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Resolution of omeprazole by inclusion complexation with a chiral host BINOL

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Abstract

Both (*S*)-(–)- and (*R*)-(+)-enantiomers of omeprazole were directly resolved by inclusion complexation with a chiral host compound (*S*)-(–)- or (*R*)-(+)-2,2′-dihydroxy-1,1′-binaphthyl in high enantiomeric excess (>99% e.e.).

1. Introduction

5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1*H*-benzimidazole, which has the generic name omeprazole **1**, is a highly potent gastric acid secretion inhibitor,[1] and was firstly marketed by Astra in 1988. Omeprazole **1** has a stereogenic center at the sulphur atom, and exists as two enantiomers, (*S*)-enantiomer and (*R*)-enantiomer (Fig. 1).

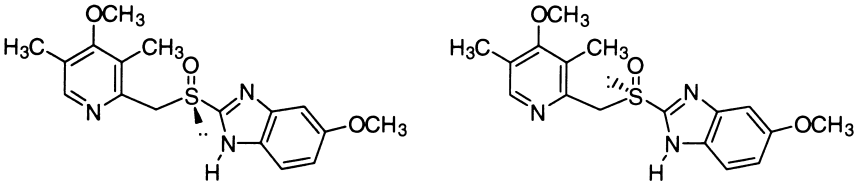

Figure 1. The structure of two enantiomers of omeprazole **1**

In January 1996, the FDA announced it would consider further incentives for developing single isomer drugs,[2] owing to their better pharmacokinetics prosperity, safety, and tolerability. Racemic omeprazole **1** has a mature preparation method and is manufactured on a large scale, but there is not yet an efficient process for the preparation of the single enantiomers. Resolutions, via

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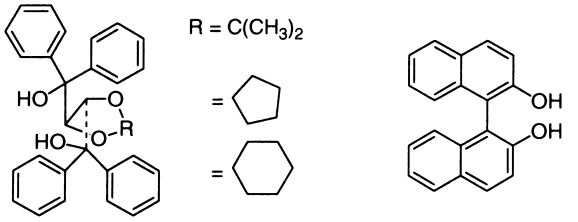
diastereomerically *N*-substituted derivatives of omeprazole, have been disclosed; however, this process involves the complicated separation and cleavage of *N*-substituents.[3] An asymmetric oxidation of the prochiral sulfide, 5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-thio}-1*H*-benzimidazole, was also described in the literature.[4] Since the early 1980s, the formation of host–guest inclusion complexes, via selectively and reversibly including chiral guest molecules in host lattices of chiral molecules, has been applied to the resolution of racemates by Toda, and many enantiomerically pure compounds have been successfully prepared by inclusion resolution.[5] Recently, we have obtained the enantiomerically pure alkylpyridyl sulfoxide by the inclusion method with chiral TADDOL **2** ($R = C(CH_3)_2$);[6] however, it is unsuccessful in resolving omeprazole **1** containing a 2-pyridylmethyl sulfinyl group with TADDOLs **2** as chiral host.[7] Here, we report the first inclusion resolution of omeprazole **1** by inclusion complexation with chiral host 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) **3**.[8]



TADDOLs **2** BINOL **3**

2. Results and discussion

An inclusion complex was obtained from the mixed solvent of benzene and hexane (see Table 1). Because racemic omeprazole **1** easily separates out on cooling, high mole ratios of **1** and the chiral host BINOL **3** are needed for high enantioselectivities, and the best results were obtained with a 1:1.5 ratio of *rac*-**1** and chiral **3** (Table 1, entries 3 and 5). The suitable volume ratio of benzene and hexane is also important for the crystallization of the inclusion complex; when the ratio of benzene and hexane increased to 6:1, no complex precipitated, and when the ratio decreased from 4:1 to 2.5:1, lower enantioselectivity was observed although a higher yield was obtained (Table 1, entry 7).

