Chapter 1
X-Ray Nanochemistry: Background and Introduction

If you are flexible, you may not get what you want; If you are adamant, you may only get what you want.

1.1 Background and Introduction

1.1.1 Ionizing Radiation and Nature

Ionizing radiation research began with the discovery of X-rays in 1895 by Röentgen, who was awarded the first Nobel Prize in Physics in 1900. Other types of ionizing radiation were discovered soon after, with the discovery of γ-rays in 1900 by Villard. After a century of studying radiation biology, and as technologies improve and the level of exposure to man-made ionizing radiation decreases, there seems to be a lack of interest in studying radiation-related topics because large doses of ionizing radiation are generally perceived as harmful to humans. Exceptions to this are in the field of crystallography and medical imaging as well as cancer treatment, areas in which ionizing radiation is still being actively researched and used.

It turns out that ionizing radiation such as X-rays and γ-rays is ubiquitous in nature, as we are constantly being irradiated by them. For example, the annual background dose received by people living in Denver is equivalent to performing several head computed tomography (CT) per year. When ionizing radiation interacts with matter, whether it is air, water, tissues or nanomaterials, one of the most important events is ionization of core electrons in atoms in these materials, hence the name ionizing radiation. When X-ray photons interact with light elements such as oxygen, another absorption process known as Compton scattering occurs, which produces energetic electrons as well. As shown in Chap. 2, these electrons and positive ions left behind on the ionized species are capable of initiating or enabling chemical reactions. Knowing that ionizing radiation is omnipresent all the time on Earth, in our bodies, and around the world, and the interactions between the radiation and matter generate reactive electrons, radicals, and ions, the question to ask is whether nature has developed any kind of chemistry that specifically responds to ionizing radiation.

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To answer this question, one may draw inspiration from a well-known process, photosynthesis. The dominating part of the electromagnetic spectrum from the sun is comprised of visible and ultraviolet photons, which interact strongly with some molecules and certain biological systems. It also can be said that nature created these molecules to respond or harvest sunlight energy delivered to Earth. Nature does this because certain biological systems need to draw energy from the sun, and this energy becomes the driving force for the growth of plants and other organisms on Earth. Biological systems such as human bodies, on the other hand, consume the organic matter but do not directly require solar energy to survive, with exceptions such as human skin absorbing UV light to produce vitamin D_3. If nature developed these molecules and photosystems to effectively respond to sunlight, can it also create any effective systems to respond to X-rays?

A possible mechanism developed in nature to respond ionizing radiation is DNA repair. Biological systems have to defend against reactive species such as hydroxyl radicals, which may be generated by UV light, ionizing radiation, or chemicals such as oxidized fats. X-rays produce these radicals when interacting with biological systems, which contain abundant water as well as other molecules that can produce radicals or react with radicals. The exact reason why biological systems developed these repair mechanisms is unknown because there are many means known to cause DNA damage. The outcome, nonetheless, is that chemicals in cells such as DNA repair proteins do exist and Lindahl, Modrich and Sancar won the Nobel Prize in Chemistry in 2015 for their work on this important topic.

Another clue that may help answer the question of whether nature created any systems to respond to ionizing radiation comes from the fact that all known natural living systems are made of light elements such as C, H, N, and O, and none of these systems contain large amounts of X-ray or γ-ray absorbing heavy elements. Based on the existing knowledge, although it is still too early to completely rule out the possibility that nature began to create proteins to repair nuclear DNA only after they were damaged by ionizing radiation billions of years ago, it is more likely that nature has not developed any specialized processes to respond to X-rays or other types of ionizing radiation. Given that ionizing radiation can generate a high local density of radicals and can directly ionize atoms in nuclear DNA molecules, it appears that nature is less prepared or that our current understanding is not advanced enough to claim that biological systems have evolved mechanisms or measures to specifically enhance or counter the effects of ionizing radiation. Even the most radioresistive bacteria such as *Deinococcus radiodurans,* which can survive 1000 Gy of irradiation, only have more efficient repair systems rather than sensitization mechanisms. In short, there is no existing enhancement mechanism in nature that harvests or thrives on ionizing radiation such as X-rays like photosystems do with sunlight.

If this reasoning is correct, much more work is needed to create artificial chemical or nanochemical systems to respond to X-rays. The upside of such a reality is this lack of natural systems may be a blessing in disguise. Rather than spending time figuring out what nature already offers, researchers can create and assemble materials that fulfill different functions. The hidden principles associated with these new materials will require investigation and creation, after which engineers can make

devices based on established principles. This is analogous to what we have done in the current digital world, beginning with the study of semiconductor materials and associated chemical and physical principles in the 1950s.

In summary, it looks certain that new materials will have to be created and principles be understood so that it is possible to use these new systems to build devices to respond to X-rays and other types of ionizing radiation. Those who are working in the discipline have to explore and create chemical and particularly nanochemical systems to do what we want them to do. Knowledge on at least two fronts will have to be advanced—creating new materials and developing novel physical and chemical principles. These new materials and systems and the principles will improve the enhancement as defined later in this book and beyond.

