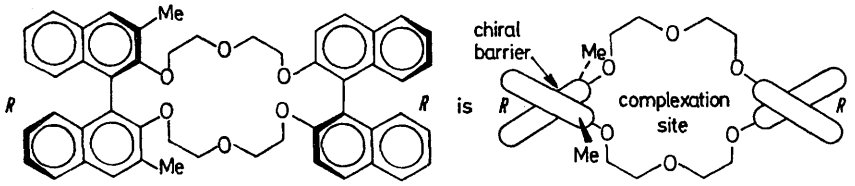
High Chiral Recognition in α-Amino-acid and -ester Complexation

By STEPHEN C. PEACOCK and DONALD J. CRAM*

(*Department of Chemistry, University of California at Los Angeles, Los Angeles, California* 90024)

Summary Chiral cyclic polyether hosts containing one 2,2′-substituted-1,1′-binaphthyl and one 2,2′-substituted-3,3′-dimethyl-1,1′-binaphthyl units in $CDCl_3$–CD_3CN or $CDCl_3$ have been used to extract from water differentially by factors of up to 52 the enantiomers of eight amino-acids and five amino-ester salts.

A PRIOR paper[1] reported two syntheses of optically pure (*RR*)-(**1**) and its use as host in differentially extracting at 25 °C into chloroform from water the enantiomers of α-amino-ester hexafluorophosphate salts as guests. The results provided enantiomer distribution constants, EDC = D_A/D_B, where D_A is the distribution coefficient of the enantiomer more complexed by (**1**) in chloroform and D_B is that of the enantiomer less complexed. Values of EDC as high as 18 were observed, which corresponds to a $\Delta(\Delta G)$ for the diastereomeric complexes of −1700 cal mol^{-1} ($\Delta(\Delta G) = -RT$ ln (EDC)). We now report that (*RR*)-(**1**) exhibits high chiral recognition in complexation of amino acid perchlorate salts.



(1)

In a standard procedure, 741 mg (1 mmol) of optically pure (*RR*)-(**1**) dissolved in 5 ml of a 23·1% (w/w) CD_3CN–$CDCl_3$ mixture was shaken at 25 °C with 2·5 ml of a D_2O solution, 4 M in $LiClO_4$, pH 1·0 ($HClO_4$), containing 3 mmol of amino-acid (organic solution, 0·20 M in host, aqueous solution 1·2 M in guest). The mixture was cooled to 0 °C with shaking, and the layers were separated. After the ^{1}H n.m.r. spectrum of the organic layer had been taken to determine the molar guest to host ratio (G/H), the solvent was evaporated off at < 25 °C, and the residue dissolved in 30 ml of HCl gas-saturated anhydrous methanol. The solution was evaporated to dryness *in vacuo*, a solution of the residual gum in anhydrous methanol was refluxed for 3 h, and the solvent was evaporated off *in vacuo*. A solution of the residual ester salt in 40 ml of dichloromethane was extracted with five 6 ml portions of 1 M hydrochloric acid, the combined extracts were brought to pH 9 with 3% aqueous ammonia, and extracted with five 10 ml portions of dichloromethane. The combined extracts were evaporated, the residual amino-ester oil was dried to constant weight, and its ^{1}H n.m.r. spectrum and rotation were recorded. The original aqueous layer was lyophilized to give a white powder, which was esterified by the procedure applied to the original organic layer to give dried amino-ester oil characterized by its weight, ^{1}H n.m.r. spectrum, and rotation. In the absence of host, no amino-acid salts were extracted. No detectable amount of host (^{1}H n.m.r. spectral probe) was distributed in the aqueous layer. No optical fractionation occurred during isolation. The EDC values were calculated from observed amino-ester rotations from each layer and their known maximum rotations. The absolute configurations of the host and guests are known and, the absolute configurations of their more stable diastereomeric complexes were determined. Table 1 reports the results. The procedure applied to the very hydrophilic lysine, cystine, and serine salts brought enough guest into the organic layer to detect with ^{1}H n.m.r. spectral probes, but too little for EDC determination.

