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Finding reaction mechanisms, intuitive or otherwise

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Chemical reaction mechanisms have been frequently studied using computational simulations, but these tools have been primarily effective at examining reaction paths within the scope of chemical intuition. To determine reaction mechanisms that were not already preconceived by chemists, nonstandard simulation tools are required. This perspective introduces new methods developed by the Zimmerman group that are designed to uncover sequences of elementary steps, from first principles and without substantial human guidance. Results from the areas of organo catalysis and transition metal catalysis indicate that new frontiers of knowledge will be gained through continued development and application of reaction discovery simulation techniques.

Reaction mechanism discovery

Reaction mechanisms are revealing. Mechanisms reveal the atomistic details of chemical transformations, provide guidance to increase rates and selectivity, vitally, and explain why a transformation occurs. Mechanisms therefore have substantial fundamental scientific importance and provide practical value for engineering and optimizing chemical reactions. With this kind of impact, we might ask: what reveals the reaction mechanism?

Since the advent of quantum chemistry it has been known that reaction mechanisms, in principle, could be studied using computation.[1] After advances in quantum chemical methods and incredible gains in computer processor speed, it has now become commonplace to use computation to investigate reaction mechanisms.[2,3] Popular electronic structure methods, such as density functional[4] or wave function theories,[5] are available to accurately evaluate the structures and energetics of a sequence of intermediates and transition states in an envisioned reaction mechanism.

With these powerful tools, researchers in the field of quantum chemistry have examined a wide scope of reactions.[6–8] When doing so, quantum chemical methods are best at evaluating previously hypothesized, chemically intuited mechanisms. In other words, computational methods do not usually discover sequences of reaction pathways, but instead evaluate reactions within the scope of existing chemical knowledge. For mechanisms where no hypotheses are available—and the researchers "just don't know"—computation has not offered practical solutions to discover these unknown mechanisms.

Recent developments are transforming the ability of quantum chemistry to discover reaction mechanisms even without prior chemical intuition. These techniques allow specification of the reactant molecules and catalyst, and proceed to determine feasible sequences of elementary reaction steps.[9–11] Unexpected reaction mechanisms[12,13] can therefore be found at reasonable computational cost, enabling a new paradigm of research in quantum chemistry. A brief overview of these methods is the subject of this perspective.

Computational reaction discovery tools

From a purely computational standpoint, the primary challenge in reaction discovery is the high dimensionality of the problem. Reactions involve motion in $3N - 6$ coordinates, where N is the number of atoms in the system. Even with efficient methods like density functional theory available to compute energies of individual structures, exhaustive searches over all these degrees of freedom are not possible.

The standard toolkit for computational reaction searches avoids the problem of dimensionality by providing, as input, specific reaction coordinates. These reaction coordinates are based on hypothetical elementary steps connecting a presupposed reactant–product pair. Fig. 1 outlines the concept alongside other representative reaction finding methods. The "by hand" approach relies on an internal coordinate system consisting of interatomic distances, angles, and torsions.[14] Over this set of chemically meaningful coordinates, a typical reaction might consist of significant changes in a few interatomic distances and a few key angles. Ultimately, however, the likelihood of discovering new reaction mechanisms with this chemical-intuition-guided approach is minimal.

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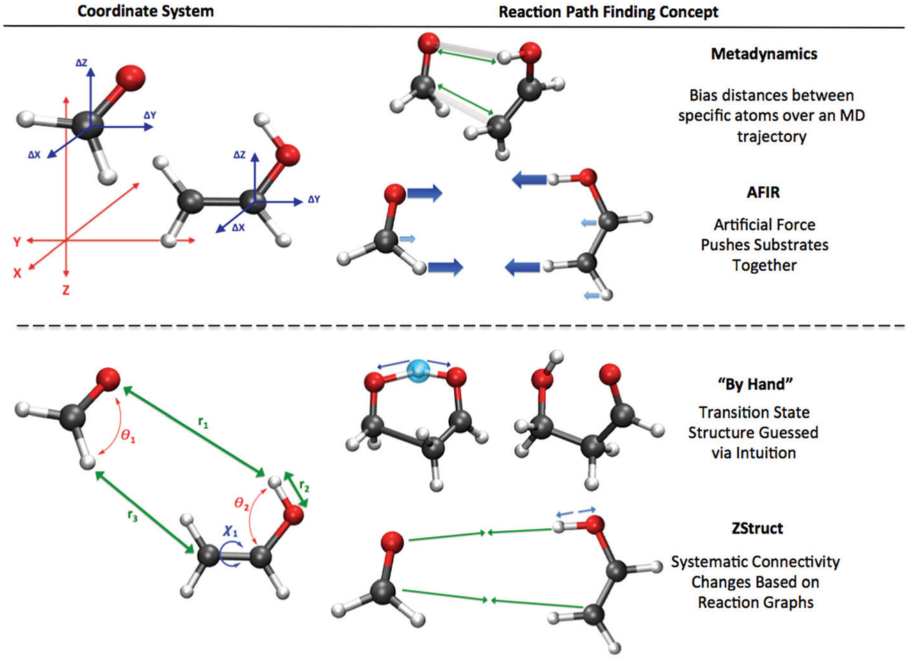

Fig. 1 Comparison of selected, computational reaction finding methods.

