

University of Nevada, Reno

**Screening Trans-Uranium Compounds for Small Molecule  
Activation Reactions**

A thesis submitted in partial fulfillment  
of the requirements for the degree of

Bachelor of Science in Chemistry and the Honors Program

by

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We recommend that the thesis  
prepared under our supervision by

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## ABSTRACT

Uranium (III) complexes have been shown to be effective for activating nitrogen<sup>1</sup> as well as other small molecules, such as water (H<sub>2</sub>O), methane (CH<sub>4</sub>), and hydrogen (H<sub>2</sub>). Given the chemical similarities between uranium (U) and neptunium (Np) as well as other trans-uranium elements, it would be straightforward to suggest that trans-uranium complexes can also effect small-molecule transformations. Unfortunately, there is little experimental evidence to support this claim. This is particularly complicated by the fact that there are various challenges associated with experimental investigations of the properties of trans-uranium complexes. In this thesis, we explore the possibility of modifying existing Np complexes in order to facilitate small-molecule activations similar to those of analogous U compounds. Furthermore, this thesis explores how implementation of modern machine learning techniques can improve the process by which viable trans-uranium compounds that can facilitate small molecule transformations are discovered.

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## INTRODUCTION

Small molecules such as H<sub>2</sub>O, O<sub>2</sub>, N<sub>2</sub>, CO<sub>2</sub> and CH<sub>4</sub> are ever present in our daily lives. Chemical reactions involving these small molecules serve vital functions required to sustain life. In many cases however, these reactions are mechanistically complex and often kinetically and thermodynamically demanding. As such, many reactions involving transformation of small molecules are done under harsh temperature and/or pressure conditions. For example, the Haber-Bosch process—which converts molecular nitrogen (N<sub>2</sub>) and molecular hydrogen (H<sub>2</sub>) into ammonia (NH<sub>3</sub>)—is a very valuable small molecule reaction. This is because ammonia is a very important industrial reagent, as well as being a key component in fertilizers. The process, however, must be performed under very high temperatures and pressures. The Haber-Bosch process consumes 1-2% of global energy production, with attendant effects for CO<sub>2</sub> emissions. Due to these limitations, transformation of small molecules into value-added intermediate chemicals under benign conditions is one of the holy grails of chemistry. As such, there is interest in alternative methods for achieving these transformations, without harsh temperature and pressure conditions. Recent progress has shown that uranium (III), U<sup>3+</sup>, metal complexes can be effective in activating small molecules, such as those mentioned above. This is particularly due to the nature of the *5f* valence electrons present in U, as well as the polarizing nature of the U center, which makes it possible to overcome the thermodynamic difficulties present in small molecule transformations.

Uranium is an actinide element. Actinide elements are found between actinium and lawrencium on the periodic table. They generally form chemical bonds with 6d and 5f

orbitals. As such, they are often referred to as the 5f elements. Due to the highly delocalized natures of the 5f orbitals, it is usually the case that the elements exhibit similar chemical properties. As such, U shares many similarities with other actinides, such as neptunium (Np), plutonium (Pu) and americium (Am). Due to these similarities, it is reasonable to expect that the trans-uranium elements (the elements beyond uranium) will show similar abilities to engage in small-molecule transformations. So far however, this has been shown to not be the case. The origins of this discrepancy are not entirely clear; however, it appears that there is a shift in the balance of redox potentials that enables uranium to perform small molecule transformations, while hindering these reactions in trans-uranium elements.

The Odoh research group at UNR uses quantum-mechanical computation to investigate the properties of trans-uranium species that are analogous to existing U complexes. Figure 1 shows the structure of four of the different uranium compounds whose Np analogues were studied by our group. The focus is on designing trans-uranium complexes that can perform small-molecule activation reactions. Density functional theory (DFT) is used to compare the electronic structure and chemical reactivity properties of Np analogues of U complexes. A paper recently published by our group shows that Np complexes can indeed facilitate small-molecule activation, albeit at a higher kinetic barrier than those of existing U complexes. The Odoh group also recently published the first literature evidence to suggest that it is possible for Np complexes to activate small molecules, with DFT calculations showing a favorable reaction of  $N_2$  to  $N_2^{4-}$  through the use of  $K_3Np-N-Np[NH]$ . Thus, it appears possible that trans-uranium complexes that can activate small molecules can be designed, using computational chemistry as a guide.

