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Efficient Construction of a Chemical Reaction Network Guided By a Monte Carlo Tree Search

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Chemical reaction networks are essential for the complete elucidation of chemical reaction mechanisms. Graph-theoretic methods combined with quantum calculations are known to be an efficient approach with broad applicability for constructing reaction networks. However, this method entails high computational cost due to quantum calculations on chemically irrelevant intermediates coming from the exploration of a large scale chemical space. To remedy this problem, we propose to apply the Monte Carlo tree search algorithm to those graph-theoretic methods. We have combined it with ACE-Reaction, our in-house graph-theoretic method, and demonstrated its performance on five organic reactions. The result shows that the computational cost for quantum calculations has been reduced by up to 75% from that of the original ACE-Reaction. Furthermore, cost reduction became more efficient for more complex reactions.

1. Introduction

For the complete elucidation of chemical reactions, it is necessary to consider a chemical reaction network composed of competitive reaction pathways from reactants to products. In order to construct the reaction network, intermediates and elementary reactions should be sampled by exploring a chemical space. However, the manual exploration of the chemical space is slow and entails a lot of trial and error. Therefore, a lot of effort has been put into developing automated methods for exploring the chemical space.

One example is to directly explore the potential energy surface (PES), starting from reactants.[1–14] This method navigates the chemical space by changing the 3D geometries of reactants. To search transition states and intermediates efficiently, it uses the local curvature or energy information obtained by quantum calculations. Although navigating PES can explore various chemical reactions based on first principles, it is challenging for dealing with chemical reactions that involve many reactive atoms and multiple steps, since its computational cost increases rapidly.

Another example is to use the graph representation of molecules, which is called the graph-theoretic method. In this method, molecules are represented as graphs. It samples intermediates by changing the molecular graphs of reactants. Therefore, it can explore a chemical space more efficiently than exploring the corresponding PES. However, allowing all possible enumerations can lead to combinatorial explosion. To prevent such combinatorial explosion, intermediates that contain chemically irrelevant molecules should be screened out by using some chemical information that can be deduced from molecular graphs.

Some employ data-driven reaction rules to screen chemically irrelevant intermediates.[15–17] For a given intermediate, it only enumerates new intermediates within possible chemical transformations obtained by heuristic rules. Therefore, this approach can significantly reduce the search scope of given chemical space and have been widely used, particularly in synthesis planning.[18–27] However, these approaches are not applicable to reactions that heuristic rules do not cover.

To overcome the lack of broad applicability, energy information can be used as screening criteria.[28–35] First, it applies reaction-free chemical heuristics, such as atomic valency or formal charge, to screen chemically unstable intermediates. Then, the molecules consisting of the remained intermediates are converted into 3D geometries, and their energies are obtained by quantum calculations. The intermediates that require high energy barriers to reach are screened out. Finally, those energetically accepted intermediates are used for constructing a reaction network. Although this method is generally applicable to various reactions, this method wastes quantum calculations for intermediates that do not necessarily lead to products throughout chemically plausible pathways, since reaction-free chemical heuristics do not have any prior information on reaction paths and so cannot remove all chemically irrelevant intermediates. Therefore, it is desirable to further exclude such irrelevant intermediates for efficient construction of a reaction network.

One possible remedy is to give priority for quantum calculation to intermediates that are likely to be a part of the plausible pathways to products. To this end, Monte Carlo tree search (MCTS) is particularly useful. MCTS is a heuristic search algorithm that provides the best choice that would give

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maximal reward among given possible choices, by performing several lookahead searches.[36–38] It is widely used in sequential decision-making problems like Go games[39] or synthesis planning.[27] Finding plausible paths can also be considered as a sequential decision-making problem, as they can be generated by taking a series of elementary reactions starting from reactants. Therefore, we expect MCTS as a useful tool for giving quantum calculation priority to intermediates.

In this work, we demonstrate the performance of MCTS for efficient construction of a reaction network. To test whether it can effectively reduce the number of quantum calculations, we combined it with ACE-Reaction,[35] one of the graph-theoretic method that uses quantum calculations to screen irrelevant intermediates. It should be noted that ACE-Reaction aims to find reaction mechanisms for given reactants and products with equal stoichiometry for homogeneous reaction systems; thus, the extension possibility of MCTS to other types of reaction needs further examination. We checked the number of quantum calculations and whether the sampled intermediates contain the known mechanism in order to assess the efficiency and reliability of the proposed method, namely MCTS-ACE-Reaction. As a test set, we used the reactions that were used to evaluate the performance of ACE-Reaction in our previous work.[40] Among 26 reactions, we chose five reactions, where three of them had a large number of intermediates in the respective reaction networks, and the other two of them had some issues in determining the major path among various mechanisms.

In what follows, we first briefly summarize the workflow of ACE-Reaction. Then, we discuss how we implemented MCTS in ACE-Reaction. Finally, we show the performance of MCTS-ACE-Reaction compared to ACE-Reaction and draw conclusions.

2. Method

2.1. Overview of ACE-Reaction

ACE-Reaction makes use of the graph-theoretic method to construct a reaction network for given reactants and products. It is based on the idea of the principle of minimal structure change (PMSC)[41,42], which states that reaction paths to products are likely to have a minimal number of bond dissociation and formation, to collect only plausible paths. Here, we briefly discuss three major steps in ACE-Reaction. More detail information is available in Refs. [35] and [40].

