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_{z^2}-d_{z^2} 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?
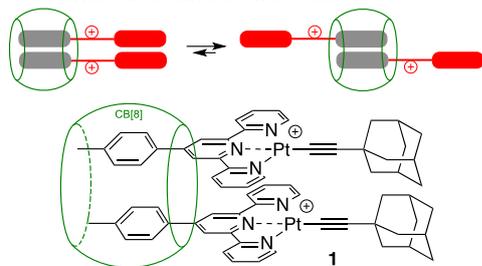
Fig. 1 Equilibrium between stacked and unstacked 2:1 guest/CB[8] assemblies. Structure of CB[8]-secured Pt dimer **1**₂·CB[8].

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-

D3[ATM] 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).
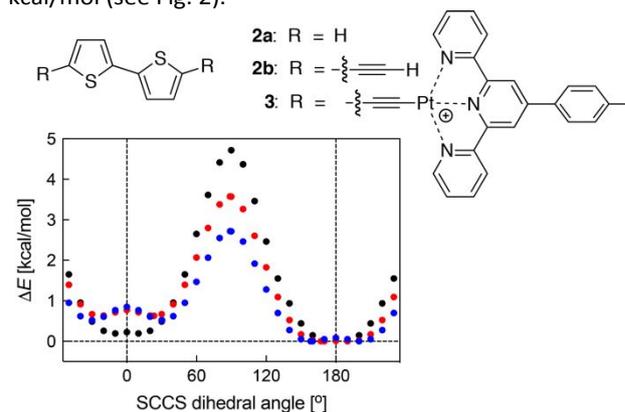

Fig. 2 Energy profile of dithiophene (**2a**; in blue) and its derivatives **2b** (in red) and **3** (in black), along their SCCS dihedral angle. Energies calculated at the B3LYP-D3[ATM]/def2-TZVP level (**2a** and **2b**) and B97-3c/def2-mTZVP level (**3**); electronic contributions only.

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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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-naphthyl 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).
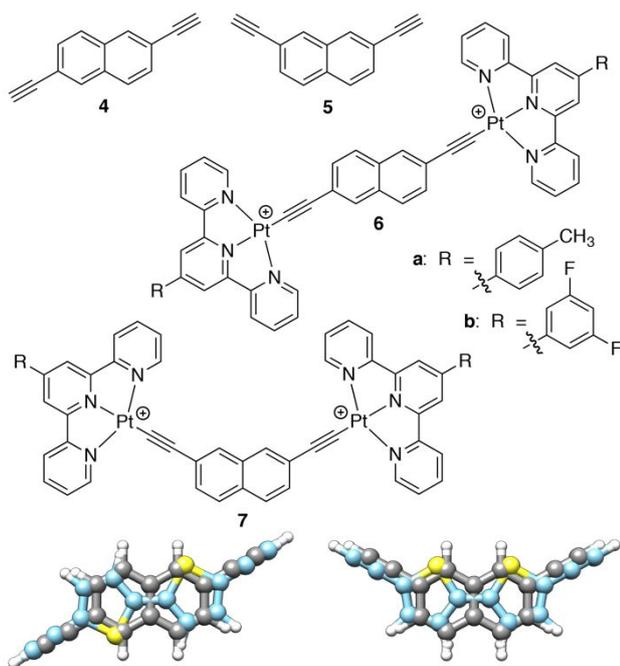

Fig. 3 Structures of disubstituted naphthalenes **4** – **7**. Superimposed structures of *trans*- and *cis*-dithiophene **2b** conformations (carbon atoms in light blue and sulfur atoms in yellow) with 2,6- and 2,7-diethynylnaphthalenes (**4**) and (**5**), respectively (carbon atoms in gray). Structure optimization carried out at the B3LYP-D3$^{\text{ATM}}$/def2-TZVP level.

