Crystals

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Investigation of an Unusual Crystal Habit of Hydrochlorothiazide Reveals Large Polar Enantiopure Domains and a Possible Crystal Nucleation Mechanism

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Abstract: *The observation of an unusual crystal habit in the common diuretic drug hydrochlorothiazide (HCT), and identification of its subtle conformational chirality, has stimulated a detailed investigation of its crystalline forms. Enantiomeric conformers of HCT resolve into an unusual structure of conjoined enantiomorphic twin crystals comprising enantiopure domains of opposite chirality. The purity of the domains and the chiral molecular conformation are confirmed by spatially revolved synchrotron micro-XRD experiments and neutron diffraction, respectively. Macroscopic inversion twin symmetry observed between the crystal wings suggests a pseudoracemic structure that is not a solid solution or a layered crystal structure, but an unusual structural variant of conglomerates and racemic twins. Computed interaction energies for molecular pairs in the racemic and enantiopure polymorphs of HCT, and the observation of large opposing unit-cell dipole moments for the enantiopure domains in these twin crystals, suggest a plausible crystal nucleation mechanism for this unusual crystal habit.*

Manifestations of molecular chirality in nucleation and growth mechanisms leading to chiral or polar crystal forms are of special interest due to their solid-state optical[1] and physical properties.[2] Attempts to control chiral nucleation phenomena via selective seeding, attrition by grinding[3] (Viedma ripening[4]), and irradiation by circularly polarized light[5] have led to efficient techniques for enantioseparation[6] and deracemization.[3c,7] Understanding the nucleation and solid-state chirality of pharmaceutical compounds is crucial in developing crystal-engineering strategies for separating eutomers (pharmacologically active enantiomers) of chiral drugs. Enantiomerically pure substances crystallize in any of the 65 Sohncke space groups (those devoid of mirror and inversion symmetry, containing only symmetry operations of the first kind).[8,9] On the contrary, and according to commonly cited monographs,[10] a racemic mixture of enantiomeric molecules usually crystallizes as an ordered racemic crystal structure (most commonly with a 1:1 composition), rarely as a conglomerate of enantiomorphs, and even more rarely as a disordered solid solution of variable composition (referred to as a pseudoracemate[9]). However, other crystalline products of racemic mixtures are known, including kryptoracemates[11] and enantiomorphous twins.[9,12] Enantiomorphic twinning is a relatively rare phenomenon, often manifested by a layered structure formed by alternating (+)- and (−)-enantiomeric domains, resulting in a pseudoracemic crystal composition. Also referred to as lamellar twinning, many examples of this have been reported[13] in the space groups $P2_1$ and $P2_12_12_1$, for which it has been observed that this form of twinning occurs frequently;[13b] a well-known example is hexahelicene.[13c] A more unusual case of enantiomorphic twinning has been reported in 1,8-dihydroxyanthraquinone,[14] where square-plate crystals exhibit intergrown mirror-image domains in space groups $P4_1$ and $P4_3$.

In this Communication, we report an unusual solid-state enantiomorphic growth observed in crystals of the antihypertensive drug hydrochlorothiazide (HCT, Figure 1). Detailed investigation combining laboratory X-ray diffraction (XRD), synchrotron micro-XRD, neutron diffraction, and circular dichroism (CD) spectroscopy has revealed intriguing structural features and an unusual domain structure of these enantiomorphic twin crystals, showing how they differ structurally from the known cases of pseudoracemates, racemic twins and lamellar twin crystals. Complementary computational approaches help to rationalize this unusual structure and suggest a plausible mechanism for the growth of these enantiomorphic twins.

Solid forms of HCT have been characterized in considerable detail since it became commercially available in 1959,

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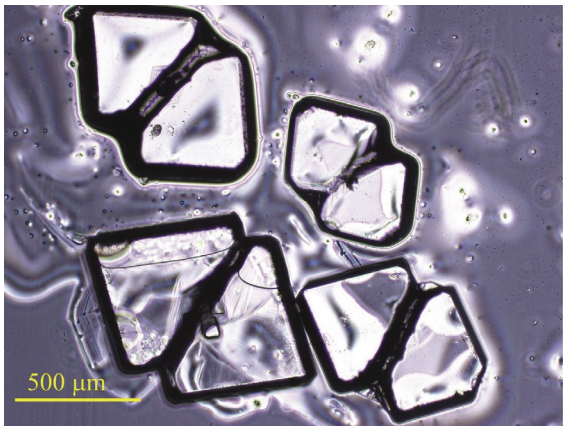

