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

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Electronic Supplementary Information

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1. Synthetic and crystallization protocols

Preparation of libraries was described in details in refs 19 and 34. In brief - separate solutions of aldehyde 1 and amine 2 were prepared in HPLC grade MeCN (both solutions were 100mM), mixed (the final concentration of each substrate was thus 50mM) and immediately added to vials containing weighted amount of 2 equivalents of templates (LiCl or LiClO₄·H₂O). Vials were capped and left to react at room temperature for 2 days. Composition of libraries and crystals was examined by HPLC according to previously presented protocols (refs 19, 34).

Figure S1. HPLC traces of the corresponding secondary libraries of amines, obtained upon NaBH₄/H₂O/TFA reduction (refs 19,34) of parent (1+2) imine libraries in MeCN. a) non-templated library, b) LiClO₄·H₂O (2 equivs) templated, c) solution taken from LiCl (2 equivs) templated library, d) 3*LiCl crystal dissolved in MeCN.

Crystallization of complexes. In case of 3*LiCl the first crystals could be spotted within 2 hours. After 2 days the solvent was carefully removed by a syringe, crystals were quickly washed with 5 portions of MeCN. Yield of reaction/crystallization: 60-70%. 3*LiCl was stored under a small amount of MeCN in a fridge.

In case of 3*LiClO₄ after 2 days of equilibration the library mixture was filtrated through 45μm syringe filter and subjected to slow diethyl ether diffusion (vapour/vapour).

Crystals of 3*NaClO₄ and 6*LiCl were described in refs 19 and 34, respectively.

Solubility of 3*LiCl was determined spectrophotometrically using (1+2) library in MeCN templated with LiClO₄·H₂O as a reference and assuming the same absorption of 3*LiCl and 3*LiClO₄ complexes. Solubility of 3*LiCl in pure acetonitrile is 0.0054M (1.85mg/ml).

3*LiCl and 3*LiClO₄ X-ray crystallography, monocrystals. Measurements of crystal were performed on a KM4CCD κ-axis diffractometer with graphite-monochromated MoKα radiation. The crystals was positioned at 62 mm from the CCD camera.

For 3*LiCl crystal, 2400 frames were measured at 0.5° intervals with a counting time of 4 sec.

For 3*LiClO₄ crystal, 1800 frames were measured at 0.5° intervals with a counting time of 10 sec.

The data were corrected for Lorentz and polarization effects. Empirical correction for absorption was applied. Data reduction and analysis were carried out with the Oxford Diffraction programs.

The structures was solved by direct methods and refined using SHELXL. The refinement was based on R² for all reflections except those with very negative F². Weighted R factors wR and all goodness-of-fit S values are based...
on \(F^2\). Conventional R factors are based on \(F\) with \(F\) set to zero for negative \(F^2\). The \(\text{F}^2 > 2\sigma(\text{F}^2)\) criterion was used only for calculating R factors and is not relevant to the choice of reflections for the refinement. The R factors based on \(F^2\) are about twice as large as those based on \(F\). All hydrogen atoms were located geometrically and their position and temperature factors were refined. Scattering factors were taken from Tables 6.1.1.4 and 4.2.4.2 in ref. S5.

\(3^*\text{LiClO}_4\) crystallized as a racemic twin with refined contribution of one component of 0.50(5). Highly disordered solvent, probably acetonitrile, was refined isotropically as carbon atoms, no hydrogens were included.

References:

\(3^*\text{LiCl}\) X-ray crystallography, powder diffraction. Chiral (from series “A”) and achiral (from series “G”) crystal samples of \(3^*\text{LiCl}\) were characterized by X-ray powder diffraction (XRD), using a Siemens D5000 device with monochromatic CuK\(\alpha\) radiation (\(\lambda = 1.5418\) Å). The tube current (40 mA), tube voltage (40 kV), step width (0.02°), preset time (0.6 s), and scan rate (1.0° min\(^{-1}\)) were applied to record the patterns in the 2\(\Theta\) range of 2-50°.

2. Circular dichroism experiments

Solid state CD experiments were carried out on JASCO J-715 with continuous rotation of a tablet. Each tablet composed of finally powdered 100mg of KCl and 0.1-0.25mg of \(3^*\text{LiCl}\) crystals. The samples were examined for linear dichroism (LD) contribution. Smoothing and baseline correction was applied prior to calculation of “normalized CD” (molar CD, Jasco Spectra Manager ver 1.52).

