Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1479–1483

TETRAHEDRON: *ASYMMETRY*

Enantioselective inclusion in bile acids: resolution of cyclic ketones

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Received 10 May 2001; accepted 25 May 2001

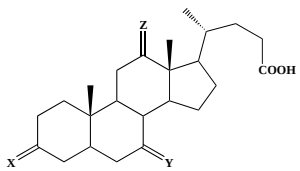
Abstract—Cholic and deoxycholic acids were found to form inclusion compounds with various racemic cyclic ketones enabling direct and straightforward enantiomer separation. The X-ray structure of the 2:1 inclusion complex between (−)-bicyclo[3.2.0]-hept-2-en-6-one and cholic acid is reported.

1. Introduction

The resolution of racemates by enantioselective inclusion in suitable chiral hosts is an interesting branch of organic stereochemistry that is receiving renewed interest in recent years.[1] This technique is based on the ability of a chiral host to incorporate enantioselectively the racemic guest within its molecular or crystal lattice cavities (Scheme 1).

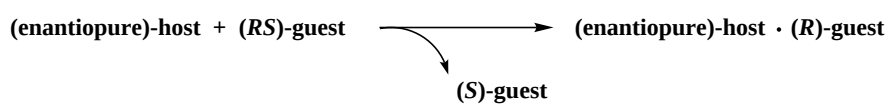
The major advantages of this methodology are its efficiency and simplicity, the mild conditions employed, the quantitative recovery of both guest and host compounds and the wide applicability of the method.[2] A number of inclusion procedures have been described in the literature that may be grouped in: (i) absorption methods[3] in which the insoluble host was simply left in the presence of the guest, or vice versa, for a given time, (ii) crystallization methods[4] in which the host is dissolved and recrystallized from the guest and (iii) solid-state inclusions[5] consisting of a co-grinding of the two solid components in an agate mortar.

Steroids are one of the best sources of chiral host compounds due to their multi-functional and rigid, although flexible, structure. Among steroids, bile acid derivatives have often been used for this purpose on account of their ability to recognize and resolve important organic substrates such as lactones,[6] alcohols,[4] sulfoxides[7] and epoxides,[8] which are otherwise difficult to resolve. These substrates have been shown to form inclusion compounds with derivatives of cholic **1**, deoxycholic **2** and dehydrocholic acid **3**, affording enriched or resolved racemates (e.e. up to 99%).



1 X=Y=Z=α-OH,H
2 X=Z=α-OH,H; Y=H,H
3 X=Y=Z=O

The efficiency of bile acids as host compounds is associated with two additional peculiarities. The majority of the bile acids are commercially available compounds, obtainable at low cost and easy to handle. Furthermore, the carboxylic function present on the steroid lateral chain permits ready removal of the host from the reaction mixture by direct acid–base treatment and facilitates recycling.[7,8] Taking into account these considerations, all classes of 'neutral' organic molecules lacking acid–base functions that are not suited to classical resolution via preparation of diastereoisomeric salts[9] are ideal candidates for host–guest resolution



Scheme 1.

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PII: S0957-4166(01)00243-9

processes. In this respect and following our previous work on the use of bile acids as host compounds for the resolution of 'neutral' organic derivatives such as epoxides and sulfoxides,[7,8] we have extended the study to cyclic and bicyclic ketones, which are useful synthons for the preparation of various important target molecules. In particular bicyclo[3.2.0]-hept-2-en-6-one, successfully resolved in optically pure form using cholic acid, is an important starting material for prostaglandin synthesis.[1a,10]

In order to learn about the structural mechanism of the efficient chiral host–guest recognition, the crystal structure of the inclusion compound between the bicyclo[3.2.0]-hept-2-en-6-one and cholic acid was analyzed by X-ray diffraction.

2. Results and discussion

All the host–guest methods described in the literature for the resolution of racemic compounds have a similar procedure consisting of the formation of the inclusion crystals, filtration and washing of the clathrate which has formed crystals and release of the guest compounds upon heating or acid–base treatment, exploiting the terminal carboxylic function when available.[7,8] In order to increase the enantiomeric excesses (e.e.s) the procedure may be separately repeated on both the preferentially included enantiomerically enriched derivative and the non-included compound recovered from the mother liquors.

The results of the optical resolution complexation experiments between the hosts cholic **1** and deoxycholic acid **2** and the guest derivatives **4**–**10** are summarized in Tables 1 and 2.

