**Templating Conformations with Cucurbiturils**

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Templating Conformations with Cucurbiturils

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The trans- and cis conformations of 5,5’-substituted 2,2’-dithiophenes can be stabilized when those are secured with two Cucurbit[8]uril macrocycles (CB[8]) on top of rigid 2,6- and 2,7-substituted naphthalenes, which respectively mimic the trans and cis conformations of the dithiophene. The substituents are Pt(II) terpyridyl groups bearing CB[8]-binding sites at their 4’-position, as those form dimers in the presence of the macrocycle through Pt-Pt and dispersive interactions between the terpyridyl ligands.

To maximize Coulombic interactions with positive guests, Cucurbit[8]uril (CB[8]) 1 forms ternary complexes that distribute the positive charges of the pair of guests over both portals of the macrocycle. 2-11 Recently, we reported the first exception to this pattern, with pairs of Pt(II) acetylides 1 sitting at the same CB[8] portal despite Coulombic repulsion between the two positive guests and a sub-optimal stabilization of both charges by only one carbonylated portal (see Fig. 1). 12 We attributed the driving force to highly favorable dispersive “π-π” interactions between the extended aryl and heteroaryl units, and possibly to Pt-Pt interactions via d z2-d z2 orbital overlap. This new motif, with the acetylide moieties pointing towards the same direction and sitting on top of one another, led us to consider the following question: can one use one of the guests to “template” the conformation of the second guest, and even force it to adopt an otherwise unstable conformation?

Fig. 1 Equilibrium between stacked and unstacked 2:1 guest/CB[8] assemblies. Structure of CB[8]-secured Pt dimer 1·CB[8].

To address the question above, we used a dithiophene derivative as the unit that is to be templated, as it can switch between a cis and a trans conformation (see Fig. 2). Similarly to biphenyl, 13 unsubstituted thiophene 2a has two stable conformers (SCCS dihedral angles 30° and 158°). Density functional theory (DFT) calculations carried out at the B3LYP-D3ATM level 14 indicate that the antiperiplanar conformer is more stable than its synperiplanar counterpart by 0.64 kcal/mol. Fully coplanar syn and anti conformations are transition states along the energy profile due to S-S, S-H(3) and H(3)-H(3) repulsion, with activation barriers of 1.2 kcal/mol relative to their respective ground states, while the interconversion barrier from the anti to the syn conformer (SCCS angle 89°) is 3.7 kcal/mol (see Fig. 2).

Fig. 2 Energy profile of dithiophene (2a; in blue) and its derivatives 2b (in red) and 3 (in black), along their SCCS dihedral angle. Energies calculated at the B3LYP-D3ATM/def2-TZVP level (2a and 2b) and B97-3c/def2-mTZVP level (3); electronic contributions only.

Attaching ethynyl groups to the 5 and 5’ positions (see thiophene derivative 2b) was found to bring the ground states of the syn and anti conformers closer to planarity (SCCS dihedral angles 23° and 167°). Linking acetylides 2b to Pt(II) terpyridyl units (see complex 3) exacerbates the trend described above, yielding very shallow energy profiles centered around the syn and anti conformations. SCCS dihedral angles of the ground state conformations are 9° and 177°, and energy differences with the coplanar transition states are less than 0.1 kcal/mol. The syn conformer is 0.79 kcal/mol less stable than the anti conformer. Due to the shallowness of the syn- and antiperiplanar region of the energy profile, we will thus consider that dithiophene 3 behaves as a simple switch between a cis and a trans state, separated in energy by 0.79 kcal/mol.

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†Electronic Supplementary Information (ESI) available: preparation of Pt(II) complexes 3, 6 and 7, their precursors, and their CB[8]-bound assemblies; self-sorting assay; computational details. See DOI: 10.1039/x0xx00000x

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As far as the “template” unit is concerned, we exploited the fact that 2,6- and 2,7-diethynylnaphthalene (4) and (5) have geometries similar to dithiophene 2b in its trans and cis conformations, respectively. The four ethynyl carbons of the 2,6- and 2,7-naphtyl derivatives can be overlapped with their counterparts in dithiophenes trans-2b and cis-2b, within 0.61 and 0.70 Å, respectively (root-mean-square deviation; see Fig. 3). We thus prepared 2,6- and 2,7-disubstituted naphthalene derivatives 6 and 7 as possible “templating” guests for the trans- and cis-conformations of guest 3, upon encapsulation of a portion of their terpyridyl units by CB[8] (see Fig. 3).