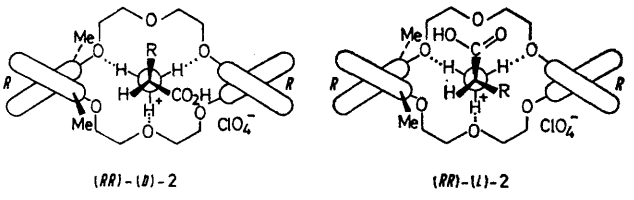
Table 1 also reports new EDC values for several amino-ester hexafluorophosphate or perchlorate salts distributed at 0 to −11 °C between $CDCl_3$–CD_3CN containing optically pure (*RR*)-(**1**) and D_2O, 4 M in $LiClO_4$ or $LiPF_6$ at pH 4·5. In all cases the esters were recovered from both layers, and their rotations taken (the procedure has been described).[1]

With phenylglycine salt as a standard amino-acid guest, the effect of polarity of the organic phase on chiral recognition was examined. As the CD_3CN content of the organic phase was increased the EDC values increased from 6·15 to a maximum of 52 at 23·1% (w/w) CD_3CN, and decreased to a constant 6·2 at higher amounts (runs 1—6). Thus maximum structuring of the complex occurs in a medium which is possibly polar enough to allow host completely to displace ClO_4^- at all N–H hydrogen bonding sites of the guest, and yet not provide enough CD_3CN to compete seriously with host for N-H sites of the guest. The other amino-acids were extracted with 23·1% (w/w) CD_3CN present.

In the amino-acid salt series, the EDC values decreased with decreasing effective size of the R substituent attached to the chiral centre (in runs 4 and 7—11) as follows: 52 (Ph) = *ca.* 48 (*p*-HOC_6H_4) > 36 ($C_8H_6NCH_2$, tryptophan side chain), > 11 (Me_2CH) > 3·2 ($MeSCH_2CH_2$) > 2·3 (Me). In this series, the more stable complexes (**2**) all possessed the (*RR*)-(D) configurations. The diastereomeric complexes differed in free energy by −2150 to −450 cal mol^{-1}. With R = *p*-$HOC_6H_4CH_2$ no chiral recognition was observed (run 13), while with R = $PhCH_2$, (*RR*)-(L)-(**2**) became the more stable complex with an EDC of 3·5 (run 14).

Examination of Corey-Pauling-Koltun (CPK) molecular models of (**1**) and (**2**) indicated in advance of experiment that (*RR*)-(**1**) possessed a chiral cavity sterically more complementary to D-amino-acid and -ester salts than to L. In (*RR*)-(D)-(**2**), the two methyl groups extend the chiral

barrier of the host, and H attached to the asymmetric centre of the guest fits well against a methyl group. The R groups of the amino-acids fit in the middle of a cavity between the two naphthalene walls of the host, and the CO_2H or CO_2Me groups lie alongside the non-methylated



(*RR*)-(D)-2 (*RR*)-(L)-2

naphthalene wall, aligned in a parallel plane. In (*RR*)-(L)-(**2**), the R and CO_2H groups are interchanged, and the complex appears more compressed.

host (**1**) bound to polystyrene resin.[2] A possible explanation involves π-complexation between the different parts of the hosts and guests. The naphthalenoxy-group is a π-base, and the $CHNH_3^+$ group strengthens the π-acidity of the attached substituents (CO_2H or CO_2Me, and Ar or $ArCH_2$). In CPK models of the (*RR*)-(D)-isomers, the CO_2H or CO_2Me substituents form a sandwich with a naphthalenoxy-group, possibly stabilizing this isomer, whereas Ar or $ArCH_2$ groups cannot become aligned this way. In models of the (*RR*)-(L)-isomers, an Ar substituent forms a sandwich with a naphthalenoxy-group but inhibits CO_2H or CO_2Me from doing so. In models of the (*RR*)-(L)-isomers, a CH_2Ar substituent can form a sandwich with one naphthalenoxy-ring and a CO_2H or CO_2Me substituent can form a sandwich with a second. This two-way π-complexation effect may outweigh pure steric effects favouring the (*RR*)-(D)-isomers.

