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Homochiral Crystal Generation *via* Sequential Dehydration and Viedma Ripening

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1,2-bis(*N*-benzoyl-*N*-methylamino)benzene (2) forms centrosymmetric hydrate crystals (2•xH$_2$O) but non-centrosymmetric anhydrous crystals. Dehydration of this hydrate (30 min at 140 °C) resulted in the formation of chiral crystals (*i.e.* a physical racemate of the conglomerate crystals) as verified using solid-state circular dichroism and powder X-ray diffraction. Subsequent attrition-enhanced deracemization, also known as Viedma ripening, was used to obtain homochiral crystals of 2 within 5 h.

The outstanding mystery of the origin of homochirality in nature has been thoroughly investigated due to the essential role it plays in chemistry, biochemistry and biology. The mechanism to generate homochiral populations can be generally separated into two steps: (*i*) the formation of an initial chiral imbalance (*i.e.* mirror symmetry breaking) and (*ii*) its subsequent amplification to homochirality. The initial imbalance may be caused by statistical fluctuations, the parity violation energy difference (PVED), the influence of circularly polarized light or selective adsorption on chiral mineral surfaces.[1] In conglomerate crystal systems, this initial imbalance can be amplified through, for example, the eutectic model,[2] Kondepudi's model[3,4] and more recently, Viedma ripening.[5]

Generating chirality in the absence of chiral reagents (*i.e.* spontaneous absolute asymmetric induction) is an attractive route to obtain chiral materials and has clear implications with regards to the origins of biological homochirality.[6] Mirror symmetry breaking and chiral amplification can be achieved by effectively utilizing the unique nature of conglomerate crystals. More specifically, attrition-enchanced deracemization, or Viedma ripening, has proven to be an effective method to obtain homochiral populations of conglomerate-forming crystals from an initial racemic state.[5,7–9] The remarkably simple process involves grinding a conglomerate crystal mixture in saturated solution. Both chiral and achiral molecules that crystallize as conglomerates, in non-centrosymmetric space groups, can undergo Viedma ripening, albeit the former require racemizing conditions in solution.[10,11] The initial broken mirror symmetry is a result of conglomerate crystallization, where the chirality of the system resides intimately and sometimes solely in the solid state. Conglomerate crystallization is often referred to as spontaneous resolution even though the chiral crystals are not physically separated.[4] In the extreme case of an achiral conglomerate-forming molecule under optimal Ostwald ripening conditions, one can envisage the formation of one homochiral crystal.[12–14]

Chiral or achiral molecules that form conglomerates must crystallize in one of the 65 non-centrosymmetric Sohncke space groups.[15,16] Our group is particularly interested in the latter case, where it was estimated in 2005 that 8-10% of chiral crystal structures are formed from achiral molecules.[17–19] A more recent survey of the Cambridge Structural Database (CSD 5.36; 2015) estimates that 5 ± 2% of chiral crystal structures are formed from achiral molecules (see ESI†).[20] Out of the 127 397 structures (chiral and achiral molecules) in a Sohncke space group, the majority crystallize in the P2$_1$ (31%) and P2$_1$2$_1$2$_1$ (44%) space groups. Out of these structures in the P2$_1$ and P2$_1$2$_1$2$_1$ space groups, 9% and 14% are formed from achiral molecules, respectively (see ESI†). These statistics represent a maximum frequency since a common early crystallographic error was to miss assign space groups to lower symmetry.[21] Marsh has noted that these errors have dropped significantly but still arise with alarming regularity.[22]

Through the 'manipulation' of crystalline structures in the solid-state, crystal chirogenesis can be achieved to obtain homochiral populations. For example, crystals that incorporate

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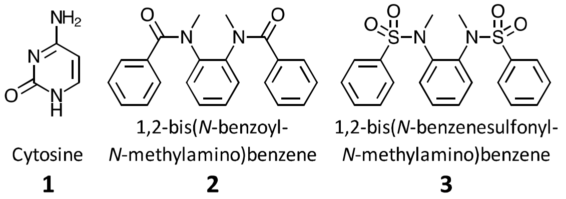
solvent molecules or host-guest inclusion crystals can undergo a crystal-to-crystal transition from centrosymmetric hydrates or solvates to non-centrosymmetric anhydrous or non-solvated crystals.[23,24] Along these lines, Soai *et al.* have elegantly demonstrated the generation of absolute crystal chirality by the face-selective removal of crystal water from *individual* achiral cytosine monohydrate crystals *via* thermal dehydration or reduced pressure conditions.[25,26]

