Racemic compound formation–conglomerate formation. Part 3.† Investigation of the acidic salts of α-phenylethylamine by achiral dicarboxylic acids. Optical resolution by preferential crystallization and a structural study of (*R*)-α-phenylethylammonium hydrogen itaconate

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Acidic salts of eight achiral dicarboxylic acids with α-phenylethylamine are prepared and investigated by IR and density measurements, and X-ray crystallography to distinguish between racemic compound and conglomerate formation. It was found that conglomerate formation takes place when the protonated and deprotonated carboxylic groups form hydrogen bonded chains rather than forming cyclic intramolecular hydrogen bonds. Racemic compound formation, and indeed intramolecular H-bond formation, seems to be preferred when the two carboxylates are constrained in the same plane close to each other by a double bond, or they are *ortho*-substituents of a planar ring. The rules found for conglomerate formation of acidic salts of α-phenylethylamine are compared with Saigo's rules for conglomerate formation. The crystal structure of the conglomerate forming (*R*)-α-phenylethylammonium hydrogen itaconate is (OARPHI) also presented and the optical resolution by preferential crystallization is described. The hydrogen bonding network of OARPHI [$N_1 = C(7)C_2^2(6)$, $N_2 = R_3^3(8)R_5^5(22)$] is very similar to the hydrogen bonding network of the other conglomerate forming salt of this series: α-phenylethylammonium hydrogen succinate [$N_1 = C(7)C_2^2(9)$, $N_2 = R_3^3(8)R_3^3(13)$].

Introduction

The problem of homochiral *versus* heterochiral packing of enantiomers has drawn substantial attention in the last few decades.[1–9] This is because it results in either a molecular compound or in conglomerate formation, which, in addition to its theoretical interest, also has important industrial implications, since the simplest resolution method for racemates, optical resolution by preferential crystallization, can be accomplished only for conglomerate formation.[10–11]

Wallach postulated[12] in 1895 that the formation of crystalline racemates takes place by contraction. The racemic compounds are more dense than the crystals of the corresponding enantiomers. Jacques *et al.* demonstrated[13] the greater stability of racemic crystals by thermodynamic calculations. Brock *et al.* stated[5] that the preference for hetereochiral packing 'could result merely from the additional possibilities for favourable packing arrangements in racemic space groups compared with chiral ones'.

Saigo *et al.*[6–9] extensively investigated the conditions required for the formation of conglomerate-type crystals. By comparison of the crystal structures of some enantiomeric salts composed from chiral bases and achiral acids, they postulated a few criteria that the achiral salt forming agents would have to comply with for conglomerate formation to occur.

We have been performing a systematic study on the occurrence of molecular compound *vs.* conglomerate formation for salts of α-phenylethylamine using achiral dicarboxylic acids as model compounds.[14–16] In this paper we report a comparative study on eight acidic salts of α-phenylethylamine, together with the optical resolution by preferential crystallization of the conglomerate forming α-phenylethylammonium hydrogen itaconate‡ and the crystal structure of its (*R*)-isomer (OARPHI), and its analysis from the point of view of conglomerate formation.

Experimental

All chemicals were purchased from Merck. Optical rotations were measured on a Perkin-Elmer 241 polarimeter and given in units of 10^{-1} deg cm^2 g^{-1} IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer in KBr. Densities were measured by flotation in a mixture of chlorobenzene and bromobenzene.

General procedure for preparation of acidic salts of racemic and (*R*)-(+)-α-phenylethylamine

Dicarboxylic acid (25 mmol) was dissolved in 20 ml boiling 96% ethanol and α-phenylethylamine (3.03 g, 25 mmol) [(*R*)-(+) or racemic] was added. The solution was evaporated to dryness *in vacuo*. The residue in all cases was a transparent oil, which crystallized after a few hours.

