

Understanding the Exceptional Hydrogen-Atom Donor Characteristics of Water in Ti^{III}-Mediated Free-Radical Chemistry

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Abstract: In recent years solid evidence of HAT reactions involving water as hydrogen atom source have been presented. In this work we demonstrate that the efficiency of titanocene(III) aqua complexes as an unique class of HAT reagents is based on two key features: (a) excellent binding capabilities of water toward titanocene(III) complexes and (b) a low activation energy for the HAT step. The theory has predictive capabilities fitting well with the experimental results and may aid to find more examples of this remarkable radical reaction.

Introduction

Reduction of carbon-based radicals is an essential and widely spread process in organic chemistry (Scheme 1).¹ It lies at the heart of many fundamental reactions in organic synthesis, such as the Barton–McCombie deoxygenation reaction, reductive radical cyclizations, low valent metal-mediated carbonyl reductions, etc. Two main mechanisms have been proposed to carry out this essential step: (a) a direct hydrogen atom transfer (HAT) from common donors (1,4-cyclohexadiene (1,4-CHD), thiols, hypophosphorus acid and its salts, HSnR₃ and silicon-based derivatives) to the carbon-centered radical² or (b) a stepwise electron and proton transfer (ET/PT).³ The synthetic methods based on the first process are limited by the availability of suitable hydrogen atom donors, which are usually unstable, toxic, expensive, and/or foul smelling, thus seriously restricting the application for large scale preparations.

In this context, water would be a remarkable, safe, and cheap HAT reagent. Nevertheless, it is generally believed that the high bond dissociation energy (BDE) of the H–OH bond (117.59

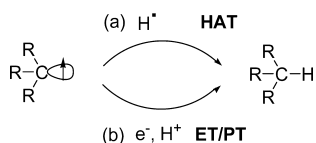
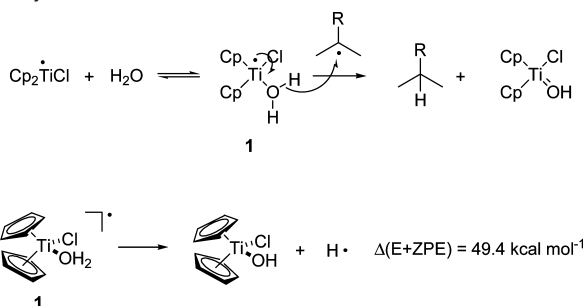
± 0.07 kcal mol^{−1})⁴ would preclude any potential HAT reaction to carbon-centered radicals. Despite this general assumption, we have recently described that, in fact, water becomes an excellent hydrogen atom donor in the presence of bis(cyclopentadienyl)titanium(III) chloride (Cp₂TiCl)⁵ toward aliphatic carbon radicals.^{6–8} To explain the experimental results, we proposed that the H–OH bond is weakened upon coordination to titanocene(III), acting the corresponding aqua-complex **1** as an efficient hydrogen atom donor (Scheme 2). The reaction energy for the process was computed at DFT level, showing

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- (5) The single-electron-transfer reagent bis(cyclopentadienyl)titanium(III) chloride can be generated *in situ* by stirring commercial Cp₂TiCl₂ with Mn dust in THF, where it exists as a mixture of the mononuclear Cp₂TiCl(THF) and the dinuclear (Cp₂TiCl)₂ species; see: (a) Rajan-Babu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986–997. (b) Enemark, R. J.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. *J. Am. Chem. Soc.* **2004**, *126*, 7853–7864. (c) Half-open dimers are also active compound for binding Lewis-bases and can be considered as the real precursor of monomeric Cp₂TiCl(THF) and others Cp₂TiCl(L) related species: Gansäuer, A.; Barchuk, A.; Keller, F.; Schmitt, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359–1371.
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- (7) For other precedent of water acting as HAT reagent: Spiegel, D. A.; Wiberg, K. B.; Schacherer, L. N.; Medeiros, M. R.; Wood, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12513–12515.
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[†] University of Granada.

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- (2) HAT mechanism is a subfamily of the more general proton-coupled electron transfer (PCET) mechanism: (a) Mayer, J. M. *Annu. Rev. Phys. Chem.* **2004**, *55*, 363–390. (b) Huynh, M. H. V.; Meyer, T. J. *Chem. Rev.* **2007**, *107*, 5004–5064.
- (3) Organometallic compounds, derived from a radical heterocoupling between a carbon radical and metallic species, can be involved in the initial reduction step, leading the global ET/PT after a subsequent protonolysis.

Scheme 1. Commonly Accepted Mechanisms for Carbon-Centered Radical Reduction**Scheme 2.** Mechanism of Carbon-Centered Radical Reduction by Aqua-Complex **1** and Calculated Reaction Energy for the Homolytic O–H Bond Dissociation

that the homolytic O–H bond dissociation is extraordinarily favored by coordination of H₂O to Cp₂Ti^{III}Cl. Reaction energy decreases from a calculated value of 108.1 kcal mol^{−1} for H₂O to 49.4 kcal mol^{−1} for **1**. This fact was strongly supported by kinetic measurements. In accord with our proposal, Newcomb et al. have determined the rate constant for the HAT reaction of Cp₂TiCl–H₂O to secondary alkyl radicals using indirect kinetic methods ($k_{25} = 1.0 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$).⁹ Although with the actual experimental data a direct comparison with widely used Bu₃SnH is not possible, it is worth noting that the rate constant is only 1 order of magnitude lower ($k = 1.4 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$).¹⁰

This remarkable behavior of water further facilitated the development of an efficient synthesis of alcohols and β -deuterated alcohols from epoxides with anti-Markovnikov regiochemistry,^{6b} the control of the ending step in titanocene-catalyzed radical cyclizations in the straightforward synthesis of complex polycyclic terpenoids,¹¹ and the development of a new hydrogenation reaction of alkenes and alkynes based on an unprecedented HAT reaction from water to common hydrogenation catalysts (Pd/C, Rh/C, Wilkinson catalyst, etc.), avoiding the use of potentially dangerous hydrogen gas.¹² All these results might also have important consequences on fundamental mechanistic considerations of organic reactions in aqueous media. Moreover, from a practical point of view, water can be used as a safe and inexpensive HAT reagent instead of actual ones.

Nevertheless, the general scope of this uncommon radical reduction is unknown despite of its interest. Simple alkyl radicals seem to be suitable substrates for this transformation, but related

allyl or benzyl radicals as well as alkenyl and aryl radicals might also undergo the same process. Additionally, related reduction reactions of carbon-centered radicals using methanol activated by B-alkylcatecholboranes have been also reported.¹³ Taking into account our mechanistic hypothesis and this result, other compounds with hydrogen-heteroatom bonds, able to coordinate to Cp₂TiCl, might also be potential radical reducing reagents. Bearing this idea in mind, we present in this paper an in depth study of the exceptional hydrogen atom donor behavior of water toward different carbon-centered radicals in the presence of titanocene(III) complexes compared to other potential hydrogen atom donors containing hydrogen-heteroatom bonds.

