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Title : Synthesis and Chelation Study of a Fluoroionophore and a Glycopeptide based on an Aza Crown Iminosugar Structure

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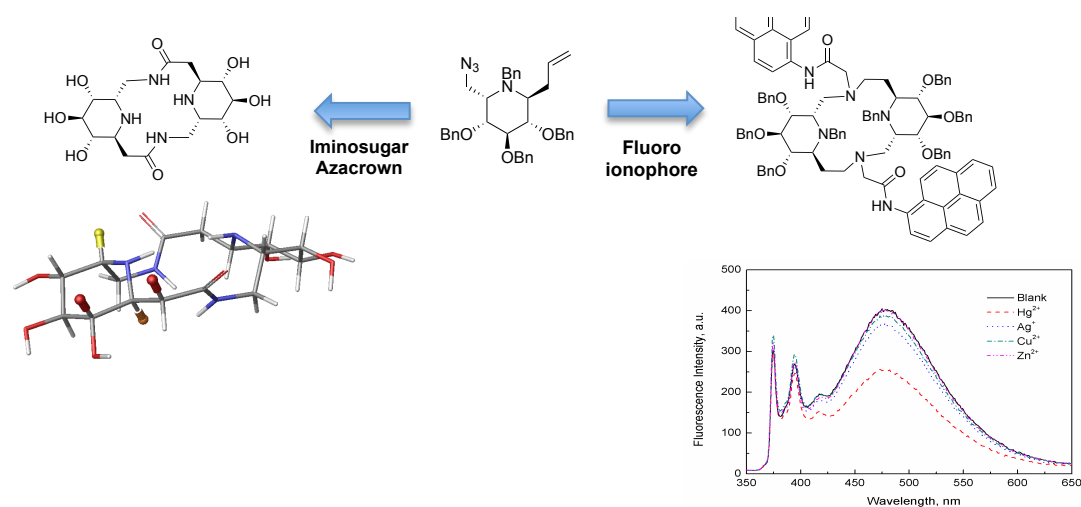
Highlights

- First synthesis of fluoroionophore based on an iminosugar scaffold
- The fluoroionophore shows selectivity for Hg⁺⁺ cations
- First synthesis of iminosugar azacrown (ISAC) with amide pending arms
- Introduction of amide arms abolishes the chelation properties observed for ISAC with amine arms

Abstract

Capitalizing on a recently reported iminosugar-based aza-crown (ISAC) accessed by a double Staudinger azaWittig coupling reaction, we have expanded the structural diversity of this new family of sweet cyclam analogs. Replacement of the two secondary amines linking the iminosugar units by two amide bonds obtained a cyclodimerization with BOP and DIPEA led to a macrocycle that did not demonstrate efficient Zn^{2+} chelation unlike the parent ISAC. Introduction of two pyrene moieties on the secondary amines of the parent ISAC yielded a new fluoroionophore that selectively binds Hg^{2+} in methanol.

Graphical abstract



Keywords

Iminosugar, ionophore, macrocycle, NMR analysis

Acknowledgements

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Introduction

Aza-crown ethers and cyclams are important molecular receptors for molecular or ionic recognition studies that find applications notably in analytical chemistry as well as nuclear medicine.^{1,2} The inherent chirality of carbohydrates is very suitable for the design of chiral receptors and ligands for asymmetric synthesis or chemosensors. Accordingly, chiral aza-crown ethers incorporating various carbohydrate motifs have received much attention in recent years^{3,4} and demonstrated biological, environmental, and medical properties. Here are some representative examples (Figure 1) in which a pyranose **1**,⁵ a disaccharide **2**,⁶ two furanoses **3**⁷ or two pyranoses **4**⁸ have been used to delineate a macrocycle. Depending on the size of the macrocycle and/or the number of oxygen and nitrogen donor atoms, different guests have been accommodated, including ammonium cations,⁶ alkali metal cations,⁹ and transition metal cations, such as cadmium(II), mercury(II), and copper(II) using a fluorescent sensor.^{10,11} Very recently, we disclosed the synthesis of the first amine-linked iminosugar macrocycles **5** and **6** (Scheme 1), coined iminosugar-aza-crowns (ISACs), obtained by dimerization of an iminosugar-based aminoaldehyde by reductive amination.¹² Alternative dimerization of a related iminosugar-based amino acid through amide bonds formation is of interest to generate more rigid cavities that may lead to exquisite specificity of recognition and catalyst.^{13,14,15} Herein we report the synthesis, conformational analysis and complexation study of such cyclic C2-symmetric glycopeptides **7** and **8** as well as the study of a fluorescent ISAC **9** bearing two pyrenyl arms (Figure 1).

