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Creating a ‘Compass’ for Deuterium Chemistry through Theoretical Calculations

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On Earth, hydrogen contains only 0.015% deuterium, which has about twice the mass of regular hydrogen. Until now, deuterium has only been used in basic research, but recently, “deuterated molecules,” in which hydrogen in the molecule is replaced with deuterium, have been found to have improved functionality and are beginning to be used as new materials. However, the mechanism behind why the molecule becomes more functional when its hydrogen is converted to deuterium has hardly been elucidated. Amid growing expectations for theoretical research, Prof. Tachikawa is using HPCI (High-Performance Computing Infrastructure) to elucidate the mechanisms underlying the manifestation of deuterium effects.

It All Started as a Calculation for Fun

“Actually, I started research on deuterium playfully,” Prof. Tachikawa recalls. “I tried changing the hydrogen (H) nucleus in a molecule to a positron using a molecular calculation program I developed during my doctoral studies, and got some interesting results. So, next, I tried doubling the mass of the hydrogen nucleus. If you double the mass, you get deuterium (D). This significantly changed the computational results.” In other words, it suggested that changing hydrogen in a molecule to deuterium could change the properties of the molecule. He thought, “Maybe the ‘common sense’ that hydrogen and deuterium have the same chemical properties is wrong,” and immediately began calculations on molecules in which hydrogen had been replaced with deuterium (deuterated molecules) to quantitatively elucidate the differences between hydrogen and deuterium.

The behavior of extremely small particles, such as molecules, follows the principles of quantum mechanics. However, when trying to calculate the shape and energy of molecules using quantum mechanics, the amount of computational cost required becomes enormous. Therefore, when calculating molecules, it is usually assumed that only the electrons in the molecule follow quantum mechanics, and the atomic nucleus, which is very heavy and has a high charge density compared to the electrons, is considered to be a stationary point charge, thereby reducing the amount of computational cost.

However, Prof. Tachikawa focused on the difference between hydrogen and deuterium. Both have one electron, but the difference lies in the atomic nucleus (Fig. 1). In order to express such a difference, the atomic nucleus must be calculated using the theory of quantum mechanics, rather than as a stationary point charge. To address this, Prof. Tachikawa developed a new “quantum multi-component molecular theory” to calculate not only electrons but also atomic nuclei using quantum mechanics, and implemented his unique program. The components here refer to types of particles, including not only electrons and atomic nuclei, but also positrons and muons.

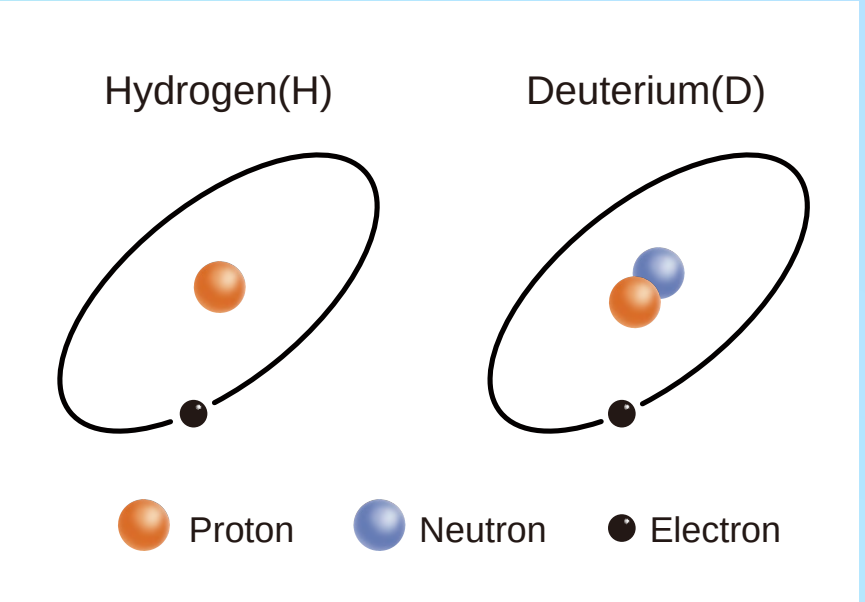

Fig. 1 : Differences between hydrogen and deuterium

The nucleus of hydrogen contains only one proton, but the nucleus of deuterium (also called a deuteron) contains one proton and one neutron, so they have different masses. This difference in mass creates differences in the properties of normal molecules and deuterated molecules. (Original figure provided by: Associate Professor Hiroshi Naka, Kyoto University)