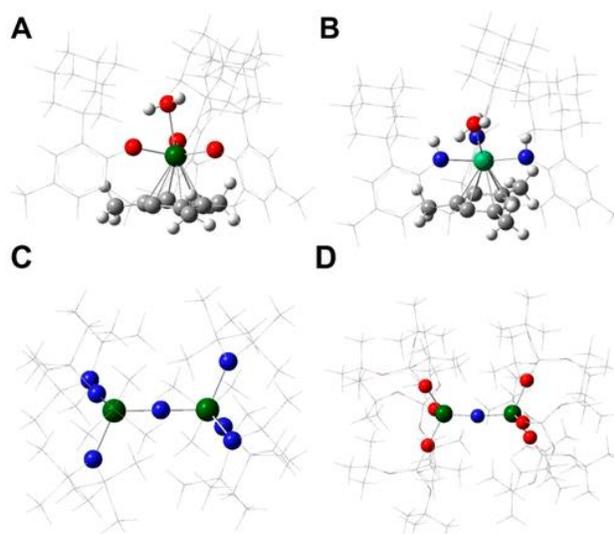


Figure 1: Four uranium complexes being for which the Np analogue is being studied by the Odoh Group. Reprinted from Adeyiga, et al., Activating Water and Hydrogen by Ligand-Modified Uranium and Neptunium Complexes: A Density Functional Theory Study. *Inorg. Chem.* **2020**.

Going forward, the greatest challenge involves identifying which ligands allow for the most favorable interactions between the Np center and the target molecule. We are interested in ligands that lead to lower rate-determining barriers for small-molecule transformations by Np complexes. By performing DFT calculations on a variety of different Np complexes, each with a different ligand (a ligand-modulation approach), we can get an idea of how different ligands affect the ability of Np complexes to facilitate small molecule transformations. The goal of this project is to determine whether a ligand-modulation approach produces *general* results that can be seen across the trans-uranium elements. As such, I will be investigating the thermodynamics and kinetics of small molecule activation processes by certain trans-uranium species, with the primary reaction being hydrogen evolution from water. This thesis also serves to provide ideas for future research projects to build from the research carried out herein. The conclusion of the most

recent paper published in the Odoh group is that a “large-scale computational screening of Np complexes that can be useful for catalytic activation of various small molecules”<sup>2</sup> is needed in order to find the most promising candidates for small molecule activation using trans-uranium elements. Given the way we perform DFT calculations and the power of modern computers and computing technologies, I believe that machine learning algorithms could play a pivotal role in identifying potential species that could prove effective in small molecule activation.

## LITERATURE REVIEW

### 1. Uranium Complexes

Uranium (U) is an element in the actinide series on the periodic table. Its most common oxidation states are U(IV) and U(VI).<sup>3</sup> Despite this, we find that the high reactivity of U(III) makes it an ideal candidate for forming large coordination complexes. Uranium's six (6) valence electrons allow it to form a variety of bonds with many different ligands, including both d-block elements, as well as organics.<sup>4</sup> Common ligands of uranium complexes include CO, CO<sub>2</sub>, N<sub>2</sub>, and organic alkyls and alkynes.<sup>4</sup>

Because uranium has from three (3) to six (6) valence electrons available<sup>3</sup>, it is able to form complexes with a wide variety of geometries ranging from linear and “sandwich” species, to octahedral complexes. Linear dioxide compounds (Shown in Figure 2) are the most common for U(V) and U(VI) oxidation states<sup>5</sup> with the other oxidation states allowing for different geometries. Uranium complexes tend to bond covalently using their 5f and 6d valence electrons.<sup>3</sup> Because of the wide variety of geometries and coordination complexes that uranium can form, it can be the center of a wide variety of catalysts that can be used for small molecule activation reactions.

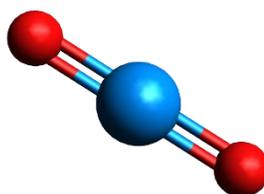


Figure 2: Linear dioxide uranium species structure (UO<sub>2</sub><sup>2+</sup>).

