UNIVERSITÉ DE NAMUR

NISM
Namur Institute of Structured Matter

« Investigation of the vibrational signatures of molecules having specific interactions with the solvent such as chiral induction »

1 PhD position at the University of Namur on quantum chemistry simulations of Raman optical activity.

Outstanding candidates are sought to work at UNamur (Namur, Belgium) in the frame of the project called "Investigation of the vibrational signatures of molecules having specific interactions with the solvent such as chiral induction". In summary, it aims at providing a deeper knowledge of the influence of the surrounding, namely the solvent, on the vibrational signatures and more particularly on the Raman optical activity (ROA) spectra. The full project is joined to this announcement. Starting date is envisioned to be as soon as possible.

JOB REQUIREMENTS:

Candidates should hold a MSc (or equivalent) in Chemistry, Physics or Materials Science. The candidate should have obtained recently (no more than 4 years) the MSc. The candidate can also be finishing her/his Master degree and should therefore mention the approximative date of availability.
Good knowledge of English, both written and oral, is compulsory. An experience in quantum chemistry and on the usage of quantum chemistry codes such as Gaussian, Dalton, Turbomole, QChem, … is a plus. Having some coding experience is also a bonus (FORTRAN and/or Python).

CONTRACT DETAILS:

The PhD position is a 1-year contract renewable up to 4 years. Salary follows the legal scale for doctoral positions in Belgium (indicatively around 2350 €).

ABOUT THE GROUP:

The retained candidates will join the group of V. Liégeois at the laboratory of theoretical chemistry (http://www.unamur.be/en/sci/chemistry/lct) of the UNamur and the newly-established Namur Institute of Structured Matter (http://nism.unamur.be). The lab comprises two senior researchers, Prof. B. Champagne and Dr. V. Liégeois, three post-docs, eight PhD students, two Master students. Within the group, we have access to computational facilities provided by the HPC consortium of the Fédération Wallonie-Bruxelles, including those of the Scientific Computing Platform of our University.

HOW TO APPLY:

Applicants should send their CV, including their scientific achievements, list of publications, coding skills, as well as a brief motivation letter explaining why they feel being the right perform for this position to vincent.liegeois@unamur.be (in a single PDF file) as soon as possible. They should also arrange for one letter of recommendation to be sent to the same address. The candidates that have been selected upon their CV will be auditioned by videoconference during 30'.

2) DESCRIPTION OF THE RESEARCH PROJECT

2.1 Goals of the research

The goal of this proposal is to provide a deeper knowledge of the influence of the surrounding, namely the solvent, on the vibrational signatures, more particularly on the Raman optical activity (ROA) spectra. One of the most intriguing effect this project aims at understanding is the chiral induction (IC) on an achiral solvent which has been observed experimentally. For instance, very strong solvent signals (up to 100 times more intense than that of the solute) were observed for nickel (II) complex in polar solvents on their ROA spectra.[1]

While the simulation of ROA[2,3] spectroscopy can now be routinely done and is used in industry to unravel the stereochemistry (configuration) of chiral molecules (a molecule that cannot be brought to coincide with its mirror image), the solvent effect is mainly considered implicitly through polarizable continuum model (PCM). However, it was shown that treating the environment of the molecules under study is very important to reproduce the experimental spectrum, that implicit solvent model is not enough and that explicit solvent molecules need to be considered.[4–7]

In this regard, our objective is to assess the performance and reliability of the most recently published strategies to simulate ROA spectra of flexible solute molecules in their environment. More particularly, two types of systems will be investigated in close collaboration with experimentalists for their synthesis and characterization (ROA recorded spectra among other techniques) through an ANR project called CAORSS: cryptophane derivatives and Extended Metal Atom Chains (EMACs) derivatives. These systems are known to present ROA signatures due to encapsulation of guest molecules/atoms or solvent effects. This interplay between theory and experiment will help us design an accurate methodology to simulate the ROA signatures of these systems in various environments. The ultimate goal is to understand the exact influence of the surrounding on the vibrational signatures, and more particularly the phenomenon of chiral induction.

