Isotope Exchange

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Regiospecific C–H Bond Activation: Reversible H/D Exchange Promoted by Cu^{I} Complexes with Triazamacrocyclic Ligands**

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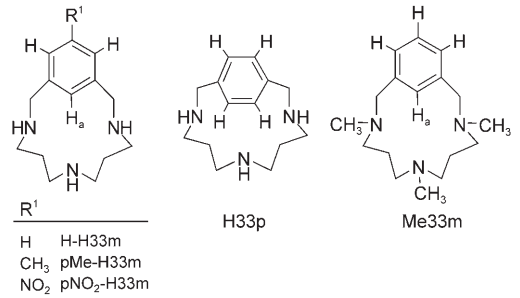
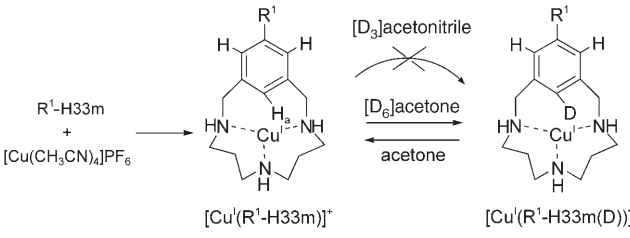
Selective C–H bond activation by metals under mild conditions is a major subject of research targeting the final functionalization of organic substrates.[1] The characterization of the usually unstable intermediates of the C–H bond activation prior to functionalization is crucial for the mechanistic comprehension of the reaction.[2] Different mechanisms, such as oxidative addition, electrophilic metalation, or agostic bonding, have been proposed in extensive work published on the C–H activation of aromatic or aliphatic compounds catalyzed by second- and third-row transition metals (TMs; i.e., Pd and Pt,[3] and Ru, Rh, and Ir[4]). However, much less work is found with first row TMs (i.e., Ni,[4c,5] Co,[6] Fe,[7] and Mn[8]) and even less for the biologically relevant metal copper.[9] We have already reported an example of intramolecular aromatic C–H activation by Cu^{II} in a disproportionation reaction and characterized an aryl copper(III) species as a reaction product.[10] Herein, we report on the reactivity of five triazamacrocyclic ligands with Cu^{I} and the study of these reactions by ^{1}H and ^{2}H NMR spectroscopy, ESI mass spectrometry, and density functional computations.

The reaction of the ligands H-H33m, pMe-H33m, and pNO_2-H33m (Scheme 1) with one equivalent of $[Cu^{I}(CH_3CN)_4]PF_6$ in CD_3CN under N_2 afforded the corresponding $[Cu^{I}(R^{1}\text{-H33m})]^{+}$ complexes (Scheme 2). The ^{1}H NMR spectra of these complexes are very similar to those of the free ligands. However, when performing the reaction in $[D_6]$acetone, we observed a gradual decay of the singlet corresponding to H_a in the ^{1}H NMR spectra, with no other integration changes in the rest of the signals. The ESI mass spectra of deuterated acetone solutions show a peak corresponding to $[Cu^{I}(R^{1}\text{-H33m})]^{+}+1$, compared to the peak for $[Cu^{I}(R^{1}\text{-H33m})]^{+}$ in the case of CD_3CN solutions, which clearly suggests the substitution of H_a by a deuterium atom (Scheme 2). This result was confirmed by demetalation of the deuterated complex by adding an excess of 1,10-phenanthro-



Scheme 1. Ligands used for Cu^{I} complexation.



Scheme 2. Synthesis of the copper complexes and their solvent-dependent reversible isotope exchange.

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line (phen) to form the highly stable complex $[Cu^{I}(phen)_2]PF_6$, the free deuterated ligand remaining in solution. Chromatographic purification afforded the deuterated ligands H-H33m(D), pMe-H33m(D), and pNO_2-H33m(D), which were characterized by ^1H and ^2H NMR spectroscopy and ESI mass spectrometry to confirm the regiospecific deuteration at the inner-macrocyclic aromatic position.

