic carbonates by a cholic acid host: structure and enantioselection

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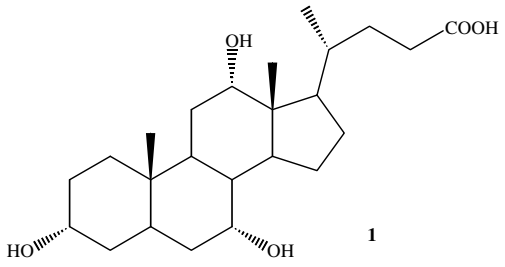
Abstract—The optical resolution of some model monosubstituted cyclic carbonates, by inclusion in cholic acid, is described. The X-ray analysis of the host–guest crystal structures provide a rationale for molecular recognition.

1. Introduction

Bile acid derivatives, in particular cholic **1** and deoxycholic acids, are classical host compounds that form inclusion complexes with various organic substances.[1] Some of these inclusion compounds have crystal structures able to selectively enclathrate either of the enantiomers of a guest racemate into the host framework, thus performing efficient chiral resolution. Numerous examples have been reported in the literature, which include the resolution of lactones, alcohols, sulfoxides, epoxides, amines, prochiral ketones and cyclic amides.[1] The characteristic features of this resolution method are simple handling, low cost, mild conditions and eco-friendliness, since little or no loss of substance is associated with a recycle of the host.[1]

Following our recent work in this field, we extended the bile acid-based host–guest resolution protocol to cyclic carbonates, important molecules both as CO_2 synthons[2] and as intermediates to polyfunctional derivatives of interest.[3,4] The routes to optically active cyclic carbonates are based on the cyclization of chiral diols with phosgene or activated carbonates, and on the insertion of CO_2 into epoxides and allylic epoxides catalyzed by Zn(II) or Pd(0).[3] Enzymatic enantioselective reactions have also been described, and the hydrolysis of cyclic carbonates using Porcine Pancreas Lipase[5] and *Pseudomonas diminuta*[6] was particularly efficient.

Herein we report the inclusion of some monosubstituted cyclic carbonates **2a**–**f** with **1** that give rise to a particularly efficient resolution for **2a** and **2b**.



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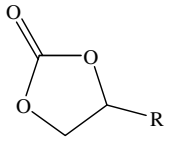

2a: R = Me
2b: Et
2c: n-Pr
2d: n-Bu
2e: Ph
2f: CH_2OAc

X-ray crystal structures of the related inclusion complexes are presented and discussed. The steric dimensions of the host cavities control the size and shape of the included molecules with particular attention to the guest substituent length.

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2. Results and discussion

The resolution of racemic cyclic carbonates via host–guest enclathration using cholic acid **1** is a straightforward procedure that occurs according to Scheme 1, drawn for the inclusion of an unspecific (*S*)-enantiomer. Substrates **2a**–**f** were simply added to solid **1** either as neat samples or dissolved in the appropriate alcohol, at room temperature. After 2 days, the crystals were washed with ether and the included guest separated, recovered and submitted to analysis (^{1}H NMR, GC, $[\alpha]_D$, see Section 3 for details). The results are shown in Table 1. Short length substituted cyclic carbonates **2a** and **2b** enantioselectively include into cholic acid both in the absence or presence of the solvent with enantiomeric excesses of 35% and 71%, respectively. The excessive enlargement of the host cavity, requested for the enclathration of carbonates with longer chains, prevents the inclusion of **2c**, **2d** and **2f**, as proven by the X-ray analysis of the complexes **1**·**2a** and **1**·**2b** discussed below.

Table 1. Resolution of cyclic carbonates using cholic acid **1** as a chiral host

Cyclic carbonate	Host–guest ratio	Solvent	ee % (opt. rot. sign)
2a	1:1	Neat	35 (+)
	1:1	2-Butanol	30 (+)
2b	1:1	Neat	63 (−)
	1:1	*t*-Butanol	61 (−)
	1:1	2-Butanol	63 (−)
	1:1	3-Buten-2-ol	71 (−)
2c	—	Neat	—
	—	2-Butanol	—
2d	—	Neat	—
2e	4:1	Neat	41 (+)
2f	[a]	Neat	2

[a] Not determined.