2.2 State of the art

At the harmonic approximation, the simulation of non-resonance vibrational spectroscopies (IR, Vibrational Circular Dichroism (VCD), Raman, ROA) requires the evaluation of first-order derivatives of the various properties (the molecular responses toward the electromagnetic field perturbations) with respect to the vibrational normal coordinates (Q_p) as well as the calculation of the Hessian. All these quantities are calculated within a given level of approximation: Hartree-Fock, Density functional theory (DFT), Moller-Plesset (MP), coupled cluster (CC), … Along with the developments of the spectroscopies, methods have been developed to evaluate these molecular quantities using the Time-Dependant Hartree Fock iterative cycle[8–11], the quasienergy formulation[12], the Lagragian approach[13], and even coupled cluster response theory[14]. A review by Helgaker *et al.* summarizes the recent advances in wave function-based methods to calculate molecular properties[15]. When resonating with an excited state, the so-called Resonant ROA (RROA) signals can be greatly intensified, as is the case with metal complexes with d and f orbitals. Nafie[16] proposed a so-called single excited state theory. It states that the RROA intensity associated with a single excited state (i) is monosignate, (ii) has an opposite sign to that of the maximum ECD, (iii) has the same relative intensities as the parent Resonance Raman spectrum (RR) , and (iv) for all the ROA bands, shows an RROA / RRaman intensity ratio equal to the ratio ECD/(2*UV). Other approaches, such as using the time-dependent (TD) formulation and real time propagation DFT[17,18] and the finite lifetime[19] methods have also been developed.

Before being able to simulate vibrational signatures, or any molecular properties, it is of crucial importance to generate a representative ensemble of low-energy structures, generally referred to as conformers. As stated by Barone in his last review[20] about computational molecular spectroscopy, “a current challenge for computational spectroscopy tools is represented by large flexible molecules, for which the analysis of the conformational PES is the first obstacle to be overcome”. To tackle this issue, the group of Grimme has recently developed a new scheme called “Conformer-Rotamer Ensemble Sampling Tool” (CREST) based on a meta-dynamics approach and using a semi-empirical tight binding (GFN2-xTB) level of theory.[21] Even at this relatively cheap level of quantum chemistry, the generated structures often match quite well with the experimentally observed conformations.

Next, one needs to consider the effects of the environments (such as the solvent). The simplest way to consider its effects is via an implicit approach using a polarizable continuum model (PCM)[22–24] where the effect of the solvent is mimicked by a cavity possessing an electric permittivity. However, this model lack of direct interactions between solute and solvent such as hydrogen bonds. For ROA, several studies have demonstrated that many solvent molecules are required to reproduce the experimental spectrum.[5–7,25] For these reasons, some researchers advocate a molecular dynamics (MD) simulation approach and sample several thousand snapshots to catch dynamics in modelling water solvent effects.[25,26] In addition, a multiscale approach has also been proposed combining quantum mechanics, polarizable molecular mechanics and polarizable continuum model[27] and has been successfully applied for two test systems: (R)-methyloxirane and (L)-alanine[28]. Contrary to this approach, the "clusters-in-a-liquid" methodology[29] relies on the fact that only some small chiral hydration clusters, rather than the chiral solutes themselves, are the dominant species in aqueous solution. In this model, one builds the necessary explicit H-bonded chiral solute-$(water)_n$ clusters, and then places the clusters in an implicit solvent model, for example PCM, or a more sophisticated ONIOM model of MM water molecules. The methodology also provides some insight about how to build these important chiral hydration clusters. The "clusters-in-a-liquid" approach can also be utilized for other protic solvents than water. The approach was further validated by simulating IR, VCD, Raman and ROA spectra of methyl glycidate in CCl_4 and water.[30] In a recent article,[31] the ROA signatures of n-acetyl-L-cysteine, a flexible chiral system, in water and methanol have been simulated and compared to experiment. Two approaches to include the solvent effect have been compared. The first one couples the "clusters-in-a-liquid" model with the recently developed conformational search tool CREST[21] by Grimme and coworkers. The second one uses the *ab initio* molecular dynamics (AIMD) approach.[32,33] According to the authors,[31] the AIMD ROA approach was only applied so far to rigid chiral molecule, propylene oxide. Their conclusions were that implicit solvation model captures most of the spectra signatures in the 700-1400 cm^{-1} region while adding one explicit water molecule ("clusters-in-a-liquid" method) further improves the agreement with the experimental measurement. However, some discrepancies still appear in the low frequency region, below 400 cm^{-1}. This is where the AIMD approach brings considerable improvements since it considers the influence of the entire bulk solvent as well as some anharmonic effects. At last, building on their CREST algorithm, S. Grimme and coworkers have just introduced their new methodology called "quantum cluster growth" (QCG).[34] It is a fully automated approach to build molecular clusters of the solute with a given number of solvents generated by adding one solvent molecule at a time to an energetically favorable position. The underlying growing process is physically motivated by computing the leading-order solute−solvent interactions first and can account for conformational and chemical changes due to solvation for low-energy barrier processes. This approach is very similar to the "clusters-in-a-liquid" method presented earlier.