In the first step, intermediates are gathered by enumerating the molecular graphs of reactants, just like other graph-theoretic methods. To prevent combinatorial explosion, active atoms are assigned for the given reactants, and only those active atoms are considered in the enumeration. Also, it restricts the number of maximal bond formation and dissociation to a certain value. Normally the value is 2 for both. After the enumeration step, new molecular graphs are first screened by using reaction-free heuristics. Then, the remained ones are converted to the corresponding 3D geometry at a molecular mechanics level accuracy.[43] Those converted molecules are subjected to 3D-on-the-fly screening by semi-empirical calculations like DFTB[44] or PM6[45] calculations. Either molecules that are not converged or whose connectivities change after optimization are excluded. Intermediates that only contain the remaining molecules are regarded as chemically plausible intermediates and hence used in the next enumeration cycle. This process is repeated until it reaches the termination criteria.

In the second step, irrelevant intermediates are screened from the gathered intermediates. It first removes the intermediate whose energy is higher than the sum of the given tolerance (E_{tol}) and the energies of reactants. After screening by energy, it further screens intermediates that are not a part of plausible paths with respect to the PMSC. To measure the extent of structure change, we use chemical distance (CD)[35,41,42], which is defined as the sum of the number of minimal bond dissociation and formation to interconvert between the two intermediates. By using this CD, it removes intermediates that are far from both reactants and products by applying elliptic inequality given as [Eq. (1)]:

$$\mathrm{CD}(\mathrm{R},\mathrm{I}) + \mathrm{CD}(\mathrm{I},\mathrm{P}) \leq \mathrm{CD}(\mathrm{R},\mathrm{P}) + \Delta \quad (1)$$

where Δ denotes a digression factor that controls the search range of reaction paths with respect to the CD.

In the final step, a reaction network is generated with the remaining intermediates. The method collects the shortest pathway in terms of CD that passes through each intermediate using the Dijkstra algorithm[46] and combines those of all intermediates and elementary reactions within the collected shortest pathways to make a reaction network. It can flexibly consider the 2nd and the 3rd shortest paths and so on by employing the Yen's algorithm.[47]

2.2. Overview of Applying MCTS to the Graph-Theoretic Method

As shown in Figure 1-a, our method finds a single pathway from reactants to products at a time by sequentially determining the most plausible next intermediate, starting from the reactants. To decide the next intermediate, we utilize MCTS and quantum calculations. We search for another pathway iteratively until the obtained pathway meets the termination criteria. Then, we construct a reaction network with all intermediates within those sampled pathways. We describe the overview of our method with a flowchart in Figure 1-b. Each step of the flowchart proceeds as the following:

1) *Step 1:* Our method obtains the atom connectivities and the sum of the energies of reactants by quantum calculation. (Initialize Reactant)
2) *Step 2:* It conducts MCTS with the current intermediate as the root node to find the priorities of intermediates. (Do MCTS)
3) *Step 3:* Based on the MCTS result, it selects a high-priority intermediate and performs a quantum calculation for the selected intermediate. (Quantum Calculation)

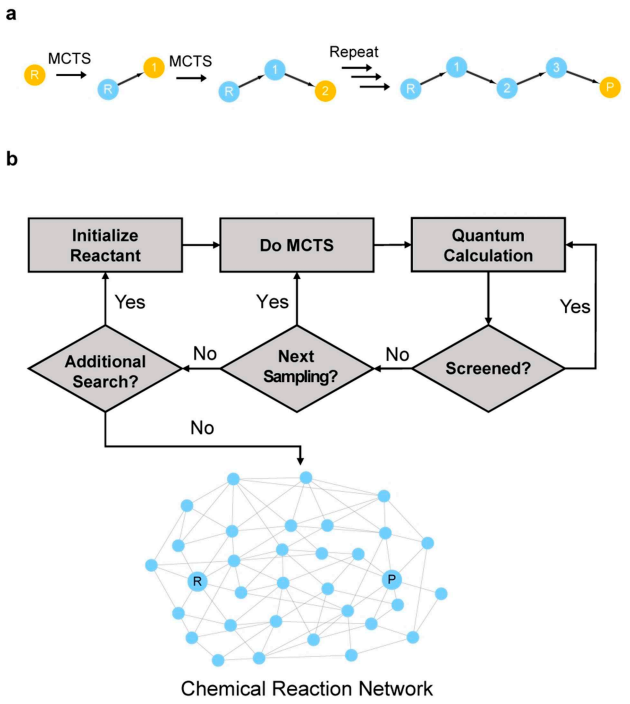

Figure 1. a) Illustration of finding a pathway from reactants (R) to products (P) by sequentially selecting the next intermediate from the current intermediate, colored in yellow. The number (n) denotes the nth sampled intermediate. b) The flow chart of MCTS-ACE-Reaction. It starts with initializing reactants on the left top and proceeds in a clockwise order.

