Total Optical Resolution of Amino Esters by Designed Host-Guest Relationships in Molecular Complexation[1]

Sir:

Previous papers[2] established that host molecules such as **1** exhibited chiral recognition in complexation of primary alkylammonium salts as guests. Experiments were performed in which the enantiomers of racemic amine salts were distributed between aqueous inorganic salt solutions and chloroform solutions of optically pure hosts. The results provided enantiomer distribution constants, EDC = D_A/D_B, where D_A is the distribution coefficient of the more and D_B of the less complexed enantiomer in the chloroform phase. Values of EDC varied between 1.5 and 18, depending on host-guest complementary structural relationships.[2b] This paper reports a method for the complete optical resolution of racemates of primary amine salts, particularly those of amino esters.

Liquid–liquid chromatography was used with water–$NaPF_6$ or water–$LiPF_6$ solutions supported on Celite (John Manville Purified) or silica gel (Davison No. 56) as the stationary phase. The mobile phase was a chloroform solution of optically pure (*RR*)-**1**.[2] Racemic amine salt was introduced at the top of a jacketed constant temperature column packed with the (wet) stationary phase equilibrated with the mobile phase. The appearance of complexed amine salt in the column eluate was monitored by passing it through a conductivity cell.[3] Figures 1–3 are plots of the relative conductance *vs.* millimeters of eluate for chromatographic resolutions performed on α-phenylethylammonium hexafluorophosphate (**2**), methyl phenylglycinate hexafluorophosphate salt (**3**), and methyl *p*-hydroxyphenylglycinate hexafluorophosphate salt (**4**), respectively. Table I describes the column conditions and parameters[4] derived from the plots. Pure enantiomers were recovered from each peak of Figures 1–3, their rotations were equal in magnitude and opposite in sign, and their configurations were determined by reference to authentic materials.[5] The configurational and steric relationships of the more stable diastereomeric complexes found in the lead chromatographic fractions (A peaks) are formulated.

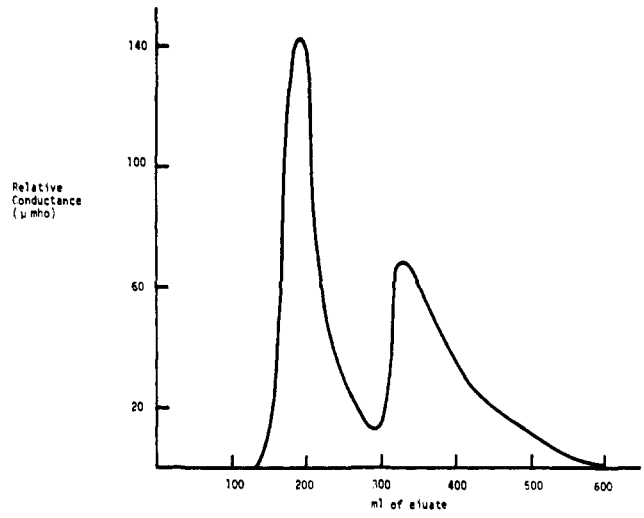

Figure 1. Chromatographic optical resolution by (*RR*)-**1** of α-phenylethylammonium hexafluorophosphate.

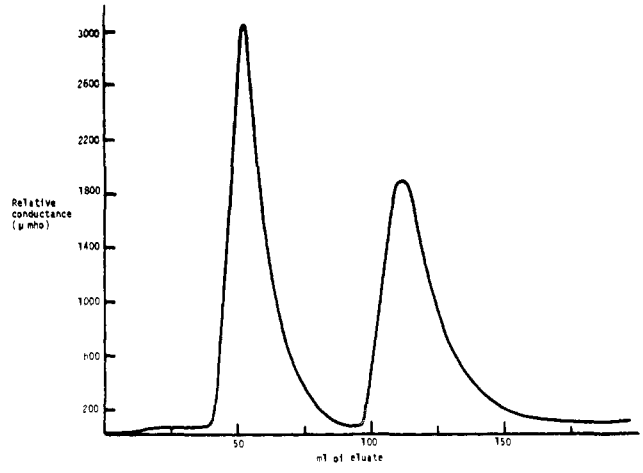

Figure 2. Chromatographic optical resolution by (*RR*)-**1** of methylphenylglycinate hexafluorophosphate salt.

If the columns had the characteristics of liquid–liquid countercurrent extraction, then $\alpha = (D_A/D_B) =$

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(2) (a) E. P. Kyba, K. Koga, L. R. Sousa, M. G. Siegel, and D. J. Cram, *J. Amer. Chem. Soc.*, **95**, 2692 (1973); (b) R. C. Helgeson, J. M. Timko, P. Moreau, S. C. Peacock, J. M. Mayer, and D. J. Cram, *ibid.*, **96**, 6762 (1974).

(3) Two brass plates held apart by a Teflon gasket, 0.1 ml capacity, gave a cell constant of ~0.017 cm^{-1}. The cell was attached to a Philips PR 9501 direct reading conductivity bridge attached to a recorder. The relative conductivity (μmho) of 0.0375 *M* solutions of (*RR*)-**1** in chloroform containing α-phenylethylammonium hexafluorophosphate was found proportional to the salt concentrations over the range 8.25×10^{-3} to 7.72×10^{-4} *M*.

