

Seventeen-Membered Water Cluster Resulting from Recognition of Solvated Anions on Brucinium Corrugated Layers

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Supporting Information

ABSTRACT: Formation of diastereomeric salts remains the most important method for the separation of racemic acids and bases. Selection of a suitable resolving agent in this method is a key for successful resolution. There are primary, secondary, and tertiary chiral amines among frequently used resolving agents for the separation of racemic acids. Cations of most of them and anions of resolved acids are linked to each other by a characteristic system of hydrogen bonds resulting in common cationic-anionic self-assemblies. In this respect, brucine and



strychnine are unique, because incorporation of anionic species into a crystal lattice of their salts usually does not affect common cationic self-assembly. The uniqueness of both resolving agents is also reflected in a high frequency of solvated salt formation. In this paper, we show that the presence of water molecules incorporated into the crystal lattice of the brucinium salt may result from recognition of the resolved compound together with its closest aqueous environment on the common brucinium corrugated layers. Performing racemic resolution of model compounds and studying structural relations between succeeding crystalline fractions, we also point out factors responsible for the successful separation of N-(4-nitrobenzoyl)alanine by fractional crystallization of brucinium diastereomeric salts.

■ INTRODUCTION

Pasteur's (1853) resolution of racemic compounds via formation and fractional crystallization of diastereomeric salts of chiral resolving agent remains the most practically important method for the preparation of enantiopure compounds.^{1,2} During such resolution, any chiral amine can be used as a resolving agent. However, for some reasons, such as accessibility or price, some chiral amines are more frequently used for the separation of racemic acids than others. Among them, there are primary, secondary, and tertiary chiral amines. Usually, they form common hydrogen-bonded cationicanionic self-assemblies.³⁻⁷ For example, cations and anions are linked to each other by an ionic hydrogen bond system defined by an $R_4^{3}(10)$ graph set^{8,9} in 72% of 324 chiral crystal structures of 1-arylethylammonium salts (CSD 5.35).¹⁰ The $C_2^{2}(6)$ or $C_2^{1}(4)$ graph sets define ionic hydrogen bond patterns between cations and anions in 67% of 46 crystal structures of ephedrinium, pseudoephedrinium, or deoxyephedrinium salts. Characteristic of chininium, chinidinium, cinchoninium, or cynchonidinium salts (54% of 66 structures) is the presence of cationic-anionic chains defined by the $C_2^{2}(9)$ graph set. In this respect, brucine and strychnine are unique, because incorporation of anionic species into the crystal lattice of their salts usually does not affect common cationic self-assembly. Similar, stabilized by hydrophobic interactions only, cationic self-assemblies are observed in 79% of 34 crystal structures of strychnium salts and 70% of 102 crystal structures of brucinium salts.

It indicates that driving forces, leading to molecular recognition of an acid by brucine or strychnine, may be different from those leading to molecular recognition of the acid by other resolving agents. Previously, we showed that both enantiomers of resolved N-(4-nitrobenzoyl)- or N-(3,5dinitrobenzoyl)amino acids (alanine, serine, asparagine, and aspartic acid) are recognized in a similar way by hydrophobic interactions of the N-protected group in deep rows of common strychninium corrugated layers.^{11,12} In these cases, diastereomeric diversification has been realized by different hydrogen bond patterns observed in both strychninium diastereomeric salts. On the other hand, in cases in which both diastereomeric salt cations and anions are linked to each other by a similar hydrogen bond network, as has been observed in many crystal structures of salts of many other resolving agents, diastereomeric diversification is often related to differences in hydrophobic interactions in both diastereomeric salts.^{13,14}

The different driving forces leading to recognition in strychninium or brucininium salts and in salts of many other resolving agents are reflected in the frequency of solvates formation. Contrary to the others, brucine and strychnine reveal a strong tendency to form solvated salts. Nearly 82% of strychninium, 89% of brucinium, and only 6% of 1arylethylammonium salts are solvates. Among brucinium and strychninium salts, 61 and 64% are hydrates, respectively. If

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Scheme 1



only hydrates are taken into account, these values are far from the frequency of hydrates that resulted from database analysis, which for the presence of a carboxylate group is equal to 35%.¹⁵ It is worth mentioning that the percentage of solvated 1arylethylammonium salts is comparable to the frequency of solvated cocrystals.¹⁶

