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# Synthesis, Conformational Analysis, and Complexation Study of an Iminosugar-Aza-Crown, a Sweet Chiral Cyclam Analog

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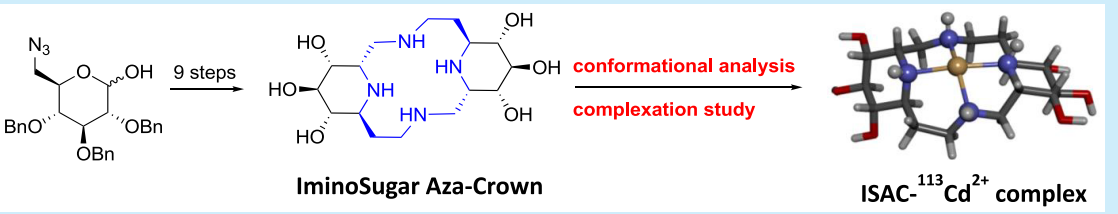


**ABSTRACT:** A new family of chiral $C_2$ symmetric tetraazamacrocycles, coined ISAC for IminoSugar Aza-Crown, incorporating two iminosugars adopting a $^4C_1$ conformation is disclosed. Multinuclear NMR experiments on the corresponding $Cd^{2+}$ complex show that the ISAC is a strong chelator in water and its tetramine cavity adopts a conformation similar to that of the parent Cd−cyclam complex. Similar behavior is observed with $Cu^{2+}$ in solution, with enhanced stability compared to the Cu−cyclam complex.

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Oxygen- and nitrogen-based macrocycles, often referred to as "crowns", have been long known for their coordinating abilities toward anions and cations. In this context, sugar-based macrocyclic compounds are of high interest and demonstrated biological, environmental, and medical properties.[1] Several advantages are associated with their glycosidic nature including their availability from natural sources and their polyhydroxylated pattern allowing the modulation of their physicochemical properties. Furthermore, their chirality combined with the geometric constraints brought by the five- or six-membered sugar rings is useful for the design of conformationally restricted chiral cavities. Thus, the design of sugar-based macrocycles bearing a combination of O- and N-donors is appealing and a vast array has been reported,[2] incorporating furanoses, pyranoses, and disaccharides. Depending on the size of the macrocycle and/or the number of oxygen and nitrogen donor atoms, different guests can be accommodated. Large 15- to 19-membered rings bearing up to three nitrogen atoms (**1**−**3**, Figure 1) have been used as excellent ligands for large and/or hard (according to HSAB theory) guests, such as amino acids[3] or ammonium[4−7] and alkali metal cations.[8] Smaller 14-membered rings with two oxygen and two nitrogen donors (**4**−**5**, Figure 1) have been designed to accommodate softer or smaller transition metal cations, such as cadmium(II), mercury(II), and copper(II).[9−11]

Tetra-azamacrocycles, such as cyclam (1,4,8,11-tetraazacyclotetradecane), constitute another specific class of ligands that have been extensively studied for their complexation properties.[12,13] They have been exploited for the selective

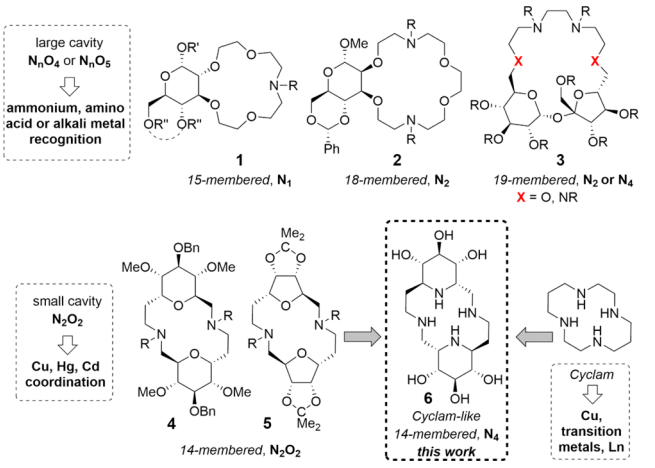


**Figure 1.** Structures and targeted guests of known and new polyaza sugar-based macrocycles **1**−**6**.

binding of transition metals, heavy metals, and lanthanides, especially after their mono- or poly-N-functionalization. In particular, cyclam is one of the azamacrocycles that has been

