Studies on crystal structure of inclusion chiral crystal of (*S*)-α-cyclopentyl-α-hydroxyl-α-thienylacetic acid with (*R*)-α-methyl benylamine

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The optically active α-cyclopentyl- α-hydroxyl-α-thienylacetic acid is obtained by the optical resolution of racemates with the chiral host α-methylbenylamine. The structure of the inclusion salt complex of two compounds was first elucidated by X-ray analysis.

Keywords: inclusion chiral crystal, optical resolution

The optical resolution of racemates via diastereoisomeric salt formation is a common way for the preparation of optical isomers.[1,2] The tertiary hydroxy acids and esters are highly important components in the asymmetric synthesis of a variety of natural products and medicinal agents.[3,4] Our recent drug candidate: 9α-(3-azabicyclo[3,3,1]nonyl)-2-cyclopentyl-2-hydroxyl-2-thienylacetate(thiencynonate), is a potent selective M_1 antagonist. It is composed of a tertiary hydroxy acid as a key component like many of the muscarinic receptor antagonists. It exhibits classical antimuscarinic side effects, such as a dry mouth. The biology results suggest that the (*S*)-configuration of thiencynonate displays an improved therapeutic profile compared to its racemic counterpart. In our efforts to have a production of the enantiopure tertiary acid, we found that inclusion crystallisation with α-methylbenzylamine as a chiral host with the tertiary hydroxyl acid is an effective method for the resolution of α-cyclopentyl-α-hydroxyl-α-thienylacetic acid. The optically active tertiary hydroxy acid with high enantiomeric excess is obtained through this new and practicable method, and this key intermediate can be effectively synthesised as the optically pure thiencynonate.

The X-ray ORTEP structure of the inclusion salt complex of (*S*)-α-cyclopentyl-α-hydroxyl-α-thienylacetic acid and (*R*)-α-methylbenylamine with atomic labelling is shown in Fig. 1. X-ray structure analytical data showed that inclusion complexes of two compounds are produced by the formation of hydrogen bonds. The tertiary hydroxy acid is deprotonated to form the acetate anion. The C–O bond lengths of the carboxyl group are homogenized being 1.2424(2)Å(C1A–O1A) and 1.2354(4)Å(C1A–O2A), they are shorter than the C–O bond of hydroxyl groups(C2A–O3A, 1.4187(3) Å). The amino group of α-methylbenylamine is protonated, and the N–H group participates in N–H···O hydrogen bonds involving the O atom

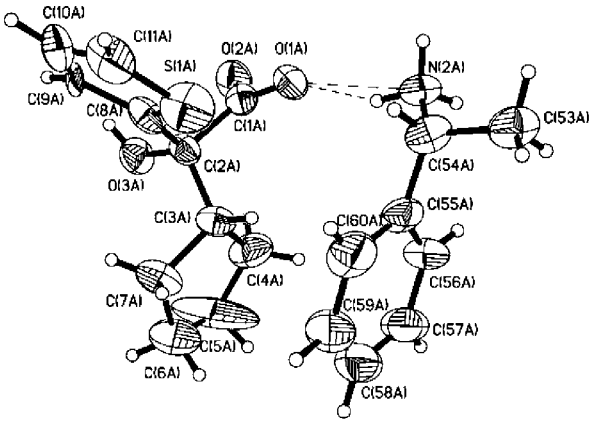

Fig. 1 The ORTEP structure of the inclusion salt complex with atom labeling.

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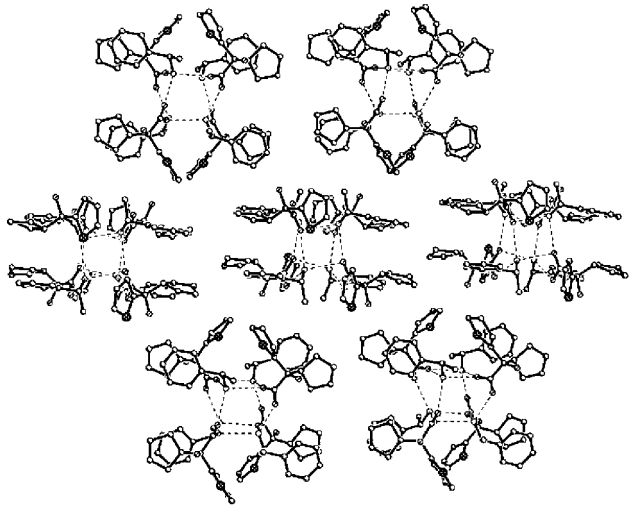

Fig. 2 Packing diagram for tetrapolymer cage structures of the inclusion salt complexes showing the hydrogen bonding.

of the acetate anion. The N···O separation is 2.761 Å with the H···O separation 1.930 Å, falling into the normal range of the N···O separation for hydrogen bonding,[5] the smallest bond angle is 153.32°.

