Diketobile Acids as New Hosts in Solid-state Enantioselective Resolutions

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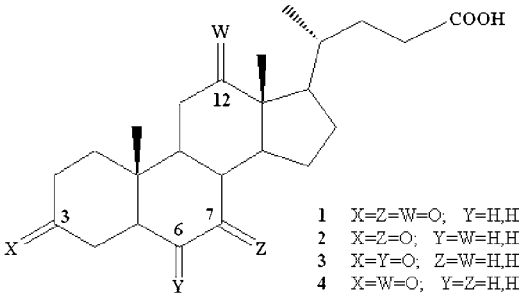
New diketobile acid derivatives have been evaluated as hosts in the resolution of aryl methyl sulfoxides. The guest molecules are linked to the host ones via hydrogen bonds with the SO group. The 3,6-diketo derivative is also effective for the resolution of γ-lactames.

Bile acids, in particular derivatives of cholic acid, are classical host compounds that form crystalline inclusion clathrate complexes with various organic guest derivatives. Due to their asymmetry, these hosts are expected to construct assemblies with chiral cavities able to accommodate chiral organic guests, thus allowing optical resolution of racemic compounds.[1] In the enantioselective inclusion complexation of a racemic guest with a chiral host, in fact, one enantiomer of the former is separated as an inclusion host–guest complex crystal. From the inclusion crystal, an optically active guest can be isolated by an appropriate method.[1]

During our search for new host compounds for racemate resolution we have evaluated the capability of three diketobile acid derivatives **2**–**4**,[2] comparing their resolution performances with those of dehydrocholic acid **1**, derivative extensively used in many host–guest resolutions (Scheme 1).[3,5]

Table 1 reports the pertinent results based on the use of methyl tolyl sulfoxide as model guest, included within the selected host **2**–**4** by the co-grinding method.[1] According to this methodology a host–guest mixture is ground in a mortar at room temperature for 20 min; the solid is washed with Et_2O, dissolved using aqueous $NaHCO_3$ and extracted with Et_2O to afford enriched (*R*)-methyl tolyl sulfoxide. Hosts **2** and **3** showed superior results in terms of enantioresolution, however, host **3** displayed a more pronounced resistance during work-up and, consequently, has been selected to investigate the resolution ability toward different classes of organic racemates i.e. aryl methyl sulfoxides and cyclic amides. Table 2 collects the pertinent results.

In this case, to obtain host–guest inclusion complexes, the guest was either dissolved in Et_2O and added to **3** or vaporized



Scheme 1. Ketobile acids of this study.

Table 1. Optical resolution of methyl tolyl sulfoxide using **2**–**4** as chiral host

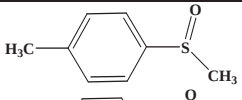
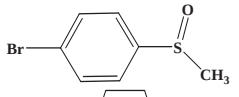
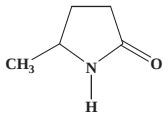
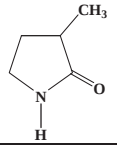
Host	Host:Guest ratio[a]	ee%[b]	abs. config.[c]
2	1:1	96	(+)-R
3	1:1	93	(+)-R
4	1:1	85	(+)-R

[a]Determined by ^{1}H NMR on the formed crystals. [b]Determined by GC using a chiral column. [c]cf. Ref. 3.

at 50 °C in the presence of **3**. The inclusion compounds were then treated as described in previous paragraphs. Compared with dehydrocholic acid the new host gives rise to comparable or slightly better results, particularly in the case of cyclic amides, and may be proposed as suitable host for the resolution of these compounds.

In previous publications, we have reported and discussed the crystal structure of the 1:1 inclusion compound between dehydrocholic acid **1** and (*R*)-methyl tolyl sulfoxide[6] and the X-ray powder diffraction (XRPD) of **1** with *p*-$XC_6H_4SOCH_3$, X = CH_3 and Br, respectively.[7,8] In both cases, the packing diagrams showed the guest molecules linked to the carboxylic group of the host by means of a hydrogen bond with the sulfoxide moiety, stabilized by COOH···OS contacts of 2.63 Å for methyl tolyl sulfoxide and of 2.65 Å for *p*-bromophenyl methyl sulfoxide.[8] Unpublished IR data obtained on isolated compounds

Table 2. Optical resolution of organic racemates using **3** as host and comparison with the data obtained with dehydrocholic acid **1**

Guest	ee %[a] (abs. conf.)[b]	Prev. work
	96 (R)[c] 67 (R)[d]	99 (R)[3]
	85 (R)[c] 83 (R)[d]	84 (R)[3]
	40 (R)[c] 23 (R)[d]	64 (R)[5]
	60 (S)[c] 36 (S)[d]	42 (S)[5]

[a]Determined by GC using a chiral column. [b]For absolute configurations cf. Ref. 3. [c]Guest dissolved in Et_2O and added to **3**. [d]The guest is vaporized at 50 °C in the presence of the solid host.