The first calculation was for the hydrogen molecules. After calculating H_2, which consists of two hydrogen atoms, HD, which consists of one hydrogen and one deuterium, and D_2, which consists of two deuterium atoms, the results showed that the electron density, nuclear density, and

internuclear distance were all different (Fig. 2). Interestingly, it was found that the charge distribution of the electrons in the HD molecule is polarized toward D. Upon seeing this result, Prof. Tachikawa was surprised and wondered, "How is it so different?" When he reported the computational results to the experimental researchers and asked for their opinion, they say, "We knew this result through experimental measurement, but we didn't have a theory that could explain the reason." Prof. Tachikawa made it possible to theoretically calculate the difference between hydrogen and deuterium by treating atomic nuclei quantum mechanically.

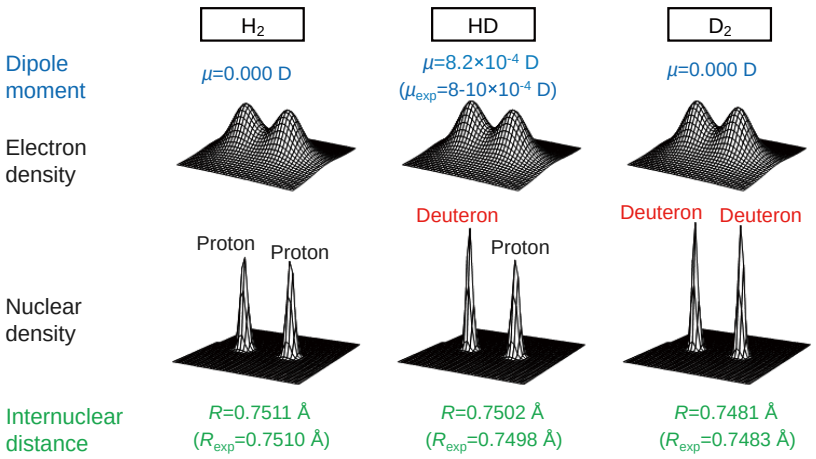

Fig. 2 : Differences between hydrogen and deuterium revealed by quantum multi-component molecular theory

In the HD molecule, it was found that the electron charge distribution is polarized toward D. The degree of this polarization (dipole moment, unit D [debye]) also closely reproduced the experimental value (μ_{exp}). Additionally, it was found that the distance between atomic nuclei decreases in the order of H_2 > HD > D_2 (the experimental value is in parentheses).

Revealing How Deuteration Changes a Substance's Properties

Prof. Tachikawa developed a series of computational methods that treat atomic nuclei quantum mechanically, and gradually became able to calculate larger deuterated molecules. One of these was squaric acid, a substance in which four carbon atoms are bonded in a square ($C_4H_2O_4$). Squaric acid crystals, which are formed via hydrogen bonding, become antiferroelectric at low temperatures and paraelectric at high temperatures. Simply put, the properties of a crystal when an electric field is applied change drastically depending on the temperature, and the phase transition temperature (the temperature at which the property changes) rises from 373K (100℃) to 520K (247℃) when hydrogen is replaced with deuterium. Squaric acid crystals were chosen as the subject of calculations because they are a representative example of crystals whose properties change significantly when deuterated.

One of the methods for treating atomic nuclei quantum mechanically is the "path integral (PI)" method (Fig. 3). In quantum mechanics, atomic nuclei are represented as a superposition of various quantum states. In the PI method, each quantum state is represented as a "bead" that obeys the classical laws of physics, and the "superposition" of quantum states is reproduced by a "necklace" made by connecting these with springs. The interactions between different necklaces are then calculated for each bead and added together.