Resolution of racemic α-phenylethylammonium hydrogen itaconate by preferential crystallization

(*R*)-(+)-α-Phenylethylammonium hydrogen itaconate. Racemic α-phenylethylammonium hydrogen itaconate (9.0 g) and (*R*)-(+)-α-phenylethylammonium hydrogen itaconate (1.0 g) were dissolved in 18 ml of water at 45 °C in a thermostatted double walled flask. The solution was cooled to 19 °C and seeded with finely-pulverized (*R*)-(+)-α-phenylethylammonium hydrogen itaconate (0.05 g). The solution was allowed to stand undisturbed at this temperature for 120 min. The precipitated crystals were filtered off and dried. (*R*)-

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† Part 2. Z. Böcskei, D. Kozma, K. Simon and E. Fogassy, *J. Chem. Res.* (*S*), 1995, 160.

‡ IUPAC name for itaconic acid: 2-methylidenebutanedioic acid.

Table 1 Crystal data and a summary of data collection and structure refinement results for OARPHI

Empirical formula	$C_{13}H_{17}NO_4$
Formula weight	251.28
T/K	293(2)
λ/Å	1.541 78
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a/Å	11.049(5)
b/Å	18.758(4)
c/Å	6.317(3)
V/Å^3	1309.2(9)
Z	4
D_c/Mg m^{-3}	1.275
μ/mm^{-1}	0.785
F(000)	536
Crystal size/mm	0.50 × 0.30 × 0.20
θ Range/°	4.64–75.12
Index ranges	$0 \leqslant h \leqslant 13, 0 \leqslant k \leqslant 23, 0 \leqslant l \leqslant 7$
Reflections collected	1555
Independent reflections	1555
Absorption correction	Semi-empirical from psi-scans
Max. and min. transmission	0.997 and 0.848
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1549/0/175
Goodness-of-fit on F^2	1.072
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0397$, $wR2 = 0.1013$
R indices (all data)	$R1 = 0.0838$, $wR2 = 0.1763$
Extinction coefficient	0.0100(11)
$\Delta\rho$/e Å^{-3}	0.182, −0.187

(+)-α-Phenylethylammonium hydrogen itaconate (1.31 g) was obtained; $[\alpha]_D^{20}$ +4.4 (*c* 1 in ethanol); optical purity 92.0%.

(*S*)-(−)-α-Phenylethylammonium hydrogen itaconate. Racemic salt (1.3 g) was dissolved in the mother liquor at 45 °C, then cooled to 19 °C and seeded with finely-pulverized (*S*)-(−)-α-phenylethylammonium hydrogen itaconate (0.05 g). The seeded solution was allowed to stand undisturbed at this temperature for 90 min. The precipitated salt was filtered off and dried. (*S*)-(−)-α-Phenylethylammonium hydrogen itaconate (0.47 g) was obtained. $[\alpha]_D^{20}$ −4.1 (*c* 1 in ethanol); optical purity 85.0%.

X-Ray crystal structure analyses

Crystals of OARPHI were grown from ethanol. Crystal data are listed in Table 1. Data were collected on a Rigaku AFC6S diffractometer. The structures were solved using the TEXSAN[17] program package, while refinement was done by SHELEX-93[18] running on a Silicon Graphics R3000 workstation. No absorption correction was applied. Hydrogen atoms with known geometry were generated, except for N–H and O–H atoms which were taken from difference Fourier calculations. The numbering scheme of the molecules is shown in Fig. 1 and the hydrogen bonding system is shown in Fig. 2. Full lists of atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and reference number 188/8. The applied weighting scheme was $w = 1/\sigma^2(F_0)$.

Discussion

The optically active and racemic forms of the acidic salts of α-phenylethylamine with eight different achiral dicarboxylic acids were prepared (Table 2). Oxalic acid forms only a neutral salt with α-phenylethylamine, even with a molar ratio of base to acid of 1 : 1.[16] To determine the type of crystallization all the salts were subjected to IR and density measurements since the IR spectra and the density values of the optically active and the racemic form should be identical for conglomerate formation and different for racemic compounds. Fig. 3 shows an example of the IR spectra of a conglomerate-forming and a molecular compound-forming salt. The results from these two methods were in agreement indicating that only the hydrogen succinate and the hydrogen itaconate form conglomerates (see Table 2).‡ A comparison of the densities of the racemic compounds indicated that in five out of six cases the active forms are more dense than the racemate. The racemate is denser only in the case of the salt formed with malonic acid, which was the shortest chain, with only a CH_2 group between the two carboxylate groups. These results indicate that for this series of salts the Wallach rule is not valid.

