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Metal-Induced Supramolecular Chirality Inversion of Small Self-Assembled Molecules in Solution

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Zoran Kokan,[a,*] Berislav Perić,[a] Mario Vazdar,[a] Željko Marinić,[a] Dražen Vikić-Topić,[a] Ernest Meštrović,[b] and Srećko I. Kirin[a,*]

Non-covalent self-assembled chiral alanyl aminopyridine ligand exhibits supramolecular chirality in solution, independent of the organic solvent used. The supramolecular chirality of the assemblies is completely inverted by complexation to zinc ions. Up to now, such supramolecular metal-ligand system has not been reported in the literature.

Controlling the chirality of supramolecular systems is essential not only for understanding the role of chirality in biological environment, but also due to its increasing importance in the fields of sensing, optics, electronics, and catalysis.[1] Especially appealing is the precise regulation of the chirality inversion, successfully achieved by employing metal coordination,[2a] anions,[2b,c] host-guest interactions,[2d] solvent,[2e] concentration,[2f] redox reactions,[2g] sonication,[2h] pressure,[2i] temperature,[2j] and light irradiation.[2k,l] However, research on the chirality inversion of self-assembled systems driven by weak non-covalent interactions (*e.g.* hydrogen bonding, aromatic, and ionic interactions) has been conducted mostly for large discotic,[3a] dendritic,[3b,c] and gelator molecules.[3d] Metal mediated chiral inversion in solution on the other hand is exclusive to oligo- or polymeric compounds.[2a,4]

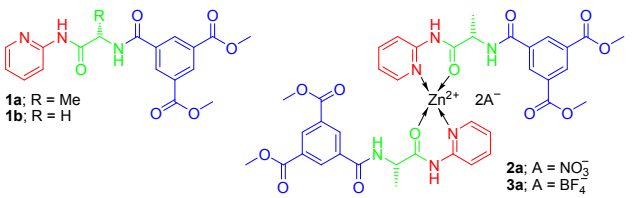
Amino acids represent a convenient source of chirality and are known to induce helicity in aromatic foldamers,[5a] as well as form chiral supramolecular assemblies.[5b–d] Also, strong enantioselective recognition has been reported for simple amino acid derivatives, in the solid state.[6,7] In addition, 2-acylaminopyridine derivatives self-organise in a predictable fashion in both solution and solid state.[8] Despite these findings, amino acid derivatives of acylaminopyridines in supramolecular systems are extremely scarce.[9]

In recent literature on chiral supramolecular catalytic systems,[10] hydrogen bonding plays a prominent role in inducing selectivity of the reaction. Therefore, it is of great importance to investigate the chiral properties of such hydrogen-bonded ligand systems.

Herein, we present an unprecedented hydrogen-bonded system exhibiting supramolecular chirality which can be inverted by zinc complexation. The system is comprised of cheap and readily available building blocks (*e.g.* amino acids, pyridines, simple organic acids, and metal salts), allowing fast and robust synthesis in comparison to large macromolecular systems where tedious synthetic and purification procedures are often necessary. To the best of our knowledge, this is the first example of a metal-induced supramolecular chirality inversion of weak, non-covalent, small molecule assemblies in solution.[1a,2a,4]

The organic ligands (**1**) were synthesized by standard peptide coupling procedures and purified by automated flash chromatography. The complexes (**2** and **3**), prepared by shortly heating the acetonitrile solution of the ligand and zinc salt in 2:1 ratio, were obtained in quantitative yield, as determined by ^{1}H NMR spectroscopy. The ligands are coordinated to zinc in a bidentate fashion through acylaminopyridine moieties (Scheme 1), indicated by ^{13}C NMR (amide shifted downfield for 4.9 ppm and pyridine carbon atoms up to 1 ppm) and FT-IR measurements (see later in text).

Single crystals of D-**1a** were obtained by slow diffusion of hexane into a dichloromethane solution. Crystals with identical unit cell parameters were also obtained from acetonitrile. Infinite *P*-helical hydrogen-bondedpattern was found in the crystal structure of D-**1a** (Figure 1). According to the Bernstein-Davis notation,[12] a single pseudo-4_1-helix turn is comprised of four $R_2^2(10)$ hydrogen-bonded dimers, adopting a "Herick



Scheme 1. The ligands (**1**) and complexes (**2** and **3**). Detailed synthetic procedures are given in the Electronic Supplementary Information (ESI).

