Theoretical Calculations in Reaction Mechanism Studies

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In recent decades, quantum chemistry calculations have been used for various chemical fields such as reaction pathway analysis and spectroscopic assignments due to the theoretical developments, especially accuracy improvement of functionals in density functional theory (DFT), and high-speed parallel computers. However, the functionals in DFT should be appropriately employed for a target system or phenomenon because its reproducibility depends on the functionals used. Therefore comparison among obtained results with available experimental data or high-level computations is necessary to avoid misleading. In this review, we report the DFT-based mechanistic studies and spectroscopic analyses on reaction intermediates of catalytic reactions.

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Introduction

The homogeneous catalysts with transition-metal complex are widely used for olefin polymerization, and for manufacturing of fine chemicals, medical and agricultural chemicals, and electronic materials. With the use of the catalysts, many types of compounds have been synthesized to bring new functional materials into the market. In addition, organometallic catalytic reactions occur in living organisms to play an important role for sustaining life. It is known that the reaction mechanism with organometallic catalyst consists of more than one intermediate and transition state. To control the reactions, it is necessary to correctly understand the complicated mechanisms. The development of highly-active catalysts is significantly important for chemical companies because the consumed amount of transition metals will be reduced and environmentally-friendly and cost-cutting processes will be established.

1. Tasks of Theoretical Calculation

From the perspective of molecular theory, a variety of chemical phenomena come out mainly from changes of electronic state in molecules. Compared with theoretical and experimental data, this is easily understood. For example, irradiation of compounds by specific light from UV or XPS rays causes electron excitation from occupied to virtual orbitals. Chemical reactions are also one of the chemical phenomena along with bond formations and cleavages from changes of electronic states among reactants, reagents, and catalysts. A wide variety of performances of transition-metal catalysts are considerably dependent on the electronic states belonging to d-orbital electrons having different oxidative or spin states designed by coordinated ligands. To explore high-performance catalysts, analytical investigation based on electronic states is necessary, and theoretical calculations are indispensable for determining the electronic states.

2. Methods of Theoretical Calculation

The number of articles relating to theoretical calculation has recently increased in the fields of spectroscopy assignments, study of electronic states and structures, and elucidation of reaction mechanisms. This trend is due to improvements in CPU speeds and the development of advanced molecular theories. **Table 1** lists major theoretical methods which are available in many program packages. By the 1980s, most of the major *ab initio* molecular orbital theories had been established, and nowadays they precisely reproduce spectroscopic parameters for molecules with a couple of dozen atoms. Among these, the use of density functional theory (DFT) has rapidly progressed after 1990, and DFT makes an important contribution to promotion of theoretical calculations. With DFT, the electronic state of the chemical compounds is expressed by electron density functionals, which have been modified and proposed by many types of approaches for improving computation accuracy. The DFT method realizes a high accuracy that

Table 1 List of major theoretical calculation methods

Method	Scaling factor for Basis set	Content
HF	N^4	The simplest *ab-initio* method
DFT	$N^{3\sim4}$	The DFT reproduces a high level *ab-initio* MO with reasonable computational costs, but depends on the accuracy of functional.
MP2	N^5	The MP2 is the simplest method to take account of dynamical electron correlation and describe the weak interaction energy such as van der waals.
CASSCF	N^5	The CASSCF is the one of the multi-configurational method and used for the analyzing the reaction pathway.
MRMP2	N^6	The MRMP2 is quantitatively multi-reference method to take account to statical and dynamical electron correlations.
CCSD	N^6	The CCSD utilizes the exponential cluster operator to efficient take account an electron correlation with single and double excitations.
CISD	N^6	The CISD is a popular multi-configurational method including electron correlation and its procedure is very simple.
CCSD(T)	N^7	The CCSD(T), added perturbative triple excitation term to CCSD, is current gold standard of *ab-initio* MO method.

*) N refers to the number of basis functions. For example, the computational cost of HF method is proportional to the fourth power of the N.

is comparable to the relatively state-of-the-art *ab initio* calculations without high computational costs. It is noteworthy that DFT calculation is widely applied not only to the assignment of experimental spectra, but also to the study of reaction mechanisms. There are many articles about the guidelines for catalyst design discussed by synthetic chemists with the support of theoretical chemistry. DFT calculation is now readily performed owing to low-cost computing, convenient programs, and many high-performance functional developments.

In fact, the number of papers describing DFT calculations in coupling reactions with complex catalysts has rapidly increased since 2000 (**Fig. 1**). For example, 25% of all the papers of the ACS journal Organometallics in 2007 has reported articles relating to theoretical calculations.1) While catalytic reaction mechanisms studied by theoretical calculations have become popular in recent years as described above, the number of papers that fully discuss the adequacy of reaction mechanisms obtained from theoretical calculations in light of experimental data is still limited.