We studied the kinetics of this H/D exchange reaction in the R^1-H33m systems by following the decay of the H_a NMR signal. The three ligands were chosen in order to study the influence of the electronic effect exerted by the R^1 substituents on the isotopic exchange. The decay of the signal intensity was fitted by pseudo-first-order kinetics, and the reaction rates ($k_{obs,H/D}$) are listed in Table 1. The deuterium atom comes from [D_6]acetone (see discussion below), so the pseudo-first-order kinetics are explained by the large excess of the deuterium source. In order to extract kinetic information we measured kinetic isotope effects (KIE). We prepared the Cu^{I} complexes of the pure monodeuterated ligands ($[Cu^{I}(R^1\text{-H33m(D)})]^+$), which allowed us to follow the decay of the deuterium signal by performing ^2H NMR experiments in nondeuterated acetone. We noticed that, apart from the gradual disappearance of the aromatic-deuterium singlet, a triplet corresponding to monodeuterated acetone (CDH_2COCH_3) at $\delta = 2.05$ ppm gradually increased in intensity, also following first-order kinetics, with the same rates (Figure 1 and Table 1), to finally give the complexes with the original nondeuterated ligands (see Supporting Information).

Table 1: Kinetic data for the H/D ($k_{obs,H/D}$) and D/H ($k_{obs,D/H}$) isotopic substitution at 300 K obtained for a first-order rate law.

	$[Cu^{I}(H\text{-}H33m)]^+$	$[Cu^{I}(pMe\text{-}H33m)]^+$	$[Cu^{I}(pNO_2\text{-}H33m]^+$
$k_{obs,H/D}$ [min^{-1}][a]	0.0144(5)	0.0134(2)	0.00033(1)
$k_{obs,D/H}$ [min^{-1}][b]	0.0164(4)	0.0165(8)	0.000054(5)
overall KIE	0.88	0.81	6.1

[a] From ^1H NMR studies in CD_3COCD_3. [b] From ^2H NMR studies in CH_3COCH_3 for monodeuterated $[Cu^{I}(R^1\text{-H33m(D)})]^+$ complexes.

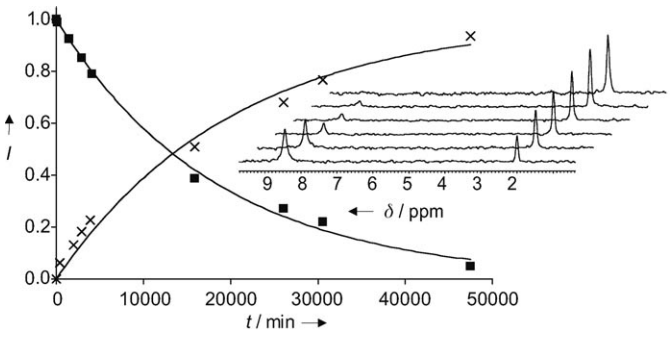

Figure 1. Plot of normalized signal intensity versus time for the decay of the aromatic-deuterium signal at $\delta = 8.45$ ppm (■) and the growth of the CDH_2COCH_3 signal at $\delta = 2.05$ ppm (×) in the ^2H NMR spectrum of the $[Cu^{I}(pNO_2\text{-H33m(D)})]^+$ complex in CH_3COCH_3 (inset: evolution of the ^2H NMR spectrum with time).

In order to gain more insight into the nature of this C–H activation, we studied the isotopic exchange reaction for the H-H33m system in different deuterated solvents. The reaction proceeds in CD_3OD[11] but does not proceed in CD_3CN or CD_2Cl_2, thus clearly manifesting the need for an acidic deuterium atom. We also performed theoretical studies, and DFT geometry optimizations in the gas phase were carried out for the free H-H33m ligand, the $[Cu^{I}(H\text{-H33m})]^+$ complex, and the same Cu^{I} complex starting with two axially coordinated molecules of acetonitrile, acetone, or methanol.[12] We found an agostic interaction between Cu^{I} and the C–H_a bond for $[Cu^{I}(H\text{-H33m})]^+$, with a lengthening of the C–H_a bond (1.098 Å) compared to that in the free ligand (1.092 Å) and an angle of 11.8° between this bond and the plane of the aromatic ring (Figure 2a).

