

Substituent Effects and Supramolecular Interactions of Titanocene(III) Chloride: Implications for Catalysis in Single Electron Steps

Andreas Gansäuer,^{*,†} Christian Kube,[†] Kim Daasbjerg,[‡] Rebecca Sure,[§] Stefan Grimme,[§] Godfred D. Fianu,^{||} Dhandapani V. Sadasivam,^{||} and Robert A. Flowers,^{II*||}

[†]Kekulé-Institut für Organische Chemie und Biochemie, Universität Bonn, Gerhard Domagk Str. 1, 53121 Bonn, Germany

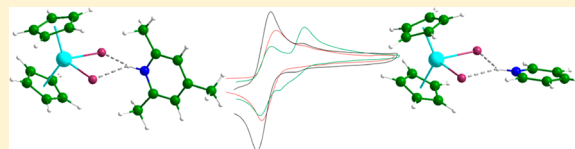
[‡]Department of Chemistry, Aarhus University and Interdisciplinary Nanoscience Center, Langelandsgade 140, 8000 Aarhus C, Denmark

[§]Mulliken Center for Theoretical Chemistry, Institut für Physikalische und Theoretische Chemie der Rheinischen-Friedrich-Wilhelms-Universität Bonn, Beringstraße 4, D-53115 Bonn, Germany

^{||}Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania 18015, United States

Supporting Information

ABSTRACT: The electrochemical properties of titanocene(III) complexes and their stability in THF in the presence and absence of chloride additives were studied by cyclic voltammetry (CV) and computational methods. The anodic peak potentials of the titanocenes can be decreased by as much as 0.47 V through the addition of an electron-withdrawing substituent (CO₂Me or CN) to the cyclopentadienyl ring when compared with Cp₂TiCl. For the first time, it is demonstrated that under the conditions of catalytic applications low-valent titanocenes can decompose by loss of the substituted ligand. The recently discovered effect of stabilizing titanocene(III) catalysts by chloride additives was analyzed by CV, kinetic, and computational studies. An unprecedented supramolecular interaction between [(C₅H₄R)₂TiCl₂]⁻ and hydrochloride cations through reversible hydrogen bonding is proposed as a mechanism for the action of the additives. This study provides the critical information required for the rational design of titanocene-catalyzed reactions in single electron steps.



INTRODUCTION

The design of novel and efficient catalytic transformations is at the heart of chemistry.¹ Radical-based transformations offer attractive features such as ease of generation, high functional group tolerance, and ability to add to unsaturated functional groups.² In view of these advantages, it is surprising that their potential as key intermediates in catalytic atom-economical C–C bond formation is largely untapped.³ Among the rare examples of such reactions are atom-transfer radical addition reactions, especially those catalyzed by Ru complexes,⁴ the highly important Cu-catalyzed atom-transfer radical polymerizations,⁵ and H₂-mediated Cr- or Co-catalyzed reductive cyclization of dienes.⁶ We have introduced reagent-controlled examples⁷ of atom-economical catalytic radical reactions with our titanocene-catalyzed tetrahydrofuran synthesis⁸ and radical arylations of epoxides.⁹

In all of the aforementioned processes, radical generation and trapping can be regarded as oxidative additions and reductive eliminations in single electron steps.¹⁰ Thus, catalysis of atom-economical radical chemistry should be considered as catalysis in single electron steps and is therefore part of the framework of classical organometallic catalysis.¹¹ In line with this notion, the titanocene-catalyzed tetrahydrofuran synthesis and radical arylation are critically influenced by the electronic properties of

the ligands. Moreover, in reactions with the most efficient electron-deficient catalysts, thermal stability of the catalyst was a serious issue. Addition of chloride sources resolved this issue and allowed a significant reduction of catalyst loading. Thus, the success of these transformations is due to an intricate interplay of thermodynamic properties of the titanocene(III) reagents and their kinetic stability under highly specific reaction conditions. As a consequence, it is essential to unravel the interplay between catalyst stability and reactivity in order to provide a toolbox for the design of efficient reactions.

Here we describe our efforts to achieve this goal with the aid of cyclic voltammetry (CV), kinetic, and computational studies. CV is ideally suited for the identification of the components of mixtures of redox-active compounds and the study of their properties and the kinetics of their reactions.¹² CV has been applied to resolve the composition and reactivity of parent Cp₂TiCl-derived reagents in a number of solvents and transformations.¹³ Computational studies provide the relative stabilities of the complexes between Ti(III) catalysts and amine hydrochlorides, and kinetic studies show the impact of additives on catalyst reactivity.

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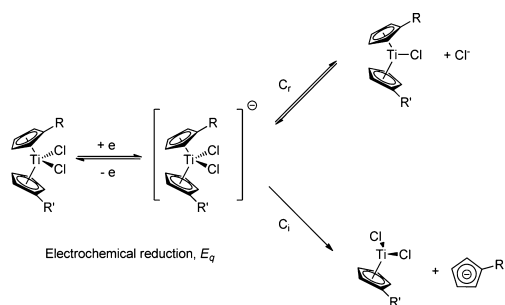
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RESULTS AND DISCUSSION

The CV investigations were divided into three parts. First, the electrochemical reduction of the titanocenes was studied. In this manner, the properties of $[(C_5H_4R)_2TiCl_2]^-$ could be studied, providing benchmarks for examining the impact of chloride additives. Second, the influence of ligand substitution on solutions of Zn-reduced $(C_5H_4R)_2TiCl_2$ was investigated. These solutions contain $(C_5H_4R)_2TiCl$, the active species in titanocene(III)-catalyzed reactions, and its dimer. Finally, since chloride sources are often employed in catalytic applications of Ti(III) reductants, the effect of chloride additives to solutions of Zn- $(C_5H_4R)_2TiCl_2$ was probed. In addition to the CV experiments, kinetic and computational studies aimed at understanding the nature of the interactions of these additives and catalysts were examined.

