Conformational Isomerization as a Key Selectivity-Determining Step

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Abstract

Organic reactions take place in one or more elementary processes, and their product selectivity is determined by which elementary processes are involved in a reaction and how they occur. Among the elementary processes, bond-forming and cleaving processes are typically the only steps drawn in the proposed organic reaction mechanisms and are generally considered to be more important than other processes such as conformational isomerization, which have rarely been recognized as key steps such as selectivity-determining steps. We report herein on an example where a conformational isomerization process, propeller-like alkene rotation, is considered to determine the selectivity over the reaction pathways in a catalytic reaction. The transition state with the highest energy barrier in some palladium chain walking events was indicated by DFT calculations to correspond to alkene rotation in an alkene hydride palladium species, rather than bond-cleaving b-hydride elimination or bond-forming migratory insertion, even when there is only one transition state between an alkyl complex and an alkene hydride complex. It was also suggested both theoretically and experimentally that the chain walking over internal carbons in alkyl chains proceeds via cis alkene intermediates, rather than thermodynamically more stable trans alkene intermediates, due to their relative ease of undergoing alkene rotation.

Main Text

Catalytic organic transformations proceeding via organometallic intermediates constitute one of the major categories in organic reactions, and many of them have become indispensable to modern organic synthesis. Each of the catalytic cycles of these reactions consists of a sequence of a variety of elementary processes. When the mechanisms of the catalytic cycles are described, much attention has been paid to the processes involving a bond-forming or cleaving event, including migratory insertion and \( \beta \)-elimination (Fig. 1a). In contrast, elementary processes proceeding without forming or cleaving a bond are rarely considered an important step because they are mostly assumed to have low energy barriers and proceed smoothly. Conformational isomerization is one of those non-bond-forming/non-bond-cleaving processes whose kinetic preference is hardly examined, although the relative thermodynamic stability of conformers is discussed frequently.

Propeller-like alkene rotation (Fig. 1b, hereinafter referred to as alkene rotation), in which an alkene bound to a metal center revolves around the metal-(alkene centroid) axis, is an elementary process considered to be involved in countless reactions using transition metal catalysts but only changes the conformation of the metal complex. Although alkene rotation as an elementary process has been studied for various transition metal complexes for many decades, it has received little attention in the mechanistic analysis of catalytic reactions. For example, the alkene rotation process may be involved in alkene insertion into metal-ligand (M–Z) bonds, as it may proceed via alkene coordination, rotation (depending on the orientation of the coordinating alkene), and migratory insertion (Fig. 1c). In general, however, the alkene rotation step is not considered carefully and not depicted in the alkene coordination/insertion
process. Even in the case where alkene rotation was discussed, it was not recognized as a key step, such as turnover-limiting or selectivity-determining steps, in catalytic cycles.

Chain walking of metal centers on alkyl chains has been one of the key processes utilized in recent developments of olefin polymerization and catalytic organic reactions and is a process in which alkene rotation on the metal may occur frequently. While there have been multiple mechanisms considered for chain walking processes of various metals, that of most transition metals, such as palladium, is generally considered to proceed via \( \beta \)-hydride elimination from an alkylmetal species, alkene rotation, and migratory insertion of the coordinating alkene into the metal-hydrogen bond (Fig. 1d). The metal migration process requires a net 180° rotation of the alkene ligand. Even for the chain walking process, however, alkene rotation has generally not been considered a key step, partly because it is assumed to proceed without any difficulty. In 1997, Morokuma and coworkers reported on the DFT calculation of chain-walking ethylene polymerization catalyzed by a palladium catalyst with a simplified \( \alpha \)-diimine ligand and suggested that the energy barriers for the alkene rotation process are less than 1 kcal/mol. While many palladium-catalyzed organic transformations via chain walking have been reported recently and DFT calculations have been conducted for some of these reactions, the transition states of the alkene rotation process have not often been located in the calculation. As a rare example, Baudoin, Clot and coworkers reported a palladium-catalyzed arylation of esters via metal migration and DFT calculations on the reaction to show that metal migration proceeds smoothly because the energy barrier for alkene rotation is higher than that for \( \beta \)-hydride elimination/insertion but lower than that for rate-determining reductive elimination.