NMR and elemental analysis showed that the molar ratio of **1** and **3** in the inclusion complexes is 1:1.[10] IR analysis of inclusion complex, chiral host and guest shows a shift of O–H and S=O stretching vibrational region.[11] The chiral host, (*S*)-(–)-**3**, exhibits sharp and strong bands at 3509 (intermolecular hydrogen bonding) and 3433 cm^{-1} (intramolecular hydrogen bonding), and *rac*-**1** exhibits the sulfinyl absorption band at 1018 cm^{-1}, while complex (–)-**1**–(–)-**3** shows a broad band around 3058 and 1028 cm^{-1} which is compared with the sulfinyl absorption band (1028 cm^{-1})[11] of the (*S*)-enantiomer of omeprazole **1**. We also obtained a crystal of *rac*-**1** from butanone solution,[12] and X-ray crystallographic structure analysis[13] shows it to be a dimer of two enantiomers (Fig. 2), which forms by intermolecular N–H···O=S hydrogen bonding (distance between O2 and N1, 1.900 Å). These results show that the chiral sulfinyl group does not attribute the formation of hydrogen bonding in the inclusion complex,[8b] and the chiral recognition in the inclusion complex may occur via formation of hydrogen-bonded supramolecular chiron[14,15] between chiral BINOL **3** and chiral omeprazole **1**. Unfortunately, we have not obtained a suitable crystal of the inclusion complex.

Table 1
Resolution of omeprazole **1** by inclusion complexation

entry	Solvent Ratio[a] (V/V)	Chiral Host	Mole Ratio of Rac-**1** and **3**	Product[b]	Yield(%)[b]	E.e.(%)[c]
1	4:1	(*R*)-(+)-**3**	1:0.55	(*R*)-(+)-**1**	71.8	58.9
2	4:1	(*R*)-(+)-**3**	1:1	(*R*)-(+)-**1**	77.2	80.6
3	4:1	(*R*)-(+)-**3**	1:1.5	(*R*)-(+)-**1**	91.9	90.2
4	4:1	(*R*)-(+)-**3**	1:2.0	(*R*)-(+)-**1**	91.5	89.7
5	4:1	(*R*)- (-)-**3**	1:1.5	(*S*)- (-)-**1**	92.4	90.3
6	6:1	(*R*)- (-)-**3**	1:1	–[d]	–[d]	–[d]
7	2.5:1	(*R*)-(+)-**3**	1:1	(*R*)-(+)-**1**	105.3	14.9

a) The solvent system is a mixture of benzene and hexane.

b) The enantiomers of **1** were separated from inclusion complex on SiO_2 column and the yield was based on a half of rac-**1**.

c) The enantiomeric excess of **1** was determined by HPLC and further separation of **1** and **3** is not necessary.[9]

d) No inclusion complex precipitated.

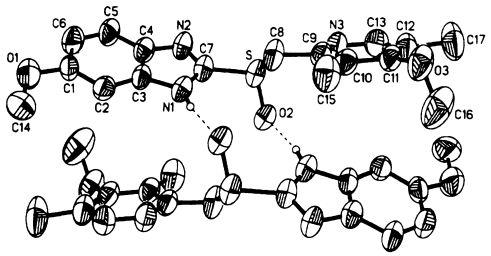


Figure 2. X-Ray ORTEP drawing of racemic omeprazole **1**

3. Conclusion

An inclusion complex (–)-**1**–(–)-**3** or (+)-**1**–(+)-**3** was first obtained from racemic omeprazole **1** with chiral host (*S*)-(–)- or (*R*)-(+)-2,2′-dihydroxy-1,1′-binaphthyl **3** in high selectivities, and thus both enantiomerically pure enantiomers of omeprazole **1** were prepared by direct resolution with more than 99% enantiomeric excess.

4. Experimental

At 110°C, (*S*)-(–)-**3** (1.248 g, 4.35 mmol) and *rac*-**1** (1.000 g, 2.90 mmol) were dissolved in 36 mL of benzene:hexane (v/v = 4:1), and then the mixture was cooled and kept at 0°C for 12 h. A complex of (*S*)-(–)-**1**[3c] and (*S*)-(–)-**3** was obtained as a grey–blue powder with 90.3% e.e. (determined by HPLC analysis[9]) of (*S*)-(–)-**1**. Then, one recrystallization of the complex in benzene:hexane (v/v, 1:1) and separation of the resulted complex (0.769 g) on a SiO_2 column gave (*S*)-(–)-omeprazole **1** with 98.9% e.e. and 84.1% overall yield as a red syrup. After recrystallization in water, (*S*)-(–)-**1** was obtained as a white powder with 99.2% e.e.[16] Similarly, by using chiral (*R*)-(+)-BINOL **3** as host, a white powder of (*R*)-(+)-omeprazole **1** can be obtained with 99.5% e.e.[16]

