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Lipophilic Tartaric Acid Esters as Enantioselective Ionophores

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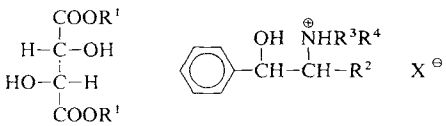
Tartaric acid esters with lipophilic alcohol moieties can discriminate between enantiomeric ammonium ions such as norephedrinium ions. Quantitative results were obtained by partitioning the components between water and 1,2-dichloroethane. The stereoselectivity was characterized by the free energy difference of the partition process ($\Delta\Delta G$). Diamond-lattice sectors were used to construct models of the (unstable) lipophilic ester/ammonium salt complexes from X-ray structures of the individual components (esters and ammonium salts). These models can be used to interpret the effect of structure and configuration of the alcohol moiety on the stereoselectivity and enantioselectivity towards 1-phenyl-2-amino-1-propanol (norephedrine) salts.

1. Introduction

Lipophilic tartaric acid esters (**1**–**29**; cf. Tables 1 and 2) display a remarkable enantioselectivity towards salts of 1-phenyl-2-amino alcohols (β-hydroxyphenethylammonium salts **31**–**35**; cf. Table 3),[1–4] which is interesting for several reasons. These esters are simple enantioselective ionophores whose structure can easily be varied and can often be determined by X-ray analysis. The 1-phenyl-2-amino alcohols include important, medicinally useful alkaloids (including the components of the addictive stimulant Kath, widely used in the Orient), synthetic drugs, and other biologically active



1–**29**

31–**35**

substances whose enantiomers differ greatly in activity.[5] Because of their ready accessibility, some of these lipophilic tartaric acid esters are well suited for analytical and preparative enantiomer separation of the salts of 1-phenyl-2-amino alcohols by iterative methods (chromatography, partitioning, etc.[1, 2, 4, 6]). With the help of tartaric acid esters, these hydrophilic ammonium salts can also be rapidly and enantioselectively transported through lipophilic phases or membranes.[4]

The enantioselectivity of lipophilic tartaric acid esters toward hydrophilic ammonium salts can readily be determined by partitioning the two components between an aqueous phase and a lipophilic phase. This process can be characterized by the ratio of the partition coefficients of the two enantiomers ($Q = k_A/k_{\bar{A}}$), or by the corresponding free energy difference of the partition process ($\Delta\Delta G = RT\ln Q$). The esters and salts appear to form diastereomeric complexes ("supermolecules") in the lipophilic phase, and the observed enantioselectivity may be traced back to differences in the stability of these complexes. These differences are reflected in the free energy difference of the partition process.

Since it was not possible to crystallize these unstable complexes, direct X-ray analysis could not be used to determine the structural basis of the enantioselectivity. The X-ray structures of several crystalline tartrates[7] and of two diastereomeric 1-phenyl-2-amino-1-propanols (norephedrines)[8] were therefore determined, and models of the complexes were constructed based on the structures of their com-

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ponents. This allowed an interpretation of the observed enantioselectivities.

2. Electrochemical Prologue

In 1974, work in our laboratory showed that enantioselective electrodes for chiral ammonium salts could be constructed using membranes composed of 1/3 polyvinyl chloride and 2/3 of a plasticizer containing 2–5% of a chiral ionophore. Since then, many ionophores (e.g., the crown ethers prepared in our laboratory and elsewhere) have been electrochemically tested for enantioselectivity.[9–14]

When lipophilic chiral tartrates were used as plasticizers in an attempt to improve the enantioselectivity of such membranes, we discovered, to our surprise, that remarkable enantioselectivity is observed for certain biologically interesting compounds (e.g., salts of 2-amino alcohols, 1,2-diamines, and certain α-amino acid esters) even in the absence of crown ethers. Since the mechanism of "molecular recognition" was not evident in this case, we investigated it further by preparing a number of tartaric acid esters of readily available alcohols and determining their enantioselectivity towards several α-amino alcohol salts.

