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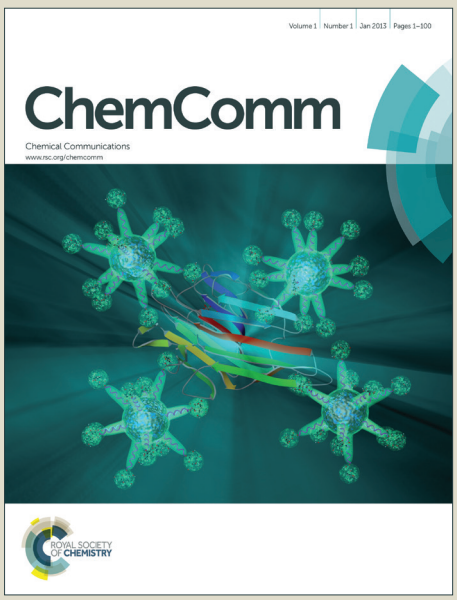

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ARTICLE TYPE

One hydrogen bond does not a separation make, or does it? Resolution of amines by diacetoneketogulonic acid

Nikoletta B. Báthori,[a]* Luigi R. Nassimbeni[a] and Jacco van de Streek[b]

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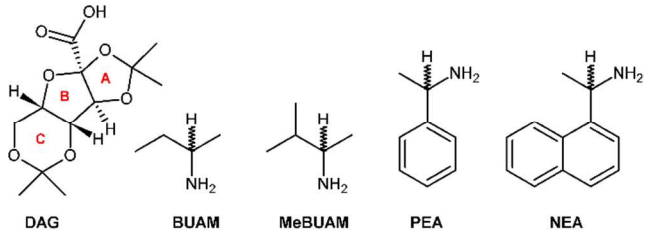
Diacetoneketogulonic acid was used to separate primary amines from their racemic modifications and the selectivity of the acid was rationalized by lattice energy calculations and analyzing the weak interactions around the captured amines.

Selectivity arises from the phenomenon of molecular recognition and depends on such factors as complementarity of binding sites, the strengths of the relevant non-bonding interactions between the reactants and the conformational adaptability of the molecules. Supramolecular selectivity, whereby a host shows preference for a particular guest and separates it from a mixture, is relevant in many applications, such as petroleum chemistry or pharmaceutics. In this way one can segregate a given constitutional isomer from a solution containing several components which have similar boiling points (e.g. xylene isomers[1], tautomers[2]) where distillation techniques would be inefficient. A most demanding form of separation is that of enantiomeric resolution. This because the physical properties of the *R* and *S* forms of the two optical isomers have identical characteristics such as melting point, boiling point, vapour pressure and density and differ only in their reactions toward homo-chiral compounds and polarized light. Resolution of racemic modifications of organic molecules is of considerable importance to the pharmaceutical industry because 90% of drugs currently used are chiral.[3] These compounds represents close to 30% of all drug sales worldwide[4], thus substantial effort has been put into developing efficient resolution methods.

The most common procedure for resolving a racemate is *via* diastereomeric salt formation, a method which has been reviewed.[5] The most famous resolution experiment was carried out by Pasteur, in which he manually separated crystals of sodium ammonium tartrate tetrahydrate and showed that, when dissolved, they turned polarized light in opposite directions.[6] It is interesting to note that after 166 years of research, although there is a constant interest in this topic,[7] the mechanism of the enantiomeric resolution via diastereomeric salt formation is still not fully understood.

In this work, a sugar derivative was employed to resolve racemic chiral amines (Scheme 1[8]) and the non-bonding interactions which give rise to the structures of the diastereomeric salts were analyzed.

(−)-2,3:4,6-Di-O-isopropylidene-2-keto-L-gulonic acid, (diacetoneketogulonic acid, DAG[9]) is a useful resolving agent because it is relatively inexpensive, is water soluble, and forms



Scheme 1 Molecular structure of (-)-2,3:4,6-Di-O-isopropylidene-2-keto-L-gulonic acid, (diacetoneketogulonic acid, DAG), 2-butylamine (BUAM), 3-methyl-2-butylamine (MeBUAM), 1-phenylethylamine (PEA) and 1-naphthylethylamine (NEA).

crystalline salts with a variety of amines (Kozma lists 10 references and 8 patents for the resolution of various amines with this acid[5]).

The structures of six diastereomeric salts were elucidated which crystallized from solutions of DAG with 2-butylamine (BUAM), 3-methyl-2-butylamine (MeBUAM), 1-phenylethylamine (PEA) and 1-naphthylethylamine (NEA). The experimental details of the crystallization, the crystal data and refinement parameters are reported in Table S1 and their prominent intermolecular interactions are summarized in Table S2 in the Electronic Supplementary Information (ESI).

