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Computational Modeling of Renewable Molecules. Ruthenium Alkylidene-Mediated Metathesis of Trialkyl-Substituted Olefins

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The metathesis reaction of (*Z*)-3-methyl-2-pentene (**2**) mediated by the first- and second-generation Grubbs catalysts has been studied at the PBE0/LACV3P**// PBE0/LACVP* level of theory using 1,2-dichloroethane as a solvent. Calculations established direct correlation between the activation energy of the metathesis and the number of substituents at the double bond of an olefin. The relative stabilities of secondary and tertiary metallacarbenes depend on the interplay between steric and electronic factors. Thus, for the first-generation Grubbs catalyst the contribution of steric factor dominates, while for the second-generation Grubbs catalyst both the stabilizing electronic factors and the destabilizing steric effects are equally important. Secondary metallacarbene was found to be more active in the metathesis reaction due to less sterically hindered transition states, and therefore, secondary metallacarbene **8b** is the principal reactive intermediate in the reaction under kinetic control. The higher activity of the second-generation Grubbs catalyst was confirmed, which is reflected in lower activation energies of the metathesis for the latter. Calculations also demonstrated the low stereoselectivity of Ru-alkylidene catalysts in the metathesis reaction of trialkyl-substituted olefins.

Introduction

Trisubstituted olefins are essential components of many biobased products. Thus, various plant *cis*−*trans* (*Z*,*E*)-polyprenols and dolichols,[1] tocotrienols,[2] vitamin K_1,[3] and natural rubber[4] are some of the examples of trisubstituted olefinic carbon−carbon bond containing compounds. Trialkyl-substituted olefins are also very important key intermediates for the synthesis of many natural products, in particular for the preparation of vitamin E molecules. It is worth noting that the metathesis of these molecules is challenging[5] due to the presence of an alkyl group directly linked to the double bond, which can impede the coordination with a metal active center. Thus, relatively few reports exist on the metathesis reaction of natural rubber (NR) or *cis*-1,4-polyisoprene (*cis*-PI).[6−12] This may be explained by the fact that NR is very sensitive to the side reactions,[7] and this polymer, with trisubstituted unsaturations, degraded much slower than *cis*-polybutadiene and other polyalkenamers with disubstituted unsaturations.[9] The authors[9a] reported that *cis*-PI degradation occurs very slowly using the classical tungsten-based catalyst. Hence, sterically hindered substrates require highly stable and selective metathesis catalysts. The development of highly active Ru-alkylidene catalysts opens vast new possibilities in olefin metathesis and their application to controlled synthesis of desired products.[13]

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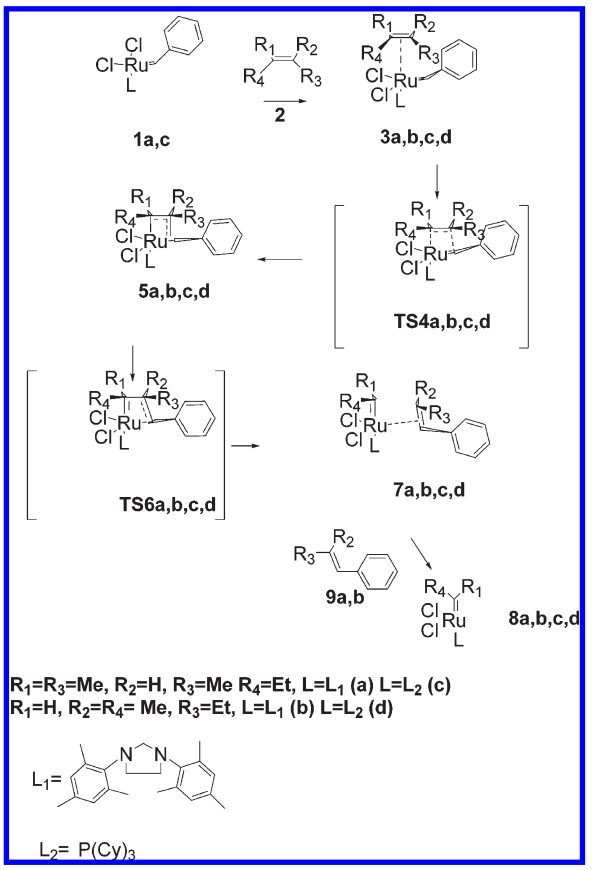
Thus, cross-metathesis of 2-methyl-2-butene using highly active ruthenium alkylidene catalysts containing an N-heterocyclic carbene ligand[14,15] converts a vinyl group to a dimethylethenyl group in the synthesis of several natural products, ring-opening metathesis polymerization transforms trisubstituted *cis,cis*-1,5-dimethyl-1,5-cyclooctadiene to polyisoprene, and cross-metathesis degradation of isoprene-containing copolymers gave oligomers.