Figure 1. Conjoined two-winged habit observed for the enantiomorphic pairs of form-I HCT crystals.

and two crystalline forms are known. A preliminary crystallographic study of the commercially available form I ($P2_1$, $Z' = 1$) was reported in 1970,[15] and a full crystal-structure determination appeared two years later.[16] The centrosymmetric form II ($P2_1/c$, $Z' = 1$) was not observed until 2005.[17] The enantiomorphs of HCT discussed in this report correspond to the $P2_1$ polymorph, form I. Single-crystal structures of both forms have since been re-determined.[18] One of those studies[18a] has suggested that form II is metastable with respect to form I on the basis that crystallizations from a large number of solvent combinations yielded exclusively form I in 91% of the attempts and form II in only 6% (the remainder yielded either a mixture of forms or no crystalline sample), and also because form II has almost twice the solubility of form I in ethanol. Solvated forms and co-crystals of HCT have also been synthesized via numerous crystal engineering approaches, typically aimed at improving its water solubility.[19]

While observing under an optical microscope, we found that crystals of HCT exhibited a two-winged twin-crystal morphology (akin to a butterfly, but with characteristic flattened triangular wings; Figure 1).[20] To understand the persistent occurrence of this twin-crystal habit in crystallization experiments from methanol (Supporting Information, Section S.1), we set out to investigate the crystal structures of both the intact twin and the separated wings of a twin-crystal. X-ray diffraction data (100 K, CuKα radiation) measured for an intact twin crystal resulted in a diffraction pattern with sharp spots, and the structure refinement indicated the presence of inversion twinning (Table S1 and Figure S2).

The crystal pair was separated under an optical microscope (Figure S1) and X-ray diffraction data for the separate wings yielded essentially the same cell parameters and space group as form I (Supporting Information, Section S.2, Table S1). Indexing of the faces of the separated form-I crystals (Figure S1) revealed the junction face between the crystal wings to be (010). Near-zero Flack and Hooft parameter[21] values obtained in these refinements also indicated enantiopurity of each of the individual wings (Table S1). Further evidence for the enantiopurity of the wings came from solid-state CD spectra, obtained by separating the wings of a twin-crystal (size $\approx 5 \times 8 \times 2$ mm) and grinding them into powder samples. Mirror symmetry observed in the CD spectral features from opposite crystal wings again indicated their opposing chirality (Figure 2 and Supporting Information, Section S.3).

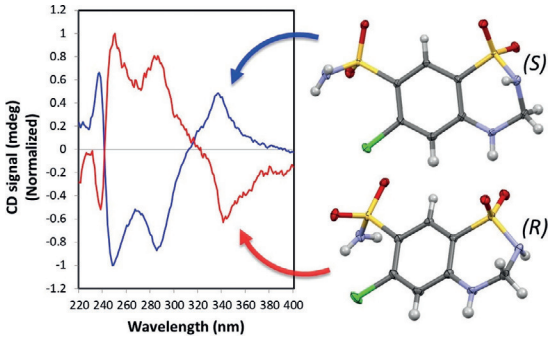

Figure 2. Solid-state CD spectra for separated wings of a conjoined HCT twin crystal, along with corresponding structures for the *R* and *S* enantiomers present in the two enantiomorphs.

The conformational flexibility of HCT with respect to the sulfonamide functional group ($-SO_2NH_2$) has been extensively studied using computational methods.[18a] However, HCT also incorporates a subtle chiral center and, rather surprisingly, this seems to have eluded observation or comment in the literature to date. Close inspection of the molecule reveals that flipping of the saturated ring, coupled with inversion of the sultam N adjacent to the sulfone group and appropriate rotation of the sulfonamide moeity, results in a molecular conformation with the opposite absolute configuration (Figure 2). This inversion is only possible if the sultam nitrogen atom is significantly nonplanar and pyramidal, and this was unambiguously established by a neutron-diffraction experiment on a form-I crystal; the sum of the bond angles at the sultam N atom is only 335.1° (Supporting Information, Section S.2). Together with the evidence from the other experiments described above, this indicates that the individual wings of the twin-pair are homochiral crystals, with opposite enantiomers dominant in the separate wings. Assigning the non-bonding electron pair on the sultam N the lowest priority, the molecular structures belonging to the enantiomorphs were designated *R* and *S* (Figure 2).