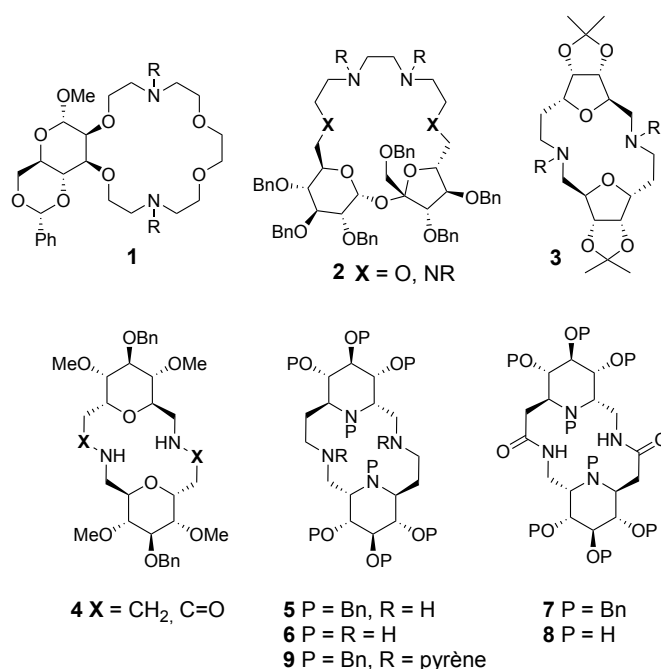


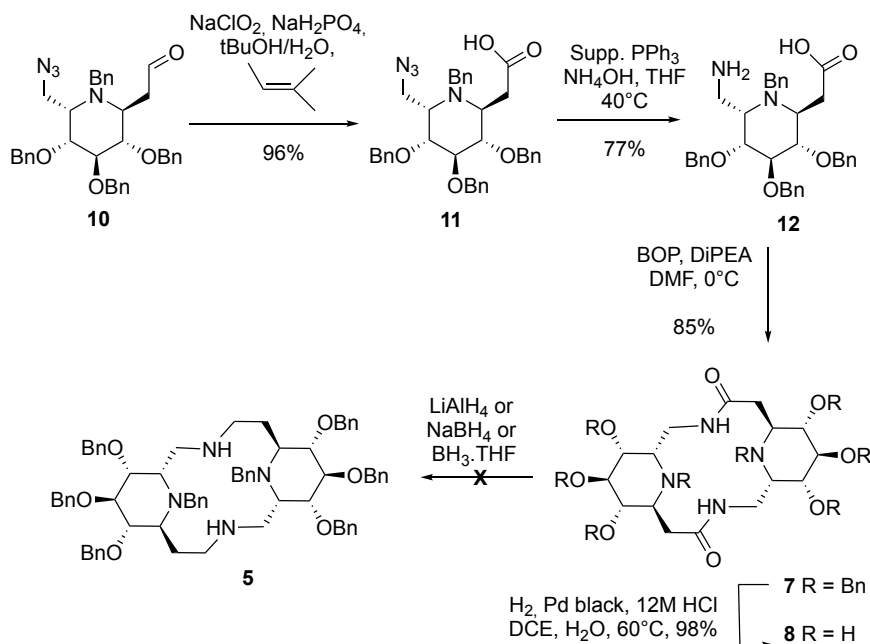
Figure 1: Structure of known **1-5** and new **6-9** diazasugar-based macrocycles