Metathesis of trisubstituted olefins, in general, proceeded with poor *cis*−*trans* (*Z*,*E*) selectivities.[5,16−18] The computational modeling also demonstrates that the low stereoselectivity of olefin metathesis is due to close activation energies for the *cis* and *trans* isomer formation and the fast *cis*−*trans* isomerization caused by the catalyst.[19a] Numerous experiments demonstrated that the metathesis reaction is accompanied by the *cis*−*trans* isomerization, reaching, in general, the equilibrium state.[20]

Recently, it has been demonstrated that computational modeling can be used as a powerful tool in the elucidation of the reaction mechanism[21] and in the reactivity prediction of many challenging olefins.[22] Various theoretical aspects of ruthenium-mediated olefin catalysis have been touched on.[23] However, little attention has been paid to the peculiarities of the metathesis mechanism of highly substituted biobased molecules.

The goal of this study is the computational modeling of ruthenium-mediated metathesis of biobased molecules using (*Z*)-3-methyl-2-pentene (**2**) as a model compound. Nowadays, the dissociative mechanism is widely accepted for the olefin metathesis. It starts with the dissociation of one phosphane ligand to form a tetracoordinated 14-electron complex. The most recent investigations[24] clearly favor the dissociative path. The tetracoordinated 14-electron intermediates were unambiguously identified for both Grubbs-type catalysts with a cationized phosphane ligand.[25] Therefore, a dissociative mechanism for the olefin metathesis was assumed in the current study.

Scheme 1. Initiation Step of 2 Metathesis by the First- and the Second-Generation Grubbs Catalyst



Computational Details

All calculations were carried out using Gaussian 03 Revision E.01 suit of programs.[26] Test calculations were carried out to establish the most appropriate theoretical model. Three different functionals, B3LYP, M05, and PBE0, were tested to compare the optimized and experimental structures of recently synthesized ruthenium-alkylidene complexes[27] using double- and triple-ζ quality basis sets: LACVP* (pseudopotential LANL2DZ basis set for Ru[28] and 6-31G* for other elements) and LACV3P* (triple-ζ contraction of the LACVP basis set for Ru[29]) and the 6-311G* all-electron basis set for other elements,

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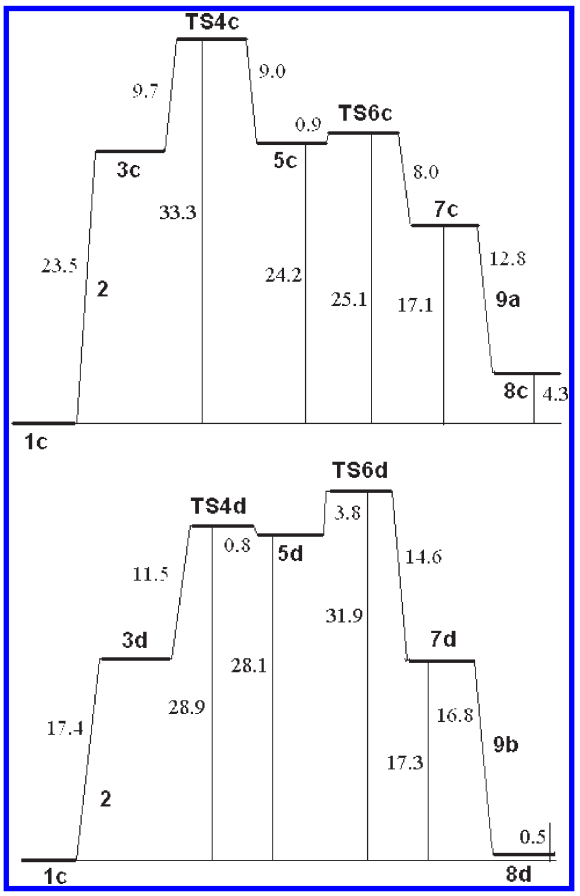

Figure 1. Gibbs free energy profile (kcal/mol) of **2** metathesis by the first-generation Grubbs catalyst.

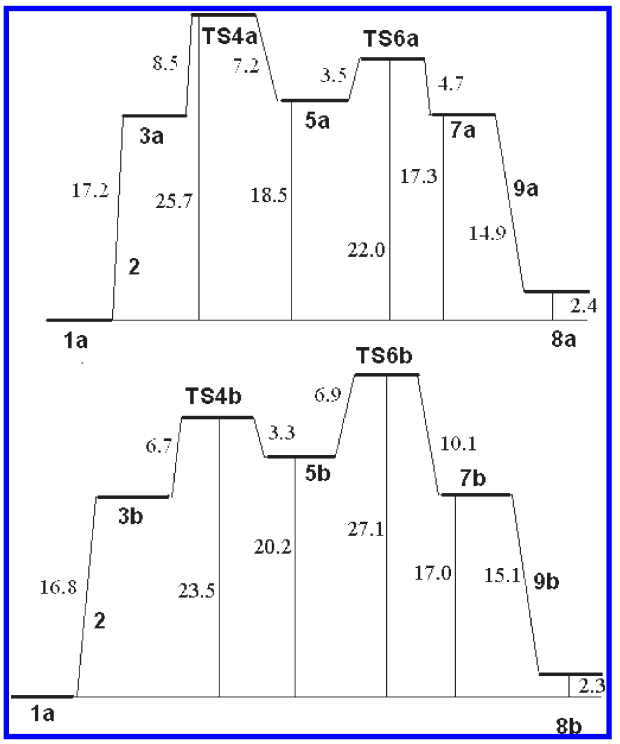

Figure 2. Gibbs free energy profile (kcal/mol) of **2** metathesis by the second-generation Grubbs catalyst.

