Conformational Analysis of Olefin−Carbene Ruthenium Metathesis Catalysts

Diego Benitez, Ekaterina Tkatchouk, and William A. Goddard III*

Materials and Process Simulation Center, Beckman Institute (139-74), Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

Summary: We settle a long-standing disagreement of DFT with experiment (both solution and gas phase) for the phosphine dissociation process in Grubbs metathesis catalysis. Our findings with the M06 functional provide further support to gas-phase experimental work, concluding that for the ring-closing metathesis of norbornene, the resting state is the alkylidene−olefin complex and the rate-determining step is the loss of norbornene as a ligand and generation of the 14-electron activated species. Comparing to recent solution NMR data on olefin−carbene Ru complexes relevant to olefin metathesis, we find that the M06 density functional leads to accurate predictions for the stability of conformers, ∼0.5 kcal/mol better than is found by B3LYP. Using this methodology, we suggest that Piers and co-workers observed the cis-dichloro "down" isomer exclusively following the ring opening of acenaphthalene.

Ruthenium-catalyzed olefin metathesis[1] has become a powerful tool for forming organic carbon−carbon double bonds, making it useful for synthetic challenges ranging from natural products[2] to novel polymeric architectures.[3] The nature of the general mechanism has been explored[4,5] experimentally in solution by variable-temperature NMR spectroscopy and in the gas phase by tandem ESI-MS,[6] leading to conclusive observations of intermediates presumed to be part of the catalytic pathway. The mechanism has also been studied[7] quantum mechanically (QM), with many reports of degenerate and nondegenerate metathesis reactions involving full and simplified models using density functional theory (DFT) and high-level ab initio QCISD(T) methods. However, the geometrical details and the relative stability of the intermediates and transition states remain under debate.[8]

We recently reported[7e] DFT studies using B3LYP and M06 functionals and concluded that the general mechanism involves only intermediates that retain the *trans*-dichloro Ru geometry. The M06 functional is a hybrid meta-GGA exchange-correlation functional[9] developed to include attractive medium-range (van der Waals or London dispersion) interactions. Truhlar and Zhao reported[10] that, using the M06-L (no Hartree−Fock exchange) functional, the relative ruthenium tricyclohexylphosphine (PCy_3) bond dissociation energies for both the first- and second-generation Grubbs catalysts were predicted with much higher accuracy than for B3LYP when compared to solution activation parameters measured by Grubbs and co-workers.[4] Chen et al. reported[11] also that M06-L predicted phosphine dissociation energies for Ru and Au complexes were in better agreement with gas-phase threshold collision-induced dissociation (T-CID) data than were B3LYP values. To resolve these issues, here we report validation for the new M06 functional.

There has been a longstanding question about the accuracy of DFT methods for predicting the bond dissociation energy of Ru phosphine in Grubbs catalysts.[10] We have extended the M06-L studies of Truhlar to the M06 level. Using M06 and the LACV3P++**(2f) small-core pseudopotential and basis set (see the Supporting Information for detailed computational methods), we find that the PCy_3 dissociation (Scheme 1) energy for the second-generation Grubbs catalyst is $\Delta H_{298} = 39.0$ kcal mol^{-1} ($\Delta G = 32.1$ kcal mol^{-1}) in the gas phase. Using the "0 K model",[12] we calculate $\Delta H = 37.1$ kcal mol^{-1}, in excellent agreement with the experimental collision-induced dissociation

---

* To whom correspondence should be addressed. E-mail: wag@wag.caltech.edu.

(1) (a) Hoveyda, A. H.; Zhugralin, A. R. *Nature (London)* **2007**, *450*, 243–251. (b) Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760–3765. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (d) Calderon, N. *Acc. Chem. Res.* **1972**, *5*, 127–132. (e) Michrowska, A.; Grela, K. *Pure Appl. Chem.* **2008**, *80*, 31–43. (f) Bieniek, M.; Michrowska, A.; Usanov, D. L.; Grela, K. *Chem. Eur. J.* **2008**, *14*, 806–818.

(2) (a) Nicolau, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527. (b) Furstner, A.; Nevado, C.; Waser, M.; Tremblay, M.; Chevrier, C.; Teply, F.; Aissa, C.; Moulin, E.; Muller, O. *J. Am. Chem. Soc.* **2007**, *129*, 9150–9161. (c) Becker, M. H.; Chua, P.; Downham, R.; Douglas, C. J.; Garg, N. K.; Hiebert, S.; Jaroch, S.; Matsuoka, R. T.; Middleton, J. A.; Ng, F. W.; Overman, L. E. *J. Am. Chem. Soc.* **2007**, *129*, 11987–12002.