Substituent Effects for Electrochemically Reduced Titanocene(IV) Dichlorides in THF. In general, the electrochemical reduction of Cp_2TiCl_2 (Scheme 1, $R = R' = H$) can be

Scheme 1. E_qC_r and E_qC_i Schemes for the Electrochemical Reduction of Titanocene Dichlorides



described according to an E_qC_r reaction scheme as originally proposed by Laviron and co-workers.¹⁴ The quasi-reversible electrochemical reduction of Cp_2TiCl_2 (E_q) is followed by a chemically reversible cleavage of chloride from $[Cp_2TiCl_2]^-$ (C_r).^{13b,f} Scheme 1 also includes a chemically irreversible step (C_i), namely, loss of a cyclopentadienyl anion ligand rather than chloride upon electrochemical reduction, which has never been observed until this point.

Previously, it was shown that the most characteristic feature of the cyclic voltammogram of Cp_2TiCl_2 at a low sweep rate ($\nu < 1 \text{ V s}^{-1}$), is the presence of the $Cp_2TiCl_2/Cp_2TiCl_2^-$ wave in tetrahydrofuran (THF) (vide infra).^{13b} This is due to the fact that the second-order back association reaction between Cp_2TiCl and Cl^- in the C_r step is fast, thus leaving $[Cp_2TiCl_2]^-$ as the only species detectable on the reverse sweep. In principle, at sufficiently high sweep rates a situation can be reached where the back association reaction is outrun before regeneration of $[Cp_2TiCl_2]^-$. Indeed, cyclic voltammograms recorded at $\nu = 20 \text{ V s}^{-1}$ show a small additional oxidation wave pertaining to the oxidation of Cp_2TiCl .^{13b}

Ring-substituted titanocenes have only recently been employed in catalytic electron transfer applications.^{9,10} It was assumed that ring substitution would strongly influence the redox behavior of the complexes. Until now only a few such examples have been investigated.¹⁵ Therefore, in this study we decided to investigate various mono- and disubstituted titanocene complexes of the type $(C_5H_4R)(C_5H_4R')Ti(IV)Cl_2$ with $R = tBu, H, Cl, COOMe$, or CN and $R' = tBu, H, Cl$, or $COOMe$ (see Scheme 1).

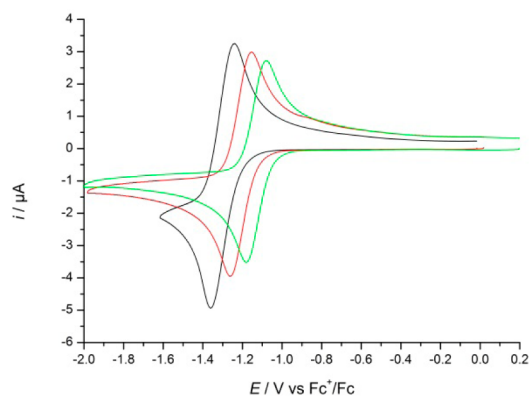


Figure 1. Cyclic voltammograms of 2 mM Cp_2TiCl_2 (black), $(C_5H_4Cl)CpTiCl_2$ (red), and $(C_5H_4Cl)_2TiCl_2$ (green) recorded at a glassy carbon disk electrode with $\nu = 0.1 \text{ V s}^{-1}$ in 0.2 M Bu_4NPF_6/THF .

Figure 1 shows cyclic voltammograms of Cp_2TiCl_2 , $(C_5H_4Cl)CpTiCl_2$, and $(C_5H_4Cl)_2TiCl_2$ recorded at $\nu = 0.1 \text{ V s}^{-1}$ in 0.2 M Bu_4NPF_6/THF . As can be seen, the overall electrochemical behavior of the two substituted complexes follows that of Cp_2TiCl_2 in which the characteristic redox wave of $(C_5H_4R)(C_5H_4R')TiCl_2/[(C_5H_4R)(C_5H_4R')TiCl_2]^-$ is the only one observable at low ν . However, the position of the wave is shifted in a positive direction when chlorine is introduced as a substituent. Hence, CV constitutes a good method of choice for studying the properties of the anionic complexes $[(C_5H_4R)(C_5H_4R')TiCl_2]^-$.

Table 1 summarizes the effect of ligand substitution on the redox properties of the titanocene complexes. The potential of the reduction peak ($E_{p,c}$) varies from -1.44 V vs ferrocenium/ferrocene (Fc^+/Fc) for the reduction of Kagan's complex (**1**) to -1.06 V vs Fc^+/Fc for the reduction of $(C_5H_4CN)CpTiCl_2$ in THF (recorded at $\nu = 0.1 \text{ V s}^{-1}$); the pertinent anodic potentials ($E_{p,a1}$) were found to be 100–160 mV less negative. The standard potentials of the $(C_5H_4R)(C_5H_4R')TiCl_2/[(C_5H_4R)(C_5H_4R')TiCl_2]^-$ systems (E_1°) were determined by digital simulations and are included in the last column of Table 1.¹⁶

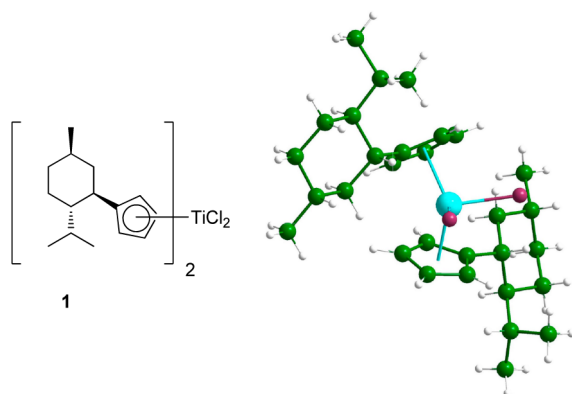
The order of the potentials is substituent-dependent, displaying a reasonable correlation with the Hammett substituent coefficient σ_p ($\sigma_p = -0.20, 0, 0.22, 0.45$, and 0.66 for the $tBu, H, Cl, COOMe$, and CN substituents, respectively).¹⁷ In addition, the substituent effect on the potential shift is seen to be almost additive for Cl (compounds **5** and **7**) with, on average, 75 mV per substituent and also for $COOMe$ (compounds **6** and **8**) with, on average, 130 mV per substituent, as deduced from the E_1° values. In contrast, the tBu substituent (complexes **2** and **3**) exerts much less than the expected effect ($\leq 20 \text{ mV}$) on the measured potentials. For Kagan's complex **1** (Scheme 2),¹⁸ a precatalyst in highly enantioselective electron transfer reactions,¹⁹ the effect on E_1° is larger. This is due to destabilizing steric interactions between the two Ti-bound chlorides and the conformationally locked^{18b} and sterically congested cyclopentadienyl ligands.

