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Switching of inherent chirality driven by self-assembly

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Dynamic chirality of iminoresorcin[4]arenes that originates from regioselective and diastereoselective keto-enol tautomerisation, was switched by non-covalent interactions with achiral molecules, as demonstrated by experimental electronic circular dichroism (ECD) spectra supported by TD DFT calculations.

Dynamic chirality[1] and supramolecular chirality[2] are closely related (but not equivalent) stereochemical terms that arose in response to growing complexity of supramolecular architectures. These terms introduce non-covalent and reversible components into the initial meaning of chirality, changing the common perception of chirality from being a static parameter into a stimuli-responsive switchable parameter. Effective switching of chirality requires controllable racemization/epimerization under the given conditions, *i.e.* proper balance between kinetic and thermodynamic parameters. Examples of stimuli-responsive modulation of chirality has been reported for foldamers,[3] photoswitches,[4] molecules with memory of chirality[5], liquid crystals[6] and supramolecular polymers.[7] In the current paper we show that inherent chirality of resorcin[4]arene derivatives that is based on tautomeric equilibrium retains the dynamic character which enables adaptation to environmental changes. We also show that such inherently chiral structure can be switched by self-assembly with achiral molecules.

Recently, we have reported that reaction of tetraformylresorcin[4]arene **1** with various amines leads iminoresorcin[4]arenes **2** that exist exclusively as keto-enamine tautomers in the solution and in the solid state (Fig. 1).[8,9] The tautomerization proceeds in a highly regioselective manner, *i.e.* all carbonyl atoms are directed to the same side

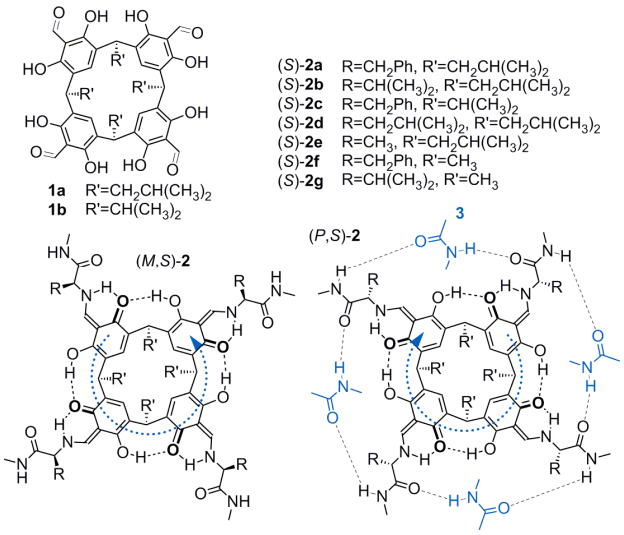

Fig. 1. Structures of tetraformylresorcin[4]arene **1**, keto-enol tautomers of iminoresorcin[4[arenes **2** with inherent chirality descriptors and the structure of **3**.

of the macrocyclic ring, leading to exclusive formation C_4-symmetric inherently chiral structures.[8,9,10] For aliphatic chiral amines two inherently chiral *M* and *P* diastereoisomers were clearly visible in NMR spectra and chemical exchange between them was slow on the NMR timescale (EXSY, no exchange detected using mixing time 1.5 s).[8,§] When (*S*)-amino acid derivatives were used as amine components of this reaction, presence of only single diastereoisomers was observed for (*S*)-**2a** and (*S*)-**2b**, meaning that tautomerization proceeded not only in a highly regioselective but also diastereoselective way (d.e. >95%). It is important to note that such amino acid iminoresorcin[4]arenes have a high propensity towards self-assembly.[9] For example, (*S*)-**2a** exists as a concave monomer in a homochiral form, however, upon addition of its enantiomer (*R*)-**2a**, it self-assembles to form a centrosymmetric capsular dimer ((*S*)-**2a**)((*R*)-**2a**).[9]

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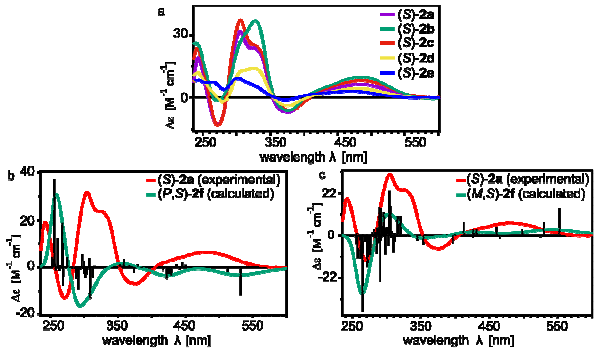

Fig. 2. a) Experimental ECD spectra for iminoresorcin[4]arenes; b), c) comparison of experimental spectrum of (*S*)-**2a** and calculated spectra for (*S*)-**2f** based on crystal structures of: b)((*P*,*S*)-**2a**)(*M*,*R*)-**2a**) and c) (*M*,*S*)-**2c**. Vertical bars represent calculated rotatory strengths.

