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Metathesis

The Key Role of the Nonchelating Conformation of the Benzylidene Ligand on the Formation and Initiation of Hoveyda–Grubbs Metathesis Catalysts

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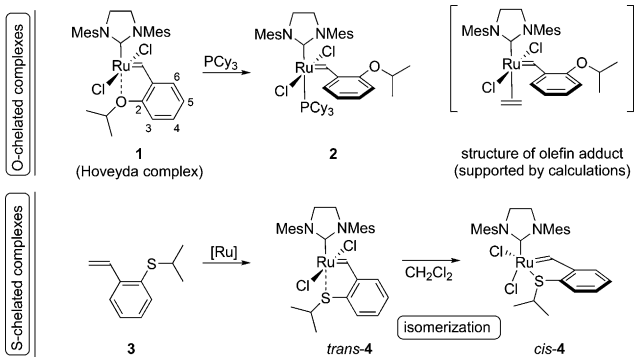
Abstract: Experimental studies of Hoveyda–Grubbs metathesis catalysts reveal important consequences of substitution at the 6-position of the chelating benzylidene ligand. The structural modification varies conformational preferences of the ligand that affects its exchange due to the interaction of the coordinating site with the ruthenium center. As a consequence, when typical S-chelated systems are formed as kinetic *trans*-Cl_2 products, for 6-substituted benzylidenes the preference is altered toward direct formation of thermodynamic *cis*-Cl_2 isomers. Activity data and reactions with tricyclohexylphosphine (PCy_3) support also a similar scenario for O-chelated complexes, which display fast *trans*-Cl_2⇄cis-Cl_2 equilibrium observed by NMR EXSY studies. The presented conformational model reveals that catalysts, which cannot adopt the optimal nonchelating conformation of benzylidene ligand, initiate through a high-energy associative mechanism.

Mechanistic studies play a dominant role in development of catalytic systems, and olefin metathesis is one of the main areas of the frontier research.[1] For the family of Hoveyda–Grubbs complexes (e.g., **1**), numerous studies that focused on the catalytic cycle[2] revealed the importance of the initiation step as a key process[3] responsible for release of active species, and involved in the bimolecular deactivation pathway.[4] In kinetic studies Plenio demonstrated that the initiation proceeds by dissociative (D) or interchange mechanism (I_a), depending on structure of the substrate and coordinating alkoxy group of the catalyst.[5] In both scenarios the chelate ring opens and olefin binds preferably in a *trans* position to the N-heterocyclic carbene (NHC).[6] Further insights were delivered by reaction of **1** with excess of PCy_3, in which pentavalent adduct **2** adopts a nonchelating conformation of benzylidene ligand (Scheme 1, top).[7] As supported by ab initio calculations, in a real catalytic cycle the system rearranges in a similar way, distancing the O*i*Pr coordinating site from the metal center; the so-formed



Scheme 1. Selected reactions of O- (top) and S-chelated (bottom) Hoveyda-type complexes.[7,9] Mes = 2,4,6-trimethylphenyl; Cy = cyclohexyl

olefin adduct evolves further into metallacyclobutane (MCB), starting the initial turnover of the metathesis reaction.[2b,8] Intriguingly, as the initiation process was studied in detail, much less is known about the formation of Hoveyda-type complexes. Important details of the mechanism delivers synthesis of sulfur-chelated analogs (e.g., **4**).[9] Replacement into the heavier coordinating heteroatom offers a unique opportunity to follow conformational changes of the systems, which usually form as kinetic *trans*-Cl_2 products, slowly isomerizing to the thermodynamic *cis*-Cl_2 structures (Scheme 1, bottom).[10] Recently, we observed that a S-chelating ligand with extended aromatic framework adjacent to the olefinic substituent favors direct formation of the *cis*-Cl_2 isomer.[9b] In the current report we explain the data by providing a concise mechanism based on conformational considerations of the chelating benzylidene ligand and its exchange in metathesis reactions. The presented model is validated by experimental studies of formation and initiation of S- and O-chelated Hoveyda–Grubbs complexes bearing substituted benzylidene ligands.

