New Insights into the Mechanism of Ruthenium-Catalyzed Olefin Metathesis Reactions

Melanie S. Sanford, Michael Ulman, and Robert H. Grubbs*

Arnold and Mabel Beckman Laboratories of
Chemical Synthesis, California Institute of Technology
Pasadena, California 91125

Received October 4, 2000

Over the past two decades, olefin metathesis has emerged as a mild and efficient method for the formation of carbon−carbon double bonds.[1] In particular, $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (**1**)[2] has found extensive use in organic and polymer chemistry due to its high reactivity with olefins in the presence of a diverse array of functional groups.[3] Recently, a new family of ruthenium-based olefin metathesis catalysts have been prepared by the substitution of a single PCy_3 ligand of **1** with an N-heterocyclic carbene.[4−6] These new alkylidenes, particularly **2** [Figure 1], exhibit dramatically increased activity over the parent system in ring-opening metathesis polymerization,[7] ring -closing metathesis,[4a] and cross metathesis reactions.[8] The mechanism of olefin metathesis reactions catalyzed by **1** has received intense investigation in our group[9] and others,[10,11] and early studies established that phosphine dissociation is a crucial step along the reaction coordinate.[9a] As such, it has been suggested that the high activity of **2** and its analogues is due to their increased ability to promote this critical phosphine dissociation step.[4−6] We report herein a detailed mechanistic study of phosphine exchange and initiation kinetics in alkylidenes **1** and **2**. This study provides new and surprising evidence concerning the origin of the large activity differences between these two catalysts.

To better understand the differences in reactivity between **1** and **2,** we examined the mechanism of the ligand substitution of phosphine with olefinic substrate [Scheme 1]. In the two limiting cases, this substitution could take place in an associative [Scheme 1a] or a dissociative [Scheme 1b] fashion. The associative pathway involves initial binding of substrate to form the coordinatively saturated intermediate **3**, while the dissociative substitution proceeds by initial loss of PCy_3 to generate the 14-electron intermediate **4**.[12] To distinguish between these possibilities we focused on the degenerate exchange reaction between free and bound PCy_3 in alkylidenes **1** and **2** [Scheme 2]. We reasoned that this exchange, which is the simplest example of ligand substitution in these catalysts, should provide a model system for the phosphine/olefin substitution.

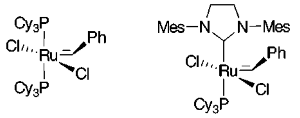
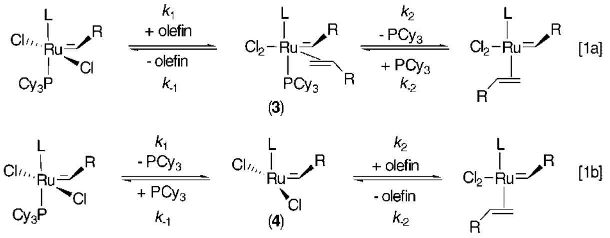
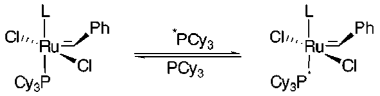


Figure 1.

Scheme 1



Scheme 2



^{31}P NMR spectroscopy was used to examine the rates of phosphine exchange in **1** and **2**. Initial experiments indicated that this exchange is relatively slow, and in both cases coalescence of the free and bound phosphine signals was not observed up to 100 °C in toluene-d_8. As such, ^{31}P magnetization transfer studies were utilized to obtain exchange rate constants in these systems.[13] In a typical experiment, the free phosphine (P_F) resonance was selectively inverted, and the peak heights of free and bound phosphine (P_B) were observed at variable mixing times. The time-dependent magnetization data was analyzed using the computer program CIFIT,[14] and rate constants for the exchange of P_B with P_F (k_B) were determined for each catalyst. The exchange rate constants (per coordinated phosphine ligand) at 80 °C for **1** and **2** are 9.6 ± 0.2 and $0.13 \pm 0.01\ s^{-1}$, respectively. These results are surprising, since they show an *inverse* relationship between phosphine exchange rate and olefin metathesis activity.[15] In fact, alkylidene **2**, which exhibits very rapid propagation rates surpassing some early transition metal catalysts in the ROMP of cyclooctadiene,[7] exchanges phosphine almost 2 orders of magnitude slower than **1**.

An examination of the exchange rate constant as a function of phosphine concentration established a dissociative mechanism for this reaction. For both catalysts, k_B is independent of $[PCy_3]$ over a wide range of concentrations. Activation parameters for phosphine exchange were determined from the temperature dependence of k_B (at a constant $[PCy_3]$), and the results are summarized in Table 1. In both cases, the values for $\Delta H^‡$ and $\Delta S^‡$ are large and positive in sign, also consistent with dissociative substitution. Taken together, these data indicate that phosphine exchange proceeds via a dissociative pathway [Scheme 3], in which initial formation of a 14-electron intermediate is followed by fast trapping with free PCy_3.

While the phosphine exchange rates do not correlate with the propagation rates of **1** and **2**, we thought that they might be related to the initiation rates of the two catalysts.[16] To probe this possibility, the reaction of alkylidenes **1** and **2** with ethyl vinyl ether

---

[1] Ivin, K. J. and Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, CA, 1997.

