Racemic Compound Formation–Conglomerate Formation. Part. 1. Structural and Thermoanalytical Study of Hydrogen Malonate, Hydrogen Phthalate and Hydrogen Succinate of α-Phenylethylamine

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The crystal structure of (*R,S*)-α-phenylethylammonium hydrogen phthalate (RACPHP) [$P2_1/a$; a = 8.503(3), b = 16.748(5), c = 10.544(3) Å, β = 104.48(2)°; Z = 4; R = 0.058 based on 2412 observed reflections] and (*R,S*)-α-phenylethylammonium hydrogen malonate (RACPHM) [$P\bar{1}$; a = 8.768(1), b = 9.014(1), c = 7.485(1) Å, α = 104.31(1), β = 96.95(1), γ = 91.68(1)°; Z = 2; R = 0.069 based on 2061 observed reflections] were determined and compared with each other and with the known crystal structure of the (*R*)-α-phenylethylammonium hydrogen succinate (KACBEV). The structural and thermoanalytical investigations of the salts proved that the hydrogen phthalate and hydrogen malonate anions form racemic compounds while the hydrogen succinate anion forms a conglomerate, the latter being the only one which could be resolved by preferential crystallization.

The comparison of the structures revealed that the hydrogen bonding network of RACPHP [$S(7)C_2^2(9)R_4^4(18)R_8^8(30)C_4^4(12)$] and RACPHM [$S(6)C_2^2(8)R_4^4(12)R_4^4(16)$] are very similar (represented by graph theory), while KACBEV [$C_1^1(7)C_2^2(9)R_3^3(8)R_3^3(13)$] is different. Intramolecular hydrogen bonds through acidic hydrogens are formed only between the carboxylic groups of the racemic compounds.

From a solution of a racemic substance either homochiral or heterochiral crystals can precipitate. The heterochiral crystals contain both the *R* and *S* isomers in equal amounts (racemic compound), while the eutectic mixture of the homochiral *R* and *S* crystals is a conglomerate.[1]

'Under what conditions does a given racemate, racemic compound or conglomerate form?' is an interesting theoretical question, but it has some practical importance too, because only conglomerate forming racemates can be resolved by preferential crystallization, which is one of the most frequent ways for separating optical isomers of racemates.[2] Statistical[3–6] and crystallographical[7–9] considerations show that the racemic compound formation is more frequent than conglomerate formation. Saigo *et al.*[10] investigated the structural basis of the conglomerate formation in a particular case.

We performed a structural and thermoanalytical study on three closely related α-phenylethylammonium salts [(*R,S*)-α-phenylethylammonium hydrogen phthalate (RACPHP); (*R,S*)-α-phenylethylammonium hydrogen malonate (RACPHM); (*R*)-α-phenylethylammonium hydrogen succinate (KACBEV)]† in order to get an insight into the mechanism of conglomerate–racemic compound formation.

Experimental

All chemicals were purchased from Merck.

Preparation of Acidic Salts of Racemic and (R)-(+)-α-*Phenylethylamine.*—Dicarboxylic acid (2.60 g malonic, 2.95 g succinic and 4.15 g phthalic acid; 25 mmol) was dissolved in boiling 96% ethanol (20 cm^3) and α-phenylethylamine (3.03 g, 25 mmol) [(*R*)-(+) or racemic] was added. The solution was evaporated to dryness *in vacuo*. The residues in all cases were transparent oils, which crystallized after a few hours. These samples were used for DSC measurements. For the single crystal X-ray diffraction study the salts were recrystallized from ethyl acetate. All salts gave good quality single crystals except the optically active hydrogen malonate and hydrogen phthalate.

Resolution of the Racemic α-Phenylethylammonium Hydrogen Succinate by Preferential Crystallization.—Racemic α-phenylethylammonium hydrogen succinate (11.46 g) and (*R*)-(+)-α-phenylethylammonium hydrogen succinate (1.15 g) were dissolved in a mixture of acetone (190 cm^3) and water (10 cm^3) at 40 °C in a thermostatted double walled flask. The solution was cooled down to 20 °C and seeded with 0.05 g finely-pulverized (*R*)-(+)-α-phenylethylammonium hydrogen succinate. The solution was allowed to stand undisturbed at this temperature for 170 min. The precipitated crystals were filtered and dried. (*R*)-(+)-α-Phenylethylammonium hydrogen succinate (1.53 g) was obtained; $[\alpha]_D^{20}$ = +5.7 (*c* 1; ethanol), optical purity 90.5%.

