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How Important Is the Release–Return Mechanism in Olefin Metathesis?

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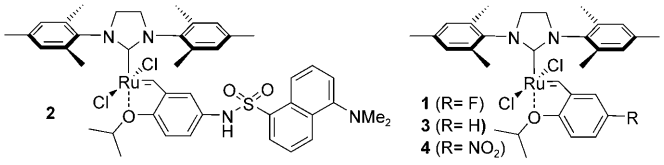
Hoveyda[1] and later Blechert[2] first reported on stable ruthenacarbenes derived from Grubbs II complexes, in which benzylidene and PCy_3 are replaced by a bidentate benzylidene ether ligand.[3] Such complexes combine excellent stability with remarkable catalytic activity in various types of olefin metathesis reactions.[3b,4] It was claimed, that the initiation step involves dissociation of the benzylidene ether and that following the olefin metathesis reaction, the bidentate isopropoxy styrene returns to the ruthenium as a benzylidene ligand; this was termed boomerang or release–return mechanism.[1,5] Based on the observation of deuterated and non-deuterated benzylidene ether ligand crossover between bead-immobilized Grubbs–Hoveyda complexes, Hoveyda et al. provided evidence that the initially proposed release–return mechanism is operative.[6] Even though this mechanism has been recognized by numerous others with various Grubbs–Hoveyda-type olefin metathesis catalysts,[5,7] the important question of whether this mechanism contributes substantially or only marginally has not been resolved.[8] Recently, Grela et al. reported on exchange experiments between deuterated and non-deuterated benzylidene ether ligand and styrene ether. First the background reaction between styrene ether and deuterated benzylidene ether ligand in complexes **3** and **4** was probed. During ring-closing metathesis (RCM) reactions the deuterated and non-deuterated labels were equilibrated much faster than the background reaction. Based on this, it was concluded that the whole amount of precatalyst applied was involved in the catalytic reaction and was then regenerated by the release–return mechanism.[9]



We and others recently discovered that tagging of ligands in metal complexes with fluorescent dyes can provide useful information on ligand dissociation reactions due to changes in the fluorescence intensity during the catalytic reactions.[10] Transition-metal ions often quench the fluorescence of such dyes and consequently fluorophore-tagged ligands coordinated to such metals, render weakly fluorescent complexes.[11] However, upon dissociation of the tagged ligand from a metal complex, the fluorescence is restored due to the spatial separation between the two components. When the dissociation of such a tagged ligand represents a key step in the catalytic cycle, the monitoring of the fluorescence intensity will provide detailed mechanistic information. This could thus become a key experiment for probing the release–return mechanism.

We want to report here on the release of the benzylidene ether ligand under real catalytic conditions during olefin metathesis reactions using Hoveyda-type precatalysts and (more importantly) whether a return of this ligand occurs to a significant extent. To enable the monitoring of such reactions, in addition to the normal Grubbs–Hoveyda complex **3,** closely related complexes with different spectroscopic reporter groups were needed. The fluorine substituted complex **1** was obtained according to a known procedure;[12] the new fluorophore-tagged complex **2** was synthesized in good yields using the respective dansyl-tagged styrene.

It was important, to first show that the dansyl fluorophore and the fluorine groups located *para* to the ether oxygen do not disturb the RCM activity of complexes **1** and **2** to a significant degree. With a view to the Hammett constants $\sigma_p(NHSO_2Me) = 0.03$ and $\sigma_p(F) = 0.06$ this appears to be unlikely.[13] RCM reactions for the conversion of DEDAM (diethyl diallyl malonate) catalyzed by the tagged complexes **1** and **2** and Grubbs–Hoveyda complex **3** were monitored and the respective conversion-time curves found to be compara-

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ble (Figure S1 in the Supporting Information), with complex **3** showing the slowest and **1** the fastest conversion. Apparently, neither the dansyl nor the fluorine tag interferes with the olefin metathesis reaction to a really significant extent.