Our group has been working on the development of palladium-catalyzed reactions via chain walking. 1,10-Phenanthroline and its derivatives have mostly been used as ligands in our reactions, such as cycloisomerization and addition/cyclization of 1,\( n \)-diienes as well as remote arylative substitution. To gain an understanding of the mechanism, we explored the theoretical investigation of the chain walking process of alkylpalladium species possessing a 1,10-phenanthroline ligand. It should be noted that DFT calculations on the chain walking mechanism of the 1,10-phenanthroline palladium have partly been reported by other groups, but complete analysis including the structures and modes of the imaginary vibration at the transition states as well as the possible pathways involving all of the stereoisomers was not conducted. Therefore, entirely novel findings and conclusions were drawn from our investigations.

Our theoretical studies employing density functional theory (M06-D3/cc-pVDZ, SDD (only for Pd) and PCM (dichloroethane)) were initiated by using a simple model of a palladium complex containing two ligands: 1,10-phenanthroline and an \( n \)-propyl group, which would give the smallest terminal alkene, propene, upon \( \beta \)-hydride elimination. We postulated that the chain walking of the 1,10-phenanthroline palladium catalyst would follow a pathway involving the same sets of elementary processes as depicted in Fig. 1d: \( \beta \)-hydride elimination of an agostic \( n \)-propyl complex to form a hydride complex possessing a propene ligand with the carbon-carbon double bond oriented horizontally to the square plane around the palladium center (hereinafter referred to as a horizontal alkene complex), alkene rotation to give a
complex with a vertically oriented propene ligand (hereinafter referred to as a vertical alkene complex), further rotation of propene to provide another horizontal alkene complex, and migratory insertion of propene into the palladium–hydrogen bond to form an agostic isopropyl complex. It should be noted that the way each process was expressed here was based on the classical description of the organometallic elementary processes and may not be the same as the calculated elementary steps, the single-step processes from an intermediate to another with only one transition state.

The calculated mechanism of the chain walking of the 1,10-phenanthroline palladium catalyst on the three-carbon chain and its Gibbs free energy diagram are shown in Fig. 2. Analyses of the intrinsic reaction coordinates (IRCs) suggested that the reaction proceeds essentially via the pathway depicted in Fig. 1d, although intermediates corresponding to the horizontal alkene complexes were not found in our calculation, and the agostic n-propyl (1) and isopropyl (3) complexes are directly transformed into vertical alkene complexes (Fig. 2a). There are two possible pathways for the conversion of complex 1 to 3 depending on the direction of the alkene rotation, and the isomerization by clockwise alkene rotation via vertical alkene complex 2 was indicated to proceed more easily by 1.2 kcal/mol than by counterclockwise rotation via complex 4. The vibration modes with imaginary frequencies were then carefully examined (Fig. 2b), and the direction of the vibration vector of each atom suggested that the transition states between the alkyl complexes (1 and 3) and the vertical alkene complexes (2 and 4) are located during the alkene rotation processes, particularly where the methyl or a hydro group on the propene ligand is placed on the palladium plane to create possible steric repulsion with either the hydride ligand or the hydrogen at the 2-position of the 1,10-phenanthroline ligand. The closest distances between the 1,10-phenanthroline hydrogen and an alkene substituent in all four transition states are 1.93–2.05 Å (Fig. 2c), which are less than the sum of the van der Waals radii of two hydrogen atoms. While the distances between the alkene ligand and the palladium center at the transition states were slightly longer than those of vertical alkene complexes 2 and 4 (Fig. 2d), the transition state structures showed larger angles between the Pd–N bond and the Pd–(alkene centroid) axis. The alkene ligands are more distorted at the transition states, as the pyramidalization angles around the alkene carbons were mostly larger than those of complexes 2 and 4. Therefore, the repulsive interaction between the hydride/1,10-phenanthroline ligands and the alkene substituents may lead to the creation of energy barriers for alkene rotation. The highest energy barrier during alkene rotation was observed at TS(4 – 3), where the methyl hydrogen on the alkene ligand becomes close to the 1,10-phenanthroline hydrogen (1.93 Å), and the most significant pyramidalization around the alkene carbon was found at this transition state.