Recognition on the surface of a resolving agent self-assembly supplies interesting information about fruitful or fruitless racemic resolution, like two possible mechanisms of double-salt formation.¹⁷ or factors governing the kinetics of salt precipitation.¹⁸ However, it also can supply information about the resolved compound itself. Governed by the dielectric constant of the solvent, the ability of spontaneous racemic resolution of *N*-(3,5-dinitrobenzoyl)asparagine is the best example of it.¹² In this paper, we present racemic resolution of *N*-(4-nitrobenzoyl)alanine by formation of brucinium diastereomeric salts (Scheme 1).¹⁹

EXPERIMENTAL SECTION

N-(4-Nitrobenzoyl)alanine was synthesized in a reaction of 4nitrobenzoyl chloride with DL-alanine in water by applying standard procedures.²⁰ Racemic resolution of the alanine derivative was performed by fractional crystallization of brucinium salts. Anhydrous brucine (100 mg, commercially available) and an equimolar amount of *N*-(4-nitrobenzoyl)alanine were dissolved in 10 mL of methanol (p.a.). The sample was left for solvent evaporation at room temperature. Pale yellow crystals of brucinium *N*-(4-nitrobenzoyl)-D-alaninate methanol disolvate [**B4NBDA(1**)] precipitated as a first fraction in a few hours. Crystals of **B4NBDA(1**) were separated from the mother liquid. Yellow crystals of brucinium *N*-(4-nitrobenzoyl)-L-alaninate 4.8hydrate [**B4NBLA(2**)] precipitated from the filtrate as a further fraction after 1 day.

X-ray data for both crystalline fractions were collected on a Kuma KM4CCD diffractometer (Mo K α radiation; $\lambda = 0.71073$ Å). X-ray data for each compound were collected at 100 K using an Oxford Cryosystems device. Data reduction and analysis were conducted with the CrysAlis "RED" program.²¹ Space groups were determined using XPREP.²² Structures were determined by direct methods using SHELXS-2013 and refined using all F^2 data, as implemented in SHELXL-2013.²³ Non-hydrogen atoms were refined with anisotropic displacement parameters. In B4NBLA(2), one of four crystallographically unrelated anions, the carboxylate O atom of another, and eight of 19 crystallographically unrelated water molecules reveal twoposition disorder. Preliminary, occupancy factors were calculated separately for each of the crystallographically unrelated components. It allowed us to group particular components of the disorder into two groups, depending on occupancy factors. The occupancy factor of the major components is equal to 0.70, and the occupancy factor of the minor components is equal to 0.30. Besides, two maxima on the $\Delta \rho$ map were interpreted as an additional two water molecules, both with occupancy factors equal to 0.10. Displacement parameters of the disordered atoms with occupancy factors of <0.5 were restrained to be approximately isotropic (ISOR). For partially overlapping atoms, the SIMU restraint was applied. H atoms of a majority of water molecules

with occupancy factors of <0.5 were not found in the $\Delta\rho$ map. All other H atoms were found in $\Delta\rho$ maps or placed at calculated positions. Before the last refinement cycle, all H atoms were fixed and allowed to ride on their parent atoms. The absolute structures were chosen on the basis of the known absolute configuration of brucine.²⁴

Crystal data for brucinium *N*-(4-nitrobenzoyl)-D-alaninate methanol disolvate [**B4NBDA**(1)]: $C_{23}H_{27}N_2O_4^+ C_{10}H_9N_2O_5^- 2CH_4O$, M = 696.74, orthorhombic, $P2_12_12_1$, a = 7.668(2) Å, b = 12.341(3) Å, c = 35.548(4) Å, V = 3363.9(13) Å³, Z = 4, $D_c = 1.376$ Mg m⁻³, T = 100(2) K, R = 0.059, wR = 0.107 [4773 reflections with $I > 2\sigma(I)$] for 451 variables. Crystal data for brucinium *N*-(4-nitrobenzoyl)-L-alaninate 4.8-hydrate [**B4NBLA**(2)]: $C_{23}H_{27}N_2O_4^+ C_{10}H_9N_2O_5^-$ 4.8H₂O, M = 719.13, monoclinic, C2, a = 31.826(6) Å, b = 12.510(3) Å, c = 35.668(3) Å, $\beta = 104.98(3)^\circ$, V = 13718(5) Å³, Z = 16, $D_c = 1.393$ Mg m⁻³, T = 100(2) K, R = 0.095, wR = 0.155 [16741 reflections with $I > 2\sigma(I)$] for 2097 variables.

