

Resolution of alkyl pyridyl sulfoxides by complexation with a chiral host compound derived from tartaric acid

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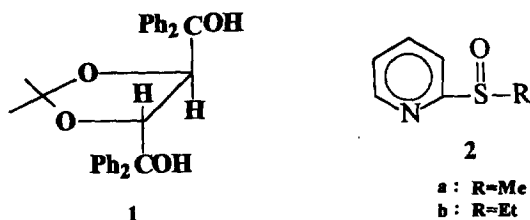
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Abstract: Alkyl pyridyl sulfoxides **2** were prepared in high enantiomeric excess by resolution through inclusion complexation with a chiral host compound, (2*R*,3*R*) or (2*S*,3*S*)-(-)-trans-4,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxolane **1**. The X-ray crystallographic structure analysis of complex (R,R)-(-)-**1** and (R)-(-)-**2b** is reported.
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Chiral sulfoxides are useful synthons for asymmetric carbon–carbon bonds formation.¹ The preparation of non-racemic chiral sulfoxides has been developed.^{2–11} However, reports about the preparation of alkyl pyridyl sulfoxides with high enantiomeric excess are few,^{8,10} despite their great potential for the development of new ways for asymmetric carbon–carbon bonds formation.^{12–14}

Inclusion crystallization has been used since the early 1980s, to selectively and reversibly include chiral guest molecules in host lattices of chiral molecules.¹⁵ Recently, we found this method is effective for the resolution of alkyl pyridyl sulfoxides **2**, which form inclusion complexes with chiral host compounds **1**, and optically active alkyl pyridyl sulfoxides with high enantiomeric excess are obtained (Table 1).



A solution of (R,R)-(-)-**1** (1.174 g, 2.52 mmol) and rac-**2b** (0.776 g, 5 mmol) in toluene (3 ml) was kept at room temperature for 12 h, a 1:1 inclusion complex of (R,R)-(-)-**1** and (R)-(-)-**2b** was obtained as colourless crystals (1.265 g, 81% yield). Two recrystallizations of the crystals from toluene gave pure inclusion crystals (1.060 g, 68% yield, mp 122–123°C), and (R)-(-)-**2b** of 100% e.e. [0.240 g, 62% yield, $[\alpha]_D^{16}$ –168 (c=0.78, MeOH)] was obtained by chromatography on silica gel. A crude (S)-(+)-**2b** (0.39 g, 15% e.e.) was recovered from the filtrate by column chromatography on silica gel, and then the crude (S)-(+)-**2b** (0.39 g, 2.5 mmol) and (S,S)-(+)-**1** (1.166 g, 2.5 mmol) were dissolved in toluene (2 ml) and kept at room temperature for 12 h. The crude inclusion complex of (S,S)-(+)-**1** and (S)-(+)-**2b** was recrystallized twice from toluene and subsequently separated by column chromatography on silica gel to give (S)-(+)-**2b** of 98% e.e. [0.210 g, 54% yield, $[\alpha]_D^{16}$ +167 (c=0.79, MeOH)]. The recovered compounds **1** could be recycled and affect on the resolution was observed.

X-Ray structure analytical data showed that inclusion complexes of compounds **1** and **2** are produced by the formation of hydrogen bonds between the two components. The X-ray ORTEP drawing of

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Table 1. Resolution of **2** through inclusion complexation with **1** by crystallization from toluene

sulfoxide	chiral host compound	mp of inclusion complex (°C) ^a	product ^b	yield (%)	e.e (%) ^c
2a	(R,R)-(-)- 1	119-123	(R)-(+)- 2a	61	95
	(S,S)-(+)- 1	132-133	(S)-(-)- 2a	42	96
2b	(R,R)-(-)- 1	122-123	(R)-(-)- 2b	62	100
	(S,S)-(+)- 1	122-124	(S)-(+)- 2b	54	98

a. Inclusion complex was purified by two recrystallizations from toluene.

b. The absolute configuration was confirmed by X-ray analysis.

c. The enantiomeric excess of **2** was determined by HPLC using Chiralcel OB as the chiral solid phase and n-hexane /2-propanol (85 : 15) as elute.

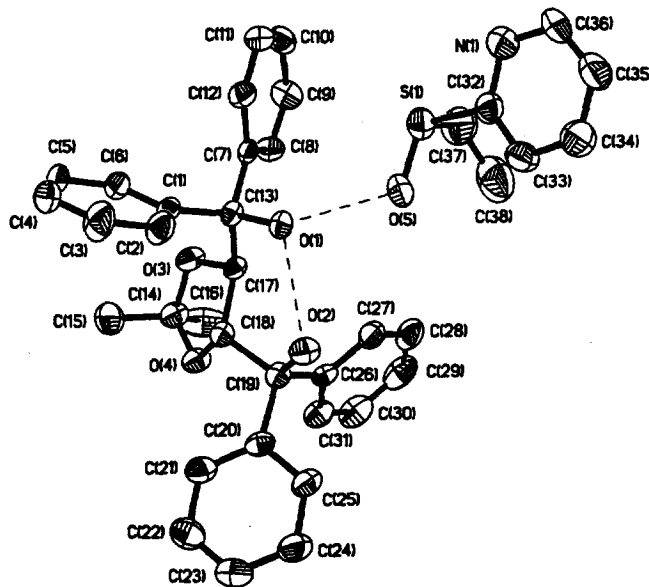


Figure 1. X-Ray ORTEP drawing of inclusion complex of (R,R)-(-)-**1** and (-)-**2b**.