TABLE 1. Enantiomer distribution constants (EDC) for α-amino acid and ester salts between CD_3CN–$CDCl_3$ solutions of host (**1**) and D_2O–salt solutions at 0 °C

Run no.	$R\overset{*}{C}H(\overset{+}{N}H_3)CO_2R'X^-$ R	R′	X^-	% (w/w) CD_3CN in $CDCl_3$	Org. phase, G/H	More stable complex	EDC (D_A/D_B)	$\Delta(\Delta G)$/cal mol^{-1} for diaster. complexes
1	Ph	H	ClO_4^-	0	*ca.* 0	—	—	—
2	Ph	H	ClO_4^-	9·1	0·15	(*RR*)-(D)-(**2**)	6·15	−990
3	Ph	H	ClO_4^-	16·7	0·58	(*RR*)-(D)-(**2**)	9·32	−1210
4	Ph	H	ClO_4^-	23·1	0·92	(*RR*)-(D)-(**2**)	52	−2150
5	Ph	H	ClO_4^-	28·6	1·0	(*RR*)-(D)-(**2**)	6·15	−990
6	Ph	H	ClO_4^-	33·3	1·0	(*RR*)-(D)-(**2**)	6·25	−1000
7	*p*-HOC_6H_4	H	ClO_4^-	23·1	0·80	(*RR*)-(D)-(**2**)	48	−2100
8	$C_8H_6NCH_2$[a]	H	ClO_4^-	23·1	0·71	(*RR*)-(D)-(**2**)	36	−1950
9	Me_2CH	H	ClO_4^-	23·1	0·68	(*RR*)-(D)-(**2**)	11	−1300
10	$MeS[CH_2]_2$	H	ClO_4^-	23·1	0·82	(*RR*)-(D)-(**2**)	3·2	−630
11	Me	H	ClO_4^-	23·1	0·42	(*RR*)-(D)-(**2**)	2·3	−450
12	*p*-$HOC_6H_4CH_2$	H	ClO_4^-	23·1	0·78	—	1	0
13	$PhCH_2$	H	ClO_4^-	23·1	0·89	(*RR*)-(L)-(**2**)	3·5	−680
14	Ph	Me	ClO_4^-	0	0·91	(*RR*)-(D)-(**2**)	21	−1650
15	Ph	Me	ClO_4^-	9·1	1·0	(*RR*)-(D)-(**2**)	23	−1700
16[b]	Ph	Me	PF_6^-	0	0·84	(*RR*)-(D)-(**2**)	31	−1870
17	*p*-HOC_6H_4	Me	ClO_4^-	0	0·72	(*RR*)-(D)-(**2**)	25	−1750
18	*p*-HOC_6H_4	Me	ClO_4^-	9·1	0·81	(*RR*)-(D)-(**2**)	24	−1730
19	*p*-HOC_6H_4	Me	PF_6^-	0	0·76	(*RR*)-(D)-(**2**)	38	−1980
20[c]	Me_2CH	Me	PF_6^-	0	0·75	(*RR*)-(D)-(**2**)	5·3	−870
21[d]	$MeS[CH_2]_2$	Me	PF_6^-	0	0·95	(*RR*)-(D)-(**2**)	2·2	−420
22	$PhCH_2$	Me	PF_6^-	0	1·0	(*RR*)-(L)-(**2**)	2·3	−450

[a] Tryptophan side chain. [b] D_2O solution 2M in $LiPF_6$, pH 4·5. [c] Extraction temperature, −11 °C. [d] Extraction temperature, −5 °C.