Results and Discussion

Based on our mechanistic hypothesis, two key factors seem to control the success of the reduction step: (i) the coordination of the potential hydrogen atom donor to the titanocene(III) complex and (ii) the efficiency of the HAT process. Interestingly, the influence of both factors is accessible from both experimental and theoretical point of views.

Study of the Coordination Capabilities of Potential Hydrogen Atom Donors toward (Cp₂TiCl)₂. (Cp₂TiCl)₂ (**2**) is a highly air-sensitive complex, which can be prepared in pure form. The coordination capabilities of different potential hydrogen atom donors toward this complex were evaluated experimentally using UV–vis spectroscopy.¹⁴ In our present study, we selected ligands with H–O bonds, such as water, methanol, and phenol, and with H–N bonds, such as primary (*N*-octylamine) and secondary (*N,N*-dibutylamine) amines. Ammonia gas was excluded because it is difficult to handle properly and reproducibly in the glovebox. We initially chose tetrahydrofuran (THF) as solvent since it is the usual one in Cp₂TiCl mediated reactions.

Addition of water and primary or secondary amines (octylamine and dibutylamine, respectively) to 10 mM solutions of (Cp₂TiCl)₂ in THF promoted marked changes in the corresponding spectra (Figure 1–3). In the case of water, the disappearance of the absorption band at 456 nm, characteristic of complex **2**, is observed upon addition of relatively low amounts of additive (8 equiv of water).¹⁵ A similar trend is observed using both amines (1 equiv).

On the other hand, the addition of methanol or phenol only promoted slight variations in the UV–vis spectra in the same conditions (Figures 4a and 5a). In the case of methanol, up to 17 equiv of additive were necessary to promote similar changes to that observed with water or amines. With phenol, we only obtained minor changes in the UV–vis spectra. Competitive experiments also confirmed that water has better coordination ability toward Ti(III) than methanol and phenol. Addition of 8 equiv of water to 1:8 mixtures of (Cp₂TiCl)₂/methanol and (Cp₂TiCl)₂/phenol yielded the same UV–vis spectrum as complex **2** in the presence of same amounts of water (Figures 4b and 5b).

A similar UV–vis study of methanol and phenol in benzene was carried out to avoid any competitive binding process with the solvent (Figures 6 and 7). Water had to be excluded from the study due to its immiscibility with benzene. The behavior

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(14) For a previous spectroscopic study (mainly UV–vis and ¹⁷O NMR) of titanocene(III) aqua complexes see reference.⁸

(15) Taking into account that (Cp₂TiCl)₂ is a dimer, 1 equiv of water means a molar ratio (Cp₂TiCl)₂: H₂O of 1:2.

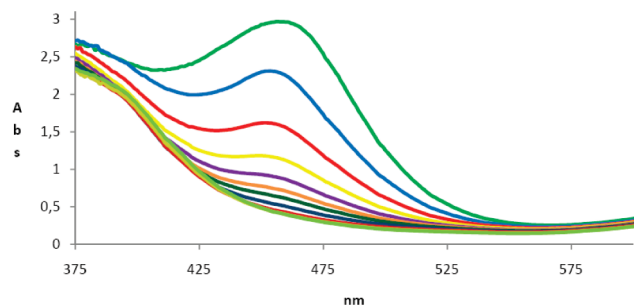


Figure 1. UV-vis spectra of **2** (green) in THF (0.01 M) with increasing amounts of H₂O: 0.5 equiv (blue), 1 equiv (red), 1.5 equiv (yellow), 2 equiv (purple), 2.5 equiv (orange), 3 equiv (dark green), 4 equiv (dark blue), 6 equiv (dark red), 9 equiv (dark yellow), and 13 equiv (light green).

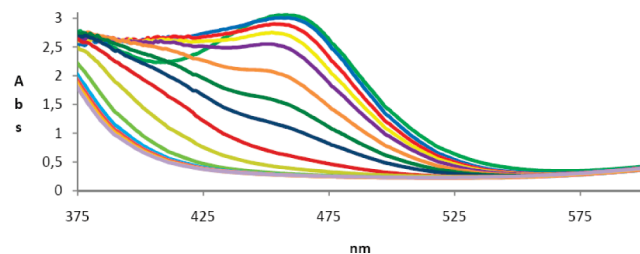


Figure 2. UV-vis spectra of **2** (green) in THF (0.01 M) with increasing amounts of *N*-octylamine: 0.05 equiv (blue), 0.1 equiv (red), 0.15 equiv (yellow), 0.2 equiv (purple), 0.3 equiv (orange), 0.4 equiv (dark green), 0.5 equiv (dark blue), 0.7 equiv (dark red), 0.9 equiv (dark yellow), 1.2 equiv (light green), 1.5 (light blue), 2 (light red), and 3 (light purple).

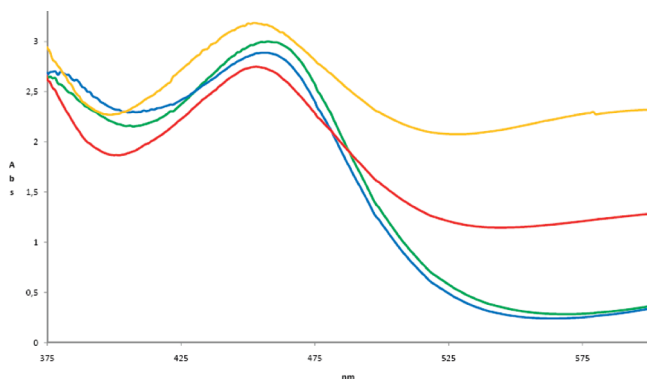
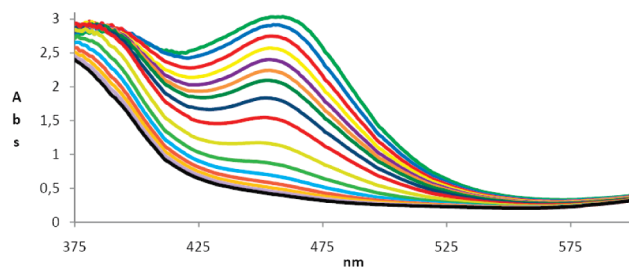


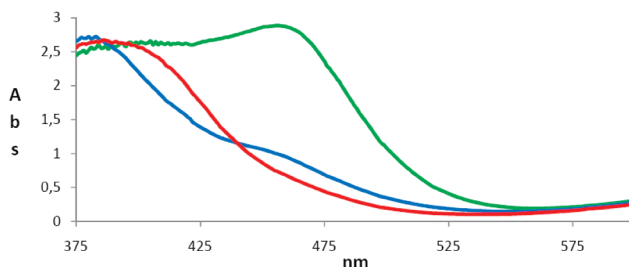
Figure 3. UV-vis spectra of **2** (green) in THF (0.01 M) with increasing amounts of di-*N*-butylamine: 0.1 equiv (blue), 0.9 equiv (red), and 2 equiv (orange).

of both additives in benzene and THF was very similar. This fact suggests that, at least, THF is not a competitive ligand when methanol is used as additive. Moreover, the independence of the behavior of both additives from the solvent used, strongly supports that the titanocene(III) complex has similar structure in both solutions at those concentrations. A dimeric structure, (Cp₂TiCl)₂, seems to be plausible in benzene solutions of complex **2**, according to the low coordination ability of benzene. Therefore, the dimeric structure is retained in THF solutions even in the presence of a large excess of a potential ligand, as THF molecules.¹⁶ Under this assumption, we could obtain the

(16) The corresponding UV-vis study of a 0.01 M solution of complex **2** in benzene in the presence of increasing amounts of THF was also carried out. We did not observe significant changes in the UV-vis spectrum even in the presence of high amounts of THF. See Supporting Information for details.

