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H₂O Activation for Hydrogen-Atom Transfer: Correct Structures and Revised Mechanisms**

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The reduction of radicals to hydrocarbons through hydrogen-atom transfer (HAT) is a fundamental radical reaction.^[1] Recent developments in the field concentrate on alcohols and H₂O as HAT reagents in the presence of boranes^[2] and [Cp₂TiCl],^[3] (Cp = C₅H₅) the use of H₂ as the final reductant,^[4] and on BH₃–NHC complexes (NHC = N-heterocyclic carbene).^[5] All cases feature a weakening of otherwise strong H–X bonds.

The propensity of H₂O to act as a HAT reagent has been explained by a reduction of the bond dissociation energy (BDE) of the O–H bond by about 60 kcal mol^{–1} in the presence of [Cp₂TiCl].^[3] Herein, we demonstrate by EPR spectroscopy and cyclic voltammetry (CV) that the proposed HAT reagent **1**^[3c] is not present in zinc-reduced THF solutions of [Cp₂TiCl₂] and H₂O. Instead, our results suggest that **2** and **3** are the active HAT reagents (Figure 1). Moreover, we show that previous data in support of **1**^[3c] are also in agreement with **2**, **3a**, and **3b**, and that an older computational study^[3c] needs extension and refinement.

Electron paramagnetic resonance (EPR) spectroscopy and the hyperfine resolving techniques electron spin echo envelope modulation (ESEEM)^[6] and hyperfine sublevel

correlation (HYSCORE) spectroscopy^[6d,7] are excellent methods for studying interactions between H₂O and [Cp₂TiCl]. The *g* values provide direct information about which orbital is occupied by the unpaired electron. The ESEEM and HYSCORE methods are well suited for examining the coordination sphere of the [Cp₂TiCl]–H₂O system by the detection of magnetic hyperfine couplings with surrounding nuclear spins. Thus the binding of chloride (*I* = 3/2) and the coordination of H₂O or D₂O can be studied through their coupling to protons (*I* = 1/2) or deuterons (*I* = 1).

Pulsed EPR spectra of zinc-reduced [Cp₂TiCl₂] in THF were recorded. Without H₂O, they are in agreement with a previous study^[8] on [Cp₂TiCl] and show that the unpaired electron resides in a 3d_{z²} orbital at Ti^{III}. This is also the case upon addition of H₂O. However, the shape of the spectrum and especially the *g_x* value change significantly upon addition of various molar equivalents of H₂O (see the Supporting Information for the spectra).

To understand these effects, ESEEM spectra of Zn-reduced [Cp₂TiCl₂] in THF with different amounts of added H₂O (Figure 2, left panel) and D₂O (Figure 2, right panel) were recorded. Under the experimental conditions (microwave frequency of 34 GHz) they contain nuclear modulations derived from chloride (*I* = 3/2) and from deuterons (*I* = 1). Protons (*I* = 1/2) do not contribute, because their Zeeman frequency is 50 MHz and their modulations have zero amplitude.^[9]

The frequency of the nuclear modulations changes noticeably upon addition of 10 or 20 equivalents of H₂O (Figure 2;

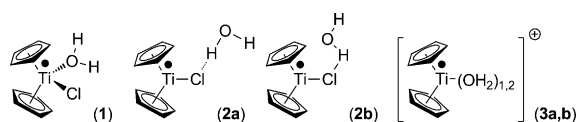


Figure 1. Proposed modes of complexation of [Cp₂TiCl] by H₂O.

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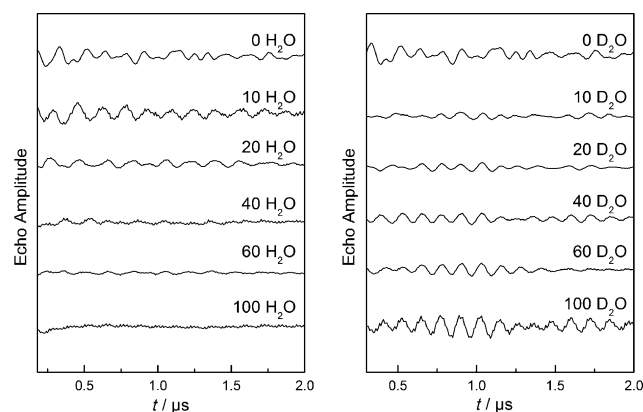