Crystallization and seeding experiments in methanol (Supporting Information, Section S.1) suggested reasonably rapid racemization in the solutions, and hence a racemic solution at all times. This was confirmed by solution-state CD spectroscopy of separated wings of HCT, which upon dissolution gave no CD spectral peaks, but a flat spectrum indicating racemization in solution. To explore this further, we probed the molecular conformation of HCT via computational analysis using the G4(MP2) method. Here, the transition states and energy barriers associated with conformational inversion between the *R* and *S* enantiomers in the gas phase were computed (Supporting Information, Section S.4). Analysis of the intrinsic reaction coordinates showed that i) the envelope flipping of the six-membered ring around S–(NH)–C bonds and ii) pyramidal inversion

about the sultam N atom are not concerted in the conversion pathway. The free-energy barrier obtained for (i) is 47.3 kJ mol^{-1}, while that for (ii) is 18.6 kJ mol^{-1} (Figure S7). The modest upper barrier estimate of ≈47 kJ mol^{-1} is in accord with the observation of racemization in methanol solution, since interactions with the polar protic solvent are likely to lower this barrier considerably.[22]

The outcomes from the X-ray, neutron, and solid-state CD experiments are consistent with a picture of enantiopure domains of the wings of each twin component, and certainly inconsistent with a lamellar domain structure, where alternate layers of enantiomers lead to a near-racemic macroscopic composition. However, they do not exclude the possibility that each wing may incorporate localized domains of opposite chirality. To investigate this further, we undertook micro-domain mapping studies using a micro-collimated synchrotron beam (FWHM cross-section of 7.5 × 11.25 μm), focusing on micron-sized regions within each of the crystal wings (Figure 3 and Supporting Information, Section S.2). Flack parameters obtained for each of these regions (Table S2) clearly showed that all domains comprising *S*-enantiomers are in one wing, while the domains comprising *R*-enantiomers are in the opposite wing.

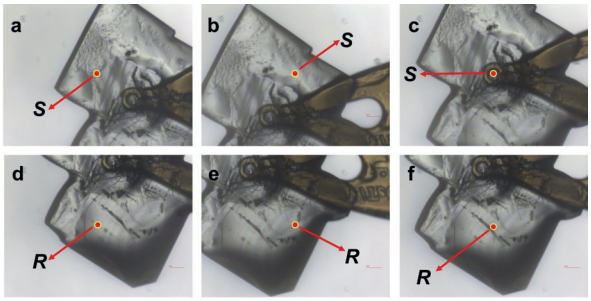

Figure 3. The twin crystal mounted for micro-XRD measurements. The small red dots represent regions where the synchrotron X-ray beam is focused. a)–c) highlight regions in the top crystal wing which show *S*-configuration and d)–f) show regions in the bottom wing which show *R*-configuration.

In an attempt to rationalize this unusual enantiomorphic growth as conjoined crystal twins, and to gain insight into the significance of the (010) twin plane, we examined the strength and directionality of the nearest-neighbor intermolecular interactions in the $P2_1$ and $P2_1/c$ forms of HCT.[16–18] Intermolecular interaction energies for the strongest molecular pairs in forms I and II (Figure S8) and energy framework analyses (Figure S9) revealed that the nature and topology of intermolecular interactions in form I are strikingly different from those in form II. Most notably, the strongest pairwise interaction in form II is a centrosymmetric π···π stacking interaction (−93 kJ mol^{-1}), and it is considerably stronger than any pairwise interaction in form I. A closer look at these two crystal structures reveals that this centrosymmetric π···π stacking interaction may form the junction between the enantiomorphic wings (Figure 4), and is likely to be important in the early nucleation steps that lead to the twin boundary.[23] This observation is supported by recent research on substituted benzoic acids, which demonstrated that aromatic stacking—not hydrogen bonding—is a key step in nucleation and cluster growth in solution.[24]