respectively. Test calculations demonstrated that PBE0 reproduced best the experimental geometry (the largest deviation from experiment was found to be around 0.04 Å for Ru−Cl and Ru−P bonds for the LACVP* basis set). The use of the LACV3P* basis set does not lead to substantial improvement of optimized geometries. Thus, the bond length differences between LACV3P* and LACVP* optimized geometries do not exceed 0.005 Å for the PBE0 functional. Considering the fact that the PBE0/LACV3P*//PBE0/LACVP* model reproduces very well the experimental enthalpy of the phosphine ligand dissociation in $(IMesH_2)(PCy_3)Cl_2Ru{=}CHPh$ (23.8 (theory) and 25 ± 4 kcal/mol (experiment), respectively[24b]), this model was adopted for all calculations.

Although the reaction energies are barely affected by solvation,[22d] this is not the case for activation energies. Our test calculations reveal that taking into account solvation effects increases the Gibbs free activation energy by 3−5 kcal/mol. The origin of this phenomenon is that in the transition states each part of the catalytic system is solvated only from the one side, while in the reactants two separated molecules are completely solvated.

To take into account solvation, single-point energy calculations were carried out at PBE0/LACVP* optimized geometries using the LACV3P* basis set and dichloroethane as a solvent using the PCM solvation model. The molecular cavity was defined using the united atom topological model applied on radii optimized for the PBE0/6-31G* level of theory (radii = uaks keyword).

The total Gibbs energies (G) in solution of all molecules were calculated as follows: $G = E_t + \Delta G$, where E_t is the total electronic energy in solution calculated at the PBE0/LACV3P* level using the PBE0/LACVP* gas phase optimized geometry, and ΔG is the Gibbs energy correction calculated as the difference between the total electronic energy and the Gibbs energy estimated at the PBE0/LACVP* level using the PBE0/LACVP* optimized geometry in the gas phase.

Frequency calculations at 298.15 K were run for all structures to make sure that a transition state (one imaginary mode) or a minimum (zero imaginary modes) is located and to estimate zero-point energy correction and thermodynamic properties.

Results and Discussion

First- and the Second-Generation Grubbs Catalysts Comparison. Scheme 1 shows the metathesis of **2** mediated by the first-generation Grubbs catalyst. Figure 1 depicts the corresponding Gibbs free energy profiles. There are two possible orientations of **2** in the catalytic complex, leading to two different products and two different metallacarbenes, secondary (**8d**) and tertiary (**8c**). As seen from the reaction energy profile, the formation of secondary metallacarbene **8d** is slightly favored both thermodynamically and kinetically compared to **8c**; the Gibbs free reaction energies for the formation of **8c** and **8d** are 4.3 and 0.5 kcal/mol, respectively, and the effective Gibbs free activation energies (the difference between the lowest and highest points on the energy profiles) are 33.3 and 31.9 kcal/mol, respectively.

Generally, the stability of metallacarbenes increases from primary to secondary.[19a] It is expected that the tertiary metallacarbene should be more stable than the secondary one. However, our calculations demonstrated that the tertiary carbene is less stable compared to the secondary one due to additional steric hindrance caused by bulky substituents. Thus, the Gibbs free reaction energy in the gas phase

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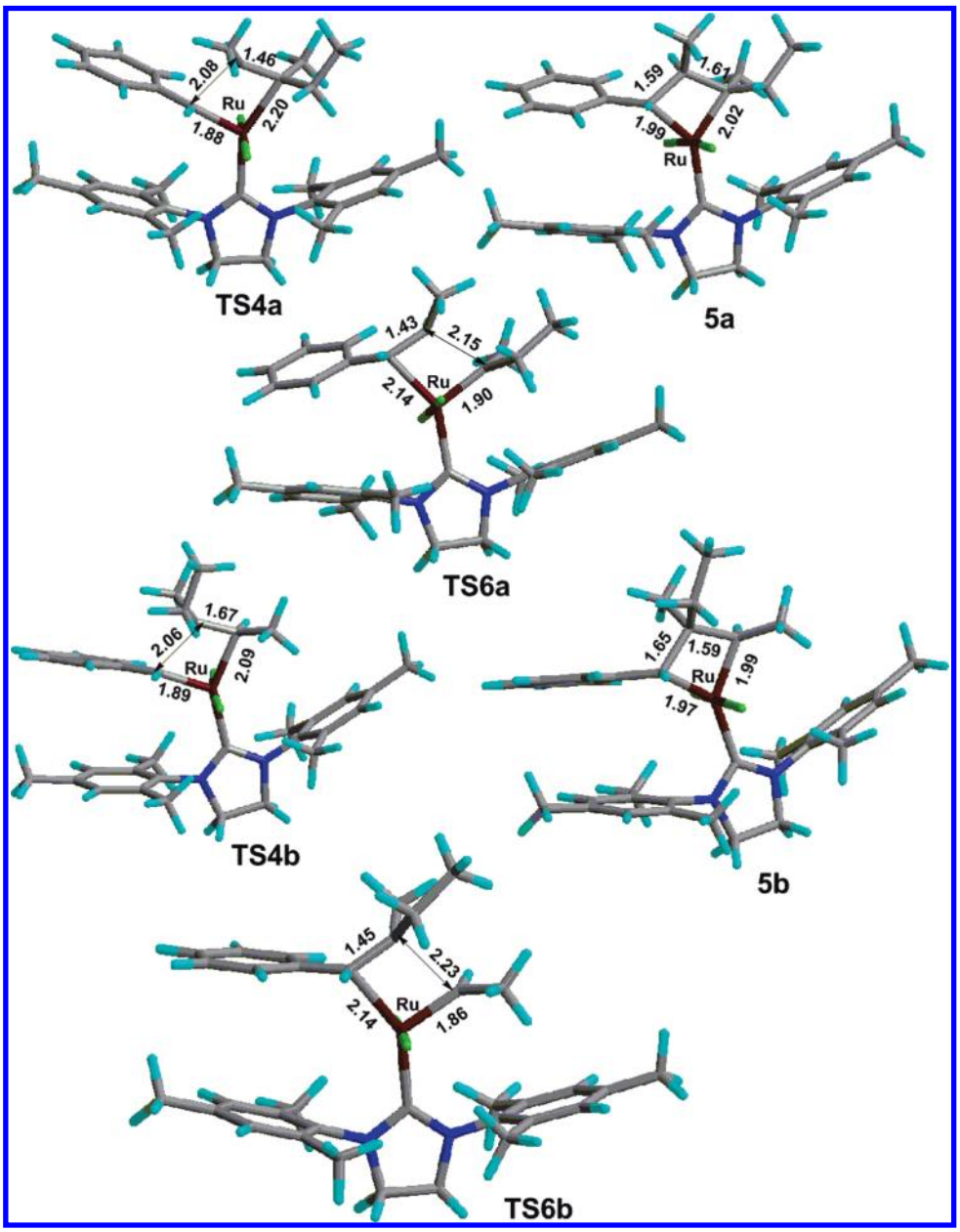