Prof. Tachikawa further developed this computational method and performed calculations on squaric acid crystals using Kyushu University's Supercomputer system ITO. He said, "The algorithm of PI method can be divided for each bead, so they are inherently easy to parallelize. Furthermore, we succeeded in increasing the efficiency of parallelization by applying a quantum mechanical application that allows parallelization

to the calculation of interactions between beads. As a result, we were able to complete a massive amount of calculations, which improved the accuracy of the calculations."

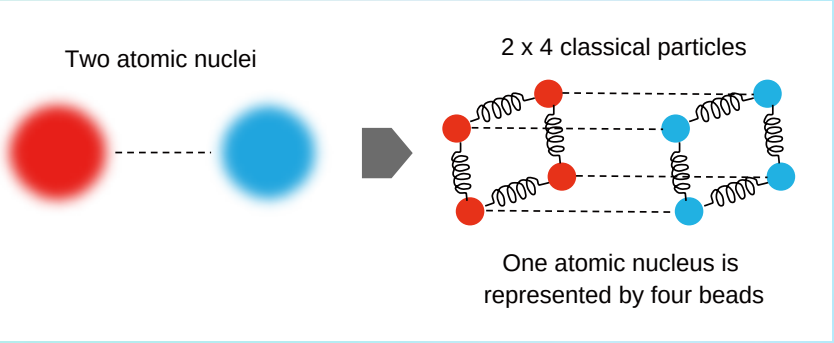

Fig. 3 : Schematic illustration of the path integral (PI) method

Two atomic nuclei interacting quantum mechanically (left) are represented in the PI method as shown on the right. In the figure on the right, as an example, one atomic nucleus is represented by a necklace of four beads connected by a spring (the number of beads is 8, 16, 32, etc. depending on the purpose of the calculation). The dotted lines connecting the beads of the two necklaces indicate the interaction between atoms involving electrons (calculated by a quantum mechanical application). By incorporating all of these effects, it becomes possible to treat all particles quantum mechanically, and the structure and physical quantities of the molecule can be calculated with high accuracy..

As a result of the calculations, it was found that when atomic nuclei are included in quantum mechanical calculations, both hydrogen and deuterium tend to exist near the middle of two oxygen atoms, and that the positions of hydrogen and deuterium involved in hydrogen bonds change as the temperature increases (Fig. 4). Prof. Tachikawa achieved this result by developing and implementing a method to improve the parallelization efficiency of the PI method, and for this achievement, his project was awarded the 9th HPCI Excellent Achievement Award (Matter, material, and chemistry research field) in 2022.