(3) (a) Hadjichristidis, N.; Iatrou, H.; Pitsikalis, M.; Mays, J. *Prog. Polym. Sci.* **2006**, *31*, 1068–1132. (b) Bielawski, C. W.; Grubbs, R. H. *Prog. Polym. Sci.* **2007**, *32*, 1–29. (c) Bielawski, C. W.; Benitez, D.; Grubbs, R. H. *Science* **2002**, *297*, 2041–2044. (d) Carnes, M.; Buccella, D.; Decatur, J.; Steigerwald, M. L.; Nuckolls, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2982–2985.

(4) (a) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749–750. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554. (c) Booyens, S.; Roodt, A.; Wendt, O. F. *J. Organomet. Chem.* **2007**, *692*, 5508–5512.

(5) (a) Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2007**, *129*, 1698–1704. (b) Wenzel, A. G.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 16048–16049. (c) van der Eide, E. F.; Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2008**, *130*, 4485–4491.

(6) (a) Chen, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 2832–2847. (b) Adlhart, C.; Chen, P. *Helv. Chim. Acta* **2003**, *86*, 941–949.

(7) (a) Straub, B. F. *Adv. Synth. Catal.* **2007**, *349*, 204–214. (b) van Rensburg, W. J.; Steynberg, P. J.; Kirk, M. M.; Meyer, W. H.; Forman, G. S. *J. Organomet. Chem.* **2006**, *691*, 5312–5325. (c) Piacenza, M.; Hyla-Kryspin, I.; Grimme, S. *J. Comput. Chem.* **2007**, *28*, 2275–2285. (d) Vyboishchikov, S. F.; Bühl, M.; Thiel, W. *Chem. Eur. J.* **2002**, *8*, 3962–3975. (e) Benitez, D.; Tkatchouk, E.; Goddard, W. A., III. *Chem. Commun.* **2008**, 6194–6196.

(8) (a) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441–444. (b) Correa, A.; Cavallo, L. *J. Am. Chem. Soc.* **2006**, *128*, 13352–13353. (c) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225–3228.

(9) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157–167.

(10) Zhao, Y.; Truhlar, D. G. *Org. Lett.* **2007**, *9*, 1967–1970.

(11) (a) Torker, S.; Merki, D.; Chen, P. *J. Am. Chem. Soc.* **2008**, *130*, 4808–4814. (b) Fedorov, A.; Moret, M.-E.; Chen, P. *J. Am. Chem. Soc.* **2008**, *130*, 8880–8881.

(12) The "0 K model" is used, since the energy threshold corresponds to the formation of products with no internal energy. See: Dalleska, N. F.; Honma, K.; Armentrout, P. B. *J. Am. Chem. Soc.* **1993**, *115*, 12125–12131.


Scheme 1. Grubbs-II Tricyclohexylphosphine Dissociation Reaction

Scheme 2. Formation of Olefin−Carbene Complexes
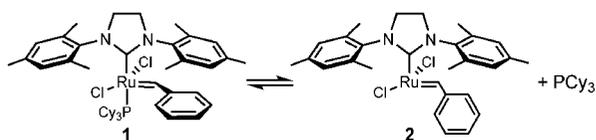
(T-CID) threshold energy of 36.9 ± 2.3 kcal mol^{-1} for a similar benzylidene complex reported by Chen and co-workers.[13] Applying the PBF Poisson−Boltzmann continuum solvation correction for toluene, we calculate $\Delta H = 35.7$ kcal mol^{-1}. However, Grubbs reported[4b] that, in toluene solution, the dissociative PCy$_3$ exchange activation energy is $\Delta H^{\ddagger} = 27$ kcal mol^{-1}. To test whether this discrepancy might be caused by the lack of a solvent molecule in the coordination site of our computational model, we included an explicit benzene molecule in the vacant site of the computational model. This leads to $\Delta H = 28.4$ kcal mol^{-1} ($\Delta G = 23.4$ kcal mol^{-1}) for PCy$_3$, remarkably close to the solution-phase experimental value ($\Delta H^{\ddagger} = 27 \pm 2$ kcal mol^{-1} and $\Delta G^{\ddagger} = 23 \pm 0.4$ kcal mol^{-1}) in toluene. These results validate that the M06 DFT leads to accurate dissocation energies for phosphine ligands for both solution and gas-phase conditions. In contrast, using the same methodology, B3LYP DFT leads to $\Delta H = 3.9$ kcal mol^{-1}. Including the full counterpoise correction (CP) for the basis set superposition error (BSSE) with a similar basis set reported[10] by Truhlar and co-workers of ~ 2 kcal mol^{-1}, M06 predicts $\Delta H = \sim 26.4$ kcal mol^{-1} and B3LYP $\Delta H = \sim 1.9$ kcal mol^{-1} compared to $\Delta H^{\ddagger} = 27 \pm 2$ kcal mol^{-1} from experiment.[4b]