Figure 3. Optimized geometries of **2** metathesis intermediates by a second-generation Grubbs catalyst.

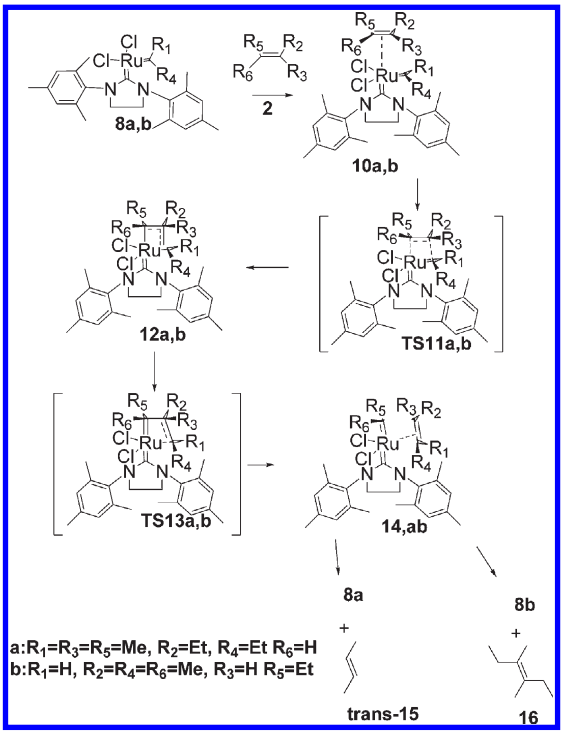
of the model reaction where ethyl group in **2** is replaced by methyl is reduced by 0.8 kcal/mol, suggesting that the more positive Gibbs free energy for the formation of tertiary metallacarbene **8c** is related to steric hindrance caused by bulky substituents at the carbene atoms. The contribution of steric factors is seen comparing angles $C_{carbene}$−Ru−P in **8c** and **8d** (105.6° and 97.5°, respectively), reflecting a higher steric effect for **8c**.

Apart from steric hindrance, electronic factors play an important role in the relative stability of metallacarbenes too. Thus, it has been found[19b] that the stability of a metallacarbene decreases with charge at a metal center. For **8c** and **8d** the Mulliken charges at Ru atoms are +0.15 and +0.25, respectively. Therefore, the tertiary carbene stabilizes the Ru center electronically, but destabilizes it sterically.

Scheme 1 and Figure 2 show the metathesis of olefin **2** mediated by the second-generation Grubbs catalyst. It is seen that the absolute activation energies are notoriously lower for the second-generation catalyst. Thus, the effective activation energies for the formation of two different products are 25.7 and 27.1 kcal/mol, respectively. These data confirm the known experimental fact that the activity of a second-generation catalyst is higher compared to the first-generation one.[14] It is generally accepted that the activity of a reactive intermediate decreases with its stability. Since the stability of metallacarbenes decreases with the charge at a Ru center,[19b] one can relate the reactivity of a metallacarbene with the charge at the Ru atom. Thus, the Mulliken charges at Ru atoms of **8c**, **8d**, **8a**, and **8b** are +0.15, +0.25, +0.40, and +0.55, respectively, revealing that metallacarbene active centers of the second-generation Grubbs catalysts are more active compared to those of the first generation. On the other hand, secondary metallacarbenes **8d** and **8b** are more active compared to tertiary ones.