3. Determination of Stereoselectivity by Partitioning between Two Phases

Observations of the relatively high enantioselectivity of lipophilic tartaric acid esters towards ammonium salts in electrochemical experiments prompted us to study their stereoselectivity through partition experiments. When an aqueous solution of the hydrophilic, racemic ammonium salt is shaken in the presence of a lipophilic anion (e.g., $PF_6^{\ominus}$) with a solution of the tartaric acid ester in a lipophilic solvent (1,2-dichloroethane), some of the ammonium salt is stereoselectively transferred from the aqueous phase (aq.) into the lipophilic phase (lp). The amount remaining in the aqueous phase, c^{aq}, is measured spectrophotometrically, and the excess of one enantiomer, Δc, is determined by circular dichroism measurements. From these values, the ratio Q of the enantiomeric partition coefficients k_A and $k_{\bar{A}}$ may be calculated. If the volumes of the two phases are equal, then

$$Q = \frac{c^{aq} + \Delta c}{c^{lp} - \Delta c} \cdot \frac{c^{lp} + \Delta c}{c^{aq} - \Delta c}; \quad c^{lp} = c^0 - c^{aq}$$

A second procedure for determining Q values measures the partition coefficients k separately and has been preferred recently. Either the two enantiomeric ammonium salts are partitioned separately, under standard conditions, with an enantiomerically pure tartaric acid ester or an enantiomerically pure ammonium salt is treated with the two enantiomeric esters. In either case, the concentrations in the aqueous phase are measured spectrophotometrically before and after partition. Although this and the previous procedure are two fundamentally different processes, the Q values obtained are the same, to within the limits of experimental error, as those previously determined.

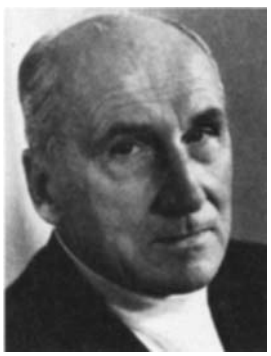
$$Q = \frac{k_A}{k_{\bar{A}}}; \quad k_A = \frac{c_A^{lp}}{c_A^{aq}}; \quad k_{\bar{A}} = \frac{c_{\bar{A}}^{lp}}{c_{\bar{A}}^{aq}}$$

One practical advantage of the second procedure is that one does not require expensive apparatus for measurement of circular dichroism. One can also choose between the two variants of the procedure, according to whether the two enantiomeric esters or the two ammonium salts are more readily available.

The second procedure also has the advantage that one can measure not only the Q values of enantiomers, but also, quite simply, those of diastereomers or even of constitutionally different compounds. Indeed, there is an advantage in calculating Q values by dividing the partition coefficient k of a compound by that (k_s) of a very precisely measured pair, since, in this case, $Q_s = 1$. In the following, di-(1*R*,2*S*,5*R*)-menthyl (2*R*,3*R*)-tartrate **17** and (1*S*,2*R*)-1-phenyl-2-amino-1-propanol (norephedrine) as its ammonium salt **32** are used as such a pair.

$$Q_1 = \frac{k_A}{k_s}; \quad Q_2 = \frac{k_B}{k_s}; \quad Q_s = \frac{Q_1}{Q_2}; \quad Q = \frac{k_A}{k_B}$$

The Q values obtained are dependent on several parameters (tartaric acid ester concentration, initial concentration of the ammonium salt, concentration of other ions present, and temperature).[3] To obtain comparable values, the partition experiments must be carried out under strictly analogous conditions. Since these conditions must be suitable for as broad a range of compounds as possible, they do not necessarily yield the highest Q values.



Vladimir Prelog was born in 1906 in Sarajevo. He completed his doctoral work in 1929 under E. Votocek at the Czechoslovakian Technical University in Prague. After working in industry, he became docent and later professor in Zagreb, then at the ETH in Zürich. He has received numerous awards, culminating in the 1975 Nobel Prize in Chemistry (together with J. W. Cornforth). The C(ahn)-I(ngold)-P(relog) nomenclature for chiral compounds, developed over twenty years ago, is just one of his diverse contributions to scientific knowledge.

4. Results of the Partition Experiments

In the absence of lipophilic tartaric acid esters, the ammonium salts studied are practically insoluble in lipophilic solvents like 1,2-dichloroethane, even when a lipophilic anion like $PF_6^{\ominus}$ is present. One can therefore assume that the enantiomeric salts form diastereomeric complexes with tartaric acid esters in the lipophilic phase, and that the enantioselectivities observed are due to differences in stability of these complexes. In discussing the selectivities, instead of the Q values, the free energies of partitioning, $\Delta\Delta G = RT\ln Q$, are used. These represent the difference in stability of the diastereomeric complexes in the lipophilic phase.

