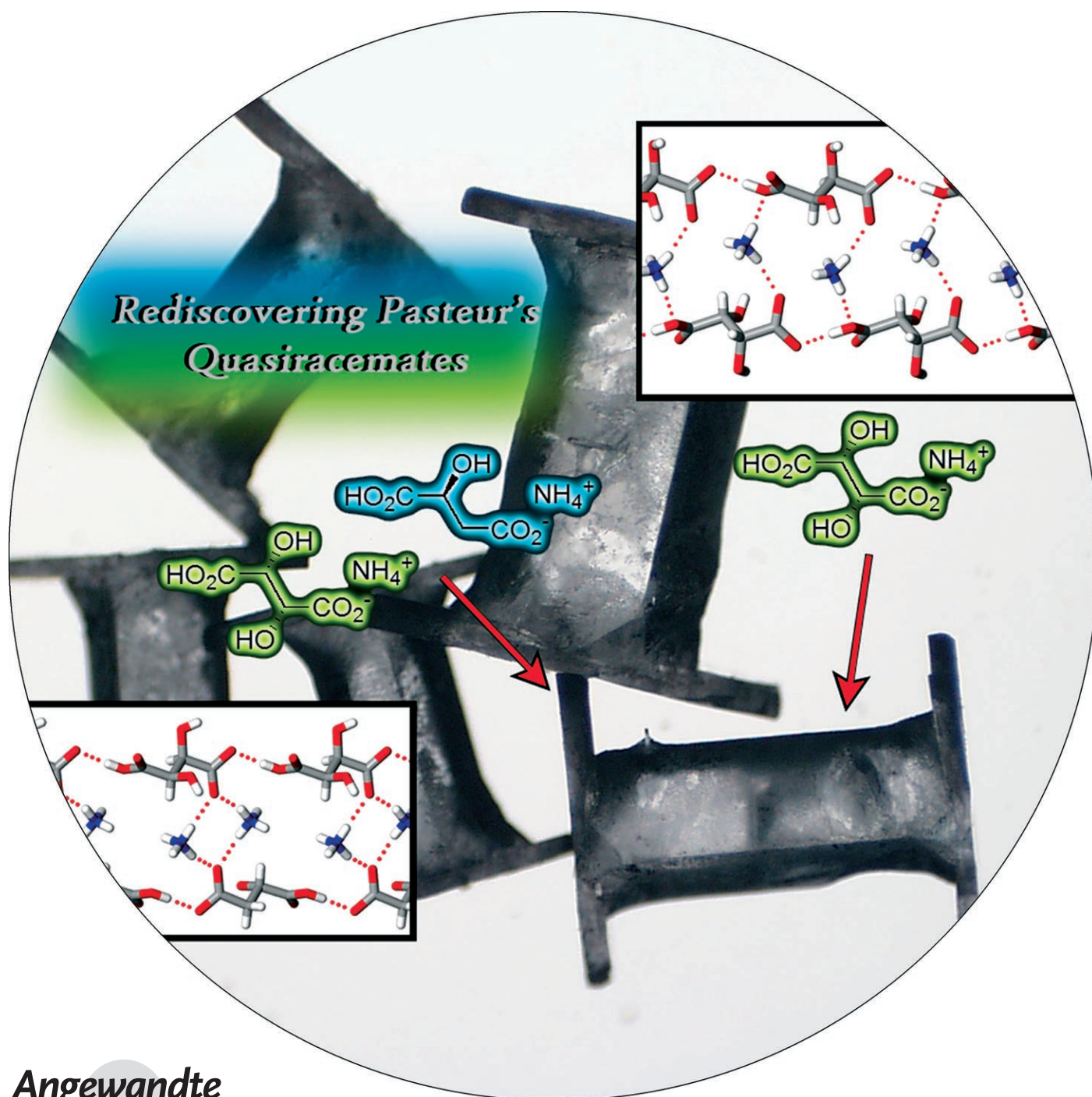


Rediscovering Pasteur's Quasiracemates**

Kraig A. Wheeler,* Rebecca C. Grove, Raymond E. Davis, and W. Scott Kassel



In recent communications we reported that cocrystallization of isosteric molecules that differ in handedness consistently mimic the centrosymmetric 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

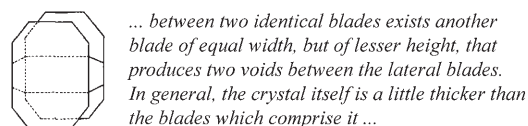


Figure 1. Pasteur's 1853 account^[5] of the ammonium (+)-bitartrate and ammonium (−)-bimalate combination compound.

