

**Chemical Separations for Actinide Chemistry and CO₂ Capture Applications using
Quantum Mechanics and Machine Learning**

A Dissertation Presented for the
Doctor of Philosophy
Degree
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*Dedicated to my parents Dr. Jeffrey William Laub and Lisa Gail Laub, my grandparents Donald
A. Laub and Mary Ann Laub, and my late grandparents Silas Young Jr. and Carolyn Stidham
Young*

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Abstract

Nuclear energy is a promising and powerful alternative to providing energy to assist in alleviating current energy demands. With the growing concern of climate change due to an increase in CO₂ atmospheric concentration, many nations have made a commitment to reaching net zero carbon emissions by 2050. Nuclear energy is a key component in providing clean energy for global energy demands with a prominent disadvantage of producing radioactive waste which is a subject of interest to overcome in the nuclear community. However, reducing carbon emissions alone will not reduce the pre-existing CO₂ in the atmosphere from past emissions. Due to this, direct air capture (DAC) technologies provide a pivotal instrument for helping to reduce the carbon concentration in the atmosphere. The utilization of nuclear energy and DAC technologies together will help in reaching net zero emissions as well as reducing the overall carbon concentration in the atmosphere. This dissertation is focused on the modeling and predictions of actinide ligation for the treatment of nuclear waste as well as the separation of actinium from various sources for repurposing in nuclear medicine and on molecular discovery for ligand-based actinide separations for nuclear waste treatment and CO₂ adsorption thermochemical analysis utilizing host-guest chemistry for solid-DAC applications.

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Chapter 1 Introduction to Chemical Separations for Radiochemical and CO₂ Applications

“The nuclear age began with the detonation of the world’s first atomic bomb at the Trinity Site on July 16, 1945.” -Roadside historic marker near the Trinity Site in Socorro county, NM

1.1. Nuclear Energy and the Production of Nuclear Waste

Since the end of World War II, nuclear science has made significant scientific advancements, especially in the utilization of nuclear energy. In the United States, the generation of nuclear energy has consistently been above 700 million MWh since 1999 (**Figure 1.1**),¹ with 9% of the total energy consumption in the US being from nuclear energy in 2023.² Other countries, such as Sweden and France, consumes a greater percentage of nuclear energy for their national energy needs for example, Sweden had 29% of their energy needs from nuclear energy in 2022³ and France with 68% of their electricity needs by nuclear power in 2021, with plans to expand and upgrade their nuclear industry already underway.⁴ Indeed, France has already produced 12.2% more electricity generated from nuclear power in 2024 compared to the same cumulative time period from 2023 (January-June), however less than 2021 due to reactor outages in 2022.^{4, 5} These advances and consumption of nuclear energy are key for not only the reduction of carbon emissions to help counter climate change and reach net-zero by 2050,⁶ but also due to the high output of energy from a single UO₂ ceramic fuel pellet. One fuel pellet containing 2-5%⁷ of fissile ²³⁵U that is approximately 1.6 cm in length with a diameter of 0.95 cm⁸ produces the energy equivalent of about 149 gallons of oil.⁹

Two different types of nuclear reactors are used in the United States: boiling water reactors (BWRs) and pressurized-water reactors (PWRs). Since, approximately 67% of the operational reactions in the U.S. were PWRs in 2023, the focus on how nuclear energy works will be discussed with PWRs as the example reactor with an illustration of a PWR demonstrated by **Figure 1.2**.¹⁰ PWRs contain a closed system of water that surrounds the zirconium alloy fuel rods and the control rods composed of neutron absorbing materials with a large cross section to maximize the probability of neutron absorption within the reactor core.⁷ Within the reactor vessel,



Figure 1.1. Nuclear electricity generation and capacity from 1957 to 2022. Figure slightly modified from reference [1].

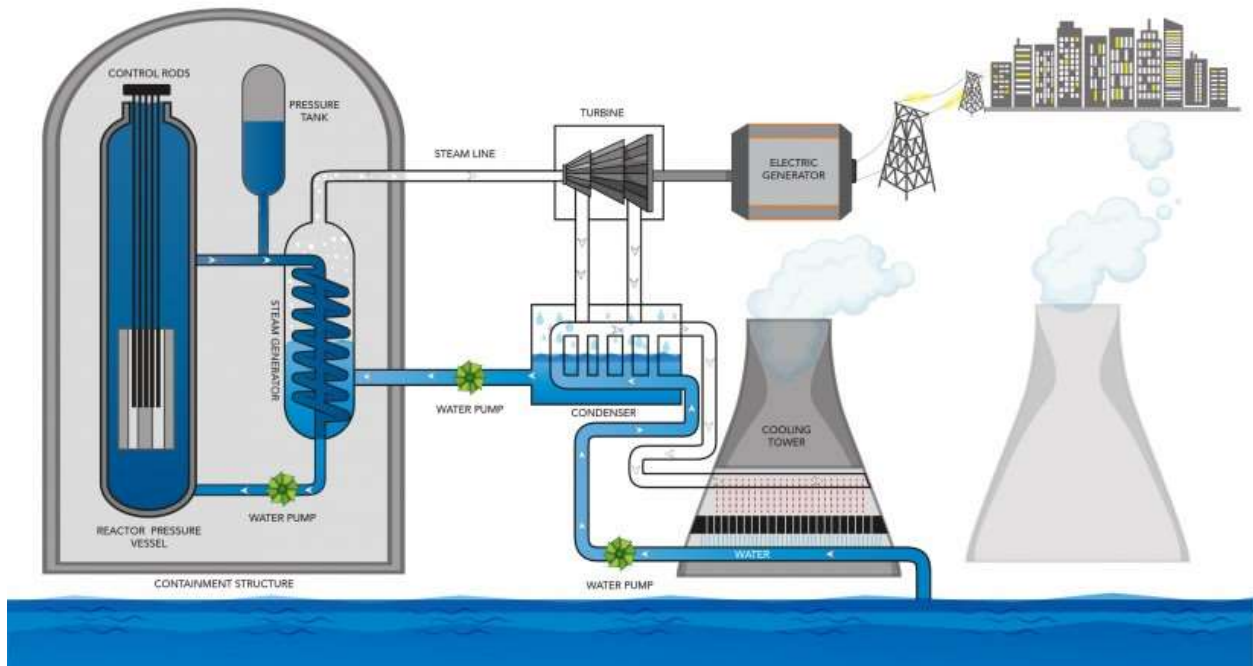


Figure 1.2. Pressurized-water nuclear reactor (PWR) illustration. Slightly modified from reference [10].

there is also typically a neutron absorbing solvent such as boric acid to maintain controlled fission.⁷ Controlling fission in a state called *critical* is crucial for nuclear reactors. The *critical* state is defined as having a neutron multiplication factor (k) equal to 1.⁷ Having a k value equal to 1 means that the number of initial neutrons used for the bombardment of fissile ^{235}U is equal to the number of generated neutrons used for further bombardment within the reactor vessel. Thus, it is the ratio of neutrons in generation 2 with respect to generation 1. If the reactor is *subcritical*, this means that the k value is less than 1 which means there is a lack of neutrons for further bombardment, while a *supercritical* reactor ($k > 1$) is producing too many neutrons that are not being absorbed which increases the chain reaction within a reactor, illustrating the importance for reactors to be kept in a *critical* state for energy generation and why neutron absorbing materials are crucial for reactor usage.

Upon bombardment of a ^{235}U nuclei by a neutron, the neutron can either be absorbed by the nuclei to create ^{236}U or cause immediate fission of the nuclei to produce fission products and approximately 2.418 neutrons.⁷ As mentioned early, since PWRs need to be operated in the *critical* state, also known as a self-sustaining state, only 1 generated neutron will go on to bombard another ^{235}U nuclei causing another nuclear fission event while the rest are absorbed by the neutron absorbing material.⁷ These fission events produce a large amount of kinetic energy in the form of heat which will heat the water within the closed system surrounding the reactor core. This heated water will then flow to steam generator under a pressurized system to prevent boiling (**Figure 1.2**) and boil water within a secondary closed system to generate steam that then turns a turbine to generate electricity. The steam is then condensed by the flow of an external water source through the condenser so that the condensed water can be reused within the secondary closed system. The heated water from the reactor core will then act as a coolant as it returns to the reactor core to then be reheated to continue the cycle of electricity generation until the fuel needs to be replaced or another factor causes the reactor to stop production.⁷

The spent nuclear fuel from these reactors is one of the major disadvantages of nuclear energy since it creates radioactive waste comprised of fission products, activation products, lanthanides, and actinides.¹¹ One of the major concerns of this waste is the radiotoxicity of the radioactive nuclei present in the waste towards human health. Of these radioactive nuclei, the actinides constitute a majority of the radiotoxicity¹²⁻¹⁹ within the radioactive waste and are one of

the focus points of this dissertation. The actinides present in nuclear waste as determined in PWR fuel after burnup includes ^{227}Ac , ^{229}Th , ^{231}Pa , $^{233/235}\text{U}$, ^{237}Np , $^{238/239/240/241}\text{Pu}$, $^{241/243}\text{Am}$, ^{244}Cm , Bk, and Cf.⁷ Currently, U and Pu are typically extracted from the waste for repurposing, however, the remaining actinides are usually disposed in long-term storage to decay over a long period of time.¹⁹ Treating nuclear waste by developing more efficient separation strategies for U and Pu and methods for separation of the actinide nuclei from the waste, especially trivalent actinide separation from trivalent lanthanides, would significantly decrease the radiotoxicity of the waste, reduce the amount and time required of long-term storage necessary for decay, and provide nuclei that can be repurposed for other applications ranging from nuclear medicine to space exploration.^{13, 18-20}

1.2. Separations of Actinides in Nuclear Waste

There are different techniques for the treatment of nuclear waste such as ion exchange, chromatographic, and solvent-based extraction methods. Since solvent-based extractions of actinides for the treatment of nuclear waste is one of the main focuses of this dissertation, this section will focus on solvent-based actinide separations with discussions on lanthanide separations from actinides as these are crucial for selectively separating trivalent actinides from trivalent lanthanides. It is also important for the separation of lanthanides from U and Pu particularly, due to the large neutron cross sections of lanthanides which will hinder nuclear fission of recycled U and Pu for energy production.²¹⁻²³ Indeed, mixed oxide fuel (MOX) is a type of nuclear fuel developed by Orano that mixes spent ^{235}U and ^{239}Pu as oxides, repurposing these radionuclides and reducing nuclear waste.²⁴ With the focus on solvent-based methods, a discussion on ligand design and hard-soft acid-base theory will first be introduced since this is one of the key theories behind the treatment of nuclear waste.

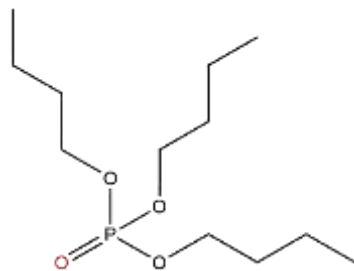
Ligand design is crucial for selective extraction of specific radionuclides such as Ac, Th, U, Np Pu, Am, and Cm as examples. The aforementioned trivalent actinides Ac, Am, and Cm, are less hard (softer) Lewis acids than trivalent lanthanides due to the larger atomic radius of the actinides under identical oxidation states as the lanthanides.²² Thus, for the selective extraction of trivalent actinides from lanthanides, softer ligands need to be utilized for selectively extracting the trivalent actinides over the lanthanides. Such ligands include N-donor and S-donor ligands that are soft ligands that have been utilized for selective actinide extraction.^{13, 18-21, 23} This means

that the trivalent lanthanides would prefer to be extracted by hard ligands such as O-donor ligands.¹⁸ Consequently, the other actinides not discussed as examples, U, Np, and Pu preferably all exist at oxidation states greater than 3+.⁷ This makes these actinides harder Lewis acids than the trivalent actinides which makes O-donor, hard ligands be the preferable ligands for extracting these actinides. **Figure 1.3** demonstrates examples of hard and soft ligands commonly used in current treatment of waste (such as tributyl phosphate (TBP)) or major topics of research (such as 6,6'-bis(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-benzo-1,2,4-triazin-3-yl)-2,2'-bipyridine (CyMe₄-BTBP)).^{18, 22, 25} However, utilizing hard ligands to separate U, Np, and Pu from a solution containing lanthanides and lower oxidation state actinides, U, Np, and Pu would be extracted leaving the solution of trivalent actinides and lanthanides behind to be selectively extracted. It should be stated that ligand design for nuclear waste treatment does not just fall upon the donor group of the ligand, the ligand structure also plays a key part in the extraction process which is what will be presented later in this dissertation. However, these fundamentals of ligand design for nuclear waste treatment lie as the basis for the different solvent-based extraction processes that are utilized for various different radionuclide isolation.

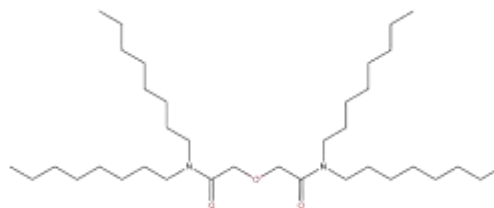
There are multiple different solvent-based extraction processes that utilize ligand design for selective radionuclide isolation. For instance, there is the plutonium uranium redox extraction (PUREX) which is currently a key U and Pu repurposing and separation process used in nuclear powerplants as part of the back end of the nuclear fuel cycle.^{19, 25-28} Other separation processes include but are not limited to the transuranic extraction (TRUEX), uranium extraction (UREX+), diamide extraction (DIAMEX), selective actinide extraction (SANEX), and the group actinide extraction (GANEX) methods. For a discussion on how some of these processes are utilized for the treatment of nuclear waste, a discussion will begin with the PUREX process as most of the separation techniques are typically focused on the removal of the remaining actinides from the PUREX raffinate.

As stated, the PUREX process is focused on the removal of U and Pu to reuse these radionuclides for further energy generation. This process is typically accomplished by utilizing TBP (**Figure 1.3A**) in an organic solvent, such as kerosene, which selectively isolates Pu⁴⁺ and UO₂²⁺ from the overall nuclear waste solution.^{25, 26} The PUREX raffinate is usually placed into long-term storage due to the radiotoxicity and difficulty in selectively isolating the remaining

O-Donor

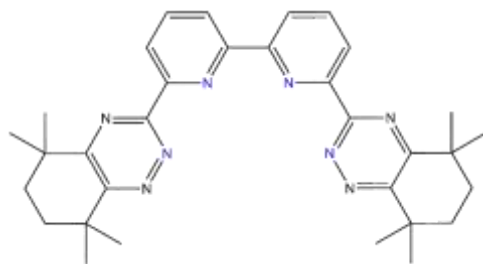


A

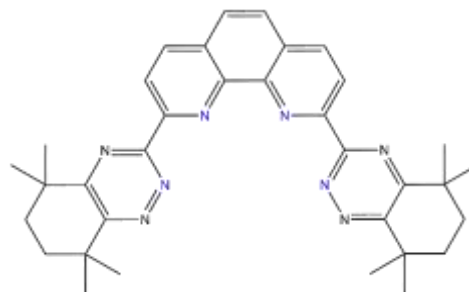


B

N-Donor

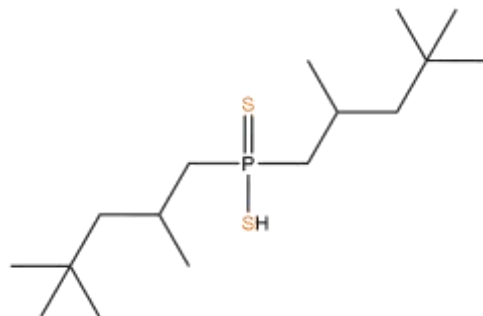


C

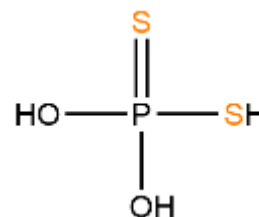


D

S-Donor



E



F

Figure 1.3. Example of ligands that are O-donor, N-donor and S-donor with the coordinating atom color coded for each ligand. **A** is tributyl phosphate (TBP), **B** is N,N,N',N'-tetraoctyl diglycolamide (TODGA), **C** is 6,6'-bis(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-benzo-1,2,4-triazin-3-yl)-2,2'-bipyridine (CyMe₄-BTBP), **D** is (2,9-bis(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-1,2,4-benzotriazin-3-yl)-1,10-phenanthroline) (CyMe₄-BTPhen), **E** is sulfanyl-sulfanylidene-bis[(2r)-2,4,4-trimethylpentyl]-phosphane (Cyanex 301), and **F** is dithiophosphoric acid (DPAH).

actinides from the raffinate.²² This is where other nuclear waste processing methods come to fruition. For example, the SANEX process focuses upon separation of the minor actinides within the PUREX raffinate from lanthanides with some processes utilizing ligands derived from the CyMe₄-BTBP (**Figure 1.3C**) and CyMe₄-BTPPhen (**Figure 1.3D**) ligand family^{17, 18, 29} for transmutation of the actinides into less stable and shorter-lived species to reduce the time needed for storage. This approach is commonly referred to as “Partitioning and Transmutation.”^{11, 13, 15} In a similar manner, the GANEX process is focused on maximizing the separations of the actinide species from the nuclear waste solution replacing the PUREX process.¹⁹ Optimizations of these extraction processes typically involves using different combinations of ligands that are dissolved in the aqueous phase and the organic phase to try and maximum separations by using ligands, for example, that has a stronger affinity for actinides in the organic phase, while using a different ligand in the aqueous phase that has a stronger affinity for lanthanides. While this is just a brief overview for some of the nuclear waste treatment processes, the improvement of methodology,^{25, 30} optimization of extractions,^{17, 18, 21, 23} and the development of new ligands^{13, 22} continues to be crucial goals for radiochemists as the goal to closing the nuclear fuel cycle continues.

1.3. Applications and Importance of Computational Methods for Actinide Chemistry

Computational applications for actinide chemistry have been making great strides over the last 15 years, with research ranging from benchmark studies of small actinides complexes,³¹⁻³³ general computational analysis of the actinides,^{34, 35} on actinide covalency,^{22, 36-40} studies related to actinide ligation, speciation, and extraction for solvent-based actinide partitioning applications,^{17, 19, 21, 23, 41-44} and more recently, studies utilizing artificial intelligence and machine learning for the prediction of actinide properties and rare-earth chemistry.⁴⁵⁻⁵⁵ Indeed, in 2021, an eBook was published as part of the *ACS Symposium Series* titled “Rare Earth Elements and Actinides: Progress in Computational Science Applications” that included contributions by some of the leading experts in the field.⁵⁶ As these demonstrate, computational actinide chemistry is a growing field of study, with new advancements happening consistently to assist in the elucidation of actinide properties, as well as assist in computational modeling to improve many different applications involving actinides, and for the purpose of this dissertation, actinide separations from nuclear waste for repurposing or transmutation.

While there are many different applications for the actinide elements, the following discussion on the importance for computational methods of actinides will focus solely on ligand-based actinide separations for nuclear waste treatment but the principles can still represent other actinide chemistry applications. When it comes to the optimization of ligand-based actinide separations for the treatment of nuclear waste, the traditional approach includes the synthesis and experimental evaluation of new inorganic ligands in a trial and error methodology.⁵⁶ This is consequently an expensive and chemical intuition-driven process. In addition, such studies are limited due to the fact that radioactive materials require specialized facilities.⁵⁶ Additionally, there is no guarantee that the ligand being studied will perform better than existing ligands. Thus, having computational protocol and modeling for the separation of actinides from nuclear waste would provide radiochemists with an invaluable methodology for aiding in the screening of ligands to optimize extractions, reduce the cost spent in the lab for experimentation that may prove ineffective, and aid in ligand design for selective isolation of targeted radionuclides. This is the driving force for the work presented in this dissertation which utilizes quantum mechanical and machine learning methods to provide radiochemists with a computational protocol for the study of actinide ligation (**Chapter 2**), ligand design (**Chapter 2** and **Chapter 3**), and data-driven screening of ligands (**Chapter 3**) for the optimization of actinide separations with an emphasis on nuclear waste treatment.

1.4. From Radiochemical Separations of Actinides to Carbon Capture

During the literature search of ligand-based actinide separations, a family of ligands stood out that could be excellent candidates for an alternative purpose, CO₂ (carbon) capture from the atmosphere. This family of ligands that have had extensive actinide and heavy metal chelation and host-guest interactions are organic cyclic oligomers such as the molecules of interest for this dissertation, calix[*n*]arenes.⁵⁷⁻⁷⁴ Calix[*n*]arenes and other cavitand ligands have been attractive molecules for CO₂ capture due to their host-guest interaction phenomenon and their high tunability which can include the incorporation of CO₂-philic functional groups.⁷⁵⁻⁹⁶ Since this dissertation is focused on functionalized calix[4]arenes examples of the highly tunable conformations are provided in **Figure 1.4**. As demonstrated by **Figure 1.4**, calix[4]arenes can adopt 4 different conformations the cone shape which is the typical chalice conformer observed when discussing calix[*n*]arenes, the partial cone conformer which involves the rotation of a

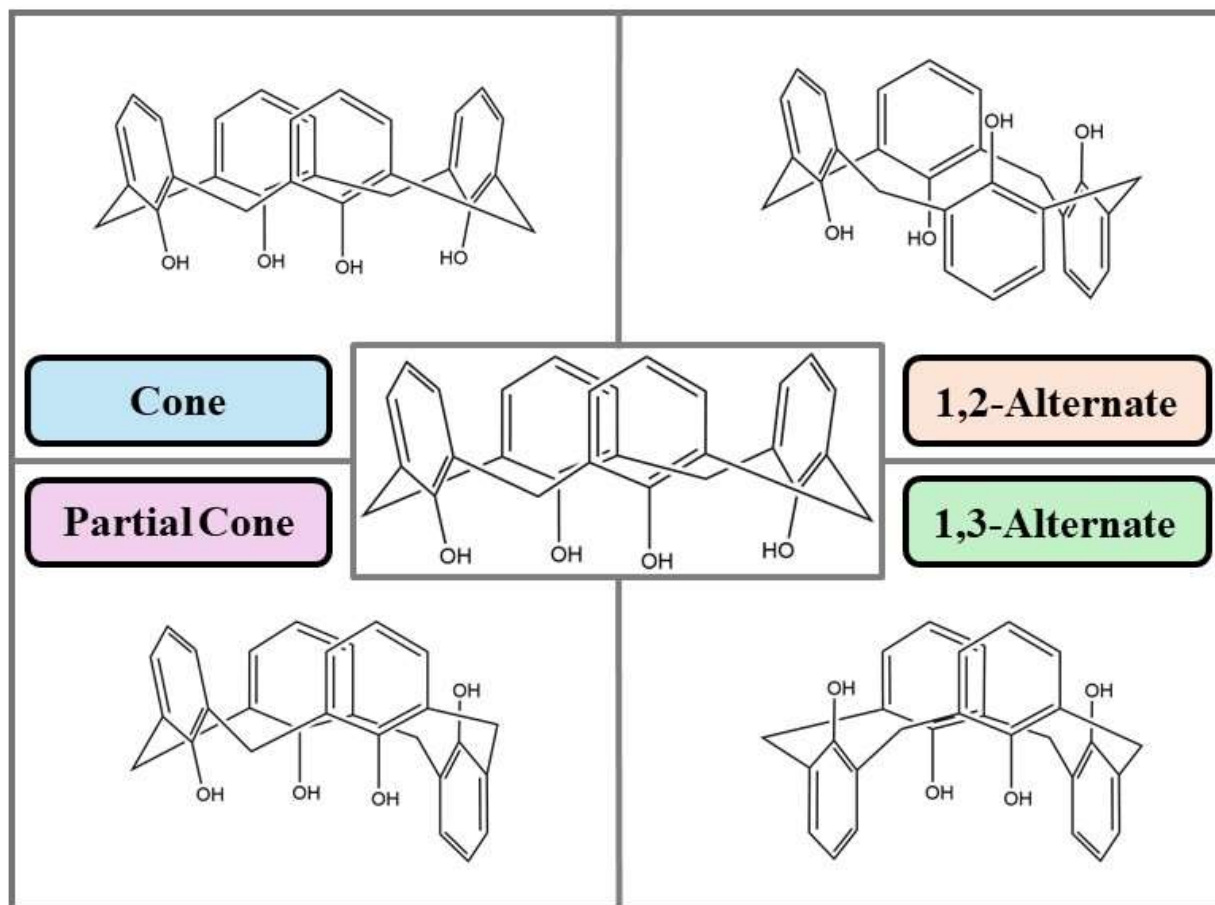


Figure 1.4. The different calix[4]arene conformations with labels demonstrating the versatility and tunability of this class of molecules.

singular phenol group, the 1,2-alternate conformer that has two adjacent phenol groups rotated, and the 1,3-alternate conformer which also involves the rotation of two phenol groups, just not adjacent to each other. Each conformer has multiple substitution sites (the lower rim with the hydroxyl groups, the methylene bridge, and the upper rim which can be considered as the *para* and *meta* positions of the phenol rings with respect to the hydroxyl group) that can all alter the host-guest interacting systems. This allows rich computational exploration and optimization of functionalized calix[4]arenes for host-guest interacting systems for carbon capture which will be discussed further in **Chapter 4**.

1.5. Climate Change and Direct Air Capture

Since writing my Master's thesis at Eastern Kentucky University, *Structural Investigation on the Thermal Degradation of Aqueous Amines in Post-Combustion CO₂ Capture*,⁹⁷ in 2020, the concentration of atmospheric CO₂ has increased from 410.27 ppm to 425.55 ppm in July 2024.⁹⁸ The abundance of CO₂ in the atmosphere has contributed to the increase in global temperature with 2023 having an average temperature 1.36°C higher than the combined average preindustrial era (1850-1900) global temperatures according to NASA's Goddard Institute for Space Studies.⁹⁹ The increase in global temperature has led to adverse climate changes, including ocean life.^{100, 101} Efforts have been made to reduce the quantity of anthropogenic CO₂ sources such as the retrofitting of carbon-based power plants with alkanolamine scrubbers for the sequestering of CO₂ from the produced flue gas.^{97, 100} This technology is energy demanding for the stripping of CO₂ from amine for regeneration and reuse and can unfortunately result in the degradation of the alkanolamine itself.⁹⁷ However, even with these drawbacks, this technology has been proven to be successful at reducing CO₂ emissions from carbon-based power plants.¹⁰² With promising technologies for the reduction of CO₂ emissions from a major anthropogenic source, there still remains the problem of the pre-existing CO₂ in the atmosphere. To combat this, direct air capture (DAC) technologies are being explored and implemented to remove atmospheric CO₂.^{6, 100, 103-106}

Current DAC technologies can be categorized into two different categories, liquid DAC (L-DAC) and solid DAC (S-DAC).^{101, 105, 106} Each technology focuses on extracting CO₂ from ambient air by utilizing a fan to collect the air and then have it interact with either the solvent-based chemicals or the solid sorbents to selectively isolate the CO₂ and allowing the filtered air to then be released back into the atmosphere.¹⁰¹ Both technologies have had recent success with

the company Holocene utilizing L-DAC with amino acids for CO₂ capture¹⁰⁷ and Climeworks utilizing S-DAC with the first large-scale direct air capture plant located in Iceland called Orca (not to be confused with the ORCA quantum chemistry package^{108, 109} commonly utilized in this dissertation).¹¹⁰ Since, this dissertation will focus on S-DAC applications, the following discussion will be made with an emphasis on these technologies.

S-DAC technologies commonly utilize amine-based sorbents for DAC applications.^{100, 103, 104} These sorbents are classified into three different classes according to the type of immobilization these amines have been processed onto a porous support, such as an inorganic porous oxide-support.^{100, 103} The first class, class 1 sorbents, involves amines that are impregnated within the porous material, class 2 sorbents are tethered to the porous supports with aminosilanes being common molecules, and class 3 sorbents are a combination of polymeric amines and covalent immobilization, which has been referred to as a combination of class 1 and class 2 sorbents.^{100, 103}

While S-DAC, and DAC in general, are promising and proven^{107, 110} technologies for the capture of historic CO₂ in the atmosphere, there are several hindrances for their utilization. Some of these hindrances involve the cost, long-term monitoring, conversion of CO₂ into valuable products such as fuel, and potential leakage of CO₂ after geological deposition.¹⁰⁴⁻¹⁰⁶ Other hindrances are due to the ultra-dilute concentration of CO₂ in the atmosphere which consequentially leads to high-energy demands¹⁰⁵ and competition with other gas molecules, such as H₂O, for DAC technology utilization. Due to the high-energy demands, which are directly related to the cost of DAC, adsorption-based S-DAC processes are considered to be the more auspicious approach due to the relatively low energy requirements for CO₂ reprocessing and regeneration of the solid sorbent.^{6, 104} Thus, one way to reduce the cost of S-DAC technologies, would be the optimization of the utilized adsorbent material that has a favorability for CO₂ over the polar H₂O gas molecules. This is the motivation for the work presented in **Chapter 4**, where the analysis of calix[4]arenes with their host-guest capabilities and high functionalization would provide a lower energy requirement for material and CO₂ recovery and the capability of optimization of the molecule group towards CO₂ selective isolation from ambient air.

1.6. Dissertation Organization

The organization of this dissertation that follows this chapter's introduction to nuclear waste treatment and carbon capture. **Chapter 2** investigates actinide ligation with various key ligand classes for nuclear waste treatment by utilizing thermochemical methods with comparisons to experimental stability constant values. **Chapter 3** is a continuation study that takes what was learned from the study in **Chapter 2** and applies what was learning from CyMe₄-BTBP-based ligands to actinium separations from nuclear waste and other actinium sources and as an alternative methods for actinium acquisition to current processes with the aim to increase actinium supply for radiopharmaceutical and nuclear medicine purposes by utilizing quantum chemistry and machine learning methods. **Chapter 4** discusses the utilization of functionalized calix[4]arenes for CO₂ host-guest interactions for direct air capture applications. **Chapter 5** outlines two separate but related collaborative work that was performed to investigate the stereochemistry and CO₂/CH₄ separations utilizing vinyl-addition polynorbornenes, a type of polymer that can be utilized in membrane-based gas separations. Finally, **Chapter 6** provides the closing remarks for this dissertation and highlights the synergistic relationship between nuclear waste treatment and the promotion of nuclear energy coupled with direct air capture technologies and, ultimately, carbon capture itself can lead towards clean energy to supply the energy demand and a cleaner atmosphere to reduce the greenhouse effect on Earth.

Chapter 2 Actinide Ligation Analysis in Aqueous and Organic Phase Solvents for Actinide Extraction from Nuclear Waste

“People must understand that science is inherently neither a potential for good nor for evil. It is a potential to be harnessed by man to do his bidding.” -Dr. Glenn Theodore Seaborg

Disclosure: The following chapter has been slightly modified from a journal article published in *The Journal of Physical Chemistry A* in 2023, volume 127, issue 26, from pages 5523-5533. The publication is authored by myself and my principal investigator Dr. Konstantinos D. Vogiatzis. All computations and analyses were conducted and performed by myself under the guidance and supervision of Dr. Vogiatzis.

2.1. Introduction

Nuclear energy is an important source for providing our energy needs, especially in transitioning toward carbon free energy sources. However, a hindrance is the production of radioactive waste. Spent fuel pellets contain unused fissile material and fission products from the bombarded ^{235}U nuclei.⁷ The spent fuel is collected and typically treated to acquire the fissile material, such as unspent U and Pu, while the rest is placed into long-term storage and classified as radioactive waste.⁷ The treatment of the generated radioactive waste is of particular interest to radiochemists who target on the development of more efficient methods for separating U and Pu, and methods for separation of the minor actinides from the waste placed in long-term storage.^{13, 19, 25, 29, 111}

Actinide separation from nuclear waste includes ion exchange, chromatographic extraction, and solvent extraction methods. The latter involves an organic and aqueous phase such as the group actinide extraction (GANEX) process which separates U from the spent fuel that is dissolved in nitric acid followed by another extraction focusing on the group extraction of the transuranic actinides.^{26, 112, 113} One of the more common separation methods is the plutonium and uranium redox extraction (PUREX), which is implemented in many nuclear fuel cycles in nuclear power plants.^{19, 25-27} This is due to Pu and U being major actinides that can be reused for further energy production, while the rest of the fission products are placed in long-term

storage.^{25, 26} For sake of completeness, we should mention the transuranic extraction (TRUEX), uranium extraction (UREX+), and diamide extraction (DIAMEX) methods.²⁶ There are other methods such as the self-assembled metal-polyphenolic nanocages process proposed by Mei et al. that provided high efficiency and selectivity and fast kinetics for the extraction of U.¹¹⁴ While there are different separation processes, they all use organic ligands as extractants.

Use of a ligand in both the aqueous and the organic phases would allow for optimized extractions due to the different selectivities of the extractants. In a study by Deblonde et al., for the recovery of Ac(III) from Pu(IV), two separate extractions were accomplished using different aqueous phase ligands.²⁵ The ligand used in the organic phase was bis(2-ethylhexyl) phosphate (HDEHP) for both extractions, where the first separation involved the aqueous phase ligand diethylenetriaminepentaacetic acid (DTPA) and the second 3,4,3-LI(1,2- HOPO) (343HOPO, **Figure 2.1**).²⁵ DTPA and 343HOPO both have an affinity to extract tetravalent ions, with DTPA being a member of the polyaminocarboxylate chelator group while 343HOPO is with the hydroxypyridinone chelator group.²⁵ The differences in chelator groups is crucial when examining the separation factor (SF) that depends on the distribution coefficient (D) for the two different ligands for separating Ac(III) from Pu(IV).²⁵ The $SF_{Ac^{3+}/Pu^{4+}}$ for the process with DTPA was between 1 and 100, while that with 343HOPO reached 1000000.²⁵ The same study also reported that, when DTPA or 343HOPO was used in the presence of HDEHP (a trivalent extractant) in the organic phase, Ac(III) was separated from Am(III), producing a SF value of 10 (DTPA) and 130000 (343HOPO).²⁵ This difference in SF values demonstrates the need to optimize ligands used in both the organic and aqueous phases to acquire the greatest possible SF values to maximize the extraction.

