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Atomistic simulation of olefin polymerization reaction by organometallic catalyst: significant role of microscopic structural dynamics of (pyridylamido) Hf(IV) complex in catalytic reactivity

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Understanding the microscopic catalytic mechanism of the olefin polymerization reaction is crucial for the rational design of next-generation catalysts. However, the dynamic nature of the active species, including the fluctuations of the ion pair structure and the orientation of substituents, presents significant challenges for theoretical approaches. In this paper, we present an overview of our recent computational studies on the role of the structural dynamics of the active species of olefin polymerization catalyst in determining reactivity, especially focusing on a novel olefin polymerization catalyst (pyridylamido) Hf(IV) complex. Utilizing the molecular dynamics method and our Red Moon method, a novel methodology we have developed for atomistic simulation of complex chemical reaction systems, we elucidate how the dynamic features, including anion coordination and steric interaction, govern the reactivity in key steps such as ligand modification and propagation reactions. In addition, we demonstrate how machine learning techniques can be applied to extract chemically meaningful descriptors from the structural ensemble obtained from atomistic simulation data of complex chemical reaction systems, thereby identifying the substituents that play an important role in propagation reactions. Our studies highlight the importance of incorporating molecular-level dynamic features of catalysts into mechanistic models.

KEYWORDS

polymerization, ion pair, polyolefin, molecular dynamics, red moon method, (pyridylamido) Hf(IV)

1 Introduction

In today's society, polyolefins are the most extensively used polymer resins. Consequently, significant efforts have been made to develop the olefin polymerization catalyst for achieving efficient production and precise control over the microscopic structures of resulting polymers (Sinn et al., 1980; Gibson and Spitzmesser, 2003; Wilke, 2003; Baier et al., 2014). Although gaining a precise understanding of the polymerization mechanism is crucial for catalyst development, experimentally capturing the microscopic processes remains challenging due to the complexity of the reaction and the difficulty of isolating intermediates. Therefore, computational approaches have been widely adopted to investigate the detailed reaction mechanism that cannot be easily probed experimentally. For example, the reaction mechanisms have been extensively investigated using quantum chemical methods from a static point of view, particularly with respect to the origin of monomer reactivity, as well as regio- and stereoselectivity (Kawamura-Kuribayashi et al., 1992; Alt and Köppl, 2000; Angermund et al., 2000; Lanza et al., 2000; Lanza et al., 2001; Rappé et al., 2000; Resconi et al., 2000; Zurek and Ziegler, 2003; Ziegler et al., 2005; Motta et al., 2007; Motta et al., 2008; Tomasi et al., 2007; De Rosa et al., 2016). While these quantum mechanical methods provide valuable insights into the static features of the reaction mechanism, understanding the dynamic aspect of the catalytic processes requires a different set of computational tools. In this regard, various methodologies have been developed. For instance, *ab initio* molecular dynamics and molecular dynamics using machine learning potentials (MLPs), the latter of which has significantly progressed in recent years (Unke et al., 2021), have been widely used. However, bridging the gap between the timescales of chemical reactions and molecular motions remains challenging due to the high computational cost; the former, which involves the bond formation and breaking, occurs far less frequently than the latter. Another important class of approaches is reactive force fields, such as ReaxFF (van Duin et al., 2001; Senftle et al., 2016), which have been successfully applied to a wide range of systems. However, reactive force fields are sometimes difficult to parametrize accurately (Gissinger et al., 2017) and suffer from limited transferability of their parameters (Senftle et al., 2016). For these reasons, studies addressing the dynamic aspect of the polymerization reaction with organometallic catalyst remain relatively scarce, even though such dynamics are crucial for a comprehensive understanding of the catalytic behavior (Correa and Cavallo, 2006; Yang and Ziegler, 2006; Rowley and Woo, 2011).

Under such circumstances, we have investigated the microscopic dynamics of the active species and its role in the olefin polymerization reaction by employing the molecular dynamics (MD) method and the Red Moon (RM) method, a novel methodology we have developed for atomistic simulation of complex chemical reaction systems. In particular, we have focused on the (pyridylamido) Hf(IV) complex, which attracts much attention as a novel catalyst with high activity (Boussie et al., 2003; Boussie et al., 2006; Chum and Swogger, 2008; Frazier et al., 2011). In this mini-review, we present an overview of our recent computational investigations, highlighting the dynamic features of the active species and their influence on the olefin polymerization reaction (Matsumoto et al., 2016; Matsumoto

et al., 2019; Misawa et al., 2021; Misawa et al., 2023; Kanesato et al., 2023; Kanesato et al., 2024).