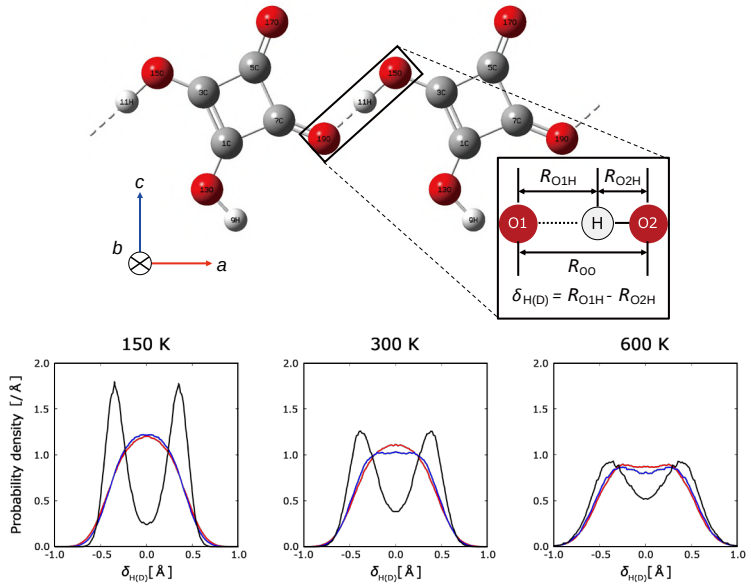

Fig. 4 : Computational results of interatomic distances of squaric acid

The upper figure shows a partial structure of a squaric acid crystal (where two molecules are hydrogen-bonded). Grey represents carbon, red represents oxygen, and white represents hydrogen or deuterium. The lower figure shows the computational results of the position of the hydrogen (deuterium) atom at three temperatures. The horizontal axis ($\delta_{H(D)}$) is an index showing where the hydrogen (deuterium) atom is located between the two oxygen atoms (see the box in the above figure). The vertical axis (probability density) is the probability that the atom exists at that position. The red curve shows the computational result using the PI method when the circled H is hydrogen, and the blue curve shows the result when it is deuterium. The black curve represents the result of calculation when the circled H is hydrogen and atomic nuclei are not included in the quantum mechanical calculations. The black curve has two peaks (bimodal distributions) at all temperatures, indicating that the hydrogen atom is located toward one of the oxygen atoms. However, at 150K using the PI method, the peak is at the center for both hydrogen and deuterium, indicating that the hydrogen (deuterium) atom is located near the center of the two oxygen atoms. At 300K, the hydrogen case shows a peak at the center, while the deuterium case starts to show a bimodal distribution. At 600K, both cases show bimodal distributions. These results reveal the structural change due to deuteration.

When Prof. Tachikawa started the calculation of squaric acid crystals, he also conducted joint research with Prof. Hatsumi Mori of the University of Tokyo. Prof. Mori discovered through experiments that a transition of a certain organic conductor to an insulator occurs only when the hydrogen is replaced with deuterium, and asked Prof. Tachikawa to collaborate on the research in order to find a theoretical explanation. Prof. Tachikawa also performed calculations on this material and elucidated the mechanism behind the phase transition that occurs specifically with deuterium.

World's First Calculation That Reveals Why Deuterated Drugs Are So Effective

The improvement in drug efficacy due to deuterium was published for the first time in 2009. At the time, everyone thought it would be impossible to commercialize. However, in 2017, deutetrabenazine was approved by the U.S. Food and Drug Administration (FDA) as a drug for Huntington's disease (Fig. 5). By simply replacing some of the hydrogen in an existing drug with deuterium, the drug's duration of efficacy improved and it became possible to take it less frequently.

It was known that by replacing hydrogen with deuterium, the reaction with the enzyme becomes less likely to proceed, and the medicinal effects last for a long time, but it was not clear why deuteration brings about such a change. Therefore, Prof. Tachikawa calculated a molecule called anisole as a model of the reaction site of deutetrabenazine, and simplified the reaction with the enzyme to clarify how the energy changes (Fig. 6). The calculation was performed on the Supercomputer system ITO using a method called multi-component density functional theory, which is one of the quantum multi-component molecular theories developed by Prof. Tachikawa.