Previous works, such as the 343HOPO study that was discussed in the previous paragraph, demonstrate the need for ligand optimization for the separation of tetravalent and trivalent actinide ions.^{13, 19, 25, 29, 111} 343HOPO has shown excellent affinities to selectively separate tetravalent ions in a mixture, it is water-soluble, highly stable when coordinated with a metal under strong acidic conditions, and is also able to oxidize Bk(III) into Bk(IV) stabilizing the ion in aqueous solution by demonstrating redox capabilities.^{25, 41, 115} 343HOPO is not the only ligand observed to have redox capabilities. The trivalent affinity 2,9-bis(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-1,2,4-benzotriazin-3-yl)-1,10-phenanthroline (CyMe₄-BTPhen) was shown to

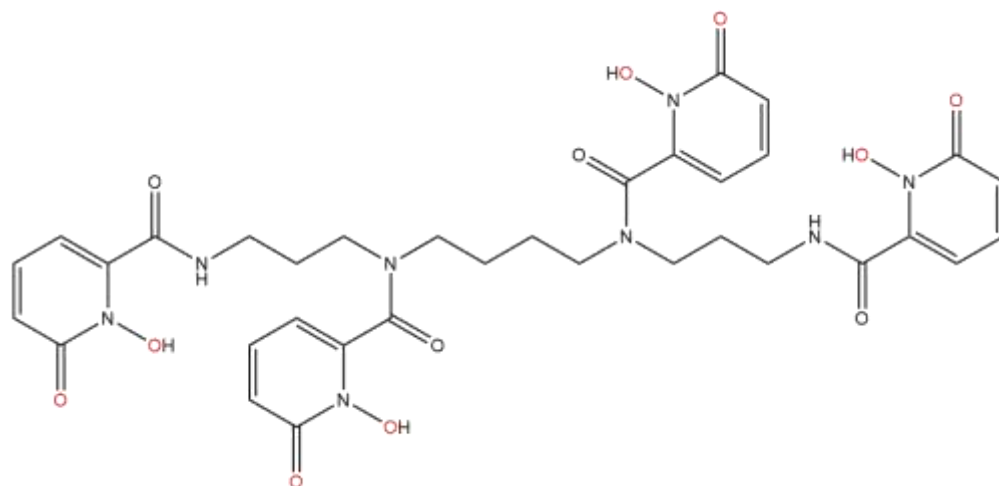


Figure 2.1. Structural representation for 343HOPO, where the red atoms represent the coordination sites.

reduce Pu(IV) into Pu(III) to produce a mixed-valence $[\text{Pu}^{\text{III}}(\text{CyMe}_4\text{-BTPhen})_2(\text{NO}_3)][\text{Pu}^{\text{IV}}(\text{NO}_3)_6]$ compound.²⁹ CyMe₄-BTPhen related ligands were also examined for actinide(III) and lanthanide(III) separations.^{13, 20, 116} A different study demonstrated that the highest SF value acquired for the separation of Am(III) from Eu(III) was achieved with Cl-CyMe₄-BTBP (124 ± 12 with 3 M HNO₃ in the aqueous phase and 1-octanol as the organic phase),¹³ although those ligands were unable to distinguish a separation of Am(III) from Cm(III), since the highest SF value was 1.9 ± 0.4 with 0.5 M HNO₃.¹³ These results demonstrate the importance of the choice of ligands being used for the extraction process, the need for optimization of ligands for actinide separations, and the need for a systematic process for predicting ligand behavior to provide a method of ligand screening.

Theoretical calculations with density functional theory (DFT) offer an effective methodology for the examination of ligand-actinide coordination in liquid-liquid extractions and predicting ligand stability and selectivity.^{41, 43, 44, 115} Since the speciation of the liquid-liquid extraction of the actinides is unknown for many different systems, computational studies consider either a hydrated form of the actinides as the reactants,⁴¹ while others incorporate NO₃⁻ coordination to the actinide before ligand coordination.²³ From a computational standpoint, the exact coordination environment of the actinides before and during the separation process is of importance since it has a significant effect on the computed Gibbs' free energies (ΔG).⁴³ In a study performed by Kelley et al., the free energy complexation of Ac-Es with 343HOPO using a hydrated form of the actinide species reacting with the deprotonated form of 343HOPO was evaluated with the PBE0¹¹⁷ functional and the PCM solvation model.^{41, 118} The computed ΔG values obtained from this study deviated from the experimentally refined stability constant values, but the overall trend between trivalent and tetravalent actinides was observed. This included the behavior of Ac that shares similarities to the later actinides (those past plutonium) as opposed to the early actinides where Ac resides.⁴¹ DFT was also used to predict a possible reduction pathway of Pu(IV) to Pu(III) from formation of the mixed-valence CyMe₄-BTPhen compound mentioned previously by evaluating different reactants and the resulting ΔG values to produce the experimentally determined mixed-valence compound.²⁹

Experimentally refined logarithmic stability constants ($\log\beta$) provide a useful characteristic of the extraction of actinides which they can be correlated to computed ΔG energies:¹¹⁹

$$\Delta G = -2.303RT \log \beta \quad (2-1)$$

In other words, determining the ΔG value of a reaction involving the coordination of an actinide with a ligand would allow for the determination of $\log\beta$ at a temperature T , which can be compared with experimental data. This work focuses on elucidating ligand-based actinide separations with quantum chemical calculations. For this purpose, four actinides were chosen for investigation, Ac(III), Th(IV), Am(III), and Cm(III), which have applications in a variety of technological applications. For example, Ac(III) can be used for targeted alpha therapy, Th(IV) is recently being explored as an alternative nuclear fuel source, Am(III) is used in smoke detectors, and Cm(III) has been used for space exploration applications. First, we explored different interplay between water and nitrate ligands coordinated to Ac(III), Th(IV), Am(III), and Cm(III). Water is a common solvent to use with nitrate as it is cheap and adds additional shielding from radiation emitted by the actinides during the separation process. In solution, water can be a competitive ligand against nitrate toward the ligation of actinides. Due to this, it is important to evaluate the energetics for specific coordination numbers for the interplay of water and nitrate ligands. The results from this first step provided the initial conditions for the accurate calculations of $\log\beta$ values for the extraction process in both aqueous (343HOPO ligand) and organic phases (BTBP ligands). The computational methodology is presented in **2.2. Computational Details**, while our results are discussed in **2.3 Results and Discussion**. The last section of the chapter (**2.4. Summary of Key Results**) includes our concluding remarks.

2.2. Computational Details

All DFT calculations were performed with the ORCA quantum chemistry package version 5.0,^{108, 109, 120} and utilized the zeroth-order regular approximation (ZORA)¹²¹ coupled with the segmented all-electron relativistically contracted (SARC)¹²² basis sets and the conductor-like polarizable continuum model (CPCM) with water (aqueous phase), methanol, and 2-propanol (organic phase).¹²³ The geometry optimizations and frequency calculations were performed with the BP86^{124, 125} density functional together with the relativistically contracted SARC-ZORA-

TZVP¹²² basis set for the actinides and the ZORA-def2-SVP^{126, 127} basis sets for the remaining atoms. The resolution of identity for the computation of the two-electron integrals together with the SARC/J auxiliary basis set was utilized. Gibbs' free energies were computed at 298.15 K by adding the zero-point energy and the thermal vibrational–rotational entropies of the lowest-energy conformers, which were computed with the quasi-harmonic approximation, as implemented in ORCA. The applied computational methodology was chosen based on a recent benchmark study for ligand-based separations of lanthanides which possess similarities with the late actinides (from americium onward).¹²⁸

The performance of different density functionals was evaluated for Th(IV) and Cm(III) extraction by 343HOPO with respect to their accuracy in the stability constant calculation. The density functional evaluation for heavy elements is important since the majority of actinide benchmark studies are typically performed on much smaller molecular structures and not on polyatomic complexes.^{32, 33} The TPSSh,¹²⁹ B3LYP,^{130, 131} BLYP,^{125, 129} O3LYP,¹³² X3LYP,¹³³ PBE0,¹¹⁷ and ω B97¹³⁴ density functionals were examined with the same computational details described in the previous paragraph. This study would also provide a comparison of the TPSSh and B3LYP density functionals, which have been demonstrated to be top performing functionals on smaller actinide molecules with different computational parameters.^{32, 33}

Next, larger basis sets were investigated using the BP86 and B3LYP functionals. This further elucidates the effects of larger basis sets with the generalized gradient of the approximated BP86 density functional. For the larger basis set investigation, ZORA-def2-TZVP was used for all atoms and in a separate case, ZORA-def2-TZVP was used for all atoms except for H atoms (ZORA-def2-SVP). In addition, the SARC-ZORA-TZVP and SARC-ZORA-TZVPP basis sets were tested for the central actinide. The Th(IV) extraction with 343HOPO was chosen for this investigation due to the larger deviation from experiment (*vide infra*). Similarly, the Cm(III) extraction with 343HOPO was examined due to the consistent agreement with experimental data, and both Th(IV) and Cm(III) results are discussed.

Since the aim of this study is to explore a variety of different chemical environments, we have selected 4 representative actinides (Ac(III), Th(IV), Am(III), and Cm(III)), two of which have a closed-shell electronic structure (Ac(III), Th(IV)) and two high-spin cases, one with a half-filled f-shell (Cm(III)) and one with an 5f⁶ configuration (Am(III)). Available experimental

data for these actinides have been used as reference for the evaluation of our computational approach. The following nitrated molecular complexes were considered in this work: $\text{Ac}(\text{NO}_3)_x^{3-x}$, $\text{Am}(\text{NO}_3)_x^{3-x}$, $\text{Cm}(\text{NO}_3)_x^{3-x}$ ($x = 3-7$), $\text{Th}(\text{NO}_3)_y^{4-y}$ ($y = 4-7$). The following hydrated complexes were considered in this work $\text{Ac}(\text{H}_2\text{O})_x^{3+}$, $\text{Th}(\text{H}_2\text{O})_x^{4+}$, $\text{Am}(\text{H}_2\text{O})_x^{3+}$ ($x = 8-10$), $\text{Cm}(\text{H}_2\text{O})_y^{3+}$ ($y = 8-9$). The following mixed nitrated/hydrated molecular complexes were considered in this work: $\text{Ac}(\text{NO}_3)_3(\text{H}_2\text{O})_x$, $\text{Cm}(\text{NO}_3)_3(\text{H}_2\text{O})_x$ ($x = 1 - 6$), $\text{Th}(\text{NO}_3)_4(\text{H}_2\text{O})_y$ ($y = 1 - 5$), $\text{Am}(\text{NO}_3)_3(\text{H}_2\text{O})_z$ ($z = 1 - 4$). The aqueous phase coordination number for 343HOPO was kept at 8 for all actinide complexes. The organic phase coordination number is 4 for CyMe₄-BTBP, and 4 for *t*-Bu-C2-BTBP. All initial structures generated with nitrates considered bidentate coordinate with the actinides. The ground spin states of the molecular complexes considered in this study are singlet for Ac(III) and Th(IV), septet for Am(III) and octet Cm(III). For the open-shell cases, energy differences from various spin states were computed and verified that the ground state multiplicities for these complexes are the more stable states.

Recent work by Bhattacharjee and Miró⁴² showed that complexes of U, Np, and Pu with water, chloride, or nitrate ligands, the speciation is impacted by varying concentrations. In our work, all stability constants were computed without taking into consideration different concentrations of the species. We should note that concentrations of the actinides and ligands used for the experimental analysis with 343HOPO were small, so insignificant variations on the experimentally determined $\log\beta$ are expected

2.3. Results and Discussion

2.3.1. Actinide Speciation Analysis in a Hydrated and Nitrated Solution

Previous computational studies have evaluated extraction reactions using hydrated actinides,^{41, 135} with some studies considering both nitrated and hydrated actinides.^{23, 136} With previous studies considering different starting reactants for actinide extractions, we wish to further examine cases where different numbers of H₂O and NO₃⁻ ligands are introduced. Thus, calculations were performed to determine the energy differences between the formation of actinide nitrates versus hydrated actinide complexes. In addition, we considered a combination of actinide complexes containing both nitrate and water ligands, which helped us evaluate the

favorability of each species in solution. A detailed list of formation reactions with water, nitrates, as well as mixed species is given in **Table 2.1**.

The most favorable nitrated actinides in solution that were found are: $\text{Ac}(\text{NO}_3)_6^{3-}$, $\text{Th}(\text{NO}_3)_6^{2-}$, $\text{Am}(\text{NO}_3)_5^{2-}$, $\text{Cm}(\text{NO}_3)_5^{2-}$. The early actinides ($\text{Ac}(\text{III})$ and $\text{Th}(\text{IV})$) demonstrate similar behavior in a nitrate-rich environment showing the highest stability constant when they are coordinated with six nitrates, while the later actinides ($\text{Am}(\text{III})$ and $\text{Cm}(\text{III})$) share similarities with each other and prefer to be coordinated to five nitrates. However, for the hydrated species, $\text{Ac}(\text{III})$ behaves similar to $\text{Am}(\text{III})$ and $\text{Cm}(\text{III})$. The most favorable hydrated actinides determined are: $\text{Ac}(\text{H}_2\text{O})_9^{3+}$, $\text{Th}(\text{H}_2\text{O})_{10}^{4+}$, $\text{Am}(\text{H}_2\text{O})_9^{3+}$, $\text{Cm}(\text{H}_2\text{O})_9^{3+}$, in agreement with experimental solid-state reports. Finally, the most favorable mixed hydrated-nitrated actinide species were: $\text{Ac}(\text{NO}_3)_3(\text{H}_2\text{O})_4$, $\text{Th}(\text{NO}_3)_4(\text{H}_2\text{O})_3$, $\text{Am}(\text{NO}_3)_3(\text{H}_2\text{O})_4$, and $\text{Cm}(\text{NO}_3)_3(\text{H}_2\text{O})_3$. Out of all these species, the nitrated actinides in all cases were shown to be the most favorably formed products. For example, the formation of $\text{Th}(\text{NO}_3)_6^{3-}$ and $\text{Th}(\text{H}_2\text{O})_{10}^{4+}$ results to $\log\beta$ values of 305.46 and 240.49, respectively. $\text{Th}(\text{IV})$ having the more stable state with six coordinated nitrate ligands agreed with expected experimental solid-state observations.¹³⁷ We also note that, a mixture of water and nitrate would result in higher stability than a solution containing just water. In all cases, the most stable hydrated actinide is less stable than the most stable mixed actinide species. For example, the determined $\log\beta$ for $\text{Th}(\text{NO}_3)_4(\text{H}_2\text{O})_3$ and $\text{Th}(\text{H}_2\text{O})_{10}^{4+}$ were found to be 290.94 and 240.49 respectively. The most stable products were then compared to the other species evaluated as starting reactants for extraction analyses by 343HOPO.

In terms of the coordination number, we found that the most favorable (larger $\log\beta$ value) hydrated actinide form in solution agrees with the observed crystal structures.¹³⁷ For fully hydrated actinide ions, a coordination number of 10 was found experimentally for $\text{Th}(\text{IV})$, and a coordination number of 9 for $\text{Cm}(\text{III})$ and $\text{Am}(\text{III})$,¹³⁷ which were verified from our computational work. The coordination number of 9 for $\text{Cm}(\text{III})$ was determined by the observed optimized structure from DFT. Each attempt to optimize 10 water molecules coordinated to $\text{Cm}(\text{III})$ resulted in the detachment of the tenth water molecule from $\text{Cm}(\text{III})$, which moved to the second solvation sphere most likely due to the smaller atomic radius of $\text{Cm}(\text{III})$. $\text{Am}(\text{III})$ can accommodate 10 water molecules in its coordination sphere, but the formed species is less stable

Table 2.1. Comparison between the Formation of Actinide Nitrates, Hydrated Actinides and the Combination of Actinides with Nitrates and Water Molecules.

Formation	ΔG (kcal/mol)	$\log\beta$
Actinide Nitrates		
$\text{Ac}^{3+} + 3\text{NO}_3^- \rightarrow \text{Ac}(\text{NO}_3)_3$	-149.04	109.25
$\text{Ac}^{3+} + 4\text{NO}_3^- \rightarrow \text{Ac}(\text{NO}_3)_4^-$	-176.77	129.57
$\text{Ac}^{3+} + 5\text{NO}_3^- \rightarrow \text{Ac}(\text{NO}_3)_5^{2-}$	-195.47	143.28
$\text{Ac}^{3+} + 6\text{NO}_3^- \rightarrow \text{Ac}(\text{NO}_3)_6^{3-}$	-196.35	143.93
$\text{Ac}^{3+} + 7\text{NO}_3^- \rightarrow \text{Ac}(\text{NO}_3)_7^{4-}$	-185.62	136.06
$\text{Th}^{4+} + 4\text{NO}_3^- \rightarrow \text{Th}(\text{NO}_3)_4$	-365.42	267.86
$\text{Th}^{4+} + 5\text{NO}_3^- \rightarrow \text{Th}(\text{NO}_3)_5^-$	-405.22	297.03
$\text{Th}^{4+} + 6\text{NO}_3^- \rightarrow \text{Th}(\text{NO}_3)_6^{2-}$	-416.72	305.46
$\text{Th}^{4+} + 7\text{NO}_3^- \rightarrow \text{Th}(\text{NO}_3)_7^{3-}$	-409.96	300.50
$\text{Am}^{3+} + 3\text{NO}_3^- \rightarrow \text{Am}(\text{NO}_3)_3$	-225.19	165.06
$\text{Am}^{3+} + 4\text{NO}_3^- \rightarrow \text{Am}(\text{NO}_3)_4^-$	-259.88	190.49
$\text{Am}^{3+} + 5\text{NO}_3^- \rightarrow \text{Am}(\text{NO}_3)_5^{2-}$	-276.94	203.00
$\text{Am}^{3+} + 6\text{NO}_3^- \rightarrow \text{Am}(\text{NO}_3)_6^{3-}$	-271.21	198.80
$\text{Am}^{3+} + 7\text{NO}_3^- \rightarrow \text{Am}(\text{NO}_3)_7^{4-}$	-250.84	183.87
$\text{Cm}^{3+} + 3\text{NO}_3^- \rightarrow \text{Cm}(\text{NO}_3)_3$	-222.16	162.85
$\text{Cm}^{3+} + 4\text{NO}_3^- \rightarrow \text{Cm}(\text{NO}_3)_4^-$	-256.81	188.25
$\text{Cm}^{3+} + 5\text{NO}_3^- \rightarrow \text{Cm}(\text{NO}_3)_5^{2-}$	-273.49	200.47
$\text{Cm}^{3+} + 6\text{NO}_3^- \rightarrow \text{Cm}(\text{NO}_3)_6^{3-}$	-265.42	194.55
$\text{Cm}^{3+} + 7\text{NO}_3^- \rightarrow \text{Cm}(\text{NO}_3)_7^{4-}$	-252.77	185.28
Hydrated Actinides		
$\text{Ac}^{3+} + 8\text{H}_2\text{O} \rightarrow \text{Ac}(\text{H}_2\text{O})_8^{3+}$	-144.76	106.11
$\text{Ac}^{3+} + 9\text{H}_2\text{O} \rightarrow \text{Ac}(\text{H}_2\text{O})_9^{3+}$	-147.68	108.25
$\text{Ac}^{3+} + 10\text{H}_2\text{O} \rightarrow \text{Ac}(\text{H}_2\text{O})_{10}^{3+}$	-144.37	105.82
$\text{Th}^{4+} + 8\text{H}_2\text{O} \rightarrow \text{Th}(\text{H}_2\text{O})_8^{4+}$	-316.63	232.09
$\text{Th}^{4+} + 9\text{H}_2\text{O} \rightarrow \text{Th}(\text{H}_2\text{O})_9^{4+}$	-326.63	239.42
$\text{Th}^{4+} + 10\text{H}_2\text{O} \rightarrow \text{Th}(\text{H}_2\text{O})_{10}^{4+}$	-328.09	240.49

Table 2.1. Continued

$\text{Am}^{3+} + 8\text{H}_2\text{O} \rightarrow \text{Am}(\text{H}_2\text{O})_8^{3+}$	-214.62	157.32
$\text{Am}^{3+} + 9\text{H}_2\text{O} \rightarrow \text{Am}(\text{H}_2\text{O})_9^{3+}$	-216.08	158.39
$\text{Am}^{3+} + 10\text{H}_2\text{O} \rightarrow \text{Am}(\text{H}_2\text{O})_{10}^{3+}$	-211.64	155.13
$\text{Cm}^{3+} + 8\text{H}_2\text{O} \rightarrow \text{Cm}(\text{H}_2\text{O})_8^{3+}$	-218.20	159.94
$\text{Cm}^{3+} + 9\text{H}_2\text{O} \rightarrow \text{Cm}(\text{H}_2\text{O})_9^{3+}$	-219.40	160.82
Mixed		
$\text{Ac}^{3+} + \text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Ac}(\text{NO}_3)_3(\text{H}_2\text{O})$	-160.16	117.40
$\text{Ac}^{3+} + 2\text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Ac}(\text{NO}_3)_3(\text{H}_2\text{O})_2$	-169.45	124.21
$\text{Ac}^{3+} + 3\text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Ac}(\text{NO}_3)_3(\text{H}_2\text{O})_3$	-176.91	129.68
$\text{Ac}^{3+} + 4\text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Ac}(\text{NO}_3)_3(\text{H}_2\text{O})_4$	-180.44	132.27
$\text{Ac}^{3+} + 5\text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Ac}(\text{NO}_3)_3(\text{H}_2\text{O})_5$	-178.20	130.62
$\text{Ac}^{3+} + 6\text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Ac}(\text{NO}_3)_3(\text{H}_2\text{O})_6$	-174.03	127.57
$\text{Th}^{4+} + \text{H}_2\text{O} + 4\text{NO}_3^- \rightarrow \text{Th}(\text{NO}_3)_4(\text{H}_2\text{O})$	-383.45	281.07
$\text{Th}^{4+} + 2\text{H}_2\text{O} + 4\text{NO}_3^- \rightarrow \text{Th}(\text{NO}_3)_4(\text{H}_2\text{O})_2$	-394.13	288.90
$\text{Th}^{4+} + 3\text{H}_2\text{O} + 4\text{NO}_3^- \rightarrow \text{Th}(\text{NO}_3)_4(\text{H}_2\text{O})_3$	-396.92	290.94
$\text{Th}^{4+} + 4\text{H}_2\text{O} + 4\text{NO}_3^- \rightarrow \text{Th}(\text{NO}_3)_4(\text{H}_2\text{O})_4$	-396.04	290.30
$\text{Th}^{4+} + 5\text{H}_2\text{O} + 4\text{NO}_3^- \rightarrow \text{Th}(\text{NO}_3)_4(\text{H}_2\text{O})_5$	-390.73	286.41
$\text{Am}^{3+} + \text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Am}(\text{NO}_3)_3(\text{H}_2\text{O})$	-241.01	176.66
$\text{Am}^{3+} + 2\text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Am}(\text{NO}_3)_3(\text{H}_2\text{O})_2$	-253.64	185.92
$\text{Am}^{3+} + 3\text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Am}(\text{NO}_3)_3(\text{H}_2\text{O})_3$	-257.04	188.41
$\text{Am}^{3+} + 4\text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Am}(\text{NO}_3)_3(\text{H}_2\text{O})_4$	-257.40	188.68
$\text{Cm}^{3+} + \text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Cm}(\text{NO}_3)_3(\text{H}_2\text{O})$	-237.93	174.40
$\text{Cm}^{3+} + 2\text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Cm}(\text{NO}_3)_3(\text{H}_2\text{O})_2$	-249.11	182.60
$\text{Cm}^{3+} + 3\text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Cm}(\text{NO}_3)_3(\text{H}_2\text{O})_3$	-255.46	187.26
$\text{Cm}^{3+} + 4\text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Cm}(\text{NO}_3)_3(\text{H}_2\text{O})_4$	-253.97	186.16
$\text{Cm}^{3+} + 5\text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Cm}(\text{NO}_3)_3(\text{H}_2\text{O})_5$	-253.86	186.08
$\text{Cm}^{3+} + 6\text{H}_2\text{O} + 3\text{NO}_3^- \rightarrow \text{Cm}(\text{NO}_3)_3(\text{H}_2\text{O})_6$	-254.67	186.68

(-211.64 kcal/mol) as opposed to the hydrated Am(III) with coordination number of 9 (-216.08 kcal/mol). A previous computational study also explored the hydration number of Cm(III) and Am(III), and concluded that the coordination number is 9.³⁷ This agreement with experimental observations demonstrates that these results can be further used as a guide for predicting the chemistry of actinides in aqueous solutions.

2.3.2. Aqueous Phase Actinide Extraction and Ligation using 3,4,3-LI(1,2- HOPO)

This section is focused on the replication of experimentally determined $\log\beta$ values to provide a methodology for screening 343HOPO derivatives in nitric media. To accomplish this, first, three different hydrated actinide extraction systems were studied for Ac(III), Th(IV), Am(III), and Cm(III), and were compared to the nitrated actinide species reactions. Since the actual extraction mechanism of actinides extracted by 343HOPO (**Figure 2.1**) is unknown, a variety of different reaction mechanisms were considered in this study. Previous computational exploration involved hydrated actinides at different oxidation states together with the eight-coordinate ligand 343HOPO.⁴¹ The first hydrated system demonstrated by reaction ((R2-1)) was used by Kelley et al. in an effort to replicate experimentally observed stability constants.⁴¹



Since the number of water molecules coordinated to the actinide can vary in solution, three different coordination numbers were investigated in our study ($x = 8, 9$, and 10). It should be noted that $x = 10$ was not acquired for Cm(III), as 10 water molecules would not coordinate to Cm(III). In reaction ((R2-1)), n represents the charge of the hydrated actinide compound, which is $4+$ for Th(IV) and $3+$ for all other actinides. The other hydrated systems evaluated in this study are shown in (R2-2) and (R2-3). The coefficients x in (R2-2) and y in (R2-3), where $x = 4 + y$, demonstrate the number of molecules needed to balance the reaction. Each reaction takes the hydrated form of an actinide and interacts with the protonated form of 343HOPO ($\text{H}_4\text{343HOPO}$) for the substitution of the corresponding water molecules per reaction. These hydrated systems were then compared to both (R2-4) and (R2-5), which consider nitrated actinides that are in agreement with experimentally determined stability constants. A detailed discussion on the hydronium Gibbs' free energy correction that was applied for all calculations involving the

hydronium ion is available in the supporting information of the original publication and will not be discussed here.

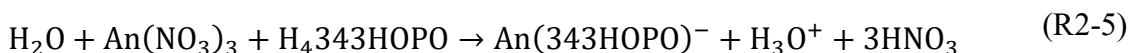
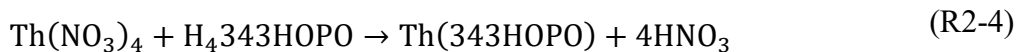
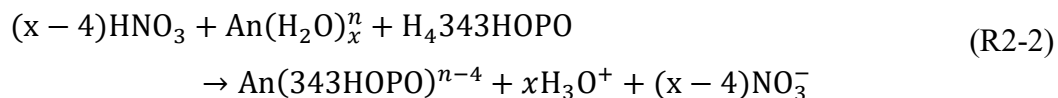


Figure 2.2 demonstrates the stability constant deviation ($\Delta\log\beta$) between the computed and experimentally determined stability constant. For **Figure 2.2A-C**, the x-axis demonstrates the number of water molecules coordinated to the central actinide. The experimental stability constants used for reference are 40.1(5), 20.4(2), and 21.8(4) for Th(IV), Am(III), and Cm(III), respectively.^{25, 41} The expected stability constant for Ac(III) is between 10 and 14, and we used the upper limit (14) as reference.²⁵ The Th(IV) constant was determined by competition titration from a stock solution of $\text{ThCl}_4 \cdot 8\text{H}_2\text{O}$ dissolved in 0.1 M H_2SO_4 with 0.1 M KOH with Ce(IV), which was prepared in 0.1 M H_2SO_4 from $\text{Ce}(\text{SO}_4)_2 \cdot 4\text{H}_2\text{O}$, where the ligand and metal concentrations were approximately 30 μM , performed at a pH of 1.0 to prevent hydrolysis at 20°C.¹³⁸ The conditional stability constant (pM) at a fixed pH of 7.4 with a Th(IV) concentration of 1 μM and a ligand concentration of 10 μM which, by taking the negative logarithm of the complexed ligand, free metal, and free ligand species, resulted in a pM value of 41.0(5).¹³⁸ The stability constants for Am(III) were also determined with three competitive titrations against varying concentrations of Eu(III) between 0 to 15 μM with Am(III) at a concentration of 3 μM , with 0.1 M KCl at a pH of 7.4 at 25°C.¹³⁹ The pM value of the Am(III)–343HOPO complex was estimated as 21.3(2). For Cm(III), the titration started at an initial pH of 1.1 and was titrated with 0.1 M KOH to a pH of 4.0 and 11.0, respectively, and were backward titrated by 0.1 M HCl, three titrations were conducted, and the pM value was estimated to be 22.7(4).¹⁴⁰ However, in an industrial scale treatment of nuclear waste where small competitive titrations would not be applicable, the use of nitric acid is crucial.^{31, 141} Thus, we chose to work with nitrated actinides to not only try and acquire a stability constant near those reported previously but also to provide computational results under identical conditions. These reported experimental results were

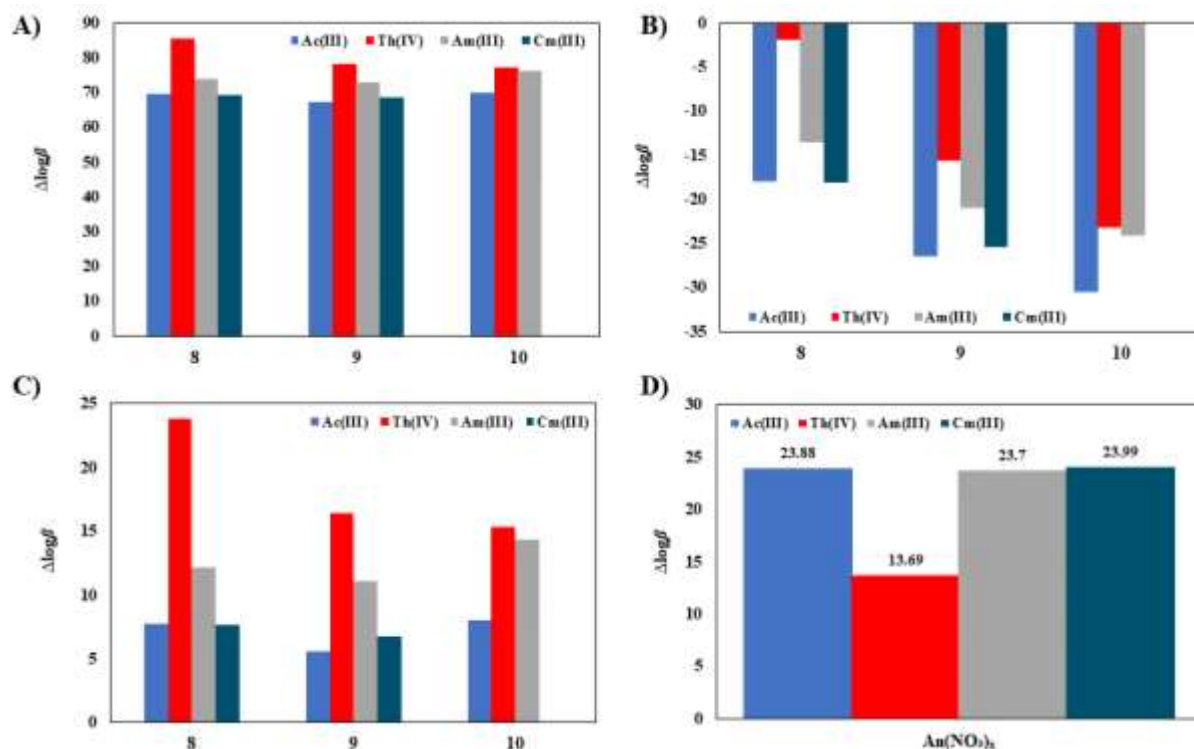


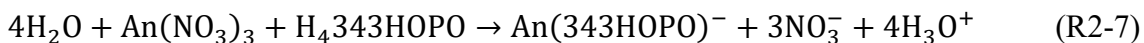
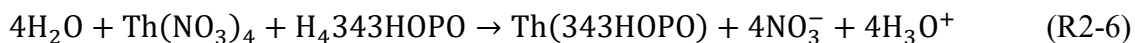
Figure 2.2. Comparison between different reactions (not in scale) involving hydrated actinides and nitrated actinides as reactants, where (A) represents the difference in stability constants from experimental results to those acquired computationally ($\Delta \log \beta$) for (R2-1), (B) is for (R2-2), (C) is for (R2-3), and (D) is for (R2-4) and (R2-5). The x-axis of (A)–(C) represents the number of coordinated water molecules. For (D), the nitrated form of the actinides is $x = 3$ for Cm, Am, and Ac, and $x = 4$ for Th.

determined under relatively proton independent environments (providing that stability constants are dependent only on the actinide, ligand, and ligated actinide). We analyzed various different proton dependent environments, but the computed $\log\beta$ values are significantly higher than the experimentally refined value.

First, we found a good agreement between this work and the computational results of Kelley and co-workers (**Figure 2.2A**),⁴¹ where Ac(III) has the lowest stability constant and Th(IV) the highest. Results from reactions (R2-4) and (R2-5) (**Figure 2.2D**) follow the expected trend with respect to the experimentally refined stability constants, which were more in agreement than those in **Figure 2.2A,B**, where Cm(III) has a higher stability constant than Am(III) (45.79 and 44.1, 1.69 difference between Am(III) and Cm(III), compared to 21.8 and 20.4, 1.40 difference between Am(III) and Cm(III), respectively) and Th(IV) (53.79 compared to 40.1) has the highest $\log\beta$ and Ac(III) (37.88 compared to 14) the lowest. Importantly, **Figure 2.2C** provided the best agreement in $\log\beta$ for all actinides considered in this study. Not only is there good agreement for (R2-3), but we also observe that the most favorable number of water molecules coordinated to the actinide provided the most accurate values with experimental findings in all cases. A coordination number of 9 with water was observed to be the most favorable for Ac(III) (19.6 compared to 14), Am(III) (31.5 compared to 21.8), and Cm(III) (28.54 compared to 20.4) and 10 for Th(IV) (55.46 compared to 40.1). We would also like to note that the various reactions reported in the supporting information of the original publication that diverge from the expected experimental $\log\beta$ values could still provide insights into the behavior of actinide extractions by 343HOPO. Each reaction mechanism is specific to experimental conditions, some with higher nitric acid concentration than others. While here we are aiming on replicating experimental $\log\beta$ values, the other reactions could be used as a guide for developing criteria for actinide behavior under nitric acid media.

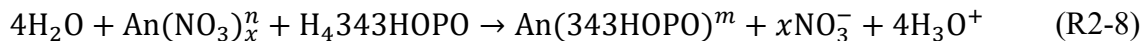
Since many of the equations evaluated here involved HNO₃ as a product, a short discussion is provided on the extraction, or coextraction, of the nitric acid into the organic phase of the extraction system. It is known that the coextraction of nitric acid into the organic phase can occur for systems such as the *N,N,N',N'*-tetra-*n*-octyl diglycolamide (TODGA), 1-octanol, inert kerosene organic phase systems containing 2-ethylhexanol, and systems containing *N,N,N',N'*-tetra(2-ethylhexyl)diglycolamide (T2EHDGA) with 2-ethylhexylphosphonic acid

mono-2-ethylhexyl ester (HEH[EHP]) in n-dodecane.^{30, 142} Based on this, it is possible that upon the decoordination of the nitrates from the actinides, the nitrates become protonated and are drawn toward the organic phase and could be coextracted into the organic phase layer. Thus, the degree of deprotonation of nitric acid should be examined for reliable simulation of the experimental conditions. We also note that conditional stability constants have a strong dependence on pH. For example, Th(IV) was shown to have a pM range from around 20 (pH of 0) to 41.0 at a pH of 6 which stays constant to a pH of 10 (experimental cutoff).¹⁴³ Since, 343HOPO has been investigated for purposes of physiological conditions at a pH of 7.4, which is around the optimum pH for the formation of 343HOPO-actinide complexation,^{25, 138-140, 144} a reaction with a minimum amount of free hydrogen would be expected. To evaluate what would be expected in lower pH reactions (unprotonated nitrate), we made comparisons between the protonated and unprotonated forms of nitrate, with reactions (R2-6) and (R2-7) and compared these with reactions (R2-4) and (R2-5).



