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Communication

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Cyclam Functionalization through Isocyanate Insertion in Zr−N Bonds

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Supporting Information

ABSTRACT: The insertion of isocyanates in $(Bn_2Cyclam)ZrX_2$ is regioselective; $(Bn_2Cyclam)Zr(OR)_2$ produces urea-like moieties by the insertion of RN═C═O in the $Zr-N_{amido}$ bonds of the cyclam ring. Depending on the bulkiness of the isocyanate R groups, O- and N-bound ureates are formed. $(Bn_2Cyclam)Zr(NH^tBu)_2$ reacts with MesN═C═O at the terminal Zr−N bonds.

The coordinating ability of cyclam to a large range of metal ions and the significant properties of many of its compounds are extensively documented.[1] Recent applications of cyclam derivatives in biological and medicinal studies[2] mainly focused on the development of (i) selective sensors for adenosine triphosphate, zinc, and NO regulation/delivering processes,[3] (ii) radiometal chelates for diagnosis and treatment,[4] and (iii) anti-HIV agents.[5] Modification of the macrocycle framework by the attachment of substituents at the nitrogen atoms is a requisite for optimization of these properties because it allows the design of highly sensitive and specific molecular probes by increasing the selectivity toward bonding and providing suitable anchoring functional groups.[6] A major drawback associated with these issues is related to the lack of efficient synthetic processes for selective functionalization of cyclam, which often involve multistep sequences and low overall yields.[7]

The work reported here extends our investigation of cyclam-based diamidodiamine zirconium complexes[8] and describes a new methodology to the syntheses of N-substituted cyclam derivatives by the insertion of isocyanates in the $Zr-N_{amido}$ bonds of the cyclam ring.

The insertion of isocyanates into Ti−N or Zr−N bonds was scarcely reported.[9] A mechanistic study carried out with zirconocene complexes revealed that previous coordination to the metal is not a requirement. The bonding of the resulting carbamide groups to the zirconium was postulated through the oxygen considering the oxophilicity of the metal, but the authors did not exclude N-coordinated ureate ligands.[9b]

The treatment of $(Bn_2Cyclam)ZrCl_2$ (**1**) with 2 equiv of LiOR (R = ^{i}Pr, ^{t}Bu) proceeds through chloride metathesis to give $(Bn_2Cyclam)Zr(OR)_2$ (**2**; R = ^{i}Pr, **2a**; ^{t}Bu, **2b**). The molecular structure of **2a** reveals coordination of the four N atoms of the macrocycle to the Zr atom in a trigonal-prismatic geometry (Figure 1) similar to other $(Bn_2Cyclam)ZrX_2$ complexes.[8a,b]

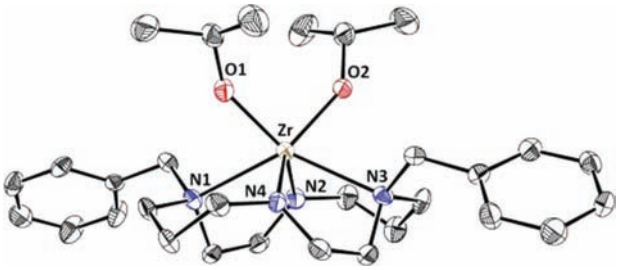
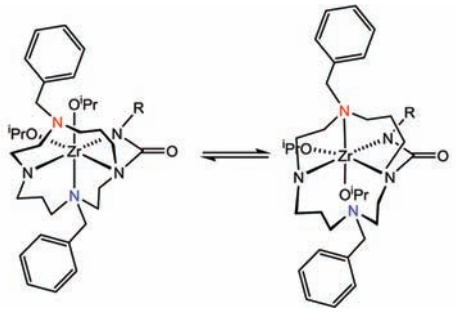


Figure 1. Molecular structure of **2a**. Displacement ellipsoids are shown at the 40% probability level. Selected bond lengths (Å) and angles (deg): Zr−O1 2.003(4), Zr−O2 2.008(3), Zr−N1 2.478(4), Zr−N2 2.097(4), Zr−N3 2.474(4), Zr−N4 2.078(4); O1−Zr−O2 91.06(13).

The reactions of **2a** with equimolar amounts of RN═C═O (R = ^{i}Pr, ^{t}Bu) result in the insertion of isocyanates into one of the $Zr-N_{amido}$ bonds of the cyclam ring, leading to the formation of N-bound urea-like fragments. The formulation of **3a** and **3b** was suggested by IR and NMR and further confirmed by X-ray diffraction of **3a**, as shown in Figure 2.