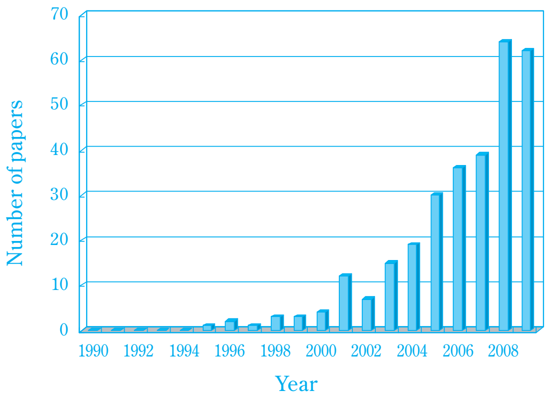


Fig. 1 Number of papers involving DFT studies on organometallic-catalyzed coupling reactions

One thing should be noted in using DFT methods. With DFT, many types of functionals with corrections to improve calculation accuracy have been proposed. Unless appropriate functionals are applied, accurate calculation results may not be obtained. So it is necessary to check whether the functionals and basis sets are appropriate before launching full calculations.

This review is focused on the discussion of homogeneous (solution system) catalytic reactions with organometallic catalysts. We describe the comparison of calculation accuracy for each functional, reaction mechanism studies with organometallic catalysts, and the detection of reaction intermediates by mean of spectroscopic measurement and theoretical calculations. In a limited number of analytical methods to identify the short-lived reaction intermediates, highly versatile stopped-flow UV spectrum measurements were applied. Before UV measurement, we predict the spectra for the corresponding intermediates by theoretical calculations. As expected, the spectra were observed to determine the reaction mechanism.

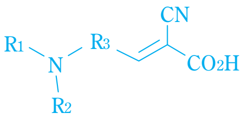
Theoretical Chemistry and Analytical Chemistry

In the developmental stages of functional materials and the related catalysts, theoretical calculations are often performed to compare with analytical experiments for complementary purposes. The analytical targets are mainly spectroscopic data, for example, IR, Raman, UV, ESR, and NMR spectra that are routinely calculated by standard program packages. It is known that experimental vibration spectra for common neutral organic molecules are reproduced by theoretical calculations within ca. 10% error or less.[2] The performance is, therefore, practical for assigning the spectra observed in the experiments. Once magnetic parameters, which consist of ESR parameters, *g*-values (*g*-tensor) and hyperfine coupling constants (A-tensor) for paramagnetic nuclei or NMR chemical shift for compounds without unpaired electron, are experimentally observed, the chemical structures are basically determined without any theoretical calculations. However, spectra for molecules such as polymers indicate sometimes that they are more complicated than the low-molecular-weight molecules which are simply predicted by theoretical calculations.[3] DFT calculation is useful for solving such problems.[4] For hydrocarbon compounds, the B3LYP functional level with DZVP and TZVP basis sets are frequently used and reproduce the experimental spectroscopic data precisely.[5] Also the hyperfine coupling constants calculated by the BHandHLYP functional with 6-31+G (3df, 3pd) basis set including a solvent effect are in good agreement with experimental values for nitroxide radicals used as spin-label agents or catalysts.[6]

On the other hand, it is difficult for DFT calculation to reproduce the experimental NMR chemical shift and ESR hyperfine coupling constants for compounds with heavy nuclei due to remarkable relativistic effects such as transition-metal complexes.[6]

With DFT methods, suitable functionals for accurate calculations depend on the types of physicochemical properties, spectroscopies, and chemical structures, so the functionals should be carefully adopted for each purpose. Here we present the reproducibility of UV spectrum maximum absorption wavelengths for pigments depending on several functionals.

As for five pigments (**Fig. 2**) reported by Grätzel et al.,[8]–[13] the reproducibility of UV spectra estimated by several theoretical calculations are summarized in **Table 2**. The semi-empirical ZINDO (Zerner's Intermediate Neglect of Differential Overlap) method and the



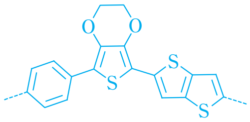
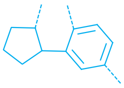
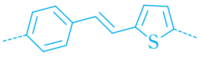
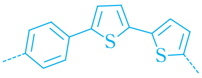
	R_1	R_2	R_3
A	*p*-methoxy phenyl	Same as R_1	
B	*p*-methoxy phenyl		
C	Phenyl	Same as R_1	
D	9,9-dimethyl -9H-fluorenyl	Same as R_1	
E	Phenyl	Same as R_1	*p*-Phenylene

Fig. 2 Dye structures, A to E

Table 2 The calculated excitation energies in eV for lowest excited state of A, B, C, D, and E using various functionals