Our studies started from the preparation of S-chelating ligands with various groups attached at the 6-position of the benzylidene ring, to probe their ligand-exchange processes (R = H, SMe, OMe, Me; **5a–d**; Figure 1).[11] The substrates were subjected to the commercially available ruthenium precursor **6** (M2), and the reactions were analyzed using ^{1}H NMR spectroscopy (CD_2Cl_2, 40 °C). As expected, 2-(thiomethyl)styrene (**5a**; R = H) led to the formation of the initial product attributed to the kinetic *trans*-Cl_2 isomer with a resonance peak of benzylidene proton observed at 17.2 ppm, which slowly converted into another one detected at 17.0 ppm (*cis*-Cl_2).[12] In contrast, for substituted ligands **5b–d** (R ≠ H) one predominant product

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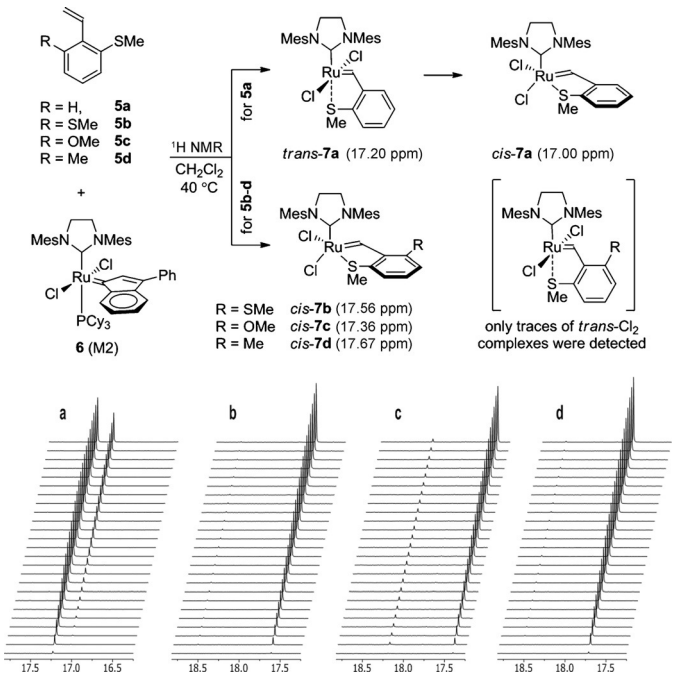


Figure 1. ^{1}H NMR studies of synthesis of complexes **7a–d**. The array experiments were conducted in CD_2Cl_2 at 40 °C, and the NMR acquisitions were repeated at 30 min intervals.[11]

was formed in each case, with only trace amounts of accompanying species. Analogously, in preparative experiments (CH_2Cl_2, 40 °C, 1 h) products **7b–d** were isolated in good yields, and characterized with NMR and X-ray studies as *cis*-Cl_2 isomers (Scheme 2). From the results we suspected that substitution of benzylidene ring in a position adjacent to the vinyl group influences mechanism of the ligand-exchange process. In a search for the missing *trans*-Cl_2 isomers complexes *cis*-**7b–d** were irradiated with UV light (366 nm), a technique used earlier for *cis*-to-*trans*-Cl_2 isomerizations.[9a] In the mixtures we detected formation of small amounts of products (expectedly *trans*-Cl_2 isomers), which remained stable under ambient conditions and only slowly decayed, as detected by ^{1}H NMR.[11] Importantly, chemical shifts of the minor forms were consistent with traces of accompanying species observed in previous NMR experiments (cf. Figure 1). In the next step the preparative experiments were repeated in toluene, which favors formation of kinetic *trans*-Cl_2 isomers of S-chelated systems.[10a] Interestingly, a reaction of ligand **5a** afforded complex *trans*-**7a**, isolated in 64% yield, whereas ligands **5b–d** displayed essentially no conversion under the same conditions (toluene, 40 °C, 16 h).[11] Attempts at forcing the processes at 80 °C overcame the inhibitory effect, but again formation of *cis*-Cl_2 products was observed, and only for ligand **5c** we isolated a small amount of product characterized with NMR and X-ray studies as *trans*-Cl_2 complex **7c** (11%).

Although all synthesized complexes *cis*-**7a–d** displayed very little activity in model metathesis reactions,[11] more pronounced differences between catalysts were observed for *trans*-Cl_2 isomers of **7a** and **7c** (Figure 2, left).