When introducing acetone and methanol molecules both axial molecules remain mostly uncoordinated ($d_{Cu\text{-}O} > 2.9$ Å) and the copper center remains in the macrocyclic plane (defined as the best fitted plane that contains the nitrogen atoms of the ligand, Figure 2b and Supporting Information), thus enabling formation of the agostic interaction between Cu^{I} and the C–H_a bond (the aromatic C–H_a bond is elongated by 0.006 and 0.004 Å with respect to the free ligand in the presence of acetone and

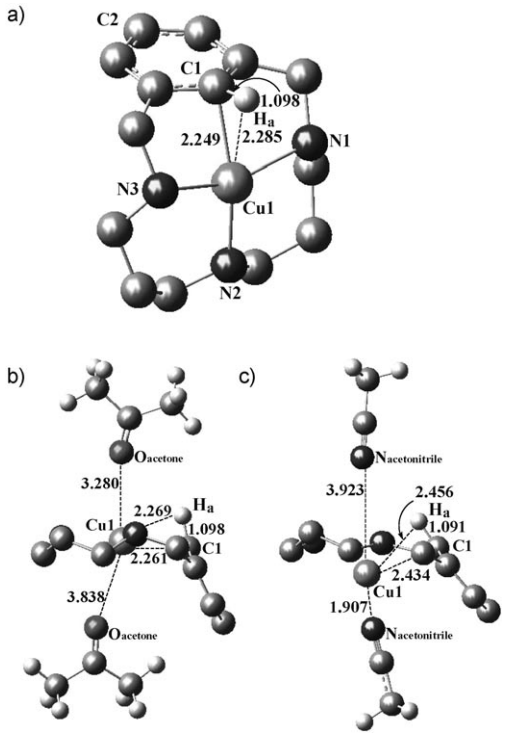

Figure 2. DFT geometry optimizations of a) the $[Cu^{I}(H\text{-H33m})]^+$ complex in the absence of solvent molecules (showing the Cu···C–H_a agostic bond), b) the complex with two axially coordinated CH_3COCH_3 molecules (the agostic interaction with C–H_a persists), and c) the complex with one coordinated CH_3CN molecule and a second uncoordinated CH_3CN (no agostic interaction observed). Ligand hydrogen atoms other than H_a are omitted. All distances are given in Å.

methanol molecules, respectively). In the case of CH_3CN, the Cu^I center is forced out of the macrocyclic plane and the metal adopts a distorted tetrahedral coordination geometry by binding to one CH_3CN molecule; the other axial solvent molecule remains mainly uncoordinated with a very weak contact (Figure 2c). Indeed, the C–H_a bond length and C2-C1-H_a angle are the same as in the free ligand, therefore no agostic interaction is found.[13]

With all these theoretical data at hand, we followed the H/D exchange for complex $[Cu^I(pMe\text{-}H33m)]^+$ by ^1H NMR spectroscopy at different concentrations of $[D_6]$acetone in an innocent solvent such as CD_2Cl_2—the concentration of the complex was kept constant—and also found first-order kinetics with respect to acetone (see Supporting Information).

The kinetics in pure $[D_6]$acetone indicate a pseudo-first-order reaction for all systems that is roughly two orders of magnitude faster ($k_{obs,H/D}$) for H-H33m and pMe-H33m than for pNO_2-H33m (see Table 1). However, when we studied the D/H exchange for the respective deuterated ligands in pure nondeuterated acetone, the $k_{obs,D/H}$ values were about three orders of magnitude higher (Table 1). These data suggest an inverse KIE for H-H33m and pMe-H33m and a direct KIE for pNO_2-H33m (Table 1), and indicate the presence of radically different rate-determining steps (rds) for these systems. It is important to note here that the addition of H^- to our previous $[Cu^{III}L]^{2+}$ complex (L: H-H33m acting as an organometallic aryl ligand) gives the corresponding $[Cu^I(H\text{-}H33m)]^+$ complex quantitatively.[14] Furthermore, the existence of inverse isotope effects for the breaking of Rh^{III}–H bonds has been well documented.[15] The presence of free D^+ caused the decomposition of the complex.[16]