inclusion complex of (R,R)-(-)-**1** and (-)-**2b** is shown in Figure 1.¹⁶ It is first report of an X-ray structure of a sulfoxide inclusion complex: a 1:1 complex of (-)-**1** and (-)-**2b** was formed. The sulfonyl oxygen of (-)-**2b** is included by forming a hydrogen bond with the hydroxyl group of (-)-**1**, and the distance between O(1) and O(5) is 2.650 Å. The other remaining hydroxyl group O(2) of host **1** also makes an intramolecular hydrogen bond with the hydroxyl group of O(1), and the distance between O(1) and O(2) is 2.650 Å. The crystal of (-)-**1**-(-)-**2b** was found to be monoclinic and the space group to be $p2_1$. The absolute configuration of (-)-**2b** was confirmed to be (R), which was assigned by the (R,R) absolute configuration of the host **1** as an internal reference. The absolute configuration of (+)-**2a** was also confirmed to be (R) by X-ray and HPLC analysis.¹⁷

NMR spectra showed that the molar ratio of compound **1** and **2** in the inclusion complexes is one to one.¹⁸ IR spectra of the inclusion complexes of **1** and **2** also showed that there is hydrogen bonding between the host **1** and guest **2** in a crystalline state.¹⁹ The IR spectrum of the inclusion complex (-)-**1**-(+)-**2a** exhibits the sulfonyl absorption band at 1028 cm⁻¹, while that of (+)-**2a** shows the corresponding band at 1036 cm⁻¹, the hydrogen bonding between the sulfonyl oxygen of (+)-**2a** and the hydroxyl group of (-)-**1** thus causes a lower wave number shift of 8 cm⁻¹. Inclusion complex (-)-**1**-(+)-**2a** exhibits a hydrogen bond around 3280 cm⁻¹, while chiral host (-)-**1** exhibits intramolecular hydrogen bond at 3434 cm⁻¹ and intermolecular hydrogen bonding 3206 cm⁻¹. The IR spectrum of the inclusion complex (-)-**1**-(-)-**2b** shows the same case.

Acknowledgements

We are grateful for the financial support of the National Natural Science Foundation of China.

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- Crystal data for 1:1 inclusion complex of (R,R)-(-)-**1** and (-)-**2b**: C₃₈H₃₉NO₅S; Mr=621.76; colorless prism (0.38×0.28×0.2 mm); monoclinic; space group P2₁, a=9.701(2), b=9.953(2), c=17.392(2) Å; V=1678.1(5) Å³; Z=2; Dc=1.230 g/cm³; F(000)=660; μ (Mo-Kα)=0.140 cm⁻¹; SIEMENS P4 diffractometer; MoKα radiation (0.71073 Å): graphite crystal monochromator; T=294 K; scan type, ω; scan speed, 6° min⁻¹; scan ring, Δ ω=1.4; scan limits, 2°<2θ<48°; standard reflection, 3 per 97 reflections; crystal stability, standard reflection decay during data collection, 0.012; total reflection collected, 2476, in which independent reflection collected, 2335 (Rint=0.012). The skeletal structure was solved by the direct method and successive Fourier syntheses. All hydrogens were found by the difference Fourier syntheses. Full matrix least-squares refinement of positional and thermal parameters, including anomalous scattering factor of oxygen and carbon atoms, lead to the final convergence with R=0.0351 and WR₂=0.0772. The absolute configuration was assigned as shown by using the (2R,3R) absolute configuration of the host **1** as an internal reference.

17. J. Zhu, J. G. Deng, A. Q. Mi, Y. Z. Jiang, unpublished results. We obtained a crystal from the filtrate of the suspension in hexane of (-)-**1** and **2a** (1:1 mol/mol) and the X-ray structure analysis shows 2:1:1 inclusion complex of (2R,3R)-(-)-**1** and (-)-**2a** and water. The absolute configuration of (-)-**2a** was confirmed to be (S) by the (2R,3R) absolute configuration of host **1** as an internal reference and retention time of (-)-**2a** is 11.3' on HPLC. However, that of (+)-**2a** resolved by the formation of inclusion complex of (2R,3R)-(-)-**1** is 17.1' on HPLC and thus the absolute configuration of (+)-**2a** was confirmed to be (R). This configuration of (+)-**2a** was also verified according to the order of elute on Chiralcel OB column.¹⁰
18. ¹H-NMR (300 MHz, CDCl₃ and D₂O). Complex (-)-**1**-(+)-**2a**: δ (ppm) 0.97 (6H, s), 2.74 (3H, s), 4.48 (2H, s), 7.16–7.48 (21H, m), 7.87–7.91 (2H, m), 8.53–8.54 (1H, m). Complex (-)-**1**-(-)-**2b**: δ (ppm) 0.96 (6H, s), 1.08 (3H, J=7 Hz, t) 2.80 (2H, J=7 Hz, q), 4.48 (2H, s), 7.12–7.47 (21H, m), 7.81–7.83 (2H, m), 8.50–8.51 (1H, m).
19. IR spectrum (film). Complex (-)-**1**-(+)-**2a** (ν_{max}): 3280, 3086, 3058, 3032, 2957, 2854, 1576, 1562, 1494, 1448, 1425, 1410, 1377, 1368, 1333, 1240, 1225, 1171, 1102, 1083, 1052, 1028, 940, 887, 794, 771, 757, 743, 723, 706 cm⁻¹. Complex (-)-**1**-(-)-**2b** (ν_{max}): 3282, 2958, 2872, 2854, 1598, 1579, 1561, 1492, 1423, 1378, 1271, 1236, 1202, 1171, 1082, 1051, 1024, 1011, 962, 887, 783, 760, 743, 722, 697 cm⁻¹.

(Received in Japan 20 May 1997)