Conformers of quaternary assemblies 3·CB[8], 6a·6b·CB[8], 7a·7b·CB[8], 3·6b·CB[8], and 3·7b·CB[8], were screened and optimized at the B97-3c/def2-mTZVP level together with the COSMO solvation model (see Fig. 4 and SI section for other optimized structures). The use of a continuum solvation model like COSMO is valid, as the cavities of CB[8] are filled with guests, and deep pockets that would necessitate the addition of discrete water molecules are not present.

Quaternary complexes 3·CB[8], 6a·6b·CB[8], 7a·7b·CB[8], 3·6b·CB[8], and 3·7b·CB[8], were prepared in a 5:2 mixture of D$_2$O and acetonitrile- $d_3$ (0.50 mM) upon addition of an excess amount of CB[8] to suspensions of the free guests; the latter are insoluble in the buffer in the absence of CB[8].

To determine whether complex 6 can template the trans conformation of dithiophene 3 in a heterodimer secured by two CB[8] units, we combined stoichiometric amounts of homoquaternary assemblies 3·CB[8] and 6b·CB[8].

The mixture of assemblies was heated to 40 °C and self-sorting was monitored over time until equilibrium was reached (180 h). Intermolecular scrambling affording heteroquaternary complex trans-3·6b·CB[8], would necessarily imply a templating effect (see Fig. 4), as complex cis-3·6b·CB[8] is geometrically unrealistic. As presented in a recent study from our group (see Fig. 5), such a self-sorting process can be characterized by a free energy term $\Delta G$ that corresponds to the equilibrium between the homo and hetero complexes (see equation 1). A strongly negative $\Delta G$ term ($<-2.3$ kcal/mol) indicates a fully social self-sorting (i.e. the quasi-quantitative formation of hetero-assembly); a strongly positive term (> 2.3 kcal/mol) indicates narcissistic self-sorting (i.e. the persistence of pairs of homo-assemblies). The scale is convenient as it allows the assessment of self-sorting patterns along the social-to-narcissistic spectrum.

$$\Delta G = -R \ln K = \frac{[AB]}{[AA][BB]}$$

1H NMR spectroscopy was used to quantify complexes 3·CB[8] and trans-3·6b·CB[8], as in the former case CB[8] encapsulates a pair of tolyl terpyridyl substituents, and in the latter case one tolyl and one 3,5-difluorophenyl unit (see Fig. 6, spectra a-c). The homo- and heterocomplexes result in different resonances for multiple hydrogen nuclei (signals at positions 3 and 3'' of the terpyridyl ligands were used for quantification). 19F NMR spectroscopy was used to quantify complexes 6b·CB[8] and trans-3·6b·CB[8], as fluorine nuclei also resonate at different frequencies in both assemblies (see Fig. 6, spectra d-e). A $\Delta G_{trans}^{2,6-Np}$ term equal to $-0.23 \pm 0.01$ kcal/mol was obtained.

Consequently, the template effect not only operates (as hetero-assembly trans-3·6b·CB[8] is detected), but is significant enough to favor the formation of the hetero-assembly over its homo counterparts (as $\Delta G_{trans}^{2,6-Np}$ is negative).
The experiment was repeated with homoquaternary assemblies 3·CB[8] and 7b·CB[8] to test the possibility of using 2,7-disubstituted naphthyl groups. A negative free energy term was obtained again (–0.58 kcal/mol), thereby indicating that templating still operates towards a less stable conformation, as is significantly lower than +0.29 kcal/mol, that corresponds to a 31% fraction of heterocomplex 3·CB[8] relative to all quaternary assemblies present at equilibrium. The formation of this heterocomplex is just not as favorable as its trans-3·CB[8] counterpart (ΔGtrans−cis = −0.23 kcal/mol, that corresponds to a 59% fraction of heterocomplex relative to all quaternary assemblies). The penalty for the templating of the cis-dithiophene unit in the stacked system is thus ΔΔG = ΔGcis−trans − ΔGcis−cis = 0.52 kcal/mol, in remarkably close agreement with the stability of cis-dithiophenes 2a and 3 relative to their trans conformers (0.64 and 0.79 kcal/mol, respectively).