The ORTEP[7] views of host–guest complexes **1**·**2a** and **1**·**2b** are shown in Figures 1a and 2a. Their crystal packings, given in Figures 1b and 2b, are isostructural and very similar to many other inclusion compounds of cholic acid **1** and organic guests.[8–13] In all these structures, the host–guest frameworks display amphiphilic bilayered structures where the layers are held together by hydrogen bonds between the hydrophilic α-faces and van der Waals interactions between the lipophilic β-faces. The guest compounds are trapped by van der Waals forces and steric complementarity within the chiral channels in the lipophilic layers. In **1**·**2a** and **1**·**2b** the molecules of cholic acid forming the supramolecular architecture exhibit the carboxylic side chain with full extended conformation *t t t t* (Table 2) and are stacked with the α-trans aggregation type.[14]

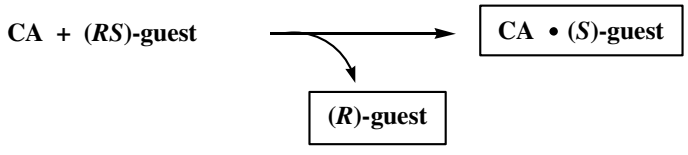
The volumes of the host cavity *per* unit cell of 347.5 and 383.3 Å^3, for **1**·**2a** and **1**·**2b**, respectively, correspond to volumes *per* guest molecule of 173.8 and 191.6 Å^3 that are comparable with those in the range of 150–200 Å^3, reported for crystals of inclusion compounds of **1** with monosubstituted benzenes.[15] Therefore, the larger ethylic substituent at the 4-position of 1,3-dioxolane-2-one cyclic carbonate **2b** induces an increase in the size of the cavity in the crystal structure **1**·**2b** with respect to that in **1**·**2a**, which contains the methylic derivative **2a**. This variation is accompanied by a weakening of all intermolecular O–H···O hydrogen bonds within the hydrophilic layers of cholic acid aggregations as shown by a systematic lengthening of the related O···O distances in **1**·**2b** with respect to those in **1**·**2a**, as reported in Table 3.

The results obtained with the phenyl derivative **2e** are noteworthy. Its unexpected inclusion into cholic acid, despite the bulkiness of the substituent, can be explained as either related to the planarity and torsion of the phenyl ring or, alternatively, due to a morphologic change of the inclusion crystals. This latter hypothesis is supported by the unusual host–guest ratio, that is 4:1, displayed by the inclusion complexes (Table 1).

A final note refers to the IR data obtained with the free and the included cyclic carbonates. In the IR spectra of compound **2b**, the carbonyl stretching was found at 1791.13 cm^{-1} in the free carbonate and at 1806.61 cm^{-1} when the molecule is included (**1**·**2b**). This considerable difference can be explained taking into account that dipolar carbonyl–carbonyl contacts occur in the free form as demonstrated by recent studies.[16,17] On the other hand these intermolecular interactions are prevented in host–guest inclusion crystals.

3. Experimental

^{1}H NMR spectra were obtained with a Varian Gemini 300; optical rotations were measured on a Perkin–Elmer 241 polarimeter; IR spectra (KBr) were obtained with a NICOLET 510P spectrometer operating in Fourier Transform mode and enantiomeric excesses were determined by GC on a Megadex DETTBS. The host–guest inclusion derivatives were obtained by adding the racemic cyclic carbonate (1 mL), either as neat sample or dissolved in the alcohols reported in Table 1, to cholic acid (0.35 g, host–guest ratio ca. 1:10) and let at room temperature for 48 h. The inclusion crystals were filtered



Scheme 1.