While specific solvent-solute interactions can explain some signature changes in vibrational spectroscopies, new observations of chiral induction (IC) have recently been revealed. In 2016, Sebestik *et al.* observed a strong induction of ROA chirality on achiral solvents by an optically active dye, helicene Helquat.[35] This effect has first been interpreted as a solvent-solute complexation. In 2019, Li *et al.* observed a strong IC ROA on the solvent by a chiral Ni complex. The authors have tentatively explained this phenomenon by a through-space solvent-solute interactions facilitated by the solute under resonance they called "ring of fire".[1] They were able to reproduce the experimental ROA patterns using their Transition Polarizability Model (TPM[36–38]) even though they were not completely convinced. After some more detailed two-cell experiments, Bour and coworkers were able to derive a quantitative formula to simulate these phenomena.[39] This new form of chiral Raman spectroscopy has first been described as interference of CD and ROA,[39] then a combination of electronic circular dichroism and circularly polarized light,[40] false ROA and ECD/ROA interference,[41] and ECD-Raman.[42] The final mechanism of the phenomenon is summarized in two very recent papers.[43,44] In addition to the RROA signal, the difference between the right-handed and left-handed circularly polarized scattered lights when an incident randomly polarized light is sent on a chiral solute molecule (SCP measurement), the solute, when in resonance, can undergo ECD and thus absorbs differently the right-handed and left-handed components of the incident randomly polarized light. The partially circularly polarized (CP) light generated can then produce CP-Raman scattering (usual Raman scattering but with 100% right-

handed or left-handed incident circularly polarized light instead of using linearly or naturally polarized light) with the achiral solvent. This phenomenon was called **e**CP-Raman to emphasize the contribution of both ECD and CP-Raman in the mechanism. While specific non-covalent interactions and coordination may still produce induced solvent chirality features, it is important to check if the **e**CP-Raman mechanism plays an important role in solvent ROA signals for resonance measurements. It is therefore crucial to understand the origin of the signatures to separate the two contributions otherwise some misleading conclusions can be drawn.[43,44]

2.3 Research project

Recently Nafie[45] one of the leading experts in the field, identified the future challenges for Vibrational Optical Activity (VOA): these consist in describing the effects of weak intermolecular interactions, the transfer of chirality, the effects of solvent, supramolecular chirality, ... To tackle these issues, one needs to sample thoroughly the PES to unravel the most energetically favorable conformers as well as to properly describe the interactions with the environment. New methodologies have recently been proposed in this regard like CREST[21] to sample the PES of flexible molecules and "clusters-in-a-liquid"[29,31] or AIMS[31–33] to evaluate the solvent effects. When measuring the ROA signals of a solute under (near) resonant condition, some peculiar signatures associated to the achiral solvent have been discovered.[1,35,42,43] After few attempts, the final explanation is a repolarization of the incident light due to the ECD of the solute which leads to CP-Raman signatures of the solvent.[39,46] However, some specific non-covalent interactions may still produce induced solvent chirality (IC) signatures. This shows more than never that a reliable quantum chemistry approach is required to unravel all these different types of signatures. In this proposal, we would like to assess the performance and reliability of the recently proposed methodologies to unravel the ROA signatures of two types of systems, cryptophane derivatives and Extended Metal Atom Chains (EMACs) derivatives, by confronting the simulations with accurate ROA measurements provided by our partners in the frame of an ANR project called CAORSS (see section 4, interdisciplinary approach of the research project). These systems are known to present ROA signatures due to encapsulation of guest molecules/atoms or solvent effects (such as chiral induction).