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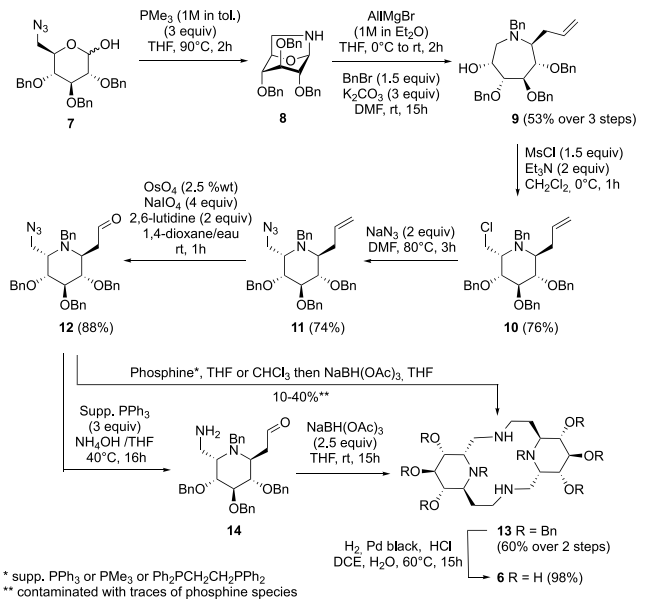
advantageously employed during these past decades in extraction,[14] catalysis,[15−17] supramolecular,[18] sensing,[19] bio-inorganic,[20] and medicinal chemistry.[21] Although they have been decorated with appended carbohydrates on side chains, for formulation or medical imaging purposes,[22−24] sugar motifs have never been, to the best of our knowledge, directly included within the skeleton of such polyazamacrocycles. In order to take the best of both worlds, we postulated that incorporation of iminosugars, sugar analogues in which the endocyclic oxygen has been replaced by nitrogen, could be of interest to generate new "sweet" constrained cyclam derivatives, which physicochemical properties could be tuned thanks to their polyhydroxylated nature. Iminosugars have thus far been almost exclusively developed as therapeutic candidates[25,26] targeting carbohydrate processing enzymes. Herein, we report the synthesis, conformational analysis, and preliminary ion-binding study of a new nitrogen-containing sugar-based macrocycle coined iminosugar azacrown (ISAC) **6** (Figure 1).

To build the tetraazamacrocyclic framework, we explored an intermolecular macrocyclization, relying either on a reductive amination or on a Staudinger-aza-Wittig (SAW) reaction, a strategy successfully applied for the construction of sugar-aza-crown (SAC) ethers.[11,27] The required iminosugar-based azidoaldehyde was prepared as follows. The known azidolactol **7**[28] was submitted to a SAW reaction using $PMe_3$[29] to provide the corresponding bicyclic hemiaminal **8**[30] that was directly treated with AllMgBr and *N*-benzylated to afford the hydroxyazepane **9**. Mesylation of the free OH in **9** provided the ring-contracted chlorinated piperidine **10**. A subsequent azide displacement yielded the azido-piperidine **11** in 74% yield. Finally, oxidative cleavage of the allylic moiety with $OsO_4/NaIO_4$ in the presence of 2,6-lutidine[31] furnished the target azidoaldehyde **12** (Scheme 1), the structure of which is guided by the necessity to have relatively flexible arms provided by the two carbon and three carbon appendages to favor dimerization and disposed in a *trans*-relationship to avoid intramolecular coupling. The dimerization of **12** was examined next, the crude expected di-imine being further reduced with $NaBH(OAc)_3$. Two solvents (THF, $CHCl_3$) and three sources of phosphine (supported $PPh_3$, $PMe_3$, and $Ph_2PCH_2CH_2PPh_2$[32]) were screened, all leading to the expected ISAC **13** albeit in poor yield (10−40%) that was contaminated with traces of phosphine species in all cases (Scheme 1). To gain insight into this unsatisfactory dimerization, the reaction was monitored by $^1H$ NMR in $CDCl_3$ at room temperature over a 4.5 h period using $PPh_3$ as the phosphine source (Figure 2). We observed the progressive