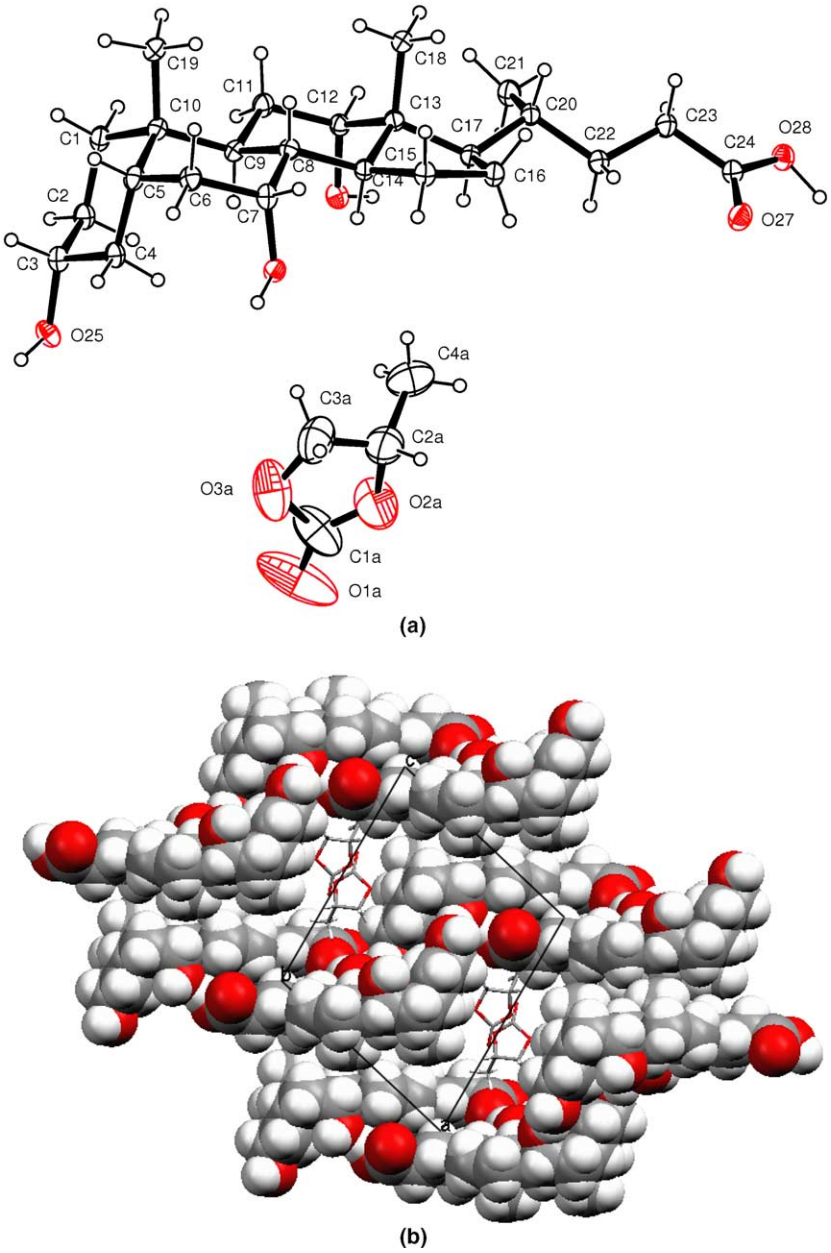


Figure 1. (a) ORTEP view and atom numbering scheme for host–guest complex **1·2a** displaying the thermal ellipsoids at 30% probability; (b) a space filling representation of crystal packing of host–guest complex **1·2a** as viewed down the crystallographic *b* axis. The guest molecules of 4-methyl-1,3-dioxolan-2-one, **2a**, included in the lipophilic channels formed by cholic acid molecules, **1**, are shown using the stick representation.

and washed with ether several times. The product was analyzed by ^{1}H NMR to determine the cholic acid–carbonate ratio, treated with aqueous $NaHCO_3$ and extracted with ether. The extracts were analyzed by GC to obtain the enantiomeric excess and polarimetric analysis for the optical rotation sign.