The (DAG^-)($BUAM^+$), obtained from the racemic BUAM, crystallizes in the space group $P2_12_12_1$ with Z=4. The three rings of DAG are *cis* fused; ring A has an envelope conformation while rings B and C can be described as a twist boat and chair conformation, respectively. (Scheme 1) The structure is a salt, with the carboxylic proton having transferred to the nitrogen of the amine, and is stabilized by (DAG)-$COO^-\cdots H_3N^+$-(BUAM) hydrogen bonds (Table 2S) which may be described as $R_2^3(10)$ graph set notation.[10] The BUAM was not resolved, and both the *R* and *S* enantiomers are present at the same site, although in slightly differing proportion (56% *R* and 44% *S*). The packing, Fig. 1a, shows the $BUAM^+$ cations (red: *R* conformer, blue: S conformer) located in channels running along a two-fold screw axis.

Crystallization of DAG from racemic MeBUAM yielded (DAG^-) (*R*-$MeBUAM^+$) crystals (space group $P2_12_12_1$ with Z=4). The structure is similar to the (DAG^-)($BUAM^+$) and is again stabilized by (DAG)-$COO^-...H_3N^+$-(MeBUAM) hydrogen bonds.

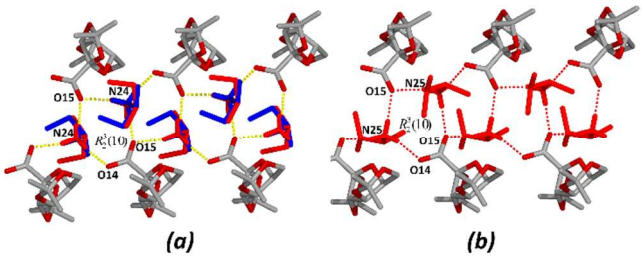


Fig.1 Hydrogen bonding motifs in a: (DAG^-)($BUAM^+$) and b: (DAG^-) (*R*-$MeBUAM^+$). The crystals are isostructural and the hydrogen bonds may be described with $R_2^3(10)$ graph set notation.

The DAG anions build an isostructural network in both the structure containing *R* and *S*-$BUAM^+$ and that containing *R*-$MeBUAM^+$ cations (Fig. 1b). Many attempts were made to crystallize DAG with *S*-MeBUAM but our efforts were unsuccessful and all experiments yielded gels. (See ESI.)

DAG was exposed to the racemic mixture of PEA and crystals of (DAG^-)(*R*-PEA^+) were obtained after 3 days ($P2_1$, Z=4). There are two DAG^- and two *R*-PEA^+ ions in the asymmetric unit. The packing is characterized by a series of hydrogen-bonded rings, each of which may be described with graph set notation as $R_2^3(10)$. This hydrogen-bonded framework of fused rings forms an infinite column running in the two-fold screw axis. (Fig. 2a) Analysis of the refined structure gave no evidence of the existence of the *S*-PEA^+ ion, thus the resolution was 100% successful. The (DAG^-)(*S*-PEA^+) structure was obtained by exposing the acid to pure *S*-PEA. The packing is similar to that of the previous structure except that now the *c* axis is halved. This results in the hydrogen bonding being symmetrical about the screw diad (Fig. S1, ESI). The host molecules build an isostructural skeleton in the two structures and the chiral amines are located in similar positions in the two structures (Fig. 2).

The (DAG^-)(*S*-NEA^+) was obtained from the racemic modification of the amine[11] and crystallizes in $P2_1$ with Z=2. The hydrogen-bonding pattern again consist of fused rings, $R_3^4(10)$. In addition there is a close contact between the chiral methyl group of the *S*-NEA^+ and one of the ether oxygen of the neighboring host (C30-H30…O6, 3.67Å, 169.5°) (Fig. 3a, green arrow). The (DAG^-)(*R*-NEA^+) arose from exposing the acid to pure *R*-NEA. Its structure is different from that of its related diastereomeric salt (space group $P2_12_12_1$, Z=4). Not only are the cell parameters different but the packing is now characterized by chains of hydrogen bonded rings running in the [010] which may be described as $R_2^2(10)$ and $R_3^3(9)$ (Fig.3). While in the (DAG^-)(*S*-NEA^+) an additional host-guest interaction was noted involving the chiral carbon, in (DAG^-)(*R*-NEA^+) a host-host interaction appears instead (C5-H5…O15, 3.37Å, 170.4°) (Fig. 3b, green arrow). Also the forced formation of the (DAG^-)(*R*-NEA^+) salt results in a significant torsional change of the carboxylate moiety (Table S3).