The NMR spectra of **3a** and **3b** reveal a fluxional process compatible with the equilibrium shown in eq 1. This process,



(1)

which corresponds to the swinging of the zirconium between the two amines of the original tetraazaring (in red and blue in eq 1), fades the difference between the syn and anti macrocyclic protons that show up as apparent triplets. The pendulum movement of the metal between the two macrocycle amines releases interaction of the zirconium with the macrocycle frame compared to complexes anchored on the four N atoms of the cyclam ring and accordingly the ring resonances display a high

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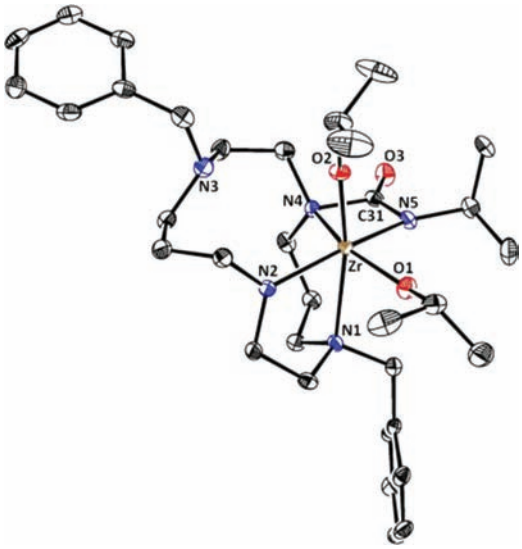


Figure 2. Molecular structure of **3a**. Displacement ellipsoids are shown at the 40% probability level. Selected bond lengths (Å) and angles (deg): Zr−O1 1.957(2), Zr−O2 1.922(2), Zr−N1 2.507(3), Zr−N2 2.099(2), Zr−N4 2.479(2), Zr−N5 2.253(2), N4−C31 1.523(5), N5−C31 1.324(5), C31−O3 1.226(4); N4−C31−N5 108.1(3), N1−Zr−O2 170.55(11), N4−Zr−O1 151.19(10), N2−Zr−N5 154.18(12).

average symmetry,[10] even though the O^{i}Pr ligands are inequivalent.

The further addition of ^{i}PrN═C═O to **3a** led to the insertion of a second isocyanate in the remaining Zr−N_{amido} bond of the macrocycle, **4** (Figure 3). The ^{1}H NMR spectrum

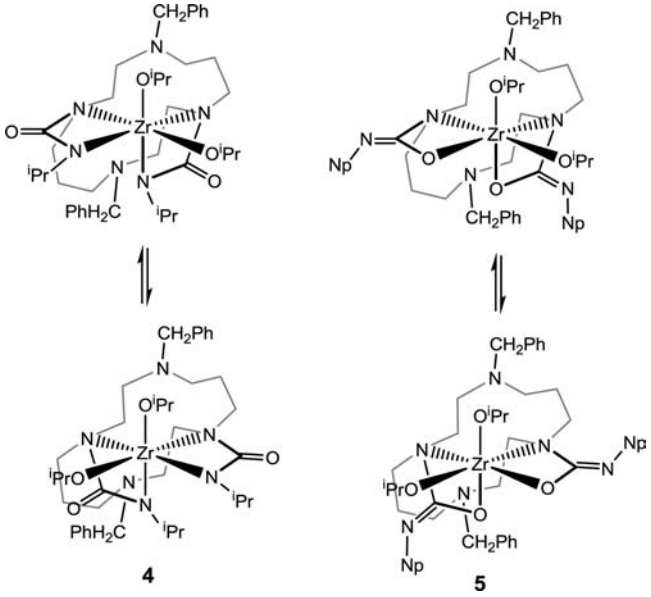
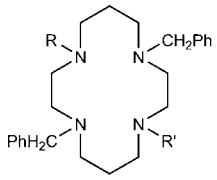


Figure 3. Complexes **4** and **5**, respectively (Np = 1-naphthyl).

displays broad resonances for the macrocyclic chains, in agreement with cleavage of the two Zr−N_{amine} bonds of the cyclam ring, and two nonequivalent O^{i}Pr and N^{i}Pr fragments. On the basis of the NMR data, the coordination geometry around the Zr atom is distorted-octahedral with two *cis*-O^{i}Pr ligands and two orthogonal four-membered metallacycles [ZrN_{cyclam}C(O)N^{i}Pr] formed upon isocyanate insertion. The set of resonances due to the cyclam ring suggests a fluxional process that interconverts the metallacycles. This process likely involves cleavage of the Zr−N_{cyclam} bond and isomerization of the pentacoordinated intermediate, followed by recoordination of the N_{cyclam} amine. This type of equilibrium was observed in titanium and zirconium azametallacycles formed by coordination of a macrocycle amine and another function (alkoxido or amido) appended to it.[11] The ^{13}C NMR spectrum displays only one resonance at δ 158.3 ppm for NC(O)N, and the IR spectrum shows one $\nu_{C=O}$ signal at 1675 cm^{-1}.

