Supramolecular Chemistry

International Edition: DOI: 10.1002/anie.201508009
German Edition: DOI: 10.1002/ange.201508009

Hexaphyrin–Cyclodextrin Hybrids: A Nest for Switchable Aromaticity, Asymmetric Confinement, and Isomorphic Fluxionality

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Abstract: *Conformational control over the highly flexible π-conjugated system of expanded porphyrins is a key step toward the fundamental understanding of aromaticity and for the development of molecular electronics. We have synthesized unprecedented hexaphyrin–cyclodextrin (HCD) capped hybrids in which the hexaphyrin part is constrained in a planar rectangular conformation in either a 26 or a 28 π-electron oxidation state (**[26]/[28]HCD**). These structures display strong aromaticity and antiaromaticity, respectively, exhibit markedly different chiroptical properties, and are interconvertible upon the addition of DDQ or $NaBH(OAc)_3$, thus affording a rare switchable aromatic–antiaromatic system with a free-base expanded porphyrin. Conformational analysis revealed discrimination of the two coordination sites of the hexaphyrin, one of which was coupled to a confined asymmetric environment, and fluxional behavior consisting of apparent rotation of the hexaphyrin cap through a shape-shifting mechanism.*

During the last two decades, expansion of the porphyrin ring to create larger homologues, including core-modified structures, has been investigated intensively.[1] In particular, larger porphyrinoids allow straightforward access to Möbius aromatic molecules owing to nonplanar π conjugation, as well as to stable antiaromatic compounds.[1b] They thus serve as precious tools in the endeavor to gain a fundamental understanding of aromaticity and form a basis for new practical applications. For example, porphyrinoids with switchable aromatic/antiaromatic character have potential applications in molecular electronics, in line with their distinctive photophysical features.[2] The relationship between the π-conjugated system of expanded porphyrins and their conformational properties (Figure 1 a) has been identified as a key issue for the development of innovative diatropic–paratropic switchable systems.[1d–f] In general, control of the aromatic state of expanded porphyrins has been explored by two main strategies (Figure 1 b). The first is to modify the topology of the π-conjugated system in a given oxidation state by changing the number of twists in the structure. This approach has led to a variety of stimuli-responsive planar-to-twisted conformational/aromaticity switches.[3] The second approach is to modify the oxidation state ($4n/4n+2$) of the macrocycle in a locked topology.[3g,4] The corresponding two-electron redox reactions, such as electrochemical processes, appear to be well-suited for the design of molecular devices, although strict conformational control is required to avoid topological changes that could convert an antiaromatic state into a more stable aromatic state.[5]

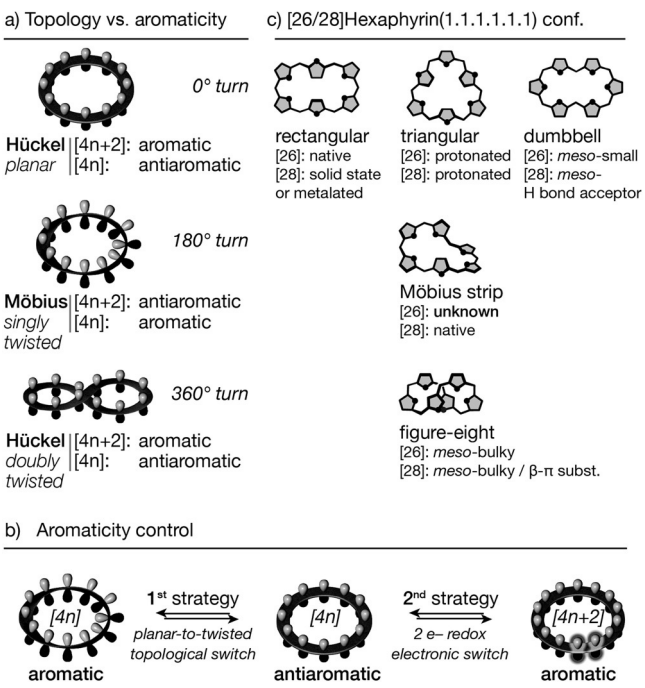

Figure 1. a) Relationship between topology and aromaticity in π-conjugated macrocycles. b) Illustration of two different strategies to design aromatic–antiaromatic switches with expanded porphyrins. c) Remarkable conformations of the hexaphyrin(1.1.1.1.1.1) macrocycle with some characteristics favoring the topologies.

