

Mass spectral and semi-empirical studies on chiral discrimination in gaseous aggregation products of protonated dialkyl tartrates

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ABSTRACT

The enantiomers (*M*) of isopropyl *threo*- and *erythro*-3-cyclohexylglycerates (**4** and **5**), 2,3-butanediol (**6**), *trans*-1,2-cyclohexanediol (**7**) and 1,4-dimethoxy-2,3-butanediol (**8**) were studied in the gas phase by chemical ionization mass spectrometry with enantiomer-labelled diisopropyl tartrates (**1c**) as chiral additive. The protonated mixed dimers $M \cdot 1c \cdot H^+$ of **4** and **8**, but not those of **5–7**, showed small but distinct chiral discriminations. The smaller number of H-bond acceptors sites in **4–8** compared with **1c** reduces or cancels the chirality effect. For the dimethyl tartrates, semi-empirical calculations predicted homochiral and heterochiral dimer structures $RR \cdot H^+$ and $RS \cdot H^+$ with four and three intermolecular H bonds, respectively. The stability increase of -0.22 kcal/mol for $RR \cdot H^+$ agrees with the chirality effect $K_{RR}/K_{RS} \approx 1.5$. Protonated trimers of **1c** showed a chiral effect $K_{RRS}/K_{RRR} \approx 1.6$ in favour of the heterochiral $RRS \cdot H^+$ and $RSS \cdot H^+$ ions compared with $RRR \cdot H^+$ and $SSS \cdot H^+$. Association of a methanol, ethanol or diol molecule (*X*) in heterogenous trimers $X \cdot 1c \cdot 1c \cdot H^+$ affected the initial chiral discrimination which occurs in the unsolvated $1c \cdot 1c \cdot H^+$ dimers.

INTRODUCTION

The first observation of a chiral discrimination of organic ions in the gas phase was reported by Fales and Wright [1] in 1977. They studied protonated dialkyl tartrates (**1**) by mass spectrometry (MS) under conditions of chemical ionization (CI) [2]. This method can be generally applied to stereochemical analysis [3]. The isobutane CI mass spectrum of a 1:1 mixture of dimethyl (*2R,3R*)-tartrate and [2H_6]dimethyl (*2S,3S*)-tartrate (d_0 -*R-1a* and d_6 -*S-1a*, or *R* and *S*) showed nearly equal abundances of the protonated species, $R \cdot H^+$ and $S \cdot H^+$, for the unlabelled and labelled molecules [1]. However, the formation of protonated dimers, $RR \cdot H^+$,

$RS \cdot H^+$ and $SS \cdot H^+$, did not show the expected 1:2:1 abundance pattern. The dimers of the same configuration (homochiral), $RR \cdot H^+$ and $SS \cdot H^+$, were relatively more stable. The dimers of a different configuration (heterochiral), $RS \cdot H^+$, showed only 78% of the calculated abundance. The chirality effect for the more bulky diisopropyl tartrates (**1c**) was enhanced to give only 46% of $RS \cdot H^+$ dimers [1].

In a more extensive study, a quantitative approach for a direct chirality assignment of an "unknown" chiral substrate applying CI mass spectrometry was demonstrated for the dialkyl tartrates in 1985 [4,5]. Meanwhile, tartrate species were probed by CI [1,4–7], fast atom bombardment (FAB) [8,9], metastable ion [8,9] and ion cyclotron resonance (ICR) [10] mass spectrometric techniques. Several other ap-

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proaches to chiral discrimination in mass spectra of organic compounds have been reported [3,11]. Generally, a chelate-type aggregation has been assumed for protonated clusters of polyfunctional species in the gas phase [4,5,12–14]. H-bond geometries of related polyhydroxy compounds have been determined in the crystal state [15]. Applications of chiral discriminations by tartrate moieties in the condensed state include chromatographic phases [16,17], ionophores [18], electrophoresis buffers [19] and crystalline clathrates [20].