[2] Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

[3] (a) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Steltzer, F. *J. Macromol. Sci., Pure Appl. Chem.* **1996**, *A33*, 941.

[4] (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.

[5] Huang, J.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674.

[6] Weskamp, T.; Kohl, F. J.; Hieringer, W.; Gliech, D.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2416.

[7] Bielawski, C. B.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903.

[8] (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (b) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751.

[9] (a) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887. (b) Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484. (c) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202.

[10] (a) Adlhart, C.; Hinderling, C.; Baumann, H.; Chen, P. *J. Am. Chem. Soc.* **2000**, *122*, 8204. (b) Hinderling, C.; Adlhart, C.; Chen, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2685.

[11] Aagaard, O. M.; Meier, R. J.; Buda, F.; *J. Am. Chem. Soc.* **1998**, *120*, 7174.

[12] Sanford, M. S.; Henling, L. M.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 3451.

[13] Morris, G. A.; Freeman, R. *J. Magn. Res.* **1978**, *29*, 433.

[14] Bain, A. D.; Kramer, J. A. *J. Magn. Res.* **1996**, *118A*, 21.

[15] An approximately inverse relationship between olefin metathesis activity and phosphine exchange rate is observed in related catalysts. Sanford, M. S.; Love, J. A.; Grubbs, R. H. Unpublished results.

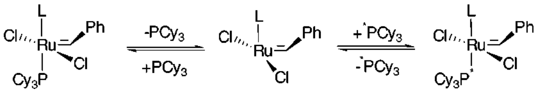
[16] The initiation step in olefin metathesis catalysis involves stoichiometric reaction of a metal alkylidene with an olefinic substrate to generate the catalytically “active species.”

10.1021/ja003582t CCC: $20.00

Table 1. Activation Parameters for Phosphine Exchange

catalyst	k_B (s^{-1}) 80 °C	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})	$\Delta G^{\ddagger}$ (298 K) (kcal mol^{-1})
1	9.6 ± 0.2	23.6 ± 0.5	12 ± 2	19.88 ± 0.06
2	0.13 ± 0.01	27 ± 2	13 ± 6	23.0 ± 0.4

Scheme 3



was chosen as a model for the initiation event. Catalysts **1** and **2** react with ethyl vinyl ether leading to the exclusive formation of the Fischer carbenes L(PCy$_3$)(Cl)$_2$Ru=CHOEt. This reaction is ideal for these studies because it is quantitative and essentially irreversible.[17] In addition, the rate is extremely rapid (significantly faster than that with less electron-rich olefins), and should provide close to an upper limit for the initiation rates in these systems.

The reaction of **2** with ethyl vinyl ether was studied by ^{1}H NMR spectroscopy at 35 °C. Under these conditions, the initiation rate constant ($k_{obs} = (4.6 \pm 0.3) \times 10^{-4}$ s^{-1}) is *independent* of olefin concentration over a wide range of concentrations (5 equiv to 60 equiv of ethyl vinyl ether relative to [Ru]).[18] These results indicate that saturation kinetics are achieved even at low olefin concentrations,[19] and suggest that the rate-determining step of the reaction is phosphine dissociation. This can be confirmed by extrapolation of the Eyring plot from the magnetization transfer data which provides the predicted phosphine dissociation rate constant at 35 °C ($k_B = (4 \pm 3) \times 10^{-4}$ s^{-1}). The values obtained for k_{obs} and k_B are identical within the error of the two measurements.

In contrast, ^{1}H NMR studies of the reaction of **1** with ethyl vinyl ether show that k_{obs} is dependent on olefin concentration over a concentration range of 30 to 120 equiv of olefin (relative to [Ru]). However, UV–vis spectroscopy, which enables monitoring of the reaction at much higher olefin concentrations, can be utilized to achieve saturation conditions. The initiation reaction was followed by the appearance of the vinyl ether product (484 nm), and the data fit first-order kinetics over 5 half-lives. Using 5300 equiv of substrate, a first-order rate constant of 0.018 ± 0.001 s^{-1} was obtained at 20 °C. This value shows excellent agreement with the extrapolated phosphine exchange rate constant ($k_B = 0.016 \pm 0.002$ s^{-1}) from the magnetization transfer data.

