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RESEARCH ARTICLE

Structure-resolvability relationship of several diastereomeric salt pairs of 1-phenylethylamine – A Cambridge Structural Database study

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Abstract

In order to study the effects of crystal structures on resolvability, a CSD (Cambridge Crystallographic Database) study has been carried out on 1-phenylethylammonium diastereomeric salt pairs with available crystal structures. The structures of the diastereomers of the salts are analyzed, compared and grouped. The structural features are set against the resolution results. The effects of three types of structural features on the resolution efficiency are demonstrated.

Keywords

optical resolution · diastereomeric structures · phenylethylammonium salts · resolvability

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1 Introduction

Enantiomers i.e. mirror image molecules behave identically in an achiral environment. For the separation of enantiomers a chiral agent (associations of the same enantiomers, a chiral surface, a chiral molecule etc.) is needed. The separation is most commonly achieved by using an optically active compound that yields diastereomeric salts with the enantiomers to be separated [13, 17, 20]. The separation of diastereomeric salts is based on their solubility difference which originates from structural differences. The molecular constitution of the diastereomers is identical. It is the different molecular shape in the diastereomeric molecule associates (ion pairs) that causes crystal structural differences. In some cases, the structural difference is large enough to make an efficient separation possible. Organic compounds usually have several possible crystal structures (polymorphs). The differences between these structures are caused by weak second order interactions and thereby their energy may be close to each other. Therefore, the prediction on any level of these crystal structures is very difficult. Although general rules can hardly be set up, some trends can be found.

The diastereomeric crystalline phases may be studied by X-ray diffraction (on a single crystal or on a powder sample), molecular modelling or quantum chemical calculations [18]. Even nowadays, the computational methods in the study of crystalline phases are strongly limited by computer capacities. X-ray powder diffraction is a very useful method in the study of diastereomeric crystalline phases. However, it does not give detailed information about the crystal structures except in favourable cases. Single crystal X-ray diffraction is the most powerful method in the study of the crystals of diastereomers but its use is limited by the availability of good quality single crystals. When the solubility difference between the two diastereomers is large, generally the more soluble diastereomer does not crystallize well. Therefore, the preparation of single crystals from both diastereomers is often difficult.

Recently, our research group published the crystal structures of the diastereomeric salts of several 1-phenylethylammonium derivatives [2–4]. For the sake of a fairly extensive study using single crystal data, a literature survey was done and all

Tab. 1. Physicochemical and crystallographic properties of the studied diastereomeric pairs vs. the resolvability (ee: enantiomeric excess; Y: yield; F: Fogassy parameter; x_{eu}: eutectic composition; n: the CIP configurations of the acid and the base are different; p: the CIP configurations of the acid and the base are identical, Sol: solubility in the solvent of the resolution, ρ : calculated density on the basis of crystallographic data; mp: melting point; ΔH_{melt}: melting enthalpy; Ra: ratio; Δ: difference)

