A new optical resolution method: coordinative resolution of mandelic acid esters. The crystal structure of calcium hydrogen (2*R*,3*R*)-*O*,*O*′-dibenzoyl tartrate–2(*R*)-(−)-methyl mandelate

András Mravik,*[a] Zsolt Böcskei,[b] Zoltán Katona,[a] Imre Markovits,[a] György Pokol,[c] Dóra K. Menyhárd[d] and Elemér Fogassy[a]

[a] *Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, POB 91, Hungary*
[b] *CHINOIN Pharmaceuticals, H-1325 Budapest, POB 110, Hungary*
[c] *Institute for General and Analytical Chemistry, Technical University of Budapest, H-1521 Budapest, POB 91, Hungary*
[d] *Eötvös University, Department of Theoretical Chemistry, H-1518 Budapest-112, POB 32, Hungary*

A new and efficient resolution, based on the finding that the calcium acid salt of *O*,*O*′-dibenzoyltartaric acid forms crystalline coordination complexes with enantiomers of α-hydroxy acid esters, is reported.

Optically pure hydroxy acids and esters are important chiral starting materials and intermediates in organic syntheses.[1,2,3] Enantiomeric syntheses incorporate esterification of the optically active hydroxy acids,[4,5] and selective reduction of the corresponding carbonyl compounds[6,7,8] or separation of the enantiomers of racemic hydroxy esters. In addition to the enzymatic reactions[9,10] the application of host–guest complexation[11] in optical resolutions has recently become of growing importance. Hydroxy acids are generally optically resolved by fractional crystallization using chiral amines which are relatively expensive and in some cases extremely toxic. Yeast reduction[8] of carbonyl compounds requires a large volume of the reaction mixture, takes a long time and exact parameters (pH, temperature). Moreover, the separation of the product is often difficult. Chemical reduction requires expensive chiral reducing agents in a large excess,[7] and the isolation or purification of the hydroxy ester needs chromatographic separation. Enzyme catalysed kinetic resolution of hydroxy acid esters is generally performed by either hydrolysis [10] of an *O*-acyl derivative or acylation[9] of the hydroxy group (transesterification). In the former case the derivative should be previously prepared. The products should be separated by chromatograph and one of the enantiomers still exists as a derivative. Chiral host compounds are very expensive resolving agents and are not available on large scale. However, they are good resolving agents for a wide variety of racemates.

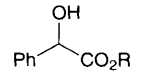
It is well known that the calcium ion has a large coordinating capacity for oxygen containing molecules. However, this phenomenon still remains unexploited in the separation of optical isomers. We report here a simple and very useful method for the resolution of mandelic esters **1a–d**.

When racemic **1** was added to a hot ethanolic solution of the calcium hydrogen (2*R*,3*R*)-*O*,*O*′-dibenzoyl tartrate [$Ca(HL_0)_2$] a complex salt separated on cooling.

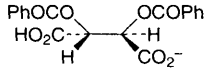
$$Ca(HL_0)_2 + n_0(rac\text{-}L_1) + [L_{aux}] \rightarrow [Ca(L_1)_{n_1}(L_{aux})](HL_0)_2 + (n_0\text{-}n_1(ent\text{-}L_1)$$

Thus, (2*R*,3*R*)-*O*,*O*′-dibenzoyl tartaric acid monohydrate (27.8 g, 74 mmol) and CaO (2.07 g, 37 mmol) were dissolved in ethanol (60 ml) by heating and then a solution of racemic **1a** (20.0 g, 120 mmol) in acetone (15 ml) was added. The stirred solution was then seeded and cooled to 5 °C and the crystalline precipitate was filtered to give 32.5 g of a salt which was recrystallized from a mixture of ethanol (100 ml) and toluene (50 ml) to give a pure 1 : 2 complex **2a** of the calcium hydrogen dibenzoyl tartrate and (*R*)-(−) **1a** (27.0 g, 24.9 mmol, 83%).

The stability constant and the solubility of the complexes, as well as the enantioselectivity (the enantiomer preference during the crystallization), is highly affected by the alkyl group being actually present in L_1 **1a–d**. Since the solubilities are quite different, solvents should be selected according to the complex (ligand) used. In most cases solvent mixtures[12] should be used rather than a pure solvent. A very interesting property of this type of complexes was also observed. An auxiliary ligand (L_{aux}) like ethyl acetate when used (in the equation above square brackets mean that the use of the auxiliary ligand is optional)



1a R = Me
b R = Et
c R = CH_2Ph
d R = CH_2CH_2Ph



HL_0

Table 1 Coordination complexes $[Ca(L_1)_{n_1}(L_{aux})](HL_0)_2$ formed with mandelic esters **1a–d** during the resolution