1.1.2 History of Nanochemistry

Nanochemistry is a scientific discipline that studies chemical processes made available by nanomaterials. The latter contain a vast number of materials, from simple nanoparticles or nanowires to hybrid, complex nanomaterials that support exotic functions such as sensing and catalysis. Like ionizing radiation, nanomaterials have existed for millennia. Many kinds of nanoparticles have probably existed in nature for billions of years. Simple, man-made, or engineered nanomaterials existed for thousands of years, dating back to ancient times when silver was used to stain glass. More recently, Faraday made gold and silver nanoparticles in the 1850s.

Nanochemistry is closely related to another field of work—nanotechnology, which is a more popular term. Nanotechnology is the applied form of nanochemistry, although the two are closely intertwined. The beginning of the nanotechnology era dated back to almost a century ago. There were several accounts in the 1920s where platinum nanoparticles were studied. Then, starting in the 1970s, platinum nanoparticle catalysts were further developed and widely used for automobiles and have continued to be used till now. The actual arrival of modern nanoscience, which is almost a synonym of nanochemistry, occurred in the late 1980s and early 1990s, when many new studies and nanomaterials emerged. For example, fullerenes were discovered by Smalley et al. [1]. Following this was the discovery of carbon nanotubes by Ijima [2]. Quantum dots were discovered by Bawendi et al. [3]. Studying these materials soon became popular in research laboratories around the world. Gold nanoparticles were synthesized by Brust et al. [4] with specialized sizes and coatings. In another effort, gold nanoparticles were used as a contrast agent in transmission electron microscopy by Hainfeld [5] and others in the late 1980s. Starting in the 1990s, almost every chemistry department in the United States has had some activities of nanoscale research. This created the basis for the nanotechnology boom in the 2000s when the United States began to invest heavily in infrastructures for nanotechnology. The establishment of the National

Nanotechnology Initiative (NNI) led by Roco and Tech [6] signaled the formal arrival of the true nanoscience era at the national level. Despite all these achievements, the era of nanotechnology probably has not yet arrived because there have been only a handful of real applications developed, such as using quantum dots in display devices.

1.1.3 Early Histories Related to X-Ray Nanochemistry

From what are shown above, simple nanoparticles and ionizing radiation may have existed for a long time. The study of catalysis using ionizing radiation and synthesis of nanomaterials using ionizing radiation has been ongoing since the 1920s. From very early times, the idea of using nanoparticles to catalytically improve the yield of relatively simple chemical reactions was examined. The radiation was usually γ-rays, and nanoparticles were either platinum black or oxide nanoparticles. In retrospect, these efforts were connected to the enhancement of the effectiveness of irradiation of ionizing radiation that is discussed in this book, which is formally defined as one of the main goals of X-ray nanochemistry research. The scope of the impact, however, has been significantly expanded from molecular hydrogen production in the early times to generation of reactive oxygen species, DNA damage, and polymerization at present. All of these research topics belong to X-ray nanochemistry research.

As stated earlier, research on interactions of ionizing radiation with nanomaterials began in the 1920s when interactions of electrons, γ-rays, α particles, and other types of ionizing radiation with catalysts and nanoparticles were used to investigate catalytic production of chemicals, such as hydrogen. More studies were undertaken after the invention of nuclear technologies capable of producing intense ionizing radiation and nuclear waste, the latter of which presents a storage problem. Motivations for work in this area are the same now as they were then. For example, it is important to understand if and how nanomaterials can be used to produce or stop the generation of hydrogen gas when irradiated with ionizing radiation.

These studies comprised part of the early history of systematic study of ionizing radiation nanochemistry. Most results obtained using other types of ionizing radiation can help X-ray nanochemistry, and, conversely, most of the principles developed in X-ray nanochemistry can be used to improve the outcome of these early works. Though the radiation types are interchangeable, the content contained in these early works encompassed only a small part of X-ray nanochemistry. As this book shows, the scope of X-ray nanochemistry extends far beyond those early studies involving γ-rays and nanoparticle catalysts.

A related area in early studies that does not fall into the current scope of X-ray nanochemistry research was the production of nanomaterials using ionizing radiation. X-ray synthesis of nanoparticles is different from X-ray nanochemistry because it only involves reduction of ions by X-ray-generated species in solutions to form nanoparticles and has not considered using nanomaterials under X-ray irradiation to

augment the effects of X-ray irradiation. If the synthesis of nanomaterials using ionizing radiation were proven to be dependent on nanomaterials under irradiation, then this process would belong to X-ray nanochemistry.

1.1.4 Early Works Outside UC Davis

Interactions of ionizing radiation with nanomaterials may not have led to the creation of X-ray nanochemistry so quickly if not for the immense medical application potential of X-ray nanochemistry, ranging from imaging to treatment. Development of nanomaterials, nanochemistry, nanoscience, and nanotechnologies has been accelerated by the desire to use these techniques in medical applications. Several experimental demonstrations that helped create or accelerated the creation of the discipline of X-ray nanochemistry are described here.