Next the fluorescence of complex **2** was monitored in toluene, in the absence of RCM substrate, to obtain information on the stability of **2** under the experimental conditions (blank experiment). The initial fluorescence intensity is weak and only a very slow increase with time was observed (Figure 1, trace a). This experiment was repeated with

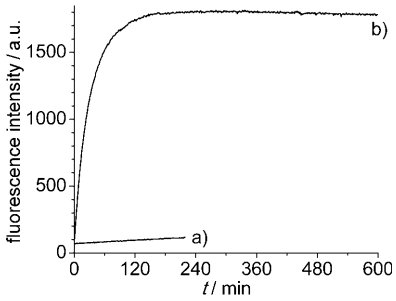

Figure 1. Fluorescence evolution of a toluene solution of complex **2** (trace a, blank) and during the RCM of DEDAM (trace b).

added RCM substrate (DEDAM, 0.5 mol% of **2**).[14] Within a few minutes a strong increase of the fluorescence intensity occurred, until after about 120 min a plateau was reached and held for the next 18 h (Figure 1, trace b, only the first 10 h are shown). To probe whether this fluorescence intensity corresponds to the liberation of all dansyl-tagged benzylidene ether, the dansyl-tagged complex **2** was reacted with 1000, 2500, and 5000 equivalents of ethyl vinyl ether. All of those reactions lead to the same final fluorescence intensity, corresponding to quantitative initiation and full liberation of the fluorophore (Figure S3 in the Supporting Information).[15]

The weak initial fluorescence of a solution of complex **2** is indicative of efficient fluorescence quenching. The initiation of the olefin metathesis reaction leads to the dissociation of the fluorophore tag and thus to the spatial separation of ruthenium and the fluorophore. Consequently, the fluorescence of the dansyl group is restored. However, a release–return mechanism also requires that the liberated fluorophore-tagged styrene returns to the ruthenium. Under the conditions employed here, this should result in the partial quenching of the fluorescence. However, the fluorescence intensity remains virtually constant after the RCM reaction. The same type of fluorescence–time curve was observed for two additional RCM reactions with *N*, *N*-diallylcarbamate and *N*, *N*-tosyldiallylamide carried out under the same conditions (Figures S9 and S10 in the Supporting Information). For the three RCM reactions with different substrates catalyzed by pre-catalyst **2** the full fluorescence evolution can be slower or faster, due to different rates of the initiation reactions for the three olefinic substrates. This also indicates that the increase of fluorescence intensity is related to the nature of the substrate and not caused by a separate decomposition reaction independent from substrate conversion. It is also evident that fluorophore-tagged ligands can be highly useful tools for mechanistic studies in transition-metal catalysis. The RCM reaction with DEDAM and catalyzed by **3** was also monitored by UV/Vis spectrometry. The UV/Vis spectra of **1** and **2** are characterized by a distinct absorbance at 380 nm. This absorbance disappears during the RCM reaction, but does not return after the RCM reaction. Therefore an independent UV/Vis experiment provides no evidence for a return of the isopropoxy styrene.

To obtain a better picture of the RCM reaction, the fluorescence experiments were repeated for different olefin concentrations, at constant concentrations of complex **2** (5.3×10^{-5} M). In contrast to UV/Vis experiments, providing a metal-centered view of olefin metathesis event, the fluorescence experiments furnish information on the (liberated) fluorophore, which is formed after the first olefin metathesis reaction. For an analysis of the initiation reaction the same kinetic model as reported before is used.[16] Accordingly, the Grubbs–Hoveyda complex is first activated by the olefinic RCM substrate. The activated complex then allows substrate molecules to react to the product. The derived rate expression for the fluorescence intensity I for conversion of the substrate is: $I=(I_0-I_\infty)/(1+k_{obs}t)+I_\infty$. The fitting of the fluorescence–time curves for the DEDAM reactions yields the respective k_{obs}, and a linear fit of the various k_{obs} versus substrate concentration provides the second-order rate constant for catalyst initiation $k_1=(15.0\pm2)\times10^{-3}\,M^{-1}s^{-1}$ of **2**. This rate constant for the initiation is close to the initiation rate obtained from UV/Vis experiments $k_1=(23.8\pm3\times10^{-3}\,M^{-1}s^{-1})$ for complex **3**,[16] which shows that the fluorescence and the UV/Vis experiments report on the same event. For the same reaction of the fluorine-tagged complex **1** a faster $k_1=(57.5\pm2)\times10^{-3}\,M^{-1}s^{-1}$ was obtained from UV/Vis experiments.

When using UV/Vis and fluorescence spectroscopy with complexes **2** and **3** it is difficult to obtain precise data on the identity of the species formed in the course of olefin metathesis reactions. The ^{19}F NMR signals in **1** and other fluorine-containing derivatives can provide such information and consequently the evolution of the ^{19}F NMR signal in the RCM reaction of DEDAM with **1** was recorded. The excellent sensitivity of ^{19}F NMR spectroscopy allows the performance of these experiments under the same conditions as before. Initially the ^{19}F signal of complex **1** ($\delta=-126.2$ ppm) was observed, but the ongoing initiation reaction leads to a single new signal ($\delta=-125.4$ ppm), which corresponds to that of the free 3-fluoro-6-isopropoxy styrene and which is also the only ^{19}F NMR signal observed at the end of the RCM reaction. Again there is no evidence supportive of a release–return mechanism.

