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Synthesis and characterization of a novel imidazole cyclic trimer

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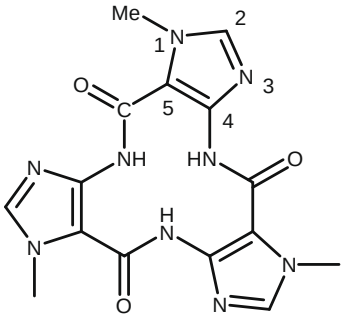
ABSTRACT

A novel cyclic trimer of imidazole **1**, in which imidazole rings are connected by amide bonds, has been synthesized with the help of LiCl as a template for the cyclization. The absorption spectra of **1** indicate the extension of conjugation between imidazole rings and amide bonds. The addition of 3 M equiv of $MgCl_2$ solubilizes **1** in polar organic solvent, suggesting the chelating ability of **1** to Mg cation.

The design and synthesis of cyclopeptides have been an active field of research in supramolecular chemistry. Cyclopeptide scaffolds are adopted in a number of artificial anion receptors as a key structure for their molecular recognition.[1,2] Tubular structures are constructed from cyclopeptides as nanostructured channels.[3] The design of cyclopeptides with various functional groups opens the possibility of a wider range of applications. Despite the significance of imidazole rings in many chemical and biological processes, they have been incorporated in only a few cyclopeptides as a part of their macrocycles.[4,5] In this Letter, we show the synthesis and characterization of a novel imidazole cyclic trimer **1** based on the condensation of 4-amino-1-methylimidazole-5-carboxylate ethyl ester (**2**). In **1**, the arrays of N1, C2, and N3 of imidazole rings project outward from the cyclic platform. This novel design provides free N3 atoms for protonation and alkylation.



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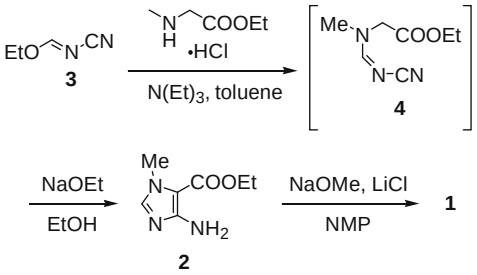

Scheme 1. Preparation of imidazole-based cyclic trimer **1**.

Cyclic trimer **1** was synthesized as shown in Scheme 1. Monomer **2** was synthesized from readily accessible ethoxymethylene cyanamide (**3**).[6] Treatment of **3** with free sarcosine ethyl ester, which was generated in situ from commercially available hydrochloride salt of it by addition of triethylamine, gave intermediate **4**,[7] which was cyclized with NaOEt to give monomer **2**.[8] The reaction of **2** in the presence of 1.2 equiv of NaOMe and 3.2 equiv of LiCl provided **1** in 53% yield.[9] The FAB-MS spectrum of the product has the peak corresponding to **1** (*m/z* 370.3 [MH], $C_{15}H_{15}N_9O_3H$, calcd 369.34): the spectrum has no peaks corresponding to dimmers, tetramers or larger oligomers of **2**. The ^1H NMR spectrum of the product shows no signals ascribable to linear oligomers. Therefore, a clear preference for the cyclic trimer in the condensation reaction of **2** was confirmed. We have further investigated the role of NaOMe and LiCl in the condensation of **2**. The results are summarized in Table 1. One molar equivalent of NaOMe was required for the production of **1** (entries 1–3).[10] In the absence of LiCl, **1** was not obtained (entry

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5). The substitution of $CuCl_2$, $ZnCl_2$, or $MgCl_2$ for LiCl also did not give **1**. Therefore, Li cation probably plays a role as a template for cyclization.[11] Three molecules of **2** should form a steric arrangement of cyclic trimer with the aid of Li cation.

