Is it all in the hinge? A kryptoracemate and three of its alternative racemic polymorphs of an aminonitrile†

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Four polymorphs of 2-(perfluorophenyl)-2-(phenylamino)acetonitrile have been crystallized and structurally analyzed: in addition to three racemic crystals, a rare kryptoracemate has been obtained. The central single bonds allow for conformational flexibility: the kryptoracemate as well as two of the remaining polymorphs contain several independent molecules with different conformation. In contrast to these uncommon packing modes, the fourth phase is unexceptional and crystallizes with a single molecule in the asymmetric unit. Individual crystallization batches may contain several crystal forms concomitantly.

Four alternatives exist for the crystallization of racemic solutions: (a) Ordered racemic structures with both enantiomers in the unit cell represent the most common result. (b) The less frequent second alternative consists in spontaneous resolution; in such conglomerates each crystal is homochiral and hence necessarily belongs to one of the 65 chiral space groups or Sohncke groups. Statistics prove that racemic crystals occur more frequently than conglomerates. This preference for heterochiral crystals has long been associated with better space filling and Wallach’s rule. Even predates X-ray diffraction. Preferred mirror image recognition in crystalline solids is not limited to exact enantiomers but extends to quasiaromatics, in which opposite enantiomers of chemically related molecules co-crystallize. The remaining two possibilities are only rarely observed: (c) Pseudoracemates are solid solutions of opposite enantiomers; these heterochiral crystals may adopt any space group. (d) Finally, so-called kryptoracemates or false conglomerates may form; these racemic crystals crystallize in chiral space groups. In their enantiomorphic crystals the opposite enantiomers are “hidden” (such is the meaning of the Greek prefix krypto) as independent molecules in the asymmetric unit. Z, the number of molecules per asymmetric unit, is therefore necessarily larger than one when the enantiomers occupy general positions.

Reviews for kryptoracemate crystallization were published by Fábián & Brock10 covering organic and by Bernal & Watkins11 covering metal–organic compounds with a stereogenic metal atom. These authors identified approximately 200 credible kryptoracemates in the Cambridge Structural Database12 and mentioned the difficulties in performing an exhaustive search for this class of compounds. In this contribution we communicate the kryptoracemate of 2-(perfluorophenyl)-2-(phenylamino)acetonitrile (1) and the alternative polymorphs of this compound. The chemical constitution of 1 as well as the space groups and the content of the asymmetric unit are compiled in Fig. 1.

Prakash et al. showed that z-aminonitriles are accessible in high yields and purity by a three-component Strecker type
reaction from aldehydes and amines with trimethylsilyl cyanide using gallium triflate as catalyst. In the course of analogous reactions starting from highly fluorinated benzaldehydes, we came across the racemic compound 2-(perfluorophenyl)-2-(phenylamino)-acetonitrile (1). Details concerning synthesis and crystallization have been compiled in the ESI.† The first crystalline appearance of 1 turned out to contain both enantiomers in the asymmetric unit of the chiral space group P2\textsubscript{1}2\textsubscript{1}2\textsubscript{1}, thus corresponding to a kryptoracemate (krypto-1). Fig. 2 underlines that the symmetrically independent molecules of opposite chirality adopt very different conformations.

Crystals of krypto-1 are rod-shaped and of good quality; their diffraction pattern extends to high resolution. Very slow isothermal evaporation from hexane at room temperature allowed to grow a single huge elongated crystal (maximum dimension 1.75 cm, weight 13.01 mg, see Fig. S1, ESI†).

After the serendipitous discovery of the unexpected solid krypto-1, we set out in search for potential alternative polymorphs. The next two modifications of 1 encountered belong to the most frequent case (a) and correspond to racemic crystals. Crystals of rac-1a are very thin plates in the popular space group P2\textsubscript{1}1/c, those of rac-1b thin needles in the polar space group Pna\textsubscript{2}1; in either case the quality of the associated intensity data is modest. The solids rac-1a (Z′ = 2) and rac-1b (Z′ = 4) both crystallize with more than one independent molecule. Upon closer inspection, they share another peculiarity with krypto-1: all three polymorphs feature symmetrically independent molecules which adopt more or less different conformations with respect to the soft internal degrees of freedom. The single bonds between the perfluorinated and the unsubstituted phenyl rings act as a flexible hinge and allow for different dihedral angles between these aromatic systems. The torsion angle C\textsubscript{2} – C\textsubscript{3} – N – C\textsubscript{4} (Fig. 1) represents a second soft internal degree of freedom. The symmetrically independent molecules of 1 in each of its alternative solid forms krypto-1, rac-1a and rac-1b cover a relevant part of the conformational space thus available. Fig. 3 provides a color-coded synopsis of all individual molecules in the polymorphs of 1, and Fig. 4 allows to visually inspect the variance of the aforementioned degrees of freedom within each modification.

