Reactivity Prediction Through Quantum Chemical Calculations

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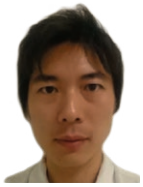

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The main challenge in chemistry is understanding and controlling the movement of atoms, which play a leading role in chemical reactions. In principle, one could predict the movement of atoms by solving the Schrödinger equation, however, which for many-particle systems is too complicated to solve with high accuracy. Thanks to advances in quantum chemical calculation methods, the Schrödinger equation for the motion of electrons is solvable with reasonable accuracy under various approximations.[1] Among the approximation algorithms, the density functional theory (DFT) based on the Kohn-Sham equation is routinely used in calculations of the potential energy surface (PES) for a system of several hundred atoms.

DFT-BASED REACTION mechanism study is currently popular. By performing DFT calculations for each ever-changing nuclear configuration, molecular dynamics (MD) calculations simulate the motion of atoms while solving Newton's eqation of motion based on the gradient of the PES.[2] Nevertheless, MD calculations require DFT calculations every 10^{-15} seconds in the simulation step width, and as many as 10^{6} DFT calculations are necessary to run a simulation of 10^{-9} seconds.

Many reaction mechanism studies discuss energy profiles.[3-5] After geometry optimization obtains the transition state (TS) of each elementary reaction process,[6] the movement of atoms during the reaction is visualized by the intrinsic reaction coordinate (IRC) calculated from the TS.[7,8] Then, an energy profile can be drawn using the energy levels of the TS and the two end-points along the IRC path. Since several tens to several hundreds of DFT calculations are needed for one geometry optimization and one IRC calculation each, the calculation cost is much lower than MD calculations. On the other hand, the TS obtained by geometry optimization depends on the initial structure, which is generally created based on the computators' own experience and intuition. Therefore, it is necessary to repeat DFT-based geometry optimization calculations for the mechanism assumed by the computators until the energy profile becomes consistent with the experimental result.

Recently, several automated reaction path search methods that do not require the initial structure of TS have been developed.[9-11] The methods enable systematic analysis of reaction mechanisms without relying on the computators' experience or intuition. In addition, the automated reaction path search methods are opening the way to *ab initio* prediction of new chemical reactions passing through unknown reaction paths. This article outlines the artificial force induced reaction (AFIR) method, which has been developed by the authors.[12-15] Further, by applying the rate constant matrix contraction (RCMC) method, a kinetic analysis method developed by the authors, to the reaction path network obtained by the AFIR method, the products and their formation paths can be elucidated.[16,17] Combined usage of the AFIR and RCMC methods also facilitates on-the-fly kinetic simulation to explore elementary reaction processes while solving the chemical kinetics.[18] Finally, this article introduces quantum chemistry aided retrosynthetic analysis (QCaRA), which searches reaction paths backward from a product to possible reactants, and its application to chemical reaction discovery.[19]

Artificial Force Induced Reaction (AFIR) Method

The basic idea behind the AFIR method is quite simple, as explained below. The fragments in a molecule or complex are repeatedly pushed against each other or pulled apart by an artificial force. Fig. 1(a) shows the AFIR function F^{AFIR} applying an artificial force between fragments A and B, where **Q** is a set of variables describing the molecular structure, E is PES, α is a parameter defining the strength of the artificial force, R_i is the covalent radius of the i-th atom, r_{ij} is the distance between the i-th and j-th atoms, and p is a parameter (after adjustment, it is set p = 6). This procedure for minimizing F^{AFIR} corresponds to the application of an artificial force between substructures A and B. The three examples in Fig. 1(b) indicate that different molecules can be obtained by specifying various fragments, A and B, in each case and minimizing F^{AFIR}. In other words, by systematically generating combinations of A and B and minimizing F^{AFIR} for each instance, new