Figure 2. Normalized Q-Band 3-pulse modulation patterns (*T* = 30 K) of Zn-reduced [Cp₂TiCl₂] in THF with different molar equivalents of H₂O and D₂O added. For the spectra in the frequency domain see the Supporting Information.

left panel) indicating an interaction of the halide with H₂O. The modulations become weaker for 40 and more equivalents of H₂O. This result suggests that the Ti–Cl bond is eventually cleaved through the generation of hydrated chloride and a titanocene cation. However, from this particular ESEEM spectrum it is not clear if the titanocene cation is hydrated or not.

Therefore, to study the interaction of water with the titanocene moiety directly, ESEEM spectra of Zn-reduced [Cp₂TiCl₂] in THF with different equivalents of D₂O added were recorded (Figure 2, right panel). Addition of 10 equivalents D₂O resulted in similar, albeit not identical, initial changes of the chloride modulations. This result is related to the different hydrogen-bonding propensities of H and D and to a beginning superposition of the modulations caused by D and Cl. Starting from 20 molar equivalents D₂O, the modulations with a frequency of 8 MHz became clearly observable. In the presence of more than 40 equivalents these signals dominate the appearance of the ESEEM spectrum. This coupling constitutes the direct experimental evidence for the coordination of D₂O to titanium through a Ti–O bond. Moreover, the combination of the ESEEM experiments highlights that coordination of water is especially favorable after dissociation of the halide ligand.

These conclusions were further verified by HYSORE experiments. At the employed microwave frequency (X-band, 9.7 GHz) all proton signals appear in the spectral region around 14 MHz, off-diagonal signals (cross-peaks) appear between nuclear transition frequencies that belong to the same proton, similar to 2D NMR spectroscopy experiments. Striking differences are observed between the spectra of Zn-reduced [Cp₂TiCl₂] without added H₂O and those with 10 and 100 equivalents H₂O (Figure 3). This result is especially apparent at the frequency coordinates (11, 19) MHz and (19, 11) MHz. Cross peaks are absent for Zn-reduced [Cp₂TiCl₂] but weak signals appear with 10 equivalents of H₂O. With 100 equivalents H₂O these cross-peaks become very intense. Interestingly, the line shape of the signals observed with 10 equivalents and 100 equivalents of water is essentially identical.

Moreover, the HYSORE technique allows an estimation of the distance between the protons of the bound H₂O and the Ti center. The ridges of these cross-peaks do not form straight lines, but are rather bent, indicative of the presence of anisotropic hyperfine interaction.^[10] Careful analysis allows a determination of the dipolar hyperfine coupling constant T_{\perp} of 5.7 MHz. This value is comparable to that found for the equatorial protons of [Cu(H₂O)₆]²⁺ and indicates that the effective distance between the protons of H₂O and the unpaired electron is less than 3.3 Å.^[10]

To verify these conclusions, the Zn-reduced THF solutions of [Cp₂TiCl₂] with added H₂O were investigated by cyclic voltammetry (CV) with concentrations of all the reagents being identical to those of the EPR samples. The voltammograms recorded at sweep rates of 0.1 and 1 V s^{−1} are shown in Figure 4 (for CVs with higher sweep rates, see the Supporting Information). For both sweep rates two oxidation waves were observed for all the cases investigated. For Zn-reduced [Cp₂TiCl₂] these are assigned to the oxidation of