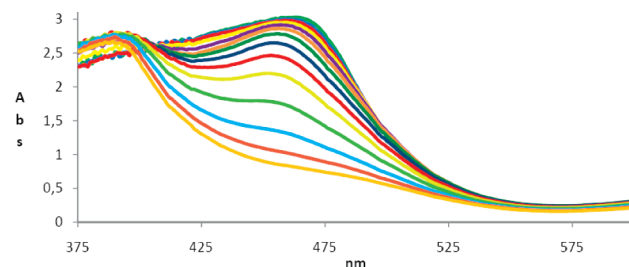


a

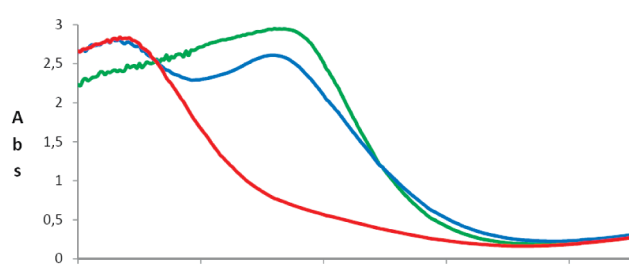


b

Figure 4. (a) UV-vis spectra of **2** (green) in THF (0.01 M) with increasing amounts of MeOH: 0.5 equiv (blue), 1 equiv (red), 1.5 equiv (yellow), 2 equiv (purple), 2.5 equiv (orange), 3 equiv (dark green), 4 equiv (dark blue), 6 equiv (dark red), 10 equiv (dark yellow), 15 equiv (light green), 21 (light blue), 28 (light red), 45 (light purple), and 55 (black). (b) Competitive experiments: **2** (green), **2** + 13 equiv of phenol (blue), and **2** + 13 equiv of phenol and water (red).



a



b

Figure 5. (a) UV-vis spectra of **2** (green) in THF (0.01 M) with increasing amounts of PhOH: 0.5 equiv (blue), 1 equiv (red), 2 equiv (yellow), 4 equiv (purple), 8 equiv (orange), 14 equiv (dark green), 22 equiv (dark blue), 32 equiv (dark red), 47 equiv (dark yellow), 77 equiv (light green), 122 (light blue), 182 (light red), and 262 (light orange). (b) Competitive experiments: **2** (green), **2** + 13 equiv of phenol (blue), and **2** + 13 equiv of phenol and water (red).

corresponding binding constants from the titration curves.¹⁷ Consequently with the UV-vis spectra, the highest binding constant in THF corresponds to *N*-octylamine ($K_{\text{octylamine}} = 1412 \text{ M}^{-1}$). Water and methanol have binding constant values of 101.6 and 2.5 M^{-1} , respectively. For phenol we could only determine

(17) We could not obtain a titration curve for *N,N*-dibutyl amine.

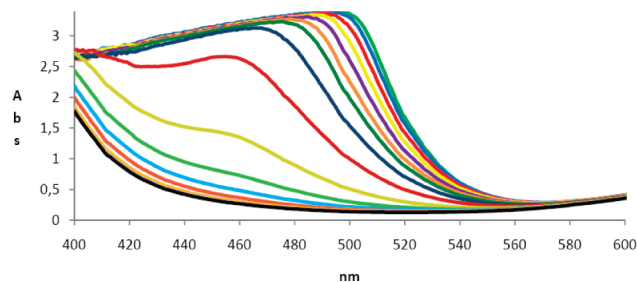


Figure 6. UV-vis spectra of **2** (green) in benzene with increasing amounts of MeOH: 0.5 equiv (blue), 1 equiv (red), 1.5 equiv (yellow), 2 equiv (purple), 2.5 equiv (orange), 3 equiv (dark green), 4 equiv (dark blue), 6 equiv (dark red), 10 equiv (dark yellow), 15 equiv (light green), 21 (light blue), 28 (light red), 45 (light purple), and 55 (black).

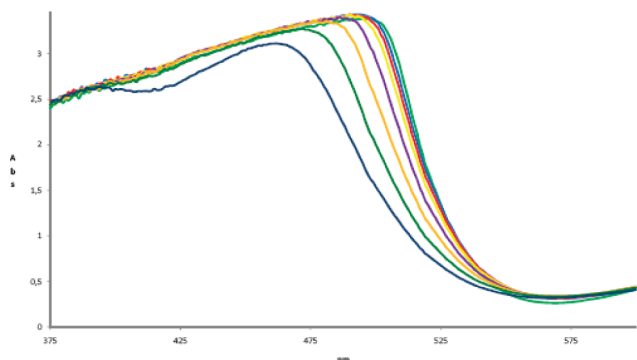


Figure 7. UV-vis spectra of **2** (green) in benzene with increasing amounts of PhOH: 22 equiv (blue), 32 equiv (red), 47 equiv (yellow), 77 equiv (purple), 122 equiv (orange), 182 equiv (dark green), and 262 equiv (dark blue).

that the binding constant is in the range of 10^{-2} M^{-1} . We could also determine the binding constant value for methanol in benzene, which increases up to 6.7 M^{-1} .

Binding Energies. The experimental results suggest that only water, amines, and, to a lesser extent, methanol are able to dissociate the dimeric $(\text{Cp}_2\text{TiCl})_2$. To clarify this key point we performed a computational study using density functional theory (DFT). The (relative) binding energies of water and the others potential hydrogen atom donors to Cp_2TiCl were calculated at the B3LYP/6-31G(d) level. In this theoretical study, we have included water, methanol, phenol, and methyl- and dimethylamine as simplified structures of the primary and secondary amines. Ammonia and THF have been also included for comparison. The binding energy of the dimeric $(\text{Cp}_2\text{TiCl})_2$ was also calculated because it is another essential parameter for the understanding of the nature of the hydrogen atom donor species in solution.

