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Quantum Chemical Insights into the Mechanism of the TADDOL−$TiCl_2$ Catalyzed Diels−Alder Reactions

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Quantum chemical calculations have been carried out for the first time on model compounds of TADDOL−$TiCl_2$ (1,4-butanediol−$TiCl_2$) complexed with an *N*-alkenoyl-1,3-oxazolidin-2-one. The results of these calculations have shown that the intermediate in which the carbonyl oxygen atom of the enoate moiety is in *trans*-position with respect to a chlorine atom experience a higher degree of Lewis acid activation, and therefore it is the most reactive, although it is not the most stable. These results are in agreement with the experimental observations, as well as with a previous hypothesis based on the mechanism of the Diels−Alder reactions of this kind of complex.

TADDOL (α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol), first reported by Seebach,[1] and its derivatives have frequently been used as chiral ligands in Ti^{IV}-catalyzed Diels−Alder reactions.[2] In particular, the $TiCl_2$−TADDOLates promote Diels−Alder[3−6] and 1,3-dipolar cycloadditions[7,8] with high enantio- and diastereoselectivities.

The mechanism of the cycloadditions catalyzed by this kind of complex has been the subject of controversy. In all these reactions one of the reagents is an *N*-alkenoyl-1,3-oxazolidin-2-one (**1**). The coordination of this compound to the catalyst can lead to five diastereomeric complexes and, in each case, **1** can adopt an *s-cis* or *s-trans* conformation (Figure 1), although theoretical and experimental studies have shown that in chelate complexes the *s-cis* conformation is preferred over the *s-trans*.[9,10]

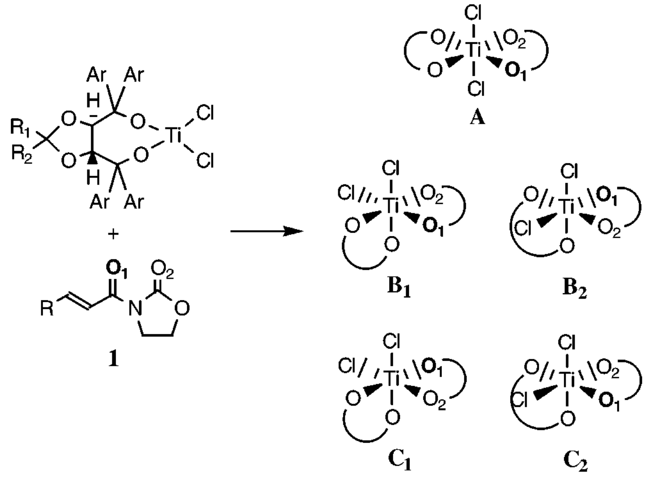

Figure 1. The five possible diastereomeric complexes formed between an *N*-alkenoyl-1,3-oxazolidin-2-one and a $TiCl_2$−TADDOLate.

X-ray studies of the complex formed between a $TiCl_2$−TADDOLate and (*E*)-3-(3-cinnamoyl)-1,3-oxazolidin-2-one,[9] as well as NMR spectra of the complexes formed in solution between (*E*)-3-hex-2-enoyl-1,3-oxazolidin-2-one and several $TiCl_2$−TADDOLates,[10] have shown that the complex bearing both chlorine atoms in the relative axial position (**A**) is the most abundant. The NMR studies[10] have also shown that the unsymmetrical intermediate **B** is the second one most abundant species.

Seebach,[6] DiMare,[10] and their respective co-workers have proposed that those intermediates in which the carbonyl oxygen atom of the enoate moiety is in the *trans*-position with respect to a chlorine atom (**B_1** and **B_2**) experience a higher degree of Lewis acid activation, and hence they are more reactive. On the other hand, Gothelf and Jørgensen have studied the reactions between (*E*)-3-butenoyl-1,3-oxazolidin-2-one and benzylidenephenylamine *N*-oxide, catalyzed by $TiCl(O^iPr)_3$ and $TiCl(O^iPr)$−TADDOLate,[8] and they have concluded that the inter-