(4) B. L. Karger in "Modern Practice of Liquid Chromatography," J. J. Kirkland, Ed., Wiley, New York, N. Y., 1971, pp 8–14.

(5) Optical fractionation was avoided during isolation. The column eluate from run 1 (Figure 1) from 125 to 245 ml was washed with dilute HCl, and the extracted amine salt was converted to its tosylamide (42% of starting racemate), $[\alpha]^{25}_{546}$ −102°, *c* 1.5, CH_2Cl_2 (here and below). Eluate from 360 to 560 ml similarly yielded tosylamide (30%), $[\alpha]^{25}_{546}$ +101°. Conversion on the same scale of optically pure (−)-(*S*)-α-phenylethylamine (W. Leithe, *Chem. Ber.*, 64, 2827 (1931); W. Theilacker and H. J. Winkler, *ibid.*, 87, 690 (1954)), $[\alpha]^{25}D$ −40.8° (neat, 1 dm), gave (90%) tosylamide, $[\alpha]^{25}_{546}$ −102°. A larger scale preparation of tosylamide which was recrystallized gave mp 99–100°, $[\alpha]^{26}_{546}$ −108° (*c* 0.9, CH_2Cl_2), comparable to values of M. B. Watson and G. W. Youngson, *J. Chem. Soc.*, 2145 (1954). The column eluate from run 3 (Figure 2) was cut at the point of base line separation into fraction A (first 90 ml) and B (90–200 ml). Appropriate extractions gave the amino esters: from A, 40% of starting racemate, $[\alpha]^{25}_{546}$ −180°, *c* 2.4–2.9, CH_2Cl_2 (here and below); from B, 38%, $[\alpha]^{25}_{546}$ +180°. Optically pure (−)-(*R*)-methyl phenylglycinate (M. Goodman and J. M. McGahren, *Tetrahedron*, **23**, 2031 (1967); H. Reihlen and L. Knöpfle, *Ann.*, **523**, 199 (1936)) of $[\alpha]^{26}_{546}$ −185° when subjected on the same scale to the isolation procedure gave 77% recovery, $[\alpha]^{25}_{546}$ −181°. The column eluate from run 4 (Figure 3) was cut from 50 to 116 ml (fraction A) and from 160 to 330 ml (fraction B). The fraction from 116 to 160 ml gave a negative ninhydrin test, whereas those of A and B were strongly positive. Fraction A was washed with 0.1 *N* HCl, the aqueous layer was washed free of host with CH_2Cl_2, the pH of the aqueous layer was adjusted to 9 (Na_2CO_3) and extracted with ethyl acetate. The ester was reextracted into HCl and back into ethyl acetate as before and isolated, 27% of starting racemate $[\alpha]^{25}_{546}$ −153°, *c* 1.2, 1 *N* HCl (here and below). Similarly, fraction B gave 17%, $[\alpha]^{25}_{546}$ +153°. Optically pure (−)-(*R*)-methyl *p*-hydroxyphenylglycinate of $[\alpha]^{25}_{546}$ −171° derived from optically pure (−)-(*R*)-*p*-hydroxyphenylglycine (A. A. W. Long, J. H. C. Nayler, H. Smith, T. Taylor, and N. Ward, *J. Chem. Soc. C*, 1920 (1971)) when subjected on the same scale to the isolation procedure gave 72% recovery, $[\alpha]^{26}_{546}$ −149°.

Table I. Characteristics of Liquid–Liquid Chromatographic Runs with (*RR*)-**1** as Host Compound in Mobile Phase

Run no.	Comp resolved No.	mg	*T*, °C	Separation factor (α)	EDC[a] (D_A/D_B)	Theoretical plates (N)	Resolution R_s	Area A/ Area B[b]	$([H]/[G])_{max}$[c] A	B
1[d]	2	200	0	1.76	1.78	24	0.6	0.94	4.5	8
2[e]	2	25	25	1.52	1.48	19	0.6		65	136
3[f]	3	100	−13	2.48	2.48	18	1.25	1.08	2.1	3.3
4[g]	4	108	−15	3.6	5	18	1.57	0.83	8.6	25
5[h]	4	100	−15	2.4		74	1.28		2.7	4.1

[a] Reference 2. [b] Ratios of integrated areas under peaks with A the faster and B the slower moving enantiomer. [c] Ratios of concentrations of host to guest at the tops of peaks of plots. [d] Column, 57 by 2.5 (i.d.) cm, packed with (by weight) 66% Celite and 5% $NaPF_6$ (0.94 *M*) in 29% H_2O, gravity flow (0.30 ml/min), host 0.0375 *M* in $CHCl_3$. [e] Column, 60 by 0.76 (i.d.) cm, packed with (by weight) 34% silica gel and 9% $NaPF_6$ (0.94 *M*) in 57% H_2O, pressure drop 30 psi (0.15 ml/min), host 0.0375 *M* in $CHCl_3$. [f] Column, 60 by 0.76 (i.d.) cm, packed with (by weight) 40% silica gel and 19% $NaPF_6$ (2.4 *M*) in 41% H_2O, pressure drop 80 psi (0.50 ml/min), host 0.0375 *M* in $CHCl_3$. [g] Column, 60 by 0.76 (i.d.) cm, packed with (by weight) 41% silica gel and 26% $LiPF_6$ (4.0 *M*, pH 4) in 33% H_2O, pressure drop 22 psi (0.52 ml/min), host 0.0750 *M* in $CHCl_3$. [h] Column identical with run 4 except dichloromethane was substituted for chloroform.