Results and discussion

1. Iminosugar azacrown linked by amide bonds

1.1 Synthesis of C-2 symmetric iminosugar azacrown **8**

A range of C-2 symmetric glycopeptides have been synthesized either by solid phase¹⁶ or solution phase^{17,18} peptide synthesis from a sugar amino acid (SAA) precursor. Using a similar methodology, the corresponding iminosugar amino acid was synthesized as follows. Iminosugar azidoaldehyde **10**, easily available from the corresponding C-allyl iminosugar,¹⁹ was oxidized to the azidoacid **11**. Conversion of the azide group into the amine with supported PPh₃ and NH₄OH provided the iminosugar-based aminoacid **12**. While solution phase peptide coupling with EDC and HOBt furnished the expected glycopeptide **7** in modest 32% yield, cyclodimerization of **12** using BOP and DIPEA under diluted conditions in DMF¹⁴ provided macrocycle **7** in excellent 85% yield. Its hydrogenolysis under classical conditions furnished the glycopeptide **8**. Attempts to convert **7** into **5** through reduction of the amides either with NaBH₄, BH₃.THF or LiAlH₄ failed (Scheme 1).



Scheme 1: Synthesis of ISAC **8**

1.2 Study of the stability and geometry of ISAC **8**

The geometry in water of ISAC **8** was then 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 C2 symmetry in the chemical shift NMR time scale. Both iminosugar rings adopts the typical ⁴C₁-type chair geometry with equatorial OH groups as deduced from the large coupling constants (J_{1,2}, J_{2,3}, J_{3,4} ≥ 9.0 Hz, see SI). The stability of ISAC **8** was then evaluated in D₂O

and DMSO at various temperatures. Only slight changes in the chemical shifts of the exchangeable protons were observed upon heating, evidencing the existence of intramolecular hydrogen bonds (Figure 2).

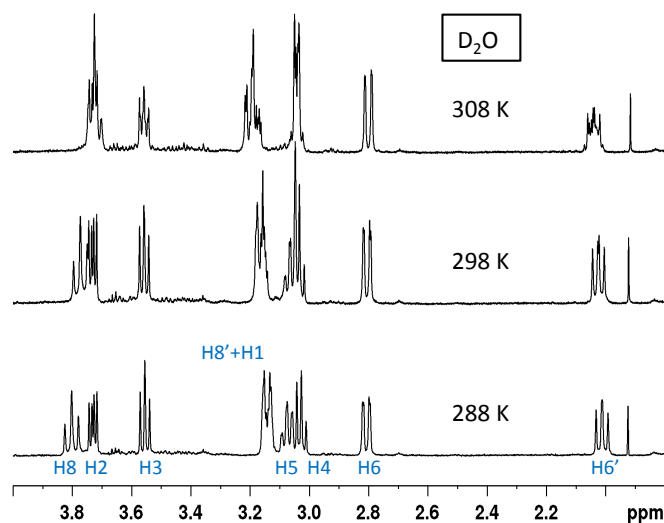


Figure 2: ^1H NMR study of the structure and stability of ISAC **8** at 1mM in D_2O at 288, 298 and 308K.

1.3 Study of the ability of ISACs **6** and **8** to chelate Zn^{2+}

The ability of ISAC **8** to chelate Zn^{2+} was then examined by NMR and compared to that of ISAC **6** that has been previously shown to bind Cu^{2+} and Cd^{2+} metal cations.¹² As already observed for Cu^{2+} and Cd^{2+} (Figure 3) with **6**, the formation of a zinc-bound macrocycle takes place in slow exchange in the chemical shift time scale. Moreover, the conformation of **6** does not change much upon binding as the coupling constants are very similar in the free state and when bound to Zn^{2+} , suggesting a preorganization in the free state and an interesting interplay between preorganization and flexibility.

