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## New Chiral Selectors Derived from Lactic Acid. Cocrystalline and Sorptive Optical Resolutions, and the Crystal Structure of an Inclusion Complex with 3-Methylcyclohexanone

**Edwin Weber,*[a] Claus Wimmer,[a] Antonio L. Llamas-Saiz[b] and Concepcion Foces-Foces[b]**

[a] *Institut für Organische Chemie und Biochemie der Universität Bonn, Gerhard-Domagk-Strasse 1, D-5300 Bonn-1, Germany*

[b] *Instituto de Quimica-Fisica Rocasolano, Consejo Superior de Investigaciones Cientificas, Serrano, ES-28006 Madrid, Spain*

A new type of optically active clathrate formers derived from lactic acid, **1**, is described, enabling useful enantiomer separations of different chiral compounds *via* cocrystallization and, for the first time, *via* sorption; the X-ray structure of the 2 : 1 inclusion complex between **1a** and 3-methylcyclohexanone is reported.

Although asymmetric synthesis has achieved great success during the last two decades,[1] optical resolution[2] has lost no attraction.[3] Often it is the economic way to obtain optically active substances.[1,4] However, the classical racemate resolution (formation of diastereoisomeric salts of different solubility) only works with molecules having acidic or basic groups.

We report here a useful expansion of this method, enabling easy separation of enantiomers from substance classes other than acids and bases. It rests on cocrystallization[5] using optically pure clathrate formers of type **1**. These bulky molecules[6] are readily obtained from the ethyl ester of natural lactic acid by Grignard addition; **1a**: yield 94%, m.p. 92–93 °C, $[\alpha]_D^{20}$ −125.4 (*c* 18, MeOH); **1b**: yield 38%, m.p. 89–90 °C, $[\alpha]_D^{20}$ −86.0 (*c* 14, MeOH); **1c**: yield 44%, m.p. 177 °C, $[\alpha]_D^{20}$ −22.0 (*c* 12, $CHCl_3$). Compounds **1a** and **b** have recently been described in a different context.[7]

Crystallization of the clathrate formers **1a** and **c** from solutions of racemic ketones, alcohols, sulfoxides and other important chiral building blocks yield enantiomeric excesses (e.e.), in one step, as given in Table 1 (**1b** is less efficient). With 3-methylcyclohexanone and **1a** we obtained an e.e. > 99%; *i.e.* this method renders possible easy preparation of pure enantiomers on a large scale.† In general, **1a** and **c** are superior to other clathrate formers[8,9] in enantioselectivity (see Table 1), *e.g.* for racemic methyloxirane and methyl phenyl sulfoxide, which are both difficult to separate. They yield 9.3 and 32.8% e.e. (mean of three tests), respectively, using cocrystallization with **1a**. Recrystallization of the clathrates from suitable solvents can improve the e.e. values significantly. Thus, recrystallization of the **1a**·β-butyrolactone clathrate from $Et_2O$ raised the e.e. from 12 to 87%.

Table 1 compares the efficiencies of **1a** and **c** in resolving both 2-methylcyclohexanols: **1a** gave the higher e.e. More remarkable—and particularly important—is the result that **1a** and **c** favour different enantiomers of these compounds. Thus, it is shown that inversion of enantioselectivity is possible simply by changing substituents at the clathrate former, without departing from the configuration (*S*) of the natural lactic acid.

The X-ray crystal structure of the 2 : 1 inclusion complex between **1a** and 3-methylcyclohexanone (e.e. >99%) has been determined,‡ showing high steric fit between **1a** and the ketone (Fig. 1) (by way of contrast, 2-methylcyclohexanone does not cocrystallize with **1a**). The ketone, with the carbonyl group, is clamped between two H-bonded molecules **1a** of the same chirality (*S*) and is bound there by an H-bridge. The methyl group projects into a lipophilic niche of the framework, which explains the complete enantiodifferentiation of the ketone (*R* configuration). Modification of the substituents at the clathrate former may create different voids which, in an analogous manner, could offer optimum space to other chiral organic compounds.