A comparison of the $\Delta\log\beta$ values from the four different equations is shown in **Figure 2.3**. We conclude that the presence of nitrate decreases the $\log\beta$ deviations, while the modeling of reactions that include nitric acid ((R2-4) and (R2-5)) diverges more when compared with experimental observations. Thus, the proposed approach provides a computational methodology for screening actinides with 343HOPO-based ligands and a demonstration of the possible behavior and speciation of actinide separations in a nitric media.

If the most stable nitrate molecules and mixed nitrate/water complexes were compared with (R2-6) and (R2-7) using a similar approach, we obtained stability constant values that further diverge from the experimental findings than the neutral actinide nitrate complexes. By using reactions (R2-8) and (R2-9), where the variable x is the number of nitrate molecules coordinated



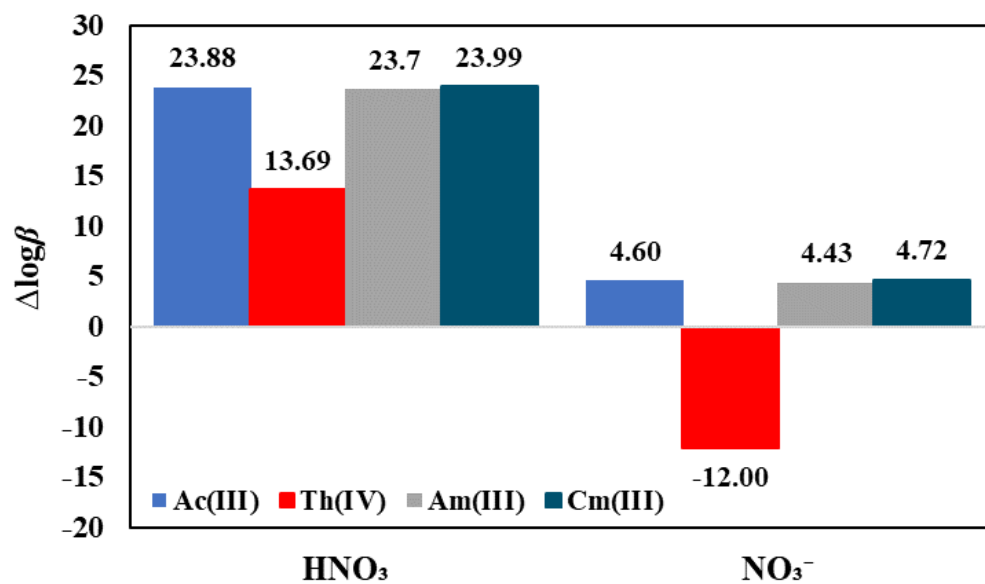
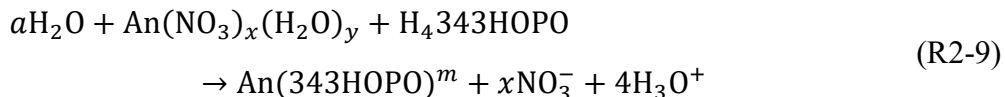
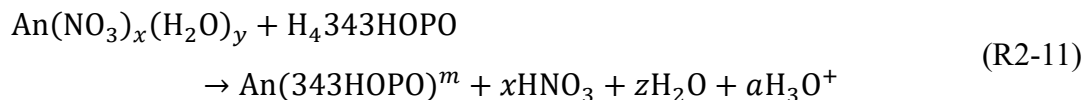


Figure 2.3. A comparison between the computed stability constants with the experimentally determined stability constants for select actinide extractions with 343HOPO using a protonated ((R2-4) and (R2-5)) and unprotonated ((R2-6) and (R2-7)) nitrate model.



to the actinide (An), n is equal to the oxidation state of the actinide minus x , m is equal to the oxidation state of the actinide minus four, a is the number of water molecules used to balance the equation (which is either one or zero for this instance), and y is the number of coordinated water molecules. To reiterate, the most favorable actinide nitrates were found to be $\text{Ac}(\text{NO}_3)_6^{3-}$, $\text{Th}(\text{NO}_3)_6^{2-}$, $\text{Am}(\text{NO}_3)_5^{2-}$, and $\text{Cm}(\text{NO}_3)_5^{2-}$ and the most favorable combined nitrate and water actinide complexes were $\text{Ac}(\text{NO}_3)_3(\text{H}_2\text{O})_4$, $\text{Th}(\text{NO}_3)_4(\text{H}_2\text{O})_3$, $\text{Am}(\text{NO}_3)_3(\text{H}_2\text{O})_4$, and $\text{Cm}(\text{NO}_3)_3(\text{H}_2\text{O})_3$. **Figure 2.4** demonstrates the differences in stability constants between the computed and experimental values using (R2-8) and (R2-9) with the most favorable actinide complexes. These results demonstrated that while the mixed nitrate and water complexes provide better agreement with experimental observations, both reactions demonstrated unfavorability (negative stability constants for (R2-8), and very low positive values and a negative value for $\text{Ac}(\text{III})$ for (R2-9)) for further consideration.

Better agreement with experimental stability constants was found when deprotonation was combined with protonated nitrates. We also found better agreement for the mixed nitrate and water complexes when treating the nitrates as protonated as opposed to deprotonated. For this analysis, reactions (R2-10) and (R2-11) were used where the variables that were used are identical to those described for (R2-8) and (R2-9), except here x has to be greater than or equal to 4 from the four protons of 343HOPO , a was used to represent the hydronium ions used to balance the reaction (either one or zero for this purpose), and z is equivalent to y minus a .



We treat the protons lost by 343HOPO to coordinate with all of the nitrates, and if there are only three nitrates, then the fourth forms a hydronium ion in (R2-11). Here we found very good agreement when using (R2-11) with the most favorable mixed nitrate and water actinide

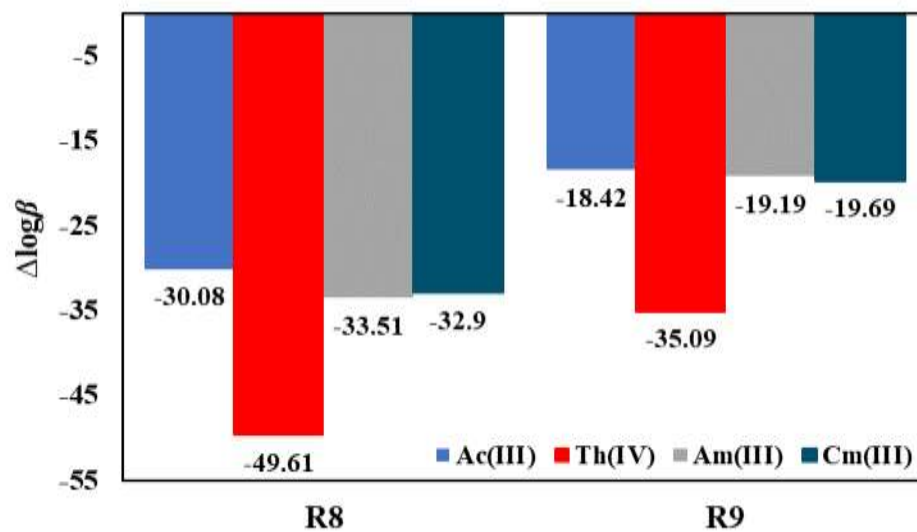


Figure 2.4. Comparisons between the change in stability constants from reactions (R2-8), or R8 in the figure, and (R2-9), or R9, with the actinides used in this study.

complexes and an improvement of results using (R2-10) compared with (R2-8) (**Figure 2.5**). Th(IV) was shown to be significantly underestimated for both cases compared to the experimental stability constant of 40.1.

2.3.3. Density Functional Dependency Analysis on Various Reactions in the Aqueous Phase

We also explored the density functional dependence on the $\log\beta$ computation for Th(IV) and Cm(III). We applied reactions (R2-4)-(R2-7) for the evaluation of Th(IV) and Cm(III), respectively, and all results are summarized in **Figure 2.6**. Overall, all density functionals overestimated the Cm(III) stability constants using (R2-5), with deviations ($\Delta\log\beta$) that range from 15.30 (B3LYP) up to 23.99 (BP86). On the contrary, $\Delta\log\beta$ values for Th(IV) spanned from 9.86 (O3LYP) to 13.69 (BP86) using (R2-4). For reactions (R2-6) and (R2-7), a significant underestimation was found for all cases, with less significance for the BP86 functional, for Th(IV), and an underestimation for all cases for Cm(III), except with the BP86 functional, which slightly overestimated the stability constant. For (R2-4) and (R2-5), the O3LYP functional performed the best for Th(IV), and the B3LYP functional performed the best for Cm(III). For (R2-6) and (R2-7), the BP86 functional performed best for both Th(IV) and Cm(III). We also explored the consistency of B3LYP for Am(III) since this functional was shown to have good performance in previous benchmark studies.^{33, 129} The difference between computed and experimental stability constants is 16.62 (15.30 for Cm(III)) for (R2-5) and -15.78 (-17.09 for Cm(III)) for (R2-7). B3LYP is consistent in performance for both Cm(III) and Am(III), however, the difference is still significant from experimental expectations. We conclude that BP86 would be an acceptable density functional due to the consistent behavior across four different reactions, which agrees with the lanthanide benchmark study,¹²⁸ and also that, depending on the reaction being studied, the functional chosen has a significant impact on large actinide complexes, demonstrating the crucial importance of benchmarking these complexes.

Following the density functional benchmark study, we examined whether the basis sets choice would improve the accuracy of the calculated stability constants. First, different basis sets were evaluated in conjunction with the BP86 density functional and the computed $\Delta\log\beta$ values by implementation of reactions (R2-4) for Th(IV) and (R2-5) for Cm(III), with the corrected H_3O^+ values being utilized, are shown on **Figure 2.7**. From these results, it was shown that the chosen computational protocol deviated the most from the experimentally refined values for

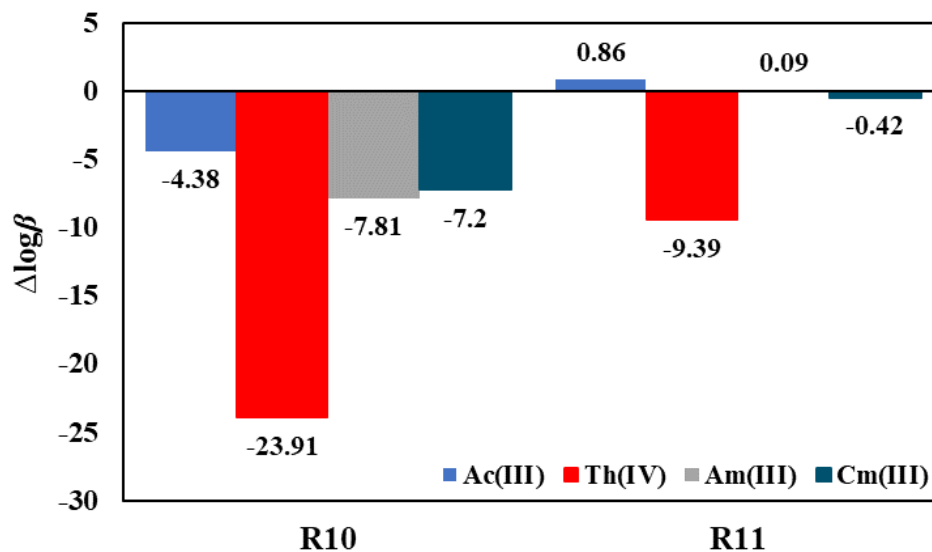


Figure 2.5. Comparisons between the change in stability constants from reactions (R2-10), or R10 in the figure, and (R2-11), or R11, with the actinides used in this study.

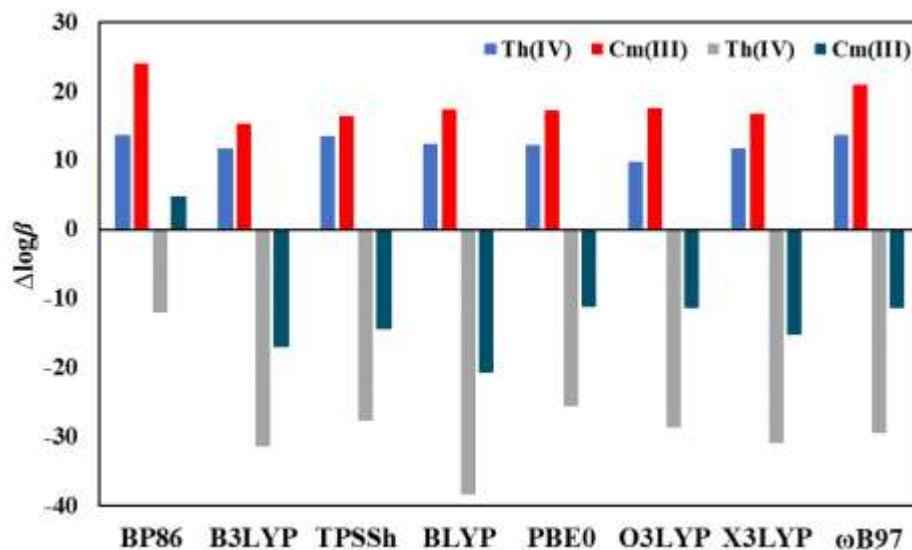


Figure 2.6. Accuracy assessment of different density functionals Th(IV) and Cm(III) coordination to 343HOPO using equations (R2-4) and (R2-5) [blue and red] and (R2-6) and (R2-7) [grey and dark teal].

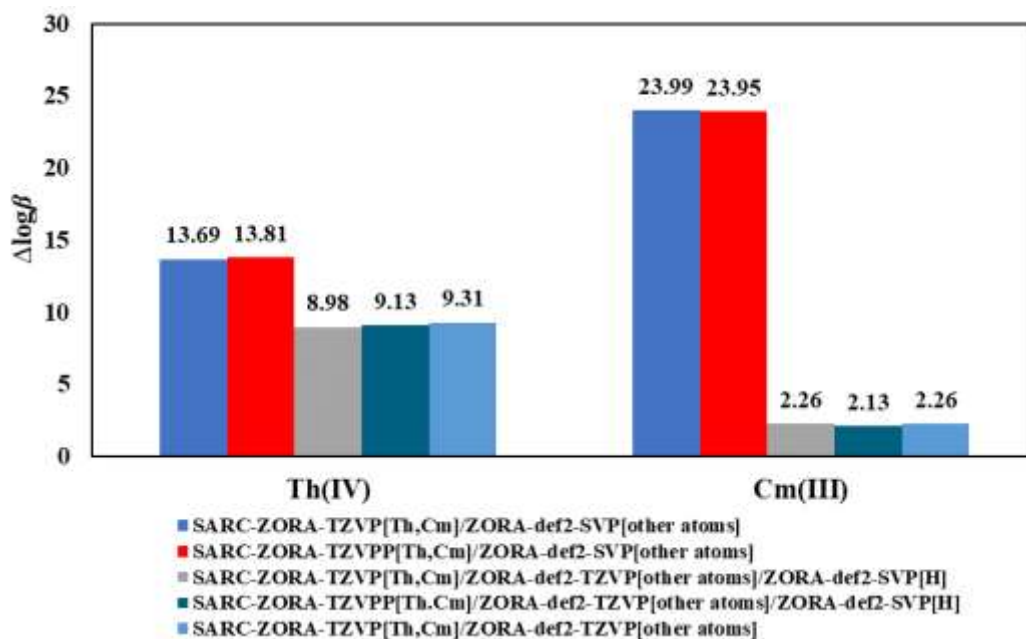


Figure 2.7. Calculated $\Delta\log\beta$ values for the different basis sets for Th(IV) and Cm(III) using the BP86 density functional. Recall, for the combinations involving three different basis sets, the H atoms were the atoms described by the ZORA-def2-SVP basis set in the complex. The legend describes the implemented basis set for specific atoms shown in brackets.

these actinide extraction systems. Additionally, it was observed that adding triple- ζ basis sets to the system increased the accuracy for both Th(IV) and Cm(III). The use of triple- ζ valence polarization basis sets greatly increases the computational cost of these systems. These same observations were made when utilizing the B3LYP density functional (**Figure 2.8**) with a more noticeable decrease being observed for the SARC-ZORA-TZVP/ZORA-def2-SVP and SARC-ZORA-TZVPP/ZORA-def2-SVP basis sets.

The best combination for Th(IV) using (R2-4) was demonstrated to be with the BP86 density functional with the SARC-ZORA-TZVP/ZORA-def2-TZVP/ZORA-def2-SVP basis sets combination with a difference of 8.98. For Cm(III), the B3LYP density functional with the SARC-ZORA-TZVP/ZORA-def2-TZVP basis sets combination was shown to provide the least deviations from the experimental stability constant providing a difference of -1.19. We also note that the expected computational intuition of using a larger basis set to provide more accurate chemical information was observed with the decrease in deviations as the basis set size were increased. There was little change when going from the SARC-ZORA-TZVP basis set on the actinide to the SARC-ZORA-TZVPP basis set upon utilization of the BP86 functional, demonstrating absolute differences ($\Delta\Delta\log\beta$) of 0.12, 0.15, 0.04 and 0.13, while the absolute differences utilizing the B3LYP functional were 0.76, 0.39, 0.42 and 0.83.

2.3.4. Organic Phase Actinide Extraction and Ligation using 6,6'-bis(1,2,4-triazin-3-yl)-2,2'-bipyridine Ligands

After the aqueous phase 343HOPO analysis with nitrates, we turned our attention to organic phase-based ligands and their use for extracting actinides from an acidic solution. Organic BTBP ligands are popular ligands used for the extraction of trivalent actinides¹⁴⁵ and the ability to screen these ligands computationally could aid chemists toward the development of ideal extractants to close the nuclear fuel cycle. Three organic phase ligands were examined for the evaluation and implementation of a systematic method for organic phase ligand screening. Two BTBP ligand variants are the *tert*-butyl-C2-6,6'-bis(1,2,4-triazin-3-yl)-2,2'-bipyridine (t-Bu-C2-BTBP, or **A**) and 6,6'-bis(5,5,8,8-tetramethyl-5,6,7,8-tetrahydrobenzo-1,2,4-triazin-3-yl)-2,2'-bipyridine (CyMe₄-BTBP or **B**), see **Figure 2.9** (top). A 2:1 ligand:Cm(III) ratio was considered for both **A** and **B** based on BTBP studies by Panak and Geist.¹⁸ The BP86/ SARC-ZORA-

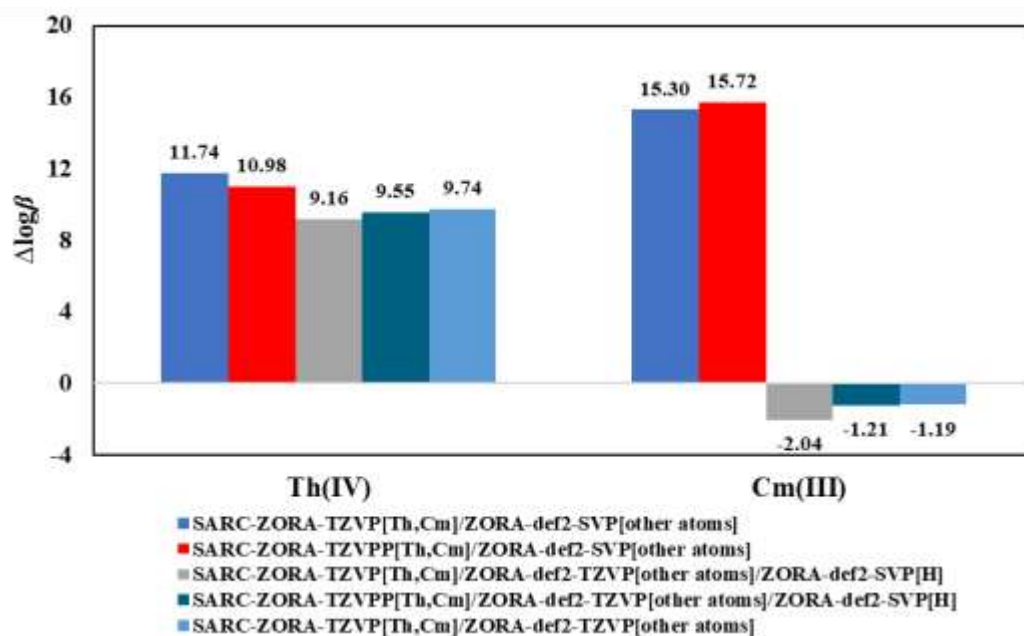


Figure 2.8. Calculated $\Delta \log \beta$ values for the different basis sets for Th(IV) and Cm(III) using the B3LYP density functional. Recall, for the combinations involving three different basis sets, the H atoms were the atoms described by the ZORA-def2-SVP basis set in the complex. The legend describes the implemented basis set for specific atoms shown in brackets.

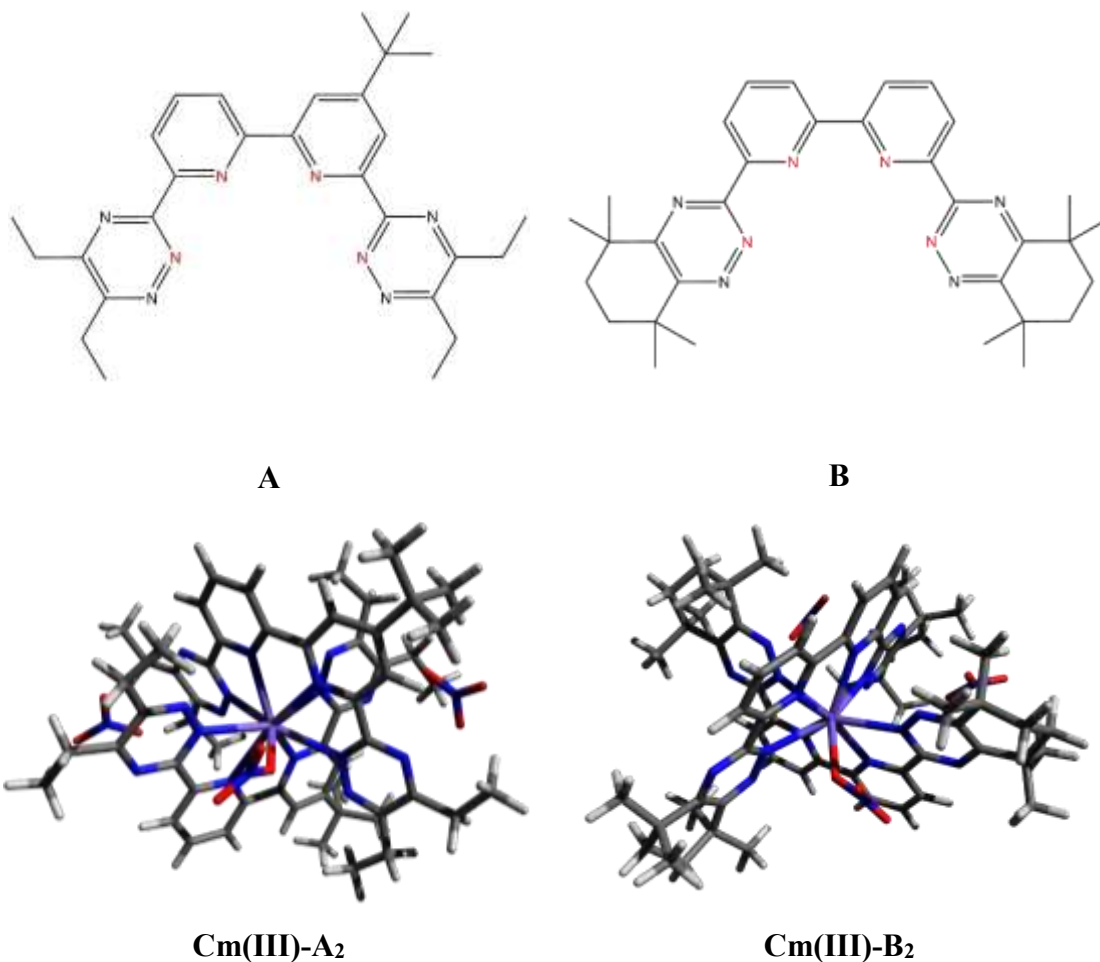


Figure 2.9. Top: the two organic ligands t-Bu-C2-BTBP (**A**) and CyMe₄-BTBP (**B**) evaluated with experimental stability constant values for Cm(III) extraction. Atoms indicated with red font are the binding sites of the ligands. Bottom: Optimized structures of **Cm(III)-A₂** (**A**: t-Bu-C2-BTBP), and **Cm(III)-B₂** (**B**: CyMe₄-BTBP). Hydrogens atoms are shown in white, blue is nitrogen, grey is carbon, red is oxygen, and purple is Cm(III).

TZVP/ZORA-def2-SVP optimized geometries for the complexes are provided in **Figure 2.9** (bottom).

We have used reaction (R2-12) to probe the ligand coordination in the organic phase, which implies that the nitrates are detached from Cm(III) upon ligand coordination but remain within the solvation sphere of the complex:



Using (R2-12) for the two organic ligands, the computed $\log\beta$ values at 25°C for **A** and **B** are 14.52 and 13.14, respectively. The experimental $\log\beta$ value for Cm(III) ligation by *t*-Bu-C2-BTBP (**A**) in a 1:1 volume solution of 2-propanol/H₂O with a nitrate concentration range of 1.85×10^{-4} to 1.74×10^{-3} M at 20°C was found to be 11.1 ± 0.15 ,¹⁸ giving a $\Delta\log\beta$ with respect to the computationally determined $\log\beta$ value of 3.42. For CyMe₄-BTBP (**B**), the experimentally determined $\log\beta$ value in a methanol mixture with 3.3 mol% H₂O, with an initial Cm(ClO₄)₃ concentration of 5×10^{-8} M and the HClO₄ concentration of 91.2 mM, was found to be 12.4(3).^{12, 18, 141} When compared with the computed $\log\beta$ values, we obtain a deviation of $\Delta\log\beta = 0.74$. Here, we note that the computational values are given at a 5°C higher temperature than those from the experimental value. This difference is not expected to alter the stability constant values by a dramatic extent, as demonstrated by the ligation of Eu(III) with CyMe₄-BTBP where at 20°C in methanol and 0.01 M nitrate the $\log\beta$ value was 11.9 ± 0.5 while under similar conditions as the reported Cm(III) ligation was 11.3 ± 0.3 .¹⁴¹ Likewise, the use of nitrate versus HClO₄ was also observed with the previous example, indicating a small difference in stability constants, most likely due to the structural similarities, similar denticities, and identical coordination atoms between HNO₃ and HClO₄. However, we also chose to use nitrate for this present study due to the importance of nitric acid in the treatment of nuclear waste.^{31, 141}

When we attempt to coordinate more than nine atoms to the actinide cation, one ligand was detached so that the complex will maintain a coordination number of nine. For example, when nine water molecules were coordinated to Cm(III), a tenth water molecule is moved to the first solvation sphere of Cm(III). The coordination number for each of the three systems was shown to be nine, where Cm(III)-**A**₂ and Cm(III)-**B**₂ had an oxygen atom from a nitrate molecule become the ninth coordinated atom (**Figure 2.9**, bottom). Spectroscopic data of CyMe₄-BTBP

supported the coordination of a nitrate molecule to the Cm(III) center of the BTBP complexes.¹⁴¹ This observation could also entail a limitation of Cm(III) to typically have a maximum coordination number of nine in solution.

Since there was agreement between experimental and computed stability constants, three different BTBP ligands that have been synthesized¹⁴⁵ were tested alongside of CyMe₄-BTBP for Cm(III), Ac(III), and Th(IV). Our aim was the evaluation of structural similarities and the prediction of the stability constant using methanol as a solvent at 25°C. We have applied the methodology that was described in the previous section and provided accurate results for CyMe₄-BTBP. These four ligands are shown in **Figure 2.10**, with the binding site being emphasized by red nitrogen atoms. Each ligand was evaluated based on the generalized form of (R2-12), (R2-13), where x is the number of nitrate molecules that give a total charge of 0, using a 2:1 ratio of ligand ($n = 2$) to actinide nitrate.



The stability constant values ($\log\beta$) for all of the systems are demonstrated by **Figure 2.11**. Initial observations from this plot demonstrated that Th(IV) is unfavorable for extractions with these four ligands, which was expected considering the harder acid nature of Th(IV) as opposed to the trivalent actinides. Also, all four ligands were predicted to be more favorable for the extraction of Cm(III) over Ac(III). Based on these results for the trivalent actinides, CyMe₄-BTBP was shown to be the best extractant for both. For the functionalized BTBP ligands, **BTBP-II** was shown to be the second best extractant for Cm(III), with a $\log\beta$ of 10.89, but less applicable for Ac(III) ($\log\beta$ of 1.88). **BTBP-I** was shown to be the second best extractant for Ac(III), with a $\log\beta$ of 4.51, while it showed lower performance for Cm(III) ($\log\beta$ of 7.16). **BTBP-III** was shown to be the least favorable extractant for Ac(III), with a $\log\beta$ value of 1.82 and the third best extractant for Cm(III) being 8.87. Therefore, we conclude that if a selective extraction is desired for a Cm(III) and Ac(III) mixture, **BTBP-II** should be preferred due to the $\Delta\log\beta = 9.01$ between the two radionuclides, which is a difference of approximately $-12.29 \text{ kcal mol}^{-1}$.

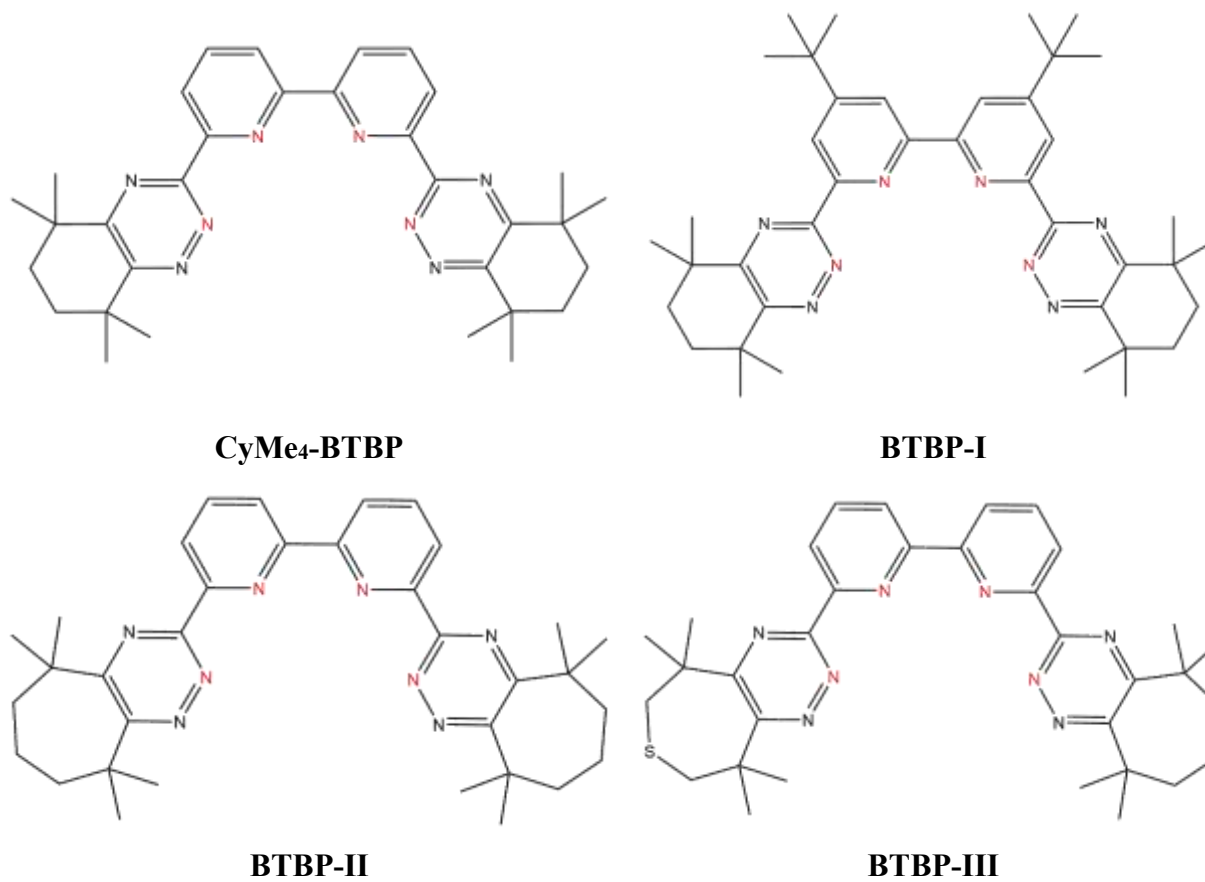


Figure 2.10. BTBP ligands used for the prediction of 2:1 ligand to actinide interactions for Ac(III), Th(IV), and Cm(III) nitrates. CyMe₄-BTBP is included here for reference.

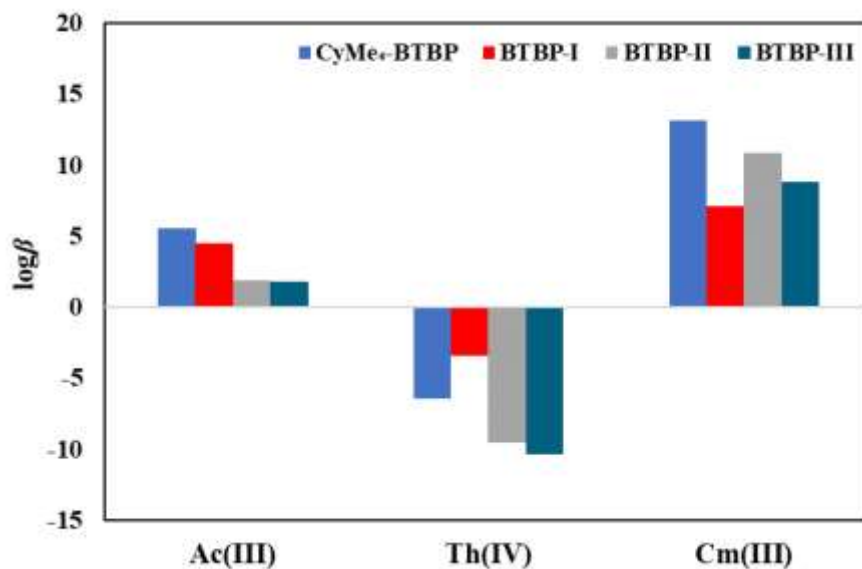


Figure 2.11. The computed $\log\beta$ for the prediction of what should be expected upon experimental analysis using the same protocol used for the BTBP ligands studied. The $\log\beta$ value for Cm(III) and CyMe₄-BTBP has been compared with the experimental value in methanol and shown to be within experimental accuracy. All reactions shown were for the 2:1 ratio with methanol as the solvent.

