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Chiral Crystals from Porphyrinoids Possessing a Very Low Racemization Barrier†

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The unique solid state NMR technique Very Fast MAS with a sample spinning rate over 40 kHz was employed for screening and selection of crystals of porphyrinoid derivatives – corroles, suitable for X-ray diffraction studies. The host-guest approach and formation of inclusion complexes were efficient methods for the synthesis of chiral crystals from free base corroles possessing an extremely low racemization barrier. Our data show that the intrinsic features of corroles, including the dihedral angle saddling effect and distortion of the macrocyclic rings out of planarity have no crucial influence on the tendency for symmetry breaking.

An intriguing phenomenon related to the origin of life is the formation of proteins and nucleic acids from homochiral L-amino acids and D-sugars.[1] Theories for the stochastic origin of single chirality in the biological world fall into two major categories, biotic and abiotic.[2] According to the biotic theory, the selection of one of the enantiomers took place at a later stage in the biological evolution of living matter. The abiotic concept assumes that homochiral materials had been formed prior to biopolymers and asymmetric synthesis was induced by chiral inorganic/organic matrices.

Numerous papers showing the formation of chiral templates have been published and different strategies have been recently reviewed[3] and discussed.[4] One of the methods leading to the formation of chiral matter is crystallization of achiral molecules. This approach, known as "Mirror Symmetry Breaking" has a long history.[5] The best known example of

formation of chiral crystals (CCs) from achiral compounds is nucleation of sodium chlorate which was reported over a hundred years ago by Kipping and Pope.[6] To date, a number of achiral species have been tested with success as potential substrates for the synthesis of chiral templates.[7] Surprisingly, only a few such examples are found among porphyrinoid derivatives which belong to some of the most important natural products. Ribo and co-workers have shown that porphyrin derivatives functionalized by sulfonyl residues employing electrostatic interactions can be organized into chiral fibers (J-aggregates).[8] Yamaguchi *et al.* have reported self–assembly of dendritic zinc porphyrin which under spin-coating conditions are organized into a chiral material.[9] The literature reporting the CCs formed by non-decorated ("naked") porphyrin derivatives is rather limited. Alternatively, the good candidates for formation of chiral crystals can be found in the big family of chemically modified porphyrinoid derivatives.[10] Among them, corroles (Fig. 1) constitute a special case since all non-planar conformations of free base corroles are chiral.[11] This feature is simply a consequence of the lack of any symmetry element in such conformers. On the other hand, the calculated energy barrier associated with enantiomerization is very low (~0.2 eV).[11a] This low energy barrier is not only a consequence of the lack of steric hindrance, but also of the ground-state proton transfer (tautomerization)[12] and presumably the excited-state proton transfer (analogous to the one studied for porphycenes).[13] The low racemization barrier for free base corroles has been overcome by introduction of one alkyl substituent on the nitrogen atom in the core, first by Gross and co-workers[11b] and then by Koszarna *et al.*,[14] a modification which led to separation of the two enantiomers *via* chiral HPLC.[11b]

Recently Ghosh and co-workers discussed the problem of chirality and enantiomerization for free base corroles, porphyrin analogues that are composed of four pyrrolic rings connected by three *meso* carbons and one direct pyrrole–

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pyrrole link (Fig. 1).[11a] These authors have investigated 2, 3, 7, 8, 12, 13, 17, 18 – octabromo – 5, 10, 15-tris(penta-fluorophenyl)corrole, $H_3[Br_8TPFPCor]$, which exhibits the strongest nonplanar distortions observed to date for any free base corrole structure. Due to the presence of heavy atoms (bromines) and due to the significant nonplanar distortions, energetics barrier for enantiomerization is high. In light of the mentioned above discussion, the outcomes raise the question of whether a significant distortion of the molecular structure of corroles is a sufficient and decisive prerequisite for formation of CCs and further what strategy can be employed for synthesis of CCs of corroles with very low racemization barrier.
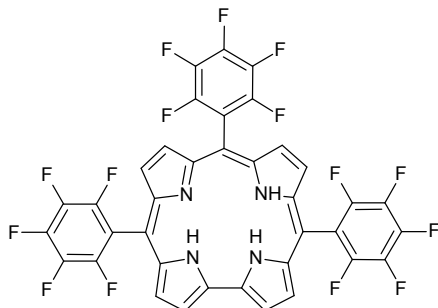