Racemic salt (1.55 g) was dissolved in the mother liquor at 40 °C, then cooled down to 18 °C and seeded with 0.05 g finely pulverized (*S*)-(−)-α-phenylethylammonium hydrogen succinate. The seeded solution was allowed to stand undisturbed at this temperature for 150 min. The precipitated salt was filtered and dried. *S*-(−)-α-Phenylethylammonium hydrogen succinate (0.55 g) was obtained; $[\alpha]_D^{20}$ = −5.2 (*c* 1; ethanol), optical purity 82.5%.

The optical rotations were measured on a Perkin-Elmer 241 polarimeter. The DSC curves were recorded and integrated with a DuPont 1090B Thermal Analysis System. Samples of 2–3 mg were run in hermetically sealed aluminium pans with a heating rate of 5 K min^{-1}. The temperature range of thermal decomposition was determined by thermogravimetric measurements (carried out on the same system).

† The structure of (*R*)-(+)-α-phenylethylammonium (2*R*)-[2-^{2}H]succinate (KACBEV) has been published[11] without detailed analysis of the hydrogen bonding interactions. [This structure is practically identical with (*R*)-(+)-α-phenylethylammonium hydrogen succinate. We used that structure in our study.]

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

Parameter	RACPHP	RACPHM
Formula	$C_8H_{12}N^+C_8O_4H_5^-$	$C_8H_{12}N^+C_3O_4H_3^-$
M_w	287.31	226.23
a/Å	8.503(3)	8.768(1)
b/Å	16.748(5)	9.014(1)
c/Å	10.544(3)	7.485(1)
α/°	90	104.31(1)
β/°	104.48(2)	96.95(1)
γ/°	90	91.68(1)
V/Å^3	1453.9(7)	567.9(1)
Space group	$P2_1/a$	$P\bar{1}$
Z	4	2
D_x/g cm^{-3}	1.313	1.323
N_{tot}	2916	2401
N_{obs}	2412 [$I > 3.00\sigma(I)$]	2061 [$I > 3.00\sigma(I)$]
R	0.058	0.069
R_w	0.039	0.134
$2\theta_{max}$/°	150	150
λ/Å	1.5418	1.5418
μ/cm^{-1}	7.83	8.43

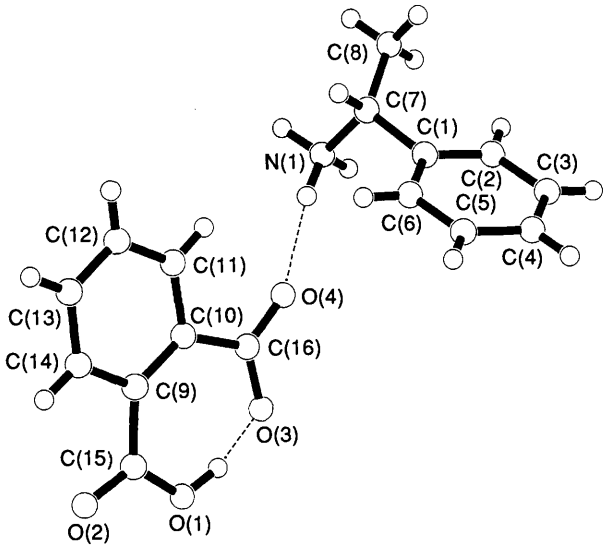

Fig. 1 PLUTO drawing illustrating the molecular geometry and the atomic numbering scheme of RACPHP

X-Ray Crystal Structure Analyses.—Crystals of RACPHP and RACPHM were grown from ethyl acetate. Crystal data are listed in Table 1. Data were collected on a Rigaku AFC6S diffractometer. The structures were solved using the TEXSAN[12] program package, running on a Silicon Graphics R3000 workstation. An empirical absorption correction was applied to all reflections, using the DIFABS program.[13] 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 can be seen on Figs. 1 and 2. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre. See 'Instructions for Authors (1994)', *J. Chem. Soc., Perkin Trans. 2*, 1994, Issue 1. The applied weighting scheme was $w = 1/\sigma^2(F_o)$.