Alternative approaches, such as metadynamics[15] and the artificial-force-induced reaction (AFIR) method,[16,17] have been developed to overcome these deficiencies. These techniques introduce biases into the reaction search to force reactions to occur, and require less chemical intuition than the "by hand" approach (Fig. 1). Methods in the class of metadynamics and AFIR, however, do not systematically search over a comprehensive set of possible reaction coordinates, which limits their scope of discoverable reactions.

Our research group has developed new reaction discovery tools to overcome limitations in previous methods (Fig. 1, bottom). The method, called ZStruct,[9–11] uses a graph-based approach to sample a combinatorial set of hypothetical reaction pathways. ZStruct, named after the Z-matrix type of internal coordinates,[18] systematically drives reactions to occur in inter- and intramolecular systems using the basic chemical structures of the substrates (and catalyst) as input. The success and efficiency of this procedure is enabled by the growing string method (GSM),[10,19,20] which is a low-cost computational tool that reliably constructs a reaction path connecting two intermediates. Recent developments in GSM, which are currently being distributed online at GitHub,[21] allow location of intermediates, transition states, and minimum energy reaction pathways starting only from the reactant state and a set of reaction coordinates.

The ZStruct procedure for discovering bimolecular reactions involving a transition metal and a substrate is outlined in Fig. 2. The two species and a selection of their reactive atoms are provided as input, and ZStruct automatically performs the remainder of the reaction discovery. ZStruct thus identifies the

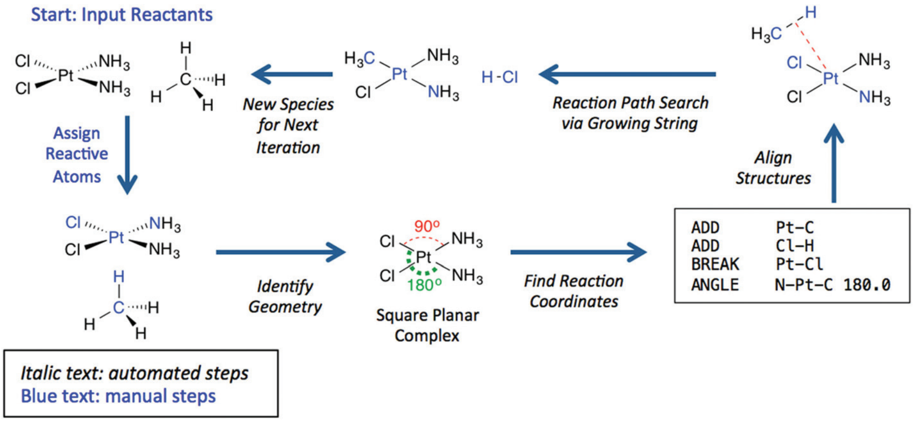

Fig. 2 ZStruct process for reaction pathway discovery.

