

Unidirectional helical assembly via triple hydrogen bonds between chiral tris(oxazoline) and achiral tris(imidazoline)

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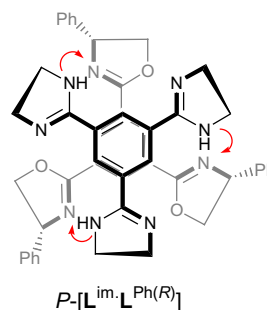
Abstract—Tris(imidazolines) are assembled via triple hydrogen bonding interactions to give rise to a stacked polymeric structure. A mixture of chiral tris(oxazoline) and achiral tris(imidazoline) generates a helical assembly in which the helical direction of the assembly is unidirectionally induced by the chirality of tris(oxazoline).

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Hydrogen bonding and aromatic stacking interactions are the main forces for the assembly of biomolecules such as nucleic acids and proteins. Many artificial helices have been constructed for mimicking natural helical structures using H-bonding and/or metal–ligand coordination interactions.¹ In this paper we report on helical structures self-assembled via H-bonding and π – π stacking interactions between chiral tris(oxazoline) and achiral tris(imidazoline) as seen in a real DNA duplex system, and the unidirectional helicity induced by the chiral oxazoline unit (Scheme 1).

In a previous study, we have found that the chiral tris(oxazoline) unit in a metal-mediated supramolecule of $[\text{Ag}_3\text{L}_2^{\text{Me}}]$ induces the helical direction in a predictable way: The $\text{L}^{\text{Me}(S)}$ unit drives *M*-helicity whereas the $\text{L}^{\text{Me}(R)}$ unit drives *P*-helicity in the self-assembled supramolecule.² Molecular modeling revealed that replacing metal–ligand interactions with H-bonding interactions would also generate a helical assembly. Tris(imidazoline)³ and tris(oxazoline)⁴ were prepared as H-bond donors/acceptors and acceptors, respectively.

Nonpolar solvents were employed throughout the study in order to maintain H-bonds and render the aromatic



Scheme 1. Schematic representation of hydrogen-bonded and π – π stacked helical structure. Note the induced helicity of tris(imidazoline) by the chirality of tris(oxazoline). L^{im} is tris(imidazoline) ligand and $\text{L}^{\text{Ph}(R)}$ is tris(oxazoline) ligand that has a Ph group with *R* configuration.

stacking interaction between tris(imidazoline) and tris(oxazoline) effective. Whilst the tris(oxazoline) seems to exist in a monomeric state, the tris(imidazoline) is likely to be in a dimeric or polymeric state through intermolecular H-bonds in a nonpolar solvent such as chloroform. However, because the tris(imidazoline) is highly insoluble in nonpolar solvents such as chloroform, dichloromethane, or acetonitrile, methanol was used as solubilizing solvent. Solvent polarity was varied by changing the composition of methanol and chloroform in NMR spectroscopy. Both aromatic and ethylene protons of tris(imidazoline) shift downfield when the chloroform ratio in a methanol solution is increased: $\Delta\delta$

Keywords: Helical assembly; Hydrogen bond; Tris(oxazoline); Tris(imidazoline).

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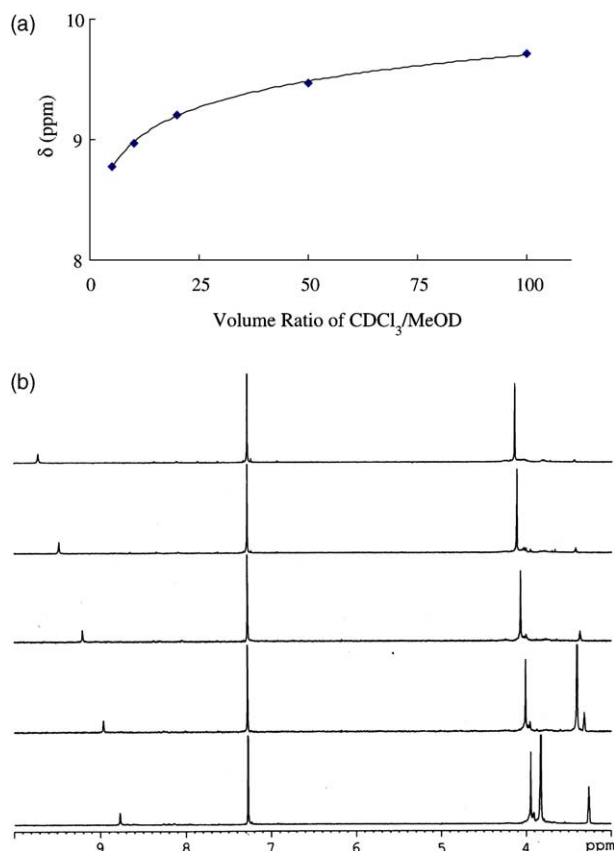