Discussion

In our comparative study first thermoanalytical and preferential crystallization experiments were performed on the three salts.

None of the salts were solvated, thermal decomposition did not disturb the determination of the melting point and the heat of fusion. The hydrogen succinate seems to be more stable,

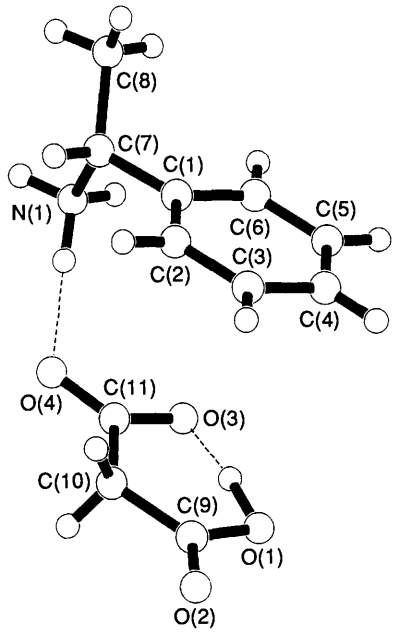

Fig. 2 PLUTO drawing illustrating the molecular geometry and the atomic numbering scheme of RACPHM

Table 2 Thermal data of the α-phenylethylammonium salts

		M.p./K	ΔH_{fus}/kJ mol^{-1}
Hydrogen succinate	active	383 (1)	30.5(12)
	racemic	358(1)	30.6(12)
Hydrogen malonate	active	372(1)	18.2(7)
	racemic	406(1)	25.3(10)
Hydrogen phthalate	active	375(1)	16.2(6)
	racemic	403(1)	21.6(9)

having the highest heat of fusion values and the highest melting point among optically active salts (Table 2). The heat of fusion values of the optically pure and racemic hydrogen succinate are practically the same, the melting point of the racemate is lower than the active salt, which indicates conglomerate formation. The melting point of the racemate (357 K) calculated from the thermal data of the active salts by the Schröder–VanLaar equation[1] agrees well with the measured 358 K.

The racemates of the hydrogen malonate and hydrogen phthalate have higher melting points and heats of fusion than the active salts, which show that the racemic form is more stable and forms a racemic compound. In the preferential crystallization experiments we were able to get separation only in the case of hydrogen succinate, which is in agreement with the thermoanalytical results.

Unfortunately the optically active hydrogen phthalate and hydrogen malonate do not form good quality crystals for single crystal X-ray diffraction study, only the structure of the two racemic salts were determined. The RACPHP crystallizes in the $P2_1/a$ while the RACPHM crystallizes in the $P\bar{1}$ space group.

The bond lengths and angles of the α-phenylethylammonium moiety are very similar in all cases. The torsion angles of the α-phenylethylammonium cation are also quite close in all the three salts that we considered for comparison in agreement with our previous study on the torsion angles of α-phenylethylammonium cation.[14] The N(1)–C(7)–C(1)–C(2) torsion angle is 112.2(4)° for the hydrogen malonate, 101.3(5)° for the hydrogen phthalate and 124° for the hydrogen succinate salt.

It is interesting to note that both racemic dicarboxylate salts that we determined the crystal structure of, are planar anions and form an intramolecular hydrogen bond. A similar conformation in the case of KACBEV would require a