In this respect, it is also interesting to note that for complexes **1–5** and **7** we found that $i_{p,a1}/i_{p,c1} > 0.8$ at $\nu = 0.1 \text{ V s}^{-1}$, where $i_{p,a1}$ is the anodic peak current of the first anodic wave and $i_{p,c1}$ is the cathodic peak current. Such high values of $i_{p,a1}/i_{p,c1}$ show that the chemical reactions present are quasi-reversible. As mentioned previously, by increasing ν substantially it is possible

Table 1. CV Data for the Reduction of Titanocene Dichlorides 1–9 in THF in Terms of Peak Potentials for the Cathodic Wave ($E_{p,c}$) and the Two Anodic Waves ($E_{p,a1}$ and $E_{p,a2}$) Along with the Determined Standard Potential (E_1°)^a

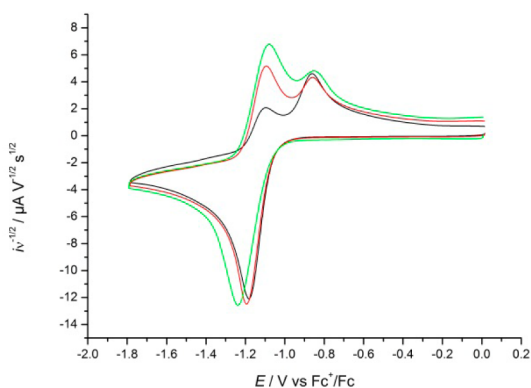
compound	$E_{p,c}$ ^b	$E_{p,a1}$ ^b	$E_{p,a2}$ ^b	E_1° ^c
Kagan's complex (1) ¹⁸	-1.44	-1.32		-1.37 ^{13f}
(C ₅ H ₄ tBu)CpTiCl ₂ (2) ²⁰	-1.39	-1.27		-1.36
(C ₅ H ₄ tBu) ₂ TiCl ₂ (3) ²¹	-1.36	-1.25		-1.34 ^{13f}
Cp ₂ TiCl ₂ (4)	-1.36	-1.24		-1.27 ^{13b}
(C ₅ H ₄ Cl)CpTiCl ₂ (5) ²²	-1.26	-1.15		-1.20
(C ₅ H ₄ COOMe)CpTiCl ₂ (6) ²³	-1.20	-1.09	-0.85	-1.15
(C ₅ H ₄ Cl) ₂ TiCl ₂ (7) ^{22,24}	-1.18	-1.08		-1.12
(C ₅ H ₄ COOMe) ₂ TiCl ₂ (8) ²⁵	-1.08	-0.92	-0.74	-1.01
(C ₅ H ₄ CN)CpTiCl ₂ (9) ¹⁰	-1.06		-0.85	-1.00

^aAll potentials are given in units of V vs Fc⁺/Fc and can be converted to V vs SCE by adding 0.52 V.^{13b,26} ^bRecorded at a glassy carbon disk electrode with $\nu = 0.1$ V s⁻¹ in 0.2 M Bu₄NPF₆/THF. ^cDetermined by digital simulation (see the Supporting Information).

Scheme 2. Structure of Kagan's Complex (1)

to reach a situation where the back association reaction in the C_r step is outrun and can be disregarded. Experimentally, this is seen as a decrease in $|i_{p,a1}/i_{p,c}|$ and the appearance of a new peak at less negative potentials pertaining to the oxidation of (C₅H₄R)(C₅H₄R')TiCl. In a specific study of Cp₂TiCl itself, its oxidation wave recorded at $\nu = 0.1$ V s⁻¹ appeared at about -0.8 V vs Fc⁺/Fc.^{13b}

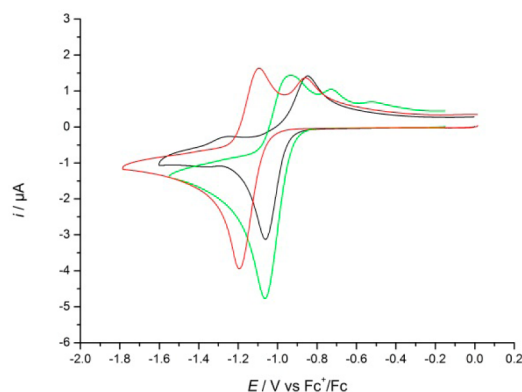
In contrast to the findings described above, the reduction of 6, 8, and 9 follows a different course as evidenced by CV. Figure 2 shows cyclic voltammograms recorded for (C₅H₄COOMe)CpTiCl₂ (6) at three different sweep rates. Besides an oxidation wave appearing at $E_{p,a1} = -1.09$ V vs Fc⁺/Fc, a second wave at $E_{p,a2} = -0.85$ V is seen.

**Figure 2.** Cyclic voltammograms of 2 mM (C₅H₄COOMe)CpTiCl₂ (6) recorded at a glassy carbon disk electrode with $\nu = 0.05$ (black), 0.1 (red), and 0.5 V s⁻¹ (green) in 0.2 M Bu₄NPF₆/THF.

Unambiguously, this shows that the generated anionic Ti(III) species 6⁻ is unstable and undergoes a chemical follow-up reaction.

Two observations preclude that the mechanism can be the “expected” E_qC_r mechanism. First, the addition of a chloride source (Bu₄N⁺Cl⁻) did not affect the voltammograms (see the Supporting Information), even though the C_r follow-up reaction should be greatly suppressed by the presence of Cl⁻.^{13b} Second, the first anodic wave grows at the expense of the second wave (after background subtraction) as ν is enhanced from 0.05 to 0.5 V s⁻¹. This behavior is the opposite of what would be expected if the rate-controlling step had been the back association in a C_r step. Rather, this behavior would be in much better agreement with the existence of another rate-controlling chemical follow-up step in which the cyclopentadienyl anion, [C₅H₄R]⁻, rather than chloride is lost irreversibly,²⁷ as included in Scheme 1.

