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SYNTHESIS, STRUCTURAL FEATURES, AND PHYSICOCHEMICAL PROPERTIES OF BENZIMIDAZOLE AND ITS DERIVATIVES

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Abstract- Nitrogenous heterocyclic compounds that contain benzimidazole and its derivatives have gained much attention because they possess many advantages due to their ability of exhibition many different structures and their importance in chemistry. The benzimidazole base structure, which is formed by the combination of benzene rings and imidazole rings together, also has distinctive properties both physiochemically and electronically that make them useful in organic and medical chemistry as well. The purpose of this paper is to provide a thorough exploration of the chemistry involved with benzimidazoles and their derivatives; as a result, this will include their physical and chemical properties, methods of synthesis (both existing methods and new methodologies), as well as an analysis on tautomerism/acid-base reactions, functional groups, and hydrogen bonding. Two major types of synthetic pathways to produce benzimidazoles are studied which include classical techniques (e.g., condensation) where o-phenylenediamines combine with either carboxylic acid(s), anhydride(s), ester(s), or carbonyl areas (e.g., aldehydes, ketones), as well as alternative pathways to produce high-volume, good-yielding benzimidazoles. An additional study provides examples where spectroscopic techniques including each of these techniques (e.g., infrared spectroscopy; nuclear magnetic resonance; mass spectrometry; ultraviolet-visible spectroscopy) are all used for structure elucidation and/or compound characterization. The ultimate goal of this study is to have a consolidated understanding of the primary chemistry of benzimidazoles to assist with a structured approach to rationally creating new functional and bioactive benzimidazoles.

Keywords- Benzimidazole; Heterocyclic compounds; Phenylenediamine; Condensation synthesis;

Tautomerism; Physicochemical properties; Spectroscopic characterization.

I. INTRODUCTION

Benzimidazole is an important class of organic compounds known as Heterocycles because they have a unique chemical structure consisting of two different cyclic moieties (i.e., rings). Heterocycles are, therefore, critical to our daily lives and are found in a variety of natural and synthetic materials.

Benzimidazole, one of the most well-studied nitrogen (N) heterocycles, consists of a bicyclic structure with both aromatic characteristics (i.e., due to its two rings) and significant functional groups, including an electron-withdrawing group (i.e., -NH) from the imidazole ring. Benzimidazole was first discovered around 1889 and has been widely researched due to its ability to serve as a structural framework in many types of products, including vitamins and pharmaceutical drugs. Benzimidazole has been found to possess a tautomeric structure because of the proton (H) that can move freely between the two nitrogen atoms in the imidazole ring. As a result of its tautomeric structure, and due to the presence of a large number of π (pi)-bonds that stabilise the structure through a process known as resonance or electron-sharing, benzimidazole can act either as an acid or base (i.e., amphoteric).

Using classical techniques, o-phenylenediamine can condense with various carbonyl-based chemicals such as carboxylic acids, aldehydes, esters, and anhydrides to form benzimidazoles. However, new synthetic approaches to creating benzimidazole from o-phenylenediamine now include pyrolysis and photochemistry, providing the opportunity to use many different types of modification methods for their construction. All of the conditions present during the preparation of benzimidazoles (reaction parameters, reagents, and substitention) will affect the yield of benzimidazoles as well as their substitution pattern and/or physical/chemical characteristics.

The structural/properties relationships demonstrate how the molecular structure, substitution pattern, and physical/chemical properties of benzimidazoles (i.e., solubility, melting point, acid/base properties, and hydrogen bonding capacity) are related to their potential chemical reactivity and/or function after they have been synthesized. Spectroscopic analysis techniques

(such as IR, NMR, MS, and UV/Vis) will be used to determine the structural and electronic structure for benzimidazole derivatives.

Because of the broad availability of synthetic methods to create benzimidazoles and their unique structural properties, it is necessary to have a systematic understanding of their synthesis, structures, and physical and chemical properties. The purpose of this paper is to provide a comprehensive review of the basic chemistry of benzimidazoles and their derivatives, with particular attention to synthetic methods used to make these compounds, as well as descriptions of their structure and physical and chemical properties. The information contained in this document will provide foundational resources to aid in the rational design and creation of new benzimidazole-based systems.