2.4. Summary of Key Results

In this article, we present computational findings from quantum chemical calculations on the actinide coordination in organic and aqueous phases. Our work is organized into three sections. In the first, actinide ligation with varying nitric acid environments was considered, where different coordination of H₂O, NO₃⁻ and H₂O/NO₃⁻ mixtures to Ac(III), Th(IV), Am(III), and Cm(III) were examined. Observations from this study were in agreement to crystal structures including the favorability of Cm(III) and Am(III) to coordinate with nine water molecules while Th(IV) preferred a coordination environment of ten H₂O molecules. In a nitrate rich environment, our calculations showed higher stability of a hexa-ligated [Th(IV)(NO₃)₆]²⁻, which is in agreement with experimental structures. We also computed actinide complexes with mixed nitrate-water ligands which showed higher stability than a purely aqueous coordination sphere, and more accurate stability constants than starting complexes with only nitrates. From the first section of this work, we concluded that mixed nitrate-water ligated actinide complexes can serve as starting point for the computation of stability constants upon coordination of actinides with organic chelators.

We then focused on the computational evaluation of experimentally determined log β values related to ligand-based separation and capture in the aqueous phase by 343HOPO. As in the first step of this project, we considered actinides with different coordination environments (H₂O, NO₃⁻ and H₂O/NO₃⁻ mixtures) as starting reactants. By screening a variety of different possible reactions, we identified two cases which are in good agreement with experimentally refined values. These cases are (R2-6) and (R2-7) and (R2-11), three reactions but two cases since (R2-6) and (R2-7) are similar reactions just specific to Th(IV) and the trivalent actinides, respectively. We highlight first the results for the trivalent actinides reporting differences from (R2-7) first then (R2-11). For Ac(III), the differences between the computational stability constants and experimental were 4.60 and 0.86, Am(III) was 4.43 and 0.09, and Cm(III) was 4.72 and -0.42. Less accurate results were found for Th(IV) with differences from (R2-6) being -12.00 and (R2-11) -9.39. To further assess the effect of the selected density functional on these results, we evaluated the accuracy of 8 common functionals which helped us justify the choice of BP86.

In the third section, we evaluated two organic phase ligands (*t*-Bu-C2-BTBP, CyMe₄-BTBP) and their ability to coordinate Cm(III). Overall, our computed stability constants are

consistent with experimentally determined values, where our results indicate that all ligands extract Cm(III) in a 2:1 ratio. We then considered three variants of the BTBP ligand scaffold (**BTBP-I**, **BTBP-II**, and **BTBP-III**) with the aim to predict their stability constants and guide future experimental work on the optimization of organic phase extractions for trivalent actinides. From this short-scale ligand screening, we concluded that all ligands showed lower stability constants for the trivalent actinides when compared to the parent CyMe₄-BTBP ligand. However, a remarkable reduction of the $\log\beta$ value was found for the Ac(III)-**BTBP-II** (from 5.62 to 1.88) which is disproportional to the Cm(III)-**BTBP-II** (from 13.14 to 10.89). Considering that the computed $\log\beta$ value for Ac(III) is close to zero, the **BTBP-II** ligand forms an interesting target for future experimental and computational examination for extraction between trivalent actinides. In addition, this study forms the base for large-scale computational screening of ligand libraries for the treatment of nuclear waste which are currently underway in our research group.

Chapter 3 Ligand Design for ^{227}Ac Extraction by Active Learning and Molecular Topology

“What we observe is not nature itself, but nature exposed to our method of questioning.” -Dr. Werner Karl Heisenberg

Disclosure: The following chapter is the current manuscript to be submitted in Fall 2024. All of this work was performed by myself under the guidance of Dr. Konstantinos D. Vogiatzis.

3.1. Introduction

Targeted α -therapy (TAT) is a promising radiotherapeutic technique for the treatment of various cancers.¹⁴⁶⁻¹⁵³ The effectiveness of TAT is due to the high linear energy transfer ($50\text{-}230\text{ keV}\cdot\mu\text{m}^{-1}$)^{146, 154} and the short path lengths ($50\text{-}100\text{ }\mu\text{m}$)¹⁴⁶ of α particles (^4He nucleus) allowing for the destruction of cancer cells in a confined region leaving healthy cells relatively unaffected.^{146, 147, 150, 154} There are, however, only a select few α -emitters that are able to be used for TAT since the α -emitters need a half-life sufficient enough to be effective and cannot contain daughters that emit γ rays but ideally contain daughters that also emit α particles.¹⁵⁵ Of the acceptable radioisotopes for radiopharmaceutical applications, ^{223}Ra ($t_{1/2} = 11.4\text{ d}$),^{146, 150, 152, 156} ^{224}Ra ($t_{1/2} = 3.6\text{ d}$),^{154, 155} ^{225}Ra ($t_{1/2} = 14.9\text{ d}$),¹⁵⁴ and ^{225}Ac ($t_{1/2} = 9.9\text{ d}$)^{146, 147, 151, 154, 155} are of interest due to their origination from ^{227}Ac ,¹⁵⁷ the longest living, naturally occurring actinium isotope ($t_{1/2} = 21.77\text{ y}$) being a great-granddaughter of ^{235}U .^{148, 158} Indeed, the first and only radioisotope currently approved by FDA is ^{223}Ra in the form of $^{223}\text{RaCl}_2$ (Xofigo, Bayer HealthCare Pharmaceuticals)¹⁵⁶ for the treatment of prostate cancer. This radioisotope is known to be produced through the isolation of ^{227}Ac and ^{227}Th .¹⁵⁹ The radioisotope ^{225}Ac is also a promising α -emitter since the daughters of ^{225}Ac are also all α -emitters, allowing for increased radiation dosage to the cancer cells.^{146, 160, 161} However, one of the major hindrances with the implementation of TAT is with the supply of α -emitting radioisotopes.^{149, 154, 160, 161}

Isotope production for TAT applications is a growing industry, such as the ^{225}Ac generation by BWXT Medical Ltd. to supply Fusion Pharmaceuticals Inc. to advance their FPI-2265 program that would be the first actinium-based radiopharmaceutical treatment for the

prostate-specific membrane antigen (PSMA) available commercially.^{162, 163} The production of ^{225}Ac from Fusion Pharmaceuticals Inc. comes from β^- -decayed ^{225}Ra , which is an α -decay product of ^{229}Th ($t_{1/2} = 7932\text{ y}$).^{162, 163} A thorium generator was recently constructed at the Canadian Nuclear Laboratories for the isolation of ^{225}Ac .¹⁵⁴ This generator takes historic stock supplies of ^{233}U , a strictly regulated radioisotope, that contains daughter ^{229}Th , great-granddaughter ^{225}Ra and great-great-granddaughter ^{225}Ac and selectively isolates the radioisotopes using anion exchange resin separations by milking the separated ^{229}Th , that was extracted from ^{233}U , acquiring ^{225}Ac and ^{225}Ra which can then be separated using ion exchange chromatographic resins in a nitric acid medium.¹⁵⁴ This process of removing ^{225}Ac and other radioisotopes from ^{229}Th that originated from ^{233}U sources using ion exchange chromatographic resins in a process known as “milking the thorium cow” that was developed at Oak Ridge National Laboratory (ORNL) is a well-established method for the acquisition of ^{225}Ac for TAT.^{151, 152, 160} A similar process as the thorium generator at the Canadian Nuclear Laboratories is utilized at the High Flux Isotope Reactor (HFIR) at ORNL in Oak Ridge, TN for the production of ^{229}Th .¹⁴⁹ The production of ^{229}Th is accomplished through the neutron bombardment and inevitable transmutation of ^{226}Ra through the following nuclear reaction: $^{226}\text{Ra}(n, \gamma)^{227}\text{Ra}(\beta^-, t_{1/2} = 42\text{ min})^{227}\text{Ac}(n, \gamma)^{228}\text{Ac}(\beta^-, t_{1/2} = 6.2\text{ h})^{228}\text{Th}(n, \gamma)^{229}\text{Th}$.¹⁴⁹ This process also demonstrated that there was an increase in ^{228}Th yield and a decrease in uncertainty when ^{227}Ac was used directly as a neutron bombardment source due to decreased neutron capture by other radioisotopes.¹⁴⁹ The ^{223}Ra isotope is generated from α -decay of ^{227}Th ($t_{1/2} = 18.7\text{ d}$) which is a β^- -decayed daughter of ^{227}Ac .^{148, 152} Each of these processes utilize the ^{227}Ac radioisotope whether directly from legacy sources or from the transmutation of ^{226}Ra , however, each of the radioisotopes previously mentioned have ^{227}Ac as a parent nuclide emphasizing the focus of this study on ^{227}Ac extraction.

An alternative method for the extraction of actinide(III) radioisotopes is by solvent-based extraction with 6,6'-bis(1,2,4-triazin-3-yl)-2,2'-bipyridine (BTBP, **Figure 3.1A**) ligands.^{13, 16, 18, 116, 141, 164} These ligands were designed for the selective extraction of trivalent actinides over trivalent lanthanides from a nitric acid medium.^{16, 18} They were also designed to be more resistant to radiation degradation than the 2,6-bis(1,2,4-triazin-3-yl)-pyridine (BTP) ligands.¹⁸ The BTBP ligands coordinate to trivalent actinides in a 1:2 (actinide-to-ligand) ratio with instances of

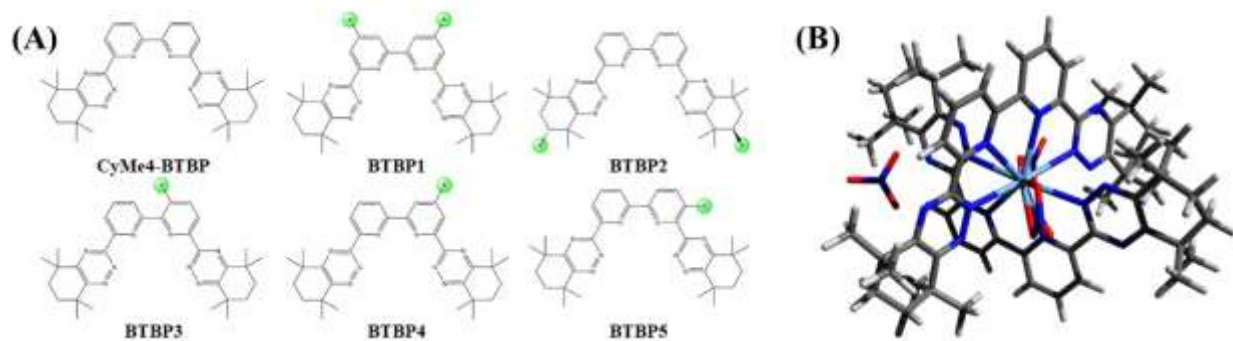


Figure 3.1. A) The reference **CyMe₄-BTBP** ligand and the five analogs labeled **BTBP1 - BTBP5** considered in this study. Nitrogen atoms in blue font demonstrate the coordination sites of the BTBP ligands, R groups represent the substitution position(s) of the molecules. **B)** Optimized geometry of the $[\text{Ac}(\text{CyMe}_4 - \text{BTBP})_2(\text{NO}_3)_2]^+ \text{NO}_3^-$ coordination complex. (color code: light blue = Ac(III), red = O, blue = N, grey = C, and white = H).

extractions in nitric acid solution possessing a coordinated nitrate ligand in the inner coordination sphere with the remaining charge balancing nitrates in the outer solvation sphere of the coordinating complex (**Figure 3.1B**).^{18, 141, 165} Extractions with selected BTBP complexes have been shown to be diluent dependent and importantly, structurally dependent. For example, extractions with 6,6'-bis(5,6-dipentyl-[1,2,4]triazin-3-yl)-[2,2']bipyridine (C5-BTBP) were shown to be dependent upon the utilized diluent showing an increase in the distribution ratios between Am(III) and Eu(III) with an increase in dielectric constant of the diluent.^{18, 166} Likewise, 6,6'-bis(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-benzo-1,2,4-triazin-3-yl)-2,2'-bipyridine (or **CyMe₄-BTBP**, in short), the current trivalent actinide/lanthanide extraction European reference ligand,¹⁶⁷ when used for extraction in 1-octanol/kerosene and 1-octanol of Am(III) and Eu(III) were shown to indeed selectively extract Am(III) over Eu(III). Unfortunately, the kinetics of these extractions were shown to be inadequate to justify industrial applications.^{18, 168} Structural modifications of BTBP ligands plays an important role in optimization of actinide extractions.¹⁸ As an example, Cm(III) and Eu(III) extractions were evaluated with **CyMe₄-BTBP** in methanol/3.3 mol% water using TRLFS¹⁴¹ which demonstrated conditional stability constants ($\log\beta$) of 12.4 ± 0.3 and 11.3 ± 0.3 , respectively, while C5-BTBP in 1-octanol/water/0.04 M nitrate using TRLFS^{18, 169} was shown to be 10.8 ± 0.6 and 9.4 ± 0.4 , respectively. Another study focused on the synthesis of two BTBP molecules (Cl-CyMe₄-BTBP and Br-CyMe₄-BTBP) with the halogen substituted on the *para* carbon with respect to the coordinating nitrogen atom on one of the bridging pyridine groups¹³. Comparing the behavior of both of these ligands to each other for Am(III) separations from Eu(III) demonstrated a maximum separation factor^{15, 141} of 124 ± 12 and 112 ± 11 at 3 M HNO₃ for Cl-CyMe₄-BTBP and Br-CyMe₄-BTBP, respectively.¹³ This demonstrates that small structural changes in the functionalization of BTBP ligands can have significant changes towards the binding affinity of the BTBP ligands to actinides (actinium in this study) and the need to have a protocol for the screening of thousands of different BTBP ligands for evaluation can be vital towards separation optimization and ligand discovery.

Since current industrial processes utilize ligands, in the form of resins, for the selective separation of Ac(III) from a mixture of different isotopic quantities of Th(IV) and Ra(II) dissolved in nitric acid, solvent-based extractions methods have the potential to selectively separate Ac(III) from a mixture of impurities by utilizing highly selective BTBP ligands in the organic phase for Ac(III) separations while utilizing a masking agent that can be used to reduce

divalent impurities (such as Ra(II))¹⁸ from being extracted or a secondary ligand, such as the hydroxypyridinonate 3,4,3-LI(1,2-HOPO) ligand,²⁵ that can be used to selectively extract tetravalent impurities (such as Th(IV)). Indeed, one such ligand utilized in resin-based extraction is N,N,N',N'-tetraoctyl diglycolamide (TODGA)^{154, 161} ligand which has been explored in solvent-based separation processes with **CyMe4-BTBP** for SANEX applications.^{18, 170} Utilizing solvent-based extractions as an alternative method for the extraction of ²²⁷Ac could reduce the number of processes providing a simpler extraction process that can assist in the development of novel methods for extracting trace amounts of Ac found in the ocean,¹⁷¹ uranium ore during the uranium processing stage instead of leaving it to decay, and from nuclear waste.⁷ This would be advantageous for assisting in an increase in radioisotope supply for applications in targeted radiotherapy.

Artificial intelligence and machine learning (ML) methodologies have shown promise in the analysis and prediction of actinide properties and rare-earth element separations.⁴⁵⁻⁵⁵ A recent study utilized ML to make thermochemical binding predictions from computational data of La(III) and Ac(III) with carboxylic acids.⁵⁵ More specifically, this study utilized supervised ML methods based on decision tree regression to predict ΔG_{rxn} values for the complexation of La(III) and Ac(III) with carboxylic acids by using Coulomb matrices of the coordinated complexes with inner shell coordination of solvent molecules (water). The most accurate results acquired in this study, in terms of mean absolute error (MAE), derived from the XGBoost¹⁷² method resulting in an MAE of 6.93 kcal mol⁻¹.⁵⁵ Overfitting was observed in all the ML models trained in this study, which was hypothesized to be reduced upon the addition of a larger dataset. Liu and coworkers developed ML models for the prediction of log*D*, which is the logarithm of the distribution ratio, acquired from experimental analysis for La(III) separations.⁵³ This study utilized fully connected neural networks with the extended-connectivity fingerprints¹⁷³ and a descriptor input vector extracted by RDKit¹⁷⁴ for the individual ligands and the log*D* values with their respective experimental conditions such as temperature and concentration as examples, as inputs for the neural network. From this study, they were able to acquire a MAE of 0.34 and a root mean square error of 0.53 for their validation set.⁵³ Both studies have specific limitations but are relevant to our study as we aim towards thermochemical predictions based on the structure of the ligand to generate a simple method for screening unexplored ligands for ²²⁷Ac extractions.

The present study explores ^{227}Ac extractions using **CyMe₄-BTBP**-based variants as an alternative to current industrial processes and provides a general methodology for BTBP-based ligand discovery and design through scalar relativistic density functional theory (DFT) and ML. The workflow for this study is graphically illustrated by **Figure 3.2** which highlights the three major sections that are presented and discussed: calibration, model development, and impact of the ML results. Application of active learning enabled an extended and reliable screening of thousands of unexplored functionalized BTBP analogs. The interpretability of the ML methodology presented here, as well as its transferability to functionalized **CyMe₄-BTPhen** ligands, is discussed.

3.2. Computational Details

3.2.1. Molecular Structure Database

A molecular library that includes five BTBP analog ligand classes used for functionalization to use for data generation and machine learning analysis was generated by using molSimplify¹⁷⁵ that applies OpenBabel^{176, 177} in the backend to create molecular substitutions. The substitutions were made at symmetrical and asymmetrical positions of a parent structure (**CyMe₄-BTBP**) creating five uniquely substituted BTBP molecule types (**Figure 3.1A**). This was done by using a semi-automated refinement of the GDB8 database (subspace of the GDB11).^{178, 179} Each GDB8 entry is represented as a SMILES string. For example, structures that began with a F atom were excluded, since a terminal fluorine cannot coordinate to a heavy metal. Thus, a total of 350,875 unique BTBP molecules were generated for this study. The distribution of the composition for the functional groups used for ligand substitution of the BTBP analogs are demonstrated by **Table 3.1** where H atoms are excluded. Note that the sum of these generated ligands is not the sum of the total database by one ligand and that is simply due to the unsubstituted **CyMe₄-BTBP** ligand not being included.

Since the creation of the coordination complexes for Ac(III) with the individually functionalized BTBP molecules would be an arduous task, the same protocol was utilized for the creation of the Ac(III) 1:2 ratio BTBP complexes but with a pre-optimized $[\text{Ac}(\text{CyMe}_4 - \text{BTBP})_2(\text{NO}_3)_2]^+ \text{NO}_3^-$ (shown in **Figure 3.1B**). The same molecular substitutions were used for the two BTBP molecules shown in this complex as those from **Figure 3.1A** creating coordination

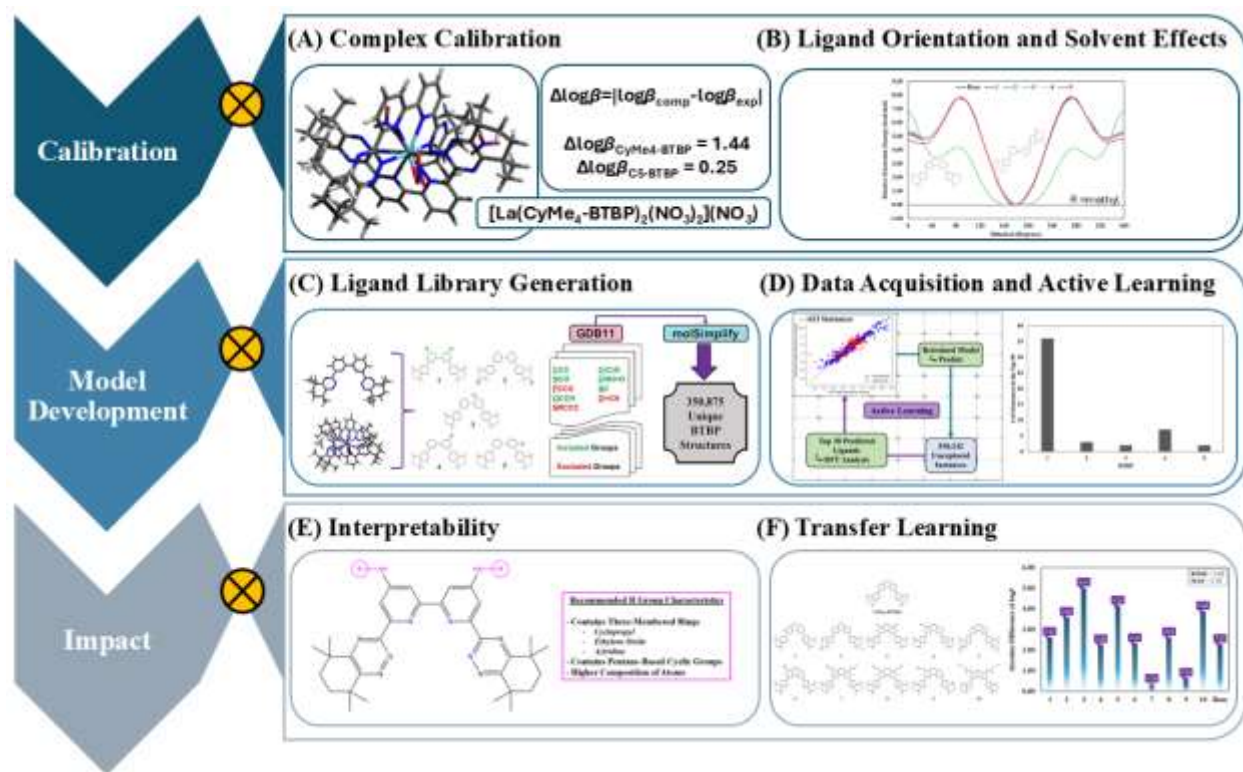


Figure 3.2. Schematic overview of the individual steps considered in this study. The methodology calibration includes (A) examination of the coordination complex with the assistance of experimental data and (B) the orientation and solvation effects of the BTBP analogs using dihedral rotations with methyl groups as substituents. The model development focuses on (C) the generation of the ligand library that were used for this study and (D) the collection of stability constants ($\log \beta$) for the initial dataset used for training the machine learning algorithm. The active learning process enabled us to augment the training dataset by taking the top 30 performing ligands as predicted by ML and computing their respective $\log \beta$ value. The model's impact is evaluated based on (E) the interpretability from the ML results to provide targeted functional groups that were computationally predicted to improve ^{227}Ac complexation and (F) transfer learning where predictions were made on eleven **CyMe₄-BTPhen** ligands using ML algorithms trained with BTBP ligands.

Table 3.1. Distribution of Functional Group Scaffold Composition used for Ligand Generation

Atoms	1	2	3	4	5	6	7	8
Ligands	20	35	90	340	1,525	7,995	46,096	294,773

complex counterparts to the individual BTBP molecules for further DFT calculations.

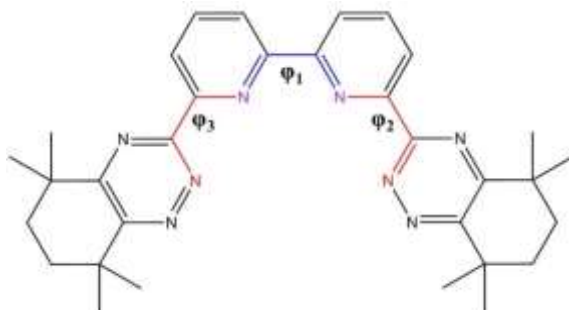
3.2.2. Ligand Orientation - Calibration

Dihedral analysis was accomplished by using the built-in scan function in ORCA 5.0^{108, 109, 120} to investigate the energy barriers of the different conformers of the **CyMe₄-BTBP** molecule and the BTBP analogs from **Figure 3.1** using methyl as the substituent. The energy barrier analysis utilized water, methanol, 1-octanol, and kerosene as solvents to show solvation effects on the organization and energy barriers of the BTBP ligands.^{16, 164, 180} These energy barriers were calculated with respect to the most stable conformer (lowest electronic energy). **Figure 3.3A** demonstrates the dihedral angles investigated in this study. The dihedral angle ϕ_1 was used for **CyMe₄-BTBP** as well as the methyl substituted BTBP ligands to investigate the steric effects between the transitions between the *ctc* (cis, trans, cis) and the *ccc* conformers (**Figure 3.3B**). The dihedral scan was performed with 10° intervals from 0° to 360° making 37 conformers of each ligand. An additional analysis was conducted for **CyMe₄-BTBP** which took each ϕ_1 conformer, fixed the dihedral, and did 37 scans at 10° intervals from 0° to 360° for ϕ_2 producing the *cct*, *ctc*, *ctt*, and *ccc* excluding the *ttt* and *tct* conformations. Further analysis was conducted by taking the minimum *ctt* and *cct* conformers along the path towards the most favorable *ccc* conformer of each potential energy surface and rotating the previously unrotated 1,2,4-triazine group (ϕ_3) by 180° at 10° intervals starting at 0° to analyze all possible BTBP conformers and acquire the full energy profile of each BTBP.

3.2.3. Quantum Chemical Calculations

Density functional theory (DFT) computations were performed with the ORCA 5.0 quantum chemistry package^{108, 109, 120} which allows the incorporation of scalar relativistic effects using the zeroth-order regular approximation (ZORA)¹²¹ and the segmented all-electron relativistically contracted (SARC)¹²² basis sets. The conductor-like polarizable continuum model (CPCM)¹²³ was utilized for the incorporation of solvation effects using the built in solvents methanol, 1-octanol, and water. For kerosene, the dielectric constant and refractive index used were 1.998 and 1.44, respectively.¹⁸¹ All molecular geometry optimizations used the BP86^{124, 125} density functional with the SARC-ZORA-TZVP¹²² basis set for Ac(III)/La(III), both with a closed-shell electronic structure, and the ZORA-def2-SVP^{126, 127} basis set for all other atoms. Each

(A)



(B)

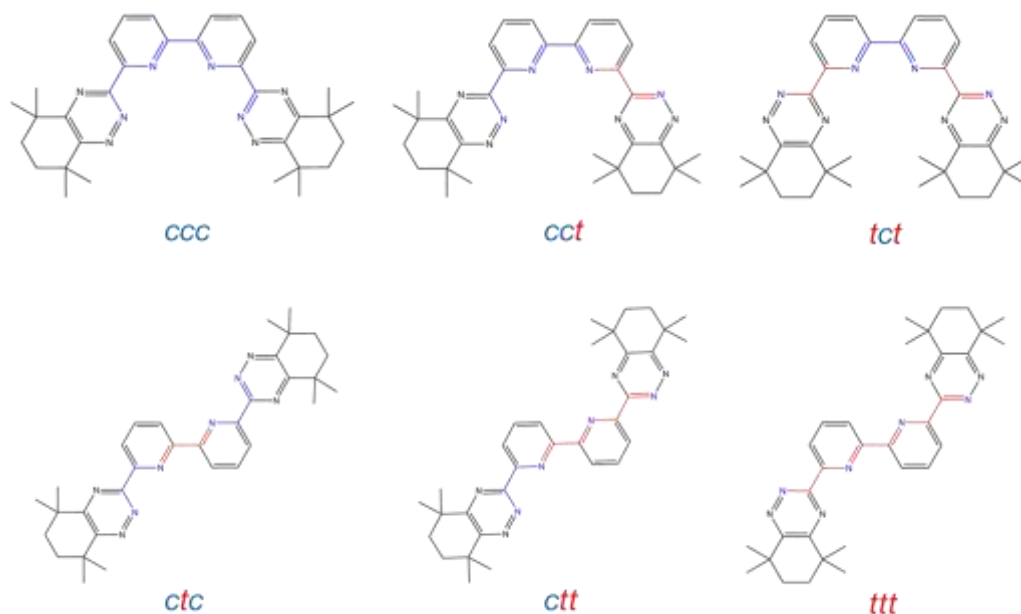
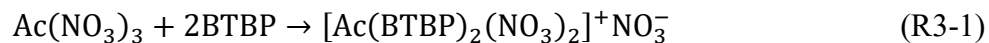


Figure 3.3. A) Labelled dihedral analysis for the BTBP ligands with CyMe₄-BTBP as an example. ϕ_1 (blue) shows the dihedral angle used for the rotation of the 2,2'-bipyridine group while the ϕ_2 and ϕ_3 (red) shows the dihedral angle for the rotations about the connecting dihedral between 2,2'-bipyridine and 1,2,4-triazine groups. B) The six different conformers for the CyMe₄-BTBP ligand. The cis conformations are color coded as blue and the trans are red.

calculation also utilized the resolution of identity for the calculation of the two-electron integrals with the SARC/J auxiliary basis set. The quasi-harmonic approximation was used to compute the Gibbs' free energy at 298.15 K by the addition of the zero-point energy with the thermal vibrational-rotational entropies of the lowest-energy conformers. This methodology has been used in our previous studies which proved to provide good agreement between computed and experimentally determined stability constants of Cm(III) ligation with **CyMe4-BTBP** and *t*-Bu-C2-BTBP.^{182,128}

Automated data curation was mandatory to screen the large number of calculations performed for this project. Any calculations that failed due to poor starting geometry or that finished but contained negative frequencies below -50 cm^{-1} were filtered out of the usable structures for thermochemical analysis. The Gibbs' free energy values were utilized for the calculation of $\log\beta$ at a specific temperature T using (3-1).^{18, 119} The reaction used for this study for both Ac(III) as determined by the complexation calibration with La(III) is shown in (R3-1).

$$\Delta G = -2.303RT \log \beta \quad (3-1)$$



3.2.4. Machine Learning

The machine learning input vectors utilized molecular descriptors of the individual BTBP ligands by using persistence homology^{183, 184} coupled with the smooth overlap of atomic positions (SOAP).^{185, 186} This involved the generation of persistence images (PIs) by the vectorization of persistence diagrams to incorporate ligand topology as the input vectors. Utilizing persistence homology for machine learning in chemistry has been used by previous studies^{187, 188} and shown to be an effective descriptor for regression. This study utilized Ripser¹⁸⁹ for the generation of persistence images (PIs) that include connected components, 1- (holes), and 2-dimensional (voids) homological descriptors by generating 100×100 square persistence images with a standard deviation of the Gaussian kernel (spread) of 0.009, an upper boundary of the PIs of 2.5 Å, and a lower boundary of the PIs of -0.1 Å. The SOAP descriptor used the positions of the H, C, N, O, and F atoms present for each individual structure and constructed the descriptor with a local region cutoff value of 4 Å, 6 radial basis functions, a maximum degree of spherical

harmonics as 4, and set the output as a dense array as opposed to a sparse matrix. The persistence images coupled with the SOAP (SOAP+PI) for each ligand were used as the input vector with their respective $\log\beta$ values as y for Random Forest Regression as implemented in the Scikit-learn package¹⁹⁰ using Python 3.10. The ML model utilized a 5-fold cross validation process with 200 trees, the mean absolute error loss function criteria, and six minimum samples per leaf for the analysis. The root-mean-squared error was also calculated for each fold with the standard deviation of the error.

3.3. Results and Discussion

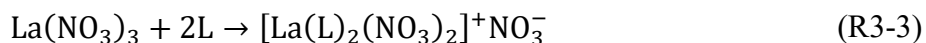
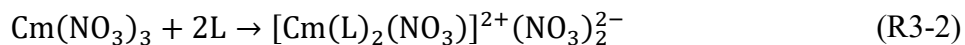
3.3.1. 6,6'-bis(1,2,4-triazin-3-yl)-2,2'-bipyridine Ligand Library Generation

The aim of this study was the effective prediction of $\log\beta$ values for more than 350,000 molecular units by using only the BTBP ligand geometries and without performing expensive geometry optimization of the full complex (2:1 ratio between the ligand and actinide cation). This was achieved by using DFT-generated data from a small subset of the full ligand library. In particular, a ligand library of 350,875 unique molecular structures were generated (see Computational Details). Each class of atom size functional groups with respect to SMILES strings has approximately equal amounts of **BTBP1-5** generated. Hereafter, when discussing the atom size of a functional group it will be implying the size of the SMILES string which excludes the hydrogen atoms. The five different families that were used for the generation of the ligand library included two families that were symmetrically functionalized and three that were asymmetrically functionalized. The two symmetrical families involved the functionalization of the *para* sites of the 2,2'-bipyridine unit of the **CyMe₄-BTBP** scaffold with respect to the coordinating N atoms (**BTBP1**), and the functionalization of the lower C atom that is positioned between the tetramethyl substituted cyclohexene unit of the scaffold (**BTBP2**). The asymmetric functionalization included the single substitution of one side of the 2,2'-bipyridine portion of the **CyMe₄-BTBP** scaffold by substitution of the *meta* site with respect to the coordinating N atom closest to the other half of the 2,2'-bipyridine group (**BTBP3**), substitution of the *para* site (**BTBP4**), and substitution of the other *meta* site, which is closest to the 1,2,4-triazine group of the BTBP scaffold (**BTBP5**).

3.3.2. Ligand Orientation and Complexation Calibration

Before the generation of the necessary data, we first wanted to determine the most stable conformation of the BTBP ligands and the Ac(III) complexation with BTBP. The most probable Ac(III) complexation was determined by using La(III) for select ligand complexation analysis due to its chemical similarity to Ac(III).^{55, 191} This was accomplished by taking known experimental $\log\beta$ values of La(III) ligation since, to the best of our knowledge, Ac(III) has no known experimental $\log\beta$ values for these systems. This calibration allowed us to make inferences about the expected performance of Ac(III) ligation with BTBP ligands.

Table 3.2 demonstrates experimental $\log\beta$ values for the 1:2 ratio of Cm(III) (from our previous study,¹⁸² shown here for comparison) and La(III) using different BTBP ligands. The $\log\beta$ values were computationally determined from the chemical reactions (R3-2) and (R3-3) for the complexation with Cm(III) and La(III), respectively (L represents the BTBP variants). We note that the predicted $\log\beta$ values for La(III) were overall in better agreement with the experimental values than the Cm(III) values. Thus, we infer that due to the chemical similarity between La(III) and Ac(III), that the $\log\beta$ values from our computational protocol should provide reasonable agreement with the actual value from future experiments.



We then used computationally determined stability constants and electronic energies to evaluate the trends from rotations about dihedral angles of **CyMe4-BTBP** as well as substituted **CyMe4-BTBP** analogs. The full dihedral rotation study discussion can be found in the supporting information of our publication and our key findings are summarized here. First, we evaluated the $\log\beta$ associated with Ac(III) ligation with each BTBP analog (**Figure 3.1A**) using methyl as the substituent and then computed the energy barrier between all BTBP conformations of the individual analog to compare thermodynamic favorability with respect to the rotational barriers. Analysis of the computed $\log\beta$ for these analogs demonstrated the following trend from most favorable to least favorable: **CyMe4-BTBP** > **BTBP2** > **BTBP4** > **BTBP1** > **BTBP5** > **BTBP3**. Comparison of the $\log\beta$ values with respect to the energy barrier of the BTBP analogs

Table 3.2. Selected Experimental Stability Constants Compared to Computationally Determined Stability Constants for Cm(III) and La(III) Ligation with BTBP Ligands.