Figure 1. Stacked ^1H NMR spectra of 2.0 mM tris(imidazoline). The peaks at 8.7–9.7 ppm is for aromatic protons, 3.9–4.1 ppm for ethylene protons, and 3.0–3.9 ppm for methanol protons. The solvent ratio of $\text{CDCl}_3/\text{CD}_3\text{OD}$ (v/v) from bottom to top: 5/1; 10/1; 20/1; 50/1; 100/1. Chemical shifts of the aromatic proton of tris(imidazoline) are plotted against volume ratio of $\text{CDCl}_3/\text{CD}_3\text{OD}$ in the inset.

(ppm) = +0.94, +0.20 for aromatic and ethylene protons, respectively. These phenomena are attributable to the increased population of π – π stacked hydrogen-bonded dimeric or polymeric structures of tris(imidazoline) in nonpolar solvent. Whereas the monomer structures are presumably prevalent in a polar solvent of 5:1 CDCl_3 and CD_3OD , the dimeric and polymeric structures are more effectively formed when increasing the ratio of nonpolar solvent, such as chloroform, which is clearly shown in the inset of Figure 1.

We then performed NMR experiments in nonpolar solvent to obtain the evidence for H-bonding interaction in the heterodimer between tris(imidazoline) and tris(oxazoline): three samples of 4 mM of tris(imidazoline), 4 mM of tris(oxazoline) and a mixture of 4 mM of tris(imidazoline) and 4 mM of tris(oxazoline) in chloroform were prepared. NH protons in the mixture of tris(imidazoline) and tris(oxazoline) displayed an upfield shift (–0.31 ppm) with a broadening of the peak relative to the tris(imidazoline) solution. This implies that H-bonds in the tris(imidazoline) dimer or oligomer are stronger than those in the heterodimer of tris(imidazoline) and tris(oxazoline). Two samples were prepared in $\text{CDCl}_3/\text{MeOD}$ (100/1, v/v): 1 mM of tris(imidazoline) and a mixture of tris(imidazoline) and tris(oxazoline)

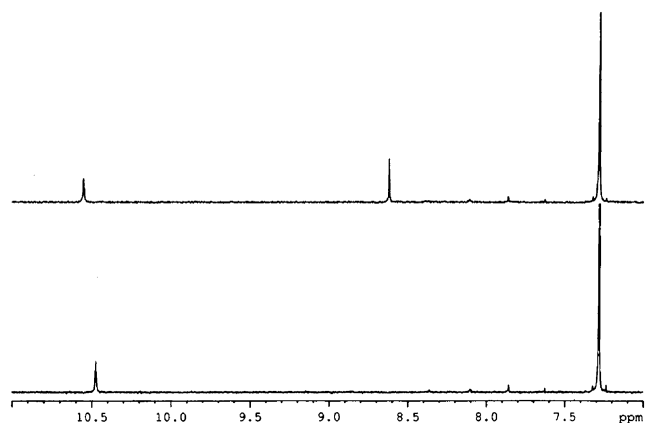


Figure 2. ^1H NMR spectra of tris(imidazoline) (1.0 mM, bottom) and a mixture of tris(imidazoline) and tris(oxazoline) (each in 1.0 mM, up) in $\text{CDCl}_3/\text{CD}_3\text{OD}$ (100/1, v/v).

