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Catalyzed Ring Opening

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Elucidation of the Mechanism of Titanocene-Mediated Epoxide Opening by a Combined Experimental and Theoretical Approach**

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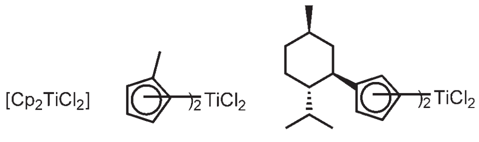
Titanocene-mediated[1] and -catalyzed epoxide ring opening[2] continues to be a highly pertinent synthetic transformation in organic chemistry. However, despite its preparative usefulness nothing is known about its mechanism. Herein, we present a study to elucidate this mechanism by a combination of electrochemical, kinetic, computational, and synthetic methods.

The determination of catalyst composition and the kinetics of the ring opening are the essential experimental basis for any mechanistic discussion. Thus, Zn-reduced THF solutions of [Cp_2TiCl_2] (**1**; Cp = cyclopentadiene), **2**, and **3**[3] were first analyzed by cyclic voltammetry, a technique uniquely suited for the investigation of redox-active species.[4]



1 **2** **3**

The solution derived from **1** consists of two species, [Cp_2TiCl] (**1b**) and the dimer [$Cp_2TiCl]_2$ (**1a**), which are in rapid equilibrium ($K = 3000\,\text{M}^{-1}$).[5] Herein, we demonstrate

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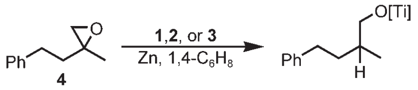
that for **2** the dimer **2a** remains an important constituent ($K = 1000\,\mathrm{M}^{-1}$), but to a noticeably lesser extent. The presence of the bulkier ligand in **3** makes the monomer **3b** the only species detectable by cyclic voltammetry ($K < 100\,\mathrm{M}^{-1}$, as deduced from digital simulations; see Supporting Information). For 2-mM Zn-reduced solutions of **1**, **2**, and **3**, this implies that the dimer/monomer ratio is 1.5, 0.8, and < 0.15, respectively.

Kinetic analysis of the opening of **4**[2a] with Zn-reduced solutions of **1**, **2**, and **3** was then carried out (Table 1). The rate constants, k, were extracted by monitoring the disappearance of the $\mathrm{Ti^{III}}$ species with a UV dip-probe in the presence of an excess of **4** (see Supporting Information). As in the synthetic work, 1,4-cyclohexadiene (1,4-$\mathrm{C_6H_8}$) was added in order to chemically reduce the radical intermediate formed upon electron-transfer-mediated ring opening. The kinetics were unaffected by the concentration of 1,4-$\mathrm{C_6H_8}$. Thus, electron transfer is the rate-controlling step of the overall reduction. This renders any mechanism with a quick and reversible ring opening before radical trapping unlikely.

Table 1: Rate constants k [$\mathrm{M^{-1}\,s^{-1}}$] of the reductive ring opening of **4** with Zn-reduced THF solutions of **1**–**3**.

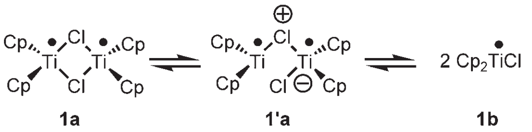


catalyst	k(monomer)	k(dimer)
1	0.5	1.4
2	1.3	3.9
3	0.8	–

To establish the nature of the reductant, with specific emphasis on the influence of the monomer/dimer distribution, kinetic traces were recorded at different $\mathrm{Ti^{III}}$ concentrations in the range 1–8 mM. In the case of **3** no effect was observed on the extracted pseudo-first-order rate constants, thus indicating that the monomer is the only reducing agent. This is consistent with the cyclic voltammetry studies, where no dimer constituent could be detected. Also, the reaction rate is relatively low in this case ($k = 0.8\,\mathrm{M^{-1}\,s^{-1}}$), which can be attributed to larger steric constraints during substrate binding or in the transition state (TS). In contrast, in the case of **1** and **2** the Zn-reduced solutions contain appreciable amounts of the dimer, and the reaction rate is strongly affected by the $\mathrm{Ti^{III}}$ concentration. This was interpreted as though both monomer and dimer have a measurable reactivity towards **4** under these conditions, in agreement with the kinetic analysis of the reaction between Zn-reduced **1** and benzaldehyde or benzyl chloride.[5]

By numerically fitting the decay curves pertaining to the concentration of $\mathrm{Ti^{III}}$ (see Supporting Information) we established that the dimers ($k = 1.4$ and $3.9\,\mathrm{M^{-1}\,s^{-1}}$ for **1** and **2**, respectively) open **4** faster than the corresponding monomers ($k = 0.5$ and $1.3\,\mathrm{M^{-1}\,s^{-1}}$). For an employed concentration of $\mathrm{Ti^{III}}$ of 10 mM for instance, this implies that 84 % and 75 % of **4** will be opened by the dimers, respectively.