The data obtained by the second procedure are compiled in Tables 1–3, which contain the measured k_A and $k_{\bar{A}}$ values, Q values, $\Delta\Delta G$ values, and $\Delta\Delta S$ values. Representative examples are also presented graphically in Figures 1–3, together with the formulas of the alcohol residues of the tartaric acid ester.

Table 1. Results of partition experiments with 1 M solutions of tartaric acid esters **1** to **22** in $ClCH_2CH_2Cl$ at 4 °C. Aqueous phase: 0.05 M *u*(*erythro*)-norephedrine hydrochloride **32**, 0.5 M $NaPF_6$.

Ester	Alcohol moiety	k_A	$k_{\bar{A}}$	Q	$\Delta\Delta G$ [kcal mol^{-1}]	$\Delta\Delta S$ [cal mol^{-1} K^{-1}]
1	Isopropyl alcohol	5.13	3.98	1.29	0.14	1
2	1-Butanol	6.81	5.05	1.35	0.16	2
3	*tert*-Butyl alcohol	6.77	3.85	1.76	0.31	6
4	(*R*)-2-Methylbutanol	4.97	3.72	1.34	0.16	–
5	(*S*)-2-Methylbutanol	4.53	3.27	1.39	0.18	–
6	1-Octanol	5.08	3.73	1.36	0.17	2
7	(*S*)-2-Octanol	4.57	3.71	1.23	0.12	–
8	(*R*)-2-Octanol	3.17	2.29	1.38	0.18	–
9	5-Nonanol	1.54	0.88	1.75	0.31	7
10	Cyclopentanol	9.81	6.73	1.46	0.21	–
11	Cyclohexanol	9.81	6.25	1.57	0.25	4
12	(1*S*,2*R*,5*S*)-Myrtanol [a]	4.21	2.84	1.48	0.22	–
13	(1*R*,2*S*,5*R*)-Myrtanol [a]	3.79	2.61	1.45	0.21	–
14	(1*R*,2*S*,4*R*)-Borneol [a]	5.29	3.26	1.62	0.27	5
15	(1*S*,2*R*,4*S*)-Borneol [a]	3.99	2.45	1.63	0.27	4
16	(1*S*,2*R*,5*S*)-Menthol [a, b]	1.61	1.11	1.45	0.20	3
17	(1*R*,2*S*,5*R*)-Menthol [a, b]	**1.89**	0.88	2.15	0.42	8
18	Benzyl alcohol	2.31	1.76	1.31	0.15	–
19	(1*S*,2*R*,4*R*)-Fenchol	2.21	1.63	1.36	0.17	–
20	3,3,5,5,-Tetramethylcyclohexanol	2.61	1.69	1.54	0.24	–
21	(1*R*,2*S*,5*S*)-Isomenthol [b]	1.64	1.05	1.56	0.25	–
22	(1*R*,2*R*,5*S*)-Neomenthol [b]	1.01	0.69	1.46	0.21	–

[a] Configuration established by X-ray structure analysis. [b] The locants 1,2, and S correspond to locants 3,4, and 1, respectively, in the conventional numbering system.

Table 2. Results of partition experiments with 0.25 M solutions of tartaric acid esters **16**, **17**, **23**, to **25** in $ClCH_2CH_2Cl$ at 4 °C. Aqueous phase: 0.05 M *u*(*erythro*)-norephedrine hydrochloride **32**, 0.5 M $NaPF_6$.

Ester	Alcohol moiety	k_A	$k_{\bar{A}}$	Q	$\Delta\Delta G$ [kcal mol^{-1}]	$\Delta\Delta S$ [cal mol^{-1} K^{-1}]
16	(1*S*,2*R*,5*S*)-Menthol [a, b]	0.08	0.06	1.33	0.16	–
17	(1*R*,2*S*,5*R*)-Menthol [a, b]	**0.14**	0.09	1.56	0.24	
23	1-Nonanol	0.26	0.20	1.30	0.14	–
24	(1*S*,2*R*,5*R*)-Isomenthol [b]	0.14	0.12	1.17	0.08	–
25	4-*cis*-*tert*-Butylcyclohexanol [a]	0.12	0.11	1.09	0.05	–
26	(1*R*,2*S*,4*S*)-Fenchol	0.12	0.08	1.50	0.22	–
27	(1*S*,2*S*,5*R*)-Neomenthol [a, b]	0.11	0.05	2.20	0.43	> 10
28	(1*R*,2*S*,5*R*)-Phenylmenthol [c]	0.10	0.08	1.25	0.12	–
29	(1*S*,2*R*,5*S*)-Phenylmenthol [c]	0.42	0.30	1.40	0.19	–

[a, b] See Table 1. 8-Phenylmenthol (conventional numbering).