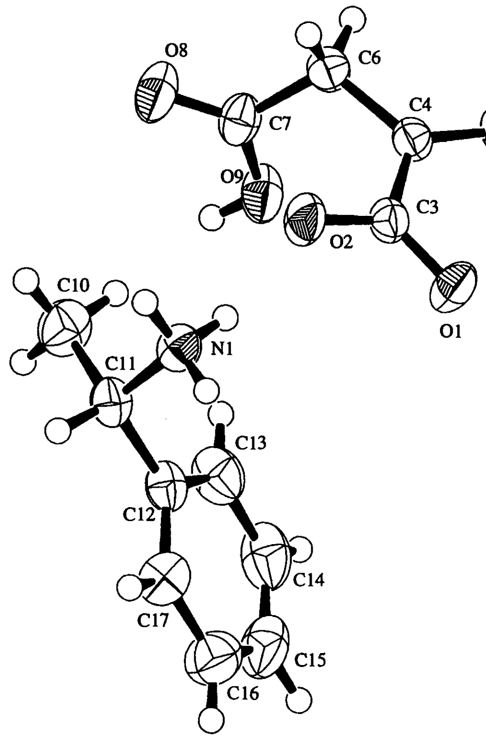

Fig. 1 PLUTO drawing illustrating the molecular geometry and the atomic numbering scheme of OARPHI

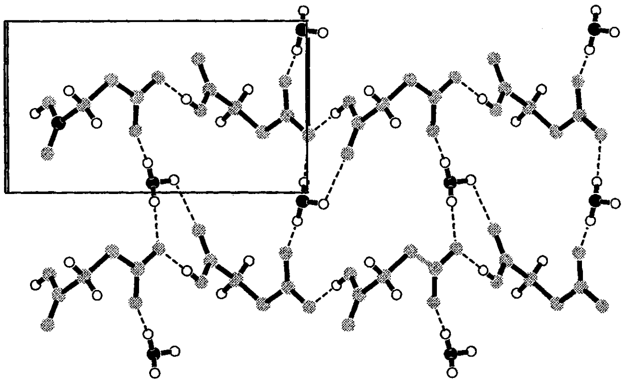

Fig. 2 Hydrogen bonding system of OARPHI; to give a better view all the atoms of α-phenylethylamine were removed except the N and the connected hydrogens

Since α-phenylethylammonium hydrogen succinate has already been analysed in detail,[15] we selected the other conglomerate forming salt: α-phenylethylammonium hydrogen itaconate for detailed study.

As a final proof of conglomerate formation, optical

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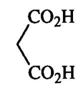
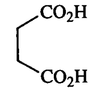
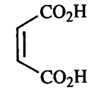
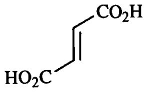
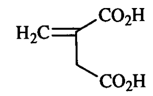
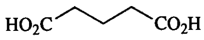
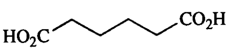
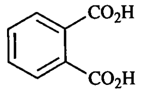
‡ Nohira *et al.*[19] published the optical resolution of the acidic salt of α-phenylethylammine *cis*-cyclohexane-1,2-dicarboxylic acid by preferential crystallization, which is also proof of conglomerate formation.

Table 2 Summary of the density and IR measurements

Dicarboxylic acid	Density/g cm^{-3} (*R*)	Density/g cm^{-3} (*R*,*S*)	Comparision of IR spectra of (*R*) and (*R*,*S*) salts
	1.305	1.320	Different
	1.301	1.301	Identical
	1.271	1.237	Different
	1.309	1.256	Different
	1.281	1.281	Identical
	1.228	1.192	Different
	1.185	1.179	Different
	1.320	1.317	Different