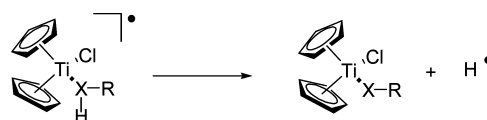
We were pleased to find that theoretical results fit with the experimental ones (see Table 1). We can clearly observe that ammonia and methylamine have binding energies, -13.6 and $-12.1 \text{ kcal mol}^{-1}$, respectively, similar to water ($-12.3 \text{ kcal mol}^{-1}$). Methanol ($-6.4 \text{ kcal mol}^{-1}$) and phenol ($-4.6 \text{ kcal mol}^{-1}$) possesses a coordination capability close to THF ($-4.6 \text{ kcal mol}^{-1}$), while a secondary amine, such as dimethylamine, presents intermediate values ($-8.7 \text{ kcal mol}^{-1}$). Interestingly, the binding energy of the titanocene(III) dimer is $-10.4 \text{ kcal mol}^{-1}$, which is between the calculated energies for water and methanol or phenol.

Table 1. Binding Energies of Potential Hydrogen Atom Donors to $\text{Cp}_2\text{TiCl}^{19}$

ligand (L)	$\Delta(E+\text{ZPE}), \text{ kcal mol}^{-1}$
H ₂ O	-12.3
D ₂ O	-12.8
Cp_2TiCl	-10.4
MeOH	-6.4
PhOH	-4.6
NH ₃	-13.6
MeNH ₂	-12.1
Me ₂ NH	-8.7
THF	-4.6

These (relative) values of binding energies could explain the profile of the titration experiments. That is, dimeric $(\text{Cp}_2\text{TiCl})_2$ is stable in the presence of methanol and phenol, and low concentrations of the corresponding $\text{Cp}_2\text{TiCl}(\text{HXR})$ active hydrogen atom donor species is expected in these cases. Consequently, the rates of HAT for methanol and phenol will be masked by this unfavorable coordination step. In the case of phenol, the situation is even less favorable owing to an efficient competence of THF molecules toward the binding sites. According to the calculated values, water and primary amines are able to yield the monomeric structures, which explains the marked UV-vis changes. Nevertheless, the interpretation of the UV-vis spectra of mixtures of titanocene(III) and amines might be not so simple, since subsequent deprotonation steps of the initial amine complexes could yield the corresponding amido complexes.¹⁸ Noteworthy, deuterium oxide has a slightly better coordination ability than H₂O and this fact could have some influence when water-based or D₂O-based experiments are compared. In this sense, free titanocene(III) concentration would be lower in experiments using D₂O, and thus, slightly slower reaction rates are expected.

Thermodynamic Profile of the HAT Process. The second key parameter to consider is the intrinsic HAT capabilities of the studied additives after coordination to titanocene(III). We have previously suggested that the unprecedented ability of water as hydrogen atom donor is due to a decrease of the O-H BDE favored by coordination to $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$. We wondered whether the above-mentioned closely related systems, including amines, alcohols, or phenols, would show the same trend. Theoretical calculations gave us the (relative) BDE values for the free species HXR and for the corresponding $\text{Cp}_2\text{TiCl}(\text{HXR})$ complexes, which let us estimate the H-X bond weakening. The results are summarized in Table 2.



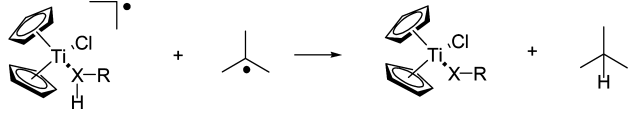
As can be seen, water is the species showing the highest bond weakening by coordination with Cp_2TiCl ($\Delta(\text{BDE}) = 58.6 \text{ kcal mol}^{-1}$).

(18) For a recent reference see: Paniagua, C.; Mosquera, M. E. G.; Jacobsen, H.; Jimenez, G.; Cuenca, T. *Organometallics* **2009**, *28*, 6975–6980.

(19) This study has been restricted to Cp_2TiCl . Nevertheless, it has been described that changes in the Cp substitution in titanocene(III)-complexes have significant variations in their chemical reactivity and consequently coordination capabilities can be also affected: Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807–832. In fact, calculated binding energies for water and $(t\text{BuCp})_2\text{TiCl}$ and Cp_2^*TiCl are -10.63 and $-8.30 \text{ kcal mol}^{-1}$, respectively.

Table 2. BDE Values of the X–H Bond in Cp₂TiCl(HXR) Complexes

HXR	BDE, kcal mol ⁻¹	Cp ₂ TiCl(HXR)	BDE, kcal mol ⁻¹	Δ(BDE), kcal mol ⁻¹
H ₂ O	108.1	H ₂ O	49.4	58.6
D ₂ O	110.3	D ₂ O	51.4	58.8
MeOH	93.5	MeOH	42.6	50.9
PhOH	74.3	PhOH	39.6	34.7
NH ₃	100.4	NH ₃	65.0	35.4
MeNH ₂	92.4	MeNH ₂	63.7	28.7
Me ₂ NH	86.7	Me ₂ NH	67.6	19.1

Table 3. Δ*H* for the Reduction of *t*-Butyl Radical by Cp₂TiCl(HXR) Complexes


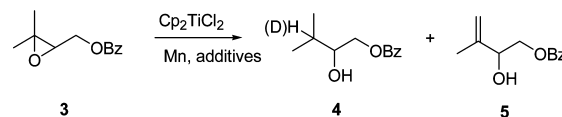
HXR	Δ <i>H</i> , kcal mol ⁻¹
H ₂ O	–42.1
D ₂ O	–42.2
MeOH	–48.9
PhOH	–54.9
NH ₃	–26.5
MeNH ₂	–27.8
Me ₂ NH	–23.2

mol⁻¹). Of the other two oxygenated systems studied, only methanol has a similar behavior (Δ(BDE) = 50.9 kcal mol⁻¹). Phenol, ammonia, and primary and secondary amines showed a significantly lower bond weakening (Δ(BDE) = 19.1–35.4 kcal mol⁻¹).

Nevertheless, the feasibility of the HAT reaction is related to not only the bond weakening but also the exothermicity of the global reaction. In that case, the creation of the new H–C bond has to be taken into account. Consequently, the endothermicity of the H–X bond dissociation in the titanocene(III) complex can be surpassed more easily with low values of BDE. By this reasoning methanol (BDE of Cp₂TiCl(MeOH) = 42.6 kcal mol⁻¹) and phenol (BDE of Cp₂TiCl(PhOH) = 39.6 kcal mol⁻¹) would be the best HAT reagents and not water. In this sense, we have computed the enthalpy change of a model HAT reaction. For simplicity, we selected the reduction of *t*-butyl radical using the corresponding Ti(III)-complexes. In all cases, the reaction was exothermic, and as we expected based on the values in Table 3, phenol and methanol showed the higher exothermicities.