RESULTS

B4NBDA(1) is quasi-isomorphous with the previously reported crystal structure of brucinium *N*-(4-nitrobenzoyl)-D-serinate methanol disolvate and the solid solution of brucinium *N*-(4-nitrobenzoyl)serinate methanol disolvate.²⁵ Brucinium cations form common corrugated layers, stabilized by hydrophobic interactions (Figure 1).^{26–28} *N*-(4-Nitrobenzoyl)-D-



Figure 1. Orientation of N-(4-nitrobenzoyl)-D-alaninate anions and methanol molecules to the surface of the common corrugated brucinium layer (blue) in B4NBDA(1).^{30,31}

alaninate anions are bonded to the layer by ionic N–H⁺···O⁻ hydrogen bond and hydrophobic C–H···O interactions. The nitro group of the anions, located in shallow holes in the brucinium layer, participates in the C–H···O interactions. Consecutive anions, bonded to one brucinium layer, are linked to each other by C–H···O hydrogen bonds. In turn, anions, bonded to neighboring brucinium layers, are linked to each other by N–H···O⁻ hydrogen bonds. Methanol molecules are located in narrow channels formed between the corrugated cationic and relatively flat anionic layer. Methanol molecules are involved in O–H···O hydrogen bonds, in which the O4 amide atom of cations and the O7 amide atom of the anions are acceptors.

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In **B4NBLA(2)**, there are four crystallographically unrelated brucinium N-(4-nitrobenzoyl)-L-alaninate ion pairs and 19 water molecules (the major components of the disorder) in an asymmetric part of the unit cell. Brucinium cations form two crystallographically unrelated corrugated layers. The cationic layers in **B4NBLA(2)** are somehow modified as compared to the common corrugated brucinium layers. Two corrugated brucinium ribbons are assembled in a way in which concave parts of one meet concave parts of the other (like in the common corrugated layers). However, the two consecutive ribbons are shifted, so their concave parts meet convex parts of the former. Anions, linked by ionic $N-H^+\cdots O^-$ hydrogen bonds to one brucinium layer, form N4(nitro)…O4(amide) and other hydrophobic interactions with the neighboring brucinium layer (Figure 2). Crystallographically unrelated



Figure 2. Packing of B4NBLA(2). Corrugated brucinium layers (blue) are separated by N-(4-nitrobenzoyl)alaninate anions bonded to the water dimer and the 17-membered water cluster.^{30,31}

water molecules are assembled as a dimer and a 17-membered water cluster (see Scheme 2). The carboxylate O and the amide N atoms of the anions are bonded to the 17-membered water

Scheme 2. Representation of the 17-Membered Water Cluster (red) Presented in B4NBLA(2) and the Hydrogen-Bonded Carboxylate O and Amide N Atoms of the Anions (R is a 4-nitrobenzoyl group)¹⁹



cluster, and their amide O atom is bonded to neighboring water clusters or the water dimer. The water dimer forms hydrogen bonds with the carboxylate and the amide O atoms of three anions bonded to the same 17-membered water cluster.

DISCUSSION

The crystal structures described above result from fruitful racemic resolution of N-(4-nitrobenzoyl)alanine by fractional crystallization of brucinium diastereomeric salts. It seems that the most important factor driving the separation of both the brucinium diastereomeric salts is related to recognition of the carboxylate and the nitro groups of N-(4-nitrobenzoyl)-D-alaninate anions by the same brucinium corrugated layer. It results in a relatively flat surface and in a fast precipitation of brucinium N-(4-nitrobenzoyl)-D-alaninate methanol disolvate.

Similar recognition of the carboxylate and the nitro group of anions on the same brucinium corrugated layers was observed in solid solutions of brucinium diastereomeric salts with N-(3nitrobenzoyl)amino acids (alanine, serine, and threonine) or N-(4-nitrobenzoyl)serine. On the basis of the crystal structures of related brucinium salts with N-(4-nitrobenzoyl)serinate methanol disolvate, it seems that N-(4-nitrobenzoyl)-L-alaninate anions could be recognized in a similar way and form a solid solution as was observed for the serine analogue. However, if the statistical analysis is taken into account (CSD 5.35), the conformation of N-(4-nitrobenzoyl)-L-serinate [here the H- $C(\alpha)$ -N-H torsion angle] in the solid solution of brucinium N-(4-nitrobenzoyl)-(D_{0.85}L_{0.15})-serinate methanol disolvate is unfavorable. Unlike the alanine analogue, the intermolecular O-H…O hydrogen bond, in which the hydroxyl group of the serine derivative is involved, may stabilize the unfavorable conformation. The lack of such a stabilizing factor leads to racemic resolution of N-(4-nitrobenzoyl)alanine by fractional crystallization of brucinium salts.