Similar to other olefin polymerization catalysts with group 4 metal, (pyridylamido) Hf(IV) complex **1** requires an activation process. As shown in Figure 1A, when neutral complex **1** reacts with such as $[B(C_6F_5)_3]$ or $[HNMe(C_{18}H_{37})_2][B(C_6F_5)_4]$, called cocatalyst, one of the Me groups is abstracted and results in the ion pair (IP) of the cation **2** and the anion. Afterwards, monomeric olefin is inserted into the Hf-C_{aryl} bond, which is known as ligand modification reaction. It is widely accepted that the **3** referred to as "monomer-inserted active species" is the genuine active species for the following propagation reaction (Froese et al., 2007; Zuccaccia et al., 2009).

This mini-review is organized as follows. In Section 2, we present molecular dynamics study on the structural dynamics of the active species in the ligand modification reaction. We revealed a characteristic dynamic of the anion dissociation from the active site, which we refer to as the associative active site opening (AASO) mechanism. Next, in Section 3, we focus on the structural dynamics of the active species in the propagation reaction. For this purpose, we utilized the RM method. Our study reasonably reproduced the anion-dependent reactivity of the catalyst and clearly illustrated how the structural dynamics of the active species is interwoven with the propagation reaction. Then, in Section 4, we present an application of our RM method, especially focusing on the role of structural dynamics in the mechanism of steric hindrance. By combining machine learning techniques, we successfully identified the key substituents and elucidated how they govern the steric hindrance around the active site. Finally, in Section 5, we conclude with emphasis on the importance of capturing dynamic features of the active species in mechanistic analysis of olefin polymerization reaction.

2 Associative active site opening mechanism in the ligand modification reaction

Experimental evidence indicates that the active site, i.e., the Hf atom on the cation species **2** is occupied by the anion due to its strong interaction with the Hf atom (Zuccaccia et al., 2008; Zuccaccia et al., 2009). Thus, the anion dissociation from the active site is a prerequisite for the ligand modification reaction. However, active site opening process is hard to statically investigate with such as quantum mechanical method because it is a dynamic process. We, therefore, developed a molecular model of the IP of the cation **2** and the counter anion $[MeB(C_6F_5)_3]^-$, and investigated its structural dynamics by MD method (Matsumoto et al., 2016).

From our simulation, it was revealed that the counter anion exhibits characteristic dissociation from the active site when monomeric ethylene molecules are present in the system (Figure 1B). Initially, the counter anion $[MeB(C_6F_5)_3]^-$ interacts with the Hf atom using a single F atom and Me group (structure α in Figure 1B). Subsequently, the anion interacts with the Hf atom solely via F atoms, leading to the structure β in Figure 1B. Then, the borate anion can move along the cation's surface while staying coordinated to the Hf atom, thereby yielding enough coordination space for the monomeric ethylene to access the active site (structure γ in