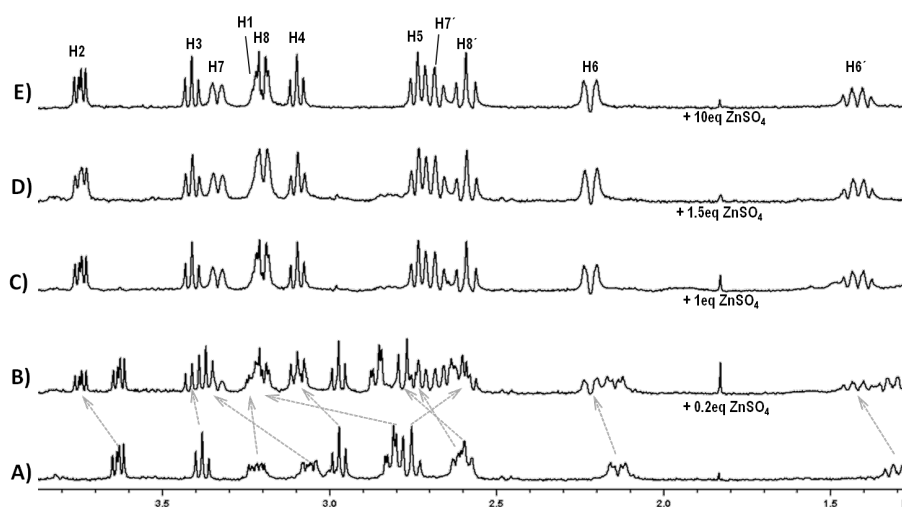


Figure 3: Study by ^1H NMR of the complexation of ZnSO_4 by ISAC **6**. A) ^1H NMR spectrum of ISAC **6** at 1mM in $\text{Na}_2\text{CO}_3/\text{NaHCO}_3$ buffer at pH=11 in D_2O and 298K. B)-E) ^1H NMR spectra of ISAC **6** upon increasing additions of ZnSO_4 (0.2, 1, 1.5 and 10 equivalents). The arrows indicate the shifts of the ^1H resonances upon binding to Zn(II).

The results obtained with ISAC **8** were strikingly different. Unlike ISAC **6**, neither changes in chemical shifts nor new NMR signals were observed upon addition of increasing amounts of ZnCl_2 . This fact supports the existence of a weak interaction between ISAC **8** and Zn^{2+} (Figure 4).

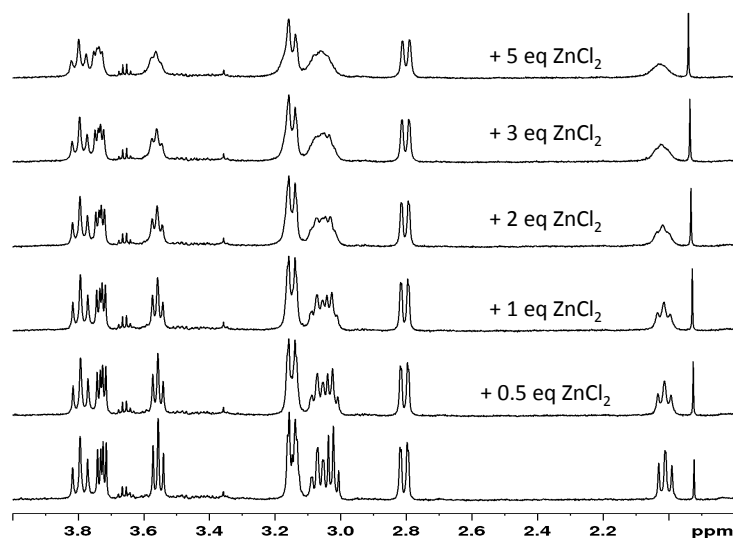


Figure 4: Study by ^1H NMR of the complexation of ZnCl_2 by ISAC **8**. A) ^1H NMR spectrum of ISAC **8** at 1mM in $\text{Na}_2\text{CO}_3/\text{NaHCO}_3$ buffer at pH=11 in D_2O and 298K. B)-E) ^1H NMR spectra of ISAC **8** upon increasing additions of ZnCl_2 (0.2, 1, 1.5 and 10 equivalents).