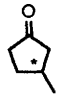
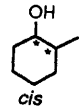
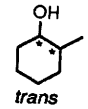
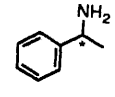
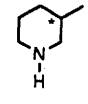
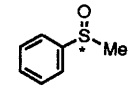
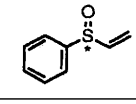
Moreover, and rather unexpectedly, we found that solid **1a** and **c** could effect enantiomer separations of vaporized compounds by sorptive clathrate formation[10] on a preparative scale (Table 1). For this purpose, the solids **1a** or **c** are exposed

† Optical resolution of racemic 3-methylcyclohexanone was carried out as follows: (*S*)-**1a** (5.0 g, 22 mmol) was dissolved in 3 ml boiling racemic 3-methylcyclohexanone. Slow cooling gave crystals of the clathrate which were collected and washed with a few ml of light petroleum, b.p. 40–60 °C. On heating the crystals in vacuum [(100 °C, 15 Torr; 1 Torr = 133.3 Pa)], 1.1 g (86%) of optically pure (*R*)-3-methylcyclohexanone with $[\alpha]_D^{20}$ = 15.0 (*c* 0.24, $CHCl_3$) {lit.[8] $[\alpha]_D^{20}$ = 14.4 (*c* 0.01, $CHCl_3$)} was obtained as distillate.

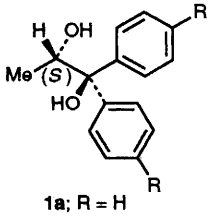
‡ *Crystal data*: 2(**1a**)·(*R*)-3-methylcyclohexanone, $2(C_{15}H_{16}O_2)\cdot C_7H_{12}O$, $M$ = 568.32, orthorhombic ($P2_12_12_1$), $a$ = 25.0880(22), $b$ = 21.7182(17), $c$ = 5.8776(2) Å, $V$ = 3202.5(4) Å$^3$, $Z$ = 4, $D_c$ = 1.180 g cm$^{-3}$ and $\mu$ = 5.74 cm$^{-1}$. 3150 independent reflections with $\theta$ < 65° (Cu-K$\alpha$ radiation). Sample of 0.60 × 0.23 × 0.17 mm sealed into a Lindemann capillary containing solvent; 38% decay in 27 h; direct methods. Refinement was carried out on $F_o$ values with two blocks matrix (555 parameters) and anisotropic thermal parameters for the non-hydrogen atoms. The H atoms were kept isotropic. $R$ = 0.054, $R_W$ = 0.060 for 2742 observed reflections [$I > 3\sigma(I)$]. Three reflections suffer from secondary extinction and were not included in the last cycles of refinement. Final $\Delta F$ peak 0.20 eÅ$^{-3}$.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

**Table 1** Enantioselective clathrate formation

| Racemic compound | Clathrate former | Stoichiometry (clathrate)[a] | Yield (%)[b] | Enantiomeric excess (% e.e.)[b,c] *via* crystallization[d] | *via* sorption |
|---|---|---|---|---|---|
|  | **1a** | 2:1 | 90 | 14.5 (*R*) | 3.0 (*R*) |
|  | **1a** | 2:1 | 86 | >99 (*R*) [28.0][8] | 71.0 (*R*) |
|  | **1a** | 2:1 | 67 | 12.0 (*R*) [3.1][9] | 15.0 (*R*) |
|  | **1a** | 2:1 | 90 | 9.3 (*R*) [5.0][8] | 25.0 (*R*) |
|  *cis* | **1a**<br>**1c** | 1:1<br>1:2 | 50<br>80 | 53.0 (*S*)<br>2.1 (*R*) | —<br>— |
|  *trans* | **1a**<br>**1c** | 1:1<br>1:2 | 64<br>85 | 35.3 (*S*)<br>18.3 (*R*) | —<br>— |
|  | **1a** | 1:1 | 75 | 8.0 (*R*) | 2.7 (*R*) |
|  | **1a**<br>**1c** | 2:1<br>2:1 | *e*<br>*e* | *e*<br>*e* | 8.5 (*S*)<br>16.2 (*R*) |
|  | **1a** | 1:1 | 72 | 32.8 (*S*) [4.4][8] | — |
|  | **1a** | 1:1 | 77 | 30.0 (*R*) | — |

[a] Clathrate former: secondary component. [b] Secondary component distilled from the clathrate. [c] Determined by polarimetry (mean of three tests.). [d] In brackets are the e.e. obtained by other clathrate formers. [e] Difficult to crystallize.