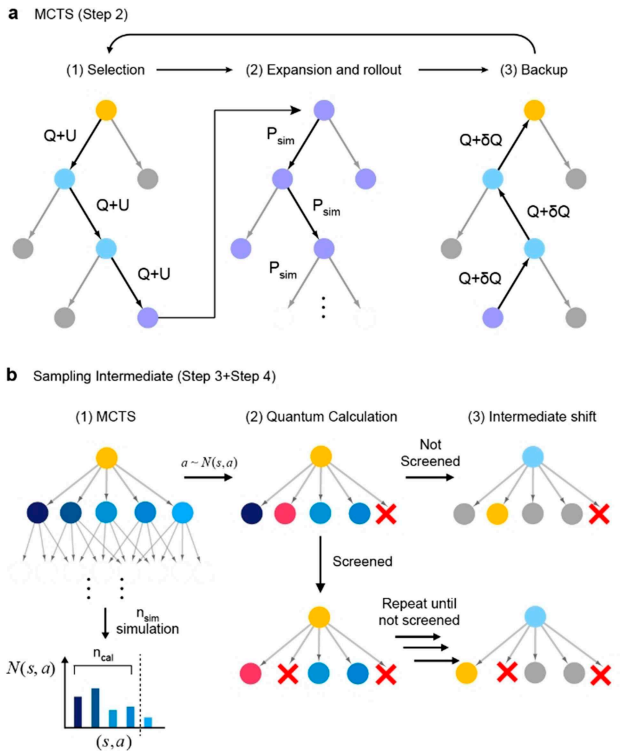

Figure 2. Major processes that are related to sampling intermediates. a) MCTS. MCTS is composed of 3 phases: Selection, Expansion and rollout, Back-up. (1) Selection. Selection starts from the root node colored in yellow. It chooses an action that has the maximal expected reward (Q + U). The visited nodes in selection are colored in blue. (2) Expansion and rollout. In this stage, it adds new edges and nodes to the tree and chooses the next node based on the simulation policy (P_{sim}). Nodes that are related in this stage are colored as purple. (3) Back-up. After termination, it updates the statistics of visited edges. b) Sampling Intermediate. In this phase, our method considers only n_{cal} number of the most visited intermediates for choosing a next intermediate, where n_{cal} is set to 4 in the figure case. It gives a higher probability to more visited elementary reactions and performs quantum calculations for the intermediate (colored in pink) generated by the selected elementary reaction. If the selected intermediate is screened, it selects the other intermediate with a higher probability for more visited elementary reactions and repeats until it finds an intermediate that is not screened by quantum calculation. When such an intermediate is found, it considers the found intermediate as the current intermediate, colored in yellow.

4) *Step 4:* If the selected intermediate is screened by the quantum calculations, it picks up another high-priority intermediate, and this process is repeated until the selected intermediate is verified. We call an intermediate is verified if it is not screened by quantum calculation. (Screened?)
5) *Step 5*: For the verified intermediate, our method repeats steps 2, 3, 4 to sample the next intermediate. It is continued until the reaction path composed of the sampled intermediates satisfies a termination condition. (Next sampling?)
6) *Step 6:* When the sampling is terminated, our method decides whether to search another pathway by referring to the score of the sampled reaction pathway. If no further search proceeds, then it constructs a reaction network with all sampled verified intermediates. (Additional Search?)

Among the six steps, steps 2, 3, and 4 are the most important steps that are related to reducing quantum calculations. The other steps are just related in deciding whether to terminate further sampling. In the following section, we will discuss the detailed procedure of steps 2, 3, and 4 to show how we combined MCTS with ACE-Reaction to develop MCTS-ACE-Reaction. The details of the other steps are discussed in Supporting Information.

2.3. Implementation of the MCTS-ACE-Reaction

The details of steps 2, 3, and 4 are illustrated in Figure 2. Figure 2-a describes MCTS, which is performed in step 2 to give priorities to intermediates. MCTS searches reaction pathways starting from a root node and builds up a search tree composed of nodes and edges. The nodes and edges represent states (s) and actions (a), respectively. In our method, those states and actions represent intermediates and elementary reactions described by the change in atom connectivity, respectively. Each edge (s, a) in the search tree stores prior probability $P(s,a)$, which represents the initial priority of (s, a), a visit count $N(s,a)$ which is related to the actual priority of (s, a), and an action value $Q(s,a)$, which shows the average received reward of (s, a) during MCTS simulations. Using these statistics, MCTS iteratively searches throughout 3 phases for n_{sim} times, where n_{sim} is the maximal number of MCTS simulations. Those 3 phases are conducted as follows:

(1) Selection

In this phase, it selects an action (a) that has the maximal expected reward referring to the statistics stored in each edge (s_t, a) connected to the current node (s_t). For every current node, it selects the action $a_t = \mathrm{argmax}(Q(s_t,\ a) + U(s_t,\ a))$, using a variant of the polynomial upper confidence trees (PUCT) algorithm [Eq. (2)]:[48]

$$U(s_t,\ a) = c_{puct} P(s_t, a) \frac{\sqrt{\sum_b N(s_t,\ b)}}{1 +\ N(s_t,\ a)} \tag{2}$$

where c_{puct} is an exploration constant. It encourages exploration, as c_{puct} gets higher.

For statistically meaningful selection, we activate the selection only if the visit counts of edges meet the following condition: $\max_a N(s_t, a) > n_{thre}$, where n_{thre} denotes the minimum required value to activate the selection process. If $N(s_t, a) \le n_{thre}$ for all action a, it starts the rollout phase. Therefore, at an early stage, the selection does not occur since the visit counts of the edges are smaller than n_{thre}.

(2) Expansion and Rollout

After the selection phase, the rollout phase starts. Here, it simply selects the next action based on a simulation policy (P_{sim}). If the current node is first visited, it undergoes expansion, since there aren't any edges connected to the current node. It expands possible elementary reactions by applying the heuristic rules used in ACE-Reaction. The expanded edges and their successor states are added to the tree. The statistics of each edge are initialized as $\{W(s_t, a) = 0,\ Q(s_t, a) = 0,\ N(s_t, a) = 0,\ P(s_t, a) =\ P_{sim}(s_t, a)\}$. To reduce the tree complexity, the successor states that are already present in the tree are not added to the tree, and edges that produce those successor states are connected to the corresponding successor states. After expansion, one of the edges connected to the current node is randomly selected, with its probability proportional to $P(s_t, a)$. This process is repeated until it meets the termination condition.