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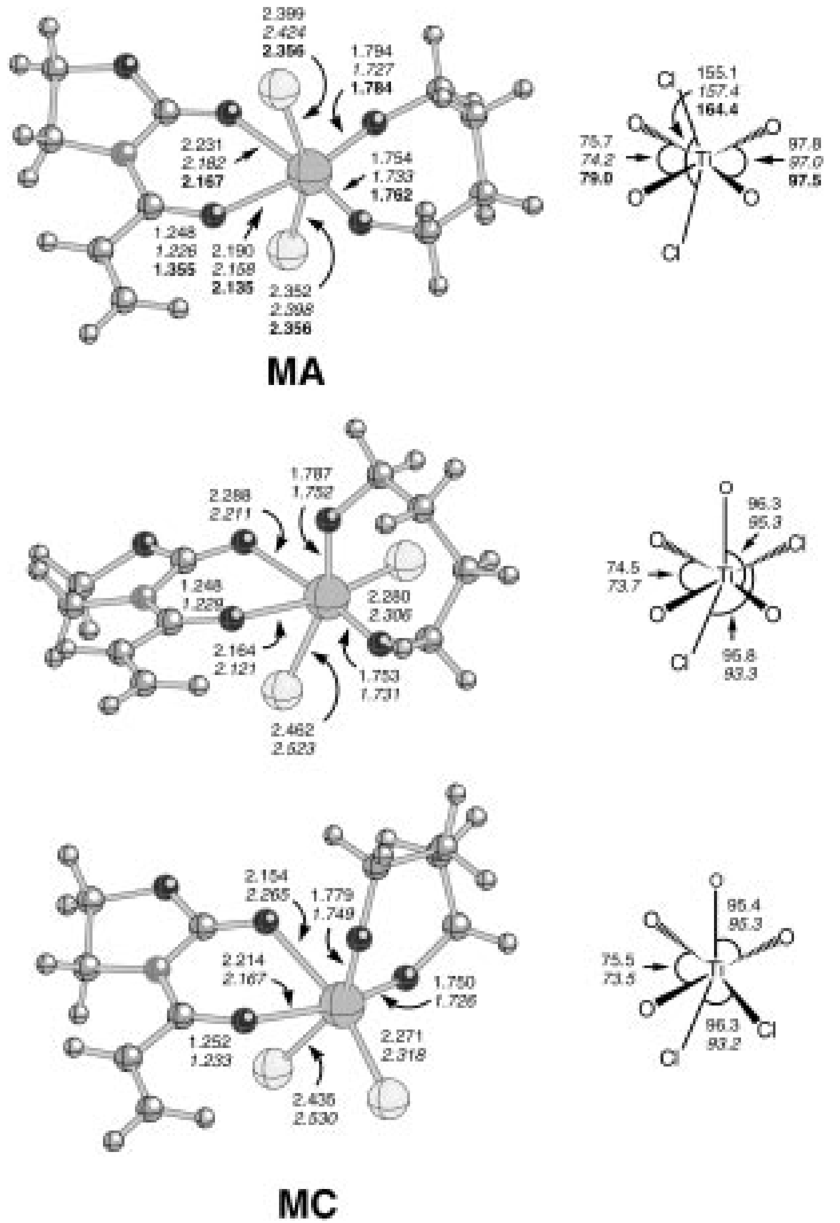

Figure 2. Some selected geometrical parameters of the $TiCl_2$−TADDOLate complexes **MA**, **MB**, and **MC**, calculated at the B3LYP/3-21G(d) (normal typeface) and HF/3-21G(d) (italic) theory levels, and, in the case of **MA**, obtained from X-ray diffraction measurements (boldface).

Table 1. Total and LUMO Relative Energies (in kcal mol^{-1}) of the $TiCl_2$−TADDOLate Complexes MA, MB, and MC, Calculated at Several Theoretical Levels

	MA		MB		MC	
theoretical level	ΔE	ΔE_{LUMO}	ΔE	ΔE_{LUMO}	ΔE	ΔE_{LUMO}
HF/3-21G(d)//HF/3-21G(d)	0.0	4.5	7.6	0.0	5.6	4.6
B3LYP/3-21G(d)//B3LYP/3-21G(d)	0.0	4.2	7.8	0.0	6.8	2.2
B3LYP/6-311+G(d)//HF/3-21G(d)	0.0	4.1	6.2	0.0	5.7	3.5
B3LYP/6-311+G(d)//B3LYP/3-21G(d)	0.0	3.6	5.2	0.0	4.5	2.3

mediates having an axial chlorine atom are more reactive. They have extrapolated this conclusion to say that the intermediate (**A**) is not only the most abundant, but also the most reactive.

On the basis of the nonlinearity observed between the asymmetric induction and the enantiomeric purity of the TADDOL, Seebach and co-workers have proposed[11] the existence of a cationic intermediate. However, given the lack of direct experimental evidences about this intermediate, it will not be further considered in this first quantum mechanical work about these catalysts.

