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Preparation and Characterization of a Halogen-Bonded Shape-Persistent Chiral Alleno-acetylenic Inclusion Complex

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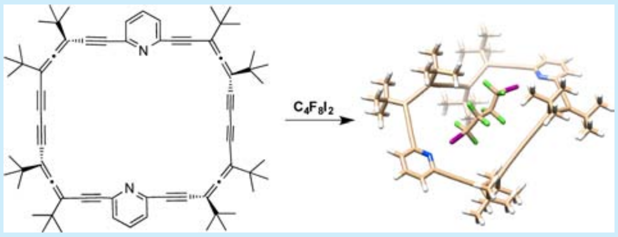
Supporting Information

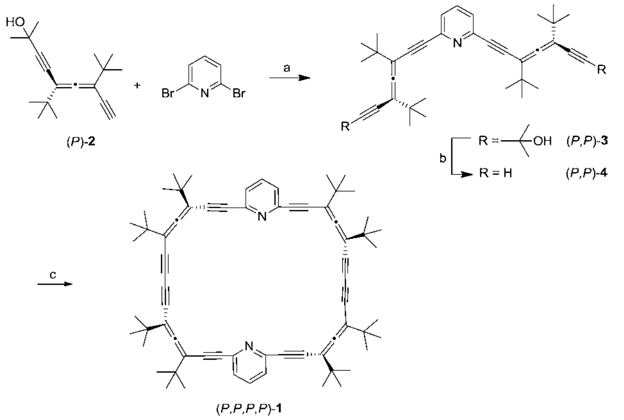
ABSTRACT: A chiral bidentate inclusion complex has been formed by halogen-bond interaction between the pyridyl moieties of a pyridoallenoacetylenic host and octafluorodiiodobutane. X-ray crystallography showed that the guest adopts a chiral conformation inside the molecular channels formed by stacking of the host units. A 10 ppm shielding of the ^{15}N NMR resonance for the pyridil units provided evidence of the formation of the halogen-bond complex in solution.



Shape-persistent macrocycles (SPMs),[1−5] commonly based on acetylenic structural units, present as one of their principal characteristics their ability to self-assemble in solution, giving rise to liquid crystal phases,[6−8] or when crystallized form molecular channels by suited alignment of the macrocycles cavities.[9] Most of the reported SPMs have an achiral nature since they are based on nonstereogenic arene-acetylene or arene-bisacetylene motifs. However, the introduction of a stereogenic allene unit leads to chiral allenoacetylenic or allenophanic structures.[10−16] Noteworthy, these allene-based structures present very intense Cotton bands in their electronic circular dichroism (ECD) spectra,[17,18] which makes them suitable as potential chiral sensors, especially if polar groups, pointing toward the inner cavity, were present in the molecule as, for instance, in our previously reported allenoacetylenic (2,5)-[19] and (2,6)-substituted[20] pyridine rings. Recently, the formation of chiral molecular channels in the solid state from an allenoacetylenic macrocyle decorated with phenols in its periphery has been reported by the group of Diederich.[21] Allenoacetylenic or allenophanic SPMs have been postulated in many cases as potential hosts for formation of inclusion complexes. So far, reported examples have been limited to solvent inclusion in crystallized compounds.[20−22] We report here the preparation of (2,6)-pyridophane in an enantiopure homochiral form, either (*P*,*P*,*P*,*P*)-**1** or (*M*,*M*,*M*,*M*)-**1**, and its use as a host for the formation of a chiral bidentate inclusion complexes through halogen-bonding interaction with octafluorodiiodobutane.

As the first step of the synthesis toward (*P*,*P*,*P*,*P*)-**1** (Scheme 1), Sonogashira cross-coupling reaction between 2,6-dibromopyridine with enantiopure allene (*P*)-**2** afforded (*P*,*P*)-**3** in 79% yield (Scheme 1). Removal of the acetonide protecting group gave (*P*,*P*)-**4** in 80% yield. Intermolecular ring closure under Breslow conditions afforded the desired (*P*,*P*,*P*,*P*)-**1** in 62% yield. Similarly, the enantiomer (*M*,*M*,*M*,*M*)-**1** was obtained from the corresponding (*M*)-**2** allene. It is worth noting the stability of homochiral **1**, which did not show signs of decomposition or isomerization on its ^1H NMR spectrum after weeks at room temperature under day light.

Scheme 1. Synthesis of Enantiopure (*P*,*P*,*P*,*P*)-1[a]



[a]Reagents and conditions: (a) $[PdCl_2(PPh_3)_2]$, CuI, TMEDA, toluene, 110 °C, 20 h, 79%; (b) NaOH, toluene, 110 °C, 2 h, 80%; (c) $CuCl_2$, CuCl, pyridine, 25 °C, 72 h, 57%.