## 2. Small-Molecule Activation by U Complexes

U(III) compounds are known to be strongly reducing. Furthermore, this strong reduction character has been shown to be affected by the ligands involved in the compound.<sup>4</sup> U complexes show promise for small-molecule activation because of this highly reducing, oxophilic nature, which allows them to mediate processes requiring one or more electrons.<sup>6</sup> Research conducted in 1986 showed success in activating CO<sub>2</sub> with U(III) complex by reducing it to a bimetallic U(IV/IV) complex.<sup>7</sup> As such, the small-molecule activation ability of U has been known for quite some time. By bridging more than one U(III) center, it has been shown that the activation of nitrogen, N<sub>2</sub>, is possible.<sup>8</sup>

U(III) complexes are not the only ones that have shown success in small molecule activation. Research has shown that higher valent U compounds are equally capable of performing these small molecule activation reactions. For example, Bart et al. reported success in activating CO<sub>2</sub> with U(IV) and U(V) complexes.<sup>6</sup> While these compounds are equally as capable of mediating small-molecule activation reactions, they act on different classes of substrates. For example, while U(III) compounds have shown success in activating compounds such as CO<sub>2</sub>, CO, and N<sub>2</sub> compounds, U(IV) and U(V) have been shown to mediate reactions centered around alkanes and alkynes, as well as support insertion of carbon oxides, rather than their reduction.<sup>4</sup>

Since the 1980's, uranium compounds have shown promise in small-molecule transformations. Because of the similarities between U and Np, it would follow that Np complexes should be able to perform similar small-molecule activation reactions. In

practice however, it has been hard to find trans-uranium compounds that would be viable at performing these types of reactions. As such, a new search technique may be necessary.

### **3. Quantum-Mechanical Computations/Methodology**

Computational chemistry attempts to learn more about processes that are generally not well understood. In order to better understand these processes, researchers turn to a multitude of different computational methods, each with its own strengths and weaknesses. The first quantum computational chemistry method developed was Hartree-Fock Energy (HF). HF solves the Schrödinger equation to determine the wavefunction of a quantum system as well its energy. HF uses a Slater determinant to approximate the wavefunction of a system. This simplification comes at the expense of accuracy but make HF computationally inexpensive. As such HF theory is not as accurate as other quantum mechanical methods. This is because HF theory does not account for electron correlation effects, and treats each electron as being independent, when this is not the case in the real world where electrons would be interact instantaneously with each other.<sup>9</sup>

Perhaps the most ubiquitous quantum computational chemistry method is Density Functional Theory (DFT).<sup>10</sup> DFT allows for prediction of the properties of atoms and molecules by looking at their electron density.<sup>11</sup> Modern DFT comes from the work of Kohn and Hohenberg and their development of their two Hohenberg-Kohn (H-K) theorems.<sup>9</sup> These theorems express the electronic Hamiltonian as functionals of the electron density (functions of electron densities that are dependent on other functions). This approach is computationally cheaper than handling the electronic wavefunction. Kohn and Sham later modified the original H-K theorems in order to develop Kohn-Sham (KS)

DFT<sup>12</sup> which would go on to win the Nobel prize in chemistry in 1998.<sup>13</sup> KS DFT uses a system of non-interacting electrons that is set to have the same electron density as the true system.<sup>12</sup> This means that while KS DFT will produce energies similar to the exact energy (full solution of the Schrodinger equation) if all terms in its Hamiltonian are solved exactly. However, not all terms in KS DFT can be solved exactly. The largest errors are found in the exchange-correlation (XC) energy, as the XC term is approximated.<sup>12</sup> Many modern DFT functionals provide approximations to the exact XC energy.<sup>14</sup>

DFT calculations often involve a choice of two things: the XC density functional as well as the one-electron basis sets used to describe the density. As stated above, functionals are functions of the electron density of a system that use functions as their own parameters. Many different types of functionals exist. They are divided into numerous categories, including Local Density Approximation (LDA), Generalized Gradient approximation (GGA), and Hybrid.<sup>14</sup> In practice, the Hybrid functional B3LYP is the most common functional used. Hybrid functionals use some exact HF exchange.<sup>15</sup> The result is a more accurate calculation that maintains its efficiency. Becke devised this system in 1992, and ever since it has been one of the most popular functionals in use. B3LYP is an improvement on Becke's original functional that combines three parameters from Becke's functional to calculate the exchange, and the Lee Yang Parr (LYP) correlation calculation.

In addition to functionals, basis sets are a set of functions that represent the wave function of an orbital in any given atom.<sup>16</sup> These basis sets are generally treated as vectors, which are then mapped to scalars by the functional in order to be used in calculations. As

such, a functional gives a snapshot of the electronic structure/density of an atom at one time (unless time dependent DFT is being used, but that is not in the scope of this thesis).

