Research Article

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Supramolecular encapsulation of 1,3-bis(1-adamantyl)imidazolium chloride by β-cyclodextrins: towards inhibition of C(2)-H/D exchange

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The study of the hydrogen/deuterium exchange reactions of the C(2)-proton for different carbene precursors has been carried out in the absence and presence of β-cyclodextrin in D_2O at 25°C. Formation of the inclusion complexes of imidazolium salts with the native β-cyclodextrin and the β-dimethylcyclodextrin is demonstrated by 1D and 2D ^1H NMR, ESI/HRMS and a molecular modelling study. Formation of the inclusion complexes of imidazolium salts with the native β-cyclodextrin and the β-dimethylcyclodextrin is a simple and efficient method to modify the acidity of the imidazolium H(2) and to modify its environment. Encapsulation of 1,3-disubstituted imidazolium chloride by β-cyclodextrins results in the inhibition of the H(2)/D exchange in the complex. Copyright © 2008 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: cyclodextrins; imidazolium salt; H/D exchange; supramolecular chemistry; encapsulation

INTRODUCTION

Since the description of stable carbenes by Bertrand and Arduengo, the exploration of their chemical reactivity has become a major area of current main group chemistry.[1] Significant improvements of the catalyst performance have recently brought benefits to fine chemistry via simple substitution of a phosphine by an imidazolylidene ligand. Various examples are found in many catalytic reactions: cyclopropanation, hydrogenation, hydroformylation, etc.[2] For example, in alkene metathesis, attempts to mimic the influence of bulky electron-rich phosphines in ruthenium catalysts using sterically hindered imidazolylidenes have revealed a dramatic activity increase.[3–8] The best way to coordinate a sterically hindered *N*-heterocyclic carbene to a metal centre involves the *in situ* deprotonation of the H(2) of an imidazolium salt with a base in the presence of a metal complex.[3–8] This deprotonation can be evidenced by the H/D exchange of the proton in D_2O solution.[9] The imidazolium salts have also been used as ionic liquids solvent for organometallic reaction,[10] but in this case the formation of the carbene is avoided. Because ligand metathesis can occur in the ionic liquid media, the simple modification of the environment of the imidazolium salts can be an interesting way to inhibit the carbene formation in these conditions.[11]

In supramolecular chemistry,[12,13] host–guest chemistry describes complexes that are composed of two or more molecules or ions held together in unique structural relationships by non-covalent bonds. Classical hosts are cyclodextrins (**CDs**), cyclic oligosaccarides forming a truncated cone with hydrophilic annulus and relatively hydrophobic cavity.[14] A methylation of the native **β-CD** can occur on the alcohols to form the 2,6-dimethyl-β-cyclodextrin (**β-DIME**, see Fig. 1). Use of supramolecular chemistry can be a very simple way to modify the acidity of the imidazolium H(2) by the formation of an inclusion complex and by modifying its environment. We present here the supramolecular encapsulation of 1,3-disubstituted imidazolium chloride by β-cyclodextrins and the inhibition of the H(2)/D exchange in the complex.

Due to the salt nature of the 1,3-disubstituted imidazolium cation, various complexes can be designed by changing the nature, the size or the shape of the imidazolium substituents. In fact, the introduction of hydrophobic groups on the imidazolium cation can allow the formation of very stable inclusion complexes with **CDs**.[15,16] In this study we have used imidazolium salts employed as carbene precursor for organometallic catalysis, possessing very common residues such as adamantyl, 2,6-di-*iso*-propylphenyl and 2,4,6-trimethylphenyl attached directly to the nitrogen atom of the imidazolium cation (Fig. 2). In all cases, chloride counter ion has been used.