In this paper, chiral CI mass spectrometric studies of tartrate related compounds are extended to isopropyl *threo*- and *erythro*-3-cyclohexylglycerates (**4** and **5**), *threo*-2,3-butanediol (**6**), *trans*-1,2-cyclohexanediol (**7**) and *threo*-1,4-dimethoxy-2,3-butanediol (**8**). Structures of protonated dimethyl tartrate dimers ($RR \cdot H^+$ and $RS \cdot H^+$ of **1a**) are calculated by semi-empirical methods. Specific aggregations of protonated trimers and tetramers of tartrate species are probed.

EXPERIMENTAL

Compounds **1** and **6** were available from earlier work [4–7] and **7** and **8** were obtained from Fluka (Buchs, Switzerland). The enantiomer-labelled isopropyl and [2H_7]isopropyl *threo*- and *erythro*-3-cyclohexylglycerates[(*2R*)- d_0 - and (*2S*)- d_7 -**4**, (*2R*)- d_0 - and (*2S*)- d_7 -**5**] were synthesized by mixed Kolbe electrolysis [21] of *O,O'*-diacetyl (*2R,3R*)- and (*2S,3S*)-tartaric acid monomethyl ester, respectively, and cyclohexanecarboxylic acid. Details will be reported elsewhere [22].

Chiral CI mass spectrometry was performed with a Varian MAT 112 instrument with an electron impact (EI)-CI source. Under a 0.15-mbar isobutane flow, the enantiomer-labelled racemic mixtures (**1c** and **4**) without or with analytes (**4** and **8**) were evaporated from a temperature-controlled direct probe (90–100°C). Low ion-source temperatures of 50–140°C were necessary to obtain sufficient abundances of protonated dimers and clusters. Sample introduction by gas chromatography (**4–8**) was done

with a 20 m \times 0.3 mm I.D. directly coupled DB-1 capillary column (80–200°C) with 2.5 or 5 s per scan and 20 scans per peak. The fast atom bombardment (FAB) mass spectra of the alkylated (alkali metal ion attached) dimers were obtained with an MAT CH5-DF instrument. An Ion Tech FAB source with xenon atoms of 8 kV energy was used; LiCl or KCl was added to the sample without a matrix or in a thioglycerol matrix. All spectra were scanned 10–20 times and averaged values for the chirality effects were determined. The spectra in Figs. 1–3 are single-scan raw data (50°C).

The semi-empirical calculations on the dimers $RR \cdot H^+$ and $RS \cdot H^+$ of **1a** were done with the neglect of diatomic differential overlap (NDDO) method [23–25] in the program HyperChem. The Parametric Method 3 (PM3) and Austin Model 1 (AM1) parameters were chosen for the neutral and protonated species, respectively, as suggested from proton affinity studies of diols by this approach [22].

RESULTS AND DISCUSSION

Internal chirality effects in protonated dimers and trimers

Table I summarizes the observed chiral discriminations of protonated self-dimers in the CI mass spectra of dialkyl tartrates and related compounds from previous [1,4–8] and the present experiments which were done with enantiomer-labelled racemic mixtures. The chiral discrimination of the self-dimers is described by the *internal chirality effect* (or the chiroselective ratio of the virtual equilibrium constants), as defined by $K_{RR}/K_{RS} = K_{SS}/K_{RS} = 2([RR \cdot H^+][SS \cdot H^+])^{1/2}/[RS \cdot H^+]$ for a 1:2:1 statistics of diastereomeric dimers, $RR \cdot H^+$, $RS \cdot H^+$ and $SS \cdot H^+$ [1,4,5]. Arbitrarily, the stability of the homochiral dimers, $RR \cdot H^+$ and $SS \cdot H^+$, versus the stability of the heterochiral dimers, $RS \cdot H^+$, is stated and not its reciprocal.