#### **4. Machine-Learning**

The field of machine-learning is expanding daily, with new advancements in technology helping to make machine-learning algorithms faster, more optimized, and more accurate. Machine-learning, at its core, works by analyzing patterns found in data, then using statistics and other mathematical methods to infer something about the data based on the patterns found. For machine-learning models to be accurate, a wealth of training data is needed so that meaningful patterns in the data can be found. With the current state of computational chemistry, there has never been a better opportunity to harness chemical data into powerful machine-learning models. Indeed by taking data from known chemical reactions, we can use machine-learning to predict how chemicals will react before a reaction is ever done. This prospect could save countless hours of both wet-chemistry reactions and simulation time.

Using computer programs to predict chemical outcomes is not a novel idea. In 1969, a software program called the Organic Chemical Simulation of Synthesis was designed to perform retrosynthetic analysis on an organic compound in an attempt to determine the steps to synthesize it.<sup>17</sup> Unfortunately, this program lacked popularity because there was a small amount of collected, computerized data at the time, and computer performance was not good enough to perform the desired calculations within reasonable times. Much has changed since these early days. Current Artificial Intelligence (AI) systems are being used by bench chemists in order to interpret their data in ways that humans alone would not be

able to do, or would take much too long to do.<sup>18</sup> Most of the research done in applications of machine learning and artificial intelligence in chemistry have focused on the same idea: retrosynthetic analysis.

Much less well studied, but equally useful (especially for the subject of this thesis) is reaction product yields. Specifically, we are looking at the prediction of reaction conditions, such as rate-determining barriers, as these are the reaction features that directly affect the viability of transition metal complexes' abilities to perform small molecule transformations. These types of reactions are ideal for computational methods as they're generally small enough to be able to simulate in reasonable times, with good enough accuracy to reliably predict real world performance.<sup>19</sup>

Machine-learning methods generally involve two phases: training and testing. The first phase is the training phase. In order to be effective, machine-learning models need large quantities of data in order to interpret patterns<sup>20</sup> and identify relationships between chemical structures and the energy of a system. There are many algorithms used to train machine-learning models, each with different goals. Some algorithms attempt to preserve as much of the original data as possible (a technique known as principal component analysis), while reducing the amount that is needed to make accurate predictions, while others attempt to transform the data in a way that makes it as easy to process as possible, discarding any original information that may not be needed (a technique known as linear discriminant analysis).<sup>20</sup>

The amount of data needed to adequately train a system is exponentially proportional to the complexity of the system being trained<sup>20</sup>. The complexity of a model is typically

measured by its *dimensionality*, that is, the number of variables in the training data that have an influence on the results. For simple image recognition problems, generally the dimensionality of the model is the same as the number of pixels, though it could be even higher<sup>20</sup>. For more complex systems such as modelling molecular interactions and energies, these models could have many more dimensions, and thus require an enormous amount of training data. For example, Ramakrishan *et. al.* used energy data from six thousand structural isomers of C<sub>7</sub>H<sub>10</sub>O<sub>2</sub> before they were able to predict molecular energy of new isomers to within 1 kcal/mol (a threshold they describe as “chemically accurate”, implying the accuracy is good enough to be taken as a true value).<sup>21</sup> This problem with massive amounts of training data needed is a commonly called the “curse of dimensionality<sup>20</sup>”, and is commonly seen in pattern classification problems. Fortunately, using existing computational methods such as DFT, generating the amount of training data needed for accurate energy prediction is possible.

Once the machine learning model is trained, the second phase—the testing phase—can begin. In this phase, input data with a known output is fed into the machine learning model in order to test the accuracy of the model.<sup>20</sup> If a model is not accurate enough, then it obviously cannot be used for high-accuracy scientific work, and thus would need to be retrained, or the algorithm may have to be altered. Once a model has been shown to work with a reasonable degree of accuracy, it can begin to work on actual experimental data.

## **5. Ideas for Machine-Learning in Actinide Chemistry**

While not well studied, predictions of reaction conditions is a problem that is well-tailored for machine-learning applications. Accurate chemical simulations boil down to the

accurate prediction of one thing: energy.<sup>21</sup> Energy stored within bonds, transferred between molecules, and shared between systems are paramount to chemistry as a science. Energy is especially important in quantum chemistry such as predicting rate-determining-step barriers in a chemical reaction, as an activation energy barrier, by definition, is focused on energy. Thus, if one can accurately model the energy of a chemical system, then one can accurately predict how other chemical systems will interact with one another. Using this information pattern recognition, neural networks, and big data analytics can be used as valuable tools to model almost any possible chemical system.<sup>21</sup> Using the two-step machine-learning model presented previously, I will provide an example for how a machine-learning algorithm could be implemented for actinide quantum chemistry focusing on a ligand modulation approach.