We have attempted to quantify the attribute “more or less different conformations” in our preceding statement: the pairwise least-squares overlay of the nine independent molecules in the different crystal forms of 1 results a matrix\textsuperscript{15} of root mean square (rms) deviations for each of the 36 combinations which allow to address the observed conformations as more or less different. The full matrix is available in the ESI†; we here only summarize the main results: (a) one of the molecules in krypto-1, three in rac-1b and the molecule in rac-1c are conformationally similar, with rms values below 0.4 Å; these molecules have been marked with an asterisk * in Fig. 3. The two independent molecules in rac-1a and the fourth molecule in rac-1b are conformationally related, albeit to a lower extent. The second molecule in krypto-1 (top row in Fig. 3, middle) stands out completely; it may also readily be identified as the “lone” green dot in the left-hand part of Fig. 4. Up to this point, one might conclude that 1 suffers from a serious packing problem. Its conformational polymorphs krypto-1, rac-1a and rac-1b can then be perceived as the necessarily elaborate answers to this challenge. We recall that structures with an elevated number of independent molecules can be associated with packing conflicts\textsuperscript{16} and that several structures with very high Z\textsuperscript{17} are based on conformationally flexible constituents. Are the Z′ > 1 solids the brute force solution to the packing problem of 1? Can we hold the central hinge in the molecules of 1 responsible for the manifold and at least in part exotic answers to the packing problem?

We have good reason to doubt the preceding hypothesis. The most simple solution to the packing issue was found by discovering a fourth solid form, rac-1c. It seems to support the often-quoted statement by McCrone\textsuperscript{18} that “... in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound”. During a series of crystallization experiments on 1 and after the structural characterization of krypto-1, rac-1a and rac-1b, we detected the unexceptional polymorph rac-1c. It crystallizes in form of apparently hexagonal, well-diffracting plates in the most popular space group P2\textsubscript{1}1/c with just one molecule in the asymmetric unit. The soft conformational degrees of this only residue fit those of the polymorphs described earlier: this

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Fig. 2 Overlay (PLATON\textsuperscript{14}) of the opposite enantiomers in krypto-1

Fig. 3 All independent nine conformations of the molecules in the asymmetric units of krypto-1 (green), rac-1a (blue), rac-1b (magenta) and rac-1c (orange).
along the c groups of different residues with N–H independent residues. In leads to an infinite chain along the chain through stacking contact (F7-cg) amounting to 3.3293(14) Å is present. There is different substituted aryl rings of the (R2.876(2) Å for the two independent molecules. Between the two nearest fluorine neighboring atoms amount 2.8481(19) Å and one-dimensional structure is generated. Intra-molecular hydrogen amounting to 3.4975(11) Å and no slippage (Fig. S2, ESI†). The flexible hinge allows for different conformations, but this conformational flexibility is no prerequisite for crystallization.

Table 1

<table>
<thead>
<tr>
<th>Polymorph</th>
<th>Space group, Z′</th>
<th>Filled space [%]</th>
<th>Density [g cm−3]</th>
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<tr>
<td>krypto-1</td>
<td>P212121, 2</td>
<td>70.1</td>
<td>1.583</td>
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<tr>
<td>rac-1a</td>
<td>P21/c, 2</td>
<td>69.3</td>
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<td>rac-1b</td>
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<td>70.9</td>
<td>1.603</td>
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<tr>
<td>rac-1c</td>
<td>P21/c, 1</td>
<td>72.8</td>
<td>1.651</td>
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Notes and references


12 WebCSD, 791,568 entries, 9th of Sept. 2015.