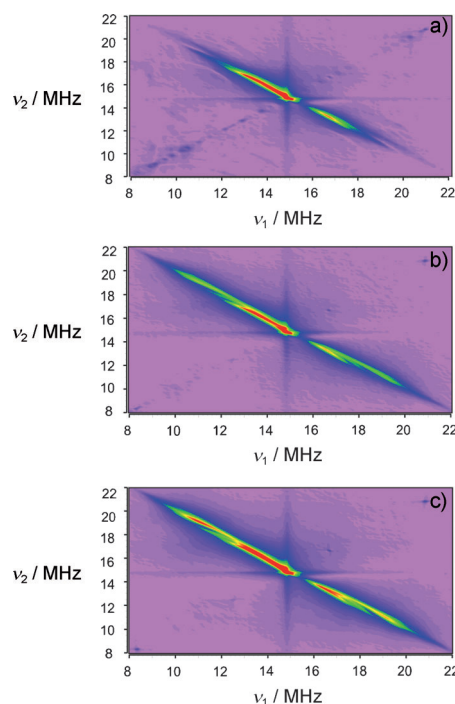


Figure 3. X-band HYSORE spectra (9.68 GHz, 30 K) of Zn-reduced [Cp₂TiCl₂] in THF a) without H₂O b) with 10 equivalents of H₂O, c) with 100 equivalents of H₂O, recorded at the g_y canonical orientations.

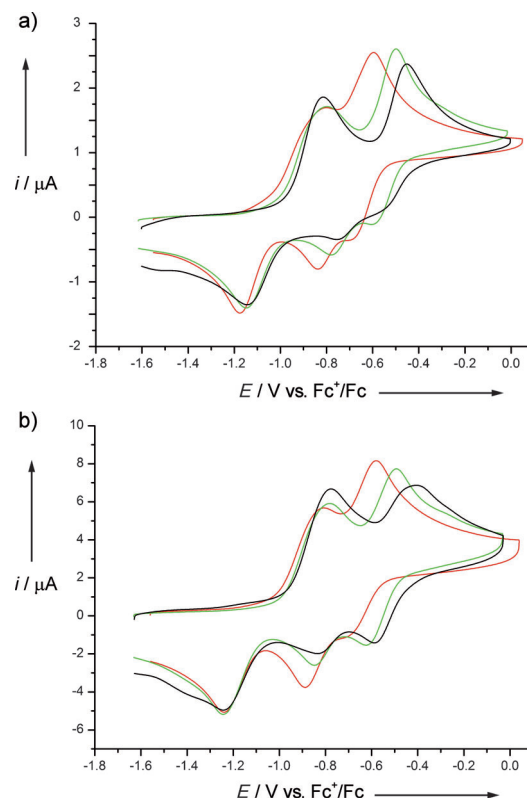


Figure 4. CV of Zn-reduced [Cp₂TiCl₂] a) 0.1 V s^{−1}, b) 1 V s^{−1} in 0.2 M TBAPF₆/THF with 0 (black), 10 (green), and 100 equivalents (red) of added H₂O.

$[(\text{Cp}_2\text{TiCl})_2]$ and $[\text{Cp}_2\text{TiCl}]$ (first wave) and $[\text{Cp}_2\text{Ti}]^+$ (second wave) in analogy to previous studies.^[11] Several features of the CVs obtained upon addition of H_2O deserve closer attention:

First, in the presence of H_2O the peak current ratio of the two oxidation waves remains essentially independent of the sweep rate, suggesting that $[\text{Cp}_2\text{Ti}]^+$ derived species are present in Zn-reduced solutions in THF with added H_2O . This is not the case without H_2O .^[11] It should be noted that not even the addition of the strongly coordinating HMPA (HMPA = hexamethyl phosphoramide) to Zn-reduced solutions of $[\text{Cp}_2\text{TiCl}_2]$ results in the generation of solvated $[\text{Cp}_2\text{Ti}]^+$.^[12] Thus, the solvation of chloride ion through hydrogen bonding by H_2O is essential for generation of the titanocene cation.

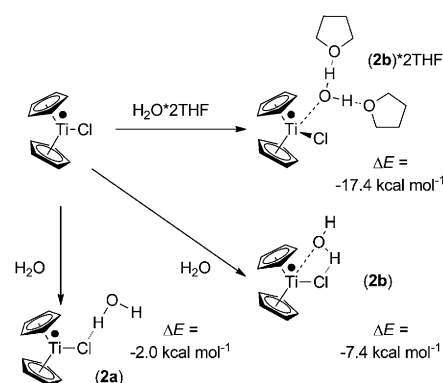
Second, the first oxidation wave of Zn-reduced $[\text{Cp}_2\text{TiCl}_2]$ in the presence of H_2O does not consist of two individual processes (oxidation of $[\text{Cp}_2\text{TiCl}]$ and $[(\text{Cp}_2\text{TiCl})_2]$) because no second oxidation peak appears at higher sweep rates.^[11a] These results indicate that $[(\text{Cp}_2\text{TiCl})_2]$ dissociates into monomeric species upon addition of H_2O .