Method	Dye					MAE*c)
	A	B	C	D	E	(%)
ZINDO	2.93	4.13	3.39	3.20	4.24	11.7
CIS	2.87	3.87	3.03	3.03	3.96	8.7
MPWB1K*a)	2.50	3.46	2.70	2.60	3.40	3.6
CAM-B3LYP*a)	2.64	3.48	2.97	2.78	3.45	4.4
BLYP*b)	2.08	2.44	1.60	2.22	2.45	11.8
BPBE*b)	2.08	2.43	1.61	2.24	2.46	11.7
BPW91*b)	2.08	2.43	1.61	2.24	2.45	11.7
LC-BLYP*b)	2.78	3.44	2.90	2.93	3.56	5.5
LC-BPW91*b)	2.80	3.45	2.92	2.96	3.57	5.7
L-BPBE*b)	2.80	3.45	2.92	2.96	3.57	5.8
B3LYP*b)	1.79	2.85	2.01	2.64	2.82	7.8
BHandHLYP*b)	2.41	3.30	2.54	2.53	3.32	3.4
(Experimental)	2.25	3.18	2.81	2.84	3.21	–

a) Calculated by Grätzel group with 6-31G basis set in vacuum[13].
*b) Our results calculated with 6-31G** basis set in vacuum.
*c) The percentage of the mean absolute errors.

CIS (Configuration Interaction Singles) method, which are the simplest *ab initio* calculation methods for excited states, overestimated the wavelength by ca. 1eV. Besides the ZINDO and CIS methods, TD-DFT (Time-Dependent DFT) methods were used with various functionals. The results of TD-DFT calculation indicated that the reproducibility for experimental UV significantly depends on the functionals. In a vacuum, pure DFT functionals without HF exchange terms, such as BLYP, are at almost the same values. The functionals with long-range correction resulted in all of them shifting toward the higher energy side (toward shorter wavelengths). The hybrid functionals B3LYP including 20% HF exchange term underestimated, however, BHandHLYP (including 50% HF exchange) estimated to be within ca. 0.3eV error.

The excitations corresponding to the pigment's maximum absorption wavelength are π-π^* transition between the frontier orbitals (**Fig. 3**). With respect to the solvent effect in the excited state, the linear response (LR) model[14), 15)] indicated a trend to shift to the lower energy side (shift to longer wavelengths) than the vacuum, and the State Specific (SS) model, which is treated as self-consistent for each electron state,[16), 17)] indicated that the absolute deviation was improved due to the relaxation of the electronic state in the solvent. In spite of the presence or absence of the solvent effect, the BHandHLYP hybrid functional was found to be in the best agreement with the experimental data.

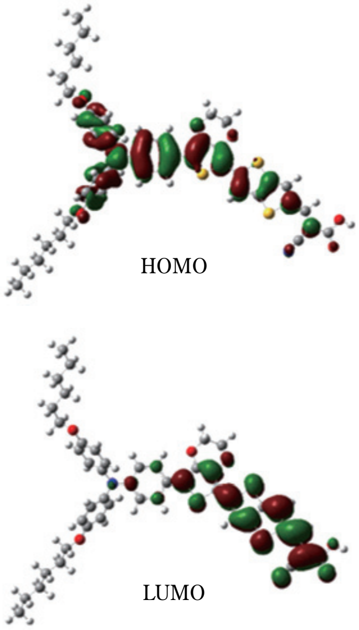
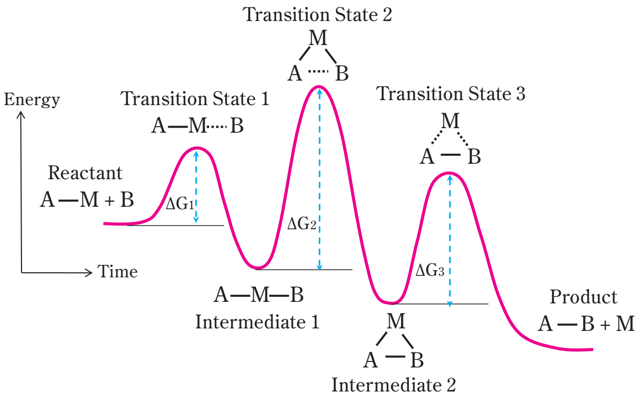


Fig. 3 Frontier orbitals of A estimated by BHandHLYP/6-31G**

Theoretical Chemistry and Chemical Reaction

1. Energy Diagram

When the reaction mechanism in the presence of a complex catalyst is successfully elucidated by theoretical calculations, an energy diagram of the mechanism is generally illustrated as shown in **Fig. 4**, which indicates that the reactant located on the left side in the diagram reaches the product on the right side via several intermediates and transition states. In **Fig. 4**, three transition states are depicted as saddle points, and the energies required to go over each barrier (ΔG_1, ΔG_2, and ΔG_3) are called activation energies.