The homochiral dimers $RR \cdot H^+$ and $SS \cdot H^+$ are more stable than the heterochiral dimers $RS \cdot H^+$ for all examples in Table I [1,4–8]. The chirality effects K_{RR}/K_{RS} for the dimers of the dialkyl tartrates **1a–c** show increasing values in the range 1.3–2.3 for increasing size of the alkyl

TABLE I

INTERNAL CHIRALITY EFFECT K_{RR}/K_{RS} OF PROTONATED SELF-DIMERS IN THE CI MASS SPECTRA OF TARTRATE-TYPE SYSTEMS

No.	Compound	A ^a	COOR ^a	K_{RR}/K_{RS}	Ref.
1a	Dimethyl tartrate	COOMe	COOMe	1.3–1.5	1,6,8
1b	Diethyl tartrate	COOEt	COOEt	1.5–1.8	6,8
1c	Diisopropyl tartrate	COOiPr	COOiPr	1.5–2.3	1,4–8
1d	Tartaric acid dipyrrolidide	CONC ₄ H ₈	CONC ₄ H ₈	1.11	6
2	Isopropyl glycerate	H	COOiPr	1.005	6
3	Isopropyl <i>threo</i> -3-methylglycerate	Me	COOiPr	1.08	6
4	Isopropyl <i>threo</i> -3-cyclohexylglycerate	cHx	COOiPr	1.02 ± 0.02	
5	Isopropyl <i>erythro</i> -3-cyclohexylglycerate	–	–	0.97 ± 0.02	
6	<i>threo</i> -2,3-Butanediol	Me	Me	1.0	5

^a A and COOR are structural subunits as shown in Fig. 1. cHx = Cyclohexyl.

group. An inverse temperature dependence affects K_{RR}/K_{RS} for the homologues at 50–150°C [4–7]. The more complex tartaric acid dipyrrolidide (**1d**) reduces the chiroselectivity to $K_{RR}/K_{RS} = 1.1$ compared with the diesters. The replacement of one of the ester functions in **1** by an H, Me or cyclohexyl group in **2–4** results in negligible or absent chirality effects. This applies also for the enantiomers of the *erythro*-ester **5**. In addition, the chiral discriminations in the deprotonated diastereomeric (**1c**·**1c**·H)[–] species and in the MMH⁺ dimers of *threo*-2,3-butanediol {with [1,4-²H₂](*S*)-2,3-butanediol} are completely cancelled [4,5].

The Dreiding molecular models suggested in Fig. 1 show structures with protonation on a carbonyl oxygen. Optimum proton solvation can be achieved by five H-bonds which interlock to a framework with H-bridge angles of *ca.* 132° and

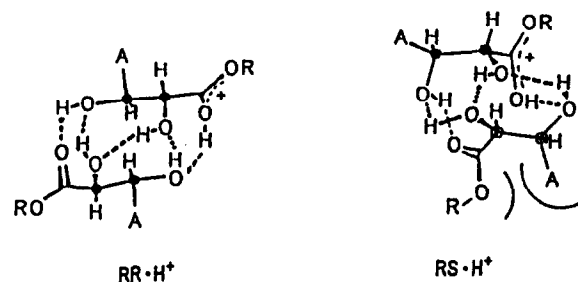


Fig. 1. Dreiding models of homochiral and heterochiral dimers $RR \cdot H^+$ and $RS \cdot H^+$ of tartrate-type species. ● = R and ○ = S configurations at C-2 and C-3.

$H \cdots O$ lengths of *ca.* 200 pm. These H-bond structures could explain the decreased stability of the heterochiral dimer by an RO/A repulsion, compared with the homochiral dimer. However, this explanation only agrees with some and not all of the above results. The results on **2–4** indicate that the second ester group A, which is not essential for the Dreiding models, cannot be omitted and cannot be replaced with a cyclohexyl group of comparable size. The importance of the H-bond acceptor site A for the chirality effect will be discussed in more detail below.