DFT calculation of transition states for the associative alkene exchange processes showed that their lowest energy barrier was higher than that for the alkene rotation, while the dissociative alkene exchange would be even harder, as the three-coordinate hydride palladium complex 6 is much more thermodynamically unstable (Fig. 2e). The 1,3-exchange of agostic β-hydrogen was also considered to proceed by an associative mechanism, in which both carbon–hydrogen bonds weakly interact with the metal center in the transition state (TS(3–3')), and its energy barrier was lower by 2.4 kcal/mol than that of the alkene rotation process. Therefore, the chain walking process examined here is suggested to
proceed easily without dissociating propene, and the highest energy barrier is found at the alkene rotation process.

Examination of the chain walking processes on the four-carbon alkyl chain suggested an interesting selectivity of the chain walking pathways. While the calculation results obtained for chain walking over the terminal carbon–carbon bond are similar to those over three carbons (Fig. 2), chain walking over the two internal carbons indicated its preference for a pathway via a cis alkene intermediate over a trans alkene intermediate (Fig. 3a). Calculation of the pathway via a trans alkene complex showed the presence of horizontal alkene intermediate $8_t$ after β-hydride elimination, and it is considered to be easily converted to vertical alkene complex $9_t$. In contrast, vertical cis alkene complex $9_c$ is directly formed from the corresponding agostic sec-butyl complex $7_c$ similar to the formation of 2 from 1, and is thermodynamically less stable than trans alkene complex $9_t$. Analyses of the transition states suggested that the cis alkene pathway is more preferred than the trans alkene pathway because the trans alkene is harder to rotate by 180° than the cis alkene. The rotation of the trans alkene needs to proceed via transition state $\text{TS}(8_t-9_t)$, where both of the methyl substituents pass through the palladium face simultaneously to make significant steric interactions with the hydride and the 1,10-phenanthroline ligands, while the cis alkene can rotate by 180° while avoiding close contact between the methyl substituents and the 1,10-phenanthroline ligand. Conversion between complexes $7_c$ and $7_t$ via $\text{TS}(7_c-7_t)$ was found to possess a slightly higher energy barrier than the cis alkene rotation but was still lower by 3.0 kcal/mol than the trans alkene rotation. The observed preference for the cis alkene pathway was counterintuitive because trans alkenes are generally more thermodynamically stable than cis alkenes, and chain walking processes have presumably been described in the literature to proceed via trans alkene intermediates.

DFT calculations were also conducted for the chain walking over the internal carbons at the 3- and 4-positions of the six-carbon alkyl chain, and the process proceeds via similar pathways to those on the four-carbon chain (Figs. 3b and 3c). Conversion of 1-ethylbutyl complexes $10_c$, $11_t$, and $13_t$ to vertical alkene complexes $12_c$ or $12_t$ occurs directly via a single transition state. The elementary processes corresponding to the transition states are either β-hydride elimination or alkene rotation, but the transition state with the highest energy barrier for the trans alkene pathway, $\text{TS}(11_t-12_t)$, corresponds to the aforementioned trans alkene rotation. As a result, chain walking via cis alkene intermediate $12_c$ is again more facile by 4.6 kcal/mol than that via a trans alkene.