We used $CD(R, I)$ and $CD(I, P)$ to design the simulation policy. According to PMSC, an intermediate that has a low value of $CD(R, I) + CD(I, P)$ $(= CD_{sum}(I))$ and $CD(I, P)$ is preferred in order to reach products through the shortest path in terms of CD. To reflect this preference, we used those two values as a variable to measure the priority of a selected elementary reaction. We defined $E_a(s, a)$, which corresponds to a kind of activation barrier, in terms of those two values as follows in order to generate a non-negative value [Eqs. (3), (4)]:

$$\begin{aligned} &\delta CD_{sum} = CD_{sum}(s') - CD_{sum}(s),\ \ \delta CD_P \\ &=\ CD(s', P) - CD(s, P) \end{aligned} \tag{3}$$

$$E_a(s, a) = \max(\delta CD_{sum},\ \delta CD_P,\ -1) + 1 \tag{4}$$

where s′ is a successor state of elementary reaction (s, a). Then, we expressed the simulation policy (P_{sim}) in terms of softmax function to reflect its probabilistic nature with exponential dependence on activation barrier [Eq. (5)]:

$$P_{sim}(s, a) = \frac{\exp(-\beta E_a(s, a))}{\sum_b \exp(-\beta E_a(s, b))} \tag{5}$$

where β is a unitless parameter which determines the search scope of chemical space.

(3) Termination and Backup

We consider the total reaction pathway: $\{R(= I_0),\ I_1,\ \ldots,\ I_m\ (= s_0),\ s_1,\ \ldots,\ s_t\}$, the union of previous sampled intermediates $[R\ (= I_0),\ I_1,\ \ldots,\ I_m\}$ and the visited nodes $\{I_m(= s_0),\ s_1,\ \ldots,\ s_t\}$ during the MCTS simulation, to determine the termination of simulation and the reward value, where I_n is the n-th sampled intermediate during the pathway search, $I_m = s_0$ is the root node of MCTS, and s_i is the i-th visited node within a single MCTS simulation.

We use the plausibility of the total reaction pathway in order to determine the reward value and termination condition. We defined a path is plausible when it satisfies the following three conditions based on the PMSC:

Condition A. A pathway that leads to defined products;

Condition B. A pathway that only contains short elementary reactions. Here, we consider that elementary reaction is short if its CD is less than or equal to 2, where the CD of elementary reaction is defined as the CD between the two intermediates of the elementary reaction;

Condition C. A pathway whose CD is short, where the CD of a reaction pathway is defined as the sum of the CDs of the elementary reactions within the reaction pathway.

To find those paths efficiently, we prepared two termination conditions to avoid unnecessary searches:

For the given total reaction pathway [Eq. (6)]:

$$\{R(= I_0),\ I_1,\ \ldots,\ I_m\ (= s_0),\ s_1,\ \ldots,\ s_t\} \tag{6}$$

If [Eq. (7)]:

$$\begin{aligned} &\sum_{i=0}^{m-1} CD(I_i, I_{i+1}) +\ \sum_{i=0}^{t-1} CD(s_i, s_{i+1}) + \\ &CD(s_t, P) >\ L_{best} + \Delta \end{aligned} \tag{7}$$

the simulation is terminated, where L_{best} is the CD of reaction pathway from reactants to products which has the highest reward, and Δ is the digression factor used in ACE-Reaction. L_{best} is updated if the new obtained highest rewarded reaction pathway is shorter than the previous highest one. This termination condition prevents unnecessary exploration by terminating further search for reaction pathways whose CDs are long enough, since those pathways would not satisfy the condition C.

(ii) If a current node (s_t) (except the root node) is linked to a verified path to products ($\{s_{t+1}, s_{t+2}, \ldots, s_n(=P)\}$, s_is are verified intermediates) satisfying [Eq. (8)]:

$$\sum_{i=t}^{n-1} CD(s_i, s_{i+1}) = CD(s_t, s_n(=P)) \tag{8}$$

with each [Eq. (9)]

$$CD(s_i, s_{i+1}) \leq 2 \tag{9}$$

then the simulation is terminated.

This condition helps to find plausible pathways efficiently. The CD of the shortest reaction pathway from an intermediate to products is equal to the CD between the intermediate and products. Thus, if the current node is linked to the shortest reaction pathway to products with each elementary reaction whose CD is short, we directly obtain a plausible pathway by combining a pathway produced by the pathway search and the MCTS simulation ($\{R\ (=I_0), I_1, \ldots, I_m\ (=s_0), s_1, \ldots, s_t\}$) with the shortest pathway ($\{s_{t+1}, s_{t+2}, \ldots, s_n\ (=P=\}$) composed of verified intermediates to both satisfy condition B and C. Figure 3 shows an example of a total reaction pathway and finding a termination condition.

After the termination, back-up proceeds. In this phase, the statistics of visited edges are updated with the evaluated reward. We give a higher reward, if the total reaction pathway is more plausible pathway in terms of the three conditions. If the simulation is terminated by the condition (i), the reward is -1, since it failed to reach the desired products through a plausible pathway. If it was terminated by the condition (ii), we evaluate the path reward (R_{path}) with some added penalty (P_B, P_C) defined as [Eq. (10)]:

$$R_{path} = 1 - P_B - P_C \tag{10}$$

Where P_B, P_C are defined as [Eqs. (11), (12)]:

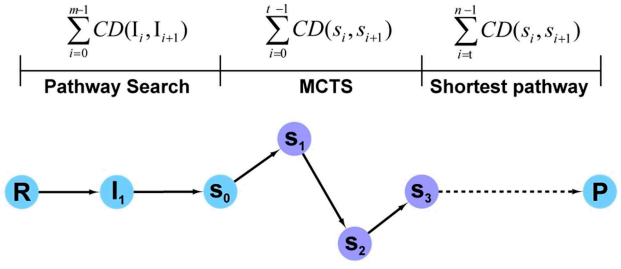

Figure 3. Example of a total reaction pathway used in the determination of termination and the evaluation of reward. In this case, the total reaction pathway is an intermediate sequence: $\{R(=I_0), I_1, I_2(=s_0), s_1, s_2, s_3\}$, where the sampled intermediates are R, I_1, I_2, and s_0, s_1, s_2, s_3 are visited nodes during a single MCTS simulation. The dotted line is the shortest pathway that provides the second termination condition.

$$P_B = \frac{\sum_{i=0}^{m-1} \max(CD(I_i, I_{i+1}) - 2, 0) + \sum_{i=0}^{t-1} \max(CD(s_i, s_{i+1}) - 2, 0)}{N_{max}} \tag{11}$$

$$P_C = \frac{max(\sum_{i=0}^{m-1} CD(I_i, I_{i+1}) + \sum_{i=0}^{t-1} CD(s_i, s_{i+1}) + CD(s_t, P) - L_{best}, 0)}{\Delta + 1} \tag{12}$$

where Δ is the digression factor used in ACE-Reaction, N_{max} is the allowed number of elementary reactions whose CDs are bigger than 2 and $P_{B/C}$ is the penalty for not satisfying the condition B/C. P_B gets higher if more and more elementary reactions whose CDs are larger than 2 are present in the total reaction pathway. In the same way, P_C becomes higher if the CD of the total reaction pathway gets larger.

To prevent a negative penalty, we give a maximum function to give a penalty at least zero. If those P_B and P_C gets bigger, the reward could be negative.

Our method aims to find multiple plausible paths. We introduce a uniqueness reward (R_{uniq}) to avoid sampling pathways that were sampled previously [Eq. (13)];

$$R_{uniq} = \frac{n_{new}}{n_{path} - 1} \tag{13}$$

where n_{new} is the number of new sampled intermediates that were not sampled in the previous pathway searches, and n_{path} is the number of intermediates in the total reaction pathway.

'-1' term in the denominator is used for the correction for excluding reactants, as the reactants are always present in the total reaction pathway that are not new sampled intermediates. This correction helps R_{uniq} to achieve its maximal value to 1.

After evaluating the two rewards, the minimum value is used as the final reward value, and the statistics of visited edges are updated using this final reward: $R_f = \min(R_{uniq}, R_{path})$, $N(s_t, a_t) = N(s_t, a_t) + 1$, $W(s_t, a_t) = W(s_t, a_t) + R_f$, $Q(s_t, a_t) = W(s_t, a_t)/N(s_t, a_t)$, for all visited elementary reactions during a single MCTS simulation.

After n_{sim} times of MCTS simulations, only n_{cal} number of the most visited actions (s,a) are considered as a candidate for the next intermediate state, as shown in Figure 2-b. For those n_{cal} actions, an elementary reaction is selected according to the policy given as $\pi(a|s) = \frac{N(s,a)}{\sum_b N(s,b)}$. Then, the corresponding intermediate by the selected elementary reaction (s,a) is subjected to the 3D-on-the-fly screening process as implemented in ACE-Reaction. If the intermediate is screened, another action is selected with the policy redefined as $\pi(a|s) = \frac{N(s,a)}{\sum_{b \neq a_{sel}} N(s,b)}$, where a_{sel} is the previously selected action. Note that $\pi(a|s)$ is different from the prior probability $(P(s,a))$. $P(s,a)$ considers only a single elementary reaction during a single MCTS simulation. It is already determined using CD.

However, $\pi(a|s)$ is always determined after a large number of MCTS simulations, in terms of $N(s,a)$. Thus, $\pi(a|s)$ is a probability distribution that considers a large number of reaction pathways, whereas $P(s,a)$ only considers a single elementary reaction.

This sampling is repeated until the intermediate produced by the selected action is not screened. If all n_{cal} intermediates are screened out, the pathway search is terminated immediately. If not, our method restarts MCTS from the selected intermediate and chooses the next intermediate. This process is repeated until the pathway search satisfies the termination condition which is discussed in Supporting Information. For every MCTS, we keep reusing the previous search tree generated by MCTS for the sake of efficiency. When reusing the tree, we reset the statistics of edges to their initial values and remove nodes that were screened by quantum calculations.

3. Computation Details

For sampling intermediates, we applied the same heuristic rules, parameters, and digression inequality to both MCTS-ACE-Reaction and ACE-Reaction for the fair comparison of performance. We stored the results of quantum calculations in order to avoid performing quantum calculations on the same molecules. The geometries of molecules were optimized at the PM6 semi-empirical calculation level, as implemented in Gaussian 09.[49] The solvation effect was considered with the CPCM solvation model. The details of the screening process are available on Supporting Information.

Due to the stochasticity of MCTS, our method can sample a different set of intermediates for each trial. Therefore, we conducted MCTS-ACE-Reaction simulation three times and considered the union of sampled intermediates from those three trials to find plausible pathways as many as possible. We obtained those unions of sampled intermediates 50 times to check the reproducibility of our method. For every union of sampled intermediates, we checked the number of quantum calculations defined as the number of different molecules within the unions that were undergone quantum calculations and whether the known mechanism was found to evaluate the efficiency and reliability of our method.