(each in 1 mM).⁵ The equilibrium between the tris(imidazoline) dimer or oligomer and the heterodimer of tris(imidazoline) and tris(oxazoline) is fast on the NMR time scale. As the heterodimeric composition increases, the aromatic proton of tris(imidazoline) moves downfield, as shown in Figure 2.

We wondered how chiral substituents in tris(oxazoline) could induce the direction of the helicity of the heterodimer or heteropolymer by H-bonding and aromatic stacking interactions. To ascertain the unidirectional helicity induced by chiral tris(oxazoline), computational calculation was performed in a chloroform solvation model.⁶ A heterodimer, consisting of one tris(imidazoline) and one chiral tris(oxazoline), was calculated to be a model structure of H-bonded and aromatic-stacked dimeric or polymeric structure. Compared with the *P*-helicity derived from a chiral tris(oxazoline), $L^{*\text{Me}(\text{R})}$, helicity inversion to *M*-form evidently showed doubly repulsive steric effects between the chiral substituents of tris(oxazoline) and the NH protons of tris(imidazoline): av NH \cdots CH distances are 2.85 and 1.80 Å for *P*-form and *M*-form, respectively (Fig. 3). Therefore, the helicity was induced in a predictable manner: $L^{*\text{Me}(\text{S})}$ induces *M*-helicity whereas a $L^{*\text{Me}(\text{R})}$ unit induces *P*-helicity in the supramolecule.^{2,7}

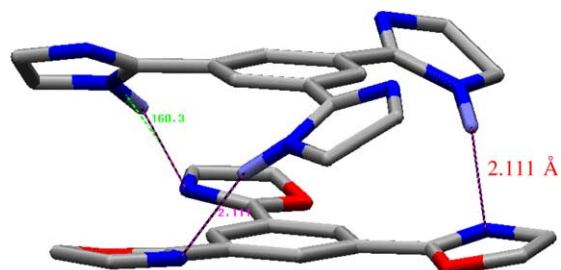


Figure 3. Global minimized heterodimer structure of tris(imidazoline) and tris(oxazoline) in chloroform global solvation model, MacroModel 7.0. H-bond angle and bond length of N–H \cdots N: 160.3° and 2.111 Å, respectively.

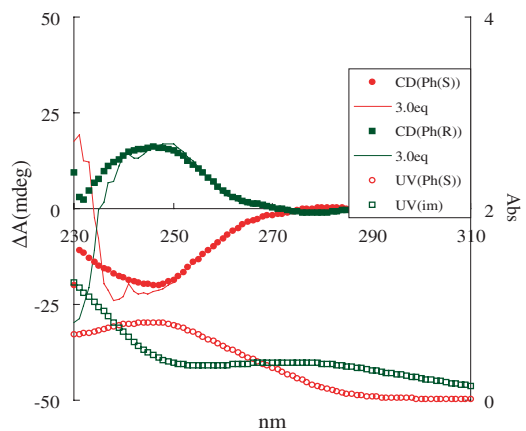


Figure 4. Circular dichroic spectra at 293 K. To a 20 μ M solution of tris(oxazoline) ($L^{*Ph(R)}$) as filled rectangle in black and $L^{*Ph(S)}$ as filled circle in red in dichloromethane/methanol (1000/1, v/v) was added 3 equiv of tris(imidazoline) (solid lines). UV-vis spectra were indicated as open circle ($L^{*Ph(R)}$) and open rectangle (tris(imidazoline)).

To address the unidirectional helicity induced by chiral tris(oxazoline) through H-bonding and aromatic stacking interactions, circular dichroism (CD) spectroscopy was used. When a 1:3 mixture of chiral tris(oxazoline), $L^{*Ph(S)}$ (20 μ M) and tris(oxazoline) (60 μ M) was compared with the chiral tris(oxazoline) (20 μ M) itself, the CD intensity of the mixture significantly increased around 230 nm in the strong UV-visible absorbance region of tris(imidazoline), owing to the proposed chiral tris(oxazoline)-induced unidirectional helicity in tris(imidazoline) (Fig. 4).