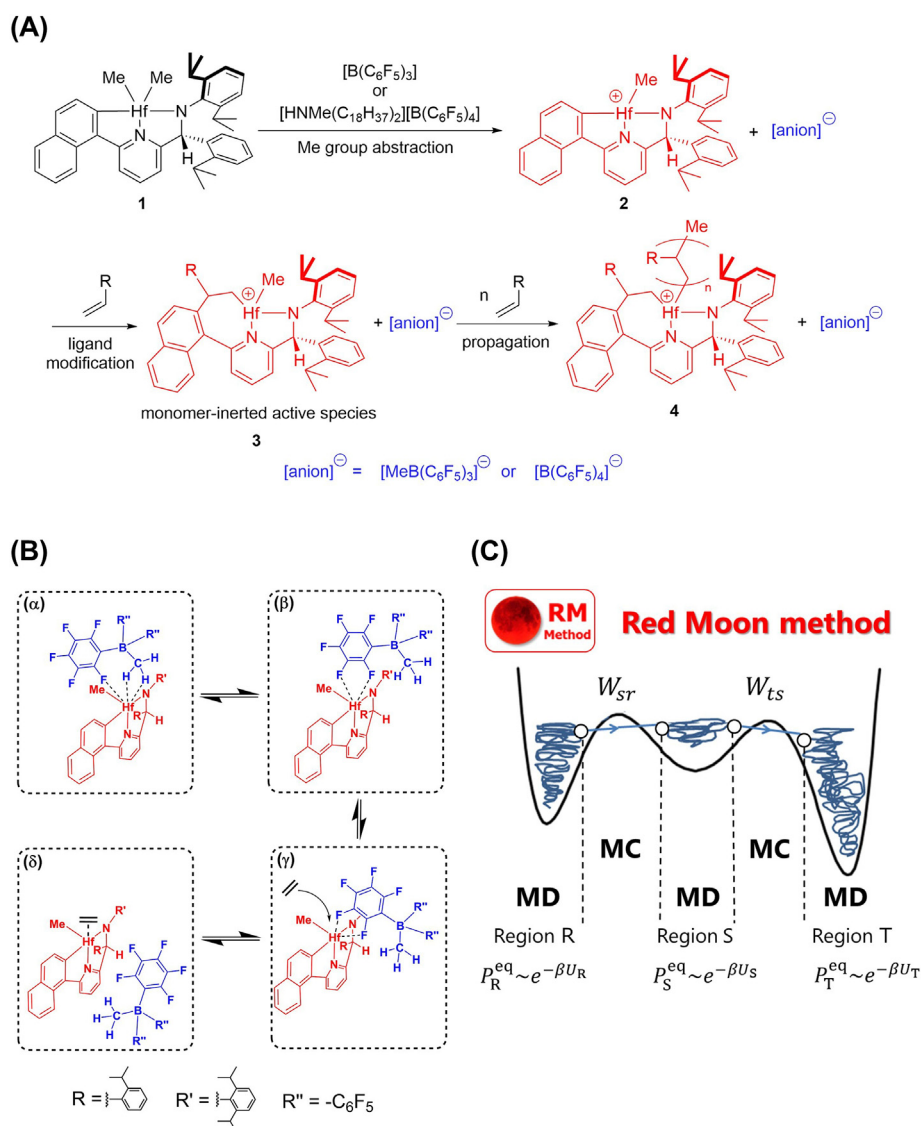


FIGURE 1

(A) Schematic representation of activation (Me group abstraction and ligand modification) and propagation reaction of (pyridylamido) Hf(IV) complex. (B) Schematic representation of the associative active site opening mechanism. Adapted with permission from *Organometallics*, 2016, 35, 24, 4099–4105. Copyright 2016 American Chemical Society. (C) A schematic representation of the Red Moon method. In three regions R, S, and T, the configurational distribution p_x^{eq} ($x = R, S, T$) is proportional to the exponential factor $e^{-\beta U_x}$, where U_x is the potential function in each region. W_{sr} and W_{ts} are the transition probabilities from a configuration state r in region R to s in region S, and from s in region S to t in region T, respectively.

Figure 1B). Such a behavior arises from the planar geometry, and the orthogonal alignment of pyridylamide ligand and perfluorophenyl group. In the final step, the anion dissociation and the monomer coordination occur associatively (structure δ in Figure 1B), which we refer to as the associative active site opening (AASO).

According to the free energy barrier, structural change from structure α to β in Figure 1B is the slowest step in the AASO mechanism, involving the Me group dissociation. It is inferred, therefore, that the ligand modification occurs more rapidly if the anion is $[B(C_6F_5)_4]^-$ because of the lack of Me group strongly interacting with the active site. In fact, it is experimentally shown that the polymer growth initiation proceeds more slowly with $[MeB(C_6F_5)_3]^-$ (Cueny et al., 2017), which supports the validity of the AASO mechanism.