Fig. 1 Structure of 5,10,15-tris(pentafluorophenyl)corrole

The best way to designate the chirality and absolute structure of crystals is to perform X-ray crystallographic analysis in properly determined space group. Of the 230 space groups theoretically obtained, there are 65 space groups containing only proper (first kind) symmetry operations producing chiral crystal structures.[7a] In searching the X-ray structures deposited in the Cambridge Crystallographic Data Center (CCDC) for free base corroles, we found that the solvates of 5,10,15-tris(pentafluorophenyl)corrole[15] with ethyl acetate and chloroform included in the crystal lattice belong to the group of chiral crystals with space groups $P2_12_12_1$ and $P2_1$ respectively. In general, the chiral crystals can be obtained by employing subtle host–guest interactions. For instance, the achiral molecules of urea and tri-o-thymotide crystallize as enantiomorphous inclusion hosts in the presence of achiral guest molecules, driving the latter to assume a homochiral environment.[16]

In this paper we address the question of whether a host-guest strategy can be used to obtain the chiral crystals of corroles. Our studies were carried out in several stages. First, we optimized the crystallization conditions by testing different solvents (guests). Subsequently, we applied solid-state NMR for screening of crystals and selection of material with quality acceptable for single crystal X-ray Diffraction (XRD) studies. We then solved, refined and determination of the absolute structure of the selected crystals by means of XRD and finally, we confirmed the chirality of crystal employing the circular dichroism (CD) method.

As a primary tool we used the Very Fast Magic Angle Spinning (VF MAS) NMR technique which has several advantages.[17] Due to the small size of the rotor, it is possible to work with minimal amounts of sample (*ca* few mg). Moreover, the sample can be spun up to 70 kHz which greatly improves the resolution of the proton spectrum. Searching the large collection of crystals grown during crystallization with different solvents, we found that the most interesting samples were obtained when deuterated methylene chloride was applied as a guest molecule.

Fig. 2 shows the ^{1}H NMR spectra recorded with a spinning rate of 42 kHz in a 1.3 mm rotor for crystals of 5,10,15-tris-(pentafluorophenyl)corrole. Sample **1** was obtained by slow isothermic evaporation of deuterated methylene chloride (CD_2Cl_2) at room temperature. Sample **2** was crystallized from a mixture of deuterated methylene chloride (CD_2Cl_2) with pentane (vol:vol 1:1). 1D NMR spectra clearly prove that with the mixed solvent, the pentane molecules were not incorporated into the crystal lattice. Notable differences between the ^{1}H spectra were apparent, which suggested a distinct arrangement of molecules in the solid phase. These differences were more clearly seen in 2D mode. The 2D Back-to-Back correlation (Fig. 2a, 2b) showed the connectivity between the group of individual signals. The most striking feature was the distinction of ^{1}H chemical shifts and spectral patterns for the H-N protons. Furthermore, results confirming the high crystallinity of the obtained material and dissimilarity in the molecular packing of crystals were obtained by 1D and 2D ^{13}C NMR measurements. Fig. 2c, 2d displays the [1]H-^{13}C HETCOR correlations for both crystals recorded in the inverse mode with the contact time of 50 μs in order to observe direct carbon-proton correlations.

Having obtained the roughly characterized and selected crystals, we then carried out the XRD measurements. Sample **1** crystallized in the $P2_12_12_1$ space group while sample **2** was in the $P2_1$/c group. Fig. 3 shows the crystal and molecular structures for both polymorphs. The asymmetric unit of the crystal consists of one molecule of corrole and two molecules of solvent. In both cases, two guest molecules (methylene chloride) were in close contact with corrole matrix. The X-ray studies further confirmed that pentane was not incorporated into the crystal lattice. The molecular packing for **1** and **2** is determined by the space group symmetry despite that the Z equal to four independent units (each containing one corrole molecule and two methylene chloride molecules) per unit cell for both crystals they differs in molecules arrangement. For sample **1**, the corrole rings were aligned in almost parallel planes (face to face) with a significant offset between the center of rings. For corrole **2**, the macrocyclic cores were located in perpendicular planes (T-shape).

The distortion from coplanarity of the pyrrole rings is thought to be a crucial factor leading to an increase of the enantiomerization barrier for corroles.[11a] The measure of nonplanar distortions is shown by the saddling dihedral angles labeled as χ_1, χ_2, χ_3, χ_4. Thus, to understand the correlation between molecular structures and chirality of crystals, we compared (Table 1) the values of these angles for the inclusion complexes of 5,10,15-tris(pentafluorophenyl)corroles, as deposited with the CCDC, with the data reported in this study.