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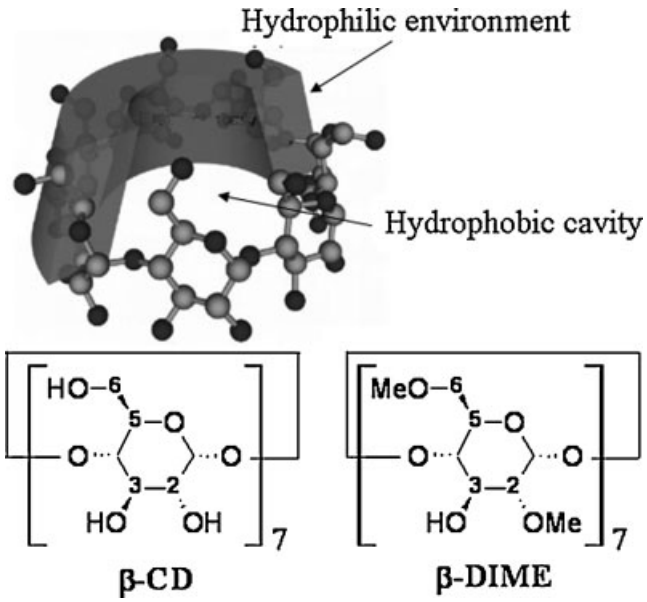

Figure 1. Structure and schematic representation of the cyclodextrins used in this work

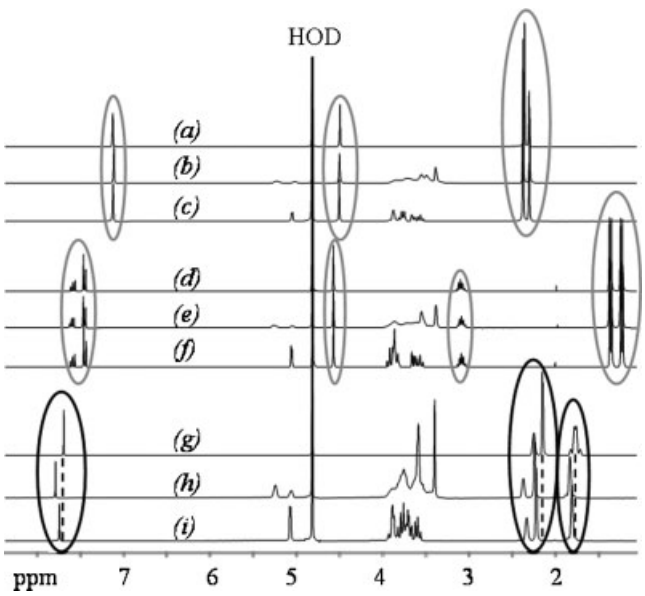

Figure 3. ^{1}H NMR spectra at 298 K in D_2O (equimolar mixture at 8 mM) for: *(a)* **[1][Cl]**, *(b)* **[1][Cl]** and **β-DIME**, *(c)* **[1][Cl]** and **β-CD**, *(d)* **[2][Cl]**, *(e)* **[2][Cl]** and **β-DIME**, *(f)* **[2][Cl]** and **β-CD**, *(g)* **[3][Cl]**, *(h)* **[3][Cl]** and **β-DIME**, *(i)* **[3][Cl]** and **β-CD**

Recently the H/D exchange rate constants for the C(2)-proton of a series of imidazolium cations with alkyl, aryl and calixarene substituents in CD_3OD containing 3% H_2O were reported.[17,18] Buncel and coworkers have demonstrated that the lability of the C(2)-proton in aqueous solution is increased by protonation or metalation of imidazoles compared with the neutral substrate.[19] More recently, the effect of supramolecular inclusion of imidazolium cations on the lability and acidity of the C(2)-proton has been investigated. The study of the hydrogen/deuterium exchange reactions of the C(2)-proton for α,α'-bis(3-(1-methyli-1-methylimidazolium))-*p*-xylene dication has been carried out in the absence and presence of cucurbit[7]uril (**CB[7]**) in D_2O at 25°C.[20] The **CB[7]** host molecule acts as a hydrogen bond acceptor for the C(2)-protons, by positioning the guest in the cavity of **CB[7]** for optimal hydrogen bonding interactions.