In this context, the conformational control of expanded porphyrins is crucial. Their capping, yet unexplored, would offer such control and also generate a confined space around the coordination sites, which could be useful for the development of artificial bioinspired molecular receptors and catalysts.[6] To tackle the synthesis of such hybrids, we focused on the association between an α-cyclodextrin and a regular hexaphyrin(1.1.1.1.1.1) (Figure 1 c),[7] as both units possess attractive native properties. We describe herein the synthesis

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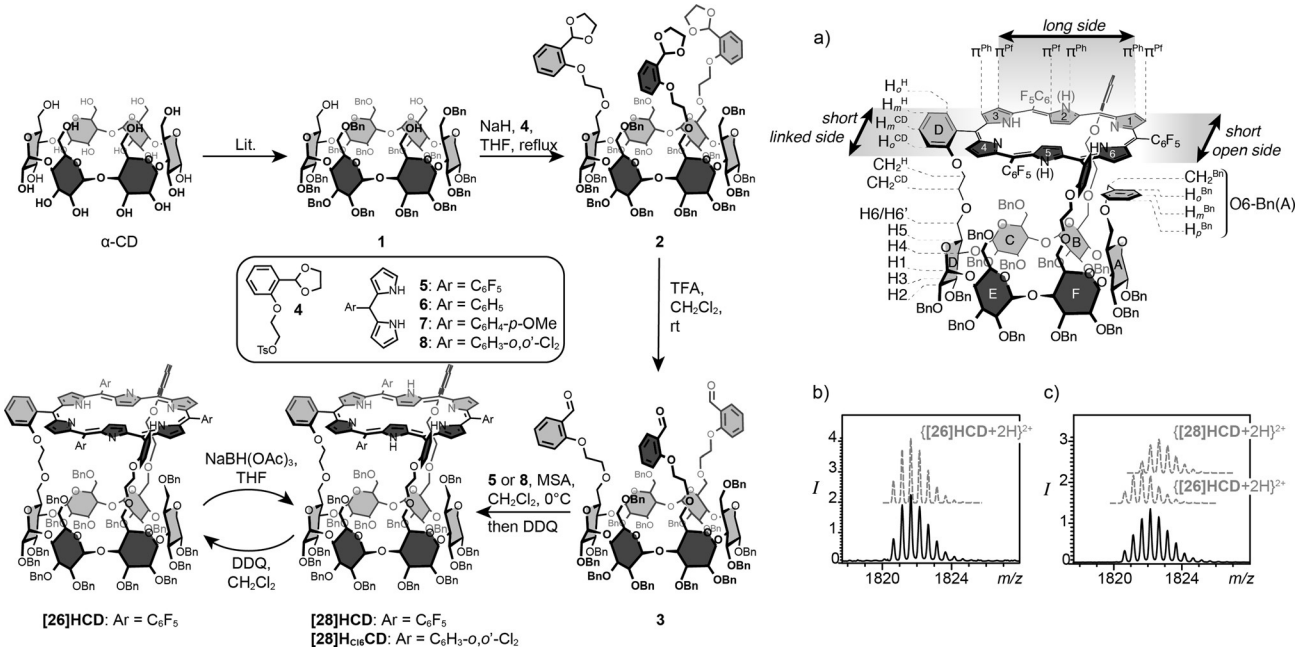
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201508009.

and conformational characterization of unprecedented triply linked hexaphyrin–cyclodextrin (HCD) hybrids, and a study of their dynamic behavior.