Figure 3 further compares the CV behavior of 6, 8, and 9 for ν fixed at 0.1 V s⁻¹. Since the reductions of both 6 and 9 would

**Figure 3.** Cyclic voltammograms of 2 mM (C₅H₄CN)CpTiCl₂ (9) (black), (C₅H₄COOMe)CpTiCl₂ (6) (red), and (C₅H₄COOMe)₂TiCl₂ (8) (green) recorded at a glassy carbon disk electrode with $\nu = 0.1$ V s⁻¹ in 0.2 M Bu₄NPF₆/THF.

be expected to proceed exclusively through loss of the cyclopentadienyl ligand possessing the electron-withdrawing group to achieve the highest possible stabilization of the released anion, this would in both cases result in the formation of CpTiCl₂ as the other product. This was indeed the case, as the peak potential of the second oxidation wave was the same for both complexes ($E_{p,a2} = -0.85$ V vs Fc⁺/Fc) and identical to that measured for the oxidation peak of CpTiCl₂ generated by

electrochemical reduction of CpTiCl_3 (see the Supporting Information).

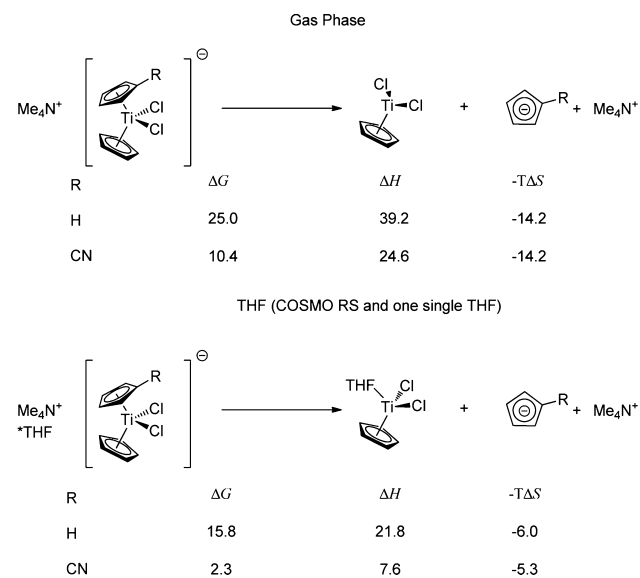
Loss of $[\text{C}_5\text{H}_4\text{CO}_2\text{Me}]^-$ was also observed after reduction of **8**. In this case, the second anodic wave has a lower potential ($E_{p,a2} = -0.74$ V vs Fc^+/Fc) than for **6** because of the formation of $(\text{C}_5\text{H}_4\text{CO}_2\text{Me})\text{TiCl}_2$, in agreement with the $E_q\text{C}_1$ mechanism in Scheme 1. A third anodic wave (-0.52 V vs Fc^+/Fc) was also observed. It seems reasonable to assume that this is due to the formation of TiCl_3 through ligand loss from $(\text{C}_5\text{H}_4\text{CO}_2\text{Me})\text{-TiCl}_2$, even though this was not further investigated.

Hence, for **6**, **8**, and **9** we propose the $E_q\text{C}_1$ mechanism in Scheme 1, where the quasi-reversible electrode process is followed by an irreversible loss of the cyclopentadienyl anion. The time frame for the follow-up reactions in the case of **6** and **8** can be easily monitored in CV by varying the sweep rate as illustrated in Figure 2. From such studies of the voltammetric response recorded as a function of sweep rate, the dissociation rate constant (k_{dis}) may be extracted using digital simulations (see the Supporting Information).¹⁶ Using this approach provided k_{dis} values of 0.11 and 10 s^{-1} for the anions of **6** and **9**, respectively. Thus, the more electron-deficient cyano-substituted cyclopentadienyl ligand²⁸ dissociates faster than the corresponding ester-substituted one as a consequence of the enhanced ability of the cyano group to stabilize the negative charge in the cleaved $[\text{C}_5\text{H}_4\text{R}]^-$ anion.

The thermodynamic features of the loss of the cyclopentadienyl ligands were studied computationally²⁹ for the model systems with Bu_4N^+ replaced by Me_4N^+ shown in Scheme 3 in the gas phase (TPSS-D3/def2-TZVP)^{30–32} and in solution with the COSMO continuum solvation model for real solvents (RS) (TPSS-D3-COSMO-RS³³/def2-TZVP//TPSS-D3/def2-TZVP).

In the gas phase, both dissociation reactions are unfavorable ($\text{R} = \text{H}$, $\Delta G = +25.0$ kcal mol^{-1} ; $\text{R} = \text{CN}$, $\Delta G = +10.4$ kcal mol^{-1}). The difference between the ΔG values is caused by the difference in ΔH and is a reflection of the weaker binding of $[\text{C}_5\text{H}_4\text{CN}]^-$.

Scheme 3. Model Systems for the Thermodynamic Features of Cyclopentadienyl Ligand Loss (R = H, CN) at 298.15 K (All Energies in kcal mol^{-1})



The effect of solvation was studied by employing two modifications. First, COSMO-RS was included to simulate the effect of bulk solvent. Second, one molecule of THF was introduced in order to understand its interactions with NMe_4^+ of the substrate and the Lewis acidic product CpTiCl_2 on a molecular level. The results clearly show that dissociation of the cyclopentadienyl ligands is more advantageous in solution than in the gas phase. This is mainly due to a more favorable ΔH that is caused by coordination of THF to the Lewis acid CpTiCl_2 . The differences between the ΔG values (14.6 and 13.5 kcal mol^{-1} , respectively) in the gas phase and in solution are almost identical. This suggests that binding of $[\text{C}_5\text{H}_5]^-$ to Ti is more favorable than binding of $[\text{C}_5\text{H}_4\text{CN}]^-$ by about 14 kcal mol^{-1} .