Solubility of **1** in various solvents has been investigated. Trimer **1** is poorly soluble in common organic solvents, while it is highly soluble in aqueous acids. In addition, when 3 M equiv of $MgCl_2$ is added to the solution, **1** becomes readily soluble in polar organic solvents such as methanol, ethanol, and dimethyl sulfoxide. Excess amount of LiCl also acts as a solubilizer in these solvents. Other metal salts such as $CuCl_2$ and NaCl did not show any solubilizing effect. Though the exact working mechanism of $MgCl_2$ and LiCl is not yet clearly understood, we suggest that three Mg cations bind to the carbonyl oxygen and N3 of **1** to form a chelate complex.

Figure 1 shows the absorption spectra of **1** in ethanol containing $MgCl_2$ (3 equiv) and in H_2SO_4. Cyclic trimer **1** has a strong peak at ca. 280 nm and a small broad one at ca. 400 nm. The former corresponds to the absorption by the building block **2** (see Fig. 1(a)). The latter indicates the extended conjugation between the amide bonds and the imidazole rings in **1**. When the concentration of H_2SO_4 is changed from 0.18 M to 1.26 M, the former peak shifts by about −20 nm, showing that the protonation of basic N3 atoms in **1** occurs in strong acid solution.

Single crystals of the sulfate salt of **1**·$3H_2SO_4$ suitable for X-ray analysis was obtained by slowly evaporating the solution of **1** in 3.6 M H_2SO_4. The X-ray structure (Fig. 2)[12] shows that the three N3 imidazole nitrogens in **1**·$3H_2SO_4$ are protonated, which corresponds to the observation in the absorption spectra. The three amide hydrogens point toward the center of the macrocycle, while two of them direct slightly upward and the other one slightly downward from the macrocycle. The distance between the amide hydrogens is 2.19–2.69 Å. As mentioned above, the absorption spectra indicate that the imidazole rings and the amide bonds are conjugated in **1**. The conjugation state can be evaluated through the analysis of the planarity and the amide bond length of **1**. The three imidazole rings of **1** lie nearly on the same plane: the root-mean-square deviation of the imidazole N and C atoms from their mean plane is 0.136 Å. However, the amide bonds are tilted on average 38.4° out of the mean plane of the imidazole rings. Further, the lengths of the amido bond and the carbonyl bond are 1.368 and 1.216 Å, respectively. The double bond character of the amide bonds in **1** is weaker than that of typical amide bonds in proteins, of which the C–N and C–O lengths are in the ranges of 1.325–1.350 Å and 1.245–1.220 Å, respectively.[13] So, the conjugation between imidazole rings and amide bonds in **1** is rather weak.

In conclusion, we have synthesized and characterized a novel imidazole based cyclic trimer **1**. The cyclic trimer was prepared by one-step condensation reaction of ethyl-4-amino-1-methylimidazole-5-carboxylate, **2** in the presence of LiCl as a template for the cyclization. Three imidazole rings construct a macrocycle with arrays of N1, C2, and N3 of imidazole rings projecting outward from the macrocycle. The basic N3 at the outer accessible site will allow further chemical modifications, which would contribute to the development of new classes of liquid crystals and metal chelators.

Table 1
Effect of NaOMe and LiCl in preparation of **1**

Entry	Equiv of NaOMe	Equiv of LiCl	Yield (%)
1	1.2	3.2	53
2	2.0	3.2	59
3	0.5	3.2	0
4	1.2	0	0

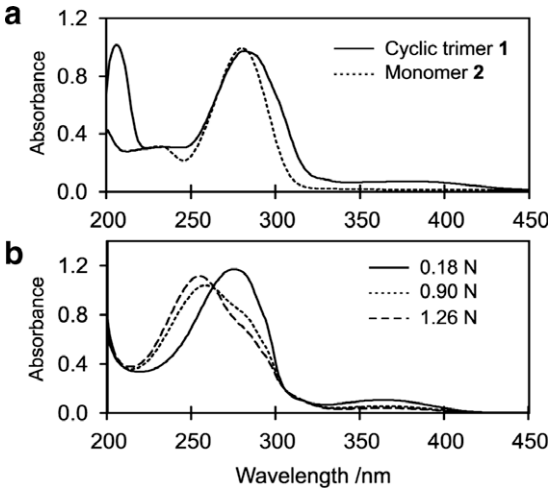

Figure 1. Absorption spectra of (a) **1** and **2** in ethanol containing 3 M equiv of $MgCl_2$ and (b) **1** in 0.18, 0.90, and 1.26 N H_2SO_4.

