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Homogeneous Catalysis

Probing the Mechanism of Olefin Metathesis in Grubbs–Hoveyda and Grela Type Complexes[**]

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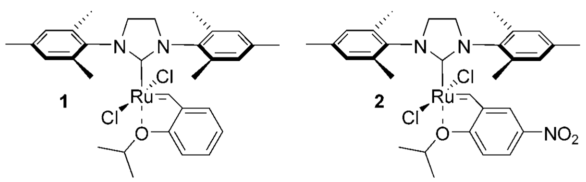
Dedicated to Prof. Dr. Heinrich Vahrenkamp on the occasion of his 70th birthday

Progress in catalysis critically relies on detailed mechanistic understanding. The development of olefin metathesis over the last decades from ill-defined, low-activity catalysts to powerful synthetic tools is an excellent example.[1] Detailed studies on the mechanism of Ru-mediated olefin metathesis were done for Grubbs first- and second-generation complexes and variants thereof.[2] One conclusion of these experiments was that dissociation of the phosphine ligand is the rate-limiting step for olefin metathesis. Hoveyda et al.[3] first reported on stable ruthenacarbenes derived from Grubbs-type complexes, in which benzylidene and PCy_3 are replaced by a bidentate benzylidene ether ligand (Scheme 1). Such complexes are very important, as they combine excellent stability with remarkable catalytic activity in olefin metathesis.[4] Nonetheless, they are mechanistically less well explored. Most studies focused on the release/return (boomerang) mechanism. It was claimed that the initiation step involves dissociation of the benzylidene ether and that, following the olefin metathesis reaction, the bidentate ligand returns to the Ru complex.[3,5]

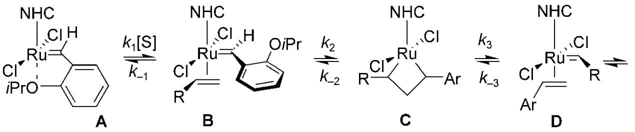


Scheme 1. Grubbs–Hoveyda complex **1** and Grela complex **2**.

Recently, Dorta et al.[6] and Grubbs et al.[7] demonstrated that, in the presence of very high olefin concentrations, Grubbs–Hoveyda-type complexes are extremely efficient in ring-closing metathesis (RCM) reactions. Clearly, this behavior cannot be explained by the accepted mechanism for Grubbs second-generation complexes. Our present work attempts to resolve this question by studying the mechanism of olefin metathesis with complex **1** and the well-known Grela subtype **2**, with an electronically modified benzylidene ether ligand (Scheme 1). We studied the initiation reaction, since olefin metathesis with Grubbs second-generation and Grubbs–Hoveyda complexes are normally initiation-limited.[2a]

Complexes **1** and **2** display absorption bands at around 380 nm. Ring-closing metathesis reactions lead to a decrease in this band and growth of a new one at around 500 nm, which both provide excellent spectroscopic handles.[2a,8,9] To obtain a detailed picture of the initiation event in Grubbs–Hoveyda- and Grela-type complexes, experiments were performed at different olefin concentrations and fixed concentrations of complexes **1** and **2** (1.09×10^{-4} M) and analyzed by UV/Vis spectroscopy.

The following study makes use of the established general mechanism for the initiation reaction (Scheme 2). Complex **A** is activated by the olefinic substrate to result in **B**. The initial reaction of **A** with an olefin can occur by an associative, dissociative, or interchange mechanism. Hoveyda et al. suggested a dissociative mechanism for such complexes,[4a] similar to the established mechanism for Grubbs second-generation complexes,[2a] while an associative mechanism based on negative activation entropies was suggested by Grubbs and Vougioukalakis.[10] Complex **B** then undergoes ruthenacyclobutane formation to give **C**, which after cycloreversion leads to complex **D.** Following olefin exchange this complex then enters the catalytic cycle, in which species closely related to **C** and **D** occur.



Scheme 2. Basic mechanism for the initiation reaction.

