Theoretical and Computational Chemistry

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Importance of Theoretical and Computational Chemistry in State-of-the-art Chemistry Research

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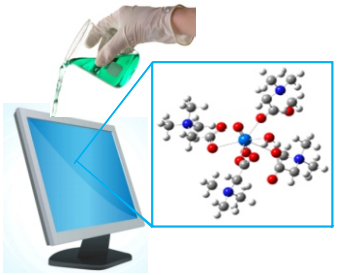

ABSTRACT

There is no doubt that research in chemistry plays an extremely important role in our day-to-day lives. For example, some of the products we use routinely, including toothpaste, soaps, clothes, medicines, and also the food we consume are all related in some or the other manner to chemistry. Therefore, research in chemistry helps us in developing and advancing various aspects of our daily life. Conventionally, chemistry is considered as an experimental subject. So, it is pertinent enough to raise the question – whether and how Theoretical and Computational Chemistry actually works; and also whether there is a need for a specialized branch of theoretical chemistry research. In this article, we shall briefly discuss these issues and, in the process, also highlight the needs of Theoretical and Computational Chemistry in the modern-day start-of-the-art research in chemistry. The important roles that Theoretical and Computational Chemistry can play in areas of interdisciplinary research related to the programs of DAE are also highlighted.

KEYWORDS: *Theoretical and Computational Chemistry, Medicines*

Introduction

Theoretical Chemistry is a branch of chemistry in which generalizations based on theoretical principles and concepts are developed and these doctrines are used to understand the fundamental physical principles in underlying chemical processes. Within the framework of theoretical chemistry, one can construct chemical laws, principles and their modifications and their hierarchy. A major place in theoretical chemistry is occupied by the dogma of the interconnection between the structure and the property of chemical systems. Theoretical chemistry uses mathematical methods with appropriate physical assumptions to explain the structures, dynamics and thermodynamics of a chemical system and correlate between them. In doing so, theoretical chemists often use computers and computational methods to solve equations numerically wherever analytical solution is not possible or perform simulations of the actual system and phenomena. However, the bottleneck in early years was the non-availability of supercomputing machines to handle large chemical systems.

With the advent of high-performance supercomputing (HPC) machines, the field of theoretical chemistry has seen a paradigm shift and has changed into Theoretical and Computational Chemistry. Because of the availability of large-scale computational facilities, now fairly large and complex chemical and physical systems can be handled computationally. However, extent of largeness of the system depends on the computational technique we use. The first step in any theoretical method is to map the actual physical system into a model system by choosing constituent basic units appropriately. Depending on the chosen length scale of the basic unit, various branches of theoretical chemistry have evolved. If electrons and nuclei of the atoms constituting the system are the basic units, the methods we need to apply should be based on the principles of well-known Quantum Chemistry/Mechanics and the system size that we can handle in such cases can be up to a few hundred atoms. However, due to the inherent periodicity of the lattice structure, some of the computational methods such as periodic density functional theory (DFT) [1] using plane waves can be used to study bulk solids. Similarly, in atomistic lengthscales in which atoms are the basic units, statistical mechanical principles are used for any many-body system and larger system sizes such as proteins and DNAs in water or for that matter any macromolecule in a solvent can be handled in this domain. At the mesoscopic length scale, where clusters of atoms are the basic units, statistical mechanical principles are used to describe and the system sizes relevant to biological systems like cell membranes, complete cell, multi protein interactions in the cell matrix can be studied easily. The question that we ask here is whether Theoretical and Computational Chemistry is important in chemistry research.

