OPEN JOURNAL OF

NANO

ISSN:2147-0081

Volume:5, Issue: 1, Year: 2020

A JOURNAL ABOUT NANOSCIENCE

Volume 5 / Issue 1

Open Journal of Nano

OPEN JOURNAL OF
NANO

Contents
Volume: 5, Issue: 1, Year: 2020

Open Journal of Nano
(2020) 5–1

Regulatory Policies For Safety Of Nanomaterials

[1]Arife Kübra Demirbaş ,*[1]Sinem Çevik

[1]. Department of Metallurgical and Materials Engineering Ondokuzmayıs University, Samsun, Turkey.
Corresponding author, e-mail: akubrademirbas@gmail.com

Submission Date: 15.11.2019 Acceptation Date: 18.01.2020

Abstract - Nanoparticles can cross cell boundaries or move from the lungs directly to the bloodstream and ultimately reach all organs in the body due to their unique features including small size, shape, high surface area, chemical characteristics, solubility and degree of agglomeration. Nanoparticles entering the body through the skin, air or different ways have shown toxic properties and harming human health. In areas such as cosmetics, textiles and food, nanostructured materials may be used under specific standards, as nanostructured materials may have toxic properties. Because of the risks posed by nanomaterials, important rules and the methods have been established for the use and storage of these materials. Developed countries have established and become members of international organizations for the safe use of nanomaterials. These organizations have established regulatory policies and standards for using of nanomaterials in the different fields. The countries comply with the standards established by these organizations and implement policies for the use of nanomaterials in this direction. It is crucial to use nanomaterials according to these regulatory policies for the environment and human health. This paper discusses the regulatory policies established and used for nanomaterials in various countries of the world and the organizations that make up these regulations. It is mentioned that these regulations and policies should be taken into consideration for the use of nanomaterials and that these rules should be followed.

Keywords: Nanomaterials, Safety, Regulatory aspects, Nano toxicity, Health and risk

Nanomalzemelerin Güvenliği ile İlgili Düzenleyici Politikalar

Öz - Nanoparçacıklar vücut içerisinde hücre sınırlarını aşabilir veya akciğerlerden doğrudan kan dolaşımına geçebilir ve bunun sonucunda küçük boyut, şekil, yüksek yüzey alanı, kimyasal karakteristikleri, çözünürlük ve yığılma derecesi gibi benzersiz özellikleri nedeniyle vücuttaki tüm organlara rahatlıkla ulaşabilir. Vücuda deri, hava ya da farklı yollarla giren nano parçaçıklar toksik özellik göstererek insan sağlığına zarar vermektedir. Kozmetik, tekstil ve gıda gibi nanoyapılı malzemeler belirli standartlar altında kullanılabilir, çünkü nanoyapılı malzemeler toksik özelliklere sahip olabilmektedir. Nanomalzemelerin oluşturduğu risklerden dolayı bu malzemelerin kullanılması ve saklanması için önemli kurallar ve yöntemler oluşturulmuştur. Gelişmiş ülkeler nanomalzemelerin güvenli kullanımı için uluslararası organizasyonlar kurmuşlardır ve bu organizasyonlara üye olmuşlardır. Bu organizasyonlar nanomalzemeler için düzenleyeci politikalar ve standartlar oluşturmuşlardır. Ülkeler bu organizasyonların oluşturduğu standartlara uymaktadırlar ve bu doğrultuda nanomalzeme kullanımı için politikalar yürütmektedirler. Çevre ve insan sağlığı için nanomalzemeleri bu düzenleyici politikalara (yönetmeliklere) göre kullanmak çok büyük önem arz etmektedir. Bu çalışma dünyanın çeşitli ülkelerinde nanomalzemeler için oluşturulan ve kullanılan düzenleyici politikalardan ve bu düzenlemeleri oluşturan kuruluşlardan bahsetmektedir. Nanomalzeme kullanımı için bu yönetmeliklerin ve politikaların dikkate alınması ve bu kurallara uyulmasının gerekliliğinden bahsedilmiştir.

Anahtar kelimeler: Nanomalzemeler, Güvenlik, Düzenleyici hususlar, Nano toksisite, Sağlık ve risk

1. Introduction

Nanomaterials are particles that have at least their one dimension smaller than 100 nm. Nanomaterials are very important in the field of nanotechnology. European Commission define a nanomaterial containing about particles size 50% or more has one or more external dimensions is in the range 1–100 nm as any natural, or manufactured materials [2]. Because of these new and improved features, nanomaterials affect us in many areas of our lives, including automotive, electronics, cookware, cosmetics, pharmaceuticals and dyeing. Future and current applications of nanotechnology are expected to provide enormous benefits with new diagnostic and medical treatment methods, as well as increasing employment and economic development, improving materials with environmental improvement and less resources [1,3]. Nanotechnology and its applications were worth between $1-2.6 trillion in manufacturing industry by 2010 and have been keep growing rapidly [4].

Nanomaterials having the same composition in bulk state may have different physical or chemical properties in which the same materials are in bulk and therefore, these nanomaterials maybe show different behaviors if they enter the body and generate different important hazards [5]. The continued use of nanomaterials has raised concerns about whether these materials are safe for the environment. The first publication that considers and investigates the possible ecological effects of designed nanomaterials emerged more than 15 years after the worldwide spread of nanotechnology [6-7].

Nano ecotoxicology, a new discipline, examines the environmental impact of nanoscale materials. Evaluating the behavior and effects of nanomaterials in complex environmental conditions is an extremely difficult and necessary problem [8]. Attention should be paid to the release of nanoparticles to the environment in a way that encompasses the entire life cycle, including the production, use and disposal of a product. Nanoparticles can have not only advantages over bulk materials, but also have unique toxic properties. Potential undesirable effects that may occur should be considered at the cellular level to the entire ecosystem. Hazard of environmental assessment on a mass dose basis may not be applicable to nanomaterials and the question regarding the relevant dose measurements in nano ecotoxicology is still unclear. How to use the benefits of nanotechnology and how to protect the environment from potential hazard is the most urgent problems of our time. It is essential to understand and manage these risks well, to effectively commercialize products containing nanotechnology and determine their potential [9].

This paper discusses the regulatory policies established and used for nanomaterials in various countries of the world and the organizations that make up these regulations. It is mentioned that these regulations and policies should be taken into consideration for the use of nanomaterials and that these rules should be followed. The aim of this study is to introduce the organizations established in the world for the safe use of nanomaterials. This study is about the rules and policies that individuals and companies who want to use nanomaterials should follow and where they can access this information. These policies and rules must be known in order to minimize the damages of the use of nanomaterials and to create safer products and environment.

2. The Reasons of Nanomaterials Cause Eco-toxicity

Nanoparticles can be categorized by size, morphology, physical and chemical properties into different types. Some of these materials are carbon-based nanoparticles, ceramics nanoparticles, metallic nanoparticles, nanoparticles with semiconductors, polymer nanoparticles and lipid-based nanoparticles. Nanoparticles physiochemical properties affect their contact with cells and their overall potential toxicity. With the same mass, smaller nanoparticles have a larger special area (SSA) and therefore a greater area available for interacting with cellular elements, such as nucleic acids, proteins, grade acids and carbohydrates. It is also possible to enter the cell because of its smaller size and it can generate cell damage.

Research reports and articles about nanomaterials have shown that they have some properties that play a decisive role in their toxicity properties. It includes chemical and physical properties such as size, increased agglomeration, dissolution and surface area. Many studies and reports have shown the toxicity levels of nanomaterials [1-8]. The degree of toxicity of each component in the ecosystem varies. Even low concentrations of nanoparticles may show toxic properties for living things. Therefore, it requires detailed examination of various factors that play an important role in determining the toxicity of nanomaterials. However, there are relatively a few reports on the eco-toxicity of different nanomaterial types [3-15]. For examples; Aluminum based nanoparticles alter mitochondrial function, disturb the cell viability, increase oxidative stress, and also alter tight junction protein expression of the blood brain barrier. Copper oxide is genotoxic and cytotoxic with disruptive integrity of the cell membrane and oxidative stress. Silver nanoparticles show a higher toxicity for cell viability, production of reactive oxygen species and lactate dehydrogenase leakage. Zinc oxide nanoparticles have adverse effects such as changes in cell morphology, DNA damage, and changes in mitochondrial activity in human hepatocytes. In addition, many nanomaterials such as titanium oxide, carbon-based nanomaterials, silica have toxic properties.

When nanoparticles are released into the environment, living and non-living components interact with them in various ways. When humans and animals are exposed to nanomaterials, these nanomaterials are absorbed by the feeding channels. Similarly, respiratory and skin exposure occurs by inhalation and injection, respectively. Due to gravity, nanomaterials emitted in the air may condense or collect. Agglomeration in nanomaterials leads to an increase in particle sizes. Thus, the nanomaterials can enter the respiratory system by air, suspended or agglomerated. However, the collected nanoparticles from the air can settle in the soil and therefore they can be spread or transported through soil and water to the environment [9].

The identification of hazards is the first step in determining risk and exposure of nanomaterials. This step involves identifying toxic, physical and physicochemical hazards of chemicals or nanomaterials associated processes. The following primary hazard categories may be considered when assessing risk associated with nanomaterials.

2.1. The Size

It is important to know the size of the particles to determine the toxicity levels of the nanomaterials. The nanoparticles' shape and size in the range of 1–100 nm is of interest for biological interface. Many articles and reports [7-14] have shown that nanomaterials with particle sizes below 100 nm have detrimental effects on the biological system. The nanometer sized particles generate more damage when compared to their bulk state. Toxicity studies for inhalation of 20 and 250 nm size of titanium dioxide nanoparticles have shown that smaller nanoparticles exert high inflammatory reaction when compared to the bigger particles. Further investigations have shown that when the nanomaterial exposure prolonged in the body, their retention in tissue increases, more tissue damage and augmented translocation occurs.

Blood-brain barriers are highly sensitive to nanomaterials below 12 nm in size, so these particles can easily pass through this barrier. Similarly, cells can be endocytosed to the nanoparticles of the 30 nm or less in diameter [10-12]. Furthermore, nanomaterials with smaller sized particles have a higher surface area. Smaller nanoparticles cause the dose-dependent increase in DNA damage and oxidation when compared to large particles with similar dose [14]. Therefore, the biological application or release of this nanoparticles into the environment is really dangerous and should be considered.

2.2. The Agglomeration

Nanomaterials may behave differently under different environmental conditions. Therefore, it is likely that the nanoparticles undergo agglomeration in the test environments. Furthermore, it is very difficult to distribute the nanoparticles in water. Because of the high surface activity of the nanomaterials, agglomeration usually occurs in almost all nanoparticles. In order to avoid agglomeration problems, an anti-dispersing material must be used in the production of nanomaterials. Therefore, it implies that nanoparticles can easily get agglomerated when released into blood and body fluid. In such cases, they can compose harmful effects on biological components present in the water ecosystem since nanoparticles will appear as a pollutant. Other conditions affecting the degree of agglomeration and sedimentation rate of nanomaterials in the dispersion medium are the degree of ions, inorganic salts and pH. Nanoparticles agglomeration depends on the surface charges and the pH of the surrounding environment. The natural pH of the body varies as the alkaline and acidic. However, the pH level of the organism changes according to the environment. When pH and ionic strength of the stomach change, it may affecting their uptake and cause the nanoparticles agglomeration. Agglomeration can prevent the bioavailability of nanomaterials under laboratory conditions. However, if nanomaterials (particles) are thrown into the environment or passed through air, water or food, this can cause dangerous effects. In such cases, nanoparticles can form homogeneous and heterogeneous agglomeration with natural colloidal components in the ecosystem [15]. It must be known that it is very difficult to prevent intracellular agglomerating of nanoparticles. In the study of Kim et.al. (2009), it can be concluded that the agglomeration leads to a reduction in the all surface area of the nanoparticles and these agglomeration effects were reported in lysosome, vesicles and endosomes of cell [16].

2.3. The Dissolution

It is generally known that the dissolution of nanomaterials in the environment causes ion release and plays an important role in the biological system. When nanomaterials pass through natural water of body, they bind to release the corresponding ions. Silver nanoparticles (AgNPs) ion concentrations have been reported to be three times more lethal than silver ions in terms of absolute silver content. The concentration of ion release is determined by the rate of dissolution in the environment. Therefore, it is an important component in the application of the toxic effect to the target. In addition, the release of ions depends mainly on the size of the particles, the chemical structure, the surface functionalization, the crystal structure of the particles, the temperature and presence of the biomolecules and salts in the dissolution medium [17]. Poly (vinyl pyrrolidone) (PVP) stabilized nanoparticles are better soluble than citrate stabilized nanoparticles. The citrate coating is claimed to reduce outgoing silver ions, thereby preventing their release. [18]. Similarly, increased Cu^{+} ion release in cowpea seeds of copper oxide nanoparticles (CuONPs) is largely toxic to the plant [19]. Prolonged storage of nanoparticles results in a reduction in particle sizes, causing the release of ions in the environment. The release of ions into the environment can lead to a 33% reduction in nanoparticle diameter [18]. Freshly prepared nanoparticles of AgNPs have less lethal concentration 20 times smaller compared to stored particles for 6 months in dispersion environment. This clearly shows the role of silver ions in their toxicity when stored for a long period of time.