The formation of triply bridged HCD conjugates was investigated according to a [1+3] macrocyclization strategy involving the α-CD-trisaldehyde **3** and various 5-aryl dipyrromethanes (Scheme 1). Nucleophilic substitution of the perbenzylated 6^A,6^C,6^E-α-CD-triol **1**[8] with the tosylate derivative **4**, followed by acidic treatment, enabled isolation of the trisaldehyde **3** in 76% yield over two steps. Next, the [1+3] macrocyclization reaction was attempted from a mixture of **3** and dipyrromethane **5** in a 1:3 molar ratio, with a catalytic amount of methanesulfonic acid (MSA).[9] The oxidation of an aliquot with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was monitored by MALDI-TOF MS and TLC, and to our delight, the mass spectra showed an isotopic pattern corresponding to the targeted triply bridged hybrids (Scheme 1 b,c). Thus, the conjugate **[28]HCD** was isolated in moderate but reproducible 5% yield (Scheme 1), which is comparable to that of other hexaphyrin syntheses.[9] Both desired oxidation states (26 and 28 π-electron circuits) were accessible, as **[28]HCD** was readily oxidized with DDQ to **[26]HCD** (78% yield); importantly, **[26]HCD** could also be reduced back to **[28]HCD** with $NaBH(OAc)_3$ (75% yield; Scheme 1). These conditions were further applied to three other 5-aryl dipyrromethanes, **6**, **7**, and **8** (Scheme 1); however, only the **[28]H_{Cl6}CD** conjugate could be isolated (Scheme 1; see the Supporting Information). The higher stability of **[26/28]HCD** and **[28]H_{Cl6}CD** is in accordance with previous observations in investigations of hexaphyrins(1.1.1.1.1.1), in which *meso*-aryl groups substituted with large *ortho* groups or electron-withdrawing substituents increased the stability of the macrocycle.[9]

[26]HCD is characterized by a deep purple color similar to that of *meso*-hexakis(pentafluorophenyl)[26]hexaphyrin-(1.1.1.1.1.1) (**[26]H**),[9] and the UV/Vis absorption spectra of the two compounds are almost superimposable, with a sharp Soret-like band at 568 nm and weak Q-type bands at 717, 780, 901, and 1035 nm (Figure 2 a,c). These observations indicate that the [26]hexaphyrin subunit is aromatic, in line with either a planar or a figure-eight conformation (Figure 1).[1e] Conversely, the red-brown color of **[28]HCD** contrasts with the blue color generally observed for free-base [28]hexaphyrins. Instead of the sharp Soret-like band at 591 nm displayed by the aromatic *meso*-hexakis(pentafluorophenyl)[28]hexaphyrin(1.1.1.1.1.1) **[28]H**,[7] an ill-defined blue-shifted spectrum with maxima at 486 and 573 nm was observed for **[28]HCD**, without Q-bands (Figure 2 b,d). Such a spectrum is a general feature of antiaromatic expanded porphyrins,[2a] thus suggesting a conformation that differs from the Möbius strip topology. Furthermore, the circular dichroism spectra of both HCDs revealed Cotton effects with $\Delta\varepsilon_{max}$ values at 582 and 570 nm, which indicate a transfer of chirality from the enantiomerically pure cyclodextrin subunit to the hexaphyrin core (Figure 2 a,b).

The ^{1}H NMR spectra of **[26]HCD** and **[28]HCD** are characteristic of C_1-symmetrical species (see the Supporting Information). **[26]HCD** displays eight deshielded β-pyrrolic hydrogen atoms (8.45–9.55 ppm) and four shielded β-pyrrolic hydrogen atoms (between −2.74 and −3.32 ppm), whereas **[28]HCD** displays the reverse distribution: four deshielded (19.81–20.65 ppm) and eight shielded β-pyrrolic hydrogen



Scheme 1. Synthesis of triply bridged hexaphyrin–cyclodextrin hybrids through a [1+3] macrocyclization pathway. Bn = benzyl, TFA = trifluoroacetic acid, Ts = *p*-toluenesulfonyl. a) Labeling of HCDs (π^{Ph} and π^{Pf} define β-pyrrolic protons close to an aryl linker and a C_6F_5 *meso*-substituent, respectively). b,c) ESI-TOF high-resolution mass spectra of **[26]HCD** (b) and **[28]HCD** (c). The isotopic pattern of **[28]HCD** corresponds to the sum of both oxidation states, probably as a result of partial oxidation during mass analysis. Gray dashed lines: theoretical patterns.