Conformation of ISAC **8** in the presence of ZnCl_2 was studied by NMR and strongly suggests a macrocycle where the piperidines adopt a $^4\text{C}_1$ chair conformation and in which the C=O groups of the amide bonds point outside the cavity delineated by the four amines (Figure 5 and SI).

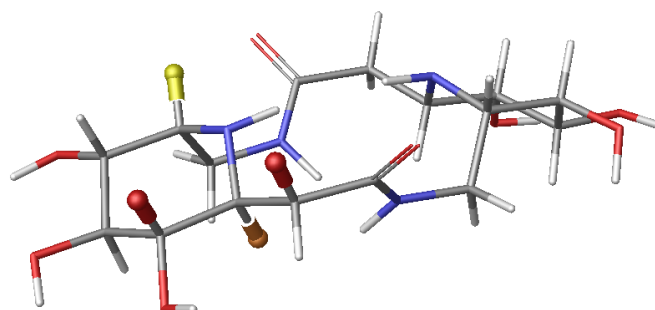
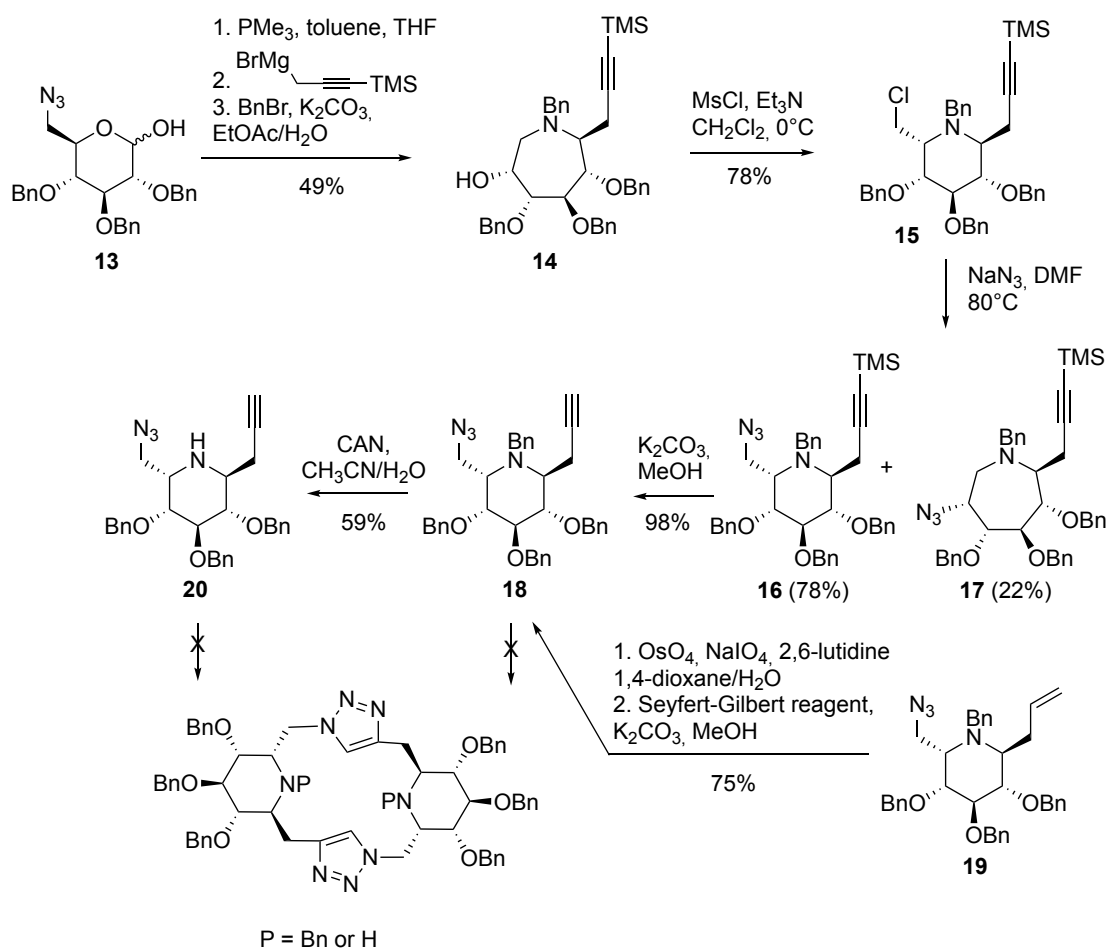