However, the above-mentioned studies indicate that nanomaterials have toxic effects on almost all components of the ecosystem, but none have produced a simple result. This may include variation in particle properties, choice of toxicological model, dosing parameters, the type of biochemical methods and cell type used in toxicity tests [9].

3. The Standardization and Nano-safety Assessment of International Organizations

Governments around the world are seriously looking at nanomaterials and answering questions about “if” and “how” about the regulation of nanomaterials. Countries such as the USA, Canada, United Kingdom and Australia have begun to ask companies to disclose information about nanomaterials found in different products. Taiwan's nanoMark program certification has evaluated more than 200 products from 19 companies in 19 categories since its launch in November 2004 [3].

3.1. Organization for Economic Cooperation and Development (OECD)

In 2006, the OECD in order to assess the safety of manufactured nanomaterials, has established the Working Party on Manufactured Nanomaterials (WPMN). To determine the safety of nanomaterials and to examine their effects on and the ecosystem and human health, it is requires to make risk assessments [20]. Many countries are member of organizations such as, Sound Management of Chemicals (IOMC), International Organization for Standardization/Technical Committee 229, Business and Industry Advisory Committee (BIAC) for the industrial circles and Non-Governmental Organization (NGOs) and also member of OECD.

There are also non-member countries like China. These countries are participating in the sponsorship programs as co-sponsor, lead sponsor and contributor to programs as can be seen in Table 1. The Republic of Korea has been a lead sponsor, contributor, co-sponsor for these programs. OECD members work for nano-toxic endpoints by making specific nanomaterials to examine and investigate OECD test guidelines (TGs). For this reason, OECD test programs are progressively working on the definition of nanomaterials, their physicochemical properties and their characterization, safety and their effects on environment and the humans. To discuss OECD test guidelines, OECD members also meet with expert workshops [21].

Table 2 shows OECD test guidelines manufactured nanomaterials list. OECD WPMN projects are included in the guidance group (SG) test programs of OECD WPMN's Priority Area (PA) 9 on nanomaterials produced [23]. The OECD, WPMN projects have been focused on the OECD database construction, test guidelines and safety testing, strategic regulatory programs, risk assessment and alternative different methods of nano toxicology and mitigation and exposure measurement on manufactured nanomaterials. The OECD sponsorship program first reported a guidebook on testing nanomaterials produced in 2009. From an environmental point of view (SG 9), test guidelines discussing environmental sustainability, ecotoxicology and environmental fate of the produced nanomaterials were published in 2013 and 2014, respectively. In 2014, OECD expert meetings reported on physicochemical properties and toxic properties and test guidelines of nanomaterials [21].

OECD continues to work on test guidelines for assessing nanomaterials to ensure sustainable economic growth. In addition, these OECD test rules help in reviewing the risk assessment of nanomaterials and provide important information about the probable risks posed to nanomaterials on human health and the environment. To provide new information, a series of safety reports on nanomaterials produced in 2015 have been published [21].

Table 1. OECD test guidelines manufactured nanomaterials list [22].

Contributors-Lead sponsors/Nanomaterials
Austria, Korea/Dendrimers
Canada, Germany, France, China, EC, BIAC-Japan, US/MWCNTs
Canada, Denmark, Germany, Japan, Netherlands, Spain, EC-UK/BIAC/Zinc oxide (ZnO)
Canada, Nordic Council of Ministers-China, US, BIAC/Iron nanoparticles
China-Japan, Denmark, US/Fullerenes (C60)
Denmark, US, EC-BIAC/Nanoclays
Denmark, UK, Japan, China-France, Germany/Titanium dioxide (TiO_2)
Denmark, Japan-France, EC/Silicon dioxide (SiO_2)
Denmark, Japan, Germany , EC, Switzerland-US, UK/BIAC/Cerium oxide (CeO_2)
France, Netherlands, China, EC, BIAC-Korea, US/Silver nanoparticles
Germany , Canada, EC, China, BIAC-Japan, France, US/SWCNTs
Germany, Japan, US-BIAC/Aluminum oxide
Korea, EC-South Africa/Gold nanoparticles

3.2. International Organization for Standardization (ISO)

In June 2005 the ISO technical committee TC 229 of nanotechnologies was established. In Table 3, the member countries of the technical committee can be seen and this countries are composed of 33 participating and 15 observing countries [24]. On behalf of the Korean government, Korean Technology and Standards Agency (KATS) is the participating agency. ISO / TC 229, which consists of four working groups, realized the ISO standardization of nanotechnologies and nanomaterials [25]. As shown in Table 4, the ISO/TC 229 includes terminology and nomenclature (Working Group 1), measurement and characterization (Working Group 2), safety of health and environmental aspects of nanotechnologies (Working Group 3), and material specifications (Working Group 4) [26].

Table 2. List of the steering group of priority area 9 [23].

Steering Group 1/2	OECD Database on Nanomaterials Produced to Inform and Analyze EHS Research Activities
Steering Group 3	Safety Testings of Nanomaterials
Steering Group 4	Test Guidelines and Nanomaterials
Steering Group 5	Voluntary Schemes and Regulatory Programs related studies
Steering Group 6	Co-operation on Risk Assessment
Steering Group 7	The importance of Alternative Methods in Nano Toxicology
Steering Group 8	Exposure Mitigation and Measurement
Steering Group 9	Sustainable Use research of Manufactured Nanomaterials

Working Group 1 which focused on the terminology and definitions of nanomaterials like nanofibers, nanoparticles and nanoplates, published as a standart of ISO/TS 27687 in 2008. Working Group 2 focuses on measurement (e.g., and characterization including SEM, TEM, TGA and UV-VIS-NIR spectroscopy. When characterization tests were performed for nanomaterials, they were found to have different structure and properties than their bulk state due to their physico-chemical properties [27]. Working Group 3 is about the environment and health safety standarts was established in 2008. In its report, Korea has stated the requirements for the health and safety requirements of nanomaterials used in the workplace or laboratory based on ISO/TR 12885. Working Group 3 guidance documents recommended that nanomaterials should be identified according to their characterization and measurements, because the toxicology report of nanomaterials is usually based on parameters obtained by their characterization [25].

Table 3. Member countries of ISO/TC 229 [21].

Participating countries			
Australia Canada Denmark India Israel Malaysia Poland Spain United States	Austria China Finland Indonesia Italy Mexico Russian Federation Sweden	Belgium Colombia France Iran Japan Netherlands Singapore Switzerland	Bulgaria Czech Republic Germany Ireland Korea Norway South Africa United Kingdom
Observing countries			
Argentina Hong Kong Mongolia Romania	Egypt Jamaica Morocco Sri Lanka	Estonia Kazakhstan Portugal Thailand	Greece Kenya Romania

Table 4. Working groups of ISO/TC 229 [27].

Working Group 1	Working Group 2	Working Group 3	Working Group 4
Terminology and Nomenclature	Measurement and Characterization	Safety of Health and environmental aspects of nanotechnologies	Material specifications

A list in Table 5 compiled by Working Group 3 shows toxicity testing methods of nanomaterials and products, standards and workplace safety and health measures, and various consumer products [28]. The last Working Group 4 works on material specifications. This study group had difficulty in determining the properties of nanomaterials like calcium carbonate ($CaCO_3$) and titanium dioxide (TiO_2) due to the change in the standardization of nanomaterials according to their application areas [27]. The ISO technical committee of nanotechnology has a big role in establishing the foundations of risk management, risk assessment and standardization for global nanotechnologies [26].

Table 5. List of WG3 of ISO/TC 229 nanotechnology standards development [28].

Toxicity: Testing methods
ISO 29701:2010 related to endotoxin test in vitro systems – Test of Limulus amebocyte lysate.
ISO/TS 19337 related to characteristics and measurement methods of nano-objects in vitro toxicity testings.
ISO/TS 19057 related to use and application of nanomaterials cellular in vitro tests and methodologies to assess nanomaterial biodurability.
ISO 10801:2010 related to metal nanoparticles for inhalation toxicity testing.
ISO/TS 19007 related to cell viability of modified MTS assay.
ISO 10808:2010 related to characterization and toxicity testing of nanoparticles in inhalation exposure.
ISO/TS 18827 related to toxicity properties of synthesized zinc oxide nanomaterials by using physicochemical characterization.
ISO/TR 13014:2012 related to guidance on physical and chemical characterization of nanomaterials materials.
ISO/TR 16196 related to dosing methods and sample preparation for manufactured nanomaterials.
ISO/TS 14101:2012 related to surface characterization and toxicity testing of gold nanoparticles by FT- IR method.
ISO/TS 16550:2014 related to investigation of silver nanoparticles.
ISO/TR 16197:2014 related to determination of toxicology test methods for produced nanomaterials.
Workplace safety and health
ISO/TR 12885:2012 related to health and safety applications in nanotechnology related occupational environments.
ISO/TS 18637 related to studies on the development of exposure limits for nanomaterials and their aggregates.
ISO/TR 13121:2013 related to Nanomaterials risk.
ISO/TS 12901-2:2014 related to risk management applied to nanomaterials.
ISO/TR 13329:2012 related to preparations safety data sheet (SDS) for nanomaterials.
ISO/TS 12901-1:2012 related to Guidelines for risk management of engineered nanomaterials.
Consumer products
ISO/TS 13830:2013 related to consultancy on voluntary labeling of consumer nanomaterials.

3.3. The Other Developments

The World Health Organization (WHO) has developed guidelines to determine the risks of nanomaterials ‘To protect employees from the risks of nanomaterials produced’ (NANOH/ WHO). An important member of the ISO / TC229 standards committee, Iran has published national standards to provide safety guidelines. These guidelines help ensure the safety of the environment and the works in which nanotechnology is used. A guideline on new chemical requirements for the notification of Australian industrial nanomaterials, effective since early 2011, has been published. Japan and Korea use a REACH-like approach to proactively assess and manage risks associated with nanomaterials [3].

3.4. Industry Initiatives

While countries are dealing with insufficient and conflicting scientific data to formulate a policy to manage risks related with nanomaterials, industrial organizations and companies follow a proactive approach to managing risks related with uncertainty about this policy.

In 2006, The Royal Community has developed the Responsible Nano code, which sets out seven principles for the governance of nanomaterials. DuPont and the Environmental Defense Fund on the potential risks of nanomaterials and products have developed a Nano risk framework that defines a six-stage process to identify, characterize and communicate information [3]. BASF Dialogue Forum Nano developed recommendations on how to ensure information and transparency throughout the product lifecycle [29].

In a decisive move to self-governance, a global electronic stock market, called INSCX [19], was uttered in early 2011, accredited and approved for nano objects, products and capacities. Assured Nano is a leading safety health and environmental accreditation program for organizations producing nanomaterials, nano-efficient products and nanotechnology users in general [3].

A general way for businesses to handle risks, particularly in the United States, is to use quantitative methods to identify risks related with nanomaterials, using insurance products and insurance companies [3, 30] and consulting companies [3] in infancy. The insurance industry is also exploring potential collaborative opportunities and ways to handle the risks associated with nanomaterials to ensure the efficient and safe use of nanotechnology [31, 32].

For companies producing and using nanomaterials, the Good Nano Guide [3] is a good collaboration platform. It is intended to be an interactive forum that meets the need of new information on the current good business practices to manage nanomaterials in an occupational setting. http://www.nanoceo.net another good site with best practices for adaptation. NanoConsulting (http://www.nanoconsulting.com.sg/whatWeDo/nanosafety.php.), in addition, the weekly news broadcast at nanosafety provides new information on all aspects of nano security.

4. Regulation of Nanomaterials

4.1. The United States of America (USA)

In the USA, by a variety of national organizations have been established nano-regulations and this organizations including the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and Consumer Product Safety Commission (CPSC) [33]. Toxic Substances Control Act (TSCA) and Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) organizations regulations controlled the EPA’s policy for nanomaterials [34]. The regulation of the TSCA requires the collection of information about both new and existing nanomaterials produced. It has announced Significant New Use Rules (SNUR) of pre-manufacture notices (PMNs) for 13 chemicals, including carbon nanotubes and fullerenes regarding EPA’s regulation [21]. In addition, new nanomaterials manufacturers should report all previous and existing production. In the case of the manufacture of nanomaterials, the manufacturers must supply the EPA with all information of the nanomaterials within 90 days.