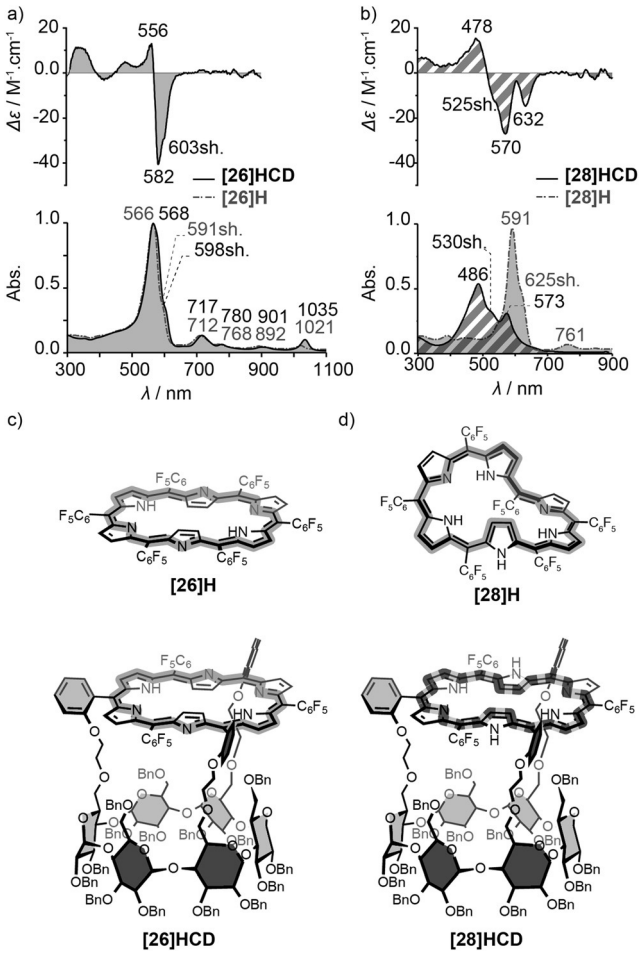


Figure 2. a,b) Circular dichroism (top) and UV/Vis spectra (bottom) of **[26]HCD** (a) and **[28]HCD** (b) in CH_2Cl_2. The UV/Vis spectra of **[26]H** and **[28]H** are superimposed in gray dashed lines as indicated. c,d) Structures of **[26]H** and **[26]HCD** (c) as well as **[28]H** and **[28]HCD** (d), with their π-electron circuits highlighted with solid and dashed gray lines for the aromatic and antiaromatic species, respectively.

atoms (3.36–2.51 ppm). Furthermore, the NH hydrogen atoms follow the same trend and are located upfield for **[26]HCD** (inner NHs: −2.37, −3.13 ppm) and both downfield and upfield for **[28]HCD** (inner NHs: 26.96, 26.49 ppm; outer NHs: 1.88, 1.49 ppm). These patterns correspond to a planar rectangular conformation with two inverted pyrrole rings facing one another. The inner hydrogen atoms of **[26]HCD** are strongly shielded owing to the diatropic ring current of the 26 π-electron circuit (Figure 2c, Hückel aromaticity), whereas those of **[28]HCD** experience the paratropic ring current of the 28 π-electron circuit (Figure 2d, Hückel antiaromaticity) and are therefore strongly deshielded. The chemical shifts of the hexaphyrin unit of **[26]HCD** are similar to those of **[26]H** (see the Supporting Information). In contrast, the chemical shifts of **[28]HCD** differ strongly from those of **[28]H** and show opposite trends with strong variations (see the Supporting Information; the symmetrical pattern of **[28]H** reflects the rapid equilibrium between Möbius structures: average $\delta_{\pi in} = 2.63$ ppm, average $\delta_{\pi out} = 7.62$ and 7.71 ppm).[7] Clearly, the triple linkage prevents antiaromatic-to-aromatic conformational adaptation, thus affording a rare example of purely Hückel antiaromatic [28]hexaphyrin in its free-base form.[10] These HCD derivatives thus enable aromatic–antiaromatic switching through two-electron redox reactions (Scheme 1) that can be monitored by circular dichroism, which provides a clear chiroptical readout (Figure 2a,b; at 570 nm, $\Delta\varepsilon^{[26]HCD} = 0$ and $\Delta\varepsilon^{[28]HCD} = -27\ M^{-1}\,cm^{-1}$).

