

UNIVERSIDAD AUTÓNOMA DE NUEVO LEÓN

FACULTAD DE INGENIERÍA MECÁNICA Y ELÉCTRICA



HAFNIUM OXIDE NANOCRYSTALS GRAFTED WITH  
ORGANIC MOLECULES SYNTHESIZED IN SUBCRITICAL  
WATER

POR

**LIC. MARIEL QUINTANILLA RODRÍGUEZ**

T E S I S

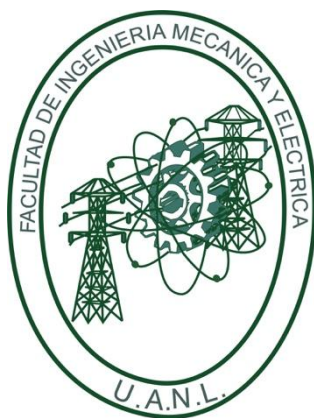
EN OPCIÓN AL GRADO DE MAESTRÍA EN CIENCIAS DE LA  
INGENIERÍA CON ORIENTACIÓN EN NANOTECNOLOGÍA

CIUDAD UNIVERSITARIA

29 DE MAYO DE 2026

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**Posgrado**

Los miembros del Comité de Evaluación de Tesis recomendamos que la Tesis "Hafnium Oxide Nanocrystals Grafted with Organic Molecules Synthesized in Subcritical Water", realizada por el estudiante Mariel Quintanilla Rodríguez, con número de matrícula 1866983, sea aceptada para su defensa como requisito parcial para obtener el grado de Maestría en Ciencias de la Ingeniería con Orientación en Nanotecnología.

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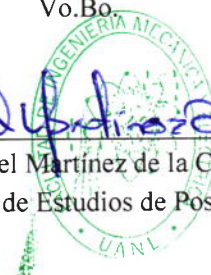
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The members of the Thesis Evaluation Committee recommend that the thesis entitled “HAFNIUM OXIDE NANOCRYSTALS GRAFTED WITH ORGANIC MOLECULES SYNTHESIZED IN SUBCRITICAL WATER”, carried out by the student Mariel Quintanilla Rodríguez, student ID 1866983, be accepted for its defense as a partial requirement for obtaining the degree of Master of Science in Engineering with a Specialization in Nanotechnology.

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October 2026

## Dedication

To God, Jesus Christ, and the Virgin Mary, for their eternal love and constant guidance. With gratitude and humility, I dedicate my life to you, my efforts, my work, and everything I do.

To my grandfather, Loreto, who was one of the people who loved me the most and taught me so much. Even though you are no longer here, you continue guiding me every day. You were my example of kindness, wisdom, courage, and perseverance. Your words still resonate in my mind, and your advice continues to guide my steps. Throughout this master's degree, I often wondered what you would have said if you had known that one day I would travel to Japan and fulfill a dream that once seemed so far away. I hope you will be proud.

To my parents, Mario and Elena, for their unconditional love, support, and dedication. Thank you for everything you have done for me and for always believing in my dreams. I love you with all my heart.

To my family, thank you for your constant support, encouragement, and love throughout every stage of my life.

To Sofia and my nieces and nephews, thank you for filling my life with joy and laughter. I hope that one day I can be an example for you, just as so many people have been for me.

I dedicated this thesis to everyone who believed in me, supported me, and walked beside me throughout this journey. This achievement represents not only years of study and research, but also growth, resilience, friendship, faith, and the fulfillment of a dream.

大丈夫さ 時計のように  
巡り巡って元の場所へと

*Everything will be alright. Like a clock, we go around and around, eventually returning to where we belong.*  
— SEVENTEEN, Circles

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# **Hafnium Oxide Nanocrystals Grafted With Organic Molecules Synthesized In Subcritical Water**

## **Abstract**

Hafnium oxide nanoparticles were synthesized through a hydrothermal process under subcritical water conditions to obtain highly crystalline and morphologically uniform structures. This environmentally friendly approach allows control over key synthesis parameters such as temperature, reaction time, and pH, minimizing the use of harmful organic solvents. The influence of these variables on the structural and surface properties of  $\text{HfO}_2$  was systematically investigated.

The resulting nanoparticles exhibited a stable monoclinic phase and improved crystallinity under optimized conditions. Following synthesis, the materials were surface modified with biocompatible organic molecules, modifying their surface chemistry and potential for future biomedical applications. Comprehensive physicochemical characterization confirmed the structural integrity, surface functionalization, and stability of the modified nanoparticles.

These findings highlight the effectiveness of subcritical water as a sustainable synthesis medium and demonstrate that controlled hydrothermal processing can produce hafnium oxide nanoparticles with tunable properties. The obtained materials are promising for future biomedical applications, particularly as promising candidates for future biomedical applications, particularly as radiosensitizer nanomaterials or drug delivery.

## **Keywords**

Hafnium oxide · Nanoparticles · Surface Modification · Subcritical Water · Hydrothermal Synthesis · Functionalization.

# Chapter 1 Introduction

## 1.1. Hafnium oxide

Hafnium oxide ( $\text{HfO}_2$ ), also known as hafnia, is a metal oxide characterized by outstanding chemical and physical properties, which make it a material of high interest for a wide range of technological applications.

Regarding its crystalline structure,  $\text{HfO}_2$  can exist in monoclinic, tetragonal, and cubic phases, with the monoclinic phase being the most thermodynamically stable at ambient conditions. The remaining phases typically require elevated temperatures or specific synthesis environments for stabilization and can be identified through techniques such as X-ray diffraction (XRD) and other crystallographic methods [1]. Thermodynamic analyses have demonstrated that phase stability in  $\text{HfO}_2$  strongly depends on parameters such as temperature and pressure, which directly influence the crystallinity of the synthesized material [2].

Among the most remarkable intrinsic properties of  $\text{HfO}_2$  are its high melting point, chemical inertness, and wide band gap, characteristics that define its dielectric behavior, which is significantly higher than that of many conventional oxides. These attributes have promoted its adoption as a high-k dielectric material in semiconductor devices, where it has been employed, for instance, as a replacement for silicon dioxide in gate insulation layers to reduce leakage currents and enable continued device scaling [3].

Beyond microelectronic applications,  $\text{HfO}_2$  has also been extensively studied due to its optical properties, particularly its high refractive index and transparency across visible to infrared wavelengths. These features make it suitable for optical coatings, waveguides, and various optoelectronic structures that require stable, low-loss dielectric layers [4]. Thin-film studies have shown that variations in processing conditions and microstructure can significantly influence both optical transmittance and refractive index, highlighting the importance of crystalline and morphological control to achieve tailored optical performance [5].

Collectively, these properties establish  $\text{HfO}_2$  as a versatile material with strong relevance in both electronic and optoelectronic applications. Consequently, the ability to tailor its phase composition and microstructure through controlled synthesis strategies is essential not only for device performance but also for advancing research in high-k dielectrics and photonic materials [6].

In addition to electronic and photonic technologies, hafnium oxide has also gained relevance in biomedical and nanomedical research.

Metal oxide nanoparticles have received considerable attention in recent years due to their applications in catalysis, optics, electronics, and biomedicine. Among them, Hafnium oxide stands out for its high thermal stability, dielectric properties, and potential in nanomedicine and radiotherapy [7].

In the biomedical field,  $\text{HfO}_2$  nanoparticles have demonstrated outstanding performance as radiosensitizer in cancer therapies, and the possibility of tuning their size and surface area through aqueous synthesis offers advantages for improving biocompatibility and tumor selectivity [8]. These characteristics make  $\text{HfO}_2$  a key candidate for nanomedical applications, especially when combined with emerging targeting and localized release technologies.

Hafnium oxide nanoparticles have attracted considerable attention due to their excellent physicochemical stability, high atomic number, favorable biocompatibility, and versatile surface chemistry. In the biomedical field,  $\text{HfO}_2$  nanoparticles have demonstrated outstanding advantages as radiosensitizers in cancer therapy, while the ability to adjust their size and surface properties via aqueous synthesis offers significant advantages for improving biocompatibility and tumor selectivity [8]. These characteristics make  $\text{HfO}_2$  a promising nanoplatform for cancer nanomedicine, particularly when combined with targeted drug delivery and localized therapeutic strategies. More generally, recent advances in nanomedicine have established nanoparticles as versatile platforms for cancer diagnostics, drug delivery, imaging, and immune stimulation [9]. In particular, nanoparticle-based systems enable the localized and controlled delivery of therapeutic agents, improving treatment efficacy and reducing systemic toxicity [10–14]. Furthermore, the combination of nanotechnology with conventional therapeutic approaches has demonstrated greater antitumor efficacy in preclinical studies, although significant challenges remain regarding biocompatibility, tumor heterogeneity, intratumoral penetration, controlled drug release and clinical translation [10,11,15–17].

## **1.2.Synthesis strategies and surface functionalization**

In terms of synthesis, the use of water under subcritical conditions and supercritical conditions has established itself as a green and efficient strategy for producing nanomaterials, as it allows morphology and crystallinity to be controlled by regulations parameters such as temperature, pressure, pH, while reducing the use of toxic organic solvents [18]. An outstanding example was

reported by Garcia Montes et al. (2020), who successfully synthesized  $\text{HfO}_2$  nanoparticles with shape control (Spherical, cylindrical and eruciform) under supercritical conditions, using organic molecules as surface modifiers. This study demonstrated that carboxylic acids not only stabilize the surface but also directly influences crystal growth and the final morphology of  $\text{HfO}_2$  [19].

Although the most recent literature on  $\text{HfO}_2$  also focuses on nonaqueous solvothermal routes [20], several studies have shown that high-pressure aqueous methods are a promising avenue for obtaining highly crystalline nanostructures with advanced applications. Indeed,  $\text{HfO}_2$  nanoparticles synthesized under these conditions exhibit improved dispersion properties and high potential for biomedical and optoelectronic applications [8,19].

Overall, recent research highlights that combining sub/supercritical water chemistry with  $\text{HfO}_2$  nanoparticles design opens an attractive prospect for technological and biomedical applications, although challenges related to scalability and precise control of crystalline phases remain [18,21].

### **1.3.Scope of the research**

This research focuses on the synthesis and characterization of hafnium oxide nanoparticles using hydrothermal synthesis under subcritical conditions. The experimental work was made at the Center for Technological Research and Development (CIDET) of the Faculty of Mechanical and Electrical Engineering (FIME–UANL), in collaboration with Nagoya University.

The scope of this study includes the use of organic molecules as surface modifiers to influence the growth and stability of the nanoparticles. Structural, morphological, thermal, and colloidal properties of the synthesized nanoparticles were analyzed using X-ray diffraction (XRD), with crystallite size estimation based on the Scherrer equation and thermogravimetric analysis (TGA).

This work is limited to fundamental experimental analysis and does not include in vitro or in vivo biological evaluations, device fabrication, or clinical assessments. The study aims to establish correlations between synthesis conditions and the resulting physicochemical properties of  $\text{HfO}_2$  nanoparticles, providing a basis for future research in biomedical and technological applications.

## 1.4.Objectives

### General Objective

synthesize and evaluate hydrothermally derived  $\text{HfO}_2$  nanoparticles under subcritical conditions, focusing on the impact of organic modification on their surface and structural properties.

### Specific Objectives

- Synthesize hafnium oxide nanoparticles grafted with organic molecules using the hydrothermal method under subcritical conditions with controlled synthesis parameters.
- Obtain crystalline monoclinic  $\text{HfO}_2$  nanoparticles and determine their crystal structure and average crystallite size using X-ray diffraction.
- Evaluate the thermal stability of nanoparticles and assess the presence of organic residues associated with surface modification using thermogravimetric analysis.
- Identify functional groups and interactions between  $\text{HfO}_2$  nanoparticles and organic modifiers using Fourier transform infrared spectroscopy.

## 1.5.Hypothesis

Hydrothermal synthesis of hafnium oxide in subcritical water under controlled conditions enables the formation of nanoparticles with a well-defined monoclinic phase and reproducible structural properties by grafting the nanostructures via the incorporation of organic molecules (selected organic molecules including carboxylic acids, catechol containing compounds, polymers and neurotransmitters) to promote chemical or physical interactions at the nanoparticle surface, modifying the surface without significantly altering the internal crystalline structure.

## Chapter 2 Literature Review

### 2.1. Nanomaterials and Nanomedicine

Nanotechnology has transformed biomedical research by enabling the design and manipulation of materials at the nanoscale, where physicochemical properties differ significantly from those of bulk materials due to increased surface-to-volume ratio and quantum-scale effects [22,23].

Nanomedicine refers to the application of nanoscale materials and devices for disease diagnosis, monitoring, prevention, and therapy. The integration of engineered nanoparticles into medical practice has enabled advancements in drug delivery, imaging, immunotherapy, and radiation-based treatments [24,25].

In oncology, nanoparticles are particularly attractive due to their ability to enhance therapeutic selectivity and reduce systemic toxicity. Smart nanoparticle systems have been developed to respond to tumor microenvironment stimulus such as pH, hypoxia, and enzymatic activity, improving therapeutic precision [9]. Furthermore, nanoparticle-mediated delivery platforms have demonstrated significant potential in enhancing in situ cancer vaccination and immune activation [11].

Multifunctional nanoplateforms combining chemotherapy, photothermal therapy (PTT), photodynamic therapy (PDT), and immunomodulation have shown promising synergistic effects in preclinical models [13,15]. The performance of these systems depends strongly on structural properties, particle size distribution, crystallinity, and surface chemistry, which must be precisely controlled during synthesis and post-functionalization.

#### Definition of Nanomaterials

Nanomaterials are defined as materials possessing at least one external dimension in the nanoscale range, typically between 1 and 100 nm. Within this dimensional regime, materials exhibit physicochemical behaviors that differ significantly from those of their bulk counterparts due to the dominance of surface and quantum-related effects [22,26].

The reduction of particle size to the nanoscale leads to a dramatic increase in the fraction of atoms located at or near the surface. This elevated surface-to-volume ratio enhances surface energy and reactivity, directly influencing

catalytic performance, adsorption phenomena, and interaction with surrounding environments [23]. In the context of biomedical systems, these surface-dominated properties determine colloidal stability, protein adsorption, cellular internalization, and overall biological response [24].

Beyond geometric considerations, nanomaterials may also exhibit size-dependent modifications in electronic structure, optical absorption, and radiation interaction. Such effects are particularly relevant for inorganic nanoparticles employed in therapeutic applications, where energy absorption and transfer mechanisms depend strongly on nanoscale structural characteristics [25].

Therefore, the definition of nanomaterials extends beyond a simple dimensional threshold; it encompasses a regime in which surface phenomena, phase stability, and size-dependent physicochemical properties govern material behavior. Understanding these foundational principles is essential for the rational design of inorganic oxide nanoparticles intended for advanced biomedical applications.

### **Size-Dependent Physicochemical Properties**

When materials are reduced to the nanoscale, their physicochemical properties deviate significantly from those of bulk solids due to the increasing dominance of surface atoms and the modification of thermodynamic stability. One of the most critical parameters is the surface-to-volume ratio, which increases dramatically as particle size decreases. This effect leads to higher surface energy, enhanced reactivity, and altered phase [22,23].

From a thermodynamic perspective, nanoscale materials exhibit size-dependent changes in Gibbs free energy. The contribution of surface energy becomes comparable to bulk lattice energy, influencing structural stability and potentially favoring metastable polymorphs over thermodynamically stable bulk phases [27]. Such behavior is particularly relevant in metal oxide systems, where polymorphism can directly affect electronic structure, mechanical properties, and radiation interaction efficiency [28].

Crystallinity and particle size are also strongly correlated. As particle size decreases, peak broadening in X-ray diffraction (XRD) patterns become evident due to finite crystallite size and lattice strain effects. This relationship is commonly described by the Scherrer equation [29], which allows estimation of

crystallite size from diffraction peak broadening [30]. Control of crystallite size is therefore essential in tailoring nanoparticle performance.

Optical and electronic properties may also shift at the nanoscale due to quantum confinement effects. Although more pronounced in semiconductor nanoparticles below the 10 nm, such modifications can influence absorption cross-sections and energy transfer mechanisms. In the context of high-atomic-number (high-Z) inorganic oxides, nanoscale structuring can enhance interaction with ionizing radiation, improving secondary electron generation and localized energy deposition [25].