Rac-L_1 **1**	Solvent	L_{aux}[a]	Recryst.[b]	n_1	Yield (%)[c]	Mp[d]/°C	Config.	Ee[e] (%)
a	Ethanol > acetone	—	1	2	83	176–177	(*R*)-(−)	>99
b	Ethanol > acetone	H_2O	1	2	41	147–148	(*S*)-(+)	62
b	Ethanol–ethyl acetate	EtOAc, H_2O	1	1	74	152–153	(*S*)-(+)	>99
c	Toluene ≫ ethanol	toluene	–	4	136	135–139[f]	(*S*)-(+)	16
c	Ethyl acetate ≫ ethanol	H_2O	2	1	42	145–146[g]	(*R*)-(−)	87
d	Ethanol > acetone	H_2O	2	1	68	135–137	(*S*)-(+)	74

[a] L_{aux}: auxiliary ligands. [b] Number of recrystallizations. [c] Yield of the crystalline complex calculated with respect to half the amount of the starting racemic **1**). [d] Each melting accompanied by decomposition of the complex. [e] After work-up, ee determined by comparing the optical rotation values to those given for pure enantiomers (*R*) **1a**, lit.,[4] $[\alpha]_D^{25}$ = −174 (*c* 1.23, chloroform), (*R*) **1b**: lit.,[5] $[\alpha]_D^{25}$ = −126 (*c* 2.0, chloroform), (*S*) **1c**† and (*S*) **1d**.‡ [f] Decomp. at 96 °C. [g] Decomp. at 85 °C.

highly affects the composition and therefore the solubility of the complex formed.

Thus, to a hot solution of the acid salt [prepared from 14.6 g (2*R*,3*R*)-*O*,*O*′-dibenzoyl tartaric acid monohydrate and 1.09 g CaO] in ethanol (25 ml) racemic **1b** (6.0 g) and ethyl acetate (25 ml) were added. The stirred solution was seeded and cooled (3 h) to 0 °C. The salt was filtered, dried and recrystallized from the mixture of ethanol and ethyl acetate (38 ml, 1 : 1) to give 12.8 g of the salt [Ca{(*S*)-(+)-**1b**}(EtOAc)(H_2O)](HL_0)$_2$.

The results obtained with mandelic esters **1a–d** are summarized in Table 1. As can be seen, methyl mandelate forms a very stable complex with the acid salt affording the pure complex in high yields. Mandelates having alkyl groups larger than methyl form less stable complexes owing to their bulky character and tend to form complexes of other structures. In addition, the configuration of the coordinated ester is affected by other ligands. In contrast to the moderate ee's of ethyl mandelate obtained from the complex crystallized from ethanol–toluene, enantiomerically pure ester can be obtained in good yield by crystallizing a mixed ligand complex formed with ethyl mandelate and ethyl acetate. Benzyl mandelate forms a complex containing four ester molecules being slightly *S*-isomer enriched. Crystallization from a solvent mixture containing ethyl acetate gave only one mandelate coordinated and the configuration changed to *R*. Interestingly, ethyl acetate is not present in the salt after drying under an infra-red lamp. Work-up of such complexes can be done in good yields. In the case of methyl and ethyl mandelate the complex was suspended in toluene, acidified with conc. hydrochloric acid and then water was added (toluene–water, 3 : 1). After gentle warming the free dibenzoyltartaric acid separated as an oil. The cold mixture seeded with dibenzoyltartaric acid monohydrate. After filtration of the acid, the toluene layer was washed with $NaHCO_3$ and water, dried and evaporated. Pure mandelic esters were obtained in 80–90% yield. Owing to the lower solubility of the benzyl and 2-phenylethyl mandelate in tolune, they were isolated by suspending the complex in organic solvents (*e.g.* ether, chloroform) and removing the Ca^{2+} with aqueous hydrochloric acid and extracting the organic layer with alkali carbonate. The organic layer was then washed with water, dried and evaporated to dryness. The yields were in the range 85–92%.

In the crystal structure§ of [Ca{(*R*-(−)-**1a**}$_2$](HL_0)$_2$ the molecules are organized around a central column of Ca^{2+} ions coordinated according to a distorted square antiprism geometry (Fig. 1). Two methyl mandelate molecules coordinate the Ca^{2+} ions as bidentate ligands on opposite sides of the same ion. On the contrary two carbonyl oxygens of a single tartrate ion are in contact with two different Ca^{2+} ions. Thereby they provide an opportunity for the formation of an endless chain through the crystal structure. Also, there are two of these endless chains on opposite sides of the Ca^{2+} ion. The stability of the above chain is further reinforced by hydrogen bonds between the OH of the methyl mandelate molecules and the carbonyl oxygen of one of the benzoyl groups as well as by another hydrogen bond between the carboxylates of two neighbouring semiprotonated tartrate ions. Difference Fourier calculations locate the hydrogen almost exactly in the middle between the two oxygens, which might point to possible disorder. Also, all the C–O bond lengths are practically equal and don't facilitate unequivocal assignment of the hydrogen to any of the oxygen atoms. However, the two rival oxygens must be hydrogen bonded since they are close to each other. In summary, the crystal structure of **2a** consist of columns of Ca^{2+} ions coordinated by eight O atoms. These hydrophilic columns are surrounded by 'lakes' of phenyl groups and are practically isolated from each other. A possible explanation for the stability of the crystal of **2a** formed by the given pair of chiral moieties might arise from the crystal structure. The central hydrophilic column is thought to be a very well stabilized component. Since the constituting elements of this column are also present in the compound formed by the dibenzoyltartaric acid and the other enantiomer of methyl mandelate, the well stabilized central Ca^{2+} containing column can easily be formed by a similar molecular recognition process. However, a hydrogen atom and a phenyl group has to change position in the methyl mandelate as compared to the structure presented here. This change might not be compatible with frequently occurring space group symmetries, therefore the formation of a crystal by these components is severely hindered.