The salient question which arises from this work is why does DAG select *R*-MeBUAM, *R*-PEA but *S*-NEA from their respective racemic modifications?

In the case of the MeBUAM selectivity experiment, the answer remains hidden; the comparison of the salt structures are impossible because of the lack of the structure of the opposite diastereomer salt.

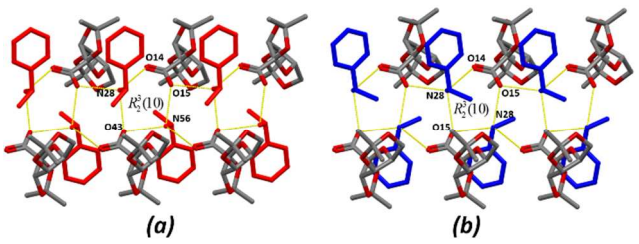


Fig. 2 Hydrogen bonding in (DAG^-)(*R*-PEA^+) (DAG^-)(*S*-PEA^+), *a* and *b* respectively.

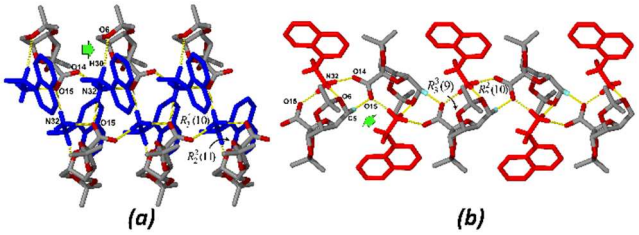


Fig.3 Packing diagram of (DAG^-)(*S*-NEA^+) *(a)* and (DAG^-)(*R*-NEA^+) *(b)*. The green arrows indicate the main difference in the interactions.

Analysis of fingerprint plots[12], and the 2D representation of the Hirshfeld surface[13] for the PEA and NEA cations generated with the program Crystal Explorer[14] revealed a significantly higher percentage of O···H interactions in the favored salt structures. The *R*-PEA^+ cation has *ca*. 4% more, while the *S*-NEA^+ cation has 7% more O···H interaction with the surrounding crystal phase and the % of the generally repulsive H···H interactions are less in the favored structures (Fig. 1S and S2, ESI).

Lattice energy calculation is a viable tool to search for the thermodynamically more stable structure of a given compound.[15] The method is commonly employed to analyse polymorphs and this is relevant to the current work because enantiomers and diastereomeric salts have the same chemical composition and the same covalent connectivity.[16] Lattice energy calculations with dispersion-corrected density functional theory were conducted on the PEA and NEA diastereomeric pairs employing the program *GRACE*[17], details are given in the ESI. In case of the PEA salts, the calculated lattice energy of the (DAG^-)(*R*-PEA^+) structure is 1.5 kcal mol^{-1} lower than the (DAG^-)(*S*-PEA^+). For the NEA salt pair, the difference in the energies is 0.5 kcal mol^{-1} favoring the (DAG^-)(*R*-NEA^+) structure, which is not significant because the method carries *ca*. 0.5 kcal mol^{-1} error.

The previously discussed selectivity experiments with PEA and NEA were repeated by exposing DAG to the vapor of the racemic modifications for 30 mins at 50 °C (Fig. S4, ESI). The reaction was followed by PXRD and it revealed that DAG is selective towards the *R* enantiomer of the PEA, similar to the crystallization experiments (Fig. S5). In case of exposing DAG to *rac*-NEA, the XRD indicated no formation of diastereomeric salts in solid-vapor sorption experiments under 30 mins (Fig. S6). This is due to the low vapour pressure of NEA (ca. 4 mmHg for PEA and 0.02 mmHg for NEA at 50°C).

This finding supports the results of the lattice energy calculations and suggest that the discrimination process is subtle, meaning that the crystals that are obtained from the crystallization are likely to be the thermodynamic product.

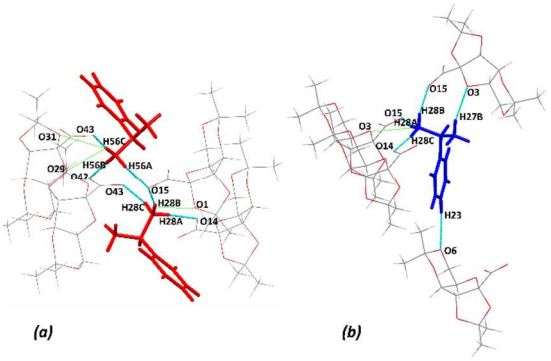


Fig.4 *(a)* The hydrogen bonding of *R*-PEA$^+$ (red) with the three charge assisted bonds between the amino and the carboxylate moieties and the extra interaction between the chiral carbon of the cation and the ether oxygen of the anion. (b) The hydrogen bonding of *S*-PEA$^+$ (blue) with the three charge-assisted bonds between the amino and the carboxylate moieties and the extra interaction between the two neighboring anions. Charge-assisted hydrogen bonds are light blue and hydrogen bonds with ether oxygen atoms are green.