Additionally, surface chemistry becomes increasingly influential as size decreases. Surface charge, defect density, and hydroxylation state determine colloidal stability, dispersion behavior, and interfacial interactions in aqueous environments. These parameters are critical for materials synthesized via hydrothermal or subcritical water methods, where reaction conditions directly impact nucleation, growth kinetics, and final nanoparticle morphology [31].

Altogether, size-dependent physicochemical properties form the scientific foundation for the rational design of inorganic oxide nanoparticles for advanced technological and biomedical applications.

### **Inorganic Nanoparticles in Biomedical Applications**

Inorganic nanoparticles are a major class of nanomaterials distinguished by their structural stability, tunable surface chemistry, and diverse functional properties, making them particularly suitable for biomedical applications. These materials include metal oxides, noble metals, and other inorganic frameworks that can be engineered to perform targeted therapeutic and diagnostic functions.

Metal oxide nanoparticles, such as iron oxide ( $\text{Fe}_3\text{O}_4$ ), cerium oxide ( $\text{CeO}_2$ ), and  $\text{HfO}_2$ , have garnered significant attention due to their inherent physicochemical properties and biocompatibility. Iron oxide nanoparticles, for instance, have been extensively studied as magnetic resonance imaging (MRI) contrast agents and hyperthermia mediators due to their superparamagnetic behavior and controllable size distributions [32]. Cerium oxide nanoparticles have demonstrated antioxidant activity with potential applications in oxidative stress mitigation and tissue [33].

The functional versatility of inorganic nanomaterials extends to therapeutic delivery, where their robust cores serve as platforms for the conjugation or encapsulation of drugs, genetic material, or imaging agents. This capability has enabled combination therapies in which inorganic nanoparticles act both as carriers and active agents, enhancing therapeutic index while reducing systemic toxicity [34].

Recent advances also emphasize the integration of inorganic nanoparticles with biological systems for immunomodulation and vaccine delivery. For example, certain oxide nanoparticles can be engineered to interact with immune cells to promote antigen presentation or controlled cytokine release, contributing to improved immune responses in cancer immunotherapy [35].

Furthermore, inorganic nanoparticles are increasingly being investigated for theragnostic purposes, integrating therapeutic and diagnostic functions within a single platform. Materials such as gold nanoparticles, quantum dots, and doped metal oxides enable simultaneous imaging and treatment monitoring, enhancing the precision and real-time assessment of therapeutic outcomes [36].

Overall, the unique properties of inorganic nanomaterials underpin their widespread exploration in diverse biomedical applications, from imaging and drug delivery to immunotherapy and combined modality treatments.

## **2.2. Hafnium Oxide**

Hafnium oxide is a transition metal oxide characterized by its high density, wide band gap, strong chemical inertness, and exceptional thermal stability [37]. Owing to these properties,  $\text{HfO}_2$  has been extensively investigated in microelectronics [38], catalysis, and high-temperature applications. In recent years, its high atomic number ( $Z = 72$ ) and favorable radiation interaction properties have also positioned it as a promising material for biomedical applications, particularly in radiation-enhanced cancer therapy [37,39].

$\text{HfO}_2$  is a polymorphic material whose physicochemical behavior depends strongly on crystal structure, particle size, and synthesis conditions. At the nanoscale, modifications in phase stability, surface chemistry, and defect density may significantly influence functional performance. These characteristics are especially relevant when  $\text{HfO}_2$  is engineered in nanoparticulate form for biomedical use.

The combination of structural robustness, high density (approximately  $9.68 \text{ g}\cdot\text{cm}^{-3}$ ) [40], and large photoelectric absorption cross-section makes  $\text{HfO}_2$  particularly attractive for applications requiring efficient energy deposition under ionizing radiation[39]. Furthermore, its chemical stability minimizes unwanted degradation or ion release, contributing to favorable biocompatibility profiles reported in many studies [41].

Given these properties,  $\text{HfO}_2$  nanoparticles represent a material-science-driven approach to enhance radiotherapeutic efficiency while maintaining structural and chemical stability under physiological conditions. A detailed understanding of its physicochemical characteristics, crystalline phases, and biological interactions is therefore essential for rational material design.

### **Physicochemical Properties**

Hafnium oxide is a wide band gap transition metal oxide characterized by high density, chemical inertness, and strong structural stability. In its bulk form,  $\text{HfO}_2$  exhibits a band gap in the range of 5.3–5.9 eV, classifying it as an electrical insulator with excellent dielectric properties [42]. These electronic characteristics have historically positioned  $\text{HfO}_2$  as a high-k dielectric material in microelectronic devices.

One of the most significant physicochemical attributes of  $\text{HfO}_2$  is its high density ( $\sim 9.68 \text{ g}\cdot\text{cm}^{-3}$ ) combined with a high atomic number ( $Z = 72$ ). This combination contributes not only to its mechanical robustness but also to enhanced interaction with ionizing radiation. The mass attenuation coefficient of hafnium-based compounds is higher than that of low-Z materials, making nanoscale  $\text{HfO}_2$  particularly attractive for radiation-mediated applications.

From a thermodynamic perspective,  $\text{HfO}_2$  exhibits strong lattice energy due to the highly stable Hf–O bonds. The enthalpy of formation is significantly negative, reflecting its intrinsic chemical stability and resistance to decomposition under normal conditions. This stability contributes to its corrosion resistance and low solubility in aqueous environments, which are essential properties for biomedical implementations [43].

At the nanoscale, surface energy plays a dominant role in determining physicochemical behavior. As particle size decreases, the proportion of surface atoms increases, influencing defect concentration, hydroxylation state, and surface charge. Oxygen vacancies are common point defects in  $\text{HfO}_2$  and can modify electronic structure, local charge distribution, and catalytic or redox

behavior [44]. These surface-related phenomena are especially relevant for hydrothermally synthesized nanoparticles, where reaction conditions directly impact nucleation, growth kinetics, and final particle morphology.

Additionally,  $\text{HfO}_2$  demonstrates high hardness and mechanical strength, with reported Vickers hardness values exceeding 10 GPa in bulk form. Such mechanical resilience contributes to structural integrity under irradiation and thermal cycling conditions.

In nanoparticulate systems, physicochemical properties such as crystallite size, phase composition, surface chemistry, and defect density become strongly interdependent. Therefore, careful control of synthesis parameters directly determines the final functional performance of  $\text{HfO}_2$  nanoparticles.

### **Crystalline Phases**

Hafnium oxide is a polymorphic material that exhibits multiple crystalline phases depending on temperature, pressure, particle size, and synthesis conditions. In bulk form,  $\text{HfO}_2$  presents three primary crystallographic phases: monoclinic, tetragonal, and cubic. At ambient conditions, the monoclinic phase (space group  $P2_1/c$ ) is thermodynamically stable. Upon heating,  $\text{HfO}_2$  undergoes a phase transition to the tetragonal structure around the 1700 °C, followed by transformation to the cubic fluorite-type phase at temperatures above the 2600 °C [43].

The monoclinic phase is characterized by distorted  $\text{HfO}_7$  coordination polyhedral and lower symmetry, which contribute to its thermodynamic stability at room temperature. In contrast, the tetragonal and cubic phases exhibit higher symmetry and more uniform Hf–O coordination environments. These structural differences significantly influence mechanical properties, dielectric response, and defect distribution within the lattice [42].

At the nanoscale, phase stability strongly becomes dependent on size. The increased surface energy associated with small crystallites can stabilize metastable phases, particularly the tetragonal phase, at temperatures well below their bulk transition points. This phenomenon arises because the surface energy contribution to total Gibbs free energy becomes comparable to bulk lattice energy as particle size decreases [45]. Experimental and computational studies have shown that below a critical crystallite size (typically below approximately 20–30 nm), tetragonal  $\text{HfO}_2$  can be stabilized at room temperature without external pressure or dopants.

Oxygen vacancies and lattice defects also play a significant role in phase stabilization. Defect chemistry can alter local bonding environments and reduce the energy barrier between polymorphs. In doped systems or nanoparticles synthesized under non-equilibrium conditions, such as hydrothermal or solvothermal processes, mixed-phase compositions are commonly observed [44].

Understanding phase behavior is particularly important in nanoparticulate  $\text{HfO}_2$  systems because crystalline phase influences density, mechanical strength, dielectric properties, and radiation interaction mechanisms. Control over synthesis parameters directly determines crystallite size and phase composition, thereby affecting functional performance in advanced applications.

### **Thermal and Chemical Stability**

Hafnium oxide is widely recognized for its exceptional thermal and chemical stability, properties that arise from the strong ionic–covalent character of the Hf–O bond and its highly negative enthalpy of formation. The standard enthalpy of formation of  $\text{HfO}_2$  is approximately  $-1080 \text{ kJ}\cdot\text{mol}^{-1}$ , reflecting the high thermodynamic stability of the oxide phase and its resistance to decomposition under ambient and elevated temperatures [46].

Thermally,  $\text{HfO}_2$  exhibits one of the highest melting points among metal oxides (around  $2758^\circ\text{C}$ ), which makes it suitable for extreme-temperature applications. Its high lattice energy and strong metal–oxygen bonding contribute to remarkable structural integrity under thermal cycling conditions. These characteristics are particularly relevant for nanoparticle systems subjected to calcination or post-synthesis treatments, where phase transformations and crystallite growth may occur [43].

Chemically,  $\text{HfO}_2$  demonstrates strong resistance to corrosion and oxidation. It is insoluble in water and exhibits high stability in physiological environments, which is a critical requirement for biomedical applications. Dissolution of hafnium ions under neutral conditions is minimal due to the oxide's low solubility product, reducing the risk of unwanted ion release and cytotoxicity. However, under highly acidic or strongly basic conditions, partial surface dissolution or hydroxylation may occur, modifying surface chemistry without compromising bulk stability [44].

In aqueous synthesis routes, such as hydrothermal or subcritical water methods,  $\text{HfO}_2$  stability is influenced by pH, temperature, and precursor speciation. Hydrolysis and condensation reactions govern nucleation and particle growth, while subsequent thermal treatment enhances crystallinity and phase purity. Importantly, despite its chemical inertness, surface hydroxyl groups can form during aqueous synthesis, enabling further functionalization without altering the intrinsic oxide core.

Under ionizing radiation,  $\text{HfO}_2$  maintains structural integrity due to its high displacement energy and strong lattice bonding. While radiation may induce point defects such as oxygen vacancies, the material exhibits high resistance to amorphization compared to less stable oxides [42]. This radiation tolerance further supports its suitability in applications involving high-energy exposure.

Overall, the combination of high melting temperature, strong lattice energy, corrosion resistance, and radiation tolerance establishes  $\text{HfO}_2$  as a robust inorganic material platform. These properties are particularly advantageous for nanoparticle systems intended for radiation-enhanced biomedical applications, where both structural stability and chemical inertness are essential.

### **High Atomic Number and Radiosensitization Potential**

Hafnium oxide has attracted considerable attention in radiation-enhanced cancer therapy due to the high atomic number of hafnium ( $Z = 72$ ) and its high mass density. Materials composed of high- $Z$  elements exhibit significantly larger photoelectric absorption cross-sections compared to soft biological tissues, particularly in the kilovoltage (kV) and lower megavoltage (MV) energy ranges commonly used in radiotherapy. The probability of photoelectric interaction is proportional to  $Z^3/E^3$ , where  $Z$  is the atomic number and  $E$  is photon energy, highlighting the strong dependence of radiation absorption on atomic composition [47].

When exposed to ionizing radiation,  $\text{HfO}_2$  nanoparticles can locally amplify energy deposition through enhanced photoelectric absorption, followed by emission of secondary electrons such as photoelectrons, Auger electrons, and Compton electrons. These low-energy electrons deposit energy within nanometric distances, increasing localized DNA damage and promoting the formation of double-strand breaks in tumor cells [48]. This phenomenon is commonly referred to as physical dose enhancement.

In addition to physical interactions,  $\text{HfO}_2$  nanoparticles may contribute to chemical radiosensitization mechanisms. Secondary electron cascades generated at the nanoparticle surface can promote radiolysis of water molecules, leading to increased production of reactive oxygen species (ROS), including hydroxyl radicals (OH). Elevated ROS concentrations amplify oxidative stress within cancer cells and further enhance cytotoxic effects induced by radiation [49].

The high density of  $\text{HfO}_2$  (approximately  $9.68 \text{ g}\cdot\text{cm}^{-3}$ ) further supports its radiosensitization potential by increasing mass attenuation coefficients relative to surrounding tissues. Compared to lower-Z oxides, Hafnium-based materials demonstrate superior radiation interaction efficiency, which allows therapeutic enhancement without increasing the delivered radiation dose to healthy tissues [50].

Importantly,  $\text{HfO}_2$  nanoparticles combine this radiation-interaction capability with strong structural and chemical stability. Unlike metallic nanoparticles that may undergo surface oxidation or dissolution, the oxide form provides intrinsic chemical robustness while preserving high-Z characteristics. This dual advantage makes  $\text{HfO}_2$  a promising inorganic nanomaterial for radiotherapy enhancement strategies.

Overall, the radiosensitization potential of  $\text{HfO}_2$  arises from a synergistic combination of physical dose amplification, secondary electron emission, and enhanced ROS generation, all supported by its high atomic number and density. These properties provide a strong materials-science rationale for the development of  $\text{HfO}_2$  nanoparticles as radiation-enhancing agents.

### **Biological Interactions of $\text{HfO}_2$ Nanoparticles**

The biological behavior of  $\text{HfO}_2$  nanoparticles is governed by a combination of physicochemical parameters including particle size, crystallinity, surface charge, aggregation state, and surface functionalization. Unlike soluble metal salts,  $\text{HfO}_2$  exhibits low aqueous solubility and strong chemical inertness, which significantly limits ionic release under physiological conditions. This intrinsic stability contributes to favorable biocompatibility profiles reported in both vitro and in vivo studies [50].

Cellular internalization of  $\text{HfO}_2$  nanoparticles typically occurs through energy-dependent endocytic pathways, including clathrin-mediated and caveolae-mediated mechanisms. Once internalized, nanoparticles are commonly localized within endosomal and lysosomal compartments. Their biological

response is strongly dependent on surface chemistry; hydroxylated or functionalized surfaces may influence protein corona formation, which in turn modulates cellular uptake, immune recognition, and biodistribution [51].

Cytotoxicity studies indicate that non-functionalized  $\text{HfO}_2$  nanoparticles exhibit low intrinsic toxicity at therapeutically relevant concentrations. In radiotherapy-enhancement applications, cytotoxic effects are observed under irradiation conditions, where nanoparticles function as radiation amplifiers rather than independent toxic agents [48]. This selective activity is a critical advantage, as it minimizes off-target effects in non-irradiated tissues.

In vivo investigations have demonstrated that  $\text{HfO}_2$  nanoparticles can remain localized within tumor tissues following intratumoral administration, with limited systemic redistribution. Their high density and chemical stability reduce degradation and clearance rates compared to more reactive nanomaterials. Additionally, surface modification strategies have been explored to improve colloidal stability, circulation time, and targeting efficiency [52].

Another important consideration is oxidative stress. While  $\text{HfO}_2$  is chemically stable, under irradiation conditions secondary electron emission can enhance reactive oxygen species (ROS) generation. However, in the absence of ionizing radiation,  $\text{HfO}_2$  nanoparticles exhibit minimal ROS induction compared to transition metal oxides capable of redox cycling. This distinction is essential for ensuring biosafety in clinical contexts.

Overall, current evidence suggests that  $\text{HfO}_2$  nanoparticles combine chemical inertness, low baseline cytotoxicity, and irradiation-dependent therapeutic activation. These characteristics position  $\text{HfO}_2$  as a promising high-Z nanomaterial platform for radiation-enhanced cancer therapy, with controllable biological interactions through surface engineering and formulation design.

### **2.3. Hydrothermal Synthesis**

Hydrothermal synthesis is a solution-based crystallization method conducted in aqueous media at temperatures above the atmospheric boiling point of water, typically in sealed reactors that generate autogenous pressure. Under these conditions, water exhibits modified physicochemical properties that significantly influence reaction pathways, solubility behavior, and crystallization kinetics. This method has been extensively employed for the preparation of metal oxide nanomaterials due to its ability to promote controlled nucleation

and direct crystallization without requiring extremely high external temperatures [31].

One of the defining characteristics of hydrothermal systems is the temperature-dependent variation in water properties. As temperature increases, the dielectric constant decreases while the ionic product of water ( $K_w$ ) increases. These changes enhance hydrolysis reactions and facilitate acid–base equilibria, which are particularly relevant for highly charged metal cations such as  $Hf^{4+}$ . The enhanced reactivity of water under hydrothermal conditions accelerates precursor transformation into oxide phases, enabling crystallization at temperatures significantly lower than those required in solid-state reactions.