Unlike the first-generation catalysts, the stability difference of tertiary **8a** and secondary **8b** metallacarbenes for the

Scheme 2. Metathesis of 2 Mediated by Metallacarbenes 8a and 8b



second-generation catalyst is minimal (ΔG = 2.4 and 2.3 kcal/mol, respectively). Since the $IMesH_2$ ligand is less bulky compared to PCy_3, the steric factor is less important for the second-generation catalysts, and the destabilizing steric factor only slightly overperforms the stabilizing electronic factor in **8a**. Therefore, the stability and the rate of the formation for tertiary metallacarbene **8a** and secondary **8b** are very close. Similar to **8c** and **8d** the steric hindrances in metallacarbenes **8a** and **8b** are reflected by their geometry. Thus, the $C_{carbene}-Ru-C_{ligand}$ angle increases from 104.1° for **8b** to 116.2 for **8a**, due to the repulsion between a methyl group of the carbene and a mesityl group of the ligand, indicating stronger steric hindrance for the latter.

Figure 3 shows optimized geometries of transition states and metallacyclobutane intermediates for **2** metathesis mediated by a second-generation Grubbs catalyst. As can be noted from Figure 3, the stronger steric hindrances in the formation of **8b** are manifested by the longer C−C bond in metallacyclobutane intermediate **5b**, achieving 1.65 Å.

Self-Metathesis of 2 Mediated by Ruthenium Complexes 8a and 8b. The reaction route shown in Scheme 1 is an initiation step. Once formed, metallacarbenes **8a** and **8b** can participate in the metathesis reaction with olefin **2**. Each of the metallacarbenes can produce two different products depending on the orientation of the olefin at the active site. As a result, one of the products for each metallacarbene is always the same olefin **2**. Therefore, only the reaction route of nondegenerative metathesis will be considered. Scheme 2 shows these reaction routes, and Figure 4 depicts the corresponding energy profiles.

The first reaction route transforms tertiary metallacarbene **8a** to a secondary one (**8b**), while the second reaction transforms **8b** to **8a**. Tetrasubstituted olefin **16** is a product of the first reaction, while the product of the second reaction route

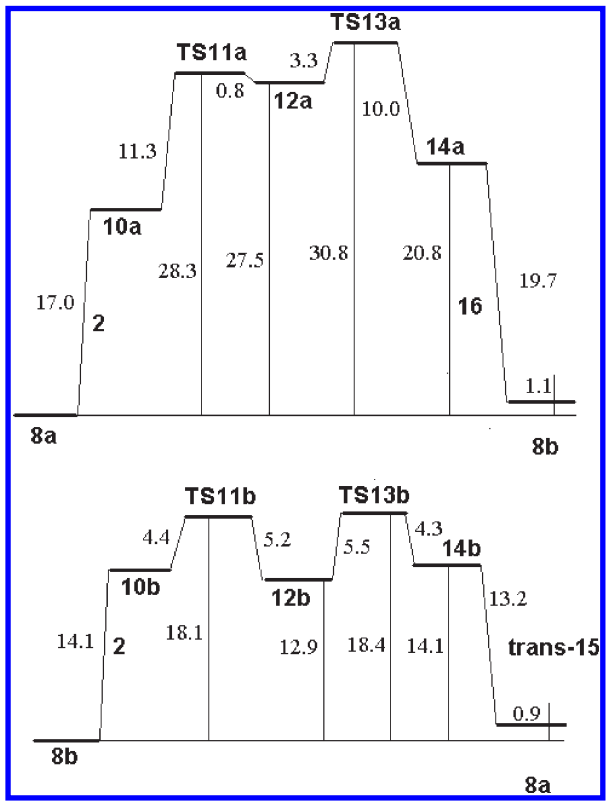


Figure 4. Gibbs free energy profiles (kcal/mol) of **2** metathesis by metallacarbenes **8a** and **8b**.

is *trans*-butene (***trans*-15**). As seen, the formation of olefin **16** proceeds with a relatively high activation energy (30.8 kcal/mol), while the formation of *trans*-butene is much easier from the kinetic point of view, requiring only18.8 kcal/mol. The high activation energy for the first reaction route is due to the strong steric hindrance between the olefin substituents. As seen from Figure 4, metallacyclobutane intermediate **12a** is only slightly lower in energy compared to two neighboring transition states, which is a result of steric hindrance between closely positioned olefin substituents. The reaction energies are very close for both reactions (1.1 and 0.9 kcal/mol, respectively). Therefore, mostly kinetic control favors the second reaction route.

The analysis of the reaction profiles demonstrates that in the case of the initiation step of **2** metathesis the reaction energies for the formation of **8a** and **8b** are very close. On the other hand, the formation of tertiary metallacarbene **8a** is slightly kinetically preferred. However, while the difference between the activation energies in the initiation step does not exceed 1.5 kcal/mol (Figure 1), the difference between the activation energies for **2** self-metathesis is 12.0 kcal/mol (Figure 4). Therefore, secondary metallacarbene **8b** shows higher overall reactivity compared to tertiary metallacarbene **8a**. The inspection of optimized molecular geometries demonstrates the importance of steric factors for the reactivity of different metallacarbenes. As seen from Figure 5, the longest C−C bond in a metallcyclobutane complex increases to 1.66 Å, while for the alternative route this bond length is 1.60 Å.

cis*-Butene Metathesis Mediated by Ruthenium Complexes 8a and 8b.** Scheme 3 and Figure 6 depict the reaction route and the energy profile for *cis*-butene (cis*-15**) metathesis mediated by metallacarbenes **8a** and **8b**.