ΔG_1, ΔG_2, ΔG_3: Activation Energy

Fig. 4 Reaction energy diagram

The activation energies include electronic and steric effects, and the energy values represent quantitative reactivity. According to the theory of absolute reaction rates, the reaction rate constant k is calculated from the activation Gibbs free energy ΔG^* using equation (1). A smaller ΔG^* provides a larger reaction rate (equal to a faster reaction), and a larger ΔG^* provides a smaller reaction rate (equal to a slower reaction).

$$k = \frac{k_B T}{h} e^{-\frac{\Delta G^*}{RT}} \qquad (1)$$

In equation (1), k_B, h, T, ΔG^*, and R represent Boltzmann's constant (1.38×10^{-23} J/K), Planck's constant (6.62×10^{-34} J s), the reaction temperature (K), the activation Gibbs free energy (J/mol), and the gas constant (8.31 J/mol K), respectively.

To synthesize the key intermediate of vancomycin, for example, a Suzuki coupling reaction was applied to make a new C-C bond between two aromatic rings (**Fig. 5**).[18a)] At present computer power, it is possible to elucidate this reaction mechanism by DFT calculation without downsizing the target structure as shown in **Fig. 6**. **Fig. 6** illustrates an energy diagram of the transmetalation step in the Suzuki coupling reaction with a catalytic ligand PPh_3.18b) From the results of theoretical calculations, the transmetalation step proceeds from the oxidative-addition intermediate via two transition states into the reductive-elimination intermediate. The activation Gibbs free energy was estimated to be 24.8 kcal/mol. From the result, if the activation free energy of a certain ligand is estimated to be lower than 24.8 kcal/mol, the ligand is regarded as more reactive than PPh_3. In the case of a catalytic reaction of the same size as shown in **Fig. 6**, theoretical calculations contribute to catalyst design, because the reactivity for candidate catalysts may be quantitatively estimated.

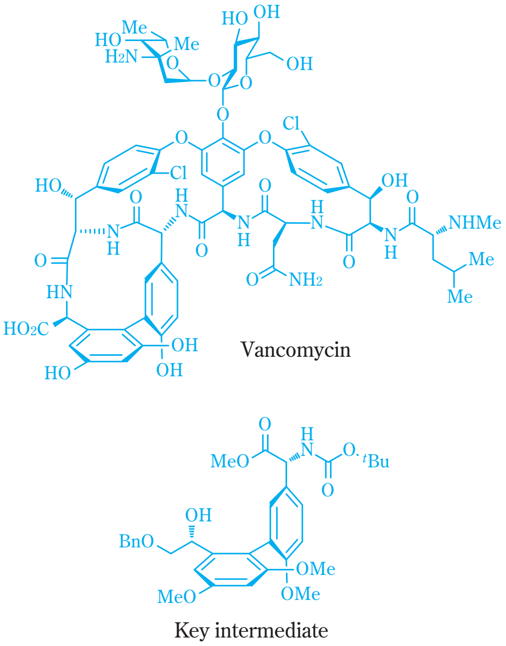


Fig. 5 Vancomycin and key intermediate

2. Current Reaction Mechanism Analysis by Theoretical Calculation

At this moment, it is impossible to reproduce automatically the real catalytic reaction occurring in a flask by computational simulation in a rational time scale. To analyze reaction mechanisms, researchers have made assumptions of possible intermediates and transition states, and subsequently the assumptions are carefully evaluated using the energies of the reaction path estimated by theoretical calculations.

In most existing theoretical calculation programs, the search algorithms generally look for only energetically optimized intermediate and transition state structures which are closest to the initial input structures (so-called "local minimum" structures), and they cannot automatically find the global minimum structures in the reaction path. Since the theoretical calculation of intermediates and transition states depends on the initial structures manually prepared by researchers, it is quite difficult to determine a reliable mechanism without knowledge and information with respect to the catalytic reactions. All possible intermediates and transition states are examined by theoretical calculations, and then the energetically lowest reaction path is regarded as the final catalytic reaction mechanism.

