Effects of Structural Changes on Chiral Selectivity in Molecular Complexation

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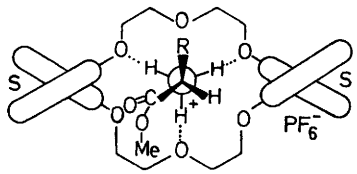
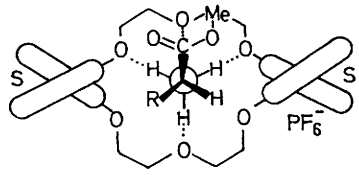
Summary Seven macrocyclic ethers containing 2,2′-substituted-1,1′-binaphthyl units as chiral barriers connected through different combinations of $OCH_2CH_2OCH_2CH_2O$, $O[CH_2]_5O$, *m*-$C_6H_4(CH_2O)_2$ and 2,6-$C_5H_3N(CH_2O)_2$ (substituted pyridyl) units complex differently with the enantiomers of the hexafluorophosphate salts of racemic methyl phenylglycinate and methyl valinate.

STRUCTURES (*SS*)-(**1**)·(*S*)-(**2**) and (*SS*)-(**1**)·(*R*)-(**2**) apparently explained the ^1H n.m.r. spectral differences between the one-to-one complexes of host cycle (*SS*)-(**1**) and guest (*S*)-phenylglycine methyl ester salt [(*S*)-(**2**)] and (*SS*)-(**1**) and (*R*)-phenylglycine methyl ester salt [(*R*)-(**2**)]. Of the two diastereoisomers, (*SS*)-(**1**)·(*S*)-(**2**) is the more stable, probably for steric reasons (three-point binding model). With valine methyl ester salt (**3**) as guest, diastereoisomer (*SS*)-(**1**)·(*R*)-(**3**) is the more stable. Possibly the steric requirements of the isopropyl group are less than those of the phenyl group, and a fourth binding site (four-point binding model) helps to stabilize the complex.[1] To test this hypothesis, several analogues of (*SS*)-(**1**) whose CH_2OCH_2 groups are replaced by other groups have been examined

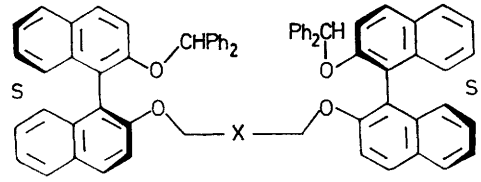


Three-point binding model
(*SS*)-(1)•(*S*)-(2), R = Ph
(*SS*)-(1)•(*S*)-(3), R = Pr^i



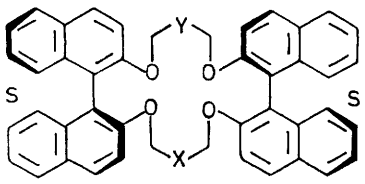
Four-point binding model
(*SS*)-(1)•(*R*)-(2), R = Ph
(*SS*)-(1)•(*R*)-(3), R = Pr^i

for their stereoselective and complexing powers toward (**2**) and (**3**).



Comp.	X	$[\alpha]_{258}^{25}$ (c 0·8, $CHCl_3$)	Yield/%
(**4**)	CH_2OCH_2†‡	−3·04°	73
(**5**)	$CH_2CH_2CH_2$†‡	−20·8°	54
(**6**)	m-C_6H_4†‡	−8·9°	67

Optically pure (*SS*)-compounds (**4**), (**5**), and (**6**) were prepared from the optically pure monobenzhydryl derivative[2] of (*S*)-2,2′-dihydroxy-1,1′-binaphthyl[1] and diethyleneglycol ditosylate, pentamethyleneglycol ditosylate and 1,3-bisbromomethylbenzene, respectively. The reactions were conducted in refluxing solutions in tetrahydrofuran of KOH or $KOBu^t$ (24—36 h), and the products were purified by chromatography on alumina. The benzhydryl groups were removed from (**4**), (**5**), and (**6**) by treatment with hydrochloric acid–methanol in CH_2Cl_2 (20 h at 25°) to give the respective diols, which were used without characterization to prepare the cyclic compounds. From (**4**) and diethyleneglycol ditosylate was obtained (*SS*)-(**1**)[1] (47%), $[\alpha]_{578}^{25}$ −215° (c 0·3, CH_2Cl_2); from (**5**) and diethyleneglycol ditosylate, (*SS*)-(**7**)†‡ (41%), $[\alpha]_{578}^{25}$ −203° (c 0·15, $CHCl_3$); from (**4**) and 2,6-bischloromethylpyridine,[3] (*SS*)-(**8**)† (43%), $[\alpha]_{578}^{25}$ −242° (c 0·7, $CHCl_3$); from (**4**) and 1,3-bisbromomethylbenzene, (*SS*)-(**9**)† (13%), $[\alpha]_{578}^{25}$ −231° (c 0·5, $CHCl_3$); optically pure (*SS*)-(**10**) was available;[4] from (**6**) and 2,6-bischloromethylpyridine,[3] (*SS*)-(**11**)†‡ (43%), $[\alpha]_{578}^{25}$ −283° (c 0·54, $CHCl_3$); from (**5**) and 2,6-bischloromethylpyridine, (*SS*)-(**12**)†‡ (29%), $[\alpha]_{578}^{25}$ −250° (c 0·5, $CHCl_3$). The reactions were conducted for 24—69 h in refluxing tetrahydrofuran solutions of $KOBu^t$, and the cyclic hosts after chromatography on alumina were obtained as amorphous solids.