In our study, the inclusion of **[1][Cl], [2][Cl]** and **[3][Cl]**, frequently used as carbene precursors, with **CDs** was considered. In fact, the formation of symmetrical inclusion complexes with two **CDs** with one imidazolium salt can protect the H(2) H/D exchange. The formation of inclusion complexes with **β-CD** and **β-DIME** was investigated by 1D, 2D NMR study, mass spectrometry and molecular modelling simulation.

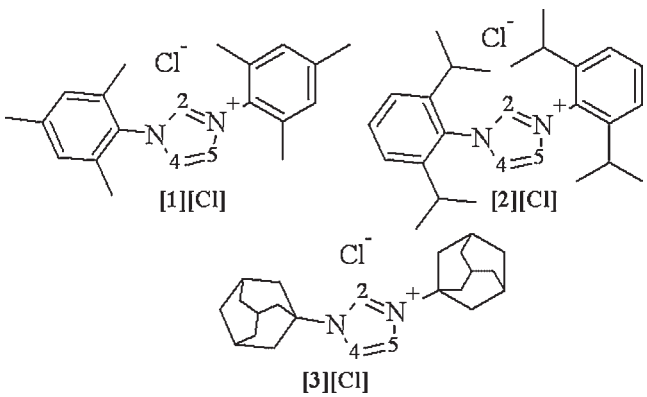

Figure 2. Structure of different imidazolium salts used in this work

RESULTS AND DISCUSSION

Initially, the imidazolium salts have been studied by ^{1}H NMR spectrometry to observe the formation of the inclusion complexes with the native **β-CD** and the **β-DIME** (Fig. 3). For a mixture of **β-CD** or **β-DIME** with **[1][Cl]** or **[2][Cl]** no changes are observed for the imidazolium protons (see grey ellipsis). The non-complexation of **[1][Cl]** or **[2][Cl]** by the **CD** is probably due to steric hindrance of the aromatic residues. A strong modification of the chemical shifts of **[3][Cl]** can be monitored after the addition of **β-CD** or **β-DIME** (see black ellipsis). In fact for **[3][Cl]**, the aromatic protons show different downfield shifts after the addition of **β-CD** or **β-DIME**. These variations confirm the formation of **[3][Cl]** · **CD** complexes for both cyclodextrins.

Figure 4 presents ^{1}H NMR spectra of **[3][Cl]** in the presence of the two **CDs**. The signals of **β-CD** or **β-DIME** recorded in the presence of **[3][Cl]** show some differences with respect to those of **β-CD** or **β-DIME** alone. In particular, both the internal H(3) and H(5) protons of both **CDs** underwent upfield shifts in the presence of equimolar amounts of **[3][Cl]**. This observation indicates a 'host–guest' interaction.[21] H(2) and H(4) outer protons also underwent downfield shifts; this result can be attributed to an interaction other than an inclusion phenomenon. Since **[3][Cl]** contains adamantyl residues, the binding interaction in the $\mathbf{[3][Cl]_x \cdot CD}$ complexes in aqueous solution may be dominated by hydrophobic forces.

To gain more insights into the molecular interactions and the geometry of the host–guest complexes, we performed a 2D NMR study in addition to the 1D NMR data presented above. ROESY experiments are well suited for the purpose (Fig. 5). The spatial distance must be less than 5Å to observe cross peak between two

