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# Mirror symmetry breaking upon spontaneous crystallization from a dynamic combinatorial library of macrocyclic imines†

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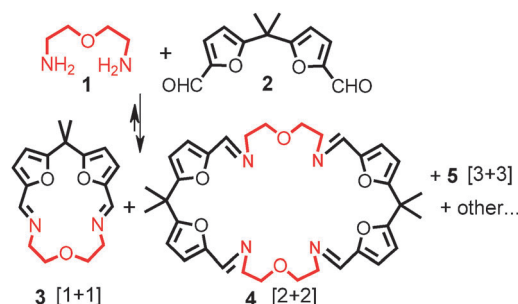
**Spontaneous emergence of solid state chirality and mirror symmetry breaking occurred upon crystallization from a small templated dynamic combinatorial library (DCL) of achiral macrocyclic imines, and depended strongly on the nature of library building blocks (amines, aldehydes, template cations and anions) and crystallization temperature.**

Chiral crystal formation from an achiral species is a well-known phenomenon, occurring commonly in Nature. Cambridge Crystal Structure Database (CCSD) surveys show that approximately 10%<sup>1,2</sup> of achiral substances crystallize in chiral space groups. For some classes of compounds, such as sterically hindered biaryls or species forming supramolecular helices, this occurs more often.<sup>1</sup> However, there is no clear rational explanation for these facts and, consequently, crystal engineering towards solid state chirality is still very limited. Such structural studies are directly concerned with identifying sources of chirality on Earth<sup>3</sup> and developing methods for achieving absolute asymmetric synthesis.<sup>4,5</sup> Consequently, of more importance are those rare cases in which the mirror symmetry is broken, leading to the predominance of one enantiomeric form. Sodium chlorate(v) seems to be the best examined example in this regard;<sup>6–9</sup> however, more complex organic compounds of this sort are of high relevance, paving the way for easy and controllable structural modifications supplying data for crystal engineering.<sup>10</sup> Substantial crystal enantiomeric excess (CEE) in the crystallization of various achiral organic compounds has recently been reported by several groups.<sup>11–16</sup> In 2006, we reported the first example of an achiral macrocyclic polyamide crystallizing with substantial CEE.<sup>17</sup> This finding encouraged us to search for other, more synthetically available systems. Macrocyclic imines and their complexes, typically providing high crystallinity, offer such advantages.<sup>18</sup> We have recently<sup>19</sup> described a reaction of diamine **1** with dialdehyde **2**

that leads to a dynamic combinatorial library (DCL) of macrocyclic imines, shown in Scheme 1. In this communication, we present the results of our studies on this reaction, carried out in the presence of lithium salts, leading to potentially chiral crystalline complexes.

Simple mixing of dialdehyde **1** with diamine **2** and LiCl in acetonitrile led to an expected DCL, from which spontaneous crystallization of a complex of [1+1] macrocyclic imine **3** with LiCl occurred. Although solubility of LiCl in acetonitrile is very low (0.14 g/100 g)<sup>21</sup> and it initially remained at the bottom of the flask, it was slowly extracted from the solid by a minute amount of **3**, which immediately crystallized.<sup>22</sup> The first crystals of the complex could be seen after just two hours. X-ray analysis revealed that 3·LiCl crystals were chiral, belonging to the space group *P*<sub>2</sub><sub>1</sub><sub>2</sub><sub>1</sub><sub>2</sub><sub>1</sub>.