The project is divided into two tasks (presented below). Their schedule and interplay are given as a Gantt chart in Section 2.4.

Task 1 consists in the simulation and interpretation of ROA spectra of flexible molecules taking into account the surroundings. Our model system will be the cryptophane derivatives since Nicolas Daugey (in collaboration with Thierry Brotin for the synthesis) can provide us with very accurate experimental spectra in different solvents.[47,48] Cryptophane molecules consist in two hemispheres each made of three benzene rings connected in ortho by three methylene groups. The two hemispheres are themselves bound with three -O$(CH_2)_n$O- linkers to form a quite rigid cage. Function of the arrangement of the linkers and of the substitution of the benzenes, the molecule can be chiral. Moreover, it is known that cryptophanes can encapsulate solvent molecules as well as a Xe atom and that this has an influence on the ROA spectrum. For instance, the ROA intensity of the heart breathing mode at around 150 cm^{-1} diminishes by 80% when Xe is present in the cavity (Figure 1).[49] Contrary to rigid molecules, more than one conformers need to be taken into account in the simulation of vibrational spectra for flexible molecules such as cryptophane derivatives. A preliminary investigation in the frame of the master work of Lou D'haese has shown that CREST[21] is suitable to obtain starting conformer structures. However, cryptophane-111 (Cr-111), which was the subject of this investigation, is still very rigid while cryptophane with longer linkers such as Cr-222 and Cr-223 are known to be more flexible. Thus, **Task 1a** will investigate the performance of CREST on these other Cr-derivatives. From the ensemble of conformers generated by CREST, a DFT optimization step will be performed. The effect of adding dispersion correction such as D3[50] from Grimme on the energy of the conformers will also be assessed since the preliminary study has shown that the relative energy of the two more stable conformers is reversed when adding D3 correction on top of B3LYP or when using ωB97X-D XC functional. This was in contradiction with MP2 relative energies and with ROA measurement. In **Task 1b**, various implicit solvent models will be tested to consider the solvent effects such as the IEF-PCM method or the more recent SMD approach[51,52] which is supposed to better described the solvation free energy. After geometry optimization in the implicit solvent, the Raman and ROA spectra will be calculated and compared to experimental data provided by

our collaborator using different solvents such as chloroform, dichloromethane, acetonitrile, DMSO, DMF, Toluene. Next, explicit solvent molecules will be added to our simulation (**Task 1c**). Various methodologies will be tested: (i) molecular dynamics (MD) simulation approach to sample several thousand snapshots for catching dynamics of the solute-solvent interactions, (ii) "clusters-in-a-liquid" by manually adding up to 3 explicit solvent molecules since it has been demonstrated that small solvent clusters are usually enough to reproduce vibrational spectra,[29,31] even in water, (iii) or by using the new automated scheme to grow explicit solvation clusters.[34] **Task 1d** will be dedicated to the AIMD approach to simulate ROA spectra.[33] To our knowledge, this approach was only used a couple of times to simulate ROA spectra while it was shown to produce spectra consistent with experimental observations, especially at low wavenumbers where harmonic-based approaches usually fail.[31,33] It is important to reproduce the ROA signatures in this region since it was shown for instance that the encapsulation of xenon atom on Cr-111 only affects the intensity of the ROA band at 150 cm^{-1} associated to a breathing mode of the cage (Figure 1).[49]

In **Task 2**, we will focus on the ROA spectra of molecules that are in resonance with the incident laser light. The molecule under study will be Extended Metal Atom Chains (EMACs) derivatives such as tri-cobalt $Co_3(dpa)_4(MeCN)_2](PF_6)_2$ that exhibit an helicoidal structure. We except them to show **e**CP-Raman signatures[44] from the solvent in addition to their intrinsic RROA ones. Indeed, a preliminary investigation by Nicolas Daugey together with Patrick Rosa and Elizabeth Hillard (unpublished results) has shown that they present exceptional optical activity properties (ROA/RAMAN > 0.01, Figure 2) and induce optical activity on the solvent even at long range (low dilution, Figure 3). These observations are complementary to those of Bour and coworkers.[1,35] In the frame of the CAORSS project, new EMAC compounds will be synthetized and characterized by ROA spectroscopy. Our simulations are necessary to separate this newly found **e**CP-Raman component, which sometimes dominate the overall signal, from the RROA signatures (**Task 2a**). **Task 2b** will used the same methodology to account for explicit solvent molecules as in Task 1c to investigate inter/intramolecular bonding interactions that may still produce induced solvent chirality RROA signatures.