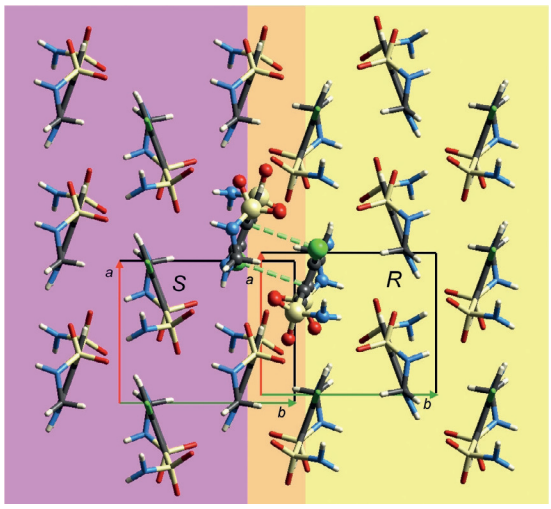

Figure 4. Illustration of the possible boundary between *S* and *R* enantiomorphs of form-I HCT. Unit cells for the two enantiomorphs have parallel axes and the view is along *c*. The magenta region includes a portion of the *S* enantiomorph and the yellow region a portion of the *R* enantiomorph. The strong centrosymmetric pairs found in form II are located in the orange overlap region, with a single pair highlighted by a ball-and-stick model. Green dashed lines indicate close C···Cl contacts of 3.66 Å in the central dimer.

Because $P2_1$ is a polar space group, we also explored the relationship between the unit-cell dipole moment (μ_{cell}) of HCT form I and the observed twin crystal habit. The calculated molecular dipole moment of HCT in form I is 11.1 D (B3LYP/6-31G(d,p)), and the vector sum of these molecular dipoles gives $\mu_{cell} = 16.8$ D along the *b* axis. The formation of polar domains in crystals is a fundamental problem in current crystal-nucleation research.[25] Polar crystals formed by dipolar molecules can build up substantial electric polarity, leading to instability during crystal growth. Monte-Carlo simulations suggest that the formation of monodomain polar crystals is unfeasible, while the growth of opposite polar domains within polar single crystals is very likely during crystal nucleation in order to reduce the net electric polarity of the growing crystals.[26] Figure 5 illustrates two different orientations of unit-cell dipole moments in polar crystals that exhibit conjoined twin growth and where the

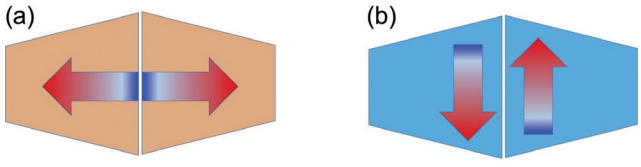

Figure 5. Different orientations of unit-cell dipole moments in twinned polar crystals that exhibit conjoined growth and where the dipole moments of opposite twin domains mutually cancel: a) Opposite polarity orientation in *R* and *S* wings of HCT twin crystal determined in this study; b) Observed antiparallel orientation of electric polarity in a ZNPPA twin crystal.[22]

dipole moments of opposite domains mutually cancel. The enantiomorphs of HCT demonstrate one way of circumventing this polarity problem, with opposite polar domains growing into physically separable wings of enantiopure crystals. The twin arrangement suggested by Figure 4 implies that crystal growth occurs such that the cell dipole-moment vectors along the *b* axes of both enantiomorphs are oriented in opposite directions and effectively cancel the net electric polarity of the macroscopic twin (Figure 5a). A striking example of the second possibility, antiparallel side-by-side orientation of unit-cell dipoles, has actually been reported for (4-pyrrolidinopyridyl)bis(acetylacetonato)zinc(II) (ZNPPA).[27] Although this molecule is not chiral, it crystallizes in both centrosymmetric (*C*2/*c*) and non-centrosymmetric polar (*Fdd*2) forms. Bipyramidal crystals of the polar form could be split along the (010) cleavage plane to reveal two domains of equivalent size but opposite polarity. The calculated dipole moment of ZNPPA (B3LYP/6-31G(d,p)) is 10.0 D, aligned along the *c* axis of this space group, resulting in the net cancellation of crystal polarity in Figure 5b.