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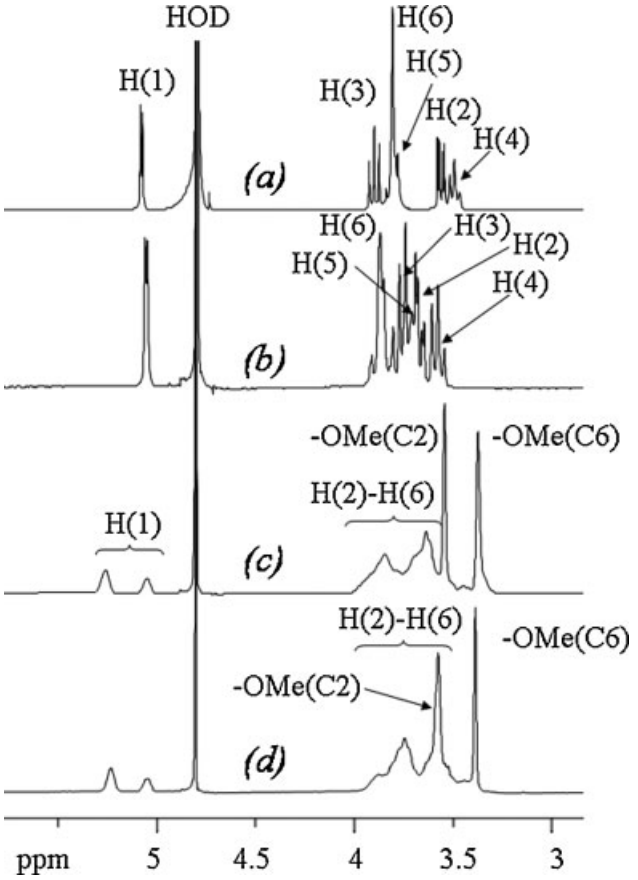

Figure 4. Partial ^{1}H NMR spectra at 298 K in D_2O (8 mM) for: *(a)* **β-CD**, *(b)* **[3][Cl]** and **β-CD**, *(c)* **β-DIME**, *(d)* **[3][Cl]** and **β-DIME**

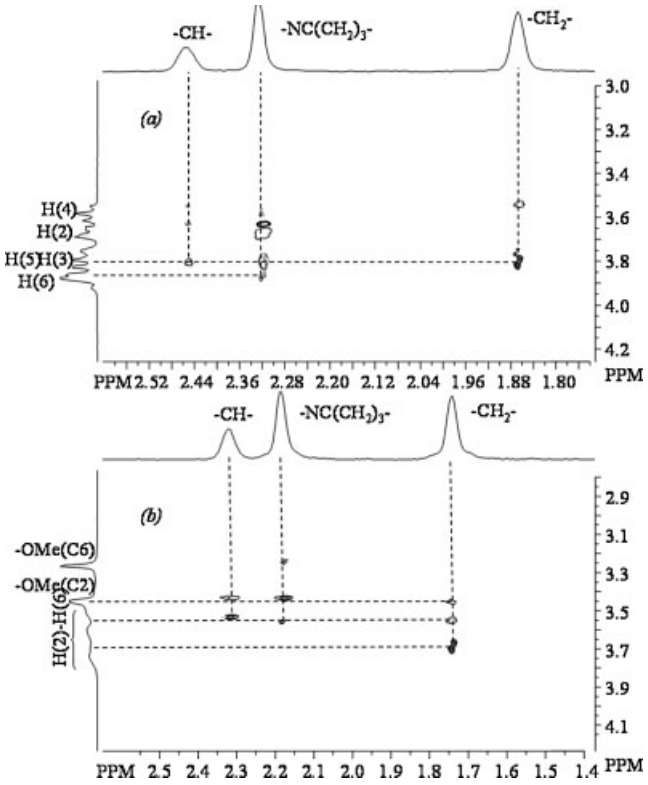

Figure 5. Partial NOESY NMR spectra at 298 K in D_2O of: *(a)* 8 mM **[3][Cl]** and 8 mM **β-CD** (D_2O); *(b)* 8 mM **[3][Cl]** and 8 mM **β-DIME**

protons. For **[1][Cl]** and **[2][Cl]**, any spatial cross peaks are detected with **β-CD** or **β-DIME** and these results confirm the absence of an inclusion complex.