4. Results and Discussion

Table 1 summarizes the effect of MCTS to ACE-Reaction. First of all, it shows that our method can effectively reduce the number of quantum calculations, and its effect is more significant as the number of quantum calculations in the original ACE-Reaction increases. For example, the total number of quantum calculations in benzoin condensation which performed only 40 quantum calculations, was decreased to 74.0% on average. For Cannizzaro, which performed 51 quantum calculations, the total number of quantum calculations was decreased to 54.1%, more effective than the benzoin condensation. Moreover, for three reactions that had more than 300 quantum calculations, the number of quantum calculations was decreased to less than 40% on average. Also, the ratio of the number of quantum calculations did not show a large deviation implying that our method consistently reduces the number of quantum calculations. For more detail, we attached the distributions of N_{QC} of 50 trials for tested five organic reactions in supporting information section.

Table 1. The performance of MCTS-ACE-Reaction on 5 organic reactions.

Reaction	$N_{QC}^{[a]}$	$N_{QC}^{[b]}$	Ratio [%]	Success rate[d] [%]	$T_3^{[e]}$ [min]
benzoin condensation[c]	40	29.6 ± 1.4	74.0 ± 3.5	100	2.6 ± 0.1
Cannizzaro	51	27.6 ± 1.4	54.1 ± 2.7	100	2.6 ± 0.1
diazotization	301	80.4 ± 7.8	26.7 ± 2.6	94	17.9 ± 1.7
oxy-Cope rearrangement	380	138.5 ± 8.9	36.4 ± 2.3	100	31.5 ± 2.0
Bischler-Napieralski	447	111.9 ± 5.1	25.0 ± 1.1	100	38.9 ± 2.1

[a] The number of quantum calculations in the original ACE-Reaction, [b] The average number of quantum calculations in MCTS-ACE-Reaction for 50 independent unions of sampled intermediates from 3 trials of MCTS-ACE-Reaction. The error denotes the standard deviation, [c] The reaction uses CN^- as a catalyst. [d] The success rate is defined as the number of unions that successfully contain all intermediates of known mechanisms out of 50 unions. [e] T_3 is the total time taken spent on MCTS during three consecutive searches performed by MCTS-ACE-Reaction. MCTS was conducted on an Intel Xeon workstation with just a single core (CPU = 3.20 GHz).

Secondly, it shows that our method is reliable. Except for three failures in diazotization, our method successfully found the intermediates of known mechanisms for all independent 50 unions.

Lastly, it does not spend much time giving priority to intermediates. The most complex three reactions took less than 40 minutes in average on an Intel Xeon workstation with just a single core (CPU = 3.20 GHz), and the other two reactions took less than 3 minutes. More time should be taken for more complex reactions since more time is consumed in graph enumeration, and more plausible intermediates are needed to be sampled. Nevertheless, it does not take more than an hour to reduce the number of quantum calculations, showing the high efficiency of our method.

We also visualized the sampling process of ACE-Reaction and MCTS-ACE-Reaction to see how MCTS reduces unnecessary quantum calculations. Figure 4 shows the progress of the sampling intermediates of each method for Cannizzaro Reaction. The sampled intermediates are represented as colored circles and are arranged according to the $CD(R,I)$ and the $CD(I,P)$. As shown in Figure 4-(a), the number of sampled intermediates in ACE-Reaction increases explosively after each enumeration step, because ACE-Reaction samples all intermediates that satisfy elliptic inequality. On the other hand, Figure 4-(b) shows that MCTS-ACE-Reaction first samples intermediates that have a small value of CD_{sum}.

Table 2 and Table 3 show the sampling progress more in detail. They summarize the change in the number of sampled intermediates according to the given CD_{sum} during sampling.

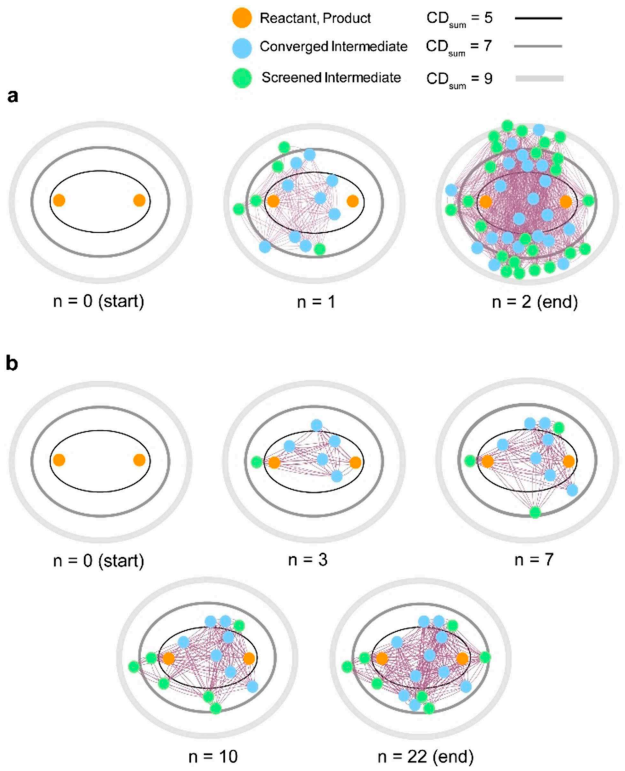

Figure 4. a) Visualization of the intermediate sampling progress of ACE-Reaction. n is the number of enumeration step in ACE-Reaction. b) Visualization of the intermediate sampling progress in MCTS-ACE-Reaction. Each n is the number of conducted pathway searches. Colored circles represent the sampled intermediates during exploration, and edges represent the possible elementary reactions between two intermediates under ACE-Reaction heuristics. The ellipse indicates the boundary of CD_{sum}. If the given intermediate is located outside of the boundary, its value of CD_{sum} is bigger than the boundary value. If it is inside of the boundary, its value of CD_{sum} is less than or equal to the boundary value.