As one of the most commonly prescribed antihypertensive and diuretic drugs, it is surprising that the subtle conformational chirality and the persistent appearance of symmetric conjoined twin crystals of HCT form I had escaped notice until this report. The chirality of HCT molecules arises from the pyramidal nature of the sultam nitrogen atom adjacent to the sulfone group, combined with a barrier to flipping of the saturated ring. Crystallization and dissolution studies have confirmed that there is a low barrier to interconversion of enantiomers in solution at room temperature. The individual wings of the conjoined twin crystals reported here comprise large polar enantiopure domains and a nucleation mechanism for their formation is suggested by the most strongly bound molecular pair in the two HCT forms, a centrosymmetric $\pi\cdots\pi$ stacking interaction in form II. The orientation of the strongly dipolar HCT molecules in the unit cell of form I results in substantial unit-cell dipole moments, precisely opposed in the two wings of the twin crystal. We are aware of only one other report of a pseudoracemic twin crystal exhibiting a boundary between two physically separable twin domains, namely that of hydrobenzoin (1,2-diphenyl-1,2-ethanediol) in its $P2_1$ crystal form. Unlike HCT, hydrobenzoin has three possible stereoisomers which do not interconvert readily in solution (The considerable literature on the habit and optical purity of hydrobenzoin crystals is summarized in the Supporting Information, Section S.6). However, molecular hydrobenzoin in its polar crystal form (CSD refcode VABVAV) has a smaller dipole moment of 1.9 D, giving $\mu_{cell} = 3.0$ D along the *b* axis. We are therefore unable to speculate on the extent to which the magnitude of the unit-cell dipole moment (or perhaps the polarization density) contributes to the creation of conjoined enantiomorphic twins or determines a limit to their growth in different solvents. However, the present study has demonstrated that there is clearly much more to be learned about macroscopic polar domains in molecular crystals and that further studies on HCT are clearly desirable.

Experimental Section

CCDC 1568967, 1568968, 1568971 and 1905989 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. Table S1 (Supporting Information) contains the supplementary crystallographic data. The Supporting Information also includes CIF files for the microXRD experiments in Table S2.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: chiral resolution · crystal engineering · crystal growth · enantiomorphs · X-ray diffraction

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[1] a) T. P. Radhakrishnan, *Acc. Chem. Res.* **2008**, *41*, 367 – 376; b) M. Jin, T. Seki, H. Ito, *J. Am. Chem. Soc.* **2017**, *139*, 7452 – 7455.

[2] a) E. Meirzadeh, I. Azuri, Y. Qi, D. Ehre, A. M. Rappe, M. Lahav, L. Kronik, I. Lubomirsky, *Nat. Commun.* **2016**, *7*, 13351; b) M. K. Panda, T. Runcevski, A. Husain, R. E. Dinnebier, P. Naumov, *J. Am. Chem. Soc.* **2015**, *137*, 1895 – 1902.

[3] a) W. L. Noorduin, T. Izumi, A. Millemaggi, M. Leeman, H. Meekes, W. J. P. Van Enckevort, R. M. Kellogg, B. Kaptein, E. Vlieg, D. G. Blackmond, *J. Am. Chem. Soc.* **2008**, *130*, 1158; b) W. L. Noorduin, P. van der Asdonk, H. Meekes, W. J. P. van Enckevort, B. Kaptein, M. Leeman, R. M. Kellogg, E. Vlieg, *Angew. Chem. Int. Ed.* **2009**, *48*, 3278 – 3280; *Angew. Chem.* **2009**, *121*, 3328 – 3330; c) W. L. Noorduin, E. Vlieg, R. M. Kellogg, B. Kaptein, *Angew. Chem. Int. Ed.* **2009**, *48*, 9600 – 9606; *Angew. Chem.* **2009**, *121*, 9778 – 9784.

[4] C. Viedma, J. M. McBride, B. Kahr, P. Cintas, *Angew. Chem. Int. Ed.* **2013**, *52*, 10545 – 10548; *Angew. Chem.* **2013**, *125*, 10739 – 10742.

[5] W. L. Noorduin, A. A. C. Bode, M. van der Meijden, H. Meekes, A. F. van Etteger, W. J. P. van Enckevort, P. C. M. Christianen, B. Kaptein, R. M. Kellogg, T. Rasing, E. Vlieg, *Nat. Chem.* **2009**, *1*, 729 – 732.

[6] H. Lorenz, A. Seidel-Morgenstern, *Angew. Chem. Int. Ed.* **2014**, *53*, 1218 – 1250; *Angew. Chem.* **2014**, *126*, 1240 – 1274.