With regard to the asymmetric induction using homochiral $TiCl_2$−TADDOLate complexes, Seebach[6] and DiMare[10] assumed that the differential shielding of both faces of the carbon−carbon double bond in complex **A** is not sufficient to account for the high enantioselectivity observed in some cases. Very recently, we have carried out molecular mechanics studies on the complexes formed between (*E*)-3-butenoyl-1,3-oxazolidin-2-one and several

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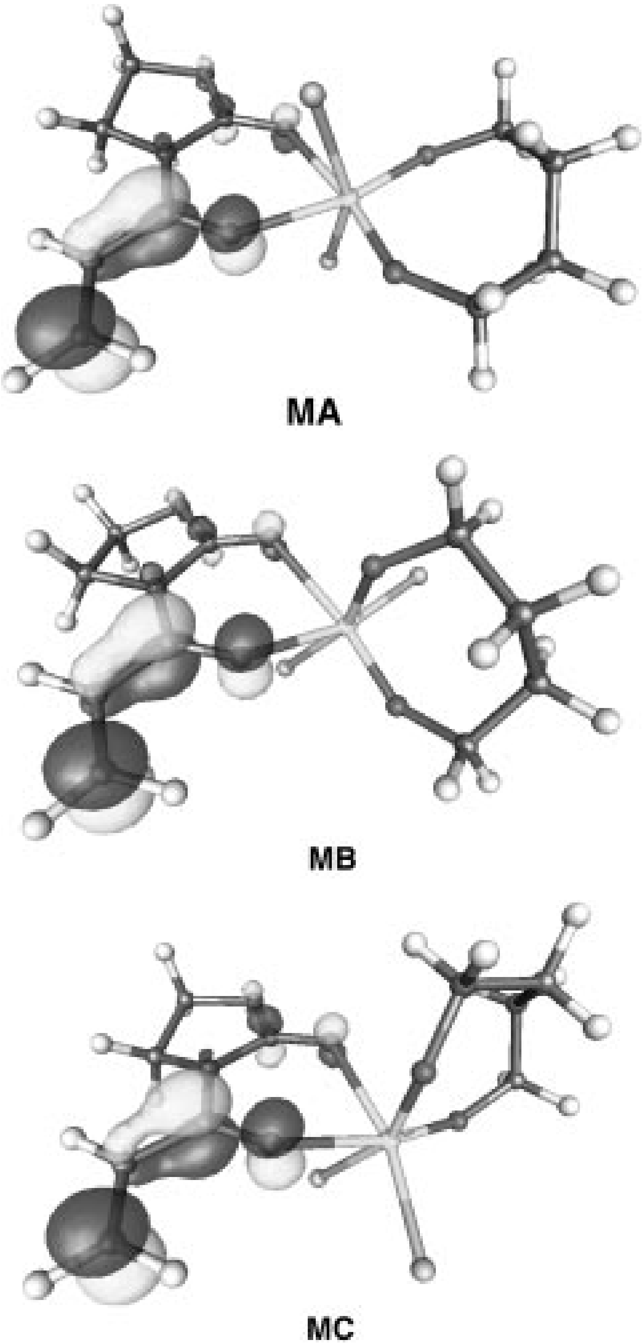

Figure 3. LUMO isovalue surface (at the 0.075 au level) of of the TiCl$_2$–TADDOLate complexes **MA**, **MB**, and **MC**, calculated at the B3LYP/6-311+G(d)//B3LYP/3-21G(d) theory level.

TiCl$_2$–TADDOLates.[12] The results obtained agree with the hypothesis that the intermediates of type **A** do not account for the extent, and in some cases even for the direction, of the asymmetric induction of the reactions of this dienophile with cyclopentadiene promoted by these catalysts. On the other hand, Jørgensen et al. have explained the enantioselectivity observed in some TiCl$_2$–TADDOLate-promoted Diels–Alder reactions on the basis of the X-ray structure determined for the intermediate **A**.

These results indicate that although the relative stabilities of the different intermediates **A**–**C** seem to be clear, the situation is not the same with regard to their relative reactivities. Quantum chemical calculations on the possible transition states of simple Lewis acid-catalyzed Diels–Alder reactions can be helpful to determine the reaction course.[13] However, in this case, the size of the system raises a computational challenge that is difficult to overcome. Given the fact that, according to the FMO theory, all these reactions are controlled by the LUMO of the 3-alkenoyl-1,3-oxazolidin-2-one, if a rapid equilibrium between the different intermediates (Curtin–Hammett principle conditions), knowledge of the energies of the π^* orbitals of the different intermediates can help to clarify this key point. This can be accomplished by means of theoretical calculations at a suitable theory level.

The TiCl$_2$–TADDOLate complexes are too big to allow full ab initio theoretical calculations, and we have therefore used model complexes, **MA**, **MB**, and **MC**, formed between 3-acryloyl-1,3-oxazolidin-2-one and an achiral analogue of TiCl$_2$–TADDOLate, namely that derived from 1,4-butanediol (Figure 2). It should be noted, however, that even these "simple" model complexes are rather big in terms of ab initio standards.