Table 3. Results of partition experiments with 1 M solutions of tartaric esters **16** and **17** in $ClCH_2CH_2Cl$ at 4 °C. Aqueous phase: 0.05 M chlorides of ammonium salts **30**–**36**, 0.5 M $NaPF_6$.

Salt	Amine	Ester	k_A	$k_{\bar{A}}$	Q	$\Delta\Delta G$ [kcal mol^{-1}]
30	1-Phenylethylamine	**17**	2.06	2.05	1.00	0.00
31	1-Phenyl-2-aminoethanol	**16**	1.28	1.07	1.20	0.10
31	1-Phenyl-2-aminoethanol	**17**	2.16	1.09	1.98	0.38
32	*u*(*erythro*)-Norephedrine [a]	**16**	1.61	1.11	1.45	0.20
32	*u*(*erythro*)-Norephedrine [a]	**17**	1.89	0.88	2.15	0.42
33	*l*(*threo*)-Norephedrine [a]	**16**	1.11	0.91	1.22	0.11
33	*l*(*threo*)-Norephedrine [a]	**17**	2.08	1.35	1.54	0.24
34	*u*(*erythro*)-Ephedrine	**17**	4.39	2.44	1.80	0.32
35	*u*(*erythro*)-*N*-Methylephedrine	**17**	7.39	4.74	1.56	0.24
36	*l*-(*threo*)-1,2-Diamino-1,2-dihydrostilbene	**17**	1.36	0.71	1.92	0.36

[a] See Table 1.

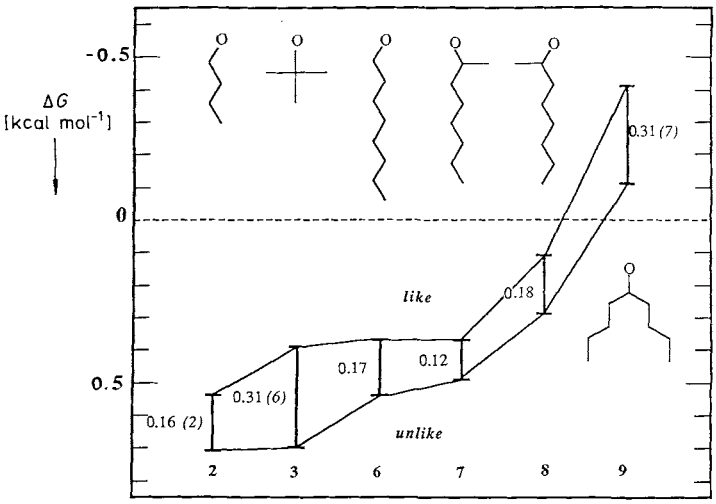


Fig. 1. $\Delta\Delta G$ values [kcal mol^{-1}] and (in parentheses) $\Delta\Delta S$ values [cal mol^{-1} K^{-1}] of representative tartaric acid esters of aliphatic alcohols (1 M solutions), relative to the pair **17** and (1*S*,2*R*)-**32** ($\Delta G = 0$). The alcohol moiety of the tartaric acid ester is shown.

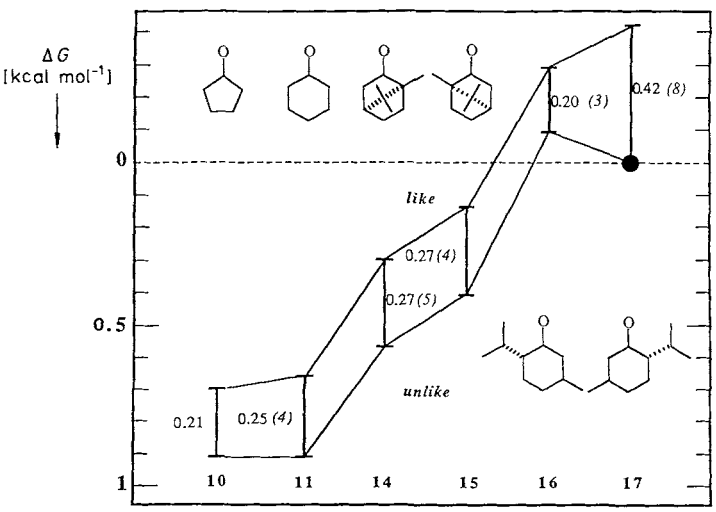


Fig. 2. $\Delta\Delta G$ values [kcal mol^{-1}] and (in parentheses) $\Delta\Delta S$ values [cal mol^{-1} K^{-1}] of representative tartaric acid esters of alicyclic alcohols (1 M solutions), relative to the pair **17** and (1*S*,2*R*)-**32** ($\Delta G = 0$). The alcohol moiety of the tartaric acid ester is shown.