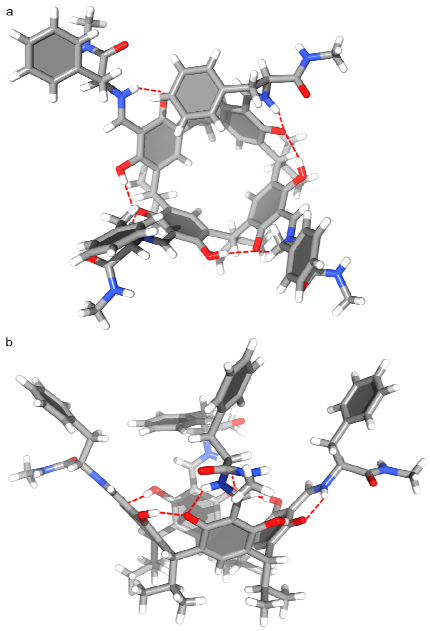

Fig. 3. X-ray structure of (*M*,*S*)-**2c**.

In order to determine which of the inherently chiral diastereoisomers is induced by stereogenic centres of amino acids we have synthesised a series of iminoresorcin[4]arenes (*S*)-**2c** ÷ (*S*)-**2e**. Electronic circular dichroism (ECD) spectra for all iminoresorcin[4]arenes composed of (*S*)-amino acids exhibit highly analogous patterns (Fig. 2a), suggesting that in all the cases, the inherent chirality induced by (*S*)-configuration of amino acids is the same. The inherent chirality of (*S*)-**2a** in dimer (*S*-**2a**)(*R*-**2a**) was unambiguously determined by X-ray crystallography as (*P*,*S*)-**2a**[9] and we used this geometry (as (*P*,*S*)-**2f**, see ESI for further details) for calculation of an ECD spectrum (TD DFT B3LYP).[11] The calculated spectrum was substantially different than the experimental spectrum of (*S*)-**2a**, with most bands having opposite signs (Fig. 2b). This result suggested that (*S*)-**2a** has different inherent chirality in the "non-assembled form" than in the "self-assembled form". Indeed, the X-ray structure confirms that for (*S*)-**2c** the "non-assembled form" has the (*M*,*S*) configuration (Fig. 3), as opposed to (*P*,*S*) configuration observed for "self-assembled form". We calculated the ECD spectrum using molecular geometry retrieved from the current X-ray structure of "non-assembled form", *i.e.* (*M*,*S*), which proved to be in a good agreement with the experimental spectrum (Fig. 2c). Combined experimental and theoretical results suggest that inherent chirality of **2** changes upon self-assembly.

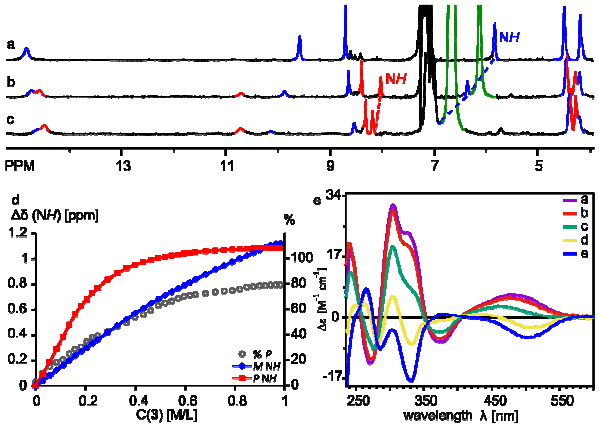

Fig. 4. ^{1}H NMR spectrum of: a) (*M*,*S*)-**2a** (32.5 mM); b) (*S*)-**2a** + **3** (11 equiv.); c) (*S*)-**2a** + **3** (30 equiv.); d) changes in relative abundance of both forms and NH chemical shifts detected by NMR titration. All NMR spectra in $CDCl_3$, 298 K, blue (*M*,*S*)-**2a**, red (*P*,*S*)-**2a**, green - **3**. e) ECD titration (a – (*S*)-**2a** (0.1 mM), b – (*S*)-**2a** + **3** (68 mM), c – (*S*)-**2a** + **3** (131 mM), d – (*S*)-**2a** + **3** (267 mM), e – (*S*)-**2a** + **3** (534 mM)).

