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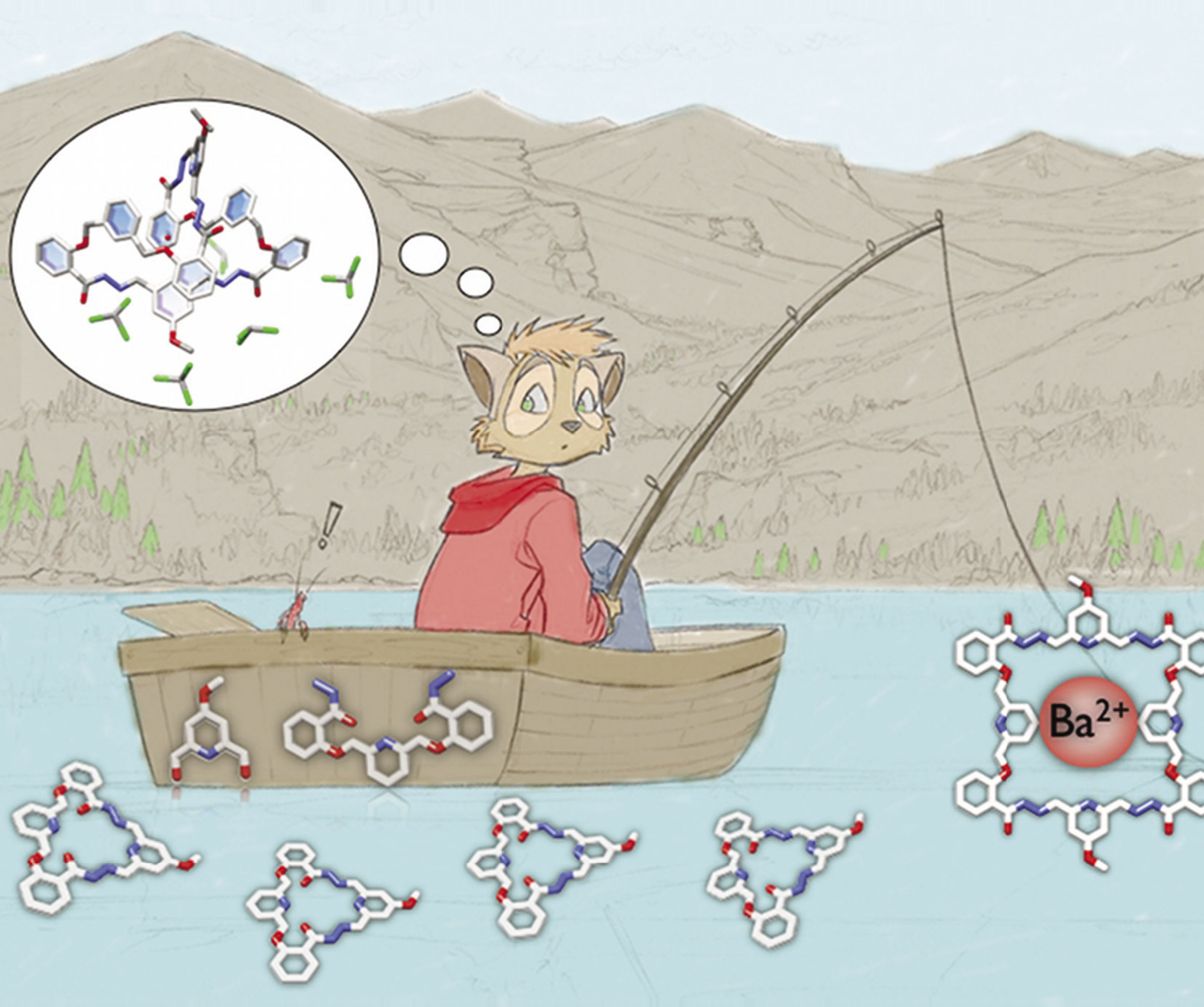

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COMMUNICATION

A remarkably flexible and selective receptor for Ba^{2+} amplified from a hydrazone dynamic combinatorial library†‡

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A new [2+2] tetra-hydrazone macrocyclic receptor was significantly amplified in a dynamic combinatorial library upon templation with alkaline earth metal ions. After optimisation the product could be isolated in 95% yield and its interaction with ions was investigated by NMR and UV-Vis spectroscopy.

