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What is the initiation step of the Grubbs-Hoveyda olefin metathesis catalyst?†

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Density function theory calculations reveal that the Grubbs-Hoveyda olefin metathesis pre-catalyst is activated by the formation of a complex in which the incoming alkene substrate and outgoing alkoxy ligand are both clearly associated with the ruthenium centre. The computed energies for reaction are in good agreement with the experimental values, reported here.

The ground-breaking advances in catalytic olefin metathesis by Grubbs and others have revolutionized many aspects of organic synthesis, ensuring a high general level of interest in the key metal alkylidene catalysts.¹ The mechanism of ruthenium-mediated olefin metathesis catalysed by first (**1a**) and second generation (**1b**) Grubbs complexes has been extensively studied both by experiment^{2,3} and by computational modelling.^{4,5} The rate constants for the initiation of the phosphane-containing catalysts are independent of the olefin concentration. The corresponding activation parameters for phosphane exchange have been measured and it is accepted that the initial dissociation of the phosphane ligand is the highest barrier on the potential energy surface.³ An important class of pre-catalyst in which both the phenyl group and the PCy₃ ligand are replaced by an iso-propoxystyrene (*e.g.* **1c**), and which displays excellent thermal stability and oxygen- and moisture-tolerance was synthesised by Hoveyda *et al.*^{6,7} There is much current interest in the initiation mechanism, because it is central to a detailed understanding of the catalytic activity. Indeed, the timing of the events around the metal centre is critical for a fundamental understanding of the interplay of structure and reactivity in alkene metathesis chemistry. Plenio and co-workers have studied the kinetics of the initiation step

using ethyl vinyl ether (EVE) as the substrate,⁸ which leads to catalytically inactive Fischer-type carbenes following a single olefin metathesis event,² and with diethyl diallylmalonate (DEDAM) which leads to a ring-closing metathesis (RCM) reaction. For both substrates the kinetics are complex, with the rate constants depending upon olefin concentration, suggesting that the olefin is involved in the rate determining step.⁸ The rates for the initiation reactions differ by only a factor of 4 (though highly electron deficient haloalkenes are less reactive by a factor of up to 10²), so that the reaction energetics are relatively insensitive to the structure of the substrate.⁸

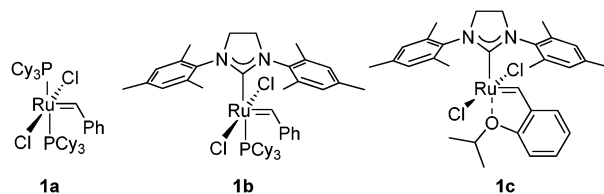
The initiation mechanism of the Grubbs-Hoveyda pre-catalysts is less well understood than those of Grubbs' first and second generation pre-catalysts. Three possible initiation mechanisms for the Grubbs-Hoveyda pre-catalyst termed dissociative, associative and interchange have been discussed in the literature.⁸ The simplest initiation mechanism (dissociative) involves rupture of the Ru–O(alkoxy) bond to create a vacant Ru binding site for the incoming olefin substrate. This behaviour resembles the mechanism favoured for the first and second generation Grubbs complexes, which is supported by evidence from computational and solution experimental studies.⁹ Alternative mechanisms involve the olefin itself. Thus we can envisage a mechanism in which the olefin forms a six-coordinate intermediate with the Ru complex (associative), or an interchange mechanism involving simultaneous olefin binding and alkoxy dissociation. No computational studies of the alternative initiation mechanisms have been reported, although a barrier in the range 17–25 kcal mol⁻¹ has been calculated for the dissociative step.¹⁰

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We present density functional theory (DFT) calculations of the initiation mechanism of the Grubbs-Hoveyda catalyst, focussing on both the alternative initiation steps, and the comparative energetics of the subsequent catalytic reaction. We have modelled these reaction steps for the catalyst (**1c**),

Table 1 Computed energies for reactions of ethene and EVE with **1c**

Mechanism	ΔH^\ddagger (kcal mol ⁻¹)	ΔS^\ddagger (cal mol ⁻¹ K ⁻¹)	ΔG^\ddagger (298.15 K) (kcal mol ⁻¹)
Dissociative	24.6	2.0	24.0
Associative	19.5	-7.2	21.6
Interchange ^a	13.9 (13.2)	-14.3 (-8.5)	18.2 (15.8)
Experiment ^b	nd (14.1 ± 1.2)	nd (-18.5 ± 5)	nd (19.6 ± 2.0)

^a Values for EVE in parentheses. ^b Determined at 283–303 K in DCM.

