

## Dynamic combinatorial libraries for the recognition of heavy metal ions†

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We present the use of hydrazone dynamic combinatorial libraries (DCLs) to identify macrocyclic receptors that are selective for alkaline earth metal ions over alkali metal ions. In particular, the toxic heavy metal ions  $\text{Sr}^{2+}$  and  $\text{Ba}^{2+}$  induce characteristic changes in the DCLs. Four macrocycles were isolated and characterised by LCMS, HRMS, NMR and X-ray crystallography; binding studies by UV-Vis spectroscopy confirm the selectivity observed in the DCLs.

## 1 Introduction

Heavy metal ions are part of everyday life and much research has focussed on the extraction of heavy metal ions from organic or aqueous effluents.<sup>1–7</sup> In particular, radioactive isotopes such as  $^{90}\text{Sr}$  and  $^{137}\text{Cs}$  have gained renewed attention following recent accidents in the nuclear power plants in Japan. As recently pointed out by Chen *et al.*, new organic ligands are needed to further optimise the extraction and make it a greener process.<sup>8</sup> Non-covalent interactions play an important role in the recognition between the metal and the organic ligand and have been found to be a way of tuning the extractant strength.<sup>9</sup> We now present the use of dynamic combinatorial chemistry (DCC) to discover new organic ligands that are selective for heavy metal ions and could contribute to more efficient extraction processes; some of these results have previously been presented in preliminary form.<sup>10</sup>

Dynamic combinatorial chemistry is concerned with mixtures of building blocks under thermodynamic control.<sup>11,12</sup> The building blocks can assemble to give different combinations (in this case macrocycles). The assembly process is reversible thus making the mixture dynamic. These adaptable mixtures are called dynamic combinatorial libraries (DCLs) and adapt to external stimuli (*e.g.* temperature, pressure, the presence of a template *etc.*) by changing the product distribution to minimise the total energy of the system. The increase in concentration of a particular species is referred to as amplification. Amplification reflects stabilisation of a particular species and has guided the discovery of new receptors.<sup>13–27</sup>

The reversible interactions used in this study are hydrazone exchange<sup>23–27</sup> and metal–ligand interactions.<sup>28</sup> Recently, we exploited the reversibility of the hydrazone linkage in ligands containing a 2,6-bis-hydrazonepyridine core (here referred to as  $\text{N}_3\text{O}_2$  ligands)<sup>29–35</sup> to study their behaviour in dynamic combinatorial libraries (DCLs).<sup>10</sup> Dialdehyde **1** and dihydrazide **2a** (Fig. 1) were combined to generate two different macrocycles. We developed a protocol for the easy isolation of the first macrocyclic hydrazone  $\text{N}_3\text{O}_2$  ligand and presented its characterisation. Binding studies showed a striking selectivity of this host for  $\text{Ba}^{2+}$  over  $\text{Ca}^{2+}$  and alkali metal ions, and proved the potential of macrocyclic  $\text{N}_3\text{O}_2$  ligands.<sup>10</sup>

Here we extend the family of macrocyclic  $\text{N}_3\text{O}_2$  ligands by introducing a new dihydrazide building block **2b** (with a diethyleneglycol linker) and study DCLs that were templated with alkali and alkaline earth metal ions (Fig. 1). The heavy metal ions  $\text{Sr}^{2+}$  and  $\text{Ba}^{2+}$  induced characteristic changes in the product distribution of the DCLs that were not observed when other metal ions were added. After the isolation and characterisation of four different  $\text{N}_3\text{O}_2$  macrocycles, binding studies of the larger 2 + 2 macrocycles by HRMS, NMR and UV-Vis confirmed the selectivity of the macrocycles for  $\text{Sr}^{2+}$  and  $\text{Ba}^{2+}$ .