Scheme 1



Herein, we address the *bulk* conversion from an achiral crystalline sample into a homochiral sample using two compounds: cytosine, **1** and 1,2-bis(N-benzoyl-N-methylamino)benzene, **2** (Scheme 1).[23,25–28] Specifically, centrosymmetric hydrate crystals of **1**•H_2O and **2**•xH_2O were subjected to thermal dehydration. Viedma ripening was subsequently used to obtain homochiral crystal populations of **1** and **2** (Figure 1).[7,23] Our approach is somewhat reminiscent to that of Vlieg *et al.*, where Viedma ripening of alanine and phenylalanine was achieved by non-centrosymmetric salt formation, while the deracemization of glutamic acid was enabled *via* a metastable conglomerate.[29,30]

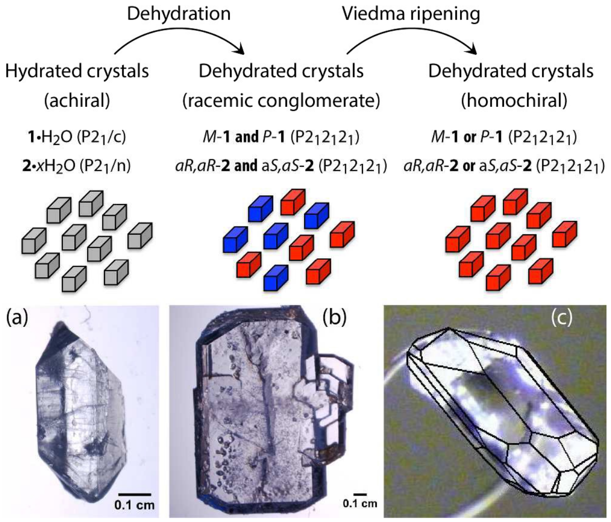


Figure 1: Top - general scheme. Bottom - (a) achiral hydrated crystal of **2**•xH_2O, (b) chiral crystal and (c) indexed chiral single crystal of **2**.

Anhydrous **1** was commercially available, while **2** was synthesized through generation of a secondary anilide followed by *N*-methylation from *ortho*-phenylenediamine and benzoyl chloride (see ESI†).[23] 1,2-bis-(*N*-benzenesulfonyl-*N*-methylamino)benzene, **3** (Scheme 1), was synthesized using a similar procedure as that of **2**, where benzenesulfonyl chloride was substituted for benzoyl chloride as a starting reagent (see ESI†).[23,27,31] Compound **3** crystallizes in either the $P4_12_12$ or $P4_32_12$ enantiomorphic space groups. The absolute structure of **3** was determined by single-crystal X-ray diffraction (ESI†).[31] In this case, a solvated crystal structure of **3** has not been reported.[31] Viedma ripening at 2400 rpm for *ca.* 24 hours yielded homochiral crystals of **3**.

Compounds **1** and **2** can form either achiral or chiral crystals depending on the solvent used during crystallization. Crystallization of compound **1** from water results in the formation of achiral crystals of **1**•H_2O with space group $P2_1/c$, whereas crystallization in anhydrous methanol yields chiral crystals of **1** with space group $P2_12_12_1$.[25,26] Similarly, crystallization of compound **2** from water-saturated ethyl acetate or aqueous ethanol results in the formation of achiral crystals of **2**•xH_2O with space group $P2_1/n$. DSC measurements of **1**•H_2O and **2**•xH_2O confirm the loss of water with broad endothermic peaks at *ca.* 96°C and 152°C, respectively. The non-stoichiometric water occupancy in **2**•xH_2O was determined by TGA analysis ($x = 0.67$) and is in agreement with the values estimated from single-crystal X-ray diffraction ($x = 0.59$ to 0.78 for an old and a freshly picked crystal, respectively; see ESI†). Crystallization of **2** from dry solvents, such as anhydrous ethyl acetate, absolute ethanol, benzene and chloroform, yields chiral crystals of **2** with space group $P2_12_12_1$.[23,28] Upon crystallization of these achiral molecules, a racemic mixture of enantiomorphic conglomerate crystals should be obtained. However, the commercial sample of **1** used in these experiments was found to be scalemic (6% ee [CD(−)290 nm]).[7] Similarly, slow crystallization of **2** (from anhydrous ethyl acetate in the presence of a drying tube, see ESI†) resulted in a unequal distribution of chiral crystals, as observed by Azumaya *et al.*.[23] In our hands, separate crystallization dishes typically yielded crystals of only one chirality of **2**. This non-stochastic mirror symmetry breaking observed in **1** and **2** can be attributed to crystallization in a cryptochiral environment.[8,9,32–35]