Additionally, it is shown in Table 6 that FIFRA (6(a) (2) or 3(c) (2) (b)) requires that must be registered for pesticide products that contain nanomaterials [34]. For instance, in May 2015 the EPA has announced that it is a conditional record for the production of pesticide products containing nano silver material (Nanosilva). This registration requirement is based on the EPA's assessment of the effects of silver nanoparticles on environmental safety and human health. Most of these materials are used in antimicrobial products, household items, hospital equipment and sports gear regarding to the registration of nano-silver materials [35].

Table 6. TSCA and FIFRA nanomaterial regulations [34].

Regulation	Description
TSCA 5(a)(2)	This amendment concerns the manufacturing of some new nanomaterials to create a important new use of the objects. Manufacturers must inform EPA at least 90 days before the production of nanomaterials.
FIFRA 6(a)(2) or 3(c)(2)(b)	About the classification of an application for registration of a pesticide product containing nanomaterials as an application for a "new" active or inert component.
TSCA Section 5	The TSCA has taken many actions to control and limit the risk of exposure to chemicals according to the competences in Sections 5 (e) and 5 (a) (2).
TSCA 8(a)	This amendment relates to production volume, exposure and release information, production and processing methods and available health and safety data.

FDA's website disseminated The FDA's regulation of nanotechnology products [21]. The FDA's regulatory approach is described as follows:

(1) Based on a scientific approach, the FDA maintains both regulatory policies and product-focused for nanotechnology products.

(2) FDA respects the diversity of nanotechnology products within legal limits. Human safety affect differently with different nanomaterial product classes.

(3) FDA conducts pre-market examinations of nanotechnology products. Pre-market investigations include various substances related to nanotechnology products such as medicines, food, dietary supplements and cosmetic products. In addition, the FDA will continue to monitor after market. Therefore, the FDA seeks to reduce animal or human health risks caused by nanotechnology products.

(4) The standards applied for industrial safety must meet all legal requirements and the FDA is responsible for ensuring this safety. In addition, the FDA cooperates with domestic and foreign colleagues according to regulatory policy.

(5) The FDA provides technical advice and guidance for the use of nanomaterials for the industry [21].

CPSC cooperates with EPA to identify the safety risks of consumer products for materials such as nanosilver. The CPSC formally joined the National Nanotechnology Initiative (NNI) in 2011 [36]. They work with several organizations to create the following:

(1) Evaluation protocols on the release of nanomaterials products into air from consumer and how people are affected.

(2) Using nanomaterials, produce advanced sports safety equipment

(3) Establish reliable protocols for assessing the risks of exposure of nano-silver materials to young children who extend consumer product testing.

(4) Research on how products containing nanomaterials affect human health.

In June 2009, the US Environmental Protection Agency (EPA) announced important SNUR for 23 different chemicals which is including multi-wall and single-wall carbon nanotubes and different modifications of films containing metal oxide. The EPA recommended that a 90-day respiratory toxicity test be performed at SNUR to ensure their safety. In addition, SNUR asked carbon nanotube manufacturers to wear protective masks and clothing that meet the requirements of the National Institute for Occupational Safety and Health (NIOSH). However, SNUR had to withdraw later due to legal techniques, and the same proposal was published in the Federal Register in May 2011, but it took much longer to provide the route than the original approach. EPA also announced that they have awarded a US $ 5.5M grant to three consortium of researchers from the United States and the UK to investigate the potential leakage of nanomaterials from products that are not used or discarded from products such as plastics, paints and fabrics [3].

In the last session of the congress, where the invoices were entered, such as the Nanotechnology Security Act of 2010 and the Safe Cosmetic Act of 2010, they were never entered. The National Institute for Occupational Safety and Health (NIOSH) [37] is a leading federal institution that conducts research and guidance on safety and health practices in the field of nanotechnology. In 2009, based on the notifications received and updated research, they published a strategic plan to direct research into current nanotechnology issues. The third revision of this plan is still ongoing. NIOSH has developed an updated and improved web resource that includes its recommendations and research results on the human health and safety impacts of nanotechnology. The Federal Drug Agency (FDA) regulates a variety of medicines, cosmetics, food products, medical devices available to the US market, taking into account the claims of the product sponsor [38].

The central coordinator of all federal research funds in the United States is the National Nanotechnology Initiative (NNI). NNI updated the EHS research strategy provides guidance to different federal institutions at the beginning of 2011 for funding research and developing regulations on managing EHS risks related to nanotechnology [3].

ASTM, the world's largest voluntary standards organization, published its standards for non-bonded nanomaterials in work environments in 2010 [39], disclosure of measures to ensure minimal exposure to nanoparticles in 2010 (UNP) research, production, laboratory and other professional environments where UNP is expected to be reasonably available.

4.2. Canada

Canadian legislators proposed to incorporate nanotechnology into the Canadian Environmental Protection Act [40]. According to this bill, risk assessment procedures will be applied before a nanomaterial or nano product is placed on the market, in the environment or in Canadians. A nanotechnology and nanomaterials inventory will also be created in Canada. As of February 2011, it received support from both the government and the public for the regulation of nanotechnology and nanomaterials, but this change was not approved [41].

4.3. European Union (EU)

A definition of the nanomaterials of the EU was defined in 2011 after the Commission's recommendation that the nanomaterials had one or more dimensions between 1 nm and 100 nm. [42]. The EU regulatory committee is the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) used to register substances produced or imported at a rate greater than one tone per year. In addition to nanomaterials, these substances contain carcinogenic, mutagenic and permanent reproduction and bioaccumulative toxic substances. According to CLP, the European Chemical Agency (ECHA) should categorize nanomaterials according to how dangerous they are. In addition, inventory containing nanomaterials should be labeled to inform consumers [43].

ECHA tried to establish a specific framework for the legislation of nanomaterials. Nanomaterials under REACH (RIP-oN) Implementation Project was launched in 2009. They completed the final report in three steps, respectively: identification of substances in nanomaterials (RIP-oN 1) [44], information requirements (RIP-oN 2) [45] and safety assessment of chemical materials (RIP-oN 3). Apart from this, Already Registered Nanomaterials Assessment Group held a meeting in 2013. GAA RN focused on human exposure of nanomaterials and assessed the risks to which nanomaterials were exposed to the environment and human health. At the GAARN meetings, the IUCLID guidelines for REACH registration provided best practices to assess the safety of version 5 of IUCLID, including nanomaterials of the Competent Authorities for REACH and CLP (CASG Nano) [46].

Alternatively, the EU legislation on electrical and electronic equipment is covered by the Regulation on the Restriction of Hazardous Substances (RoHS). RoHS limited the use of hazardous materials such as heavy metals like mercury, hexavalent chromium and cadmium and flame retardants materials like polybrominated biphenyls, polybrominated diphenyl ethers or PBBs; PBDEs [47]. Carbon nanotubes and nano-silver used in electronic equipment are proposed to be regulated by RoHS, but the proposal is excluded from the nanomaterial laws [48].

Cosmetic products in the European Union were evaluated by the Scientific Committee for Consumer Products (SCCP). SCCP applied animal tests to examine the safety of cosmetic products containing nanomaterials [49]. The European Commission has proposed that the nanomaterials contained in cosmetic products should be regulated and before six months a manufactured product should be notified to the commission before distribution [50]. Since 2013, the cosmetic regulation has tightened the control of nanomaterials produced in the European Union market [51].

In November 2009, the Council of the European Union approved a regulation on cosmetics, which stated that the contents of all cosmetic products containing nanomaterials should be specified in these nanomaterials [3]. In addition, without knowing the effects of these nanomaterials, labeling them as potentially dangerous leads to potentially unnecessary and new fears among consumers.

In 2009, members of the EU parliament [3] approved that foods containing nanomaterials should be included with the labeling, definition and specific risk assessments of these foods under the new food regulation. In 2010, the environmental committee of the EU parliament voted to remove foods that contain nanomaterials from the EU authorized list until an accurate risk assessment was made on their potential health impacts [52]. The European Risk Safety Authority (EFSA) has prepared a guidance document for engineering nanomaterials for food and feed in order to define how this safety assessment can be made and opened it to public consultation [53].

However, this arrangement did not ultimately fail in March 2011 due to a lack of consensus on cloned food as part of the regulation. Accordingly, the United Kingdom Food Standards Agency (FSA) to investigate a secret nanotechnology-related food industry in 2010 approved the creation of the database [3]. The French Food Safety Agency (AFSSA) [3] establish a working group to assess the risks of food products and monitor developments containing nanomaterials and emphasized the principles for the use of nanomaterials in the food industry.

In June 2009, the The European Parliament approved the inclusion of nanomaterials in the REACH 'no data, no market' principle. The Innovation Community has proposed a Nano Information Pyramid to facilitate the transport information and data across the value chain to meet consumer needs. The ENRHES FP7 project conducted a critical and comprehensive scientific review of the environmental and health safety of carbon nanotubes, fullerenes and metals and metal oxide nanomaterials for the fulfillment of REACH directives by industry and regulatory agencies This project ended in 2010 [3].

In addition, at the end of 2009 and in December 2010, the European Commission initiated public and scientific consultations to define the nanomaterials. The Scientific Committee for Emerging and Newly Defined Health Risks (SCENIHR) claimed that the nanomaterials define is based on its dimensions, but an upper limit is not sufficient for it. Before 2011, the Commission sought to define the definition of nano before, but there was strong disagreement and debate among those who made different definitions [3].

4.4. Japan

Every five years, the CSTI (Council for Science, Technology and Innovation) which is a pioneering council for the development of basic technology and science have made plans in Japan. Recently, the 4th basic plan has been established; It consists of four main plans: 1. Realizing sustainable growth and social development, 2. Taking measures against the key problems faced by Japan, 3. Developing basic research and human resources, 4. Establishing policies with society [3,54].

The development of nanotechnology materials has been one of the four main plans found in basic plans 2 and 3. These plans recommend three promotional strategies: 1.Developing scientific technologies to solve social problems with innovative materials with 'True Nano', 2.Developing scientific technologies to produce innovations with 'True Nano', 3.Developing technological structures to accelerate innovation.

The fourth plan had not include a major plan, whereas the co-operation task group for nano technological materials proceeds with the cross-work of nanotechnologies currently underway at CSTI (Table 7). [3].

Table 7. Some important properties of nanotech-materials [3].

Description of nanotech-materials	
Performance	Future steps
Progress in the X-ray free electron laser. New findings of superconducting materials containing ions. Development of different materials used for practical uses. İmprovement on molecular imaging.	Development of nanotechnology materials related to energy applications, environmental. Cluster validation to form the basis of nano electronic research and to promote convergence with other areas.

However, there is no legal check for the implementation of certain nanomaterials safety regulations in the present system. In order to improve nano-safety, the Japanese government used the Ministry of Economy, Trade and Industry (METI) to gather information about the nano industry and assessed the negative effects of nanomaterials by the environment ministry (ME). In terms of security measures, they are currently studying a new system for dealing with nanomaterials. Table 8 shows some research projects that analyze the hazards of nanomaterials by the Japanese government [21].

Table 8. The research projects about the negative risks of nanomaterials (2009-2014) [20].

Research projects
Improvement of performance testing and test equipment for risk experiments related to inhalation of nanomaterials. Genotoxicity tests of nanomaterials. Participation in the negative risks of the group of nanomaterials OECD (eg, fullerene (C60), SWCNTs and MWCNTs). Measurement and evaluation of nanomaterials in application environment areas and gathering information to prevent exposure of nanomaterials.

4.4. Japan

Safety practices for dealing with nanomaterials is the new trend in the world and the world currently focused on in terms of their effect on the environment and human health. The existing and newly produced chemicals trade on the market for the promotion of international trade has been redeveloped due to the safety risks of these materials. Therefore, in 2015, the Korean government proposed the Law on the Registration and Evaluation of Chemicals in the Republic of Korea (Korea REACH) to promote the European Union's REACH program [55]. In particular, the Republic of Korea is a competitive country in the field of nanotechnology and has patents and SCI documents related to nanotechnology. In addition, the Republic of Korea is the only Asian country capable of dealing with the Nanotechnology Development Incentive Act in order to develop nanotechnology and industrial applications of nanotechnology [56, 57-21].

On the other hand, although not properly regulated in the past, some parts of the Republic of Korea have been able to regulate and manage nanomaterials. These chapters include: 1) Ministry of Environment, waste control law and chemicals toxicity control law; 2) Labor and labor law, occupational health and safety law; and 3) the ministry of drug and food safety, the cosmetic law and the food sanitation law [21]. Although only nano-security laws have not yet been agreed, several government-wide efforts are currently being undertaken to implement nano-security management plans.