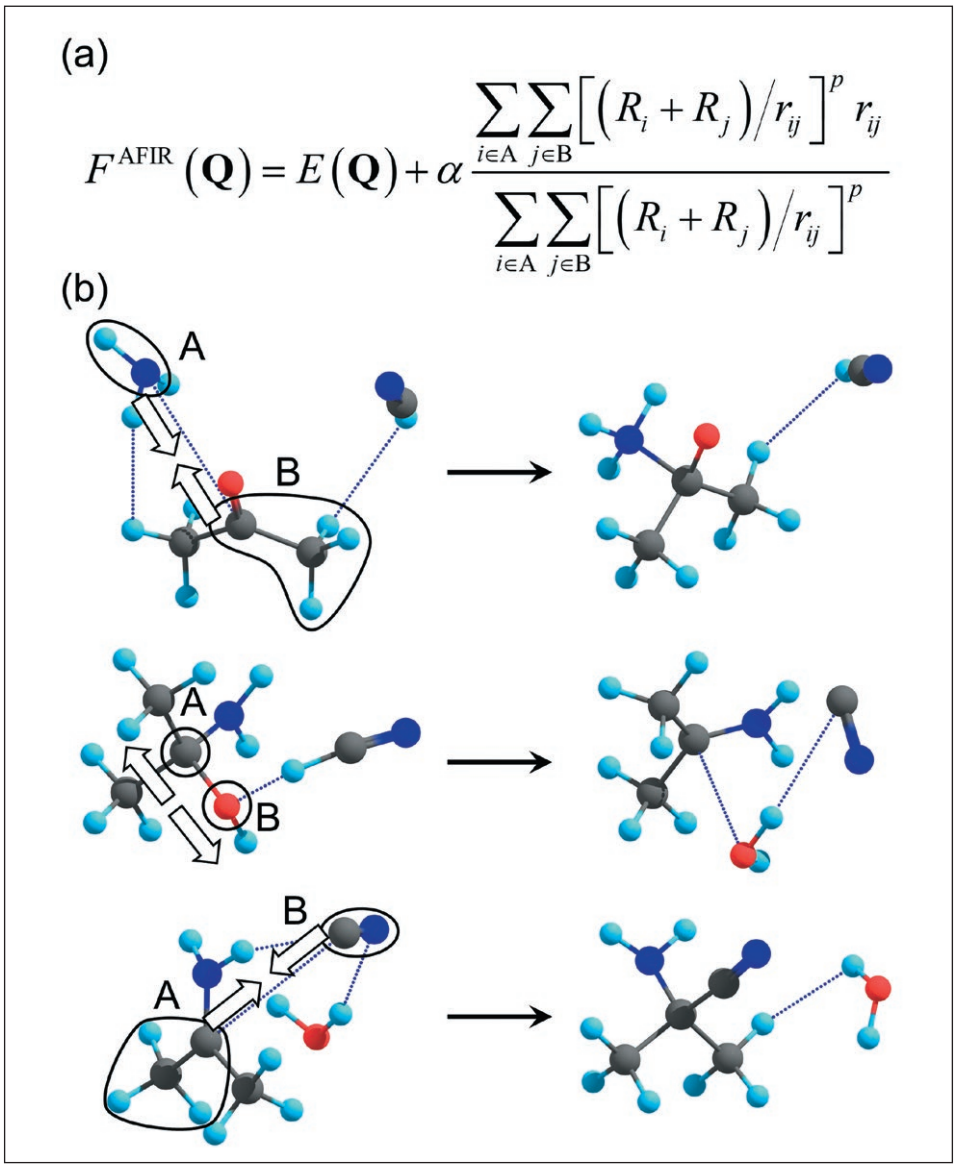


Figure 1 (a) AFIR function applying an artificial force between fragments A and B, (b) reactions induced by the artificial force between different fragment pairs.

molecules can be assembled on a computer as if building up Lego brocks. Moreover, it is possible to efficiently calculate and automatically search for the actual reaction path based on the path followed by the system in the process of minimizing F^{AFIR}.

The AFIR method has made it possible to automatically search for stable structures that the system can adapt in its chemical composition, isomerization paths among them, and their decomposition and formation paths, by starting from a set of input molecules. The connections between stable structures via reaction paths can be visualized as a reaction path network, where each node in the reaction path network represents a stable structure, and the edges between them represent the connections between stable structures. In the reaction path network, an enormous number of paths exist between the node of the reactant and that of the product, so are energy profiles. Among them, the path that gives the most favorable energy profile is the one for the actual chemical reaction.

The reaction path network obtained by the AFIR method often contains over 1000 stable structures. Kinetic analysis is necessary to identify the product among those structures, considering the experimental conditions. To easily analyze a huge reaction path network, the RCMC method was devised. The RCMC method, which is a kinetic analysis method, forms superstates by clustering stable structures that the system moves back and forth within below or equal to a time constant t_{MAX} given by a user. Each superstate is represented as a linear combination of stable structures as if each stable structure was distributed into multiple superstates. While the stable structure is distributed into superstates, by distributing the initial population given to a specific stable structure in the same way, one can simulate how the population propagates during the thermal equilibration process for t_{MAX} seconds. Thus, one can obtain the population after thermal equilibration for t_{MAX} seconds. The magnitude of the population of each stable structure is comparable to the reaction yield of the stable structure; therefore, one can identify the stable structures corresponding to the major and minor products. From the propagation of the initial population, one can also identify the path that contributes the most to the reaction.