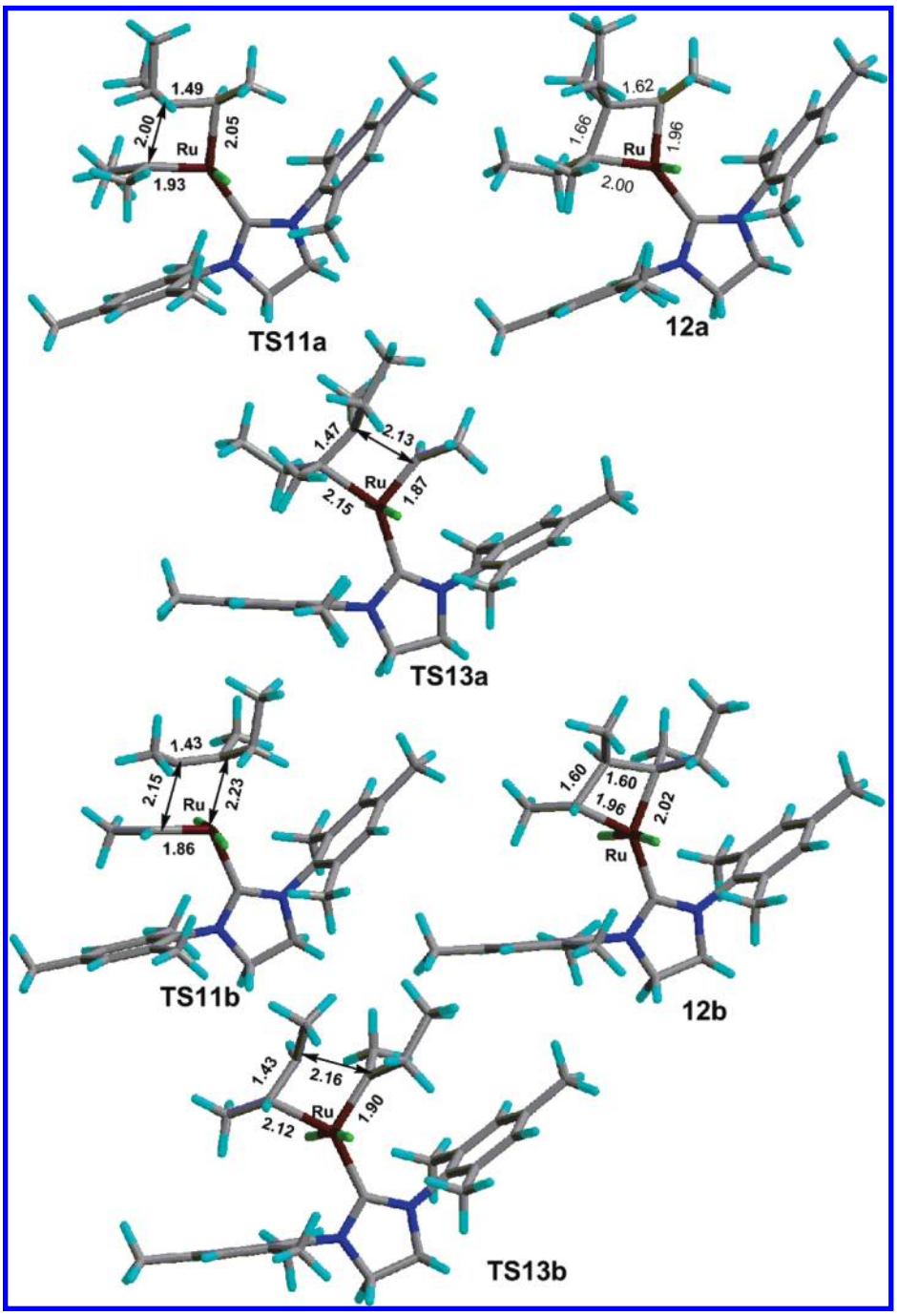


Figure 5. Optimized geometry of **2** metathesis intermediates mediated by metallacarbenes **8a** and **8b**.

The first process is exergonic ($\Delta G = -2.1$ kcal/mol), while the other one is slightly endergonic ($\Delta G = 0.1$ kcal/mol) with relatively low effective activation energies (16.7 and 10.1 kcal/mol, respectively). As seen, the activation energy of the first reaction mediated by tertiary metallacarbene **8a** is significantly higher compared to the second one.