All of these theoretical results suggest that water, methanol, and phenol should be good HAT reagents in the reduction of tertiary radicals, with phenol or methanol being the best. Nevertheless, the coordination capabilities described before must be also taken into account in real experiments.

Influence of the H-Atom Donor on the Reduction of Epoxides Mediated by Titanocene(III). Fortunately, these theoretical predictions could be tested experimentally. We selected epoxide **3** as the model substrate^{20,21} and carried out a set of experiments to guarantee that a HAT reaction from titanium(III)

Scheme 3. Mechanistic Studies of Titanocene(III)-Mediated Reduction of Epoxide **3**

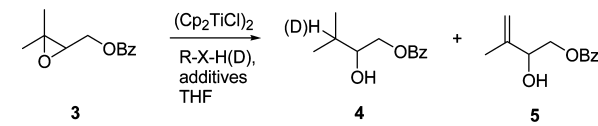
aqua complexes actually takes place (Scheme 3). Under anhydrous standard conditions (Cp₂TiCl₂/Mn), the main product is the allylic alcohol **5** (58%) and not the expected deoxygenated product derived from a potential Ti(IV) organometallic intermediate.²² However, when we treated epoxide **3** in the presence of D₂O (10 equiv) under the standard conditions, reduced derivative **4** (69%, 83% deuterium incorporation) was obtained. This result indicated that the water-mediated reduction of the transient tertiary radical was faster than the potential radical trapping by a second Cp₂TiCl species. Additionally, when we repeated the experiment in the presence of an equimolar mixture of D₂O and 1,4-CHD (10 equiv each), we obtained **4** (78%) with a 83% deuterium incorporation, revealing that the transfer of deuterium from D₂O was even faster than that of hydrogen from 1,4-CHD.²³ This kinetics ruled out the possibility of **4** being formed by the hydrolysis of an alkyl–Ti^{IV} complex.

We explored the reactivity of epoxide **3** (1 mmol) using pregenerated **2** (1 mmol)²⁴ and different potential hydrogen atom donors (5 mmol) in THF. The amount of additive was selected to ensure the presence of unbound titanocene(III) in the reaction media, which is essential for the epoxide radical opening. The results are summarized in Table 4.

Although the reactions are not quantitative, the total yields of isolated compounds are similar and consistent. Therefore, conclusions derived from the relative relationships of **4** and **5** can be assumed. First of all, the results clearly show that a direct relationship between the acidity of the hydrogen donor and the efficiency of the reduction process does not exist, although it should be expected if a protonolysis of an alkyltitanium intermediate had been involved.²⁵ As we can see, water is the

- (21) The benzoate group was introduced to avoid losses by evaporation, guaranteeing the homogeneity of the results and as a UV marker for an easy detection by analytical techniques.
- (22) Although it has been described that bis(cyclopentadienyl)titanium(III) chloride, generated in situ by stirring commercial Cp₂TiCl₂ with Mn dust in anhydrous THF, exists as an equilibrium mixture of the monomer Cp₂TiCl and the dinuclear species (Cp₂TiCl)₂, we postulate that monomeric Cp₂TiCl is the active species in the mixed disproportionation process; Justicia, J.; Jiménez, T.; Morcillo, S. P.; Cuerva, J. M.; Oltra, J. E. *Tetrahedron* **2009**, *65*, 10837–10841.
- (23) A control experiment using 1,4-CHD (10 equiv each) as HAT reagent gave a mixture of **4** (40%) and **5** (32%). Although the calculated kinetic values of *t*-butyl radical and 1,4-CHD (Δ*H* = –21.6 kcal mol⁻¹, *E*_a = 6.9 kcal mol⁻¹) suggest that should be better than water, it can not coordinate with Cp₂TiCl. In this situation the concentration of free Cp₂TiCl is high enough to promote secondary reactions such as deoxygenation processes. Pre-association processes between aqua complex and the tertiary radical cannot be ruled out either: Hammerum, S. J. *Am. Chem. Soc.* **2009**, *131*, 8627–8635. See also: Miyazaki, S.; Kojima, T.; Mayer, J. M.; Fukuzumi, S. *J. Am. Chem. Soc.* **2009**, *131*, 11615–11624.
- (24) In the usual experimental conditions, interferences owing to the presence of both Mn dust (usually required for the in situ generation of titanocene(III) from titanocene(IV) precursors) and stoichiometric amounts of MnCl₂ (formed upon oxidation of the metallic co-reductor) have to be taken into account. Therefore, for comparison, we carried out the same experiments in the presence of Mn dust or MnCl₂ obtaining similar results.
- (25) In such a case, according to the p*K*_a values, a higher amount of reduced product should be expected in the reaction with phenol compared with water. Nevertheless, the actual yields follow the opposite trend (17% and 84%, respectively).

(20) In our preliminary communication (ref 6a), we selected 6,7-epoxyneryl acetate as model substrate for tertiary radical generation and study. It presented some unique characteristics which helped us to distinguish between different mechanisms. Nevertheless, we obtained mixtures of cyclized and uncyclized products complicating the comparison between experiments.

Table 4. Yields of Compounds **4** and **5** Using Different Hydrogen Atom Donors and Experimental Conditions in THF


entry	R–X–H (D)	yield (%)	4:5	D inc. (%)
1	H ₂ O	84	100:0	
2	D ₂ O	87	90:10	84
3	MeOH	83	55:45	
4	MeOD	80	33:66	58
5	PhOD	85	20:80	47
6	Bu ₂ NH	71	0:100	
7	CH ₃ (CH ₂) ₇ NH ₂ ^a	81	20:80	

^a We used a 1:2 CH₃(CH₂)₇NH₂:**2** molar ratio to ensure the presence of active **2**. When we used a 10:1 CH₃(CH₂)₇NH₂:**2** molar ratio, only starting material was recovered.

best hydrogen atom donor among the tested compounds, and its behavior is significantly different compared with closely related MeOH and PhOH. This apparent contradiction with the theoretical findings can be easily explained by taking into account that the concentrations of the corresponding titanocene(III) complexes of methanol and phenol in THF must be very low, compared to free titanocene (Cp₂TiCl)₂, as we have previously determined. These experimental results suggest that the remarkable behavior of water as HAT reagent in Ti(III) chemistry is due to not only the weakening of the H–OH bond but also the high affinity of water for Ti(III) complexes.

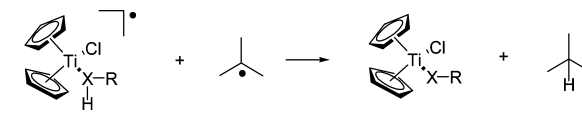
Deuterium oxide gave similar global yields although low amounts of alkene **5** could also be isolated. This is a relevant result, since it suggests that the hydrogen atom transfer is the slowest step in the overall reaction mechanism. In fact, we could determine an estimated isotopic effect of 4.7, which is consistent with our proposal.