Conformers of quaternary assemblies **3**$_2$·CB[8]$_2$, **6a**·**6b**·CB[8]$_2$, **7a**·**7b**·CB[8]$_2$, **3**·**6b**·CB[8]$_2$ and **3**·**7b**·CB[8]$_2$ were screened and optimized at the B97-3c/def2-mTZVP level[15] together with the COSMO solvation model[16] (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**$_2$·CB[8]$_2$, **6a**$_2$·CB[8]$_2$, **6b**$_2$·CB[8]$_2$, **7a**$_2$·CB[8]$_2$ and **7b**$_2$·CB[8]$_2$ 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**$_2$·CB[8]$_2$ and **6b**$_2$·CB[8]$_2$.
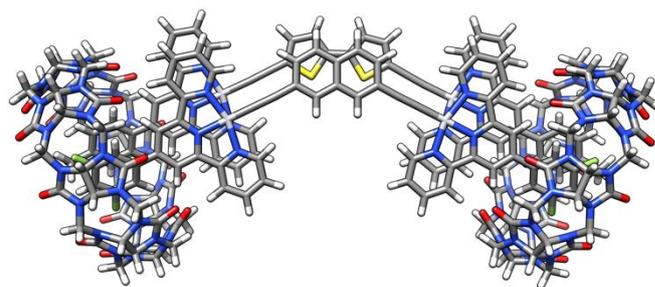
Fig. 4 Heteroquaternary complex **3**·**7b**·CB[8]$_2$ optimized at the B97-3c/def2-mTZVP level with the COSMO solvation model.

The mixture of assemblies was heated to 40 ºC and self-sorting was monitored over time until equilibrium was reached (180 h). Intermolecular scrambling affording heteroquaternary complex *trans*-**3**·**6b**·CB[8]$_2$ would necessarily imply a templating effect (see Fig. 4), as complex *cis*-**3**·**6b**·CB[8]$_2$ is geometrically unrealistic. As presented in a recent study from our group[17] (see Fig. 5), such a self-sorting process can be characterized by a free energy term ΔG that corresponds to the equilibrium between the homo and hetero complexes (see equation 1). A strongly negative ΔG 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.[17]
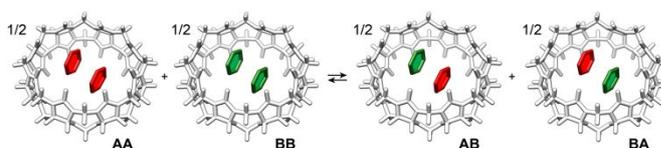

Fig. 5 A narcissistic-to-social self-sorting scale for CB[8] and a pair of guests **A** and **B**. Self-sorting is partially social when the free energy term associated with the equilibrium is negative, and partially narcissistic when the free energy term is positive.

$$\Delta G = -RT\ln K = \frac{[\text{AB}]^{1/2}\,[\text{BA}]^{1/2}}{[\text{AA}]^{1/2}\,[\text{BB}]^{1/2}} = \frac{[\text{AB}]/2}{[\text{AA}]^{1/2}\,[\text{BB}]^{1/2}} \quad (1)$$

^{1}H NMR spectroscopy was used to quantify complexes **3**$_2$·CB[8]$_2$ and *trans*-**3**·**6b**·CB[8]$_2$, 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). ^{19}F NMR spectroscopy was used to quantify complexes **6b**$_2$·CB[8]$_2$ and *trans*-**3**·**6b**·CB[8]$_2$, as fluorine nuclei also resonate at different frequencies in both assemblies (see Fig. 6, spectra d-e). A $\Delta G^{2,6-\text{Np}}_{\text{trans}-\text{Dt}}$ term equal to −0.23 (± 0.01) kcal/mol was obtained.

Consequently, the template effect not only operates (as hetero-assembly *trans*-**3**·**6b**·CB[8]$_2$ is detected), but is significant enough to favor the formation of the hetero-assembly over its homo counterparts (as $\Delta G^{2,6-\text{Np}}_{\text{trans}-\text{Dt}}$ is negative).