Currently being developed in the 1st nano-safety management plan is the domestic policies of nanomaterials in the Republic of Korea. This plan was implemented under the control of the government with the cooperation of ministries of five different departments. The Korean government intensified on four areas: (1) the establishment of nano-safety assessment techniques; (2) the construction of nano-measurements, analysis techniques and databases, (3) institutionalization and introduction of safety management, and (4) professional workforce training and construction partnerships [21, 58].

The Korean government plans to continue its 2nd nano security management plan. This second plan will be implemented by at least eight chapters. According to the results of Plan 1 and Plan 2, results will be obtained about the aim, vision and the strategy promoted. The first plan is limited to examining the institutionalization method of safety and ethics management guidelines, and the second plan aims to prepare the implementation methods for safety management as well as to promote the legal institutionalization of life cycle assessments of nanomaterials [58]. In addition, the Republic of Korea government made a gradual progress in professional labor training. Plan 2 provided personalized professional manpower training to consumers.

The Korean government has worked to establish a domestic policy for the nano-security management plan and has also endeavored to join other international organizations. The Korean government joined OECD's Working Group on Produced Nanomaterials (WPMN) as an OECD member. As shown in Table 1, it has an important role on safety tests. They are also participating in OECD WPMN SG 7's joint research with the Korean Standards and Science Research Institute (KRISS) and the EU Joint Research Center (JRC), and OECD WPMN SG 8's joint research with KRISS and National Metrology. South African Institute (NMISA) (KRISS) [3].

In addition to international activities, they are involved in ISO / TC 229 for the standardization of nanoTable's ISO / TC 229, in joint research projects with the KRISS and Swiss Federal Nano-toxicology Materials Testing and Research Laboratory (Swiss EMPA) [3]. With these methods, the Korean government has built a strategic way to create a nano-safety plan.

However, the Republic of Korea should use legal force to regulate consumers' nanomaterial products, and for this, domestic policies have developed more rapidly. According to the consumer awareness survey, in Korea most consumers do not understand clearly because they do not have information about nanomaterials or nanotechnology. However, many consumers have positive responses and uncertain expectations about nanomaterials and nanotechnology products [59]. That's why, Republic of Korea have continued to production of nanomaterials with many companies and have sold a variety of nanomaterials even though there is no policy for nanomaterials in the market.

5. Conclusions

The use of nanomaterials constantly increases consumer products in worldwide sales. Producers in countries all over the world should pay attention to the quantities and uses of nanomaterials due to their toxic properties. Policies published by organizations such as The World Health Organization (WHO), International Organization for Standardization (ISO), and Organization for Economic Cooperation and Development (OECD) indicate the uses and areas of use for nanomaterials. These regulatory policies provide the benefit of the safer use of nanomaterials.

Compared to this increase, most of the global market for example Republic of Korea, have not different regulations regarding nanomaterial consumer products. Each country must establish policies for the use of nanomaterials and impose sanctions on the implementation of these regulations. These policies will protect the health of society and the environment and will make a major contribution to the economy.

As a result, new regulatory policies should be developed by conducting further tests and researches for nano materials. Because the usage of nanomaterials is increasing day by day and new properties of them have been discovered.

References

[1] Vishwakarma V., Samal S.S., Manoharan N., (2010), Safety and Risk Associated with Nanoparticles - A Review. J. Minerals & Materials Characterization & Engineering. 9: 455-459.

[2] European Commission, (2011), REACH implementation Project substance identification of nanomaterials (RIP-oN 1). Advisory Report.

[3] Vedam H., (2011), NanoSafety Policy Overview.

[4] Lux Research, (2004), The Nanotech Report 2004. New York: Lux Research

[5] Chattopadhyay GP., (2018), Technologies in the era of singularity. Notion Press, Chennai, India,.206.

[6] Colvin VL, (2003), The potential environmental impact of engineered nanomaterials. Nat. Biotechnol. 21:1166–1170.

[7] Skjolding L.M., Sørensen S.N., Hartmann N.B., Hjorth R., Hansen S.F., Baun A., (2016), Aquatic ecotoxicity testing of nanoparticles—The quest to disclose nanoparticle effects. Angew. Chem. Int. Ed. 55:15224–15239.

[8] Boyes W.K., Thornton B.L.M., Al-Abed S.R., Andersen C.P., Bouchard D.C., Burgess R.M., Hubal E.A.C., Ho K.T., Hughes M.F., Kitchin K., Reichman J.R., Rogers K.R., Ross J.A., Rygiewicz P.T., Scheckel K.G., Thai S.F., Zepp R.G., Zucker R.M., (2017), A comprehensive framework for evaluating the environmental health and safety implications of engineered nanomaterials. Crit. Rev. Toxicol. 47:767–810.

[9] Rai M., Biswas J.K., (2018), Nanomaterials: Ecotoxicity, Safety, and Public Perception, chapter1, p3, Springer, https://doi.org/10.1007/978-3-030-05144-0.

[10] Oberdörster G., Sharp Z., Atudorei V., Elder A., Gelein R., Kreyling W,. Cox C., (2004), Translocation of inhaled ultrafine particles to the brain. Inhal. Toxicol. 16:437–445.

[11] Sarin H., Kanevsky A.S.,Wu H., Brimacombe K.R., Fung S.H., Sousa A.A., Auh S., Wilson C.M., Sharma K., Aronova M.A., Leapman R.D., Griffiths G.L., Hall M.D., (2008), Effective transvascular delivery of nanoparticles across the blood-brain tumor barrier into malignant glioma cells. J. Transl. Med. 6:80. https://doi.org/10.1186/1479-5876-6-80.

[12] Sonavane G., Tomoda K., Makino K., (2008), Biodistribution of colloidal gold nanoparticles after intravenous administration: effect of particle size. Colloids. Surf. B. 66:274–280.

[13] Conner S.D., Schmid S.L., (2003), Regulated portals of entry into the cell. Nature. 422:37–44.

[14] Donaldson K., Stone V., (2003), Current hypotheses on the mechanism of toxicity of ultrafine particles. Ann Ist Super Sanità. 39:405–410.

[15] Rana S., Kalaichelvan P.T., (2013), Ecotoxicity of nanoparticles. ISRN Toxicol. Article ID 574648, 2013:11. http://dx.doi.org/10.1155/2013/574648.

[16] Kim S., Choi J.E., Choi J., Chung K.H., Park K., Yi J., Ryu D.Y., (2009), Oxidative stress-dependent toxicity of silver nanoparticles in human hepatoma cells. Toxicol. In Vitro. 23:1076–1084.

[17] Li M., Zhu L., Lin D., (2011), Toxicity of ZnO nanoparticles to Escherichia coli: mechanism and the influence of medium components. Environ. Sci. Technol. 45(5):1977–1983.

[18] Kittler S., Greulich C., Diendorf J., Köller M., Epple M., (2010), Toxicity of silver nanoparticles increases during storage because of slow dissolution under release of silver ions. Chem. Mater. 22:4548–4554.

[19] Yuan J.S., Galbraith D.W., Dai S.Y., Griffin P., Stewart C.N. Jr., (2008), Plant systems biology comes of age. Trends. Plant. Sci. 13:165–171.

[20] OECD, (2012). Six years of OECD work on the safety of manufactured nanomaterials: Achievements and future opportunities.

[21] Park H.G., Yeo M.K., (2016), Nanomaterial regulatory policy for human health and environment. Mol. Cell Toxicol. 12:223-236.

[22] OECD, (2010), List of manufactured nanomaterials and list of endpoints for phase one of the sponsorship programme for the testing of manufactured nanomaterials: Revision, ENV/JM/MONO, 46.

[23] Fadeel B., Pietroiusti A., Shvedova A.A., (2012), Adverse Effects of Engineered Nanomaterials: Exposure, Toxicology, and Impact on Human Health. West Virginia, USA, 98.

[24] ISO/TC 229 Nanotechnologies, Available online at http://www.iso.org/iso/iso_technical_committee?commid=381983.

[25] Murashov V., Howard J., (2011), Nanotechnology standards. New York: Nanostructure Science and Technology.

[26] Murashov V., Howard J., (2009), International standards for risk management in nanotechnology. Nat. Nanotechnol. 4:205-206.

[27] Oh K.H., Lee H.S., (2009), Standardization trends and Technologies for carbon nanotubes. Korean Ind. Chem. News 12:20-25.

[28] Nano ontarioi, (2015), Nanotechnologies Standards Development List.

[29] Nanowerk, (2011), BASF Dialogueforum Nano - Information and transparency along the product life cycle of nanomaterials final report. Avaiable at http://www.nanowerk.com/news/newsid=21028.php

[30] TinyTechIP, (2011), US Patent 7890357 - Determining nanomaterial related risk. Avaiable at http://tinytechip.blogspot.com/search/label/Hartford%20Fire%20Insurance%20Company

[31] Nanowerk, (2010), Nanotechnology safety remains a concern says Llody's. Avaiable at http://www.nanowerk.com/news/newsid=18385.php

[32] Nanowerk, (2011), Insurance and risk management industry briefing on nanotechnology. Avaiable at http://www.nanowerk.com/news/newsid=19789.php

[33] Suh J.D., (2014), Study of the Introduction of a nanomaterials regulatory policy for product safety. J. Korea Acad. IndustrCoop. Soc. 15:4987-4998.

[34] US EPA, (2011), EPA needs to manage nanomaterial risks more effectively. U.S. Environmental Protection Agency, EPA report 12-P-0162, 1-23

[35] Nanotech. Available online at http://nanotech.lawbc.com/2015/05/epa-conditionally-registers-nanosilverpesticide-product/

[36] NNI CPSC. Available online at http://www.nano.gov/node/139

[37] The National Institute for Occupational Safety and Health (NIOSH), (2019), Nanotechnology. Available at https://www.cdc.gov/niosh/topics/nanotech/

[38] Aza Nano, (2010), NIH Awards $9.4 Million to Support Research Projects in Regulatory Science. Available at https://www.azonano.com/news.aspx?newsID=19721

[39] ASTM E2535, (2018), Standard Guide for Handling Unbound Engineered Nanoscale Particles in Occupational Settings.

[40] Nanowerk, (2010), Canadian legislator proposes to include nanotechnology in the Canadian Environmental Protection Act. Available at http://www.nanowerk.com/news/newsid=15358.php

[41] Frogheart, (2010), Canada's Bill C-494, Nanotechnology Safety in Canada: an update. Avaiable at https://www.frogheart.ca/?p=2841

[42] European Commission. (2012). Communication from the commission to the European parliament, the council and the European economic and social committee, second regulatory review on nanomaterials. COMM 572.

[43] European Commission (Nanomaterials). Available at https://ec.europa.eu/environment/chemicals/nanotech/index_en.htm

[44] European Commission (REACH). Available online at http://ec.europa.eu/growth/sectors/chemicals/reach/index_en.htm.

[45] Hankin, S. M. et al., (2011), Specific advice on fulfilling information requirements for nanomaterials under REACH (RIP-oN 2) - Final Project Report.

[46] Aitken, R.A. et al., (2011), Specific advice on exposure assessment and hazard/risk characterisation for nanomaterials under REACH (RIP-oN 3) - Final Project Report.

[47] European Commission (RoHS Directive). Available online at http://ec.europa.eu/environment/waste/rohs_eee/index_en.htm.

[48] Kim S.A., Kim H.J., Hong, Y.S., (2013), Safety management system on nanomaterials with regulatory scheme. J. Environ. Pol. Plan. 12:49-71.

[49] Raj S., Jose S., Sumod U. S., Sabitha M., Nanotechnology in cosmetics: Opportunities and challenges. J. Pharm. Bioallied Sci. 4:186-193.

[50] Henkler F. et al., (2012), Risk assessment of nanomaterials in cosmetics: A European Union perspective. Arch. Toxicol. 86:1641-1646.

[51] Regulation (EC) No 1223/2009 of the European parliament and of the council. Available online at https://ec.europa.eu/health/sites/health/files/endocrine_disruptors/docs/cosmetic_1223_2009_regulation_en.pdf

[52] Nanowerk, (2010), European Parliament votes to regulate food nanotechnology. Avaiable at http://www.nanowerk.com/news/newsid=16196.php

[53] Nanowerk, (2011), European Food Safety Authority launches public consultation on risk assessment of nanomaterials in food and feed. Avaiable at http://www.nanowerk.com/news/newsid=19710.php

[54] MEXT, (2011), The 4th Science and Technology Basic Plan (FY2011-FY2015), Ministry of Education, Culture, Sports, Science and Technology of Japan, 1-3.