## 2 Templating of DCLs with metal ions

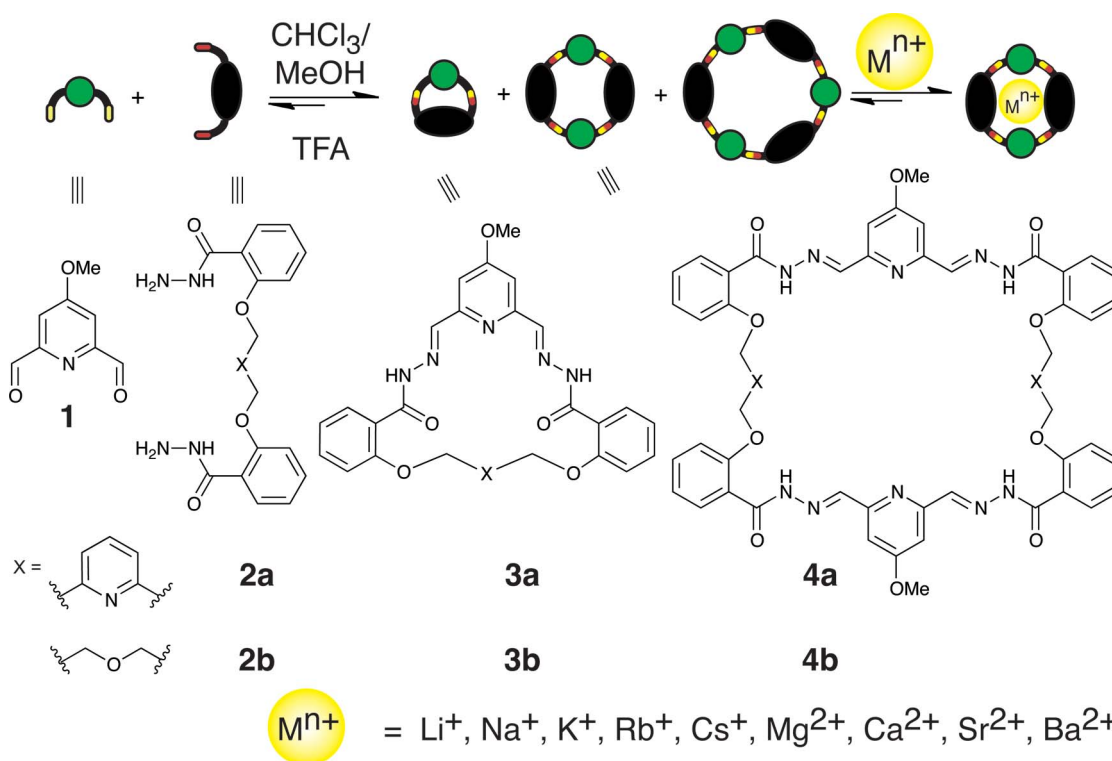
The building blocks were synthesised according to published procedures<sup>10,36</sup> or as described in the ESI.† Dissolution of dialdehyde **1** and dihydrazide (**2a** or **2b**) in mixtures of  $\text{CHCl}_3/\text{MeOH}/\text{F}_3\text{CCO}_2\text{H}$  generated two different sets of DCLs (Fig. 2 and ESI†). As shown by LCMS analysis, both sets of untemplated DCLs consisted of almost exclusively 1 + 1 macrocycle (**3a** and **3b**); therefore these smallest macrocycles, which are inevitably favoured on entropic grounds, represent the thermodynamically most stable species (Fig. 2 and ESI†). Addition of alkali metal ions had essentially no effect on the product distribution whereas addition of alkaline earth metal ions stabilised larger macrocycles and increased their abundance in the DCLs. Interestingly, the small differences in the linker unit of **2a** and **2b** led to distinctly different responses of the DCLs to

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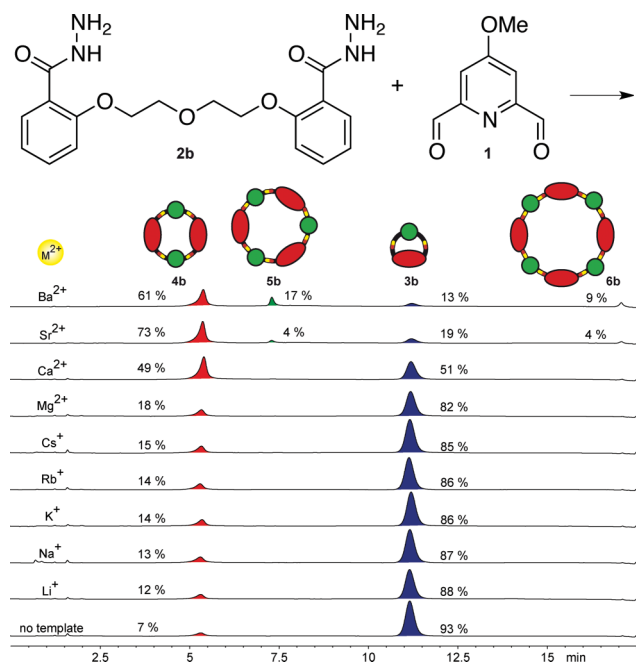
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† Electronic supplementary information (ESI) available: Synthetic and DCL set up methods, LC-MS, NMR, HRMS and UV-Vis data. CCDC reference numbers 827938 and 827939. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05976a

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**Fig. 1** Schematic representation of the experiment. A mixture of macrocycles is formed by combining a dialdehyde with a dihydrazide. Addition of a metal ion leads to the selection of the macrocycle that binds the metal ion better.