Here, I list a number of important reasons why Theoretical and Computational Chemistry (TCC) is important and an integral part of modern chemistry research

Computational Chemistry Predicts Reaction Mechanisms and Transition States

For any newly discovered chemical reaction, establishing the mechanism by identifying the transition state (TS) and the pathway connecting the reactants to the products via TS is a very important step in chemistry. Identifying the TS and the reaction pathway using experiments is not so easy. Here arises the need of quantum chemical calculations to understand the reaction mechanism, which helps chemists to modify the reaction and thereby improve the yield, productivity and

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specificity of the reaction [1-8]. The citation of 2013 Noble prize in Chemistry, which was awarded to three theoretical scientists Martin Karplus, Michael Levitt and Arieh Warshelon their works on Theoretical and Computational Chemistry reads, *"Today the computer is just as important a tool for chemists as the test tube. Simulations are so realistic that they predict the outcome of traditional experiments."*

Computational Chemistry Is Used for Calculating Reaction Rates

Not only the detailed chemical reaction pathway, but the rate and direction of a chemical reaction, which occurs at lightning speed of the order of picoseconds or fem to seconds can also be predicted from quantum mechanical calculations. Aided by advanced theoretical methods, computers can now unveil chemical processes independently, and also can complement data obtained from expensive experimental laser spectroscopy to a meaningful conclusion [9-11].

Computational Chemistry Is Key for Designing Newer Molecules and Exotic Materials

Computational chemistry can predict new molecules of importance. It helps us to design new ligands, and molecules with tunable properties.By a-priori deducing the structure-property correlations, ne wer and unconventional molecules and compounds with exotic chemistry and properties can be designed. The use of modern day periodic DFT based quantum mechanical methods has made the application of Computational Chemistry possible towards design of suitable materials for energy, healthcare and catalysis. A tremendous amount of peer reviewed research papers [12-15] is coming out recently on computational design of materials in those fields. Better predictability with respect to experimental results have been established in these studies.

Computational Chemistry helps in Analyzing and Rationalizing Experimental Data

Many experimental results in chemistry require theoretical and computational chemistry to interpret the experimental data and the observation. Be it experiment on thermodynamics, or kinetics, or spectroscopy, theoretical and computational chemistry assists in interpreting experimental results. Most of the experimental observations are macroscopic in nature and therefore an atomic or molecular level understanding of those observations require theoretical and/or computational supports. Here theoretical and computation chemistry works in consonance with the experimental research [16].

Computational Chemistry in Drug Design in the Pharmaceutical Industry

Theoretical and Computational Chemistry plays an astounding role in the pharmaceutical industry. Computational chemistry, in particular, is extensively used in many stages of drug development. Computational Chemistry using QM calculations, docking and simulations provides a complete in-silico route to design a new drug. Computational chemistry can very accurately predict the binding site of a drug in a protein molecule and thereby helps in sensing a disease or deactivating a particular enzyme causing a disease [17-20]. Computational chemistry has devised method like QSAR (Quantitative Structure Activity Relationship), through which a few molecular candidates are chosen form a large library of compounds suitable to be drug molecules and any other molecules with suitable characteristics.

Theoretical and Computational Chemistry enables us to venture into experimentally inaccessible or difficult to access domains.

One of the profound roles of Theoretical and Computational Chemistry has been to pervade those domains either not accessible or difficult to access by experiments.[21-23]Evaluating physic-chemical properties of materials at high temperature, pressure and radiation through experimental research is difficult to achieve but Theoretical and Computational research can easily predict those properties with extremely high predictability. This kind of theoretical and computational research is very important in nuclear industry. Any experiment at astro-physical condition is very difficult to perform, but theory and simulations can easily mimic those condition in computers and predict useful results [24]. That's why Theoretical and Computational chemistry plays a vital role in astronomical chemistry research, cloud formation etc.

Theoretical and Computational Chemistry enables us to understand bio-molecular phenomena in Biochemistry and Biophysics.

Biomolecules are macromolecules such as proteins, DNA, lipids etc. Due to their large size, the exact conformational structure of such molecules very much depends on environment such as salt concentration, pH, temperature, pressure etc. The properties of these molecules also depend on their structure. Phenomenon like protein folding can be better understood using molecular simulation. Molecular simulations using classical force field are now extensively used to study protein-ligand interaction, protein aggregation, drug binding etc. Therefore, theoretical and computational chemistry is a major tool to study biophysical systems [25-27].

Theory and Computations in Nuclear Energy

Roughly 15% of the electrical power in the world is produced from nuclear reactors, without significant emissions of CO2,one of the major components of greenhouse gas. That's why nuclear energy is the most attractive avenue to achieve Net Zero Emission target within a reasonable timeframe. One of the major components in the nuclear reactor operation is the formulation of a proper fuel cycle. Below are the different stages of nuclear reactor operation, in each of which Theoretical and Computational Chemistry can play a major role [28-33]. The advancement in computational chemistry has reached a stage where it can be used for a process design. [34].