One specific work closely related to X-ray nanochemistry was the use of externally introduced materials, such as implants, in the human body. Castillo et al. [7] noticed increased damage near the implants. Another closely related study that helped with the conception of X-ray nanochemistry was the use of a radiosensitizer iododeoxyuridine (IUdR) for Auger electron therapy. IUdR and related compounds containing radioisotopes were delivered into the body, after which Auger electrons were released to destruct cells. IUdR research could be traced back to the 1960s, although Auger therapy, which was still being understood in the late 1990s, overlapped with some of the early studies in X-ray nanochemistry, which began in the early 2000s. Hunting et al. [8] studied bromodeoxyuridine (BrdU) in causing single-strand breaks in DNA. The idea of using these compounds to make cancer cells more sensitive to radiation, unfortunately, has not reached its promised potential in the early days as it is difficult to make these materials target tumors or to deliver large enough quantities to tumors in the body without causing serious side effects. It was around this time when Guo began his career in the Department of Chemistry at UC Davis. The nanomaterials proposed by Guo starting from 2001 were aimed to overcome these serious problems facing IUdR or BrdU.

The work performed by Das et al. [9] was also connected to the development of X-ray nanochemistry. The study, although employing gold microspheres and not nanomaterials, was the closest to using nanomaterials in cancer treatment at the time. It is evident that the results by Das et al. [9] were medical application oriented and many cellular and medical works presented within the realm of X-ray nanochemistry resembled the work by Das et al.

Studies carried out by Meisel and LaVerne at the University of Notre Dame Radiation Laboratory and other researchers around the world helped create X-ray nanochemistry as well. For example, radiation nanochemistry was studied in Meisel's lab in the 1990s and 2000s. Works by Meisel and Laverne were generally conducted using γ-rays, which were different from many works covered by X-ray nanochemistry even though there were similarities between how nanomaterials

interact with the two types of ionizing radiation. Differences between the two are explained in Sect. 1.1.8.

These developments were seeds sown by researchers that would later grow and ripen into the then little-known field of X-ray nanochemistry. Yet like many chemical reactions, there usually is a catalyst for a major event to occur, and this catalyst was the passing of Wilson in 2001.

1.1.5 Development of X-Ray Nanochemistry in the Guo Lab at UC Davis

The stories behind the development of X-ray nanochemistry are associated with many groups, but here, the events as they happened in the Guo laboratory at UC Davis are recounted. X-ray nanochemistry work in the Guo laboratory at UC Davis commenced in 1999, two years before Guo's postdoctoral adviser Wilson passed away from cancer in 2001. Wilson had a dream of using X-rays to visualize chemical reactions, a dream shared by 16 postdoctoral scholars he hired in the early 1990s. Guo studied the synthesis of nanotubes and transition metal clusters in Smalley's laboratory at Rice University and then ultrafast X-ray spectroscopy in Wilson's lab at the University of California, San Diego. At UC Davis, he studied chemical reactions using tabletop ultrafast X-ray pulses. Many problems arose, and one of them was that the number of ultrafast X-ray photons was not enough to allow measurements of dynamics in solutions of regular metal complexes, severely limiting the number of chemical systems the technique could study. Construction of the fourth-generation synchrotron sources, such as the Linac Coherent Light Source (LCLS) at the Stanford Radiation Laboratory, had begun, which made the tabletop ultrafast X-ray measurements less appealing. At that time, Wilson passed away, and his passing gave Guo both a reason and a clue. It also seemed natural to combine nanomaterials with X-rays to increase the interaction cross-sections so that ultrafast X-rays have a better chance to be used to interrogate important chemical reactions.

In late 2001, Guo submitted his first proposal on studying X-ray nanochemistry. The proposal was turned down. The proposed work was to use sub-3 nm diameter gold nanoparticles and X-rays to damage DNA molecules, and the work was carried out by students who also worked on several other projects including ultrafast X-ray spectroscopic investigations of dynamic structures of metal complexes in solutions, a project supported by the National Science Foundation. Supported by the University of California, Guo and his students were able to demonstrate that DNA molecules were damaged with enhancement using small gold nanoparticles. The results were published in 2005, and the lead author was an undergraduate student Foley [10].

Their work was helped by several other faculty members at UC. Their generosities accelerated the pace of research. Still, it took nearly 4 years before the results were published in 2005, which came out a few months after Hainfeld et al. published

their paper, showing that nanoparticles could be used to increase the survivability of cancer-bearing mice under X-ray irradiation.

Knowing all these happened in one laboratory, one can speculate how much more effort was needed in other laboratories around the world, including Hainfeld's, which had worked for nearly 20 years on using gold clusters as a contrast agent for electron microscopy prior to their animal work published in 2004. These are speculations by the author of this book (Guo) since the author does not have first-hand experience with other laboratories.