There was another interesting and new observation in the isobutane CI mass spectrum of the enantiomer-labelled racemic mixture of diisopropyl (*S*)-tartrate [(*S*)-**1c**-d₀ or *S*] and [²H₁₄]diisopropyl (*R*)-tartrate [(*R*)-**1c**-d₁₄ or *R*] as shown in Fig. 2a. At an ion source temperature of 50°C, the high-mass region of the spectrum contains protonated trimeric cluster species. The major peaks of the trimers are close to 4% relative abundance. The four diastereomeric protonated trimers, $SSS \cdot H^+$, $SSR \cdot H^+$, $SRR \cdot H^+$ and $RRR \cdot H^+$, should have a 1:3:3:1 abundance pattern in terms of statistics. Obviously, there is a chiral discrimination which favours the major peaks of the heterochiral trimers $SSR \cdot H^+$ and $SRR \cdot H^+$ and/or which disfavors the minor peaks of the homochiral trimers $SSS \cdot H^+$ and $RRR \cdot H^+$.

The internal chirality effect for the trimers is here arbitrarily stated as the relative stability of

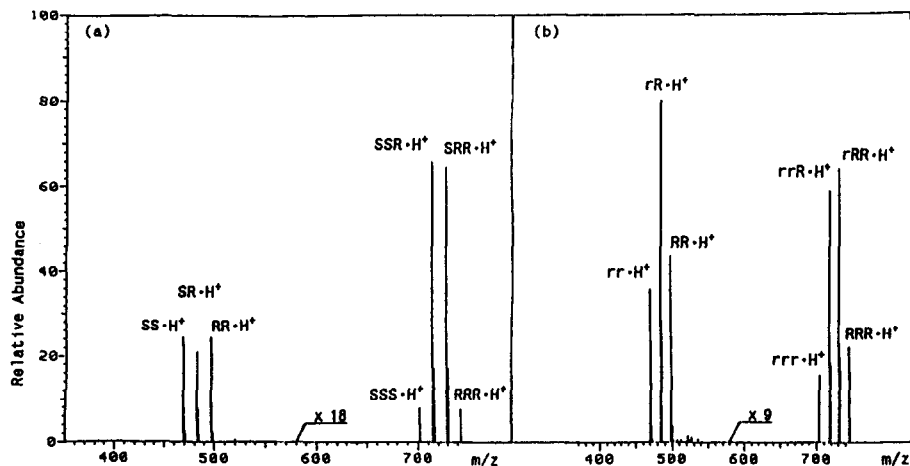


Fig. 2. (a) Partial isobutane CI mass spectrum of a racemic mixture of diisopropyl (*S*)-tartrate (*S*) and [²H₁₄]diisopropyl (*R*)-tartrate (*R*). (b) Partial isobutane CI mass spectrum of a monochiral mixture of diisopropyl (*R*)-tartrate (*r*) and [²H₁₄]diisopropyl (*R*)-tartrate (*R*).

the heterochiral *versus* the homochiral clusters and is then defined by $K_{RRS}/K_{RRR} = ([RRS \cdot H^+][RSS \cdot H^+])^{1/2} / 3([RRR \cdot H^+][SSS \cdot H^+])^{1/2}$. The observed value for K_{RRS}/K_{RRR} was 1.84 ± 0.07 . Hence the heterochiral trimers are more stable than the homochiral trimers. This means that the chirality effect for the protonated trimers of the dialkyl tartrates goes in the opposite direction to that observed for the protonated dimers. An explanation for this behaviour is very difficult.

For a more critical quantitative treatment of the trimers, a reference spectrum (Fig. 2b) of an enantiopure or monochiral mixture of unlabelled (*R*)-**1c-d**₀ and labelled (*R*)-**1c-d**₁₄ was measured. The observed value of the general discrimination effect for the two constituents was $K_{RRr}/K_{RRR} = 1.14 \pm 0.06$. Its minor deviation from 1.0 may be due to an instrumental error which disfavours peaks of very low absolute intensity. In any case, this experiment limits the upper size of the isotope effect for the trimers due to the deuterium labelling. The above value of the trimer chirality effect has to be adjusted accordingly to give $K_{RRS}/K_{RRR}(\text{corr.}) = 1.84/1.14 = 1.61 \pm 0.13$. This slightly lower value is still a substantial chiral discrimination which is comparable to the absolute value of the dimer chirality effect. For the dimers in the spectra in Fig. 1, the values of $K_{RR}/K_{RS} = 2.76 \pm 0.10$ and $K_{RR}/K_{Rr} = 0.99 \pm 0.01$ which exclude any interfering isotope

effect agree with those of previous studies [1,4,5].