[7] F. Yagishita, H. Ishikawa, T. Onuki, S. Hachiya, T. Mino, M. Sakamoto, *Angew. Chem. Int. Ed.* **2012**, *51*, 13023 – 13025; *Angew. Chem.* **2012**, *124*, 13200 – 13202.
[8] Although only 11 pairs among the 65 Sohncke groups are chiral space groups, crystals belonging to all 65 Sohncke groups are chiral.
[9] H. D. Flack, *Helv. Chim. Acta* **2003**, *86*, 905 – 921.
[10] a) E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**; b) J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates, and Resolutions*, Wiley, New York, **1981**.
[11] a) L. Fábián, C. P. Brock, *Acta Crystallogr. Sect. B* **2010**, *66*, 94 – 103; b) R. Laubenstein, M. D. Serb, U. Englert, G. Raabe, T. Braun, B. Braun, *Chem. Commun.* **2016**, *52*, 1214 – 1217.
[12] R. Bishop, M. L. Scudder, *Cryst. Growth Des.* **2009**, *9*, 2890 – 2894.
[13] a) S. Furberg, O. Hassel, *Acta Chem. Scand.* **1950**, *4*, 1020 – 1023; b) R. H. Martin, M. J. Marchant, *Tetrahedron* **1974**, *30*, 343 – 345; c) B. S. Green, M. Knossow, *Science* **1981**, *214*, 795 – 797; d) G. A. Potter, C. Garcia, R. McCague, B. Adger, A. Collet, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1666 – 1668; *Angew. Chem.* **1996**, *108*, 1780 – 1782; e) M. Berfeld, D. Zbaida, L. Leiserowitz, M. Lahav, *Adv. Mater.* **1999**, *11*, 328 – 331; f) S. Beilles, P. Cardinael, E. Ndzie, S. Petit, G. Coquerel, *Chem. Eng. Sci.* **2001**, *56*, 2281 – 2294; g) C. Gervais, S. Beilles, P. Cardinael, S. Petit, G. Coquerel, *J. Phys. Chem. B* **2002**, *106*, 646 – 652; h) V. Y. Torbeev, K. A. Lyssenko, O. N. Kharybin, M. Y. Antipin, R. G. Kostyanovsky, *J. Phys. Chem. B* **2003**, *107*, 13523 – 13531; i) R. J. Davey, G. Sadiq, C. C. Seaton, R. G. Pritchard, G. Coquerel, C. Rougeot, *CrystEngComm* **2014**, *16*, 4377 – 4381.
[14] K. Claborn, E. Puklin-Faucher, M. Kurimoto, W. Kaminsky, B. Kahr, *J. Am. Chem. Soc.* **2003**, *125*, 14825 – 14831.
[15] L. Dupont, O. Dideberg, *Acta Crystallogr. Sect. B Chem.* **1970**, *26*, 1884 – 1885.
[16] L. Dupont, O. Dideberg, *Acta Crystallogr. Sect. B* **1972**, *28*, 2340 – 2347.
[17] A. Florence, A. Johnston, P. Fernandes, K. Shankland, H. N. E. Stevens, S. Osmundsen, A. B. Mullen, *Acta Crystallogr. Sect. E* **2005**, *61*, o2798 – o2800.
[18] a) A. Johnston, A. J. Florence, N. Shankland, A. R. Kennedy, K. Shankland, S. L. Price, *Cryst. Growth Des.* **2007**, *7*, 705 – 712; b) C. K. Leech, F. P. Fabbiani, K. Shankland, W. I. David, R. M. Ibberson, *Acta Crystallogr. Sect. B* **2008**, *64*, 101 – 107; c) A. Saini, R. Chadha, A. Gupta, P. Singh, S. Bhandari, S. Khullar, S. Mandal, D. S. Jain, *Pharm. Dev. Technol.* **2016**, *21*, 611 – 618.