The situation was different when deuterated phenol was used as the additive. The low deuteration incorporation in compound **4** showed that the reduction product cannot derive exclusively from a HAT from a titanocene(III):phenol complex. This is also consistent with the absence of such species as we previously determined by UV–vis and theoretical calculations. Under these conditions, a HAT reaction from the solvent could take place.²⁶ A direct disproportionation reaction between the corresponding tertiary radicals cannot be excluded either.

Both binding energy to Cp₂TiCl and H–N bond dissociation energy suggest that amines could be good candidates. Therefore, we carried out the reaction with model primary (octyl amine) and secondary (dibutyl amine) amines. In the first case, the starting epoxide was recovered unaltered. The higher coordination abilities of nitrogen ligands compared to oxygen ones led octylamine and (Cp₂TiCl)₂ to form a stable complex, and consequently, the amounts of unbound (Cp₂TiCl)₂ are so low that the initial radical epoxide opening cannot occur. In order to observe the behavior of octyl amine as HAT reagent, we changed the reaction conditions by lowering the amount of amine below the (Cp₂TiCl)₂ concentration. In these new conditions, the reaction could be carried out, but only low yields of reduction product **4** were obtained. Dibutyl amine could be used in the standard proportion, but as in the case of octylamine, allylic alcohol **5** was the main product. These experiments rule

Table 5. Yields of Compounds **4** and **5** Using Different Experimental Conditions and Hydrogen Atom Donors in Benzene

entry	R–X–H (D)	yield (%)	4:5	D inc. (%)
1	H ₂ O	77	100:0	
2	D ₂ O	86	78:22	92
3	MeOH	84	100:0	
4	MeOD	75	60:40	73
5	PhOD	60	40:60	72

Table 6. Activation Energies for the Reduction of the *t*-Butyl Radical by Cp₂TiCl(HXR) Complexes


HXR	ΔE _a , kcal mol ^{−1}
H ₂ O	8.8
D ₂ O	9.8
MeOH	7.9
PhOH	4.0
NH ₃	14.7
MeNH ₂	12.4
Me ₂ NH	15.3

out that amines can be used as efficient hydrogen atom donors in this reaction, despite their excellent coordination capabilities.

The above shown binding constant of MeOH to titanocene(III) in benzene suggests that the amount of the active species, Cp₂TiCl(MeOH), in that solvent should be higher. Therefore, an increase of saturated alcohol **4** is expected. Although pure benzene cannot be used directly as solvent in titanocene(III)-mediated transformations, the experiments using pregenerated (Cp₂TiCl)₂ could be carried out. We were pleased to find that, in benzene, alcohol **4** is the sole product when methanol is used as an additive. MeOD showed the same profile confirming that the hydrogen atom also comes from methanol in benzene solutions. When phenol-*d*₆ was used as an additive in benzene, small amounts of deuterated **4** could be isolated. This result can be explained taking into account that a direct HAT process from uncoordinated phenol can also take place as previously reported.²⁷ Consequently with the absence of THF, the deuterium incorporations are higher in benzene. It is worth noting that incomplete deuteration can be correlated with an increase of alkene **5**, which can derive from a direct disproportionation process (Table 5).

Theoretical studies can be used again to understand the experimental results. The corresponding activation energies (*E*_a) for triplet transition state (TS) were calculated (Table 6). A correlation between the exothermicity and the *E*_a of all of the reactions exists, as it is predicted by the Evans–Polanyi equation. The higher exothermicities correlate with the minor activation energies. Therefore, phenol showed an activation energy of only 4.02 kcal mol^{−1}, whereas the HAT process involving dimethylamine has an activation energy of 15.33 kcal mol^{−1}. The activation energy for water is placed in the intermediate value of 8.82 kcal mol^{−1}. We also calculated the key thermodynamic and kinetic parameters of the HAT reaction from THF to *t*-butyl radical since it cannot be excluded in principle (Δ*H* = −2.1 kcal mol^{−1}, *E*_a = 11.9 kcal mol^{−1}). These values suggest that HAT processes from THF cannot compete

(26) Newcomb et al. have reported that under similar conditions significant HAT reactions from THF (2–4 × 10³ M^{−1} s^{−1}) are operative: see ref 9.

(27) Franchi, P.; Lucarini, M.; Pedulli, G. F.; Valgimigli, L.; Lunelli, B. *J. Am. Chem. Soc.* **1999**, *121*, 507–514.

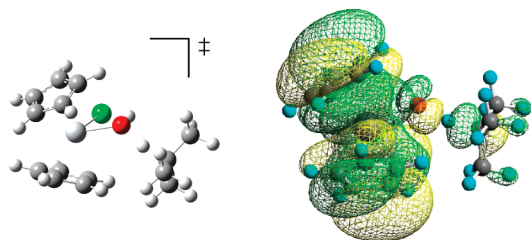


Figure 8. Calculated transition state for the H-atom transfer from **1** to *t*-butyl radical (DFT level).

efficiently with water, methanol or phenol Cp_2TiCl complexes, even in the presence of high molar relationship.

If we compare the E_a values for the reduction of the *t*-butyl radical with deuterium oxide or water, we can also conclude that this transformation has a high isotopic effect, estimated at 5.08 based on the calculated values at 298 K (assuming the same frequency factor). The only experimental values of isotopic effect for this transformation are 3.35,^{6a} 4.4,⁹ and 4.7 obtained in the reduction of primary, secondary, and tertiary radicals (this work), respectively, which are in good agreement with the calculated one.

HAT reactions are considered to be a subfamily of proton-coupled electron transfer (PCET) reactions. Although PCET processes avoid high energy intermediates such as carbanions derived from a stepwise electron transfer, in this case, a careful inspection SOMOs of the TSs suggests a HAT mechanism rather than a proton-coupled electron transfer. The electron density between O and H and the absence of connection between the metal complex and the carbon radical imply that the proton and the electron are being transferred involving the same set of atomic orbitals.²⁸

Reduction of Other Carbon-Centered Radicals. From the above exposed results, we now know that two key factors are at the heart of the success of water as hydrogen atom donor in titanocene(III) chemistry: a strong coordination between water and the titanocene(III) complex and a low activation energy (estimated at less than 8.8 kcal mol⁻¹ based on the calculated values). Nevertheless, little is known about the generality of this reaction since a systematic study of the nature of the carbon-based radical has not been performed to date. For that reason, we paid attention to the reactivity of **1** toward different carbon-centered radicals to study the scope of the reaction. Bearing in mind the solid concordance between the experimental and theoretical results until this moment, we carried out theoretical calculations over a range of HAT reactions from aqua complex **1** and different carbon-centered radicals (Figure 8). We have used hydroxyl radicals instead of the corresponding titanoxyl species in the modelization of the process for computational convenience. The results are summarized in Table 7.