Zn–Titanocene(IV) Dichlorides in THF. In stoichiometric and catalytic applications of titanocene(III) complexes, the active reagent is practically always generated by reduction of the titanocene dichlorides with Mn or Zn dust.⁷ The understanding of the influence of ligand substitution on the redox properties of the titanocene species is therefore of high practical relevance and was investigated next. Previous studies of solutions of metal– Cp_2TiCl_2 in THF by CV have shown that these solutions consist of the Cp_2TiCl monomer and the $(\text{Cp}_2\text{TiCl})_2$ dimer.¹³ The Cp_2Ti^+ cation is also observed in the voltammograms but is generated only in the diffusion layer during sweeping from the oxidized products of Cp_2TiCl and $(\text{Cp}_2\text{TiCl})_2$.¹³

Figure 4 shows cyclic voltammograms recorded for Zn–**4**, Zn–**5**, and Zn–**7**. In line with the previous assessment, the first

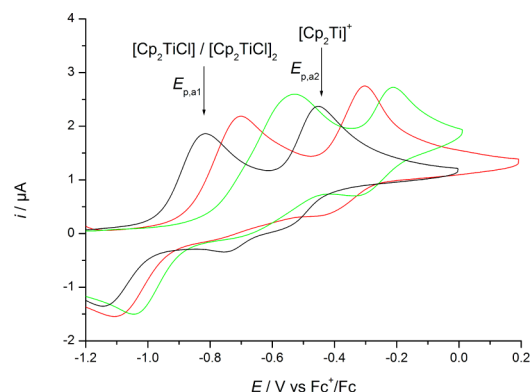


Figure 4. Cyclic voltammograms of 2 mM Zn–**4** (black), Zn–**5** (red), and Zn–**7** (green) recorded at a glassy carbon disk electrode with $\nu = 0.1$ V s^{-1} in 0.2 M $\text{Bu}_4\text{NPF}_6/\text{THF}$.

oxidation wave is assigned to the monomer/dimer couple and the second one to the cation. Furthermore, it was noted that the second wave diminishes with increasing ν , thus confirming that the cation indeed is formed in follow-up reactions induced by the sweeping and thus is not present in any substantial amount for any of the compounds **1–9**.

To determine the exact monomer/dimer composition, a detailed analysis of the first wave as a function of ν and concentration involving digital simulation would be required. Since this is not the purpose of the present investigation, the focus is rather addressed at describing the redox properties of the Ti(III) species by determining the peak potentials. At the same time, it would be pertinent to elucidate whether the cyclopentadienyl ligand is lost in the chemical reduction of **6**, **8**, and **9** as was seen for the electrochemical reduction.

Table 2 summarizes the CV data in terms of the anodic peak potentials $E_{p,a1}$ and $E_{p,a2}$ obtained for Zn-1 through Zn-9 in

Table 2. CV Data for the Oxidations of Zn-1 through Zn-9 in Terms of Peak Potentials for the Anodic Waves, $E_{p,a1}$ and $E_{p,a2}$ ^a

compound	$E_{p,a1}$	$E_{p,a2}$
Kagan's complex (1)	-0.82	-0.47
(C ₅ H ₄ tBu)CpTiCl ₂ (2)	-0.84	-0.44
(C ₅ H ₄ tBu) ₂ TiCl ₂ (3)	-0.74	-0.45
Cp ₂ TiCl ₂ (4)	-0.83	-0.42
(C ₅ H ₄ Cl)CpTiCl ₂ (5)	-0.71	-0.32
(C ₅ H ₄ COOMe)CpTiCl ₂ (6)	-0.58	-0.23
(C ₅ H ₄ Cl) ₂ TiCl ₂ (7)	-0.54	-0.20
(C ₅ H ₄ COOMe) ₂ TiCl ₂ (8)	-0.43	-0.10
(C ₅ H ₄ CN)CpTiCl ₂ (9)	-0.35	-0.20

^aPotentials were recorded at a glassy carbon disk electrode with $\nu = 0.1 \text{ V s}^{-1}$ in 0.2 M Bu₄NPF₆/THF; the values are given in V vs Fc⁺/Fc and can be converted to V vs SCE by adding 0.52 V.^{13b,26}

THF. Notably, the potentials of Zn-1¹⁸ and Zn-4 are very similar. The success of Zn-1¹⁸ in enantioselective and regioselective epoxide opening reactions¹⁹ is therefore due to steric and not electronic effects. This should also be the case in the recently described enantioselective cyclizations of ketyl radicals catalyzed by Brintzinger's complex.³⁴

The introduction of electron-withdrawing substituents has a dramatic effect on $E_{p,a1}$, which changes from -0.84 to -0.35 V vs Fc⁺/Fc. For the cationic titanocenes, the effect of ligand substitution is less dramatic, with the $E_{p,a2}$ values ranging from -0.47 to -0.20 V vs Fc⁺/Fc.

A very important finding is that for the Zn-reduced solutions the loss of electron-deficient cyclopentadienyl ligands, which is a major decomposition pathway for the electrochemically reduced complexes, was never observed. This is likely due to the efficient abstraction of chloride from [(C₅H₄R)CpTiCl₂]⁻ by Zn²⁺ ions in THF. The same is true for Mn²⁺ ions.

Zn-Titanocene(IV) Dichlorides in THF in the Presence of Chloride Additives. The increased use of Cp₂TiCl as a reagent is a consequence of the development of conditions catalytic in the reagent. In most of these reactions, turnover is mediated by protonation or silylation of Ti-O bonds through the addition of stoichiometric amounts of either Coll*HCl or Coll*Me₃SiCl (Coll = 2,4,6-trimethylpyridine).⁷ In order to understand the impact of added chloride ions on the coordination sphere and the redox properties of titanocene(III) chlorides, we studied the CV behavior of Zn-Cp₂TiCl₂ in the presence of various chloride donors, namely, Bu₄N⁺Cl⁻, Hex₃N*HCl, LiCl, Py*HCl (Py = pyridine), and Coll*HCl.