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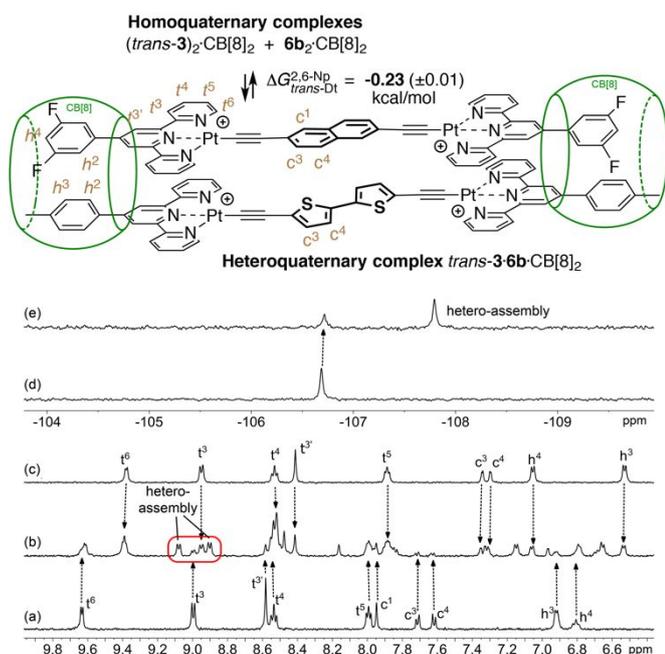
Fig. 6 Self-sorting between assemblies $6b_2 \cdot CB[8]_2$, $trans\text{-}3_2 \cdot CB[8]_2$ and $trans\text{-}3 \cdot 6b \cdot CB[8]_2$ and corresponding free energy term. ^{1}H NMR spectra of (a) homoassembly $6b_2 \cdot CB[8]_2$, (b) a self-sorting mixture of assemblies $6b_2 \cdot CB[8]_2$, $trans\text{-}3_2 \cdot CB[8]_2$ and $trans\text{-}3 \cdot 6b \cdot CB[8]_2$, (c) homoassembly $trans\text{-}3_2 \cdot CB[8]_2$. The red rectangle highlights the signals used for the quantification of the homo- and hetero-assemblies. ^{19}F NMR spectra of (d) homoassembly $6b_2 \cdot CB[8]_2$, and (e) a self-sorting mixture of assemblies $6b_2 \cdot CB[8]_2$, $trans\text{-}3_2 \cdot CB[8]_2$ and $trans\text{-}3 \cdot 6b \cdot CB[8]_2$.
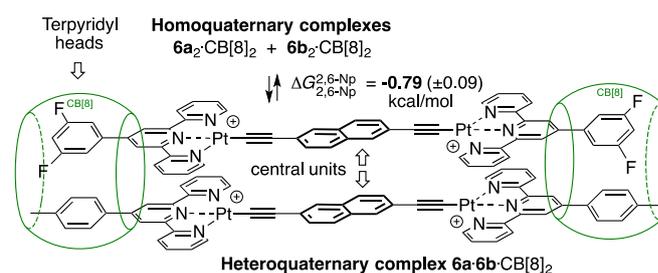
The experiment was repeated with homoquaternary assemblies $3_2 \cdot CB[8]_2$ and $7b_2 \cdot CB[8]_2$ to test the possibility of using 2,7-disubstituted naphthalene derivative **7b** to template the less stable *cis* conformation of complex **3** (see Fig. 7). This time, partially narcissistic self-sorting is observed, with a positive free energy term $\Delta G_{cis-Dt}^{2,7-Np}$ equal to +0.29 (± 0.02) kcal/mol. This indicates that templating still operates towards a less stable conformation, as $\Delta G_{cis-Dt}^{2,7-Np}$ is significantly lower than +2.3 kcal/mol (the threshold for 99% narcissistic