The theoretical values show that an increase of the stabilization of the radical results in an increase of the activation energy. The reduction of phenyl and vinyl radicals (entries 7 and 8) is predicted to take place in an essentially barrierless pathway (0.4–3.0 kcal mol⁻¹). The activation energy of simple alkyl-type radicals is also low (6.3–8.8 kcal mol⁻¹, entries 1, 3, and 4) compatible with fast reaction rates. Although we have considered mainly non polar radicals, that is, with no heteroatom placed near the carbon-centered radical, in radical reductive opening of epoxides an oxygen atom is present in the α -position

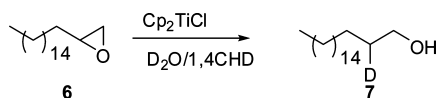
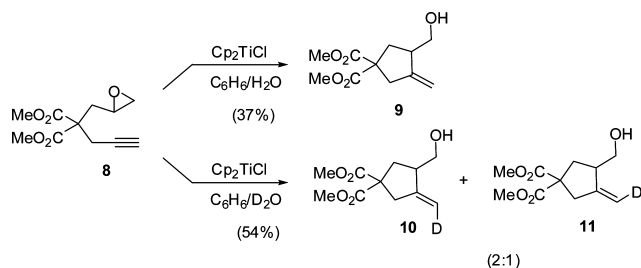
Table 7. Enthalpies and Activation Energies for the Reduction of Different Carbon-Centered Radicals by $\text{Cp}_2\text{TiClOH}_2$

entry	R	ΔH , kcal mol ⁻¹	ΔE_a , kcal mol ⁻¹
1	$\text{CH}_3\text{--CH}_2$	−48.5	6.3
2	$\text{CH}_2\text{OH--CH}_2$	−51.6	5.5
3	$\text{CH}_3\text{--CH--CH}_3$	−45.0	7.2
4	$(\text{CH}_3)_3\text{C}$	−42.1	8.8
5	$\text{CH}_2\text{OH}(\text{CH}_3)_2\text{C}$	−43.5	8.4
6	CH_2CHCH_2	−34.2	16.1
7	$\text{CH}_2=\text{CH}$	−58.3	0.4
8	C_6H_5	−59.6	3.0
9	$\text{C}_6\text{H}_5\text{CH}_2$	−37.2	12.4
10	<i>p</i> -F- C_6H_5	−37.1	12.2
11	<i>p</i> -OMe- $\text{C}_6\text{H}_5\text{CH}_2$	−36.9	7.5
12	<i>p</i> -OAc- $\text{C}_6\text{H}_5\text{CH}_2$	−37.0	12.1
13	<i>p</i> -CO ₂ Me- $\text{C}_6\text{H}_5\text{CH}_2$	−36.6	13.9

and therefore should be considered. In this case, the E_a values are slightly lower than the corresponding to non polar radicals (entries 2 and 5). A decrease of 0.8 and 0.4 kcal mol⁻¹ is observed in primary and tertiary radicals, respectively. The highest calculated E_a was obtained in the HAT to allyl radical (16.1 kcal mol⁻¹). Benzyl radicals were also studied, showing values of E_a in between those calculated for alkyl and allyl ones (12.1 kcal mol⁻¹). In this case, substitution in para position might affect the E_a because of an expected π -interaction between the π -type radical and the π -aromatic.²⁹ Nevertheless, we could not find a simple relationship between the exothermicity of the reaction or any other parameter and the E_a . All of E_a values are in the range of 12.1–13.9 kcal mol⁻¹ with the exception of *p*-OMe substituted benzyl radical which calculated E_a is 7.5 kcal mol⁻¹. This abnormally low value suggests that the TS is affected by important polar effects or a change of mechanism is taking place. Again, inspection of the SOMO's of the corresponding TS's suggests a HAT mechanism rather than a proton-coupled electron transfer. If our mechanistic hypothesis based on HAT processes from titanocene aqua complex is correct, the experimental results should fit with the above-mentioned theoretical predictions. Low E_a must be correlated with efficient HAT processes at room temperature. However, experiments are complicated in this case by the fact that side reactions can become the main reaction with some substrates. While in the study of tertiary radicals the interference of side reactions could be avoided, the study of secondary and primary radicals is more complex. As an example, primary radicals can be efficiently captured by a molecule of Cp_2TiCl and a subsequent hydrolysis the alkyl–Ti(IV) intermediate can mask a real HAT mechanism. In our preliminary communication,^{6a} we could demonstrate unequivocally that titanocene(III)–aqua complex is able to promote a HAT reaction from coordinated water to primary alkyl radicals generated by a cyclization of caryophyllene oxides. Noteworthy, this result fits the predicted E_a calculated for the HAT transfer to primary radicals.

(28) For a similar analysis of the transition state, see: DiLabio, G. A.; Johnson, E. R. *J. Am. Chem. Soc.* **2007**, *129*, 6199–6203.

(29) In the literature, there are some cases where the activation energy in HAT processes can be correlated with Hammett σ parameters. In that case the activation energies, the spin densities and the HOMO levels of the TS correlated well with the σ parameters: Wang, Y.; Kumar, D.; Yang, C.; Han, K.; Shaik, S. *J. Phys. Chem. B* **2007**, *111*, 7700–7710.

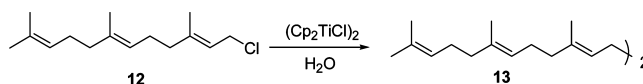
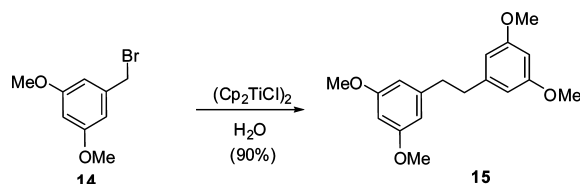
Scheme 4. Reduction of Epoxide **6****Scheme 5.** Ti^{III}-Promoted Cyclization of Epoxyalkyne **7** in the Presence of H₂O or D₂O

The reduction of secondary radicals, with a predicted E_a value of 7.2 kcal mol⁻¹, may also occur by a HAT mechanism. When simple epoxide **6** was used as model substrate, a similar kinetic reasoning to that for compound **3** could not be performed. Although alcohol **7** is the only isolable product in the presence of water (Scheme 4), 1,4-CHD is unable to promote such reduction and competitive experiments between D₂O and 1,4-CHD were not conclusive. Nevertheless, the isotopic effect of this reduction was 4.4, which is similar to described for this HAT process.

Related to this result, in 2008, Newcomb et al. determined experimentally the E_a of the HAT reaction from Cp₂TiClOH₂ to a secondary radical. The obtained value (5.5 kcal mol⁻¹) is in excellent agreement with the calculated one (7.2 kcal mol⁻¹) within the error expected for calculations.