Structure	M(III)	Experimental $\log\beta$	Computed $\log\beta$	$\Delta\log\beta$
<i>t</i>-Bu-C2-BTBP	Cm	11.1 ± 0.15^a	14.52^d	3.42
CyMe₄-BTBP	Cm	12.4 ± 0.3^b	13.14^d	0.74
	La	8.8 ± 0.1^c	10.24^e	1.44
C5-BTBP	La	10.0 ± 0.3^c	9.75^e	0.25

^a From reference (15)

^b From reference (141)

^c From reference (192)

^d From reference (182)

^e This work

demonstrated that the thermodynamic stability constants are dependent upon the coordination complex itself and are not affected by complexation kinetics that are dependent upon the organizational penalty. This phenomenon was observed experimentally when comparing the experimentally determined $\log\beta$ for La(III) with the formation rate constant, which was too rapid of a reaction to acquire interpretable results for **CyMe₄-BTPhen**, whereas **CyMe₄-BTBP** was measured to be $70.5 \pm 0.8 \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$ with the stability constants for **CyMe₄-BTBP** (8.6 ± 0.2) and **CyMe₄-BTPhen** (8.5 ± 0.2) in acetonitrile showing only a difference of 0.1 for these relatively similar ligands.¹⁷

To elucidate the solvation effects on the selective complexation between Ac(III) and La(III), the separation factor (SF) for La(III)/Ac(III) ligation using **CyMe₄-BTBP** was evaluated since it has been shown experimentally that the SF increases with decreasing relative permittivity of the solvent when analyzed with Am(III)/Eu(III) separations.¹⁶ We also chose to compare Ac(III) with La(III) as the separation between these two radionuclides would be the most challenging if La(III) is present in an analyte with Ac(III). The $\text{SF}_{\text{La(III)/Ac(III)}}$, the ratio of the $\beta_{\text{M(III)}}$ ¹⁵ values, was calculated using (3-2):

$$\text{SF}_{\text{A/B}} = \frac{10^{\log \beta_{\text{A}}}}{10^{\log \beta_{\text{B}}}} = \frac{\beta_{\text{A}}}{\beta_{\text{B}}} \quad (3-2)$$

Interestingly, the $\text{SF}_{\text{La(III)/Ac(III)}}$ was shown to have the opposite effect for the following $\text{SF}_{\text{La(III)/Ac(III)}}$ values with the solvent and their respective relative permittivity in parentheses: 5024.52 (methanol, 32.63), 1976.47 (water, 80.4), 793.32 (1-octanol, 10.3), and 2.58 (kerosene, 1.998). This inverse in the behavior demonstrated by Am(III)/Eu(III) separations can be summarized by stating that in general the SF decreases with decreasing relative permittivity between La(III) and Ac(III), however methanol was an exception providing the highest SF value out of the four solvents. Indeed, water, which has a higher relative permittivity value than methanol, resulted in a significantly smaller SF. This computational finding implies that for optimizing the SF between specific actinides and lanthanides requires solvent dependent investigations. These results also demonstrate that the commonly used kerosene in industrial

applications would be ineffective at removing Ac(III) from La(III) and instead methanol should be utilized since it possessed the highest SF value.

3.3.3. *Density Functional Theory Thermodynamic Data Collection and Analysis*

We began this study with the consideration of a small subset of 623 ligands evaluated with DFT from this library. We followed a bottom-up procedure where the initial data were collected from molecular geometries of BTBP variants with small functional groups, with the aim to develop ML models that predict properties of larger molecular structures. More precisely, we have utilized all BTBP variants with substituents consisting of 1, 2, 3, and 4 non-hydrogen atoms, together with a small subset of substituents with 5 non-hydrogen atoms. The total number of the selected ligands was 640. DFT computations were performed to determine the $\log\beta$ values of each ligand in this subset, but 17 computations were not completed successfully and were returned to the ligand library. Thus, a total of 623 DFT data were used for training in a ML algorithm for making predictions on the full ligand library (**Figure 3.4**).

A short analysis was carried out on the 50 molecular complexes with the highest computed $\log\beta$ values (out of the 623 total examined by means of DFT). We note some common features present in the functional groups of these top 50 ligands, such as 27 of the top 50 containing amine groups, 12 contain a hydroxyl group, 6 contain a cyclic group, and 4 contain a carboxyl group. These results demonstrated that the addition of polar groups increases the favorability for complexation with Ac(III) since only two ligands out of 50 contain nonpolar functional groups (cyclobutyl). We also identified the symmetrical **BTBP1** and the asymmetrical **BTBP4** ligand scaffolds as the more preferable functionalization sites. In both cases, the substituent is in the *para* site with respect to the coordinating nitrogen of the 2,2'-bipyridine group within the BTBP analog.

3.3.4. *High-Throughput Screening via Active Learning*

A major objective of this study was to provide the tools necessary for the screening of unexplored BTBP ligands for the prediction of reliable $\log\beta$ values. The computational workflow presented here avoids the explicit computation of each molecular complex (350,875 in total) by means of DFT and active learning, which can provide directions for the targeted synthesis of the next generation of BTBP-based ligands. For that purpose, we utilized the computational data

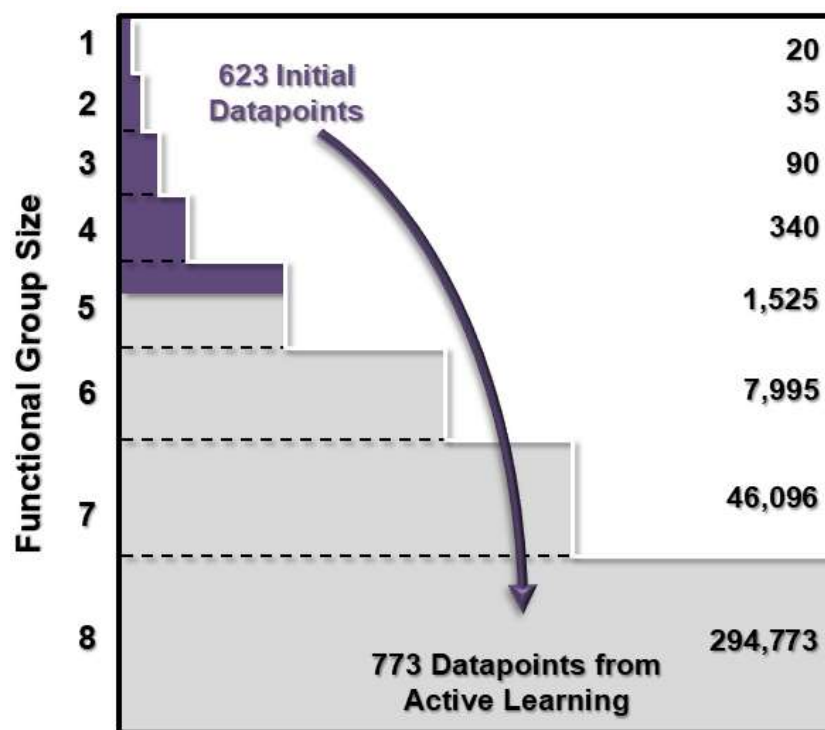


Figure 3.4. Schematic representation of the bottom-up active learning process followed in this study. An initial subset of 623 ligands with functional group size of 1, 2, 3, 4, and 5 non-hydrogen atoms was used as the initial set for ML model training (space shown in purple). Active learning steps systematically increased the training set with data from molecular units with larger functional group (5, 6, 7 or 8 non-hydrogen atom substituents). The number of ligands for each functional group size is given at the right (total of 350,874, the parent BTBP ligand is not included in this scheme), figure not in scale.

collected from the 623-ligand dataset and progressively increased the size of the ligand dataset in each active learning step (**Figure 3.4**). The active learning process includes the following phases: training, database screening, validation, data augmentation, and retraining. The model trained on the 623-ligand dataset was used for screening the unexplored 350,242 ligand dataset, and predicted $\log\beta$ values were obtained for each molecular unit.

The validation of these predictions was performed by using a *validation set* composed of 10 randomly selected structures from the remaining 350,252 unexplored molecules. Of these 10 BTBP ligands, six consisted of functional groups with an eight-atom scaffold, two contained seven, and two consisted of functional groups with a five-atom scaffold. Three of the BTBP ligands were members of the **BTBP1** analog, four were of the **BTBP2** analog, one from the **BTBP3** analog, and two from the **BTBP5** analog. We first optimized the geometry of all ten structures and then determined the $\log\beta$ values computationally to then be used as comparisons for the predictability of the trained algorithms on new ligands. Note that the validation set was kept unchanged during the active learning steps to track the performance and the increased accuracy of the retrained models (*vide infra*).

Data augmentation was performed by collecting the 30 ligands from the unexplored extended ligand library with the highest $\log\beta$ values, as those predicted by the trained ML model. Additional DFT geometry optimizations were performed for the full molecular complexes with these 30 additional ligands, new $\log\beta$ values were computed, and comparisons between the ML and DFT $\log\beta$ values were used as an additional control of the models' performance. The predicted $\log\beta$ values for each of the 10 molecules of the validation set with respect to the actual DFT values are shown in **Figure 3.5**, while the inset demonstrates the improved predictability as the training dataset increased from the initial 623-ligand instances to the 803-ligand dataset, after 6 active learning steps. The grey arrows show the shift of the predicted values during the active learning steps. For example, we identified three outliers that are located in the upper right region of the plot and have significantly higher DFT values ($\log\beta$ is 10 or higher). Surprisingly, these three cases belong to the **BTBP1** family of functionalized ligands. As the ML models are trained with more data (from 623 to 803), the model's accuracy is increased, as it is shown with the value shift towards the diagonal. We also note that similar behavior was found for the rest of the validation set. This resulted in an increase in predictability of approximately $4.45 \text{ kcal}\cdot\text{mol}^{-1}$

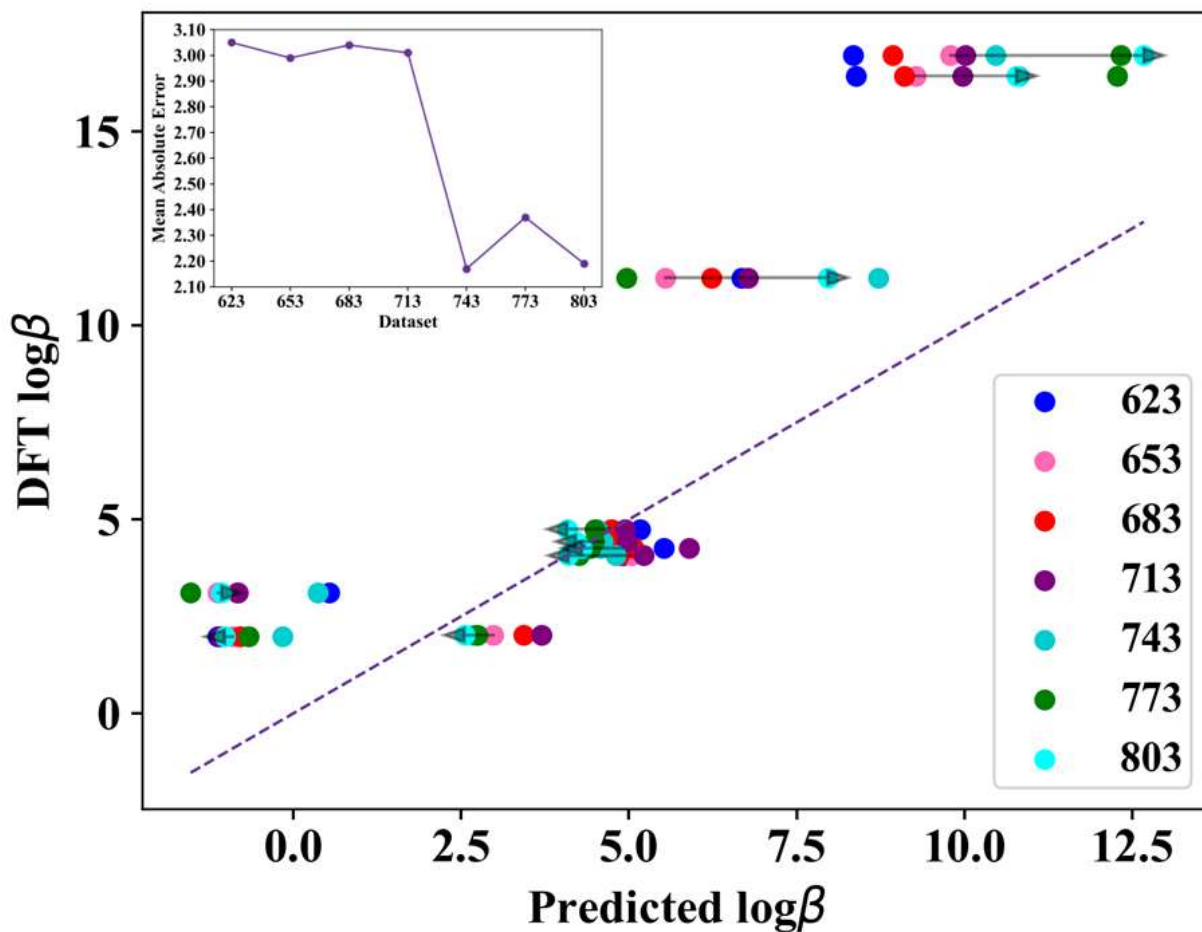


Figure 3.5. Parity plot between the DFT and the predicted $\log\beta$ values from the ML models trained during the data augmentation from active learning. The grey arrows demonstrate the evolution of the $\log\beta$ values during the active learning process. The inset graph demonstrates the learning curve of the 10-molecule validation dataset with respect to the mean absolute error of the predicted and DFT $\log\beta$ values starting from the initial 623-ligand dataset to the 803-ligand dataset with each of the active learning steps in between.

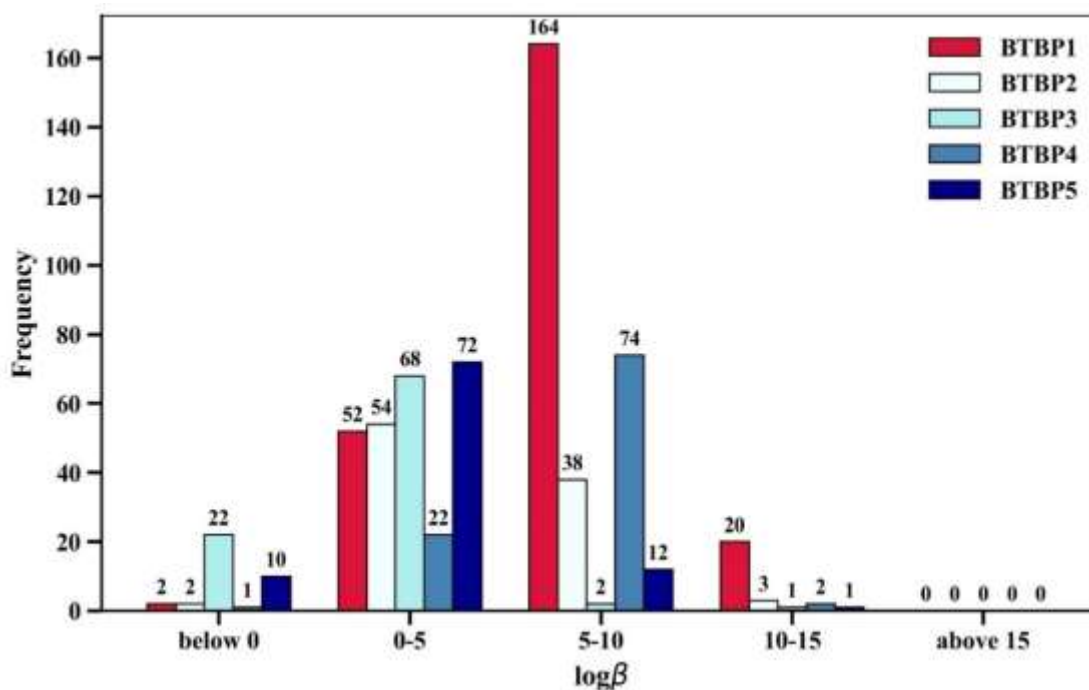
($\Delta\Delta\log\beta$ difference between the average of the upper 4 and lower 3 points of 0.78). The drop shown in the inset of **Figure 3.5** further demonstrates the improvement in the model with a $\Delta\Delta\log\beta$ value of 0.84 which equates to 4.79 kcal·mol⁻¹.

To further elucidate the predictability improvement during the active learning steps, we report the evolution of the data distribution, as we augmented the training set from 623 instances (**Figure 3.6**, top) to 803 instances (**Figure 3.6**, bottom). The 5 different families of ligands are organized into 5 groups based on their $\log\beta$ values, i.e. below 0, between 0-5, between 5-10, between 10-15, and above 15. We highlight that the distribution associated with the **BTBP1** analog demonstrated that before the inclusion of the active learning molecules, there were no reported $\log\beta$ values above 15, whereas active learning provided 27 **BTBP1** ligands above a $\log\beta$ value above 15. This assisted in improving the predictability of the *validation set* since the two significant outliers were both **BTBP1** analogs with stability constants above 15. We also note the increase in ligands with a $\log\beta$ value in the 10-15 range by 56 during the active learning process for the **BTBP1** analog. Thus, active learning helped the model to adapt and be trained on datapoints with higher $\log\beta$ values improving the validation set performance.

The active learning process also identified that symmetrically functionalized BTBP ligands significantly improve ²²⁷Ac complexation (**BTBP1** and **BTBP2** families). From the 623 ligands of our initial dataset, 20 **BTBP1** and 3 **BTBP2** variants had a $\log\beta$ value above 10, while after the four active learning steps, these numbers increased to 103 and 7 variants from the **BTBP1** and **BTBP2** families, respectively. The top-10 performing ligands discovered by active learning are presented in **Figure 3.7**. All ligands are symmetrical, they belong to the **BTBP1** family and contain functional groups that are bonded to the BTBP scaffold through a nitrogen (with the exception of ligand 664 that is connected through a carbon atom). Additional observations include that these ligands contain (a) cyclic functional groups (ligands 769, 785, and 792 are exceptions), (b) at least one double bond (ligands 774 and 795 are exceptions), and (c) contain polar functional groups. These functional groups are also all composed of 8 atom scaffolds (excluding H atoms).

Finally, we provide a set of recommendations for the functional groups and functionalization site (**Figure 3.8**) based on analysis of the ligand characteristics that produced high $\log\beta$ values for ²²⁷Ac complexation in methanol. We first note the preferred functional site

623-Ligand Dataset



803-Ligand Dataset

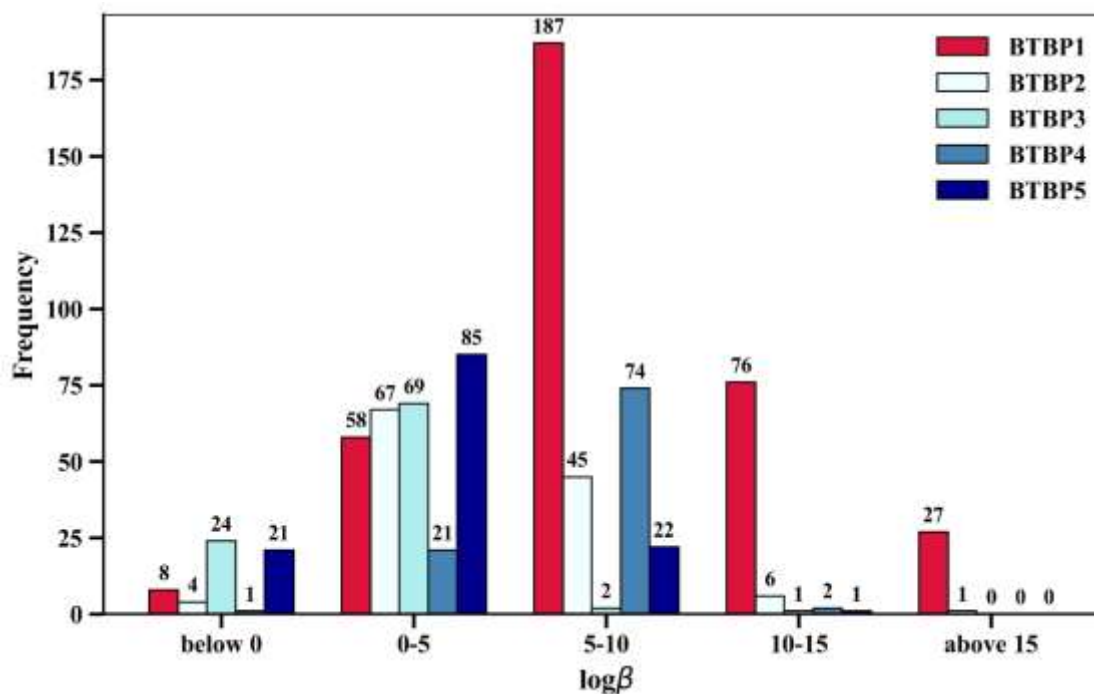


Figure 3.6. Distribution of the $\log\beta$ values for each BTBP analog using the initial 623-ligand dataset (top) and the 803-ligand dataset (bottom). The range for each frequency counter is below 0, between 0 and 5, between 5 and 10, between 10 and 15, and above 15.

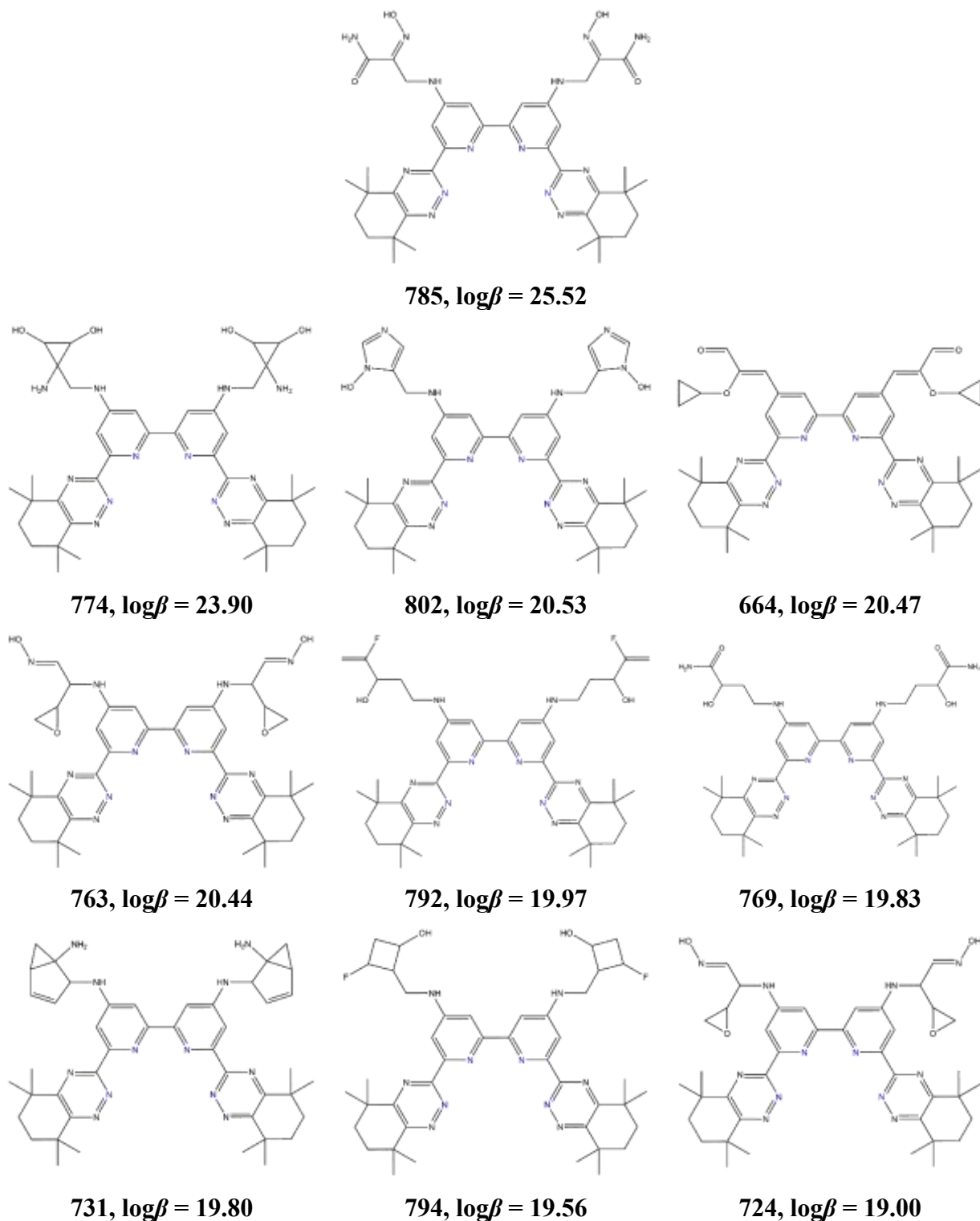


Figure 3.7. The top ten ligands out of the 743 ligands analyzed through this study.

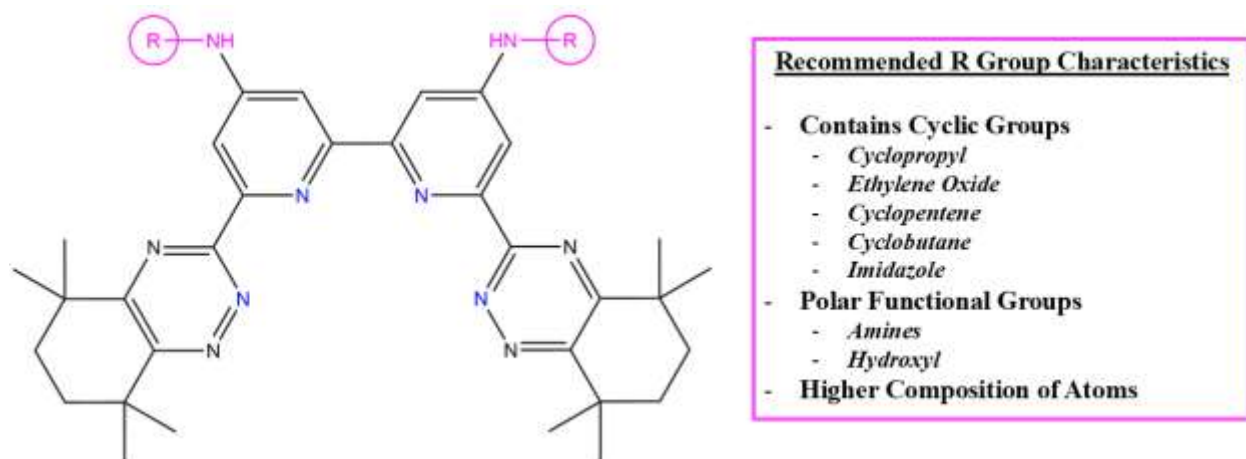


Figure 3.8. Proposed ligand design for synthesizing ligands to optimize ^{227}Ac extractions in methanol determined from this study. The functional group design is demonstrated in the magenta box and the preferred functional sites are demonstrated by the magenta functional groups.

of the BTBP analogs studied in this work. We found that the symmetrical *para* positions of the coordinating nitrogen atoms of the 2,2'-bipyridine group enhance the ligation with actinium. The recommended R groups providing the largest $\log\beta$ values from this study are shown on the right side of **Figure 3.8** in the magenta box. Our first recommendation is to bridge the BTBP scaffold to the functional group by using a -NH- linker coordinated to the BTBP core. This was a characteristic demonstrated by nine of the top ten ligands. The rest of the functional group branching from the amine bridge has several recommendations for design. The first is the use of cyclic groups such as cyclopentene, cyclopropyl, ethylene oxide, cyclobutane, and imidazole groups. We also recommend minimally branched functional groups, such as a single branch from the linear chain with minimal steric strain. The presence of double bonds was observed to be significant as well, being present in eight of the top ten ligands with a maximum of two double bonds being observed in a functional group. The functional groups should also be polar and contain oxygen and nitrogen groups, especially hydroxyl groups that were in eight of the ten ligands. Finally, we observed that functional groups containing a higher composition of atoms provided stronger favorability for ^{227}Ac complexation than when functionalized with smaller functional groups.

3.3.5. Transfer Learning with 2,9-bis(1,2,4-triazin-3-yl)-1,10-phenanthroline Ligands

Finally, we evaluated whether the trained model could make predictions on the structurally similar BTPPhen-based ligands on Ac(III) complexation. To do so, we used the ML model trained on the 743-ligand dataset to predict $\log\beta$ values of the BTPPhen parent ligand together with 10 BTPPhen variants using only their molecular structure (and not the full coordination complex) which are shown in the **Figure 3.9**. The resulting absolute differences in $\log\beta$ values with respect to the DFT computed values and the predicted values from the trained ML algorithms are demonstrated by **Figure 3.10**. To evaluate model performance, the mean absolute error (MAE, 2.70) and the root-mean-squared error (RMSE, 3.02) between the DFT and predicted $\log\beta$ value are also reported. Since DFT-optimized BTBP ligands were used, the DFT optimized BTPPhen-based ligands were also used for making predictions. Overall, we found that for the qualitative prediction of BTPPhen molecules, an algorithm trained on DFT optimized BTBP ligands can provide reasonable agreement for the expected DFT stability constants without the computation of the computationally demanding coordination complexes.

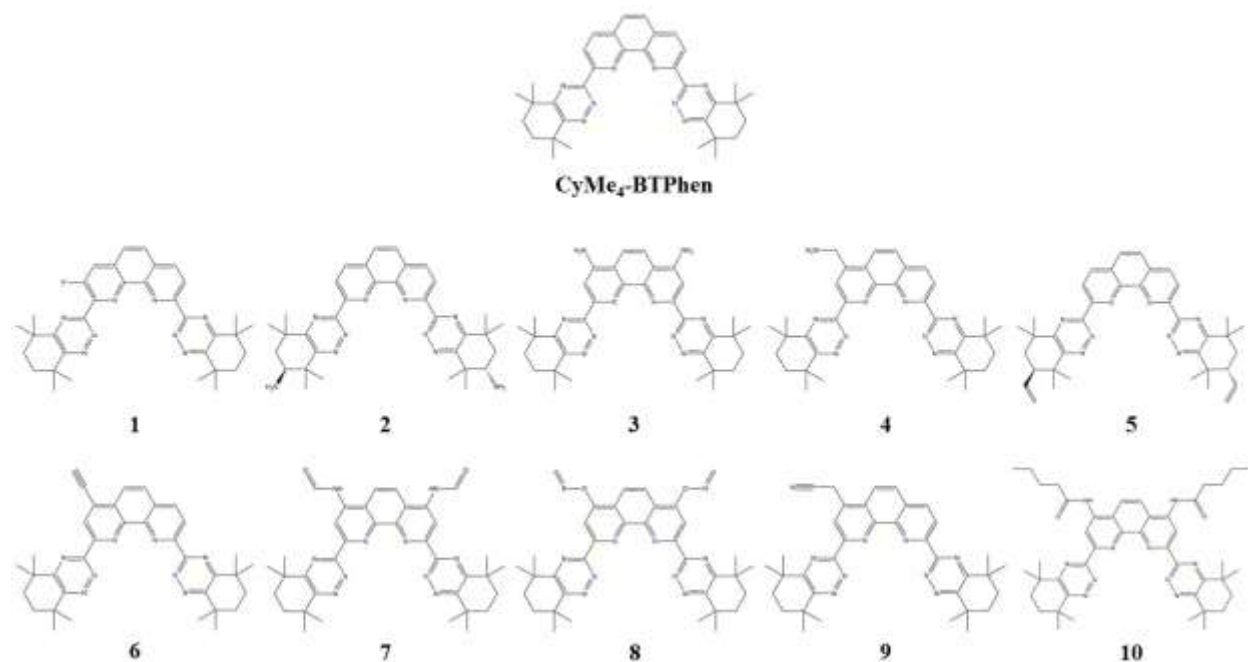


Figure 3.9. Molecular Representations of the 10 BTPhen analogs and the base CyMe₄-BTPhen molecule set used for the transfer learning analysis in this study. The DFT $\log\beta$ values for each ligand were 7.56 for **CyMe₄-BTPhen**, 6.92 for **1**, 8.45 for **2**, 13.05 for **3**, 8.01 for **4**, 9.37 for **5**, 7.22 for **6**, 7.37 for **7**, 9.60 for **8**, 6.12 for **9**, and 8.60 for **10**.

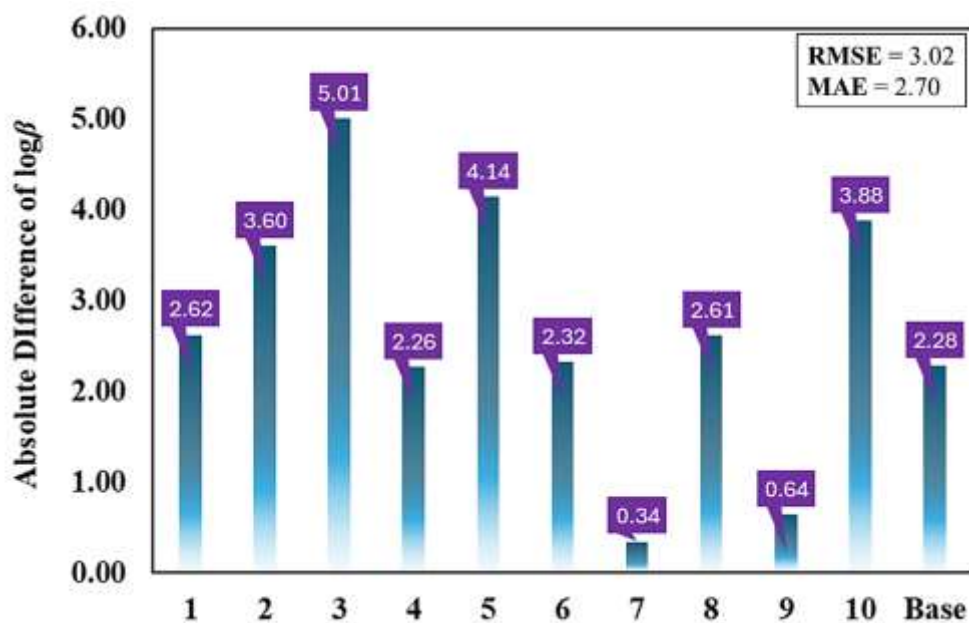


Figure 3.10. Transfer learning results using the model trained on 743 BTBP ligands for predicting $\log\beta$ values of 10+1 CyMe₄-BTPPhen derivatives. The y-axis shows the absolute difference between the DFT-computed and the predicted $\log\beta$ values.

3.4. Summary of Key Results

The *in silico* optimization of the tetradentate BTBP ligands for enhancing ligation with ^{227}Ac using active learning and ligand topology was discussed in this article. The study involved three stages: calibration, model development, and chemical interpretation. The calibration included the molecular complex ligation and the consideration of the correct coordination environment between two BTBP units and ^{227}Ac , conformation search of the bare ligand, and solvent effects. These tasks were important for the accurate modeling of the full molecular complexes by DFT.