Most importantly, the RCMC method can be used as kinetic navigation for automated reaction path search. Starting from a single stable structure, the AFIR method searches and obtains another stable structure. The AFIR method, then, is applied to the obtained stable structures successively to construct a reaction path network. However, applying the AFIR method to all the obtained stable structures is extravagant. Kinetic navigation solves this problem by applying the RCMC method periodically to the reaction path network during the search, where stable structures that cannot be accessed kinetically from the input structure are excluded from the search target. This process reduces the number of stable structures to which the AFIR method is applied, and hence dramatically cuts down the cost. This can be referred to as on-the-fly kinetic simulation, which performs kinetic simulation without any prior information. In the backward search from a product to various reactant candidates, the kinetic navigation for backward search is also available, where the search target is narrowed down based on the yield of products from each reactant candidate.[20]

Strecker Synthesis

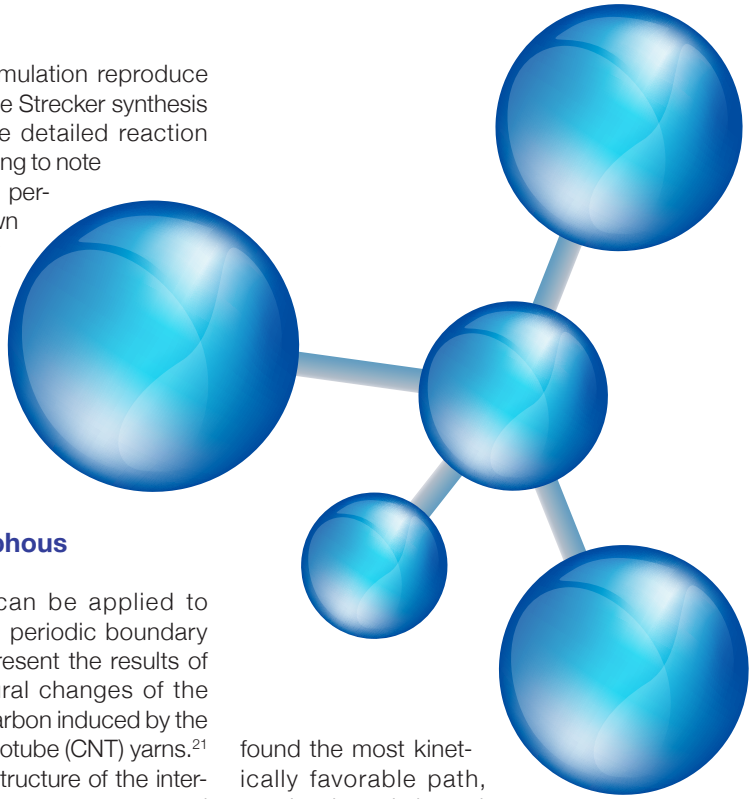
First, we discuss the application to the Strecker synthesis, which is one of the classical organic reactions and is still used in the chemical synthesis of α-amino acids. The typical Strecker synthesis employs a carbonyl compound, ammonium chloride, and cyanide to yield aminonitrile. In this calculation, acetone as a carbonyl compound, ammonium chloride, and sodium cyanide were mixed in water at three different reaction temperatures, 250 K, 300 K, and 350 K, and reacted for one day. The initial structure of the search was generated by the random arrangement of acetone, ammonium cation, cyanoanion, sodium cation, and chloroanion. The initial search was performed by DFT calculations using the ωB97X-D functional, where SV basis functions were used for H, C, N, and O atoms, and Def2-SVP basis functions for Na and Cl atoms. Subsequently, single-point calculations at the ωB97X-D/Def2-SVP level were performed for all discrete points on all paths obtained in the search, where the solvent effect of water was considered by the SMD method.

Fig. 2(a) shows the obtained reaction path network. The above procedure yielded 8042 stable structures and 19543 reaction paths

connecting them. The stable structures were categorized based on the bonding pattern, and the nodes and the edges in the network represent the groups and the reaction path connecting them, respectively. When the RCMC method was applied to the reaction path network, we predicted cyanohydrin ($Me_2C(OH)CN$) would be produced in 97.49 % yield at 250K, while at 300 K and 350 K, the targeted aminonitrile ($Me_2C(NH_2)CN$) would be produced in 97.96 % and 93.28 % yield, respectively. In addition, the examination of the most feasible reaction path revealed that first cyanohydrin was formed even at 300K and 350K, then it returned to the reactant by the retro-cyanation, and finally, aminonitrile was formed.

The white arrows on the reaction path network in Fig. 2(a) illustrate the path from the reactant to aminonitrile, while Fig. 2(b) shows the structural changes along this path. The reactant is a complex consisting of acetone, ammonium cation, cyanoanion, sodium cation, and chloroanion. The reactant undergoes the following steps on the reaction path: (1) the addition of cyanoanion to the carbonyl carbon followed by the proton transfer from the ammonium cation to the carbonyl oxygen generates cyanohydrin, (2) a retro reaction of the step (1) regenerates the reactant complex, (3) the proton transfers from the ammonium cation to the cyanoanion generates ammonia and hydrogen cyanide, (4) ammonia is added to acetone, (5) the proton transfers from hydrogen cyanide to the carbonyl oxygen, (6) the proton elimination by the chloroanion generates a hemiaminal intermediate, (7) the dissociation of water from the hemiaminal intermediate generates an iminium cation, and (8) the addition of cyanoanion to the iminium cation generates aminonitrile.

