Highly diastereoselective amplification from a dynamic combinatorial library of macrocyclic oligoimines†

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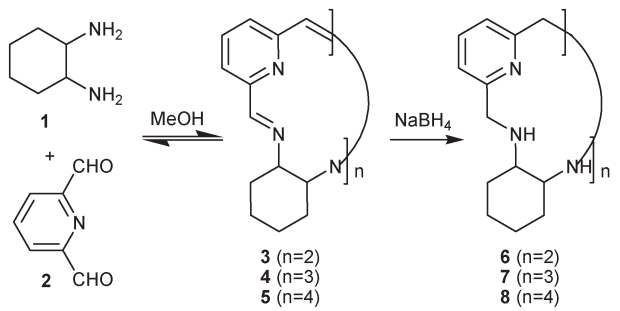
Cadmium promoted diastereoselective amplification of a single member from a dynamic combinatorial library of stereoisomeric oligoimines of different sizes allows the efficient preparation of a new macrocyclic polyamine.

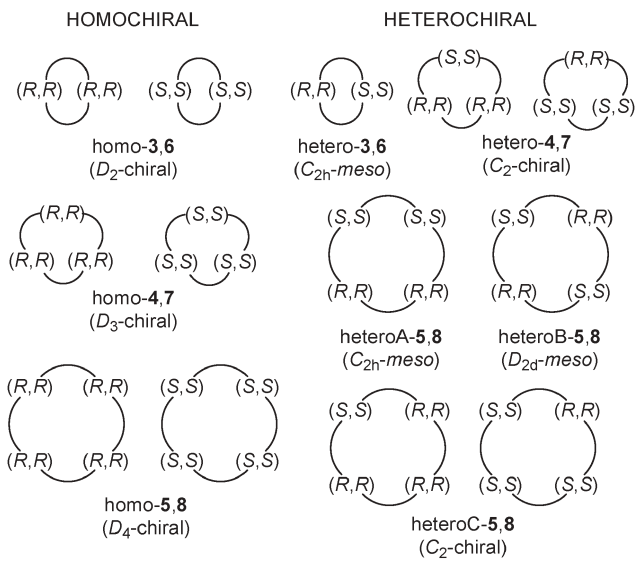
Dynamic combinatorial chemistry (DCC)[1] has proved to be a very powerful tool for the discovery of new molecular receptors,[2] metal ligands and complexes,[3] biologically interesting compounds[4] or chemosensors.[5] The interconversion of species connected through reversible equilibria generates a dynamic combinatorial library (DCL), from which a given constituent can be amplified upon the addition of an external template. Despite the large number of papers dealing with this topic over the last couple of years,[1–5] the stereoselective amplification of a member from a DCL of stereochemically different components has been scarcely reported.[6]

In a previous paper, we described the generation of a DCL of macrocyclic oligoimines starting from enantiopure *trans*-cyclohexane-1,2-diamine [(*R*,*R*)-**1** or (*S*,*S*)-**1**] and dialdehyde **2** (Scheme 1).[7] Besides, we found that this mixture can be quantitatively biased to either [2 + 2] (**3**) or [3 + 3] (**4**) cyclic products by addition of Ba(II) or Cd(II) salts, respectively. Thus, after the quenching of the exchange by *in situ* reduction, the corresponding macrocyclic polyamines (**6** or **7**) could be isolated in high yields and purities, even in preparative scales. On the other hand, a recent work reported that reaction between racemic *trans*-cyclohexane-1,2-diamine (*rac*-**1**) and **2** leads to an interconverting mixture of dimer (**3**), trimer (**4**) and tetramer (**5**).[8] A careful analysis and exhaustive purification processes allowed determining that the main components were the corresponding dimer (**3**) and tetramer (**5**). Interestingly, all of them showed to be *meso* compounds, namely hetero-**3** and heteroB-**5** (for assumed terminology, see Scheme 2). This can be probably due to a higher stability of alternating configurations in the diamine moieties and lower solubility of the obtained species, as a precipitate was observed during the reaction. As a matter of fact, theoretical calculations[9] showed that hetero-**3** is 1.14 kcal mol^{-1} more stable than homo-**3**, in accordance with the experimental results, regardless the differential solubility properties of the corresponding compounds. Additionally, a trimeric counterpart was detected in the solution as a trace compound, being its stereochemistry tentatively assigned to be heterochiral (hetero-**4** in Scheme 2),[8] but not isolated from the reaction mixture. Taking into account the additional molecular diversity due to the different stereochemical possibilities (see Scheme 2), we decided to investigate the effect of the presence of both enantiomers of **1** and the metal templates on the DCL composition.