In front-end of the fuel cycle:

Theory and computation can be applied to various problems of nuclear energy. This methodology can be used efficiently in both front end and back end of the fuel cycles [35,36]. In the front end of the fuel cycle, computational methods can predict the properties of fuels at extreme conditions of temperature, pressure and radiation almost accurately without performing any experiment, which is, in any way, very difficult to perform. Similarly, this method can be very successfully used to design newer fuels[37-38] for advanced nuclear reactors.

In operating phase of nuclear reactors

When a nuclear reactor runs for a longer time, because of the extreme condition at which it runs, a number of problems arises, such as, the degradation of fuel quality due to presence of fission products in the fuel matrix, radiation damages in nuclear structural material like RPV steel. In both the cases theoretical and computational chemistry/physics plays a very vital role in identifying the root cause of the degradation or

damage process. By performing computational and experimental studies at tandem, such problems can be solved very cost effectively. In fact, many computational studies have been conducted in the above two areas. In fact, a large number of investigations is carried out in our section in evaluating fuel properties in presence of fission products [39,40]. Computational chemistry using DFT has also been used in finding the origin of early onset of Cu precipitation causing radiation damages in RPV steel [41,42].

In front-end of the fuel cycle:

Although, nuclear energy is a very sustainable source of energy with very little emissions, but the wastes produced in nuclear reactors are radio toxic in nature and therefore isolation and safe disposal of both low-level and high level wastes (HLWs) are extremely essential [43]. In a close fuel cycle like the one in India, nuclear fuel recycling is an essential and integral part of it. In order to extract useful fuel materials from the spent nuclear fuel, liquid-liquid solvent extraction process is one of the most widely used techniques. Use of an organic ligand for complexation with the ions is an essential step in this method. Although Tri Butyl Phosphate (TBP) is a very effective ligand for complexation of actinide ions, there are many drawbacks associated with the use of TBP. Therefore, the search for a better ligand for the extraction of these ions is a major field of research in DAE. In fact, apart from many experimental investigations [44], many computational investigations [45] have also been employed to design novel ligands for better efficiency. In fact, a seamless use of experimental and computational methods will make the progress faster.

The liquid-liquid biphasic solvent extraction technique uses a large amount of organic solvent like dodecane, and after the extraction, the radiotoxic solvents are to be discarded to the environment, causing an environmental concern. Therefore, search for an alternative technique is going on. For example, solid-liquid extraction using a solid adsorbent like carbon nanotubes, graphene, graphene oxide etc. with suitable functionalization can be used as an alternative. In this method, actinide ions adsorbed on the adsorbent can be easily separated from the rest of the solution without going through the cumbersome liquid-liquid extraction process. In a recent molecular dynamics study, adsorption of uranyl ions on -COO^- functionalized carbon nanotubes has been shown[46] to follow Langmuir type of isotherms. Such studies are now in the R&D stage and theoretical and computational techniques are of huge help in designing suitable adsorbent. It also can screen a large number of possible candidates to a smaller set, on which experiments can be performed. In this way, theory and computation can make the process cost effective and hassle free contributing significantly to the circular economy of the nation.

In nuclear waste disposal and environmental safety

Due to long-lived radioactivity associated with the remains of the recycled fuels, the safe disposal of these high-level remnants is an extremely important matter and therefore, a lot of research and development is underway in this direction. There are two major areas of nuclear waste disposal, in which theoretical and computational chemistry can contribute significantly. The HLW are generally vitrified by mixing it with a suitable material capable of forming a glass, a state of matter, in which diffusion of atoms, molecules and ions are extremely slow. However, there are many lacunas in the fundamental knowledge about the diffusion mechanism and other properties of the glass. Therefore, theoretical and computational chemistry [47] can be used to get atomistic level understanding of these processes. The vitrified HLW is finally disposed in deep geological repositories, whereas low and intermediate level wastes are deposited in surface disposal facilities. In these facilities, waste containers are placed in constructed vaults made up of protective cover walls of a few meters thick to avoid leaching of radioactive ions into the ground water confined in clay layers. The knowledge of interaction with clay and the diffusion of these ions in the interlayer clay spaces are extremely important in assessing the environmental issues. Theoretical and computational chemistry plays [48] a dominant role in such studies before any actual experiments are carried out.