Similar trends are observed with the amino-esters (runs 14—22), with PF_6^- counterions providing somewhat more structured complexes [$\Delta(\Delta G)$ values 200 cal mol^{-1} more negative than ClO_4^-; compare run 14 with 16, and run 17 with 19]. The EDC values ranged from 38 for R = *p*-HOC_6H_4 with the (*RR*)-(D) complex the more stable (run 19) to 2·3 for R = $PhCH_2$ with the (*RR*)-(L) complex the more stable (run 22). The similar results obtained with esters and acids as guests indicate that hydrogen bonding of the carboxyl-group with host or counterion plays no important role in differentiating the energies of the diastereomeric complexes.

The fact that the remote *p*-hydroxy-groups on aryl rings affect the EDC values for both amino-acids and esters (compare run 12 with 13, and run 16 with 19) indicates that electronic effects are superimposed on steric effects in controlling EDC values. Even the relative stabilities of the diastereomeric complexes switch away from that predicted by the strictly steric model when R = $PhCH_2$ in the amino-acid or -ester, both in these and other experiments involving

The increased steric constraints imposed by the two methyl groups attached to (**1**) over that of its analogue (**3**) without methyl groups[1] are interestingly shown by comparisons of changes in free energies for the diastereomeric complexes of the ester salts (Table 2). When R of $R\overset{*}{C}H$-

TABLE 2. Effects of methyl groups in hosts on free energy differences between diastereomers of amino-ester hexafluorophosphate salts in $CDCl_3$ at 0 to −15 °C

Run nos. involved	Guest, R of $R\overset{*}{C}H(\overset{+}{N}H_3)CO_2MePF_6^-$	ΔG(Me)[a] − ΔG(H)[b] /cal mol^{-1}
16[c] + 2[d]	Ph	−1300
19[c] + 4[d]	*p*-HOC_6H_4	−1150
20[c] + 6[d]	Me_2CH	−1080
21[c] + 7[d]	$MeS[CH_2]_2$	−700
22[c] + 5[d]	$PhCH_2$	+130

[a] $\Delta G(Me) = \Delta G[(RR)\text{-(D)}] - \Delta G[(RR)\text{-(L)}]$; host is (**1**). [b] $\Delta G(H) = \Delta G[(RR)\text{-(D)}] - \Delta G(RR)\text{-(L)}]$; host is (**3**), identical to (**1**) with H's in place of two Me's. [c] Table 1, this work. [d] Table 1, ref. 1.

$\overset{+}{N}H_3)CO_2Me$ is Ph, *p*-HOC_6H_4, Me_2CH, and $MeS[CH_2]_2$, the stabilities of the diastereomers are moved respectively toward the (*RR*)-(D) configurations by 1300, 1150, 1080, and 700 cal mol^{-1}. Extension of the chiral barrier with a methyl group favours the model predicted on the basis of steric effects alone. When R of $R\overset{*}{C}H(\overset{+}{N}H_3)CO_2Me$ is $PhCH_2$, extension of the chiral barrier stabilizes the (*RR*)-(L) configuration by 130 cal mol^{-1}. Clearly $PhCH_2$ possesses complex-stabilizing capacities not available to the other R groups (see above explanation).

The highest EDC value of Table 1 (and in the literature for synthetic hosts) is 52, which means that if an aqueous solution of a large amount of racemic amino-acid salt is shaken with a $CHCl_3$–CH_3CN solution containing much less (*RR*)-(**1**), the optical purity of the extracted enantiomer would be about 96%. The $\Delta(\Delta G)$ of the diastereomeric complexes is only -2150 cal mol^{-1}, less than the binding energy of a single hydrogen bond. Should chiral hosts be designed to produce $\Delta(\Delta G)$ values of -5000 cal mol^{-1}, EDC values of *ca.* 10,000 would result, and the extracted enantiomer would be *ca.* 99·98% optically pure. Currently the challenge and a few leads exist for designing such a system.

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[1] R. C. Helgeson, J. M. Timko, P. Moreau, S. C. Peacock, J. M. Mayer, and D. J. Cram, *J. Amer. Chem. Soc.*, 1974, **96**, 6762.
[2] G. D. Y. Sogah and D. J. Cram, *J. Amer. Chem. Soc.*, in the press.