Figure 5 shows the cyclic voltammograms recorded for the selected chloride donors at a glassy carbon disk electrode with $\nu = 0.1 \text{ V s}^{-1}$ in 0.2 M Bu₄NPF₆/THF. The full collection of voltammograms obtained for sweep rates in the 0.05–50 V s⁻¹ range is available in Figures S13–S33 in the Supporting Information. A common effect of all of these additives is that they make the oxidation wave of [Cp₂TiCl₂]⁻ appear at low sweep rates. In fact, in the presence of Bu₄N⁺Cl⁻, LiCl, and to a large extent also Py*HCl, the voltammograms recorded are by and large identical to those of electrochemically reduced Cp₂TiCl₂ in 0.2 M Bu₄N⁺PF₆⁻/THF, as essentially no other wave but that for [Cp₂TiCl₂]⁻ is detectable. This implies that the association of chloride to either Cp₂TiCl or (Cp₂TiCl)₂

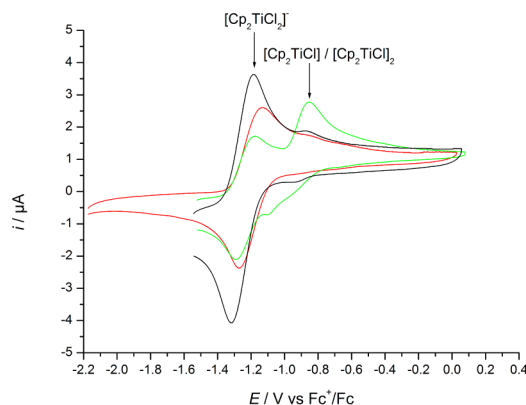


Figure 5. Cyclic voltammograms of 2 mM Zn-Cp₂TiCl₂ containing 2 equiv of Hex₃N*HCl (red), Coll*HCl (green), or Py*HCl (black) as an additive. Recordings were performed at a glassy carbon disk electrode with $\nu = 0.1 \text{ V s}^{-1}$ in 0.2 M Bu₄NPF₆/THF.

cannot be outrun in the presence of these additives, at least for the sweep rates employed (Scheme 1).

The same is true to some extent for Hex₃N*HCl, although the Cp₂TiCl/(Cp₂TiCl)₂ oxidation wave becomes dominant in the high sweep rate range. In general, Coll*HCl leads to the formation of a distinctly lower amount of [Cp₂TiCl₂]⁻ in the CV compared with Py*HCl, and interestingly, the peak current ratio of the two oxidation waves was found to be constant over the range of sweep rates from 0.05 to 20 V s⁻¹.

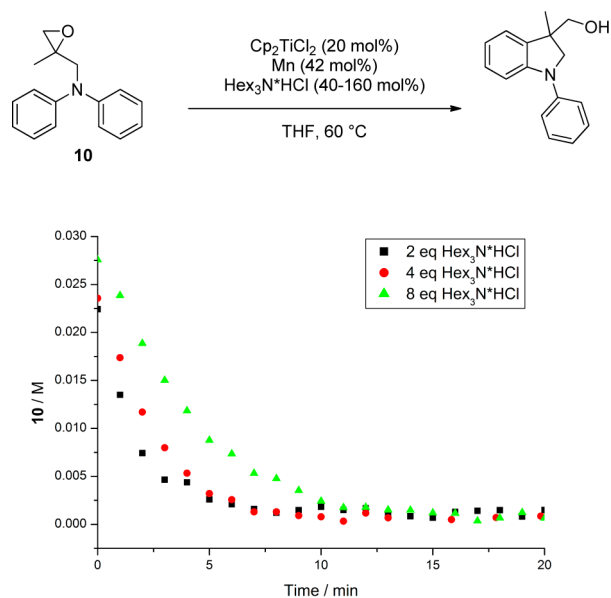
This tuning of the kinetics of the formation of [Cp₂TiCl₂]⁻ and its concentration through additives is to the best of our knowledge unprecedented. Since Coll*HCl is distinctly less soluble in THF than Hex₃N*HCl and Py*HCl, a straightforward explanation for this behavior is the smaller concentration of Coll*HCl in THF.

However, this analysis does not take into account the stability of the hydrochloride adducts, which should not be a function of the concentration of the hydrochloride. This issue was further investigated by computational means after the study of the kinetic effects of adduct formation.

In order to further understand the effect of ligand substitution on the interaction of the titanocenes with additives experimentally, we studied the voltammetry of Zn-(C₅H₄tBu)₂TiCl₂ and Zn-(C₅H₄Cl)₂TiCl₂ in the presence of Coll*HCl (see the Supporting Information). Compared with Cp₂TiCl₂, the experiments at higher sweep rates show a more rapid decline in the intensity of the oxidation wave of [(C₅H₄tBu)₂TiCl₂]⁻, and therefore, the complexation of Cl⁻ is slower for the bulky (C₅H₄tBu)₂TiCl than for Cp₂TiCl. In agreement with intuition, a higher proportion of [(C₅H₄Cl)₂TiCl₂]⁻ was observed for the more Lewis acidic (C₅H₄Cl)₂TiCl over all sweep rates.

The formation of [(C₅H₄R)₂TiCl₂]⁻ reduces the concentration of Cp₂TiCl, the active species in titanocene-catalyzed reactions. Therefore, there should be an inverse kinetic order of chloride concentration on rate caused by addition of the hydrochloride salts. This was probed for the Cp₂TiCl-catalyzed radical arylation of **10** (Scheme 4).⁹ In these experiments Hex₃N*HCl was chosen as the chloride source rather than Coll*HCl because of the limited solubility of the latter in THF.

The observed rate constants for the catalytic reaction were measured at constant initial substrate and catalyst concentrations and three concentrations of Hex₃N*HCl by following the decay of epoxide **10**. The decays (Scheme 4) fit well to a

Scheme 4. Effect of Hex₃N⁺HCl on the Rate of the Radical Arylation of **10**^a

^aFor concentrations and experimental details, see the Supporting Information.

single exponential. The k_{obs} values from the decays are given in Table 3.

Table 3. Observed Rate Constants for the Arylation of **10** at Different Concentrations of Hex₃N⁺HCl

equiv of Hex ₃ N ⁺ HCl ^a	k_{obs} (min ⁻¹)
2	0.57 ± 0.04
4	0.39 ± 0.01
8	0.24 ± 0.01

^aWith respect to catalyst concentration.

With higher amounts of Hex₃N⁺HCl, lower values of k_{obs} were observed. This finding is consistent with a reduction of the Cp₂TiCl₂ concentration through the formation of [(C₅H₄R)₂TiCl₂]⁻*Hex₃NH⁺. Moreover, the radical arylation of **10** proceeds faster in the presence of Coll⁺HCl than in the presence of Hex₃N⁺HCl. This is consistent with the CV data showing a lower amount of adduct formation.

Computational Study of the Hydrochloride Adducts.