[55] CIRS, KOREA REACH. Available online at http://www.cirs-reach.com/KoreaTCCA/Korea_REACH_The_Act_on_the_Registration_and_Evaluation_of_Chemicals.html.

[56] Karim M.D., Munir A.B., (2014), Nanotechnology in Asia: A preliminary assessment of the existing legal framework. KLRI Journal of Law and Legislation. 4:75-131.

[57] Milanović V., Bučalina A., (2013), Position of the countries in nanotechnology and global competitiveness. JSTP. 68:69-79.

[58] Ministry of Environment, (2015), A comprehensive plan study of nano-safety management by the 2nd governmental departments ('17-'21). Ministry of Environment of Republic of Korea, Chemical Safety Division, ME report, 1-10.

[59] Kim, S.A., Kim, H.J., Hong, Y.S., (2013), Safety management system on nanomaterials with regulatory scheme.J. Environ. Pol. Plan 12:49-71.

2–Amino–5–Bromobenzoic Acid: A Dft Study for Structural and Molecular Orbital Analysis of Tautomeric Forms

[1]Ahmet Kunduracıoğlu

[1] Bursa Uludağ University, Mustafakemalpaşa Vocational School, Organic Agriculture Program, 16500, M. Kemalpaşa, Bursa, Turkey.
Corresponding author, e-mail: akunduracioglu@uludag.edu.tr, ahmet_kunduracioglu@yahoo.com.

Submission Date: 17.10.2020 Acceptation Date: 05.01.2021

Abstract - 2–Amino–5–bromobenzoic acid (ABBA) and its tautomeric forms have been investigated for structural properties and molecular orbitals. HOMO–LUMO surfaces and FT–IR, FT–RAMAN analysis were carried out in an integrated approach. The molecule was handled as a sum of three tautomeric forms one of which has four isomers. The molecule was examined as a whole and partially according to tautomeric forms and geometrical isomers. For quantum chemical calculations, DFT was used in the B3LYP level and 6.31G* basis set. Computations were carried out via SPARTAN 14 software.

Keywords: benzoic acid derivatives, DFT, Spectral analysis, HOMO LUMO, tautomery

2–Amino–5–Brom Benzoik Asidin Tautomerik Formlari:Yapisal Ve Moleküler Orbital Analizi İçin Bir Dft Çalişmasi

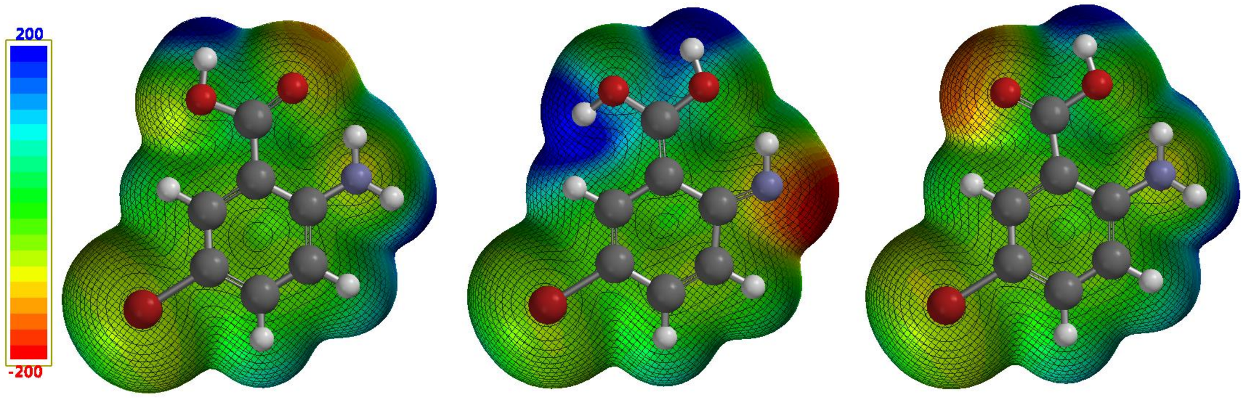
[1]Ahmet Kunduracıoğlu

Bursa Uludağ Üniversitesi, Mustafakemalpaşa Meslek Yüksekokulu, Organik Tarım Programı, 16500, M. Kemalpaşa, Bursa

Öz - 2–Amino–5–brom–benzoik asit (ABBA) ve tautomerik formlarını yapısal özellikleri, molekül orbitalleri bakımından incelenmiştir. HOMO–LUMO yüzeyleri ve FT–IR, FT–RAMAN analizleri tümleşik bir yaklaşımla gerçekleştirilmiştir. Molekül, içlerinden biri dört geometrik izomere sahip olan üç tautomerik formun bir toplamı olarak ele alınmıştır. Molekül bir bütün olarak ve kısmen de geometrik izomerlere göre araştırılmıştır. Kuantum kimyasal hesaplamalarda B3LYP düzeyinde ve 6.31G* temel setinden yararlanarak DFT (YFK) kullanılmıştır. Tüm hesaplama işlemleri SPARTAN 14 yazılımıyla gerçekleştirilmiştir.

Anahtar kelimeler: Benzoik asit türevleri, DFT, Spektroskopik analiz, HOMO LUMO, Tautomerlik

GRAPHICAL ABSTRACT: Tautomeric Forms of 2–Amino–5–Bromobenzoic Acid: A DFT Study for Structural and Molecular Orbital Analysis



1. Introduction

Benzoic acid (BA) is an organic compound that is widely found in animal and plant tissues and is used in a wide area of applications. Benzoic acid and derivatives are mostly used for their miticidal activities and pharmacological activities. Also, they are used as co–anesthetics [1].

BA is particularly found in plants, free and in the form of compounds. Gum benzoin from where BA was obtained for the first time contains 20% benzoic acid. BA is found in most of the fruits (approximately 0.05%) in the urine of the herbivorous mammals as the form of benzoyl glycine (hippuric acid) derivative. BA is easily soluble in hot water, alcohol and ether. BA is slightly soluble in cold water as well. Its solubility in water increases in the presence of alkali substances such as borax and trisodium phosphate. It also dissolves in substances such as chloroform, acetone, carbon tetrachloride, benzene, carbon sulfide, turpentine, essential oils [2–4]. The aqueous solution is acidic and slightly stronger than acetic acid. It has irritant effects on the skin, eyes and mucous membranes, causes coughs when breathed. It is commercially manufactured by the chemical reaction of toluene with oxygen at temperatures around 200°C using cobalt and manganese salts as catalysts. Pure benzoic acid melts at 122°C. BA derivatives and BA esters are used for the protection of foods, oils, juices, alkaloid solutions, etc., producing benzoates, benzoyl compounds and colorants, as mordants in fabric printing, tobacco processing. Also, it is used as a standard in volumetric and calorimetric analyzes in analytical chemistry. Some prominent derivatives of benzoic acid are sodium benzoate, used as a food preservative, benzyl benzoate, used as a miticide, and benzoyl peroxide, used in initiating chemical reactions for producing plastics materials and in bleaching flour [5, 6].

Due to the prevalence and widespread use of benzoic acid, many studies have been conducted both structural and to find new uses by researchers from every corner of the world. Experimental and theoretical chemists carried out a large number of studies on BA and its substituted derivatives. A computational and experimental study on 2–amino–5–halogeno–Benzoic acid (X= F, Cl and Br) was carried on by Xavier and Joe, they also investigated biological activities of the AXBA[7]. The crystal structure of m–bromobenzoic acid [8], 3,5–dibromo–4–aminobenzoic acid [9] and 4–amino–3–bromobenzoic acid were published by Tanaka et al., Pant and Arshad et al respectively [10]. Ferguson and Sim analyzed the molecular structure of 2–bromobenzoic acid in detail [11]. Swaminathan et al. carried out a spectroscopic and theoretical study on the vibrational spectra of 2–bromobenzoic acid

[12]. Sundaraganesan et al. [13–15] have experimentally studied the FT–IR and FT–Raman spectra of 5–amino–2–chlorobenzoic acid, methyl benzoate and 2–amino–4,5–difluorobenzoic acid. The antibacterial activity and effect on bacterial DNA synthesis of 4–aminobenzoic acid were examined by Richards and Xing [16]. 4–aminobenzoic acid and 2–aminobenzoic acid were investigated for their toxicity on cell suspension cultures of Solanum mammosum by Syahrani et al. [17].

Swislocka et al recorded the vibrational and NMR spectra of 4–aminobenzoic acid and its alkali metal salts [18]. 2,3,4–chlorobenzoic acids' IR and Raman spectra were investigated for the effect of the position of chloride in the aromatic ring [19]. Both spectroscopic properties and biological activities of the compounds similar to 2–amino–5–bromobenzoic acid (ABBA) were investigated by Xavier and Joe with F, Cl and Br [8]. The vibrational behaviors of ABBA were examined by Sundaraganesan et al. [20].

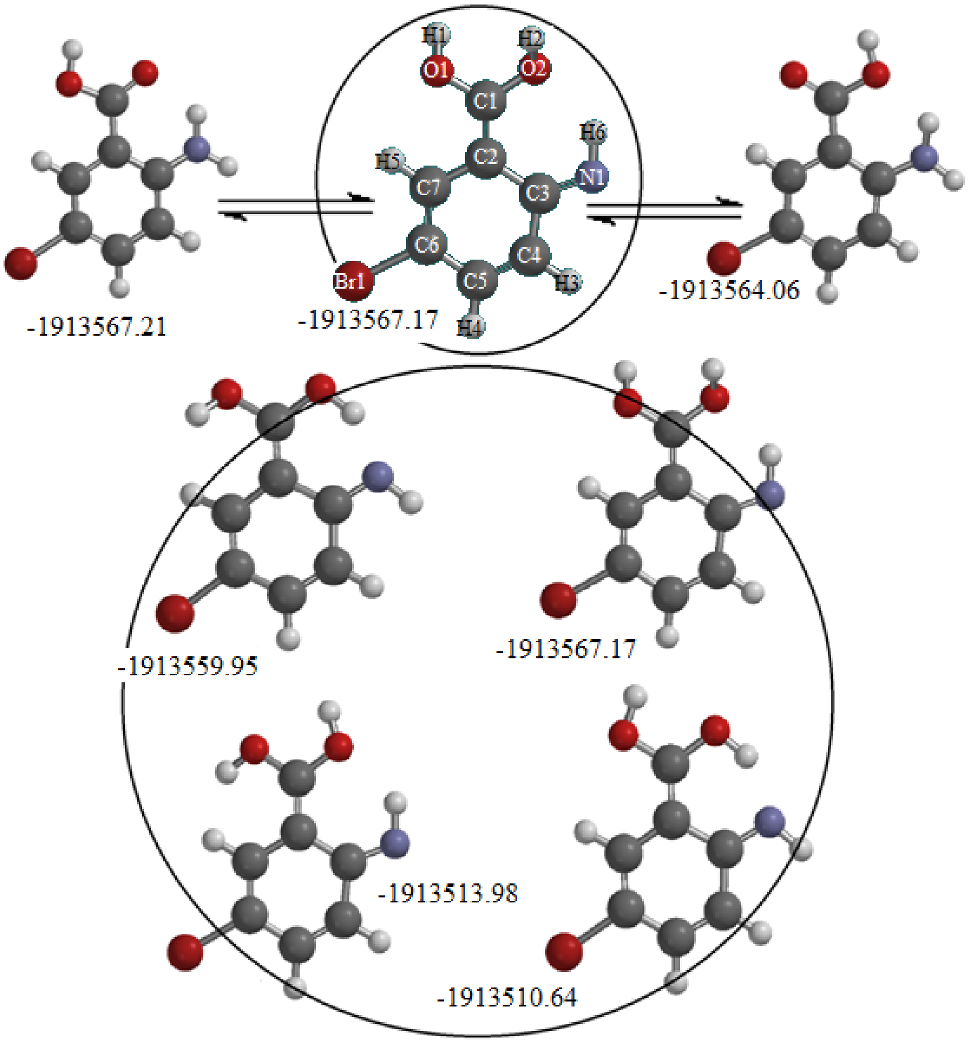


Figure 1. Tautomeric forms of compound ABBA and isomers of the hypotethical tautomer 2 (energies in kcalmol^{-1})

2. Experimental Part

2.1. Computational details

For computational analysis of the compound ABBA, the SPARTAN–14 quantum chemistry suite was used [21,22]. For the theoretical calculations, 6–31G* basis set was used in the B3LYP level of DFT method [23–25]. There are two reasons for choosing the method and basis set; first, the former studies handled the same molecule so that an opportunity for comparison was obtained. Later, this system is widely used for reducing the time needed [26]. ABBA has three tautomeric forms one of which has four conformations; Cis–Cis, Cis–Trans, Trans–Cis and Trans–Trans (Figure.1). For this reason, all calculations for the second tautomer has been repeated for each of these conformations separately. Although it is claimed in the literature that this tautomeric form does not exist, this fact does not prevent us from examining this isomer, at least hypothetically. The obtained results have been tabulated under corresponding divisions. MO surfaces and spectral graphics are depicted in corresponding figures in the following parts of this manuscript. The results which software produced were used as they were obtained without any scaling factors or any further refined corrections. To keep the study simple and to focus on some certain details some detailed studies were left out for further studies such as more complicated computational studies or medical applications etc.

