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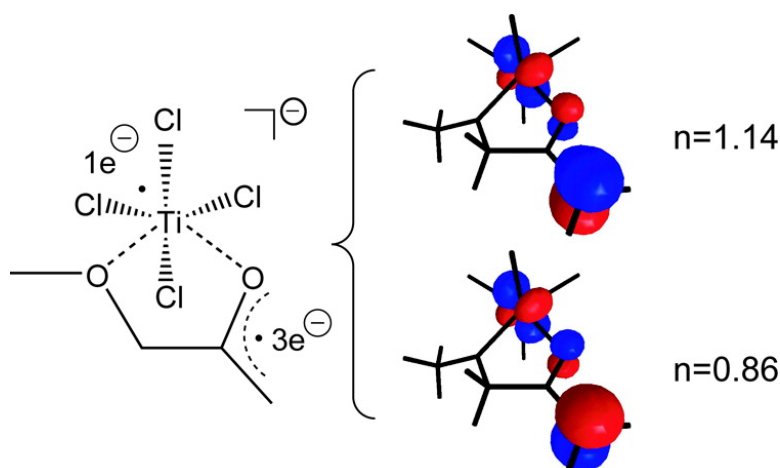
Communication

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Unconventional Biradical Character of Titanium Enolates

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Metal enolates have become foremost intermediates for the construction of structurally complex molecular architectures.[1] In particular, lithium, boron, and Ti(IV) enolates play a crucial role in the stereoselective formation of carbon−carbon bonds.[2] Thus, lithium and boron enolates have been extensively studied.[3] However, there is a scarce number of similar studies concerning Ti(IV) enolates, which have provided a poor knowledge about the aggregation state or the coordination sphere of titanium as well as the nature of its electronic ground state.[4] Recent studies of titanium-mediated aldol reactions based on chiral α-hydroxy ketones[5] have shown the tremendous impact of the enolization step on the stereochemical outcome of these processes. This is especially dramatic for lactate-derived α-benzyloxy ketones.[5] In this communication we provide strong experimental and theoretical evidence that the TiCl$_4$-mediated enolization of these ketones results in a biradical titanium enolate.

Since the seminal studies reported by Evans et al.,[4g] the TiCl$_4$-mediated enolization of ketones is performed in two consecutive steps in anhydrous and apolar media (see Scheme 1): (1) formation

Scheme 1. General Process of Formation of Titanium Enolates
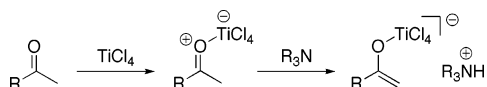
of the complex between TiCl$_4$ and the carbonyl and (2) extraction of the activated acidic proton in the α position with respect to the carbonyl group by a tertiary amine.

For simplicity, we have selected the two representative protected α-hydroxy ketones depicted in Figure 1, namely, 2-benzyloxy-3-pentanone (**1**) and 3-benzyloxy-2-butanone (**2**), to develop an experimental analysis to obtain detailed information about the structure and electronic state of the corresponding enolate.

^{1}H and ^{13}C NMR as well as EPR spectroscopic studies on the enolization process of ketones **1** and **2** using TiCl$_4$ have been performed (see Supporting Information). Comparison of NMR spectra of the Lewis acid−carbonyl complex[6] and the enolate proves that they contain a chelated structure as depicted in Figure 2.

To investigate the electronic structure of these complexes and the corresponding molecular structures, we have considered a simplified molecular model representative for the description of the enolization process by means of ab initio wave function electronic structure calculations. Hence, α-methoxyacetone was adopted as a model system to represent ketones **1** and **2**, and the diisopropyl-ethylamine was replaced by ammonia (see Supporting Information).