Substrate/reagent chirality effects in protonated mixed dimers

In Table II are shown reported [4–8] and new data for the chiral recognition of an “unknown” enantiomer (*R*)-*M* or (*S*)-*M* of a substrate which is exposed to isobutane CI mass spectrometry under chiral additive conditions. In these measurements, an enantiomer-labelled racemic mixture of (*S*)-**1c-d**₀ and (*R*)-**1c-d**₁₄ is co-introduced into the ion source, and provides the chiral selector species *R*·*H*⁺ and *S*·*H*⁺. Within the group of dialkyl tartrate analytes **1a** and **b** [4–8], the absolute configuration of a homologue *M* is indicated by the more abundant homochiral species among the competitive mixed dimers, *M*·*R*·*H*⁺ and *M*·*S*·*H*⁺, which are observed in the spectrum.

The corresponding *substrate/reagent chirality effect* or *analyte/selector chirality effect* is defined by $K_{MR}/K_{MS} = ([M \cdot R \cdot H^+]/[M \cdot S \cdot H^+]) / ([R \cdot H^+]/[S \cdot H^+])$ or the reciprocal term K_{MS}/K_{MR} . The values in Table I are listed as K_{MR}/K_{MS} and K_{MS}/K_{MR} for the (*R*)-*M* and (*S*)-*M* enantiomers, respectively. This presentation gives values >1.0 within the group of the *threo*-diol compounds and thus emphasizes the com-

TABLE II

SUBSTATE/REAGENT CHIRALITY EFFECTS OF PROTONATED MIXED DIMERS IN THE CHIRAL-ADDITIVE CI MASS SPECTRA OF TARTRATE-TYPE SYSTEMS

Chiral additive: *R* and *S* [(*R*)-1c and (*S*)-1c]. Substrate/reagent chirality effect: K_{MR}/K_{MS} and K_{MS}/K_{MR} for the (*2R*)-M and (*2S*)-M enantiomers, respectively; see text.

No.	Substrate M	(<i>2R</i>)-M: K_{MR}/K_{MS}	(<i>2S</i>)-M: K_{MS}/K_{MR}	Ref.
1a	Dimethyl tartrate	1.37	1.54	4,5
1b	Diethyl tartrate	1.46–1.85	1.45–1.92	4–8
1d	Tartaric acid dipyrrolidide	1.23	–	4
4	Isopropyl <i>threo</i> -3-cyclohexylglycerate	1.17 ± 0.05	–	
5	Isopropyl <i>erythro</i> -3-cyclohexylglycerate	0.97 ± 0.02	–	
6	<i>threo</i> -2,3-Butanediol	1.06 ± 0.10	1.01 ± 0.04	
7	<i>trans</i> -Cyclohexane-1,2-diol	1.02 ± 0.02	1.05 ± 0.02	
8	<i>threo</i> -1,4-Dimethoxy-2,3-butanediol	1.27 ± 0.05	1.21 ± 0.06	

mon homochiral stabilization of the mixed dimers.

The homochiral stabilization effects for the mixed dimers of the dimethyl and diethyl tartrates 1a and b (Table II) show values of 1.4–1.9. Similar, but less pronounced, effects are found for the corresponding mixed adducts of the enantiomers of tartaric acid dipyrrolidide (1d), isopropyl *threo*-3-cyclohexylglycerate (4) and *threo*-1,4-dimethoxy-2,3-butanediol (8) (Fig. 3). The chiral discrimination is virtually cancelled for the substrates isopropyl *erythro*-3-cyclohexylglycerate, *threo*-2,3-butanediol and *trans*-cyclohexane-1,2-diol (5–7) (Table I) and, in addition, for monohydroxy analogues, such as alkyl lactates and malates [7]. The latter failure of chiral recognition can be predicted from the structure of the diastereomeric dimers in Fig. 1, because the steric or structural requirements are not met.

