Quasiracemic Materials

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Rediscovering Pasteur's Quasiracemates**

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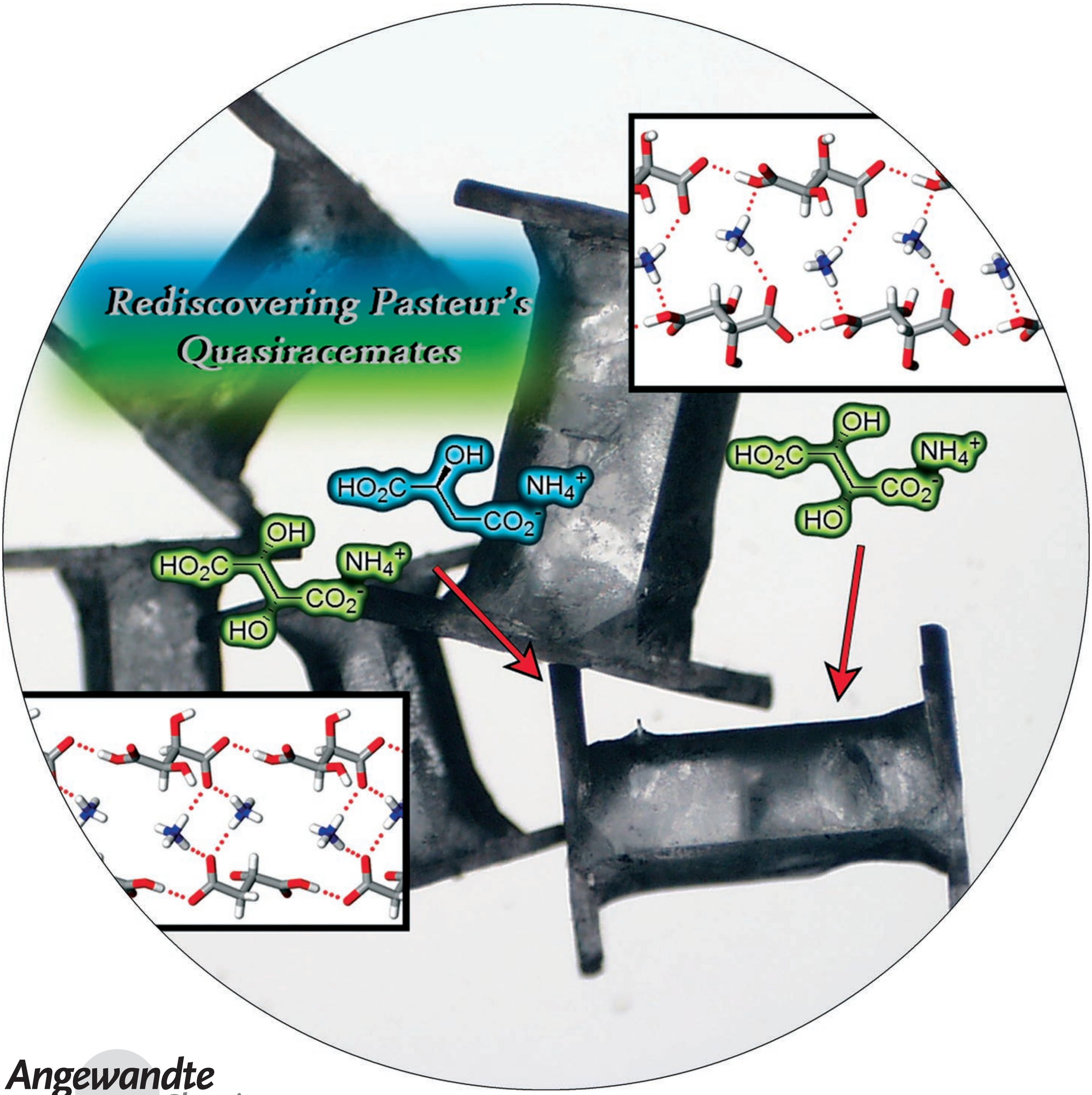
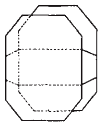