**Scheme 1. Synthesis of ISAC 6**



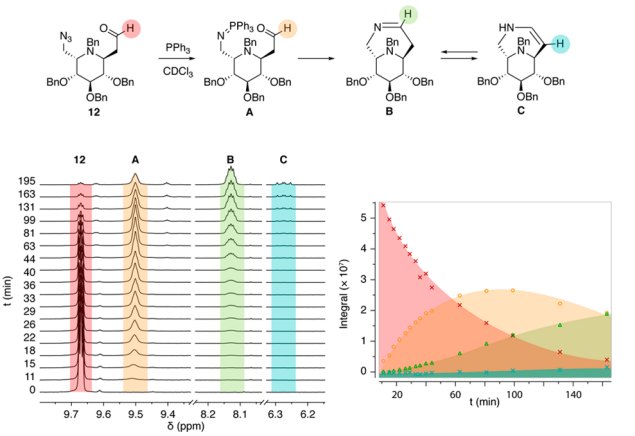




**Figure 2.** Monitoring of the Staudinger−aza-Wittig reaction of azidoaldehyde **12**. Top: Proposed reaction pathway for the Staudinger/Aza-Wittig reaction of azidoaldehyde **12**. Bottom: selected regions of the $^1H$ NMR monitoring ($CDCl_3$, 400 MHz, 300 K) of the reaction of **12** with $PPh_3$ and graph of the integrals intensity variation during the reaction

consumption of the starting azidoaldehyde **12** (1H at 9.7 ppm) affording the transient iminophosphorane **A** (1H at 9.6 ppm). This latter converts to the bicyclic imine **B** (1H at 8.2 ppm) that slowly equilibrates with the detrimental bicyclic enamine **C** (1H at 6.3 ppm). The ESIMS analysis of the mixture after 195 min confirms the hypothesis, showing not only the different intermediates but also the expected cyclic imine dimer (see Supporting Information (SI)). These results forced us to examine the alternative reductive amination route. Azidoaldehyde **12** was reduced to the crude aminoaldehyde **14** that was directly engaged in a double reductive amination in the presence of $NaBH(OAc)_3$ identified as the reagent of choice for imine reduction for such a motif.[27] Satisfyingly, the protected ISAC **13** was isolated in 60% yield after preparative HPLC purification, its hydrogenolysis affording the target ISAC **6** (Scheme 1).

The geometry in water of ISAC **6** was next studied through extensive NMR analysis, supported by molecular modeling protocols. The relative simplicity of its $^1H$ NMR spectrum associated with the presence of only one set of sugar protons confirmed its $C_2$ symmetry in the chemical shift NMR time scale. Both iminosugar rings adopts a chair conformation with the OH groups in the equatorial position as deduced from the observed large coupling constants ($J_{2,3} = J_{3,4} = J_{4,5} = 9.5$ Hz) (Figure 3A) and intraresidue NOEs (H1/H2, H2/H4, H3/H5) (see SI). Analysis of the coupling constants of the aminated arms connecting the iminosugar units suggested some flexibility around the C6−C7−N moiety. In fact, larger temperature coefficients were observed for the $^1H$ NMR signals at positions 7 and 8, while the rest of the $^1H$ NMR signals were barely altered (see SI). Moreover, medium size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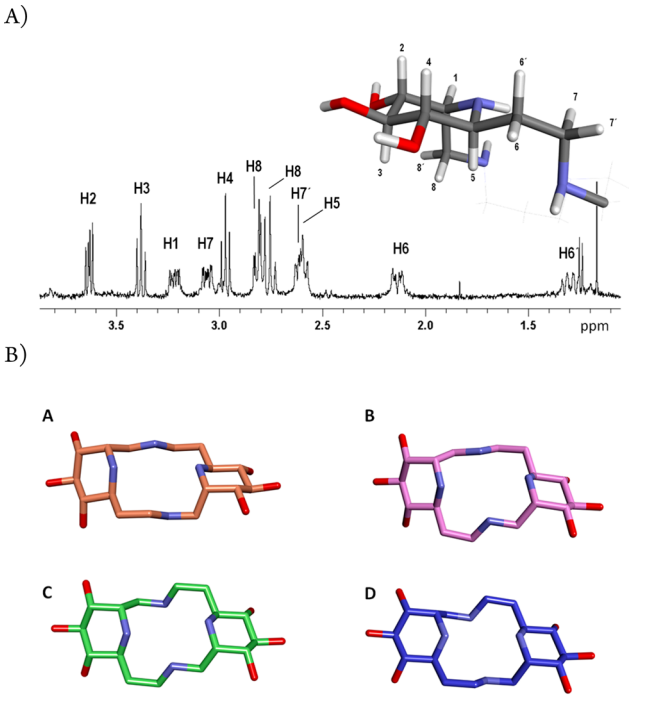