[a] Ruđer Bošković Institute, Bijenička c. 54, 10000 Zagreb, Croatia
[b] PLIVA Croatia d.o.o., Prilaz baruna Filipovića 25, 10000 Zagreb, Croatia
*E-mail: zoran.kokan@irb.hr, srecko.kirin@irb.hr

Electronic Supplementary Information (ESI) available: Synthetic procedures, crystallographic data in cif format, CCDC 1511324, comprehensive spectroscopic characterisation, and computational details. See DOI: 10.1039/x0xx00000x

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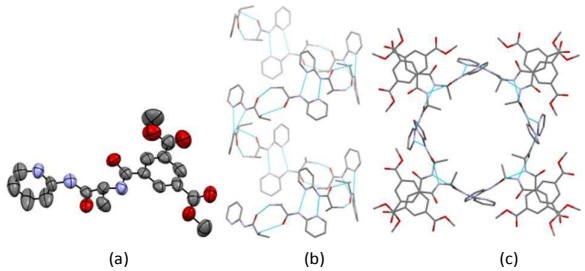

Figure 1. (a) Molecular structure of D-**1a** (space group $P2_12_12_1$); (b) side (phenyls omitted for clarity) and (c) top view of alternating hydrogen bond patterns showing *P*-helicity and pseudo-4_1-symmetry in the single crystal structure.

conformation",[13] interconnected through $R_2^2(8)$ hydrogen-bonded aminopyridine moieties. It is interesting to mention that the "Herrick conformation" is often found in the structures of small organic[7] and inorganic[10b–d,13] bioconjugates.

Molecular dynamics (MD) simulations were performed for ligands **1a** in chloroform or acetonitrile, with the total simulation length of 500 ns. Initial configuration was generated using independently dissolved molecules. After 100–200 ns, the molecules of **1a** start to associate through intermolecular hydrogen bonding and π-π stacking (Figure S4) forming linear supramolecular assemblies in solution (Figure S3),[14] similarly observed in the solid state (Figure 1b).

Intermolecular hydrogen bonding for ligand **1a** and complex **2a**, in chloroform or acetonitrile, was confirmed by variable concentration and temperature ^{1}H NMR measurements. Noticeable disposition of the amide NH proton signals was observed (Figure 2), strongly indicating molecular association.[15] Two-dimensional ROESY and NOESY NMR measurements of **1a** in chloroform (Figures S22–24) at 40 mM showed cross-peaks not observed at 4 mM concentration, also confirming molecular association at higher concentration. These spectra indicate similar arrangement of **1a** molecules in solution and solid state (Figure S26). In addition, ROESY spectra of **2a** in acetonitrile at high concentration exhibit minor differences with respect to **1a** (Figures S25,27), also indicating similar arrangement of the molecules in solution.

Diffusion ordered NMR measurements[16a] of **1a** and **2a** in acetonitrile at two different concentrations showed the reduction of diffusion coefficients upon increasing concentration,[17] further supporting molecular association.[16b]

A more detailed insight into the hydrogen bonding of **1a** was obtained by variable concentration FT-IR measurements in chloroform or dichloromethane. The amide N–H vibrations

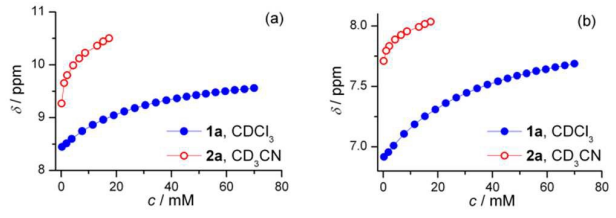

Figure 2. Variable concentration ^{1}H NMR of **1a** and **2a**, showing intermolecular hydrogen bonding of (a) pyridine and (b) alanine NH amides. The solvents and concentration ranges were chosen in accordance with solubility.

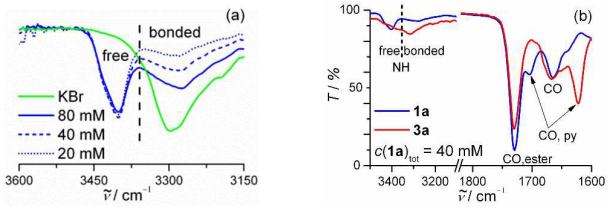

Figure 3. FT-IR: (a) N–H vibrations **1a**, showing intermolecular hydrogen bonding in solution (dichloromethane; corrected for concentration) and solid state (KBr); (b) hydrogen bonding and pyridine C=O amide shift of **3a** in dichloromethane.

were observed at 3407 and 3275 cm^{-1} indicating free and hydrogen-bonded amide, respectively (Figure 3a).[18] For the zinc complex it was necessary to use the tetrafluoroborate salt (**3a**) to rule out a possible interference of the nitrate ion in hydrogen bonding. The FT-IR of **3a** in dichloromethane (Figure 3b) shows a broad peak at 3315 cm^{-1} also indicating hydrogen-bonded amide protons. Acylaminopyridine derivatives often act as bidentate ligands, supported by the crystal structures of various complexes.[19] The shift of the amide C=O band from 1704 in **1a** to 1622 cm^{-1} in **3a** is characteristic of amide coordination through the oxygen atom, in support to the bidentate coordination mode. Since tetrafluoroborate and dichloromethane are very weakly coordinating species,[20] a tetrahedral zinc coordination sphere is implied, commonly found in biological systems.[21]