3 Structural dynamics of the ion pair active species interwoven with the propagation reaction

The anion-dependent reactivity is also observed in the propagation as well as in the ligand-modification. In fact, it has been experimentally observed that active species **3** with $[B(C_6F_5)_4]^-$ tends to show higher polymerization rate of 1-octene than that with $[MeB(C_6F_5)_3]^-$ (Cueny et al., 2017), which indicates that the dynamic features of the IP active species has an effect on the propagation reaction as in the case of the ligand modification. However, it is still challenging to computationally investigate how the propagation reaction and the IP dynamics influence each other because these phenomena differ significantly in

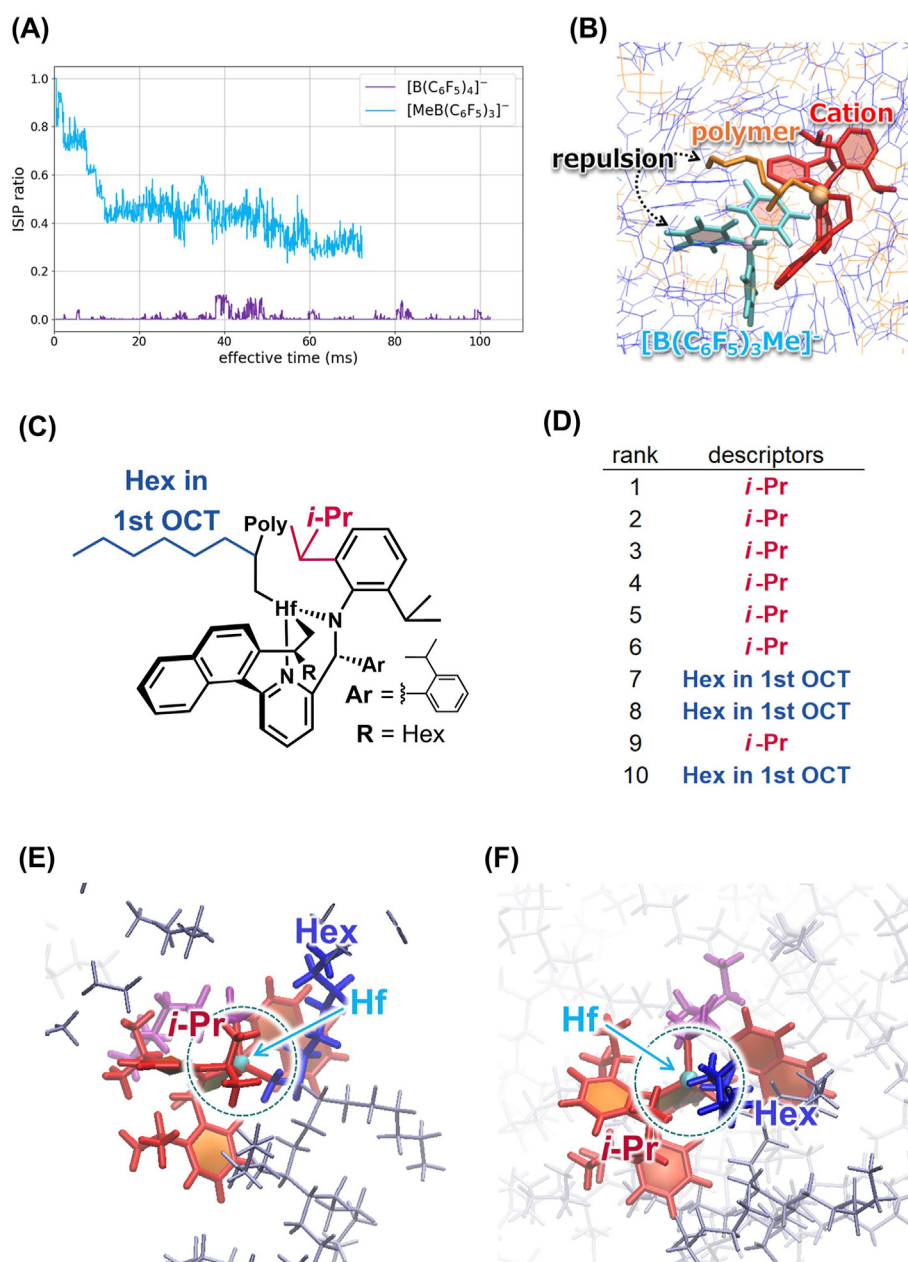


FIGURE 2

(A) Averaged ISIP ratio as a function of the effective real-time in each IP system. (B) OSIP structure of the IP system with $[MeB(C_6F_5)_3]^-$ anion after the first monomer insertion, where the steric hindrance between the inserted monomer and the counter anion induces the structural transition from the ISIP to OSIP. Adapted with permission from J. Phys. Chem. B 2023, 127, 5, 1209–1218. Copyright 2023 American Chemical Society. (C) Schematic representation of the cation showing the *i*-Pr and Hex groups in the 1-octene unit adjacent to the Hf atom (Hex in 1st OCT) which affect the propagation reaction. (D) Results of descriptor extraction with machine learning techniques. Typical snapshots of steric hindrance around the active site due to (E) the *i*-Pr group and (F) the Hex group. Adapted with permission from Phys. Chem. B 2024, 128, 25, 6178–6188. Copyright 2024 American Chemical Society.

timescale. The former, characterized by the formation and breaking of chemical bonds, takes place much less frequently than the structural changes seen in the latter. To tackle this problem, the RM method (Nagaoka et al., 2013; Nagaoka et al., 2019; Nagaoka, 2024) was employed. In the RM method, the molecular motions over a relatively short time scale are handled with the MD method, while the chemical reaction processes involving formation and breaking of chemical bonds over a relatively long time scale are handled with

Monte Carlo (MC) method. A single cycle comprising these two methods is referred to as the “RM cycle”. Repeating the RM cycle allows stochastic simulation of a series of propagations (Figure 1C). Moreover, by employing the time transformation theory (Suzuki and Nagaoka, 2017; Nagaoka et al., 2019), the RM cycle is mapped onto an effective real-time domain. Some independent groups have recently adopted the same spirit of the RM method and reasonably applied their methods in the field of lithium-ion batteries

(Biedermann et al., 2021b; Biedermann et al., 2021a; Abbott and Hanke, 2022). Furthermore, Okabe et al. employed a treatment similar to the RM method to primarily study the cross-linking reactions and physical properties of epoxy resins (Takaba et al., 2008; Okabe et al., 2013; Oya et al., 2021). We believe that these works further support the validity of the direction pursued by our RM method.