Figure 5: Possible conformation for ISAC **8** in the presence of ZnCl₂ according to NMR data; the ¹H that are the more affected/ broadened by the addition of ZnCl₂ are highlighted.

Therefore these observations suggest that aminated arms are required to generate an efficient di-cation binder. As the aim of this strategy is to develop new iminosugar-based macrocycles for chelation studies devoided of glycosidase inhibition potency, the two ISACs **6** and **8** were further assayed on a panel of twenty-one glycosidases. Satisfyingly and as expected regarding the structure of these dimeric iminosugars in which the iminosugar unit is sterically hindered by the other unit, neither **6** nor **8** did demonstrate significant glycosidase inhibition at 1 mM concentration (see SI).

2. Attempted synthesis of an ISAC linked by triazole arms

A convenient alternative to amide bonds to link sugar units in sugar-based macrocycles is the use of triazoles exploiting click chemistry. Several groups have reported such cyclic oligosaccharides in which the glycosidic bond has been replaced by a triazole moiety.^{21,22,23} To generate a cyclic iminosugar dimer displaying two triazole-based tethers requires the introduction of azide and alkyne moieties of the iminosugar scaffold in a trans relationship to avoid intramolecular cyclization. Introduction of the alkyne moiety was performed as follows. Known azidolactol **13**^{24,25} was first converted to a crude bicyclic hemiaminal under Staudinger-azaWittig conditions²⁶ that was subsequently opened by silylated propargyl organomagnesium bromide, synthesized according to literature²⁷ to afford azepane **14** as a single diastereoisomer in 49% yield over three steps after N-benylation. The introduction the azide function started with the ring contraction of **14** with mesyl chloride to furnish, in a stereoretentive manner, the chloropiperidine **15** in 78% yield. The chlorine atom was displaced with sodium azide to produce the expected azidopiperidine **16** (78%) along with the corresponding azidoazepane **17** (22%). Removal of the silyl protecting group under slightly basic conditions yielded the target piperidine-based azidoalkyne **18**. Compound **18** was also efficiently obtained from known azidoallyl derivative **19**¹⁹ though alkene oxidative cleavage with OsO₄/NaIO₄ combination followed by olefination with the Seyfert-Gilbert reagent.²⁹ Azidoalkyne **18** was then submitted to several click chemistry conditions including conditions that proved successful for the synthesis of iminoglycoconjugates from *N*-benzyl iminosugars.³⁰ Unfortunately, whatever the conditions used (CuI, DIPEA, toluene; CuSO₄, sodium ascorbate, methanol or EtOAc/H₂O; [(CH₃CN)₄Cu]PF₆, CH₂Cl₂) over a range of temperatures, no trace of expected dimer was detected by TLC or MS. Application of the same click conditions to the NH free azidoalkyne **20**, obtained by removal of the *N*-benzyl group with CAN, were also unsuccessful.