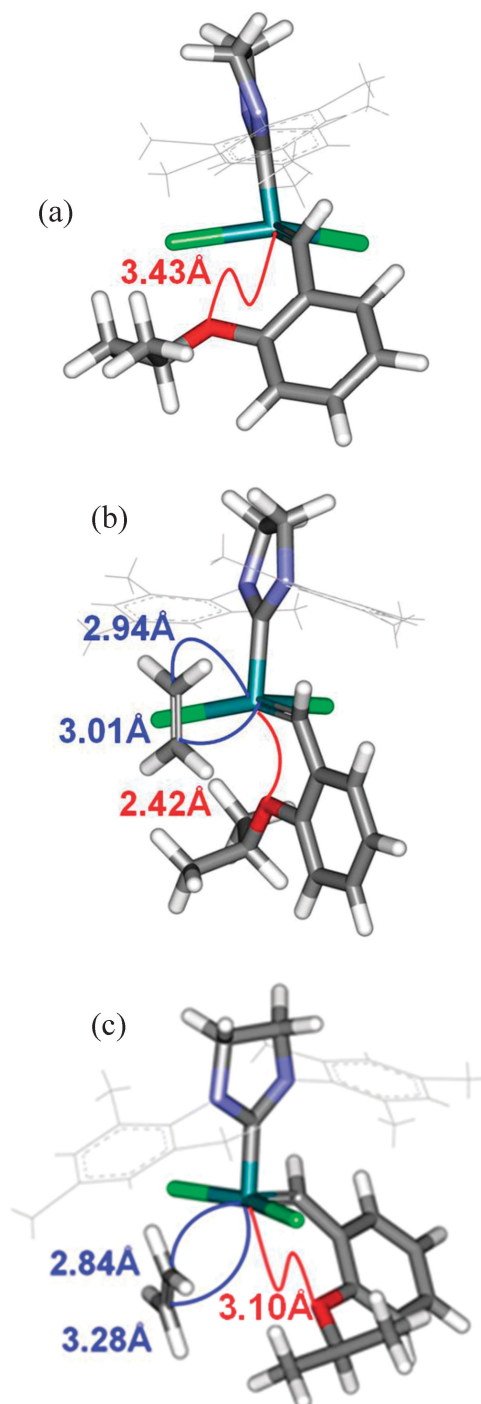
interacting with both ethene and EVE. We have employed the M06-L functional (implemented locally in Gaussian03¹¹) which unlike traditional functionals such as B3LYP, correctly describes the weak intermolecular interactions which may occur in these systems.^{12,13} We use a basis set, previously denoted B2⁵ which consists of the SDD ECP and corresponding basis on Ru, with additional *f*-functions, and with a 6-311G** basis on all other atoms. Solvation is included by the use of the Conductor-like Polarizable Continuum Model (C-PCM) with a dielectric of 8.93 (dichloromethane, DCM).¹¹ Details of the strategy used to locate transition structures (TS) are given in the ESI.

We have measured the second-order rate constants for the reaction between EVE and **1c** by UV-Vis spectrophotometry and derived activation parameters from an Arrhenius treatment (283–303 K).

In Table 1 we show our computed values for the enthalpy, entropy, and free energy of activation for **1c**. Both the enthalpy and free energy values include solvation at the C-PCM level, so that the free energy of solvation is included in the enthalpy values. However, the differential solvation energies are quite small at ~0.1 kcal mol⁻¹. The TS for the three possible initiation mechanisms involving ethene and **1c** which we have considered are shown in Fig. 1, with the corresponding coordinates being given in the ESI.

The TS for the dissociative mechanism (Fig. 1a), which does not involve ethene, is formed by rotation of the Ru–C bond by 36°, which lengthens the Ru–O distance from 2.32 Å in the reactant to 3.43 Å in the TS. The corresponding free energy barrier is 24.0 kcal mol⁻¹. The barrier for the associative mechanism involving the binding of ethene to form a six coordinate complex (Fig. 1b), is somewhat lower, at 21.6 kcal mol⁻¹. In the TS for this mechanism the Ru–O distance (2.42 Å) is changed by only 0.1 Å from the value in the reactant, but the approach of ethene has caused the Cl–Ru–Cl bond angle to decrease from 156° in the reactant to 111° in the TS, the distance of the Ru atom from the closest ethene carbon atom being 2.94 Å. The TS for the interchange pathway (Fig. 1c) involves an extension of the Ru–O distance to 3.10 Å, which allows the ethene to approach to a distance of 2.84 Å from the ruthenium atom, and has the smallest free energy barrier (18.2 kcal mol⁻¹) of the three mechanisms investigated. The closer approach of ethene in the TS on the interchange pathway is consistent with an higher degree of Lewis acidity at ruthenium caused by extensive scission of the Ru···O interaction.

We have also studied the interchange reaction involving EVE. The activation parameters (Table 1) are close to those for the ethene substrate, in line with the experimental finding that the actual initiation rates do not depend strongly on the details of the substrate (*vide supra*).⁸ The TS structures for

**Fig. 1** Transition structures for the (a) dissociative, (b) associative and (c) interchange mechanisms for the activation of **1c**.