As discussed previously, a wealth of training data is needed in order to get an accurate prediction model. Thus, the data from prior DFT calculations run by our group, as well as data from other groups who have done DFT studies on actinide compounds, can be fed into a machine-learning model in order for the model to extract features that could prove useful for predicting future reactions. Here, the specific features of focus are the ligands in the compound, as the ligand modulation approach that we have been using up to this point most supports that model. The model would look at the rate determining barrier of the reaction in the context of the ligands present in the complex. As such, the model would assume a causal relationship between the ligands in the complex and the rate-determining-barrier. Though, the machine-learning algorithm will most likely look at other aspects of the reaction as well.

When predicting the activation energy barrier of a reaction, every step of the reaction is computed using DFT calculations, including reactants, all transition state species, intermediates, and products. Thus, in order to train a machine-learning model to give information that would be useful for the prediction of activation energy barriers for actinide chemistry, one would need to have DFT data from every step of the reaction, using the base state as the training data, and the transition states and products as the resultant data. This way, the machine-learning algorithm becomes trained in how the base state of a reaction influences the reaction, and as such, its activation energy barrier. If the model is not accurate enough after training, it may be necessary to create more training data by running various other reaction steps for different actinide metal complexes through DFT computations in order to get their energies, then use that as training data in order to better train the model.

Once the model has been trained appropriately, it can be tested and validated using even more pre-calculated samples as testing data. If the model is validated, then one could easily write a computer program to automatically generate new actinide metal complexes based on ones that have shown the most promise for small molecule activation. These complexes can then be sent into the machine learning model which can validate with relative certainty whether the complex would be a good match for small molecule activation reactions. Since this process can be done automatically, many potentially viable actinide complexes can be found. Once the machine-learning model has identified the most likely ligands for use with small molecule activation reaction, full DFT calculations can be ran on these complexes in order to determine whether the complexes are viable. Once the

DFT calculations have been run, these compounds can be used again as training data, to improve the model further.

Choi et. al. were able to use machine learning to predict activation energies of reactions to within 1.95 kcal/mol using kinetic information from 12,704 chemical reactions.<sup>22</sup> Their results indicate that more complicated chemical reactions (those involving many products or reactants and changing the total number of bonds by >4) are generally far less accurate, with simple chemical reactions generally the most accurate.<sup>22</sup> Since small-molecule activation reactions tend to deal with simple molecules (with the exception of the catalysts used) and do not produce a multitude of different products, these reactions would most likely perform well with current machine-learning techniques.

## REFERENCES

- (1) Panthi, D.; Adeyiga, O.; Dandu, N. K.; Odoh, S. O. Nitrogen Reduction by Multimetallic Trans-Uranium Actinide Complexes: A Theoretical Comparison of Np and Pu to U. *Inorg. Chem.* **2019**, *58* (10), 6731–6741. <https://doi.org/10.1021/acs.inorgchem.9b00129>.
- (2) Adeyiga, O.; Panthi, D.; Suleiman, O.; Stetler, D.; Long, R. W.; Odoh, S. O. Activating Water and Hydrogen by Ligand-Modified Uranium and Neptunium Complexes: A Density Functional Theory Study. *Inorg. Chem.* **2020**. <https://doi.org/10.1021/acs.inorgchem.9b03433>.
- (3) Duward Shriver; Mark Weller; Tina Overton; Fraser Armstrong; Jonathan Rourke. *Inorganic Chemistry*, 6th ed.; W. H. Freeman, 2014.
- (4) Arnold, P. L. Uranium-Mediated Activation of Small Molecules. *Chem. Commun.* **2011**, *47* (32), 9005–9010. <https://doi.org/10.1039/C1CC10834D>.
- (5) Arnold, P. L.; Jones, G. M.; Odoh, S. O.; Schreckenbach, G.; Magnani, N.; Love, J. B. Strongly Coupled Binuclear Uranium-Oxo Complexes from Uranyl Oxo Rearrangement and Reductive Silylation. *Nature Chemistry; London* **2012**, *4* (3), 221–227. <http://dx.doi.org.unr.idm.oclc.org/10.1038/nchem.1270>.
- (6) Bart, S. C.; Anthon, C.; Heinemann, F. W.; Bill, E.; Edelstein, N. M.; Meyer, K. Carbon Dioxide Activation with Sterically Pressured Mid- and High-Valent Uranium Complexes. *J. Am. Chem. Soc.* **2008**, *130* (37), 12536–12546. <https://doi.org/10.1021/ja804263w>.