Self-assembly of (*S*)-**2a** with its enantiomer (*R*)-**2a** results in cancelling out of Cotton effects. Therefore, for further studies we used *N*-methylacetamide **3**, that retains recognition binding sites (Fig. 1), however without electronic absorption in the diagnostic region (550–250 nm). Interaction of (*S*)-**2a** with **3**, detected by NMR, was very weak, however, appearance of a second diastereoisomer upon addition of **3** was evident (Fig. 4a-c) The diastereoisomers (*M*,*S*)-**2a** and the newly formed (*P*,*S*)-**2a** are kinetically stable on the NMR timescale. However, the equilibrium is reached within few minutes (as checked by remeasuring the spectrum after 24h). In addition to appearance of a new set of signals, signals of amide protons gradually shifted upfield upon addition of **3**. This is in agreement with co-existence of a second process that is fast on the NMR timescale – assembly with **3**. The shape of the titration curves demonstrated that assembly of the newly formed diastereoisomer (*P*,*S*)-**2a** with **3** is much more efficient than assembly of diastereoisomer (*M*,*S*)-**2a** with **3** (Fig. 4d). It is consistent with the hypothesis that assembly is the driving force that induces switching between diastereoisomers. Additionally, it can be concluded that the chirality switching is concerted, since we did not observe any unsymmetrical intermediates (*e.g.* with one or two arms inverted).

Titration experiments were also performed using ECD. Upon gradual addition of **3** to the solution of (*S*)-**2a** or (*S*)-**2b** we observed gradual inversion of the sign of Cotton effects (Fig. 4e and S7). It should be noted that upon switching of inherent chirality, all bands within detection region inverted

even though (*M*,*S*)-**2a** and (*P*,*S*)-**2a** are not enantiomers. It points out the dominating role of inherent chirality on electronic transitions in this region.

Numerous studies have shown that conformation has a pronounced effect on ECD spectra.[12] Although the inherently chiral chromophore of iminoresorcin[4]arenes has a well-defined geometry, the upper rim fragments are highly flexible. In order to estimate the influence of conformational flexibility on the current ECD spectra, we performed a conformational search using (*S*)-**2g** as a model compound. (*S*)-**2g** has lower flexibility of the side chains than the other amino acids and lacks additional chromophores. By 60° rotation about two bonds (N-C_α and C_α-$C_{carbonyl}$) and assuming C_4 symmetry (simplification based on the observed symmetry in NMR spectra) 36 starting structures were generated, which converged into a set of eight conformations for each of the diastereoisomers (Table S1 and S2, DFT B3LYP). Meaningful contributions (> 0.01 %) were predicted only for two conformations for each of the diastereoisomers. Comparison of the calculated ECD spectra for these different conformations indicated that changes caused by flexibility of the upper rim parts are small. All bands exhibit the same signs of Cotton effects, only their relative intensities are different (Fig. S9). Additionally, we compared ECD spectra for structures with imposed C_4 symmetry (obtained by conformational search) with the ones having substantial deviations from C_4 symmetry (obtained from X-ray structures). For the same diastereoisomer deviations from symmetry only changed relative intensities of ECD bands but not their signs (Fig. S10).

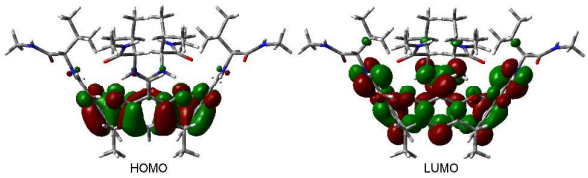

Fig. 5. HOMO and LUMO orbitals of (*M*,*S*)-**2g** involved in the lowest energy electronic transition (TD DFT B3LYP).

Combined experimental and theoretical results suggest that all ECD bands in the range of 550-250 nm are sensitive to inherent chirality of a keto-enamine chromophore. However, DFT calculations indicate that the lowest energy band is most reliable for the determination of inherent chirality. It derives from HOMO→LUMO transition and the orbitals involved in this transition are located directly at the inherently chiral chromophore (Fig. 5). Therefore, the influence of other parts of the molecule (*e.g*. flexible amino acids) on the sign of this band is negligible. It is also important to note that this band is present only for keto-enamine tautomers (it does not occur in enol-imine tautomers). These observations enable time-efficient semi-theoretical determination of inherent chirality based on ECD spectra.‡

In conclusions, we have shown that inherent chirality based on tautomeric equilibrium of iminoresorcin[4]arenes is a stimuli-responsive switchable parameter. Thus, iminoresorcin[4]arenes can enter the scant pool of molecular scaffolds chirality of which can be modulated, and, due to persistent concave shape, they can potentially be a part of functional systems. On the other hand, our results have also demonstrated that self-assembly has a power to modulate the structure of molecules to much higher extend than it is commonly perceived.

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Notes and references

§ Distinction between configuration and conformation in this case is ambiguous. We use “configuration” since isomers cannot interconvert by simple rotation about single bonds.

‡ VCD measurements were also performed. However, very low signal-to-noise precluded reliable determination of chirality.

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