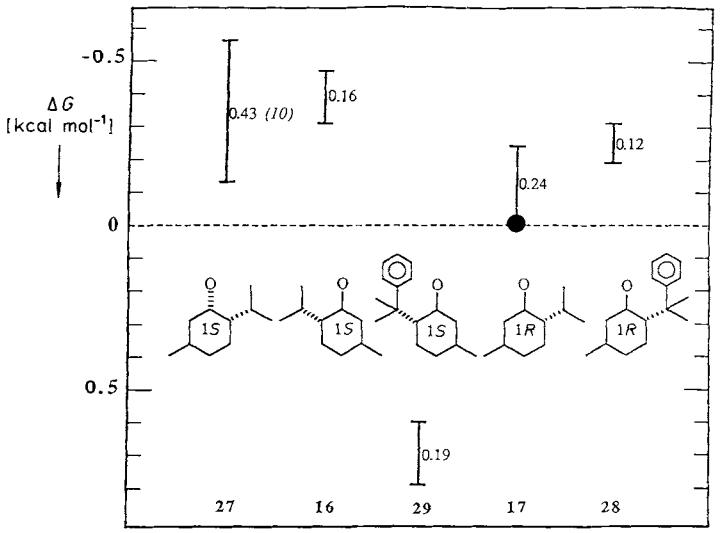


Fig. 3. $\Delta\Delta G$ values [kcal mol^{-1}] and (in parentheses) $\Delta\Delta S$ values [cal mol^{-1} K^{-1}] of less soluble tartaric acid esters (0.25 M solutions), relative to the pair **17** and (1*S*,2*R*)-**32** ($\Delta G = 0$). The alcohol moiety of the tartaric acid ester is shown.

5. Discussion of the Results

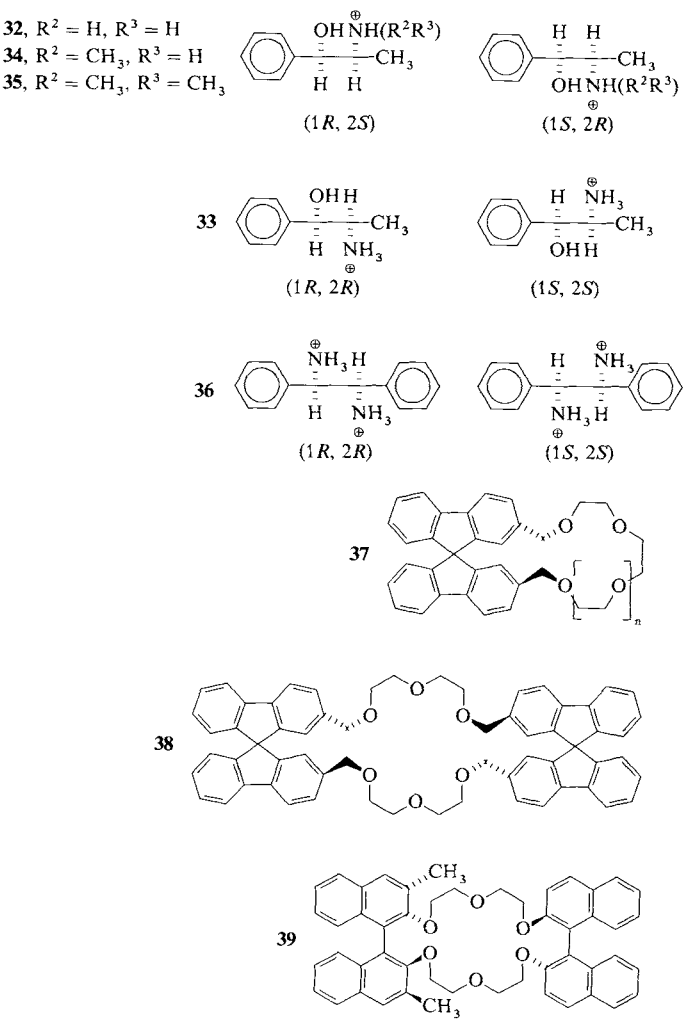
As the comparison of $\Delta\Delta G$ values (Table 4) shows, the enantioselectivity of the readily available tartaric acid ester **17** towards the salts of 1-phenyl-2-amino alcohols is quite comparable with those of the best chiral crown ethers we have studied.