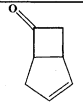
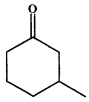
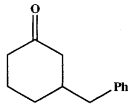
As shown in the second column of Tables 1 and 2, the bile acid-to-ketone ratios of the inclusion complexes are generally 2:1. However, some noticeable differences demonstrate the independence of the steric dimensions of the guest with respect to bile acid and inclusion stoichiometry. Hosts showed varying degrees of specificity in the complexation. In particular cholic acid **1** formed inclusion derivatives only with **4**, **7** and **9**, all characterized by high enantioselectivity. On the other hand deoxycholic acid **2** is less specific, forming host–guest complexes with all the above guest varieties, despite the lower level of resolution. No relationship emerged between resolution and the detailed structure of the guest. As an example **1** enabled the enantioselective resolution of **7**, but did not include either **6** or **8**, which have a similar structure. As expected repetition of the procedure on the partially resolved substrate increases the e.e. up to complete resolution, depending on the number of cycles.

The results obtained with bicyclo[3.2.0]-hept-2-en-6-one **4**, a derivative not easy to obtain, at least by resolution in high e.e. values,[2] deserve some comments. As shown in Tables 1 and 2, when (±)-**4** is included in cholic acid, the resolution is quite effective, affording the (−)-(1*S*,5*R*) enantiomer in 95% e.e. after two cycles, whereas if deoxycholic acid is used as host compound the opposite (+)-(1*R*,5*S*) enantiomer is obtained. These observations suggest that fine structural details play, among other factors, an important role in the chiral discrimination process. In this context the crystal structure of the inclusion complex of **1** with bicyclo[3.2.0]-hept-2-en-6-one **4** has been analyzed.

The ORTEP[11] view of both host–guest molecules is shown in Fig. 1. The crystal packing (Fig. 2) consists of an amphiphilic layered structure of cholic acid molecules and displays channels containing molecules of bicyclo[3.2.0]-hept-2-en-6-one arranged around a 2_1 axis.

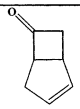
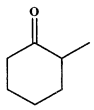
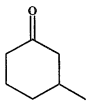
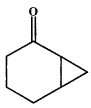
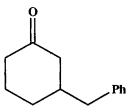
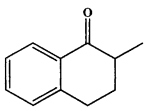
The three hydroxy groups and the carboxylic one are α oriented determining the hydrophilic layers through the formation of four intermolecular hydrogen bonds: O25–H···O26 [$d_{O\cdots O}=2.866(5)$ Å], O26–H···O27 [$d_{O\cdots O}=2.878(6)$ Å], O28–H···O29 [$d_{O\cdots O}=2.693(4)$ Å] and O29–H···O25 [$d_{O\cdots O}=2.685(6)$ Å]. The two methyl groups, $C(18)H_3$ and $C(19)H_3$, are β oriented and define

Table 1. Resolution of ketones by absorption method using cholic acid **1** as chiral host

substrate	bile acid/ketone ratio[a]	e.e.% after one cycle	e.e.% after two cycles	configuration
 **4**	2:1	65	95	(-)-(1*S*,5*R*)
 **7**	3:1	90	>99	(+)-(*R*)
 **9**	2:1	70	96	(+)-(*S*)

a. determined by ^{1}H NMR on the formed crystals

Table 2. Resolution of ketones by absorption method using deoxycholic acid **2** as chiral host

substrate	bile acid/ketone ratio[a]	e.e. % after one cycle	e.e. % after two cycles	configuration
 **4**	1.5:1	11	20	(+)-(1*R*,5*S*)
 **5**	2:1	7	13	(+)-(*S*)
 **6**	2:1	40	70	(+)-(*S*)
 **7**	1:1	4	10	(+)-(*R*)
 **8**	2:1	26	60	(+)-(1*R*,6*S*)
 **9**	4:1	20	35	(+)-(*S*)
 **10**	2:1	15	30	(+)

a. determined by ^{1}H NMR on the formed crystals

the lipophilic layers alternating with the hydrophilic ones. The guest molecules are included in the lipophilic layers and interact with cholic acid only by means of weak van der Waals contacts. This crystal packing is isomorphous with many other inclusion complexes built up by cholic acid and ketones, esters or phenyl derivatives.[12]

Work is currently in progress to widen the scope of the above-described applications to the resolution of 'neutral' organic molecules using low cost and readily accessible host compounds, as well as to improve the structural interpretation by comparable crystallographic studies.

3. Experimental

3.1. Materials and methods

^{1}H NMR spectra were obtained from a Varian Gemini 300; optical rotations were measured on a Perkin–Elmer 241 polarimeter. E.e.s were determined by GC on a Megadex DETTBS. The absolute configurations were determined by comparison of the specific rotations with literature values.