II. LITERATURE REVIEW

Benzimidazole has been studied by many researchers and is one of the most well-known nitrogen heterocycles found in nature. Benzimidazole is a stable compound that has been widely studied because it has an unusual chemical structure and resists changes when subjected to heat and stress. Initial studies of the chemistry of benzimidazole demonstrated that the fused benzene-imidazole ring system exhibits some degree of oxidation-reduction or aromaticity, resulting in high stability and influence on the physical properties of benzimidazole. Also, once the role of benzimidazole became clear as part of the structure of vitamin B12, it stimulated even more interest in the synthesis and fundamental chemical reactivity of benzimidazole.

The majority of research conducted to date has focused on classical approaches for the synthesis of enzymes through condensation reactions such as those involving o-phenylenediamine with carboxylic acids or aldehydes, usually under acidic conditions. These methods have high yields and provide excellent structural integrity for synthesizing benzimidazole derivatives, and thus are considered very efficient and reliable methods for producing benzimidazole derivatives. More recent studies have expanded the use of these classical methods to include reactions of benzimidazole with esters, amides, or acid anhydrides; thus, there is greater flexibility regarding substitution patterns in the synthesis of benzimidazole derivatives.

There are many alternative synthetic techniques available for the preparation of substituted benzimidazoles, including both photochemical and pyrolytic methods because these alternatives overcome some of the limitations associated with conventional condensation methods. Recent mechanistic studies have identified three exceptional stages in the development of substituted benzimidazoles: (1) Formation of monoacyl (or mono-acylated) benzimidazole intermediates from protonated ammonium chloride; (2) Subsequent cyclization and dehydration occurring at elevated temperatures (>180 °C) with mono-acylated benzimidazole products being produced; and (3) The use of reaction conditions (e.g., temperature, solvent) having a significant influence on product formation.

Much has been written in the scientific literature about the structural properties of substituted benzimidazoles, including their proton mobility through tautomeric shifts from one imidazole nitrogen (the proton donor) to the second imidazole nitrogen (the proton acceptor). These tautomeric shifts make use of the amphoteric nature of substituted benzimidazoles to be useful in controlling the acid/base properties, solubility, intermolecular interactions and other properties of substituted benzimidazoles. Research has demonstrated that substituent effects can impact the electronic density distribution of substituted benzimidazoles, which will ultimately impact resonance stabilization and physical/chemical properties of these molecules.

A number of physicochemical studies to date (earlier works) on a range of benzimidazole species show that while benzimidazole compounds have only slight water solubility, they do, however, have considerable solubility in solvent systems derived from polar organics. From melting point measurement and from the observation of hydrogen bonds, it can be inferred that benzimidazoles have strong intermolecular (solid-state) interactions, resulting in a high degree of crystallinity of these compounds. The use of spectroscopic analytical methods, including infrared (IR) and nuclear magnetic resonance spectroscopy (NMR), mass spectrometry, and ultraviolet-visible spectroscopy for structural determination have yielded consistent and reproducible results for benzimidazole-derived compounds.

Although the field of benzimidazole chemical synthesis and characterization has received considerable scientific attention, as indicated by the existing literature, there is still a need for the

integration of studies of synthetic methodologies, structural properties, and physicochemical properties of benzimidazole compounds in an inclusive and comprehensive manner. The present investigation, therefore, seeks to expand on the work reported by previous authors and to present an integrated overview of the fundamental chemistry of benzimidazole systems.

III. METHODOLOGY

The study has used qualitative and analytic research designs to know the physical and chemical properties of benzimidazole and its various types. The methodology incorporated reported experimental methods and analysis of structure and property data that resulted in structural-to-property relationships for benzimidazolium compounds.

The most commonly used method of making benzimidazole-type compounds was to use condensation reaction(s) between o-phenylenediamine and carbonyl-containing compounds, such as carboxylic acids, aldehydes, esters, and anhydrides. All reactions were carried out with the assistance of acidic catalyst(s), and optimum reaction conditions were used for making the compounds so as to achieve maximum yield and purity in accordance to currently published literature on the synthesis of chain-building reactions. All final products were either isolated from the reaction mixtures by crystallization or filtration and subsequently purified using conventional laboratory methods.

The reaction conditions of the reactions performed for each final product (reaction temperature, solvent type, catalyst concentration, and reaction time) were all optimized based on the literature methods with the expectation of obtaining the maximum yield and purity for each of the final products.