The treatment of **2b** with 2 equiv of 1-naphthyl isocyanate led to the insertion of isocyanate in the two macrocycle Zr−N_{amido} bonds (**5** in Figure 3). In contrast to compounds **3** and **4**, **5** displays O-bonded ureate moieties that give rise to one ν_{C-O} band at 1388 cm^{-1} and two $\nu_{C=N}$ bands at 1582 and 1570 cm^{-1}. The ^{1}H NMR spectrum of **5** displays very broad resonances that spread from δ 1.23 to 3.22 ppm, and the quaternary carbon of the ureate group shows up at δ 166.7 ppm in the ^{13}C{^{1}H} NMR spectrum.[12] It was not possible to attain a limit spectrum until −80 °C. The NMR pattern observed for the cyclam protons of **5** suggests that, analogously to **4**, an exchange between the two four-membered metallacycles, responsible for the magnetic equivalence of the two C2 and two C3 chains of cyclam, is taking place in the solution. The naphthyl groups in **5** are responsible for the fluorescent behavior observed when the compound is exposed to sunlight. The UV−vis spectrum of **5** shows an absorption band at 297 nm and a fluorescence emission band at 375 nm. Hydrolysis of complexes **3**−**5** afforded **6**, **7**, and **8** in almost quantitative yield (Scheme 1). While NMR data for **7** reveal a C_1 symmetry species, the NMR spectra of **6** and **8** indicate C_2 symmetry.

Scheme 1. Compounds 6−8



R = H, R' = C(O)N(H)^{i}Pr, **6**
R = R' = C(O)N(H)^{i}Pr, **7**
R = R' = C(OH)=N(Np), **8**

The results described show that the Zr−OR bonds of **2** are inert toward isocyanate insertion, and regardless of the bulkiness of RN═C═O, the insertion is regioselective and takes place at the Zr−N bonds of the cyclam ring; the formation of N- or O-bonded ligands is likely determined by the steric bulk of the nitrogen substituent in the isocyanate.

In order to compare the reactivity of a terminal primary amido ligand with a cyclam-based amido moiety, we performed the reaction of (Bn_2Cyclam)Zr(NH^{t}Bu)$_2$ (**9**) with MesN═C═O. (Bn_2Cyclam)Zr(NH^{t}Bu)$_2$ may be described as a particular tetraamidozirconium(IV) species displaying two terminal N(H)^{t}Bu ligands and two secondary amido groups incorporated in the cyclam frame. The Zr−N_{amine} distances are very elongated, and the geometry around the metal is best described as tetrahedral with two capped Zr−N_{amine} groups.[8c] The 1:1 reaction of **9** with MesN═C═O led to isocyanate insertion in the terminal amido ligand with formation of (Bn_2Cyclam)Zr(NH^{t}Bu){OC(NH^{t}Bu)═NMes} (**10**), displaying an O-bonded carbamide fragment (Figure 4). The IR spectrum of **10** displays a ν_{C-O} band at 1330 cm^{-1} and a $\nu_{C=N}$ band at 1655 cm^{-1}, which attests to electron delocalization along the N−C−N fragment. The NMR data of **10** are

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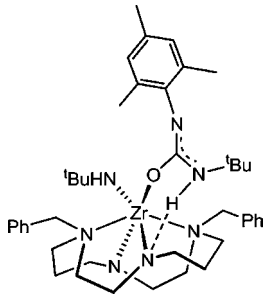

Figure 4. Complex **10**.

compatible with a C_1 symmetry species. The ^{1}H chemical shift of the N(H)^{t}Bu moiety is appreciably shifted to low field (δ 6.45 ppm). The resonance assigned to this proton shifts to high field when the temperature is raised, thus suggesting that it is involved in a hydrogen bridge. Further information on this interaction was provided by the NOESY NMR spectrum that shows cross peaks between the bridging proton (δ 6.45 ppm) and protons belonging to one C2 and one C3 macrocyclic chains, as well as the benzylic protons of one AB system. On the basis of the spectroscopic information, it is possible to assign a structure to **10** that is represented in Figure 4. It is noteworthy that, although isocyanate insertion took place at the terminal NH^{t}Bu group, the establishment of a hydrogen bridge with the macrocyclic amido function points out the availability of its electron pairs. Thus, it is not surprising that the insertion reactions in **2** and **3** occur at the cyclam N_{amido} functions alternatively to the Zr−OR bonds that are less reactive in view of the high oxophilicity of zirconium.

In conclusion, the reactions described disclose a new reactivity pattern based on the insertion of isocyanates in the Zr−N bonds of dianionic cyclam derivatives of **2**. The high oxophilicity of the zirconium is likely responsible for this behavior, which allows the selective functionalization of cyclam with one or two urea fragments. The stoichiometric ratio between RN═C═O and the complex controls mono- or diinsertion, and the type of product obtained, O- or N-bonded ureates, seems to be dictated by the bulkiness of the isocyanates. To the best of the author's knowledge, this is the unique reliable method for the syntheses of these types of compounds. If $(Bn_2Cyclam)Zr(NH^tBu)_2$ reacts with MesN═C═O, the insertion in the terminal Zr−N bonds is favored. The reactions of other polar molecules (CS_2, CO_2, allenes, isocyanides, and cyclic esters) with $(Bn_2Cyclam)ZrX_2$ complexes are currently under study. It is noteworthy that the insertion of isocyanates does not take place in **1**. The results demonstrate that the bonding of diamido/diamine cyclam ligands to zirconium is sensitive to the nature of the two additional ligands that may regulate the reactivity of the macrocycle toward insertion and, in this way, determine the significance of this method in cyclam functionalization.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details concerning the syntheses and characterization of all new compounds and crystallographic data for **2a** and **3a** (CCDC 826142 and 826143). This material is available free of charge via the Internet at http://pubs.acs.org.

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