An important question at this point pertains to the actual structure of the dimer. Both **1a** and **2a** have no vacant coordination site and should be unable to complex **4**. We therefore propose the half-open structure **1′a** as the species responsible for epoxide binding to **1** (Scheme 1), with a similar structure in the case of **2**. Complex **1′a** is a highly Lewis acidic intermediate in the formation of **1a** according to the principle of activation of electrophiles through dimeric association.[6]



Scheme 1. Dimeric (**1a** or **1′a**) and monomeric species (**1b**) present in Zn-reduced THF solutions of **1**.

On the basis of the above experimental results, we turned our attention towards calculations to gain further insight into the reaction mechanism. Activation and reaction energies were determined along with the structures of all pertinent intermediates and transition states by density functional theory (DFT) calculations[7] with the BP functional and a TZVP basis set. The [$\mathrm{Cp_2TiCl}$]-derived complexes, which are valuable models for higher-substituted titanocenes, were investigated first. As model compounds for the epoxide we focused on the simpler propene oxide (**5**) and isobutene oxide (**6**) rather than **4**.

The results concerning the binding of **5** and **6** with [$\mathrm{Cp_2TiCl}$] to afford the corresponding complexes **7** and **8** (see Table 2) proved to be interesting as there is a binding-energy difference in favor of **7** by about 4 $\mathrm{kcal\,mol^{-1}}$. The calculations show that this is because the hydrogen atom at the substituted carbon atom of the epoxide part in **7** cannot be replaced by a second methyl group (giving **8**) without causing geometrical changes: For steric reasons the epoxide has to be rotated by 90° in **8** compared to **7** in order to enable complexation by titanium. Despite this structural change the Ti–O bond length in **8** is slightly shorter than in **7**. Illustrations of complexes **7** and **8** are given in Figure 1.

All activation energies, $\Delta E^{\neq}$, are in the range 7.0–9.4 $\mathrm{kcal\,mol^{-1}}$, thus indicating that radical generation should be facile at room temperature, in agreement with the experimental results. It should also be noted that $\Delta E^{\neq}$ for the formation of **7a** and **8a** is lower than for **7b** and **8b**, and that the higher-substituted radicals are the thermodynami-

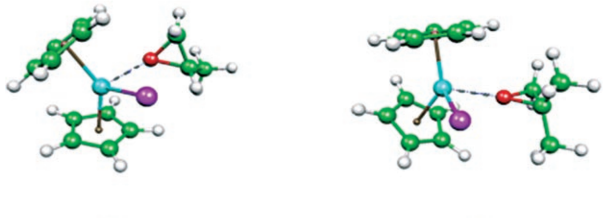
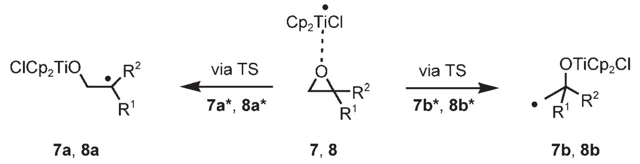

7 8

Figure 1. DFT-calculated structures of **7** and **8**.

cally favored products. These results are summarized in Table 2.

Table 2: Reaction and activation energies [kcal mol^{-1}] of the ring opening of **7** (R^1 = Me, R^2 = H) and **8** (R^1 = R^2 = Me) by **1b**.



ΔE(7)		ΔE‡ (7)		ΔE(8)		ΔE‡ (8)	
a	b	a	b	a	b	a	b
−4.0	−1.8	8.2	9.4	−8.5	−1.3	7.0	9.0

In all transition-state structures (i.e., **7a**‡, **7b**‡, **8a**‡, and **8b**‡) the spin density on the evolving radical center is lower (approximately 0.3) than on titanium (approximately 0.7), thereby suggesting that radical stability should not be as important an issue as steric effects. Steric effects have also been found to be significant in other titanocene-catalyzed reactions.[8] In the less-favored transition-state structures **7b**‡ and **8b**‡ the methyl group of the epoxide part is indeed in closer proximity to one of the cyclopentadienyl ligands (see Figure 2 for a comparison of **7a**‡ and **7b**‡). Thus, substituted cyclopentadienyl ligands should increase the steric effects.