There is a huge archive of spectral data for the compound ABBA which had been studied by several researchers so far. For this reason, in this study, the existing experimental spectroscopic data have been used.

2.2. Structure of the compound

As mentioned before the title compound has three tautomeric forms (T1, T2 and T3) and one of these tautomeric forms has four geometrical isomers which will be called CC, CT, TC and TT (C for Cis– and T for Trans–) respectively in the following lines (Figure 1). As can be seen from Figure 1, the least energetic tautomer of the compound was found to be the first form which has a carboxylic and a primary amine moieties together. In this study, the molecular structure of the title compound and spectral data is going to be examined according to this fact [28]. Although the second tautomer is only a hypothetical form it is worth to be examined for understanding the reason for its absence in real conditions.

Molecular Structure: Like any other compound, the molecular structure of ABBA is determined by bond lengths, bond angles and dihedral (torsion) angles. In corresponding tables and figures, these properties have been depicted comparatively.

There is no experimental data for the molecular structure of the compound as of today. But in literature, some very similar molecules were elucidated in terms of molecular structures. From literature, the compound 4–amino–5–bromo benzoic acid was chosen due to its similarities in structure [9, 10] and after some adaptations, these values were used.

Calculated and experimental bond lengths are tabulated in Table 1 comparatively. As seen in Table 1, among the calculated values, T1 is the closest to the experimental results comparing with the others. It is an expected reflection of the fact that T2 is an intermediate step with different conformers. In table 1 some relatively abnormal values that are made evident by being underlined and italicized reflect migrations of H atoms between tautomeric forms. Another notable point in Table 1 is that the T1 and T2/TC values are comparatively close to each other among the other ones.

Table 1. Calculated and experimental bond lengths(Ǻ) for the compound ABBA.

BOND	T1	T2					T3	Exp*
		CC	CT	TC	TT	Total		
O1,C1	1.356	1.358	1.352	1.357	1.360	1.352	1.215	1.234
O2,C1	1.227	1.218	1.340	1.227	1.358	1.340	1.371	1.312
C1,C2	1.470	1.487	1.373	1.469	1.364	1.373	1.479	1.462
C2,C7	1.409	1.408	1.452	1.409	1.455	1.452	1.409	1.376
C7,C6	1.381	1.384	1.353	1.381	1.350	1.353	1.380	1.382
C6,Br1	1.920	1.917	1.919	1.921	1.920	1.920	1.920	1.888
C6,C5	1.402	1.400	1.443	1.402	1.446	1.443	1.401	1.407
C5,C4	1.383	1.384	1.352	1.382	1.351	1.352	1.383	1.377
C4,C3	1.415	1.415	1.467	1.416	1.467	1.467	1.415	1.365
C3,N1	1.363	1.365	1.294	1.358	1.293	1.294	1.372	1.376
C3,C2	1.426	1.427	1.495	1.427	1.499	1.495	1.424	1.402
H1,O1	*2.240*	0.970	0.971	0.975	0.974	0.971	0.975	0.820
H2,O2	*5.230*	0.986	0.974	*1.928*	0.974	0.974	*5.246*	**
H6,N1	1.013	1.009	1.020	1.007	1.021	1.020	1.009	0.920
H5,C7	1.082	1.086	1.087	1.083	1.083	1.087	1.083	0.930
H4,C5	1.085	1.085	1.085	1.085	1.085	1.085	1.085	0.930
H3,C4	1.087	1.087	1.085	1.087	1.085	1.085	1.087	0.930

*= borrowed from ref (5 and 10)   **= not exist for this conformer/isomer

Computationally found and experimentally measured bond angles of the compound ABBA have been tabulated comparatively in Table 2. In this table again some comparatively abnormal values that are underlined and italicized, reflect migrations of H atoms between tautomeric forms. These values are not stable between conformers. Except for these unstable values which reflect the immigrant H's the general results are in a close agreement with experimental ones. However, the most plausible results were seen surprisingly at T3 excluding H1O1C1 and H2O2C1 angles.

As a presupposition, any small compound with a benzene ring can be expected to be perfectly planar. But the compound ABBA has slightly deviated from this rule. When Table 3 was revised in a sketchy way, the first point to be noticed is; T2/TC column is filled with 180 and 0.00 degrees which shows the molecule is perfectly planar. But in other columns, there are different degrees even less or more. The experimental values are very near to 180° (and/or 0.00°) with about 7.1 (172.9)° as the biggest torsion degree.

HOMO–LUMO analysis and Electronic Transitions: As the T1 Tautomeric form has the minimum energy according to calculations, it has been accepted as the reference point and other values have been compared according to this value. In Table 5 calculated energies and energy differences have been presented comparatively. In the table, the data are presented in two parts. In the first part, the energy values and the differences in the T1 form are shown. In the second part, the values of the T2/TT isomeric form are presented. The energy differences can be calculated using Eq.1.

$\Delta E = E(C0) - E(T1)$ or

$\Delta E = E(C0) - E(TC)$ Eq. 1

Table 2. Calculated and experimental bond angles (°) for the compound ABBA

BOND ANGLE	T1	T2					T3	Exp*
		CC	CT	TC	TT	Total		
H1,O1,C1	110.14	108.61	110.12	102.63	109.12	110.14	*6.49*	109.5
H2,O2,C1	108.28	107.33	108.27	106.40	109.01	108.28	*56.57*	109.5(!)
O1,C1,O2	110.68	114.01	110.68	114.35	114.72	110.68	120.38	121.8
O2,C1,C2	123.15	123.09	123.16	124.15	123.30	123.15	125.80	123.4
O1,C1,C2	126.17	122.90	126.15	121.50	121.97	126.17	113.81	114.7
C2,C7,C6	120.96	121.90	120.96	121.71	120.44	120.96	120.61	120.2
C7,C6,Br1	120.26	121.68	120.28	121.79	120.25	120.26	120.00	119.5
Br1,C6,C5	118.17	117.46	118.16	117.53	117.70	118.17	119.66	119.0
C7,C6,C5	121.56	120.86	121.55	120.68	122.04	121.56	120.35	121.5
C6,C5,C4	119.62	122.47	119.63	122.59	119.74	119.62	119.79	117.1
C5,C4,C3	123.74	120.70	123.73	120.62	123.38	123.74	121.64	121.8
C3,C2,C7	119.09	117.55	119.10	118.21	119.23	119.09	119.81	118.5
H6,N1,C3	111.60	110.78	111.58	110.40	111.09	111.60	117.67	116.0
N1,C3,C2	128.93	122.27	128.92	122.04	128.49	128.93	122.22	121.6
N1,C3,C4	116.32	121.31	116.34	121.77	116.48	116.32	119.96	121.3
C3,C2,C1	122.57	118.85	122.57	119.24	119.23	122.57	120.22	120.7
C1,C2,C7	118.30	123.59	118.29	122.54	117.56	118.30	119.96	120.7
H3,C4,C5	121.35	121.16	121.35	121.20	121.52	121.35	119.61	119.1
H4,C5,C6	119.18	118.17	119.17	118.02	119.10	119.18	120.25	119.6
H5,C7,C2	120.18	118.76	120.18	117.62	118.32	120.18	118.82	119.9
*= borrowed from ref (5 and 10)								

TORSION ANGLE	T1	T2					T3	Exp*
		CC	CT	TC	TT	Total		
H1,O1,C1,O2	–169.90	–167.70	164.20	0.00	42.72	164.20	–152.79	x
H2,O2,C1,O1	0.00	164.11	–9.14	0.00	36.38	–9.04	–0.10	x
H1,O1,C1,C2	9.78	12.40	–16.15	180.00	–138.00	–16.15	26.68	x
H2,O2,C1,C2	–179.64	–16.00	171.19	180.00	–142.89	171.31	–179.63	x
O2,C1,C2,C3	–0.92	17.08	–8.55	0.00	8.58	–8.55	–2.21	–5.3
O2,C1,C2,C7	178.08	–161.01	173.77	180.00	–173.43	173.77	177.22	178.0
O1,C1,C2,C7	–1.58	18.89	–5.84	0.00	7.36	–5.84	–2.28	–3.7
O1,C1,C2,C3	179.41	–163.02	171.83	180.00	–170.64	171.85	178.29	172.9
C1,C2,C3,N1	–3.21	1.68	7.58	0.00	–6.26	7.56	–3.61	175.6
C1,C2,C7,C6	–178.63	–179.92	173.16	180.00	–175.32	173.12	–178.95	176.3
C2,C7,C6,Br1	–179.94	179.97	179.31	180.00	179.75	179.13	179.77	179.5
C2,C7,C6,C5	0.18	–0.23	0.26	0.00	–0.02	0.27	0.01	–0.9
C2,C3,C4,C5	0.58	1.53	–4.16	0.00	3.25	–4.13	0.43	–3.2
H4,C5,C4,H3	0.33	–0.19	–0.37	0.00	0.35	–0.38	0.53	x
H6,N1,C3,C4	–171.89	15.23	–178.63	0.00	178.31	–178.65	–167.53	x
C1,C2,C3,C4	178.26	179.31	–171.39	180.00	173.78	–171.38	178.69	–176.8
C1,C2,C7,H5	1.07	2.97	–10.25	0.00	4.01	–10.32	0.73	x
C2,C3,N1,H6	9.60	–167.19	150.08	180.00	–1.65	2.43	14.79	x
C2,C3,C4,H3	–179.88	–178.69	176.98	180.00	–178.01	177.00	179.90	x
N1,C3,C4,H3	1.55	–1.62	–2.13	0.00	2.03	–2.08	2.07	x
H4,C5,C6,Br1	–0.14	–1.58	2.28	0.00	–0.58	2.47	0.01	x
Br1,C6,C7,H5	0.37	–1.43	2.67–	0.00	0.44	2.53	0.10	x
H2,O2,O1,H1	**	48.79	146.04	180.00	74.57	146.14	**	**
*= borrowed from ref (5 and 10) **= not exist in this conformer/isomer x=not found in literature								

Table 3. Calculated and experimental Dihedral angles (°) for the compound ABBA.

Table 4. Calculated Energies of the MO surfaces.

E_{MO} (Ev)	T1	T2						T3
		CC	CT	TC	TT	Ave	Total	
LUMO{+1}	–0.0	–0.4	–0.2	0.0	0.0	**–0.15**	–0.2	–0.1
LUMO	–1.4	–1.6	–1.9	–1.4	–2.0	**–1.725**	–1.9	–1.4
HOMO	–5.7	–5.9	–5.3	–5.7	–5.4	**5.575**	–5.3	–5.8
HOMO{–1}	–7.4	–7.5	–6.7	–7.3	–6.8	**–7.15**	–6.7	–7.3
HOMO{–2}	–7.7	–7.8	–7.4	–7.7	–7.4	**–7.575**	–7.4	–7.7
HOMO{–3}	–7.8	–8.0	–7.7	–7.8	–7.7	**–7.8**	–7.7	–7.8
HOMO{–4}	–7.9	–8.1	–8.0	–7.9	–7.8	**–7.95**	–8.0	–7.8
HOMO{–5}	–8.8	–8.8	–9.1	–8.8	–9.0	**–9.025**	–9.1	–8.9
HOMO{–6}	–9.5	–9.7	–9.9	–9.5	–9.8	**–9.775**	–9.9	–9.5
HOMO{–7}	–10.0	–10.2	–10.1	–9.9	–9.9	**–10.025**	–10.1	–9.9
HOMO{–8}	–10.3	–10.5	–10.3	–10.3	–10.1	**–10.3**	–10.3	–10.1
HOMO{–9}	–10.8	–10.9	–10.6	–10.8	–10.4	**–10.675**	–10.6	–10.9

According to these results, T1 was found to be 56.57 and 3.15 kcalmol^{-1} more stable than T2 and T3, while TT isomeric conformer of T2 was found to be 7.22, 53.19 and 56.53 kcalmol^{-1} more stable than the conformers CC, CT and TC respectively.

Due to these relations between energy values T1 form has been chosen as a symbol for representing the electronic transitions and visualization of e^- transfer between MO's in Figure 2.