The nanochemistry component did not emerge until 2007, when the surface of nanoparticles was modified to accommodate targeting ligands. The term X-ray nanochemistry was first mentioned in a publication by Guo et al. [11]. Although one may debate about the influence of the timing of these events on the creation of X-ray nanochemistry, it was definitely in that time span when the theme of X-ray nanochemistry emerged. It may be unimportant to pinpoint the exact time when X-ray nanochemistry was established. Knowing the content of those proposals by Guo in 2001, which was to use sub-3 nm gold nanoparticles to replace IUdR or equivalents as a highly specialized method to destruct cancer or cancerous DNA, it is prudent to state that these two early efforts from Guo's laboratory and from Hainfeld's laboratory/company only revealed a glimpse of the essence and full scope of current day X-ray nanochemistry, which is still quickly growing.

1.1.6 Formal Introduction of X-Ray Nanochemistry

X-ray nanochemistry is a brand new discipline. As stated in the preface, X-ray nanochemistry studies X-ray-driven chemical reactions in nanosystems, starting with X-ray ionization of atoms to create reactive chemical species such as electrons and reactive oxygen species. X-ray nanochemistry also includes the creation of nanomaterials to enable these reactions as well as methods to characterize these reactions. In other words, X-ray nanochemistry creates, utilizes, and links atomic, molecular, and nanoscale events and studies how to use these events to transform X-ray energy into other forms of energy, a definition given earlier in this chapter. X-ray nanochemistry also contains current applications in biology, cancer treatment, catalysis, sensing, and environmental science. Future applications in other areas are also possible.

X-ray nanochemistry can be regarded as being introduced over a few years, depending on how it is viewed. For example, Guo et al. [12] and Guo et al. [13] both discussed relevant aspects of X-ray nanochemistry. In a few publications in 2011 and 2012, the concept of X-ray nanochemistry became clearer. Finally, in a publication in 2012, Guo et al. [11] performed the first experiment that was directly connected to X-ray nanochemistry. Regardless of the exact time when X-ray nanochemistry or X-ray nanotechnology began, three facts are clear.

Firstly, Hainfeld et al. [14] were the first to use nanoparticles to enhance the effectiveness of X-ray irradiation in radiotherapy, and Guo et al. [10] were the first to

report on using nanomaterials to enhance damage of DNA by X-rays. Secondly, X-ray nanochemistry was only formally introduced and described by Guo et al. [11]. These three publications mark the arrival of a scientific and technological era that was different from the past. There is a vast amount of literature describing many different aspects of using nanomaterials to improve all aspects of X-ray applications, and it is the aim of this book to discuss these aspects. Thirdly, while these early works in X-ray nanochemistry are the foundation of X-ray nanochemistry, the content described in these early publications does not fully represent the scope of X-ray nanochemistry. The number of nanochemical processes in these early works was limited, and other works have since greatly expanded the scope. As shown in this book, many areas have been simultaneously developed. The scope of the work performed to date in the area of X-ray nanochemistry is broad, ranging from imaging to treatment to catalysis and sensing. Theoretical work is also a major part of X-ray nanochemistry.

The application aspects of X-ray nanochemistry are often emphasized over the fundamental chemistry or nanochemistry. However, one must realize that the depth and future of X-ray nanochemistry rely on chemistry and especially nanochemistry. For example, improved understanding of the surface chemistry of nanomaterials has helped advance X-ray imaging through improved uptake and delivery. Therefore, it is critical to continue to develop these fundamental understandings. Formal introduction and creation of X-ray nanochemistry has helped emphasize the study of fundamental chemical processes that may eventually revolutionize many applications in X-ray nanochemistry. Although nanomaterials can increase the effectiveness of X-ray irradiation, it is now clear that merely using simple nanomaterials to replace existing or traditional materials does not significantly increase the effectiveness. This means that primitive nanomaterials are not the novel solution people have been looking for to solve many problems, as Guo, the author of this book, had naively imagined in the 2001 proposal. At that time, the full impact of nanomaterials was unclear. As this book shows, X-ray nanochemistry may eventually support novel applications desired by many researchers.

This book attempts to define the scope of X-ray nanochemistry, which is a discipline that continues to grow and expand. Fundamental science will be critical to the future development of X-ray nanochemistry. Although it is difficult to foresee the future, one thing is almost certain: new developments will largely rely on the development of theories and complex nanomaterials. The next edition of this book will be quite different. However, there will be strong overlap between this edition and the next because the most fundamental processes, such as physical and chemical enhancement, will be the same. Therefore, this book tries to find a balance between fundamental studies and applications as well as between simple, primitive studies and experiments using elaborate nanomaterials.