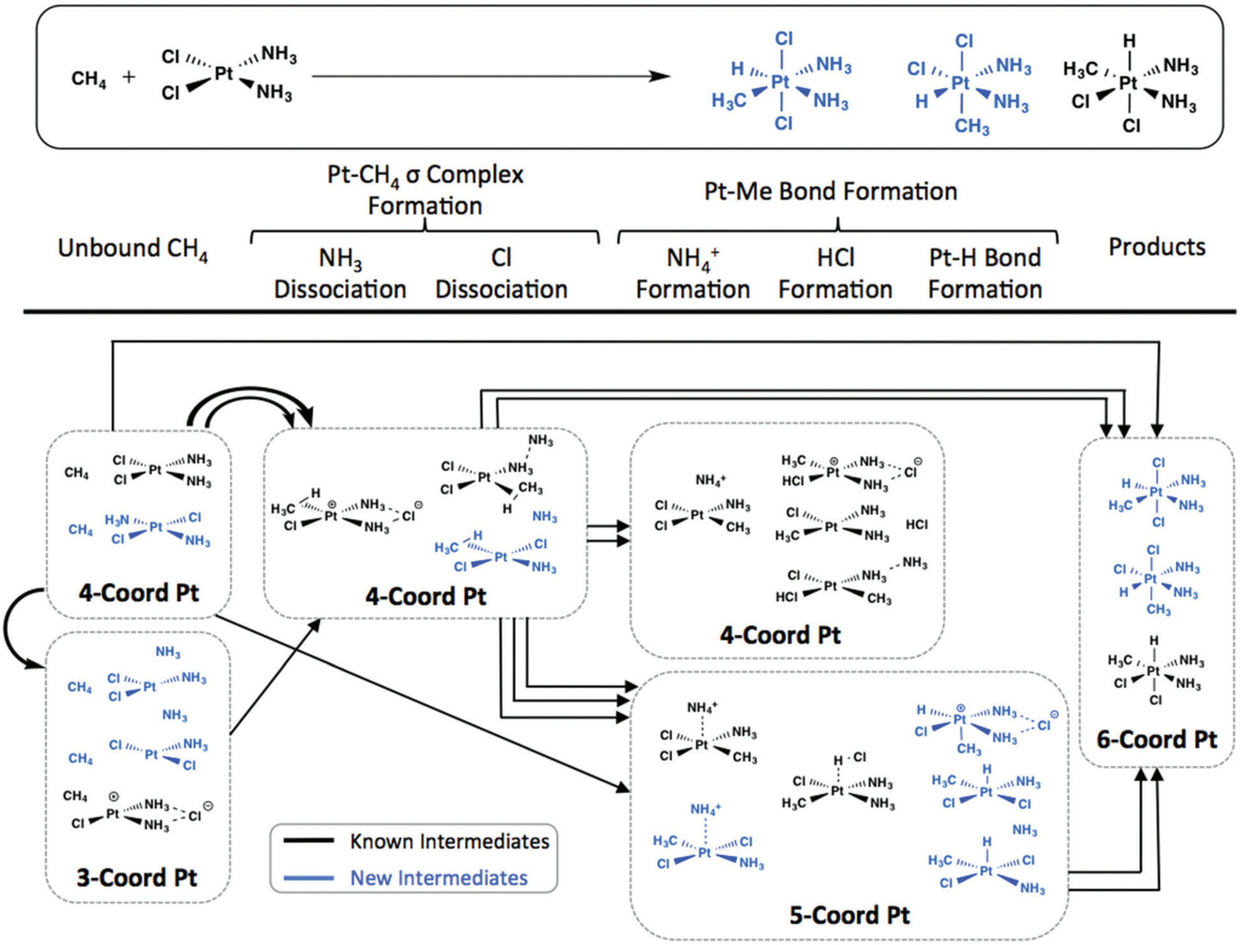

Fig. 3 Reaction networks from ZStruct for methane activation by cisplatin.

basic structure of the metal complex, creates a combinatorial set of reaction coordinates (one set shown in Fig. 2, bottom right), aligns structures for reaction, and then performs a reaction path search (*via* GSM) to find the transition state and subsequent intermediate. These intermediates are used as input to the next ZStruct run to construct an entire reaction network,[11] including thermodynamic quantities and activation barriers for each elementary step, all without input of reaction coordinates or hypotheses from intuition. Recent work with ZStruct has allowed study of systems with ~170 atoms,[27] where up to ~15 of those atoms were selected as reactive. The partitioning of the system into reactive (*e.g.* catalytic active site atoms) and unreactive atoms (*e.g.* ligand backbone) is vital to approaching such large systems because the graphical method would otherwise identify more reaction coordinates than could be feasibly computed.

To demonstrate the power of ZStruct, it was applied to the reaction of methane with cisplatin ($PtCl_2(NH_3)_2$). This system's activity for C–H functionalization has been examined by experimental[22] and computational studies,[23–25] where chemical intuition was used to hypothesize intermediates and reaction pathways. Despite the apparently simple structure of the reaction precursors, this reaction contains significant complexity due to the formation of 3-, 4-, 5-, and 6-coordinate structures enabled by the redox activity of Pt(II/IV). ZStruct was applied to the first few elementary steps of this reaction leading to the oxidative addition product of C–H activation (Fig. 3). After screening for low barrier and thermodynamically reasonable reactions, ZStruct's thorough search found 21 intermediates without help from chemical intuition, 10 of which were not previously reported in the literature. This result is especially surprising given that this reaction is particularly well known and well studied. In this case, all of these reaction paths could have been identified using chemical intuition, but the large number of plausible paths prohibited them from being studied in full using standard simulation techniques. For reactions with less studied mechanisms, unidentified reactive events are even more likely to be found.[12,13]

Outlook

Chemical reaction mechanisms are powerful conceptual tools. Methods that quickly reveal new mechanisms are therefore extremely useful, and are likely to become more and more popular as advances in these techniques allow increased predictive power and reduced computational costs.

While this perspective focused on recent developments in the ZStruct program and its application to methane activation, other studies by our group have demonstrated the predictive ability of ZStruct in a variety of different chemistries. For instance, an unexpected mechanism for C(sp^3)–N reductive elimination was found in a Pd(IV) complex, which resulted in successful prediction of non-Hammett rate behaviors.[13] In another example, a Ni-based C–H functionalization catalyst was designed using mechanistic insight from computation, enabling efficient reactivity at room temperature.[12] Additionally, surprising mechanisms for organo catalyzed stereoselective transformations were found.[26,27] These successful collaborations between experiment and simulation are providing evidence that computational reaction discovery approaches will remain a powerful avenue for advancing the study of reactions and catalysis.

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