First of all, it is important to determine which is the most suitable theoretical level that must be used to model this system. Fortunately, the X-ray structure of intermediate **A** provides a good benchmark for geometrical comparisons. We have carried out full geometrical optimizations on the model complex **MA** at several theoretical levels (Hartree–Fock, Density Functional Theory, using the Becke3LYP hybrid functional[14]), with different basis sets (3-21G(d),[15] 6-311+G(d),[15,16] LANL2DZ[17]), by means of the Gaussian 94 program.[18] The comparison between the experimental and the calculated geometries indicates that all the theoretical methods lead to reasonable geometries for the complex. If only the titanium octahedral coordination sphere is considered, the agreement between X-ray and theoretical results is, in average, better with the HF/3-21G(d) and B3LYP/3-21G(d) basis sets. Some selected geometrical parameters for complexes **MA**, **MB**, and **MC** are shown in Figure 2.

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Table 1 shows the relative energies of complexes **MA**, **MB**, and **MC**, calculated at the HF/3-21G(d), B3LYP/3-21G(d), B3LYP/6-311+G(d)//HF/3-21G(d), and B3LYP/6-311+G(d)//B3LYP/3-21G(d) levels. It can be seen that **MA** is the most stable complex at all the theoretical levels considered. **MC** is the next most stable complex, but with an energy difference of more than 5 kcal mol^{-1} with respect to **MC**, Finally, **MB** is the most unstable complex, although it is close in energy to **MC** (within 1−2 kcal mol^{-1}). These results are in good agreement with the previous experimental observations.[9,10]

Figure 3 shows the LUMO of complexes **MA**, **MB**, and **MC**, calculated at the B3LYP/6-311+G(d)//B3LYP/3-21G-(d) theory level.[19] In all cases the LUMO essentially corresponds to the π^* molecular orbital of the α,β-unsaturated carbonyl moiety of the dienophile and exhibits a strong polarization toward the carbonyl carbon, as one would expect from the coordination to a Lewis acid. Concerning the relative reactivity of these complexes, Table 1 shows the corresponding calculated LUMO energies. As can be seen, **MB** has the lowest LUMO energy at all the theoretical levels, followed by **MC**, and finally, at a greater distance, by **MA**.

These theoretical results are complemented by the analysis of the charge transfer between the dienophile and the Lewis acid complex, which was carried out by means of a Natural Population Analysis.[20] In the case of **MA**, the dienophile transfers 0.144 electrons to the TADDOL−TiCl_2 complex, whereas in the case of **MB** and **MC**, the extent of the charge transfer is of 0.162 and 0.148 electrons, respectively. It can then be concluded that **MB** experiences the highest degree of Lewis acid activation by the TADDOL−TiCl_2 complex, which is in line with the calculated LUMO energy values.

Therefore, as follows from the theoretical results, **MA** is the most stable complex, but is also the most unreactive intermediate. This means that **MA** can be easily observed in solution and even isolated and crystallized. On the other hand, **MB** is more unstable than **MA**, but is much more reactive by far, so that it normally exists only in small concentrations under the reaction conditions. Furthermore, if we assume[10] that the cycloaddition of the diene to the intermediates **MA**−**MC** is the step that determines both the rate and stereochemistry of the reaction, the Curtin−Hammett principle prevails, and most of the products will come from the reaction of the diene with **MB**.

In conclusion, we present for the first time high-level theoretical results that support the hypothesis put forward by DiMare and Seebach in the sense that intermediate **MB**, in which the carbonyl oxygen atom of the enoate moiety is in the *trans*-position with respect to a chlorine atom, experiences a higher degree of Lewis acid activation and is therefore it is the most reactive. As a consequence, the stereochemical results of the Diels−Alder reactions catalyzed by this kind of complex can be explained in the light of this observation.

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Supporting Information Available: HF/3-21G(d) and B3LYP/3-21G(d) optimized Cartesian coordinates for **MA**, **MB**, and **MC**. HF/3-21G(d), B3LYP/3-21G(d), B3LYP/6-311+G(d)//HF/3-21G(d), and B3LYP/6-311+G(d)//B3LYP/3-21G(d) total and LUMO energies for **MA**, **MB**, and **MC** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(19) There is some controversy about whether the Kohn−Sham orbitals have a physical meaning, although it is generally accepted that they are good approximations to the Hartree−Fock orbitals. However, recently it has been established that the Kohn−Sham orbitals are physically sound and can be expected to be more suitable for use in qualitative molecular orbital theory than either Hartree−Fock or semiempirical orbitals. See, for instance: Baerends, E. J.; Gritsenko, O. V. *J. Phys. Chem. A* **1997**, *101,* 5383.

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