The magnitude of Cotton effects at 280nm (as “normalized CD”) form S1 independent crystallizations (Figure 3, main text) are as followed:

Series A (5°C); unstirred samples: 1.96, 1.22, -0.38, 0, 0; stirred samples: 0, -0.52, 0.30, 0.
Series B (20°C); unstirred samples: 1.63, -0.40, -0.91, -0.37, 0.19, -0.48; stirred samples : 1.36, 0.63, -0.43.
Series C (30°C); unstirred samples: 0.71, 0, 1.56, 0, 0.47; stirred samples: -0.46, 0.24, 1.74, -1.24, 1.60.
Series D (35°C), unstirred samples: 1.03, -1.14, -1.37, 0.53; stirred samples: 0, 0, 1.49, -0.66, -0.60.
Series E (35°C), unstirred samples: 0, 0, 0, -0.23.
Series F (40°C), unstirred samples: 0, 0.43, 0, -0.26.
Series G (40°C), unstirred samples: 0, 0, 0, 0; stirred samples: 0, 0, 0, 0.
3. Crystal data for $3\text{ LiCl}$, $3\text{ LiClO}_4$ and packing comparison for $3\text{ LiClO}_4$ and $3\text{ NaClO}_4$

Crystal data for $3\text{ LiCl}$: Empirical formula: $C_{17}H_{20}ClLiN_2O_3$, Formula weight: 342.74, Temperature: 100(2) K, Wavelength: 0.71073 Å, Crystal system: rhombic, Space group: $P2_12_12_1$, Unit cell dimensions: $a$ 7.7015(2) Å, $b$ 12.0371(3) Å, $c$ 18.2095(6) Å, $\alpha$ 90°, $\beta$ 90°, $\gamma$ 90°, Volume: 1688.09(8) Å$^3$, Z: 4, Absorption coefficient $i$: 0.243 mm$^{-1}$, F(000): 720, Crystal size: 0.53 x 0.20 x 0.18 mm, Theta range for data collection: 2.81 to 28.70°, Limiting indices: -10 ≤ h ≤ 10, -15 ≤ k ≤ 15, -24 ≤ l ≤ 24, Reflections collected / unique: 31607 / 4191 [R(int) = 0.0206], Absorption correction: not applied, Refinement method: Full-matrix least-squares on F$^2$, Data / restraints / parameters: 4191 / 0 / 297, Goodness-of-fit on F$^2$: 1.003, Final R indices [I>2sigma(I)]: R1 = 0.0221, wR2 = 0.0531, R indices (all data): R1 = 0.0254, wR2 = 0.0536, Absolute structure parameter: 0.00(3), Largest diff. peak and hole: 0.204 and -0.175 e*Å$^{-3}$. CCSD refcode: 1039906.

Crystal data for $3\text{ LiClO}_4$: Empirical formula: $C_{37}H_{40}Cl_2Li_2N_4O_{14}$, Formula weight: 849.51, Temperature: 100(2) K, Wavelength: 0.71073 Å, Crystal system: monoclinic, Space group: $Pn$, Unit cell dimensions: $a$ 7.6122(2) Å, $b$ 18.1368(6) Å, $c$ 14.7510(5) Å, $\alpha$ 90°, $\beta$ 96.894(2)°, $\gamma$ 90°, Volume: 2021.81(11) Å$^3$, Z: 2, Absorption coefficient $i$: 0.232 mm$^{-1}$, F(000): 884, Crystal size: 0.55 x 0.17 x 0.16 mm, Theta range for data collection: 2.64 to 28.73°, Limiting indices: -10 ≤ h ≤ 10, -24 ≤ k ≤ 24, -19 ≤ l ≤ 19, Reflections collected / unique: 28166 / 9508 [R(int) = 0.0189], Absorption correction: Semi-empirical, Refinement method: Full-matrix least-squares on F$^2$, Data / restraints / parameters: 9508 / 271 / 593, Goodness-of-fit on F$^2$: 1.034, Final R indices [I>2sigma(I)]: R1 = 0.0454, wR2 = 0.1220, R indices (all data): R1 = 0.0601, wR2 = 0.1261, Largest diff. peak and hole: 0.788 and -0.534 e*Å$^{-3}$. CCSD refcode: 1039907.

Figure S2. Packing in crystals of $3\text{ LiCl}$. Projections along: a) $x$, b) $y$, and c) $z$ crystallographic axes. Hydrogens omitted for clarity.
Figure S3. Packing in crystals of 3*LiClO$_4$ (left) and 3*NaClO$_4$ (right). Green and blue colors correspond to: two crystallographically independent molecules of complex for 3*LiClO$_4$ ("A" green, "B" blue) and the same (one) independent molecule for 3*NaClO$_4$ colored to highlight similarities between the two structures. Hydrogens omitted for clarity. Projections along: a) $x$, b) $y$, and c) $z$ crystallographic axes.
4. Powder diffraction patterns of 3*LiCl crystal

Figure S4. 3*LiCl powder diffractograms; X-axis: 2Θ, Y-axis: normalized intensity, independently for 5-30° and 30-50° angles; a) calculated from the monocrystal, b) measured for the combined chiral samples c) measured for the combined achiral samples