Acknowledgements

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7. Using (*R*,*R*)-(–)-TADDOLs **2** as chiral host, in benzene, toluene, acetonitrile, ethanol, hexane, chloroform and a mixture of benzene or toluene and hexane, no inclusion phenomena was observed.
8. Also, see: (a) Toda, F.; Tanaka, K.; Nagamatsu, S. *Tetrahedron Lett.* **1984**, *25*, 4929–4932; (b) Toda, F.; Tanaka, K.; Mak, T. C. W. *Chem. Lett.* **1984**, 2085–2088; (c) Toda, F.; Mori, K. *Chem. Commun.* **1986**, 1059–1060.
9. Condition of HPLC: KR100-5 CHI-TBB as chiral column, and hexane:2-propanol:triethylamine:acetic acid (92:8:0.15:0.05) as elute.
10. The inclusion complex (–)-**1**–(–)-**3**: 98.9% e.e.,[9] mp 115°C; ^{1}H NMR (400 MHz, DMSO), δ: 2.146 (3H, s), 2.187 (3H, s), 3.672 (3H, s), 3.792 (3H, s), 4.670 (1H, d, J = 13.6 Hz), 4.758 (1H, d, J = 13.6 Hz), 6.904 (1H, s), 6.925 (1H, s), 7.071 (1H, s), 7.071–7.238 (6H, m), 7.306 (2H, s), 7.522 (1H, s), 7.851–7.829 (4H, m), 8.178 (1H, s), 9.198 (2H, s) ppm; elemental analysis, calcd for $C_{37}H_{33}N_3O_5S$: C 70.34%, N 6.65%, H 5.26%, S 5.07%; found: C 70.11%, N 6.62%, H 5.29%, S 4.91%.
11. IR (paraffin oil), *rac*-**1**, ν_{max}: 2924, 2853 (br), 1618, 1590, 1462 (s), 1204, 1145, 1077, 1018 (s), 810 cm^{-1}; (–)-**1**, ν_{max}: 2921, 2852 (br), 1625, 1588, 1567, 1463, 1205, 1152, 1076, 1028 (s), 829 cm^{-1}; (–)-**3**, ν_{max}: 3509 (s), 3433 (br), 2924 (s), 2854, 1617, 1595, 1510, 1465, 1378, 1318, 1218, 1182, 1148, 823, 748 cm^{-1}; complex (–)-**1**–(–)-**3**, ν_{max}: 3058 (br), 2953, 2854 (br), 1618, 1595, 1462 (s), 1378, 1270, 1186, 1145, 1072, 1028 (s), 812 cm^{-1}.
12. Also, see: Ohishi, H.; In, Y.; Ishida, T.; Inque, M. *Acta Crystallogr.* **1989**, *C45*, 1921–1923.
13. Crystal data for *rac*-**1**: $C_{17}H_{19}N_3O_3S$; *M*r = 345.41; colorless cubical crystal (0.50×0.36×0.32 mm); triclinic; space group P·, a = 9.700(3), b = 10.284(3), c = 10.649(3) Å; α = 91.43(2)°, β = 112.08(1)°, γ = 115.85(2)°; V = 862.9(5) Å^3; Z = 2; Dc = 1.329 g/cm^3; $F(000)$ = 364; μ(Mo-Kα) = 0.208 mm^{-1}; SIEMENS P4 diffractometer; Mo-Kα radiation (0.71073 Å), graphite crystal monochromator; T = 296 K; scan type, ω; scan speed, 7° min^{-1}; scan ring, $\Delta\omega$ = 1.55; scan limits, 4° < 2θ < 50°; standard reflection, 3 per 97 reflections; crystal stability, standard reflection decay during data collection, 0.0066; total reflection collected, 3332, in which independent reflection collected, 3024 (R_{int} = 0.024). The direct method and successive Fourier synthesis solved the skeletal structure. All hydrogen atoms were found by the difference Fourier synthesis. Full-matrix least-squares refinement of positional and thermal parameters led to the final convergence with R = 0.0577 and $wR2$ = 0.1728.
14. The formation of a supramolecular layer in the homochiral inclusion complex of lansoprazole and BINOL **3** was recently observed by an X-ray analysis: Deng, J. et al., unpublished result.
15. Hanessian, S.; Saladino, R.; Margarita, R.; Simard, M. *Chem. Eur. J.* **1999**, *5*, 2169–2183.
16. (*S*)-(–)-**1**: 99.2% e.e. $[\alpha]_D^{25}$ = –188 (*c* 0.5, $CHCl_3$); (*R*)-(+)-**1**: 99.5% e.e. $[\alpha]_D^{25}$ = +189 (*c* 0.5, $CHCl_3$).[3,4]