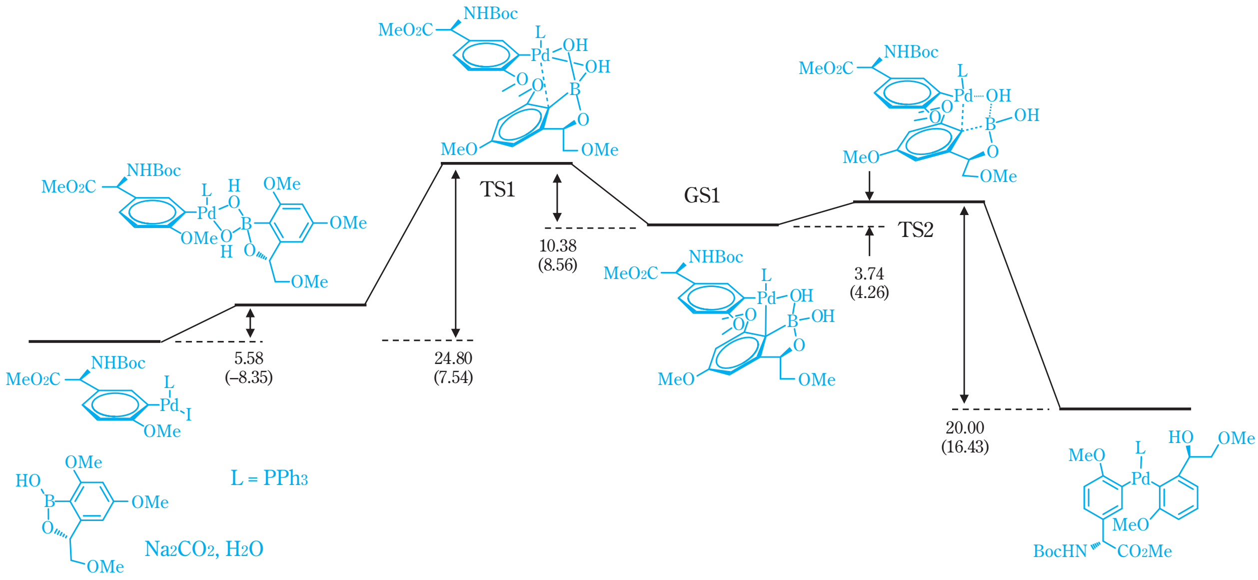


Fig. 6 Energy diagram of transmetalation step in kcal/mol

Even for computationally-optimized reaction mechanisms through such an enormous amount of tasks, verification is still needed by means of comparison with experimental data. Next, we report on the method to analytically verify the results obtained by theoretical calculations.

3. Verification of Reaction Mechanism obtained by Theoretical Calculation

To confirm whether the reaction mechanism obtained by theoretical calculations is correct or not, if there are experimental data with several reaction yields, the correlations between the experimental data and the calculated activation energy are examined first. In the case of a shortage of experimental data for correlational analysis or poor correlation between experimental and computational data, observation of the reaction intermediates suggested by theoretical calculations is a practical and reliable method.

Experimental observation of intermediates is conclusive evidence for elucidation of the reaction mechanism, but it is not easy. Identification of a reaction intermediate structure by means of X-ray crystallography is very rare, and identification of all intermediates appearing in the reaction is almost impossible. In a series of intermediates, the most likely detectable intermediate is the last one before the rate-determining transition state step which indicates the highest activation energy in the reaction. In other words, through spectroscopic observation of the intermediate, the rate-determining step is indirectly observed. This is very important information for understanding and confirming the reaction mechanism estimated by theoretical calculations. We can afford to say that if the analytically observed intermediate is not included in the reaction mechanism proposed by theoretical calculations, the mechanism should be reconsidered.

Identification of Reaction Intermediates

1. Observation Methods for Reaction Intermediates

To observe the reaction intermediates with the help of analytical chemical techniques, the reaction rate should be decreased enough to observe, or alternatively analysis equipment for short-time period measurement should be employed. According to equation (1), one can see that one of the effective ways of reducing the reaction rate is to decrease the reaction temperature. Meanwhile typical analytical methods using short-time measurements are summarized in **Table 3**. NMR measurement is useful and can easily identify structures when successfully observed. NMR is, however, difficult for paramagnetic nuclei and for low concentration solutions due to its sensitivity. Identification of structures by the UV spectrum is uncommon because the shape of the spectrum is too simple to assign structures. However, absorption wavelengths of the organometallic complex (d-orbital-electron-derived excitation) are generally different from those of organic

Table 3 List of major analytical methods for observation of reaction intermediates

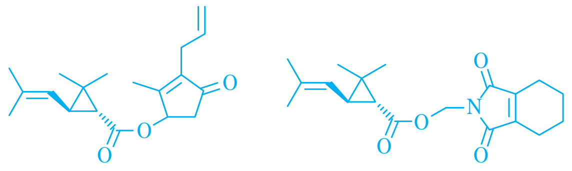
Method	Content
Flow NMR	Flow NMR techniques are superior for determination of chemical structures without paramagnetic substances. The measurement needs a certain level of concentration, and the time is on the second time scale. Example of application: chlorination of thioamide derivatives19), the synthesis of imidazole rings20), and the metallocene-catalyzed polymerization of alkene21).
Stopped Flow UV	Stopped flow UV techniques are wide-range application of intermediate observation in homogeneous reactions, however the spectrum is simple with little structure information. The measurement time is on the millisecond time scale. Example of application: synthesis reaction of Cu complexes with active oxygens22), oxidation reactions with Iron binuclear complexes23), and Diels-Alder reactions of tetradines24).
Stopped Flow ESR	Stopped flow ESR (Electron Spin Resonance) is technique only for observation of paramagnetic chemicals. The sensitivity of chemical concentration is better than NMR. Example of application: ligand exchange reactions of Cu complexes25), degradation of active oxygen species26), and Fenton reaction27).
React IR	React IR (Infrared spectroscopy) technique is one of the most popular ones, however the spectrum is sometimes too complicate to assign the intermediates.
Direct ESI-MS	Direct ESI-MS (Electrospray Ionization Mass Spectrometry) needs ionization of reaction intermediates, and the measurement of time-dependent change is difficult. The measuring objects are sometimes affected by ionizations.
Pulse Laser	The low-molecular-weight intermediates are observed with ultrashort laser pulse and gas phase-molecular beam on the femtosecond time scale, which is equal to 10^{-15} of a second time scale.