In recent communications we reported that cocrystallization of isosteric molecules that differ in handedness consistently mimic the centrosymmetic patterns observed in the crystal structures of their racemic counterparts.[1] These materials, termed quasiracemates, offer important evidence of the role of molecular shape in the construction of molecular assemblies[2] and have recently been utilized for their molecular-recognition behavior.[3]

The first likely occurrence of quasiracemates in the literature dates back one hundred and sixty years to Pasteur's celebrated tartaric acid work.[4] In addition to providing extensive details of the recrystallization outcomes for tartaric acids, Pasteur described the formation of unusual compounds he referred to as "combination isomers".[5] The two examples cited in his 1853 paper were derived from ammonium (+)-bitartrate/(−)-bimalate and (+)-tartramide/(−)-malamide components. These materials showed diminished optical behavior and notably different solubilities relative to the enantiopure building blocks. An additional curiosity resulting from this work includes the crystal morphologies of the ammonium salts. As shown in Figure 1, Pasteur's account of this material draws attention to the intergrowth of three distinct crystals. The central portion was assigned as ammonium (+)-bitartrate and the outer two crystals as the combination isomer. These results raise several important questions such as: Are these combination isomers quasiracemic compounds? What structural features are responsible for this peculiar crystal morphology?



... between two identical blades exists another blade of equal width, but of lesser height, that produces two voids between the lateral blades. In general, the crystal itself is a little thicker than the blades which comprise it ...

Figure 1. Pasteur's 1853 account[5] of the ammonium (+)-bitartrate and ammonium (−)-bimalate combination compound.

Since Pasteur's tartrate discoveries, at least two studies report the crystal structures of quasiracemates constructed from tartrate and malate components. These structures—tartaric acid/malic acid[6] and calcium tartrate/malate tetrahydrate[7]—show molecules assembled with approximate inversion relationships. Because tartrate and malate moieties differ by -OH and -H chemical functions, their successful use as quasiracemate synthons is somewhat surprising. In each case, the -OH and -H groups reside in comparable crystal environments with only the hydroxy group participating in hydrogen bonds.

In view of the historical significance of Pasteur's work and potential application to quasiracemates, we set out to explore and crystallographically assess his combination isomers. We wish to report herein our efforts to reconstruct one of his bimolecular compounds assembled from ammonium (+)-bitartrate and ammonium (−)-bimalate components.

By following Pasteur's procedure, we were able to prepare crystalline samples that resemble the description in his 1853 account.[5,8] These transparent colorless samples consist of unusual, but uniform crystal morphologies that appear to be derived from the deliberate combination of three distinct crystals (Figure 2). The central segment of this assembly is a well-formed six-sided block with two equidistant sides. The third dimension is roughly twice as long and forms an interface with the two contiguous laths of lesser quality. Sizes of these mature three-part crystals range up to 3 mm.

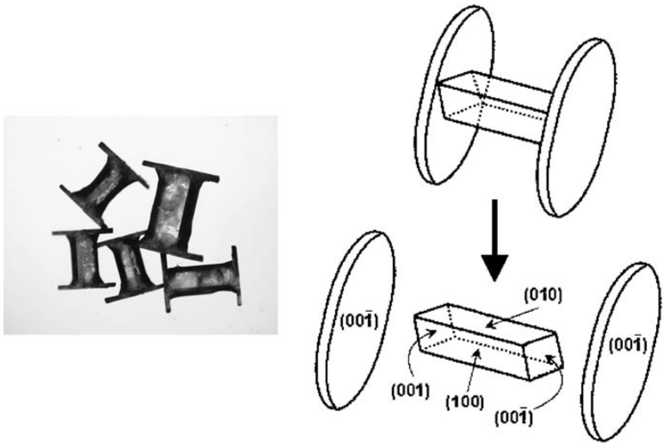


Figure 2. Photograph (left) and sketch (right) of three-component crystals formed from recrystallization of ammonium (2*R*,3*R*)-(+)-bitartrate and ammonium (*S*)-(−)-bimalate.