self-sorting, i.e. without any template effect). A free energy term of +0.29 kcal/mol corresponds to a 31% fraction of heterocomplex *cis*-**3·7b**·CB[8]$_2$ relative to all quaternary assemblies present at equilibrium. The formation of this heterocomplex is just not as favorable as its *trans*-**3·6b**·CB[8]$_2$ counterpart ($\Delta G_{trans-Dt}^{2,6-Np} = -0.23$ 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 $\Delta\Delta G = \Delta G_{cis-Dt}^{2,7-Np} - \Delta G_{trans-Dt}^{2,6-Np} = 0.52$ 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 $6a_2 \cdot CB[8]_2$ and $6b_2 \cdot CB[8]_2$, the first one bearing a tolyl head, and the second a 3,5-difluorophenyl one, while both have the same 2,6-disubstituted
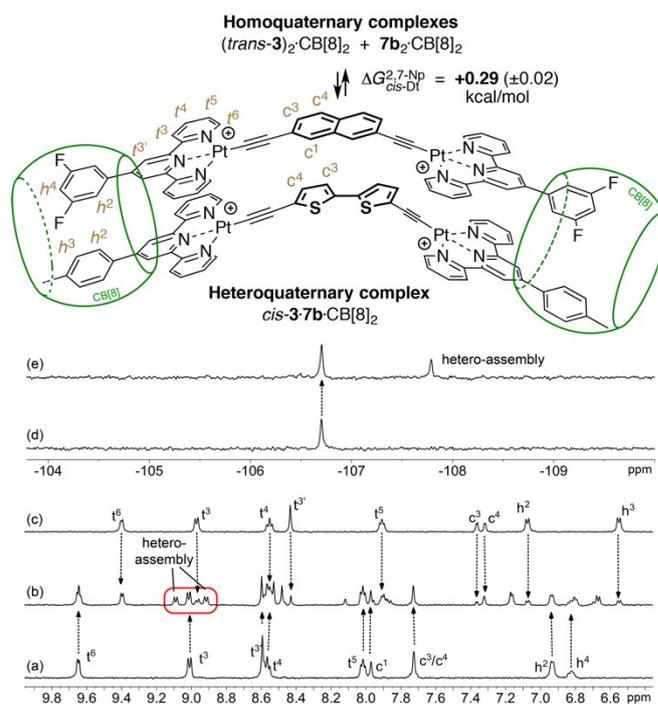
Fig. 7 Self-sorting between assemblies $7b_2 \cdot CB[8]_2$, $trans\text{-}3_2 \cdot CB[8]_2$ and $cis\text{-}3 \cdot 7b \cdot CB[8]_2$ and corresponding free energy term. ^{1}H NMR spectra of (a) homoassembly $7b_2 \cdot CB[8]_2$, (b) a self-sorting mixture of assemblies $7b_2 \cdot CB[8]_2$, $trans\text{-}3_2 \cdot CB[8]_2$ and $cis\text{-}3 \cdot 7b \cdot CB[8]_2$, (c) homoassembly $trans\text{-}3_2 \cdot CB[8]_2$. The red rectangle highlights the signals used for the quantification of the homo- and hetero-assemblies. ^{19}F NMR spectra of (d) homoassembly $7b_2 \cdot CB[8]_2$, and (e) a self-sorting mixture of assemblies $7b_2 \cdot CB[8]_2$, $trans\text{-}3_2 \cdot CB[8]_2$ and $cis\text{-}3 \cdot 7b \cdot CB[8]_2$.