Racemic guest amino-ester salts (1·2 M) of glycine and valine were distributed between $CDCl_3$ (0·2 M in host) and D_2O (4 M in $LiPF_6$), and the amount of guest drawn into the $CDCl_3$ layer was determined by ^1H n.m.r. spectroscopy.[1,2] From the rotations of the amino-ester salts isolated from the two layers at equilibrium, the enantiomer distribution constants were determined (E.D.C. = D_A/D_B where D_A is the distribution coefficient for the more, and D_B that for the less complexed enantiomer).[1,2]

Hosts (**1**) and (**7**)—(**12**) possess C_2 axes, and a guest bound to each of them from either side produces the same complex. The absence of the sixth heteroatom in hosts (**7**), (**9**), (**11**), and (**12**) decreases their complexing power as expected, below the detection point for (**7**) and (**9**) toward both guests, and for (**11**) and (**12**) toward the valine ester salt. Host (**12**) showed lowered chiral recognition compared to (**1**) toward phenylglycine ester salt, and the three-point binding model correlates the result, as with standard host (**1**). Substitution of one pyridyl for a CH_2OCH_2 group [*cf.* (**1**) and (**8**)] increased the binding power of the host, but substitution of two [*cf.* (**1**) and (**10**)] reduced it. Both mono- and disubstitution by a pyridyl unit reduced the chiral recognition toward phenylglycine ester salt but left the direction unchanged. These substitutions reversed the direction of chiral recognition toward valine ester salt from that of the four- to that of the three-point binding model. Major factors that influence the binding power and extent and direction of chiral recognition are probably the greater basicity and more rigid positioning of the heteroatom of the pyridyl *vs.* that of the CH_2OCH_2, and the one electron pair on nitrogen *vs.* the two electron pairs on oxygen available

Host			Guest + $RCHNH_3CO_2CH_3$				
Comp.	X	Y		T/°C	[Guest]/[Host]	E.D.C.	Favoured enantiomer
(**1**)	CH_2OCH_2	CH_2OCH_2	R = Ph	−10	0·9	2·8	S
(**1**)			R = Ph	−18	1·0	3·1	S
(**1**)			R = Pr^i	−10	0·6	1·5	R
(**7**)	CH_2OCH_2	$CH_2CH_2CH_2$	R = Ph	−15	~0	—	—
(**7**)			R = Pr^i	−16	~0	—	—
(**8**)	CH_2OCH_2	2,6-$C_5H_3N(CH_2)_2$	R = Ph	−10	1·2	1·7	S
(**8**)			R = Pr^i	−10	0·8	1·24	S
(**9**)	CH_2OCH_2	m-$C_6H_4(CH_2)_2$	R = Ph	−14	~0	—	—
(**9**)			R = Pr^i	−16	~0	—	—
(**10**)	2,6-$C_5H_3N(CH_2)_2$	2,6-$C_5H_3N(CH_2)_2$	R = Ph	−16	0·7	2·0	S
(**10**)			R = Pr^i	−16	0·3	1·3	S
(**11**)	2,6-$C_5H_3N(CH_2)_2$	m-$C_6H_4(CH_2)_2$	R = Ph	−17	0·3	1·0	—
(**11**)			R = Pr^i	−16	~0	—	—
(**12**)	2,6-$C_5H_3N(CH_2)_2$	$CH_2CH_2CH_2$	R = Ph	−13	0·4	1·35	S
(**12**)			R = Pr^i	−16	~0	—	—

† Carbon and hydrogen analyses were within 0·30% of theory; the ^1H n.m.r. spectra were as expected.

‡ The mass spectra exhibited molecular ions.

for binding. Although the E.D.C. values reported here are small, they have been enlarged for (**1**) to values as high as 30 by extension of the chiral barrier of one binaphthyl unit by substitution of methyl groups in the 3- and 3′-positions.[5] Substantial increases should accompany similar substitutions in the other compounds.

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