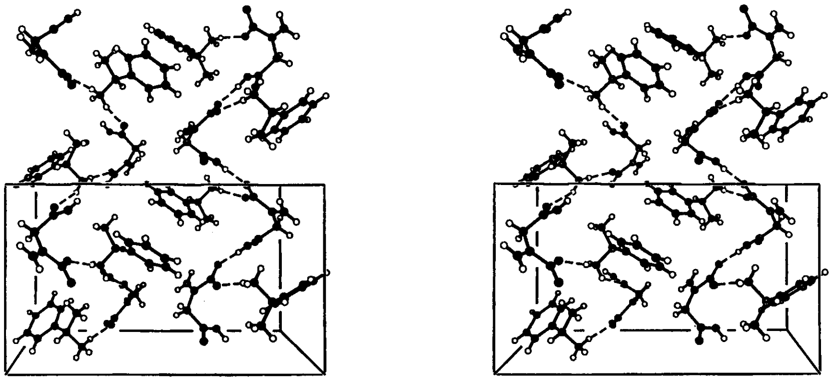


Fig. 3 ORTEP stereodiagram of the molecular packing in the crystal structure of OARPHI; H-bonds, ----

resolution by induced crystallization was attempted and carried out successfully. Similar results were achieved with hydrogen succinate, except that due to the lower solubility of the hydrogen itaconate in water, it was possible to accomplish the resolution in pure water instead of in an acetone–water (95:5) mixture. The latter solvent mixture was used for the preferential crystallization of the hydrogen succinate.

Discussion of the crystal structure

The OARPHI crystallizes in the orthorhombic $P2_12_12_1$ space group which is the most frequently found space group among chiral molecules.[13] In the crystal structure itaconic acid is protonated on one of its two carboxylate groups (Fig. 1). This is nicely demonstrated by the C–O bond length of the structure (Table 3). While the ionized carboxylate containing the O1 and O2 atoms has C–O bonds of very similar length, in the protonated carboxylate C7–O9 is very significantly longer than C7–O8 corresponding to a protonation on O9 and a more pronounced single bond character of the C7–O9 bond. Interestingly, the C3–C4 bond [1.498(5) Å] is not much shorter than a normal C–C single bond, so no real delocalisation between the C4=C5 double bond and the carboxylate group is evident from the bond length data. This is also true for the crystal structure of the pure itaconic acid.[20]

The most important force component in the crystal structure seems to be a hydrogen bonding network formed by a pleated sheet of the itaconic acid molecules into which the ammonium groups of the base sink (Figs. 2 and 4). The ammonium groups are situated between the rows of the itaconic acid moieties, which are connected into rows by hydrogen bonds formed by

O9–H9 • • • O1 atoms. The ammonium ions connect the itaconic acid rows by forming one or two hydrogen bonds alternatively to one or the other neighbouring itaconic acid rows (Figs. 2, 4 and Table 4).

Hydrogen bonding

From the hydrogen bond data it is clear that the O9–H9 • • • O1 hydrogen bond is by far the strongest one. Both the bridgehead atom distances and the almost linear hydrogen bond angle are in favour of this claim. The chain composed by this type of hydrogen bond alone can be characterized by the graph theoretical notion introduced by Etter[21] as follows: $C(7)$, where $C(7)$ means that unit of the chain built up by seven atoms with one donor and one acceptor atom (not shown in this special case). Out of the three hydrogen bonds originating from the ammonium nitrogen, two have reasonably good geometry, while for the third a much less favourable geometry is formed. Topologically, we can find the following first-order network with the participation of the two strong hydrogen bonds: $C_2^2(6)$. From the second-order networks containing both types of hydrogen bonds, the most important looks to be the eight-membered ring with the graph set symbol $R_3^3(8)$ and the large ring with the graph set symbol $R_5^5(22)$ is also worth mentioning. In conclusion we say that the hydrogen bond network of this crystal can be characterised by the following graph set: $N_1 = C(7)C_2^2(6)$, $N_2 = R_3^3(8)R_5^5(22)$. In a previous publication, we analysed the hydrogen bond networks of the α-phenylethylammonium salts of the hydrogen malonate, phthalate and succinate anions out of which the last one forms conglomerate crystals, while the first two form racemates. We concluded with the statement that the networks for the two racemate forming crystals are similar to each other, while those for the conglomerate forming one are very different from the other two. Now we can add that the present conglomerate forming crystal structure has very similar hydrogen bond characteristics to the one published earlier, $N_1 = C(7)C_2^2(9)$, $N_2 = R_3^3(8)R_3^3(13)$. Apart from the similarity in the graph sets of the conglomerates other qualitative structural features are quite similar too. It looks as though in racemate forming salts the hydrogen atom of the non-ionized carboxylate group prefers to form an intramolecular hydrogen bond, creating a six- or seven-membered ring with the participation of the ionized carboxylate, while in both of the conglomerate forming structures a linear hydrogen bonded chain of the acids can be found. It is not easy to find the structural reasons behind this behaviour. Etter, in her paper, says that it is a general rule for hydrogen bond formation in crystals that six-membered intramolecular rings form in preference to intramolecular hydrogen bonds. It is also added that five- and seven-membered intramolecular rings are also common but there are no data about competition between these bonds and intramolecular hydrogen bonds. In our racemate forming crystals in one case a six-membered intramolecular ring is present, while in the other case a seven-membered intramolecular ring is formed, but in the latter case the intramolecular ring is preformed since it is made of the two carboxylate groups of the hydrogen orthophthalate ion. In the two conglomerate forming crystals, seven-membered intramolecular rings could also be formed but the rings are not preformed.