**1a**; R = H
**b**; R = Me
**c**; R = Bu$^t$

to vapour of the racemic compound at room temperature until saturation (several hours). In some cases, vapour sorption yields higher e.e. than a single cocrystallization (*cf.* Table 1), in others the order is reversed. With respect to the favoured configuration of the secondary component, though, there is no difference between sorption and crystallization. However, certain substances given in Table 1 that form cocrystals are inefficient at sorption which points to kinetic hindrance by the crystalline framework, *e.g.* for the alcohols and the sulfoxides.

The powder diffractograms of solid (*S*)-**1a**, obtained either by crystallization from an inert solvent or by evaporation of the ketone from the clathrate, show that both samples are the same species. In the same way, the powder diffractograms of the clathrates formed by cocrystallization and by vapour sorption are also identical. This means that the crystal structures of the pure compound (*S*)-**1a** and of the clathrate with (*R*)-3-methylcyclohexanone are interconvertible by absorption or desorption of the ketone.

Apart from the chiral compounds listed in Table 1, **1a–c** yield selective stoichiometric cocrystalline complexes (a total of more than 50 examples) with many other ketones, ethers,

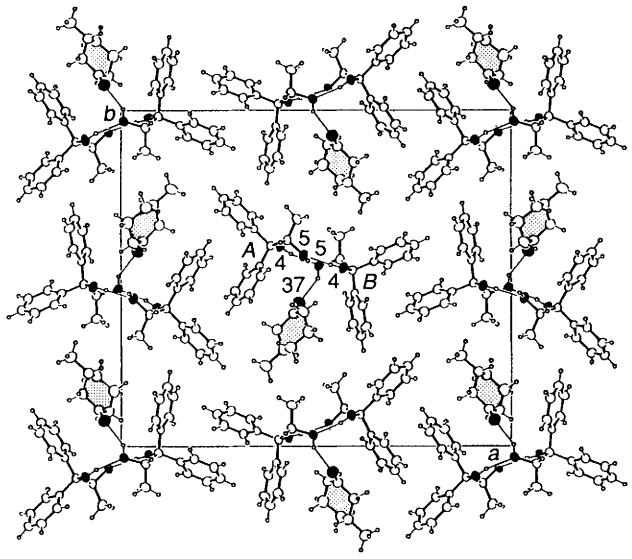



**Fig. 1** Packing illustration (ORTEP) of (*S*)-**1a**·(*R*)-3-methylcyclohexanone (2:1) viewed down the *c*-axis. The thermal ellipsoids are plotted at 50% probability level; H atoms have an arbitrary radius. O atoms are represented as filled ellipsoids; the ketone space is shaded. All the hydroxy groups are involved in H bonds joining together the two independent molecules A and B (*S* configuration) and the ketone (*R* configuration), while the intermolecular H(5A)···O(5B) contacts are responsible for chain formation along the *c*-axis. O(4A)–H(4A)···O(5B) = 2.936(3)–2.18(4) Å, O(4A)–H(4A)···O(5B) = 148(5)°; O(5A)–H(5A)···O(5B) ($x$, $y$, $z-1$) = 2.902(4)–2.00(8) Å, O(5A)–H(5A)···O(5B) ($x$, $y$, $z-1$) = 168(6)°; O(4B)–H(4B)···O(5A) = 2.886(3)–2.12(6) Å, O(4B)–H(4B)···O(5A) = 146(6)°; O(5B)–H(5B)···O(37) = 2.725(5)–2.01(6) Å, O(5B)–H(5B)···O(37) = 143(5)°.

alcohols and amines, but also with nitriles and aromatic or heteroaromatic compounds. In the future, therefore, further preparative enantiomer resolutions are to be expected using these and similar (differently substituted) clathrate formers of type **1**. Because of their selective sorption properties, the present clathrate formers are also promising for the analysis of volatile compounds (*e.g.* odorous compounds) and for the development of chemical sensors.[11]

In our opinion, the design of crystalline chiral selectors based on optically active natural compounds is a great challenge since the known advantages of chiral auxiliaries in asymmetric synthesis[1] may be transferred to the clathrate field.[5] Very recently natural tartaric acid has been modified correspondingly and used with great success.[12]

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