To evaluate our hypothesis of hydrogen bonding and to understand the nature of the interactions of the hydrochlorides with titanocene(III) complexes on a molecular level, a computational study was performed using the TURBOMOLE 6.4 program package.²⁹ All of the DFT structures were fully optimized at the TPSS-D3/def2-TZVP level including the COSMO model. Final reaction free energies were obtained via single-point calculations on the PW6B95³⁵-D3//def2-QZVP³² level in the gas phase and applying the COSMO-RS model to include solvation. For further details, see the Supporting Information.

For all of the titanocenes, the Et₃NH⁺HCl adducts are the most stable (Table 4). The Coll⁺HCl adducts are enthalpically more favorable than the Py⁺HCl adducts and also thermodynamically more stable except for the case of [(C₅H₄Cl)₂TiCl₂]⁻*PyH⁺. These results can be explained by a modulation of chloride binding through hydrogen bonding.

Table 4. Computed Free Energies (PW6B95-D3-COSMO-RS/def2-QZVP//TPSS-D3-COSMO/def2-TZVP) of Formation of Hydrochloride Adducts in THF at 298.15 K^a

[Ti]	additive	ΔH	$-T\Delta S$	ΔG
Cp ₂ TiCl	Py ⁺ HCl	-4.9	+4.0	-1.0
Cp ₂ TiCl	Coll ⁺ HCl	-9.6	+6.9	-2.6
Cp ₂ TiCl	Et ₃ N ⁺ HCl	-15.2	+6.6	-8.6
(C ₅ H ₄ Cl) ₂ TiCl	Py ⁺ HCl	-8.0	+3.8	-4.2
(C ₅ H ₄ Cl) ₂ TiCl	Coll ⁺ HCl	-10.4	+6.6	-3.7
(C ₅ H ₄ Cl) ₂ TiCl	Et ₃ N ⁺ HCl	-17.2	+6.9	-10.3
(C ₅ H ₄ tBu) ₂ TiCl	Py ⁺ HCl	-0.0	+4.5	+4.5
(C ₅ H ₄ tBu) ₂ TiCl	Coll ⁺ HCl	-5.4	+8.1	+2.7
(C ₅ H ₄ tBu) ₂ TiCl	Et ₃ N ⁺ HCl	-9.2	+8.8	-0.4

^aAll energies are given in kcal mol⁻¹. For details, see the Supporting Information.

The stronger acid Py⁺HCl will interact more strongly with the basic chloride ligands than the weaker acids Coll⁺HCl and Et₃NH⁺HCl. This is in agreement with the calculated bond lengths for H-Cl(1) and Ti-Cl(1) shown in Table 5. The

Table 5. Selected Structural Data for **11**, **12**, and **13**

adduct	H-Cl(1) (Å)	H-Cl(2) (Å)	Ti-Cl(1) (Å)	Ti-Cl(2) (Å)	dihedral angle (deg) ^a
11	2.34	2.34	2.53	2.53	-14.2
12	2.07	2.73	2.51	2.55	79.9
13	2.06	3.24	2.50	2.55	NA

^aDihedral angle between the Cl-Ti-Cl and C(2)-N-C(6) planes.

shortest of the “short” Ti-Cl bonds is found in [(Cp₂TiCl₂)⁻*Et₃NH⁺ (2.50 Å) and the longest in [(Cp₂TiCl₂)⁻*PyH⁺ (2.53 Å). The notion that chloride binding makes the most important contribution to ΔH is also supported by the observation that the most Lewis acidic titanocene, (C₅H₅Cl)₂TiCl, forms the most stable adducts. The contributions of entropy are less relevant and are caused by differences in the entropy of solvation.

Analysis of the adduct structures (Table 5) also supports the idea that supramolecular interactions modulate the Ti-Cl bonding. In all of the structures, hydrogen bonding between the N-H and the chlorides is observed. The Coll⁺HCl adduct **12** and Py⁺HCl adduct **11** are distinguished by the orientations of the respective arenes. While in **11** the arene is almost in the plane containing both chlorides and Ti, in **12** the arene is nearly perpendicular to this plane (Figure 6). This is consistent with unfavorable steric interactions between the methyl groups at the 2- and 6-positions of collidine and the two chlorides that disfavor the “in-plane” binding. As a consequence, the hydrogen bonding in **11** is distinctly different from that in **12**. In **11** the two N-H-Cl hydrogen bonds have the same length, and the arrangement is symmetrical. In **12** the two N-H-Cl hydrogen bond lengths are significantly different. In **13**, the hydrogen bonding pattern is similar to that **12**. Therefore, Et₃NH⁺ is best regarded as a cation with a steric bulk similar to CollH⁺. This notion is further corroborated for the adducts of (C₅H₄Cl)₂TiCl and (C₅H₄tBu)₂TiCl (see the Supporting Information for details).

The slightly less favored formation of [(C₅H₄Cl)₂TiCl₂]⁻*CollH⁺ compared with [(C₅H₄Cl)₂TiCl₂]⁻*PyH⁺ is a consequence of “out-of-plane” binding, which results in an unfavorable interaction between