As the formation of chiral crystals of 3·LiCl proceeds directly from the mixture of building blocks, it involves the shifting of a series of interconnected dynamic equilibria. These dynamic processes involve: (a) the reversible reaction of aldehyde with amine to form the imine bond, (b) mutual interconversion of macrocyclic and linear imines, which constitute the multiproduct dynamic combinatorial library, (c) formation of imine complexes with a template, in this case Li<sup>+</sup>, which strongly favours [1+1] macrocycle **3**, and (d) deposition of the complex in the form of crystals (Scheme 2). The first three stages (a)–(c) were common to DCL experiments under thermodynamic control<sup>19</sup> and proceeded in the solution, while the crystallization step occurred when LiCl



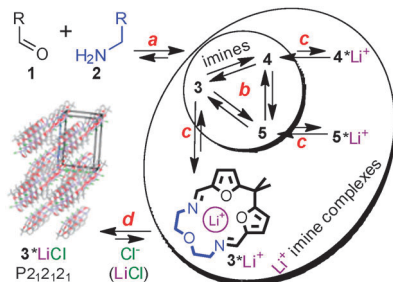
Scheme 1 Formation of (1 + 2)<sup>20</sup> library of macrocycles in MeCN.

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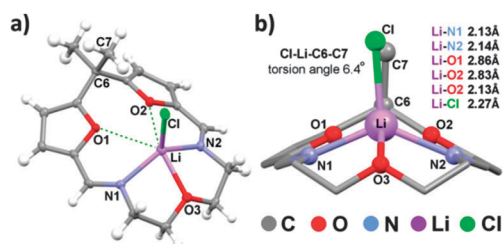
**Scheme 2** Cascade of reversible processes leading to the formation of chiral crystals of **3**-LiCl in a (**1** + **2**) DCL (a) imine formation, (b) imine exchange, (c) complex formation, (d) crystallization.

was used as the template, breaking the “all-in-one-phase” paradigm of Dynamic Combinatorial Chemistry (DCC)<sup>23–25</sup> and ultimately leading to the spontaneous crystallization of **3**-LiCl.

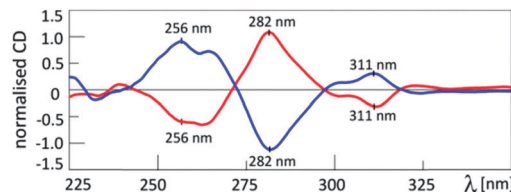
In the solid state, the macrocyclic imine in the **3**-LiCl complex (Fig. 1) adopts a rigid, nearly flat conformation. Despite the fact that a molecule of **3** formally possesses a plane of symmetry, in the solid state it adopts an unsymmetrical conformation (Fig. 1b). **3**-LiCl crystals are composed of a single ‘enantiomer’ of the complex, and are consequently chiral due to the chiral space group symmetry ( $P2_12_12_1$ ). Despite that, the deviation from planar symmetry of **3**-LiCl was rather small, solid state chirality was fully reflected in the chiroptical properties of crystals as measured by circular dichroism (CD), showing bands at  $\sim 260$  nm,  $\sim 280$  nm, and  $\sim 310$  nm (Fig. 2).

Randomly selected crystals showed Cotton effects of opposite sign, clearly evidencing that two enantiomorphs were formed. However, because of the strong absorption<sup>26</sup> and small size of the crystals, which made it necessary to work with very small quantities (0.1–0.2 mg) of **3**-LiCl, and moreover, due to the known limitations of quantitative solid state CD,<sup>27</sup> we were unable to reliably determine the molar CD value. Hence, CD is numerically presented as “normalized CD” (Fig. 2 and 3) and should not be regarded as a precise molar parameter, even though these values were calculated according to the formula for molar CD (and numerically correspond to molar CD). As envisaged, no CD bands were observed for a solution of **3**-LiCl, even immediately after dissolving the crystal (MeCN or DMSO).

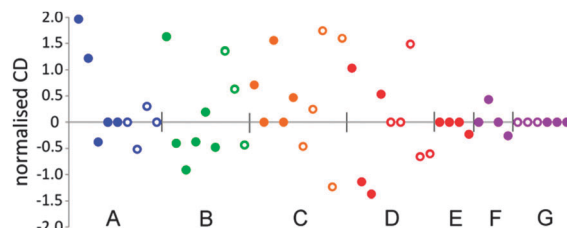
The most unique feature of **3**-LiCl was the CEE we observed for the whole population of crystals from one experiment. We performed 43 reactions in five series, with differing temperatures of crystallization (5, 20, 30, 35, and 40 °C), with or without continuous stirring of the samples during the whole process; in



**Fig. 1** X-ray structure of **3**-LiCl (a) ORTEP representation ( $P = 50\%$ ), (b) “front” view with a list of selected interatomic distances and Li–Cl–C6–C7 torsion angle.