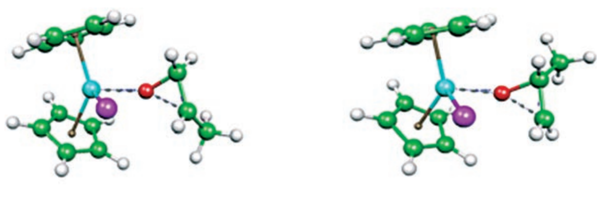
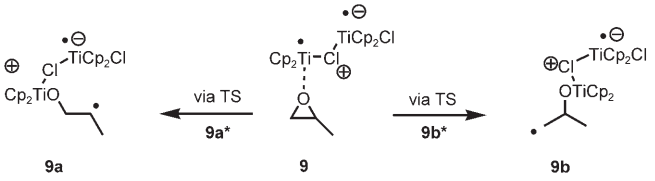

7a* **7b***

Figure 2. DFT-calculated structures of **7a**‡ and **7b**‡.

The calculations with $[Cp_2TiCl]_2$ did not provide a stable complex with propene oxide (**5**) if $[Cp_2TiCl]_2$ was assumed to be in its closed structure **1a**. However, the half-open structure **1′a** was found to readily complex **5** to give **9**, with the second Cp_2TiCl unit pointing away from the other titanocene unit. Binding of isobutene oxide (**6**) with **1′a** is less favorable as the epoxide in this case has to be rotated by 90°, which is in keeping with the results obtained for the binding of **6** with the monomer **1b** (see Supporting Information for details of all structures).

Ring opening to **9a** proceeds with $\Delta E = -6.4$ kcal mol^{-1} and $\Delta E^{\ddagger} = 6.3$ kcal mol^{-1} and to **9b** with $\Delta E = -4.6$ kcal mol^{-1} and $\Delta E^{\ddagger} = 7.5$ kcal mol^{-1} (Table 3). It is noteworthy that these activation energies are around 2 kcal mol^{-1} lower than those calculated for the corresponding reactions of **1b**. As the calculations do not include solvent effects, they reproduce the experimental finding of a higher reactivity of the dimer reasonably well.

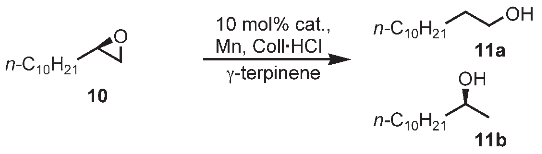
Table 3: Ring opening of **5** by **1′a**.



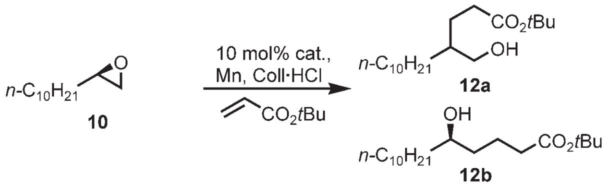
	ΔE [kcal mol^{-1}]	ΔE‡ [kcal mol^{-1}]
9a	−6.4	6.3
9b	−4.6	7.5

Although **7** and **9** are energetically quite different, the differences in reaction and activation energies of secondary and primary radical generation from these species are surprisingly similar. Moreover, all complexes originating from **7** and **9** are structurally very similar at the reaction center. The calculated activation energies were therefore used to compare the predicted (88:12 for both **7a**:**7b** and **9a**:**9b**, and 97:3 for **8a**:**8b** at 25 °C) and experimentally determined selectivity of epoxide ring opening.

Ring opening of **10**, which is a nonvolatile analogue of **5**, with **1** proceeds with a regioselectivity of between 88:12 and 90:10 in the presence of γ-terpinene or *tert*-butyl acrylate as trapping agents (Scheme 2). As the agreement between theory and experiment is excellent and independent of the trapping reagent, our mechanistic proposal, including the irreversibility of the ring opening, is strongly supported.



cat.	Yield [%]	**11a**:**11b**
1	52	88:12
3	57	>98:<2
ent-**3**	29	47:53



cat.	Yield [%]	**12a**:**12b**
1	73	90:10
2	87	93:7
3	61	>98:<2
ent-**3**	27	67:33

Scheme 2. Reagent control in the ring opening of **10**. Coll = collidine.