X-ray diffraction data for inclusion compounds **1·2a** and **1·2b** were collected at room temperature, 295 K, on a Nonius Kappa CCD diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.7107$ Å). The structures were solved by direct methods (SIR97)[18] and refined (SHELXL-97)[19] by full matrix least squares with anisotropic non-H atoms. In both structures the hydrogen atoms of cholic acid **1** host were refined isotropically while those of guest molecules **2a** and **2b** were included on calculated positions riding on their carrier atoms. All other calculations have been performed using PARST[20] and PLATON[21] systems of programs.

Crystal data: **1·2a**, $C_{24}H_{40}O_5{\cdot}C_4H_6O_3$; monoclinic, space group $P2_1$, $a = 12.5660(4)$, $b = 7.8948(2)$, $c = 14.1488(6)$ Å, $\beta = 103.399(1)°$, $V = 1365.44(8)$ Å^3, $Z = 2$, Dc = 1.242 g cm^{-3}. Intensity data collected with $\theta \leqslant 27.5°$; 5532 independent reflections measured; 4460 observed [$I > 2\sigma(I)$]. Final R index = 0.0586 (observed reflections), Rw (all reflections) = 0.1590 and S = 1.029. **1·2b**, $C_{24}H_{40}O_5{\cdot}C_5H_8O_3$; monoclinic, space group $P2_1$, $a = 12.7241(4)$, $b = 8.0907(2)$, $c = 14.1917(5)$ Å, $\beta = 104.131(1)°$, $V = 1416.78(8)$ Å^3, $Z = 2$, Dc = 1.230