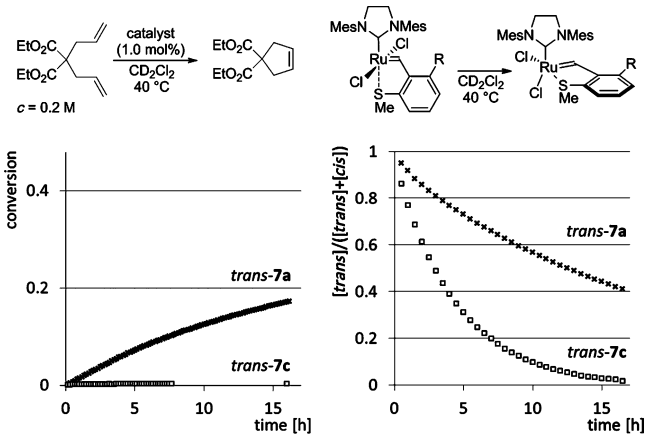
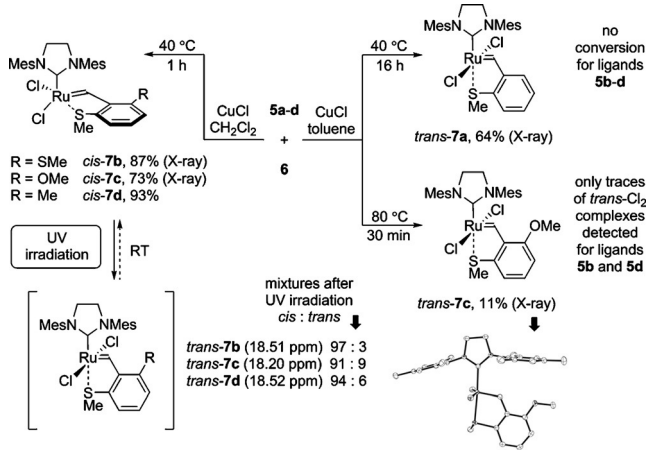


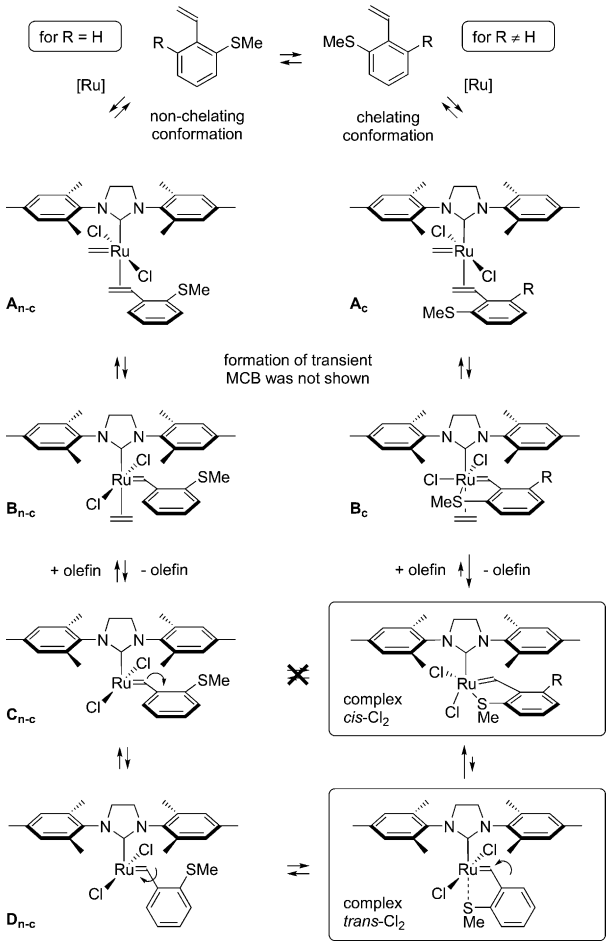
Figure 2. Activity profiles of 1.0 mol% of catalysts *trans*-**7a,c** in ring closing metathesis (RCM) of diethyl diallylmalonate (DEDAM; $c = 0.2$ M; left), and isomerization studies of the complexes detected by ^{1}H NMR (right).[11]

Complex *trans*-**7a** was moderately active, while *trans*-**7c** remained inactive at 40 °C. Moreover, NMR studies revealed that *trans*-**7c** isomerizes faster than *trans*-**7a** ($t_{1/2} = 13$ h and 3 h for **7a** and **7c**, respectively; Figure 2, right), but the difference is rather small, and thus cannot rationalize the observed lack of activity of *trans*-**7c** by fast isomerization to the latent *cis*-Cl_2 form. For the same reason, it is unlikely that in NMR and preparative experiments performed in CD_2Cl_2 (cf. Figure 1 and Scheme 2) complex *cis*-**7c** was formed by isomerization of the transient *trans*-**7c**. A more plausible mechanism should involve an alternative direct pathway to the *cis*-Cl_2 form.