**Fig. 2** CD spectra of two enantiomorphous crystals of **3**-LiCl (KCl pellet).



**Fig. 3** Cotton effects at 280 nm for 51 samples of independent reactions/crystallization of **3**-LiCl at different temperatures: 5 °C (A, blue), 20 °C (B, green), 30 °C (C, orange), 35 °C (D, E, red), 40 °C (F, G, violet), with continuous stirring (empty circles) or without (full circles).

two additional series we repeated the experiments at 35 and 40 °C (8 runs). Following an experiment duration of five days (encompassing reaction and crystallization), all crystals from each sample were powdered and subjected to CD analysis (KCl pellet). The strengths of Cotton effects, measured at 280 nm, are summarized in Fig. 3 and Table 1.

In most of the cases we observed mirror symmetry breaking in the solid state, albeit to a varying extent, depending on the temperature. While around 80% of samples (Table 1) crystallizing in the range of 5–30 °C (A–C) were chiral, this ratio dropped significantly as the temperature increased: to an average of 50% for series D, E at 35 °C and further to 20% at 40 °C (F, G).<sup>28</sup> More interestingly, the data show a small bias toward one enantiomorph (associated with a positive Cotton effect at 280 nm). Qualitatively, this corresponds to 17 *versus* 15 cases (positive *versus* negative) for all of series A–G, while for the A–C series the disparity reached 13 to 9. Importantly, the same trend was reflected by average CD at 280 nm, which was found to be +0.15 when calculated for all of the samples A–G, and +0.30 for the crystallizations performed at lower temperatures (series A–C). When only the 22 chiral samples from the 5–30 °C series (A–C) were taken into account, this value was found to be +0.38.<sup>29</sup> Although in principle, the net effect of multiple crystallizations should be zero as the lattice energy of enantiomorphs is the same, several groups have reported such phenomena for various systems, usually associated with the action of traces of some external chiral impurity.<sup>8,12,30,31</sup> The same cannot be excluded here, although the nature of such a chiral impurity remains unknown. We are aware that more experiments should be performed to confirm the chiral bias unambiguously, preferably in a different “cryptochiral environment” (*e.g.* in a different laboratory). The next important observation is that continuous stirring showed virtually no influence on the symmetry breaking phenomena. The role of mechanical stimulation in chiral amplification was first highlighted by Kondepudi<sup>6</sup> for NaClO<sub>3</sub> crystallizations and was attributed to secondary nucleation by fragments of “parent” crystal

Table 1 Average cotton effects<sup>a</sup> measured at 280 nm

Series	All samples		Only chiral samples		Only “+” 280 nm <sup>b</sup>		Only “−” 280 nm <sup>b</sup>	
	Count <sup>c</sup>	Mean CD <sup>d</sup>	Count <sup>c</sup>	Mean CD <sup>d</sup>	Count <sup>c</sup>	Mean CD <sup>d</sup>	Count <sup>c</sup>	Mean CD <sup>d</sup>
A–C (5–30 °C)	28	0.30	22 (79%)	0.38	13 (46%)	1.05	9 (32%)	−0.58
D, E (35 °C)	13	−0.07	8 (62%)	−0.12	3 (23%)	1.02	5 (38%)	−0.80
F, G (40 °C)	10	0.02	2 (20%)	0.09	1 (10%)	0.43	1 (10%)	−0.26
A–G (5–40 °C)	51	0.15	32 (63%)	0.24	17 (33%)	1.01	15 (29%)	−0.63

<sup>a</sup> As “normalized CD”. <sup>b</sup> “+” or “−” depict chiral samples associated with positive or negative sign (respectively) of Cotton effect at 280 nm.