Dynamic Combinatorial Chemistry (DCC)—combinatorial chemistry under thermodynamic control—has served as an efficient tool to discover synthetic receptors for various guests.[1] A dynamic combinatorial library (DCL) is generated by exchange and recombination of building blocks that use reversible covalent or noncovalent interconnections to build higher-order dynamic entities. Both hydrazone formation and metal–ligand interactions are dynamic, as they are labile and dissociate and reassociate under the influence of various chemical and/or physical stimuli.[2] Templating of imines by metal ions is well precedented[3] but to the best of our knowledge almost no investigations in metal-ion templated hydrazone chemistry have been published.[4]

Herein we present the efficient synthesis of a new type of a multi-hydrazone based macrocyclic receptor and the investigation of its complexation properties with alkali and alkaline earth metal ions using a dynamic combinatorial approach. Macrocycles **3** and **4** were assembled from DCLs by the reversible, acid-catalysed polycondensation of dialdehyde **1**[5] and dihydrazide **2**‡ (Fig. 1). The DCLs contained solutions of building blocks (1 mM per building block) in a mixture of $CHCl_3$/MeOH/TFA (50 : 50 : 5). Thermodynamic equilibrium was reached in 9 days.[6] The untemplated DCL of **1** and **2** formed a mixture containing only two hydrazone macrocycles **3** and **4** in a distribution of 99 : 1 (Fig. 2, no template).

The distribution of products changed significantly upon addition of a templating metal ion. Most dramatically, the addition of Ba^{2+} shifts the equilibrium position to 92% of **4**. Other metal ions had various effects depending on the charge and size of the cation (Fig. 2). Group 1 metal ions did not change the library distribution significantly whereas group 2 metal ions did. The order of amplification of **4** was $Ba^{2+} > Sr^{2+} > Ca^{2+} > Mg^{2+} \gg$ group 1. Discrimination among group 2 metal ions is clearly correlated with their size; large cations give stronger amplification, presumably due to a better fit in the binding pocket.

Thus DCC identified **4** as an interesting host for Ba^{2+}. Ironically the yields for the isolation of **4** from a templated DCL were low due to the better solubility of $Ba^{2+}\cdot$**4** compared with **4**. In the event, **4** was most easily isolated by exploiting its low solubility:[7] increasing the concentration of **1** and **2** in the DCL to 30 mM each resulted in the precipitation of pure **4** from the solution, which could be isolated by filtration in 95% yield.‡

Structural proof for receptor **4** came from X-ray analysis. Crystals suitable for X-ray diffraction were grown by slow evaporation of a solution of $CDCl_3$/MeOD.¶ $\mathbf{4}\cdot1.5H_2O\cdot4CHCl_3$ crystallises in the triclinic space group $P\bar{1}$ with one molecule in the asymmetric unit. A solvent water molecule is located within the macrocycle, forming three hydrogen bonds with the hydrazone moieties. Receptor **4** adopts a highly twisted conformation such that planar chirality is observed (Fig. 3). π–π stacking interactions and several hydrogen bonds stabilise the folding of the macrocycle (see ESI‡ for further discussion). As the space group contains inversion symmetry a racemic mixture of the two *P* and *M* enantiomers is present throughout the lattice. Adjacent pairs of enantiomers are partially intercalated and linked together through hydrogen bonding interactions between the macrocycles and their guest water.

The strongest amplification of **4** by Ba^{2+} (Fig. 2) implies that this metal is likely to form a strong complex with **4**. For this reason we decided to study this complexation process using ^1H NMR, NOESY and HRMS techniques. The number of peaks in the ^1H-NMR spectrum of **4** is consistent with a time-averaged highly symmetric structure.‡ When a substoichiometric amount of Ba^{2+} was titrated into a solution of **4** ($CDCl_3$/MeOD, 1 : 1, 1 mM) the free macrocycle and the complex were observed to be in slow exchange on the NMR timescale. Complete conversion of the host into the $Ba^{2+}\cdot$**4** complex was observed after the addition of 1.0 eq. of Ba^{2+} while further addition of Ba^{2+} did not induce any change in the ^1H-NMR spectrum.