Table 3. Assignment and wavenumbers of the vibrational bands (KBr) of free bile acids, sulfoxides and inclusion compounds[9]

Compound	ν_{SO}/cm^{-1}	ν_{CO}/cm^{-1}
1		1707
p-$CH_3C_6H_4SOCH_3$	1049	
1·*p*-$CH_3C_6H_4SOCH_3$	1001	1705, 1716
3		1704
p-$CH_3C_6H_4SOCH_3$	1049	
3·*p*-$CH_3C_6H_4SOCH_3$	1002	1692, 1717
3		1704
p-$BrC_6H_4SOCH_3$	1035	
3·*p*-$BrC_6H_4SOCH_3$	1000	1693, 1714, 1732

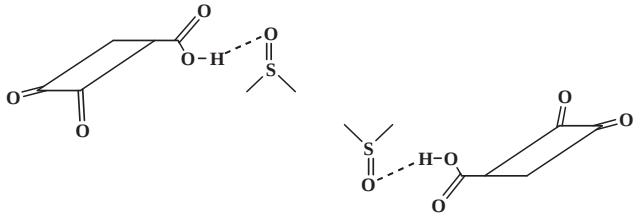


Figure 1. Pictorial representation of a possible coordination between **3** and the guest sulfoxide.

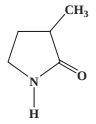
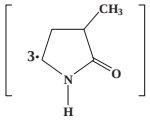
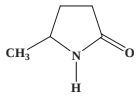
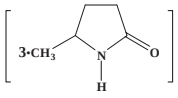
and on the 1:1 inclusion complexes showed band shifts clearly imputable to the COOH···OS contacts. Dehydrocholic acid **1** displayed, among others, a signal at 1707 cm^{-1}, assigned to a CO stretching that shifted at 1716 cm^{-1} in the inclusion complex. On the other hand, it should be noted that the sulfoxide group displays a vibrational mode at 1049 cm^{-1} that moved at 1001 cm^{-1} upon inclusion complexation, Table 3. Similar behavior may be found by comparing the IR spectra of the free bile acid **3** and of the sulfoxides *p*-$XC_6H_4SOCH_3$, X = CH_3 and Br, with those of the included complexes.

In agreement with previous interpretations[10] the lowering of the wavenumber of the sulfoxide moiety absorption upon inclusion is a clear indication that coordination within the bile acid host occurs, also for these new complexes, through the sulfoxide group, following a weakening of the bond strength, as depicted in Figure 1.

Table 4 collects the assignment and IR frequences of free and included molecules for cyclic amides. In this case, a significant increase of the NH vibrational mode frequency is observed upon complexation, associated with a small increase of the carbonyl vibrational band.

Taking into account these shifts we may assume that the coordination of **3** with the included compound is taking place

Table 4. Assignment and wavenumbers of the vibrational bands (KBr) cyclic amides and inclusion compounds[9]

Compound	ν_{NH} /cm^{-1}	ν_{CO} /cm^{-1}
	3240	1686
	3341	1706
	3244	1670
	3320	1690

through a hydrogen bond between the nitrogen of the amide and the carboxylic function i.e. COOH···NH, thus explaining the increase of the NH absorption frequency.

We are currently extending this host–guest readily accessible and low-cost resolution methodology to enantioselective hosts having ketobile acid structures.

References and Notes

1 O. Bortolini, G. Fantin, M. Fogagnolo, *Chirality* **2005**, *17*, 121, and references cited therein.
2 Compounds **1**–**4** was prepared starting from commercially available hydroxyl derivative via oxidation with the Jones' reagent; see: K. Bowden, I. M. Heilbron, E. R. H, Jones, B. C. L. Weedon, *J. Chem. Soc.* **1946**, 39.
3 O. Bortolini, G. Fantin, M. Fogagnolo, A. Medici, P. Pedrini, *Chem. Commun.* **2000**, 365.
4 V. Bertolasi, V. Ferretti, L. Pretto, G. Fantin, M. Fogagnolo, O. Bortolini, *Acta Crystallogr., Sect. B* **2005**, *61*, 346.
5 O. Bortolini, M. Fogagnolo, G. Fantin, A. Medici, *Chem. Lett.* **2003**, *32*, 206.
6 V. Bertolasi, O. Bortolini, G. Fantin, M. Fogagnolo, A. Medici, *Chem. Lett.* **2002**, 400.
7 G. Fantin, M. Fogagnolo, O. Bortolini, N. Masciocchi, S. Galli, A. Sironi, *New J. Chem.* **2003**, *27*, 1794.
8 G. Fantin, M. Fogagnolo, O. Bortolini, N. Masciocchi, S. Galli, A. Sironi, *New J. Chem.* **2004**, *28*, 1295.
9 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.
10 S. Bayari, Z. Kantarci, S. Akyüz, *J. Molec. Struct.* **1995**, *351*, 19.

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