Experimental data demonstrate that the ring-opening metathesis polymerization (ROMP) of monosubstituted cyclooctadienes using tungsten-based classical catalysts occurs only at the unsubstituted double bonds of the monomers.[20] Thus, 1-methylcycloocta-1,5-diene polymerized via ROMP to yield a polymer with alternating 1,4-isoprene units, containing *cis*-double bonds as in the monomer and 1,4-butadiene units with *cis*-double bonds of 65−70%, which are formed during the propagation reaction.[20] However, after longer reaction times, the substituted double bonds of the formed polymer participated in the intramolecular degradation reaction to form the butadiene−isoprene cyclic sesquioligomers,[21] in agreement with calculation data. The formation of trisubstituted olefins in the metathesis of 2-methyl-2-butene with monosubstituted alkenes also support the calculation data provided that the reactivity of monosubstituted olefins is higher than trisubstituted ones.[15]

The higher activation energy for the formation of olefin **16** (Scheme.2) reflects stronger steric hindrance in the transition states caused by olefin substituents. This effect

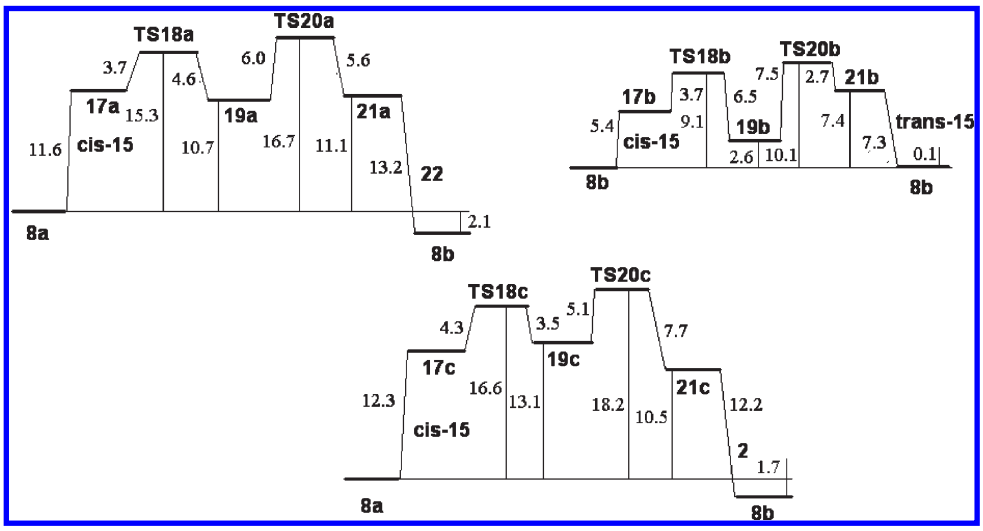
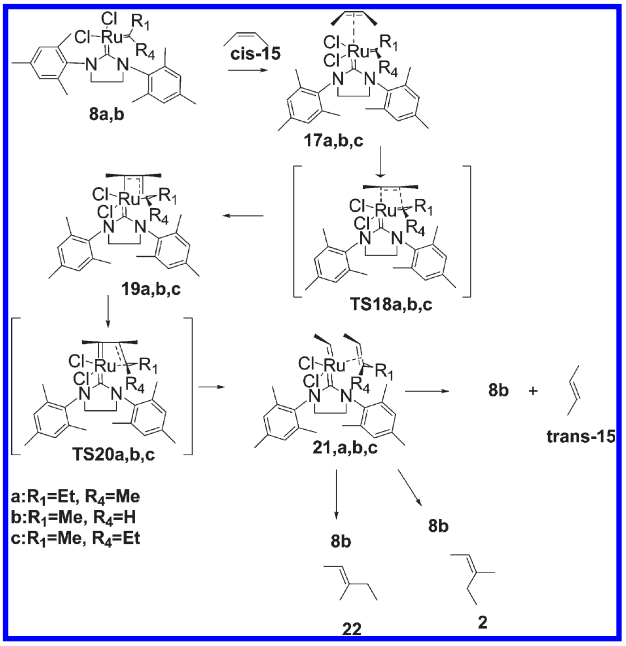


Figure 6. Gibbs free reaction energy profile (kcal/mol) of ***cis*-15** metathesis mediated by metallacarbenes **8a** and **8b**.

Scheme 3. *cis*-Butene (*cis*-15) Metathesis Mediated by Metallacarbenes 8a and 8b



is especially clear in metallacyclobutane intermediates, where the steric hindrance caused by olefin substituents is due to that caused by metallacarbene side groups. As seen from the reaction energy profiles (Figures 1, 2, 4, and 6), there is a clear correlation between the effective activation energies and the difference between the energy of the metallacyclobutane and one or two neighboring transition states.

To estimate the stereoselectivity of metallacarbene **8a**, the formation of olefins **2** and **22** from metallacarbene **8a** and ***cis*-15** has been modeled (Scheme 3, Figure 6). As seen, the effective activation energies for the olefin **22** and **2** formation are rather close (16.7 and 18.2 kcal/mol, respectively). The difference between activation energies of only 1.5 kcal/mol indicates a tiny preference for the formation of olefin **22**. This is a result of slightly greater steric hindrance in the transition states for the olefin **2** formation, where there is a close contact between the ethyl group of the metallacarbene and the methyl group in **TS18a** (Figure 7). The geometrical parameters of the transition states and metallacyclobutane intermediates are similar for the two reactions.

Therefore, it is possible to generalize that the metathesis reactions leading to the formation of highly substituted olefins or olefins with bulky side groups will always have higher activation energies compared to those leading to the formation of less substituted olefins. Moreover, metallacarbenes having a highly substituted carbene will show more elevated activation energies of metathesis compared to the less substituted ones.