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‡ Electronic supplementary information (ESI) available: Synthetic and DCL set up methods, LC-MS, NMR, HRMS and UV-Vis data. CCDC 808990. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc04863a

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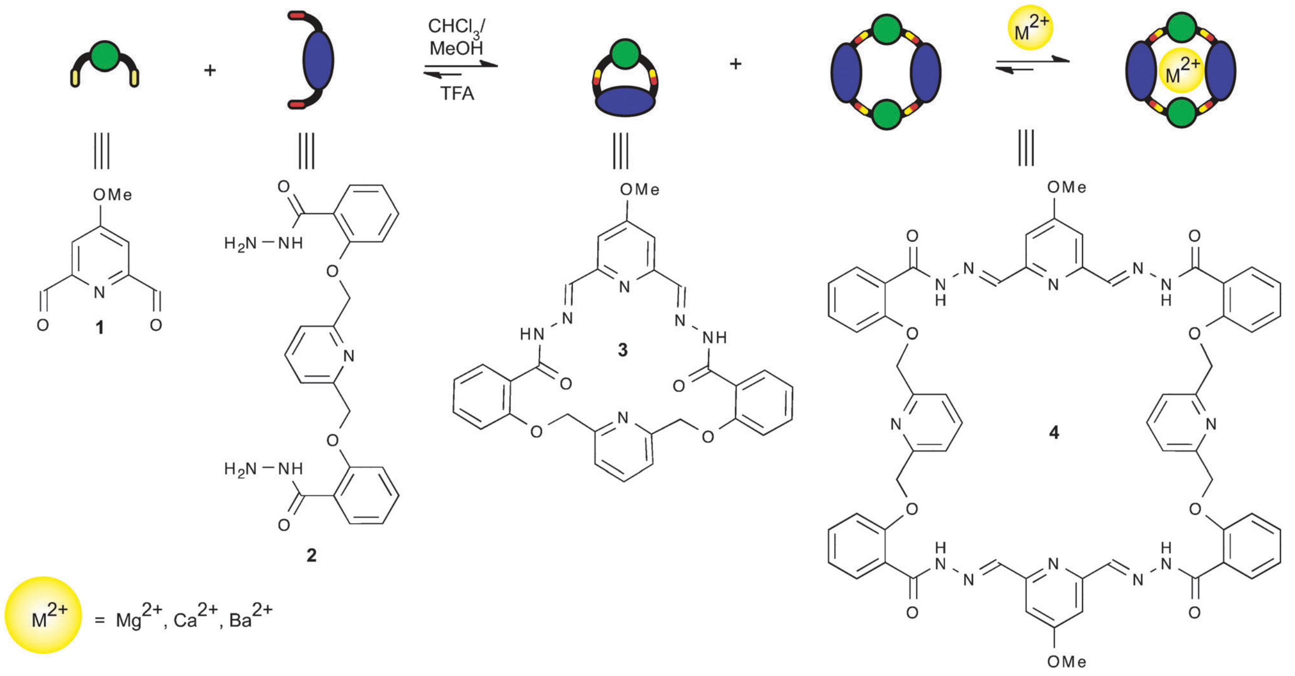

Fig. 1 Schematic representation of the selection of macrocyclic host **4** from a DCL by alkaline earth metal ions.

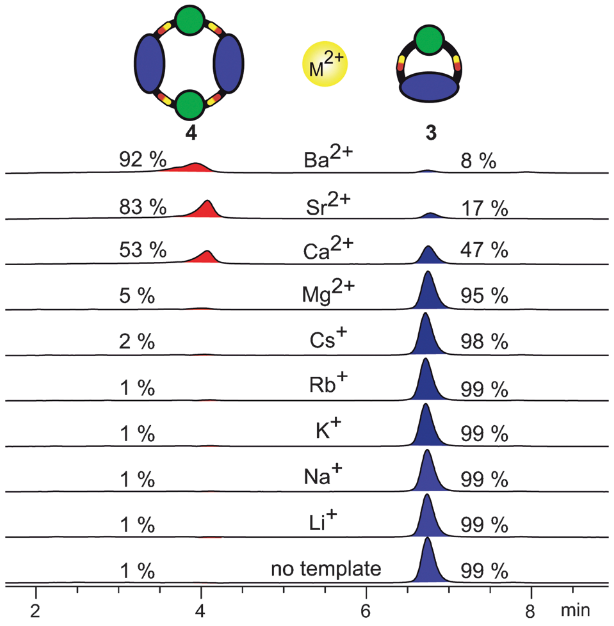

Fig. 2 HPLC traces of the DCLs with and without different chloride salts as templates after 9 days (1 mM per building block, 1 mM of template). The macrocycles present in solution are shown above the HPLC traces. The templating ions are shown in the middle of each HPLC trace. Only marginal changes were observed when monovalent cations were used. Divalent cations amplify **4** (red peaks) at the expense of **3** (blue peaks). UV traces shown were recorded at 290 nm.