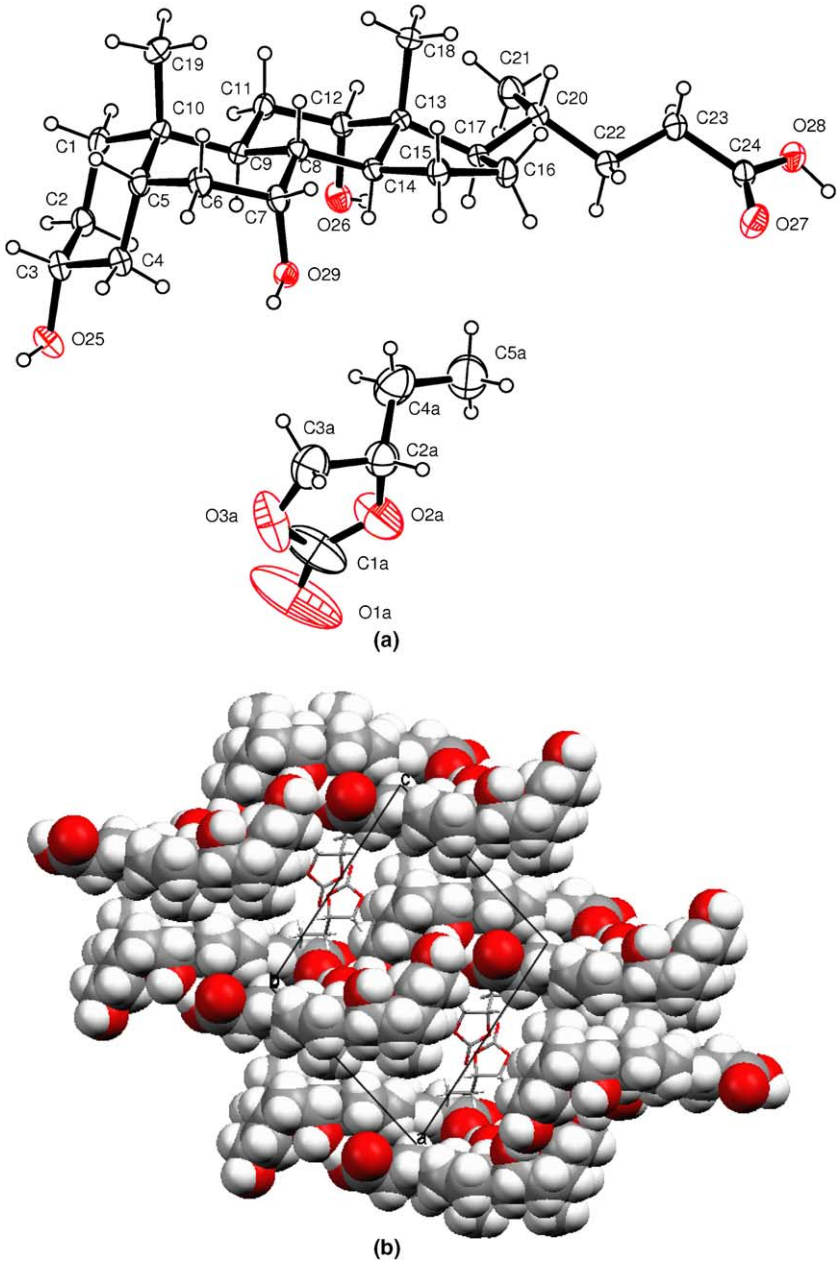


Figure 2. (a) ORTEP view and atom numbering scheme for host–guest complex **1·2b** displaying the thermal ellipsoids at 30% probability; (b) a space filling representation of crystal packing of host–guest complex **1·2b** as viewed down the crystallographic *b* axis. The guest molecules of 4-ethyl-1,3-dioxolan-2-one, **2b**, included in the lipophilic channels formed by cholic acid molecules, **1**, are shown using the stick representation.

Table 2. Selected torsion angles (°) and carboxylic side-chain conformation

Compound	ψ_1	ψ_2	ψ_3	ψ_4	Conformation
1·2a	179.4(2)	−172.7(3)	173.3(3)	153.5(3)	*t t t t*
1·2b	−179.4(2)	−170.2(2)	172.7(2)	153.6(2)	*t t t t*

ψ_1 = C13–C17–C20–C22; ψ_2 = C17–C20–C22–C23; ψ_3 = C20–C22–C23–C24; ψ_4 = C22–C23–C24–O28H.

g cm^{-3}. Intensity data collected with $\theta \leqslant 30.0°$; 6804 independent reflections measured; 5615 observed [$I > 2\sigma(I)$]. Final R index = 0.0477 (observed reflections), Rw (all reflections) = 0.1285 and S = 1.011.

Complete crystallographic data (excluding structural factors) for the structures herein have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 290735 and 290736. Copies of the data can be obtained, free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Table 3. Hydrogen bond parameters (Å, °)

D-H···A	Symm. op	D–H	H···A	D···A	D–H···A
1·2a					
O25–H25···O26	$1-x, y-1/2, 1-z$	0.99(5)	1.99(4)	2.857(3)	144(4)
O26–H26···O27	$-x, 1/2+y, -z$	1.02(6)	1.84(6)	2.821(4)	161(5)
O28–H28···O29	$-x, 1/2+y, -z$	1.00(5)	1.69(5)	2.688(4)	172(5)
O29–H29···O25	$1-x, y-1/2, 1-z$	0.87(4)	1.81(4)	2.657(3)	166(4)
1·2b					
O25–H25···O26	$1-x, y-1/2, 1-z$	0.84(3)	2.16(3)	2.906(2)	148(3)
O26–H26···O27	$2-x, 1/2+y, 2-z$	0.76(4)	2.22(4)	2.941(2)	160(4)
O28–H28···O29	$2-x, 1/2+y, 2-z$	0.89(4)	1.82(4)	2.702(2)	173(3)
O29–H29···O25	$1-x, y-1/2, 1-z$	0.74(3)	1.95(3)	2.682(2)	170(3)

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