**Fig. 2** LCMS analysis of DCLs generated from building blocks **1** and **2b** in the absence and presence of different metal ions. Cartoons as explained in Fig. 1. Method A (ESI<sup>+</sup>).

templating with Ca<sup>2+</sup>, Sr<sup>2+</sup> and Ba<sup>2+</sup>. The DCLs with the ethylene glycol linker (Fig. 2) showed amplification of 2 + 2 (**4b**), 3 + 3 (**5b**) and 4 + 4 (**6b**) macrocycles upon addition of Ba<sup>2+</sup> and Sr<sup>2+</sup> while the DCLs with the pyridyl linker showed only amplification of

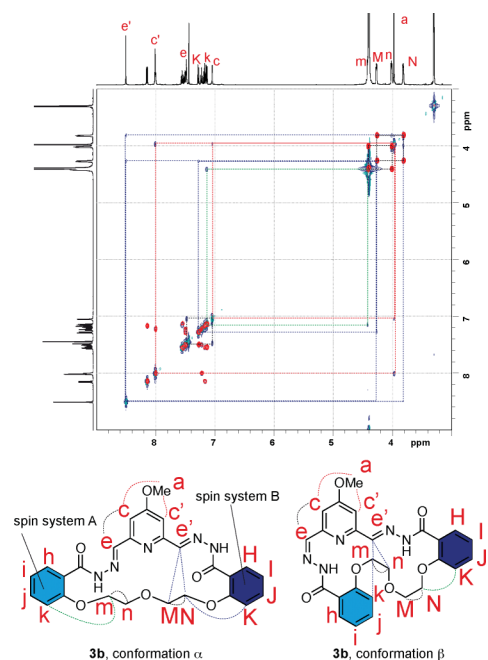
the 2 + 2 macrocycle **4a** (ESI<sup>+</sup>).<sup>10</sup> These results suggested that the 2 + 2 macrocycle with the pyridyl linker and the 2 + 2, 3 + 3 and 4 + 4 macrocycles with the ethylene glycol linker are good hosts for the doubly charged guests Ca<sup>2+</sup>, Sr<sup>2+</sup> and Ba<sup>2+</sup> while showing weak or no binding to singly charged guests (alkali metal ions). Thermodynamic control was demonstrated by reaching the same library distribution from two different starting points. When the 2 + 2 macrocycles (isolation is described below) were dissolved under the same conditions as the building blocks, an identical product distribution was reached (ESI<sup>+</sup>). The following section will present the isolation and characterisation of the two 1 + 1 macrocycles **3a** and **3b** and the two 2 + 2 macrocycles **4a** and **4b**.

### 3 Isolation and characterisation of macrocycles

#### 3.1 1 + 1 Macrocycles

The isolation and characterisation of the 1 + 1 macrocycle with the pyridyl linker **3a** was very similar to that of the 1 + 1 macrocycle with the ethylene glycol linker **3b** and only the latter is described here. The information for **3a** can be found in the ESI.<sup>†</sup> The untemplated DCL of **1** and **2b** formed almost exclusively 1 + 1 macrocycle **3b** as the thermodynamically most stable species and the 1 + 1 macrocycles were isolated in a simple three-step procedure: addition of base (to halt hydrazone exchange) followed by removal of solvent and finally removal of salts by washing with water. LCMS analysis confirmed that the isolated material was indeed the 1 + 1 macrocycle **3b** and that the purity of the obtained sample was high (ESI, <sup>†</sup> 99%).

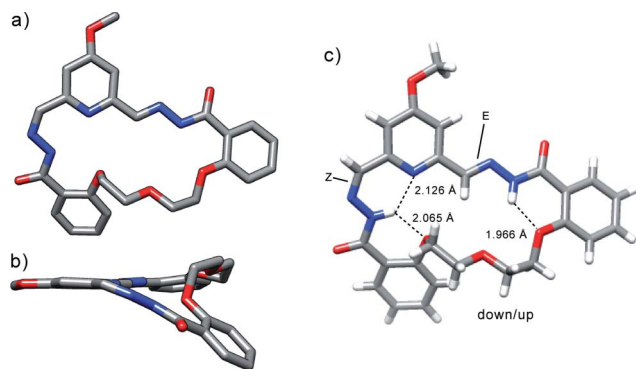
The NMR spectrum of **3b** showed that this macrocycle adopts an asymmetric conformation. NOESY cross-peaks (Fig. 3) for only one of the two imine peaks with the *meta*-pyridine protons suggested that the asymmetry arises through different orientations of the hydrazone moiety on the two sides of the MeO-pyridine ring.