To further validate the accuracy of the M06 functional, we calculated the gas-phase ring-opening metathesis (Figure 1) of norbornene with the Grubbs-II benzylidene to compare with the T-CID experiments of Chen and co-workers.[11a] Starting with the 14-electron complex (**2**) and unbound norbornene, the binding of the cyclic olefin (leading to **3**) is predicted to be $\Delta H = -18.2$ kcal mol^{-1}, in agreement with the gas-phase experimental binding value of "around 18.0 kcal mol^{-1} or perhaps slightly higher". We find that the reaction (Figure 1) proceeds via **TS$_{34}$** (-13.0 kcal mol^{-1}) leading to Ru metallacycle **4**, 8.6 kcal mol^{-1} more stable than coordinated norbornene structure **3**. The metallacycle cleaves productively via **TS$_{45}$** (-26.0 kcal mol^{-1}) to form the coordinated ring-opened product **5**, 28.5 kcal mol^{-1} lower in energy than the activated 14-electron Ru complex **2**. This compares reasonably well with the T-CID experimental energy[11a] of -33.4 kcal mol^{-1}, considering that the benzylidene used in the experiment was para-substituted by a benzyl phosphonium chloride. Our results support the findings and assumptions made by Torker et al. that the rate-limiting step
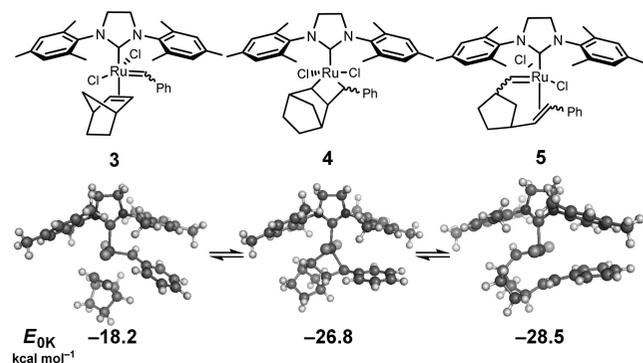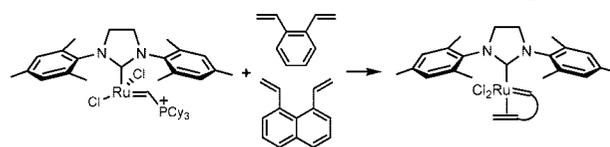
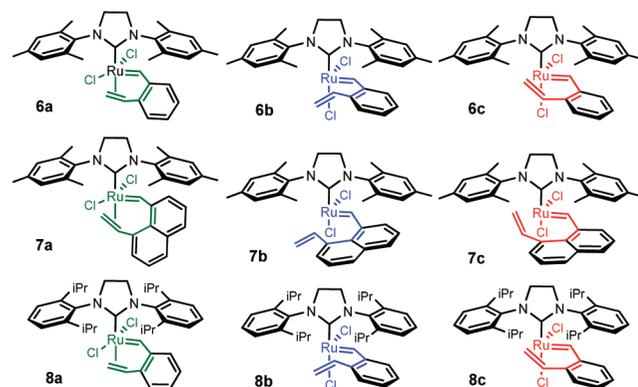for the ring-closing metathesis of norbornene is loss of co-ordinated norbornene.