**Figure 3.** Conformational study of ISAC **6** in $D_2O$ by NMR assisted by molecular mechanics. (A) $^1H$ NMR spectrum of ISAC **6** at 1 mM in $Na_2CO_3/NaHCO_3$ buffer at pH = 11 in $D_2O$ and 298 K. (B) Possible conformations of ISAC **6** according to MM3* conformational search and NMR analysis.

coupling constants (between 6.5 and 8 Hz) were also deduced (see SI). Indeed, molecular mechanics calculations showed an ensemble of structures differing in the C6−C7 and C7−N torsion angles that could be clustered into four different families (conformers **A**−**D**), conformer **A** being the global energy minimum (Figure 3B).

Because of the structural similarity between ISAC **6** and cyclam, its ability to chelate divalent cations was scrutinized. To gain insight into the metal binding event, we first investigated cadmium(II) coordination as $^{113}Cd$ is an NMR active nucleus with the potential of providing structural information through coupling constants and chemical shifts analysis.[17,33] ISAC **6** was titrated with a solution of $^{113}Cd^{2+}$ enriched (93.35%) $CdCl_2$ solution until the 1:1 complex was formed. A slow exchange process in the NMR chemical shift time scale was observed (Figure 4). Notably, the $^1H$ NMR signals of the NH groups were visible, but only when the ISAC **6**−Cd complex was formed, strongly suggesting that the exchange process with the water solvent is slowed down, the typical nitrogen inversion is blocked, and the NH orientation becomes fixed.

Thus, $^1H-^{15}N$ and $^1H-^{113}Cd$ HSQC NMR experiments were performed (Figure 5). The $^1H-^{113}Cd$ spectrum (Figure 5 red) showed only one signal for the $^{113}Cd$-containing complex ($\delta(^{113}Cd)$ = −387 ppm). Indeed, the chemical shift of this signal did not change with the addition of more $Cd^{2+}$ equivalents, strongly suggesting that only one type of complex was generated. Moreover, strong heteronuclear correlations to the $^{113}Cd$ were found for the two NH's and for only one proton of each of the two $CH_2$ groups 7 and 8, those close to NH(b), indicating that these methylene protons display an *anti* orientation with respect to the cation. Interestingly, variable

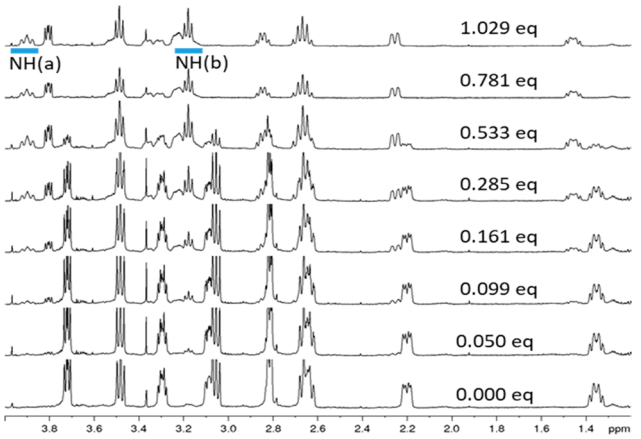


**Figure 4.** $^1H$ NMR titration of the complexation of $^{113}Cd^{2+}$ by ISAC **6** at 3.5 mM in $Na_2CO_3/NaHCO_3$ buffer at pH = 11 in $H_2O/D_2O$ (9:1) at 298 K, with increasing amounts of $CdCl_2$ (93.35% $^{113}Cd^{2+}$) solution in $D_2O$.