A three-component crystal was separated, and crystallographic studies were performed on each fragment. Assessment of these samples confirmed Pasteur's findings that the central block consists of ammonium (+)-bitartrate and the laths are "combination isomers" or quasiracemates containing ammonium (+)-bitartrate and (−)-bimalate. Each portion of a three-component crystal aligns with the *c* axis as the contact direction (Figure 2). On one side of the cluster, the (001) face of the central crystal forms a union with the $(00\bar{1})$ face of the lath. Conversely, the opposite face of the central

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crystal, $(00\bar{1})$, makes contact with the (001) face of the second lath.

The crystal structure of the laths (Figure 3) reveals ammonium cations and equal portions of (2*R*,3*R*)-(+)-bitartrate and (*S*)-(−)-bimalate anions assembled through $N^+–H\cdots O$ contacts to give $R_4^2(8)$ motifs.[9,10] The bimalate hydroxy group was found to be disordered over two sites (O9 and O9a) in a ratio of 4:1. One rationale for this observed disorder is that the bimalate component exists with the carboxy group always adjacent to the OH group. This scenario involves entire molecule disorder, with an occasional reversal of the direction of the bimalate strand. A second possibility is that the OH group is disordered over two sites. The latter rationale, which involves a less extreme alteration of the structure, seems more likely. Distinguishing between these possibilities on a crystallographic basis, however, would involve locating (and refining?) a small fraction of a hydrogen atom, which is probably beyond the reliability of the X-ray data.

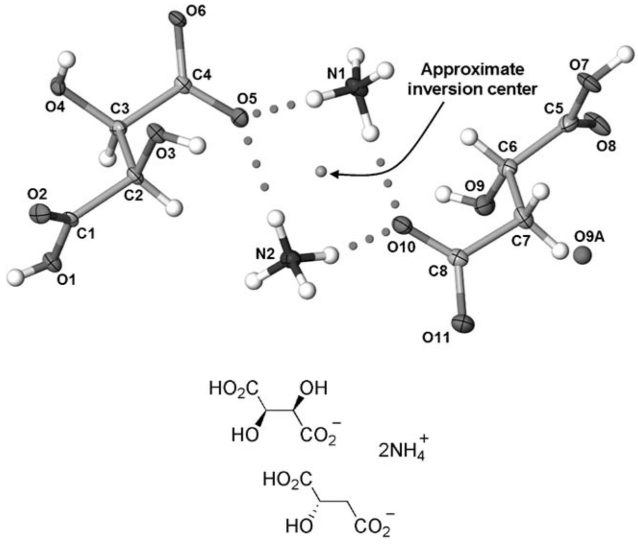

Figure 3. Crystal structure (right) of the quasiracemate dimer ammonium (+)-bitartrate/(−)-bimalate showing approximate inversion symmetry. Disorder (4:1) of the bimalate OH group is depicted as O9 and O9a.

Although the bitartrate and bimalate components of the quasiracemate are chemically distinct, this collection forms approximate inversion relationships in space group $P2_1$. The use of all hydrogen-bond donor (NH and OH) and acceptor (O atoms) groups creates an intricate network of noncovalent interactions. Each bitartrate and bimalate component participates in strong $CO_2H\cdots{}^-O_2C$ interactions with translationally related neighbors to give homomeric 1D chains along the *a* axis (Figure 4a). These motifs are antiparallel and are further linked through $OH\cdots{}^-O_2C$ and $N^+–H\cdots O$ contacts to give a molecular assembly that mimics the previously reported centrosymmetric structure of ammonium (±)-bitartrate (space group $P2_1/c$).[13]

The structure of the central ammonium (+)-bitartrate crystal corresponds to a known orthorhombic phase (space group $P2_12_12_1$).[14,15] Each bitartrate moiety forms homomeric molecular strands that are cross-linked by ammonium cations (Figure 4b). Although the overall topology of each strand and the positions of the ammonium N atoms are similar to that observed for the quasiracemate, several notable variations exist. The most striking difference is the parallel alignment of bitartrate strands. These strands are connected by $NH_4^+\cdots{}^-O_2C/HO_2C$ motifs that give rise to hydrogen bonds that differ markedly from the $R_4^2(8)$ patterns observed for the quasiracemate.