Figure 4 presents the molecules that will be synthetized and characterized within the CAORSS project and that are envisioned in our simulation within this PDR proposal. The interplay between theory and experiment will help us design an accurate methodology to simulate the ROA spectra of these systems in various environments and will aim at clarifying the different mechanisms that can be at the origin of the ROA signatures such as the induction of chirality or the **e**CP-Raman phenomenon.

2.4 Work plan (to be described for the whole duration of the project)

	Year 1		Year 2		Year 3		Year 4	
Semester	1	2	1	2	1	2	1	2
Task 1a								
Task 1b								
Task 1c								
Task 1d								
Task 2a								
Task 2b								
PhD thesis redaction								

Task 1a: Determination of the most stable conformers of cryptophane derivatives using CREST. Reoptimization of the conformers at the DFT level using various XC-functional with and without D3 dispersion correction. Comparison of the relative energies with respect to MP2 reference calculations.

Task 1b: Simulation of the Raman and ROA spectra of cryptophane derivatives using various implicit solvent models and comparison to experimental spectra recorded in different solvents such as chloroform, dichloromethane, acetonitrile, DMSO, DMF, Toluene.

Task 1c: Simulation of the Raman and ROA spectra of cryptophane derivatives using different approaches to consider explicit solvent molecules and comparison to experimental spectra.

Task 1d: Simulation of the Raman and ROA spectra of cryptophane derivatives using the AIMD approach and comparison to experimental spectra.

Task 2a: Simulation of the **e**CP-Raman signal of EMACs derivatives and comparison to experimental spectra in order to separate this signal from the RROA one.

Task 2b: Simulation of the RROA signatures taking into account solvent molecules using the different strategies of Task 1c and comparison to experimental spectra to unravel specific signals originating from inter/intramolecular bonding interactions.

References

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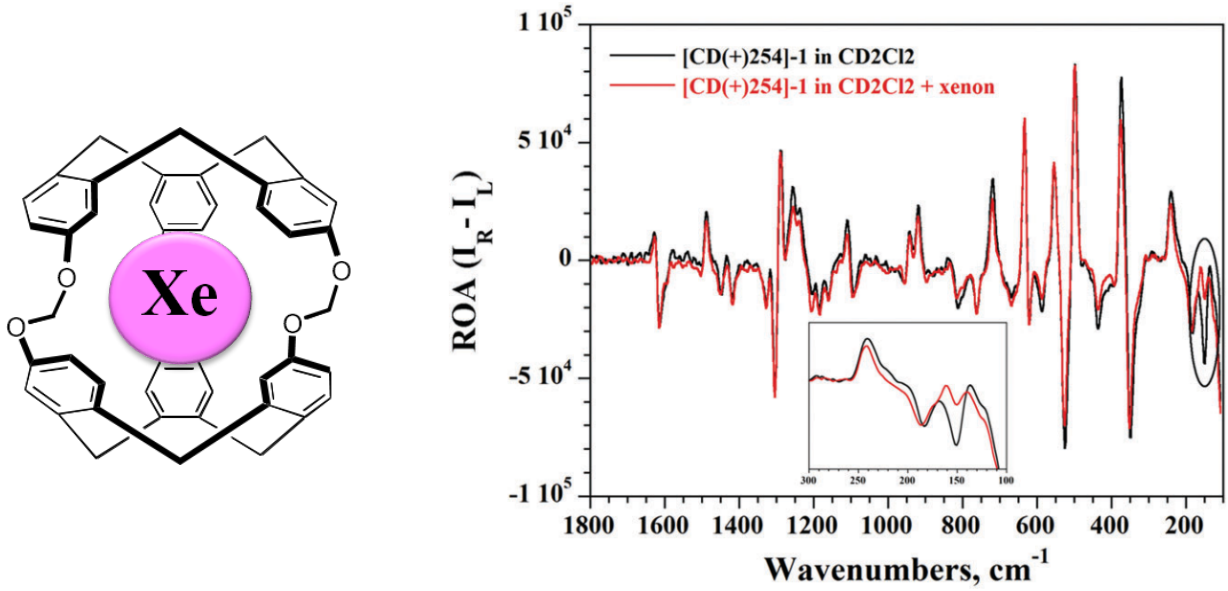


Figure 1: Sketch of the encapsulation of a Xe atom within the cavity of cryptophane-111 (left) and comparison between the recorded ROA spectra (right) with (red) and without (black) Xe atom in the cavity of PP-Cryptophane-111. The zoom region focuses on the heart breathing mode at 150 cm^{-1}. The data have been provided by Nicolas Daugey and coworkers from Ref. 49.