<sup>c</sup> Number of samples and % of total. <sup>d</sup> Mean CD value for all samples in the category.

of single chirality. More recently, Viedma<sup>7,9,32</sup> developed a universal methodology (“Viedma ripening”) that utilised constant grinding and dissolution of crystals in a saturated solution and allows for solid state enantiopurity *via* Ostwald ripening coupled with enantiomer specific oriented attachment. Applying Viedma’s approach, Cuccia<sup>16</sup> showed complete deracemisation of 10 arbitrarily selected common achiral compounds, crystallizing in chiral space groups. However, in our experiments we use no grinding medium (*e.g.* glass beads) other than a stirring bar, which may not provide sufficient attrition. Additionally, the experiment duration might have been too short,<sup>33</sup> although this is limited by imine stability.

To rule out polymorphism of the complex, chiral and achiral crystal samples were independently characterized by X-ray powder diffraction. The diffractograms (ESI) were almost identical and consistent with the simulated powder diffraction spectrum derived from the monocrystal of 3·LiCl. This proved that crystals of 3·LiCl exist in one form and the samples were not contaminated with any other crystalline material.

From our previous studies,<sup>19,34</sup> we had on hand two close analogues of the 3·LiCl complex, one differing in terms of the aldehyde used (6·LiCl, Fig. 4a) and the second being a complex of imine 3 with NaClO<sub>4</sub>. In both cases, crystallization was not spontaneous and required slow diethyl ether diffusion into the corresponding libraries. In crystals of 3·NaClO<sub>4</sub> and 6·LiCl, complexes are not symmetric on a molecular level, but the crystals are achiral (*P2<sub>1</sub>/n* and *Cc* space groups, respectively). In 6·LiCl, the more bulky ethyl (C17, C18) is located next to the chloride, rather than methyl (C16), hence we assume that steric factors (such as chloride–alkyl repulsion) are not responsible for the lack of symmetry of the complexes (6·LiCl and 3·LiCl).

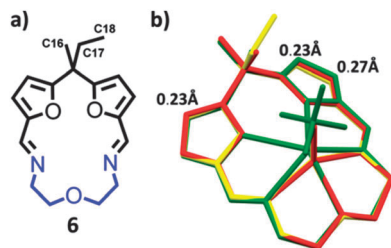


Fig. 4 (a) Imine 6 (b) superimposition of X-ray structures of 3·LiCl (yellow), 3·NaClO<sub>4</sub><sup>19</sup> (red) and 6·LiCl<sup>34</sup> (blue) using macroring heteroatoms for RMS overlay (only highest distances among the corresponding atoms presented).

Interestingly, the macrocycle geometry is virtually the same for all crystals investigated – 3·LiCl, 3·NaClO<sub>4</sub>, and 6·LiCl. Fig. 4b shows superimposition of the above structures by root mean square (RMS) overlay using the corresponding macrocycle heteroatoms; the longest distance among the equivalent non-hydrogen atoms is 0.27 Å.

We also managed to obtain monocrystals of 3·LiClO<sub>4</sub> by slow vapour–vapour diffusion of diethyl ether into a pre-equilibrated LiClO<sub>4</sub> templated (1 + 2) library in MeCN. In terms of its composition, this complex lies between 3·LiCl and 3·NaClO<sub>4</sub>. The asymmetric unit of 3·LiClO<sub>4</sub> contains two molecules of the complex (the well-defined “A”, Fig. 5a, and the disordered “B”, Fig. 5b). The geometry of both “A” and “B” macrocycles was found to be the same as in the above-described complexes of [1+1] macrocycles 3 and 6. In particular, RMS overlay by macroring heteroatoms (Fig. 5c) showed that differences in the positions of the corresponding atoms in 3·LiCl and 3·LiClO<sub>4</sub> “A” are no greater than 0.14 Å.