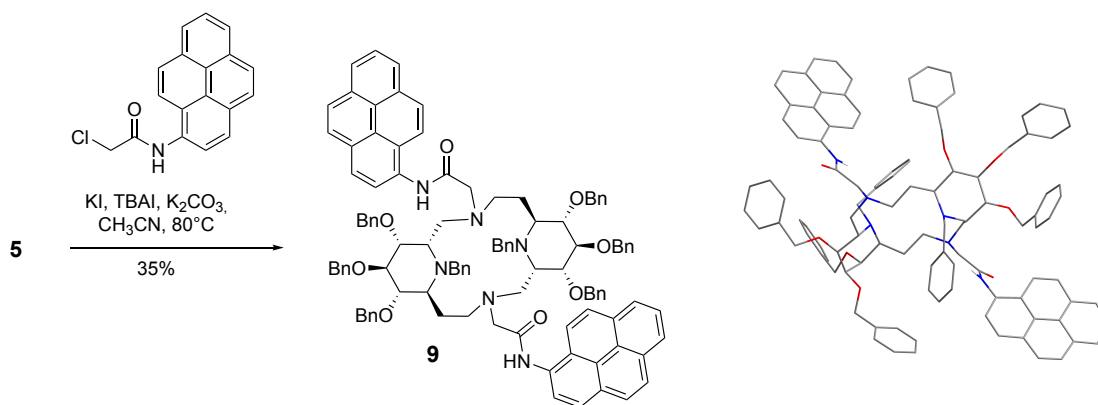


Scheme 2: Synthesis of iminosugar-derived azidoalkynes **18** and **20** and attempts to produce the corresponding cyclic dimers

3. Fluoroionophore based on an iminosugar azacrown scaffold

3.1 Synthesis of a fluorophoric iminosugar azacrown **9**

The disappointing results obtained with the strategy consisting in modifying the arms connecting the two iminosugar units forced us to turn our attention to another structural modification that could advantageously modify the properties of the ISAC structure. Combination of macrocyclic ionophores with fluorophore moieties has been often used in the preparation of fluorescent sensors and a significant number of derivatives have been developed.³¹ Amongst the wide range of fluorophores that have been reported in the literature, introduction of a pyrene moiety as the signalling unit to examine the chemosensing properties by fluorescence is well-adapted.^{32,33,34} The fluorescence enhancement can be attributed to the photoinduced electron transfer triggered by the complexation of the metal ion. In order to develop a fluoroionophore derived from ISAC **6**, compound **5** was treated with an excess of *N*-(1-pyrenyl)-chloroacetamide to provide in 70% yield the protected fluorescent ISAC **9** which crystal structure was solved and fully confirmed the structure (Scheme 3). Interestingly, here, one piperidine adopts a 4C_1 conformation with pseudoequatorial orientation of the benzyloxy groups while the other piperidine adopts a 1C_4 conformation with pseudoaxial orientation of the benzyloxy groups.



3.2 Study of the chemosensor properties of ISAC 9

The chemosensor properties of ISAC **9** were studied by fluorescence measurement. The conditions of observation of the monomer and excimer bands were optimized leading to the use of a 5 mM concentration of ISAC **9** with excitation at 341 nm. While methanol/water (1:1) allowed the best observation of the excimer band, methanol, dichloromethane and acetonitrile proved to be the best solvents to observe the monomer band (see SI). Study of the monomer band of **9** in acetonitrile in the presence of various cations (Cu^{2+} , Ag^+ , Hg^{2+} , Zn^{2+} and Cd^{2+}) was performed (Figure 6). Interestingly, while ISAC **6** has proved to bind Zn^{2+} and Cd^{2+} ,¹² introduction of two pyrene moieties on the iminosugar ring nitrogens changed the chemosensor properties of the corresponding ISAC **9** that demonstrated some selectivity towards Cu^{2+} and Hg^{2+} cations and only weak chelation of Zn^{2+} and Cd^{2+} . This result suggests the arm amine functions as handles to tune the chemosensor properties of these ISACs.