HAT processes to phenyl and vinyl radicals are usually very fast reactions with very low E_a , as theoretical calculations predict. In this situation HAT from THF becomes an important reaction, which can mask the HAT from the acuacomplex **1** in THF. In fact, calculated E_a for the HAT from THF to these radicals ranges from 2.0 kcal mol⁻¹ for vinyl radical to practically barrierless (0.1 kcal mol⁻¹) for phenyl radical.³⁰ The generation of such radicals using (Cp₂TiCl)₂ (**2**) is not a simple task. Nevertheless, vinyl radicals can be obtained after a titanocene(III)-mediated cyclization of epoxi-alkynes in THF.³¹ To preclude any potential HAT from THF,³² we decided to carry out that cyclization reaction in benzene using (Cp₂TiCl)₂. The cyclization of model epoxi-alkyne **8** in the presence of water (10 equiv) in benzene gave the cyclization product **9** albeit in moderate yield (37%, Scheme 5).

When D₂O was used instead of H₂O, we obtained isotopomers **10** and **11** with 92% deuterium incorporation (Scheme 5), confirming that the hydrogen atom came from water. The above observations strongly suggested a reaction mechanism via unprecedented H-atom transfer from water to a sp² carbon-centered radical, mediated by Cp₂Ti^{III}(OH)₂Cl. Additionally, a potential alternative mechanism via formation and subsequent hydrolysis of an organometallic vinyl-Ti^{IV} intermediate was ruled out by the following experiments. Epoxide **8** was treated

Scheme 6. Dimerization of Farnesyl Chloride (**12**) in the Presence of Water**Scheme 7.** Dimerization of Benzylic Bromide (**14**) in the Presence of Water

with (Cp₂TiCl)₂ under anhydrous conditions until all starting material was consumed (5 h, TLC analysis). Then, D₂O was added and compound **9** was obtained (66%) without any deuterium incorporation, which would have occurred in the deuterolysis of a hypothetical organometallic (or carbanion-type) intermediate.

Based on the calculated E_a values, the reduction of allylic-type radicals should be cumbersome at room temperature. Such radicals can be generated by (Cp₂TiCl)₂ from allylic halides. As model substrate we selected farnesyl chloride **12**. Consequently with the E_a values, we could not observe significant amounts of the corresponding reduction product even in the presence of high concentrations of water (20 equiv). Homodimer **13** was the only product (71%; Scheme 6).³³ This is in agreement with the reported rate constant for the dimerization of allyl radicals (4.0–8.3 × 10⁹ M⁻¹ s⁻¹).³⁴

The predicted activation energies for the reduction of benzylic radicals are also compatible with a fast reaction. Nevertheless, the rate constant for the dimerization of benzyl radical is described as being around 10⁹ M⁻¹ s⁻¹.³⁵ Therefore, the expected products in the reduction of the corresponding benzylic bromides by (Cp₂TiCl)₂ is the corresponding homodimer, even in the presence of an excess of water. In fact, when we carried out the reaction with functionalized benzyl bromide **14** in the presence of 20 equiv of water we exclusively obtained dimer **15** (90%; Scheme 7).^{36,37}

Interestingly, products derived from the homodimerization of benzylic radicals have been described in titanocene(III) chemistry when styrene oxides are used as starting materials.³⁸ As an example, the reductive opening of styrene oxide (**16**) mediated by (Cp₂TiCl)₂ in anhydrous conditions yields the corresponding dimer **17**³⁹ (48%; Scheme 8). The isolation of the dimer guarantees that organometallic intermediates are not involved in those reaction conditions. When the reaction was

(30) Cp₂TiClOD₂ showed similar profile to vinyl radical: E_a = 1.51 kcal mol⁻¹, ΔH = 58.1 kcal mol⁻¹.

(31) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3206–3208.

(32) When the reaction is carried out in THF, we only obtained the nondeuterated products in the presence of D₂O, which suggests that the HAT from THF is the main reaction.

(33) Barrero, A. F.; Herrador, M. M.; Quílez del Moral, J. F.; Arteaga, P.; Arteaga, J. F.; Diéguez, H. R.; Sánchez, E. M. *J. Org. Chem.* **2007**, *72*, 2988–2995.

(34) Throssel, J. J. *Int. J. Chem. Kinetics* **1972**, *4*, 273–276.

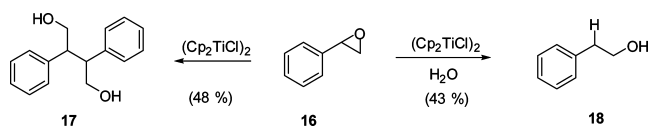
(35) k = 4.6 × 10⁹ M⁻¹ s⁻¹; Claridge, R. F. C.; Fischer, H. *J. Phys. Chem.* **1983**, *87*, 1960–1967.

(36) The functionalization was selected to obtain reduction products which would not be volatile.

(37) Barrero, A. F.; Herrador, M. M.; Quílez del Moral, J. F.; Arteaga, P.; Akssira, M.; El Hanbali, F.; Arteaga, J. F.; Diéguez, H. R.; Sánchez, E. M. *J. Org. Chem.* **2007**, *72*, 2251–2254.

(38) (a) Gansäuer, A.; Ndene, N.; Lauterbach, T.; Justicia, J.; Winkler, I.; Mück-Lichtenfeld, C.; Grimme, S. *Tetrahedron* **2008**, *64*, 11839–11845. (b) Fernández-Mateos, A.; Encinas Madrazo, S.; Herrero Tejón, P.; Rubio González, R. *J. Org. Chem.* **2009**, *74*, 3913–3918.

(39) Compound **17** was isolated as a 1:2 mixture of meso:dl stereoisomers.

Scheme 8. Dimerization and Reduction of Styrene Oxide (**16**)**Table 8.** Enthalpies, Activation Energies and Yields for the Reduction of Different Styrene-Derived Radicals by $\text{Cp}_2\text{TiClOH}_2$

epoxide	R	ΔH_f , kcal mol ⁻¹	ΔE_a , kcal mol ⁻¹	alcohol	yield, %
16	H	-36.1	13.9	18	43
19	F	-36.1	13.7	21	52
20	OAc	-39.9	18.2	22	48

repeated in the presence of water we could obtain alcohol **18** (43%) which can not derive from the protonolysis of an organotitanium. In this situation the HAT process could be operative. This study was extended to para substituted styrene oxides **19–20** and apparently the reduction process takes place even when substrates with a high E_a are used (Table 8).

Conclusions

We have demonstrated that our initial assumption that titanocene(III) aqua complexes are a unique class of HAT reagents is correct. They are able to reduce efficiently carbon-

centered radicals of diverse nature. The success of this transformation is based on two key features: (a) an excellent binding capabilities of water toward titanocene(III) complexes and (b) a low activation energy for the HAT step. Therefore, the observed reactivity can be explained in the framework of an unprecedented HAT reaction involving water. The theory has predictive capabilities fitting well with the experimental results, and may aid to find more examples of this remarkable radical reaction. We are currently working in obtaining a complete theoretical foundation of this phenomenon and in the extension of these studies to other metals such as Sm, Cr, or Co.

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Supporting Information Available: General experimental procedures and computational details. UV–vis and ¹³C NMR spectra of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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