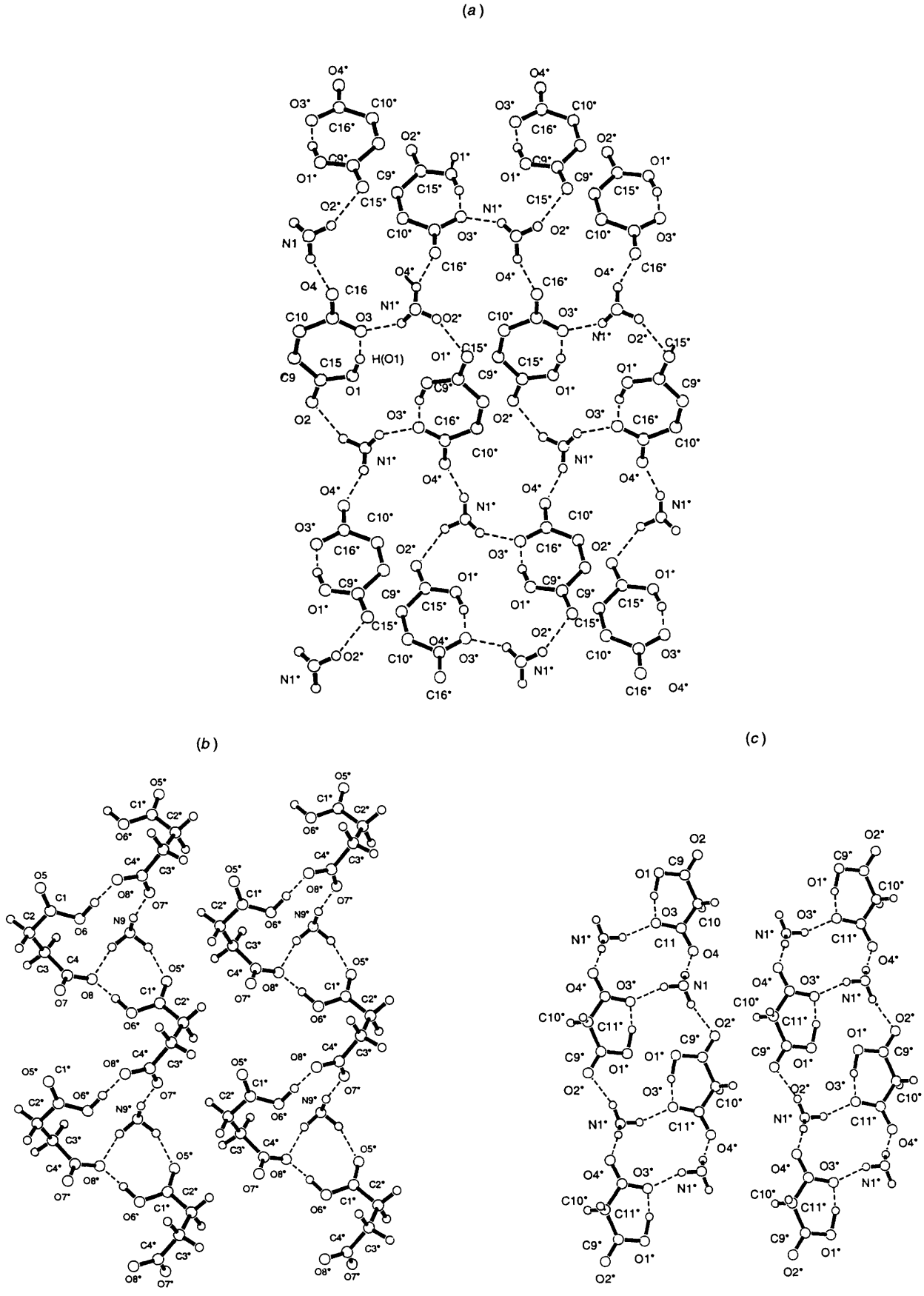

Fig. 3 Hydrogen bonding systems (for the better view all atoms of α-phenylethylamine were removed except the N and the connected hydrogens) (*a*) RACPHP (the phenyl ring removed); (*b*) RACPHM; (*c*) KACBEV

Table 3 Hydrogen bond data (Å, deg.) for the three salts

	RACPHP	RACPHM	KACBEV
H(O)···O(3)	1.569(4)	1.694(3)	1.480(3)
O(1)–H···O(3)	178(4)	154.9(5)	176.3(3)
O(1)···O(3)	2.379(5)	2.456(2)	2.542(3)
H(N)···O(2)	2.004(4)	2.032(2)	1.993(4)
N(1)–H···O(2)	153.3(1)	157.53(5)	140.8(2)
N(1)···O(2)	2.820(5)	2.875(2)	2.868(3)
H(N)···O(3)	2.023(3)	2.045(2)	1.729(4)
N(1)–H···O(3)	153.3(1)	152.83(6)	160.6(3)
N(1)···O(3)	2.846(5)	2.866(2)	2.741(3)
H(N)···O(4)	1.984(3)	1.874(2)	1.687(4)
N(1)–H···O(4)	154.8(1)	168.25(6)	162.8(2)
N(1)···O(4)	2.803(5)	2.751(2)	2.714(3)

syn-periplanar conformation along the C(1)–C(2)–C(3)–C(4) fragment, which is obviously very unfavourable. The conglomerate forming hydrogen succinate salt KACBEV structure is the only hydrogen succinate salt known to adopt a *gauche* conformation, because in most of the cases the *anti*-periplanar conformation is preferred.[15–17]