Hydrothermal synthesis also allows improved control over particle morphology and crystallinity. Because nucleation and growth occur in a homogeneous liquid phase, diffusion processes are more uniform compared to vapor-phase or solid-state routes. Furthermore, the closed reaction environment minimizes contamination and enables reproducible reaction conditions, leading to high-purity oxide materials [53].

From a thermodynamic perspective, elevated temperature reduces kinetic barriers associated with nucleation and atomic rearrangement. Increased diffusion coefficients promote crystal growth, while autogenous pressure supports phase stabilization and densification. These factors collectively enable the formation of well-defined crystalline structures without extensive post-synthesis calcination.

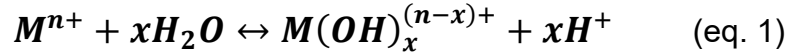
In the context of high-Z oxides such as  $HfO_2$ , hydrothermal synthesis is particularly advantageous because it provides a balance between crystallinity, particle size control, and chemical homogeneity. These characteristics are essential for applications where both structural integrity and nanoscale dimensions must be preserved.

### **Fundamentals of Hydrothermal Synthesis**

Hydrothermal synthesis is based on chemical reactions occurring in aqueous media at elevated temperatures and pressures, typically within sealed autoclaves. Under these conditions, the physicochemical properties of water deviate significantly from those at ambient temperature, profoundly influencing reaction mechanisms, solubility behavior, and crystallization kinetics.

As temperature increases toward subcritical conditions (100–374 °C), the dielectric constant of water decreases, reducing its polarity. This change enhances the solubility of partially hydrolyzed metal species and promotes interaction between inorganic precursors. Simultaneously, the ionic product of water ( $K_w$ ) increases by several orders of magnitude, facilitating acid–base equilibria and accelerating hydrolysis and condensation reactions [31]. These solvent-property modifications are central to the efficiency of hydrothermal oxide formation.

For metal cations with high charge density, such as  $Hf^{4+}$ , hydrolysis reactions occur readily due to strong Lewis's acidity. The general hydrolysis process can be expressed as:



In hafnium systems, rapid formation of hydroxylated intermediates precedes condensation reactions that generate metal–oxygen–metal (M–O–M) bridges. This stepwise transformation leads to the formation of polymeric hydroxide networks that subsequently reorganize into crystalline oxide domains under thermal activation.

From a thermodynamic perspective, nucleation under hydrothermal conditions is governed by the balance between volumetric free energy gain and surface energy penalty. The Gibbs free energy change for nucleus formation ( $\Delta G$ ) can be expressed as:

$$\Delta G = \frac{4}{3}\pi r^3 \Delta G_v + 4\pi r^2 \gamma \quad (\text{eq. 2})$$

where  $\Delta G_v$  is the volumetric free energy change,  $\gamma$  is interfacial energy, and  $r$  is the nucleus radius. Elevated temperature reduces the kinetic barrier by increasing diffusion coefficients and promoting atomic rearrangement, enabling crystallization at moderate temperatures compared to solid-state methods.

Autogenous pressure, generated within the sealed system, also contributes to phase formation and densification. Increased pressure can influence solubility equilibria and reduce activation barriers for structural rearrangement, thereby favoring crystalline oxide formation without requiring extreme external heating [53].

Another important aspect of hydrothermal systems is their capacity to produce highly crystalline nanoparticles directly from solutions. Unlike sol–gel routes, which often require post-synthesis calcination to achieve crystallinity, hydrothermal synthesis can yield phase-pure oxide nanoparticles in a single

step. This advantage arises from the combined effect of elevated temperature, pressure, and solvent-mediated diffusion.

Overall, the fundamentals of hydrothermal synthesis rely on solvent-property modification, enhanced hydrolysis–condensation kinetics, thermodynamically driven nucleation, and pressure-assisted crystallization. These principles provide the theoretical framework for controlled oxide nanoparticle formation, including high-Z materials such as  $\text{HfO}_2$ .

### **Nucleation and Crystal Growth Mechanisms**

Under hydrothermal conditions, the formation of oxide nanoparticles proceeds through nucleation and subsequent crystal growth processes governed by thermodynamic driving forces and kinetic constraints. In aqueous systems containing highly charged metal cations such as  $\text{Hf}^{4+}$ , rapid hydrolysis leads to the formation of hydroxylated species that progressively increase the supersaturation of the solution. Once a critical supersaturation threshold is reached, stable nuclei are formed.

According to classical nucleation theory, the formation of a stable nucleus requires overcoming an energy barrier associated with surface formation. The total Gibbs free energy change ( $\Delta G$ ) during nucleus formation is the sum of a favorable volumetric term ( $\Delta G_v$ ) and an unfavorable surface energy term ( $\gamma$ ). Only when the nucleus reaches a critical radius ( $r$ ) does further growth become thermodynamically favorable. Elevated hydrothermal temperatures reduce this barrier by enhancing diffusion and increasing atomic mobility, thereby accelerating nucleation rates. Additionally, the modified physicochemical properties of water under hydrothermal conditions further enhance hydrolysis and condensation reactions [31].

In hafnium systems, nucleation is often preceded by the formation of polymeric Hafnium hydroxide clusters. These intermediate species may exhibit short-range structural ordering before transforming into crystalline  $\text{HfO}_2$  domains. Because hydrolysis and condensation can continue during heating, nucleation under hydrothermal conditions is frequently continuous rather than occurring in a single burst event. This behavior contrasts with idealized monodisperse colloidal systems and results in particle size distributions that depend strongly on reaction time and precursor concentration.

Crystal growth following nucleation typically proceeds via diffusion-controlled monomer addition. Dissolved hydroxylated hafnium species diffuse toward the

surface of existing nuclei, where they incorporate into the lattice through condensation reactions. Growth rate is influenced by temperature, supersaturation, and interfacial energy. At higher temperatures, increased diffusion coefficients promote faster crystal growth and improved crystallinity.

Non-classical growth mechanisms may also contribute under hydrothermal conditions. Oriented attachment, for example, involves the alignment and fusion of adjacent nanocrystals along specific crystallographic orientations to reduce total surface energy. This mechanism can lead to anisotropic growth and the formation of larger crystalline domains without complete dissolution of smaller particles [54].

At extended reaction times, Ostwald ripening may occur. In this process, smaller particles with higher surface energy dissolve preferentially, and their material redeploys onto larger particles. This phenomenon reduces total system energy and results in progressive particle size increase and narrowing of size distribution.

Overall, nucleation and crystal growth in hydrothermal  $\text{HfO}_2$  systems are controlled by a dynamic interplay between supersaturation, hydrolysis kinetics, diffusion processes, and surface energy minimization. Understanding these mechanisms is essential for tailoring nanoparticle size, phase composition, and structural homogeneity.

### **Influence of Temperature, pH, and Precursor Concentration**

The physicochemical characteristics of hydrothermally synthesized  $\text{HfO}_2$  nanoparticles are strongly governed by reaction temperature, solution pH, and precursor concentration. These parameters directly influence hydrolysis kinetics, supersaturation level, nucleation rate, crystal growth dynamics, and phase stability. A systematic understanding of their interplay is essential for achieving controlled nanoparticle formation.

Reaction temperature plays a significant role in determining both kinetic and thermodynamic aspects of crystallization. As temperature increases, diffusion coefficients rise and solution viscosity decreases, facilitating mass transport toward growing nuclei. Higher temperatures also enhance hydrolysis and condensation rates of hafnium precursors, accelerating the transformation from amorphous hydroxide intermediates to crystalline  $\text{HfO}_2$ . In addition, the modified solvent properties of water at elevated temperatures promote faster reaction equilibria [31]. From a thermodynamic perspective, temperature

influences polymorph stability; while monoclinic  $\text{HfO}_2$  is the most stable bulk phase at ambient conditions, nanoscale systems may stabilize tetragonal domains due to surface energy contributions [45]. Thus, temperature not only controls crystalline and particle size but may also affect phase composition.

Solution pH significantly impacts hafnium speciation and hydrolysis behavior. Due to the high charge density of  $\text{Hf}^{4+}$ , hydrolysis occurs readily even under mildly acidic conditions. At low pH values, protonation of hydroxylated intermediates limits condensation reactions, slowing nucleation and promoting smaller, more dispersed particles. In contrast, alkaline conditions accelerate the formation of  $\text{Hf-OH}$  species, increasing supersaturation and promoting rapid nucleation. However, excessive alkalinity may lead to uncontrolled aggregation due to reduced electrostatic stabilization, a behavior widely observed in hydrothermal oxide systems [53]. Therefore, pH adjustment is critical for balancing nucleation rate and colloidal stability.

Precursor concentration directly determines the degree of supersaturation in the reaction medium. According to classical nucleation theory, higher supersaturation reduces the critical nucleus radius and lowers the nucleation energy barrier, leading to increased nucleation density. This relationship between supersaturation and nucleation barrier is well established in solution-phase crystallization[31]. Consequently, higher precursor concentrations typically produce smaller crystallite sizes due to competition for available growth species, whereas lower concentrations favor fewer nuclei and enhanced growth of larger particles.

Importantly, these three parameters do not act independently. Temperature affects hydrolysis kinetics, pH modifies metal ion speciation, and precursor concentration determines supersaturation levels; their combined influence defines particle size distribution, crystallinity, defect density, and surface hydroxylation state. Careful tuning of these variables enables precise structural control of hydrothermally synthesized  $\text{HfO}_2$  nanoparticles.

### **Advantages Compared to Other Synthesis Methods**

The hydrothermal synthesis of  $\text{HfO}_2$  nanoparticles offers significant thermodynamic and kinetic advantages compared to conventional solid-state, sol-gel, co-precipitation, and vapor-phase techniques. Under subcritical aqueous conditions (200–300 °C), the dielectric constant of water decreases while its ionic product ( $K_w$ ) increases, enhancing solubility and mass transport of ionic precursors. These changes facilitate controlled hydrolysis and

condensation of hafnium species under near-equilibrium conditions, promoting homogeneous nucleation and crystalline growth without requiring post-synthesis calcination [53]. In contrast, solid-state methods typically require temperatures above 800 °C, leading to uncontrolled grain growth and broad particle size distributions, which are unsuitable for biomedical applications where nanoscale uniformity is critical.

From a kinetic perspective, hydrothermal systems provide precise control over nucleation and growth rates through temperature, time (2–6 h), and pH adjustment using KOH. The high-pressure aqueous environment enhances diffusion coefficients relative to ambient-pressure aqueous systems, enabling faster crystallization while limiting aggregation [55]. Compared to sol–gel synthesis, which often involves uncontrolled gelation kinetics and requires high-temperature annealing to achieve crystallinity, hydrothermal processing yields directly crystalline HfO<sub>2</sub> nanoparticles in the 10–20 nm range. This eliminates additional thermal treatments that could induce particle coalescence or phase transformation.

Another major advantage lies in phase control. HfO<sub>2</sub> exhibits polymorphism (monoclinic, tetragonal, cubic), with the monoclinic phase being thermodynamically stable at ambient conditions, while tetragonal and cubic phases are stabilized at small crystallite sizes or elevated temperatures. Hydrothermal conditions allow phase selection through thermodynamic stabilization driven by surface energy minimization at the nanoscale [45]. By adjusting temperature within 200–300 °C and maintaining alkaline pH, it is possible to modulate supersaturation and surface energy contributions, influencing phase composition without dopants. In contrast, vapor deposition techniques such as atomic layer deposition (ALD) provide excellent thin-film control but are not suitable for bulk nanoparticle production and require complex vacuum systems.

Hydrothermal synthesis also offers superior control over surface chemistry, which is critical for biomedical functionality. The aqueous environment promotes the formation of hydroxylated surfaces, enabling subsequent functionalization with biomolecules or organic modifiers. FTIR analyses typically confirm surface –OH groups, while TGA reveals controlled organic residue content depending on precursor chemistry and washing protocols. Compared to combustion or thermal decomposition routes, hydrothermal processing avoids carbonaceous contamination and produces particles with cleaner surfaces, enhancing colloidal stability and biocompatibility [56].

Finally, scalability and reproducibility represent practical advantages. Hydrothermal systems can be adapted from laboratory-scale Teflon-lined autoclaves to continuous-flow reactors, maintaining uniform temperature and pressure profiles. The closed-system environment reduces contamination and ensures reproducible supersaturation conditions, essential for consistent particle sizes confirmed by XRD (Scherrer analysis) and TEM imaging.

Compared to microemulsion or template-based methods, hydrothermal synthesis does not require surfactant removal steps, simplifying purification and reducing cytotoxicity risks for biomedical applications. Therefore, hydrothermal synthesis provides a balanced combination of thermodynamic control, kinetic tunability, phase selectivity, and surface functionality that is particularly advantageous for producing high-purity  $\text{HfO}_2$  nanoparticles in the 10–20 nm range suitable for biomedical use.

## **2.4. Subcritical Water as a Reaction Medium**

Subcritical water refers to liquid water maintained at temperatures between 100 °C and 374 °C under sufficient pressure to prevent vaporization, thereby remaining below its critical point (374 °C, 22.1 MPa). Within this region, water undergoes profound physicochemical changes that significantly modify its solvent properties, reactivity, and transport behavior. These modifications are particularly relevant for hydrothermal synthesis of metal oxides such as  $\text{HfO}_2$ , where controlled nucleation and crystal growth occur under elevated temperature and autogenous pressure conditions [57]. In subcritical regimes typically used for  $\text{HfO}_2$  synthesis (200–300 °C), water acts simultaneously as solvent, reactant, and transport medium.

Thermodynamically, increasing temperature at constant pressure reduces the hydrogen-bonding network of water, decreasing its dielectric constant and modifying solvation dynamics. This reduction enhances the solubility of less polar species while still maintaining sufficient polarity to stabilize ionic hafnium complexes in alkaline environments. As a result, hydrolysis, and condensation reactions of  $\text{Hf}^{4+}$  species can proceed in a controlled manner, especially under pH regulation with KOH. The balance between solvation energy and lattice formation energy becomes a determining factor for phase selection and crystallinity of  $\text{HfO}_2$  nanoparticles.

Kinetically, subcritical water enhances mass transport due to reduced viscosity and increased diffusion coefficients at elevated temperatures. These changes promote faster precursor conversion and shorter induction times for nucleation

compared to ambient aqueous systems. For  $\text{HfO}_2$  nanoparticle synthesis within 2–6 h reaction windows, this kinetic acceleration enables direct crystallization of nanometric monoclinic domains without the need for post-synthesis calcination. The pressurized environment also suppresses bubble formation and concentration gradients, contributing to homogeneous nucleation throughout the reaction volume [55].

From a mechanistic standpoint, subcritical water promotes metal hydroxide formation through temperature-enhanced autoionization. The increased ionic product ( $K_w$ ) at elevated temperatures facilitates both acid- and base-catalyzed pathways, even in nominally neutral solutions. When alkaline conditions are imposed using KOH, the elevated  $K_w$  synergistically accelerates the formation of hafnium hydroxide intermediates that subsequently dehydrate and reorganize into crystalline  $\text{HfO}_2$ . This dual catalytic character distinguishes subcritical water from conventional aqueous precipitation at room temperature.

Finally, subcritical water offers advantages in terms of purity, environmental compatibility, and structural control. Unlike organic solvents or surfactant-assisted methods, hydrothermal processing in subcritical water minimizes carbon contamination and simplifies purification, as confirmed by FTIR and TGA analyses. The closed autoclave system ensures reproducible thermodynamic conditions, while temperature modulation between 200–300 °C allows tuning of particle size (10–20 nm) and crystallinity observed by XRD and TEM. Therefore, subcritical water represents a versatile and tunable reaction medium for controlled synthesis of  $\text{HfO}_2$  nanoparticles with properties tailored for biomedical applications.

### **Definition of Subcritical Water.**

Subcritical water is defined as liquid water maintained at temperatures between 100 °C and 374 °C, under sufficient pressure to prevent phase transition into vapor, thereby remaining below its critical point (374 °C, 22.1 MPa). This state preserves the liquid phase while inducing profound modifications in physicochemical properties such as dielectric constant, viscosity, and ionic product, making it a highly versatile reaction medium for hydrothermal synthesis[57]. Unlike conventional aqueous systems at ambient conditions, subcritical water provides enhanced solubility for ionic and partially polar species, allowing controlled hydrolysis and condensation reactions of metal precursors like  $\text{Hf}^{4+}$ .