For both HCDs, a thorough analysis of the NMR spectra revealed a field effect unevenly experienced by the differentiated glucose units of the cyclodextrin part. Indeed, a higher field effect occurs on half of the cyclodextrin torus (A, B, and F glucose units), with greater amplitude on the A unit located near the short open side (see the Supporting Information). This result indicates that the hexaphyrin protrudes asymmetrically over the cyclodextrin torus, with its short open side (π1 and π6) above the A unit. This hexaphyrin offset is in accordance with **[26]HCD** modeling (Figure 3). Calculations showed an interesting alignment

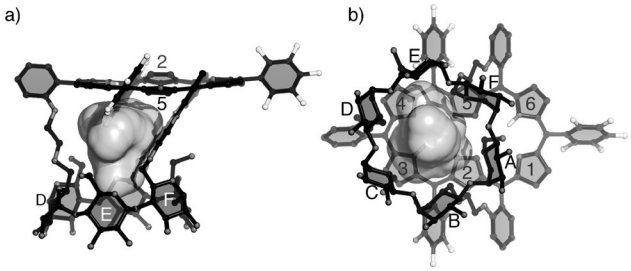


Figure 3. a) Side view and b) apical view from the cyclodextrin secondary rim of the optimized geometry of **[26]HCD** (Avogadro software, UFF parameters; benzyl groups were omitted for the modeling). The calculated Connolly solvent-accessible surface area is depicted in light gray.

between the cyclodextrin cavity and one of the two hexaphyrin coordination sites [Figure 3b: NH(π3), N(π4), CH-($\pi5^{Pf}$), CH($\pi2^{Pf}$)], which is further associated with a hydrophobic pocket delineated by the hexaphyrin cap, the three linkers, and the primary rim of the cyclodextrin (Figure 3). The cyclodextrin capping thus discriminates both the two faces of the hexaphyrin and the two coordination sites, one of which is coupled to the chiral cavity.

Interestingly, 2D NOESY spectra recorded at high temperatures revealed, for both HCDs, a drastic conformational reorganization illustrated by triads of exchange correlations. For example, there was good evidence for in/out and out/out pyrrole exchanges at 350–360 K, with selective correlations for $\pi2^{Pf}$ with $\pi4^{Pf}$ and $\pi6^{Pf}$, and for $\pi2^{Ph}$ with $\pi4^{Ph}$ and $\pi6^{Ph}$ (gray/white pyrroles delineated by dashed lines, Figure 4a). Similar correlations are observed for $\pi1^{Pf(/Ph)}$ with $\pi3^{Pf(/Ph)}$ and $\pi5^{Pf(/Ph)}$ (gray/white pyrroles delineated by unbroken lines, Figure 4a). They result from an equilibrium between three identical (degenerate) conformations, namely, state D, state B, and state F (Figure 4b), which share an identical ^{1}H NMR pattern.

The rectangular shape of the hexaphyrin thus fluctuates between three different orientations relative to the cyclodextrin, which leads to an apparent rotation of the pyrrolic