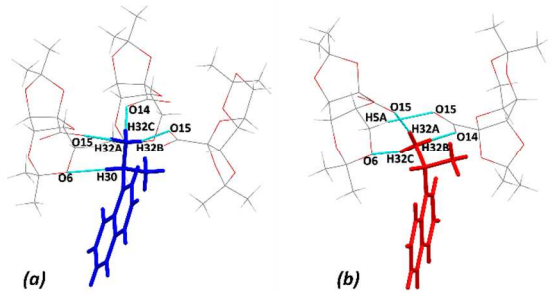


Fig. **5** *(a)* The hydrogen bonding of *S*-NEA$^+$ (blue) with the three charge assisted bonds between the amino and the carboxylate moieties and the extra interaction between the chiral carbon of the cation and the ether oxygen of the anion. (b) The hydrogen bonding of *R*-NEA$^+$ (red) with the three charge assisted bonds between the amino and the carboxylate moieties and the extra interaction between the two neighbouring anions.

Further evidence for the preferential capture of *R*-PEA and *S*-NEA maybe gained from analysis of the hydrogen bonding (metrics displayed in Table 2S, ESI). For (DAG$^-$)(*R*-PEA$^+$) each $-NH_3^+$ moiety is hydrogen bonded to a carboxylate oxygen. In addition, the interaction involving the H56B atom is trifurcated and likewise the H28B is bifurcated between carboxylate and ether oxygen atoms. Similarly, in (DAG$^-$)(*S*-PEA$^+$) the amino hydrogen atoms are involved in charge-assisted hydrogen bonds and that with H28A is bifurcated. There are two additional CH···O(ether) interactions, located between the *S*-PEA$^+$ and neighboring anions. The nature of the interactions in the two diastereomeric salts are similar but (DAG$^-$)(*R*-PEA$^+$) has the shorter hydrogen bonds with better geometries (Fig. S4).

Analysis of the (DAG$^-$)(*S*-NEA$^+$) shows that there are three distinct $-NH_3^+\cdots{}^-OOC-$ hydrogen bonds and an additional −CH···O(ether) interaction can be noted between the hydrogen of the chiral carbon (H30) and the ether oxygen of the DAG$^-$. The corresponding hydrogen bond for the (DAG$^-$)(*R*-NEA$^+$) structure has only two $-NH_3^+\cdots{}^-OOC-$ hydrogen bonds and the third hydrogen bond of the $-NH_3^+$ with an ether oxygen. An extra anion-anion interaction is noted but the cation displays no contacts via its chiral region (Fig. 5). This observation resembles recently published results of a selectivity experiment where the unsuccessful discrimination was explained with the stronger C···H interactions between the molecules of the resolving agent.[18]

In summary, the sugar derivative resolving agent diacetoneketogulonic acid, DAG, forms diastereomeric salts with the selected amines. The acid is not selective towards BUAM but shows 100% discrimination if exposed to racemic MeBUAM, PEA and NEA. In particular it forms diastereomeric salt pairs capturing *R*-MeBUAM, *R*-PEA but *S*-NEA from their respected racemic modifications from solution crystallizations. In the case of the PEA salts, the selectivity is a result of the sum of the hydrogen bonds formed between the cation and the anion while in the NEA salts the selectivity can be explained by the formation of one additional hydrogen bond between the selected guest and the host via its chiral moiety.

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Notes and references

[a] *Crystal Engineering Unit, Department of Chemistry, Faculty of Applied Sciences, Cape Town, 8000, South Africa, Fax: +27 21 460 3854; Tel: +27 21 460 8354; E-mail: bathorin@cput.ac.za*
[b] *University of Copenhagen, Department of Pharmacy, Universitetsparken 2, 2100 Copenhagen, Denmark*

† Electronic Supplementary Information (ESI) available: Preparation of diastereomeric salts and their single crystal data, hydrogen-bond metrics, fingerprint plots, details of lattice energy calcuations and XRD data for vapor sorption experiments are deposited. See DOI: 10.1039/b000000x/

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