The resulting energy profile for such model enolization is shown in Figure 3. As expected, the first step entails the formation of a
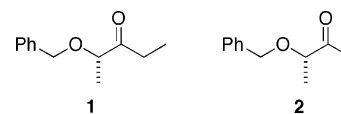
† Departament de Química Física, Universitat de Barcelona.
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Figure 1. The two protected α-hydroxy ketones studied in this work.
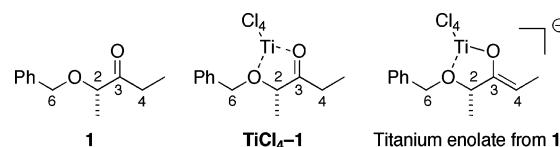
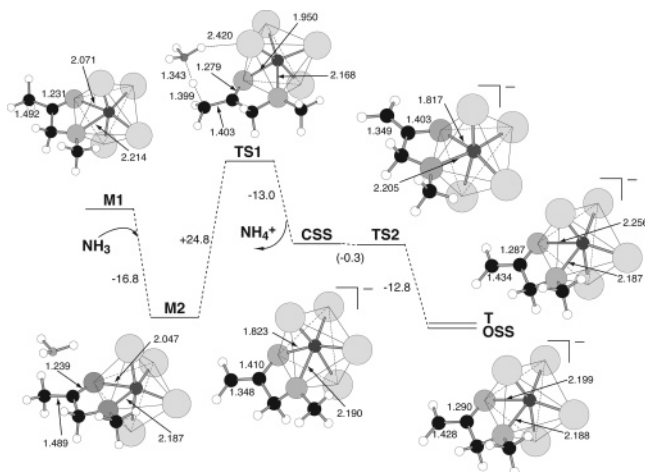**Figure 2.** Proposed structures for the complexes derived from ketone **1**.

Figure 3. Optimized geometries (HF/LANL2DZ for **M1**, **M2**, and **TS1** and CASSCF(8,10)/LANL2DZ for **CSS**, **TS2**, **OSS**, and **T**) with critical bond lengths (in Å) and potential energy profile (HF or CASSCF(8,10)/6-31G* single point energy + ZPE(LANL2DZ), in kcal mol^{-1}) for the Ti enolate formation mechanism (See Supporting Information for details.).

chelated Lewis acid−carbonyl complex, **M1**. The calculated bond distances for the carbonyl group and the MeO···Ti···O=C system are compatible with the standard lengths of this kind of bonds. Moreover, analysis of electron density of both Ti···O bonds reveals their dative character.

The next step involves proton abstraction. According to our model calculations, addition of ammonia to **M1** produces a hydrogen-bonded prereactive complex **M2** that evolves through transition state **TS1** to the final Ti(IV) enolate, labeled as closed shell singlet **CSS**. The chelated structure of this enolate encompasses four chlorine atoms directly bound to the hexacoordinated titanium and exhibits significant changes on the Ti···O bond lengths whereas the C−O distance of the carbonyl group in **M1** has been considerably enlarged. Because the electron density of the TiCl$_4$ moiety in the Ti(IV) enolate **CSS** is highly polarized toward the chlorine atoms and empty d-shells are still available for the metal, we also

π₁ [1.913]   π₂ +Ti(d) [1.143]   π₁ [1.914]   π₂ [1.005]

π₂ -Ti(d) [0.862]   π₃ [0.078]   Ti(d) [1.000]   π₃ [0.078]

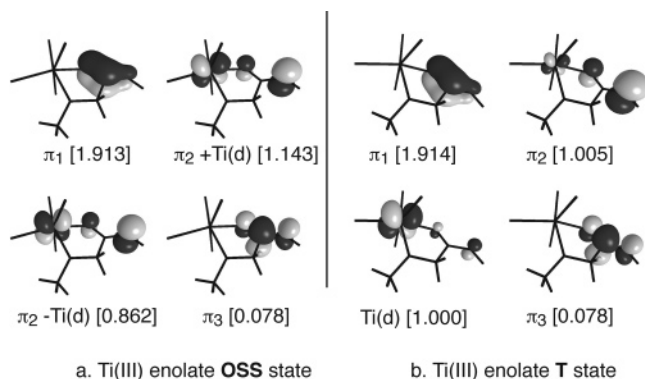a. Ti(III) enolate **OSS** state   b. Ti(III) enolate **T** state

Figure 4. The most relevant valence (natural) orbitals and the corresponding occupation numbers for the titanium (III) enolate singlet open-shell, **OSS**, and triplet, **T**, states. The most significant spin densities (unpaired electrons) in the **T** state are Ti (0.98), O (0.28), C (−0.10), and C (0.82).