CSI (cold spray ionization) mass spectrometric analysis of the polymeric structure of tris(imidazoline) (**A**) in dichloromethane showed fragmentation patterns typical for polymer structures up to 17-mer: m/z 283.3 (A^+ , BP); 565.4 (A_2^+ , A_4^+ , 35%); 847.4 (A_3^+ , A_6^+ , A_9^+ , 34%); 1129.4 (A_4^+ , A_8^+ , A_{12}^+ , 12%); 1412.3 (A_5^+ , A_{10}^+ , A_{15}^+ , 7%); 1694.6 (A_6^+ , A_{12}^+ , A_{18}^+ , 4%); 1977.4 (A_7^+ , A_{14}^+ , 2%) (Fig. 5) while a mixture of tris(imidazoline) (**A**) and tris(oxazoline) (**B**) showed the predominant formation of a

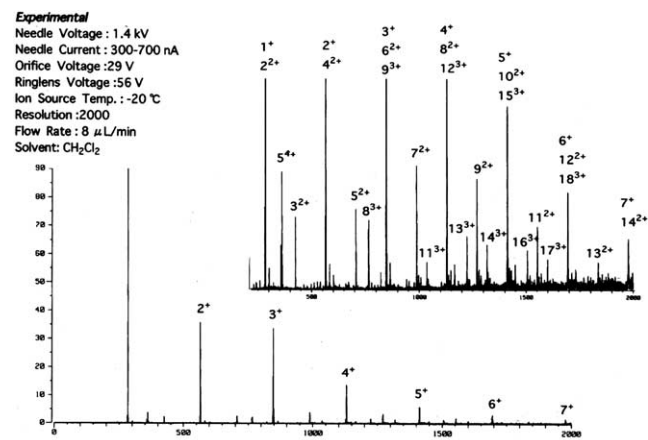


Figure 5. CSI mass spectra of trisimidazole as positive mode in CH_2Cl_2 . The figures on each peak are the number of tris(imidazoline) (**A**).

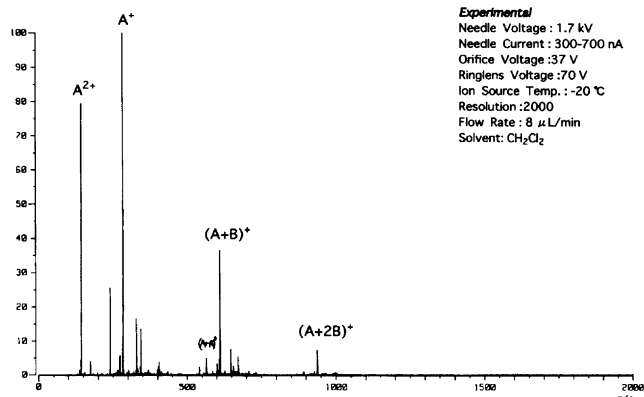


Figure 6. CSI mass spectra of tris(imidazoline) and tris(oxazoline) (positive mode in CH_2Cl_2). **A** is tris(imidazoline) ligand and **B** is tris(oxazoline) ligand.

heterodimeric complex: m/z 283.3 (A^+ , BP); 565.4 (A_2^+ , 5%); 610.4 (A^+B^+ , 35%) (Fig. 6). It is noticeable that the homo-polymeric structure of A_n was suppressed due to the formation of the heterodimer (**A**-**B**).

In conclusion, the helical information of chiral tris(oxazoline) was transferred to the achiral tris(imidazoline).

Acknowledgements

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- When solvent polarity was changed from 100/1 to 5/1 ($CDCl_3/CD_3OD$, v/v), only a mixture of monomer structures of tris(oxazoline) and tris(imidazoline) exist, to give

- no change in chemical shift of a 1:1 mixture of tris(imidazoline) and tris(oxazoline) relative to only the tris(imidazoline) solution.
6. Computational modeling study showed the dimeric structure should be D_3 symmetric, not the displaced π - π stacked structure in nonpolar solvent of chloroform. This is evidently shown in polarity-dependent ^1H NMR spectra: while a displaced π - π stacked structure should lead to low magnetic field (upfield in chemical shift) in lowering the polarity of solvent, the chemical shift moved to the downfield, coincident with D_3 symmetric π - π stacked structure.
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