Initially, we studied the effect of Ba(II) as template on this racemic DCL, as this metal ion induced the unique formation of dimeric macrocycles homo-**3** and homo-**6** when using enantiopure **1**. Addition of Ba(II) salt to the mixture of *rac*-**1** and **2** in MeOH (0.05 M final concentration) led to the complete re-dissolution of



Scheme 1 Generation of the DCL of oligoimines and subsequent reduction to the corresponding macrocyclic polyamines.



Scheme 2 Schematic representation of the stereochemical relationships and symmetries of all the possible macrocyclic oligoimines **3**–**5** and polyamines **6**–**8** virtually obtained from the racemic DCL.

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the initially obtained precipitate, after re-equilibration for 15 days. The first satisfying fact was that ESI-MS spectrum of the reduced reaction mixture showed the [2 + 2] cyclic compound (*m*/*z* 435, assigned to [**6** + H]$^+$) as the major product. This means that the templation effect of Ba ion is operative towards the formation of only one macrocyclic size, in spite of the presence of both enantiomers of diamine **1**. A simple analysis of the ^{1}H and ^{13}C NMR spectra of the reduced crude product revealed the presence of the two possible diastereomers (homo-**6** and hetero-**6**) in a 1.6 : 1 ratio (ESI†). Thus, regarding the stereochemistry, we observed a mixture very close to the statistical proportion. However, it is of note that Ba ion stabilizes the homochiral dimer more efficiently than the heterochiral one, which is the only dimeric structure observed in the absence of template.

These results encouraged us to check the effect of cadmium ion on the same racemic DCL. Thus, addition of Cd(II) template salt to the precipitate obtained from the mixture of *rac*-**1** and **2** in MeOH (0.05 M) led to a clean solution after 18 h of stirring. Once again after *in situ* reduction, three peaks were observed at *m*/*z* 652 [**7** + H]$^+$, 674 [**7** + Na]$^+$ and 326.7 [**7** + 2H]$^{2+}$ in the ESI-MS spectrum, all of them assigned to the [3 + 3] product. However, the large number of signals observed in the ^{1}H and ^{13}C NMR spectra (ESI†) implies the presence of the C_2 symmetrical heterochiral macrocycle (hetero-**7** in Scheme 2), either as a single diastereomer or mixed with the homochiral D_3 symmetrical one (homo-**7** in Scheme 2).[10] Comparison of NMR spectra of the obtained compound with those of true samples of the homochiral macrocycle, prepared from enantiopure (*R*,*R*)-**1**,[7] gave us some key data (Fig. 1). For instance, the homochiral trimer showed a doublet for the pyridine *meta* protons at 7.19 ppm. The sample with the product obtained from the racemic DCL in presence of Cd showed two overlapped doublets (δ 7.17 and 7.20 ppm) for those hydrogen atoms in a 2 : 1 ratio, respectively. Similar splitting was also observed for the triplet of protons on *para* position of the pyridine ($\delta \sim 7.54$ ppm). On the other hand, spectrum of homo-**7** showed an AB quartet centred at 3.84 ppm for the benzylic protons, while the sample from the racemic DCL again showed partially overlapped anisochronic AB quartets in a 2 : 1 ratio.

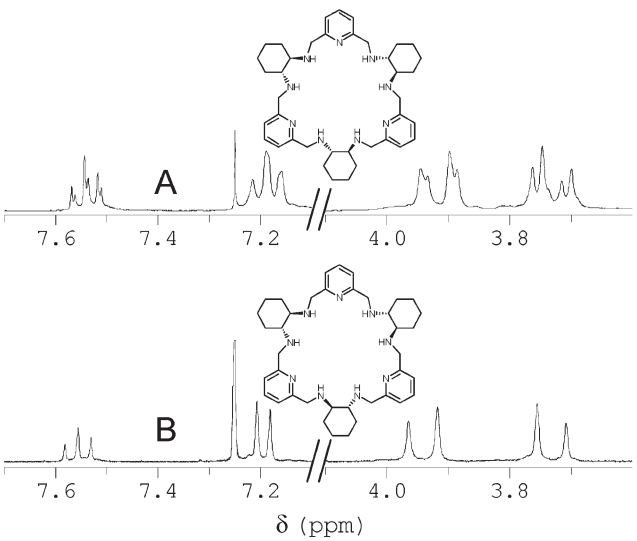

Fig. 1 Partial ^{1}H NMR spectra of hetero-**7** (A) and homo-**7** (B).

These NMR data imply the existence of two anisochronic pyridine moieties in a two to one proportion, suggesting the major presence of the C_2 symmetrical hetero-**7** macrocycle.