From a thermodynamic perspective, the elevated temperature weakens hydrogen-bond networks in water, reducing cohesive energy density and altering solvation dynamics. This enables water to solve fewer polar molecules while still stabilizing charged hafnium complexes in alkaline conditions.

Consequently, the formation of hydroxide intermediates and subsequent nucleation of  $\text{HfO}_2$  nanoparticles occurs in a homogeneous and reproducible manner. These characteristics are critical for producing uniform particles in the 10–20 nm range suitable for biomedical applications [45].

Kinetically, subcritical water accelerates reaction rates by decreasing viscosity and increasing diffusion coefficients relative to ambient-temperature water. This enhanced mass transport ensures rapid precursor conversion and facilitates controlled crystallization during the 2–6 h hydrothermal reaction window. Pressure maintenance also prevents vaporization and bubble formation, promoting uniform nucleation throughout the reaction volume. Compared to sol–gel or precipitation at room temperature, this results in directly crystalline nanoparticles without the need for post-synthesis calcination [55].

Mechanistically, subcritical water acts both as a solvent and as a medium with increased autoionization ( $K_w$ ), which supports both acid- and base-catalyzed pathways. Under controlled alkaline pH with KOH, the elevated ionic product promotes rapid formation of hafnium hydroxide clusters, which then dehydrate and reorganize into  $\text{HfO}_2$  nanocrystals. This dual catalytic role of subcritical water distinguishes it from standard aqueous systems and enhances the efficiency and reproducibility of nanoparticle synthesis.

Overall, subcritical water combines unique thermodynamic and kinetic features allowing precise control over particle size, phase, and surface chemistry. Its use in hydrothermal  $\text{HfO}_2$  nanoparticle synthesis provides a clean, environmentally benign, and scalable route for biomedical-grade nanomaterials.

### **Temperature-dependent Dielectric Constant**

The dielectric constant ( $\epsilon$ ) of water decreases significantly as temperature rises under subcritical conditions, profoundly affecting solution and reaction kinetics in hydrothermal synthesis. At ambient temperature, water has a high dielectric constant (78.5 at 25 °C), favoring the solution of ionic species. However, when heated to 200–300 °C at sufficient pressure to remain liquid,  $\epsilon$  drops to 27–35, approaching the polarity of some organic [57]. This reduction enhances the solubility of less polar and partially hydrolyzed hafnium complexes, facilitating homogeneous nucleation of  $\text{HfO}_2$  nanoparticles.

Thermodynamically, the decrease in dielectric constant reduces the stabilization of separated charges but simultaneously lowers the solvation barrier for polarizable intermediates, allowing condensation reactions to proceed more readily. For  $\text{Hf}^{4+}$  species in alkaline subcritical water, this effect promotes the controlled formation of hydroxide oligomers that will dehydrate into crystalline  $\text{HfO}_2$  [45]. The interplay between  $\epsilon$ , solubility, and reaction energetics is critical for tuning particle size and crystallinity in the 10–20 nm range without requiring high-temperature post-annealing.

Kinetically, a lower dielectric constant also influences ion mobility and electrostatic interactions among growing clusters. Reduced solvent polarity weakens repulsion between partially hydrolyzed hafnium species, promoting aggregation into uniform nuclei while preventing uncontrolled precipitation. This effect, combined with enhanced diffusion at elevated temperature, results in rapid, uniform particle growth throughout the hydrothermal reactor volume [55].

In summary, the temperature-dependent dielectric constant of subcritical water serves as a natural tunable parameter for controlling solubility, nucleation, and growth of  $\text{HfO}_2$  nanoparticles. By adjusting reaction temperature within 200–300 °C, researchers can exploit these thermodynamic and kinetic effects to achieve reproducible, phase-pure, and size-controlled nanoparticles suitable for biomedical applications.

### **Ionic Product of Water ( $K_w$ ) at Elevated Temperatures**

The ionic product of water ( $K_w$ ) increases under subcritical conditions, enhancing both the concentration of  $\text{H}^+$  and  $\text{OH}^-$  ions relative to ambient water. At room temperature,  $K_w$  is  $1 \times 10^{-14}$ , but at 200–300 °C under pressure, it rises by several orders of magnitude [57]. This elevated ionic product facilitates rapid hydrolysis of metal precursors and accelerates the condensation of hafnium hydroxide intermediates into  $\text{HfO}_2$  nanoparticles.

Thermodynamically, higher  $K_w$  reduces activation barriers for acid- or base-catalyzed pathways. In alkaline subcritical water, the increased  $\text{OH}^-$  concentration promotes uniform deprotonation and nucleation of  $\text{Hf}^{4+}$  species, improving control over particle size and crystallinity. Kinetically, the faster ion-mediated reactions reduce induction times, allowing crystallization within the 2 to 6 h reaction windows typical of hydrothermal  $\text{HfO}_2$  [55].

In practice, the combination of elevated  $K_w$  and controlled pH with KOH allows precise tuning of nucleation and growth rates, producing monodisperse

nanoparticles in the 10–20 nm range. The enhanced reactivity in subcritical water also minimizes the need for post-synthesis treatments, yielding high-purity particles with well-defined surface chemistry suitable for biomedical applications.

### **Differences between Subcritical and Supercritical Water**

Subcritical and supercritical water differ fundamentally in density, dielectric properties, and solvent behavior, which directly influence nanoparticle synthesis. Subcritical water, maintained between 100–374 °C under pressure, remains a dense liquid with a moderate dielectric constant, enabling controlled solvation of ionic and polar species [57]. In contrast, supercritical water (Less than 374 °C and 22.1 MPa) exhibits gas-like density, low polarity, and dramatically reduced hydrogen bonding, favoring rapid, less controlled reactions and solubilization of nonpolar species.

Thermodynamically, subcritical water maintains sufficient cohesion to stabilize charged hafnium complexes, allowing stepwise hydrolysis and condensation into uniform  $\text{HfO}_2$  nuclei. Supercritical water, however, reduces dielectric screening and disrupts ion pairing, often leading to faster but less homogeneous nucleation and broader particle size [55]. For biomedical applications where 10–20 nm uniform nanoparticles are required, subcritical conditions offer more precise control over crystallinity and phase purity.

Kinetically, supercritical water provides extreme mass transport and enhanced diffusion, which accelerates reactions but can compromise particle morphology. Subcritical water, while slightly slower in diffusion, balance reaction rates with controlled nucleation and growth, enabling reproducible nanoparticle synthesis without post-synthesis calcination. This balance makes subcritical hydrothermal methods particularly suitable for  $\text{HfO}_2$  nanoparticles targeted for biomedical uses.

### **Advantages of Metal Oxide Synthesis**

Subcritical water offers multiple advantages for the synthesis of metal oxides such as  $\text{HfO}_2$ , combining thermodynamic control, kinetic tunability, and environmental compatibility. Its elevated temperature and pressure conditions allow direct crystallization of nanoparticles without the need for post-synthesis calcination, preserving nanoscale size (10–20 nm) and uniform morphology. The moderate dielectric constant and enhanced ionic product under subcritical conditions enable precise control over hydrolysis and condensation of hafnium precursors, promoting homogeneous nucleation and phase-selective growth [57].

From a kinetic perspective, subcritical water accelerates diffusion and mass transport, reducing induction times and enabling rapid yet controlled particle growth. The combination of elevated temperature, pressure, and alkaline pH allows tuning of nucleation and growth rates, producing monodisperse  $\text{HfO}_2$  nanoparticles suitable for biomedical applications. Unlike supercritical water or high-temperature solid-state methods, these conditions minimize uncontrolled aggregation and broad particle size distributions [55].

Subcritical water also provides inherent advantages in surface chemistry. The aqueous environment facilitates hydroxylation of particle surfaces, which is essential for subsequent functionalization with biomolecules or organic modifiers. Additionally, the closed-system hydrothermal approach limits contamination and allows reproducible reaction conditions, ensuring consistency in particle size, crystallinity, and surface properties across batches.

Environmental and practical benefits further favor subcritical water. It is a green solvent, non-toxic, and readily available, reducing the need for organic solvents or surfactants that can complicate purification. The absence of organic residues simplifies post-synthesis processing and enhances biocompatibility, a key requirement for  $\text{HfO}_2$  nanoparticles in biomedical applications.

Overall, subcritical water provides a versatile, tunable, and environmentally friendly medium for metal oxide synthesis, allowing precise control over size, phase, and surface properties. These characteristics make it particularly suitable for producing high-quality  $\text{HfO}_2$  nanoparticles with reproducible properties for biomedical use.

## **2.5. Surface functionalization of Nanoparticles**

Surface functionalization is a fundamental strategy to control the chemical reactivity, colloidal stability, and biological interactions of  $\text{HfO}_2$  nanoparticles. Due to their small size (10–20 nm), a large fraction of atoms resides on the surface, creating high-energy, undercoordinated sites that can interact with ligands or polymers. These reactive sites are prone to hydroxylation in aqueous environments, forming  $-\text{OH}$  groups that serve as anchoring points for surface modification. Functionalization not only prevents uncontrolled aggregation but also allows tailoring of particle properties, such as hydrophilicity, charge, and biocompatibility, which are critical for biomedical applications including imaging, drug delivery, and targeted therapy [45,56]. The following subsections describe the key concepts and mechanisms underlying nanoparticle surface chemistry.

## Surface Energy and Reactivity

HfO<sub>2</sub> nanoparticles exhibit high surface energy due to the large fraction of undercoordinated surface atoms, which are thermodynamically unstable relative to the bulk [45]. This elevated surface energy drives reactions aimed at minimizing free energy, including hydroxylation, ligand adsorption, and particle aggregation. Hydroxylation produces –OH groups that act as reactive anchors for functionalization. The density of these reactive sites is inversely proportional to particle size; nanoparticles of 10–20 nm has significantly higher site density than larger particles, enhancing both reactivity and potential for dense ligand coverage.

Kinetically, surface energy governs the rate of ligand binding and the potential for particle coalescence. High surface reactivity can accelerate functionalization but also increases the risk of uncontrolled aggregation, which can broaden size distributions and reduce colloidal stability. Controlling environmental parameters such as temperature, pH, and ionic strength during functionalization is critical to managing these kinetic effects.

From a practical perspective, understanding surface energy allows for rational design of nanoparticle functionalization protocols. Proper control ensures reproducible particle size, surface chemistry, and stability, all essential for biomedical applications where predictable behavior in physiological environments is required.

## Adsorption vs. Coordination Mechanisms

Functionalization of HfO<sub>2</sub> surfaces occurs through either weak adsorption or strong coordination. Adsorption involves reversible physical interactions such as hydrogen bonding, electrostatic attraction, or van der Waals forces, which may be disrupted under changes in pH, ionic strength, or temperature. In contrast, coordination involves the formation of covalent-like bonds between Lewis-acidic surface Hf<sup>4+</sup> atoms and electron-donating ligands, creating a more stable and durable surface modification [58].

The mode of ligand attachment affects colloidal stability and surface chemistry. Monodentate ligands bind at a single site and are more easily desorbed, while bidentate or tridentate ligands occupy multiple coordination sites, enhancing stability. Hydroxylated surfaces provide nucleation points for these interactions, and the ligand density can be tuned by controlling reaction conditions, such as ligand concentration and pH.

In biomedical applications, coordination is preferred because it maintains functional moieties on the nanoparticle surface under physiological conditions. Adsorption can be used for temporary stabilization or sensing applications where reversibility is advantageous.

### **Lewis's Acid-Base Interaction**

Surface  $\text{Hf}^{4+}$  centers function as Lewis's acids, capable of accepting electron pairs from donor ligands. This acid–base interaction underpins most surface functionalization strategies [59]. Multidentate ligands, such as catechol or phosphonates, can coordinate simultaneously with multiple surface sites, creating thermodynamically favored complexes that resist desorption.

pH plays a critical role by modulating the protonation state of surface hydroxyl groups and the ligands themselves. Under alkaline conditions, surface  $-\text{OH}$  groups deprotonate, enhancing nucleophilicity and facilitating coordination with acidic ligands. Temperature also influences these interactions by affecting ligand mobility and adsorption kinetics.

This type of interaction is particularly relevant for biomedical  $\text{HfO}_2$  nanoparticles, as it allows stable anchoring of biomolecules, targeting ligands, or polymers while maintaining particle dispersion and surface accessibility.

### **Organic Acid Modification of Metal Oxides**

Carboxylic and phosphonic acids are widely used to modify  $\text{HfO}_2$  surfaces. These ligands can react with surface hydroxyls to form ester-like bonds or directly coordinate with Lewis-acidic Hf centers, reducing surface energy and preventing aggregation [56]. Coverage density and uniformity are influenced by pH, temperature, and ligand concentration, enabling tuning of surface properties for specific applications.

The modification also provides chemical handles for further functionalization. For example, carboxyl groups on the surface can be used to attach targeting moieties, fluorophores, or therapeutic molecules, expanding the versatility of  $\text{HfO}_2$  nanoparticles.

Hydrothermal conditions can favor uniform ligand coverage while preserving particle size and crystallinity, making organic acid modification a robust approach for producing nanoparticles with reproducible properties.

### **Catechol-metal Oxide Affinity**

Catechol groups exhibit strong bidentate coordination with surface  $\text{Hf}^{4+}$  centers, forming highly stable chelate complexes [59]. This interaction lowers surface energy and provides robust attachment of functional ligands, even under physiological or acidic conditions. The bidentate nature of catechol's also increases kinetic rates of binding, ensuring rapid and uniform surface coverage. Catechol-based modification is advantageous for biomedical applications because it allows direct conjugation of biomolecules or polymers without disrupting particle morphology. It is also compatible with multistep functionalization, such as attaching fluorescent probes or targeting ligands after initial chelation.

The thermodynamic stability of catechol coordination ensures that nanoparticles maintain surface functionalization over time, enhancing both colloidal stability and biological performance.

### **PEGylation and Colloidal Stability**

PEGylation involves grafting polyethylene glycol chains onto the nanoparticle surface, creating a hydrated steric barrier that prevents aggregation [60]. This steric stabilization is critical for maintaining colloidal stability in physiological media, where high ionic strength or protein adsorption could otherwise induce aggregation.

PEGylation also improves biocompatibility, reduces immune recognition, and extends circulation times in vivo. Grafting density, chain length, and conformation of PEG molecules influence the degree of stabilization and functional performance. Hydrothermal nanoparticles with prior catechol or carboxylate surface modification often achieve better PEG attachment due to stable anchoring sites.

Additionally, PEGylated  $\text{HfO}_2$  nanoparticles exhibit controlled interactions with biomolecules, enabling targeted delivery, imaging, or therapeutic applications. Proper tuning of surface chemistry, in combination with PEGylation, ensures reproducible and predictable nanoparticle behavior in biomedical contexts.

## **2.6. Influence of Organic Molecules on Nucleation and Growth**

Organic molecules play a critical role in the hydrothermal synthesis of  $\text{HfO}_2$  nanoparticles by controlling nucleation rates, growth kinetics, particle size, and morphology. Their presence influences the solubility of  $\text{Hf}^{4+}$  precursors,

stabilizes early nuclei, and prevents uncontrolled aggregation. Molecules such as carboxylic acids, catechol, or polymers can adsorb surfaces or coordinate to metal centers, altering surface energy and providing steric barriers that regulate particle growth. These effects enable the synthesis of monodisperse  $\text{HfO}_2$  nanoparticles (10–20 nm) with well-defined shapes and narrow size distributions, which is essential for biomedical applications such as imaging, drug delivery, or surface conjugation [57].

The interaction between organic molecules and forming nuclei is both thermodynamically and kinetically significant. Thermodynamically, adsorbed ligands reduce surface free energy and favor the stabilization of small nuclei, while kinetically they can slow growth rates by partially blocking reactive surface sites. This balance allows fine-tuning of particle properties, including size uniformity and crystallinity, which are crucial for reproducible performance in biomedical contexts.

### **Size and Morphology Control**

Organic molecules influence particle size by modulating the supersaturation of  $\text{Hf}^{4+}$  in solution and stabilizing nascent nuclei. Ligands like citric acid, lactic acid, and 3,4-dihydroxybenzoic acid coordinate to Hf centers, slowing condensation reactions and controlling growth rates [56]. By adjusting ligand concentration, pH, and hydrothermal temperature, researchers can systematically tune nanoparticle diameters, often achieving uniform 10–20 nm  $\text{HfO}_2$  particles.