The ROESY spectrum of an equimolar mixture of **β-CD** or **β-DIME** with **[3][Cl]** in D_2O gave intense cross peaks between the adamantyl residues and the internal H(3) and H(5) protons of the **CDs** (Fig. 5). The absence or the very weak cross peaks observed between the H(6) (and the –OMe(C6)) is an indication that the inclusion occurs by the wide rim (*i.e.* the secondary alcohols face). It can also be noted that all adamantyl protons are in spatial proximity with the **CD** protons. This could be an indication of a deep inclusion of the adamantly residue into the hydrophobic cavity of the **CD**.

The exact stoichiometry of the complexes was obtained from Job's plot titrations. For **β-CD** and **β-DIME**, the maximum value of 33% of the curve reveals a 2:1 host–guest complex stoichiometry (see Supporting Information, Figs. S2 and S3).[22–24] Moreover, the association constant and the stoichiometry could be determined by the concentration dependence of the chemical shifts ($\Delta\delta$) values of the **[3][Cl]** (Fig. 6). To extract such information, the differences of the resonance frequency of the adamantyl protons were measured from the NMR spectra because the signals were well resolved and considerably intense. The stoichiometry of the host–guest complex was confirmed to be 2:1 by the molar method[24] and the association constant can be calculated at $11000 \pm 100\ M^{-2}$ for $(\beta\text{-CD})_2 \cdot [3][Cl]$ and at $10500 \pm 150\ M^{-2}$ for $(\beta\text{-DIME})_2 \cdot [3][Cl]$. Generally, a value of $10^4\ M^{-1}$ is common for a 1:1 complex with an adamantyl guest, and a 2:1 complex may have a much higher value ($10^8\ M^{-2}$).[25] However, it was previously demonstrated that the imidazolium salts are complexed by cyclodextrin with weak binding constants, as well as native imidazole.[25–27] In this case, the adamantyl residues are directly attached to the imidazolium ring and the presence of the imidazolium close to the adamantly group may explain the obtained weaker binding constant, compared to the expected ones.

To confirm the geometry obtained experimentally, theoretical calculations have been performed using semi-empirical calcu-

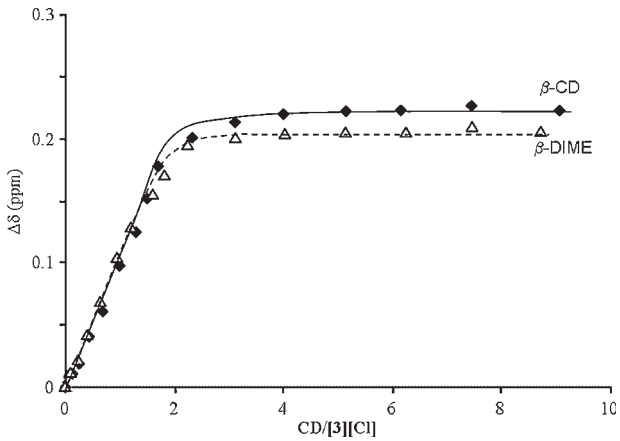

Figure 6. –CH– of **[3][Cl]** NMR titration profile in D_2O at 298 K for addition of: **β-CD** and **β-DIME**

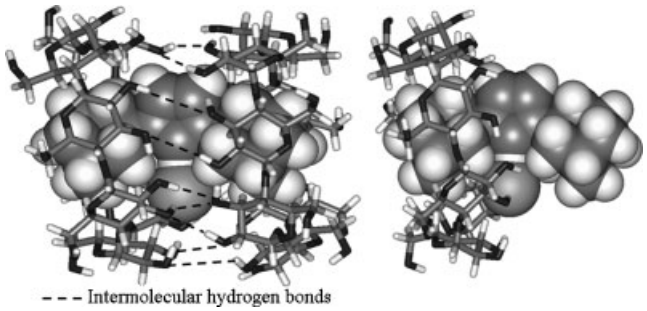

Figure 7. Minimised complexes obtained by PM3 calculation for 2:1 and 1:1 complex between the **β-CD** and **[3][Cl]**

lation (PM3, MOPAC2007^{TM}).[28] The results show that the enthalpy changes are very favourable: -57 kcal.mol^{-1} for the 2:1 complex and only -34 kcal.mol^{-1} for the 1:1 stoichiometry for **β-CD**; and respectively -64 *versus* -30 kcal.mol^{-1} for **β-DIME**. The obtained minimised geometries are shown in Fig. 7.