As shown in Fig. 2, a tetra-polymer cage structure was formed by four pairs of inclusion molecules through N-H···O hydrogen bonds in which two O atoms of the carbonyl group link the N atom of the amino group in the adjacent molecule. The N···O separations are in the range of 2.761–3.276 Å with the H···O separations in the range of 1.894–2.652Å, the bond angles are 127.20–168.83 °. The tetrapolymer cage structures were arranged with interlaced different aspects in the packing diagram.

Experimental

All the reagents for syntheses were commercially available and used without further purification or purified by standard methods prior to use. Elemental analyses were performed on a Perkin–Elmer 240C analyzer. ^{1}H-NMR spectra were measured in $CDCl_3$ using a multinuclear FT-NMR spectrometer ARX300 (Bruker). α-Cyclopentyl-α-hydroxy-α-thienylacetic acid was synthesised by addition of Grignard reagents to diethyl oxalate as described in the literature.[6]

Syntheses of the inclusion salt complex: A solution of rac-α-cyclopentyl-α-hydroxy-α-thienylacetic acid (1.13g, 5mmol) and (*R*)-α-methyl benylamine (0.6g, 5mmol) in ethanol (50 ml) was kept at 50°C for 12 h. After being cooled to room temperature, a 1:1 inclusion complex of (*S*)- α-cyclopentyl-α-hydroxy-α-thienylacetic acid and (*R*)- α-methyl benylamine was obtained as colourless crystals (1.3g, 75% yield).Three recrystallisations of the crystals from ethanol gave pure inclusion crystals (0.95g, 55% yield, mp 132–133°C). Anal. Calcd for $C_{19}H_{25}NO_3S$: C, 65.68; H, 7.25; N, 4.03. Found: C, 65.42; H, 7.21; N, 4.08. ^{1}HNMR ($CDCl_3$): 1.37– 1.57 (m, 9H), 1.59 (m, 3H), 2.85 (m, 1H), 4.39 (m, 1H), 6.87– 7.13 (m, 3H), 7.37– 7.45 (m, 5H).

Crystal data: $C_{19}H_{25}NO_3S$, M*r* = 347.46, Monoclinic, $P2_1$, *a* = 14.376(4) Å, *b* = 17.810(5) Å, *c*= 15.695(5) Å, β = 101.223(5).

V = 3942(2) Å^3, D_x = 1.171 g cm^{-3}, Z = 8, μ = 0.179 mm-1, T = 293(2) K, absolute structure parameter = 0.05(13). A colourless cube crystal with dimensions of 0.32 mm × 0.22 mm × 0.18 mm was mounted on a Bruker Smart 1000 CCD diffractometer equipped with a graphite monochromator for data collection. The determination of unit cell parameters and data collections were performed with Mo$K\alpha$ radiation (λ = 0.71073 Å). A total of 20466 reflections with 11809 independent ones with R_{int} = 0.0348 and 6549 observed reflections with $I > 2\sigma(I)$ were collected in the range of $1.32 < \theta < 25.01^o$ by an ω/θ scan mode. All data were corrected by using SADABS method. The structure was solved by direct methods with SHELXL-97 program.[7] The final refinement was performed by full-matrix least-squares methods with anisotropic thermal parameters for non-hydrogen atoms on F^2. The hydrogen atoms were added theoretically, riding on the concerned atoms and being refined with fixed thermal factors. The weighting scheme was $w = 1/[\sigma^2(F_o^2) + (0.0692P)^2 + 0.9695P]$, where $P = (F_o^2 + 2F_c^2)/3$. The refinement converged to the final R = 0.0724 and wR = 0.1485. S = 1.096. Molecular graphics were drawn with the program package XP. Full crystallographic details have been deposited with the Cambridge Crystallographic Data Center and allocated the deposition number CCDC-233062.

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