evaluated the existence of a valence tautomerism in this enolate. We found another structure, namely, open shell singlet **OSS**, with a *very strong biradical character*, so that one electron is mainly located over the titanium atom and the other electron forms an allylic-like system $[-O-C-CH_2]^{\bullet}$.[7] Thus, this intermediate might be classified as a Ti(III) enolate. The calculations predict that it is close in energy to the Ti(IV) enolate **CSS**, with transition state **TS2** connecting both species. Again, the analysis of Ti···O bonds in **CSS** and **OSS** indicates that these interactions are dative in nature. The most relevant valence (natural) orbitals of this **OSS** biradical, along with the corresponding occupation numbers, are shown in Figure 4a. The topology of these orbitals allows us to assign these orbitals to an allylic-like π-system (π_1, π_2, and π_3 orbitals) combined with the Ti d orbital, (Ti(d)). The π_1 and π_3 orbitals are clearly identified because they involve the bonding and antibonding combinations of the allyl-like π-system. However, the π_2 orbital (nonbonding in the allyl-like π-system) is mixed with the Ti(d) orbital. The orbitals, $\pi_2 + \text{Ti}(d)$ and $\pi_2 - \text{Ti}(d)$ with occupations close to unity, fulfill the biradical structure. In addition, the positive overlap between the π_2 allyl-like and Ti(d) increases as the Ti···O bond distance diminishes when **OSS** evolves to **CSS** (through **TS2**) as expected for the valence tautomerism process.

Very close in energy to the **OSS** biradical titanium enolate (at 0.9 kcal mol^{-1}), we have found a triplet state (labeled as **T**) both having almost identical geometric and electronic features as can be deduced from the topology of the most significant orbitals of the triplet state **T** in Figure 4b.

The existence of this triplet state **T** opened a way for its experimental identification, because it should be observed by electron paramagnetic resonance (EPR) spectroscopy. Therefore, we conducted EPR experiments on titanium enolates from ketones **1** and **2** at different temperatures.[8] The spectra of these titanium enolates show a clear $|\Delta m_s| = 1$ signal with hyperfine structure depending on the number of hydrogen atoms directly bonded to the O−C−C allylic-like group (see Figure 5). In both cases, the $\Delta m_s = 2$ fingerprint of an electronic triplet state is found at half field. For the EPR spectra of the enolate from ketone **1**, the expected doublet corresponding to $|\Delta m_s| = 1$ is observed. However, for the enolate from ketone **2**, the observed $|\Delta m_s| = 1$ signal is a pseudotriplet with intensities 1:1.3:1 instead of 1:2:1 because the H atoms connected to C in an α position from the carbonyl are *nonequivalent*. The significant spin densities on the O−C−C allylic-like group (see Figure 4) justify the splittings of the observed EPR signals.

In conclusion, we have reported a comprehensive mechanistic description for the titanium-mediated enolization of protected α-*hydroxy ketones and provide strong evidence of the existence of*
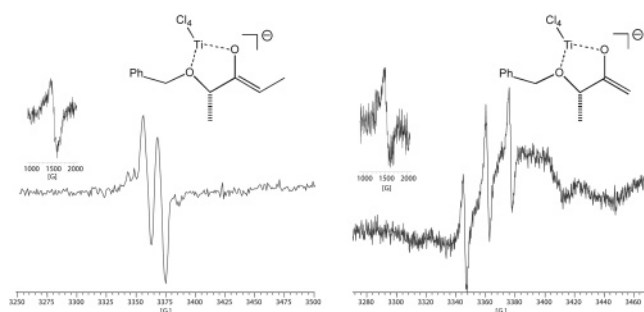

Figure 5. EPR spectra of titanium enolates derived from ketones **1** (left) and **2** (right) registered at 20 K in CH$_2$Cl$_2$. Inset corresponds to $\Delta m_s = 2$ fingerprint transition of triplet electronic state.

a biradical, which is formed through a valence tautomerism process. The implication of these biradical complexes in this and related reactions is expected to be of fundamental significance to understand the mechanism of many transition metal mediated enolizations.

Supporting Information Available: Details on the experimental procedure, ^{1}H and ^{13}C NMR spectra, and ab initio calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The EPR spectra of the titanium enolates (X-band, $\nu = 9.48408$ GHz) have been recorded at different temperatures up to 100 K in CH$_2$Cl$_2$ solution after reacting the corresponding benzyl protected α-hydroxy ketone with TiCl$_4$ and diisopropylethylamine under inert atmosphere. Blank tests on pure CH$_2$Cl$_2$ and isolated or pairs of reactants dissolved in CH$_2$Cl$_2$ (i.e., TiCl$_4$, diisopropylethylamine, or ketones **1** and **2**) do not show any EPR signal at any temperature. Consequently these signals are unambiguously assigned to the Ti(III) enolate intermediates with open shell structure.

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