Bile acids **1** and **2** are commercially available products, purified by crystallization from methanol and dried in vacuo (1 Torr) at 110 and 140°C, respectively, for one

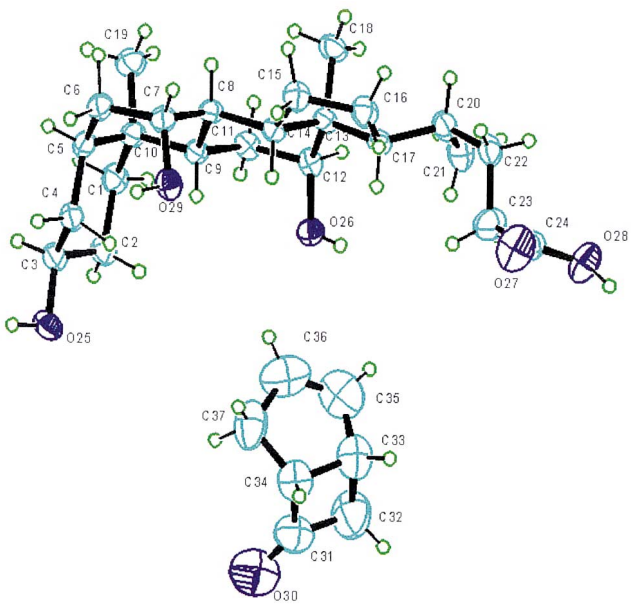


Figure 1. ORTEP view and atom numbering for host–guest molecules cholic acid/bicyclo[3.2.0]-hept-2-en-6-one.

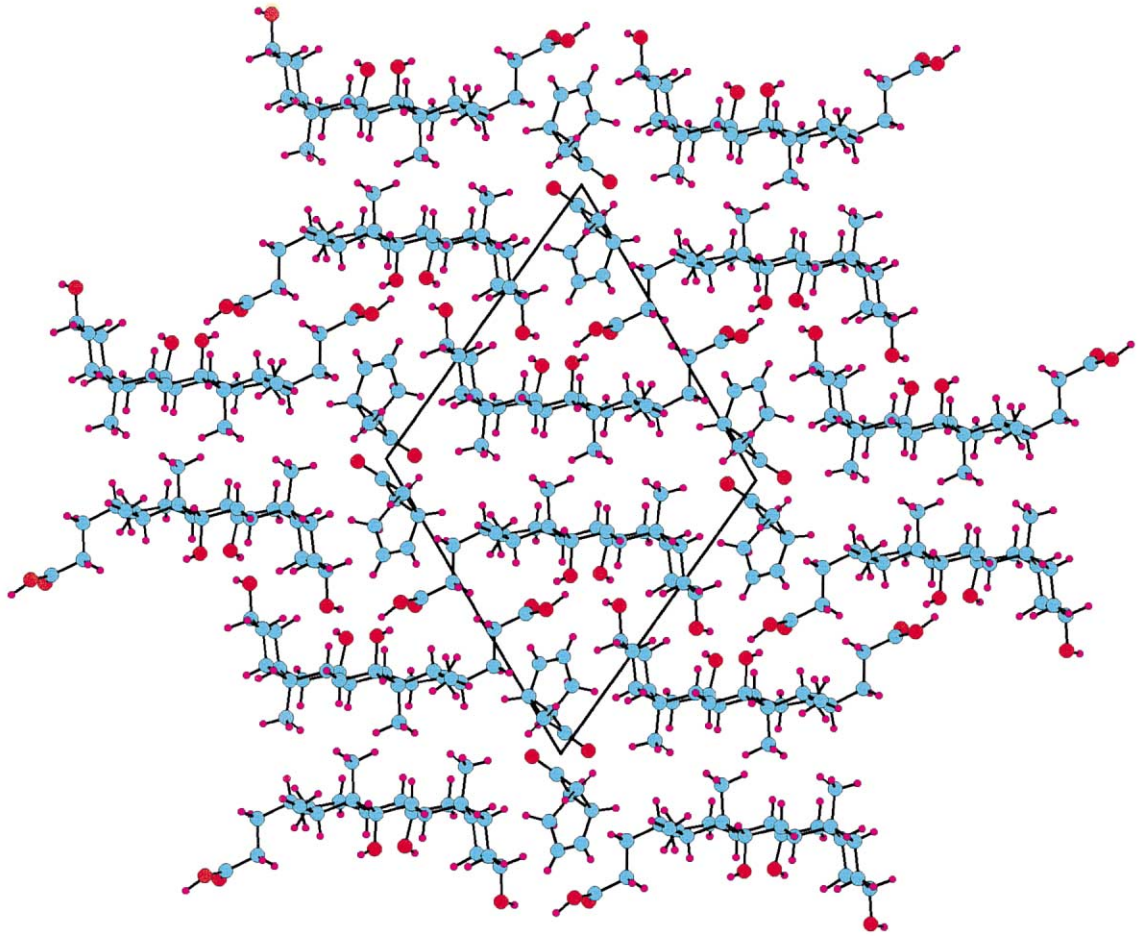


Figure 2. The crystal structure of the inclusion compound cholic acid/bicyclo[3.2.0]-hept-2-en-6-one as viewed down the crystallographic *b* axis.

