Chiral Recognition in Amino-ester Complexation by a Cyclic Polyether Host Compound

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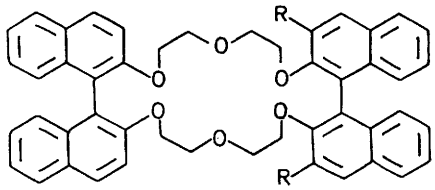
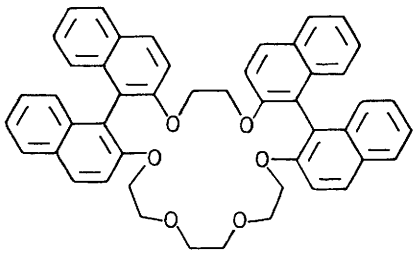
Summary A cyclic ether containing two 2,2′-substituted-1,1′-binaphthyl units as chiral barriers is described which complexes somewhat selectively the enantiomers of the hexafluorophosphate salt of racemic methyl phenylglycinate.

HOST system (*SS*)-(**1**) with D_2 symmetry complexes selectively the enantiomers of primary amine salt racemates.[1,2] The lower symmetry (C_2) host, (*SS*)-(**2**), showed higher chiral recognition toward enantiomeric guests than did (*SS*)-(**1**). The synthesis and complexing ability of a C_2 host isomeric to (**1**), (*SS*)-(**3**), are reported here.

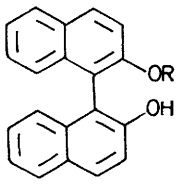
Racemic and optically pure (*S*)-(**4**)[1,3,4] with diphenylmethyl bromide in tetrahydrofuran(THF)–KOBu^t respectively gave 70% racemic (**5**)†‡ as a diethyletherate,† m.p. 103—105 °C, and 73% (*S*)-(**5**)†‡ as a glass (chromatography), $[\alpha]_{578}^{25}$ + 19·6° (*c* 0·55, $CHCl_3$). With KOH and triethyleneglycol ditosylate in THF–H_2O (25:1 v/v) at



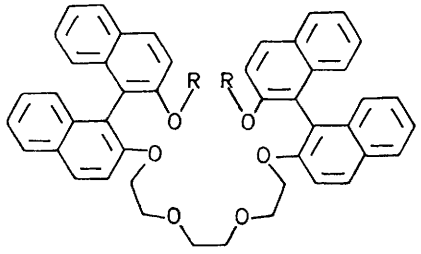
(1) R = H
(2) R = Me



(3)

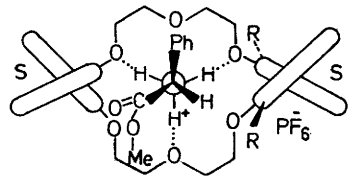


(4) R = H
(5) R = $CHPh_2$

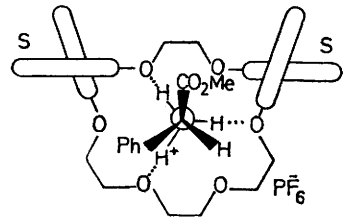


(6) R = $CHPh_2$
(7) R = H

reflux (14 h), racemic (**5**) and (*S*)-(**5**) were converted into a mixture of (*RR*)(*SS*)- and (*RS*)-(**6**)†‡ (m.p. 75—81 °C, 60%), and into (*SS*)-(**6**)†‡ as a glass (chromatography) (73%), $[\alpha]_{578}^{25}$ — 3·4° (*c* 1·08, $CHCl_3$), respectively. Each sample (0·01 mol) of (**6**) was converted (*ca.* 100%) into (**7**) (uncharacterized oils) by stirring them for 24 h with conc. HCl (10 ml), MeOH (100 ml), and CH_2Cl_2 (100 ml). Optically inactive (**7**) (0·01 mol) in THF (200 ml) containing KOH (0·028 mol), H_2O (2 ml), and ethyleneglycol ditosylate (0·01 mol) was heated at reflux (14 h). Additional KOH (0·012 mol) and ethyleneglycol ditosylate (5·4 mmol) were added, and after 24 h more at reflux, the product was chromatographed on alumina to give (50% total) first *meso*-(**3**)†‡ and then racemic (**3**).‡ Similarly, (*SS*)-(**7**) was converted (60%) into (*SS*)-(**3**)†‡ (glass after chromatography), $[\alpha]_{578}^{25}$ — 223° (*c* 4·5, $CHCl_3$), whose ^{1}H n.m.r. spectrum served to identify (*RR*)(*SS*)-(**3**) (same spectrum) and (*RS*)-(**3**) (different spectrum).