Table 4. Comparison of $\Delta\Delta G$ values [kcal mol^{-1}] for 1 M di-(1*R*,2*S*,5*R*)-menthyl (2*R*,3*R*)-tartrate **17**, 9,9'-spirobifluorene-[22]crown-5 **37** (n = 2) [15], bis(9,9'-spirobifluorene)-[32]crown-6 **38** [15], and 3,3'-dimethyl-bis(1,1'-binaphthyl)-[22]crown-6 **39** [16] in partitioning experiments (cf. Tables 1–3).

Salt	Amino alcohol	**17**	**37**	**38**	**39**
31	1-Phenyl-2-aminoethanol	0.38	0.14	0.10	0.00
32	*u*(*erythro*)-Norephedrine	0.42	0.41	0.35	0.57

From the large amount of data in Tables 1–3 and in Figures 1–3, the following general conclusions may be drawn:

1. The 29 (2*R*,3*R*)-(+)-tartaric acid esters studied all form more stable complexes with (1*S*)-1-phenyl-2-amino alcohol salts than with their (1*R*) enantiomers, and vice versa.
2. The salts with *u*(*unlike*) = *erythro* configuration form somewhat more stable complexes than their *l*(*like*) = *threo* diastereomers. This agrees with the earlier finding that the 2-phenyl-2-amino alcohol salts isomeric with the 1-phenyl-2-amino alcohol salts show only small Q values.[3] Evidently, the larger hydrocarbon residue at C-1 is critical for the enantioselectivity; the configuration at C-2 plays a lesser role.
3. Esters of secondary alcohols with fewer than eight C atoms differ little in their enantioselectivities. Their selectivity appears to be due mainly to binding interactions between the ammonium salt and the tartaric acid moiety of the ester.
4. The increased selectivity shown by esters of higher alcohols is associated with the lower stability of their complexes, and probably derives from the various destabilizing interactions between the alcohol moiety of the ester and the enantiomeric ammonium salts. Attempts to increase enantioselectivity by varying the alcohol component are limited by the poor solubility of some esters of higher alcohols. In Table 2, the data for 0.25 M solutions of the less soluble esters **23**–**29** are presented. As the values for esters **16** and **17** show, the enantioselectivity of dilute solutions is significantly less than that of 1 M solutions. In Table 2, the high enantioselectivity of di-(1*S*,2*S*,5*R*)-neomenthyl (2*R*,3*R*)-tartrate **27** is worthy of note, as is the lack of influence of the phenyl groups on the enantioselectivity of the diastereomeric 8-phenylmenthyl esters **28** and **29**, as well as their very different influence on the stability of the complexes.
5. In Table 3 the results of partitioning experiments with several chiral ammonium salts are presented in order to demonstrate the effect of their structures on the enantioselectivity of tartrate esters **16** and **17**. With the 1-phenyl-1-aminoethane salt **30** one finds no enantioselectivity, whereas the salts **31**, **32**, and **33**, involving primary alcohols, and the diamine salt **36** are most strongly discriminated. *N*-Methylation of **31** to give **34** reduces the enantioselectivity, though the enantiomers of tertiary ammonium salt **35** are still discriminated, requiring merely one hydrogen at oxygen and one at nitrogen.



6. Earlier findings have shown that di-5-nonyl (2*R*,3*R*)-2,3-dimethoxysuccinate also discriminates between the *u*-norephedrine salts ($Q = 1.27$).[11] The two hydrogens of the hydroxyl groups of the tartrates are therefore not necessary for enantioselectivity.

Any attempt to interpret the enantioselectivity of tartaric acid esters on a structural basis must take all these facts into account.

6. The Structural Basis for the Stereoselectivity of Tartaric Acid Esters

To date, all attempts to prepare crystalline complexes of amino alcohol salts with tartaric acid esters in order to determine their structures by X-ray crystallography have been unsuccessful. To gain some clue to the structure of these complexes, X-ray structural analyses were therefore carried out on their components, the hydrochlorides of (1*R*,2*S*)- and (1*R*,2*R*)-norephedrines **32** and **33**, respectively, and the crystalline esters **12**–**17**, **25**, and **27**. On the basis of these structures, models of the complexes have been constructed which permit interpretation of the observed selectivities.