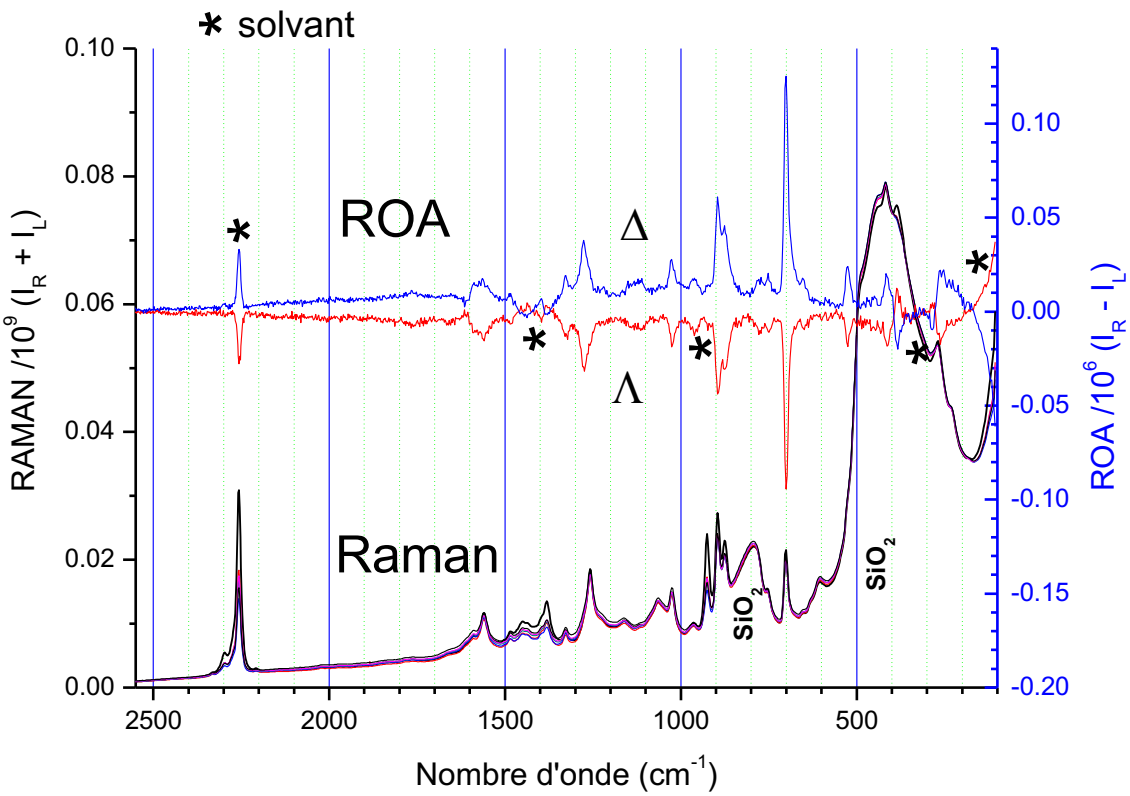


Figure 2: Recorded ROA spectra of the Δ et Λ Cobalt complexes. The asterisks indicated the ROA peaks associated to the chiral induction on the acetonitrile solvent molecule. Unpublished result provided by Nicolas Daugey and coworkers.