OPEN JOURNAL OF NANO

Table 5 The energy equivalencies for the transitions between other conformers and T1 and T2/TT

Conformers	Energy (Hartree)	Energy Diff. (Hartree)	Energy Diff. (kcalmol^{-1})	Energy Diff. (eV)	Eq. Freq. (cm^{-1})	Dip. Moment (Debye)
T1	–3049.46281	0.0	0.00	0.00	0.00	2.41
T2	–3049.37266	0.09015	56.569991	2.4531076	19785.638	4.60
T3	–3049.45779	0.00502	3.1500982	0.13660122	1101.7626	4.87
CC	–3049.45124	0.01151	7.2226356	0.3132032	2526.153	2.85
CT	–3049.37798	0.08477	53.193989	2.3067103	18604.864	4.60
TC	–3049.37266	0.09009	56.532341	2.4514749	19772.469	2.53
TT	–3049.46275	0.0000	0.0000	0.0000	0	5.39

Table 6 Molecular orbital energies and differences for conformers of the compound ABBA (* From Ref[1])

Isomers & Conformers		HOMO–1	HOMO	LUMO	LUMO+1	ΔE (eV) ΔE_1	ΔE_2	ΔE_3	λ_{max} Calc.			Exper* (Eth/water/Gas)		
	T1	–7.4	–5.7	–1.4	0.0	6.0	4.3	5.7	206.64	288.34	217.52	346 / 324 / 337.5	257 / 250 / 269.2	**217 / 210 / 249.2**
	T2	–6.7	–5.3	–1.9	–0.1	4.8	3.4	5.2	258.30	364.66	238.43			
	T3	–7.3	–5.8	–1.4	–0.2	5.9	4.4	5.6	210.14	281.78	221.40			
	CC	–7.5	–5.9	–1.6	–0.4	5.9	4.3	5.5	210.14	288.34	225.43			
	CT	–6.7	–5.3	–1.9	–0.2	4.8	3.4	5.1	258.30	364.66	243.11			
	TC	–7.3	–5.7	–1.4	0.0	5.9	4.3	5.7	210.14	288.34	217.52			
	TT	–7.4	–5.4	–2.0	0.0	5.4	3.4	5.4	229.60	364.66	229.60			

*Borrowed from Ref. (5)

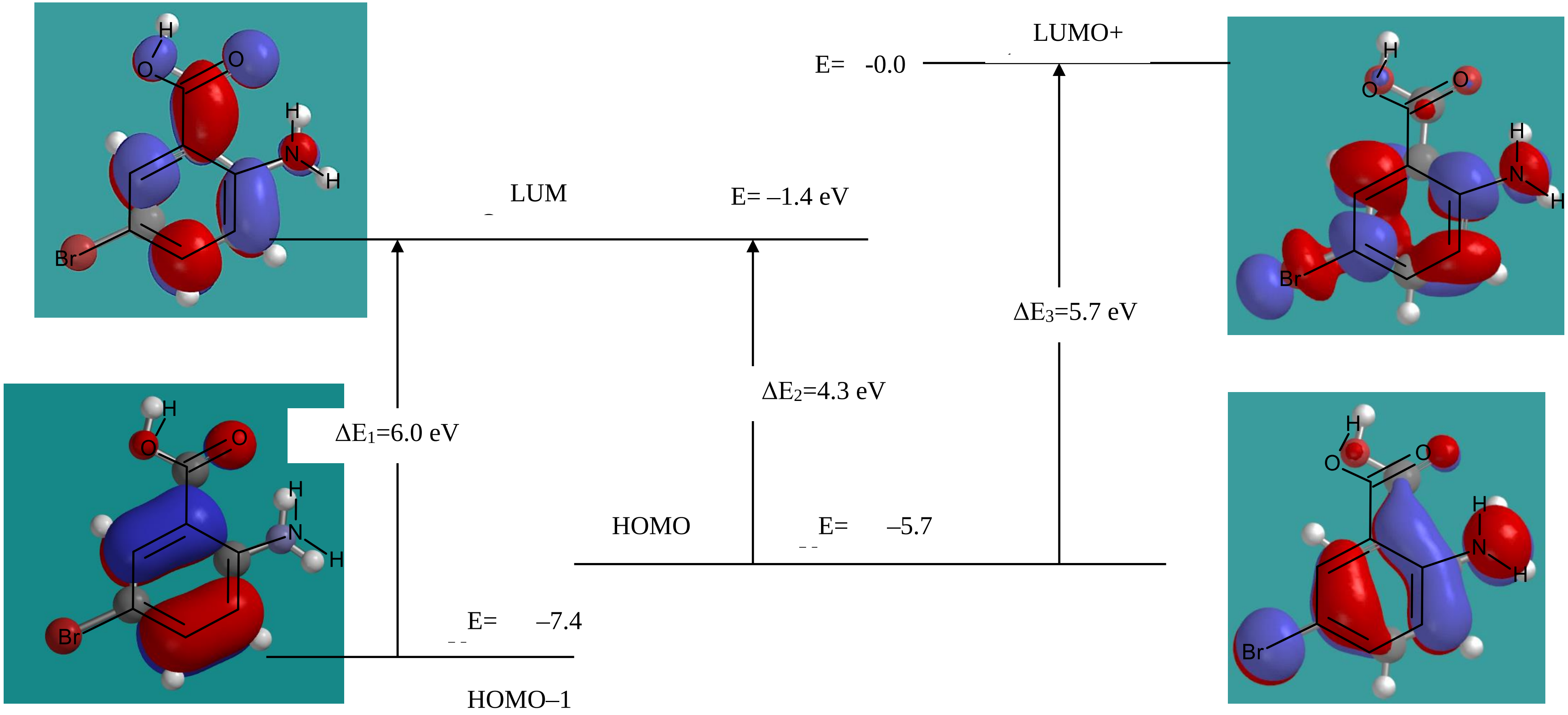


Figure 2. Electron transitions and energy differences between MO's.

Mulliken charge distribution: On a molecule, the electronic distribution causes heterogeneity of charges so that some parts of the molecule gains a negative or positive charge depending on the electronic density. The electron-rich parts of the molecule form a preferred site for electrophilic attacks.

Mulliken charge distribution was calculated according to the DFT / B3LYP method and 6.31G* basis set. The calculated values were transferred into Graph 1. As shown in the graphic, all of the H atoms have a considerable positive charge. C atoms have divided into mainly two species according to atomic charges; C6 slightly negative due to Br1 while C1,2,3 which are neighbors to O1, O2 and N1 atoms prominently have positive charges. But C4, C5 and C7 have negative charges due to the H atoms which are electropositive. The most dramatic negative charges have been observed on the O1, O2 and N1 atoms. The calculated Mulliken charge distribution graphics were depicted in Figure. 3 and Graph. 1 respectively. Also, all charge values including natural and electrostatic charges can be found in the supplementary material.

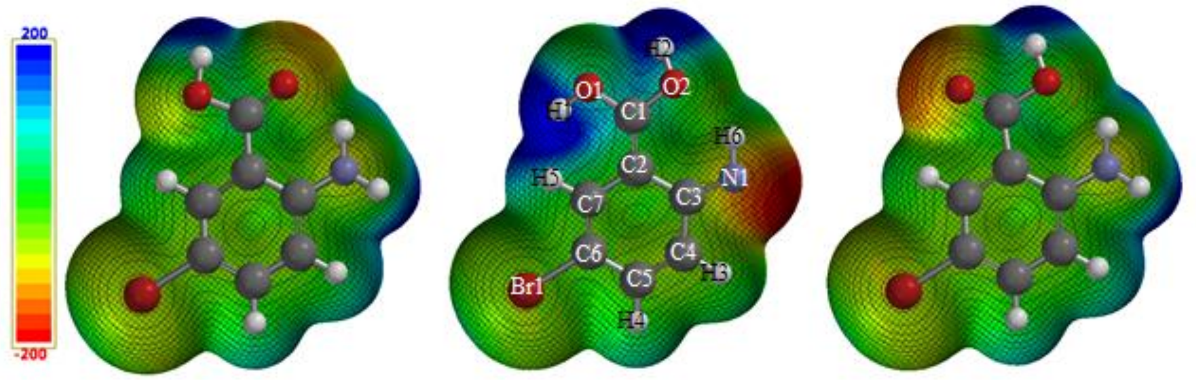
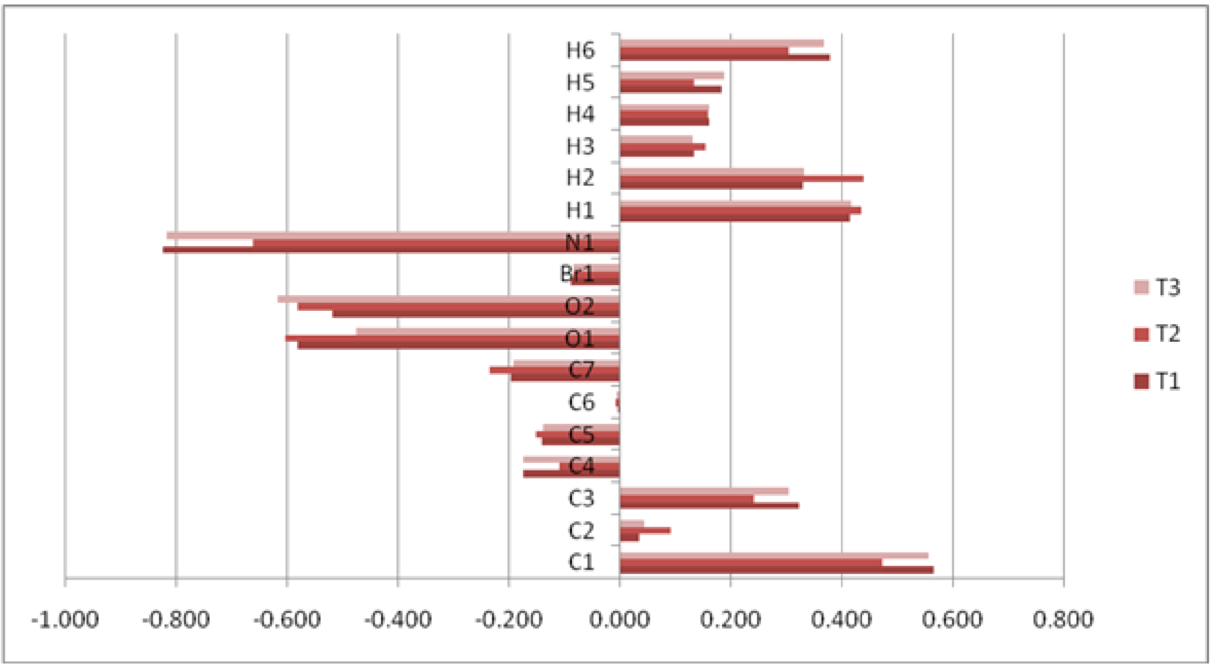


Figure 3. Electrostatic potential map (ESP Map) for the forms of the compound ABBA



Graph. 1. Calculated Mulliken charge distribution of compound ABBA

2.3. Vibrational spectroscopy (FT–IR and FT_RAMAN)

The molecule has 17 atoms and that means 45 vibrational modes in three main parts. Carboxyl group, amine group and benzene. The most mechanically active parts of the molecule are the carboxyl group and the amine group. They exhibit rocking, swinging and every kind of mechanical motions beside H immigrations between each other. For this reason, the molecule is not a simple carboxylic acid and nor a primary amine.

In the literature that ignored the tautomeric forms, F, Cl and Br analogs of ABBA were described as planar but in this study, the calculations clearly showed that some forms of the molecule have a considerable torsion.

As a brief analysis, the frequencies and their corresponding bonds have been tabulated in Table 7. In the table, the isomers of T2 were not involved. These results can be found in the supplementary material. Even so, some dramatic points should be underlined.

In T1 carbonyl C=O (C1O1) bond length is 1.227Å while the same distance 1.234Å which is 7Å longer than the former for T3. The frequency values are in agreement with this difference 1776cm^{-1} and 1810cm^{-1} respectively.

C3–N1 bond distance is 1.363 and 1.372 between T1 and T3 respectively. The frequency values which are 883cm^{-1} and 873cm^{-1} are in good agreement with them.