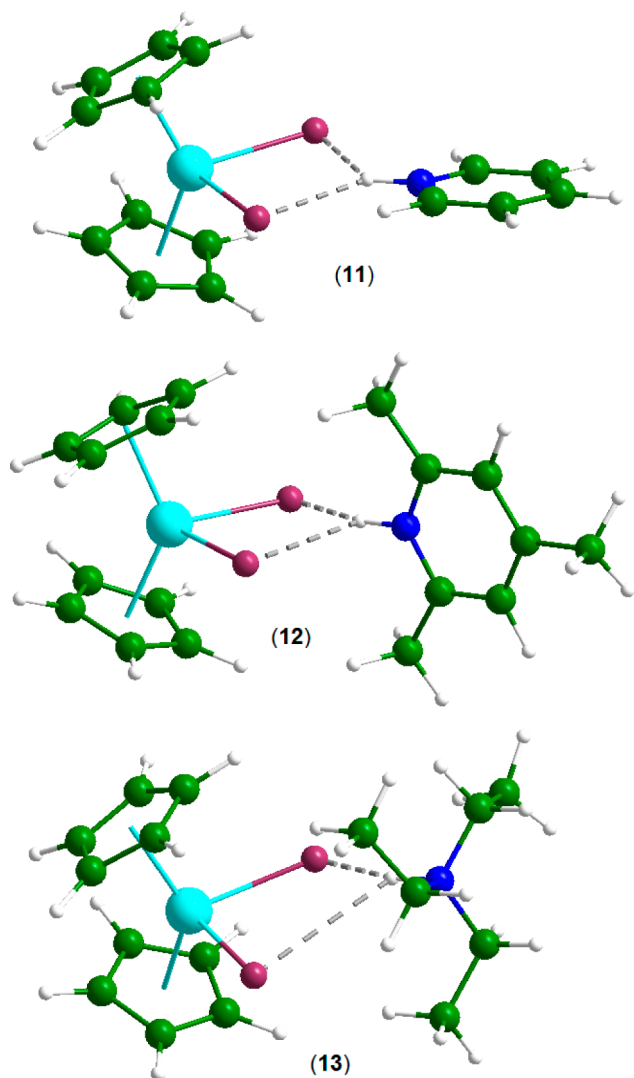


Figure 6. PW6B95-D3-COSMO-RS/def2-QZVP//TPSS-D3-COSMO/def2-TZVP-optimized structures of $[\text{Cp}_2\text{TiCl}_2]^- \cdot \text{PyH}^+$ (11), $[\text{Cp}_2\text{TiCl}_2]^- \cdot \text{CollH}^+$ (12), and $[\text{Cp}_2\text{TiCl}_2]^- \cdot \text{Et}_3\text{NH}^+$ (13).

one of the methyl groups attached to the arene and the Cl substituent of a Cp ligand in $[(\text{C}_5\text{H}_4\text{Cl})_2\text{TiCl}_2]^- \cdot \text{CollH}^+$ (see the Supporting Information).

Thus, our CV, kinetic, and computational studies clearly highlight that the addition of hydrochloride additives has a profound and unprecedented influence on the composition of metal-reduced solutions of Cp_2TiCl_2 and its substituted derivatives. Adducts are formed that consist of hydrogen-bonded tight ion pairs of $[\text{Cp}_2\text{TiCl}_2]^-$ and the ammonium ion. The stability and rate of formation of the adduct can be fine-tuned by the steric bulk and acidity of the additive's cation. The consequences of adduct formation on the performance of these reagents in catalysis will be discussed next.

Implications of Adduct Formation for Catalysis. The $\text{Cp}_2\text{TiCl}/(\text{Cp}_2\text{TiCl})_2$ couple was introduced by Nugent and RajanBabu as a very mild and chemoselective stoichiometric reagent for the reductive opening of epoxides.³⁶ In seminal contributions it was demonstrated that the epoxide-derived radicals could be employed in classical radical reactions such as 5-exo cyclizations, additions to acrylates, and radical reduction via hydrogen atom transfer.

Later, catalytic conditions employing additives such as $\text{Coll} \cdot \text{HCl}$ to mediate turnover were developed.³⁷ Even though under these circumstances the concentration of the active species Cp_2TiCl is further depleted by chloride binding, the catalytic conditions are superior for the realization of kinetically difficult radical processes. Examples include epoxypolyene cyclizations featuring slow 6-endo, 7-endo, and transannular cyclizations,³⁸ 4-exo cyclizations,³⁹ tandem processes combining cyclizations and intermolecular additions,⁴⁰ and atom-economical tetrahydrofuran syntheses.⁸

In all of these processes, the trapping of intermediate radicals by Cp_2TiCl is an undesired intermolecular side reaction. Reduction of the Cp_2TiCl concentration through reversible $[\text{Cp}_2\text{TiCl}_2]^-$ formation efficiently suppresses radical trapping and therefore increases the radical lifetime. Even better results can be obtained with electron-deficient titanocenes,^{9,10} which form the hydrochloride adducts more readily and constitute less efficient reductants. These effects can even be exploited under stoichiometric conditions, as demonstrated in a recent synthesis of (–)-maoecrystal Z.⁴¹

Another beneficial aspect of adduct formation has been described recently.⁸ After addition of hydrochlorides, Cp_2TiCl -catalyzed reactions can be run at high temperatures without catalyst decomposition. Therefore, the hydrochloride adducts are thermally more stable than Cp_2TiCl and its dimer.

CONCLUSION

We have investigated the composition and properties of solutions of electrochemically reduced $(\text{C}_5\text{H}_4\text{R})_2\text{TiCl}_2$, $\text{Zn}-(\text{C}_5\text{H}_4\text{R})_2\text{TiCl}_2$, and $\text{Zn}-(\text{C}_5\text{H}_4\text{R})_2\text{TiCl}_2$ in the presence of chloride additives by cyclic voltammetry, kinetic studies, and DFT calculations. Through this combined approach, the redox properties of representative $(\text{C}_5\text{H}_4\text{R})_2\text{TiCl}$ complexes, their dimers, and anionic chloride adducts $[(\text{C}_5\text{H}_4\text{R})_2\text{TiCl}_2]^-$ were determined. The stability of the electrochemically generated complexes depends on the substituents of the cyclopentadienyl ligands. With $-\text{CO}_2\text{Me}$ - or $-\text{CN}$ -containing ligands, $[\text{Cp}-(\text{C}_5\text{H}_4\text{R})\text{TiCl}_2]^-$ decomposes through loss of $[\text{C}_5\text{H}_4\text{R}]^-$.

In the presence of organoammonium chlorides, ammonium adducts of $[(\text{C}_5\text{H}_4\text{R})_2\text{TiCl}_2]^-$ are generated from $\text{Zn}-(\text{C}_5\text{H}_4\text{R})_2\text{TiCl}_2$. The stabilities of these adducts and the rates of their formation are determined by the extent of hydrogen bonding between the catalyst and the ammonium cation. The degree of adduct formation can also be controlled by the solubility of the hydrochloride. The fine-tuning of the supramolecular interactions provides a novel platform for the design of more efficient and sustainable titanocene catalysts and titanocene-catalyzed processes.

ASSOCIATED CONTENT

Supporting Information

Experimental protocols and further details of the CV, kinetic, and computational studies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Authors

andreas.gansaeuer@uni-bonn.de
rof2@lehigh.edu

Notes

The authors declare no competing financial interest.

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