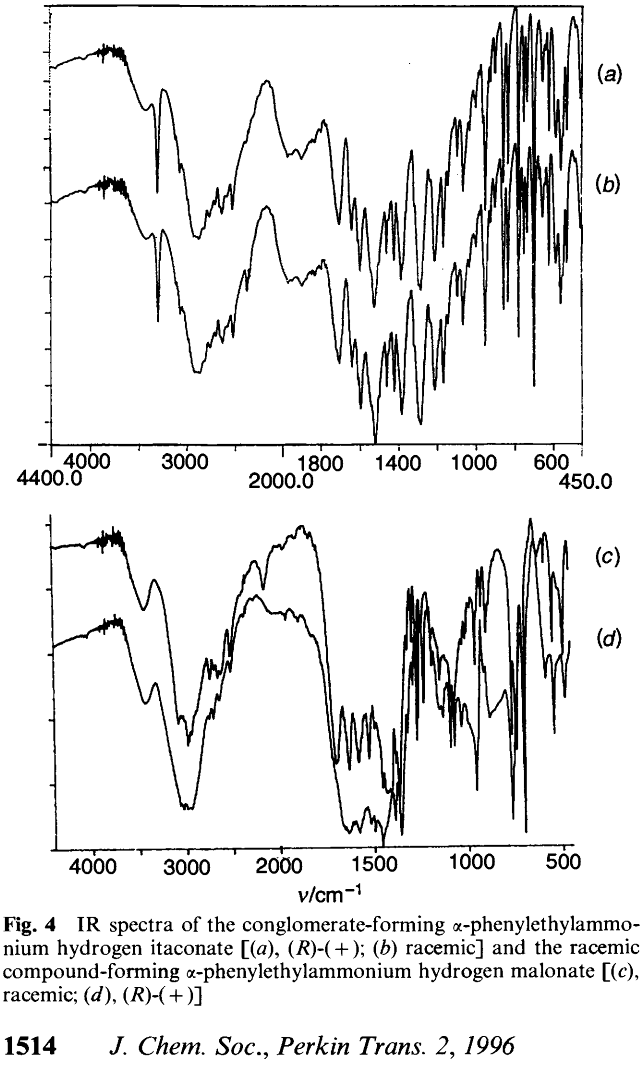


Fig. 4 IR spectra of the conglomerate-forming α-phenylethylammonium hydrogen itaconate [(*a*), (*R*)-(+); (*b*) racemic] and the racemic compound-forming α-phenylethylammonium hydrogen malonate [(*c*), racemic; (*d*), (*R*)-(+)]

Saigo *et al.* suggested[7,8] that an achiral acid should satisfy three criteria in order to be able to transform a racemic modification of an ammonium salt into a conglomerate crystal. (i) 'The achiral derivatizing agent should be able to form a helical column by forming hydrogen bonds with the molecule of the racemic compound.' This criteria is not valid for our