Moreover, the calculation reveals that both **β-CDs** are connected together via hydrogen bonds (the distance between the two **CDs** and the angles between them are comprised respectively between 2.5 and 3 Å and between 120 and 160°). The existence of these hydrogen bonds can explain the stability of the 2:1 complex for **β-CD**. For the **β-DIME**, not only intramolecular hydrogen bonds are observed but also van der Waals interactions occur between two methyl groups of the **CDs**.

As the H/D exchange in the non-complexed imidazolium salt **[3][Cl]** is fast on the NMR time scale, the precise determination of its pK_a was not possible. An indirect method to compare the H(2) acidity (pK_a) of the complexed and non-complexed imidazolium was used, based on monitoring the value of the C(2)-H(2) bond length and the H(2)'s charge during the PM3 calculation (Table 1).[29,30] Only the value of the C(2)-H(2) bond length is affected by the **CD** complexation. A reduction of approximately 0.1 Å is induced by the presence of the **CDs**, which can be an indication of the increase of the H(2) pK_a.

To complete the characterisation of the complexes of **[3][Cl]** with the **β-CD** or **β-DIME**, we have performed ESI/HRMS analysis. Only 1:1 complexes can be observed with the **β-CD** and the **β-DIME**. We found: m/z 1472.59879 (calculated: 1472.64185) for (**β-CD** · **[3]**)$^+$ and m/z 1640.83432 (calculated: 1640.82959) for (**β-DIME** · **[3]**)$^+$. This fact is not surprising, as the imidazolium charge is not visible in the 2:1 complexes, due to its encapsulation between the two cyclodextrins. A similar example was reported

Table 1. Distance C(2)-H(2) and charge of H(2)[a]

Species	Distance C(2)-H(2) [Å]	Charge of H(2)[b]
[3][Br]	1.36	0.349
[3][Br] + **β-CD**	1.24	0.349
[3][Br] + 2**β-CD**	1.26	0.351
[3][Br] + **β-DIME**	1.25	0.351
[3][Br] + 2**β-DIME**	1.27	0.353

[a] Obtained after PM3 geometry minimisation.
[b] Mulliken's charges.

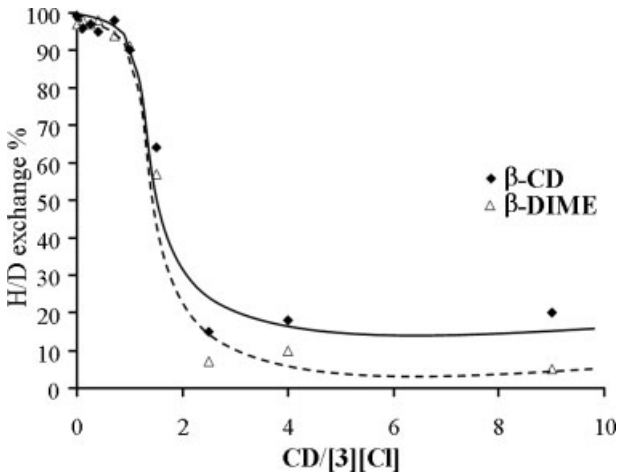

Figure 8. C(2)-proton H/D exchange after 30 min as a function of CD/**[3][Cl]** ratio for **β-CD** and **β-DIME**

for the complexation of imidazolium salts with a **CB[7]**, where the macrocycle can completely hide the charge of the complex.[31]

As the salt is totally encapsulated in the 2:1 complexes, the C(2)-H/D exchange can be monitored. The effect of the **CD**'s presence on the H/D exchange of the C(2)-proton of **[3][Cl]** in D_2O ($pD = 6.5$) at 298 K can be followed by ^{1}H NMR at different molar ratios **CD/[3][Cl]** (Fig. 8).