One motivation of writing this book is to include a more complete review and evaluation of the literature in the area of X-ray nanochemistry. The number of papers published per year in the discipline has increased significantly in recent years, as shown in Fig. 1.1. There are numerous reviews in each subfield of X-ray nanochemistry, but there is currently not a single document covering the whole

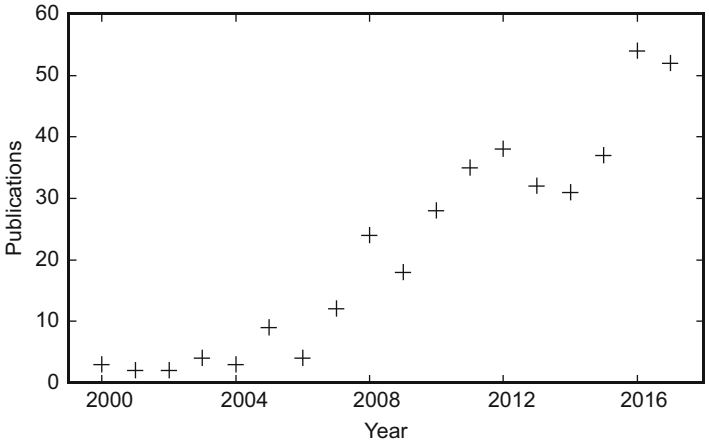

Fig. 1.1 Number of publications per year in the discipline of X-ray nanochemistry in the last 17 years, since 2000. The number of publications in 2017 is extrapolated based on the number of publications from 1/1/2017 through 6/30/2017

spectrum of work in X-ray nanochemistry. This situation is partially caused by the fast pace of the growth in the interest of cancer treatment within X-ray nanochemistry. There are many applications including imaging, treatment, catalysis, and biology that make researchers excited about the usage of nanomaterials. On the other hand, the recognition and establishment of X-ray nanochemistry, and a collection of the entire literature, as they are organized in this book, may help researchers connect with the larger community conducting X-ray nanochemistry research.

If the tradition of naming the applied side of nanoscience as nanotechnology is followed, then the applied side of X-ray nanochemistry can be called X-ray nanotechnology. As it is shown in this book, both are important, especially if the two are synergistically developed. It is important to develop the fundamental aspects of X-ray nanochemistry independent of the constraints and burdens from X-ray nanotechnology. Only then can the true potential of X-ray nanochemistry be unlocked, recognized, and reached.

1.1.7 Categories and Types of Enhancement and Enhancement Units

At the beginning of X-ray nanochemistry research, only one category of enhancement was known to researchers, and this enhancement was regarded as being caused by increased absorption of X-rays by nanomaterials. The enhancement is now categorized as physical enhancement. Other terms have been used, including dose enhancement factors or dose enhancement ratios.

Physical enhancement can be further divided into three types. The first type is the constant enhancement by electrons depositing energy in the whole sample volume. The second type is caused by electrons depositing energy near the surface of nanoparticles, and the enhancement is called nanoscale energy deposition or nanoscale enhancement. The third is caused by increased emission of UV-Vis light as the result of adding nanomaterials. All three types of physical enhancement require the added nanomaterials to strongly absorb X-rays. These concepts are described in Chap. 2.

Other categories of enhancement exist, one of which is chemical enhancement. A criterion for chemical enhancement to occur is that the enhancement has to be enabled by catalytic chemical reactions, which does not happen in physical enhancement. There are several types of chemical enhancement as well. The first is caused by catalysis enabled by reactive species generated in solution by X-rays. This type of chemical enhancement does not involve increased production of reactive oxygen species. The second type of chemical enhancement involves catalytic production or destruction of radicals. Both types are described in Chap. 3.

Another category of enhancement is biological enhancement, which is not yet well known but has been speculated in several reports. There are at least two types of biological enhancement identified in this book. The first type involves enhanced damage to biological samples such as cells without direct damage to any biological components in the cell by X-ray absorbing nanomaterials. The second type addresses responses of a biological system to direct damage of certain components in the cell, especially those next to the nanomaterials. A discussion of these types of biological enhancement is given in Chap. 4.

Accurate and conclusive proof of all these enhancement categories and types is by no means complete, and new mechanisms and nanomaterials will continuously be developed. As applications, nanomaterials, and methods used in X-ray nanochemistry continue to expand, more types and categories may be discovered.

In this book, the enhancement is gauged by dose enhancement units (DEU). Researchers have developed many ways to quantify the magnitude of enhancement, independent of the categories and types. Commonly used terms include dose enhancement factors (DEFs), dose enhancement ratios (DER), and nanoscale or microscopic dose enhancement factors (nDEFs or mDEFs). The units are times, fold, percentage, or simply unitless. DEU is introduced to mirror the Hounsfield units in X-ray imaging. All enhancement factors in X-ray nanochemistry use DEU. It is the ratio (hence can be unitless) of energy deposition with the added nanomaterials to that without the nanomaterials. This calculation of enhancement results in relative enhancement in reference to the effect of radiation without nanomaterials. As a result, 1.0 DEU relative enhancement means no enhancement. If the enhancement is calculated per weight percentage (WP) of gold in water of nanomaterials, for example, then absolute enhancement must be used, and the unit is DEU WP^{-1}. The absolute enhancement value is the relative enhancement value minus 1.0. Hence an absolute enhancement of 1.0 DEU per 1 WP of gold in water gives rise to 1.0 DEU WP^{-1}. One should not use relative enhancement values when calculating unit WP enhancement. For instance, if a relative enhancement is 1.5 DEU for 2 WP gold