A dataset of 350,875 unique BTBP variants was generated by considering 5 different functionalization sites, two of which generated symmetrical ligands (**BTBP1** and **BTBP2** ligand families) and three unsymmetrical (**BTBP3**, **BTBP4**, and **BTBP5** families). From those, we selected 640 ligands, and we computed their $\log\beta$ values by performing DFT geometry optimizations of the full complex (2:1 ration between BTBP and ^{227}Ac). A curation step reduced the number of DFT data to 623 to ensure the reliability of the data used for the training of a ML model. In all ML models, we introduced topological information of the molecular ligands together with electronic structure features via a concatenated input vector (PI+SOAP). Then, we utilized active learning to predict $\log\beta$ values of the unexplored BTBP ligands in a systematic manner. This was accomplished in six active learning steps which were augmenting the ligand set with an additional 30 ligands, followed by extra DFT computations that determined the $\log\beta$ values. Following this procedure, we increased the dataset from 623 ligands to 803 ligands. The predictability of the trained models was evaluated by comparing the ML-generated $\log\beta$ values with respect to DFT for a separate set of 10 ligands (*validation step*). Analysis of the top performers lead to the suggestion of ligand design principles. We concluded that the symmetrical **BTBP1** analog is the preferred class of ligands for ^{227}Ac extractions, with substituents that are coordinated to the BTBP body via a NH group (secondary amine).

We have also explored the transferability of the trained model to a different family of tetradentate ligands. The trained ML model on BTBP data showed good accuracy for a set of 10+1 CyMe₄-BTPhen derivatives. The importance of this becomes evident by considering that the only input information needed for the $\log\beta$ predictions are the optimized geometries of the bare ligands, an approach that surpasses the more time-consuming optimization of the larger molecular complexes ligated with Ac cations. Therefore, this methodology can be used in the

future for a large-scale study for the extraction of ^{227}Ac over Th(IV) and Ra(II) for either the optimization of the current leading extraction process with ion chromatography or for solvent-based methods. The results presented here demonstrate that solvent-based extractions of ^{227}Ac should be feasible, especially with the ligands that have $\log\beta$ values above 15, and based on the fact that Th(IV) would not favorably complex with BTBP molecules and Ra(II) interactions could be reduced by the use of a masking agent. We conclude that further optimization for the determination of the optimum ligand to use for Ac(III) would still need to be carried out as there is a vast number of unexplored ligands for Ac(III) complexation.

Chapter 4 Calix[4]arenes for Direct Air Capture Technologies

“A method is more important than a discovery, since the right method will lead to new and even more important discoveries.” -Dr. Lev Davidovich Landau

Disclosure: The following chapter will be part of a future publication. The project was conducted by myself under the guidance of Dr. Vogiatzis.

4.1 Introduction

Since the preindustrial era (1850-1900) the average global temperature has increased over 1°C, with 2023 reporting an average global temperature increase of 1.36°C by NASA’s Goddard Institute for Space Studies.⁹⁹ This increase in average global temperature has been mainly attributed the increase in atmospheric CO₂ with the concentration being reported as 410.27 ppm as of July 2024.^{76, 91, 98, 105} While there are many studies focused on the removal of CO₂ directly from flue gas in power plants,⁹⁷ emissions that were not removed from point source extraction methods remain in the atmosphere. To recover past emissions of CO₂, direct air capture (DAC) technologies are being developed and tested as promising methods to compliment point source CO₂ capture.^{6, 103-106}

DAC technologies have two areas of focus including the use of liquid sorbents for CO₂ captured (L-DAC) and solid sorbents (S-DAC). While both technologies have their strengths and weaknesses, S-DAC has the advantage due to the utilization of adsorption-based materials which reduce the cost of CO₂ and sorbent material recovery.^{6, 105} Indeed, it has been stated by Shi and coworkers that the development of adsorbent materials that can selectively isolate CO₂ from ambient air with significant CO₂ adsorption capacity will be pivotal for the future of DAC technologies.¹⁰⁵ To improve S-DAC technologies, there are some key hurdles to overcome such as, the cost of material regeneration (energy demand) and material itself, material synthesizability, material stability, material surface area and porosity, humidity, temperature, and selectivity for CO₂ over H₂O.^{6, 100, 103-106} Many of these potential hurdles can be overcome by

material selection and structural optimization/design that, for example, can directly reduce the cost and improve CO₂ selectivity from ambient air.¹⁰⁵

Calix[*n*]arenes are excellent candidates for potential implementation for DAC technologies due to their high tunability, versatility, relatively low cost for reagents and ease of synthesizability, and their ability to have host-guest interactions with guest molecules through non-covalent interactions which reduces energy demand for material and guest molecule recovery.^{76, 77, 91-96, 193} Aptly named by Gutsche and Muthukrishnan,¹⁹⁴ from the Greek *calix* meaning chalice and *arene* denoting aryl groups, calixarenes consist of a hydrophobic cavity with an upper rim, a lower rim, and the “central” aryl groups as demonstrated by **Figure 4.1**.¹⁹³ It should be noted that *n* represents the number of monomers incorporated into the cyclic oligomer which can range from 4 as the lowest to upwards of 20 cyclic chains where 4 through 8 are the more common cyclic oligomers.¹⁹³ The various R groups in **Figure 4.1** are color coded to match the coupled functionalization of the calix[*n*]arene scaffold. For instance, the black *R* groups represent symmetrical functionalization of the *meta* position with respect to the typical hydroxyl group of the monomer, the red *R* demonstrates *para* substitution with respect to the hydroxyl group, the magenta *R* associated with the hydroxyl group, while commonly just H, can be functionalized, and finally, the *X* bridging group that is commonly a methylene linker, can indeed be N, O, or S with further functionalization when this linker is C or N. **Figure 4.1** also demonstrates the different conformations of calix[*n*]arenes.

Since the initial investigation involving a hemispherical calixarene (hemicarcerand) for CO₂ capture by Cram and coworkers,¹⁹⁵ many different studies involving variously functionalized calix[*n*]arenes emerged for CO₂ capture.^{76-78, 88, 91-96, 196-199} Here, we will focus on studies that are pertinent to our theoretical application of calix[4]arenes for S-DAC adsorption purposes. One commonly utilized S-DAC technology involves class 2 sorbents which are covalently tethered amine molecules to a silica substrate.^{6, 100, 106, 200} Calix[4]arenes have been utilized as covalently tethered porous materials to silica gel as sorbents for medicinal purposes such as protein separations²⁰¹ and adiabatic drug adsorption,²⁰² for stationary phases in high performance liquid chromatography,⁷⁹ and for CO₂ adsorption.⁷⁶ The CO₂ adsorption study by Taghizadeh and coworkers investigated structural-based effects on CO₂ adsorption by linking the calixarene to silica gel by use of 2,4-toluene diisocyanate.⁷⁶ The study reported CO₂ enthalpy of

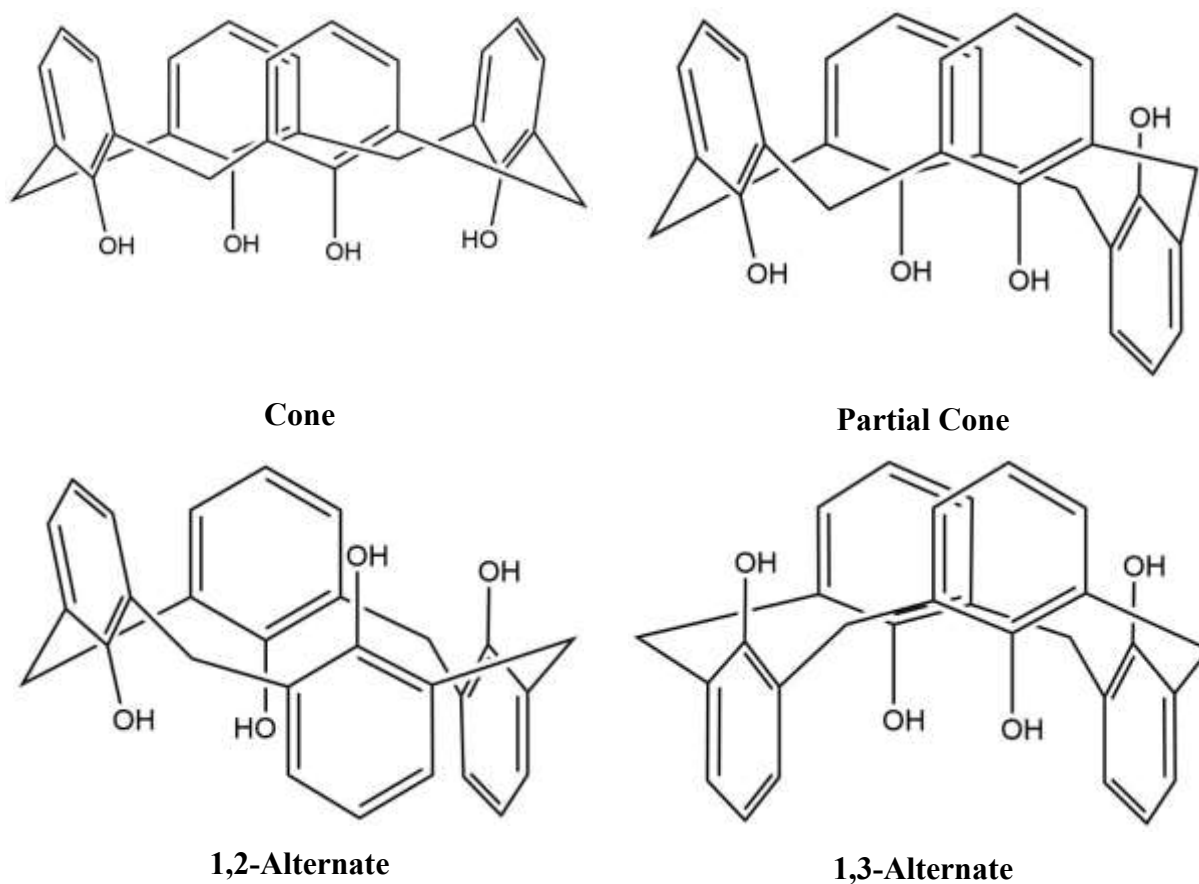
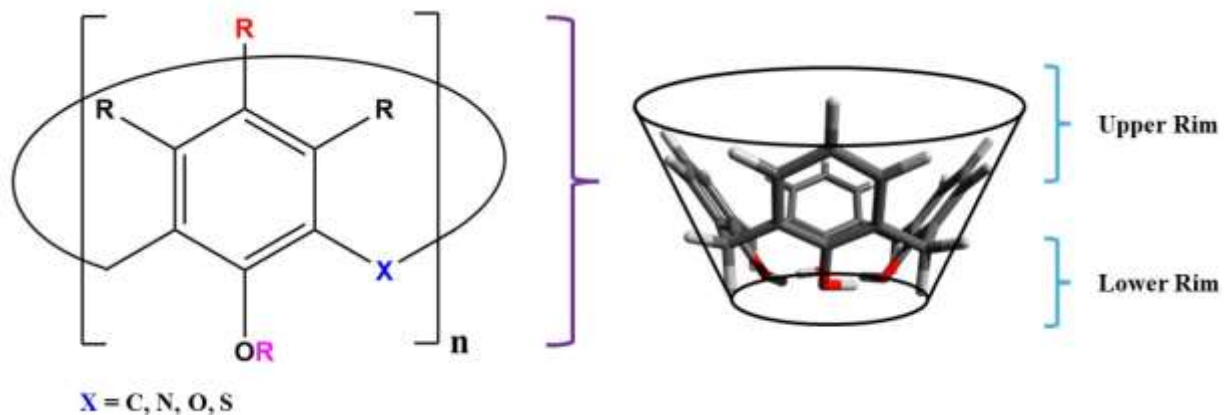


Figure 4.1. Upper: Calix[n]arene scaffold demonstrating the high tunability with various functional sites and the comparison between the base calix[4]arene with a chalice outline. The upper rim and lower rim are also demonstrated in the chalice representation where the lower rim also includes the bridging units. Lower: Conformations of calix[n]arenes including the cone, partial cone, 1,2-alternate, and 1,3-alternate.

adsorption (Q_{st}) values for the bare silica gel ($5.60 \text{ kcal}\cdot\text{mol}^{-1}$), calix[4]arene ($5.71 \text{ kcal}\cdot\text{mol}^{-1}$), *p*-*tert*-butylcalix[4]arene ($5.70 \text{ kcal}\cdot\text{mol}^{-1}$), and tetraaminocalix[4]arene prepared with a high amine loading ($9.03 \text{ kcal}\cdot\text{mol}^{-1}$) and low amine loading ($7.83 \text{ kcal}\cdot\text{mol}^{-1}$).⁷⁶ Their results, based on the Q_{st} values, demonstrated that with an increase in amine groups of the calix[4]arene scaffold that the host-guest interactions are increased while the base calix[4]arene and *tert*-butyl functionalized calix[4]arene performed slightly better than the bare silica gel however comparable.⁷⁶ They also tested the selectivity of these calixarenes for CO_2 against N_2 and CH_4 , and determined that all calixarenes exhibited a higher selectivity for CO_2 over both gases and that the calixarene (tetraaminocalix[4]arene) with the higher amine content also had the highest selectivity for CO_2 . Unfortunately, this study did not analyze the linker effect on CO_2 interactions for tethering the calixarene scaffolds to the silica substrate which can cause significant changes in the interactions as the longer the relatively linear the linker chain, the more flexible the tethered system is which could reduce CO_2 interactions with the more favorable interaction site of the calix[4]arene.

Another study by Pedrini and coworkers investigated CO_2 and CH_4 adsorption of covalent calix[4]arene-based frameworks⁹² which is a type of covalent organic framework which are commonly used for CO_2 adsorption¹⁵⁶⁻¹⁵⁹ and for S-DAC.¹⁰⁵ The study took advantage of the preorganization of the various calixarene monomers to synthesis the porous framework by utilizing tetrabrominated calix[4]arenes with different lower rim functionalities of the hydroxy groups as starting materials.⁹² Two of these frameworks were constructed using the *p*-*tert*-butylcalix[4]arene (cone conformation) and 5,11,17,23-tetrabutyl-25,26,27,28-tetramethoxy-calix[4]arene (partial cone conformation) which when analyzed using microcalorimetry and adsorption isotherms for low coverage CO_2 adsorption resulted in Q_{st} values of $8.37 \text{ kcal}\cdot\text{mol}^{-1}$ and $6.21 \text{ kcal}\cdot\text{mol}^{-1}$, respectively.⁹² Both calix[4]arenes also demonstrated selectivity for CO_2 over N_2 which was highlighted to be utilized as a possible flue gas treatment alternative.⁹²

While there are other examples and applications for CO_2 capture by calix[4]arenes,^{88, 94, 197, 203} it is not unreasonable to theorize the application of calix[4]arenes for S-DAC technologies. Calix[4]arenes are relatively inexpensive and easily synthesizable¹⁹³ and have already been demonstrated to be used in similar methods that are currently being utilized in S-DAC technologies.^{76, 92} As demonstrated by the variation in enthalpic values for CO_2 adsorption in the

aforementioned studies, by altering the structure of the calix[*n*]arenes, the strength of the noncovalent interactions varies. Custelcean of Oak Ridge National Laboratory has predicted that the enthalpy of CO₂ sorption from ambient air should be around -11.95 kcal·mol⁻¹ for DAC technologies.²⁰⁴ By exploring a large chemical space of calix[*n*]arene derivatives, improvement of the enthalpy of adsorption of CO₂ can be accomplished to determine candidates for S-DAC testing and components from the functional groups that can improve the Q_{st} values to be around the optimum enthalpy value predicted by Custelcean.²⁰⁴ Indeed, a computational study by our group, Hymel and coworkers, investigated four functional sites of calix[4]arene with 13 different functional groups.⁹¹ This study demonstrated an increase in noncovalent interactions with CO₂ occurred upon functionalization of the *para* position with respect to the hydroxyl group and had the highest change in electronic energy, as calculated by density functional theory, when methoxyamine was the functional group.⁹¹ The present study expands upon this previous computational work by exploring more functional groups, utilizing different calix[*n*]arenes such as azacalix[4]arenes, oxacalix[4]arenes, and thiacalix[4]arenes, exploration of the density functional and basis set effects on the predictability of CO₂ enthalpy of adsorption, and evaluating the predictability of the enthalpy of adsorption of these calix[4]arenes with machine learning using molecular topology descriptors for analyzing the theoretical applications of calix[4]arenes in S-DAC technologies.

4.2 Computational Details

4.2.1. Generation of Calix[4]arene Database

Calix[4]arene structures were generated by taking four unfunctionalized parent structures of calix[4]arene, azacalix[4]arene, oxacalix[4]arene, and thiacalix[4]arene with CO₂ present within the chalice of the upper rim of each structure and were functionalized in the upper rim, lower rim, and the bridging atom for the cases of calix[4]arene and azacalix[4]arenes as demonstrated by **Figure 4.2**. To generate the calix[4]arene structures by symmetrical functionalization of the *R* groups shown in **Figure 4.2**, molSimplify¹⁷⁵ was used by taking 26 SMILES^{205, 206} strings from the GDB11^{178, 179} database containing SMILES strings of atom sizes one, two, and three consisting of C, O, N, and F atoms. The following 26 SMILES strings were used for

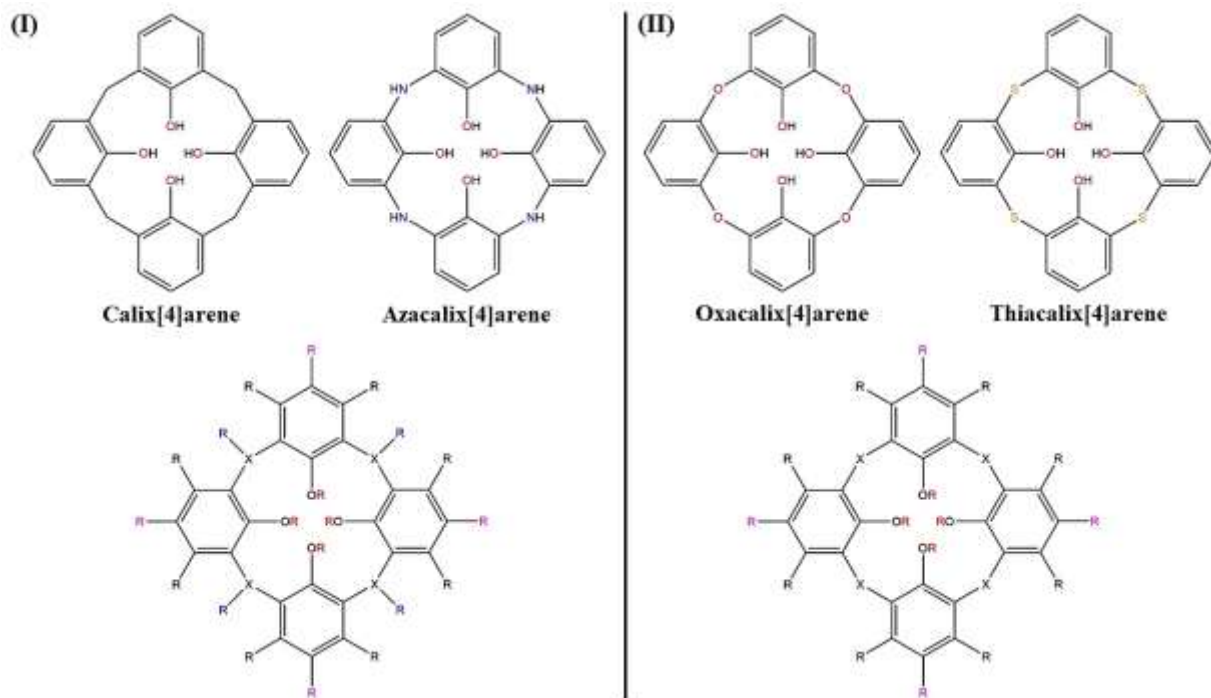


Figure 4.2. I) Molecular representations of the parent calix[4]arene and azacalix[4]arene structures with colored N (blue) and O (red) atoms. Below these two parent structures are the substitution sites utilized for each structure where each structure was functionalized symmetrically in all cases with respect to the color coded *R* groups. **II)** Molecular representations of the parents oxacalix[4]arene and thiocalix[4]arene structures with colored O (red) and S (amber) atoms. Below these two parent structures are the substitution sites for each structure which were symmetrically functionalized with respect to the color coded *R* groups.

functionalization of the calix[4]arene parent structures: C, N, O, F, CC, CN, CO, CF, C=C, C=O, CCC, CCN, CCO, CCF, CNC, COC, CC=C, CC=O, NC=N, NC=O, OC=O, NN=C, ON=C, C1CC1, C1CN1, and C1CO1. For each SMILES string, molSimplify takes the atom listed first in the string as the coordinating atom to the calix[4]arene scaffold for the color coded symmetrical functionalization at the specified positions demonstrated by **Figure 4.2**. As an example for what is meant by symmetrical functionalization with the color coded *R* groups, using **Figure 4.2(I)**, one collection of generated structures would involve the functionalization of the four blue *R* groups with the 26 SMILES strings to create 26 unique calix[4]arene structures. It should be noted that molSimplify treated the SMILES strings O and CO as a double bonded O and a carbonyl functional group (which is already included in the SMILES string list as C=O), respectively, when it should have functionalized the calix[4]arene scaffolds as a hydroxyl group and a methanol group, respectively. Due to this occurrence, manual corrections were applied to these specific cases by adding a hydrogen atom to the functional group and reducing the bond order. We should also note that the unfunctionalized forms of each calix[4]arene family as well as the *p-tert*-butyl substituted structures were used in this study by manual construction.

4.2.2. Conformation Screening and Optimization of Calix[4]arene Inclusion Compounds

Due to the flexibility and adoptable conformations that are dependent upon the type of functional group and the site of functionalization, a methodology for the screening of the conformation space of these calix[4]arenes was needed for implementation. To screen the conformational space, the Conformer-Rotamer Ensemble Sampling Tool (CREST, version 2.12)²⁰⁷ was used with the GFN2-xTB²⁰⁸ method for structure optimization. The conformational space was screened by using the inclusion compounds as the initial structure to screen the more favorable conformation of the calix[4]arene and the interacting position of CO₂ with the calix[4]arene. The most favorable inclusion compound conformation was then used for density functional theory (DFT) optimization and the base calix[4]arene derivatives were acquired by manual removal of the CO₂ from the system.

All DFT computations in this study were performed with the ORCA 5.0.4 quantum chemistry package.^{108, 109, 120} The BP86^{124, 125} density functional was used with the def2-SVP²⁰⁹ basis set, the def2/J auxiliary basis set, D4²¹⁰ dispersion corrections, and the resolution of identity for the calculation of the two electron integrals. Numerical harmonic frequency

calculations were performed on all structures to compute the enthalpy at 298.15 K with equation (4-1). The

$$\Delta H = H_{\text{Calix}+\text{CO}_2} - H_{\text{Calix}} - H_{\text{CO}_2} \quad (4-1)$$

evaluation of different density functionals was also performed with increasing basis set size. This involved the B3LYP,^{130, 131} BLYP,^{125, 130} PBE0,¹¹⁷ PBE,²¹¹ M06,²¹² and ω B97¹³⁴ density functional with the def2-SVP,²⁰⁹ def2-TZVP,^{209, 213} and the def2-TZVPP^{209, 213} basis sets. We note here that any structure that had improper structures after CREST screening or DFT optimizations were excluded from this study and so unequal numbers of the calixarene families will be observed.

4.2.3. Predictability of Host-Guest Enthalpies using Machine Learning and Molecular Topology

The supervised machine learning algorithm included persistence images¹⁸⁸ as the molecular descriptor as inputs to test the predictability of the studied calix[4]arenes. This method utilized Ripser¹⁸⁹ for the generation of persistence images (PIs) which included connected components, 1-dimensional (holes), and 2-dimensional (voids) homological descriptors by generating 50×50 square persistence images with a standard deviation of the Gaussian kernel (spread) of 0.1, an upper boundary of the PIs of 3.5 Å, and a lower boundary of the PIs of -0.1 Å. We also tested elemental PIs¹⁸⁸ which incorporates the differences in electronegativity between neighboring atoms for the connected components and 1-dimensional homological descriptors by using the same component values described previously. Random Forest Regression (RFR) was used as the machine learning algorithm as implemented in the Scikit-learn package¹⁹⁰ using Python 3.10 by used the PIs of the optimized DFT structures without CO₂ coupled with their respective enthalpy values. The RFR model utilized a 5-fold cross validation process with 200 trees, a minimum samples per leaf of four, and with the root-mean squared error calculated for each fold with the standard deviation of the error. We compared the predictability across three different persistence images (where the connected components were used in each case), the 1-dimensional PIs, 2-dimensional PIs (which also include the 1-dimensional components), and the elemental PIs.

4.3. Results and Discussion

4.3.1. Density Functional and Basis Set Effect

Before analyzing the functionalization of calix[4]arenes that increase the host-guest interaction with CO₂, a discussion on the choice of density functional and basis set is needed. To do so, the Q_{st} value of *p*-*tert*-butylcalix[4]arene covalent calixarene framework determined by Pedrini and coworkers⁹² was used since this calixarene (monomer) has been well studied for CO₂ host-guest interactions. Since Pedrini and coworkers synthesized their frameworks with spatial preorganization with respect to the calixarene monomer, the *p*-*tert*-butylcalix[4]arene would be expected to have similar behavior to the crystal structure. Udachin and coworkers¹⁹⁷ determined that at ambient temperatures and low pressure, the host:guest interaction ratio would be 1:1 which would be around the expected conditions during application of S-DAC technologies. Using the 1:1 *p*-*tert*-butylcalix[4]arene:CO₂ ratio for calculation of the CO₂ inclusion enthalpy, **Table 4.1** demonstrates the density functional and basis set effects with the targeted Q_{st} value of -8.37 kcal·mol⁻¹. We found that the basis set has greater weight on the inclusion enthalpy and that use of triple ζ basis sets provide higher accuracy. Statistical analysis across the density functionals for the different basis sets helped reinforce the choice of the level of theory. The def2-SVP basis set absolute average with the standard deviation across the density functionals was 3.97 ± 0.89 kcal·mol⁻¹, def2-TZVP was 0.50 ± 0.31 kcal·mol⁻¹, and def2-TZVPP was 0.40 ± 0.42 kcal·mol⁻¹. In terms of accuracy, the B3LYP-D4/def2-TZVPP level of theory provided the best agreement with the experimental Q_{st} value with a difference of approximately 0.02 kcal·mol⁻¹. However, using DFT with a triple ζ basis set drastically increases the amount of time required for calculation especially for these calix[4]arene molecules. Since we wished to screen many different calix[4]arene molecules, we chose to use a less accurate but significantly quicker level of theory and make note of the inherited error.

4.3.2. Structural Contributions towards Increasing CO₂ Inclusion Enthalpy of Calix[4]arenes

To discuss the structural contributions of calix[4]arenes to the CO₂ inclusion enthalpy, **Figure 4.3** demonstrates an overview of the enthalpy values, the calixarene conformation, and the family of calixarene for each set of values as a box plot. The distribution of the calix[4]arene families in

Table 4.1. Density Functional and Basis Set Dependent CO₂ Inclusion Enthalpy with Absolute Divergence from Experimental Values in Parentheses. All Values are in kcal·mol⁻¹.

Density Functional	def2-SVP	def2-TZVP	def2-TZVPP
BP86	-12.01 (3.64)	-7.96 (0.41)	-7.92 (0.45)
B3LYP	-13.12 (4.75)	-9.28 (0.91)	-8.35 (0.02)
BLYP	-13.68 (5.31)	-8.02 (0.35)	-8.44 (0.07)
PBE0	-12.71 (4.34)	-7.47 (0.90)	-8.08 (0.29)
PBE	-11.77 (3.40)	-7.78 (0.59)	-7.13 (1.24)
M06	-11.06 (2.69)	-8.19 (0.18)	-7.75 (0.62)
ω B97	-12.02 (3.65)	-8.20 (0.17)	-8.23 (0.14)

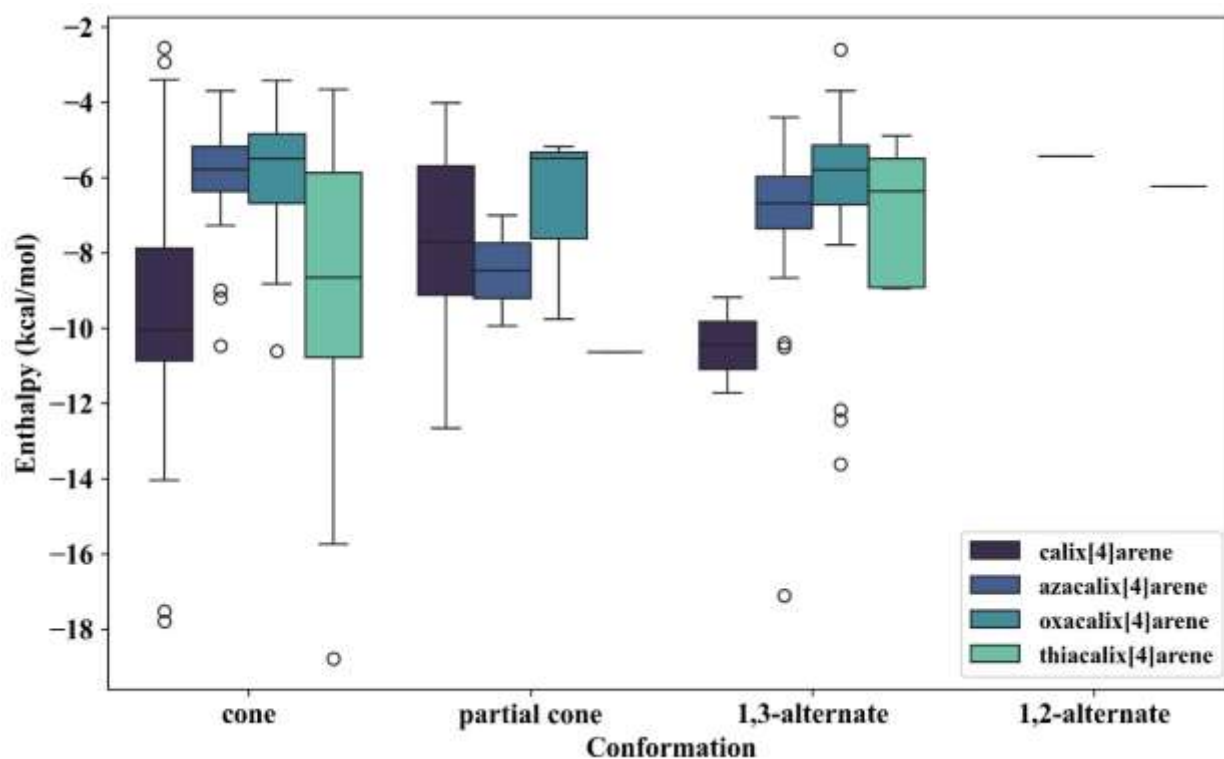


Figure 4.3. Box plots for the calix[4]arene families used in this study with respect to the conformation determined from CREST and the host-guest enthalpy of CO₂ adsorption. Potential outliers are demonstrated outside of the minimum and maximum whiskers of the plots as circles.

relation to the conformations determined from the analyzed structures are demonstrated by pie plots in **Figure 4.4**. From initial observations, it was demonstrated that calix[4]arene and thiacalix[4]arene are competitive when it comes to increasing the CO₂ inclusion enthalpy. It was also observed that the preferred conformation for calix[4]arene and thiacalix[4]arene is the cone conformation, while the oxacalix[4]arene and azacalix[4]arene is the 1,3-alternate conformation. Azacalix[4]arene preferring a 1,3-alternate conformation was observed experimentally by Tsue and coworkers who studied the crystal structure of an azacalix[4]arene functionalized with *tert*-butyl on the *para* site with respect to the lower rim methoxy group for selective CO₂ uptake.⁹⁴ This study also stated that replacement of the *tert*-butyl group with more polarizable functional groups would improve the host-guest interactions with CO₂ which we explore later in this study.⁹⁴

To explore specific cases of the functionalized calix[4]arene families, we first discuss the two common forms of the calix[4]arene families which is the base or unfunctionalized calix[4]arenes and the *p-tert*-butyl functionalized calix[4]arenes. These forms of calix[4]arenes are demonstrated by **Figure 4.5** and **Figure 4.6** with their respective DFT calculated enthalpy of adsorption values. From these interacting systems, it is clear that functionalization of the parent structures with a *p-tert*-butyl group increases the inclusion enthalpy of CO₂. It is also interesting to see that for the calix[4]arene and thiacalix[4]arene structures, the cone conformation is retained while for azacalix[4]arene and oxacalix[4]arene both are organized in the 1,3-alternate conformation. The cone conformation for these cases were also shown to have a much greater inclusion enthalpy for CO₂ than the 1,3-alternate for both the parent and *p-tert*-butyl structures. Since it is well known that it is the cavity of the calix[4]arenes that provide the favorable host-guest interactions, it can then be inferred that the decrease in inclusion enthalpy is a result of the lack of a defined cavity with the 1,3-alternate conformations essentially having two pseudo-symmetrical semi-cavities that can interact with CO₂. To support this, the “corners” (the four bridging atoms [C, N, O, S] that connect the phenol monomer) of the calix[4]arene structures were evaluated for the distance between each of the atoms. The average distance with the standard deviation for calix[4]arene was 5.114 ± 0.0012 Å, azacalix[4]arene was 4.914 ± 0.00096 Å, oxacalix[4]arene was 4.878 ± 0.00050 Å, and thiacalix[4]arene was 5.560 ± 0.00050 Å. Doing the same analysis for the *p-tert*-butyl functionalized structures, the resulting distances were 5.108 ± 0.00096 Å for *p-tert*-butylcalix[4]arene, 4.908 ± 0.0017 Å for *p-tert*-