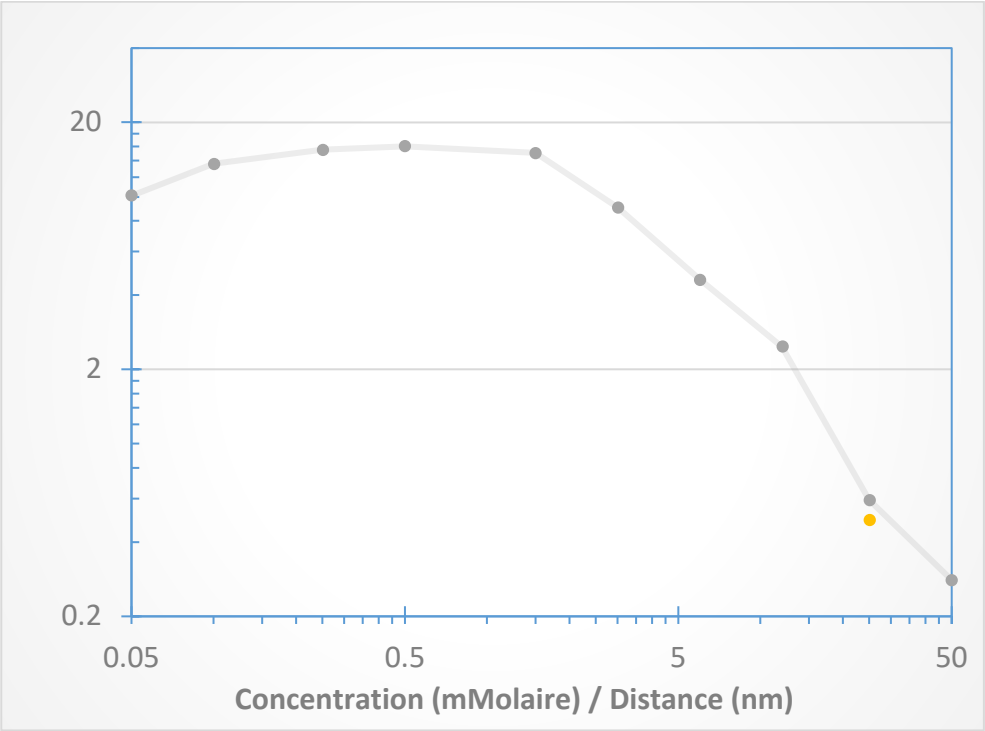


Figure 3: Effect of dilution on the ratio between the ROA bands of the solvent (acetonitrile) and those of the solute (Cobalt complex). Unpublished result provided by Nicolas Daugey and coworkers.

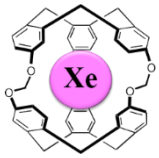
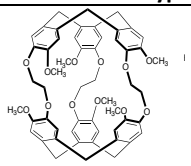
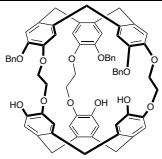
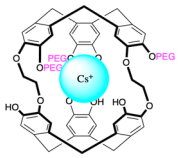
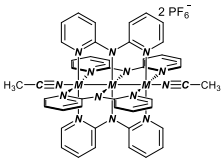
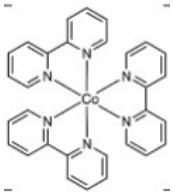
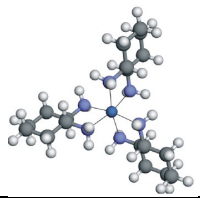
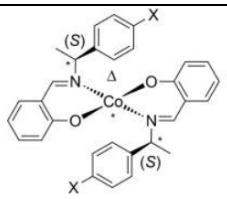
Cryptophane derivatives			
			
Anti-cryptophane 111 hosting Xenon	Anti-cryptophane A (Cr222)	Substituted Syn-cryptophane A (Cr222)	PEG substituted anti-cryptophane A soluble in H2O/CH_3CN
Model metal complexes			
			
$[M_3(dpa)_4(MeCN)_2]^{2+}$	$[M(bipy)_3)]^{2+/3+}$ Tris(2,2'-bipyridyl)cobalt(III)	$[M(chxn)_3]^{2+/3+}$	[M(bis{N-(1-(Ar)ethyl) salicylaldiminato})]
Co(II), Ni(II), Cu(II)	Mn(II), Fe(II), Fe(III), Co(II), Co(III), Ni(II), Cu(II), Zn(II)	Mn(II), Fe(II), Fe(III), Co(II), Co(III), Ni(II), Cu(II), Zn(II)	Co(II), Cu(II), Zn(II)

Figure 4: Sketch of the two types of molecular systems envisioned in this proposal.