Morphology is governed by selective interaction of ligands with specific crystallographic facets. Molecules with multiple binding groups, such as catechol's, preferentially adsorb onto high-energy facets, altering relative growth rates along different directions. This selective adsorption can produce truncated, elongated, or isotropic particles depending on the ligand structure and binding strength [59].

In practice, controlling size and morphology impacts surface area, reactivity, and colloidal behavior. For biomedical nanoparticles, these parameters influence biodistribution, cellular uptake, and functionalization efficiency. Hydrothermal conditions coupled with carefully chosen ligands enable reproducible synthesis of nanoparticles with tailored physical and chemical characteristics.

### **Steric Stabilization Mechanisms**

Steric stabilization arises when organic molecules or polymers adsorb onto the nanoparticle surface, forming a physical barrier that prevents particle–particle contact [58]. In  $\text{HfO}_2$  nanoparticles, molecules such as PEG, citric acid, or multi-hydroxyl ligands create a hydrated shell that reduces van der Waals attractions and electrostatic interactions. The thickness and density of this layer determine the degree of stabilization.

Steric hindrance also influences nucleation and growth kinetics. By limiting particle collisions and coalescence, ligands extend induction times and maintain monodispersed. High-density ligand coverage enhances stability during hydrothermal treatment and post-synthesis processing.

For biomedical applications, sterically stabilized  $\text{HfO}_2$  nanoparticles retain their size and shape in complex media, such as blood or cell culture, and prevent aggregation that could otherwise affect pharmacokinetics, targeting, or imaging performance.

### **Selective Facet Inhibition**

Organic molecules can selectively bind to specific crystallographic facets of  $\text{HfO}_2$ , inhibiting growth along these surfaces and enabling anisotropic shapes. Catechol's, carboxylates, and phosphonates exhibit high affinity for certain facets, which reduces local surface energy and slows growth in those directions. [59]

Thermodynamically, selective adsorption stabilizes high-energy facets, minimizing total surface free energy. Kinetically, it alters the relative growth rates along different axes, producing particles with controlled aspect ratios or truncated shapes. The choice of ligand and its binding mode (mono-, bi-, or tridentate) directly impacts the resulting morphology and surface chemistry.

Facet control is particularly important for applications where surface interactions dictate function. For example, specific facets may present hydroxyl groups that enhance conjugation with biomolecules or influence catalytic and imaging properties, making selective inhibition a powerful tool in nanoparticle design.[60]

Although  $\text{HfO}_2$  nanoparticles have been extensively investigated for radiotherapy enhancement, comparatively few studies have explored the influence of organic surface modifiers on nanoparticles synthesized under subcritical water conditions. Understanding how various organic molecules

interact with  $\text{HfO}_2$  surfaces is crucial for tuning surface chemistry while preserving the crystal structure. Therefore, this work focuses on evaluating the effect of various organic modifiers on the structural and physicochemical properties of hydrothermally synthesized  $\text{HfO}_2$  nanoparticles.

## Chapter 3 Methodology

### 3.1. Materials

Starting with a hafnium chloride ( $\text{HfCl}_4$ ) solution (99.99%, Wako, Japan), hafnium hydroxide ( $\text{Hf}(\text{OH})_4$ ) is formed, which is used as a hafnium precursor. Potassium hydroxide (KOH) (98%, Wako, Japan) is added to form the compounds that will be introduced into the reactor. Distilled water was used as the reaction medium in all experiments.

Organic surface modifiers consisted of different organic molecules classified into three groups: organic acids, polymers, and biomolecules. The organic acids and biomolecules included propionic acid (98%, Wako, Japan), citric acid anhydrous (98%, Wako, Japan), 3,4-dihydroxybenzoic acid (>98%, Wako, Japan), gallic acid (98.5%, Sigma-Aldrich), lactic acid (85–92%, Sigma-Aldrich), and oleic acid (98%, Sigma-Aldrich). Poly(ethylene glycol) with an average molecular weight of 4000 (PEG 4000, 98%, Wako, Japan) was used as a polymeric surface modifier. Dopamine hydrochloride (Wako, Japan) was employed as a neurotransmitter-type organic molecule for surface modification. All reagents were used as received without further purification.

### 3.2. Hydrothermal reactor setup

The hydrothermal synthesis was carried out using a laboratory-scale pressure reactor system, consisting of a temperature control unit and a stainless steel reactor, as shown in Figure 1. The heating power supplied to the reactor was manually regulated by a voltage controller, allowing for precise adjustment of the reaction temperature. This temperature was continuously monitored by a thermocouple connected directly to the reactor throughout the synthesis.

The reactor consisted of a mechanically sealed stainless steel pressure vessel, designed to withstand the high temperatures and pressures generated under hydrothermal conditions. A quartz tube placed inside the reactor served as the reaction chamber for the precursor solution, minimizing direct contact between the solution and the metal walls. Heating was provided by an external electric heating ring, while thermal insulation minimized heat loss and helped maintain a stable reaction temperature throughout the synthesis. The complete configuration of the hydrothermal reactor system and its individual components are shown in Figure 1.

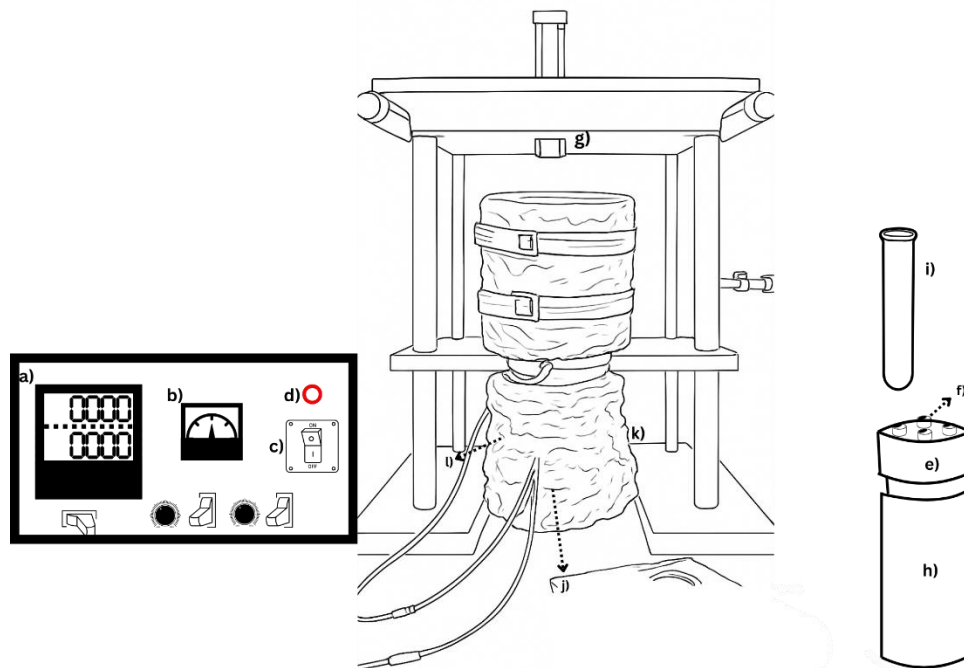


**Figure 1.** Laboratory-scale hydrothermal reactor system used for the synthesis of  $\text{HfO}_2$  nanoparticles, including the temperature control unit and the stainless-steel high-pressure reactor assembly: (a) temperature display, (b) voltage regulator, (c) power switch, (d) indicator light, (e) reactor lid, (f) sealing bolts, (g) compression frame, (h) stainless-steel reactor chamber (pressure vessel), (i) quartz reaction tube, (j) electric heating ring, (k) thermocouple, and (l) thermal insulation.

All reactions were conducted under subcritical water conditions. The internal pressure was not externally controlled but was generated autogenously by water vapor at the selected reaction temperature. Since pH was not considered a determining factor in this study, temperature was treated as the primary parameter governing nucleation, crystal growth, and surface modification processes.

### 3.3. Hydrothermal synthesis under subcritical conditions

A 0.05 M hafnium precursor solution was prepared by dissolving 3 g of  $\text{HfCl}_4$  in 187.5 mL of distilled water under continuous magnetic stirring at room temperature. The hydrolysis of  $\text{HfCl}_4$  in aqueous medium leads to the formation of partially hydrolyzed hafnium species according to:

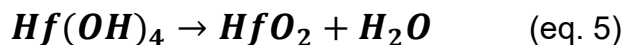


Subsequently, a 0.1 M KOH solution was added dropwise to promote further hydrolysis and precipitation. The addition of hydroxide ions facilitates the formation of hafnium hydroxide:



A white precipitate corresponding to  $\text{Hf(OH)}_4$  was formed and collected by centrifugation. The precipitate was washed three times with distilled water to remove residual chloride and potassium ions. After washing, the solid was redispersed in 10 mL of distilled water. The pH of the suspension was adjusted using 0.1 M KOH; however, pH was not treated as a controlled variable in this study.

Suspension was transferred into a quartz tube and placed inside the stainless-steel hydrothermal reactor described previously. The reactor was mechanically sealed and heated to 250 °C for 4 hours under subcritical water conditions. The internal pressure was at 3.97 MPa generated autogenously by water vapor at the selected temperature.



Under hydrothermal conditions, dehydration and crystallization of hafnium hydroxide occur, leading to the formation of hafnium dioxide (eq. 5). [61] After completion of the reaction, the system was allowed to cool helped by a fan (Makita, DCF Series) at room temperature. Solid products were washed, subjected to ultrasonic dispersion to improve particle separation, and subsequently freeze-dried (lyophilized).

In this study, temperature was considered the primary parameter governing hydrolysis, nucleation, crystal growth, and phase evolution during the hydrothermal process.

Surface-modified  $\text{HfO}_2$  nanoparticles were synthesized following a procedure like the one described in Section 1.3, with the incorporation of organic molecules prior to hydrothermal treatment.

A 0.05 M  $\text{HfCl}_4$  precursor solution was prepared by dissolving 3 g of  $\text{HfCl}_4$  in 187.5 mL of distilled water under continuous stirring. A 0.1 M KOH solution

was added to promote hydrolysis and precipitation of  $\text{Hf}(\text{OH})_4$ . After formation of the precipitate, the suspension was subsequently washed with centrifugation and distilled water three times to remove  $[\text{Cl}]^-$  and  $[\text{K}]^+$  ions, followed  $\text{Hf}(\text{OH})_4$  were resuspended in 30 mL of distilled water and the selected organic molecule was added into the suspension at a molar ratio of Hf:modifier 1:0.5. The mixture was maintained under continuous stirring to ensure homogeneous distribution of the organic species.

Suspension was subsequently subject to hydrothermal treatment under the same conditions detailed in Section 1.3 (250°C, 4 Hours, subcritical water regime under autogenous pressure).

After cooling at room temperature, the obtained solids were washed, subjected to ultrasonic dispersion to improve particle separation, and finally freeze-dried under nitrogen atmosphere to obtain surface-modified  $\text{HfO}_2$  powders.

The synthesis conditions for all modified samples are summarized in Table 1.

**Table 1.** Summary of synthesis conditions and surface modifiers.

| Sample ID                  | Organic Molecule | Functional Groups          | Hf:Modifier Ratio | Temperature (°C) | Time (h) |
|----------------------------|------------------|----------------------------|-------------------|------------------|----------|
| $\text{HfO}_2$             | None             | —                          | —                 | 250              | 4        |
| $\text{HfO}_2\text{-PA}$   | Propionic acid   | —COOH                      | 1:0.5             | 250              | 4        |
| $\text{HfO}_2\text{-CA}$   | Citric acid      | —COOH, —OH                 | 1:0.5             | 250              | 4        |
| $\text{HfO}_2\text{-DHBA}$ | 3,4-DHBA         | —COOH, —OH                 | 1:0.5             | 250              | 4        |
| $\text{HfO}_2\text{-GA}$   | Gallic acid      | —COOH, —OH                 | 1:0.5             | 250              | 4        |
| $\text{HfO}_2\text{-LA}$   | Lactic acid      | —COOH, —OH                 | 1:0.5             | 250              | 4        |
| $\text{HfO}_2\text{-PEG}$  | PEG 4000         | —OH, ether                 | 1:0.5             | 250              | 4        |
| $\text{HfO}_2\text{-DA}$   | Dopamine         | Catechol, —NH <sub>2</sub> | 1:0.5             | 250              | 4        |
| $\text{HfO}_2\text{-OA}$   | Oleic Acid       | —COOH, C=C                 | 1:0.5             | 250              | 4        |

### 3.4. Post-synthesis treatment

After completion of the hydrothermal reaction under subcritical conditions, the reactor was allowed to cool naturally at room temperature before being opened. The resulting solid products were recovered and subjected to post-synthesis purification.

Particles were washed several times with distilled water by centrifugation to remove residual chloride ions, potassium species, and unreacted precursors. The washing process was repeated until neutral conductivity of the supernatant was observed.

Following purification, the suspensions were subjected to ultrasonic treatment to improve particle dispersion and reduce agglomeration. Finally, the samples were freeze-dried (lyophilized) under nitrogen atmosphere to obtain dry powder materials suitable for structural and surface characterization.

This post-synthesis treatment ensured removal of residual by-products while preserving the crystalline structure and surface characteristics of the synthesized  $\text{HfO}_2$  nanoparticles.

## Chapter 4 Characterization Techniques

Structural, morphological, and surface properties of the synthesized pure and surface-modified  $\text{HfO}_2$  nanoparticles were investigated using complementary characterization techniques.

### 4.1. X-Ray Diffraction

The crystalline phase and structural properties of the samples were analyzed by X-ray diffraction (XRD) using  $\text{Cu K}\alpha$  radiation ( $\lambda = 1.5406 \text{ \AA}$ ). were recorded over an appropriate  $2\theta$  range to identify crystalline phases and evaluate structural evolution after hydrothermal treatment.

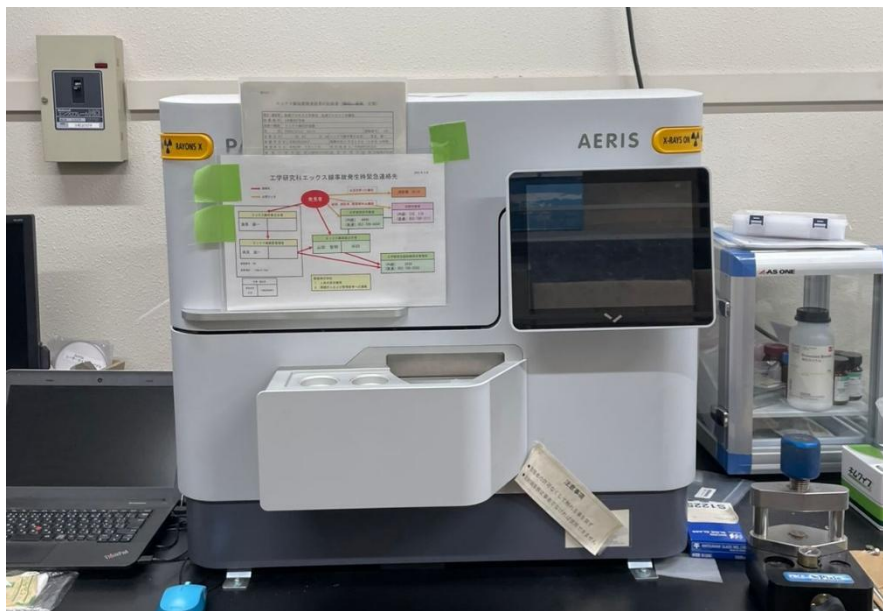


**Figure 2.** AERIS X-ray diffractometer used for the structural characterization of  $\text{HfO}_2$  nanoparticles. X-ray diffraction (XRD) measurements were performed to determine the crystalline phases and evaluate the crystallinity of the synthesized samples.

Phase identification was performed by comparison with standard reference diffraction data. The average crystallite size was estimated using the Scherrer equation:

$$L = \frac{K\lambda}{\beta \cos\theta} \quad (\text{Eq 3})$$

where:

- L: Crystal size (nm)
- K: Scherrer's constant
- $\lambda$ : X-ray wavelength (Å)
- $\beta$ : Average peak width
- $\theta$ : Angular position of DRX peaks, half of  $2\theta$

The most intense diffraction peak was selected for crystallite size estimation.

## 4.2. Thermogravimetric Analysis (TGA)

With respect to thermogravimetric analysis (TGA) was conducted to assess thermal stability and quantify the number of organic species associated with the nanoparticle surface. Samples were heated under controlled atmosphere at a constant heating rate, and weight loss was recorded as a function of temperature, while weight loss at higher temperatures was associated with decomposition of surface-bound organic molecules. This analysis allowed estimation of the relative organic content in functionalized samples.