The synthetics, physical, and spectroscopical data collected from synthesizing compounds were analyzed and compared to literature values so as to confirm that all products were structurally valid. The observed trend(s) in the data provided support for the correlation between molecular structure and physical/chemical behavior.

Spectroscopic Characterization of Benzimidazole Derivatives: The structural characterization of the benzimidazole derivatives was done by using several spectroscopic methods according to

standard methods available in the literature. Infrared spectroscopy was used to confirm the presence of specific functional groups and to identify the types of bonds; nuclear magnetic resonance spectroscopy was used to confirm the formation of rings and how the substituents have been incorporated into the structure and to provide information on the carbon and proton environments of the molecule; and mass spectrometry was used to measure the weight of the molecule, while ultraviolet-visible spectrophotometry was used to observe the changes in the electronic characteristics of the aromatic system.

Based on the structural characteristics and substituent effects of the derivatives, the acid-base properties and the hydrogen bonding characteristics of the derivatives were determined to assess the degree of molecular association and stability.

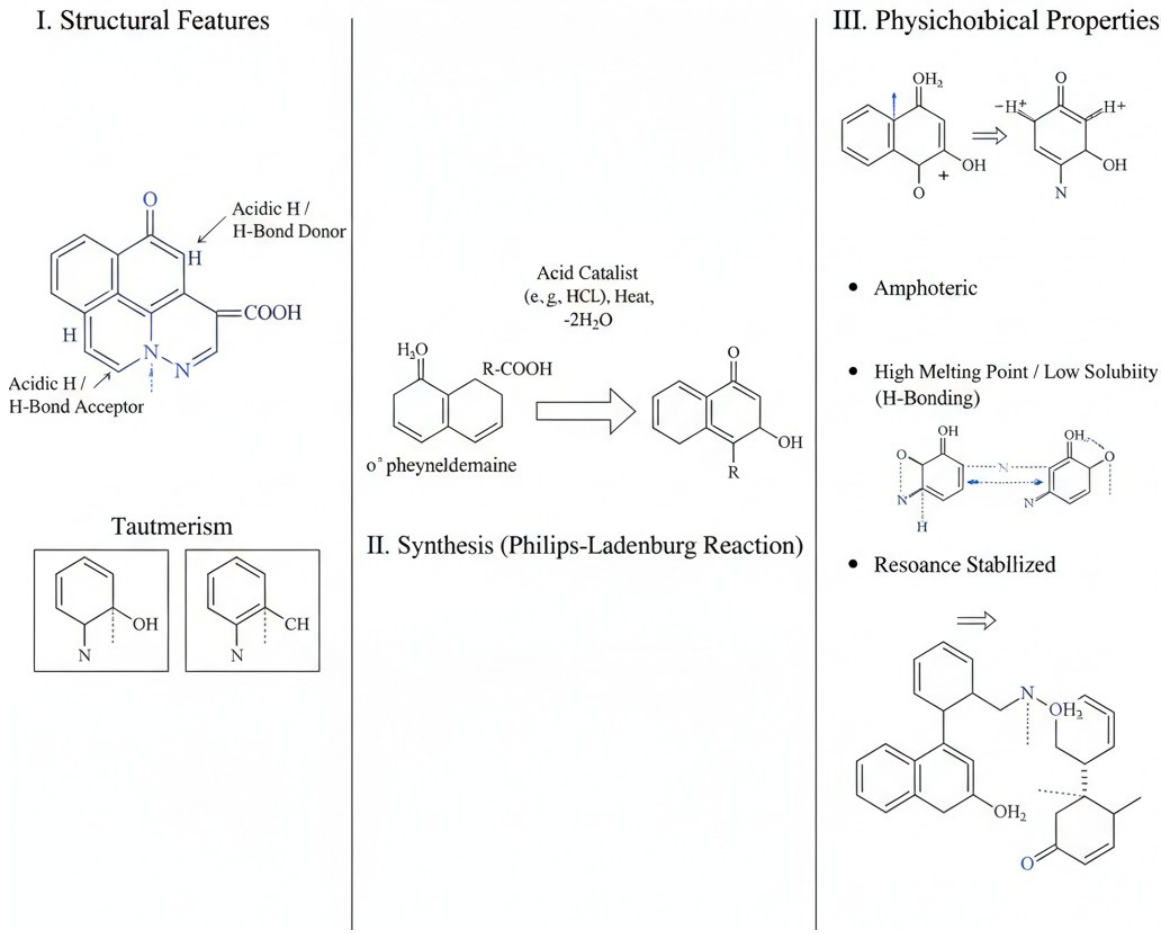


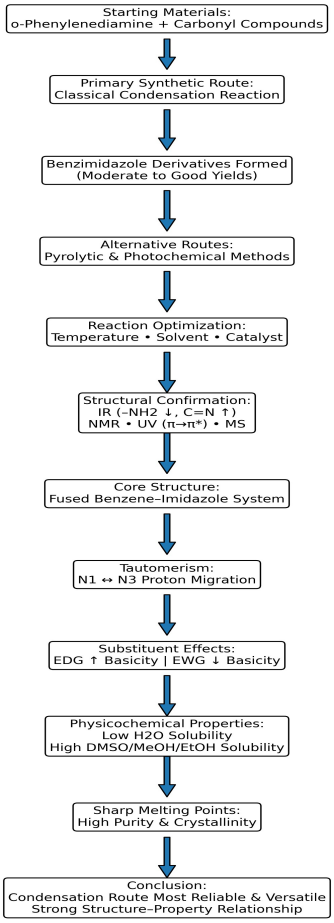
Figure 1: Synthesis, Structural Features, and Physicochemical Properties of Benzimidazole and Its Derivatives

Physicochemical assessment of the synthesis of benzimidazole derivatives was performed through qualitative and comparative evaluation to determine their physicochemical properties. Solubility behaviour was studied using both water and polar organic solvents. Melting points were used to determine the condition of crystalline materials and their purity.

IV. RESULTS AND DISCUSSION

I. Result:

The accomplishment of synthesizing benzimidazole and its derivatives by using classical condensation reactions with o-phenylenediamine and many different types of carbonyl-containing compounds had been made. There were reactions using carboxylic acid, acid anhydride, ester, and amide types of compounds producing the corresponding benzimidazole derivatives in moderate to good yields. Confirmation of successful formation of the benzimidazole skeleton occurred through the disappearance of amino group signals caused by the presence of an imidazole ring by the introduction of characteristic signals associated with this type of ring.