	Structural formula	Resolvability		Physicochemical properties				Crystallographic properties		
			Sol	ρ / gcm^{-3}	mp / °C	ΔH_{melt} / kJmol^{-1}	space group	unit cell	hydrogen-bonding	conformation
1		**ee** 0.98 **Y** 0.38 **F** 0.37 solvent acetone								
			n less soluble	1.209 **Δ 0.029**	128.9 **Δ 7.0**	20.8 **Δ 4.9**	$P2_1$	**unit cell**	**hydrogen-bonding**	**conformation**
			p more soluble	1.180	121.9	15.9	$P2_1$	different	identical	different
2		**ee** 0.99 **Y** 0.32 **F** 0.32 solvent ethanol								
			Sol	**ρ / gcm^{-3}**	**mp / °C**	**ΔH_{melt} / kJmol^{-1}**	**space group**	**unit cell**	**hydrogen-bonding**	**conformation**
			n less soluble	1.372 **Δ 0.002**	decomposition	decomposition	$P2_1$	similar	different	similar
			p more soluble	1.370	decomposition	decomposition	$P2_1$			
3		**ee** ~0 **Y** ~0 **F** ~0								
			Sol / g100cm^{-3}	**ρ / gcm^{-3}**	**mp / °C**	**ΔH_{melt} / kJmol^{-1}**	**space group**	**unit cell**	**hydrogen-bonding**	**conformation**
			n 3.27 **Ra 1.4**	1.260 **Δ 0.026**	179 **Δ 15**	-	$P2_12_12_1$	different	similar	different
			p 2.34	1.234	194	-	$P2_12_12_1$			
4		**ee** 1.00 **Y** 0.54 **F** 0.54 solvent water								
			Sol / g100cm^{-3}	**ρ / gcm^{-3}**	**mp / °C**	**ΔH_{melt} / kJmol^{-1}**	**space group**	**unit cell**	**hydrogen-bonding**	**conformation**
			n 11.4 **Ra 4.2**	1.184 **Δ 0.006**	137 **Δ 17.5**	-	$P2_12_12_1$	different	different	different
			p 48.3	1.178	119.5	-	$P2_12_12_1$			
5		**ee** 0.99 **Y** 0.63 **F** 0.62 solvent methanol								
			Sol / g100cm^{-3}	**ρ / gcm^{-3}**	**mp / °C**	**ΔH_{melt} / kJmol^{-1}**	**space group**	**unit cell**	**hydrogen-bonding**	**conformation**
			n 20 **Ra 4.5**	1.240 **Δ 0.004**	129.2 **Δ 10.4**	42.7 **Δ 26.7**	$P2_1$	similar	similar	different
			p 4.4	1.244	139.6	69.4	$P2_1$			

the available structures of the diastereomeric salt pairs of 1-phenylethylamine were compared.

2 Discussion

2.1 Crystal structures of 1-phenylethylammonium salt diastereomers in the literature

In the present study a literature survey is presented based on a CSD (Cambridge Crystallographic Database) search. The database study is concerned with the crystal structures of diastereomeric salts containing 1-phenylethylamine. The CSD contains the crystal structures of 12 diastereomeric pairs with 1-phenylethylamine base. For 9 of them, the results of the optical resolutions have been published. The crystal structures of these 9 diastereomeric salt pairs are analyzed, compared and classified. To compare the structural features with the resolution results, the resolution efficiencies are employed on the basis of the Fogassy parameter (F) that is the product of the enantiomeric excess and the yield. Some physicochemical and crystallographic properties of the diastereomeric pairs are collected in Table 1.