naphthyl central unit (see Fig. 8). The free energy term $\Delta G_{2,6-Np}^{2,6-Np}$ should mostly reflect the impact of tolyl/tolyl, tolyl/difluorophenyl and difluorophenyl/difluorophenyl interactions inside CB[8] on the self-sorting pattern. A $\Delta G_{2,6-Np}^{2,6-Np}$ 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]


Fig. 8 Self-sorting between assemblies $6a_2 \cdot CB[8]_2$, $6b_2 \cdot CB[8]_2$ and $6a \cdot 6b \cdot CB[8]_2$ and corresponding free energy term.

The experiment was repeated with a mixture of complexes $7a_2 \cdot CB[8]_2$ and $7b_2 \cdot CB[8]_2$, which both bear central 2,7-disubstituted naphthyl groups. A negative free energy term was obtained again ($\Delta G_{2,7-Np}^{2,7-Np} = -0.58$ (± 0.01) kcal/mol). The minor discrepancy between the $\Delta G_{2,6-Np}^{2,6-Np}$ and $\Delta G_{2,7-Np}^{2,7-Np}$ 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 $\Delta G_{2,6-\mathrm{Np}}^{2,6-\mathrm{Np}}$ and $\Delta G_{2,7-\mathrm{Np}}^{2,7-\mathrm{Np}}$ terms ($\Delta G_{\mathrm{heads}} = -0.69 \, (\pm 0.05)$ kcal/mol).

To test the impact of CB[8] encapsulation on the interaction between the terpyridyl heads, we compared the stabilities of dimers **8a**$_2$, **8b**$_2$ and **8a·8b** 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 **8a**$_2$ and **8b**$_2$ (0.50 equiv. each) and heterodimer **8a·8b**, in very close agreement with the experimental term $\Delta G_{\mathrm{heads}}$ (−0.69 kcal/mol). This indicates that CB[8] encapsulation barely affects the relative interactions between the aryl units.
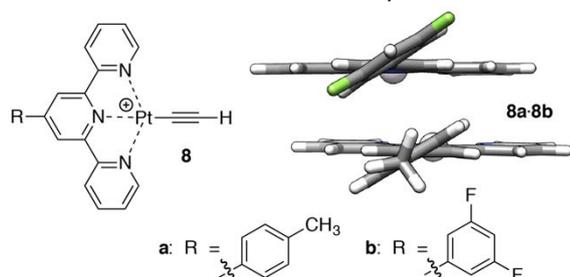

Fig. 9 Truncated Pt complexes **8a** and **8b**. Structure of the **8a·8b** dimer optimized at the B97-3c/def2-mTZVP level.

We can now isolate the impact of the central naphthyl and dithiophene units on the equilibria between complexes *trans*-**3**$_2$·CB[8]$_2$, **6b**$_2$·CB[8]$_2$ and *trans*-**3·6b**·CB[8]$_2$ (as well as *trans*-**3**$_2$·CB[8]$_2$, **7b**$_2$·CB[8]$_2$ and *cis*-**3·7b**·CB[8]$_2$). The portion of the self-sorting free energy term attributed to the interactions between the central units is $\Delta G'^{2,6-\mathrm{Np}}_{\mathrm{trans}-\mathrm{Dt}} = \Delta G^{2,6-\mathrm{Np}}_{\mathrm{trans}-\mathrm{Dt}} - \Delta G_{\mathrm{heads}}$ = +0.46 (± 0.05) kcal/mol, and $\Delta G'^{2,7-\mathrm{Np}}_{\mathrm{cis}-\mathrm{Dt}} = \Delta G^{2,7-\mathrm{Np}}_{\mathrm{cis}-\mathrm{Dt}} - \Delta G_{\mathrm{heads}}$ = +0.98 (± 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.
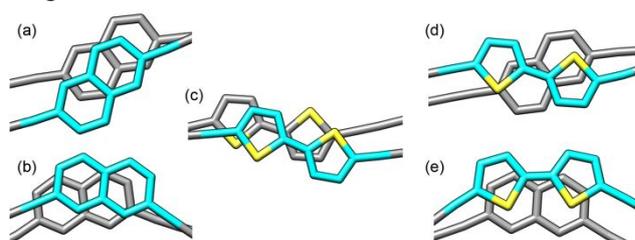
Fig. 10 Orthographic projections of the central units in complexes (a) **6b**$_2$·CB[8]$_2$, (b) **7b**$_2$·CB[8]$_2$, (c) **3**$_2$·CB[8]$_2$, (d) *trans*-**3·6b**·CB[8]$_2$ and (e) *cis*-**3·7b**·CB[8]$_2$ along a normal to the naphthyl and dithiophene units in grey. Optimization carried out at the b97-3c/def2-mTZVP+COSMO level.