Conclusions

The metathesis of (*Z*)-3-methyl-2-pentene (**2**) as a model of natural rubber and other renewables results in two metallacarbenes: a tertiary and a secondary one. The relative stability of the tertiary and secondary metallacarbenes is a product of the interplay between steric and electronic factors. Thus, for the first-generation Grubbs catalyst the secondary metallacarbene is more stable than the tertiary one due to the steric effect of the large tricyclohexylphosphine ligand. However, for the second-generation Grubbs catalyst this difference is minimal. In this case both stabilizing electronic effects and the destabilizing steric factors are important. All other things being equal, the secondary metallacarbene is always more active in the metathesis reaction due to the less sterically hindered transition states. Under kinetic control secondary metallacarbene **8b** is a principal reactive intermediate in the metathesis reaction.

The activation energies of **2** metathesis mediated by the first-generation Grubbs catalyst were found to be higher compared with the second-generation one. The direct correlation between the activation energy of the metathesis process and the number and the size of substituents at the double bond of a formed olefin was established. The calculations demonstrated that cross-metathesis of **2** proceeded with much lower activation energies compared to **2** self-metathesis. It is noteworthy that the stereoselectivity of trisubstituted olefins metathesis using Ru-alkylidene catalysts was found to be rather low.

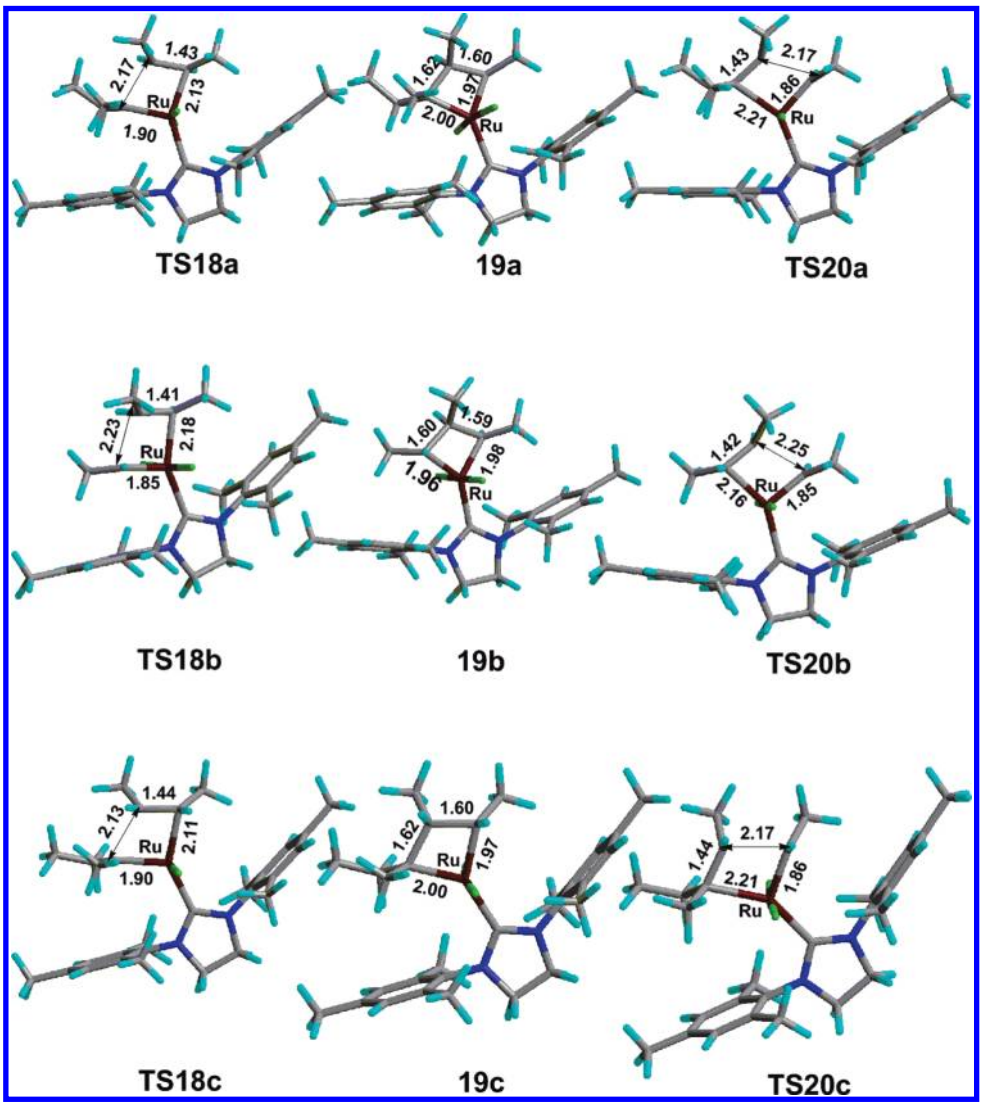


Figure 7. Optimized geometries of **2** metathesis intermediates by metallacarbenes **8a** and **8b**.

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Supporting Information Available: Optimized Cartesian coordinates and the gas phase reaction energy profiles. This material is available free of charge via the Internet at http://pubs.acs.org.