Table 7. The calculated and experimental vibrational spectra for ABBA

No	DFT / B3LYP6.31G			Experimental[1]			Total energy Distribution[2,3]
	T1	T2	T3	FT–IR[a]	FT–IR[b]	FT–RAMAN	
1*	75	66	62			68	τCOOH (79)
2*	117	94	110			103	γCNH2 (33) +γC–Br (21)
3*	140	129	144			130	γ(2A5BrBA) (83)
4*	146	150	147			186	δC–Br (53) +r(C–COOH) (29)
5*	285	268	286				ωNH2 (90)
6*	291	278	301			282	υC–Br (53)
7*	310	287	312				r(C–COOH) (63) +γC–Br (22)
8*	314	365	378			315	γ(2A5BrBA) (88)
9*	380	397	384			382	r(C–NH2)(21)+υ(C–COOH) (18)+δCCC(16)+δ(C–COOH) (16)
10*	423	414	404				δ(C–C=O) (39) + r(C–NH2)(34)
11*	429	423	434	441		435	γCCC (77)
12*	524	449	494				r(C–COOH) (37)+r(CNH2)(19)
13*	530	507	532	518			γCCC (63)
14*	596	539	550	555			γOH (81)
15*	614	612	601				τNH2 (94)
16	647	636	648	629	616	628	Ring def. (47) + υC–Br (18)
17	669.	638	650				δC=O (51)
18	707	726	706	688	676		γCCC (61) +γC–C–OH (24)
19	778	740	768	789	778	784	υCC (33) +υC–COOH (13)
20	787	825	783	816	815		δC–C–OH (72)
21	824	838	822	870	874	869	γCH (73) + δCCC (11)
22	883	877	879	888	890		δCCC (42) +υC–NH2 (10)
23	921	894	939	912	1046		γCH (87)
24	959	999	960	1089	1084	1090	γCH (82)
25	1078	1058	1076				rNH2 (40) +υCC (28)
26	1100	1068	1116				υC–OH (33) + υCC (20)
27	1135	1114	1120	1127	1124		υCC(41)+ υC–OH (12)

28	1197	1203	1194	1158	1159		δCH (40) + υCC (22) + δOH (17) + υC–COOH (10)
29	1209	1208	1207	1168	1160	1167	δCH (34) + δOH (26)
30	1313	1270	1294	1238	1230	1239	δCH(39) +υCC (26) +υC–NH2(10)
31	1351	1282	1331	1292	1256		δCH (42) + υCC (16) + δNH of NH2 (12) +υC–NH2 (11)
32	1371	1353	1357	1311	1290		υCC (31) +υC–NH2 (18)
33	1414	1411	1390	1342	1354	1339	υCC (29) +υC–COOH(16) + γOH (15) +υC–OH (14)
34	1458	1446	1469	1422	1424	1405	υCC (49)
35	1527	1461	1530	1481	1484	1484	δCH (48) +υCC (23)
36	1599	1594	1607	1547	1560	1551	υCC (52) + γNH of NH2 (18)
37	1642	1612	1658	1583	1586		ρNH2 (43) +υCC (35)
38	1678	1670	1691	1609	1618	1613	υCC (39)+ρNH2 (29) + υC–NH2 (10)
39	1776	1706	1810	1667	1692	1633	υC=O (71)
40	3186	3182	3182	2988	2521 2570 2623 2705 2834 2875 2972		1292+1583 cmb. 1167×2 o.t. CH ipb 1158+1547 cmb. (1311×2) o.t. CC str. 1481+1089 cmb. 1609+912 cmb. υCH (100)
41	3221	3212	3222				υCH (100)
42	3255	3229	3246			2722	υCH (100)
43	3542	3509	3590			2786	υ(NH2)sym. (100)
44	3692	3711	3689			2864	υ(NH2)asym. (100)
45	3700	3755	3705			2952	υOH (100)

[1]Received from Ref. 5 [2]values less then 10% omitted. [3]υ= stretching; δ= in–plane bending; γ=out of plane bending; ρ= scissoring; ω= wagging; τ= torsion; t, twisting; r, rocking. [Frequency (cm−1), a=in solid–phase b= as dissolved in 1,4–dioxane

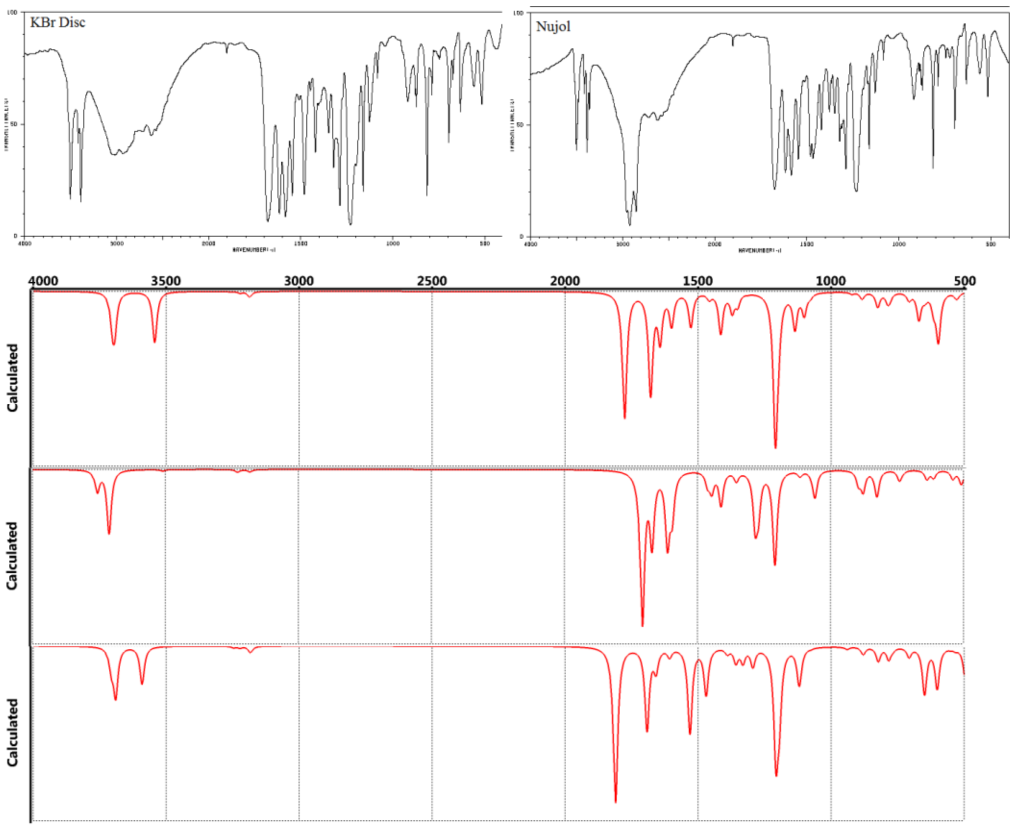


Figure 4. Calculated and experimental FT–IR spectra of compound ABBA

3. Conclusions

The molecular structure and HOMO–LUMO analysis have been carried out by using the SPARTAN 14 suite via DFT theory in the B3LYP level and 6.31 G* basis set. Also, FT–IR and FT–RAMAN spectra were calculated and compared to experimental results as well.

The compound had been studied by different research groups from different aspects but in this study, the calculations were handled in a new point of view, tautomeric transformations were examined for the first time as well.

As a result of all studies, the calculated and experimental values were found to be very close and in agreement.

Peer-review: Externally peer - reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

References

1. Hiji Y., Miyoshi M., Ichikawa O., Kasagi T., Imoto T., *Effects of butyric acid and analogues on amylase release from pancreatic segments of sheep and goats,* Arch. Int. Physiol. Biochem. 95 (1987) p. 113–120.
2. Ana del Olmo, Javier Calzada, and Manuel Nun~ez " Benzoic acid and its derivatives as naturally occurring compounds in foods and asadditives: Uses, exposure, and controversy" Critical Reviews In Food Science And Nutrition (2017) 57,(14), 3084–3103
3. Lewandowski W., Fuks L., Kalinowska M., Koczon P., *The influence of selected metals on the electronic system of biologically important ligands,* Spectrochim. Acta Part A 59 (2003) p. 3411–3420.
4. Dr Wibbertmann A., Dr Kielhorn J., Dr Koennecker G., Dr Mangelsdorf I., and Dr Melber C.,"*Benzoic Acid And Sodium Benzoate Cicad*" Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany
5. Karabacak M., Cinar M., *FT–IR, FT–Raman, UV spectra and DFT calculations on monomeric and dimeric structure of 2–amino–5–bromobenzoic acid,* Spectrochimica Acta Part A 86 (2012) p. 590 –599
6. Saxena A., Agrawal M., Gupta A., *Vibrational study, molecular properties and first-order molecular hyperpolarizability of Methyl 2–amino 5–bromobenzoate using DFT method,* Optical Materials 46, 2015, p. 154–167
7. Xavier T.S., Hubert.J., *FT–IR, Raman and DFT study of 2–amino–5–fluorobenzoic acid and its biological activity with other halogen (Cl, Br) substitution*, Spectrochimica Acta Part A, 79 (2011) p. 332–337.
8. Tanaka N., Ashida T., Sasada Y., Kakudo M., *Structural Determination, spectroscopic and nonlinear optical features of 2–acetamido–5–bromobenzoic acid by experimental techniques and quantum chemical calculations*, Bull. Chem. Soc. Jpn. 40 (1967) p. 2717–2723.

9. Pant A.K., *The crystal structure of 3,5–dibromo–p–aminobenzoic acid at room temperature (25°C approx.) and at –l50°C,* Acta Crystallogr. 19 (1965) p. 440–448.
10. Arshad M.N., Tahir M.N., Khan I.U., Shafiq M., Waheeda A., *4–Amino–3–bromobenzoic acid,* Acta Crystallogr. E 65 (2009) p. o640
11. Ferguson G., Sim G.A., *Crystal structure of 2–bromo-benzoic acid at 120 K: a redetermination* Acta Crystallogr. 15 (1962) p. 346–350.
12. Swaminathan J., Ramalingam M., Saleem H., Sethuraman V., M.T.N. *FT–IR and FT–Raman vibrational assignment of 2–bromobenzoic acid with the help of ab initio and DFT calculations* Spectrochim, Acta Part A 74 (2009) p. 1247–1253.
13. Sundaraganesan N., Joshua B.D., Settu K., *Vibrational spectra and assignments of 5–amino–2–chlorobenzoic acid by ab initio Hartree–Fock and density functional methods* Spectrochim. Acta Part A 66 (2007) p. 381–388.
14. Sundaraganesan N., Joshua B.D., *Vibrational spectra and fundamental structural assignments from HF and DFT calculations of methyl benzoate,* Spectrochim. Acta Part A 68 (2007) p. 771–777.
15. Sundaraganesan N., Ilakiamani S., Joshua B.D., *FT–Raman and FT–IR spectra, ab initio and density functional studies of 2–amino–4,5–difluorobenzoic acid,* Spectrochim. Acta Part A 67 (2007) p. 287–297.
16. Richards R.M.E., Xing D.K.L., *The effect of p–aminobenzoic acid on the uptake of thymidine and uracil by Escherichia coli* Int. J. Pharm. 116 (1995) p. 217–221.
17. Syahrani A., Ratnasari E., Indrayanto G., Wilkins A.L., *Biotransformation of o– and p–aminobenzoic acids and N–acetyl p–aminobenzoic acid by cell suspension cultures of Solanum mammosum,* Phytochemistry, 51 (1999) p. 615–620.
18. Swislocka R., Samsonowicz M., Regulska E., Lewandowski W., *Molecular structure of 4–aminobenzoic acid salts with alkali metals,* J. Mol. Struct. 792–793 (2006) p. 227–238.
19. Koczon P., Baranska H., Lewandowski W., *Vibrational and NMR studies on o–, m–and p–chlorobenzoic acids,* Asian J. Phys. 3 (1994) p. 71–79.
20. Sundaraganesan N., Saleem H., Mohan S., *FTIR and laser Raman spectra of 2–amino–5–bromobenzoic acid,* Indian J. Phys. 78 (6) (2004) p. 489–494.
21. SPARTAN'14 Wavefunction Inc. Irvine CA, USA, (2014)
22. Hehre W.,J., "*SPARTAN'14 Tutorial and User's Guide*", 2014 Wavefunction, Inc
23. Silverstein R., M., Webster F., X. Kiemle D., J. "*Spectrometric Identification of Organic Compounds*" 7th Ed. John Wiley Sons INC. 2005
24. Ramachandran K. Deepa I., G., Namboori K., "*Computational Chemistry and Molecular Modeling: Principles and Applications*", Springer–Verlag 2008 Heidelberg Berlin.
25. Jensen F., "*Introduction to Computational Chemistry*" Wiley 2016
26. Karakaş-Sarıkaya, E., "*Investigation molecular and radical structures of three-carboxyfuran by DFT and EPR on gas-phase*", Journal of Spectroscopy and Molecular Sciences 2(2) (2020),

p. 44–50

27. Peter K., Vollhardt C., Schore N., E.. “*Organic chemistry: structure and function*” 6th ed. Freeman&Comp. 2011 NY–US pp. 682,731,742,870–90