Since RACPHP and RACPHM are racemic compounds, the chiral counterparts occupy centrosymmetrically related positions at opposite sides of the crystallographic centres of symmetry present in both of these structures. Since the extensive hydrogen bonding networks present in all three cases seem to be the major factor responsible for shaping the crystal structures, we wish to analyse them in more detail.

All possible hydrogen bond donors are involved in strong or medium strength hydrogen bonds in all three salts. There are four hydrogen bond donors and eight acceptor positions per ion pair. It is worth mentioning that no bifurcated hydrogen bonds are present in any of the three crystal structures, although this has been found to be characteristic of donor deficient networks.[18]

The hydrogen bonding networks are placed in hydrophilic layers of the structures containing the carboxylate and ammonium ions and these are sandwiched between hydrophobic layers of aromatic rings (and in some cases aliphatic groups). Since the hydrogen bonding networks are extended in no more than two dimensions we cut them out of the crystal structures so that they are easier to examine in detail (Fig. 3, Table 3).

The examination of atom–atom distances reveals that the strongest hydrogen bond is formed between the carboxylate bonded acidic hydrogen and the double hydrogen bond acceptor charged oxygen of either the same (racemic crystals) or another (conglomerate) anion. The formation of the intermolecular hydrogen bond of the acidic hydrogen in the case of KACBEC, the conglomerate forming crystal may account for its extra stability (Table 3).

The O–H···O^--type hydrogen bonds are among the strongest, which is evidenced in this particular case by their short H···O^- as well as non-bonded O···O (bridgehead) distances. The strength of this hydrogen bond seems to be reflected by the fact that in two of the three hydrogen bonds of this type the O–H···O angle is very close to linearity which is another characteristic of strong hydrogen bonds. The participation of O(3) in the very strong hydrogen bond plus in an additional N–H···O type bond shields its non-bonding electrons from taking full part in the delocalization with the double bond of O(4). The C–O(3) bond lengths always show considerable single bond character, while the C–O(4) bonds are essentially double bonds. A further comparison of the C–O bond lengths in the three salts reveals that the carboxylate groups seem to be essentially equivalent in RACPHP, easier to distinguish in KACBEV, since the hydrogen atom can be assigned to O(1) barely by considering the C–O bond lengths, while RACPHM forms an intermediate step between the two mentioned previously.

Second comes the N^+–H···$O(4)^{\delta-}$ [where δ is likely to be small, since the O(4)=C–$O(3)^-$ entity does not seem to be fully delocalized as shown on the bond length], which displays the shortest N···O and H(N)···O distances in all three cases. The reason for this could be the fact that this oxygen atom takes part in only one hydrogen bond unlike O(3), but this part of the molecule still has an excess of non-bonding electrons due to the ionization as compared to the other carboxylate entity.

Using the method based on graph theory described by Etter *et al.*,[19] we characterized the hydrogen bond networks in the crystal structures. While the hydrogen bond patterns of the two racemic salts display striking similarities, both are very different from that of the conglomerate crystal. In the examined salts two types of hydrogen bonds are found, N–H···O and O–H···O. The first order graph set for RACPHP is $S(7)C_2^2(9)$-$R_4^4(18)R_8^8(30)C_4^4(12)$ while for that of RACPHM it is $S(6)C_2^2(8)R_4^4(12)R_4^4(16)$. It is not hard to see that these two graph sets are very similar to each other indeed. The graph set for the hydrogen bonding network of KACBEV is $C_1^1(7)C_2^2(9)R_3^3(8)R_3^3(13)$, which is obviously very different from the first two.

We are in the process of analysing the structures of further crystals of similar type and hope to find some rules that would account for the preferred formation of either the racemic or the conglomerate type crystal.

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