Table 3 Bond lengths (Å) and angles (°) for OARPHI

O(1)–C(3)	1.264(4)
O(2)–C(3)	1.253(4)
O(8)–C(7)	1.215(4)
O(9)–C(7)	1.319(4)
N(1)–C(11)	1.509(4)
C(3)–C(4)	1.498(5)
C(4)–C(5)	1.316(5)
C(4)–C(6)	1.502(5)
C(6)–C(7)	1.504(5)
C(10)–C(11)	1.513(5)
C(11)–C(12)	1.514(5)
C(12)–C(17)	1.387(5)
C(12)–C(13)	1.392(5)
C(13)–C(14)	1.387(6)
C(14)–C(15)	1.361(6)
C(15)–C(16)	1.360(7)
C(16)–C(17)	1.388(6)
O(2)–C(3)–O(1)	123.3(4)
O(2)–C(3)–C(4)	117.3(3)
O(1)–C(3)–C(4)	119.4(3)
C(5)–C(4)–C(3)	121.4(3)
C(5)–C(4)–C(6)	122.6(3)
C(3)–C(4)–C(6)	116.0(3)
C(4)–C(6)–C(7)	114.3(3)
O(8)–C(7)–O(9)	123.6(4)
O(8)–C(7)–C(6)	123.1(4)
O(9)–C(7)–C(6)	113.2(3)
N(1)–C(11)–C(10)	108.9(3)
N(1)–C(11)–C(12)	109.5(3)
C(10)–C(11)–C(12)	115.4(3)
C(17)–C(12)–C(13)	118.7(4)
C(17)–C(12)–C(11)	118.5(3)
C(13)–C(12)–C(11)	122.8(3)
C(14)–C(13)–C(12)	119.5(4)
C(15)–C(14)–C(13)	121.3(4)
C(16)–C(15)–C(14)	119.5(4)
C(15)–C(16)–C(17)	120.8(4)
C(12)–C(17)–C(16)	120.2(4)

Table 4 Hydrogen bond data for OARPHI

	D ··· A dist/Å	H ··· A dist/Å	D–H ··· A angle/°
O1–H9_$1–O9_$1 [a]	2.569 (0.004)	1.751 (0.046)	174.85 (0.14)
O1–H1A_$2–N1_$2 [b]	2.768 (0.004)	1.901 (0.008)	164.04 (1.41)
O8–H1C_$3–N1_$3 [c]	2.870 (0.004)	2.344 (0.020)	117.85 (1.64)
O2–H1B–N1	2.733 (0.004)	1.871 (0.007)	162.48 (2.02)

[a] $1: 0.5 + *x*, 1.5 − *y*, −*z*. [b] $2: *x*, *y*, *z* − 1. [c] $3: *x* − 0.5, 1.5 − *y*, 1 − *z*.

examples, but the anions should form a hydrogen bonded chain with each other instead of forming intramolecular hydrogen bonds. (ii) 'The derivatizing agent should be rigid and flat to limit the orientation of the molecules of the racemic compound.' The rigidity of the acid is partially fulfilled by itaconic acid, but succinic acid, our former example, is not rigid at all. It is also likely that the conglomerate forming *cis*-cyclohexane-1,2-dicarboxylic acid is less rigid than the racemate forming phthalic acid. So this criteria does not seem to be a generally necessary condition. (iii) 'The sizes of the derivatizing agent and the molecule of the racemic compound should be complementary to make the crystal packing close.' Among the nine examples of the acidic salts of α-phenylethylamine by achiral dicarboxylic acids, conglomerate formation takes place only when there is a $-CH_2-CH_2-$ group between the two carboxylic groups, while racemic compounds formed when the alkyl chain was shorter or longer, or when the double bond or the delocalised double bond connect two carbon atoms between the two carboxylic groups. This indicates that the distance between the two carboxylic groups is the most important factor for conglomerate formation, while the size of the whole molecule seems to be less important. It should be noted that the stacking of phenyl rings does not play such a prominent role in the crystal packing of our structure as can be seen in cases when both the base and the acid contain phenyl rings.

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