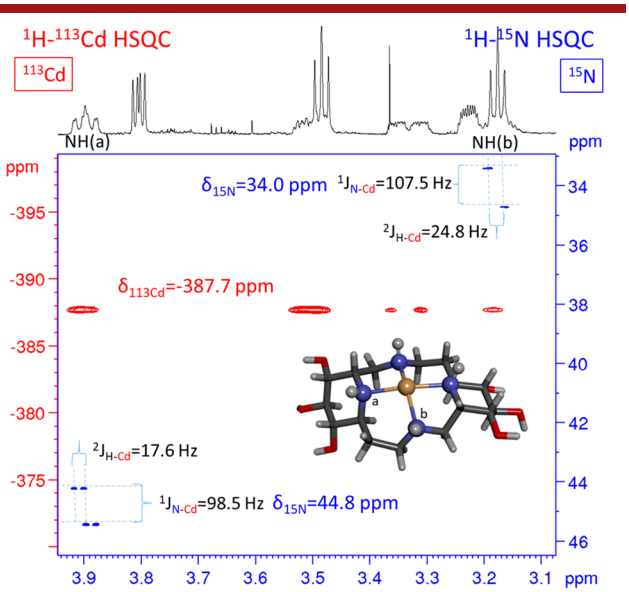


**Figure 5.** Superimposition of the $^1H-^{15}N$ HSQC (blue) and $^1H-^{113}Cd$ HSQC (red) spectra for the ISAC **6**−Cd complex.

temperature experiments showed that the exposure of the NH protons to the solvent is different. The measured temperature coefficients indicated that NH(a) is more exposed to solvent than NH(b) (see SI).

Additional NOE experiments showed strong NH(a)/H6-ax and NH(a)/H4 cross peaks confirming the axial disposition of the NH(a) further supported by the $^3J$ coupling constants with H5 (12.6 Hz, ax−ax) and H1 (3.4 Hz, ax−eq) (Figure 6). For NH(b), the ax−ax coupling pattern is evident through H5−H6ax−H7ax−NH(b), also assessing the axial orientation for this NH. Thus, the N−H bonds point toward the same face of the molecule as expected for a *trans*-I (*R,S,R,S*) type conformation, which is in full agreement with all the experimental NMR data (Figure 6 and SI).

We finally investigated copper(II) coordination by the ISAC ligand. ISAC **6** with 1 equiv of $Cu(ClO_4)_2{\cdot}6H_2O$ was placed in water at pH 6.4, and the mixture was heated for 2 h at 50 °C while adjusting the pH at 6.4. The dark blue solution suggested rapid formation of the desired complex that was isolated by precipitation in a water/acetone mixture. The targeted ISAC


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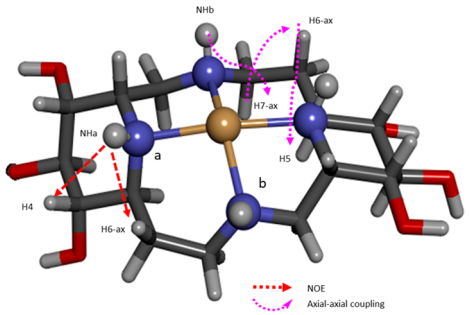


**Figure 6.** DFT calculated structure for the ISAC **6**−$Cd^{2+}$ complex according to the NMR data

**6**−$Cu^{2+}$ complex was identified through ESI-MS spectrometry (see SI) and compared to the cyclam−$Cu^{2+}$ complex prepared in parallel.[34] Its EPR analysis shows the four expected lines at low field and no superhyperfine splitting (Figure 7A) in agreement with a mononuclear copper(II) complex with a square planar geometry (see SI). Comparison with the Cu−cyclam spectrum showed high similarity in the electronic parameters demonstrating a similar conformation in these conditions. One of the main pathways in copper(II) complex demetalation, and particularly in the case of *in vivo* use, is the reduction to copper(I) and subsequent decoordination.[35] Thus, to investigate the stability of the ISAC **6**−$Cu^{2+}$ complex against reduction, electrochemical measurements were conducted. A large scan showed the contribution of the other oxidation states (Figure 7B); thus, the redox behavior of the $Cu^{2+}/Cu^{+}$ couple was assigned upon scanning from 0.3 to −0.180, with increasing scan rates (Figure 7C). Quasi-reversible behavior of the redox couple was evidenced, with $E_{1/2}$ = 0.01 V (vs Ag/AgCl) and $\Delta E_p$ ranging from 110 to 150 mV when scanning from 50 to 1000 $mV{\cdot}s^{-1}$. This demonstrates the enhanced stability of the ISAC **6**−copper(I) complex compared to its cyclam parent complex, for which an irreversible reduction wave is described in the literature.[36] To further gain insight into this ISAC **6**−copper(I) stability, a pseudoelectrolysis was conducted by scanning from 0.3 to −0.1 V and holding this potential for 30 s to trigger local generation of the $Cu^{+}$ complex (Figure 7D). When scanning back to 0.3 V, the current jump and the intact oxidation wave confirmed the stability of the $Cu^{+}$ complex at the cyclic voltammetry scale, which is very promising in this ligand family. Another important factor in the characterization of coordination complexes is the kinetic inertness of the complex when placed in competitive media. As the nitrogen-based macrocycles are highly basic (cyclam $pK_a$'s = 11.29, 10.19, 1.61, 1.91),[37] the kinetic inertness of their complexes can be assessed by competition with protons in acidic solutions and their degradation followed by UV−vis with the typical decrease of the copper d−d transition band over time. ISAC **6**−copper(I) complex inertness was assessed at 20 °C in 1.5 M HCl solution in distilled water. It proved very stable, as its UV spectrum did not change after 15 days while a half-life of 42 min was recorded for the cyclam−Cu complex (see SI).