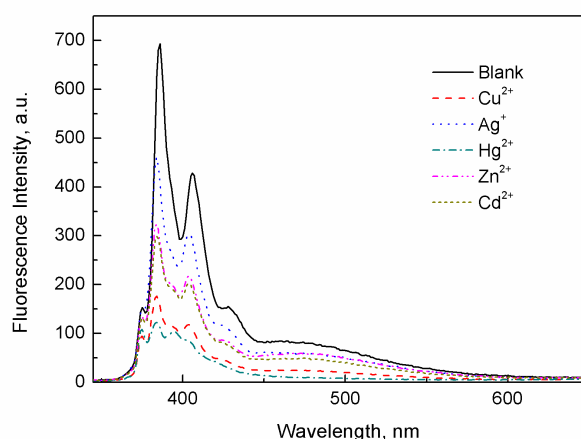


Figure 6: Fluorescence spectra of ISAC **9** in the presence of various metal ions in MeCN; $[\text{M}^{n+}] = 0.2 \text{ mM}$, $[\mathbf{9}] = 5 \text{ mM}$, $\lambda_{\text{ex}} = 341 \text{ nm}$.

A second study of the excimer band in methanol/water (1:1) in the presence of Cu^{2+} , Ag^+ , Zn^{2+} (at 0.2 mM concentrations) and Hg^{2+} (at 40 mM concentration) demonstrated a significant selective fluorescence quenching of compound **9** in the presence of Hg^{2+} ion. Interestingly, ISAC **9** exhibits a similar complexation profile as the pyrenylacetamide-functionalized cyclam²³ (Figure 7).

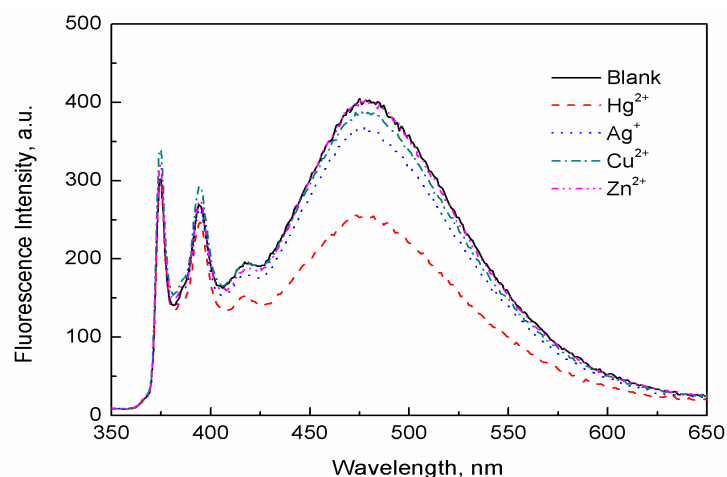


Figure 7: Fluorescence spectra of ISAC **9** in the presence of various metal ions in MeOH/H₂O (v/v= 1:1); [M^{n+}] = 0.2 mM, [Hg^{2+}] = 40 mM, [**9**] = 5 mM, λ_{ex} = 341 nm.

Conclusions

Two iminosugar azacrowns bearing either fluorescent appendages or incorporating amide bonds have been described. Preliminary chemosensor studies on the fluorescent ISAC **21** demonstrate selectivity towards Hg^{2+} ions unlike the undecorated ISAC **6**, suggesting that further structural modification of the aminated arms could control the chelation properties of these molecules. Work is now in progress to access the geometry of the **21**- Hg^{2+} complex. In parallel, the first example of a C₂ symmetric iminoglycopeptide **8** has been reported and generated from an iminosugar amino acid precursor by solution phase peptide coupling. Replacement of the aminated arms by amide bonds abolishes the Zn^{2+} complexation observed for the parent ISAC **6** suggesting a distinct geometry for the **8**- Zn^{2+} complex.

Conflicts of interest

“There are no conflicts to declare”.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:



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