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

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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 isomer from a solution containing several components which have similar boiling points (e.g. xylene isomers1, tautomers2) 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 worldwide4, 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) and the non-bonding interactions which give rise to the structures of the diastereomeric salts were analyzed. (-)-2,3,5,12-Di-O-isopropylidene-2-keto-L-gulonic acid, (diacetoneketogulonic acid, DAG)8 is a useful resolving agent because it is relatively inexpensive, is water soluble, and forms crystalline salts with a variety of amines (Kozma lists 10 references and 8 patents for the resolution of various amines with this acid9).

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 P212121 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)3COO− ions (red: R+ cations (blue: S−) and is again stabilized by (DAG)3COO−...H3N−(BUAM) hydrogen bonds (Table 2S) which may be described as R23(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)−(MeBUAM)+ crystals (space group P212121 with Z=4). The structure is similar to the (DAG)(BUAM)− and is again stabilized by (DAG)−COO−...H3N−(MeBUAM) hydrogen bonds.
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 (P21, 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
R2(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 amine11 and crystallizes in P21, with Z = 2.
The hydrogen-bonding pattern again consist of fused rings, R2(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 P212121, 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 R2(10) and R5(9) (Fig. 3b). 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.
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)+−CH···O(ether) interactions, located between the guest and the host via its chiral moiety.

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

8 Marvin was used for drawing chemical structures and substructures, Marvin 6.3.0, 2014, ChemAxon (http://www.chemaxon.com)
11 This compound was previously obtained by resolution of racemic NEA with DAG using acetone as solvent, but no structural data were obtained: E. Mohiaccsi and W. Leimgruber, Organic Syntheses, 1976, 55, 80.