Summary

Why theoretical and computational chemistry is an important component of the modern chemistry research is discussed in details. Applicability of theory and computations in various fields of chemical research are discussed. There are many facets of nuclear energy research in each of which theory and computations can be used and in fact, a few areas in which theoretical and computational chemistry has already been used are discussed. As Artificial Intelligence (AI) and Machine Learning (ML) have now pervaded the world of chemistry research, future years will see a huge upsurge in the applications of AI-ML in energy materials [49], in particular nuclear materials [50], catalysis [51,52], biology [53,54], biophysics [55], drug discovery [56] and other fields of research. Now the newer AI-ML techniques for the high throughput screening of materials required for a particular job has become a regular process and thereby reduces the experimental work, which in turn reduces the use of man powerand the cost. It is very heartening to see that not only the drug industry, but all other industries are now using AI/ML for their respective research and development.

References

[1] Parr, Robert G, and Yang Weitao, Density-Functional Theory of Atoms and Molecules (New York, 1995; online edn, Oxford Academic, 12 Nov. 2020)

[2] R. M. Langer, The Quantum Mechanics of Chemical Reaction. Phys. Rev.1929, 34, 92.

[3] Wang, L.-P. et al. Discovering chemistry with an ab initio nanoreactor. Nat. Chem.2014, 6, 1044–1048.

[4] H. F. Wangand Z. P. Liu, Comprehensive mechanism and structure-sensitivity of ethanol oxidation on platinum: new transition-state searching method for resolving the complex reaction network. J. Am. Chem. Soc.2008, 130, 10996–11004.

[5] V. van Speybroeck, and R. J. Meier, A recent development in computational chemistry: chemical reactions from first principles molecular dynamics simulations. Chem. Soc. Rev.,2003, 32, 151-157.

[6] E. Kraka and D. Cremer, Computational Analysis of the Mechanism of Chemical Reactions in Terms of Reaction Phases: Hidden Intermediates and Hidden Transition States. Accounts Chem. Res.2010 43, 591-601.

[7] E. Pieri, et al. The non-adiabatic nanoreactor: towards the automated discovery of photochemistry. Chem. Sci.2021, 12, 7294–7307.

[8] D. L. Osborn, Reaction mechanisms on multiwell potential energy surfaces in combustion (and atmospheric) chemistry. Annu. Rev. Phys. Chem. 2017, 68, 233–260.

[9] Reaction Rate Constant Computations: Theories and Applications. Edited by Han, Keli and Chu, Tianshu, Ebook, The Royal Society of Chemistry 2013

[10] UweManthe, Reaction rates: accurate quantum dynamical calculations for polyatomic systems. J. Theo.Comput. Chem.2002 01:01, 153-172

[11] D. Ferro-Costas, A. Fernández-Ramos, New computational tools for chemical kinetics: the Cathedral Package. Theor. Chem. Acc.2023, 142, 76.

[12] Stefan Grimme, Exploration of Chemical Compound, Conformer, and Reaction Space with Meta-Dynamics Simulations Based on Tight-Binding Quantum Chemical Calculations. J. Chem. Theo.Comput.2019, 15, 2847-2862.

[13] Emerging Materials and Environment. Ed. by Manoj Shukla, Elizabeth Ferguson, Jerzy Leszczynski. Springer, 2024 (Challenges and Advances in Computational Chemistry and Physics book series)

[14] Hann, M; Green, R. Chemoinformatics — a new name for an old problem? Current Opinion in Chemical Biology1999, 3, 379-383.

[15] Malyi, Oleksandr I., Dalpian, Gustavo M., Zhao, Xin-Gang, Wang, Zhi, Zunger, Alex, Realization of predicted exotic materials: The burden of proof. Materials Today, 2020, 32, 35-45.