By applying the RM method, higher 1-octene consumption with $[B(C_6F_5)_4]^-$ was reasonably reproduced (Misawa et al., 2021; Misawa et al., 2023). Furthermore, to reveal the dynamic features of the IPs, according to the location of the counter anion relative to the cation, we classified the IP structure into two classes, that is, inner-sphere IP (ISIP) state where the counter anion is coordinated to the Hf atom, and the outer-sphere IP (OSIP) where the counter anion is dissociated from the Hf atom. Figure 2A illustrates the variations of the ISIP ratio averaged over the 10 trajectories obtained from the RM simulation. It is clearly shown that the IP of $[MeB(C_6F_5)_3]^-$ forms ISIP which inhibits the coordination of the monomeric 1-octene to the active site. Notably, the ISIP ratio of the IP of $[MeB(C_6F_5)_3]^-$ drops steeply within the first 20 ms, as the inserted monomer has the steric repulsion with the counter anion after the first monomer insertion (Figure 2B). Afterwards, the ISIP ratio fluctuates between 40% and 60%, which indicates the IP of the $[MeB(C_6F_5)_3]^-$ reaches a quasi-equilibrium state. By contrast, the IP of $[B(C_6F_5)_4]^-$ predominantly retains the OSIP across the entire simulation, leading to the faster propagation. These results reveal significant differences in the dynamic features between the two IPs and illustrate how the IP dynamics is interwoven with the propagation reaction.

4 Effect of the steric hindrance on the propagation reaction: extraction of essential descriptors by machine learning techniques

In general, it is well known that the steric hindrance between a catalyst's ligands and the reacting monomers significantly affects monomer reactivity, as well as regio- and stereoselectivity in olefin polymerization reactions (Kawamura-Kuribayashi et al., 1992; Lanza et al., 2000; Lanza et al., 2001; Zurek and Ziegler, 2003; Ziegler et al., 2005; Motta et al., 2007; Motta et al., 2008; Tomasi et al., 2007; De Rosa et al., 2016). Therefore, a precise understanding of the microscopic mechanism of steric hindrance caused by substituents is essential for the rational design of catalysts that yield polymers with desired physical properties. In fact, the relationship between the catalyst structure and its reactivity has been extensively investigated using quantum mechanical methods. However, our studies presented above imply that not only the static structure of the catalyst but also its structural dynamics plays a significant role in the mechanism of steric hindrance. Motivated by these considerations, we investigated the dynamic aspect of the steric hindrance in coordinative chain transfer copolymerization of ethylene and 1-octene by (pyridylamido) Hf(IV) by combining our RM method and machine learning techniques (Kanesato et al., 2023; Kanesato et al., 2024).