After 30 min the H/D exchange is considerably affected by the introduction of **CDs** in the aqueous solution. In fact, for **CD/[3][Cl]** ratios inferior to 1, 90% of the C(2)-protons were exchanged. For ratio greater than 2, only 10% were exchanged in at the same time. The ratio range between 1 and 2 is a transition between the two previous zones. Moreover, the H/D exchange for a 2:1 complex has been followed: after 1 h, increases at 30% and after 48 h, 80% of deuterium exchange was observed. In fact, the encapsulation of the imidazolium residue between two cyclodextrins results in an inhibition of the fast kinetics of the deuterium exchange.

In our study, the supramolecular system is different from the previously reported by Macartney, as there are no direct interactions between the imidazolium H(2) and the host. The basic assumption in the analysis of H/D exchange data is that the exchange rate reflects the exposure of the imidazolium H(2) to the solvent. Thus when the imidazolium is buried between the two **CDs** the exchange is slower. As suggested by the molecular modelling results, formation of hydrogen bonds network (or methyl-methyl interactions) between the two **CDs** results in a steric barrier around the imidazolium cation. This barrier modifies the kinetics of the H/D exchange of the imidazolium acidic proton.

CONCLUSIONS

We demonstrated here that the formation of supramolecular complexes between **CDs** and imidazolium salts can be an efficient method to modify the first- and the second-coordination sphere of an organometallic precursor. Fruitful developments of these supramolecular complexes are expected in organocatalysis by controlling the reactivity and the stability of the carbene; the carbene formation can be inhibited by supramolecular encapsu-

lation in aqueous solution by an efficient shielding of cyclodextrins. Under external stimuli (addition of THF or DMSO) the supramolecular complex can be disassembled and then the carbene can be generated. Work is under development in our group for the development of fine and regulated organocatalysis in the presence of these supramolecular complexes.

EXPERIMENTAL SECTION

Materials

D_2O (99.95% isotopic purity) and all other chemicals were purchased from Aldrich or Strem and used without further purification.

NMR measurements

NMR experiments were recorded on advance 300 Brucker spectrometer (300 MHz) with the samples nonspinning. All NMR experiments (dye titration by host, Job's plot, 2D ROESY) are obtained by the use of the sequence commercially available on Brucker spectrometer. Chemical shifts are given in ppm (δ) and measured relative to the HOD signal. All NMR measurements were carried out in pure deuterated water ($pD = 6.5$) because it is known that electrolyte ions also form complexes with **CDs**.[32] Before each NMR measurement the pHs of the solutions were monitored and no change was observed, depending on the cyclodextrin or imidazolium concentration.

Molecular modelling

All calculations were performed on a Windows® XP workstation. Initial configurations of **CDs** and imidazolium cation have been obtained from UFF calculations under ArgusLab 4.0.1 software.[33] Then, each molecule or complex is transferred using Cartesian coordinates on the VEGA ZZ interface that allows running MOPAC2007™ software.[28,34] The semi-empirical method used is the PM3 parameterisation with the closed shell (restricted) (keywords used: EF GNORM = 0.100 MMOK GEO-OK PM3).

ESI/HRMS

Mass spectral data were obtained by the Université de Montréal Mass Spectrometry Facility and were recorded on a mass spectrometer TSQ Quantum Ultra (Thermo Scientific) with accurate mass options instrument.

H/D exchange

The deuterium exchange is followed by ^{1}H NMR. For various **CD**/**[3][Cl]** ratio and after 30 min at 298K, the NMR spectra are recorded. Then, the integration of the C(2)-H proton resonance (I) is compared with the integration of the protons -CH- of the adamantyl residues as non-exchanging integration reference (I_0) to give the percentage of H/D exchange.

Supporting information

Job's plots, large version of 2D-NMR ROESY profile, supramolecular structures obtained by semi-empirical calculation and archive files of calculation, example of H/D exchange calculation.

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