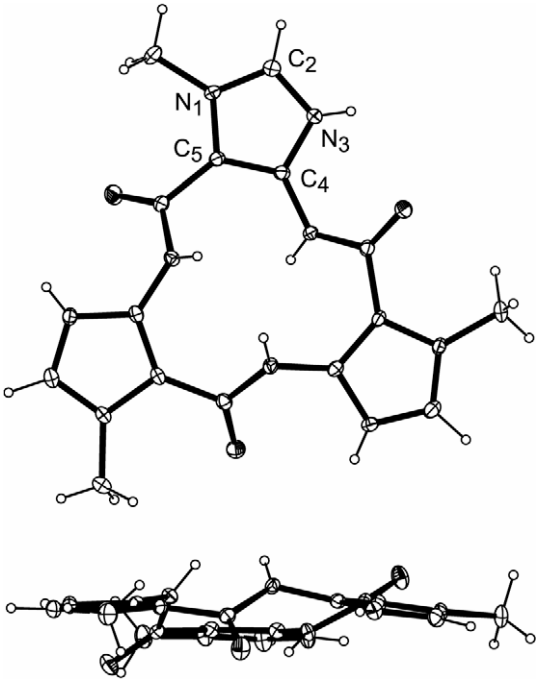

Figure 2. X-ray crystal structure of **1**·$3H_2SO_4$. Three HSO_4^- are omitted for clarity.

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8. *Preparation of 4-amino-1-methylimidazole-5-carboxylate ethyl ester* (**2**): To a mixture of **3** (16.5 g, 0.166 mol) and sarcosine ethyl ester hydrochloride (25.0 g, 0.163 mol) in toluene (100 ml) was added slowly triethylamine (25 ml) at 0 °C. After the mixture was stirred for one night at rt, the deposit was filtered off and the filtrate was concentrated under reduced pressure. To the oily residue was slowly added sodium ethoxide in ethanol (1.5 mol/l) at 0 °C and was stirred for 1 h. The precipitate was collected by filtration, dried, and suspended in saturated $NaHCO_3$. After extraction of the suspension by chloroform (100 ml × 3), the combined organic layer was dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was purified by recrystallization from ethyl acetate to give compound **2** as a pale yellow solid (16.8 g, 61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40 (s, 1H, imidazole CH), 5.57 (s, 2H, NH_2), 4.19 (q, 2H, J = 7.2 Hz, CH_2CH_3), 3.63 (s, 3H, N-CH_3), 1.25 (t, 3H, J = 7.2 Hz, CH_2CH_3); IR(KBr) 3466, 3285, 3152, 1658, 1641, 1550, 1540, 1456, 1375, 1312, 1234, 1152, 1116, 1047, 864, 767, 610 cm^{-1}.
9. *Typical procedure for synthesis of* **1**: Under a nitrogen atmosphere, a mixture of **2** (1.20 g, 7.10 mmol), sodium methoxide (470 mg, 8.70 mmol), and lithium chloride (970 mg) in *N*-methyl pyrrolidone (NMP) was stirred for 7 h at reflux temperature under reduced pressure. After cooled to rt, the mixture was neutralized with HCl(aq), reprecipitated with methanol, and collected by filtration to give the cyclic trimer **1** (200 mg, 53%) as a yellow powder. ^{1}H NMR(400 MHz, DMSO-d_6): δ 10.78 (s, 3H, amide-NH), 7.88 (s, 3H, imidazol-CH), 3.724 (s, 9H, CH_3).^{13}C NMR(D_2O): δ 157.34 (s, CO), 134.82(s, imidazole), 134.29(s, imidazole), 113.36(s, imidazole), 36.76(s, CH_3); FAB-MS: 370.3 (MH); IR(KBr) 3387, 1684, 1616, 1436, 1362, 1220, 1058, 1028, 773 cm^{-1}.
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