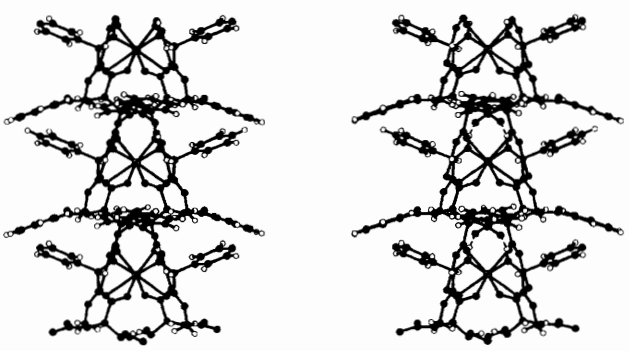


Fig. 1 Stereoview of the complex [Ca{(*R*)-(−)-**1a**}$_2$](HL_0)$_2$

The authors wish to thank Professor G. M. Sheldrick for his help in the solution of the crystal structure and acknowledge the financial support of the Hungarian Research Fund [OTKA Grant No: T014887 (E.F.) and FO19261 (D.M.)]. A. M. also thanks the Varga József Foundation for financial support.

Footnotes

† (*S*)-(+)-Benzyl mandelate: needles (benzene–hexane), mp 103–105·°C; $(\alpha)_D^{23}$ = +55.7 (*c* 1.0, chloroform).

‡ (*S*)-(+)-2-Phenylethyl mandelate: needles (toluene–hexane), mp 60–62 °C; $[\alpha]_D^{22}$ = +71.7 (*c* 1.1, chloroform).

§ *Crystal data* for [Ca{(*R*)-(−)-**1a**}$_2$](HL_0)$_2$, $C_{54}H_{46}O_{22}Ca$, *M* = 1086.99, monoclinic, *C*2, *a* = 27.86(2), *b* = 7.647(10), *c* = 24.98(2) Å, β = 103.64(2)°, *Z* = 4; total data collected = 5456, independent reflections = 5456. The initial model obtained by Patterson methods (SHELXS-86[13]), was refined against 5447 observations to convergence [final *R* indices for $I > 2\sigma(I)$: R_1 = 0.0618, wR_2 = 0.1641, for all data R_1 = 0.0848, wR_2 = 0.2166 (SHELXL-93[14])]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/157.

References

1 J. R. E. Hoover, G. L. Dunn, D. R. Jakas, L. L. Lam, J. J. Taggart, J. R. Guarini and L. Phillips, *J. Med. Chem.*, 1974, **17**, 34.
2 T. Früh and G. Ramos Tombo, *SYNLETT*, 1994, 727.
3 J. L. Charlton and K. Koh, *J. Org. Chem.*, 1992, **57**, 1514.
4 W. A. Bonner, *J. Am. Chem. Soc.*, 1951, **73**, 3126.
5 R. Roger, *J. Chem. Soc.*, 1932, 2168.
6 V. A. Burgess, S. G. Davies and R. T. Skerlj, *Tetrahedron: Asymmetry*, 1991, **2**, 299.
7 H. C. Brown and G. G. Pai, *J. Org. Chem.*, 1985, **50**, 1384.
8 B. S. Deol, D. D. Ridley and G. W. Simpson, *Aust. J. Chem.*, 1976, **29**, 2459.
9 T. Miyazawa, S. Kurita, S. Ueji, T. Yamada and S. Kuwata, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2253.
10 D. Basavaiah and P. Rama Krishna, *Tetrahedron*, 1995, **51**, 2403.
11 F. Toda, A. Sato, L. R. Nassimbeni and M. L. Niven, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1971.
12 A. Mravik, E. Fogassy, Z. Katona and I. Markovits, Hung. Pat. Appl. P 9600187.
13 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, **46**, 467.
14 G. M. Sheldrick, SHELXL-93, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1993.

Received, 25th March 1996; Com. 6/02030E