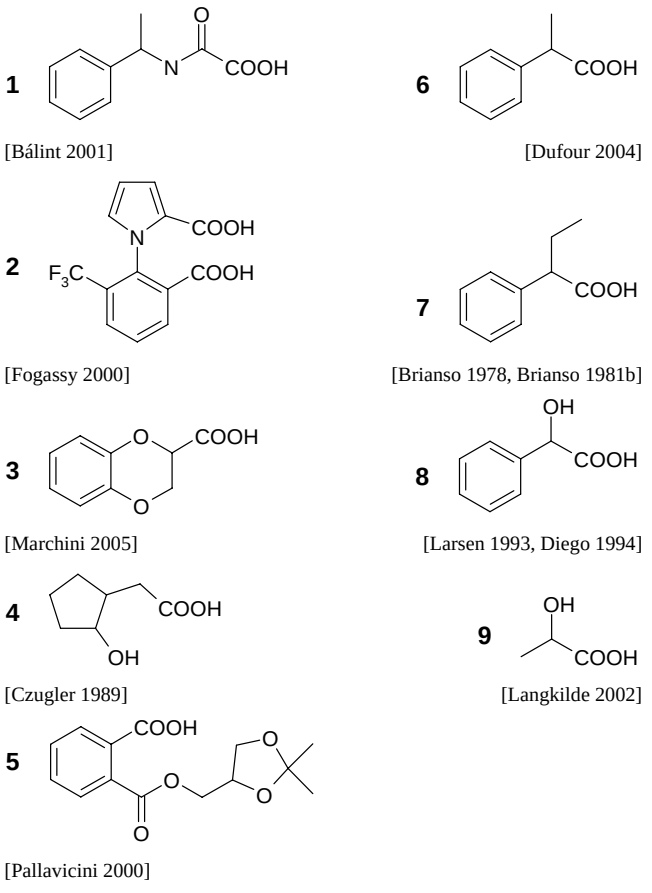

Fig. 1. Molecular structures of the acids and the reference to the original publications, single crystal data were taken from the CSD [1]

The molecular structures of the acids are shown in Fig. 1. Figs. 2, 3 and 4 were created with the ORTEP3v2 program [14].

2.2 Main structural differences in correlation with the resolution efficiency

2.2.1 Differences of the hydrogen bonding and the weak second-order interactions

The hydrogen bonding modes determine the feature of crystal structures of organic salts to a large extent. In many cases, the structures of the strong hydrogen bonds in the diastereomeric salts are similar. However, some exceptions can be found.

The best resolution (F: 0.86) in the presented literature survey was attained by Ingersoll with mandelic acid (compound **8**) a long time ago [16]. It is remarkable that the two diastereomers have a 15-fold solubility difference [22, 24]. Thus, significant structural differences including hydrogen bonds are expected, since the carboxyl and hydroxyl groups of mandelic acid are expected to create a complex hydrogen bond structure. In both diastereomers, two-dimensional hydrogen bond layers are formed but with different structures. In the less stable diastereomer, the hydrogen bond structure has a lower translational symmetry [22].

In the diastereomers of salt **4** [10], the number of hydrogen bonds is equal. However, in the more stable diastereomer, a two dimensional hydrogen bond network is formed, while in the less stable isomer, the hydrogen bond structure is one-dimensional. The ordering of the two-dimensional hydrogen bonded layers to a three-dimensional crystal lattice is easier than that of the one-dimensional rod-like units, which can give the basis of the separation (F: 0.54).

The atropisomers of salt **2** were resolved with 1-phenylethylamine by Faigl and co-workers [13]. The two diastereomers have very similar crystal structures (space group symmetry, cell parameters, calculated density, crystal packing). Notwithstanding, the differences in the hydrogen bonding make a moderately efficient (F: 0.32) diastereomer separation possible. The hydrogen bond structures are slightly different, and the more stable diastereomer has one more hydrogen bond than the less stable isomer.

The molecular conformations in the crystal lattices are influenced by weak secondary interactions. The secondary interactions stabilize the structure, while the weak interactions can force the molecules to take an energetically disadvantageous conformation.

In the case of salt **1** [2], the hydrogen bond structures in the diastereomers are similar. In the more stable salt, is formed an additional weak C(Ar)-H...O hydrogen bond which defines the molecular conformation of the acid molecules and significantly contributes to the crystal binding forces. The C(Ar)-H...O interaction ties the acids' phenyl rings into parallel position with each other (Fig. 2) and changes their conformation into a constrainted one. The energy asset of the weak C(Ar)-H...O hydrogen bond may overcompensate the conformational energy loss. The moderately efficient diastereomer separation (F: 0.37) is due to an interplay of the two effects.