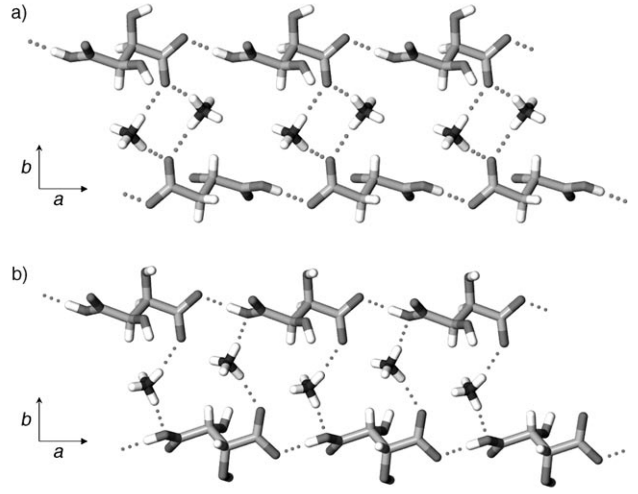

Figure 4. Molecular assemblies of a) quasiracemate ammonium (+)-bitartrate/(−)-bimalate and b) ammonium (+)-bitartrate (atomic coordinates taken from reference [15]). The hydrogen bonds linking the remaining two H atoms of each ammonium ion to strands in the *c* direction are not shown.

Curiosity of this face-specific intergrowth phenomenon and the diversity of crystal packing of the component phases led us to explore the structural relationships at the crystal interfaces. Figure 5 depicts the overlay of the quasiracemate and ammonium (+)-bitartrate crystal structures. The overall crystal packing of these phases is remarkably similar despite the variation in crystal systems, unit-cell parameters, and directionality of catemeric motifs (Figure 4). Careful comparison of the structures of the quasiracemate and (+)-bitartrate phases reveals that the alignment of crystal faces coincides with a near perfect overlap of ammonium (+)-bitartrate strands. The NH_4^+ ions provide the most discernible, albeit subtle, structural difference—a slight variation in the positions of the H atoms. This similarity of structural motifs occurs at both the (001) and $(00\bar{1})$ faces of central ammonium (+)-bitartrate crystal, and thus these faces serve as templates for the growth of the two quasiracemate laths. As ammonium (−)-bimalate is nearly 13 times more water soluble than its bitartrate counterpart,[16] it is not surprising that the crystal-growth process starts with the bitartrate phase and then more than 24 hours later the quasiracemate laths begin to form.

The variation of crystal morphologies observed for the quasiracemate and ammonium bimalate phases is likely due to the structural difference of the bimalate and bitartrate components. In the case of ammonium (+)-bitartrate, the additional hydroxy group contributes to the hydrogen-bond