[19] a) A. A. Dvorkin, Y. A. Simonov, J. Lipkowski, M. S. Fonar, T. I. Malinowski, E. V. Ganin, S. A. Kotlyar, *Kristallografiya* **1990**, *35*, 682 – 686; b) Y. A. Simonov, M. S. Fonari, G. Bocelli, G. Calestani, J. Lipkowski, K. Suwinska, E. V. Ganin, *Supramol. Chem.* **1995**, *4*, 251 – 258; c) A. Johnston, A. J. Florence, A. R. Kennedy, *Acta Crystallogr. Sect. E* **2005**, *61*, o2573 – o2575; d) A. Johnston, A. J. Florence, A. R. Kennedy, *Acta Crystallogr. Sect. E* **2005**, *61*, o2520 – o2522; e) A. J. Florence, A. Johnston, K. Shankland, *Acta Crystallogr. Sect. E* **2005**, *61*, o2974 – o2977; f) A. Johnston, A. J. Florence, A. R. Kennedy, *Acta Crystallogr. Sect. E* **2006**, *62*, o1730 – o1732; g) A. Johnston, A. J. Florence, A. R. Kennedy, *Acta Crystallogr. Sect. E* **2006**, *62*, o2288 – o2290; h) A. Johnston, A. J. Florence, A. R. Kennedy, *Acta Crystallogr. Sect. E* **2006**, *62*, o5169 – o5171; i) A. Johnston, A. J. Florence, A. R. Kennedy, *Acta Crystallogr. Sect. E* **2006**, *62*, o2926 – o2928; j) H. D. Clarke, K. K. Arora, H. Bass, P. Kavuru, T. T. Ong, T. Pujari, L. Wojtas, M. J. Zaworotko, *Cryst. Growth Des.* **2010**, *10*, 2152 – 2167; k) P. Sanphui, L. Rajput, *Acta Crystallogr. Sect. B* **2014**, *70*, 81 – 90; l) J.-R. Wang, C. Ye, X. Mei, *CrystEngComm* **2014**, *16*, 6996 – 7003; m) R. Chadha, S. Bhandari, S. Khullar, S. K. Mandal, D. V. Jain, *Pharm. Res.* **2014**, *31*, 2479 – 2489; n) P. Sanphui, V. K. Devi, D. Clara, N. Malviya, S. Ganguly, G. R. Desiraju, *Mol. Pharm.* **2015**, *12*, 1615 – 1622; o) S. P. Gopi, M. Banik, G. R. Desiraju, *Cryst. Growth Des.* **2017**, *17*, 308 – 316.
[20] We note that in the original reports by Dupont and Dideberg, crystals of HCT obtained from ethanol solution were described thus: "Les cristaux incolores se présentent sous forme de plaquettes triangulaires (001)" [The colorless crystals are in the form of triangular platelets (001)].
[21] a) H. D. Flack, *Acta Crystallogr. Sect. A* **1983**, *39*, 876 – 881; b) R. W. W. Hooft, L. H. Straver, A. L. Spek, *J. Appl. Crystallogr.* **2008**, *41*, 96 – 103.
[22] The free-energy barrier for racemisation of thalidomide is known to be $\approx 102\ kJ\,mol^{-1}$ [G. Schoetz, O. Trapp, V. Schurig, *Electrophoresis* **2001**, *22*, 3185], but enantiomers of thalidomide are known to interconvert rapidly in solution and in vivo, the rate depending on pH and availability of catalytic pathways.
[23] In a similar manner, twinning in *R*,*S*-alanine has been proposed to originate from a central nucleus of *S* enantiomers [I. Weissbuch, I. Kuzmenko, M. Vaida, S. Zait, L. Leiserowitz, M. Lahav, *Chem. Mater.* **1994**, *6*, 1258].
[24] a) E. Gaines, K. Maisuria, D. Di Tommaso, *CrystEngComm* **2016**, *18*, 2937 – 2948; b) A. J. Cruz-Cabeza, R. J. Davey, S. S. Sachithananthan, R. Smith, S. K. Tang, T. Vetter, Y. Xiao, *Chem. Commun.* **2017**, *53*, 7905 – 7908.
[25] J. Hulliger, M. Burgener, R. Hesterberg, M. Sommer, K. Brahimi, H. Aboulfadl, *IUCrJ* **2017**, *4*, 360 – 368.
[26] J. Hulliger, T. Wüst, K. Brahimi, J. C. Martinez Garcia, *Cryst. Growth Des.* **2012**, *12*, 5211 – 5218.
[27] S. P. Anthony, P. Raghavaiah, T. P. Radhakrishnan, *Cryst. Growth Des.* **2003**, *3*, 631 – 634.

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