Third, the oxidation wave of the $[\text{Cp}_2\text{Ti}]^+$ derived species is shifted to more negative values upon addition of H_2O . For 10 equivalents of H_2O this shift is 50 and 80 mV suggesting the formation of $[\text{Cp}_2\text{Ti}(\text{OH}_2)]^+$. In the presence of 100 equivalents of H_2O shifts of 130 and 180 mV were observed. This change suggests the coordination of a further molecule of water and hence at the presence of $[\text{Cp}_2\text{Ti}(\text{OH}_2)_2]^+$.

Finally, the peak potential of the first oxidation wave does not change upon addition of H_2O . This implies that H_2O does not bind to the Ti nucleus of $[\text{Cp}_2\text{TiCl}]$ because in that case a noticeably more negative peak potential shifted by 50–80 mV in analogy to $[\text{Cp}_2\text{Ti}(\text{OH}_2)]^+$ should have been observed.

The interaction of H_2O with $[\text{Cp}_2\text{TiCl}]$ was studied by computational means next. The geometries were optimized at the BP86/TZVP^[13,14] level of theory using density fitting. Stationary points were characterized by analyzing the hessian matrix.^[15] The energies were obtained by B3LYP-d/def2-TZVPP^[16] single-point calculations using COSMO^[17] with $\epsilon = 7.6$ including the zero-point energy correction of the BP86 level.

In Scheme 1 the behavior of $[\text{Cp}_2\text{TiCl}]$ in the presence of H_2O and THF is summarized. If specific interactions of H_2O with THF are excluded, the two structures **2a** and **2b** with hydrogen bonding of H_2O to the Ti–Cl bond are identified as minima. Structure **2b** is more favorable than **2a** because of a dipole–dipole interaction between O and Ti. However, the complexation energy is far too weak for a covalent Ti–O bond to be present as postulated in **1**. With the inclusion of specific interactions of H_2O and THF, the situation becomes slightly more complex. H_2O and 2 equivalents of THF form a hydrogen-bonded complex with a ΔE of $-7.8 \text{ kcal mol}^{-1}$. Both hydrogen bonds are of equal strength ($-3.9 \text{ kcal mol}^{-1}$). Based on these values it is clear that hydrogen bonding in **2a** is too weak to persist when specific THF interactions are included. For **2b**, the inclusion of $\text{H}_2\text{O} \cdot 2\text{THF}$ leads to a noticeably more favorable binding ($-7.4 \text{ kcal mol}^{-1}$ vs. $-17.4 \text{ kcal mol}^{-1}$). This change is mainly because of the increase of negative charge on the O of H_2O as a result of