On the basis of the presented data we considered the process of formation of S-chelated complexes, following a generally accepted mechanism of metathesis reaction,[2b,8] with the exchanged olefin coordinated in a *trans* position to the NHC.[6] The structure of the benzylidene ligand approaching the ruthenium center was considered in two conformations: nonchelating (n-c) and chelating (c), and the two conformations led further to parallel pathways of the ligand exchange process, as presented in Scheme 3. In a less-hindered nonchelating confor-

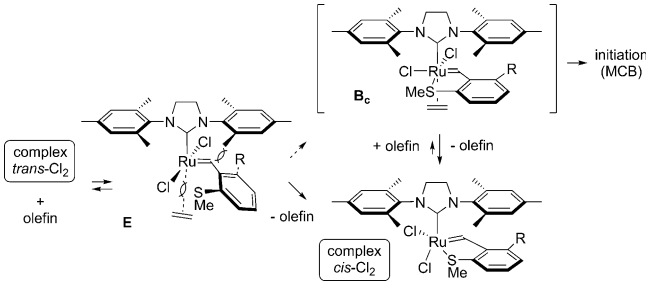


Scheme 2. Preparative syntheses of complexes **7a–d**, and results of UV irradiation experiments.[11]



Scheme 3. Proposed mechanism of formation of S-chelated Hoveyda-type complexes. Typical benzylidene ligands are exchanged in a nonchelating conformation giving kinetic *trans*-Cl_2 products (left path), whereas ligands substituted at the 6-position prefer a chelating conformation and, therefore, thermodynamic *cis*-Cl_2 isomers are formed directly (right path). Geometries of the structures and their interconversion trajectories are idealized to emphasize key conformational changes.

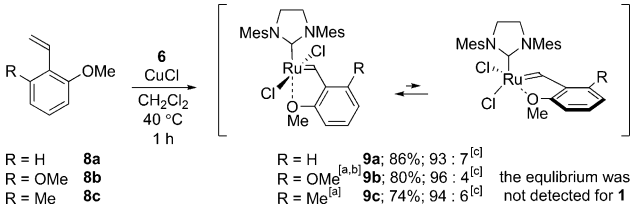
mation (available for **5a**; R = H), where interaction between the SMe coordinating site and the metal center is reduced, the olefin acts virtually as a monodentate ligand on steps $\mathbf{A_{n\text{-}c}} \rightarrow \mathbf{B_{n\text{-}c}} \rightarrow \mathbf{C_{n\text{-}c}}$. However, a close parallel orientation of NHC and benzylidene aromatic rings in $\mathbf{C_{n\text{-}c}}$ prevents a direct rotation around the $=C-C_{Ar}$ bond, and thus a rotation around the Ru=C bond leads to an intermediate $\mathbf{D_{n\text{-}c}}$, which then cyclizes to complex *trans*-Cl_2. The mechanism agrees well with the observed kinetic formation of *trans*-Cl_2 isomer of **7a**, and syntheses of similar S-chelated complexes described in the literature.[9b,10a] In contrast, for ligands substituted at the 6-position of the benzylidene ring (**5b-d**; R ≠ H) an alternative mechanism operates. Accordingly, when the chelating conformation prevails in the exchange process, the SMe coordination site of the chelating ligand begins to interact with the ruthenium center in the initial steps, giving a transient structure $\mathbf{B_c}$,[13] which decoordinates olefin directly to complex *cis*-Cl_2. As ligand **5a** (R = H) forms a kinetic *trans*-Cl_2 product, and the direct formation of *cis*-Cl_2 isomers is observed only for **5b–d** (R ≠ H), it becomes apparent that the first pathway, realized by a nonchelating conformation, is more energetically preferred. Interestingly, when considering initiation of complexes *trans*-**7a** and *trans*-**7c** the same two mechanisms remain valid. For unsubstituted catalyst **7a** (independent of olefin participation in the chelate opening) steps *trans*-**7a** $\rightarrow \mathbf{D_{n\text{-}c}} \rightarrow \mathbf{C_{n\text{-}c}}$ lead to an adduct $\mathbf{B_{n\text{-}c}}$, following a mechanism of initiation of O-chelated catalysts (cf. Scheme 1, top).[2b,7,8] In turn, opening of the chelate and coordination of the olefin in *trans*-**7c** (R = OMe) leads to an intermediate **E**, which may enter the metathesis cycle only by a rotation around the Ru=C bond, and recoordination of the SMe group[14] (Scheme 4).



Scheme 4. Proposed mechanism of initiation of 6-substituted *trans*- and *cis*-Cl_2 complexes (R ≠ H).