Another consequence of the difference between N-(4nitrobenzoyl)serine (containing the hydroxyl group) and N-(4-nitrobenzoyl)alanine (without the hydroxyl group) is the formation of various solvates of the brucinium salts with the L enantiomer of the alanine or the serine derivative. In two solvates of brucinium N-(4-nitrobenzovl)-L-serinate (methanol 1.66-solvate 1.66-hydrate and methanol tetrasolvate) obtained from a methanol solution, water and methanol, or methanol molecules form short, at most 7-membered, hydrogen-bonded chains. In B4NBLA(2), water molecules form 17-membered water clusters built up of three five-membered conjugated rings and one four-membered conjugated ring (Scheme 2). If the carboxylate group of the anions, hydrogen bonded to water molecules, is taken into account, the cluster is extended on four additional five-membered rings [two defined by $R_5^{5}(10)$ and two defined by $R_4^{4}(10)$ graph sets]. In turn, if the fact that the carboxylate O and amide N atoms of the anions are bonded to the same water cluster is taken into account, one additional $R_2^{2}(7)$ ring and three additional $R_5^{5}(13)$ rings are formed with the 17-membered water cluster. The water dimer, hydrogen bonded to the carboxylate and to the amide O atoms, also forms rings with the 17-membered water cluster [among them $R_5^4(13)$ and $R_6^5(17)$]. B4NBLA(2) seems to reflect a recognition of the anions together with their closest aqueous environment on the surface of a brucinium corrugated layer. Among the anions with their closest aqueous environment, we found one in which even the methyl group is surrounded by water molecules. Thirteen of the 19 unrelated water molecules, bonded to each other as well as to both the carboxylate O and

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the amide O and N atoms of the anion, participate in the solvation of its methyl group (Figure 3). Such connected water molecules are like a basket with the methyl group directed inward.



Figure 3. Two selected views of the methyl group surrounded by 13 water molecules in B4NBLA(2). Atoms of anions, which form hydrogen bonds with the water molecules, are shown as blue spheres.^{30,31}

The previously mentioned high percentage of solvated brucinium salts (89%) mainly results from a strong tendency of the amide O atom of the common brucinium corrugated layers to participate in hydrogen bonds, in which solvent molecules are their donors.^{27,29} Also, in **B4NBDA(1)** and in **B4NBLA(2)**, methanol molecules and the 17-membered water cluster, respectively, form hydrogen bonds with the amide O atom of the corrugated layers. Recognition of the anions together with their closest solvation sphere, as observed in **B4NBLA(2)**, may contribute to the high percentage of solvated brucinium salts.

CONCLUSIONS

We showed that, contrary to the unsuccessful racemic resolution of N-(3-nitrobenzoyl)amino acids (alanine, serine, and threonine) or N-(4-nitrobenzoyl)serine resulting in the formation of a solid solution of brucinium salts, brucine is a suitable resolving agent for racemic resolution of N-(4nitrobenzoyl)alanine. Recognition of the carboxylate and the nitro groups of N-(4-nitrobenzoyl)-D-alaninate anions on the same brucinium corrugated layers leads to the fast precipitation of the first fraction, B4NBDA(1). The recognition of N-(4nitrobenzoyl)-D-alaninate anions is similar to the recognition of suitable anions in the solid solutions mentioned above. Comparison of B4NBDA(1) with the solid solution of brucinium N-(4-nitrobenzoyl)-(D_{0.85}L_{0.15})-serinate methanol disolvate displays that probably a lack of additional stabilization of the unfavorable conformation of the alanine derivative is the main factor leading to its racemic resolution.

In the further fraction, B4NBLA(2), the carboxylate and the nitro groups are recognized by neighboring layers. B4NBLA(2) reflects a recognition of N-(4-nitrobenzoyl)-L-alaninate anions together with closest aqueous environments on the brucinium layers.

ASSOCIATED CONTENT

S Supporting Information

CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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