compounds such as reactants, products and solvents. UV spectra are relatively well reproduced by theoretical calculations. Hence, identification of structures was tried using the UV spectrum. Measurement of the UV spectrum to identify the reaction intermediates is one of the promising methods in cases where NMR measurement is difficult.

As an example of analytically detecting short-lived intermediates and determining the proposed mechanism, we wish to report that the short-lived reaction intermediate Cu(I)-carbene complex for an asymmetric cyclopropanation was identified by measurement of the UV spectrum and theoretical calculations. The catalyst has been developed by Sumitomo Chemical. We chose the stopped-flow UV spectrum measurement because the reaction system includes a paramagnetic Cu(II) complex.

2. Asymmetric Cyclopropanation Catalyst

Optically active cyclopropanecarboxylate esters are important compounds in the fields of pharmaceuticals and agricultural chemicals, and at Sumitomo Chemical the ester derivatives are used as key components in pyrethroid insecticides (**Fig. 7**). The cyclopropyl ring has two asymmetric carbons and four types of isomers, in which only *d*-trans and *d*-cis isomers demonstrate insecticidal activity and the activity of the *d*-trans isomer is higher than that of the *d*-cis isomer. For this reason, it is necessary to develop a high-performance catalyst for asymmetric synthesis. Sumitomo Chemical has discovered copper catalysts with chiral salicylaldimine ligands and has been continuously improving the activity and selectivity to develop an industrial catalytic process which is more cost-efficient than optical resolution processes.[28)]



bioallethrin tetramethrin

Fig. 7 Synthetic pyrethroids with chrysanthemate moiety

With respect to the reaction mechanism analyzed by theoretical calculations, it has been reported that the cyclopropanation reaction proceeds as follows: [1] the terminal nitrogen atom in ethyl diazoacetate coordinates to Cu(I); [2] along with detachment of N_2, ethyl diazoacetate concertedly reacts with Cu(I) to form a Cu(I)-carbene complex; [3] Cu(I)-carbene carbon attacks olefin double bonds to form a cyclopropane skeleton; and [4] finally, Cu(I) is reproduced (**Fig. 8**).[29)] The rate-determining step is that [3] Cu(I)-carbene attacks olefin to form cyclopropyl rings with two asymmetric carbon centers.

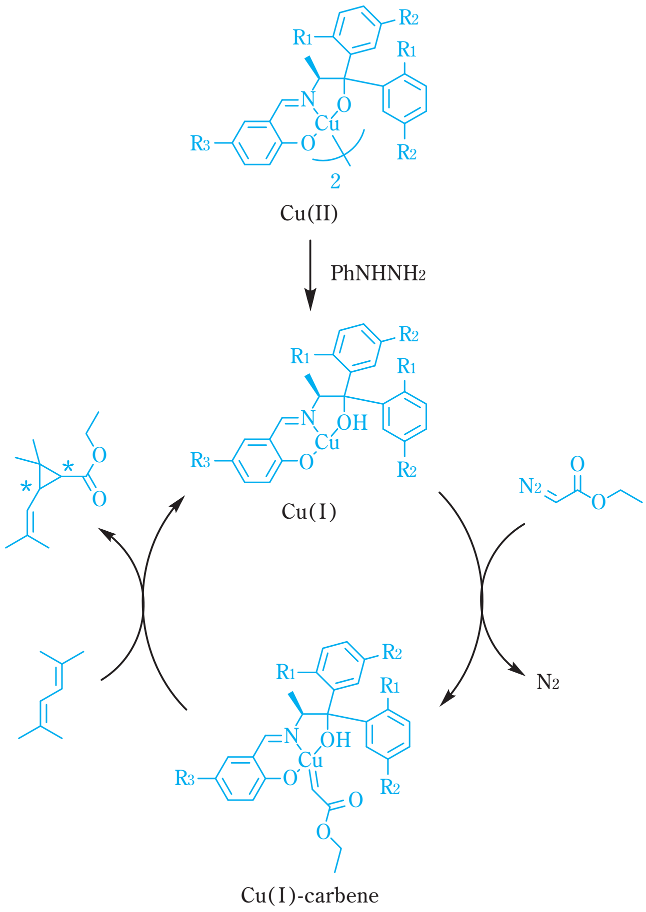


Fig. 8 Reaction mechanism of asymmetric cyclopropagation using Salicylaldimine-Copper catalyst

During cyclopropanation, diethyl maleate and diethyl fumarate are known to be formed as by-products. The side-reaction occurs in the reaction of Cu(I)-carbene with ethyl diazoacetate instead of olefin in the main reaction. Then, a Cu(I) complex is reproduced and by-products are yielded, which is a similar bond recombination to the main catalytic cycle (**Fig. 9**). In the main and side catalytic cycles, the Cu(I)-carbene complex is a detectable , and is the last intermediate before the rate-determining step suggested by theoretical calculations.