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?

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

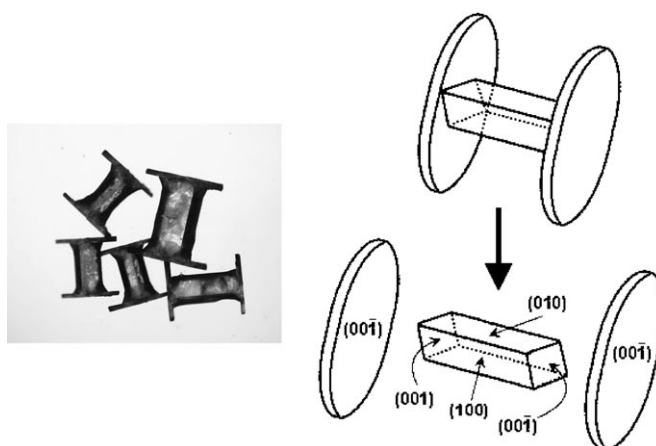


Figure 2. Photograph (left) and sketch (right) of three-component crystals formed from recrystallization of ammonium (2R,3R)-(+)-bitartrate and ammonium (5S)-(−)-bimalate.

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.

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

[*] Prof. K. A. Wheeler, R. C. Grove
Department of Chemistry
Eastern Illinois University
Charleston, IL 61920-3099 (USA)
Fax: (+1) 217-581-6633
E-mail: kawheeler@eiu.edu

Prof. R. E. Davis
Department of Chemistry and Biochemistry
University of Texas at Austin
Austin, TX 78712-0165 (USA)

Prof. W. S. Kassel
Department of Chemistry
Villanova University
Villanova, PA 19085-1690 (USA)

[**] Acknowledgements is made to the Donors of the American Chemical Society Petroleum Research Fund and to the National Science Foundation (0521062) for the support of this activity. We also wish to thank Prof. E. M. Treadwell for his helpful translation of Pasteur's original text.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

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

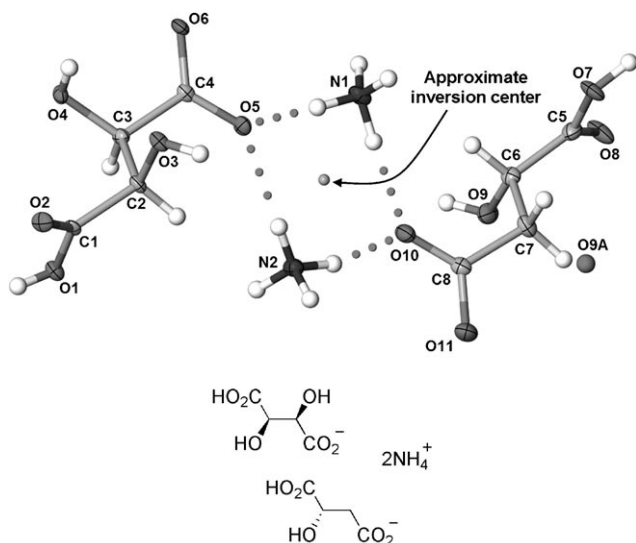


Figure 3. Crystal structure (right) of the quasiracemate dimer ammonium (+)-bitartrate/(-)-bimalate showing approximate inversion symmetry. Disorder (4:1) of the bimalate OH group is depicted as O9 and O9a.

$\text{N}^+-\text{H}\cdots\text{O}$ contacts to give $\text{R}_4^2(8)$ 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.