Table 2. The number of intermediates (N_{IM}) sampled by ACE-Reaction according to the given CD_{sum} after the nth enumeration steps.

Sum of CD	N_{IM} (n = 0)	N_{IM} (n = 1)	N_{IM} (n = 2)
$CD_{sum} = 5$	2	6	7
$CD_{sum} = 7$	0	7	19
$CD_{sum} = 9$	0	3	21

Table 3. The number of intermediates (N_{IM}) sampled by MCTS-ACE-Reaction according to the given CD_{sum} after *n* pathway searches (*n* = 0, 3, 7, 10, 22).

Sum of CD	N_{IM} (*n* = 0)	N_{IM} (*n* = 3)	N_{IM} (*n* = 7)	N_{IM} (*n* = 10)	N_{IM} (*n* = 22)
$CD_{sum} = 5$	2	6	6	6	7
$CD_{sum} = 7$	0	2	6	8	11
$CD_{sum} = 9$	0	0	0	1	1

Table 2 shows that the number of ACE-Reaction sampled intermediates with $CD_{sum} = 7, 9$ increases rapidly as the enumeration step increases. In contrast, Table 3 shows that the increase rate for MCTS-ACE-Reaction is very low. For example, it sampled only one intermediate with $CD_{sum} = 9$ up to the 22 enumeration steps. Throughout MCTS, it tries to avoid sampling intermediates that are only accessible to products through long pathways. The result shows that MCTS significantly reduces the number of sampled intermediates as we intended.

Because MCTS-ACE-Reaction effectively reduces the number of quantum calculations, we expect that the size of the final reaction network is smaller than the network produced by ACE-Reaction. Therefore, we constructed the reaction network by applying the third step in ACE-Reaction to sampled intermediates obtained by MCTS-ACE-Reaction and checked the number of intermediates and elementary reactions within the constructed chemical reaction network. Here, we present the reaction network produced by the set of intermediates that performed the maximal number of quantum calculations among 50 sets that we conducted. For diazotization, the 2nd shortest path was also considered, like the way in the previous work in Ref. [35].

Table 4 shows that MCTS-ACE-Reaction also reduces the size of the reaction network. It can be easily noted that the number of intermediates was decreased more effectively as the number of quantum calculations in ACE-Reaction increased. Therefore, it is expected that the number of elementary reactions would decrease more for complex reactions as the number of intermediates more decreases.

However, the decrease rate of the number of elementary reactions was different from the decrease rate of the number of intermediates. For example, in the case of Cannizzaro and oxy-Cope rearrangement, although there is a significant difference in the ratio of intermediates, they showed a similar ratio of elementary reactions. This is because even though intermediates are removed, elementary reactions could not be removed significantly if those intermediates contain a less number of shortest paths, and also vice versa. Nonetheless, the result tells that applying MCTS reduces not only quantum calculations but also the intermediates and elementary reactions of the reaction network.

The ultimate goal of constructing chemical reaction networks is to find all competing paths under a given condition. Therefore, we have analyzed the reaction network obtained by our new method for Cannizzaro reaction[50,51] and benzoin condensation reaction[52,53,54] in which several reaction mecha-

Table 4. Comparison of the size of the chemical reaction network for 5 organic reactions. $N_{IM/ER}$ denotes the number of intermediates/elementary reactions within the chemical reaction network.

Reaction	Method	N_{QC}	N_{IM}	N_{ER}	N_{QC} Ratio [%]	N_{IM} Ratio [%]	N_{ER} Ratio [%]
benzoin condensation	ACE	40	23	80	80	87	69
	MCTS-ACE	32	20	55			
Cannizzaro	ACE	51	23	97	61	70	47
	MCTS-ACE	31	16	46			
diazotization	ACE	301	108	1181	34	45	33
	MCTS-ACE	101	52	395			
oxy-Cope rearrangement	ACE	380	95	643	42	48	46
	MCTS-ACE	159	43	293			
Bischler-Napieralski	ACE	447	147	814	28	38	36
	MCTS-ACE	127	56	292			

nisms were proposed in literature. Here, we present Cannizzaro reaction that we have seen earlier in the visualization of sampling progress. The reaction network for the benzoin condensation reaction is available in Supporting Information.

Figure 5 shows the reaction network of Cannizzaro Reaction. In Figure 5-a, the intermediates in the network are represented in the blue-colored circles, and the elementary reactions connecting those intermediates are represented as the grey lines. The elementary reactions of reaction mechanisms that were proposed in the literature are colored in red. The directionality of the reaction is not represented. The molecular structures of each intermediate are given in Figure 5-b.

By analyzing the network, we were able to find three paths among five paths that were presented in Ref. [51]. Each elementary reaction in five paths are listed as below:

1) Path 1: R $\rightarrow$ I_4 $\rightarrow$ I_{14} $\rightarrow$ I_{11} $\rightarrow$ P
2) Path 2: R $\rightarrow$ I_4 $\rightarrow$ I_8 $\rightarrow$ *P* (Accepted Mechanism)
3) Path 3: R $\rightarrow$ I_4 $\rightarrow$ I_{14} $\rightarrow$ P
4) Path 4: R $\rightarrow$ I_4 $\rightarrow$ P
5) Path 5: R $\rightarrow$ P

Path 1 and Path 5 were not present in the obtained reaction network. However, Path 1 could be obtained by including up to the 3rd shortest paths, and the dashed line is the edge which can be included as considering up to the 3rd shortest paths. For Path 5, it is the path from reactants directly to products, which contains three bond formations, therefore screened out by heuristics used in ACE-Reaction. In conclusion, the reaction network obtained by our method included almost all elementary reactions and all intermediates in the previously reported five paths.