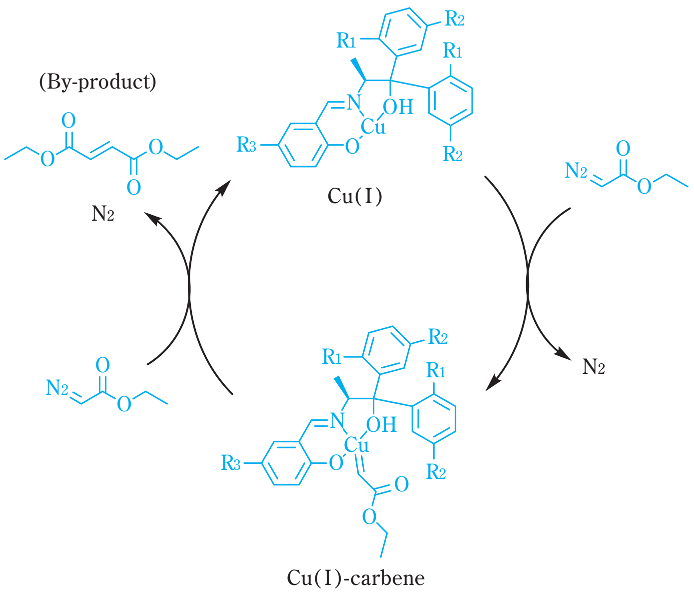


Fig. 9 Side reaction mechanism of cyclopropagation

The Cu(I)-carbene complex is extremely unstable, and there is no publication dealing with the observation of Cu(I)-carbene structures with standard ligands in asymmetric cyclopropanation, except for specific ligands utilized.30) We attempted to observe the intermediate using the stopped-flow UV31) spectrum measurement technique to confirm whether the Cu(I)-carbene complex was formed or not in the catalytic reaction.

3. Detection of Short-lived Cu(I)-Carbene Complex Intermediate

In the formation of the Cu(I)-carbene complex, the UV spectrum changes per millisecond were observed at the time of the reaction of ethyl diazoacetate and the Cu(I) catalyst with the salicylaldimine ligand. During the stopped-flow UV spectroscopy measurement, toluene solutions of Cu(I) complex and ethyl diazoacetate were mixed in the equipment by spraying with nitrogen gas.

In advance of the UV spectroscopy measurements, the spectra of intermediates, toluene, ethyl diazoacetate, and by-products diethyl maleate and diethyl fumarate were predicted by TD-DFT calculations. The calculations were conducted at B3PW91 level with m6-31G* basis set for Cu, and 6-31G* basis set for other atoms, and the solvent effect for toluene was taken into account (**Fig. 10**).

Absorptions near 500 nm were predicted for Cu(II) and Cu(I)-carbene complexes, but not for the Cu(I) complex. Since Cu(II) was reduced to Cu(I) by phenylhydrazine before the catalytic cycle started, Cu(II) and Cu(I)-carbene never exist together. It was expected that the absorption near 500 nm of the Cu(I)-carbene complex would be observed only during the ongoing catalytic cycle.

Cu(I)-carbene intermediate was measured by the stopped-flow UV spectrometer. To compare experimental data and theoretical calculations, we monitored the changes in UV spectra during reduction of the dimeric Cu(II) complex with phenylhydrazine, which is the catalyst activation step and is not included in the catalytic cycle. The result was confirmed to be reasonable as shown in **Fig. 11**. For the Cu(II) complex, the absorption disappeared near 500 nm by reduction. Next, the reduced Cu(I) complex and ethyl diazoacetate were mixed to observe the intermediate in the catalytic cycle. Soon after mixing, absorption near 500 nm appeared for several tens of seconds and then disappeared, and this was successfully observed with changes per millisecond (**Fig. 12**). The observed changes meant as follows: [1] The appearing absorption near 500 nm corresponded to formation of the Cu(I)-carbene species. [2] The carbene reacted with ethyl diazoacetate to generate diethyl maleate or fumarate. [3] The absorption of the Cu(I)-carbene complex disappeared after the consumption of all diethyl diazoacetate.