Chiral effects in alkated dimers and solvated dimers and trimers

Lithium and potassium cation attachment under FAB mass spectrometric conditions gave the alkated diastereomeric dimers of the enantiomer-labelled diisopropyl tartrates, 1c·1c·Li⁺ and 1c·1c·K⁺, respectively. Minor chirality effects of $K_{RR}/K_{RS} \approx 1.08$ were observed. This indicates that the alkated dimers only form a small portion of conformers in which mutual interactions of the tartrates similar to those in Fig. 1 are retained. The most stable conformers probably have an Li⁺ or K⁺ centre which is multiply coordinated to both separate tartrate species. Analogous conformers have been proposed for FAB-desorbed Li⁺-coordinated mixed dimers with tartrate and bi-2-naphthol enantiomers [9].

Preliminary studies on the influence of the attachment of a third or “solvent” molecule (M)

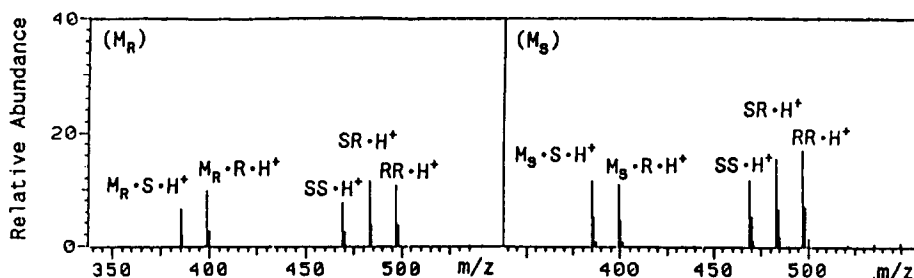


Fig. 3. Dimer regions of the chiral-additive isobutane CI mass spectra of (*2R,3R*)- and (*2S,3S*)-1,4-dimethoxy-2,3-butanediols (M_R and M_S).

to the enantiomer-labelled protonated dimers of the diisopropyl tartrates (**1c**) to give the solvate dimers, $M \cdot 1c \cdot 1c \cdot H^+$, were done with some compounds which had proton affinities (*PA*) [2] in a wide range. Ammonia is a much stronger base than **1c** and the loss of the chiral discrimination in the $1c \cdot 1c \cdot NH_4^+$ adducts has been reported [4,5]. Similarly to the alkali metal adducts above, the fully solvated NH_4^+ complex prohibits any specific interaction between the tartrate ligands.

PA values comparable to that of **1c** can be assumed for the diols *threo*- and *erythro*-2,3-butanediol [(*R*)-**6**, (*S*)-**6**; **6A**] and *trans*-1,2-cyclohexanediol [(*R*)-**7**, (*S*)-**7**]. Their chiral-additive CI mass spectra showed the mixed dimers $M \cdot 1c \cdot H^+$ and the solvated dimers $M \cdot RR \cdot H^+$, $M \cdot RS \cdot H^+$ and $M \cdot SS \cdot H^+$. As an example, the spectrum of **6A** is shown in Fig. 4. The K_{MRR}/K_{MRS} values for the solvated dimers of the above diols (0.92 ± 0.04 , 0.94 ± 0.04 , 0.95 ± 0.03 , 0.9 ± 0.05 and 1.00 ± 0.02 , respectively) were about 1.0 within experimental error. Thus, for the chiral diols **6** and **7** there is virtually no chiral discrimination of the solvated dimers; this is the same as for their mixed dimers (Table II). More importantly, the original chiral effect of the

protonated tartrate dimers is cancelled in the mixed $M \cdot 1c \cdot 1c \cdot H^+$ clusters. The *M* entity acts like a solvent which releases the conformational restrictions. This is in contrast to the behaviour of the diastereomeric self-trimers $(1c)_3 \cdot H^+$, which show a directed binding of the third monomer with reversal of the chiral discrimination. However, the $(1c)_3 \cdot H^+$ trimers can also lose their chiroselective properties in the solvated $M \cdot (1c)_3 \cdot H^+$ clusters, as shown in the CI mass spectrum of **6A** (Fig. 4). The effect $K_{RRS}/K_{RRR} = 2.14 \pm 0.08$ in the free trimers changes to $K_{MRRS}/K_{MRRR} = 1.11 \pm 0.06$ in the solvated trimers.