The RCM reactions of diethyl diallylmalonate (DEDAM) catalyzed by complex **1** or **2** were monitored by UV/Vis spectroscopy. Attempts to fit the respective absorbance–time curves with first-order exponential functions failed for low substrate concentrations. In the following kinetic analysis it is assumed that complex **A** is activated in a first step by the olefinic substrate, and the activated complex then allows substrate molecules to react to form the product. At the end of this sequence an inactive ruthenium complex is obtained. The derived rate expression for the UV/Vis absorbance A of complex **A** for conversion of the substrate is $A=(A_0-A_\infty)/(1+k_{obs}t)+A_\infty$ (second-order method).[11] The

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fitting of the respective absorbance versus time plots yields the respective k_{obs} with excellent correlation coefficients. A linear fit of k_{obs} versus substrate concentration provides the second-order rate constant for catalyst initiation of complexes **1** and **2** (Figure 1, Table 1).[12] The *y* intercept for both linear fits is close to zero. The rate of initiation for Grela complex **2** is almost three times higher than that of **1**, and this confirms that the nature of the leaving group is important.

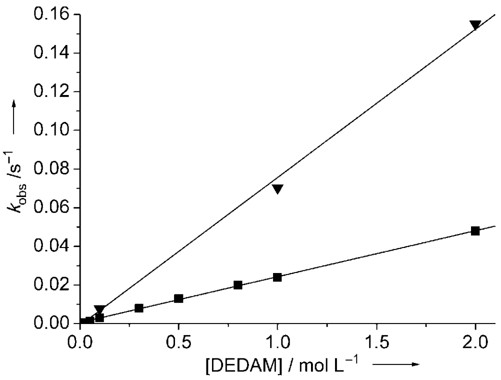


Figure 1. k_{obs} versus [DEDAM] ($c = 0.005$ M–2 M) for the RCM reaction with **1** (squares, $R^2 = 0.999$ for seven pairs of data) or **2** (triangles, $R^2 = 0.998$ for five pairs of data). $T = 40$ °C.

Table 1: Reaction rates k_1 for the first initiation reaction ($T = 40$ °C).

Reaction	k_1 [M^{-1} s^{-1}]
1 + EVE	0.069 ± 0.0023
2 + EVE	0.192 ± 0.003
1 + DEDAM	0.0238 ± 0.0032
2 + DEDAM	0.0764 ± 0.0020

This linear relationship between k_{obs} and [DEDAM] holds true even at a substrate concentration of 2 M.[13] Clearly, there is no saturation behavior, which on the other hand is well-established for Grubbs second-generation complexes.[2a,14] At this concentration of DEDAM, fading of the 378 nm absorbance in complex **1** occurs in less than 100 s. Fitting of the absorbance versus time plot with an exponential function (pseudo-first-order condition) $A = (A_0 - A_\infty)\exp(-k_{obs}t) + A_\infty$ yields k_{obs} and follows the same linear regression as for the lower concentrations.[15]

The data presented here also help to understand the drastic rate accelerations in various RCM reactions observed by Dorta et al. with an optimized Grubbs–Hoveyda complex.[6] To determine whether this is a general feature of Grubbs–Hoveyda complexes, we performed additional RCM reactions at the highest possible substrate concentration (neat DEDAM and *N,N*-diallyltosylamide, both ca. 4 M) using 0.0025 mol % of complex **1**. These reactions result in quantitative formation of the RCM products at room temperature after 30 min, without oligomer formation.[16] Thus the outstanding activities observed by Dorta et al. appear to be a general feature of this class of complexes.

From the dependence of the RCM rate on substrate concentration, it follows that the **A**→**B** reaction with 2 M DEDAM is about 400 times faster than at a 0.005 M concentration of the olefinic substrate. A consequence of this drastic rate increase is that the nature of the rate-limiting step for the RCM reaction appears to change on going from low to very high substrate concentrations. At low substrate concentrations the parallel evolution of UV/Vis absorbance and substrate conversion shows that the RCM reaction is initiation-controlled. In neat substrate (ca. 4 M DEDAM) the initiation reaction requires less than 100 s, while the RCM reaction with **1** takes approximately 30 min. The rate-limiting step now seems to occur later in the sequence of reactions defining olefin metathesis.[17]

To obtain a better understanding of the mechanism and the nature of the species involved, we carried out additional experiments aimed at probing individual steps of the initiation reaction. The reaction of Grubbs-type complexes with ethyl vinyl ether (EVE) is known to lead to catalytically inactive Fischer-type carbenes following a single olefin metathesis event.[2a] Consequently, studying the reactions of complexes **1** and **2** with EVE offers the chance to probe the sequence of reactions **A**→**D** (Scheme 1) without entering the catalytic cycle. In the UV/Vis spectrum these reactions lead to a decrease of the respective 375 nm absorbance and in a transient, broad absorbance around 500 nm. A rapid increase in this absorbance is followed by a slow decrease (Figure 2), which was observed in the EVE concentration range from 0.1 M to 2 M.