To begin with, we confirmed that the frequency of the chain transfer reaction and the ethylene content in the resulting polymers

obtained from our simulation are consistent with the experimental observations (Kanesato et al., 2023). These agreements validate the reliability of our simulation and the subsequent mechanistic analysis of the steric hindrance by the substituent. In addition, it is also shown that our methodology is applicable not only to homo polymerization but also to more complex polymerization systems such as coordinative chain transfer copolymerization.

Next, we attempted to find substituents that affect the propagation reaction by extracting essential descriptors using a machine learning technique. For this purpose, by using the Cartesian coordinate values of the cationic active species from our RM simulation as input variables, we developed random forest classification models to determine whether no reactant for the propagation reaction is found, or a reactant is found and the propagation reaction proceeds. We collected a large data set containing 4,146 structural entries from our RM simulation, and applied RMSD fitting to align the cationic active species, addressing the lack of rotational and translation invariance in Cartesian coordinates. The two hyperparameters, the number and depth of the trees, were optimized using grid search with 10-fold cross-validation.

Subsequently, based on the feature importance, we extracted the substituents whose Cartesian coordinate values are important. Figures 2C,D indicate that the *i*-Pr group of the cationic active species and the hexyl group of the inserted 1-octene adjacent to the Hf atom have significant effects on the occurrence of the propagation reaction. In fact, two snapshots from our RM simulation (Figures 2E,F), where no reactant for the propagation reaction is found, clearly show that the *i*-Pr group or the hexyl group occupies the active site and inhibits the approach of monomers.

It is worth noting that the combination of RM simulation and machine learning techniques successfully identified the substituents that affect the propagation reaction. This fact includes two important aspects: First, the RM simulation can provide meaningful information, including the reactions and dynamic features of the catalyst, for the complex reaction system that are hard to analyze using conventional approaches. Second, we have proposed a new scheme to analyze the chemical reaction dynamics by integrating molecular simulation and data science.

5 Conclusion and future perspectives

In this mini-review, we presented an overview of our recent computational studies on the role of the structural dynamics of the active species of olefin polymerization catalyst, especially focusing on the active species of (pyridylamido) Hf(IV) complex. By employing molecular dynamics method and Red Moon (RM) method, i.e., a novel methodology we have developed for the atomistic simulation of complex chemical reaction systems, we have revealed that the dynamic features such as the anion coordination and the steric interaction by the substituents significantly influence the key reaction steps, including ligand modification and propagation reactions. Furthermore, by combining machine learning techniques with our RM method, we successfully identified the substituents that govern the steric hindrance around the active site. These findings underscore the importance of capturing molecular-level dynamics in the

mechanistic analysis of olefin polymerization reactions. They also demonstrate the potential of molecular simulation and a simulation-machine learning hybrid approach for uncovering the structure-reactivity relationships that are inaccessible by static models.

Although the role of structural dynamics has not been explored enough in previous mechanistic models, we find that some experimental and theoretical observations could be viewed as consistent with our perspective. For example, it has been speculated that the bulky substituents increase the propagation rate by locking the anion into a position away from the cationic metal center (Cueny et al., 2021). In addition, the rearrangement of the backbone structure of the cationic active species during the capture of a monomeric olefin has been proposed to influence the comonomer affinity (Zaccaria et al., 2017). We consider these observations to be suggestive of the underlying role of the dynamics in determining catalytic reactivity. We believe that a deeper understanding of the dynamic features of the olefin polymerization catalysts, often overlooked in static models, will become an essential component in the mechanistic understanding and contribute to the rational design of next-generation catalysts in the future.

Author contributions

KM: Writing – original draft, Writing – review and editing. NM: Writing – review and editing. SK: Writing – review and editing. MN: Writing – original draft, Writing – review and editing.

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