6.1. The Structures of Norephedrine (1-Phenyl-2-amino-propanol) Salts[*]

X-ray structural analysis of the hydrochlorides of (1*R*,2*S*)- and (1*R*,2*R*)- norephedrines **32** and **33**, respectively, established that in both the diastereomers with (1*R*) configuration the oxygen and the nitrogen are present in a 1,2 *M* conformation, from which the *P* conformation follows for their enantiomers. As an example of the structures determined by X-ray crystallography, Figures 4 and 5 (see Section 6.2) show the structures of the (1*R*,2*S*)-norephedrinium ion and of its (1*S*,2*R*) enantiomer. Details of the norephedrine hydrochloride X-ray structures may be found in Ref. [7].

6.2. The Structures of the Tartaric Acid Esters

X-ray structural analyses were performed on a total of eleven crystalline tartaric acid esters. For a discussion of stereoselectivity the following findings are important. The two hydroxyl oxygens were found in the 2,3 *M* conformation in all the (2*R*,3*R*)-(+)-tartrates examined. In ten cases (and for **16**) the two hydroxyl and two carbonyl oxygens formed a nearly planar rectangle, with the oxygen atoms in close proximity to each other. The two alcohol moieties are situated on one face of this rectangle. A remarkable exception is the highly enantioselective di-(1*R*,2*S*,5*R*)-menthyl ester **17**, where the two hydroxyl oxygens, one carbonyl oxygen, and an ether oxygen form an almost planar rectangle (not drawn in Fig. 5). Here, the two alcohol moieties lie on opposite faces of the rectangular plane.

In Figures 4 and 5 (left), the X-ray structures of the diastereomeric dimenthyl tartrates **16** and **17** are presented as examples, so that the typical characteristics discussed can be easily recognized. Details of the X-ray crystal structures of other tartaric acid esters can be found in Ref. [8]. For further discussion it is particularly important that in all the tartaric acid esters studied the three oxygen atoms situated close to each other and forming a chiral triangle represent a potential enantioselective binding site for salts of 1-phenyl-2-amino alcohols (shown on the right in Fig. 5).

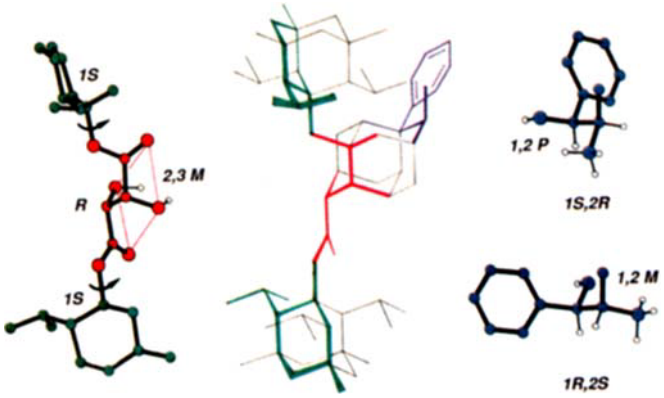


Fig. 4. X-ray structures. Left: Di-(1*S*,2*R*,5*S*)-menthyl (2*R*,3*R*)-tartrate **16**. Right: Enantiomeric *u*(*erythro*)-norephedrinium ions (cf. **32**). Center: Diamond-lattice-sector model of the (2,3 *M*)-(1,2 *P*) complex (for rectangle see text).

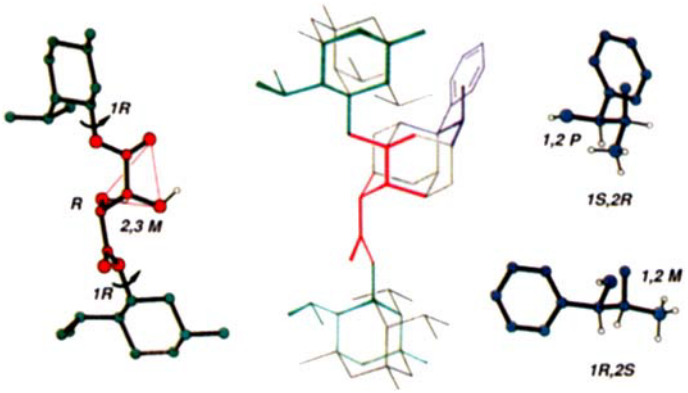


Fig. 5. X-ray structures. Left: Di-(1*R*,2*S*,5*R*)-menthyl (2*R*,3*R*)-tartrate **17**. Right: Enantiomeric *u*(*erythro*)-norephedrinium ions (cf. **32**). Center: Diamond-lattice-sector model of the (2,3 *M*)-(1,2 *P*) complex (for triangle see text).