M06 predicts a binding energy for ethylene of 16.9 kcal mol^{-1} in the gas phase at 0 K for Grubbs-II methylidene (1.3 kcal mol^{-1} weaker than for norbornene). In CH$_2$Cl$_2$, we calculate that ethylene binds exothermically by 13.5 kcal mol^{-1} (no explicit solvent) and by 9.5 kcal mol^{-1} for the CH$_2$Cl$_2$ solvento species. In order to mimic the conditions of high olefin concentrations, we used a second ethylene close to the vacant coordination site, which we found to be unbound by 0.5 kcal mol^{-1} (Ru−C = 1.8 Å), while the association of an explicit CH$_2$Cl$_2$ is only ~ 3 kcal mol^{-1} weaker (Ru−Cl = 3.1 Å). This suggests that binding to the empty coordination site trans to the alkylidene is unfavorable.

We reported[14] previously that B3LYP predicts accurately the energy of intermediates in the isomerization of *cis*- and *trans*-dichloro Ru complexes relevant to olefin metathesis. We extend here our previous studies to assess the accuracy of predicting the relative stability of *cis*- and *trans*-dichloro Ru complexes bearing chelating olefin−carbene ligands with the new M06 functional.

Grubbs et al. and Piers et al. studied[15] the reaction (Scheme 2) of metathesis initiators with bis-olefin substrates 1,2-divinylbenzene and acenaphthylene, yielding the olefin−carbene products **6−8**. The conformational equilibria of Ru metathesis catalysts **6−8** were studied using ^{1}H NMR spectroscopy, providing an excellent basis for validating the accuracy of our computational method. Figure 2 shows the *cis*- and *trans*-dichloro isomers of complexes with chelating olefin−carbene ligands we consider in this study.

Grubbs et al. studied[15a] the conformational equilibrium of the (H$_2$IMes)(Cl$_2$)Ru complex with 1,2-divinylbenzene as a chelating alkylidene−olefin ligand. They used ^{1}H NMR spectroscopy to determine that **6b,c** (Figure 2) are present in solution in a 40:60 ratio, while **6a** was not observed at 298 K. Our DFT calculations agree with experiment, since both B3LYP and M06 functionals predict (Table 1) that **6a** is present in minimal quantities (<0.05%) and that **6b,c** are are easily observable (ratios >10%). However, M06 and B3LYP disagree as to which is the major isomer. M06 predicts a 68:32 ratio, while B3LYP predicts 11:89 compared to the 40:60 ratio of **6b** to **6c** from

Figure 1. Ring-closing metathesis reaction of norbornene. Energy values are relative to **2**.

Figure 2. Isomers of olefin-coordinated Ru metathesis catalysts: (a) *trans*-dichloro; (b) *cis*-dichloro "down"; (c) *cis*-dichloro "up".

Table 1. Comparison for M06 and B3LYP Predicted Relative Free Energies[a] (kcal mol⁻¹) and Relative Abundances (%) for the Isomers of 6−8

	geometry/energy[a]						
	B3LYP/B3LYP		B3LYP/M06		M06-L/M06		
	energy	rel abund	energy	rel abund	energy	rel abund	expt rel abund
6a	4.49	∼0	7.65	∼0	7.52	∼0	N.O.[b]
6b	1.19	11	0.72	22	0.0	68	40
6c	0.0	89	0.0	78	0.44	32	60
7a	1.29	6	2.25	∼0	3.52	0.3	
7b	0.0	91	0.0	50	0.0	99.7	one major unknown
7c	1.65	3	0.0	50	3.79	∼0	product
8a	1.19	26	4.79	2	3.40	0.3	N.O.[b]
8b	3.30	5	4.41	3	1.85	4.2	3
8c	0.0	69	0.0	95	0.0	95.5	97

[a] $G_{TOT} = E_{SCF} + E_{SOLV} + E_{ZP} + H_{VIB} - TS_{VIB}$. [b] Not observed experimentally.

experiment. B3LYP predicts the correct major isomer but overestimates its stability by 0.95 kcal mol⁻¹, while M06 with the M06-L geometry predicts the wrong isomer but is only 0.68 kcal mol⁻¹ in error. Using M06 energies on B3LYP geometries leads to the correct isomer and an error of 0.48 kcal mol⁻¹. This suggests that the method introduced by Truhlar[10] and later used by us[7e] of using M06 energies with B3LYP optimized geometries is reasonably adequate for qualitative predictions. Here, we extended this methodology to M06-L geometries with M06 energies.