**Fig. 3** Overlaid COSY (red cross peaks) and NOESY (blue peaks) spectra of **3b** in  $\text{CDCl}_3/\text{MeOD}$  (3 : 1, 500 MHz, 297 K, mixing time = 800 ms). Cross-peaks are indicated by corresponding colours in the spectrum and the suggested structures below.

The resonances of the two spin systems A and B could not be assigned unambiguously by COSY/NOESY and two possible conformations are shown in Fig. 3.

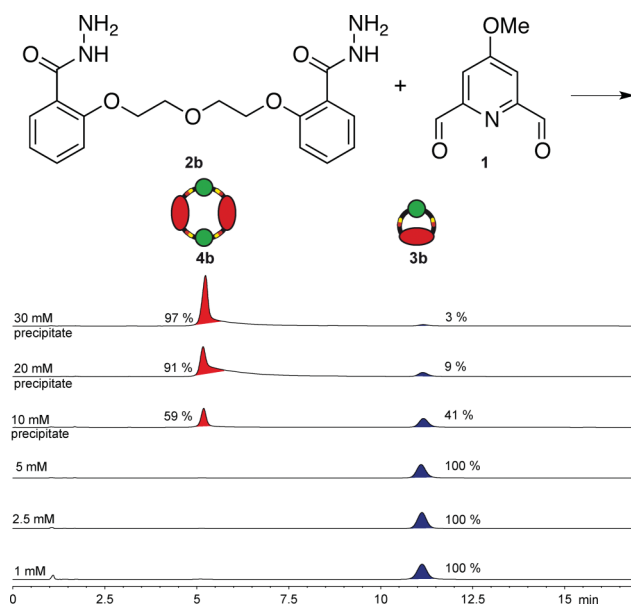
The solid state structure (Fig. 4) of the macrocycle with the ethylene glycol linker **3b** showed an asymmetric structure, the two substituents on the pyridine ring adopting different conformations. The structure obtained from X-ray crystallography is very similar to the NMR-derived conformation  $\beta$  in Fig. 3, suggesting that the macrocycle adopts similar conformations in solution and solid state.



**Fig. 4** Solid state structure of the 1 + 1 macrocycle **3b**.† a) top view; b) side view; c) different conformations of hydrazones moieties in the same macrocycle and important H-bonds (dotted lines).