[16] Gui-Juan Cheng, Xinhao Zhang, Lung Wa Chung, LipingXu, and Yun-Dong Wu, Computational Organic Chemistry: Bridging Theory and Experiment in Establishing the Mechanisms of Chemical Reactions. J. Am.Chem. Soc.2015, 137, 1706-1725.

[17] Sadybekov, A.V., Katritch, V. Computational approaches streamlining drug discovery. Nature 616, 673–685 (2023).

[18] Ou-Yang, Ss., Lu, Jy., Kong, Xq. et al. Computational drug discovery. ActaPharmacol Sin2012, 33, 1131–1140.

[19] W. L. Jorgensen The many roles of computation in drug discovery. Science2004, 303, 1813–8.

[20] Current Trends in Computational Modeling for Drug Discovery. Ed. by SupratikKar, Jerzy Leszczynski, Springer, 2023 (Challenges and Advances in Computational Chemistry and Physics book series).

[21] M. Riad Manna, Chemistry at Extreme Conditions. Elsevier B.V. 2005.

[22] Computational Approaches for Chemistry Under Extreme Conditions. Ed. By Nir Goldman, Springer, 2019 (Challenges and Advances in Computational Chemistry and Physics book series).

[23] J. M. McMahon, M. A. Morales, C.Pierleoni, and D. M. Ceperley, The properties of hydrogen and helium under extreme conditions. Rev. Mod. Phys.2012, 84, 1607.

[24] V. Barone, M.Biczysko, and C.Puzzarini, Quantum Chemistry Meets Spectroscopy for Astrochemistry: Increasing Complexity toward Prebiotic Molecules. Acc. Chem. Res.2015 48, 1413-1422.

[25] B. Roux, T. Allen, S. Bernècheand W. Im, Theoretical and computational models of biological ion channels.Quarterly Reviews of Biophysics2004, 37, 15-103.

[26] E. Jakobsson, Computational Biochemistry and Biophysics, Edited by Oren M. Becker, Alexander D. MacKerell, Jr., Benoît Roux, and Masa-katsu Watanabe, Marcel Dekker: New York and Basel. 2001.

[27] A.K. Kukushkinand K.J. Jalkanen, Role of quantum chemical calculations in molecular biophysics with a historical perspective. Theor. Chem. Acc.2010, 125, 121–144.

[28] I. S.Bushmarinov, K. A. Lyssenko and M. Y. Antipin, Atomic energy in the 'Atoms in Molecules' theory and its use for solving chemical problems. Russian Chem. Rev., 2009, 78, 283.

[29] D.Wang , W. F. van Gunsteren and Z. Chai, Recent advances in computational actinoid chemistry. Chem. Soc. Rev.,2012, 41, 5836-5865.

[30] Z. Szabó, T. Toraishi, V. Vallet and I. Grenthe, Solution coordination chemistry of actinides: Thermodynamics, structure and reaction mechanisms, Coord. Chem. Rev.,2006, 250, 784–815.

[31] G. Schreckenbach and G. A. Shamov, Theoretical Actinide Molecular Science, Acc. Chem. Res.2010, 43, 19–29.

[32] N. Kaltsoyannis, P. J. Hay, J. Li, J.-P. Blaudeau and B. E. Bursten, Theoretical studies of the electronic structure of compounds of the actinide elements, in The Chemistry of the Actinide and Transactinide Elements, ed. L. R. Morss, N. M. Edelstein, J. Fuger and J. J. Katz, Springer, Dordrecht, The Netherlands, 2008, pp. 1893–2012.

[33] Alexander V. Glushkov, Olga Y. Khetselius, Andrey A. Svinarenko, Valentin B. Ternovsky, Vasily V. Buyadzhi, 16 - Frontiers in green radiochemistry: New optimized quantum approach to laser separation of isotopes and transmutation of radioactive waste, Editor(s): LilianaMammino, In Advances in Green and Sustainable Chemistry, Green Chemistry and Computational Chemistry, Elsevier, 2022, Pages 385-402,

[34] David A. Dixon, David Feller, Computational chemistry and process design, Chem. Eng. Sci.1999, 54, 1929-1939.