Substituted catalysts **2** and **3** were investigated in the reaction of **10** next. The presence of the methyl groups in **2** results in a slightly but noticeably higher selectivity of ring opening, as expected if selectivity is dominated by steric factors in the transition state. Further evidence for this hypothesis was obtained from the reaction of (*R*)-**10** with both enantiomers of **3**. As anticipated for an irreversible ring opening, matched and mismatched cases for its regioselectivity were observed in the formation of **11a** and **11b** or **12a** and **12b**. Gratifyingly, in both matched cases complete selectivity of epoxide opening was combined with higher yields of the products (Scheme 2).

In summary, we have developed a comprehensive picture of the titanocene-mediated epoxide ring opening through electron transfer. The investigations were carried out by a combination of synthetic organic, physical organic, and computational techniques, and have resulted in unique insights into the reaction at a molecular level. We have been able to determine that the identity of the most reactive Ti^{III} species is the dimer in its half-open structure and that the selectivity of the ring opening is governed by steric effects. Moreover, in light of these results it becomes possible to develop novel reactions.

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[1] T. V. RajanBabu, W. A. Nugent, *J. Am. Chem. Soc.* **1994**, *116*, 986 – 997.

[2] a) A. Gansäuer, H. Bluhm, M. Pierobon, *J. Am. Chem. Soc.* **1998**, *120*, 12849 – 12859; b) A. Gansäuer, T. Lauterbach, S. Narayan, *Angew. Chem.* **2003**, *115*, 5714 – 5731; *Angew. Chem. Int. Ed.* **2003**, *42*, 5556 – 5573.

[3] E. Cesarotti, H. B. Kagan, R. Goddard, C. Krüger, *J. Organomet. Chem.* **1978**, *162*, 297 – 309.

[4] S. U. Pedersen, K. Daasbjerg in *Electron Transfer in Chemistry, Vol. 1* (Ed.: V. Balzani), Wiley-VCH, Weinheim, **2001**, pp. 422 – 502.

[5] a) R. J. Enemærke, J. Larsen, T. Skrydstrup, K. Daasbjerg, *J. Am. Chem. Soc.* **2004**, *126*, 7853 – 7864; b) R. J. Enemærke, G. H. Hjøllund, J. Larsen, T. Skrydstrup, K. Daasbjerg, *Organometallics* **2005**, *24*, 1252 – 1262.

[6] E.-i. Negishi, *Chem. Eur. J.* **1999**, *5*, 411 – 420.

[7] Computational details: All DFT calculations were performed with the TURBOMOLE program package.[7a] The geometries and energies were obtained with the BP functional[7b,c] and a polarized valence triple-ξ basis set (TZVP)[7d] using unrestricted wavefunctions. The transition state was obtained using an eigenvector-following algorithm.[7e] Spin densities for the transition state were calculated using the Mulliken population analysis scheme. a) TURBOMOLE 5.6: R. Ahlrichs, M. Bär, H.-P. Baron, R. Bauernschmitt, S. Böcker, M. Ehrig, K. Eichkorn, S. Elliot, F. Furche, F. Haase, M. Häser, H. Horn, C. Huber, U. Huniar, M. Kattanek, C. Kölmel, M. Kollwitz, K. May, C. Ochsenfeld, H. Öhm, A. Schäfer, U. Schneider, O. Treutler, M. von Armin, F. Weigend, P. Weis, H. Weiss, Universität Karlsruhe, **2003**; b) A. D. Becke, *Phys. Rev. B* **1988**, *38*, 3098 – 3100; c) J. P. Perdew, *Phys. Rev. B* **1986**, *33*, 8822 – 8824; d) A. Schäfer, C. Huber, R. Ahlrichs, *J. Chem. Phys.* **1994**, *100*, 5829 – 5835; e) EF routine in MOPAC6: J. Baker, *J. Comput. Chem.* **1986**, *7*, 385 – 395.

[8] a) A. Gansäuer, B. Rinker, M. Pierobon, S. Grimme, M. Gerenkamp, C. Mück-Lichtenfeld, *Angew. Chem.* **2003**, *115*, 3815 – 3818; *Angew. Chem. Int. Ed.* **2003**, *42*, 3687 – 3690; b) A. Gansäuer, B. Rinker, N. Ndene-Schiffer, M. Pierobon, S. Grimme, M. Gerenkamp, C. Mück-Lichtenfeld, *Eur. J. Org. Chem.* **2004**, 2337 – 2351.