night. Ketones **4**–**7** and **10** were obtained from Aldrich and used as received. Ketones **8** and **9** were synthesized from cyclohexen-2-one by reaction with CH_2I_2 in the presence of a zinc–copper couple[13] and by treatment with the benzylic copper reagent BnCu(CN)MgCl,[14] respectively.

3.2. Inclusion procedures

The host–guest inclusion derivatives were obtained according to absorption or crystallization methods. In the former case (±)-**4**–**10** (1 mL) were added to cholic or deoxycholic acids (0.35 g, ratio ca. 10:1) and left at room temperature for 24 h. The inclusion crystals were filtered, washed several times with pentane–ether (1:1) and dried. The product was analyzed by ^{1}H NMR to determine the bile acid–ketone ratio, treated with aqueous $NaHCO_3$ and extracted with ether. The extracts were analyzed by GC for the e.e. determination and polarimetric analysis to assign the absolute configuration. In the crystallization method the host–guest mixture was heated until complete dissolution and allowed to crystallize over 24 h. The work-up follows the sequence described above.

3.3. Multigram inclusion procedure

For resolutions on multigram scale the following modified procedure was used. A mixture of cholic acid **1** (12 g, 29.3 mmol) and bicyclo[3.2.0]-hept-2-en-6-one **4** (12.7 g, 117.2 mmol) was left at ambient temperature for 48 h. The inclusion compound was collected by filtration and washed several times with pentane–ether (20:80). Upon heating[1b,15] in vacuo (150°C, 1 Torr) 1.4 g of (−)-**4** were obtained in 65% e.e. When the same procedure was repeated on the partially resolved racemate, (−)-**4** was obtained in almost pure form.

3.4. Resolutions

When (±)-**4** is kept at room temperature in the presence of **1**, an inclusion complex with a host–guest ratio of 2:1 is obtained, that afforded (−)-(1*S*,5*R*)-**4** in 65% e.e. $[\alpha]_D = -41$ (*c* 1.2, $CHCl_3$).[16] With the same absorption procedure (+)-(*R*)-**7**, 90% e.e., $[\alpha]_D = +12.9$ (*c* 0.01, $CHCl_3$),[2,17] and (+)-(*S*)-**9**, 70% e.e., $[\alpha]_D = +20$ (*c* 1, $CHCl_3$),[18] were obtained. The remaining ketones

were partially resolved in the presence of deoxycholic acid **2** yielding (+)-(*S*)-**5**, 13% e.e., $[\alpha]_D = +16$ (*c* 1, CH_3OH);[19] (+)-(*S*)-**6**, 70% e.e., $[\alpha]_D = +12$ (neat);[20] (+)-(1*R*,6*S*)-**8**, 60% e.e., $[\alpha]_D = +11$ (*c* 2, $CHCl_3$);[21] (+)-**10**, 30% e.e., $[\alpha]_D = +10$ (*c* 1, $CHCl_3$).

3.5. X-ray structural analysis of the inclusion compound: cholic acid/bicyclo[3.2.0]-hept-2-en-6-one

$C_{24}H_{40}O_5/C_7H_8O$, $M = 516.69$, monoclinic, space group $P2_1$, $a = 13.7091(8)$, $b = 8.1499(2)$, $c = 14.0241(8)$ Å, $\beta = 114.103(2)°$, $V = 1430.3(1)$ Å^3, $Z = 2$, $F(000) = 564$, $\mu = 0.813$ cm^{-1}, $D_{calcd} = 1.200$ g cm^{-3}, graphite-monochromated Mo-Kα radiation ($\lambda = 0.71070$ Å).

Data sets were collected on a Nonius Kappa CCD diffractometer in the range $3 \leq \theta \leq 27.5°$, giving 3338 unique reflections which were corrected for Lorentz and polarization effects. The structure was solved by direct methods, using the SIR-92 system of programs,[22] and refined using the full-matrix least-squares provided by SHELXL-97.[23] The final *R* index was 0.0523 for 2552 observed reflections having $I \geq 2\sigma(I)$. All non-hydrogen atoms were refined anisotropically and the hydrogens isotropically except those of the bicyclic ketone, which were placed in idealized positions. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 163389. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

This work was financially supported by the University of Ferrara.

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