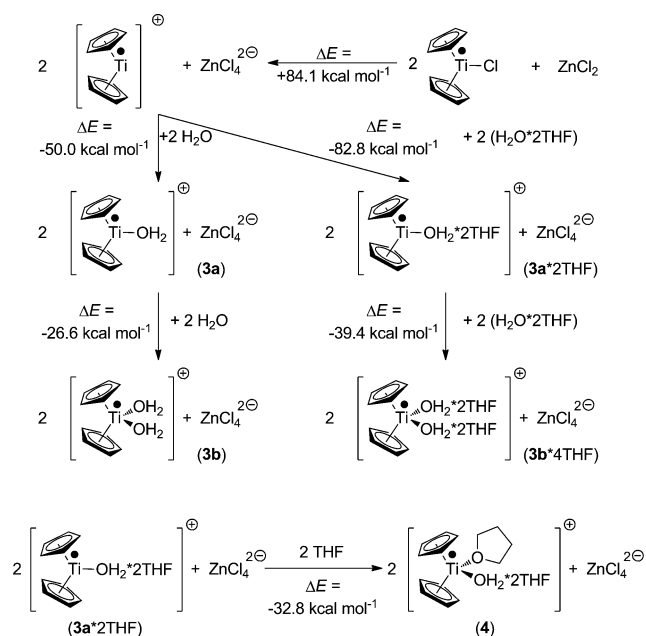


Scheme 1. Computational results on the complexation of $[\text{Cp}_2\text{TiCl}]$ by H_2O with and without THF (B3LYP-d/def2-TZVPP). COSMO^[17] with $\epsilon = 7.6$.

hydrogen bonding which leads to a stronger interaction with Ti. However, note that an interaction between an α -H of both THF molecules and Cl also contributes to the stability of **2b**·2THF (see the Supporting Information for the structure). However, even the binding of **2b**·2THF is characteristic of a dipole–dipole interaction and not of a Ti–O bond.

The computational investigation of the formation of cationic titanocenes in the presence of H_2O is summarized in Scheme 2. For our study it is important to recall that Zn-reduced solutions of $[\text{Cp}_2\text{TiCl}_2]$ contain ZnCl_2 . This strong Lewis acid makes the heterolytic cleavage of the Ti–Cl bond more favorable through the formation of ZnCl_4^{2-} . Even so, the cleavage of the Ti–Cl bonds is highly endothermic because of charge separation.

For the solvation of the titanocene cations, the inclusion of THF in the mechanistic analysis must not be neglected.

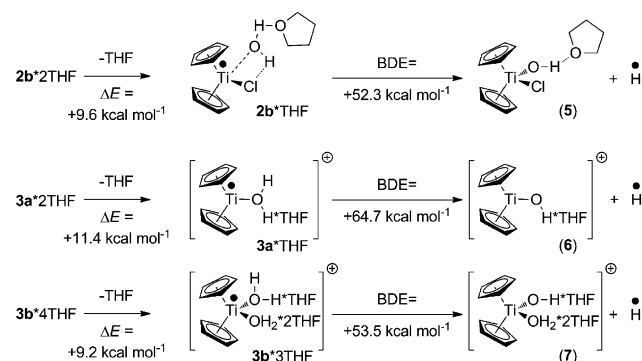


Scheme 2. Computational results on the formation of cationic titanocene(III) complexes in the presence of ZnCl_2 (B3LYP-d/def2-TZVPP). COSMO^[17] with $\epsilon = 7.6$.

Although, the complexation of a single H_2O is exothermic ($-25.0 \text{ kcal mol}^{-1}$ per Ti), the complexation of the first $\text{H}_2\text{O} \cdot 2\text{THF}$ is much more favorable ($-41.4 \text{ kcal mol}^{-1}$ per Ti). Binding of the second equivalent of $\text{H}_2\text{O} \cdot 2\text{THF}$ is less exothermic ($-19.7 \text{ kcal mol}^{-1}$ per Ti) but more advantageous than binding a single THF alone ($-16.4 \text{ kcal mol}^{-1}$ per Ti).

Therefore, the reaction of $4\text{H}_2\text{O} \cdot 2\text{THF}$ with $2[\text{Cp}_2\text{TiCl}]$ and ZnCl_2 results in an exothermic formation of solvated titanocene cations ($-19.1 \text{ kcal mol}^{-1}$ per Ti). The formation of $3\text{b} \cdot 4\text{THF}$ will become even more exothermic when solvation of ZnCl_4^{2-} is included in the analysis. While, the calculation of the complete solvation sphere of ZnCl_4^{2-} is beyond the scope of this study, the validity of our assumption is highlighted by the fact that the interaction of ZnCl_4^{2-} with 6 equivalents of H_2O is exothermic ($-30.9 \text{ kcal mol}^{-1}$).