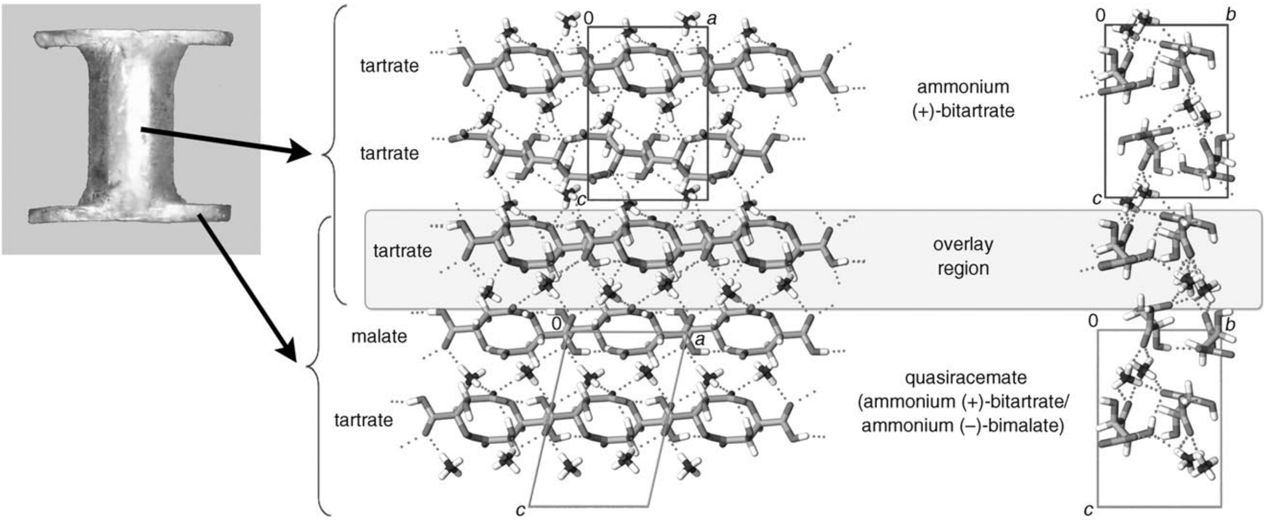

Figure 5. Crystal structure projections showing the unit cells and overlay at the crystal interface of the quasiracemate and ammonium (+)-bitartrate components (atomic coordinates taken from reference [15]).

framework along the *c* axis, which corresponds to the long crystal dimension. Although the bitartrate moiety of the quasiracemate participates in similar intermolecular contacts, the bimalate components lack this additional OH group and thus provide fewer hydrogen-bond connections along the *c* axis of the crystal. Unlike the central ammonium (+)-bitartrate phase, the quasiracemate laths grow with the long dimension along the *a* axis. This observation is consistent with fewer $OH\cdots{}^{-}O_2C$ hydrogen bonds (*c* axis) and suggests that the $CO_2H\cdots{}^{-}O_2C$ contacts that propagate along the *a* axis play a key role in the crystal-growth process.

In summary, we have reconstructed Pasteur's 1853 three-component crystals and confirmed the identities of the two phases as ammonium (+)-bitartrate (central crystal) and ammonium (+)-bitartrate/(−)-bimalate (adjoining crystal laths). Crystallographic evidence of the quasiramacemate shows that (+)-bitartrate and (−)-bimalate components organize in approximate inversion-related supramolecular assemblies in which each component (bitartrate and bimalate) forms homomeric catemeric motifs. The bitartrate strand is isostructural in the quasiracemate and (+)-bitartrate phases and likely serves as the primary structural contributor to the heteroepitaxial growth of these crystalline phases.

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[10] Crystal data: Bruker Kappa APEX II CCD diffractometer ($Cu_{K\alpha}$ $\lambda = 1.54178$ Å; graphite monochromator; $T = 173(2)$ K). Empirical absorption correction was applied by using SADABS.[11] Structure solved by direct methods and refined by full-matrix least-squares analysis on F^2 with SHELX.[12] $C_8H_{18}N_2O_{11}$, $M_r = 318.2$, monoclinic, space group $P2_1$ (No. 4), clear colorless lath, $a = 7.5996(3)$, $b = 7.7726(3)$, $c = 11.4437(4)$ Å, $\beta = 102.708(2)°$, $V = 660.25(4)$ Å^3, $Z = 2$, $Z' = 2$, $\rho_{calcd} = 1.601$ Mg m^{-3}, $\mu = 1.339$ mm^{-1}, $2\theta_{max} = 65.8°$, final *R* indices ($I > 2\sigma(I)$): $R_1 = 0.0333$, $wR_2 = 0.0812$ (9430 total reflections, 1224 unique reflections (1216 with $I > 2\sigma(I)$), $R_{int} = 0.0277$ full-matrix least-squares refinement on F^2; CCDC 657206 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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