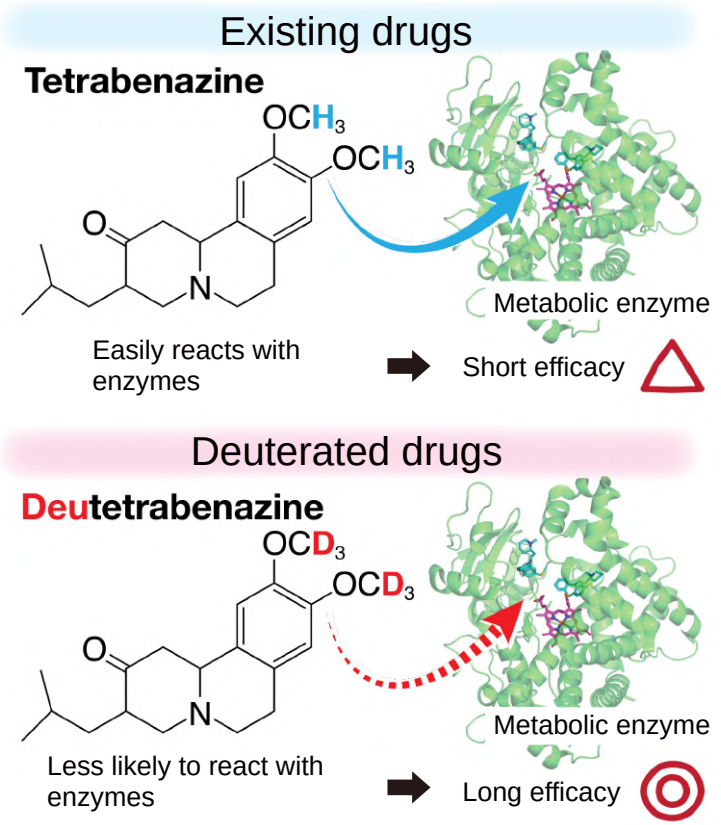

Fig. 5 : Deuterated drugs approved in the United States

Deutetrabenazine has a structure where some of the hydrogen (blue H) in tetrabenazine, an existing drug, is replaced with deuterium (red D). By replacing hydrogen with deuterium, the drug's efficacy is improved.

The results revealed that the activation energy required to remove hydrogen or deuterium from anisole is greater for deuterium. In other words, deuterium is more difficult to remove than hydrogen. This explains why the reaction with the enzyme proceeds more slowly and the drug's efficacy lasts longer. "This was the world's first calculation that elucidated the mechanism of deuteration effect in pharmaceuticals, and we received a lot of attention, including being featured on the cover of a journal and receiving several requests to contribute an article," Prof. Tachikawa says proudly.

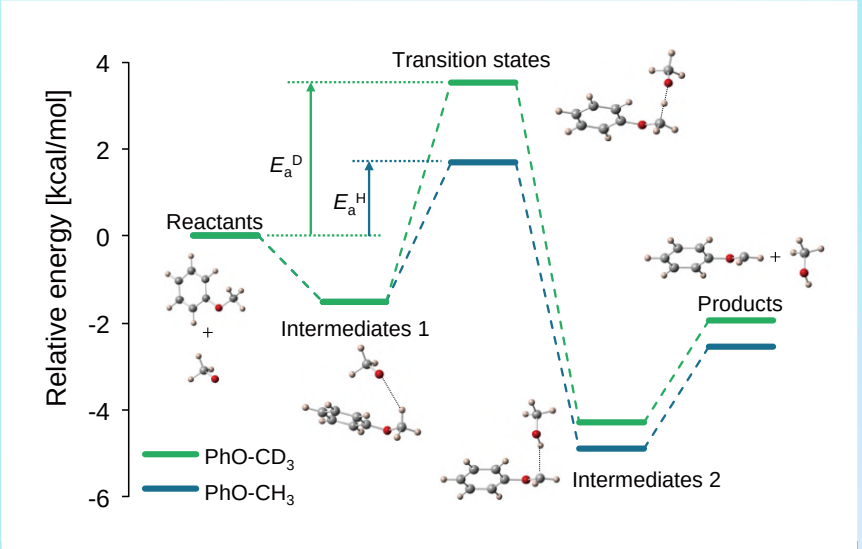

Fig. 6 : Difference in activation energy for hydrogen and deuterium abstraction reactions

Prof. Tachikawa calculated the energies of the reactants, products, and transition states of the reaction in which hydrogen or deuterium is abstracted by methoxy radical (OCH_3) from anisole ($C_6H_5OCH_3$) or deuterated anisole ($C_6H_5OCD_3$). Deuterium had a larger activation energy ($Ea^D > Ea^H$). In addition to this difference, for example, it was found that the C-D distance in CD_3 was shorter than the C-H distance in CH_3 in the reactants. Also, the number of electrons around the deuterium nucleus was greater than that around the hydrogen nucleus. This calculation can now take into account the tunnel effect, one of the quantum properties.

Introduction of Developed Computational Methods into Commonly Used Applications by Experimental Researchers

In addition to this drug, the development of deuterated drugs is booming, and several cases have been approved. Beyond pharmaceuticals, deuterated molecules are also beginning to be put to practical use in the field of materials. For example, an organic electroluminescent material for displays with improved luminous efficiency and durability due to deuteration was released in South Korea in 2021.

