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Challenges in Classifying Secondary and Tertiary Amides: A Critical Examination of IUPAC Guidelines

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Abstract Organic compounds are organized into classes or families based on their functional groups, which consist of specific groups of atoms. Similar physical and chemical properties are exhibited by compounds containing the same functional group. The classification of organic compounds according to their structure, compound naming, chemical reaction prediction, and product structure depiction is facilitated through the identification of functional groups. The amide functional group is extensively utilized in both synthetic organic chemistry and bioorganic chemistry, making it one of the most prevalent components. Its significance within the molecular sciences is profound, notably serving as the essential bond that forms the backbone of peptides, proteins, and a multitude of other biomolecules. In this study, we identify discrepancies in IUPAC's amide classification rules over the years and their lack of acceptance within the scientific community. We draw evidence from various sources, including textbooks, peer-reviewed articles, and online chemistry resources, to illustrate a lack of uniform adherence to IUPAC's amide classifications, despite complete agreement among these sources. These findings emphasize the necessity for IUPAC to reconsider these recommendations, not only to alleviate potential challenges for students and scientists but also to align with well-established scientific practices.

Keywords Functional Groups, Amide classification, IUPAC

1. Introduction and Background

Within the context of first- and second-semester undergraduate introductory organic chemistry courses, functional groups within organic compounds assume a paramount role. The nomenclature of organic compounds holds equal importance in the broader curriculum encompassing introductory organic chemistry and general chemistry. The process of naming organic compounds frequently initiates with branched alkanes and progressively incorporates substituents and functional groups [1]. Consequently, it is imperative that students possess the ability to accurately categorize functional groups to ensure precise nomenclature of organic chemical compounds. A deficiency in comprehending organic compound nomenclature can give rise to challenges in grasping other aspects of organic chemistry. The International Union of Pure and Applied Chemistry (IUPAC) has established a comprehensive set of nomenclature rules, providing the necessary framework for naming and depicting molecules and functional groups [2,3].