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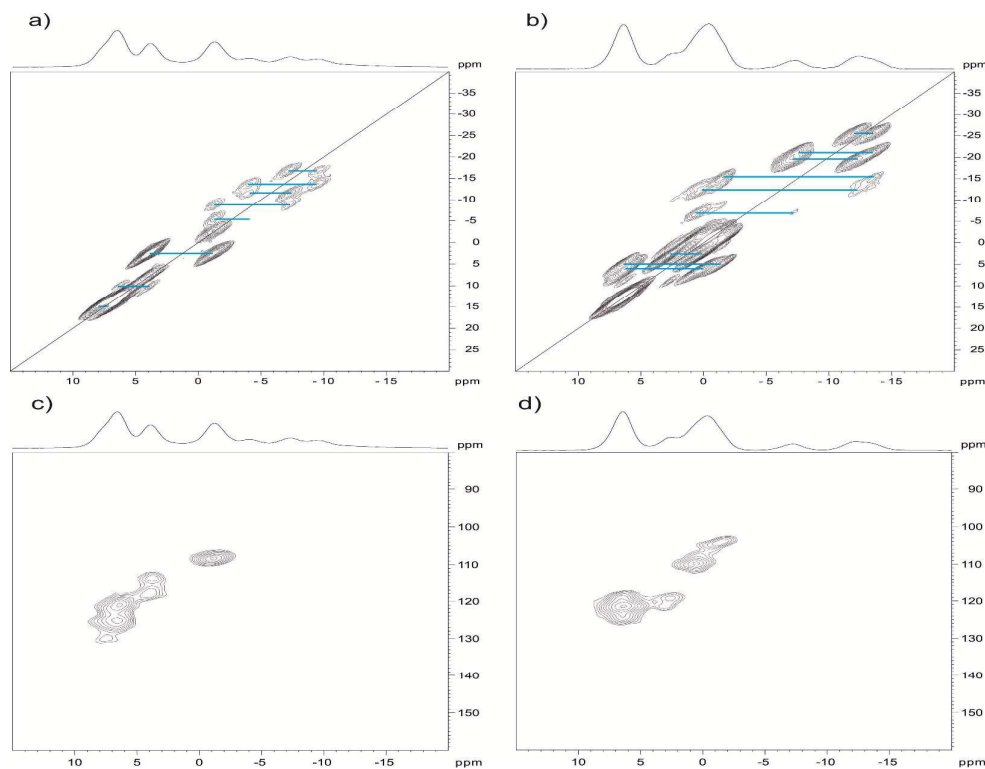
Fig. 2 2D [1]H-[1]H Back-to-Back (a, b) and [1]H-^{13}C inverse detected HETCOR (c, d) correlations for a), c) sample **1**, crystallized from deuterated methylene chloride and b), d) sample **2**, crystallized from a 1:1 mixture of deuterated methylene chloride and pentane. Spectra were measured with spinning speed equal to 42 kHz using 1.3 mm probe heads.
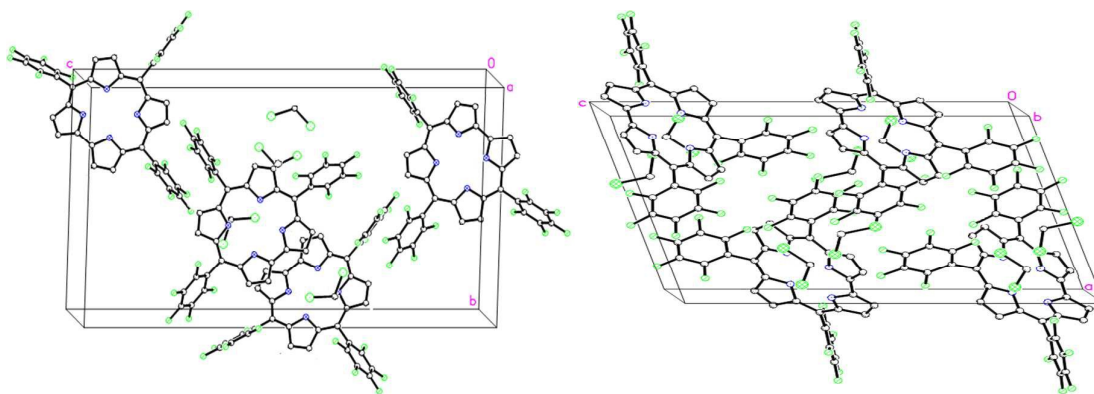
**Fig. 3** X-ray structures of sample **1** (left) and sample **2** (right). Hydrogen atoms are omitted for clarity.