Achiral crystals of **1**•H_2O and **2**•xH_2O were converted to anhydrous chiral crystals through dehydration using a heating mantle (*i.e.* 3 h at 90 °C for **1**•H_2O and 30 min at 140 °C for **2**•xH_2O; Figure 1). Starting from finely ground material reduced the time required for the crystals to transform from the centrosymmetric to non-centrosymmetric space groups. A visual indication of the transformation was possible for **1**, as **1**•H_2O crystals were initially transparent but became opaque upon dehydration. The phase transition from centrosymmetric to non-centrosymmetric space group was validated through X-ray powder diffraction (XRPD, Figures 2 and 3). Experimental XRPD data for all compounds was compared with XRPD patterns simulated from single-crystal X-ray diffraction data, either from the CSD (for **1**•H_2O and **1**, Figure 2) or remeasured (for **2**•xH_2O and **2**, Figure 3, see ESI† for experimental details). Finally, dehydration of **1**•H_2O and **2**•xH_2O yielded physical racemates, as confirmed by baseline solid-state circular dichroism (CD) signals. Our attempts at face-selective dehydration from individual achiral **2**•xH_2O were unsuccessful (see ESI†).[25]

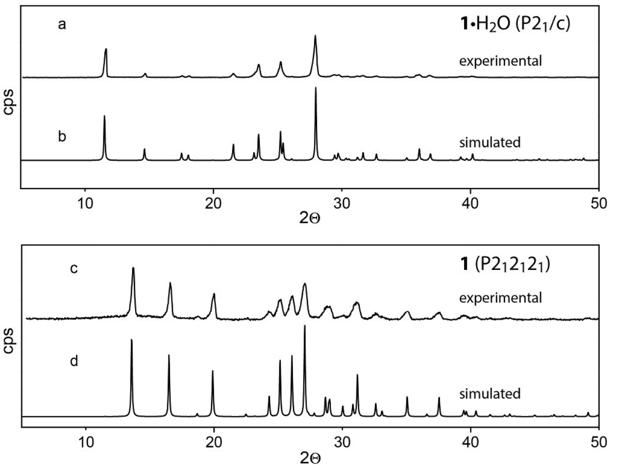


Figure 2: Transformation of $\mathbf{1}\bullet H_2O$ ($P2_1/c$) to **1** ($P2_12_12_1$) (a) Experimental XRPD for $\mathbf{1}\bullet H_2O$, (b) XRPD of $\mathbf{1}\bullet H_2O$ generated from the CSD (CYTOSM), (c) Experimental XRPD for **1** and (d) XRPD of **1** generated from the CSD (CYTSIN).

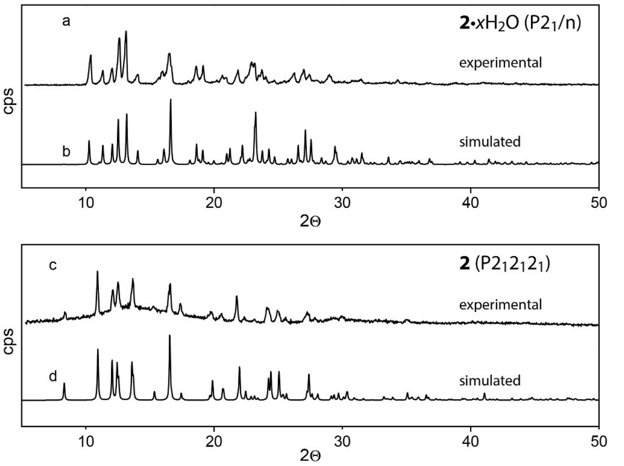


Figure 3: Transformation of $\mathbf{2}\bullet xH_2O$ ($P2_1/n$) to **2** ($P2_12_12_1$) (a) Experimental XRPD for $\mathbf{2}\bullet xH_2O$, (b) XRPD of $\mathbf{2}\bullet H_2O$ generated from single crystal data, (c) Experimental XRPD for **2**, (d) XRPD of **2** generated from single crystal data.