in water, which means the absolute enhancement value is 0.5 DEU, then the corresponding unit WP enhancement is 0.75 DEU WP^{-1} if relative enhancement is used, or 0.25 DEU WP^{-1} if the absolute enhancement value is used. The first value would mean the absolute enhancement is −0.25 DEU for 1 WP of gold, which is wrong. The second value is correct, suggesting an enhancement of 0.25 DEU for 1 WP of gold in water. For this reason, absolute enhancement is used throughout this book unless otherwise noted.

1.1.8 Similarities and Differences Between X-Rays and Other Types of Ionizing Radiation

Meisel of Notre Dame once commented to the author of this book that there is little difference between X-rays and γ-rays. This statement is correct to a degree. X-rays and γ-rays are both low-linear energy transfer (LET) ionizing radiation, meaning that they are not highly absorbed by matter. Nonetheless, interaction cross-sections of X-rays with matter are quite different from that of γ-rays with matter. As shown in Chap. 2, the interaction cross-sections of the same element, such as gold, can change nearly four orders of magnitude within the X-ray energy range of 1–100 keV. Absorption cross-sections of different elements (e.g., gold and oxygen or water) may differ by 100-fold at the same X-ray energy. In contrast, absorption cross-sections for different elements for either electrons or γ-rays are much closer, often differing by as little as a few times. This makes it much more desirable to use X-rays over other types of radiation to interact with nanomaterials dissolved in media to obtain high enhancements. Many publications have shown the advantages of using X-rays over γ-rays for enhancement purpose. Nonetheless, materials and concepts developed within X-ray nanochemistry can be readily used for γ-rays, albeit with much smaller values of enhancement.

Many features can make X-rays more favorable than other types of ionizing radiation, and four of them are shown here. First, X-rays are much safer to handle than any other types of ionizing radiation. It is easy to shield X-rays used in X-ray nanochemistry, which are often below 200 keV or even less than 100 keV. X-rays are produced with X-ray tubes, which can be switched off when not in use. For low energy X-rays such as 20 keV, using them is almost as safe as a laser pointer if safety rules are strictly followed. γ-rays are difficult to contain or shield, even though they can also be produced with electricity. Radioactive elements in large quantities are the most dangerous, although a small amount of Am241 emitting α-particles is used in smoke detectors in almost every house in the United States. This proves that small amounts of ionizing radiation can be safely used if proper science and technologies are developed.

The second advantage of using X-rays with nanochemistry is that X-ray sources are far more inexpensive and accessible than sources emitting other types of ionizing radiation. For example, a microfocus X-ray source currently costs around $30,000,

and such a source can be conveniently interfaced with other instruments such as optical microscopes to perform necessary measurements required by X-ray nanochemistry research. Furthermore, miniature sources costing less than $10,000 are adequate for a majority of experiments when lesser doses of X-rays are needed to cause measurable enhancements with the advancement in X-ray nanochemistry. Monochromatic X-rays are also available at many synchrotron sources, which are conveniently accessible to researchers around world. These user-friendly facilities are well-managed and are constantly upgraded.

Thirdly, X-rays are distinctly favored over other types of ionizing radiation because of the large interaction cross-sections between X-rays and nanomaterials of heavy elements. When γ-rays are used, although the fundamental principles are similar, the interaction is much less effective. The favorable interactions between X-rays and nanomaterials make it easier to develop advanced theories, experiments, and nanosystems. Once new nanochemical mechanisms are developed that can provide high enhancement factors, these new mechanisms can be used for all types of ionizing radiation.

The fourth advantage of using X-rays is that heavy elements such as gold absorb X-rays intensely in the water window—an energy interval between 80 and 100 keV, within which water absorbs X-rays minimally. This is not true for other types of ionizing radiation such as electrons or γ-rays—all the elements have about the same absorption cross-sections, including water.

Table 1.1 summarizes the results of comparison of several important parameters associated with X-rays and γ-rays.

One may ask why X-ray nanochemistry does not belong to the traditional field of radiation chemistry. Radiation chemistry uses mainly pure liquids, metal ions, or organic compounds in solutions. The introduction of nanomaterials, catalysis, and enhancement processes completely changes the chemistry happening in these systems. Although nanomaterials such as oxides or metal nanoparticles may have existed in nature for a long time, radiation chemistry generally does not include these particles. Many new types of nanomaterials, ranging from hybrid nanoparticles to nanocapsules, are being incorporated into X-ray nanochemistry. It is thus foreseeable that in the future, X-ray nanochemistry will be more different from radiation chemistry than now.