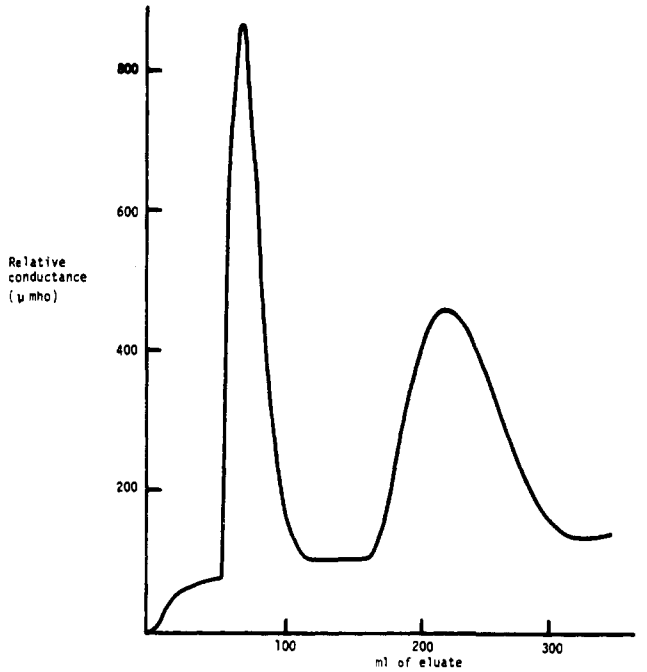
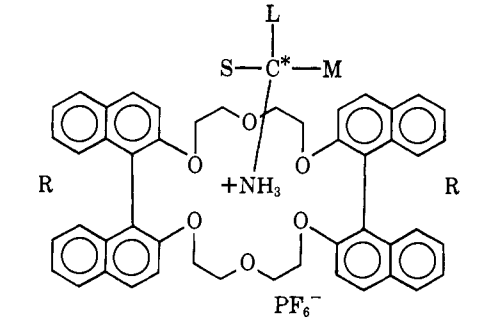


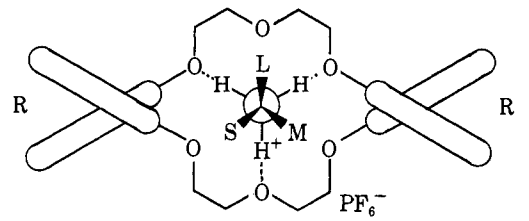
Figure 3. Chromatographic optical resolution by (*RR*)-**1** of methyl *p*-hydroxyphenylglycinate hexafluorophosphate salt.

EDC, as is nearly observed in the four runs (Table I).[4] Thus knowledge of EDC values for a variety of amino esters indicates the viability of their resolution by this technique. The values of (area A)/(area B) which ideally should be unity varied from 0.83 to 1.08, probably due to nonlinearity of the conductance. The values of $([H]/[G])_{max}$ (Table I) provide a measure of the complexing efficiency by the host of the guest. As expected, they are greater for the B component. At full complexing utility of the host, these values should approach unity. They ranged from 2.1 to 136. By choice of solvent and host concentration for the mobile phase (compare runs 4 and 5), and inorganic salt concentration in the stationary phase, the column parameters can be manipulated to best accommodate the hydrophilicity–lipophilicity and binding capacities of the guest compounds.

These results demonstrate that by rational design of host compounds, complete optical resolution by highly



Complexes of (*RR*)-**1** with generalized salts



More stable complexes of (*RR*)-**1**
(*S*)-**2**, L = C_6H_5, M = CH_3, S = H
(*R*)-**3**, L = C_6H_5, M = CO_2CH_3, S = H
(*R*)-**4**, L = *p*-HOC_6H_4, M = CO_2CH_3, S = H

structured complexation of guest compounds can be accomplished.

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Halopolycarbon Homologation

Sir:

The functional homologation of organic structures is usually limited to two or three carbon segments by virtue of the availability and cost of reagents.[1] Recently several examples of functionalized multicarbon homologation have been reported.[2] However, the construc-

(1) Two-carbon homologation: (a) RX + malonic or acetoacetic ester; (b) RX + acetylene; (c) RMgX + ethylene oxide. Three-carbon homologation: (a) RX + $^-C{\equiv}CCH_2O^-$; (b) RMgX + $ClCH_2CH{=}CH_2$.

(2) A. Suzuki, N. Miyaura, M. Itoh, H. C. Brown, G. W. Holland, and E. Negishi, *J. Amer. Chem. Soc.*, **93**, 2792 (1971); E. Negishi and H. C. Brown, *Synthesis*, 196 (1972).