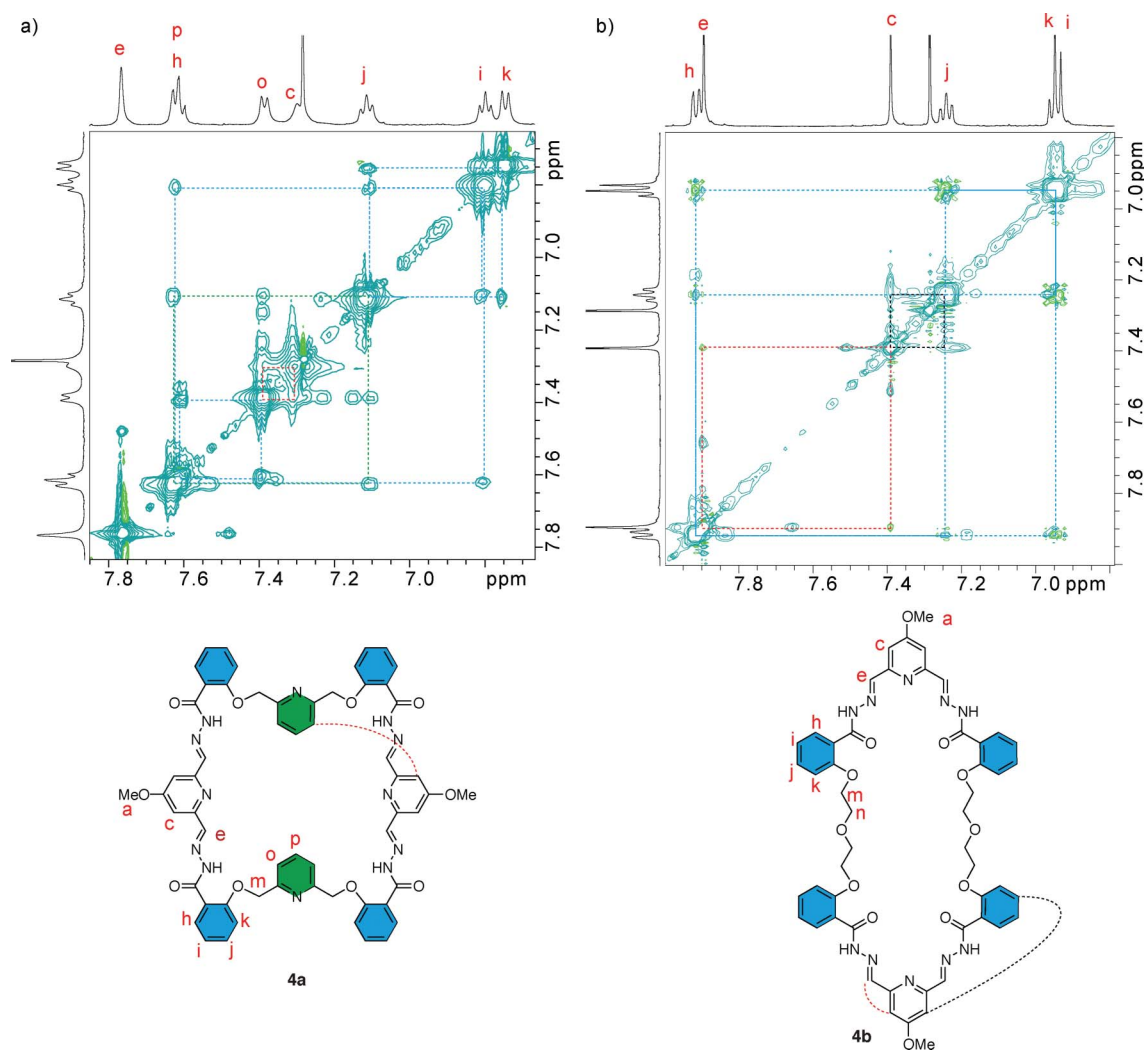
### 3.2 2 + 2 Macrocycles

Varying building block concentrations in these DCLs (Fig. 5) showed that, if the concentration of the building blocks were increased, the 2 + 2 macrocycle **4b** precipitated, creating a useful kinetic trap. The precipitation of **4b** shifts the equilibrium towards its formation, consuming all the building blocks. The 2 + 2 macrocycles were easily isolated by filtration. The group of Nitschke used this principle (*i.e.* isolation of a compound by exploiting a kinetic trap) to convert a dynamic library of six diastereomeric pairs of enantiomers into a single pair of enantiomers.<sup>37</sup> LCMS analysis of the precipitated macrocycles showed that the purity of the obtained samples was satisfactory (95% for **4b**, ESI†).



**Fig. 5** HPLC analysis of DCLs generated from **1** and **2b** at different building block concentrations. At low building block concentrations the DCLs are homogeneous and the 1 + 1 macrocycle **3b** is the only detected product. At concentrations above 5 mM the larger macrocycle **4b** precipitates, forming a kinetic trap. Analysis of the mixtures (precipitate and solution) showed that **4b** has become more abundant than **3b**.

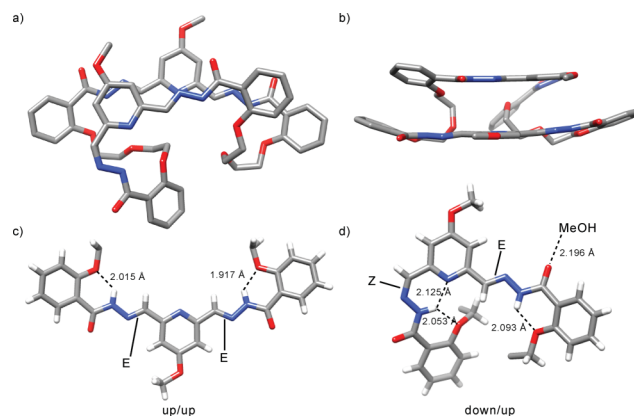
The NMR spectra of the larger 2 + 2 macrocycles **4a** and **4b** showed a time-averaged symmetrical structure exhibiting only half as many peaks as their smaller 1 + 1 analogues **3a** and **3b**. This might reflect the symmetrical orientation of the hydrazone substituents on the pyridine core or the flexibility of the macrocycles which exist as mixtures of rapidly interconverting conformations so that only a time average of these conformations is observed. The cross peak between protons *c* and *e* that was used to gain information about the conformation of the hydrazones in Fig. 3 was analysed similarly in the NOESY spectra of **4a** and **4b** (Fig. 6). However, the information from these two NOESY spectra cannot be compared easily because the spectra were recorded in different solvent mixtures to maximise the solubility of the macrocycles in the NMR solvent. A cross-peak between *c* and *e* was present in the NOESY spectrum of **4b** (Fig. 6b), but not in the NOESY spectrum of **4a** (Fig. 6a) suggesting that the conformation of the hydrazones depends on the linker unit. Both NOESY spectra showed cross-peaks between aromatic rings suggesting that