γ-rays are generally used for their high penetrating power. When a large dose is needed deep in an object and the surface dose has to be kept manageable, then γ-ray is the only option. However, X-ray nanochemistry will usher in a new platform of

Table 1.1 Comparison of X-rays and γ-rays

Properties	γ-rays	X-rays
Photon energy	>1.2 MeV	0.1–100 keV (up to 300 keV)
Penetration depth (water, 1/e)	>15 cm	Over 5 cm
Common sources	Linear accelerators	Tubes
Mass attenuation coefficients by gold	0.05 cm^2/g	5.1 cm^2/g
Access to water window (80–100 keV)	No	Yes (heavy elements)

nanomaterials, which can respond to and function with very low doses of X-rays. Under this circumstance, there is no need to use γ-rays as X-rays can deliver enough dose to activate the function of the nanomaterials anywhere in the body or elsewhere without causing side effects. Until then, there is still a place for γ-rays even though they do have many more unwanted properties than X-rays.

1.1.9 Difference Between X-Ray Nanochemistry and X-Ray Synthesis of Nanomaterials

Much work has been done in the area of using ionizing radiation to synthesize nanomaterials, especially metallic nanoparticles such as gold or silver nanoparticles. Early work in this area was demonstrated by Henglein and Meisel [15]. Belloni and Mostafavi [16] summarized works in this area more than a decade ago. A more recent example was given by Divan et al. [17] who reported the results of their study of using X-rays to deposit gold nanoparticles formed from a gold salt onto bulk SiO_2 and GaAs surfaces. Work by Hwu et al. [18] showed gold nanoparticle formation under intense X-ray irradiation. The works in this area are summarized in a recent review by Abedini et al. [19] although more reports continue to appear in the literature. All of these works are not considered as part of X-ray nanochemistry because the active role of nanomaterials is missing. Unless the synthesis of nanomaterials by ionizing radiation is influenced by nanomaterials, either pre-made or made in situ, the studies are not included in X-ray nanochemistry. However, the division between these two fields may not be final since one may find suitable nanomaterials that indeed interact with X-rays during their growth. Until then, we will distinctly call this a method of nanomaterial synthesis rather than a research component of X-ray nanochemistry.

1.1.10 X-Ray Nanotechnology and X-Ray Nanobiology

X-ray nanotechnology can be considered as applied X-ray nanochemistry. To date, the most advanced applications of X-ray nanochemistry are in X-ray imaging of nanomaterials and cancer treatment using nanoparticles, as discussed in Chap. 9. This book also describes other applications, including sensing and catalysis, which can be regarded as part of X-ray nanotechnology as well. Future work in the area of X-ray nanotechnology may include X-ray-charged batteries, X-ray writing/reading memory devices, and security materials or technologies.

One may wonder about the possibility of creating a new field called X-ray nanobiology, which is to develop nanobiological systems to maximize the effectiveness of X-ray irradiation. Such a need may exist because X-ray nanochemistry, in its current form, may not be able to create the highest magnitude of enhancement. Biochemical and especially biological systems may be used to augment physical and chemical enhancement to further increase the total enhancement.

1.1.11 The Developing Trend and Impact of X-Ray Nanochemistry

The number of research groups working in the area of X-ray nanochemistry increased from the Guo lab in 2001, to several in 2004, to more than 50 across the world in 2012. Now, the number of groups that have published in X-ray nanochemistry as defined in this book is over 200. Figure 1.2 shows a world map highlighting the groups that have conducted work in the research area of X-ray nanochemistry. The work includes theoretical, imaging, chemical, physical, and medical research, as well as clinical trials and medical treatment of patients. Between 2004 and July 2017, these groups published more than 390 papers in the area of using nanomaterials to increase the effectiveness of X-ray radiation. The annual trend of these publications is shown in Fig. 1.1, and most of these papers are cited in this book.

It is clear that X-ray nanochemistry is still in its infancy and there are many ongoing developments, as evidenced in recent publications and this book. Impacts of X-ray nanochemistry to date are still limited, with the most visible impact being in the area of cancer treatment. As shown in Chap. 9, there are many potentially powerful cancer imaging and treatment approaches derived from X-ray absorbing nanomaterials and X-ray nanochemistry. Several cases of clinical trials using rare earth oxide nanoparticles are reported.

There have been almost no publications on IUdR or similar compounds since the start of X-ray nanochemistry more than a decade ago. Nanomaterials present superior properties and seem to have completely replaced those compounds. On the other

Fig. 1.2 Groups currently conducting research in X-ray nanochemistry. The dots represent groups that work in the area and published papers cited in the book. The size of the dots is proportional to the number of publications at that location. The largest dots represent 10–20 publications per location, medium dots represent 3–9 publications per location, and small dots represent 1–3 publications at that location

hand, the Auger electron therapy that was studied prior to the development of X-ray nanochemistry may be enhanced by X-ray nanochemistry. A recent study reported the advantage of combining Auger therapy with physical enhancement by nanomaterials by Ye et al. [20]. X-ray-activated prodrugs are still being researched, but X-ray nanochemical research has also outpaced that field. In the future, it may be possible to combine both prodrugs and Auger therapy with X-ray nanochemistry to further improve the effectiveness of X-ray irradiation with nanomaterials.