Consistent with all the data reported, and taking into account the first-order kinetics with respect to complex and acetone, the mechanism outlined in Scheme 3 can be proposed. Initially, $[D_6]$acetone in its enolic form coordinates to the metal center (species **A**).[17] It then follows an oxidative type of addition to yield a formal H^- bonded to a Cu^{III} center (species **B**;[18] rds for pNO_2-H33m in agreement with a direct KIE), followed by the H/D exchange (species **C**; rds for H-H33m and pMe-H33m, in agreement with an inverse KIE) to finally generate the acetone-coordinated $[Cu^I(H\text{-}H33m(D))]^+$ complex (**D**) with an incorporated deuterium atom. Indeed, the difficulty of reaching the Cu^{III} oxidation state for the complex with the strongly electron-withdrawing NO_2 group with regard to the complexes containing pMe-H33m and H-H33m has been shown recently by ourselves[10b] and agrees with the mechanism proposed. In addition, the higher stability of the Cu^{III} complex **B** containing the pMe-H33m ligand with an electron-donating group with regard to the H-H33m complex (stronger Cu–H bond in the former) results in lower rates for the former (see Table 1). However, the stronger Cu–H bond generates a slightly larger inverse isotope effect for the H/D exchange process and thus leads to a lower KIE for the pMe-H33m system.

The precise macrocyclic coordination environment is essential for the reaction to take place, and this is evidenced by the absence of H/D exchange in the sterically hindered $[Cu^I(H33p)]^+$ system (in H33p, the aromatic ring is *para*-substituted instead of *meta*-substituted as in H-H33m), where, despite there being two inner-macrocycle aromatic C–H bonds, no reaction takes place (see Supporting Information). The $[Cu^IMe33m]^+$ system also does not undergo isotopic exchange in $[D_6]$acetone. Here, the reason is the stabilization of low copper oxidation states due to N-methylation, as described by Meyerstein et al. and Bernhardt,[19] which prevents the formation of high-oxidation-state intermediates and is therefore in line with our mechanistic proposal.

In conclusion, we have presented the first example of a reversible intramolecular H/D exchange promoted by Cu^I. The process is finely controlled by the precise coordination distance required to form the agostic interaction between Cu^I and the aromatic C–H_a bond, and thus the reactivity is sharply modified by the coordination effect exerted by the solvent used. The reactivity can also be tuned by the electronic effects of the aromatic ring and the amine substitution. The reaction is regiospecific and allows us to isolate the corresponding monodeuterated free ligands, which, in turn, have permitted us to gain insight into the isotopic exchange mechanism. Kinetic studies at different temperatures and in different solvents, as well as theoretical calculations, are currently in progress to gain further mechanistic insight into this exciting reaction.

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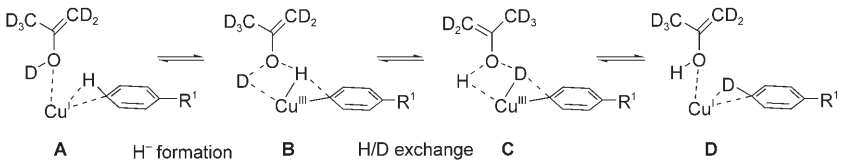
Keywords: agostic interactions · C–H activation · copper · density functional calculations · isotopic labeling



Scheme 3. Proposed H/D exchange mechanism.

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[11] Similar reactivity is found when using CD_3OD with the systems H-H33m and pMe-H33m, although with bigger reaction rates than in [D_6]acetone. In the case of CD_3OH no disappearance of the H_a signal is observed because the exchange occurs between the protons of the alcohol groups.
[12] Calculations were performed with the ADF program using the BP86 functional combined with a DZP basis set for C, N, O, and H, and a TZP basis set for Cu. See Supporting Information for further details.
[13] Several attempts to crystallize the Cu^I complexes from different solvent mixtures were performed, although crystallographic characterization was only achieved with a CH_3CN/diethyl ether mixture for a related ligand with the same R-H33m macrocyclic skeleton. The structure analysis confirmed the release of the Cu^I center out of the macrocyclic plane, due to coordination to one CH_3CN molecule, and formation of a coordination polymer (these results will be published elsewhere).
[14] The addition of 1.5 equiv of $NaBH_4$ to the corresponding organometallic $[Cu^{III}L]^{2+}$ compound (reference [10a]) leads to the Cu^I complex bearing the H_a aromatic proton (as monitored by ^{1}H NMR spectroscopy), which gives support to the formation of a transient aryl copper(III) hydride.
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[16] The addition of 0.5 equiv of CF_3COOD to a solution of $[Cu^I$(H-H33m)$]^+$ in CD_2Cl_2 (noncoordinating solvent) gives a species with broad ^{1}H NMR signals (probably partial decomplexation and oligomerization due to protonation of the amine moiety).
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