(8) R = H
(9) R = Me



(10)

In a 4 M solution of $LiPF_6$ in D_2O (9 ml; pH adjusted to 4 with LiOD) was dissolved the hydrochloride salt of racemic methyl phenylglycinate (0·0105 mol). The solution was shaken at −10 °C with 17·5 ml of a solution of (*SS*)-(**3**) (3·5 mmol) in $CDCl_3$. The ^{1}H n.m.r. spectrum of the organic layer indicated that 0·91 mol of amine salt was complexed per mol of (*SS*)-(**3**). The organic layer was washed with water, and methyl phenylglycinate was isolated without optical fractionation to give 63·5% (*R*)-amino-ester, 36·5% (*S*)-amino ester. The ester was also isolated from the originally extracted aqueous layer to give 56% (*S*)-amino ester, 44% (*R*)-amino ester (92% recovery of ester in both layers). From these data, the distribution constants between the two layers of enantiomers A (the more complexed) and B (the less complexed) were calculated (K_A and K_B), as well as the enantiomer distribution constant (EDC = K_A/K_B), which was 2·21. A similar extraction conducted at −17°C gave EDC = 2·16.

Structures (**8**), (**9**), and (**10**) represent cross sections of molecular models for the diastereoisomeric complexes between hosts (*SS*)-(**1**), (*SS*)-(**2**), and (*SS*)-(**3**), and the better complexed enantiomer of methyl phenylglycinate salt. Host (*SS*)-(**1**) at −10 °C gave EDC = 3 and (*SS*)-(**2**) at 25 °C gave EDC = 12. Hosts (*SS*)-(1) and (*SS*)-(**2**) favoured complexation of the (*S*)-amine salt[2]§ and exhibited higher chiral recognition than (*SS*)-(**3**). The three models share several common features. (i) The complexes are probably held together by electrostatic interactions between NH_3^+ and six electron pairs on the six oxygen atoms. (ii) Since the hosts all have at least one C_2 axis, the same spectrum of conformational relationships between host and guest is produced by complexation of the alkylammonium ion from either side of the oxygen atoms' best planes. (iii) The H, CO_2Me, and Ph (small, medium, and large) groups of the guest must be distributed in cavities

† Carbon and hydrogen analyses were within 0·30% of theory.

‡ The mass spectrum contained the molecular ion, and the ^{1}H n.m.r. spectrum in $CDCl_3$ was as expected.

§ In the experiments reported in ref. 2, (*RR*)-(**1**) and (*RR*)-(**2**) were used. For simplicity's sake, the enantiomeric counterparts of the compounds used are formulated here.

between the naphthalene rings, which provide planar and chiral barriers whose planes are perpendicular to the best planes of the oxygen atoms. (iv) Corey-Pauling–Koltun molecular models of structures of (**8**), (**9**), and (**10**) all appear less sterically hindered than other conformations of the same diastereoisomers or those of the other diastereoisomers. (v) The smallest group, H, occupies the most hindered position [against the end of one naphthalene wall, methyl-extended in (**9**)], CO_2Me next, and Ph the least hindered position. The methyl groups in (**2**), which extend the chiral barrier, appear to be responsible for its higher chiral recognition property, rather than the reduction of its symmetry from the D_2 to the C_2 point group. An important difference between the three sets of results is that although all three hosts are composed of (*SS*)-binaphthyl units, hosts (*SS*)-(**1**) and (*SS*)-(**2**) preferentially complex the (*S*)-amino ester salt, whereas (*SS*)-(**3**) favours the (*R*)-amino ester salt, as anticipated from molecular model examination. Host (*SS*)-(**3**) can undoubtedly be used for total amino-ester optical resolution in chromatography, as have the enantiomers of (**1**)[5]

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