As Chaps. 2, 3, 4, and 5 show, fundamental properties and principles have been discovered or developed in X-ray nanochemistry. X-ray nanochemistry has enabled chemists to investigate a completely new area of research at the interface of many disciplines. This new interdisciplinary research field will allow advanced principles and mechanisms to be developed and discovered. These research activities expand far beyond those defined by radiation chemistry using compounds. If it is possible to discover all the individual enhancements, maximize them, and constructively combine them, then it is possible to create a total enhancement that is much higher than currently measured values. If that happens, then it is possible to find a method to treat cancer without side effects of lateral damage by radiotherapy or systemic toxicity with chemotherapy. This new method can release a lethal dose of drugs from an otherwise nontoxic drug carrier with pinpoint accuracy in the body after exposing to a radiation dose that causes no side effects. In this sense, X-ray nanochemistry is bringing the dream of finding that magic bullet to destruct cancer closer to reality.

Nanomaterials in biological systems may have greater functionalities than those predicted based on their physical properties when dissolved in aqueous solutions. These nanomaterials may be excellent catalysts and may have farther-reaching functions than mere X-ray absorbers in complex environments, such as cells under ionizing radiation. As nanomaterials become more intricate and advanced in design, our understanding about biology will advance. This is another impact X-ray nanochemistry can make.

It is likely that when X-ray nanochemistry will have reached its full potential, a revolutionary change or paradigm shift will occur. Increasingly more complex nanomaterials are being developed, and improvements, although often incremental, are gradually revolutionizing applications such as radiotherapy. Currently a 30% or even 100% improvement to radiotherapy may be realized using large amounts of nanomaterials. However, many obstacles such as high costs and severe side effects exist. As shown in this book, it is possible to achieve much higher enhancement values. If enhancements can reach 100 DEU, then less than 0.1 Gy of radiation can be used to cause various, 10-Gy equivalent responses in controlled nanochemical environments such as nanoreactors. The responses include chemical, mechanical, electrical, magnetic, optical, and beyond. Other possible responses include triggering secondary processes such as drug release and sensing activities.

High local enhancements may also enable X-ray sensing and security products, although it is still too early to predict how successful these potential applications can be. In addition, several imaging methods using nanomaterials under X-ray irradiation are being developed, which may be commercialized in the future. These applications are discussed in Part IV of this book.

1.2 Other Reading Materials Related to X-Ray Nanochemistry

There are no existing reviews or books on X-ray nanochemistry prior to the publication of this book. However, there are many reviews on nanomaterial synthesis, enhanced radiotherapy using nanoparticles, and X-ray imaging assisted by nanoparticles. Many of these reviews are mentioned in various places throughout the book. For example, summaries of theoretical works are given in Chap. 2. In Chap. 6, reviews and books on nanomaterial syntheses are presented. In Chap. 9, reviews in medical applications are shown. A few reviews briefly mentioned relevant topics covered in this book. In one of these review articles, for example, Allen et al. [21] briefly mentioned the terms of physical, chemical, and biological enhancement, but the authors did not separate the types within each category as described in this book. Other reviews, including that by Chithrani et al. [22], reviewed the field of using gold nanoparticles for therapy. The content in these reviews does not fully cover X-ray nanochemistry because their emphasis is placed on cancer therapy. In several reviews on nanomaterials and their applications such as those by El-Sayed and Murphy et al. [23], the authors mentioned the idea of using nanomaterials for enhancing the performance of radiotherapy of photodynamic therapy. These discussions are informative and connected to X-ray nanochemistry although still different from X-ray nanochemistry.

1.3 Outline of the Book

This book consists of five parts. An introduction and discussion of background is described in Chap. 1, which is Part I. Part II of the book includes fundamental concepts and principles, which contain categories and types of enhancement. Part II includes Chaps. 2, 3, 4, and 5. Part III of the book covers nanomaterials and their syntheses in Chap. 6 and methods used in X-ray nanochemistry in Chap. 7. These two chapters show how enhancement in X-ray nanochemistry is measured with chemical reactions and probed with various methods. Part IV of the book, including Chaps. 8, 9, 10, and 11, discusses applications and principles related to applications. Biological, medical, radiolytic, catalytic, environmental, and sensing applications are among those discussed. In addition to these four parts, Part V, which includes Chap. 12, briefly concludes and describes future possibilities that may be investigated in X-ray nanochemistry.

Discussion of the literature is arranged chronologically in each chapter by corresponding authors; if multiple papers exist from each corresponding author, then the publications are grouped together for that author.

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