"Among the approved drugs, there is one in which replacing some of the hydrogen with deuterium changed a drug originally intended for myelofibrosis to become one for alopecia areata. Deuteration can drastically change the applicable disease. Moreover, we also know that deuteration reduces the lipid solubility of the molecule. In this way, changes in properties that are difficult to understand based on previous experience have been found. Meanwhile, in the field of materials, it is becoming increasingly difficult to develop molecules with new functions, so it is said that the last resort is to replace all hydrogen with deuterium. However, because the mechanism by which properties change is unknown, it is currently impossible to establish guidelines for molecular design, even if one tries to create molecules with new properties through deuteration. I would like to elucidate the mechanism by which properties change through theoretical calculations and provide guidelines for designing deuterated molecules," Prof. Tachikawa says.

Part of this vision has already been realized. Currently, there are several

applications for molecular calculation that use quantum mechanics for only electrons, and experimental researchers widely use these applications. The method developed by Prof. Tachikawa to calculate atomic nuclei using quantum mechanics has been incorporated into some of these applications, and plans are underway to implement it in other applications. Furthermore, Prof. Tachikawa says, “In the future, I would like to develop and implement an application that uses AI to predict the performance of deuterated molecules from their structure.” If experimental researchers can easily calculate the effects of deuterium using such an application, this will be a major step forward in putting deuterated molecules into practical use.

Regarding deuterated drugs, Prof. Tachikawa is focusing on collaborative research with Prof. Hironao Sajiki of Gifu Pharmaceutical University and Associate Professor Hiroshi Naka of Kyoto University, who are experts in the synthesis of deuterated molecules. “By developing the collaborative research, I hope to calculate the interactions between whole proteins and deuterated drugs, rather than model reactions. Not only that, but also calculate how the drug changes after it enters the body, and predict which parts of the drug should be deuterated to make it more effective. To make use of the results, it is necessary to convert only the targeted parts of the molecule to deuterium, so I want to calculate the energy of deuteration reactions, including catalysts, and propose efficient deuteration reactions. I also want to create a ‘compass’ for deuterium chemistry through theoretical calculations, and develop it into a next-generation innovative field of chemistry,” Prof. Tachikawa says.

There are many other mysteries that Prof. Tachikawa wants to solve. For example, observations have shown that the deuterated ratio reaches 10% in molecules produced in interstellar molecular clouds. “I would like to use calculations to elucidate why deuterium enrichment occurs in interstellar molecular clouds,” he says. In addition, the calculation methods that he has developed can be applied to calculations of elementary particles such as positrons and muons, so he is working on collaborative research with experimental researchers to tackle the mysteries of elementary particles. “Now that I can calculate molecules containing various particles, including deuterium, I feel like a child with a lot of toys in front of me,” he says. “There are many interesting themes that have not yet been explored in various fields, so why not join us in research at the Tachikawa Laboratory?”

About the
Researcher

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Prof. Tachikawa makes full use of HPCI to perform calculations that would be impossible for a human to do. He is also a master of the abacus. Tachikawa, whose parents were greengrocers, attended abacus classes from age 8 to 12, and obtained a third-degree abacus certificate. A few decades later, his daughter surpassed him by obtaining a fourth-degree certificate, and his passion for abacus was rekindled. In 2024, he won both the abacus and mental arithmetic divisions of the Yokohama City Youth Division II. "I can't check quantum calculations, but it's actually quite useful for my research," Prof. Tachikawa says. Using his mental arithmetic skills honed through abacus, he can quickly estimate the time it will take to conduct calculation on the HPCI system when submitting a project proposal.

Interview date: November 28, 2024

Associated Research Projects:

- Development of first-principles simulation program for crystalline system with hydrogen quantum effect (hp210077)
- Development and application of first-principles method for deuterated drugs and materials (hp220061)

Principal Investigator: Masanori Tachikawa (Yokohama City University)

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