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 $\text{CO}_2\text{H}\cdots\text{O}_2\text{C}$ 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 $\text{OH}\cdots\text{O}_2\text{C}$ and $\text{N}^+-\text{H}\cdots\text{O}$ contacts to give a molecular assembly that mimics the previously reported centrosymmetric structure of ammonium ($\pm$)-bitartrate (space group $P2_1/c$).^[13]

The structure of the central ammonium (+)-bitartrate crystal corresponds to a known orthorhombic phase (space

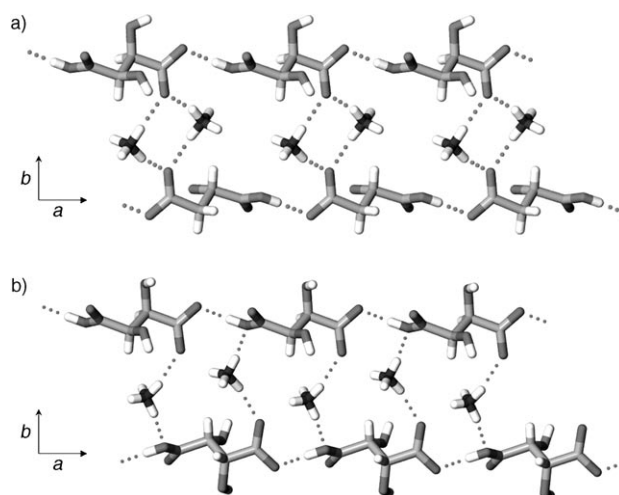


Figure 4. Molecular assemblies of a) quasiracemate ammonium (+)-bitartrate/(-)-bimalate and b) ammonium (+)-bitartrate (atomic coordinates taken from reference [15]). The hydrogen bonds linking the remaining two H atoms of each ammonium ion to strands in the *c* direction are not shown.

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 $\text{NH}_4^+\cdots\text{O}_2\text{C}/\text{HO}_2\text{C}$ motifs that give rise to hydrogen bonds that differ markedly from the $\text{R}_4^2(8)$ patterns observed for the quasiracemate.

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

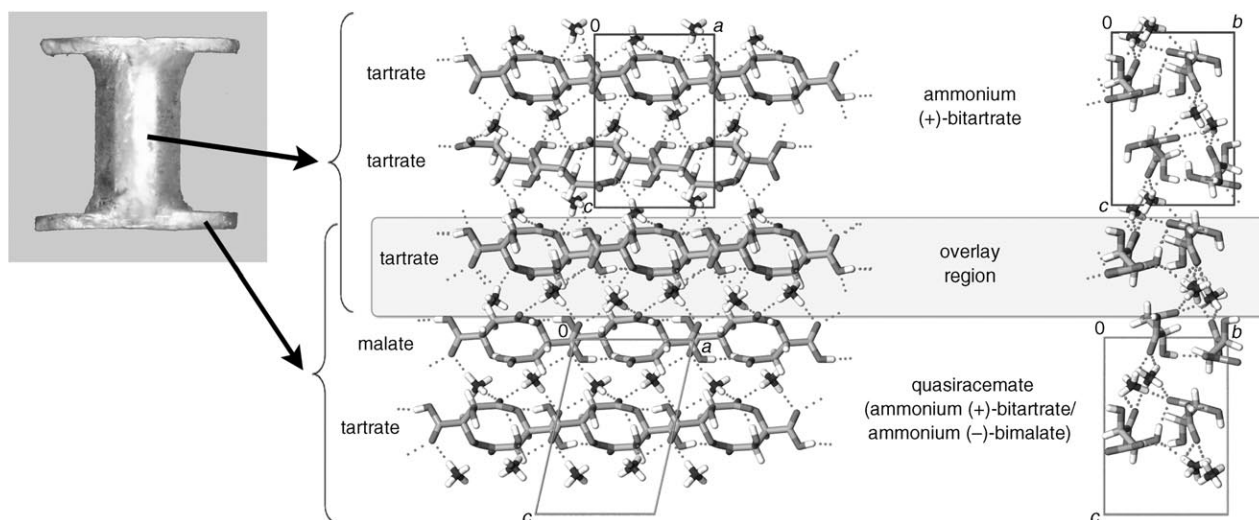


Figure 5. Crystal structure projections showing the unit cells and overlay at the crystal interface of the quasiracemate and ammonium (+)-bitartrate components (atomic coordinates taken from reference [15]).