5. Conclusion

We developed a method of applying MCTS to graph-theoretic methods to reduce unnecessary quantum calculations. To assess the performance of our method, we implemented it in ACE-Reaction that has been developed in our group for automated reaction network construction and analysis. We applied it to five reactions that were previously used to test the performance of the original ACE-Reaction in Ref. [40]. As a result, our new method was both able to effectively reduce quantum calculation and find the known mechanism for each reaction. Moreover, its performance was more efficient in complex reactions, including more intermediates as desired. The efficiency of our method also resulted in reducing the size of the reaction network, leading to a substantial reduction of computational costs in comparison to the original ACE-Reaction.

The proposed method can readily be implemented in other graph-theoretic methods, and similar performance enhancement is expected. In addition, its accuracy and reliability can be tuned by adopting appropriate metrics for the evaluation of reward in the MCTS algorithm. For instance, we adopted the chemical distance (CD) as a metric in this study. It can be replaced by other chemical metrics such as the activation energy barrier for determining plausible intermediates.

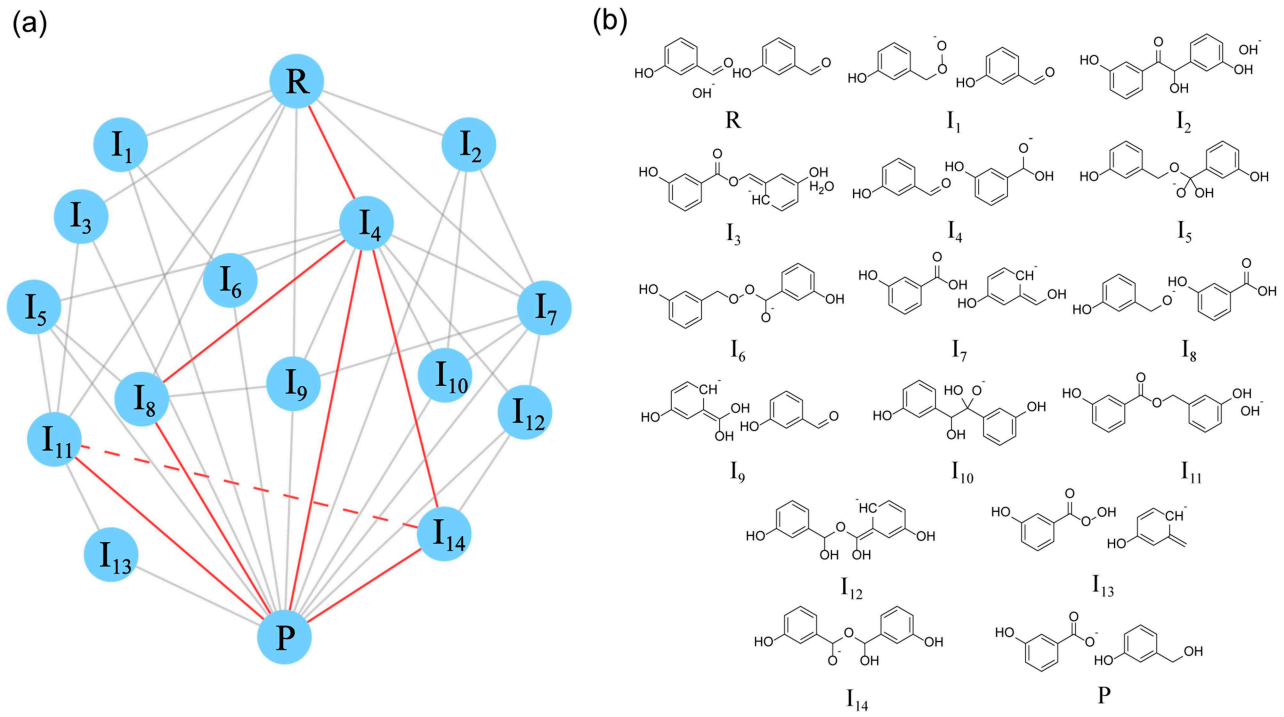

Figure 5. (a) The reaction network of Cannizzaro reaction. The red lines are the elementary reactions that are part of the reaction mechanisms proposed in literature reports. (b) The molecular structures of intermediates in the network.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: graph-theoretic method · Monte Carlo tree search (MCTS) · organic reactions · quantum calculations · reaction networks

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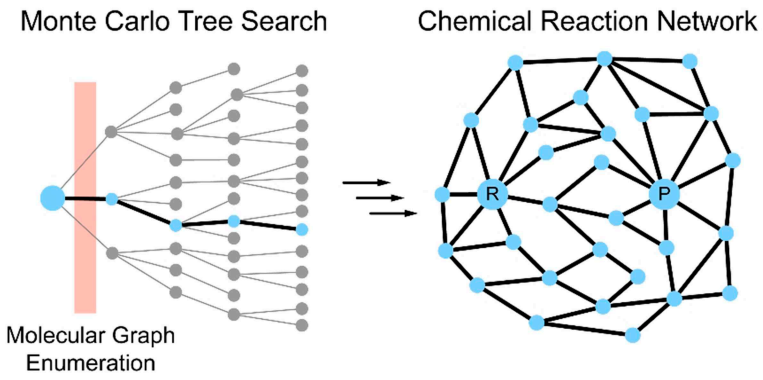

Less is more: The Monte Carlo tree search algorithm is demonstrated to significantly improve the efficiency of graph-theoretic methods for the construction of chemical reaction networks by reducing the amount of quantum chemical calculations required for sampling energetically stable intermediates.