Computational AM1 studies[20] showed that (*P*,*P*,*P*,*P*)-**1** has three conformations very close in energy, namely, C_2 boat, C_2 chair, and the highest symmetry D_2 twist form (Figure 1a−c). Here we reoptimized and computed vibrational frequencies at the DFT CAM-B3LYP/6-31G* level for these three con-

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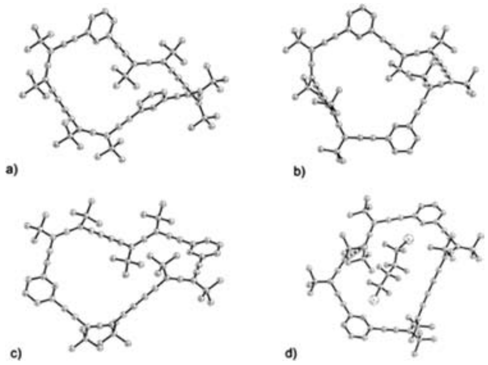

Figure 1. DFT CAM-B3LYP/6-31G* geometries for (a) C_2 boat, (b) C_2 chair, (c) D_2 twist (*P*,*P*,*P*,*P*)-**1**, and (d) $C_4F_8I_2$-(*P*,*P*,*P*,*P*)-**1** inclusion complex.

formations, confirming that they are true minima in the potential energy surface (see Supporting Information).

Crystallization of (*P*,*P*,*P*,*P*)-**1** from a $CHCl_3$/hexane solution afforded suitable crystals that after X-ray diffraction analysis show that (*P*,*P*,*P*,*P*)-**1** adopts the highest symmetry D_2 twist form in the solid state. The macrocycle molecules pack piling on top of each other, giving rise to elongated cavities that extend through the whole crystal dimension along the direction of the *b* unit cell axis forming a channel (Figure 2). The morphology of the channel was analyzed with the Caver 3.0 software[23] by using a sphere of radius 1.2 Å as a probe. The channel is formed by a sequence of ellipsoidal voids located in the centroid of the cyclic molecule, with an approximate volume of 290 Å^3. Due to blocking by the *tert*-butyl moieties, the void cavities are interconnected by three small pores, the widest being the one in the middle. Along the *c* axis, the adjacent macrocycle pyridil group intercalates between the piled molecules (Figure 3), leading to optimal π-stacking with a distance between aromatic moieties of ~3.5 Å.

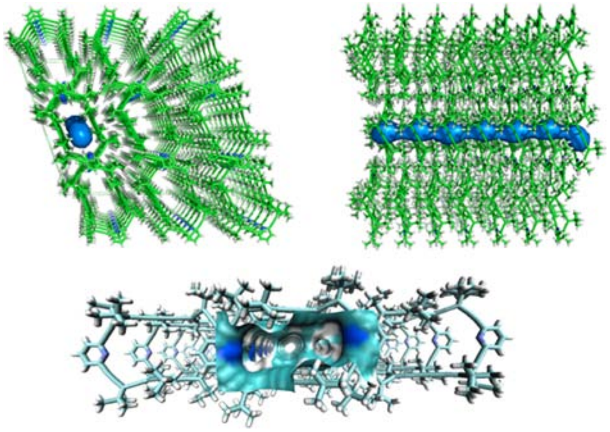

Figure 2. Three perpendicular views of the channel surface in crystallized (*P*,*P*,*P*,*P*)-**1**.

The face-to-face orientation of the pyridine lone-pairs toward the channel void in the D_2 conformation strongly suggested a great potential for the use of homochiral **1** as a bidentate host, especially for guests with linear or nearly linear geometries. Two types of noncovalent interactions come then to mind: formation of hydrogen bonds with acidic guests or the use of halogen-bond interactions. Halogen bonds are formed by donation from a lone-pair -containing donor such as amines, nitriles, and others, to the σ-hole[24] of a X−C bond (X = I, Br, Cl). Halogen bonds are becoming more and more useful[25] as part of the "non-covalent interaction toolkit" in the design of crystals structures, liquid crystal[26] and jelly[27] phases, and even medicinal chemistry.[28]

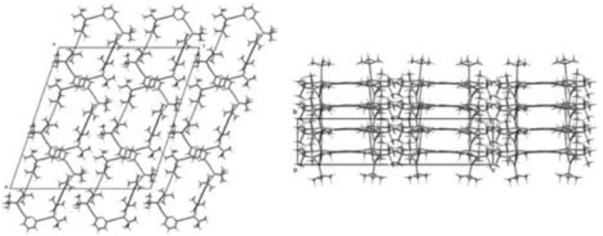

Figure 3. Packing diagram along the channel direction, *b* (left) and *a* (right) axes, displaying the $\pi-\pi$ stacking of aromatic pyridine rings and the layers of hydrophobic interactions in the *ab* plane.

Modeling of several halogen-bond bidentate complexes with different diiodinated and dibrominated guests was carried out through AM1 semiempirical computations. After trying several possible guests, we found that octafluoro-1,4-diiodobutane perfectly fitted the molecular cavity of (*P*,*P*,*P*,*P*)-**1** resulting in a bidentate halogen-bonded complex of C_2 symmetry in the AM1 potential surface as well as in higher level DFT CAM-B3LYP computations (see Figure 1d and Supporting Information for details).