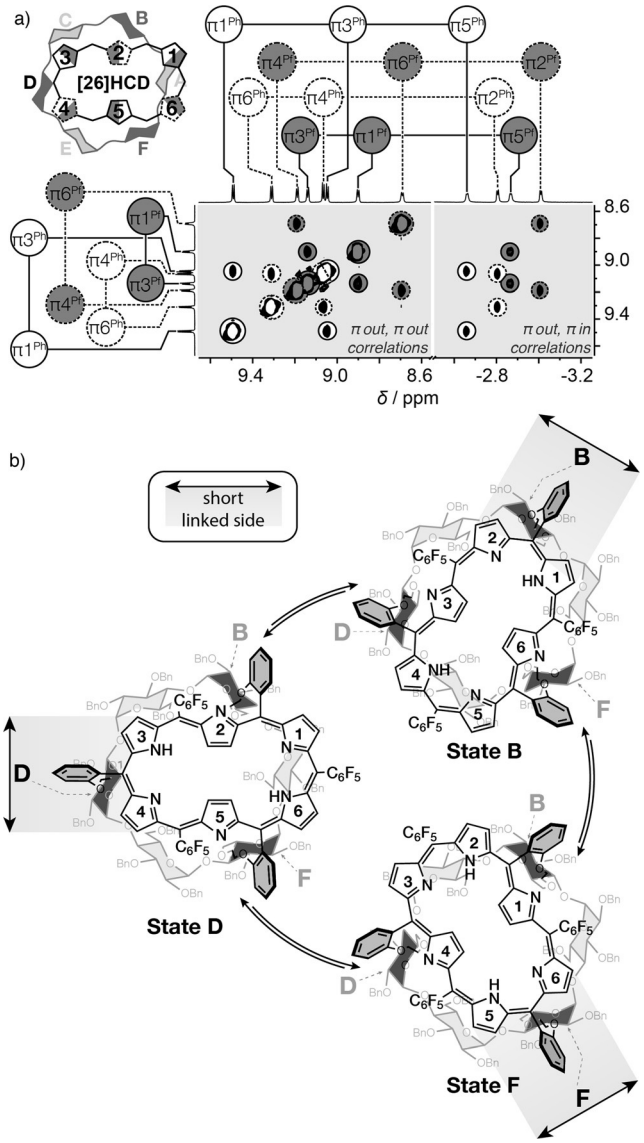


Figure 4. a) Selected exchange correlations observed in the 2D NOESY spectrum of **[26]HCD** ($CDCl_3$, 360 K, sealed tube). b) Equilibrium between the three degenerate conformations of **[26]HCD**.

macrocycle. The isomerization pathway corresponds to an isomorphing process, formally a short-side-to-long-side exchange, involving coupled in→out/out→in rotations of four pyrroles with tautomeric proton exchanges (Figure 5). For example, state D is transformed into state B through in→out and out→in inversions of π2/π5 and π3/π6, respectively. This isomerization, performed three times in a row, resets the initial orientation of the planar rectangular conformation (Figure 5). The shape shifting of the hexaphyrin is combined with a reorganization of the two subunits, thus enabling the "new" pyrrolic macrocycle to fit in one of the two other offset positions, which stresses the remarkable flexibility of the system in spite of its triple linkage. The energy barrier ($\Delta G^{\ddagger}$, Figure 5) of the degenerate exchange process of **[26]HCD** was determined according to a three-site exchange model (see the Supporting Information).[11] Quantitative analysis of the exchange correlation peaks of the 2D NOESY experiment

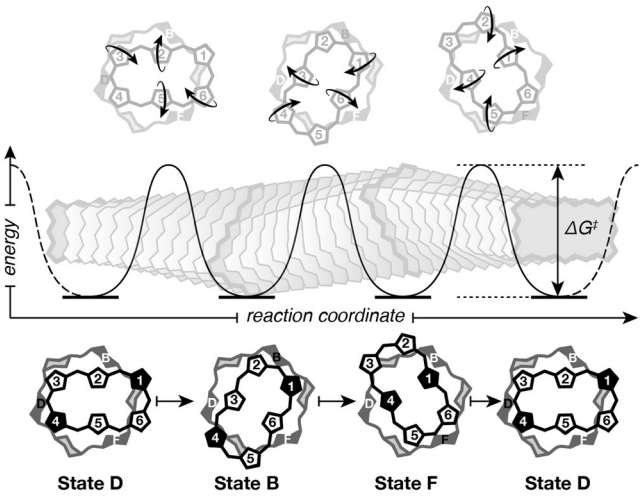


Figure 5. Idealized free-energy profile illustrating the successive pyrrole inversions for the transformation state D→state B→state F→state D.

recorded at 360 K gave a $\Delta G^{\ddagger}_{360}$ value of 23.3(±0.1) kcal mol^{-1}. To date, such conformational isomerism has only been described for nondegenerate systems [that is, $(AB_2)_2$ hexaphyrins and *meso*-bridged hexaphyrin dimers], which afford mixtures of conformational isomers.[12] In both situations, the equilibration of the separated isomers could only be frozen upon the formation of stable metal complexes.

In conclusion, the capping of a chiral hydrophobic cavity by an expanded porphyrin led to remarkable features: 1) access to switchable Hückel aromatic/antiaromatic compounds with distinctive chiroptical properties; 2) unsymmetrical capping affording coordination-site discrimination, with one site coupled to a confined asymmetric environment; 3) apparent rotational motion of the hexaphyrin cap through a short-side-to-long-side shape-shifting process. Hence, these HCD hybrids offer much potential for the fields of aromaticity, supramolecular catalysis, and switchable devices.

Acknowledgements

We are grateful to Cyclolab (Hungary) for a generous supply of α-CD and the Agence Nationale de la Recherche (research programs ANR BLANC "BIBI-CHEMAP", ANR-12-BS07-0006 and ANR BLANC "Supra-HierArchi", ANR-12-BS07-0026) for financial support.

Keywords: aromaticity · conformation analysis · cyclodextrins · degenerate equilibria · porphyrinoids

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 297–301
Angew. Chem. **2016**, *128*, 305–309

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Received: August 26, 2015
Published online: October 30, 2015