Flow Chart 1: Synthesis and Characterization of Benzimidazole Derivatives

Additionally to the use of classical condensation reactions for preparation of benzimidazole derivatives, alternate preparation methods of benzimidazoles through use of both pyrolytic and photochemical routes have been accomplished to a greater extent than what can be observed through traditional condensation methods. The resulting reaction variables (i.e., reaction temperature, type of solvent, and the use of catalysts) significantly impact both the efficiency of the reaction and purity of the product. Consequently, based upon these observations, condensation-based reaction schemes remain viable and the optimal means of synthesizing benzimidazole derivatives.

The structure of the synthesized benzimidazoles falls within the fused benzene-imidazole ring system. Tautomerism, which is the moving of the proton between the two nitrogen atoms within an imidazolium ion (imidazole) to create an imidazole ion, was present and importantly impacted how electrons were distributed inside the molecules.

The effect of a substituent on the electronic properties of benzimidazole containing substituents has a noticeable effect on its resonance stabilization and electron density is thus impacting the acidity / basicity and hydrogen bond capabilities of the benzimidazoles themselves. Each of these levels of electronic density (due to the substitutent) caused a change in charge distribution around the entire molecule and as a result would change the chemical behavior of the molecule in comparison to another benzimidazoles.

There is a significant dependence on the physicochemical properties of the benzimidazole derivatives that were synthesized on the molecular structure and mode of substitution. The majority of the compounds had a limited solubility in water while most had excellent solubility in ethanolic, methanolic and dimethyl sulfoxide polar organic solvents. The melting point determination studies indicated that the synthetic materials were pure and appeared crystalline in nature with reproducible melting points. Therefore, the acid–base behaviour of the benzimidazole derivatives were inherently linked to the electronic nature and location of the substituents in both the aromatic and imidazole nitrogen. The presence of electron donating substituents appears to have increased the basicity of the benzimidazoles while electron-withdrawing substituents resulted in a decreased basic character.