Therefore, instead of initiation by a six-coordinated structure $\mathbf{B_c}$, olefin may dissociate with the formation of *cis*-Cl_2 isomer, and thus no appreciable progress of the metathesis reaction is observed. An important consequence of this reasoning is a demand for an associative mechanism of initiation, when the nonchelating conformation of benzylidene ligand is inaccessible. This may be the case for 6-substituted benzylidenes discussed here, or complexes for which *cis*⇄*trans*-Cl_2 equilibrium is strongly shifted to the left.[9b,10a,15] Moreover, as in the dissociative and interchange mechanism, a nonchelating conformation enables a stepwise decoordination of the ligand with opening of the chelate ring separated from the metathesis cycle; in the associative mechanism, a simultaneous breaking of the Ru···heteroatom bond is required, making the process difficult.[13]

To further verify the idea we synthesized a set of O-chelated complexes **9a–c** (Scheme 5). Activity data of the catalysts were very similar to their S-chelated counterparts (Figure 3). As expected, complex **9a** (R = H) was active under ambient conditions, whereas substituted derivatives **9b** and **9c** (R ≠ H) remained intact, and required elevated temperature to initiate



Scheme 5. Syntheses of O-chelated complexes **9a–c**, and their *trans*⇄*cis*-Cl_2 equilibria detected with ^1H NMR EXSY at 80 °C.[11] [a] A longer reaction time (4.5 h) was required to complete conversion of **6**; [b] the structure of complex **9b** was confirmed with X-ray studies; [c] contents of the isomers observed in CD_2Cl_2 at RT by ^1H NMR.

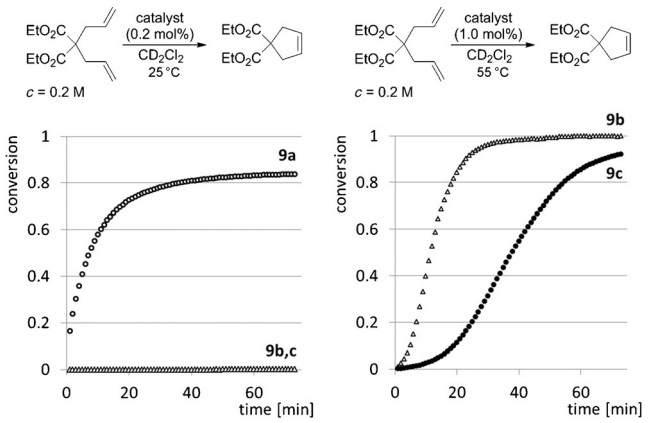


Figure 3. Activity profiles of complexes **9a**–**c** in RCM of DEDAM in 0.2 M solutions detected by ^{1}H NMR. The catalysts were tested at 0.2 mol% at 25 °C (left), and 1.0 mol% at 55 °C (in sealed tubes; right).[11]

(55 °C). Similar differences were observed also in reactions of the complexes with excess of PCy_3. As observed by ^{1}H NMR measurements, unsubstituted complex **9a** easily transformed into adduct, similar to **2** (cf. Scheme 1), whereas under the same conditions **9b** and **9c** did not react, suggesting pronounced difficulties for formation of 6-coordinated structures.[11] Interestingly, in contrast to properties of **1**, the OMe-chelated complexes existed in two forms in CD_2Cl_2 at RT, and displayed equilibria observed with NMR EXSY studies at higher temperatures. On the base of literature data[16] we assigned the dynamic process to the fast *trans*⇔*cis*-Cl_2 isomerization in solution.[9b,10,17] In this case the substitution of benzylidene ring had only a limited effect on contents of the individual forms, slightly destabilizing the minor *cis*-Cl_2 isomers for complexes **9b** and **9c** (R≠H).

In conclusion, we have presented a conformational model, which describes an exchange process of chelating benzylidene ligand in Hoveyda–Grubbs metathesis catalysts. Accordingly, the formation of S-chelated complexes proceeds through a nonchelating conformation, which minimizes interaction of the SMe coordinating site with the ruthenium center, giving kinetic *trans*-Cl_2 isomers. However, substitution at the 6-position of the benzylidene ring varies the preference toward a chelating conformation and, as a consequence, the complexes form directly as *cis*-Cl_2 structures. The differences concern also a reverse process of catalyst initiation. The nonchelating conformation of benzylidene ligand enables its stepwise decoordination by opening of the chelate ring followed by a metathesis cycle. However, when the conformation is not available, an associative mechanism operates, requiring formation of six-coordinated intermediate, and breaking of the Ru···heteroatom bond in the course of the metathesis cycle.

Experimental Section

CCDC 1044950, 1044951, 1044952, 1055099, and 1055105 (*cis*-**7b**, **9b**, *cis*-**7c**, *trans*-**7a**, and *trans*-**7c**, respectively) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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Keywords: conformers · isomerization · mechanistic studies · metathesis · NMR spectroscopy

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