Scheme 4

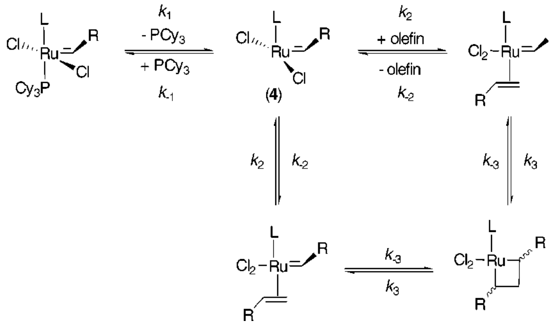


Table 2. Values for the k_{-1}/k_2 Ratio in Catalysts **1** and **2**

catalyst	T (°C)	k_1(intercept) (s^{-1})	k_B(predicted) (s^{-1})	k_{-1}/k_2
1	37	0.26	0.16	15300
2	50	0.0031	0.003	1.25

The results described above suggest that olefin metathesis reactions catalyzed by **1** and **2** proceed according to the mechanism outlined in Scheme 4.[20] In both cases, the first step of the reaction involves dissociation of bound PCy$_3$ to form a 14-electron intermediate of the general form L(Cl)$_2$Ru=CHPh, **4**. This intermediate can be trapped by free PCy$_3$ to regenerate the starting alkylidene or can bind substrate and undergo metathesis. As such, the activity of catalysts **1** and **2** is not only related to the phosphine dissociation rate k_1 [$k_1 = k_B = k_{obs}$ (saturation)], but also to the ratio of k_{-1} to k_2 which determines whether the catalyst binds olefin or returns to its resting state. An estimate of k_{-1}/k_2 in these systems can be obtained by applying the steady-state approximation to the proposed intermediate **4** (making the assumption that all of the steps following olefin binding are fast).[21] Under pseudo-first-order conditions in olefin, this approximation affords the relationship between $1/k_{obs}$ and [PCy$_3$]/[olefin] which is shown in eq 1.[19]

$$1/k_{obs} = k_{-1}[\mathrm{PCy_3}]/k_1k_2[\mathrm{olefin}] + 1/k_1 \qquad (1)$$

^{1}H NMR studies of the reaction of **1** and **2** with ethyl vinyl ether were utilized to determine $1/k_{obs}$ as a function of [PCy$_3$]/[olefin], and the data show an excellent linear correlation for both catalysts. As summarized in Table 2, the values obtained for k_1 (from the intercept of the linear curve fit) agree extremely well with those predicted by magnetization transfer experiments. This analysis provides values for the k_{-1}/k_2 ratio in catalysts **1** and **2** of 15 300 and 1.25, respectively. We believe that this difference of over 4 orders of magnitude is the reason that catalyst **2** exhibits dramatically increased olefin metathesis activity relative to **1**. While **2** does not initiate (lose phosphine) efficiently, a small amount of initiated 14-electron species is capable of cycling through multiple olefin metathesis reactions before it is deactivated by the rebinding of PCy$_3$. In contrast, catalyst **1** initiates relatively rapidly, but the rebinding of phosphine (k_{-1}[PCy$_3$]) is competitive with olefin coordination (k_2[olefin]) under typical reaction conditions. As such, the highly active 14-electron intermediate undergoes relatively few turnovers before being trapped by free PCy$_3$. Notably, the reaction of **1** and **2** with vinyl ether substrates is extremely fast and is expected to provide close to a lower limit for k_{-1}/k_2. However, we expect that the relative difference (approximately 4 orders of magnitude) between these values should be consistent across a range of olefinic substrates.

In summary, our mechanistic studies indicate that the initial substitution of phosphine for olefinic substrate in catalysts **1** and **2** proceeds in a dissociative fashion and involves a 14-electron intermediate. The high activity of the N-heterocyclic carbene-coordinated catalyst **2**, which had previously been attributed to its ability to promote phosphine dissociation (increasing k_1), instead appears to be due to its improved selectivity for binding π-acidic olefinic substrates in the presence of σ-donating free phosphine (decreasing k_{-1}/k_2). Further mechanistic investigations of catalysts with the general structure L(PR$_3$)(X)$_2$Ru=CHR^1 are currently underway to better understand the effect of the X, L, R, and R^1 ligands on the initiation rates of these catalyst systems.

Acknowledgment. We thank Dr. Ola Wendt and Dr. Jeffrey Yoder for assistance with magnetization transfer experiments. Dr. Adam Matzger, Dr. Jennifer Love, Annita Zhong, and Diego Benitez are acknowledged for helpful discussions. This research was supported by the NSF.

Supporting Information Available: Tables of rate constants, Eyring plots, and sample experimental data for both kinetics and phosphine exchange experiments (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA003582T

---

[17] The product Fischer carbene complexes do not undergo appreciable reaction with acyclic olefins under these conditions.

[18] The k_{obs} for the reaction of **2** with other vinyl ether substrates including 2,3-dihydrofuran and ethyl 1-propenyl ether is the same as that with ethyl vinyl ether [$(4.6 \pm 0.3) \times 10^{-4}$ s^{-1}] and remains so over a similar range of concentrations.

[19] Jordan, R. B. *Reaction Mechanisms of Inorganic and Organometallic Systems*; Oxford University Press: New York, 1998; pp 35–45.

[20] This catalytic cycle does not specify the geometry about the ruthenium center of the crucial catalytic intermediates. Investigations on this topic are underway. Benitez, D.; Grubbs, R. H. Unpublished results.

[21] We believe that this is a good assumption for catalyst **2**, since the Ru(IV) metallacycle is expected to be lowered in energy due to the electron donor abilities of the N-heterocyclic carbene ligand. However it may not be as good of an approximation in **1**. As such the value of k_{-1}/k_2 may be somewhat overestimated in this case since additional k_3 and k_{-2} terms are not included.