6.3. Diamond-Lattice Sector Models of the Complexes

In order to construct models of the complexes based on the structures of their components, the following reasonable assumptions must be made.

For a similar type of enantioselectivity to be achieved, one can assume that the components of the complex are bound at three analogous sites (Ogston principle[17]).

It has already been mentioned that the oxygen-atom triangle found by X-ray crystallography in all tartaric acid esters represents such a binding site. The carbonyl oxygen atom forms the negative end of a dipole, and the hydroxyl oxygens can function as hydrogen-bonding partners. The corresponding binding sites on the ammonium salt would be one hydrogen atom on the hydroxyl, at least one on the ammonium group, and the positive charge on the latter. Numerous models may be constructed on the basis of these assump-

[*] For simplicity, only the short trivial name norephedrine will be used from now on.

tions, differing considerably in their conformation and stability. If stereoelectronic effects are also taken into account, other things being equal, the most stable structures will be those displaying the largest number of tetrahedral atoms in staggered conformation. Such structures or structural fragments with staggered conformation can be visualized and depicted in an idealized fashion as sectors of the diamond lattice. In our case, one takes the structures of the components determined by X-ray analysis and attempts to build a diamond-lattice-sector model using the above-mentioned, plausible binding sites. These complex models are more stable when the characteristic conformations of their components show opposite helicities ("unlike", *M,P* or *P,M*) than when they are built of components with the same helicity ("like", *M,M* or *P,P*). (2*R*,3*R*)-Tartaric acid esters (2,3 *M*) therefore give stabler complex models with (1*S*)-amino alcohol salts (1,2 *P*) than with their (1*R*) enantiomers.

As examples, the diamond-lattice-sector models depicted in the center of Figures 4 and 5 are made up of the X-ray structures of the components with 2,3 *M* and 1,2 *P* conformations shown to left and right. The structure of the (1*R*,2*S*)-norephedrinium ion (1,2 *M*), also depicted on the right, gives less stable complex models with the same (2*R*,3*R*)-tartaric acid esters. This explains the observed preference of these esters for the (1*S*)-enantiomers.

From the X-ray structures of dimenthyl esters **16** and **17** it is not at first evident how the alcohol residues of the esters, and particularly their different configurations, can have a significant effect on the enantioselectivity, since in the crystal these residues are some distance from the amino alcohol binding site. In solutions of the ester, however, they can rotate around the C–O bond. The space taken up by the three rotamers of the alcohol residue is therefore shown in the model of the complex by the corresponding diamond-lattice sectors. With enantiomeric alcohol residues this space is chiral and penetrates into the chiral space occupied by the amino alcohol salt in the complex, thereby limiting its mobility. This explains the lower stability and occasionally increased enantioselectivity of esters of higher alcohols. The influence of size and structure of the ester alcohol residue on the entropy of the enantioselectivity ($\Delta\Delta S$ in Tables 1 and 2) also indicates that varying amounts of freedom of rotation are lost on formation of diastereomeric complexes. The entropy differences vary from 1 cal mol^{-1} K^{-1} for diisopropyl ester **1** to 10 cal mol^{-1} K^{-1} for dineomenthyl ester **27**.

7. Further Prospects

The few examples discussed here demonstrate that models of smaller molecules constructed on the diamond lattice permit one to estimate the stabilities of certain larger structures to a first approximation. Models of this sort can serve as initial structures for more complex calculations or as the basis for design of stereoselective molecules.

It should be noted that diamond-lattice sectors can be used in various areas of stereochemistry for the ordering of hypothetical structures or groups of structures. As early as 1941, before the introduction of conformational analysis, *Speakman* used diamond-lattice sectors in a discussion of the probable conformers of perhydrodiphenic acids and the influence of conformation on their dissociation constants, and expressly referred to this possibility.[18] In our laboratory, we have used the diamond lattice to interpret the transannular reaction course in cyclodecane derivatives[19] and to characterize the stereoselectivity of oxido-reductases.[20–23]

A well-known chemist close to us (*A. E.*) has described the diamond lattice as the "poor man's computer".

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