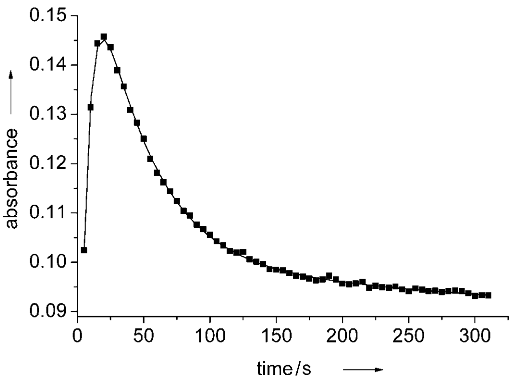


Figure 2. Absorbance versus time (complex **2**) at 500 nm for [EVE] = 0.8 M, fitted with the sum of two exponential functions ($y = a\exp(-dx) + b\exp(-fx) + gx + c$, see the Supporting Information).

The absorbance versus time data for variable EVE concentrations were fitted with the sum of two exponentials: k_1, describing the rapid increase in 500 nm absorbance, depends on olefin concentration,[18] whereas the other process leading to a decrease of this absorbance with a second rate constant is independent of EVE concentration. Consequently, in the lower concentration regime (< 0.3 M EVE) the olefin-dependent step is rate-limiting, while at very high EVE concentrations (> 0.3 M) the second, olefin-independent step is rate-limiting in the reaction of complex **1**. Again the olefin-dependent reaction is three times faster for Grela complex **2** than for Grubbs–Hoveyda-type complex **1** (Table 1). Initiation with the electron-deficient EVE is 2.5 (**1**) and 2.9 times faster (**2**) than with DEDAM (Figure 1), that is, the nature of the olefin influences the initiation rate (Table 1).In contrast, the olefin-independent step ($T = 40\,^{\circ}$C, k(indep.) = $0.0266 \pm 0.002\ \mathrm{s}^{-1}$) has virtually the same rates for **1** and for **2**, and thus the influence of the nitro group is weak.

For the A→B conversion three different pathways must be considered: an associative or dissociative mechanism or interchange with associative (I_a) or dissociative character (I_d). The initiation rate data (Table 1) obtained show that the reaction rate depends on the concentration of the olefin (Figure 1) and on its nature. A dissociative mechanism is thus unlikely, also with a view to the absence of saturation kinetics even at the highest EVE concentrations.[19] An associative mechanism is implausible since the nature of the isopropoxy benzylidene ligand in **1** and **2** also has a significant influence on k_1, the Grela-type complex is well known for its much faster initiation behavior, and binding of the olefin *trans* to the benzylidene ligand appears difficult from a steric point of view. As the incoming olefin and outgoing ether both influence k_1, we prefer an interchange mechanism. It is difficult to decide whether this has more of an I_a or I_d character. The much slower activation of the catalyst in the presence of electron-deficient alkenes[20] appears to favor an I_a mechanism.

When following the established mechanistic setup (Scheme 2), the olefin-independent step should be localized in the sequence of reactions **B**→**D**, which entail formation and reversion of the ruthenacyclobutane. Our kinetic data provide no conclusive evidence which of these steps involving the ruthenacyclobutane is rate-limiting. Piers et al. established the status of such complexes as intermediates in olefin metathesis. Low-temperature NMR spectroscopic studies provided clear evidence for the existence of unsubstituted and substituted ruthenacyclobutane in solution at low temperatures.[21] Density functional calculations led Chen and Adlhart to state that, for the first-generation catalysts, metallacyclobutane formation is the rate-limiting step, whereas for the second-generation catalysts, creation of the active species by dissociation of the phosphine is rate-limiting.[17] Obviously, the latter step is not applicable for the complexes studied here. Woo et al. suggested that cycloaddition to form the ruthenacyclobutane from the ring-opening metathesis (ROM) or RCM adducts occurs with very small barriers.[22]

To obtain additional information on the **A**→**B** conversion, we studied the reactions of **1** and **2** with an excess of PCy_3. This reaction results in a color change from green to red, typical of Grubbs second-generation complexes. Addition of a large excess of CuI, which acts as a phosphine trap, regenerates the green color of the Grubbs–Hoveyda complex. Complex **1** is characterized by a 375 nm band, which upon addition of PCy_3 shifts to 370 nm while a new band at 522 nm grows in. The time-dependent evolution of the UV/Vis spectrum of **1** and **2** was probed at different PCy_3 concentrations.