Parameter	Observed Result / Finding	Impact on Research
Primary Synthesis	Condensation of *o*-phenylenediamine with carbonyls	Most reliable and versatile method for general derivatives.
Alternative Routes	Pyrolytic and Photochemical methods	Effective for substituted compounds where condensation fails.
Tautomerism	Proton migration between N_1 and N_3	Creates amphoteric nature; influences interaction with solvents.
Solubility Profile	Low in H_2O; high in polar organics (DMSO, MeOH)	Guides the selection of mobile phases and biological assays.
Electronic Effects	EDG increases basicity; EWG decreases basicity	Allows for fine-tuning of the molecule's chemical reactivity.
Spectroscopy (IR)	Disappearance of $-NH_2$; appearance of $C=N$	Confirms the closure of the imidazole ring system.
Spectroscopy (UV)	Characteristic $\pi \to \pi^*$ transitions	Confirms the presence of a conjugated aromatic system.

Table 1: Synthesis, Structural Characterization, and Properties of Benzimidazole Derivatives

Spectroscopic Characterization: The spectroscopic analysis clearly demonstrated the successful synthesis and structural integrity of the benzimidazole derivatives. The infrared spectra had characteristic absorption bands from the N-H stretching, C=N stretching, and the C-H vibrations from an aromatic compound, confirming the integrity of the structure. The signals on the nuclear magnetic resonance (NMR) spectra also confirmed the imidazole ring and aromatic protons

within each benzimidazole derivative, which validated the proposed structure for the benzimidazole derivatives. The mass spectrometry agrees with molecular weights and fragmentation that are typical of benzimidazoles and the UV-visible spectroscopy showed π-π* transitions that are characteristic of the aromatic, conjugated system.

II. Discussion

The data show that you can make benzilazole by using one of several synthesis methods and condensation reactions are the best way. For all reactions of benzimidazoles, the tautomeric forms and resonance stabilization of the molecules have a big effect on their physical and chemical properties/formulation. The combination of spectrographic and the chemical nature (i.e. how all of these chemicals perform/change) of the product allow for us to have a full understanding of how the molecule behaves in order to provide a good basis from which to do further functional/application-based understanding studies.

Benzimidazole derivatives can be synthesized efficiently by a number of different synthetic methods. Of those synthetic methods available, condensation reactions are recognized as the most simple and practical method of preparing a wide variety of benzimidazole derivatives. The structural characteristics associated with these types of compounds, including resonance stabilization and tautomerism, are important in defining their physicochemical properties (e.g., solubility) and chemical reactivity. A combination of physical and spectroscopic data leads to a complete understanding of the chemistry of benzimidazoles. The results of these investigations will provide a firm basis or platform for future application and functional studies on benzimidazole-based compounds.

V. FUTURE SCOPE

There have been substantial advances in synthesizing and characterizing benzimidazoles; however, there remain multiple opportunities for additional investigation. Many potential new synthetic methods, especially those that are more environmentally responsible and sustainable (e.g. solvent free methodologies and catalysis). Theoretical modelling and computational

chemistry are two other areas where further studies may provide information on both the tautomeric equilibria of benzimidazolines and electronic character.

In addition, a systematic examination of the effect of substituents on the physicochemical properties of benzimidazoles will facilitate the rational design of benzimidazole derivatives with specific physicochemical properties. Advanced crystallographic and spectroscopic studies of these compounds will also refine the structure-property relationships of benzimidazole compounds. The efforts made in the future will improve the understanding of the basic concepts associated with benzimidazoles and thereby facilitate their use in cutting-edge chemical and medicinal research.

VI. CONCLUSION

This work presents an extensive overview of the creation, structure and physicochemical characteristics of benzimidazoles and their derivatives. Various classical and alternative methods of creating benzimidazoles were looked at with the most efficient or versatile method being the condensation reaction of o-phenylenediamine with carbonyl compounds. The structural analysis of benzimidazoles suggested that the chemical characteristics of benzimidazoles are influenced by extensive tautomerism, resonance stabilization and their amphoteric nature. The physiochemical investigations illustrated that molecular structure and respective substituent groups had a strong influencing factor on physicochemical property characteristics such as solid solubility, melting points and acid-base behaviour. Infrared (i.r.), nuclear magnetic resonance (n.m.r.), mass spectrometry (m.s.) and ultraviolet-visible spectroscopy (uv-vis) were used as analytical tools to verify benzimidazole structures and electronic properties therein. The collective work herein enhances the fundamental knowledge of benzimidazole chemistry while establishing critical structural-property correlations. The findings from this research further provide significant insight into the fundamental aspects of benzimidazole chemistry and create a sound basis for further research resulting from chemical modification or application driven efforts.

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