**Fig. 6** Partial NOESY spectra of **4a** and **4b** in  $\text{CDCl}_3/\text{MeOD}$  (1 : 1 and 7 : 3 respectively, 500 MHz, 297 K, mixing time = 800 ms). Cross-peaks are indicated by corresponding colours in the spectrum and the suggested structures below.

aromatic interactions influence the folding of the macrocycles in solution.

The solid state structure of the macrocycle with the ethylene glycol linker **4b** (Fig. 7) shows clearly different orientations of hydrazones in the same macrocycle. The only structural information concerning unbound  $\text{N}_3\text{O}_2$  ligands in the literature comes from two crystal structures.<sup>38,39</sup> In these (both are linear  $\text{N}_3\text{O}_2$  ligands) the hydrazones point away from each other, requiring large conformational changes upon binding of metal ion guests.<sup>29–35</sup> The differences between the published linear ligand and the macrocycles (**3a**, **3b**, **4a**, **4b**) in this study can be interpreted as a result of ring strain imposed on the  $\text{N}_3\text{O}_2$  binding motif by the linker unit. To bind the guest strongly the macrocycles need the right balance of preorganisation and flexibility. All four macrocycles (**3a**, **3b**, **4a**, **4b**) have a partially preorganised binding pocket but the 2 + 2 macrocycles **4a** and **4b** are larger and more flexible and are amplified at the expense of the 1 + 1 macrocycles. Consequently the right linker unit could increase the ability of  $\text{N}_3\text{O}_2$  ligands to bind metal ion guests by partly preorganising the binding pocket and still maintaining some flexibility. The intramolecular hydrogen bonds that are observed in the crystal



**Fig. 7** Solid state structure of **4b**.† a) top view (perpendicular to the plane of py); b) side view (parallel to the plane of py); c) and d) different conformations of hydrazones moieties in the same macrocycle and important H-bonds (dotted lines).

structure of **4b** are expected to be weakened in solution, but they might still play an important role in preorganising **4b** for binding.



## 4 Binding to alkaline earth metal ions

The binding of the 2 + 2 macrocycles **4a** and **4b** to alkaline earth metal ions was studied by NMR, HRMS and UV-Vis. To ensure stability of the isolated macrocycles, the binding studies had to be performed in a different solvent system than the DCLs (*i.e.* without acid). Since protonated species are significantly less stabilised in organic solvents compared to water we do not expect the protonation states of the macrocycles to be very different. Switching from 2-methoxyethanol/water (80/20) to ethanol decreases the  $pK_a$  values of carboxylic acid by  $\approx 4$ .<sup>40</sup> Since we work in even less polar solvent mixtures the stabilisation of charged species is not expected to be significant.

### 4.1 UV-Vis

To quantify the binding affinity between the host macrocycles (**4a** and **4b**) and metal ion guests we performed UV-Vis titrations (ESI† and Fig. 8) and fitted the obtained binding isotherms to a published model.<sup>41</sup> The macrocycle with the pyridyl linker **4a** bound weakly to  $Mg^{2+}$  and  $Ca^{2+}$  (ESI†,  $K_a \approx 10^3 M^{-1}$ ) and strongly to  $Sr^{2+}$  and  $Ba^{2+}$  (ESI†,  $K_a \approx 10^5$ – $10^6 M^{-1}$ ) with one of the best  $Ba^{2+}/Ca^{2+}$  selectivities reported to date.<sup>10</sup> Macrocycle **4b** bound  $Mg^{2+}$  with an affinity of  $K_a \approx 10^5 M^{-1}$ . The binding constants between  $Ca^{2+}$ ,  $Sr^{2+}$ ,  $Ba^{2+}$  and **4b** were too large to be determined