- (7) Brennan, J. G.; Andersen, R. A.; Zalkin, A. Chemistry of Trivalent Uranium Metallocenes: Electron-Transfer Reactions. Synthesis and Characterization of  $[(\text{MeC}_5\text{H}_4)_3\text{U}]_2\text{E}$  (E = S, Se, Te) and the Crystal Structures of Hexakis(Methylcyclopentadienyl)Sulfidodiuranium and Tris(Methylcyclopentadienyl)(Triphenylphosphine Oxide)Uranium. *Inorg. Chem.* **1986**, *25* (11), 1761–1765. <https://doi.org/10.1021/ic00231a008>.
- (8) Barluzzi, L.; Falcone, M.; Mazzanti, M. Small Molecule Activation by Multimetallic Uranium Complexes Supported by Siloxide Ligands. *Chem. Commun.* **2019**, *55* (87), 13031–13047. <https://doi.org/10.1039/C9CC05605J>.
- (9) Hohenberg, P.; Kohn, W. Inhomogeneous Electron Gas. *Phys. Rev.* **1964**, *136* (3B), B864–B871. <https://doi.org/10.1103/PhysRev.136.B864>.
- (10) Zhao, Y.; Truhlar, D. G. Density Functionals with Broad Applicability in Chemistry. *Accounts of Chemical Research* **2008**, *41* (2), 157–167. <https://doi.org/10.1021/ar700111a>.
- (11) Parr, R. G. Density Functional Theory of Atoms and Molecules. In *Horizons of Quantum Chemistry*; Fukui, K., Pullman, B., Eds.; Académie Internationale Des Sciences Moléculaires Quantiques / International Academy of Quantum Molecular Science; Springer Netherlands: Dordrecht, 1980; pp 5–15. [https://doi.org/10.1007/978-94-009-9027-2\\_2](https://doi.org/10.1007/978-94-009-9027-2_2).
- (12) Kohn, W.; Sham, L. J. Self-Consistent Equations Including Exchange and Correlation Effects. *Phys. Rev.* **1965**, *140* (4A), A1133–A1138. <https://doi.org/10.1103/PhysRev.140.A1133>.
- (13) The Nobel Prize in Chemistry 1998 <https://www.nobelprize.org/prizes/chemistry/1998/summary/> (accessed Apr 26, 2020).
- (14) Rappoport, D.; Crawford, N. R. M.; Furche, F.; Burke, K. Which Functional Should I Choose? University of California, Irvine December 15, 2008.
- (15) Becke, A. D. A New Mixing of Hartree–Fock and Local Density-functional Theories. *J. Chem. Phys.* **1993**, *98* (2), 1372–1377. <https://doi.org/10.1063/1.464304>.
- (16) Davidson, E. R.; Feller, D. Basis Set Selection for Molecular Calculations. *Chem. Rev.* **1986**, *86* (4), 681–696. <https://doi.org/10.1021/cr00074a002>.
- (17) Baskin, I. I.; Madzhidov, T. I.; Antipin, I. S.; Varnek, A. A. Artificial Intelligence in Synthetic Chemistry: Achievements and Prospects. *Russ. Chem. Rev.* **2017**, *86* (11), 1127. <https://doi.org/10.1070/RCR4746>.
- (18) de Almeida, A. F.; Moreira, R.; Rodrigues, T. Synthetic Organic Chemistry Driven by Artificial Intelligence. *Nature Reviews Chemistry* **2019**, *3* (10), 589–604. <https://doi.org/10.1038/s41570-019-0124-0>.
- (19) Houk, K. N.; Cheong, P. H. Computational Prediction of Small-Molecule Catalysts. *Nature* **2008**, *455* (7211), 309–313.
- (20) Duda, R. O.; Hart, P. E.; Stork, D. G. *Pattern Classification*, Second edition.; Wiley: New York, 2001.
- (21) Ramakrishnan, R.; Dral, P. O.; Rupp, M.; von Lilienfeld, O. A. Big Data Meets Quantum Chemistry Approximations: The  $\Delta$ -Machine Learning Approach. *J. Chem. Theory Comput.* **2015**, *11* (5), 2087–2096. <https://doi.org/10.1021/acs.jctc.5b00099>.

- (22) Choi, S.; Kim, Y.; Kim, J. W.; Kim, Z.; Kim, W. Y. Feasibility of Activation Energy Prediction of Gas-Phase Reactions by Machine Learning. *Chemistry – A European Journal* **2018**, *24* (47), 12354–12358. <https://doi.org/10.1002/chem.201800345>.