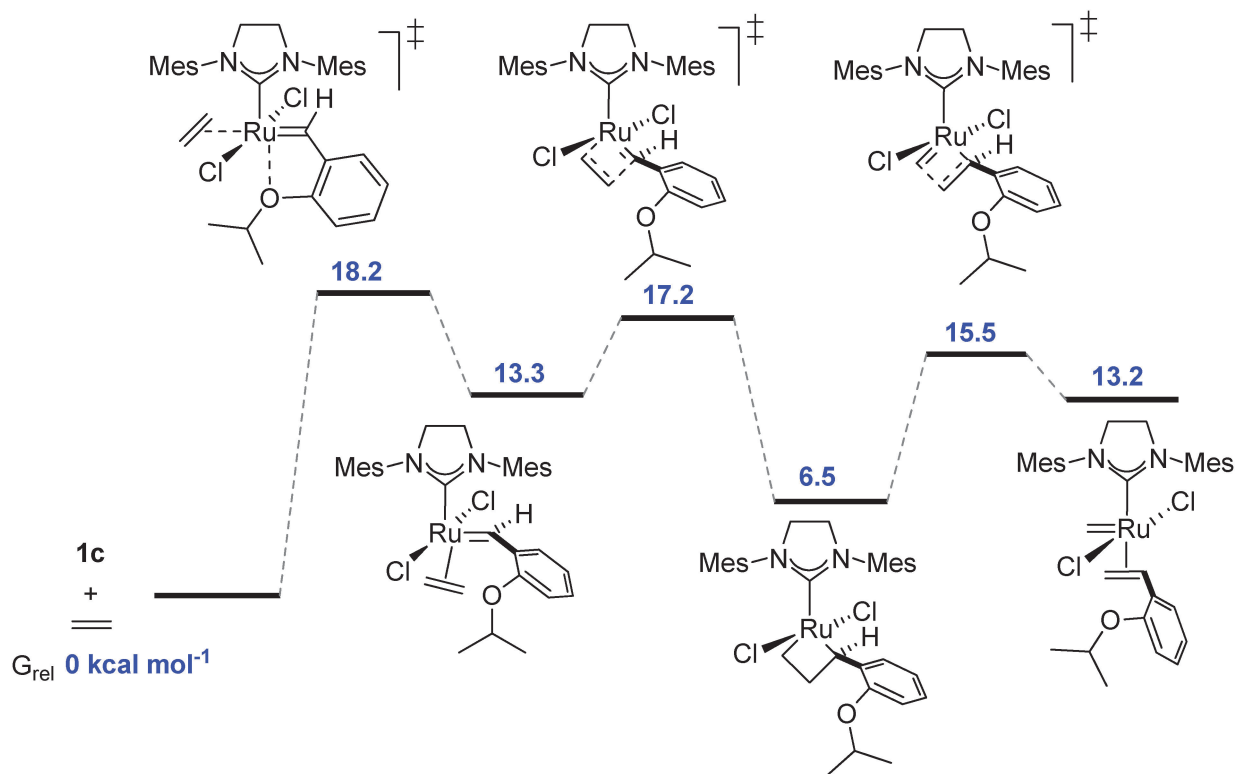


Fig. 2 Potential energy surface for the reaction of **1c** with ethene, showing free energies in kcal mol⁻¹.

both substrates are very similar, which is reflected in the closeness of the energies of the catalyst in the two TS, which differ by only 0.8 kcal mol⁻¹, in line with our prediction that ΔH^\ddagger for the two substrates differs by only 0.7 kcal mol⁻¹. The computed activation parameters are summarized in Table 1, and are also compared with the corresponding experimental values.¹⁴ As expected, the dissociative mechanism for **1c** has a positive entropy of activation, whilst for the associative and interchange mechanisms, there is a loss of entropy. Our computed activation enthalpy is very close to the value determined for **1c** and EVE, although the entropy of activation shows, not unexpectedly, a somewhat larger deviation.

For **1c**, we predict that the interchange mechanism is more favourable than the other two pathways studied. We have also computed the subsequent steps in the ethene metathesis reaction, following the formation of the η -complex by the interchange mechanism (Fig. 2). We find that the formation of the metallocycle intermediate proceeds *via* a low barrier, whilst the barrier for the final step, the formation of the styrene η -complex, is somewhat larger. However, the barrier for the initiation reaction *via* the interchange mechanism is higher than for either of these two subsequent steps, so that as in the second generation Grubbs pre-catalyst, we predict the rate determining step for the Grubbs-Hoveyda pre-catalyst to be the initiation step.

We have identified the initiation step in the Grubbs-Hoveyda metathesis pre-catalyst, shown it to be an interchange rather than a dissociative step, and to be the rate limiting step in the catalytic mechanism, and we have predicted values for the activation parameters in good agreement with experiment.

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