Supramolecular association of **1a** in different solvents could be monitored by variable concentration CD spectroscopy (Figure 4a,b). Stepwise changes in the CD spectra were observed (Figure S27), strongly indicating different association processes: 1) increase of the absorption maxima at 254 and 278 nm (< 10 mM) and subsequent disappearance, attributed to the first step of association (most probably formation of smaller aggregates, *e.g.* dimers); 2) gradual appearance of a new absorption band at 283 nm (> 10 mM), attributed to the formation of higher associates. Variable temperature CD measurements of **1a** in acetonitrile showed minor changes in the CD spectra (Figure S30). Even in methanol (a hydrogen bond competitive solvent) the CD spectra of **1a** (Figure 4c)

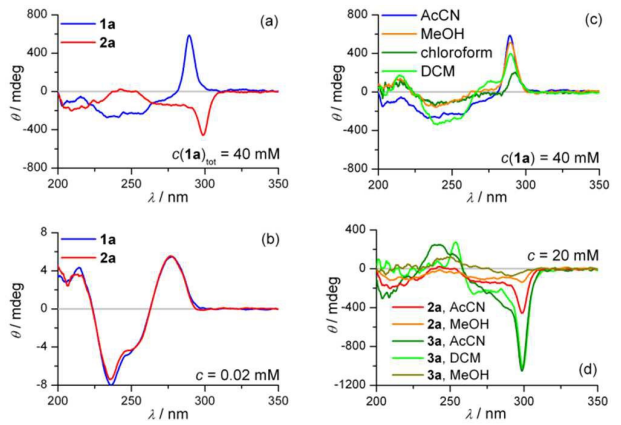

Figure 4. Variable concentration CD in acetonitrile of **1a** and **2a** at (a) high concentration and (b) dilution; (c) CD of **1a** in different solvents; (d) solvent and anion influence on the CD ofzinc complexes (**2a**, nitrate; **3a**, tetrafluoroborate).

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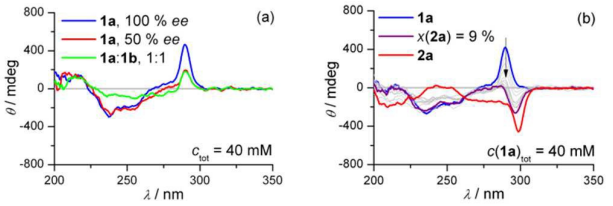
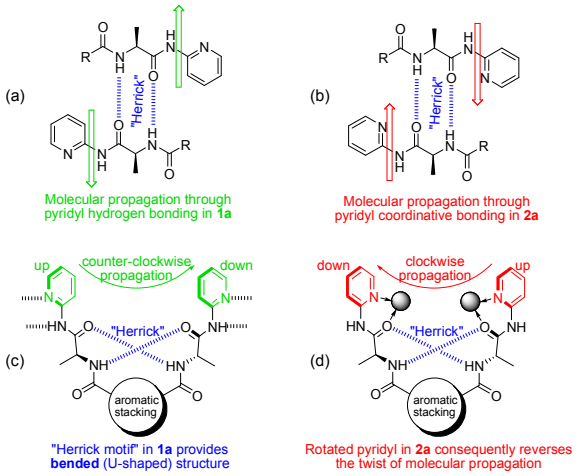


Figure 5. CD spectra in acetonitrile of (a) ligand mixtures with different content of chiral **1a**; (b) **2a** addition to **1a** exhibiting "Sergeant and Soldiers Principle".[3a,23]



Scheme 2. A plausible explanation for the origin of chiral inversion. Substituting (a) pyridyl hydrogen bonding in **1a** for (b) metal coordination in **2a** changes the direction and reverses (c, d) the twist of molecular propagation, consequently inverting supramolecular chirality of the assemblies. (R = phenyl moiety)

resemble of those in acetonitrile, showing that association is also present. CD intensities indicate that polar solvents favour molecular association. This in turn suggests that alongside hydrogen bonding, additional non-polar interactions such as π-π stacking might play a significant role in **1a** assemblies.

Very surprisingly, at higher concentrations, **2a** shows complete inversion of the CD spectra with respect to **1a** (Figure 4a). Similarity of **1a** and **2a** CD spectra at high dilution (Figure 4b) excludes the possibility of inversion being induced by conformational rearrangement of the chromophores[22] upon metal coordination. Clearly, chiral inversion is exhibited only in the supramolecular assemblies. In methanol however, the CD spectra of zinc complexes (**2a** and **3a**) show a major reduction of the 299 nm band (Figure 4d), emphasizing the importance of hydrogen bonding. This is also apparent if nitrate (**2b**) and tetrafluoroborate (**3b**) complexes are compared, since nitrate can compete for hydrogen bonding.