accurately with this method and  $K_a \approx 10^6 M^{-1}$  is given as a lower limit (ESI†, Fig. 8). Besides proving the strong affinity of the macrocyclic hosts **4a** and **4b** for selected alkaline earth metal ions the binding isotherms strongly suggested a 1 : 1 binding stoichiometry. Surprisingly, the selectivity of **4a** for  $Ba^{2+}$  over  $Ca^{2+}$  is not found in its closely related diethyleneglycol analogue **4b**. It might seem surprising that **4b** shows similar affinities for  $Ca^{2+}$ ,  $Sr^{2+}$  and  $Ba^{2+}$  while the amplification patterns in the DCL are different. The two results are consistent if one considers that the product distribution in the DCL is not only determined by the interaction of the 2 + 2 macrocycle **4b** with the template but by all interactions between the library members.<sup>42</sup> The small  $Ca^{2+}$  ion binds only to the 2 + 2 macrocycle **4b** while the larger  $Sr^{2+}$  and  $Ba^{2+}$  ions also bind to **5b** and **6b** in addition to **4b**. Therefore,  $Sr^{2+}$  and  $Ba^{2+}$  amplify **4b**, **5b** and **6b** whereas  $Ca^{2+}$  amplifies only **4b**. Furthermore, the metals that amplified **4b** in the DCLs also showed affinity in the UV-Vis study, showing that good receptors can be discovered by DCC when keeping in mind that DCLs are complex systems.<sup>43–46</sup>

Comparing **4a** with **4b** shows that small differences in the linker units can lead to unpredictably different host–guest chemistries. These differences can be observed in the DCLs as well as when the isolated compounds are studied.

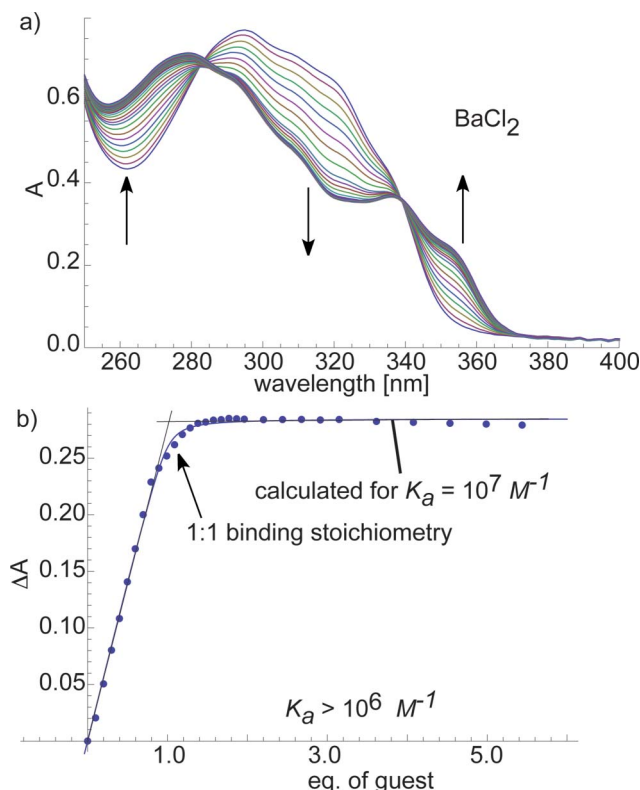
### 4.2 HRMS and NMR

After addition of 1.0 eq. of metal ion salt ( $MgCl_2$ ,  $CaCl_2$ ,  $SrCl_2$  and  $BaCl_2$ ) to **4a** and **4b**, the  $Ba^{2+}$  and  $Sr^{2+}$  complexes (1 : 1) were observed by HRMS as singly (loss of one proton) and doubly charged molecular ion peaks. The complexes of  $Mg^{2+}$  and  $Ca^{2+}$  with **4a** and **4b** were not observed by ESI-HRMS.

Well-resolved NMR spectra were obtained when  $SrCl_2$  or  $BaCl_2$  were added to solutions of **4a** (ESI†) or **4b** (Fig. 9). The largest shifts upon addition of the metal salt were observed for protons c, e and h confirming the involvement of the  $N_3O_2$  binding motif. A possible explanation for the observed shifts is that c and e are shifted through inductive effects resulting from the metal ions binding to the nitrogen lone pairs. The upfield shift of proton h, upon binding of the metal ion, can be explained by a conformational change that moves h out of the deshielding region of the carbonyl oxygens.