A comparison of 3·LiClO<sub>4</sub> with 3·NaClO<sub>4</sub> shows an even higher degree of similarity, as, in terms of crystal packing, both complexes are isostructural (ESI<sup>†</sup>), although solving and refining the 3·LiClO<sub>4</sub> structure in the *Pn* space group was numerically better

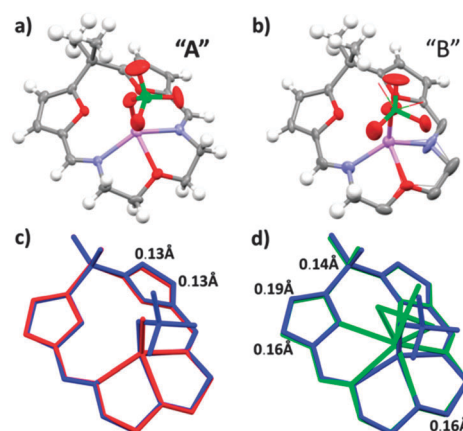


Fig. 5 X-ray structure of 3·LiClO<sub>4</sub> (a) and (b) ORTEP representation (*P* = 50%) of crystallographically independent molecules: “A” and disordered “B”, disordered hydrogens and solvent molecules omitted for clarity, atom colour codes are the same as in Fig. 1. Superimposition of X-ray structures of 3·LiClO<sub>4</sub> “A” (blue) and (c) 3·LiCl (red), and (d) 3·NaClO<sub>4</sub> (green). In (c) and (d) macroring heteroatoms were used for RMS fitting (only the highest distances between the corresponding atoms are presented).

than in the higher-symmetry group  $P2_1/n$  (as for 3-NaClO<sub>4</sub>). The packing similarity may be attributed, in this case, to the shared geometry of complexes at the molecular level (Fig. 5d), and hence to shared exposed surfaces for crystal packing interactions. It is worth noting that for the other closely structurally related pair, 3-LiCl and 6-LiCl, the same packing scheme seems to be prohibited by the steric hindrance created by an additional carbon atom in imine 6.

A major observation that can be drawn from comparing the four presented crystal structures is that the macrocycle geometry is locked and apparently independent both of the cationic guest and its counterion, and of structural modification of the aldehyde part (methyl vs. ethyl “side-chain”). Neither was the macrocycle geometry altered in different crystal lattices. Hence, conversely, the packing, and in the particular case of 3-LiCl, the emergence of solid state chirality, must be controlled to a high degree by parameters “external” to the macrocycle (cation, anion, structural variations outside the core of the macrocyclic). We believe that robust and chemically inert molecules with “stable” covalent bonds serve as convenient models to test the influence of a variety of crystallization conditions on CEE. The unique advantage of highly dynamic systems such as that presented here lies in the synthetic ease with which various structural analogues can be prepared to probe the influence of the molecular structure on solid state behaviour. In a crystallization of imine complexes, we can consider aldehyde, amine, templating cation and anion as independent and readily exchangeable constituents of a mixture, creating a 4-dimensional space for such studies. Further research, concerning mostly the role of cation and anion, is underway.

We have demonstrated that solid state chirality and the symmetry breaking phenomenon can emerge from a system consisting of very simple achiral substrates plus a template, which are involved in a set of interconnected dynamic equilibria. In this respect, there is an analogy to biological systems, where a set of simple building blocks is involved in a network of formally simple relations, the combination of which leads to advanced information (in this case, chirality). The outcome of the process cannot be simply deduced or predicted just by knowing the initial state of a system. On the other hand, the dynamic combinatorial “nature” of the 3-LiCl complex, which enables easy structural modifications *via* independent alteration of its building blocks, makes it a convenient model for studying the influence of the various aspects of molecular structure on the mirror symmetry breaking.

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