**Figure 3.** NETZSCH STA 2500 Regulus simultaneous thermal analyzer used for the thermal characterization of  $\text{HfO}_2$  nanoparticles. Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) measurements were performed to evaluate mass loss behavior.

## Chapter 5 Results and Discussion

### 5.1. X-Ray Diffraction (XRD)

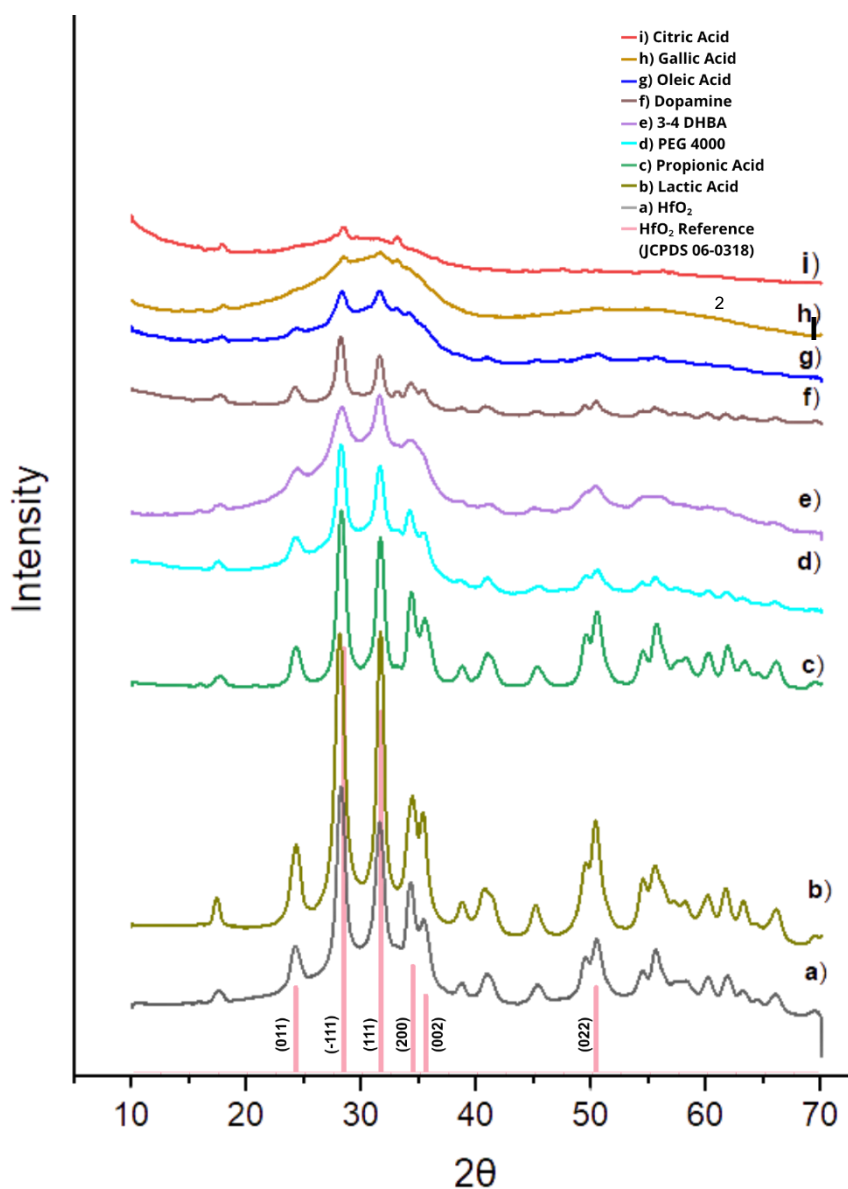


**Figure 4.** X-ray diffraction patterns of pure and surface-modified  $\text{HfO}_2$  nanoparticles synthesized under hydrothermal subcritical conditions reference JCPDS 06-0318. a).  $\text{HfO}_2$  NPs (grey), b).  $\text{HfO}_2$  NPs grafted with lactic acid (dark yellow), C.  $\text{HfO}_2$  NPs grafted with propionic acid (green), D.  $\text{HfO}_2$  NPs grafted with PEG 4000 (cyan), E.  $\text{HfO}_2$  NPs grafted with 3-4 DHBA (violet), F.  $\text{HfO}_2$  NPs grafted with dopamine (brown), G.  $\text{HfO}_2$  NPs grafted with oleic acid (blue), H.  $\text{HfO}_2$  NPs grafted with gallic acid (yellow), I.  $\text{HfO}_2$  NPs grafted with citric acid (red).

The X-ray diffraction patterns of pure and surface-modified  $\text{HfO}_2$  nanoparticles synthesized under hydrothermal subcritical conditions are presented in Figure 5. All samples exhibited diffraction peaks characteristic of crystalline hafnium oxide, with the main reflections located approximately at  $2\theta$  values near  $28^\circ$ ,  $31^\circ$ ,  $34^\circ$ ,  $50^\circ$ , and  $55^\circ$ . These diffraction features are consistent with the monoclinic phase of  $\text{HfO}_2$ , which corresponds to the thermodynamically stable polymorph at ambient conditions.

A comparison between the diffraction pattern of unmodified  $\text{HfO}_2$  and those of the organic molecule-modified samples revealed that no significant phase transition occurred after surface functionalization. Furthermore, no additional diffraction peaks associated with secondary crystalline phases, precursor residues, or crystalline organic compounds were detected. This behavior suggests that the incorporation of organic molecules did not alter the crystal structure of the hafnium oxide nanoparticles during hydrothermal synthesis. The absence of secondary phases also indicates that the added modifiers were either amorphous, molecularly dispersed on the particle surface, or present in concentrations below the XRD detection limit.

Although the overall crystal structure remained preserved, noticeable differences in peak intensity and peak broadening were observed among the modified samples. Variations in diffraction peak intensity may be associated with differences in crystallinity, preferred orientation effects, or changes in particle aggregation behavior induced by the presence of the organic molecules during nucleation and crystal growth. Samples modified with lactic acid and propionic acid exhibited sharper and more intense diffraction peaks, suggesting improved crystallinity and the formation of larger crystalline domains. This behavior may be related to the ability of carboxylic acid groups to regulate hydrolysis and condensation kinetics during particle formation.

In contrast, sample modified with dopamine showed broader diffraction peaks, whereas citric acid promoted the formation of larger crystalline domains despite preserving the monoclinic phase. Peak broadening in nanocrystalline systems is commonly associated with smaller coherent diffraction domains and increased structural disorder. In these systems, the presence of multifunctional organic molecules may partially inhibit crystal growth through surface coordination with hafnium species, limiting the growth of crystalline domains during hydrothermal treatment.

The PEG 4000 and DHBA samples exhibited intermediate diffraction behavior, maintaining well-defined monoclinic reflections while displaying moderate peak broadening. This suggests that these modifiers influenced particle growth kinetics without suppressing crystallization entirely. In hydrothermal systems, organic molecules can function as steric stabilizers or surface-coordinating agents, affecting nucleation rate, particle growth, and aggregation behavior simultaneously.

Additionally, the preservation of the monoclinic  $\text{HfO}_2$  phase in all samples indicates that the hydrothermal conditions employed (250 °C, 4 h) provided sufficient thermal energy for crystallization regardless of the presence of organic modifiers. Since monoclinic  $\text{HfO}_2$  is generally stabilized at larger crystallite sizes and lower surface energies, the observed diffraction patterns suggest that the synthesized nanoparticles reached a sufficient degree of structural ordering during the hydrothermal process.

Overall, the XRD results demonstrate that hydrothermal synthesis under subcritical water conditions successfully produced crystalline monoclinic  $\text{HfO}_2$  nanoparticles, while the presence of different organic molecules influenced crystallinity and crystallite growth without inducing structural phase transformation.

## 5.2. Crystallite Size (Scherrer Analysis)

**Table 2.** Average crystallite size values calculated from XRD diffraction peaks using the Scherrer method.

| Sample                | Average crystallite size (nm) | Average microstrain ( $\times 10^{-3}$ ) | Structural observation                          |
|-----------------------|-------------------------------|------------------------------------------|-------------------------------------------------|
| Pure HfO <sub>2</sub> | 11                            | 0.35                                     | Reference monoclinic structure                  |
| Citric acid           | 26                            | 0.10                                     | Larger crystalline domains                      |
| Propionic acid        | 12                            | 0.34                                     | Like pure HfO <sub>2</sub>                      |
| 3,4-DHBA              | 8                             | 1.43                                     | Reduced crystallite size                        |
| Dopamine              | 8                             | 1.36                                     | Higher structural strain                        |
| Lactic Acid           | 11                            | 0.52                                     | Slight crystal growth inhibition                |
| Gallic Acid           | 29                            | 0.23                                     | Larger crystalline domains                      |
| Oleic acid            | 11                            | 0.65                                     | Moderate broadening, preserved monoclinic phase |
| PEG 4000              | 8                             | 0.91                                     | Moderate crystal growth inhibition              |

The average crystallite size of the synthesized HfO<sub>2</sub> nanoparticles was estimated using the Scherrer equation based on the broadening of the main diffraction peaks observed in the XRD patterns. The calculations were performed using the full width at half maximum (FWHM) values obtained from the diffraction peaks corresponding to monoclinic HfO<sub>2</sub> reflections. A Scherrer constant (K) value of 0.9 was employed considering the monoclinic crystal structure of HfO<sub>2</sub>. The Cu K $\alpha$  radiation wavelength used for the calculations was 1.5406 Å.

Based on the XRD results discussed in the previous section, the synthesized HfO<sub>2</sub> nanoparticles are likely to consist predominantly of single crystalline domains. Under these conditions, the crystallite sizes estimated by the Scherrer equation may closely approximate the particle dimensions. Similar behavior has

been reported for hydrothermally synthesized oxide nanoparticles, where good agreement between crystallite sizes estimated by the Scherrer equation and the particle size obtained by electron microscopy was observed for predominantly monocrystalline particles[62].

It's important to note that Scherrer Equation estimates the average size of coherently diffracting crystalline domains rather than the physical particles sizes. Knowing this, the calculated values correspond to crystallite size and should not be interpreted as overall dimensions of the nanoparticles. Differences between crystalline size and particle size are commonly attributed to the presence of polycrystalline or particle agglomeration [62,63].

The estimated crystallite sizes revealed that the incorporation of organic molecules during hydrothermal synthesis influenced crystal growth behavior and crystalline domain formation. Pure  $\text{HfO}_2$  nanoparticles exhibited an average crystallite size of approximately 10.98 nm, confirming the nanocrystalline nature of the synthesized material under subcritical hydrothermal conditions. Although the crystallite size obtained in the present study is smaller than values reported in previous studies, it remains within the nanocrystalline regime and may be attributed to differences in the synthesis conditions [64].

Among the analyzed samples, the citric acid nanoparticles showed the largest crystallite size, with an average value of approximately 25.19 nm. The increase in crystallite size may indicate that citric acid promoted crystal growth during hydrothermal treatment, possibly through coordination interactions with hafnium precursor species and regulation of nucleation kinetics. Organic molecules containing multiple carboxylic groups may reduce the number of effective nucleation sites while favoring the growth of larger crystalline domains [65].

In contrast, the samples modified with 3,4-DHBA, dopamine hydrochloride, and PEG 4000 exhibited smaller crystallite sizes, with average values of approximately 7.82, 8.14, and 8.37 nm, respectively. The reduction in crystallite size observed for these systems suggests that the organic modifiers partially inhibited crystal growth during hydrothermal synthesis. Molecules containing hydroxyl and catechol functional groups may interact with hafnium hydroxide intermediates or particle surfaces, limiting crystallite growth through steric hindrance and surface stabilization effects.

The propionic acid presented an average crystallite size of approximately 11.62 nm, which remained relatively close to that of pure  $\text{HfO}_2$ . This behavior suggests that propionic acid had a comparatively weaker influence on crystal growth kinetics under the synthesis conditions employed. Due to its smaller molecular structure and lower steric effect, propionic acid may exert less restriction on crystal growth during nanoparticle formation [66].

In the case of gallic acid, one of the largest average crystallite sizes among the analyzed materials was observed, with a value of approximately 28.74 nm. This result suggests that gallic acid promoted crystal growth and the formation of larger crystalline domains during the hydrothermal treatment. The presence of multiple hydroxyl groups and a carboxyl group could facilitate coordination interactions with hafnium, influencing the nucleation and growth processes while preserving the monoclinic phase.

Meanwhile, the samples with lactic acid and oleic acid have an average crystallite size close to 11 nm, values comparable to those obtained for pure  $\text{HfO}_2$  and propionic acid. These results indicate that although both molecules interact with the particle surface, their influence on crystal growth was less pronounced than observed with citric acid or gallic acid. The preservation of crystallite size suggests that these modifying agents primarily affect the surface chemistry, rather than significantly altering the mechanism of nucleation and crystal growth during the synthesis.

The variations in crystallite size were consistent with the peak broadening behavior observed in the XRD patterns. Samples exhibiting broader diffraction peaks generally corresponded to smaller crystallite dimensions, whereas sharper diffraction peaks were associated with larger crystalline domains and improved crystallinity. These observations indicate that organic molecules influenced nucleation and growth mechanisms during hydrothermal synthesis without inducing phase transformation.

Additionally, microstrain analysis revealed comparatively higher strain values for DHBA and dopamine, suggesting greater crystal lattice distortion and increased structural disorder. This increased may be linked to the surface interactions

between the organic molecules and the  $\text{HfO}_2$  crystallites during the crystal growth process. Conversely, pure  $\text{HfO}_2$  and those modified with propionic, citric and gallic acids exhibited lower microstrain values, indicating greater structural uniformity. Meanwhile, samples modified with lactic and oleic acids showed moderate microstrain levels, higher than those observed for pure  $\text{HfO}_2$  but considerably lower than those recorded for DHBA and dopamine, suggesting limited alterations of the crystal lattice without affecting the characteristic monoclinic structure. Furthermore, there is an inverse relationship between crystallite size and microstrain. Samples with smaller crystallite sizes, specifically DHBA and dopamine, exhibited higher microstrains values, whereas larger crystallite domains, obtaining the citric and gallic acids, were associated with lower lattice distortion. This behavior is consistent with the greater contributions of surface defects and structural disorder in smaller crystallites.

It should be noted that the Scherrer analysis was preliminarily performed for samples presenting sufficiently resolved diffraction peaks and dependable FWHM values. Although crystallite size values were estimated for all samples, some modified systems have a broader diffraction peak and a lower signal intensity, which may introduce the uncertainty associated with FWHM determination and with the crystallite size estimated by the Scherrer equation.

Overall, the Scherrer analysis indicates that the incorporation of organic molecules during hydrothermal synthesis significantly affected crystallite growth behavior while preserving the monoclinic crystalline structure of  $\text{HfO}_2$  nanoparticles.

### 5.3. Thermogravimetric Analysis (TGA)

Thermogravimetric analysis (TGA) was conducted to evaluate the thermal stability and the organic composition of the synthesized  $\text{HfO}_2$  nanoparticles prepared with different capping agents. The TGA and DTA curves provide an insight into the decomposition behavior of the organic species associated with the surface of the  $\text{HfO}_2$  nanoparticles. The weight loss observed below  $120^\circ\text{C}$  will be considered attributed to the removal of physically absorbed water, while the mass loss at higher temperatures will be related to the decomposition and oxidation of organic modifiers. The magnitude and temperature range of these events strongly depends on the chemical nature of the modifier.