Compounds *M* with lower *PA* values than that of **1c** are water, methanol and ethanol. No H_2O attachment was observed, but abundant $ROH \cdot RR \cdot H^+$, $ROH \cdot RS \cdot H^+$ and $ROH \cdot SS \cdot H^+$ clusters were formed. Preliminary K_{RS}/K_{RR} and K_{MRS}/K_{MRR} values were 1.94 ± 0.02 and 1.09 ± 0.03 for MeOH studies and 2.09 ± 0.10 and 1.28 ± 0.03 for EtOH studies. Again, the tight chiroselective complex $1c \cdot 1c \cdot H^+$ is (gradually) changed to a looser aggregate $M \cdot 1c \cdot 1c \cdot H^+$. These gas-phase effects are similar to the influence of the solvent on chiral discrimination in solution [16–19].

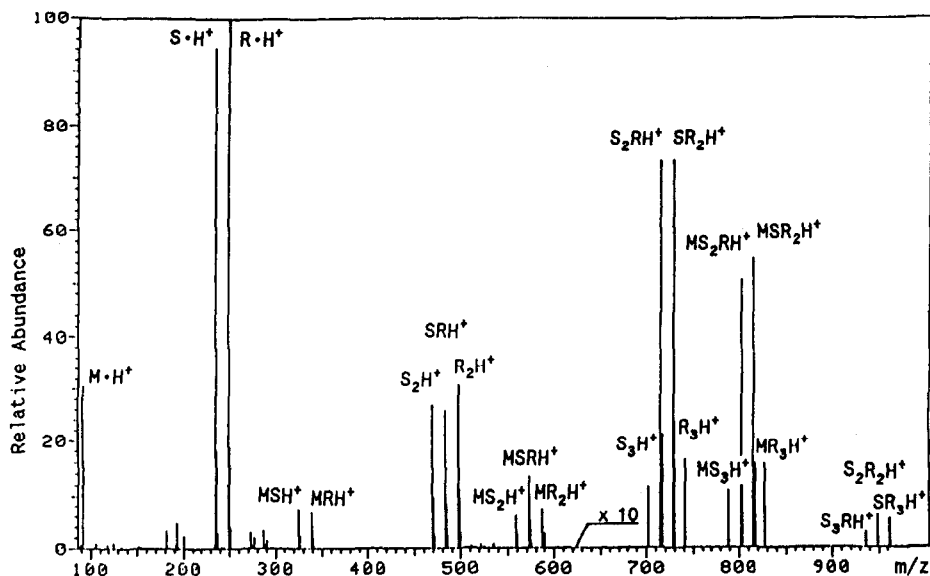


Fig. 4. Isobutane CI mass spectrum of *erythro*-2,3-butanediol (**6A**) (*M*) with diisopropyl (*S*)-tartrate and [$^2H_{14}$]diisopropyl (*R*)-tartrate (*S* and *R*) as additives.

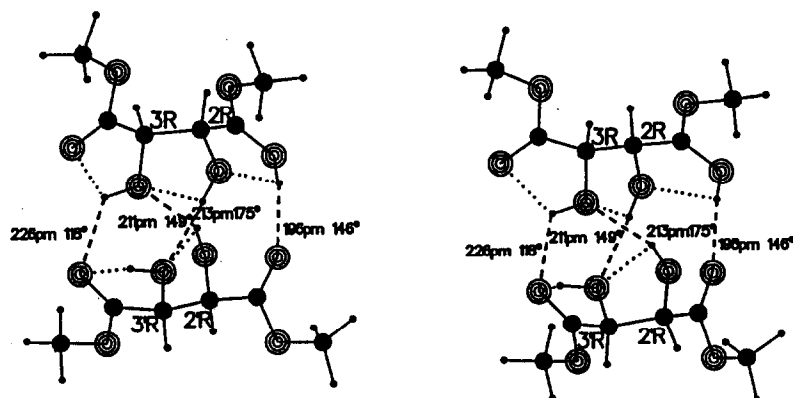


Fig. 5. Stereoscopic image of an AM1-minimized structure of the homochiral dimer $RR \cdot H^+$ of dimethyl (*R*)-tartrate [(*R*)-**1a**]. (····) Intramolecular H-bonds; (----) intermolecular H-bonds with OH----O distances and O—H----O angles.