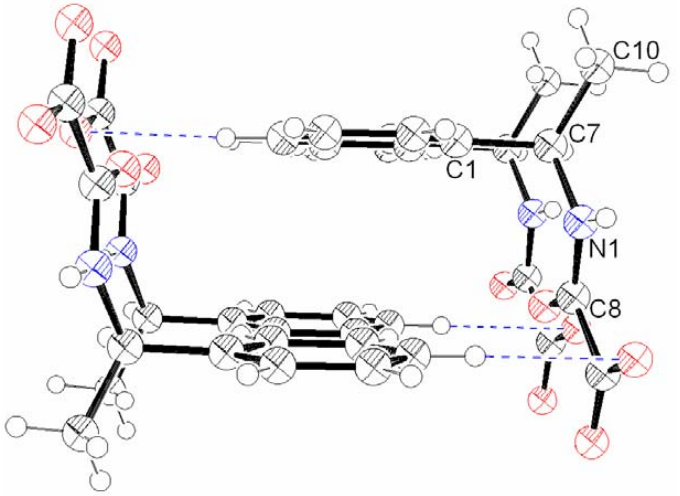

Fig. 2. C-H...O interaction of neighbouring anions in the more stable diastereomer of salt **1** (CSD reference code: YELQAH) (dashed lines mark C(Ar)-H...O hydrogen bond interactions) [1]

2.2.2 Conformational differences

The most striking difference between diastereomeric structures is observed when the molecular conformations of the two isomers significantly differ. (This is the case of salts **1**, **5** and **9**.) A characteristic example is salt **5** [26, 27] (Fig. 3). The open conformation (Figure 3.a) belongs to the more stable diastereomer. In the case of compound **5**, the presented conformational difference makes the efficient resolution possible (F: 0.62).

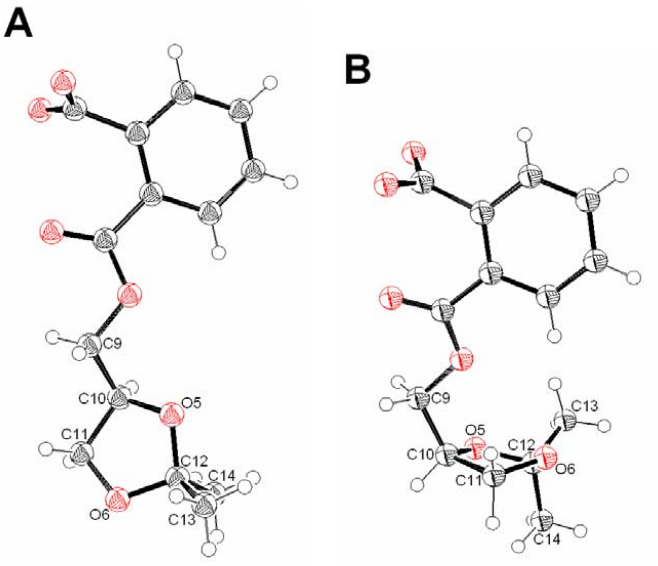

Fig. 3. Conformations of the acid molecules in the two diastereomers of compound 5 (A: in the more stable salt, B: in the less stable salt) [1]

Salt **9** [21] is exceptional, because one of its diastereomers crystallizes as a hydrate, and it is the less stable salt. (It is a rule of thumb that if one of the diastereomers is a solvate, then this will be the more stable one [19] .) However, the authors state that the solvate may be either the less stable or the more stable diastereomer with the same probability [21].) In the hydrate, the water molecule also takes part in the hydrogen bonding and more hydrogen bonds are formed than in the other isomer. Notwithstanding, it is not the difference in hydrogen bonding that makes the resolution possible since the hydrate will be the less stable salt. The second order interactions that appear in the crystal lattice of the hydrate, force the molecules of the acid **9** into a disfavoured conformation (Fig. 4.b) which considerably decreases the stability of this isomer, and makes an efficient resolution possible. The authors verified by quantum chemical calculations that the conformational energy loss can account for the solubility difference [21]. It is exceptional that the more dense structure is formed by the more soluble diastereomer, i.e. the hydrate (Table 1).