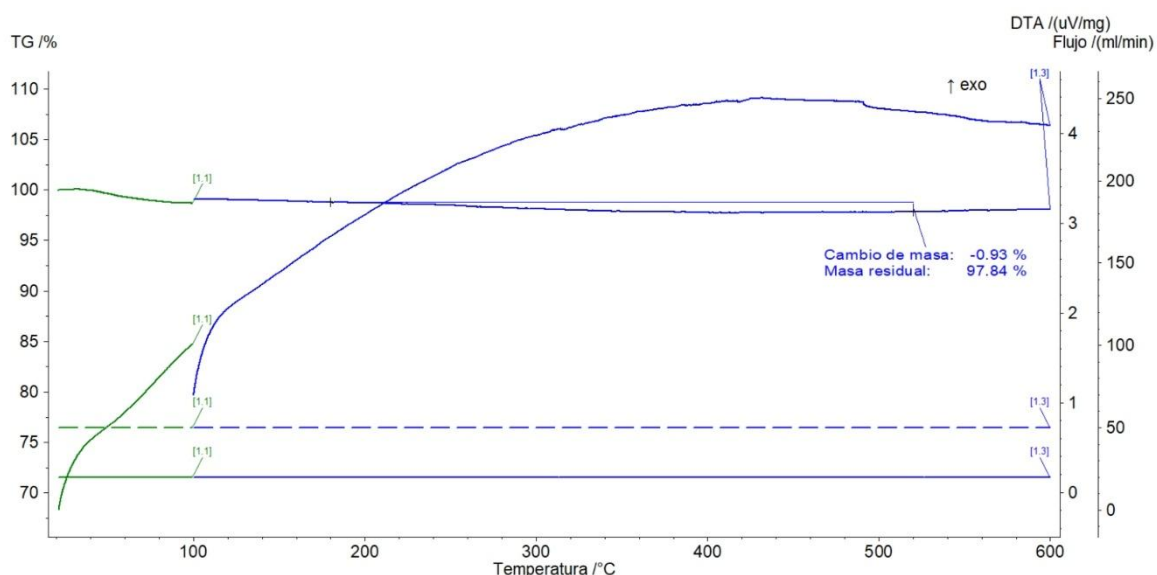


**Figure 5.** TGA and DTA curves of  $\text{HfO}_2$  nanoparticles synthesized without organic modifiers.

As shown in Figure 5, the TGA and DTA curves of  $\text{HfO}_2$  synthesized without modifying agents show a negligible mass loss across the entire temperature range, indicating the absence of significant organic content. A slight decrease in mass is observed below  $120^\circ\text{C}$ , attributed to the removal of the physically absorbed water from the material's surfaces. This is not relevant that thermal peaks are identified in the DTA curve, confirming the absence of decomposition processes or chemical reactions associated with organic species. At higher temperatures, the mass remains constant, demonstrating the material's high thermal stability and the formation of a stable inorganic phase corresponding to the  $\text{HfO}_2$ .

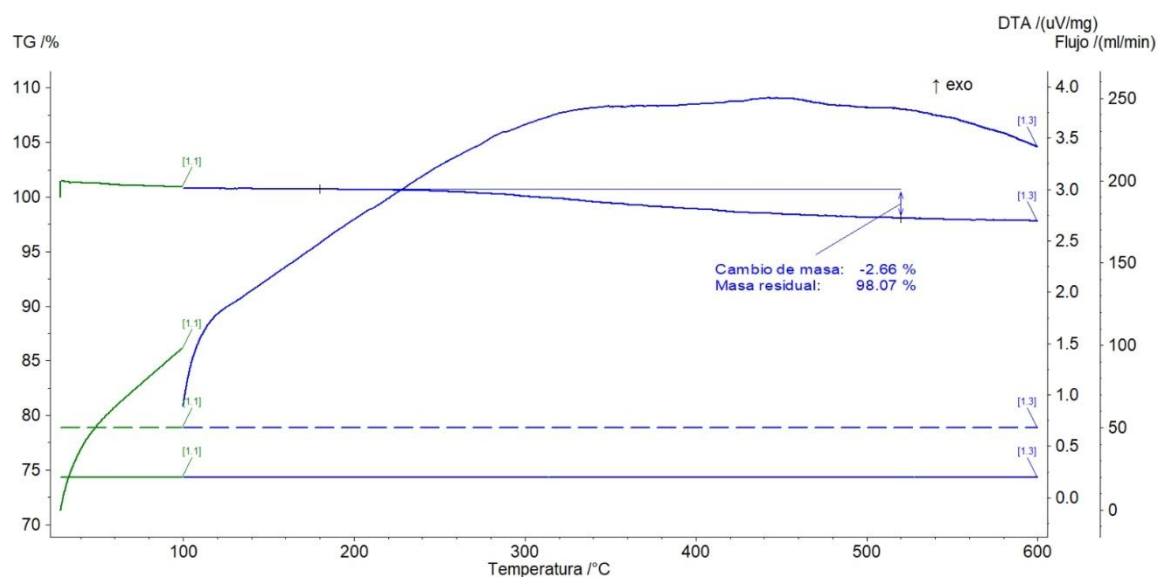


**Figure 6.** TGA and DTA curves of  $\text{HfO}_2$  nanoparticles synthesized with propionic acid.

The curves of the sample synthesized in presences of propionic acid show a very low mass loss across the entire temperature range, about 2-5%, indicating a weak interaction between the ligand and the hafnium precursor. A slight decrease in mass is observed below 120°C, attributed to the removal of absorbed water, in the 120-250°C range, a negligible mass loss occurs, associated with the removal of weakly absorbed or uncoordinated organic species. The DTA curve doesn't show pronounced exothermic peaks, suggesting the absence of relevant organic decomposition process. At temperatures above 400°C, the mass remains practically constant, indicating the formation of a thermal stable inorganic material corresponding to  $\text{HfO}_2$ . Although propionic acid can interact with the metal through its carboxylate group, the low mass loss observed in the TGA analysis suggests that this interaction is weak and doesn't lead to the formation of a stable organic on the surface of  $\text{HfO}_2$ .

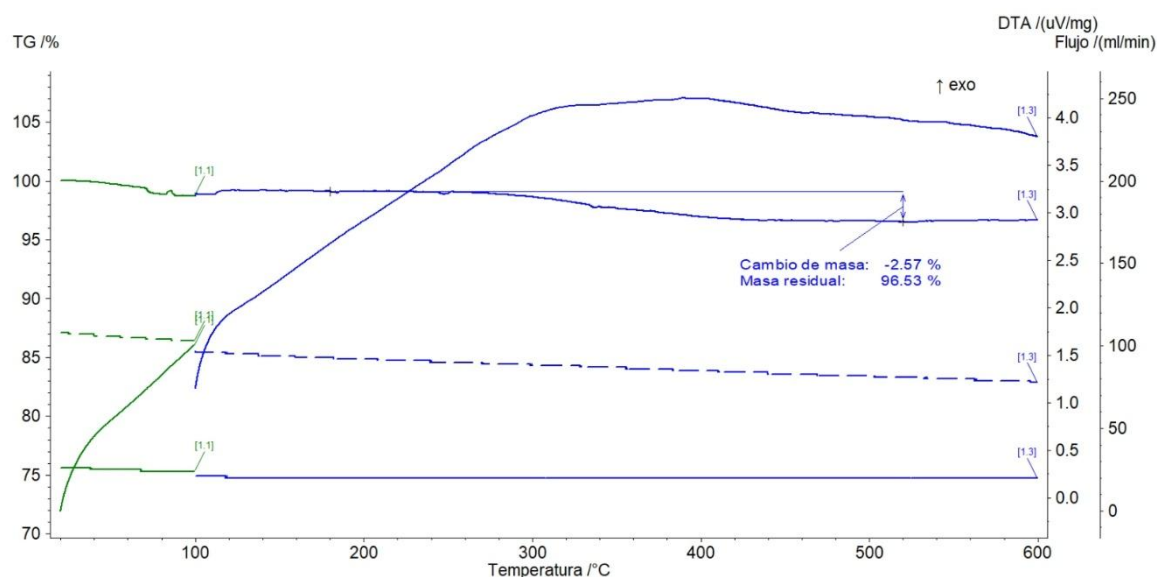


**Figure 7.** TGA and DTA curves of  $\text{HfO}_2$  nanoparticles synthesized with lactic acid.

In case of the  $\text{HfO}_2$  nanoparticles synthesized with lactic acid show a very low mass loss, about 2.3%, indicating a minimal amount of organic material associated with the nanoparticle. A slight decrease in mass is observed below 120°C, attributed to the presence of water. In 120-150°C, a marginal mass loss occurred, related to the removal of traces of weakly absorbed or uncoordinated lactic acid. The DTA shows a no significant exothermic peak, suggesting the absence of relevant organic decomposition process. Above 400°C, the mass remains practically constant, indicating the thermal stable inorganic material according to the  $\text{HfO}_2$  nanoparticles. These results suggest that the lactic acid exhibits limited interaction with the nanoparticles, without leading to the formation of a stable organic coating on the material's surface.

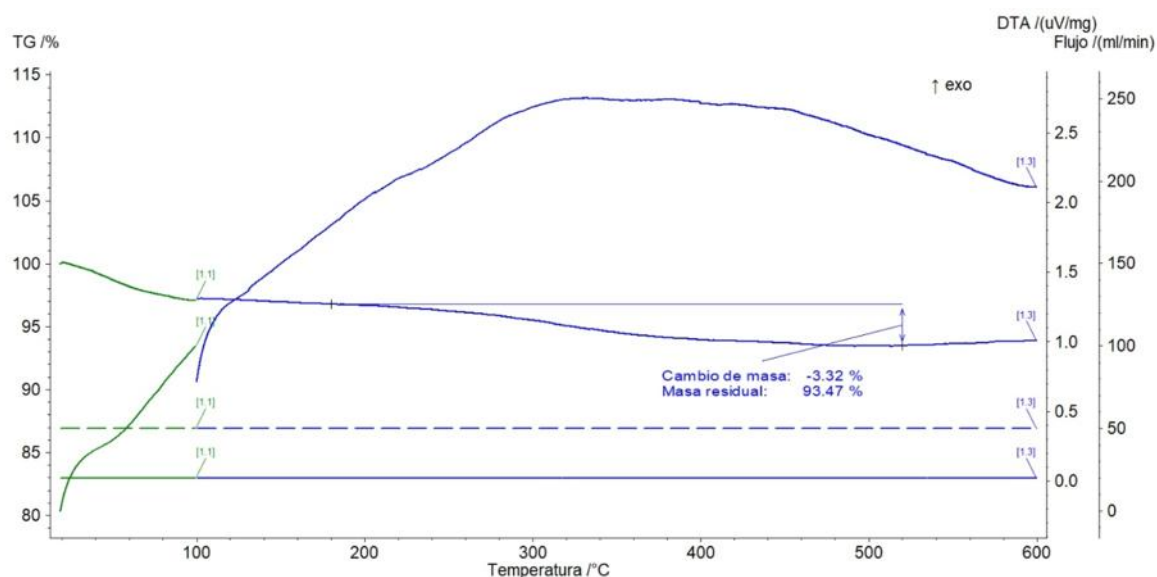


**Figure 8.** TGA and DTA curves of  $\text{HfO}_2$  nanoparticles synthesized with PEG 4000.

The particles synthesized with PEG 4000 were evaluated by TGA and DTA, revealing a high mass loss, primarily associated with the presence of a considerable amount of organic material. Above 120  $^{\circ}\text{C}$ , gradual changes linked to the initial degradation of the polymer chains were identified. The main decomposition process occurred between 250  $^{\circ}\text{C}$  and 400  $^{\circ}\text{C}$ , where the DTA curve showed an intense exothermic event that can be attributed to the rupture and oxidation of the PEG chains, as well as the combustion of carbonaceous residues that may have been generated during the heat treatment. The magnitude of the loss suggests that PEG 4000 favors the formation of a more abundant organic coating on the surface of the  $\text{HfO}_2$  nanoparticles compared to those of smaller molecular size. At 400  $^{\circ}\text{C}$ , the residual mass remained constant, indicating a thermally stable inorganic phase.

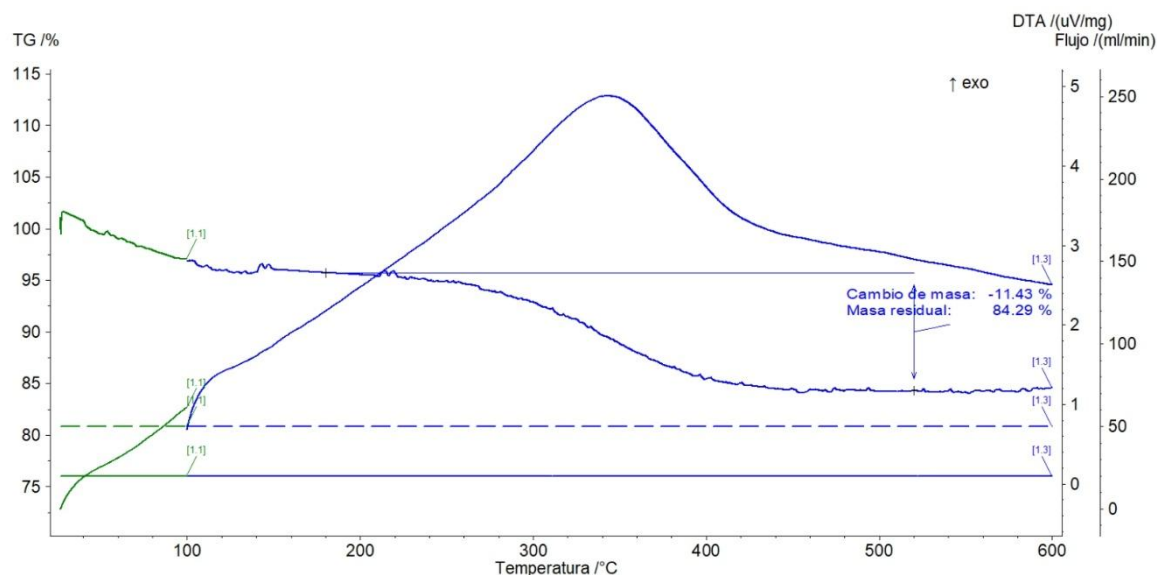


**Figure 9.** TGA and DTA curves of  $\text{HfO}_2$  nanoparticles synthesized with DHBA.

For the nanoparticles of  $\text{HfO}_2$  synthesized in the presence of 3,4-dihydroxybenzoic acid (DHBA) show a moderate mass loss, on the order around of 12%, indicating the presence of a significant amount of organic material associated with the nanoparticle. A decrease in mass is observed below 120°C, attributed to the absorbed water. In the 120-250°C range, a gradual mass loss occurs, related to the initial decompositions of organic species coordinated to the metal precursors. The main thermal event occurs between 250°C and 400°C, where the DTA curve shows a well-defined exothermic peak, associated with the oxidation of the organic ligand and the combustion of carbonaceous residues. At 400°C the mass stabilizes, indicating the formation of a thermally stable inorganic material corresponding to  $\text{HfO}_2$ . These results suggest that a stronger interaction between DHBA and the hafnium precursor, leading to the retention of organic material on the surface of the nano particles.

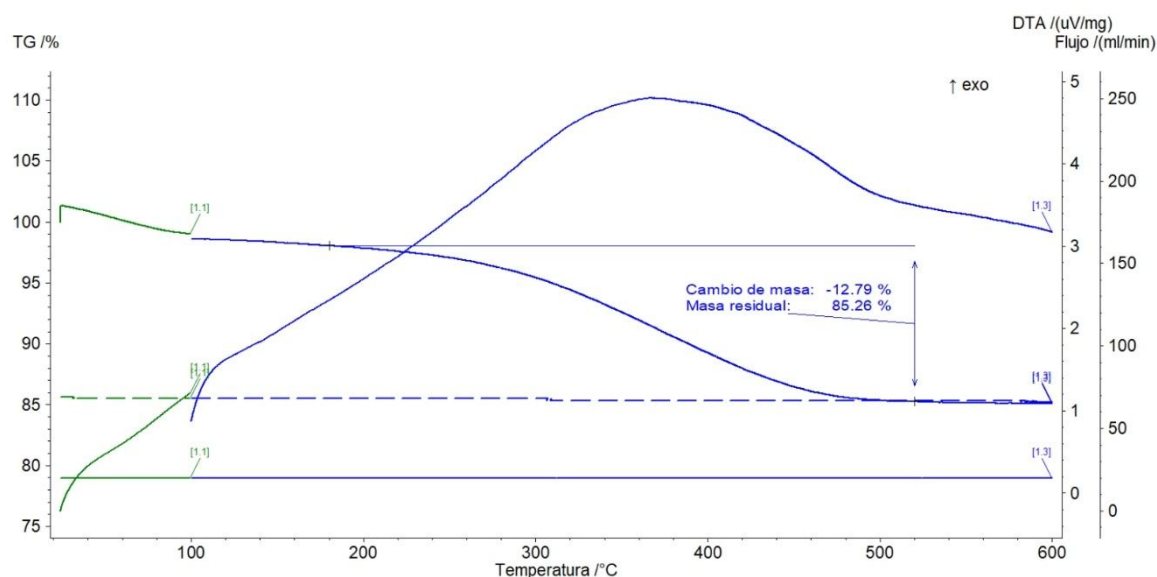


**Figure 10.** TGA and DTA curves of  $\text{HfO}_2$  nanoparticles synthesized with Dopamine.

Figure 10 shows the TGA and DTA curves of the dopamine-synthesized nanoparticles, revealing an intermediate mass loss of 12-13%, higher than that observed in short-chain acid systems. This indicates greater retention of organic species on the material's surface. Below 120  $^{\circ}\text{C}$ , a very slight decrease in mass is observed, associated with the removal of absorbed moisture. As the temperature increases, partial degradation of the organic groups derived from dopamine is observed between 120 and 250  $^{\circ}\text{C}$ . The most significant degradation occurs between 250 and 400  $^{\circ}\text{C}$ , where the DTA curve shows a marked exothermic signal. This could be related to the oxidation of the catechol group and the combustion of more stable organic residues. It may also be associated with the possible formation of polydopamine-like structures during synthesis or initial treatment. Above 400  $^{\circ}\text{C}$ , the mass remains constant, indicating a stable inorganic phase of  $\text{HfO}_2$ . These results suggest an effective interaction between dopamine and hafnium, favoring the partial retention of the ligand in the final material.