When (*M*,*M*,*M*,*M*)-**1** was allowed to crystallize from a C_6D_6 solution in the presence of an excess of the diiodinated guest, suitable small crystals were obtained for X-ray diffraction analysis, which showed the formation of a 1:1 complex between (*M*,*M*,*M*,*M*)-**1** and $C_4F_8I_2$ with a molecular geometry very similar to that obtained in the DFT computations. The $C_4F_8I_2$ guest adopts an extended conformation inside the host cavity with a N−I distance of 3.0 Å. The unit cell is formed by two equivalent C_2 forms that can be interconverted by rotation around a C_2 axis, which passes through the two nitrogen atoms of the host (Figure 4). Interestingly, the guest diiodo compound adopts a chiral conformation inside the complex with a I−C1−C4−I torsion angle of 167°. The packing of the macrocycle units is very similar to that observed for the free host crystal, being now the described molecular channels filled by the fluorinated guest.

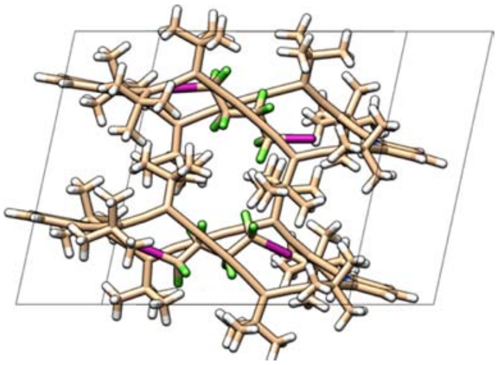

Figure 4. View of the unit cell formed by two units of the $C_4F_8I_2$−(*M*,*M*,*M*,*M*)-**1** complex.

NMR spectroscopy[29] provided strong evidence of the presence of the $C_4F_8I_2$-**1** complex also in solution. A C_6D_6 solution of (*M*,*M*,*M*,*M*)-**1** was titrated with 30, 60, 90, and 120 molar equiv of the diiodo compound. ^{1}H NMR spectrum showed some nonmonotonic changes in the chemical shifts of the pyridyl proton signals on increasing $C_4F_8I_2$ concentration (see spectra in the Supporting Information). We curiously observed that at the highest concentration (120 equiv) of the guest the meta protons of the pyridyl group become nonequivalent, while only a single set of resonances is observed in the ^{13}C spectrum. This seems to indicate breaking of the magnetic equivalence but not of chemical equivalence. This fact is remarkable since rapid exchange of guest-degenerated dispositions inside the cavity should average both *J*-couplings and chemical shifts in the host.

A stronger evidence of complex formation was obtained through analysis of the ^{15}N chemical shift, obtained, by means of HMBC ^{1}H−^{15}N experiments, at the different titration points (Figure 5). The ^{15}N shielding goes as high as 9.8 ppm with 120 equiv of guest. Fitting the ^{15}N chemical shift data to a 1:1 complexation model through Benesi−Hildebrand equation[30] furnished an association constant, $K_a = 4.2 \pm 0.2$ M, which is of the same order of magnitude than that of the previously reported perfluoroiodohexane−pyridine complex in benzene,[31] and a saturation ^{15}N shielding of 11.7 ± 0.2 ppm (see the Supporting Information for further details). GIAO/DFT PBE0 chemical shielding computations predicted a ^{15}N chemical shielding of 19.4 ppm.

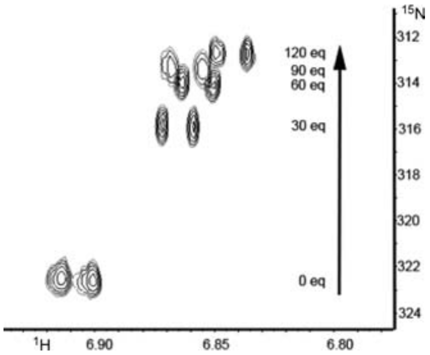

Figure 5. ^{1}H−^{15}N HMBC titration of the formation of the $C_4F_8I_2$-**1** complex in C_6D_6. The three-bond coupling cross peaks between the H_3 proton of the pyridil group and the nitrogen are shown.

In summary, we report for the first time the use of allenoacetylenic shape-persistent macrocycles as molecular hosts by exploiting halogen bonding interactions leading to specific filling of the crystal molecular channels. Applicability of these new complexes may involve the design of new chiral switchers and sensors as well as preparation of chiral chromatographic layers[32] for resolution of racemic halogenated compounds.[33] Moreover, the chiral conformation adopted by the guest presents these systems as potential ligands for asymmetric catalysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data for the synthesis of **1**. X-ray crystallography procedures, data, and CIF files for (*P*,*P*,*P*,*P*)-**1** (CCDC 877535) and $C_4F_8I_2$-(*M*,*M*,*M*,*M*)-**1** (CCDC 983222). DFT computational details and geometries of computed structures. NMR complexation studies procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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