The results of this simulation reproduce the known features of the Strecker synthesis very well, including the detailed reaction mechanism. It is interesting to note that this simulation was performed without any known information. In other words, based on a priori DFT calculations, we have succeeded in reproducing the reaction mechanism of the Strecker synthesis hitherto proposed.



Thermal Structural Transition of Amorphous Carbon

The AFIR method can be applied to periodic systems using periodic boundary conditions. Here, we present the results of calculating the structural changes of the interfacial amorphous carbon induced by the annealing of carbon nanotube (CNT) yarns.[21] In this application, the structure of the interfacial amorphous carbon was represented by 96 carbon atoms sandwiched between two parallel CNTs, as illustrated in Fig. 3(a). We assumed a one-dimensional periodicity along the two CNTs. As a reference, the same calculations were performed for the system without CNTs. For these systems, the reaction path network consisting of more than 10000 stable structures was obtained by the AFIR search using the DFTB3 method with pbc-0-3 parameters.

Fig. 3(b) illustrates the reaction path network for the structural transition of the interfacial amorphous carbon structure sandwiched between two CNTs. Among the various reaction paths predicted on the network, we found the most kinetically favorable path, passing through the region highlighted by the arrow in Fig. 3(c), was the one for the transition to a structure with more sp^2-bonds. The results of the kinetic simulation using this reaction network shown in Fig. 3(d) also indicate that the transition to the sp^2-bond-rich structure occurs during annealing at 1500 K or higher. On the other hand, in the results of the kinetic simulation for the system without CNTs shown in Fig. 3(e), which was performed as a reference calculation, we found that the transitions to the sp^2-bond-rich structure were suppressed. Amorphous carbon (without CNTs) is known to transform into the sp^2-bond-rich structure only when annealed at 2500 K or

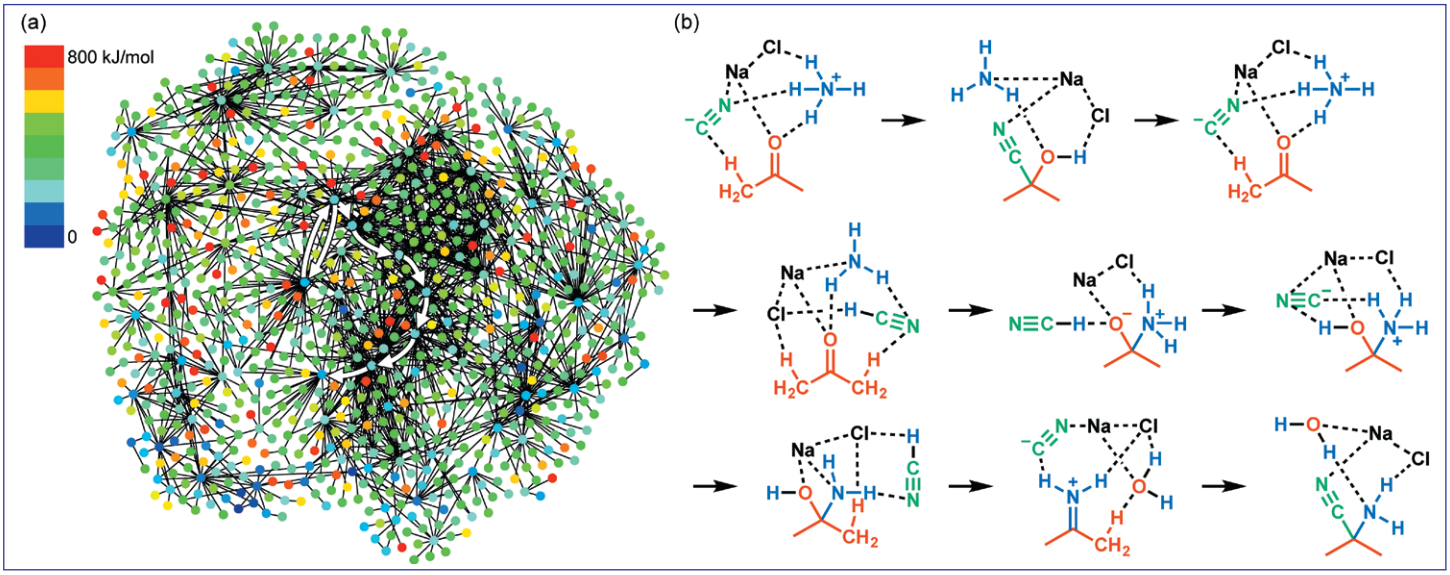


Figure 2(a) Reaction path network of the Strecker synthesis. Each node is colored based on the free energy value of each stable structure. White arrows indicate the path from the reactant to the product. (b) Reaction mechanism of the Strecker synthesis found in the reaction path network as the path highlighted by white arrows.