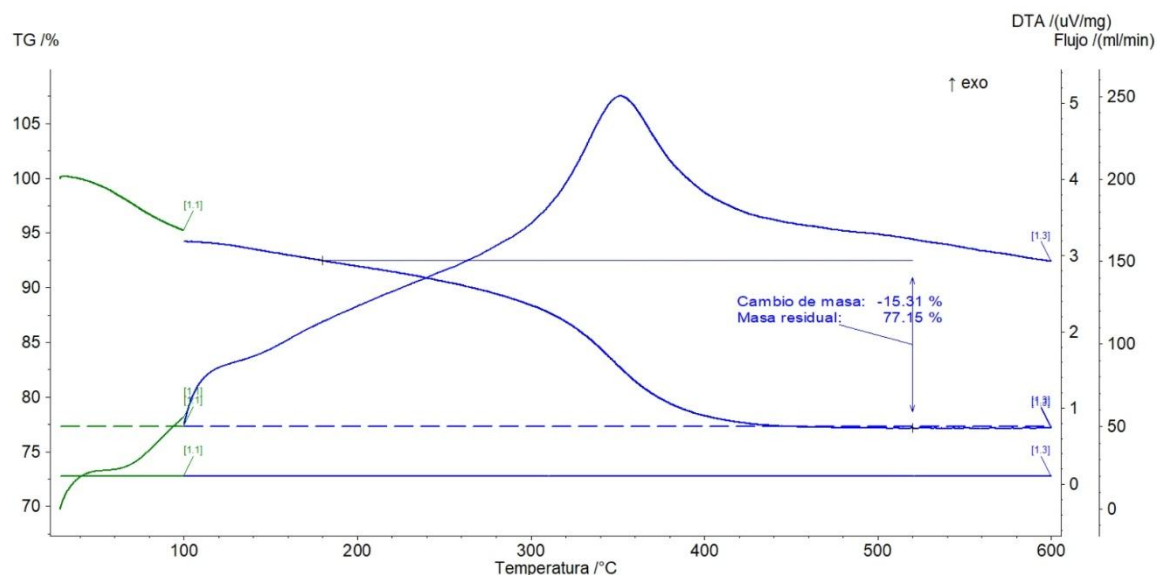


**Figure 11.** TGA and DTA curves of  $\text{HfO}_2$  nanoparticles synthesized with Citric Acid.

Figure 11 shows the TGA and DTA curves for the sample synthesized with citric acid. Compared to the previously discussed systems, there is a greater mass loss, around 15%, indicating a higher amount of organic material associated with the nanoparticles. The gradual decrease in mass loss due to the partial decomposition of the carboxylate groups attached to the nanoparticle is noticeable between 120 and 250°C. After this point, an intense exothermic peak appears on the DTA curve, associated with the oxidation of citric acid and the combustion of its residues generated during the decomposition process. This suggests a more significant interaction between the ligand and  $\text{Hf}^{4+}$ , favoring the retention of organic species on its surface. Above 400°C, the mass stabilizes, indicating a thermally stable inorganic material.

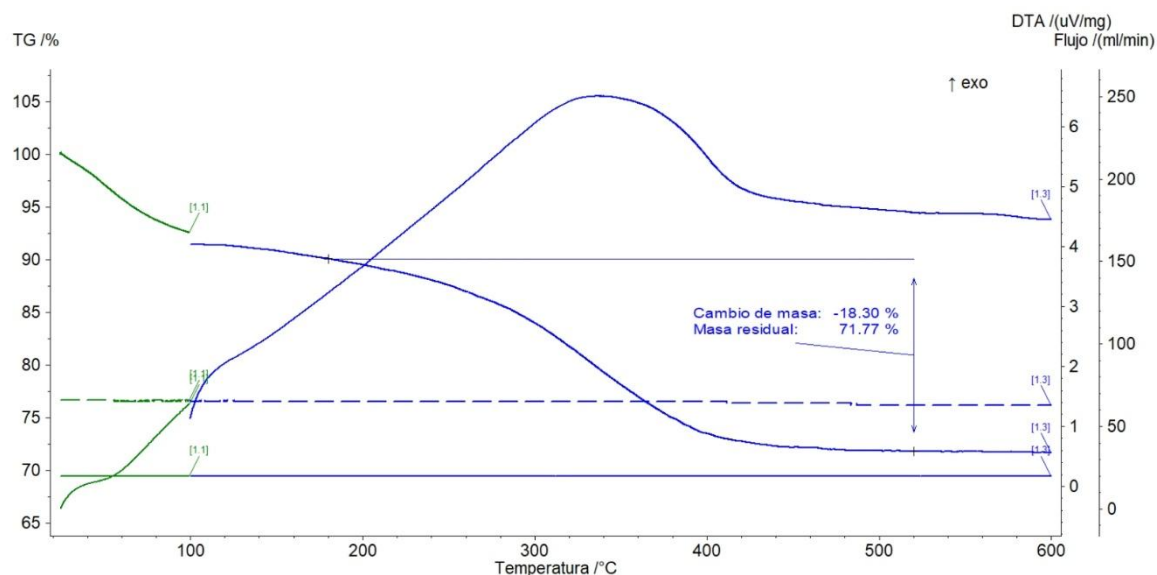


**Figure 12.** TGA and DTA curves of  $\text{HfO}_2$  nanoparticles synthesized with Gallic Acid.

The TGA and DTA graphs presented in Figure 14 correspond to the gallic acid-modified nanoparticles. This sample exhibits one of the highest mass losses among those evaluated up to this point, at approximately 18%. Progressive degradation of the organic ligand begins between 120 and 250°C. Between 250 and 400°C, the DTA curve shows an intense exothermic signal related to the oxidation of the aromatic ring of gallic acid and its multiple characteristic hydroxyl groups. The high mass loss observed suggests considerable interaction between the ligand and the nanoparticles, thus promoting greater retention of organic species compared to the previous systems. Above 400°C, the mass remains practically constant, indicating stability.

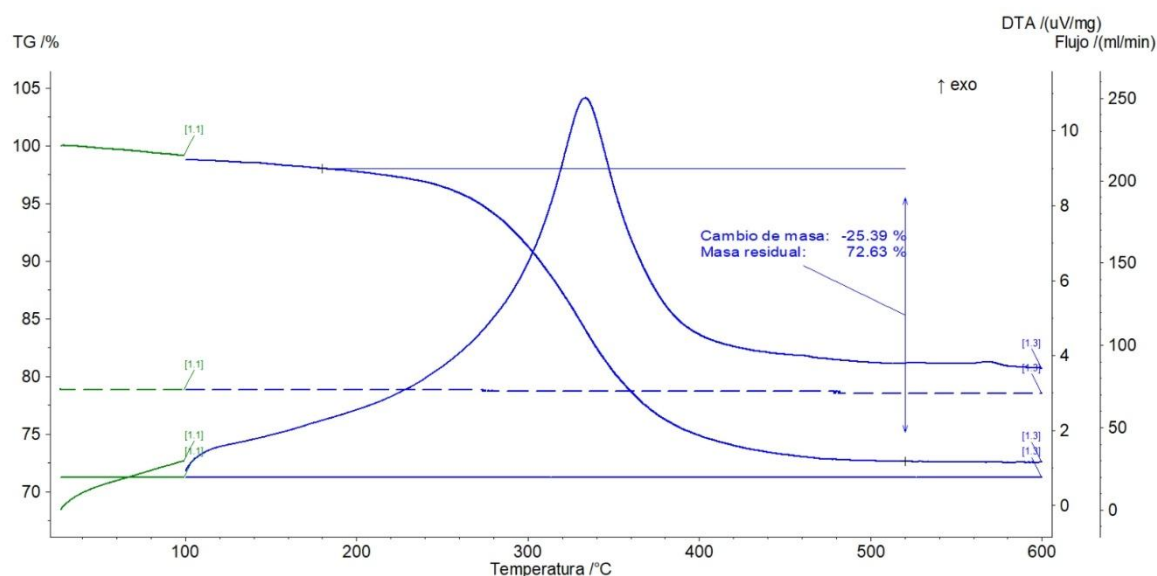


**Figure 13.** TGA and DTA curves of  $\text{HfO}_2$  nanoparticles synthesized with Oleic Acid.

Figure 13 shows the TGA and DTA curves of the sample synthesized using oleic acid as a modifying agent. This system exhibits the greatest mass loss among the analyzed samples, at 25%, indicating a high amount of organic material associated with the nanoparticles. At low temperatures below 120 °C, only a slight decrease in mass is observed, related to the removal of surface moisture, a behavior consistent with the hydrophobic nature of oleic acid. Between 120 and 250 °C, gradual variations are identified, associated with the reorganization and initial degradation of the organic chains. The main thermal event occurs between 250 and 400 °C, a range in which the DTA curve shows an intense exothermic peak attributed to the oxidation and combustion of the long aliphatic chain of oleic acid, as well as to the carbonaceous residues generated during decomposition. The high mass loss observed suggests the formation of a dense organic coating on the nanoparticle surface, favored by the ligand's surfactant properties. After 400 °C, the mass remains practically constant, indicating the formation of a stable inorganic phase corresponding to  $\text{HfO}_2$ .

In summary, the TGA and DTA results show that the chemical nature of the modifying agent directly influences the quantity and stability of the organic material associated with the  $\text{HfO}_2$  nanoparticles. Systems synthesized with short-chain acids, such as propionic acid and lactic acid, exhibit minimal mass losses, suggesting weak interactions and the absence of stable organic coatings. Conversely, aromatic

ligands such as DHBA and dopamine show intermediate mass losses, indicating greater retention of organic species due to more effective interactions with the metal precursor. On the other hand, systems modified with citric acid and gallic acid show greater losses, attributable to their high density of functional groups and greater coordination capacity. Finally, the samples synthesized with PEG 4000 and oleic acid exhibit the greatest mass losses, indicating the formation of more abundant organic coatings associated with the polymeric and surfactant nature of these modifiers. In all cases, the stabilization of the mass at temperatures above 400 °C confirms the formation of a thermally stable inorganic phase corresponding to HfO<sub>2</sub>.

**Table 3** Comparative TGA results of HfO<sub>2</sub> nanoparticles.

| Sample           | Mass loss (%) | Residual mass | Interaction level |
|------------------|---------------|---------------|-------------------|
| HfO <sub>2</sub> | <3            | High          | None/minimal      |
| Propionic acid   | 2–5           | High          | Weak              |
| Lactic acid      | 2–3           | High          | Weak              |
| PEG 4000         | 3             | Moderate      | Strong            |
| DHBA             | 11–12         | Moderate      | Moderate          |
| Dopamine         | 12–13         | Moderate      | Moderate–strong   |
| Citric acid      | 15            | Lower         | Strong            |
| Gallic acid      | 18            | Lower         | Strong            |
| Oleic acid       | 25            | Low           | Very strong       |

In general, samples are modified by oleic, gallic, citric acids and dopamine obtained the greatest mass losses associated with the presence of surface-bond organic species. TGA results support the hypothesis that the chemical nature of the modifying agent significantly influences the amount of organic material retained on the HfO<sub>2</sub> surface.

## Chapter 6 Conclusions

The present work demonstrated the successful synthesis of  $\text{HfO}_2$  nanoparticles through a hydrothermal process under subcritical water conditions at 250 °C for 4 h. The selected synthesis route enabled the production of crystalline nanoparticles while avoiding the use of organic solvents, highlighting the potential of subcritical water as a sustainable and environmentally friendly reaction medium.

X-ray diffraction analysis confirmed that all synthesized samples exhibited the monoclinic crystalline phase of  $\text{HfO}_2$ , which is the thermodynamically stable phase under ambient conditions. The incorporation of different organic molecules during synthesis did not induce phase transformation or the formation of secondary crystalline phases, indicating that the structural integrity of  $\text{HfO}_2$  was preserved after surface modification.

Scherrer analysis revealed that organic modifiers significantly influenced crystallite growth behavior during hydrothermal synthesis. Citric acid and gallic acid promoted the formation of larger crystalline domains, whereas 3,4-DHBA, dopamine, and PEG 4000 limited crystallite growth and generated smaller crystallite sizes. Furthermore, microstrain analysis showed that DHBA and dopamine exhibited higher lattice distortion, while citric acid produces larger and more structurally order crystalline domains. These results demonstrate that organic molecules can function as growth-regulating agents during nanoparticle formation.

Thermogravimetric analysis showed significant differences in the amount of organic material retained on the nanoparticle surface. Propionic acid and lactic acid exhibited very low mass losses, suggesting weak interactions with  $\text{HfO}_2$  and limited surface retention. In contrast, 3,4-DHBA, dopamine, citric acid, and other multifunctional molecules displayed higher mass losses and characteristic thermal decomposition events, indicating stronger interactions with the  $\text{HfO}_2$  surface and a greater degree of surface functionalization.

Overall, the results demonstrate that hydrothermal synthesis under subcritical conditions is an effective method for obtaining crystalline  $\text{HfO}_2$  nanoparticles and that the selection of the organic modifier plays a critical role in controlling crystallite growth, lattice strain, surface chemistry, and thermal behavior. The preservation of the monoclinic phase in all the samples confirms that surface functionalization can be achieved without compromising the structural integrity of the  $\text{HfO}_2$  nanoparticles.

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## Future and Current Work

Recommendations for future research include a more comprehensive characterization of the synthesized  $\text{HfO}_2$  nanoparticles. In particular, transmission electron microscopy (TEM) is recommended to accurately determine the morphology, size distribution, and dimensions of the crystallites, allowing for direct comparison with crystallite sizes estimated using the Scherrer equation. Furthermore, TEM analysis is necessary for a quantitative study of grafting density which is performed to determine the number of organic molecules grafted on the nanoparticle surface and to better understand the relationship between surface functionalization and the resulting physicochemical properties.

Additionally, it's extremely important to do Fourier Transform Infrared spectroscopy (FTIR) to provide evidence of surface modification of  $\text{HfO}_2$  nanoparticles through the identification of functional groups from the surfaces modifiers and evaluate the stability of these interactions between these conditions and propose new experimental conditions and hypothesis. Further evaluation of endurance of the grafting of functional groups to the nanoparticles is also recommended, particularly using different media related to biomedical applications.

Another important line of research for future work is the expansion of the biological evaluation of the synthesized nanoparticles. Because this work only demonstrated successful synthesis and surface functionalization, further in vitro studies are required to establish their suitability for biomedical applications. Biocompatibility assessments should include hemolysis essays across a wider range of nanoparticle concentrations, studies of intracellular reactive oxygen species (ROS) generation, and cell viability assays such as MTT and MTS. These experiments would provide a more comprehensive understanding of the biological response to functionalized  $\text{HfO}_2$  nanoparticles.

Finally, future research should evaluate the radiosensitizing performance of the synthesized nanoparticles under ionizing radiation. Considering the favorable physicochemical characteristics obtained in this work and the promising results reported in the literature for hafnium oxide nanoparticles, studies on radiation intensification, DNA damage, oxidative stress, and therapeutic efficacy in cancer cell models would represent a logical continuation of the present research. Such investigations would contribute to establishing structure-property-activity relationships and support the development of  $\text{HfO}_2$ -based nanomaterials for future applications in cancer therapy.

Much of the work described in this section is already underway.

## Annexes

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