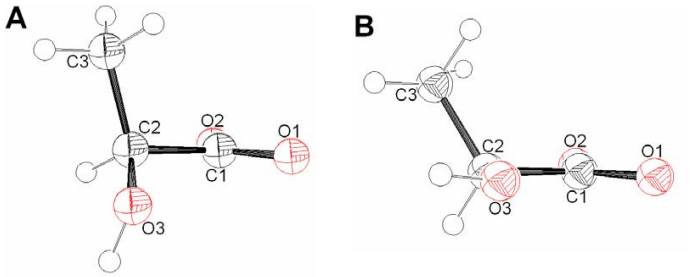

Fig. 4. Conformations of lactic acid in the two diastereomers of salt 9 (A: in the more stable salt, B: in the hydrate) [1]

The torsion angles corresponding to the presented conformational differences of salts **1**, **5** and **9** are summarized in Table 2.

Tab. 2. Main differences in the torsion angles in salts **1**, **5** and **9** (the numbering of the atoms is consistent with the Figs 2, 3, and 4)

	More stable isomer	Less stable isomer
Salt 1		
C8-N1-C7-C1	77.4(2)	152.48(13)
C8-N1-C7-C10	−157.38(16)	-81.78(17)
Salt 5		
C9-C10-C11-O6	−130.6(8)	−99.4(8)
C12-O6-C11-C10	−6.1(12)	−33.8(8)
C11-O6-C12-C13	137.9(11)	148.9(7)
C11-O6-C12-C14	−99.1(11)	−85.0(7)
C11-O6-C12-O5	21.5(12)	34.3(8)
C12-O5-C10-C9	146.4(9)	123.6(6)
C10-O5-C12-O6	−28.7(11)	−20.7(8)
C10-O5-C12-C13	−145.6(9)	−135.7(7)
C10-O5-C12-C14	90.1(10)	101.0(7)
O5-C10-C11-O6	−11.2(10)	20.3(8)
C12-O5-C10-C11	24.4(10)	-0.3(8)
Salt 9		
O1-C1-C2-O3	−32.44(12)	−1.40(11)
O1-C1-C2-C3	87.55(11)	121.36(9)
O2-C1-C2-O3	148.46(8)	179.47(8)
O2-C1-C2-C3	−91.55(11)	−57.76(11)

2.3 Differences of the stacking of the aromatic rings

The aim of the crystallization is to arrange the molecules into a compact and dense structure. The stacking of the aromatic rings can often come up as a problem. Diastereomers will

evidently crystallize in two different (more or less favourable) stacking modes.

Acids **6** [6] and **7** [7, 9] are homologous. Their phenylethylammonium salts have a similar simple ladder-shaped one-dimensional hydrogen bond sturcture for both of their diastereomers. The crystal lattices of their more stable diastereomers are almost superimposable. In these structures, the phenyl rings of the anions and the cations are parallel to each other. In their other isomers, the positions of the phenyl rings are perpendicular to each other [8] The parallel or perpendicular stacking of the phenyl rings result in a more dense structure in the more stable diastereomer and a less dense packing in the less stable diastereomer, respectively. The resolvability is related to the density difference of the diastereomers. For salt **7**, the resolution efficiency (F: 0.77) [24] twice as high as that for salt **6** (F: 0.39) [24]. The density difference of the diastereomers of salt **7** ($\Delta\rho$: 0,160 g cm^{-3}) is also more than two-fold compared to salt **6** ($\Delta\rho$: 0,072 g cm^{-3}).

In diastereomers of the salt **3** [25], there is a small difference in the direction of the benzodioxane ring of the anion *vs.* the position of the cation. This difference is not as significant as in salts **6** and **7** therefore, the density difference is also smaller ($\Delta\rho$: 0,026 g cm^{-3}). The diastereomers of salt **3** cannot be separated by crystallization [5].

In those cases, where the basis of the resolvability is the difference in the stacking of the aromatic rings, efficient diastereomer separation is attainable only when the density difference of the diastereomers is large.

3 Conclusion

Three types of structural features were found to have significant effects on the separation of the studied 1-phenylethylammonium diastereomers by crystallization. Namely, the *hydrogen bonding system*, the *conformational differences* of the anions and the *stacking of the aromatic rings*. In the case of a given salt pair, the effect of one of these features is dominant and can be regarded as responsible for the resolution of the diastereomers.

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