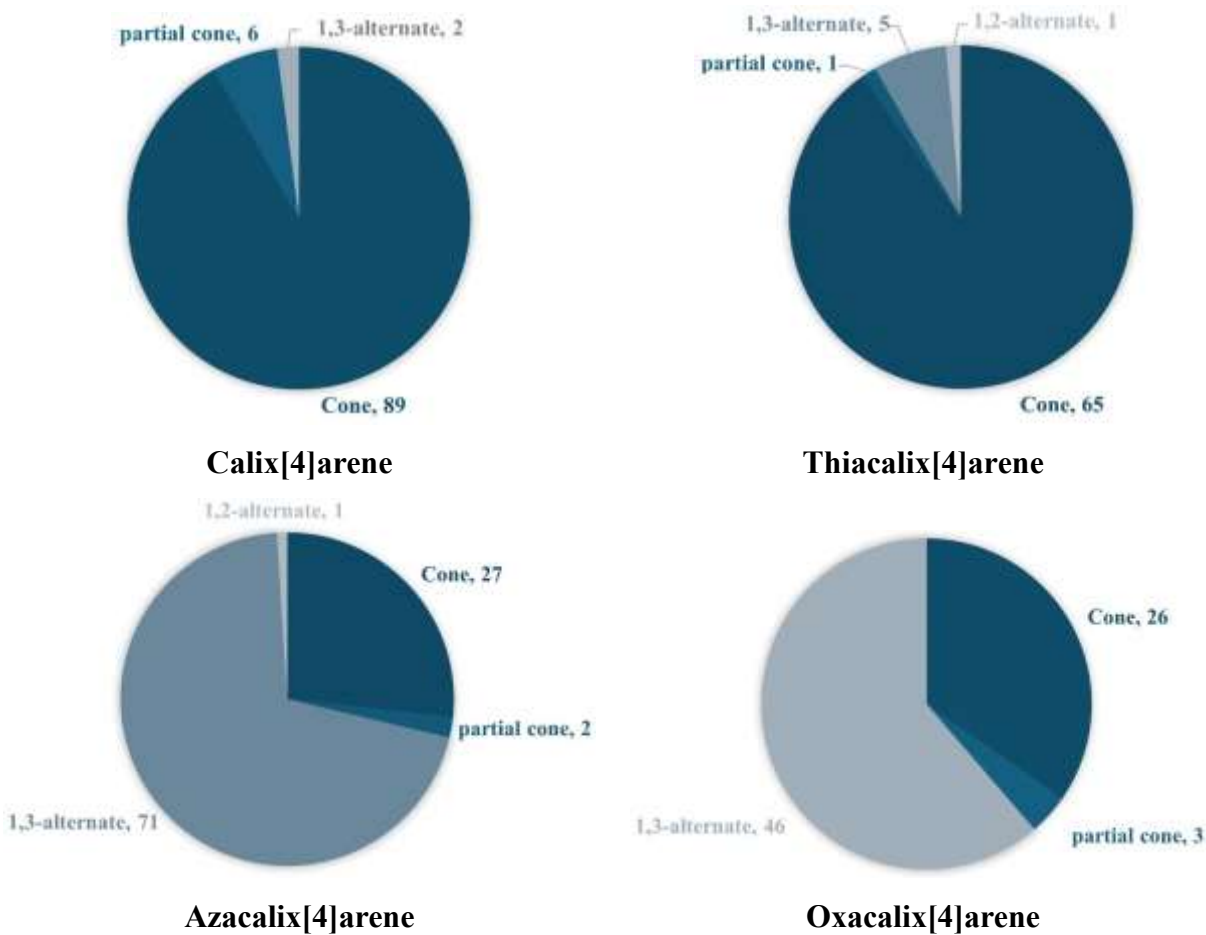


Figure 4.4. Pie plots demonstrating the conformation distribution that was predicted by CREST for the four calix[4]arene families. Each slice is labeled by the conformation being represented and the number of structures with the specified conformation being represented.



calix[4]arene

$$\Delta H = -9.95 \text{ kcal}\cdot\text{mol}^{-1}$$



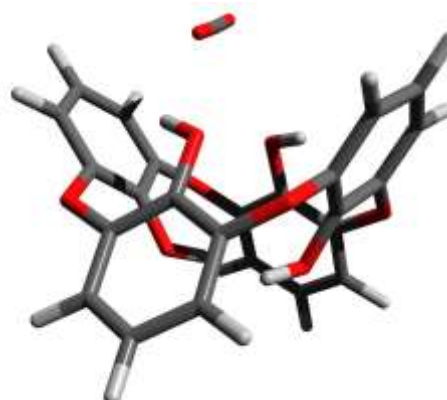
thiacalix[4]arene

$$\Delta H = -8.96 \text{ kcal}\cdot\text{mol}^{-1}$$



azacalix[4]arene

$$\Delta H = -5.85 \text{ kcal}\cdot\text{mol}^{-1}$$



oxacalix[4]arene

$$\Delta H = -4.74 \text{ kcal}\cdot\text{mol}^{-1}$$

Figure 4.5. Comparisons between the parent structures of calix[4]arene, azacalix[4]arene, thiacalix[4]arene, and oxacalix[4]arene with their respective DFT calculated CO₂ inclusion enthalpy. These structures also demonstrate the more favorable interacting site between CO₂ and the calix[4]arene structures.



p-tert-butylcalix[4]arene

$$\Delta H = -12.01 \text{ kcal}\cdot\text{mol}^{-1}$$



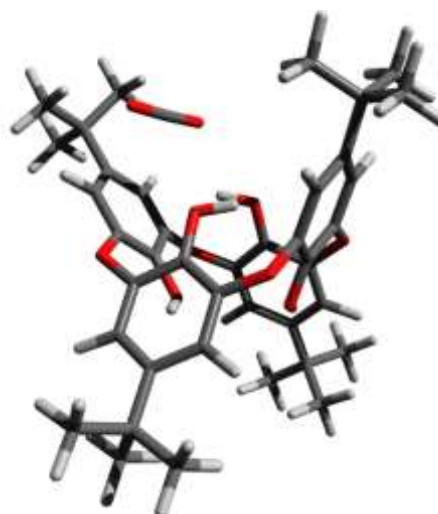
p-tert-butylthiacalix[4]arene

$$\Delta H = -11.62 \text{ kcal}\cdot\text{mol}^{-1}$$



p-tert-butylazacalix[4]arene

$$\Delta H = -7.04 \text{ kcal}\cdot\text{mol}^{-1}$$



p-tert-butylloxacalix[4]arene

$$\Delta H = -6.09 \text{ kcal}\cdot\text{mol}^{-1}$$

Figure 4.6. Comparisons with the *p*-tert-butyl functionalized structures of calix[4]arene, azacalix[4]arene, thiacalix[4]arene, and oxacalix[4]arene with their respective DFT calculated CO₂ inclusion enthalpy. These structures also demonstrate the more favorable interacting site between CO₂ and the calix[4]arene structures.

butylazacalix[4]arene, 4.870 ± 0.00050 Å for *p-tert*-butyloxacalix[4]arene, and 5.556 ± 0.0005 Å for *p-tert*-butylthiacalix[4]arene. This was an important observation as it showed that with smaller lengths between the bridging elements of the calix[4]arene chalice, the lower the inclusion enthalpy, and that having too large of the chalice, while still an effective choice, slightly decreases the interaction enthalpy. Using just these eight structures as examples, it appears that the length between bridging elements has a correlation regarding the inclusion enthalpy with the following observations. When the length is below 5 Å the cavity of the calix[4]arene prefers to take on the 1,3-alternate conformer decreasing the enthalpy of inclusion for CO₂ with further decreases in inclusion enthalpy the smaller this square is as observed with the oxacalix[4]arenes. Similarly, having a length above 5 Å results in the cone conformer being preferred and an increase in the inclusion enthalpy. It should be noted however, that comparing the two calix[4]arene and thiacalix[4]arene structures demonstrated a change in enthalpy decrease by functionalization of the parent structures with *p-tert*-butyl. The difference in enthalpy values between the calix[4]arene and thiacalix[4]arene structures decreased from $0.99 \text{ kcal}\cdot\text{mol}^{-1}$ for the parent structures to $0.39 \text{ kcal}\cdot\text{mol}^{-1}$. This decrease in the difference between enthalpy values demonstrates that it could be possible to functionalize thiacalix[4]arenes that can outperform calix[4]arenes, thus reinforcing the importance of the functional groups for CO₂ host-guest interactions.

While the distance between bridging elements of the calix[4]arenes is one possible metric for host-guest performance and conformation preference predictions, the functional group and the site of substitution also plays a crucial importance to these factors. To include the functional group and substitution site effect on the calix[4]arene structures, we first would like to provide the average CO₂ inclusion enthalpies and standard deviation across the four calix[4]arene families. The calix[4]arene family average inclusion enthalpy of the structures evaluated was $9.29 \pm 3.03 \text{ kcal}\cdot\text{mol}^{-1}$, azacalix[4]arene was $6.64 \pm 1.71 \text{ kcal}\cdot\text{mol}^{-1}$, oxacalix[4]arene was $6.12 \pm 1.94 \text{ kcal}\cdot\text{mol}^{-1}$, and thiacalix[4]arene was $8.49 \pm 3.29 \text{ kcal}\cdot\text{mol}^{-1}$. By using different functional groups at different functional sites, the calix[4]arene families will distort to a conformation or organization that reduces steric hindrance and optimizes intramolecular interactions. To continue the discussion, we provide the most promising structure from each calix[4]arene family as inclusion compounds by **Figure 4.7**. We found that the overall highest inclusion enthalpy was a result of the thiacalix[4]arene structure from **Figure 4.7** where the CO₂ guest molecule is



calix[4]arene derivative

$$\Delta H = -17.80 \text{ kcal}\cdot\text{mol}^{-1}$$

functional group: ethanol

functional site: *para*

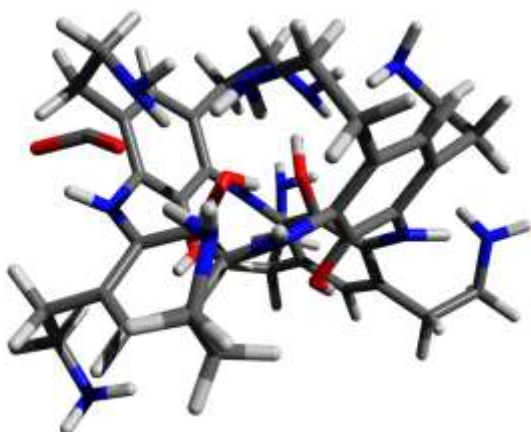


thiacalix[4]arene derivative

$$\Delta H = -18.79 \text{ kcal}\cdot\text{mol}^{-1}$$

functional group: ethanol

functional site: *para*

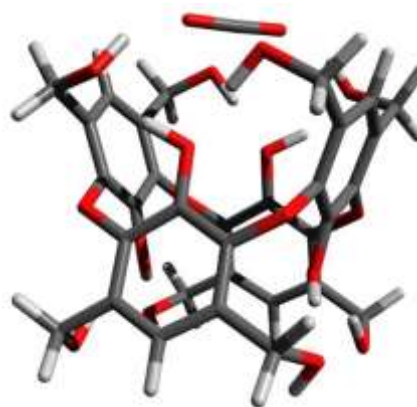


azacalix[4]arene derivative

$$\Delta H = -17.11 \text{ kcal}\cdot\text{mol}^{-1}$$

functional group: ethylamine

functional site: *meta*



oxacalix[4]arene derivative

$$\Delta H = -13.62 \text{ kcal}\cdot\text{mol}^{-1}$$

functional group: methanol

functional site: *meta*

Figure 4.7. The highest CO₂ inclusion enthalpy from DFT from the four different calix[4]arene families. The enthalpy value, functional group, functional site, and the average length between the bridging elements with the standard deviation are provided underneath each figure. Grey are carbon atoms, yellow are sulfur, white are hydrogen, blue are nitrogen, and red are oxygen.

positioned within the chalice of the molecule with a value of $-18.79 \text{ kcal}\cdot\text{mol}^{-1}$. This thiacalix[4]arene was functionalized in the *para* position with an ethanol functional group coordinated to the primary carbon of ethanol. The second overall highest enthalpy value, which is also the second highest out of the four calix[4]arene derivatives, was with calix[4]arene functionalized in the *para* site with an ethanol group functionalized on the primary carbon with a value of $-17.80 \text{ kcal}\cdot\text{mol}^{-1}$. The calix[4]arene derivative was in the cone conformation with the guest CO_2 molecule within the chalice of the calix[4]arene just like for the thiacalix[4]arene derivative. The highest enthalpy of the azacalix[4]arene family was from the *meta* substituted ethylamine coordinated to the primary carbon with a value of $-17.11 \text{ kcal}\cdot\text{mol}^{-1}$. It should be noted that this compound appears to have such a high enthalpy due to the transitioning from host-guest interactions towards a covalent bond. This was demonstrated by the bending of the CO_2 molecule in close proximity towards one of the amine groups with a C---N distance of $1.702 \text{ \AA}$ and the degree of bending for CO_2 as 139.0° . Finally, the oxacalix[4]arene family had the lowest enthalpy value out of the four calix[4]arene families, with a value of $-13.62 \text{ kcal}\cdot\text{mol}^{-1}$ from a *meta* substituted methanol group coordinated to the carbon atom. An interesting observation was made from this oxacalix[4]arene derivative in that with the *meta* substituted methanol, hydrogen bonding was demonstrated between the lower rim hydroxyl groups and the hydroxyl groups of the methanol functional groups which caused the 1,3-alternate conformation to organize towards a rectangular tube providing a more defined cavity that the CO_2 guest molecule was shown to reside within.

The top 10 structures determined from this study that do not include a transition towards covalent bonding are included five thiacalix[4]arenes, four calix[4]arenes, and one oxacalix[4]arene. All of these structures were functionalized in the *para* site with the exception of oxacalix[4]arene which was functionalized in the *meta* site which agrees nicely with previous computational work.⁹¹ The functional groups as SMILES strings with the respective calix[4]arene family being identified in parenthesis as either carbon, sulfur, or oxygen, for calix[4]arene, thiacalix[4]arene, and oxacalix[4]arene respectively, in order from highest inclusion enthalpy to lowest follows: CCO (sulfur), CCO (carbon), NC=O (sulfur), CCF (carbon), COC (sulfur), CNC (carbon), CC=O (sulfur), CO (oxygen), CC=C (carbon), and CC=C (sulfur). The inclusion enthalpy for each of these species were $-18.79 \text{ kcal}\cdot\text{mol}^{-1}$, $-17.80 \text{ kcal}\cdot\text{mol}^{-1}$, $-15.74 \text{ kcal}\cdot\text{mol}^{-1}$, $-14.05 \text{ kcal}\cdot\text{mol}^{-1}$, $-13.95 \text{ kcal}\cdot\text{mol}^{-1}$, $-13.90 \text{ kcal}\cdot\text{mol}^{-1}$, -13.88

kcal·mol⁻¹, -13.62 kcal·mol⁻¹, -13.20 kcal·mol⁻¹, and -13.19 kcal·mol⁻¹, respectively. Recall that the error from the level of theory for the CO₂ inclusion enthalpy of *p-tert*-butylcalix[4]arene was approximately 3.64 kcal·mol⁻¹. If it is assumed that this error also applied for these systems, and that the inclusions enthalpies shown here should be increased by +3.64 kcal·mol⁻¹, then we note that these are still promising candidates for CO₂ capture for S-DAC applications, especially the relatively unexplored thiacalix[4]arene molecule for CO₂ capture. Finally, we note that there is a common trend for competition between the calix[4]arene and thiacalix[4]arene that was demonstrated by the parent and *p-tert*-butyl functionalized calix[4]arene families, with both typically possessing a higher inclusion enthalpy than azacalix[4]arene and oxacalix[4]arene structures for identical functional groups and functional sites.

4.3.3. Predictability of Calix[4]arenes using Machine Learning with Molecular Topology

Since it was demonstrated that the molecular structure of the calix[4]arene has a direct dependency on the inclusion enthalpy of CO₂, machine learning was applied to investigate the predictability of these enthalpy values based on molecular topology. This investigation utilized persistence images (PIs) that vectorize the molecular topology into machine learning readable inputs, and thus, can be paired with the enthalpy values to train the algorithm. Using the three different PI methods discussed previously in the computational details section, the trained machine learning algorithms which each method were accomplished and the best parity plot and statistical analysis across the 345 structures included in this study are demonstrated by **Figure 4.8**. The machine learning results demonstrated that the 1-dimensional and 2-dimensional PIs perform nearly identically while the elemental PIs performed slightly better than both but could be argued to be about the same performance as the others. However, the machine learning results demonstrated only a slight correlation between the calix[4]arene structures and the CO₂ inclusion enthalpy with the RMSE being around 2 kcal·mol⁻¹ and the R² of the testing being around 0.5 for all three cases.

It was hypothesized that the relatively poor performance of the machine learning algorithm on the predictability of the CO₂ inclusion enthalpy could have been due to the various locations determined by CREST for the CO₂ interactions that caused different enthalpic values or due to the different characteristics of the individual calix[4]arene families included in the overall algorithm. Since, the CO₂ location was determined systematically and the screening of the

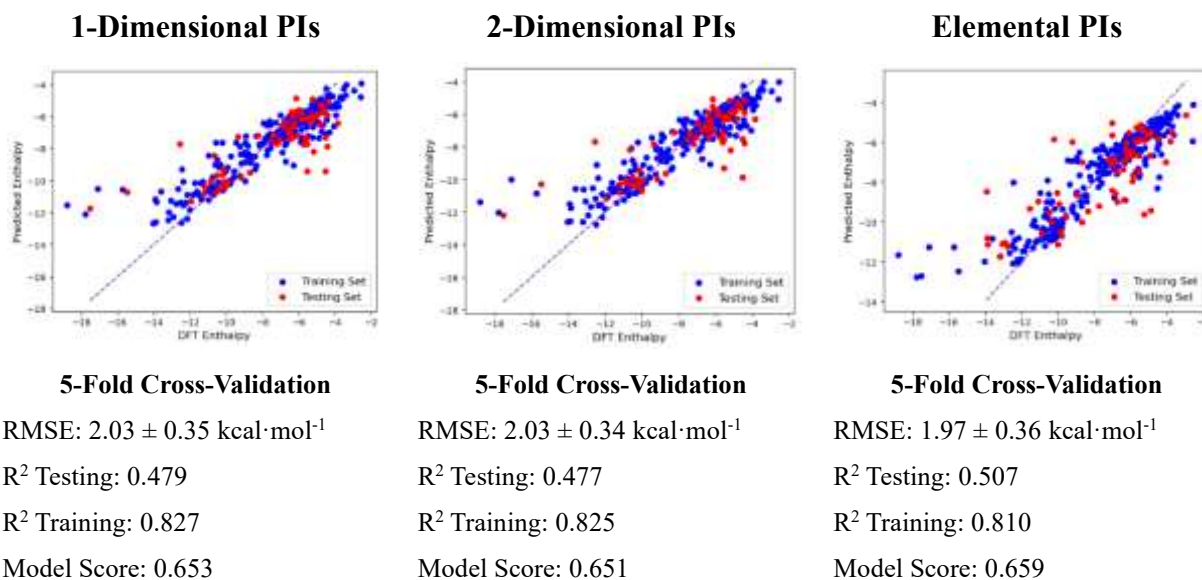


Figure 4.8. The best performing fold from each trained algorithm with different PIs are demonstrated by the parity plots, and the 5-fold cross-validation root-mean-square-error (RMSE), the average R² across all fold for the testing and training set, and the model score are demonstrated underneath the example parity plots.

individual structural cases to determine if there is a better position potentially missed by CREST would be an arduous task, it was decided to evaluate the machine learning algorithm with the elemental PI descriptions on the individual calix[4]arene families. Interestingly, when using only structures of the calix[4]arene family, the performance of the algorithm was significantly improved producing a RMSE of $1.72 \pm 0.42 \text{ kcal} \cdot \text{mol}^{-1}$ and an average R^2 testing of 0.645 and R^2 training of 0.850 across all five folds. However, while the predictability was shown to improve when only the calix[4]arene family was used, doing individual analysis with the other calix[4]arene families all produced R^2 testing values below 0.2 across all five folds. This was an interesting phenomenon that would be subject to future studies by further understanding of the chemistry and interactions with CO_2 to determine why the calix[4]arene family performs significantly better than all of the other families.

4.4. Summary of Key Results

The goal of this study was to investigate the structural effects and predictability of the CO_2 inclusion enthalpy for S-DAC technologies. This was accomplished by using four families of functionalized calix[4]arenes: calix[4]arenes, azacalix[4]arenes, oxacalix[4]arenes, and thiocalix[4]arenes. The functionalization of these calix[4]arenes involved substitution are the *para* site, *meta* site, bridging atom (calix[4]arene and azacalix[4]arene), and the lower rim using 26 functional groups, the unfunctionalized and *p-tert*-butyl substituted molecules. The inclusion compound of each functionalized structure was organized using CREST to determine the more favorable conformation of the calix[4]arenes and CO_2 location for improved interactions. We then took the best inclusion compounds from CREST, removed the CO_2 manually, and performed DFT optimizations and frequency calculations on all compounds to compute the inclusion enthalpy. A benchmark study was also performed to evaluate the error associated with the choice of theory. Finally, the predictability of the computed inclusion enthalpies was evaluated using, for the first time with calix[4]arenes, persistence images to incorporate molecular topology as descriptors.

The benchmark study elucidated that using the BP86-D4/def2-SVP level of theory would inherent an error of approximately $3.64 \text{ kcal} \cdot \text{mol}^{-1}$. This was determined by comparing an experimentally determined inclusion enthalpy of adsorption for CO_2 with respect to a *p-tert*-butylcalix[4]arene covalent calixarene framework. Comparisons were also made with other

density functionals and basis sets to determine the difference between the computed and experimental inclusion enthalpy. It was determined that the density functional choice does not have a significant impact on the inclusion enthalpy. The basis set choice, however, significantly improved the computed inclusion enthalpy reducing the error for example from $3.64 \text{ kcal}\cdot\text{mol}^{-1}$ to $0.45 \text{ kcal}\cdot\text{mol}^{-1}$ when using the BP86-D4/def2-SVP and BP86-D4/def2-TZVPP level of theory respectively. It was also demonstrated that the B3LYP-D4/def2-TZVPP level of theory provided the best agreement with the experimental value reporting a difference of only $0.02 \text{ kcal}\cdot\text{mol}^{-1}$ but at a significantly larger computational expense. This information can assist in future studies for determination on the level of theory to be implemented. If many different calculations are required, then the cheaper level of theory can be used at the expense of high accuracy, while if more accurate values are needed, then we recommend the B3LYP-D4/def2-TZVPP. We also recommend the BLYP-D4/def2-TZVPP level of theory as a less computational expense than the B3LYP functional since it resulted in a difference of $0.07 \text{ kcal}\cdot\text{mol}^{-1}$.

Evaluation of the functionalized families of calix[4]arenes provided multiple observations regarding conformational preferences dependent upon structure functionalization and calix[4]arenes recommended for S-DAC technologies. We first evaluated the unfunctionalized calix[4]arenes and *p-tert*-butyl functionalized calix[4]arenes as references. The calix[4]arene and thiacalix[4]arene structures were demonstrated to prefer the cone conformation, while azacalix[4]arene and oxacalix[4]arene preferred the 1,3-alternate conformation. This was suggested to be due to the decreased cavity size by determination of the distance between the bridging atoms of the calixarenes with distances below $5 \text{ \AA}$ preferring the 1,3-alternate conformer and above the cone. It was also observed that since the 1,3-alternate conformation does not have a full cavity, that the inclusion enthalpy is significantly lower than the cone conformation. This observation, however, would be dependent upon the functional group and the functional site. For example, the 1,3-alternate oxacalix[4]arene structure functionalized with methanol in the *meta* position was demonstrated to create a rectangular cavity due to hydrogen bonding of the hydroxyl groups of the molecule resulting in an inclusion enthalpy of $-13.62 \text{ kcal}\cdot\text{mol}^{-1}$. While this is a promising candidate for S-DAC, the two best structures recommended for S-DAC technologies would be calix[4]arene and thiacalix[4]arene functionalized with the primary carbon of ethanol in the *para* site, with resulting inclusion enthalpies of $-17.80 \text{ kcal}\cdot\text{mol}^{-1}$ and $-18.79 \text{ kcal}\cdot\text{mol}^{-1}$, respectively. Which, if assuming these

values overestimate the favorability of the inclusion enthalpy by $3.64 \text{ kcal}\cdot\text{mol}^{-1}$, would be $14.14 \text{ kcal}\cdot\text{mol}^{-1}$ and $15.15 \text{ kcal}\cdot\text{mol}^{-1}$, which are well over the estimated $11.95 \text{ kcal}\cdot\text{mol}^{-1}$ predicted enthalpy required for DAC technologies.²⁰⁴ Finally, we made two more important observations. The first, is that the findings from this study agreed with previous computational findings⁹¹ in the substitution in the para site improves CO_2 interactions for calix[4]arenes. Lastly, we discovered the effectiveness of using thiacalix[4]arenes, a relatively unexplored calixarene family for CO_2 capture, which made up five of the top ten calix[4]arenes, including the highest inclusion enthalpy spot of $-18.79 \text{ kcal}\cdot\text{mol}^{-1}$.

Testing the predictability of DFT calculated CO_2 inclusion enthalpies utilizing molecular topological descriptors as persistence images (PIs) with machine learning was accomplished using random forest regression with the DFT optimized structures. Using the 345 calixarenes that were composed of the four different families of calixarenes with the three different PIs (1-dimension, 2-dimesnional, and elemental PIs) resulted in nearly identical performance with a slight edge being given to the elemental PIs. While the elemental PIs had a slight edge, the predictability was still poor and only demonstrated a slight correlation with a RMSE across five folds of $1.97 \pm 0.36 \text{ kcal}\cdot\text{mol}^{-1}$, an average R^2 for the testing set of 0.507 and training set of 0.810. Analysis was then conducted on the individual families of calix[4]arenes to determine if the low predictability of these calixarenes is due to different characteristics and chemistry of the families. It was discovered that the calix[4]arene family had significantly improved predictability alone than with the collective structures. The RMSE across five folds decreased to $1.72 \pm 0.42 \text{ kcal}\cdot\text{mol}^{-1}$ and improved the average R^2 for the testing set to 0.645 and training set to 0.850. Interestingly, all three of the remaining calixarene families were shown to drastically decreased the predictability of the inclusion enthalpy resulting in R^2 of the testing sets below 0.2 for all cases. This is an interesting observation that could be a subject for future studies. It is hypothesized that possible reasons for this observation could be due to either the CO_2 interaction sites for some of the structures included in the dataset or the level of theory could be inadequate for these calixarene families since the methodology worked reasonably well for the calix[4]arene family. It is also predicted that the machine learning algorithm for the calix[4]arene family could be improved by adding more calix[4]arene structures, and the refinement of the already investigated structures with a higher level of theory.

Chapter 5 Structural Analysis of Vinyl-Addition Polynorbornenes for Membrane-based Applications

“The measure of greatness in a scientific idea is the extent to which it stimulates thought and opens up new lines of research.” -Dr. Paul Adrien Maurice Dirac

Disclosure: The following chapter compiles my contributions to works published from two collaboration projects. The first work presented was published in the journal *Polymers* in 2024 volume 16 on page 22243 with the title “*Multiscale Modeling of Vinyl-Addition Polynorbornenes: The Effect of Stereochemistry*” and was authored by Nobahar Shahidi, myself, Konstantinos D. Vogiatzis, and Manolis Doxastakis. My contributions for this study involved the generation of potential energy scans with density functional theory for three different conformations of unfunctionalized polynorbornene trimers. A benchmark study was also performed on two polynorbornene dimers as verification for the choice of density functional for these systems. The second work presented was published in the ACS journal *Applied Polymer Materials* in 2022 volume 4 with the title “*Vinyl-Addition Fluoroalkoxysilyl-Substituted Polynorbornene Membranes for CO₂/CH₄ Separation*” and was authored by Xinyi Wang, Trevor J. Wilson, Christopher R. Maroon, myself, Savannah E. Rheingold, Konstantinos D. Vogiatzis, and Brian K. Long. In this project, my contributions involved the use of molecular mechanics to scan the conformation space of functionalized polynorbornene monomers to perform DFT optimizations on unbiased initial structures for the calculation of CO₂ and CH₄ electrostatic interaction energies for comparisons with experimental results.

5.1 Introduction

Another technology being investigated and implemented for CO₂ capture involves the use of membrane-based separations, which are inexpensive, energy efficient, and environmentally advantageous.²¹⁴⁻²²⁴ One such polymeric material that is promising and being investigated for gas stream separations of CO₂ are vinyl-addition polynorbornenes (VAPNBs).²²⁵⁻²²⁷ The performance of VAPNBs are commonly estimated by their analysis with respect to the Robeson upper bound limit^{228, 229} which is a measure of the trade-off between permeability of, for our case, CO₂ with respect to the selectivity of the material for CO₂ over other gaseous molecules. Overcoming the

Robeson upper bound limit is a major objective²³⁰ when synthesizing these polymeric membranes for CO₂ capture and is strongly dependent upon the structure of the norbornene monomer and the stereochemistry of the polymeric backbone. It was these structure-property relationships, as well as other structure related properties, that motivated the two collaboration projects^{231, 232} where the contributions made by myself under the guidance of Dr. Konstantinos Vogiatzis will be discussed.

5.2 Computational Details

5.2.1. Multiscale Modeling of Vinyl-Addition Polynorbornenes: The Effect of Stereochemistry

DFT calculations were performed for norbornene dimers and trimers. All DFT calculations were performed using the TURBOMOLE 7.2 program package²³³ with the PBE0 density functional,¹¹⁷ the def2-TZVPP basis set,²¹³ Grimme's D3 dispersion correction²³⁴ with the Becke–Johnson damping function,²³⁵ and the resolution of identity for the two-electron integrals. Domain-localized pair natural orbital coupled-cluster singles-and-doubles with perturbative triples (DLPNO-CCSD(T))^{236, 237} calculations were performed for norbornene dimers using the ORCA 5.0 package.^{108, 109, 120} The aug-cc-pVTZ basis set,^{238, 239} was used in all DLPNO-CCSD(T) calculations while the T_{CutPNO} threshold was set to 10^{-8} . The resolution of identity approximation for Coulomb and HF exchange was applied together with the aug-cc-pVQZ/C auxiliary basis set.

A benchmark study on norbornene dimer structures was used to validate the choice of the density functional used for the larger trimer units. A potential energy surface was computed along the torsion angle for the meso and the racemo dimer conformations **Figure 5.1**. DLPNO-CCSD(T)/aug-cc-pVTZ calculations on the structures optimized with PBE0-D3(BJ)/def2-TZVPP were used as references. The accuracy of the following density functionals was evaluated: PBE0,¹¹⁷ B3LYP,²⁴⁰ BLYP,¹³⁰ BP86,^{124, 125} M06,²¹² M06-L,²⁴¹ PBE,²¹¹ and TPSSh.¹²⁹ In addition, we performed DLPNO-CCSD(T) calculations with a double-zeta quality basis set (aug-cc-pVDZ), and the error introduced by the smaller basis set size was evaluated with respect to the DLPNO-CCSD(T)/aug-cc-pVTZ energies.

Two successive dihedral angles (φ_1 and φ_2 , **Figure 5.2**) were used to generate the three-dimensional potential energy surfaces of the norbornene trimer structures which have exo-meso-

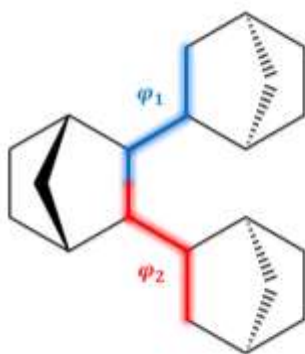


(A)

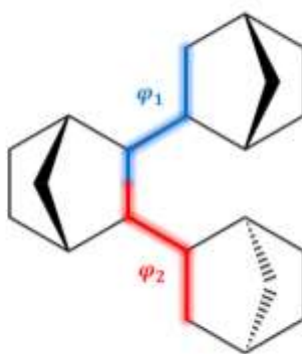


(B)

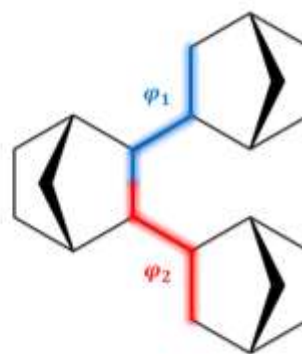
Figure 5.1. Molecular representation of **A)** the meso dimer and **B)** racemo dimer.



(A)



(B)



(C)

Figure 5.2. The **A)** meso-meso, **B)** meso-racemo, and **C)** racemo-racemo trimer structures implemented in this study.

meso, exo-meso-racemo, and exo-racemo-racemo stereochemistry. We have considered molecular geometries where φ_1 and φ_2 angles varied from -180° to 180° in intervals of 20° . Overall, a total of 324 different structures were generated per trimer. For computing the DFT energy of each structure, the dihedral angles were kept fixed while all the other degrees of freedom were allowed to relax during the geometry optimizations.

5.2.2. *Vinyl-Addition Fluoroalkoxysilyl-Substituted Polynorbornene Membranes for CO₂/CH₄ Separation*

Quantum chemical calculations were performed for the elucidation of the noncovalent interaction strength between individual repeat units of these functionalized vinyl-addition polynorbornenes (VAPNBs) **P1–P3** and **P1F–P3F** (**Figure 5.3**), and the respective gas molecules CO₂, and CH₄ (monomer–gas interactions), as well as interactions between individual repeat units (monomer–monomer interactions). When discussing only the monomer for our computations, only the number or number with **F** is used. Due to the large number of degrees of freedom and the different interaction motifs between the gas molecules and the functionalized VAPNB repeat units, a hybrid molecular mechanics/quantum chemical scheme was applied to screen a large number of near-isoenergetic conformers. The computational protocol implemented is shown in **Figure 5.4**, and allowed us to perform density functional theory (DFT) calculations with unbiased initial structures. All molecular geometries were first optimized with DFT using the PBE0¹¹⁷ functional, a small basis set (def2-SVP),²⁰⁹ and Grimme's D3 dispersion correction²³⁴ with the Becke–Johnson damping function²³⁵ as implemented within the TURBOMOLE 7.2 program package.²³³ Force-field input structures were generated from the preoptimized structures using LigParGen²⁴² for simulations using the LAMMPS²⁴³ software package. The OPLS-AA force field²⁴⁴ was used with a periodic box at 200 K in a NVT ensemble with a Nosé-Hoover thermostat using a 1.0 ps time constant and a 1.0 fs time step. For each system, 50 000 time steps were used to reduce the bias produced by the MD dependence on the initial structure and still provide a structure that is not trapped on a local minimum on the potential energy surface (PES).²⁴⁵ The 30 lowest energy structures were acquired and then optimized with DFT at the PBE0-D3(BJ)/def2-TZVPP²¹³ level of theory. Tight convergence and the resolution identity for the two-electron integrals were also applied to all DFT calculations.

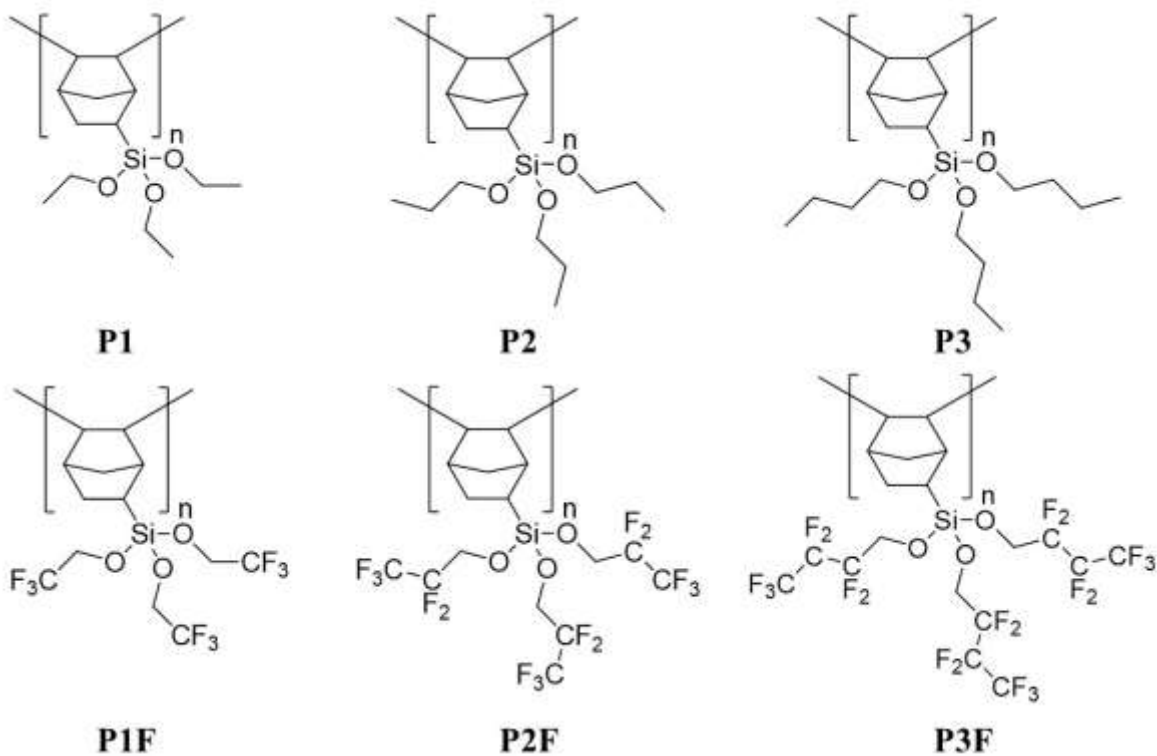


Figure 5.3. Unfluorinated (**P1-P3**) and fluorinated (**P1F-P3F**) polynorbornenes monomers used for this study.