Definitive proofs for the diastereomeric identity and purity of hetero-**7** were obtained by HPLC using a chiral stationary phase[11] (Fig. 2). Injection of the reduced sample from racemic DCL generated in the presence of Cd(II) showed two peaks at 11.5 and 13.5 min, tentatively assignable to both enantiomers of hetero-**7**. On the other hand, true samples of (*R*,*R*,*R*,*R*,*R*,*R*)-**7** and (*S*,*S*,*S*,*S*,*S*,*S*)-**7** were eluted at 10.2 and 12.2 min, respectively, confirming the previous assignation. This result implies that the Cd(II) ion induces the exclusive formation of racemic heterochiral trimer (hetero-**4** and then hetero-**7** after reduction) in the DCL prepared from *rac*-**1** and **2**. Moreover, as the trimeric species were detected as a minor compound in the absence of template, the amplification factor must be very high. Besides, homo-**7** enantiomers were not detected by HPLC, supporting that Cd(II) amplification is completely diastereoselective as only one diastereoisomer was formed in the presence of the template.

In order to get a reasonable explanation for this remarkable stereoselectivity, some molecular modelling has been also undertaken. On independent experiments, we observed that the results are identical by performing the condensation between *rac*-**1** and **2** in the presence of the metal salt or by the pre-formation of the DCL of imines and subsequent addition of the metal template. Then, we concluded that this racemic system is also a true DCL operating under thermodynamic control.[7] Therefore, the observed selectivity must emerge form the stability differences of the cadmium complexes of the diastereomeric imine intermediates. As the major species formed in the presence of Cd(II) were the corresponding alternated tris(imine)tris(α-methoxyamine) dinuclear Cd(II) metal complexes,[12] we used these species for semi-empirical PM3 quantum mechanical calculations.[9] Computed energies of the obtained minima (Fig. 3) showed that the heterochiral diastereomer is 3.24 kcal mol^{-1} more stable than the homochiral one, in a very good agreement with the experimental observations. Comparison of the obtained geometries showed that the inversion of the configuration in one cyclohexane moiety separates the α-methoxyamine NH bond from an axial γ-proton of the adjacent cyclohexane (see distances in Fig. 3). This smooth structural change would dramatically relax the steric

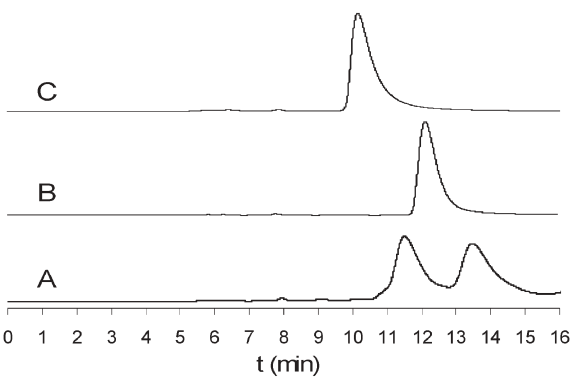

Fig. 2 HPLC traces for: hetero-**7** obtained by reduction of the Cd(II) templated racemic DCL (A), true samples of (*S*,*S*,*S*,*S*,*S*,*S*)-**7** (B) and (*R*,*R*,*R*,*R*,*R*,*R*)-**7** (C).

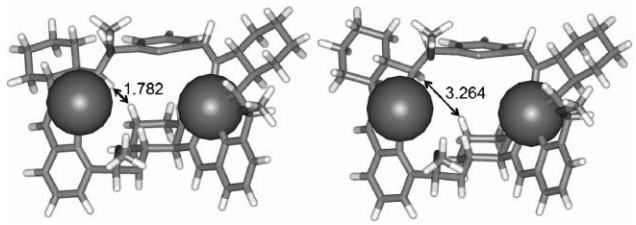

Fig. 3 PM3 optimized geometries of the Cd(II) complexes for the homochiral (left) and heterochiral (right) intermediates. Cadmium ions are represented in CPK model and selected distances are given in Å.

hindrance within the cycle, also improving the coordination geometry around the implicated metal centre.

In conclusion, unprecedented diastereoselective amplification from a DCL of macrocyclic oligoimines has been studied. The presence of Cd(II) ion efficiently promotes the unique formation of a single cycle and a single diastereomer from a virtual mixture of multiple sized and stereochemically different species. Thus, a new chiral macrocyclic ligand can be easily synthesized as a diastereochemically pure single compound. Far from being just a chemical curiosity, our results show how DCC is a powerful tool for the synthesis of new receptors which would be very difficult to prepare and isolate using more conventional approximations. Studies towards the applications of this topologically new receptor in molecular recognition processes are underway and will be reported in due curse.[13]

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