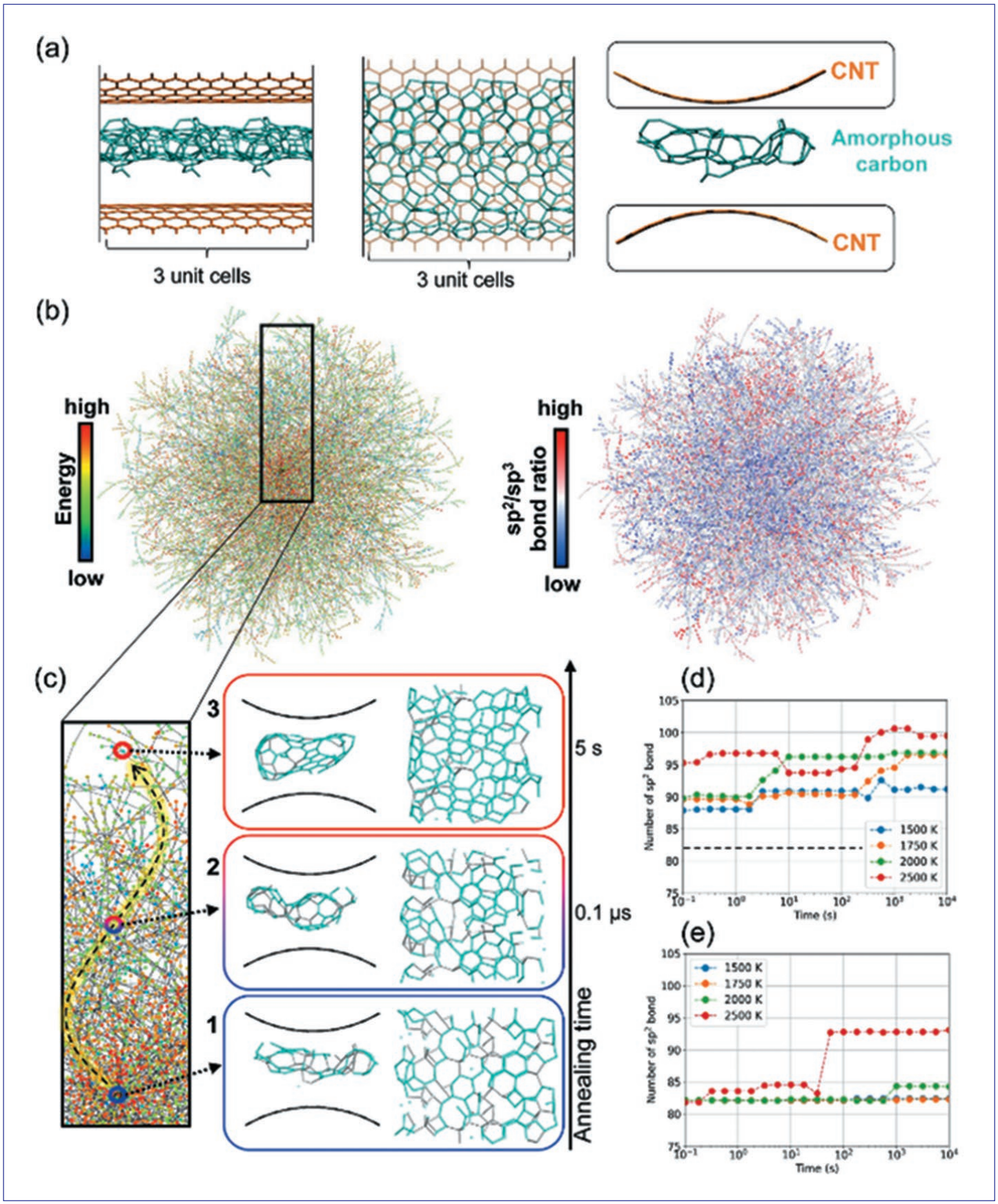


Figure 3(a) Model system used in the simulation viewed from three different directions. Only 3 unit cells are shown for the clarity. (b) Reaction path network for the structural transition of the interfacial amorphous carbon at the interface of the CNTs. The map on the left is colored by the structural energies, while that on the right is colored by the bonding type. (c) The structural transition path from the initial structure **1** to the sp^2-bond-rich structure **3** through the transient structure **2**. The sp^2-type-bonds are colored in cyan. (d) The number of sp^2-bonds with respect to the annealing time. The initial number of sp^2-bonds is shown with black dashed line. (e) Those of in vacuum simulation.

higher; Fig. 3(e) did exhibit this fact. In other words, Fig. 3(d) suggests that the amorphous carbon sandwiched between two CNTs can transform into the sp^2-bond-rich structure by annealing even at relatively low temperatures below 2000K. This prediction was verified experimentally, leading to the discovery of new carbon material with high thermoelectric properties.[21]

In the QM/MM method,the reaction center is treated by the accurate and high-cost QM calculation and the rest by the low-cost MM calculation.