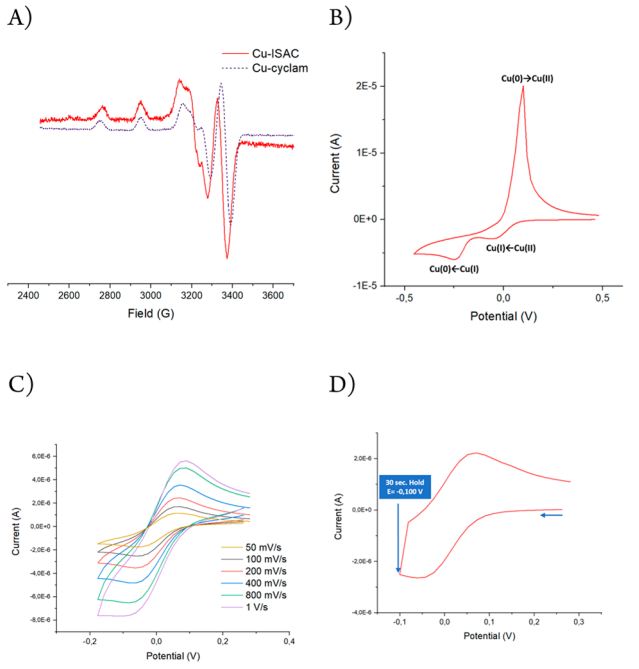


**Figure 7.** Study of the $Cu^{2+}$−ISAC **6** complex: (A) By EPR (X-band): Overlap of Cu−ISAC and Cu−cyclam at 143 K in DMF/water (1:1); (B−D) by cyclic voltammetry: (B) scan from 0.5 to −0.5 V at 100 $mV{\cdot}s^{-1}$; (C) overlap of different scan rates from 0.3 to −0.1 V; (D) pseudoelectrolysis (30 s hold at −0.1 V).

In conclusion, the synthesis of an iminosugar azacrown is disclosed. In the resulting $C_2$ symmetric macrocycle, some flexibility around the aminated arms has been observed by NMR, which disappears upon binding to $Cd^{2+}$, suggesting an interesting interplay between preorganization and flexibility. Importantly, the ISAC **6**−$Cu^{2+}$complex adopts a geometry comparable to that of the parent cyclam−$Cu^{2+}$ complex, with significantly enhanced coordination ability in solution. This constitutes a first entry in the coordination chemistry of this new class of azamacrocycles.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00503.

Experimental procedures, characterization data for compounds **7**−**13**, copies of $^{1}H$ and $^{13}C$ NMR spectra for compounds **6**, **12**, and **13**; monitoring of the Staudinger−aza-Wittig reaction with **12** by NMR and MS; study of the ISAC **6**−$Cu^{2+}$ complex (stability, analogy with cyclam−$Cu^{2+}$ complex) by EPR, cyclic voltammetry and UV−vis spectroscopy; NMR conformational study of ISAC **6** and its complex with $Cd^{2+}$ (PDF)

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## Notes

The authors declare no competing financial interest.

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