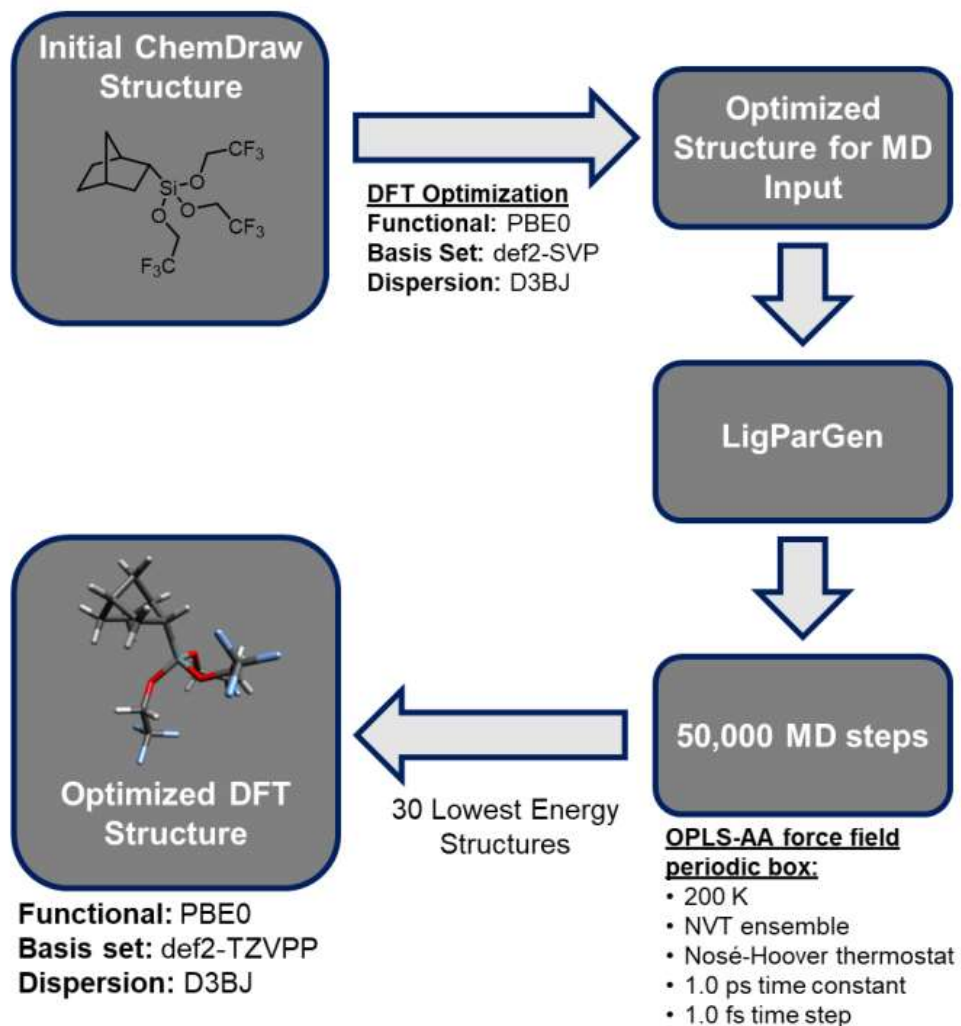


Figure 5.4. Computational methodology used for this study.

The interaction energies (ΔE_{AB}) between two structures, A and B, were computed as demonstrated by (5-1):

$$\Delta E_{AB} = E_{AB} - E_A - E_B \quad (5-1)$$

where E_{AB} represents the energy of the interacting supersystem, and E_A and E_B represent the energies of the isolated systems. For calculations on monomer–gas interactions, A corresponds to a saturated monomer analog of the repeat unit of **P1**, **P2**, **P3**, **P1F**, **P2F**, or **P3F**, and B to either CO₂ or CH₄. For the monomer–monomer examination, A = B corresponds to a saturated monomer analog of the repeat unit of **P1**, **P2**, **P3**, **P1F**, **P2F**, or **P3F**.

Due to the large number of degrees of freedom of the monomer– monomer superstructures, an additional set of geometry optimizations was performed for the further validation of the computational results. Initial geometries of the monomers with short chains were generated from the most stable structures by manually removing atoms from the monomeric units that incorporate lengthier chains, which were further optimized by the same level of theory (PBE0-D3(BJ)/def2-TZVPP).

5.3. Contributions Towards both Collaborative Polynorbornene Projects

5.3.1. Multiscale Modeling of Vinyl-Addition Polynorbornenes: The Effect of Stereochemistry

All results from the DFT benchmark study are included in **Table 5.1** and **Table 5.2**. These calculations identified that the PBE0-D3(BJ) functional provides the lowest root-mean-square error (RMSE, 0.70 and 0.89 kcal/mol for the meso and racemo dimers, respectively). The second lowest was B3LYP with and RMSE of 0.97 kcal/mol for the meso dimer and tied between B3LYP and M06-L as 0.94 kcal/mol for the racemo dimer. The two-dimensional potential energy surface with respect to the dihedral angle φ are shown in **Figure 5.5** and **Figure 5.6**. These plots demonstrate the energy change as a single norbornene unit rotates about an axis with respect to the other stationary unit. Finally, DLNO-CCSD(T) calculations with the more compact basis set (aug-cc-pVDZ) introduce a small but non-negligible error (RMSE of 0.37 kcal/mol for both dimers).

For the three norbornene trimer configurations, **Figure 5.7** demonstrates the relative energies. The relative energies were determined by subtracting all energy values from the most

Table 5.1. Benchmarking Results for the Meso Dimer (in kcal·mol⁻¹).

Functional	Mean Error	Mean Absolute Error	RMS Error	Max Absolute Error
PBE0	-0.15	0.52	0.70	1.80
B3LYP	-0.59	0.66	0.97	2.81
BLYP	-1.89	1.89	2.34	5.83
BP86	-2.20	2.20	2.66	6.34
M06	1.08	1.10	1.38	2.68
M06-L	-0.67	0.78	1.07	2.17
PBE	-1.52	1.52	2.04	5.22
TPSSh	-1.64	1.65	2.08	5.08
DLPNO-CCSD(T) aug-cc-pVDZ	0.30	0.31	0.37	0.76

Table 5.2. Benchmarking Results for the Racemo Dimer (in kcal·mol⁻¹).

Functional	Mean Error	Mean Absolute Error	RMS Error	Max Absolute Error
PBE0	-0.03	0.69	0.89	2.31
B3LYP	-0.35	0.64	0.94	2.53
BLYP	-1.57	1.60	2.08	4.90
BP86	-1.97	1.99	2.48	5.75
M06	1.75	1.75	2.08	3.82
M06-L	-0.28	0.83	0.94	1.72
PBE	-1.33	1.43	1.98	4.66
TPSSh	-1.42	1.47	1.92	4.48
DLPNO-CCSD(T) aug-cc-pVDZ	0.27	0.27	0.37	1.10

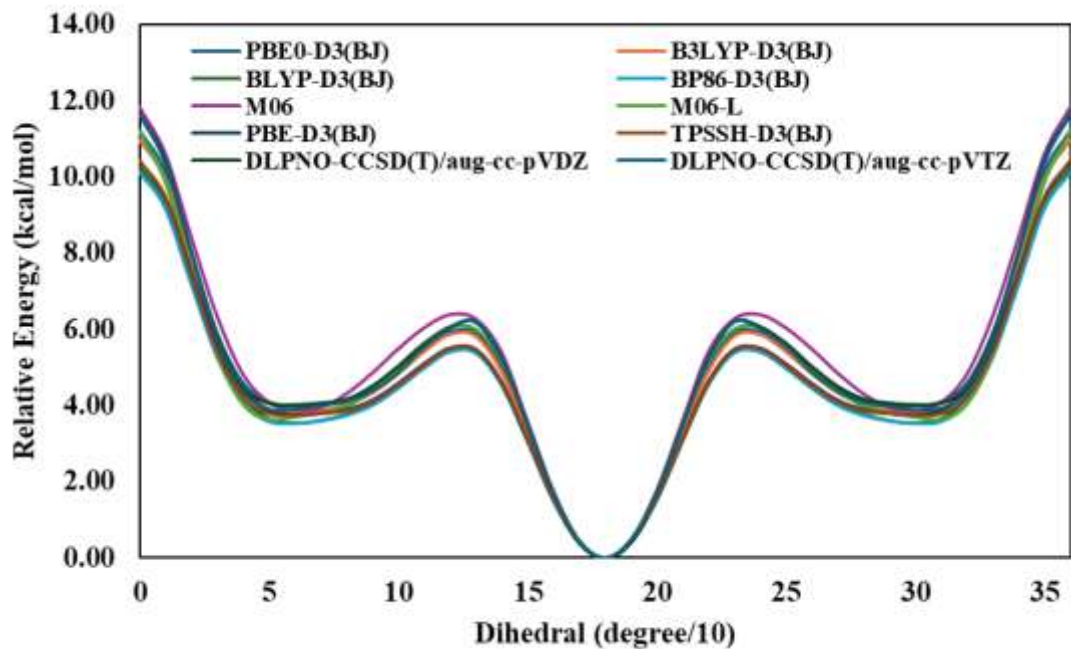


Figure 5.5. Potential energy surface for the meso dimer using the relative energy (in $\text{kcal}\cdot\text{mol}^{-1}$) with respect to the dihedral degree/10.

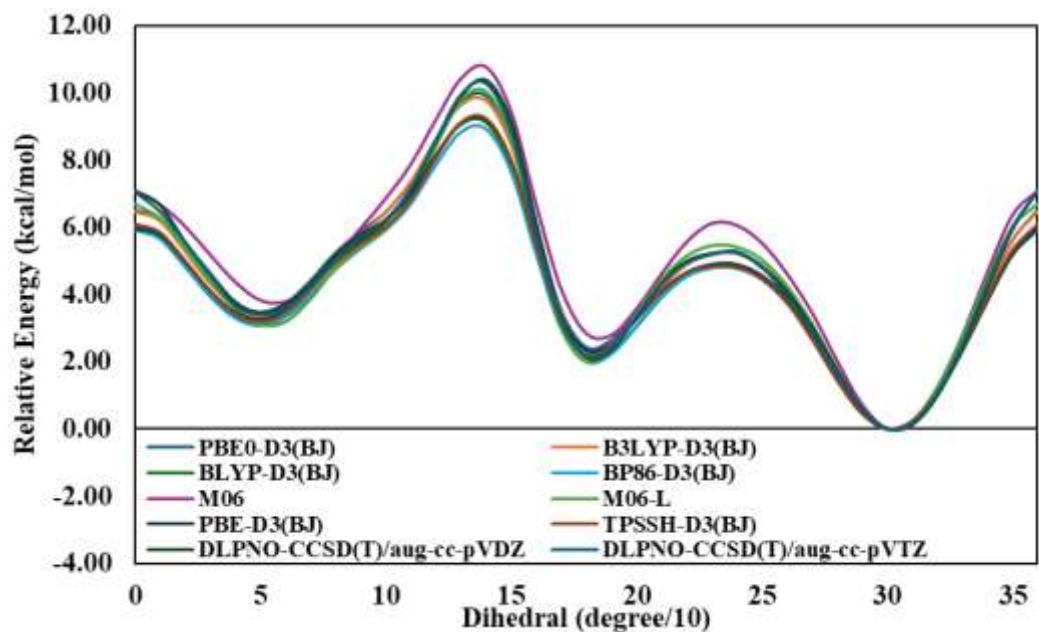


Figure 5.6. Potential energy surface for the racemo dimer using the relative energy (in $\text{kcal}\cdot\text{mol}^{-1}$) with respect to the dihedral degree/10.

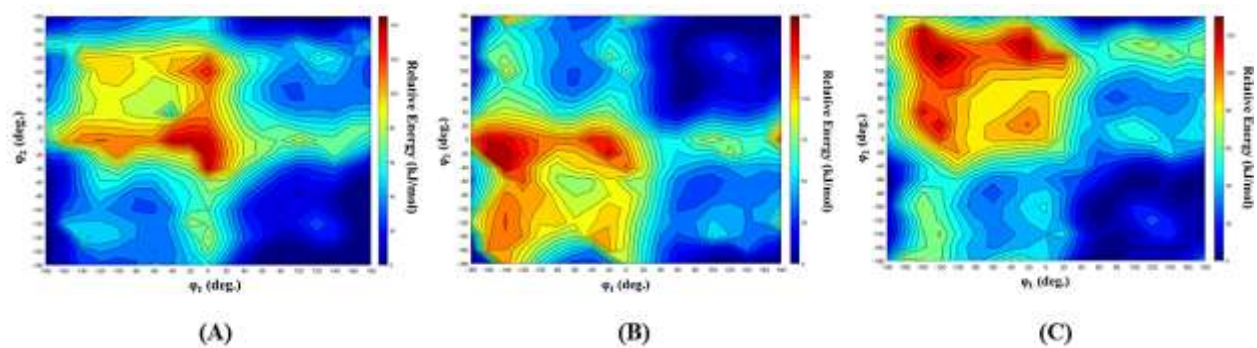


Figure 5.7. Relative energy (in kJ·mol⁻¹) contour heat plots for **A)** exo-meso-meso, **B)** exo-meso-racemo, and **C)** exo-racemo-racemo norbornene trimer configurations.

stable dihedral pair electronic energy. The plot demonstrates energy values in terms of $\text{kJ}\cdot\text{mol}^{-1}$ since this was the unit being used for the collaborative study, however our discussion will be using $\text{kcal}\cdot\text{mol}^{-1}$ to be consistent with the benchmark study. For the exo-meso-meso trimer, the lowest dihedral pair was determined to be when φ_1 was 80° and φ_2 was -160° (where the dihedral pair notation will be written as $(80^\circ, -160^\circ)$ henceforth), for exo-meso-racemo it was $(160^\circ, 160^\circ)$, and for exo-racemo-racemo it was $(180^\circ, -60^\circ)$.

Observation of the three plots hints to symmetry with respect to diagonal of the plots, from top left to bottom left for **A** and **C**, and bottom left to top right for plot **B**. It should be noted that minor imperfections to the symmetry of these plots are attributed to the manual corrections required to remove the hydrogen-hydrogen and carbon-hydrogen overlapping which was generated during the rotation of the molecules. For example, evaluation of the exo-meso-meso relative energy potential, $(120^\circ, -140^\circ)$ had a relative energy of $5.30 \text{ kcal}\cdot\text{mol}^{-1}$ compared to the equivalent $(140^\circ, -120^\circ)$ relative energy of $5.28 \text{ kcal}\cdot\text{mol}^{-1}$ showing agreement in relative energies. However, when comparing $(0^\circ, -100^\circ)$ to $(100^\circ, 0^\circ)$ the relative energies of $16.26 \text{ kcal}\cdot\text{mol}^{-1}$ and $20.53 \text{ kcal}\cdot\text{mol}^{-1}$, respectively, differed by $4.27 \text{ kcal}\cdot\text{mol}^{-1}$. **Figure 5.8** demonstrates the two structures which defer and will be used as a reference in the following short discussion. Visual observations demonstrate that the $(100^\circ, 0^\circ)$ configuration has less distance between the rotating groups of the trimer. Comparing the closest H atoms within the gap between the rotating groups, the $(100^\circ, 0^\circ)$ closest H atoms had a distance of $1.761 \text{ \AA}$ while $(0^\circ, -100^\circ)$ had a distance of $2.190 \text{ \AA}$, a difference between the two of $0.429 \text{ \AA}$. The differences in symmetry for this particular example could be due to the smaller gap in the rotating groups causing a less favorable electronic energy than the more favorable $(0^\circ, -100^\circ)$ configuration. As mentioned previously, a handful of structures had to be manually manipulated due to the overlapping of H and C atoms for specific dihedral pairs. It is possible that this manipulation caused some structures to converge to a low local minimum versus the others. It should also be noted that it could be possible for this to happen for dihedral pairs that were not manually manipulated as well, and the structures simply converged to different minimums. However, fairly decent symmetry can be observed for all norbornene trimer configurations. A reflection could also be produced where the lower minima of the plots could be used to provide plots that perfectly agree across the diagonal.

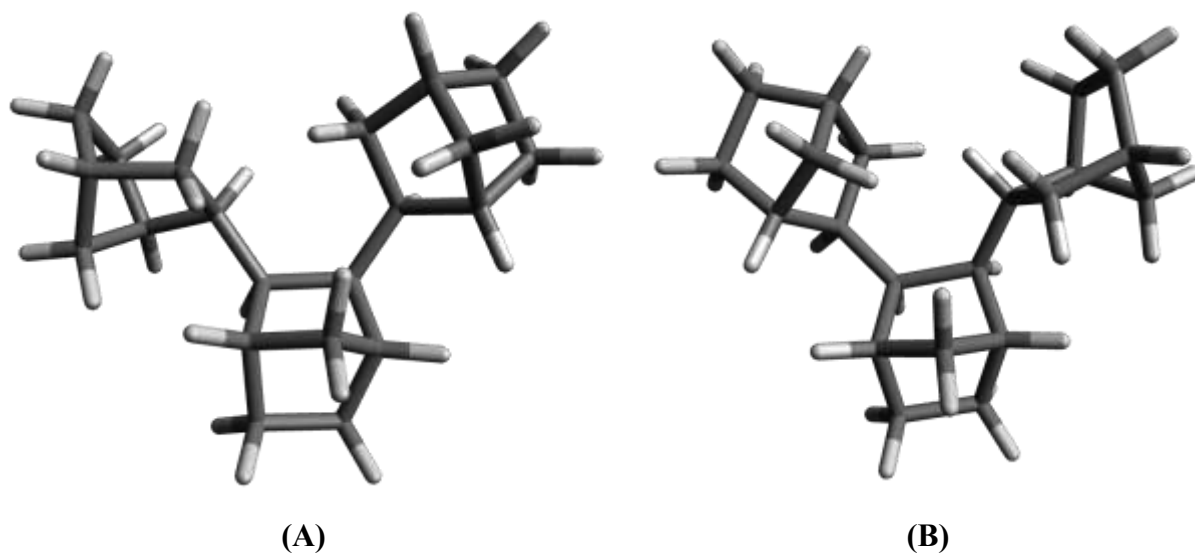


Figure 5.8. Example structures which diverged significantly from symmetry for *exo-meso-meso* **A)** (0° , -100°), and **B)** (100° , 0°).

Lastly, we state that these DFT calculations were performed since existing force fields do not allow flexibility on molecular simulations of polynorbornenes since they cannot reliably account for the rotation between two neighboring norbornenes.²⁴⁶ Previous work include the force field generated by Ahmed et al. who used quantum chemical data obtained from Hartree-Fock (HF) calculations with the STO-3G basis set to parameterize torsion angles.²⁴⁶ HF/STO-3G is a low-level of theory due to the lack of proper correlation treatment from HF. For that purpose, we utilized post-HF methods and density functional theory (DFT) for the generation of accurate potentials that assisted in the development of more accurate force fields for molecular simulations of polynorbornenes.

5.3.2. Vinyl-Addition Fluoroalkoxysilyl-Substituted Polynorbornene Membranes for CO₂/CH₄ Separation

The DFT analysis reveal that the strength of interactions for the nonfluorinated VAPNBs **P1–P3** series agrees with the experimental findings. In detail, all polymers **P1–P3** are expected to have similar interactions with both CO₂ and CH₄, as their substituents are alkoxy analogs to each other, which does not introduce additional interactions with either CO₂ or CH₄ gas molecules. As shown in **Figure 5.9**, the monomer–gas interaction ΔE is relatively consistent for both monomer–CO₂ interactions (-4.75 to -4.79 kcal·mol⁻¹) and monomer–CH₄ interactions (-2.48 to -3.11 kcal·mol⁻¹). In addition, as shown in **Figure 5.10**, the $\Delta\Delta E$ corresponds to a metric of the energy that is required to have one gas molecule perturb the monomer–monomer interaction and then form a gas–monomer interaction, which is defined as

$$\Delta\Delta E = |\Delta E_{ii} - \Delta E_{i-\text{gas}}|, \quad i = \mathbf{1}, \mathbf{2}, \mathbf{3}, \mathbf{1F}, \mathbf{2F}, \mathbf{3F} \quad (5-2)$$

where ΔE_{ii} represents the interaction energy between two monomer units and $\Delta E_{i-\text{gas}}$ the interaction energy between a simulated polymer repeat unit i and a gas molecule (CO₂ or CH₄). It is expected that a lower energy difference $\Delta\Delta E$ between gas–monomer interactions and monomer–monomer interactions correlate to relatively easier Henry’s law dissolution (k_d) of gas molecules into the polymer matrix. In regards to CO₂–monomer and monomer–monomer interactions, $\Delta\Delta E$ increased from 4.75 to 6.33 kcal·mol⁻¹ from **1** to **3**, which is in good agreement with the experimentally determined k_d that decreased from 1.43 to 0.94. For CH₄–monomer and monomer–monomer interactions, $\Delta\Delta E$ remains virtually similar for 2 to 3 (8.58 and 7.97

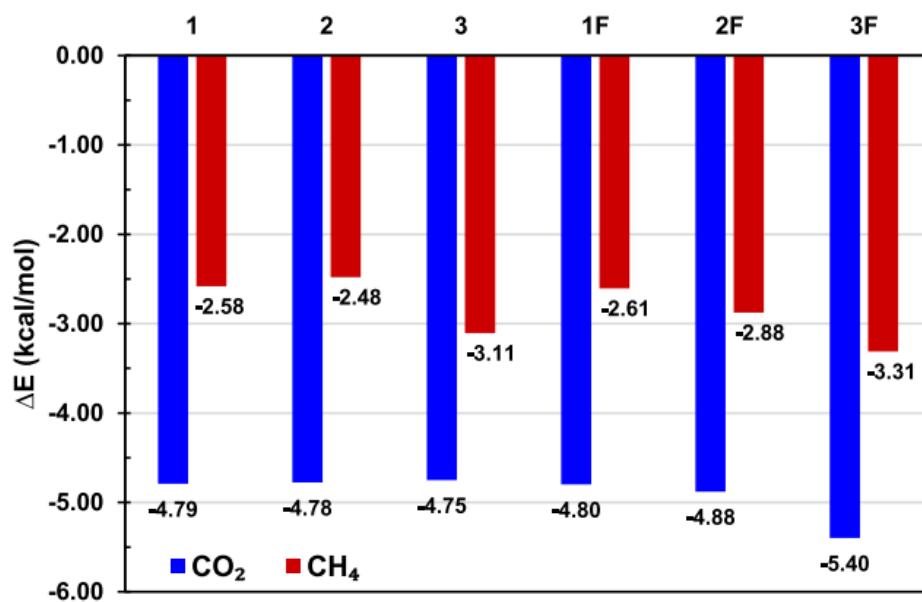


Figure 5.9. Calculated ΔE of gas–monomer interactions. Calculations were performed on saturated analogs of polymer repeat units **1–3** and **1F–3F**. Exclusion of the “P” simply is due to our computational methods only using the monomer.

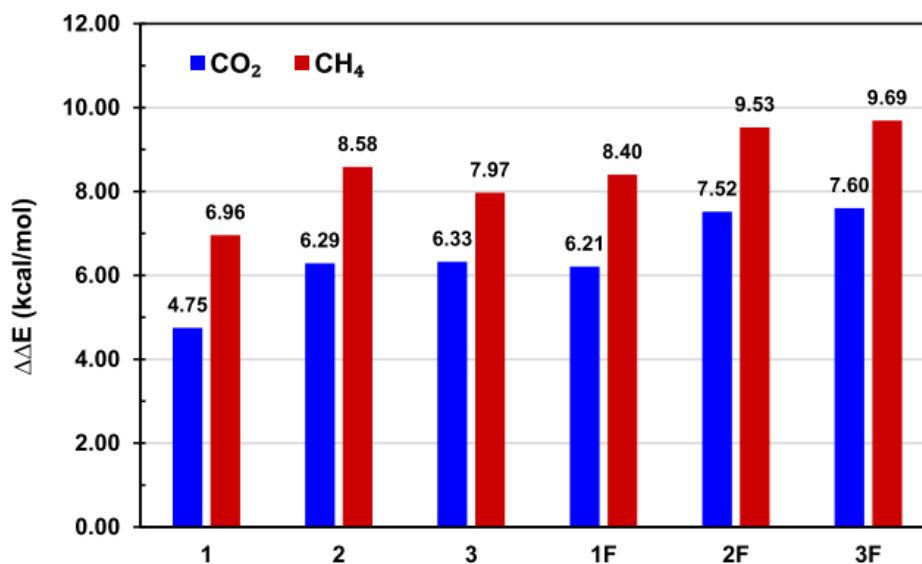


Figure 5.10. Calculated $\Delta\Delta E$ values for CO₂ and CH₄ for all nonfluorinated and fluorinated polymer series. Calculations were performed on saturated analogs of polymer repeat units **1–3** and **1F–3F**. Exclusion of the “P” simply is due to our computational methods only using the monomer.

kcal·mol⁻¹, respectively), which is in fair agreement with the experimentally measured values of $k_d = 0.48$ and 0.36 , respectively. This correlation is also in fair agreement for **P1**, if it is taken into consideration that **P1** has a significant Langmuir component that does not allow a direct comparison between **P1** and **P2/P3**.

Though the homopolymers **P2F** and **P3F** are not experimentally accessible, the computational analysis shows a decreasing ΔE for both CO₂ and CH₄ as fluorine content is increased from **1F** to **3F** (**Figure 5.9**), suggesting that favorable gas–monomer interactions are expected as the wt % of fluorinated content in the homopolymer is increased. $\Delta\Delta E$ (**Figure 5.10**), for both CO₂–monomer as well as CH₄–monomer interactions, and monomer–monomer interactions also increase from **1F** to **3F**, suggesting that the energy penalty required for both CO₂ and CH₄ molecules to disturb monomer–monomer interaction is increased. Therefore, a decreased k_d would be expected.

Though a comparison between DFT data and experimental results for **P1** and **P1F** can still be analyzed, these data do not align as well as those obtained for the nonfluorinated VAPNBs **P1–P3**. For CO₂–monomer interactions, it was previously reported that improved interactions may be observed due to the increase quadrupole–dipole/induced dipole–dipole interaction of CO₂ with fluorinated species; however, the ΔE observed in this case is similar (-4.79 and -4.80 kcal·mol⁻¹ for CO₂–**1** and CO₂–**1F**, respectively, **Figure 5.9**). For CH₄–monomer interactions, our initial hypothesis based on mutual immiscibility of fluorocarbon and hydrocarbon small molecules suggested that a decrease in ΔE may be expected; however, the observed ΔE is also similar (-2.58 and -2.61 kcal·mol⁻¹ for CH₄–**1** and CH₄–**1F**, respectively, **Figure 5.9**). Looking at $\Delta\Delta E$ (**Figure 5.10**), CO₂–monomer and monomer–monomer interactions increased from 4.75 kcal·mol⁻¹ for **1** to 6.21 kcal·mol⁻¹ for **1F**, suggesting that the energy penalty is higher for CO₂ to be inserted between two **1F** monomers and thus less likely to occur. However, the experimentally determined k_d values increase from 1.43 for **P1** to 2.01 for **P1F**, which show the opposite behavior predicted at the computational level. Similarly, looking at $\Delta\Delta E$ for CH₄–monomer and monomer–monomer interactions, these values increase from 6.96 kcal·mol⁻¹ for **1** to 8.40 kcal/mol for **1F**, which suggest that the energy penalty is higher for CH₄ to insert between two **1F** monomers (k_d values are 0.44 for **P1** to 0.43 for **P1F**). Though the presence of Langmuir component in both **P1** and **P1F** may influence a direct comparison of k_d

and $\Delta\Delta E$ values, these results indicate that this simple simulation model may not be ideal when comparing across nonfluorinated and fluorinated polymeric materials and modeling at the mesoscale can further elucidate these phenomena. We have already identified limitations in traditional force fields for atomistic simulations for the reliable modeling of polynorbornenes. For that reason, we performed the DFT calculations described in the previous collaboration project for the development a new force field based on accurate quantum chemical data that allowed us to perform large scale simulations for this class of materials.

Chapter 6 Closing Remarks

“No man should escape our universities without knowing how little he knows.” -Dr. Julius Robert Oppenheimer

The collected works presented in this dissertation, while focused on different subjects, were all aimed at providing contributions towards the resolution of global energy concerns present to modern society. The use of nuclear energy is a prominent energy source for overcoming significant environmental factors that are negatively affecting Earth's climate and as a cost efficient alternative to currently dominated fossil fuel energy sources. Nuclear energy does not emit CO₂ into the atmosphere, has a significantly higher energy output than fossil fuel-based power, and with the current production of microreactors and small modular reactors, will take a considerably smaller land space for application. While nuclear energy is imperative towards helping reduce negative environmental changes, the production of nuclear waste is an unavoidable consequence. Additionally, past CO₂ emissions that make up atmospheric CO₂ concentrations remains a problem that also needs to be addressed if a reversal of the negative climate impact is to occur. For these reasons, it was chosen to focus on both the treatment of nuclear waste by specifically focusing on actinide extractions and removal of historic CO₂ emissions by investigating calix[4]arenes as a material for implementation in direct air capture technologies.

On the subject of actinide ligation for the treatment of nuclear waste, the ligation of Ac(III), Th(IV), Am(III), and Cm(III) were investigated with relativistic quantum mechanics via density functional theory for the ligand 343HOPO and, with the exception of Am(III) with BTBP-based ligands. Using the experimentally available $\log\beta$ values (stability constants), potential extraction speciation pathways were determined by comparisons with the computationally determined stability constants. Utilizing the pathway determined for the BTBP-based ligands which agreed well with experimental observations, predictions were then made on known BTBP-based ligands with no experimental stability constants to observe the dependence of stability constants with respect to ligand structure. This first study laid the groundwork for large-scale screening of ligands for actinide extractions by providing a set of tools for the

computational determination of stability constants. Indeed, the second work presented in this dissertation took what was learned about the use BTBP ligands for actinide extractions and performed a large-scale screening of a BTBP-based ligand library that was generated. A subset of the library was used for DFT optimization to determine the stability constants for actinium extractions to use for machine learning analysis. Using the DFT data from the subset of ligands, active learning was used on the unexplored ligands in the library in pursuit of a set of guidelines to maximize the stability constant value for actinium extractions. This study determined that the symmetrical substitution at the *para* site with respect to the coordinating N atoms of the 2,2'-bipyridine group with an amine bridging functional group provided the highest stability constant values. These functional groups containing a higher composition of atoms, contained O and N atoms, especially hydroxyl groups, and contained cyclic functional groups, especially triangular-based groups. We then performed a transfer learning study to determine the transferability of trained machine learning algorithms on BTPhen-based ligands. This study concluded that DFT quality structures are required for adequate prediction of these BTPhen-based ligands when using machine learning algorithms trained on BTBP-based ligands.

On the subject of reducing the historic CO₂ emissions in the atmosphere, the use of calix[4]arenes was explored as possible materials for solid direct air capture technologies. Since, calix[4]arenes can be utilized in similar methods that are currently used in solid direct air capture technologies, a large-scale exploration of four different calix[4]arene families were explored. These families included the methylene bridging calix[4]arenes, amine bridging azacalix[4]arenes, oxygen bridging oxacalix[4]arenes, and sulfur bridging thiacalix[4]arenes. By utilizing CREST for screening the conformational space of the calix[4]arene families inclusion compound with CO₂, more appropriate starting geometries were acquired for DFT optimization. Enthalpy of adsorption values were determined from DFT calculations to compare with the estimated targeted enthalpy value for effective direct air capture applications. It was determined that the cone conformer and the symmetrical 1,3-alternate conformations are preferable for maximizing the inclusion enthalpy of CO₂, with the cone conformation performing overall better than the 1,3-alternate conformation. The optimized structures and respective enthalpy values were used to determine the structure-property prediction of these calix[4]arenes. The partial correlation across the calix[4]arene families and their respective inclusion enthalpy of CO₂ was

determined to be heavily weighted by the calix[4]arene family with the other three calix[4]arene families having virtually no correlation.

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Vita

Jeffrey Alexander Laub was born in Lexington, Kentucky but spent most of his life growing up in Claremore, Oklahoma and Amherst, VA. After graduating from Amherst County High School in 2014, Jeffrey attended Central Virginia Community College where he received his associate's degree in arts and sciences in 2016 and found a passion in Nuclear Chemistry and Physics. After CVCC, Jeffrey transferred to Randolph College where he earned his B.S. in Chemistry with an emphasis in computational chemistry under the mentorship of Dr. Jesse Kern, and a minor in History in 2018. During his time at Randolph College, Jeffrey received the American Chemical Society's 2018 undergraduate award in Physical Chemistry. Jeffrey then attended Eastern Kentucky University and earned an M.S. in physical chemistry under the mentorship of Dr. Pei Gao in 2020. During his time at Eastern Kentucky University, Jeffrey was the recipient of three awards including the Harry Smiley memorial graduate award given to the top returning graduate student, the ECU photon fellowship given for contributions towards environmental responsibility and sustainability, and the HypercubeTM Scholar award for excellence in Physical Chemistry. With a drive for Nuclear Chemistry, Jeffrey then attended the University of Tennessee – Knoxville to pursue a Ph.D. in Physical Chemistry with a graduate certificate in Radiochemistry where he worked under the mentorship of Dr. Konstantinos Vogiatzis who allowed him to pursue research in Actinide Chemistry and hone his skills. During his time at UTK, Jeffrey received the outstanding Ph.D. candidate award, an American Nuclear Society graduate scholarship, and the Eugene John Barber fellowship in Physical Chemistry. Jeffrey is hopeful that he will be able to continue into the industry of Nuclear Chemistry and apply the knowledge and skills learned throughout his entire educational experience to advance the field and contribute as much as possible in the pursuit of excellence.