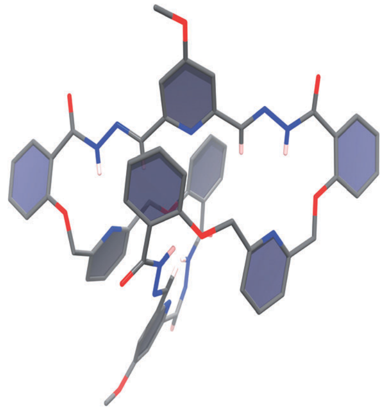

Fig. 3 A schematic representation of the crystal structure of **4**·1.5H$_2$O·4CHCl$_3$. Disorder and solvent molecules removed for clarity.

The NOESY spectrum of the Ba^{2+} complex exhibits a cross-peak between H$_c$ (6.9 ppm) and H$_e$ (8.0 ppm, Fig. 4) which is not observed in the NOESY spectrum of the unbound macrocycle. This suggests that the macrocycle undergoes a conformational change upon complexation of Ba^{2+}, a process associated with the notion of induced fit. The molecular ion peak of Ba^{2+}·**4** was observed in the HRMS after addition of 1.0 eq. of Ba^{2+} to a solution of **4**, providing further support for a 1 : 1 stoichiometry and the complete conversion of the free macrocycle into its complex.

UV titrations [in CHCl$_3$/MeOH (1 : 1) at 23 °C] confirmed the relative thermodynamic stability of the metal complexes that was indicated by the DCC experiments. For alkali metal ions changes in the UV absorption were too small to determine binding constants, while for alkaline-earth metal ions they ranged from 10^3 M^{-1} (Mg^{2+} and Ca^{2+} complexes) over 2×10^5 M^{-1} (Sr^{2+} complex) up to $> 10^6$ M^{-1} (Ba^{2+} complex). Since the binding constant for the Ba^{2+} complex was too high to be determined accurately at 23 °C, it was measured at elevated temperatures. As expected, the association constants were progressively lower as the temperature increased: K_a (33 °C) = 5×10^5 M^{-1} and K_a (43 °C) = 3×10^5 M^{-1}.

In conclusion, a DCL of multihydrazone macrocycles was templated with different metal salts. The amplification factors obtained from the DCLs represented the relative stabilities of the complexes as determined by UV-Vis titrations. A particularly