Piers et al. used[15b] NMR spectroscopy to conclude that ring opening of acenaphthalene leads to only a single product, with a yield greater than 90%. The ¹H NMR and ¹³C NMR resonances were consistent with a structure containing a Ru alkylidene with a coordinated vinyl group. The authors noted that in spite of the extensive NMR characterization, the geometry of the only observed isomer could not be determined.

We used both M06 and B3LYP DFT to predict the most stable isomer. Both functionals predict **7b** to be most stable,[16] followed by **7a** (+3.52 kcal mol⁻¹ for M06 and +1.29 kcal mol⁻¹ for B3LYP) and **7c** (+3.79 kcal mol⁻¹ for M06 and +1.65 kcal mol⁻¹ for B3LYP) in CD₂Cl₂ at 243 K. This suggests that under the experimental conditions (CD₂Cl₂ and 243 K) and at thermodynamic equilibrium, structure **7b** should be the only one observed. Since the NMR results were inconclusive as a consequence of conflicting information, we propose structure **7b** as the only isomer in solution.

We also investigated the effect that the bulkier diisopropyl-phenyl−NHC substituent (**8**) has on the accuracy of the M06 and B3LYP functionals. The increased bulk might favor the attractive dispersion forces present in M06 but not in the B3LYP functional. Experimentally **8b,c** are present in a 3:97 ratio, while **8a** was not detected by NMR in C₆D₆ at 298 K. B3LYP predicts that all three isomers should be observable by NMR spectroscopy at 298 K and a **8a**:**8b**:**8c** ratio of 26.4:4.8:68.8, while M06 predicts a ratio of 0.3:4.2:95.5 compared to experiment of ∼0: 3:97. As expected, the bulkier ligand does have a detrimental effect on the accuracy of B3LYP in predicting the relative stability for **8b,c**. In contrast, M06 predicts the relative stability of isomers of **8** with accuracy similar to that for the less bulky NHC ligand in **6** and **7**.

We find that, in polar solvents, the side-on structures are favored (compared to the gas phase) as a consequence of the higher dipole moment of the *cis*-dichloro geometry (as noted in ref 14); for example, in the gas phase, M06 predicts that **7a** is 5.2 kcal mol⁻¹ more stable than **7b** and 10.0 kcal mol⁻¹ more stable than **7c**.

In conclusion, our calculations suggest that the new M06 functional leads to improved accuracy over B3LYP (by ∼0.5 kcal mol⁻¹) for relative energies of various stable intermediates and much improved accuracy (by ∼23 kcal/mol) for PCy₃ binding. The use of B3LYP and M06-L optimized geometries with M06 electronic energies leads to reasonably accurate and practical descriptions of processes relevant to olefin metathesis. The M06 method in conjucntion with the PBF solvation methodology is also accurate for predicting relative energies of stable intermediates in CH₂Cl₂ and toluene solution. We recommend the use of an explicit solvent molecule at the vacant cordination site for calculations involving 14-electron activated Ru complexes in solution.

These results settle a longstanding disagreement of DFT with experiment (both solution and gas phase) for the phosphine dissociation process in Grubbs metathesis catalysis. Our findings with the M06 functional provide further support to the experimental work by Torker et al., concluding that for the ring-closing metathesis of norbornene in the gas phase, the resting state is the alkylidene−olefin complex **5** and the rate-determining step is the loss of norbornene as a ligand and generation of the 14-electron activated species.

Supporting Information Available: Text and tables giving detailed computational information. This material is available free of charge via the Internet at http://pubs.acs.org.

OM900041J

(13) Chen used a charged para-substituted benzylidene derivative of the Grubbs-II catalyst [(H₂IMes)(PCy₃)Cl₂Ru═CH(*p*-CH₂PCy₃)Ph]Cl as a charged analyte for the electrospray mass spectrometry experiments.[11a]

(14) Benitez, D.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2005**, *127*, 12218–12219.

(15) (a) Anderson, D. R.; Hickstein, D. D.; O'Leary, D. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 8386–8387. (b) van der Eide, E. F.; Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2008**, *130*, 4485–4491. (c) Anderson, D. R.; O'Leary, D. J.; Grubbs, R. H. *Chem. Eur. J.* **2008**, *25*, 7536–7544.

(16) M06 energies on B3LYP geometries predicted both *cis*-dichloro structures as the major species, which is not observed experimentally.