To experimentally examine the preference for the cis alkene pathway in the chain walking processes, a deuterium-labeling experiment was conducted for the remote arylative substitution reaction$^{41}$ in which alkenes possessing a distant acetoxy group react with arylboronic acids to form an arylation product via chain walking. We envisioned that the use of alkene substrate $14-d_4$ containing four deuterium atoms may suggest the cis/trans preference of the chain walking pathways, as shown in Fig. 4a. Arylpalladation of alkene $14-d_4$ gives alkylpalladium complex $A$, which then undergoes β-hydride elimination to provide either cis- or trans-alkene hydride complex $B$. Subsequent reinsertion, further chain walking, and β-acetoxy
elimination furnish product $16\text{-d}_4$, which may possess one hydrogen atom on both the $\alpha$- and $\beta$-carbons of the alkene moiety. If a 2-bromophenyl group is used as the aryl group, product $16\text{-d}_4$ may be converted to tetralin derivative $18\text{-d}_4$ using an aryne ene reaction, and the two hydrogen atoms mentioned above would be in either an anti- or syn-relationship in the six-membered ring depending on whether the chain walking proceeds via a cis- or trans-alkene intermediate, respectively (Fig. 4b). DFT calculations of the remote arylationative substitution (Supplementary Information) suggested that H/D exchange at the $\beta$- and $\gamma$-positions to the alkene moiety in the product may occur rapidly to reduce the content of H atoms at the $\beta$-position, but most of the product molecules possessing an H atom at the $\beta$-position are expected to have one H atom at the $\alpha$-position, and the stereochemical relationship between the two H atoms should suggest the main pathway of the chain walking process.

The reaction of 2-bromophenylboronic acid (15) with alkene $14\text{-d}_4$ catalyzed by a 1,10-phenanthroline palladium catalyst provided linear arylation product $16\text{-d}_4$, which was then transformed into tetralin derivative $18\text{-d}_4$ (Fig. 4b). $^1$H and $^2$H NMR analyses of product $18\text{-d}_4$ indicated that deuterium atoms did not migrate to positions other than the three methylene carbons in the six-membered ring, and the $\beta$-position of the product contains ca. 0.45 protons.

The $^1$H NMR spectrum of the product showed the signals of both the axial and equatorial positions as apparent doublets with coupling constants of 8.0 and 5.6 Hz, respectively, which suggests the axial-axial and equatorial-equatorial couplings of the two H atoms (Fig. 4c). While irradiation of the equatorial $\alpha$-proton led to the decoupling of the signal of the equatorial $\beta$-proton, the signal of the axial $\beta$-proton was decoupled by irradiating the axial $\alpha$-proton. These results showed that the product containing an H atom at the $\beta$-position mostly contains an H atom at the $\alpha$-position, and the two hydrogens are in an anti-relationship, which supports the predicted preference of the chain walking pathway via a cis alkene intermediate.

We believe the results described here are important not only for a profound understanding of the chain-walking mechanisms, which have been increasingly utilized in reaction developments, but also for upgrading strategies for mechanistic studies by carefully examining elementary processes proceeding without forming or cleaving a bond. It is difficult to consider the non-bond-forming/non-bond-cleaving processes as key processes in organic reactions, but thorough investigation by DFT calculation may provide novel insights into the reaction mechanisms that are otherwise difficult to realize.

**Declarations**

**Data availability**

The data that support the findings of this study are available within the paper and its Supplementary Information. Should any raw data files be needed in another format, they are available from the corresponding author upon reasonable request.
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Author Contributions

T.K. conceived the project. K.M. performed the calculations and the experiments. M.H. helped K.M. and T.K. choose the calculation methods, run the calculations, and analyze the calculation results. K.M. and T.K. designed and wrote the manuscript. All authors discussed the results by analyzing the data.

Supplementary Information

Computational/experimental details, characterization data, and computational results.

Supplementary Data: xyz file

Author Information

The authors declare no competing financial interests. Supplementary Information and Supplementary Data are available for this paper. Correspondence and requests for materials should be addressed to T.K. (kochi@chem.keio.ac.jp) and M.H. (hatanaka@chem.keio.ac.jp). Reprints and permission information is available at www.nature.com/reprints.

References


**Figures**
Figure 1

Elementary processes associated with the chain-walking mechanism.
Figure 2

Chain walking of a (phen)Pd catalyst on a 3-carbon alkyl chain.
Figure 3

Chain walking of a (phen)Pd catalyst on internal carbons of alkyl chains.
Figure 4

Deuterium-labeling experiments of remote arylative substitution.

Supplementary Files

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