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 $_2$ C hydrogen bonds (*c* axis) and suggests that the CO $_2$ H $\cdots$ O $_2$ C 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 quasiracemate 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.

Received: August 30, 2007

Published online: November 16, 2007

Keywords: crystal growth · history of science · molecular recognition · molecular topology · self-assembly

- [1] M. Hendi, P. Hooter, V. Lynch, R. E. Davis, K. A. Wheeler, *Cryst. Growth Des.* **2007**, *4*, 95, and references therein.
- [2] A. Fredga, *Bull. Soc. Chim. Fr.* **1973**, *1*, 173.
- [3] Q. Zhang, D. P. Curran, *Chem. Eur. J.* **2005**, *11*, 4866.
- [4] L. Pasteur, *Ann. Chim. Phys.* **1848**, *24*, 442.
- [5] L. Pasteur, *Ann. Chim. Phys.* **1853**, *38*, 437.

- [6] C. B. Aakeröy, T. I. Cooke, M. Nieuwenhuyzen, *Supramol. Chem.* **1996**, *7*, 153.
- [7] R. Warchow, *Z. Kristallogr.* **1996**, *211*, 329.
- [8] A 1:2 mixture of ammonium (+)-bitartrate and ammonium (–)-bimalate was dissolved in 15 parts water. After several weeks, slow evaporation at room temperature afforded the crystalline samples as depicted in Figure 2.
- [9] J. Bernstein, R. E. Davis, L. Shimoni, N.-L. Chang, *Angew. Chem.* **1995**, *107*, 1689; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1555.
- [10] Crystal data: Bruker Kappa APEX II CCD diffractometer (Cu $_{K\alpha}$ λ = 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 $_8$ H $_{18}$ N $_2$ O $_{11}$, *M_r* = 318.2, monoclinic, space group *P* $_2$ $_1$ (No. 4), clear colorless lath, *a* = 7.5996(3), *b* = 7.7726(3), *c* = 11.4437(4) Å, β = 102.708(2)°, *V* = 660.25(4) Å³, *Z* = 2, *Z'* = 2, ρ_{calcd} = 1.601 Mg m^{–3}, μ = 1.339 mm^{–1}, $2\theta_{\text{max}}$ = 65.8°, final *R* indices (*I* > 2 σ (*I*)): *R*₁ = 0.0333, *wR*₂ = 0.0812 (9430 total reflections, 1224 unique reflections (1216 with *I* > 2 σ (*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.
- [11] G. M. Sheldrick, SADABS—Program for area detector absorption corrections. University of Göttingen, Göttingen (Germany).
- [12] G. M. Sheldrick, SHELX—Program for the solution and refinement of crystal structures, University of Göttingen, Göttingen (Germany), **1997**.
- [13] T. Gelbrich, T. L. Threlfall, S. Huth, E. Seeger, M. B. Hursthouse, *Z. Anorg. Allg. Chem.* **2004**, *630*, 1451 (CSD ref. code PUXKAU01. Unit-cell parameters: *a* = 7.6369(7), *b* = 7.7509(4), *c* = 11.4838(11) Å, β = 102.666(4)°, *V* = 663.2(9) Å³).
- [14] A. J. van Bommel, J. M. Bijvoet, *Acta Crystallogr.* **1958**, *11*, 61.
- [15] A. L. Spek, *Acta Crystallogr. Sect. C* **1987**, *43*, 1633.
- [16] J. Timmerman, M. Dumont, *Bull. Soc. Chim. Belg.* **1931**, *40*, 689. Solubility data: 3.24 g of ammonium (+)-bitartrate in 100 g H $_2$ O and 41.72 g of ammonium (–)-bimalate in 100 g H $_2$ O.