[35] M. Stan, Discovery and design of nuclear fuels. Materials Today, 2009, 12, 20-28.

[36] R.Devanathanet al., Modeling and simulation of nuclear fuel materials. Energy Environ. Sci., 2010, 3, 1406-1426

[37] K.Srinivasu, B. Modak, T. K. Ghanty, J. Nucl. Mater.,2018, 510, 360-365.

[38] K.Srinivasu, S.Natarajanand T. K. Ghanty, J. Phys. Chem. C2019, 123, 27531−27541.

[39] T. Vazhappilly, A. K Pathak, J. Nucl. Mater.2019, 519,128.

[40] T. Vazhappilly, A.K Pathak, J. Nucl. Mater.2024, 588, 154791 and the references there in.

[41] S.Ahlawat, K.Srinivasu, A. Biswas, N.Choudhury, Compu. Mat. Sci.2019, 170, 109167.

[42] S. Ahlawat, K. Srinivasu, A. Biswas, N. Choudhury, Phys. Chem. Chem. Phys.,2021, 23, 8689–8704.

[43] Storage and Disposal of Radioactive Wastes. https://world-nuclear.org/information-library/nuclear-fuel-cycle/nuclear-waste/storage-and-disposal-of-radioactive-waste.aspx

[44] S. A. Ansari, P. Pathak, P. K. Mohapatra, and V. K. Manchanda, Chemistry of Diglycolamides: Promising Extractants for Actinide Partitioning. Chem. Rev.2012, 112, 1751-1772.

[45] D.Manna, S. Mula, A.Bhattacharyya, S.Chattopadhyayand T. K. Ghanty, Actinide selectivity of 1,10-phenanthroline-2,9-dicarboxamide and its derivatives: a theoretical prediction followed by experimental validation. Dalton Trans.2015, 44, 1477-9226.

[46] M. Chopra and N. Choudhury, Adsorption of uranyl ions from its aqueous solution by functionalized carbon nanotubes: A molecular dynamics simulation study. J. Mol. Liq.2019, 294, 111569.

[47] Y. Yu, B.Stevensson, and M.Edén, Structural Role of Sodium in Borosilicate, Phosphosilicate, and Borophosphosilicate Glasses Unveiled by Solid-State NMR and MD Simulations. J. Phys. Chem. C2019 123, 25816-25832.

[48] A. P. Singh, M. Chopra and N. Choudhury, Effect of counter ions on the interaction and complexation of uranyl ions in Lizardite clays: A MD simulation study. J. Phys. Chem. C (to be published, 2024).

[49] C. Chen, Y. Zuo, W. Ye, X. Li, Z. Deng, S. P. Ong, A Critical Review of Machine Learning of Energy Materials. 2020, 10, 1903242.

[50] D. Morgan, G. Pilania, A. Couet, B. P. Uberuaga, C. Sun, J. Li,

Machine learning in nuclear materials research. Curr.Opin.Solid State Mater.Sci. 2022, 26, 100975.

[51] Z.Yang, and W.Gao, Applications of machine learning in alloy catalysts: rational selection and future development of descriptors. Adv. Sci.2022, 9, 1–22.

[52] S.Chen, et al. Automated construction and optimization combined with machine learning to generate Pt(II) methane C-H activation transition states. Top.Catal.2022, 65, 312–324.

[53] C.J. Soelistyo, G.Vallardi, G.Charras, et al. Learning biophysical determinants of cell fate with deep neural networks. Nat. Mach. Intell.2022, 4, 636–644.

[54] J. G.Greener, S. M.Kandathil, L. Moffat, et al. A guide to machine learning for biologists. Nat. Rev. Mol. Cell. Biol.2022, 23, 40–55.

[55] J.M. Cunningham, G. Koytiger, P.K. Sorger, et al. Biophysical prediction of protein–peptide interactions and signaling networks using machine learning. Nat. Methods2020, 17, 175–183.

[56] J.Vamathevan, D. Clark, P.Czodrowski, et al. Applications of machine learning in drug discovery and development.Nat. Rev. Drug.Discov.2019, 18, 463–477.