We then questioned whether these equilibria were mostly driven by favorable interactions between (1) the naphthyl and dithiophene central units of guests 3, 6b and 7b, or (2) the tolyl and 3,5-difluorophenyl head groups when encapsulated into CB[8]. To separate both effects, we assessed the self-sorting properties of a mixture of complexes 6a·CB[8] and 6b·CB[8], the first one bearing a tolyl head, and the second a 3,5-difluorophenyl one, while both have the same 2,6-disubstituted naphthyl central unit (see Fig. 8). The free energy term should mostly reflect the impact of tolyl/tolyl, tolyl/difluorophenyl and difluorophenyl/difluorophenyl interactions inside CB[8] on the self-sorting pattern. A ΔG2,6−Np term of −0.79 (± 0.09) kcal/mol was found, thereby indicating the preferred interaction between a tolyl unit and a difluorophenyl one compared to the pair of homodimers. This effect is likely due to favorable quadrupole-quadrupole interactions between both units.11,17–20

The experiment was repeated with a mixture of complexes 7a·CB[8] and 7b·CB[8], which both bear central 2,7-disubstituted naphthyl groups. A negative free energy term was obtained again (ΔG2,7−Np = −0.58 (± 0.01) kcal/mol). The minor discrepancy between the ΔG2,6−Np and ΔG2,7−Np terms show that they are not totally independent of the central naphthyl units; this may be caused by small variations in spatial
positioning of the tolyl and difluorophenyl units in both series. The free energy contribution of the heads on the self-sorting processes is obtained from the average of both $\Delta G^{2,6}_{\text{cis}}$ and $\Delta G^{2,7}_{\text{cis}}$ terms ($\Delta G_{\text{heads}} = -0.69 \pm 0.05$ kcal/mol).

To test the impact of CB[8] encapsulation on the interaction between the terpyridyl heads, we compared the stabilities of dimers 8a₂, 8b₂ and 8a₂8b formed in the absence of CB[8], optimized using DFT calculations (see Fig. 9); complexes 8 represent the Pt(II) terpyridyl fragment of guests 3, 6 and 7. We again used the B97-3c functional and def2-mTZVP basis sets, and decided to neglect the enthalpic and entropic contributions to the stabilities as (1) vibrational frequencies calculated in non-covalent systems are subject to significant error,²¹ and (2) all components of the equilibrium are dimers with similar structures. Remarkably, a relative energy term of $-0.56$ kcal/mol was found for the equilibrium between dimers 8a₂ and 8b₂ (0.50 equiv. each) and heterodimer 8a₂8b, in very close agreement with the experimental term $\Delta G_{\text{heads}} = -0.69$ kcal/mol. This indicates that CB[8] encapsulation barely affects the relative interactions between the aryl units.

![Fig. 9](image)

**Fig. 9** Truncated Pt complexes 8a and 8b. Structure of the 8a₂8b dimer optimized at the B97-3c/def2-mTZVP level.

We can now isolate the impact of the central naphthyl and dithiophene units on the equilibria between complexes trans-3₂·CB[8]₂, 6b₂·CB[8]₂, and trans-3₂·6b·CB[8]₂ (as well as trans-3₂·CB[8]₂, 7b₂·CB[8]₂, and cis-3₂·7b·CB[8]₂). The portion of the self-sorting free energy attributed to the interactions between the central units is $\Delta G^{2,6}_{\text{cis}} - \Delta G^{2,6}_{\text{trans}} = \Delta G^{2,7}_{\text{cis}} - \Delta G^{2,7}_{\text{trans}} - \Delta G_{\text{heads}} = +0.46 \pm 0.05$ kcal/mol, and $\Delta G^{2,7}_{\text{cis}} - \Delta G^{2,7}_{\text{trans}} - \Delta G_{\text{heads}} = +0.98 \pm 0.06$ kcal/mol, respectively. Self-sorting is narcissistic in both cases, i.e. naphthyl and dithiophene homodimers are favored over their heterodimeric combinations. Templating (i.e. the formation of heterodimers) is thus enhanced by favorable interactions between tolyl and difluorophenyl terpyridyl heads.

In all homo- and heteroquaternary assemblies, the pair of central units adopt a slip-stacked arrangement (see Fig. 10). We suspect that the better overlap in the homo-assemblies (Fig. 10a-c) compared to the hetero-assemblies (Fig. 10d-e) enhances dispersive interactions between both units, and that is responsible for the observed narcissistic self-sorting pattern. In summary, despite the complex geometry of these quaternary complexes, self-sorting along the narcissistic-to-social spectrum is simply governed by (1) the relative stabilities of cis and trans dithiophene, (2) dispersive interactions between the central dithiophene and/or naphthyl units, and (3) quadrupole-quadrupole interactions between the aryl heads. The impact of CB[8] encapsulation of the heads on self-sorting is remarkably insignificant.

![Fig. 10](image)

**Fig. 10** Orthographic projections of the central units in complexes (a) 6b₂·CB[8]₂, (b) 7b₂·CB[8]₂, (c) 3₂·CB[8]₂, (d) trans-3₂·6b·CB[8]₂, and (e) cis-3₂·7b·CB[8]₂, along a normal to the naphthyl and dithiophene units in grey. Optimization carried out at the b97-3c/def2-mTZVP level.

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