To gain insight into the nature of electronic transitions around 290 nm, UV spectra of **1a** and **2a** were recorded in conjunction with TD-DFT calculations (Figures S35–40). Upon zinc complexation, red shift (6 nm) of pyridyl π-π* transition observed by calculations is also evident in the CD spectra (10 nm) of **1a** and **2a** (Figure 5b), implying that the CD maxima at ≈ 300 nm in **1a** and **2a** originate from the same pyridyl π-π* transitions.

To elucidate the origin of chirality inversion (Scheme 2), the following assumptions supported by experimental techniques were made: 1) zinc is tetrahedrally coordinated through acylaminopyridine moieties (IR, ^{13}C NMR); 2) **1a** and **2a** molecules in the assemblies are similarly arranged (ROESY, CD; *e.g.* "Herrick motif"). The minimal structural element presumably describing helical organisation of molecules in solution was taken from the X-ray crystal structure of **1a** (½ helix turn). Next, modification of the ligand conformation was done by 180° rotation of the pyridyl moiety to accommodate for zinc complexation, and the structure was optimised by DFT calculations (Figure S45). Consequently, the molecules in **2a** could only be arranged in the opposite helicity sense through distorted-tetrahedral zinc coordination with respect to **1a**, in agreement with the experimentally observed CD inversion.

We further tested whether the mixture of chiral (**1a**) and nonchiral (**1b**) or racemic ligands (rac-**1a**) could give some insight into molecular associations through chirality induction. Interestingly, a 1:1 mixture of **1a**:**1b** or **1a**:rac-**1a** in acetonitrile resulted in reduced intensity of the peak at 290 nm (Figure 5a). The CD spectra of the mixtures do not match with spectra of pure **1a** at the corresponding concentrations, but show a proportionally reduced intensity of the 290 nm peak with respect to the amount of chiral **1a**. This implies that **1b** or rac-**1a** molecules play a structural role in the **1a** assemblies but do not contribute to the CD signal – hence, no chiral induction is present.

Since concentration dependant CD spectra of ligand **1a** and complex **2a** exhibit similar features (along with the experimental and calculated data), suggesting similar structural features in solution, a test was performed whether small amounts of **2a** can control the chiral response of **1a**. Surprisingly, less than 10 mol% of **2a** was enough to completely invert the 290 nm band (Figure 5b). The region from 200 to 275 nm remained virtually intact, suggesting that one part of the supramolecular chirality is fixed (*i.e.* a "Herrick" dimer) and the other is controlled by zinc coordination (*i.e.* exchanging aminopyridyl hydrogen bonding with coordinative bonds). Similar spectra were obtained when tetrafluoroborate (**3a**) was used instead of the nitrate (**2a**) salt (Figure S34a).[1]H NMR spectrum of a **2a**/**1a** mixture (10 mol%) in acetonitrile-d_3, showed only one set of signals (Figure S29), suggesting a fast ligand exchange at zinc on the NMR time scale. If "Sergeant and Soldiers Principle"[3a,23] is applied, the zinc ions themselves, rather than the complex **2a**, play the "sergeant" in charge of the supramolecular organisation of **1a** molecules as the "soldiers".

In summary, it was shown that the non-covalent assemblies of chiral acylaminopyridine ligands exhibit supramolecular chirality in organic solvents of different polarities and hydrogen bonding propensities, as well in the solid state. When complexed to zinc, the assemblies exhibit inverted supramolecular chirality in solution, even with sub-stoichiometric zinc quantities. Hydrogen-bonding is shown to have important role in the supramolecular assemblies of both ligand and complex. A plausible explanation for the chirality inversion was assessed by experimental and computational methods. This research represents a unique system where

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supramolecular chirality of small molecule assembly in solution can be inverted by complexation to metal ions.

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17 DOSY measurements were recorded in acetonitrile-d_3 for **1a** (1.45×10^{-9} m^2 s^{-1}, 28 mM; 1.51×10^{-9} m^2 s^{-1}, 5.4 mM) and **2a** (1.09×10^{-9} m^2 s^{-1}, 14 mM; 1.26×10^{-9} m^2 s^{-1}, 2.6 mM).

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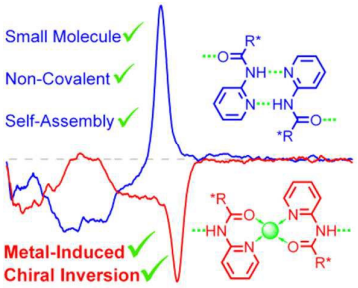

The first example of supramolecular chirality inversion of small self-assembled ligands in solution by complexation to metal ions is presented.