References

1 J. Kim, I.-S. Jung, S.-Y. Kim, E. Lee, J.-K. Kang, S. Sakamoto, K. Yamaguchi and K. Kim, *J. Am. Chem. Soc.*, 2000, **122**, 540-541.
2 H.-J. Kim, J. Heo, W. S. Jeon, E. Lee, J. Kim, S. Sakamoto, K. Yamaguchi and K. Kim, *Angew. Chem., Int. Ed.*, 2001, **40**, 1526-1529.
3 D. Jiao, F. Biedermann, F. Tian and O. A. Scherman, *J. Am. Chem. Soc.*, 2010, **132**, 15734-15743.
4 Y. H. Ko, K. Kim, J.-K. Kang, H. Chun, J. W. Lee, S. Sakamoto, K. Yamaguchi, J. C. Fettinger and K. Kim, *J. Am. Chem. Soc.*, 2004, **126**, 1932-1933.
5 Y. Liu, Y. Yu, J. Gao, Z. Wang and X. Zhang, *Angew. Chem., Int. Ed.*, 2010, **49**, 6576-6579.
6 S. Sonzini, S. T. Ryan and O. A. Scherman, *Chem. Commun.*, 2013, **49**, 8779-8781.
7 M. Ramaekers, S. P. W. Wijnands, J. L. J. van Dongen, L. Brunsveld and P. Y. W. Dankers, *Chem. Commun.*, 2015, **51**, 3147-3150.
8 H. D. Nguyen, D. T. Dang, J. L. J. van Dongen and L. Brunsveld, *Angew. Chem., Int. Ed.*, 2010, **49**, 895-898.
9 D. T. Dang, H. D. Nguyen, M. Merkx and L. Brunsveld, *Angew. Chem., Int. Ed.*, 2013, **52**, 2915-2919.
10 G. Wu, M. Olesinska, Y. Wu, D. Matak-Vinkovic and O. A. Scherman, *J. Am. Chem. Soc.*, 2017, **139**, 3202-3208.
11 R. Joseph, A. Nkrumah, R. J. Clark and E. Masson, *J. Am. Chem. Soc.*, 2014, **136**, 6602-6607.
12 K. Kotturi and E. Masson, *Chem. - Eur. J.*, 2018, **24**, 8670-8678.
13 M. P. Johansson and J. Olsen, *J. Chem. Theory Comput.*, 2008, **4**, 1460-1471.
14 E. Masson, *Org. Biomol. Chem.*, 2013, **11**, 2859-2871.
15 J. G. Brandenburg, C. Bannwarth, A. Hansen and S. Grimme, *J. Chem. Phys.*, 2018, **148**, 064104/1-13.
16 A. Klamt and G. Schueuermann, *J. Chem. Soc., Perkin Trans. 2*, 1993, 799-805.
17 M. Raeisi, K. Kotturi, I. del Valle, J. Schulz, P. Dornblut and E. Masson, *J. Am. Chem. Soc.*, 2018, **140**, 3371-3377.
18 C. R. Patrick and G. S. Prosser, *Nature*, 1960, **187**, 1021.
19 J. H. Williams, *Acc. Chem. Res.*, 1993, **26**, 593-598.
20 S. Tsuzuki, T. Uchimaru and M. Mikami, *J. Phys. Chem. A*, 2006, **110**, 2027-2033.
21 S. Grimme, *Chem. - Eur. J.*, 2012, **18**, 9955-9964.

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