Fitting of the absorbance versus time data to a single exponential gave the respective k_{obs}, which were plotted against [PCy_3] (Figure 3). The linear fit of this equilibrium reaction gave the same forward rates k_1 for the reactions of complex **1** and **2** with PCy_3, but different reverse rates k_{-1}, and consequently different equilibrium constants ($K = 72 \pm 15\ \mathrm{M}^{-1}$ for **1**[23] and $K = 380 \pm 170\ \mathrm{M}^{-1}$ for **2**).[24] NOESY spectra firmly established rotation of the substituted benzylidene group into a cofacial orientation upon coordination of PCy_3 (Scheme 3), which lead to Grubbs second-generation-like complexes. This goes along with the typical green-to-red color change and a UV/Vis band around 500 nm. The transient species observed in the reactions of EVE with complexes **1** and **2** also displays such a 500 nm absorbance, which is absent in both **1** and **2** with orthogonal six-membered rings. This provides additional support that the first intermediate in the EVE reaction is described by structure **B** in Scheme 1.

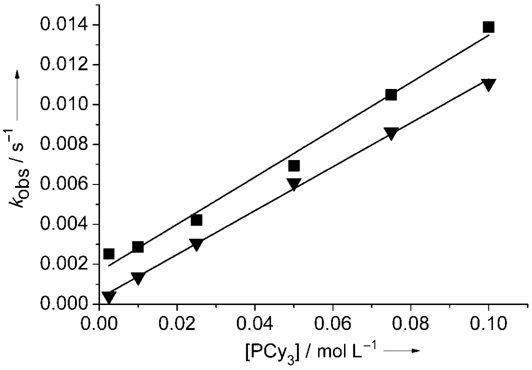
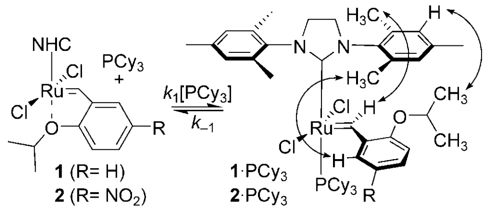


Figure 3. k_{obs} versus [PCy_3] for the reaction of PCy_3 with **1** (squares) and **2** (triangles). A linear fit for the data of complex **1** ($R^2 = 0.990$) yields $k_1 = 0.118 \pm 0.006\ \mathrm{M}^{-1}\mathrm{s}^{-1}$ and $k_{-1} = 0.00164 \pm 0.00033\ \mathrm{s}^{-1}$, and for complex **2** ($R^2 = 0.998$) $k_1 = 0.1098 \pm 0.0024\ \mathrm{M}^{-1}\mathrm{s}^{-1}$ and $k_{-1} = 0.00029 \pm 0.00013\ \mathrm{s}^{-1}$.



Scheme 3. Reaction of **1** and **2** with PCy_3; arrows denote observed NOE contacts.

In conclusion, the kinetic data reported here provide conclusive evidence for participation of the olefinic substrate in the rate-determining step of the initiation reaction. The nature of the outgoing ether as well as the nature and concentration of the incoming olefin influence the rate of the initiation reaction. We therefore prefer an interchange mechanism, possibly with associative character, for the first step of the initiation reaction. The massive acceleration of this initial event at very high olefin concentrations leads to a change in the rate-limiting step. This step occurs later in the sequence of reactions defining olefin metathesis, is independent of the incoming olefin, and also appears to be independent of the electronic nature of the benzylidene unit. Future studies will be directed towards uncovering the identity of the intermediates. This knowledge will be essential to better understand the nature of the olefin-independent step and could finally aid in the synthesis of new and improved catalysts.

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