Lactate Dehydrogenase

The hybrid quantum mechanics/molecular mechanics (QM/MM) and microiteration methods are often used together to optimize the structure of macromolecules like enzymes. In the QM/MM method,[22-24] the reaction center is treated by the accurate and high-cost QM calculation and the rest by the low-cost MM calculation. In the case of enzymatic reactions, the QM calculation is often used for regions involving chemical bond rearrangements, while the MM calculation is used for the surrounding proteins. The microiteration method is a technique to reduce the number of QM calculations in geometry optimization using the QM/MM method, where the coordinates of the MM atoms are optimized as the coordinates of the QM atoms change.[25,26] In general, the geometry optimization using the MM calculation is less expensive than a single QM calculation. Thus, the total calculation time can be significantly reduced compared to the geometry optimization when all atoms are treated equivalently.

In the microiteration method, the position of the MM atom changes according to the structural change of the QM part. Therefore, it is not applicable to the case where the structural change of the MM part promotes the reaction. To solve this problem, the multi-structural microiteration (MSM) method was proposed, in which the entire molecule is represented by a single QM structure and a weighted sum of multiple MM structures, as schematically illustrated in Fig. 4(a).[27] The weight of each MM structure is determined by a Boltzmann distribution and varies according to the QM structure.

Recently, by combining the MSM and AFIR methods, a reaction path was calculated in which L-lactate dehydrogenase (LDH) in rabbit muscle catalyzes the transformation of pyruvate to L-lactate. Fig 4(b) illustrates an experimentally proposed mechanism,[28] where (1) the open LDH binds the substrate, (2) the LDH changes from the open form to the closed one, (3) the chemical transformation of pyruvate to L-lactate occurs in the closed LDH, (4) the LDH changes from the closed form to the open one, and (5) the product is released from the open LDH. Before the calculations, we performed replica exchange molecular dynamics simulations and prepared six open-form and six closed-form structures. The MSM method was used to represent the MM structure as a weighted sum of these six open and six closed structures. The QM/MM-ONIOM method was used as the QM/MM method. The QM part was calculated at the B3LYP/6-31+G(d,p) level, and the MM part was calculated using the AMBER force field.

Fig. 4(c) shows the obtained energy profile. Among the three peaks, the middle peak corresponds to the TS for the pyruvate to L-lactate chemical transformation. At this TS, the closed-form structure was dominant as shown in Fig. 4(d), which is consistent with the mechanism in Fig. 4(b). Moreover, the transition from the open-form to the closed-form structure occurred around the first peak, and the transition from the closed-form to the open-form structure occurred around the third peak. These are again consistent with the mechanism in Fig. 4(b). Because the first and third peaks describe changes in the surrounding protein structure, these peaks are termed as surrounding structural TS (SSTS) in Fig. 4(c). The combination of the MSM and AFIR methods could be a powerful computational tool for elucidating the mechanism of enzyme reactions.

Difluoroglycine Synthesis

Finally, we introduce an attempt to propose a new synthetic method by the AFIR method. To achieve this, we adopt a new concept called Quantum Chemistry-aided Retrosynthetic Analysis (QCaRA), which systematically explores decomposition and isomerization paths of a target molecule using automated reaction path search methods like the AFIR method and proposes a synthetic method for the target molecule as a reverse reaction of the obtained path. QCaRA requires the backward search of the reaction path from the product to the reactant; hence, searching for the path through the high barrier must be considered as well. This is because a pathway that proceeds with a low barrier from the reactant may have a high barrier when traced from the product to the reactant. The AFIR method can be used as a reaction path search engine in QCaRA since its capability of exhaustive search, including high barrier paths, has been proved.[15]

QCaRA was proposed in 2013,[9] and the results of its hypothetical application to search for the formation path of glycine molecule was presented. However, over the next seven years, QCaRA was not used in actual organic synthesis. In 2020,[19] the first successful discovery of organic reaction by QCaRA was reported in the development