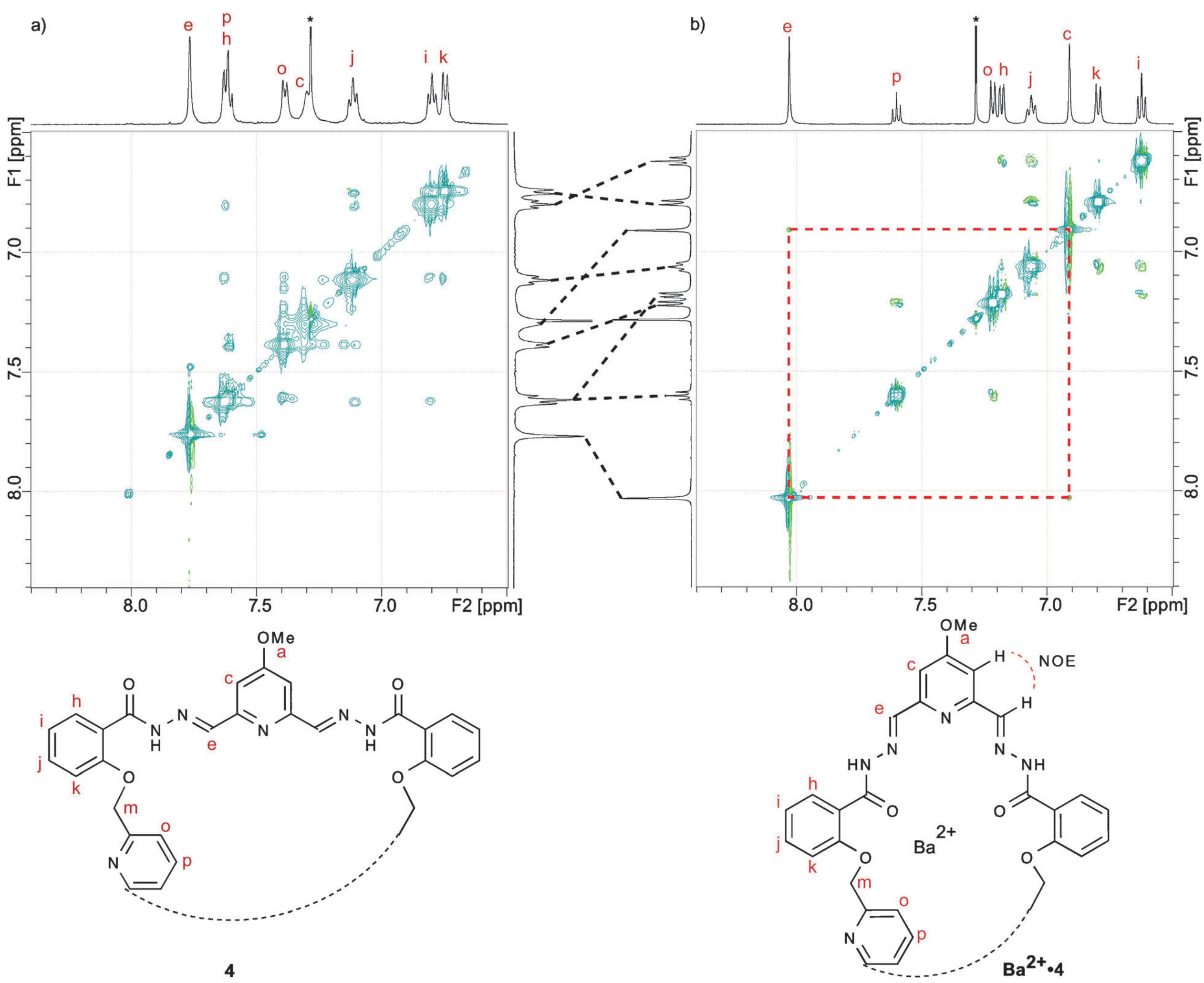

Fig. 4 Partial NOESY spectra (500 MHz, $CDCl_3$/MeOD (1/1), 300 K, d_8 = 800 ms) of (a) **4** and (b) its Ba^{2+} complex $Ba^{2+}\cdot$**4**. The appearance of the indicated cross-peak (red dashed line) suggests a conformational change upon binding. Corresponding resonances are connected by black dashed lines. Residual solvent peaks are marked with an asterisk.

strong complex is formed between **4** and Ba^{2+}. These results illustrate the ability of DCC to uncover highly flexible and therefore unpredictable macrocycles with remarkably selective recognition properties. **4** may be the most selective macrocyclic Ba^{2+} *vs.* Ca^{2+} receptor yet discovered.[8]

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Notes and references

¶ Formula: $C_{62}H_{55}Cl_{12}N_{12}O_{11.5}$, M 1577.58, triclinic, space group: $P\bar{1}$(#2), a 14.445(3), b 16.454(3), c 16.977(3) Å, α 67.62(3)°, β 73.33(3)°, γ 86.05(3)°, V 3570.8(12) $Å^3$, D_c 1.467 g cm^{-3}, Z 2, crystal size: 0.46 × 0.35 × 0.23 mm, colour: colourless, habit block, temperature: 180(2) K, λ(MoKα) 0.71073 Å, μ(MoKα) 0.532 mm^{-1}, T(SORTAV)$_{min,max}$ 0.918, 0.981, $2\theta_{max}$ 41.40°, hkl range: −14 14, −16 16, −16 16, N 31 757, N_{ind} 7245(R_{merge} 0.0244), N_{obs} 6395($I > 2\sigma(I)$), N_{var} 963, residuals: $R_1(F)$ 0.0749, w$R_2(F^2)$ 0.1992, GoF(all) 1.053, $D\rho_{min,max}$: −0.789, 0.849 e^- $Å^{-3}$.

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6 The HPLC traces remained unchanged after 9 days indicating that thermodynamic equilibrium has been reached. When **4** was dissolved under the same conditions as the DCL it reequilibrated to the library distribution obtained from the building blocks (**3** : **4**, 95 : 5, ESI‡).
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