## 5 Conclusions

In conclusion, we have presented the use of dynamic combinatorial libraries to study hydrazone receptors for metal ions. Small variations in the building block design lead to different molecular recognition properties of the DCLs. Through exploiting a kinetic trap in the system, the receptors could be isolated and characterised. Solution and solid state studies showed that the macrocycles are potent receptors for  $Sr^{2+}$  and  $Ba^{2+}$  while alkali metal ions are not measurably bound. Therefore, hydrazone DCLs provide a useful platform for the discovery of metal ion receptors with unpredictable selectivities. This opens a potential route to new receptors for the extraction of heavy metal ions.



**Fig. 8** UV-Vis titrations of ethylene glycol-based **4b** with  $BaCl_2$  in  $CHCl_3/MeOH$  (7 : 3). a) UV-Vis spectra of **4b** with different amounts of  $BaCl_2$ . Increasing and decreasing bands are indicated by arrows. b) Binding isotherm resulting from a plot of the change in absorbance  $\Delta A$  at 320 nm against the guest concentration. Experimental data represented as dots and calculated binding isotherm represented as a solid line.

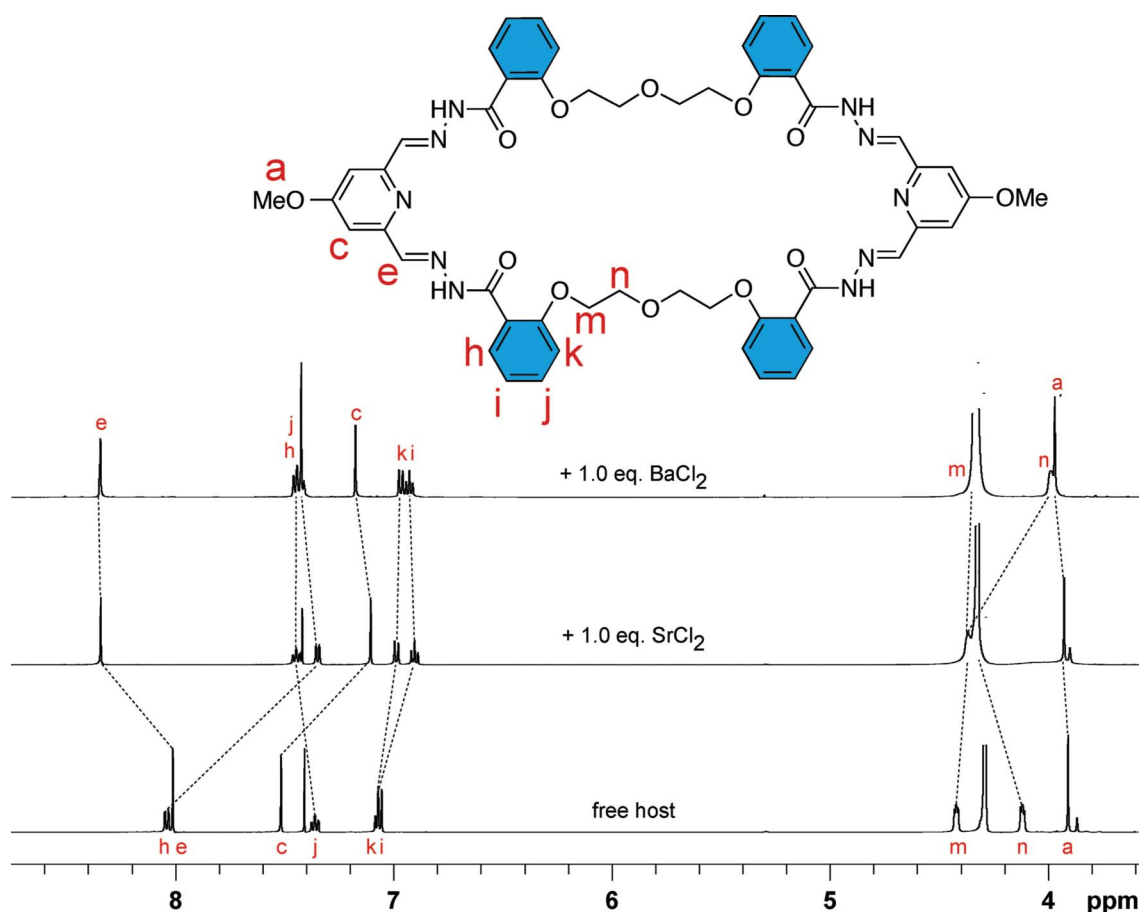


Fig. 9 NMR spectra (500 MHz, 297 K) of **4b** and its  $\text{Sr}^{2+}$  and  $\text{Ba}^{2+}$  complexes in  $\text{CDCl}_3/\text{MeOD}$  (7 : 3).

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