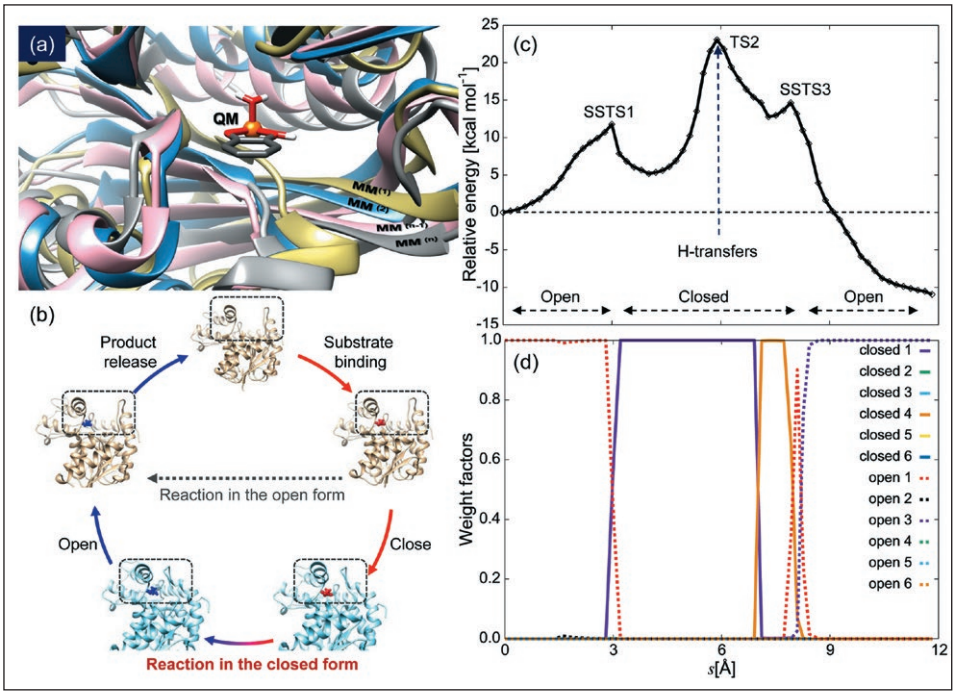


Figure 4(a) Schematic illustration of the MSM method, (b) experimentally proposed reaction mechanism of LDH, (c) energy profile along the minimum energy path for the pyruvate to L-lactate chemical transformation obtained by combining the AFIR and MSM methods, (d) variation of the weights of the MM structures along the path in (c).