Semi-empirical calculations on docking in diastereomeric dimers

The experimental studies show that the second ester group (A) is essential for strong chiral discrimination in the protonated diastereomeric dimers. This was confirmed by semi-empirical molecular orbital AM1 and PM3 calculations. The $RR \cdot H^+$ and $RS \cdot H^+$ conformations of dimethyl tartrate (**1a**) in Fig. 1 were used as starting geometries for the association or docking process. The energy minima obtained show multiple-centre H-bond structures which include all of the four ester groups (Figs. 5 and 6). There are four and three intermolecular H-bonds in the $RR \cdot H^+$ and $RS \cdot H^+$ complexes, respectively. The calculated association energies of the dimers are $\Delta\Delta H_f(RR \cdot H^+) = -16.06$ kcal/mol (1 cal =

4.1868 J) and $\Delta\Delta H_f(RS \cdot H^+) = -15.84$ kcal/mol. The stabilization increase ΔH of -0.22 kcal/mol for the homochiral dimer reflects its additional intermolecular H-bond. This ΔH term and a similar entropy term would agree with the chiroselective values of $\Delta\Delta G = -0.31$ kcal/mol for $K_{RR}/K_{RS} = 1.45$ at 140°C [4,5] and $\Delta\Delta G = -0.65$ kcal/mol for $K_{RR}/K_{RS} = 3.04$ at 20°C [10]. The geometries of the H-bond structures in the minimized dimers of **1a** are comparable to related crystal state data [15].

CONCLUSIONS

Under conditions of CI mass spectrometry, relatively small organic molecules with highly flexible conformations can show chirality effects on molecular docking reactions (self-dimers or mixed dimers), provided that there is a very large number of intramolecular and intermolecular attractions given in these species. For the protonated dimers of the dialkyl tartrates this is achieved by a total of five H-bond donor hydrogen atoms and a total of twelve H-bond acceptor oxygen atoms which can form specific and stable H-bond structures.

In addition, these dimers are capable of attaching a further third or fourth molecule. The resulting clusters can have specific aggregation properties and can show possible influences of solvent molecules on cluster structures.

Apparently, the CI method and related mass spectral techniques, with the support of semi-

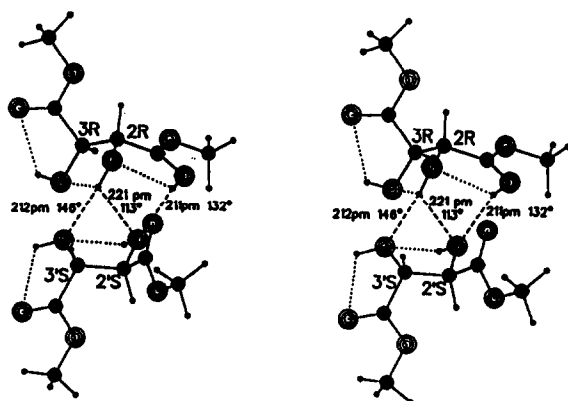


Fig. 6. Heterochiral dimer $RS \cdot H^+$ of the dimethyl tartrates (*R*)-**1a** and (*S*)-**1a**.

empirical molecular orbital calculations, can be applied to study certain aspects of chiral selector/analyte interactions in chromatographic systems and can be applied to investigate chiro-specific aggregation processes generally.

ACKNOWLEDGEMENT

Continuous support of this work by Professor H.-L. Schmidt of the Technische Universität München is gratefully acknowledged.

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