Viedma ripening was then carried out on the racemic mixtures of **1** or **2** in an attempt to yield homochiral crystals (see ESI† for experimental details).[7] In both cases, amplification to homochirality occurred. For **1**, five experiments yielded homochiral crystals with negative CD signal and five yielded homochiral crystals with positive CD signal at 290 nm (Figure 4). For **2**, four experiments yielded homochiral crystals with negative CD signal and one experiment yielded homochiral crystals with positive CD signal at 260 nm (Figure 5).

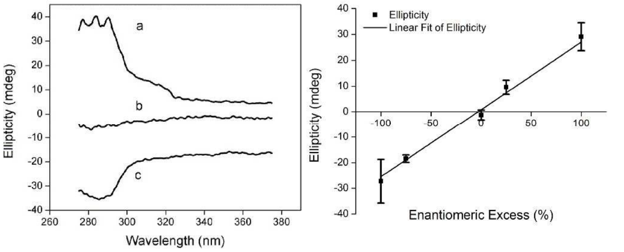


Figure 4: Left - Solid-state CD spectra of the chiral crystals of **1** in KBr: (b) After dehydration, (a) and (c) following Viedma ripening. Viedma ripening was carried out using 0.25 g sample suspended in 3 mL of saturated solution in anhydrous methanol with 3 g of ceramic grinding media (0.8 mm) stirring at 2400 rpm for *ca.* 65 hours. Right - CD calibration curve of **1** in KBr prepared from mixtures of homochiral crystals ([CD(±)290 nm]).

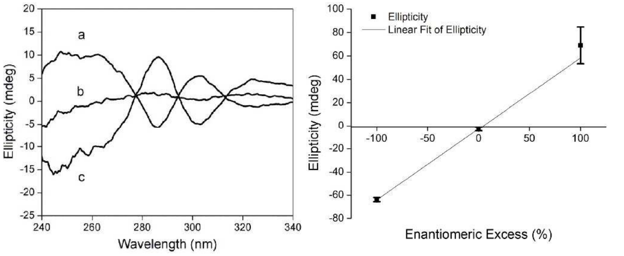


Figure 5: Left - Solid-state CD spectra of the chiral crystals of **2** in KBr: (b) immediately after dehydration, (a) and (c) following Viedma ripening. Viedma ripening was carried out using 0.25 g sample suspended in 3 mL of saturated solution in anhydrous ethyl acetate with 3 g of ceramic grinding media (0.8 mm) stirring at 1500 rpm for *ca.* 5 hours. Right - CD calibration curve of **2** in KBr prepared from mixtures of homochiral crystals ([CD(±)260 nm]).

The absolute structure of **2** was confirmed by single-crystal X-ray diffraction and solid-state CD carried out on the same single crystal. Since **2** only contains light atoms, the diffraction data was acquired with a Cu Kα radiation source. The correct enantiomer was validated by a low Flack parameter of -0.03(10) and the conformation of **2** was correlated with its respective CD signal. The chirality of **2** is due to the presence of two chiral axes (Ar-N). Crystals formed from (*aS*,*aS*)-**2** resulted in a negative CD signal at 260 nm, whereas (*aR*,*aR*)-**2** would give a positive CD signal at 260 nm (see ESI†).[23,28]

To conclude, homochiral crystals can be produced through asymmetric amplification using dehydration coupled with attrition-enchanced deracemization, as exemplified here with compounds **1** and **2**. We are currently probing the CSD for further examples of achiral molecules that form both solvated achiral crystals as well as the corresponding non-solvated chiral crystals.[36,37]

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Notes and references

§ Spectral data, experimental procedure along with characterization is available for **1**, whereas spectral data, experimental procedure, synthetic procedure, crystallographic data and characterization are available for **2** and **3** in the ESI. The resubmission of the CIF file of **2** was performed due to the incomplete entry in CSD 5.36 database.

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