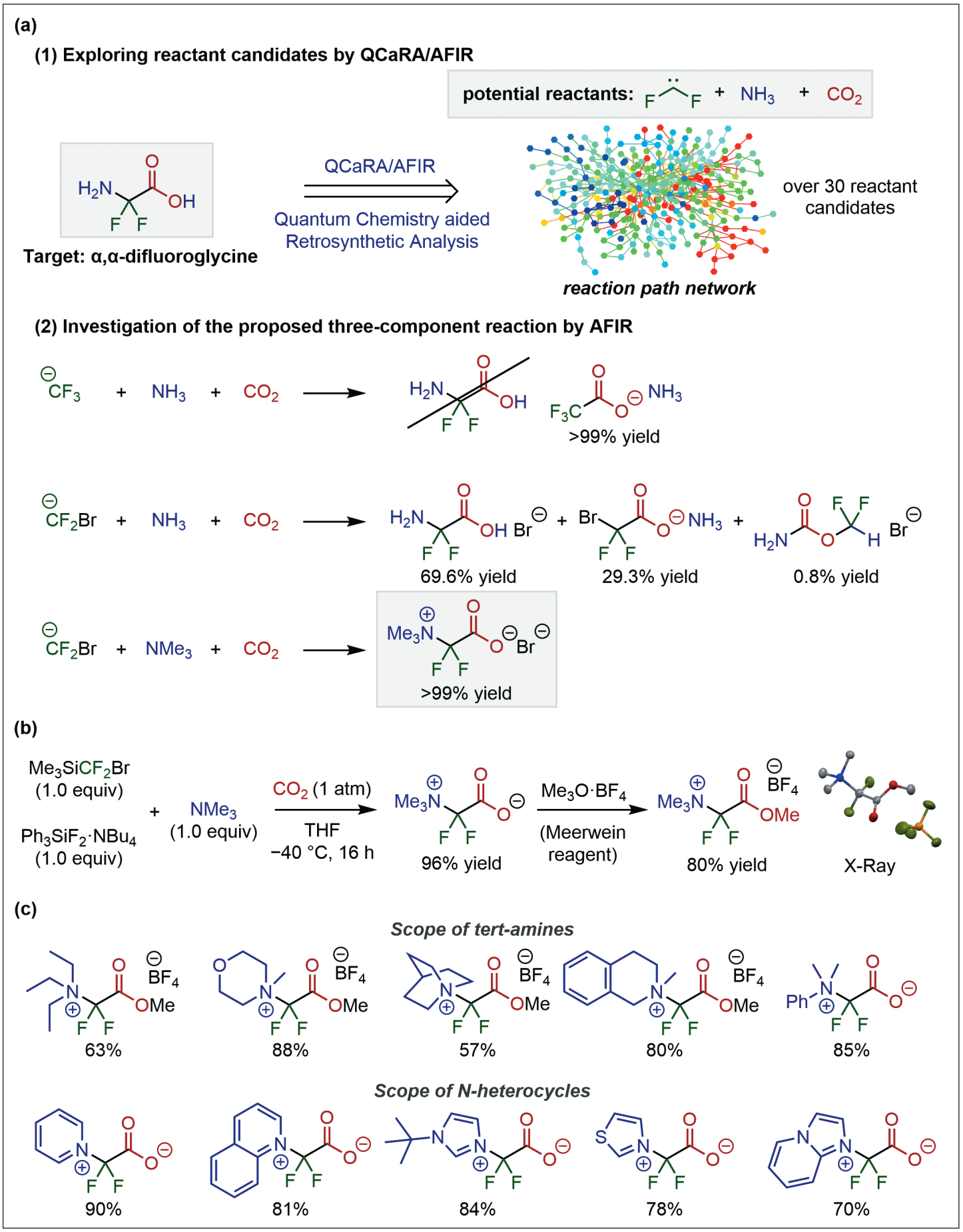


Figure 5(a) Flow of α,α-difluoroglycine derivatives synthesized from a reaction path network by (1) QCaRA/AFIR and (2) subsequent AFIR calculations, (b) scheme for the synthesis of experimentally discovered α,α-difluoroglycine derivatives, (c) examination of the substrate scope by the newly discovered synthetic method.

of a synthetic method for *α*,*α*-difluoroglycine derivatives, which are considered to be bioisosteres of natural glycine and good candidates as drug discovery resources. The flow of this discovery is illustrated in Fig. 5(a). First, the application of QCaRA/AFIR to *α*,*α*-difluoroglycine gave a reaction path network, where over 30 reactant candidates were found. Among these candidates, a set of reactants consisting of CF_2+NH_3+CO_2 was selected in consideration of the availability of the species involved. Then, assuming CF_3^- and CF_2Br^- as sources of CF_2 formation in situ, the reaction path networks for CF_3^-+NH_3+CO_2 and CF_2Br^-+NH_3+CO_2 were computed by the AFIR method. The results showed that while CF_3^-+NH_3+CO_2 gave $CF_3CO_2^-$, CF_2Br^-+NH_3+CO_2 gave a mixture of the target product and by-products. It was also found that the protons of NH_3 promoted the formation of by-products. Then, the reaction path network for CF_2Br^-+NMe_3+CO_2 with the replacement of the proton with the methyl group was obtained by the AFIR method. It was predicted that the desired *α*,*α*-difluoroglycine derivatives could be obtained from CF_2Br^-+NMe_3+CO_2 in >99% yield.

This article described the reactivity prediction by the AFIR method, which has been developed by the authors, including the latest application results. By applying virtual forces between fragments in a system and inducing chemical changes, the AFIR method gives the reaction paths based on the resulting structural changes.

Since the calculated yield of >99% was predicted, the experiment was conducted to confirm the inference. Fig. 5(b) shows the reaction scheme finally discovered experimentally. In the experiment, CF_2Br^- was generated in situ by mixing Me_3SiCF_2Br and $Ph_3SiF_2{\cdot}NBu_4$. The synthetic experiments afforded *α*,*α*-difluoroglycine derivatives from CF_2Br^-+NMe_3+CO_2 in 96% yield. Lastly, we succeeded in isolating the resulting *α*,*α*-difluoroglycine derivative as a stable solid after methyl esterification by the treatment with Meerwein reagent. Its three-dimensional structure was confirmed by X-ray crystallography. Furthermore, this three-component reaction proceeded well with various tertiary amines and nitrogen-containing heteroaromatics; hence, it became feasible to synthesize various *α*,*α*-difluoroglycine derivatives shown in Fig. 5(c).[29]

Conclusions

This article described the reactivity prediction by the AFIR method, which has been developed by the authors, including the latest application results. By applying virtual forces between fragments in a system and inducing chemical changes, the AFIR method gives the reaction paths based on the resulting structural changes. By systematically testing combinations of various fragment pairs, a systematic automated search for reaction paths is possible. The resulting reaction path network is valuable for elucidating the mechanisms of complicated chemical reactions. The complex reaction path network obtained by the AFIR method can be easily analyzed by the RCMC method based on the kinetics, which is also used to limit the scope of the AFIR search to kinetically accessible paths and to suppress combinatorial explosions.

The AFIR method can predict chemical reactions in a system consisting of 30 atoms or less with no previous knowledge. The application to the Strecker synthesis was shown as an example. Even for the system with more than 30 atoms, the reaction mechanism can be analyzed systematically by combining with calculation methods for macromolecular systems such as the semi-empirical quantum chemical calculation method and the QM/MM method. As examples, this article presented the structural transition of interfacial amorphous carbon and the conversion of pyruvate to L-lactate by LDH. Lastly, this article introduced the discovery of a synthetic method of difluoroglycine derivatives by QCaRA using the AFIR method as a reaction path search engine.

The AFIR method is now widely used in reaction mechanism analysis. This method is implemented in the GRRM20 program and is used by many users.[30] The new reaction prediction method combined with QCaRA suggests even more exciting possibilities of the AFIR method. We hope that the new AFIR features in GRRM20 will contribute to many chemical studies in the future. ◆

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