Inspection of the data collected in Table 1 clearly shows three host-guest complexes crystallized in the space groups leading to chiral crystals: the aforementioned crystal with ethyl acetate as a guest (CSD refcode JEFBIG) and sample **1**, both in the $P2_12_12_1$ orthorombic space group as well the crystal where chloroform is the guest ($P2_1$ monoclinic space group, CSD refcode UCUPOZ) According to Howard D. Flack, these space groups are not chiral themselves but they produce chiral crystal structures.[18] The saddling dihedral angles χ_1-χ_4 for

orthorhombic complexes were generally similar, with the largest difference occurring in the values of the χ_3 dihedral angles. Their packing exhibited similarities (face to face alignment with the significant offset between centers of the corrole template) even though the guests were very different and only one ethyl acetate molecule accompanied the host matrix. In the crystal with chloroform the orientation of the host molecules is angular and the space between them is filled by two chloroform molecules.

Table 1 Saddling dihedral angles of 5,10,15-tris(pentafluorophenyl)corrole

Solvent	Space group	χ_1	χ_2	χ_3	χ_4	CSD refcode
chloroform	P2$_1$	67.8	14.1	28.3	21.1	UCUPOZ[19]
ethyl acetate	P2$_1$2$_1$2$_1$	71.0	2.5	44.6	15.3	JEFBIG[20]
m-xylene	P2$_1$/c	67.3	14.6	20.0	19.1	UHEWOT[15]
methylene chloride, achiral	P2$_1$/c	70.1	17.0	3.1	28.6	Our work
methylene chloride, chiral	P2$_1$2$_1$2$_1$	68.2	3.9	48.1	14.8	Our work

Fig. 4 shows the solid-state electronic circular dichroism (ECD) spectrum of selected crystal **1** which exhibited distinct Cotton effects (CEs) in the 200-800 nm spectral range. The observed positions of the bands were typical of this class of compounds, i.e., corroles, with a Soret band occurring around 400 nm and the Q bands arising in the ~500-700 nm spectral range.[21] It should be emphasized that efforts to select even one crystal of opposite chirality from the mixture were unsuccessful.
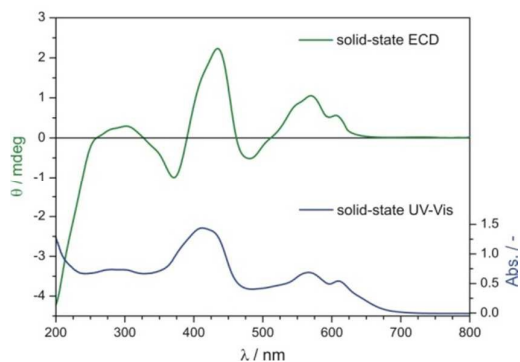
Fig. 4. Solid-state ECD (top) and EA (bottom) spectra of **1** recorded in KCl pellet.

During XRD measurements, we tested eight monocrystals of compound **1** (6 at room temperature and 2 in low temperature from two different crystallization batches) and all of them had the same chirality (Flack parameter 0 for the same atomic coordinations), which strongly suggested that only one enantiomorph grew during the crystallization process. This means that one enantiomer, if not exclusively, then in significant excess, was locally created. This outcome further indicated a radial growth of individual colonies of homochiral crystals starting from a single nucleation point direction. The process of crystallization of homochiral crystals from achiral solution was extensively studied and there are several hypotheses concerning 'symmetry breaking' in these systems. Most of them refers to a secondary nucleation process.[22] On the other hand, the collection of crystals obtained in one crystallization approach was silent in ECD, demonstrating that overall a racemic conglomerate was formed.

The unique physicochemical properties and the attractive practical applications of corroles have prompted many groups to explore new fields for their uses. The chemistry of corroles, and in particular of 5,10,15-tris(pentafluorophenyl)corrole, is well-developed and spans broad areas such as photophysical studies, coordination chemistry, self-assembly and biomedical applications.[23] For the class of compounds under discussion the stereochemistry is one of the features that can influence their further applications. Our study clearly shows that approach based on optimisation of crystal growing conditions and proper choice of the host-guest composition is the efficient way to grow chiral crystals of corroles.

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