This finally leads us to conclude, that under the conditions of the catalytic reaction, the return of the styrene ether to the ruthenium to reform the Grubbs–Hoveyda type complex does not occur to a significant extent. Nonetheless, we cannot ignore a significant number of publications, which

report on the re-isolation of Grubbs–Hoveyda complex after olefin metathesis reactions. Two scenarios are conceivable to explain this. First we take an exemplary look at a representative procedure for such a RCM reaction. We note that up to 5 mol% of the pre-catalyst **3** were used, which is much more than needed for such a conversion; as it is now known from the work of Dorta et al.[17] and from our own work[16] that Grubbs–Hoveyda type catalysts can be extremely active for RCM reactions at high concentrations of olefinic substrates. In the reaction discussed, a 0.1 M substrate concentration was utilized, which is relatively high. Secondly, the reaction workup took place after only 10 min reaction time. This time is too short to activate a significant proportion of the pre-catalyst. A consequence of this is that the initiation reaction is slower than the olefin metathesis conversion. This becomes evident in Figure 2; even at a 1 mol% loading

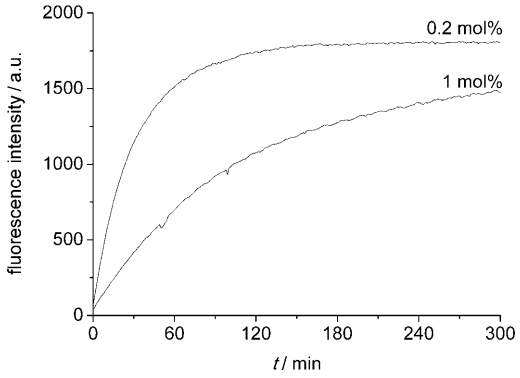

Figure 2. Fluorescence-time curves for the RCM reaction of DEDAM with complex **2** at 0.2 and 1 mol% loading.

only a small amount of catalyst is activated after 30 min. With a 5 mol% loading and 10 min reaction time, the proportion of activated catalyst will be very small. Consequently, the large majority of Grubbs–Hoveyda complex will remain unchanged and available for re-isolation. Even at 1 mol% loading (Figure 2) less than half of the complex is activated after 60 min, while at 0.2 mol% loading after 60 min activation is not quantitative.

As an alternative scenario, the concentration of the reaction mixture during the evaporation of the solvent might lead to the re-association of the isopropoxy styrene. We tested this by repeating the RCM reaction with DEDAM and 0.2 mol% of complex **3** under the conditions of the fluorescence experiment. After 6 h reaction time (quantitative initiation, Figure 2) the volatiles were evaporated. The remaining oil was dissolved in a minimum amount of CH_2Cl_2 and the solution applied to thin-layer chromatographic plates. However, the green spot indicative of the Grubbs–Hoveyda complex was not observed.

In conclusion, neither fluorescence spectroscopy, UV/Vis experiments nor ^{19}F NMR spectroscopy provide evidence supportive of a significant contribution of a release–return mechanism in RCM reactions in the Grubbs–Hoveyda-type complexes studied (**1**, **2**, and **3**). This conclusion is mainly based on three observations: 1) The highly characteristic 380 nm UV/Vis absorbance in complex **1** and **3** disappears in the course of the catalyst initiation and is not restored after the olefin metathesis reaction; 2) the dansyl fluorophore in complex **2** is released during the initiation period, the bright fluorescence is turned on and does not disappear after the RCM reaction; and 3) the characteristic ^{19}F NMR signal of the fluorine-tagged isopropoxy styrene from complex **1** grows in during catalyst initiation and is the only fluorine-containing species following olefin metathesis. We thus believe that the absence of return is much more common than previously thought. It is likely, that the re-isolation of the Grubbs–Hoveyda complex following olefin metathesis reactions is primarily caused by incomplete activation of the initial Grubbs–Hoveyda complex. This happens when the catalytic transformation is faster than catalyst initiation and occurs when much more catalyst complex is used than is required for a certain olefin metathesis reaction.[18] For low catalyst loading (just sufficient to effect the desired transformation) most of the precatalyst will undergo activation. This active olefin metathesis catalyst does not live forever and should fall victim to various decomposition reactions after a certain number of turnovers.[19]

Acknowledgements

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Keywords: fluorescence · olefin metathesis · release–return mechanism · ruthenium · UV/Vis spectroscopy

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