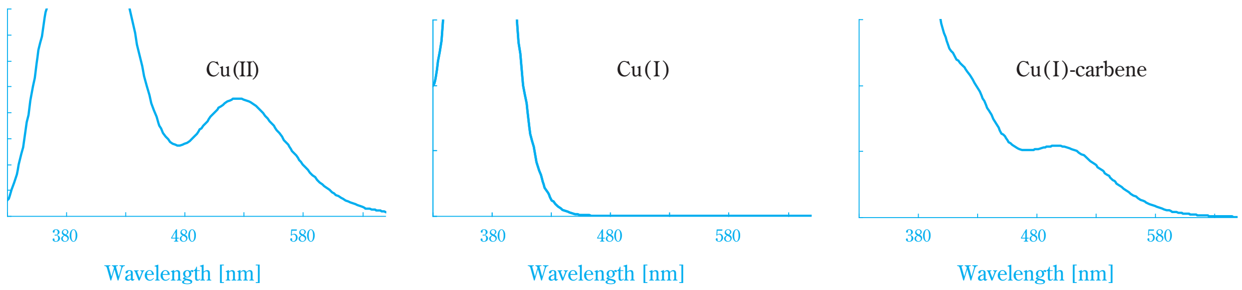


Fig. 10 Calculated UV spectra of Cu(II), Cu(I), and Cu(I)-carbene complexes

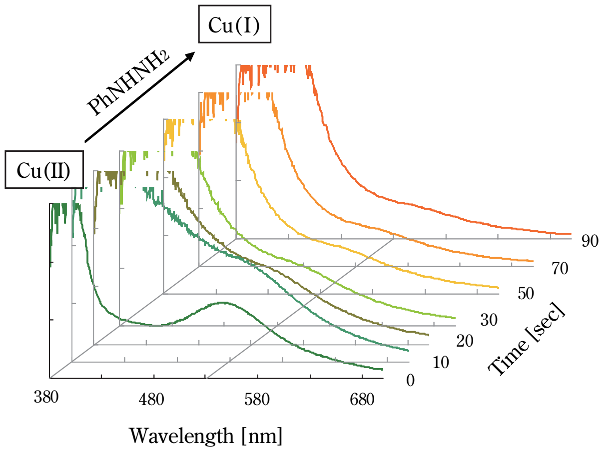


Fig. 11 UV spectral shift of Cu(II) reduced into Cu(I) complex by phenylhydrazine

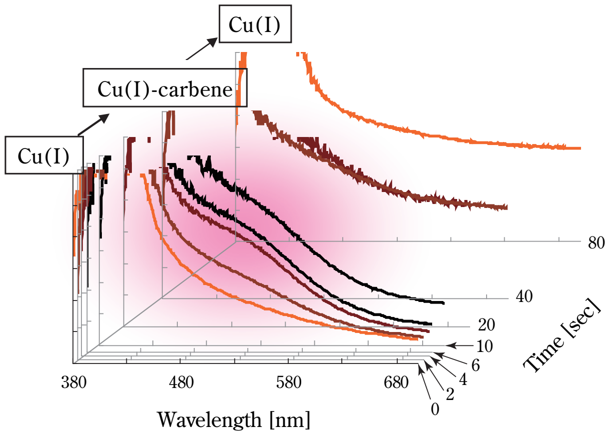


Fig. 12 UV spectral shift of Cu(I) reacting with diazoacetate to appearance of Cu(I)-carbene complex

In summary, the catalytic reaction mechanism including unstable intermediates was estimated by theoretical calculations, and the mechanism was verified by detection of the intermediates through measurement of UV spectroscopy. With the help of analytical measurements, theoretical calculations were proven to have the potential to analyze reaction mechanisms successfully.

Conclusions

The goal of uncovering reaction mechanisms with the help of theoretical calculations is to design and explore high-performance synthetic catalysts. Once the reaction mechanism is cleared, theoretical calculations can predict the quantitative reactivity of virtual catalysts and propose computationally-optimized catalysts. If the reaction mechanism is analyzed in detail, the theoretical prediction will be more accurate and thus virtual screening of catalysts will become a real possibility. In fact, computer performance has been improved tremendously and shows no sign of slowing down, and so we could argue that theoretical calculation will undoubtedly become a powerful technique in catalyst design.

On the other hand, it is time-consuming to analyze a reaction mechanism with nothing other than theoretical calculations and it is somewhat uncertain whether correct answers are obtained or not by the conventional method, which is to simply search for the reaction transition states and intermediates manually. Recently a new theoretical calculation method involving automatic searching for the reaction path has been proposed and has attracted attention.[32)] It is expected that the computational accuracy of reaction pathway analysis will improve as well as that of spectroscopic assignments. Through collaboration between analytical chemistry, synthetic chemistry, and theoretical chemistry, it is additionally expected that true reaction mechanisms can be determined in a short time and new catalysts can be discovered in silico.

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