The computed bond dissociation energies (BDEs) of $2\text{b} \cdot \text{THF}$, $3\text{a} \cdot \text{THF}$, and $3\text{b} \cdot 3\text{THF}$ (52.3, 64.7, and 53.5 kcal



Scheme 3. Bond dissociation energies (BDE) of $2\text{b} \cdot \text{THF}$, $3\text{a} \cdot \text{THF}$, and $3\text{b} \cdot 3\text{THF}$ by DFT calculations (B3LYP-d/def2-TZVPP) with COSMO^[17] ($\epsilon = 7.6$).

mol^{-1}) are summarized in Scheme 3. We propose that a dissociation of one THF from the fully hydrogen-bonded species is necessary for an unhindered backside attack of a radical on H. As expected this dissociation of THF is especially difficult for the most Lewis acidic $3\text{a} \cdot 2\text{THF}$. The difference in BDE between $3\text{a} \cdot \text{THF}$ and $3\text{b} \cdot 3\text{THF}$ is due to the better stabilization of the Ti^{IV} in **7** through complexation. All the species investigated constitute more efficient HAT reagents than traditionally employed cyclohexadienes, stannanes, silanes, and germanes.^[1]

Taking all of our experimental and computational results into account, it seems clear that addition of H_2O to Zn-reduced $[\text{Cp}_2\text{TiCl}_2]$ does not lead to the formation of **1**. The ESEEM spectra show that at a high concentration of H_2O , the chloride ligand is removed from the Ti^{III} center. The HYSCORE spectra demonstrate that with 10 and 100 equivalents of H_2O identical species are obtained. Both findings imply that even at low concentrations of H_2O no **1** is formed. This conclusion is supported by the CV measurements that also preclude a coordination of H_2O to a Ti^{III} center with a chloride ligand. Instead, the shifts of the oxidation waves of the titanocene cations demonstrate the presence of water-ligated $[\text{Cp}_2\text{Ti}]^+$ as in **3a** and **3b**. These experimental results are supported by the calculations that suggest that the

formation of hydrated titanocene cations is more favorable than the formation of **1** even in the presence of a low number of equivalents of H_2O . Moreover, it has been demonstrated that the inclusion of THF is essential for the understanding of the structures and relative stabilities of the complexes involved.

It should be noted that the previous computational study^[3c] did not consider the possibility of cationic structures. Moreover, the effects of specific interactions of H_2O with THF were neglected. None of the earlier experimental data provided direct structural data for the existence of **1**. A UV/Vis study on the interaction of H_2O with $[(\text{Cp}_2\text{TiCl})_2]$ ^[3c] has demonstrated that the addition of more than 10 equivalents of H_2O results in dissociation of $[(\text{Cp}_2\text{TiCl})_2]$. The resulting Ti species were not characterized further, though. While the observation of the dissociation is in agreement with our data, our EPR and CV measurements provide evidence for the cationic species **3**.

In a kinetic study, the rate constants for HAT from “[Cp_2TiCl]-complexed H_2O ” to alkyl radicals were reported.^[18] However, rate constants do not provide any structural information. Moreover, the measured rate constants are lower than those of stannanes even though the BDEs of the titanocene-derived species are substantially lower. This discrepancy can be readily explained with our results because an unfavorable loss of THF from $3\text{a} \cdot 2\text{THF}$ and $3\text{b} \cdot 4\text{THF}$ is required for HAT (Scheme 3). This leads to a low concentration of the active HAT reagent and hence a reduction of the observed rate constant for HAT.

The mechanism of H_2O activation by Zn-reduced $[\text{Cp}_2\text{TiCl}_2]$ is fundamentally different from that of MeOH activation by boranes.^[2] This is due to the inability of boranes to form cationic species. Thus, boranes react with alcohols by associative processes to form classical Lewis base adducts. For these species the loss of alkyl radicals during HAT is essential.^[2]

Our mechanistic proposal for the generation of Ti^{III} -based HAT reagents and the HAT itself should be valid for the activation of other molecules and electron-transfer reagents,^[19] also. This mechanism opens fascinating perspectives for the development of even more efficient and sustainable reagents. Cationic low-valent metal complexes, not necessarily derived from titanium,^[20] with donor ligands containing O–H or N–H bonds should give such HAT reagents. Amides and especially peptides or even proteins are prime candidates for such activation towards HAT.

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