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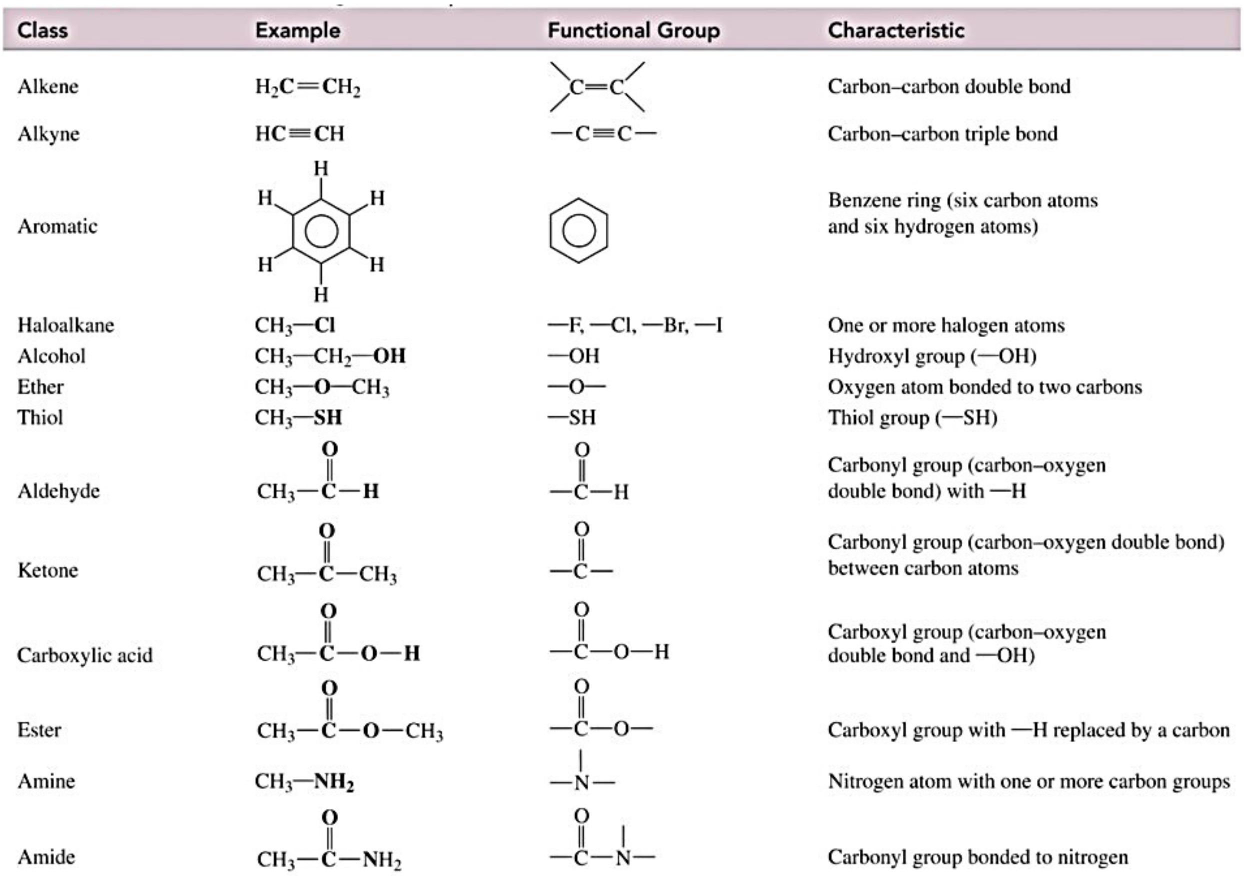
The functional group constitutes either an individual atom or a cluster of atoms exhibiting consistent chemical traits across diverse compounds. This structural element imparts distinct physical and chemical attributes to specific families of organic compounds [4]. Functional groups, at the core of organic chemistry, medicinal chemistry, toxicity assessment, and the various facets of spectroscopy, serve as the foundational concept. Within these domains, functional groups play a pivotal role by enabling specific interactions with target proteins, often through the establishment of hydrogen bonds and other less robust interactions. Additionally, functional groups significantly shape the metabolic stability and overall bioavailability of molecules, either through stereoelectronic or electrostatic considerations. Abundant scientific literature, including numerous research papers and books, is dedicated to elucidating the properties and reactivity of specific functional groups. The renowned book series titled "Chemistry of Functional Groups" provides a comprehensive exploration of various categories of organic molecules and encompasses an extensive library of over 100 volumes [5].

In high school and college-level chemistry courses, it is common practice for textbooks to introduce functional groups through a table. This table typically includes information such as the class, structure, characteristics, and a representative example (refer to Figure 1) [6]. Students are generally tasked with mastering the content presented in this chart.



Class	Example	Functional Group	Characteristic
Alkene	$H_2C{=}CH_2$	$>C{=}C<$	Carbon–carbon double bond
Alkyne	$HC{\equiv}CH$	$-C{\equiv}C-$	Carbon–carbon triple bond
Aromatic	(benzene, C_6H_6)	(benzene ring)	Benzene ring (six carbon atoms and six hydrogen atoms)
Haloalkane	CH_3-Cl	—F, —Cl, —Br, —I	One or more halogen atoms
Alcohol	CH_3-CH_2-OH	—OH	Hydroxyl group (—OH)
Ether	CH_3-O-CH_3	—O—	Oxygen atom bonded to two carbons
Thiol	CH_3-SH	—SH	Thiol group (—SH)
Aldehyde	$CH_3-C(=O)-H$	$-C(=O)-H$	Carbonyl group (carbon–oxygen double bond) with —H
Ketone	$CH_3-C(=O)-CH_3$	$-C(=O)-$	Carbonyl group (carbon–oxygen double bond) between carbon atoms
Carboxylic acid	$CH_3-C(=O)-O-H$	$-C(=O)-O-H$	Carboxyl group (carbon–oxygen double bond and —OH)
Ester	$CH_3-C(=O)-O-CH_3$	$-C(=O)-O-$	Carboxyl group with —H replaced by a carbon
Amine	CH_3-NH_2	$-N(-)-$	Nitrogen atom with one or more carbon groups
Amide	$CH_3-C(=O)-NH_2$	$-C(=O)-N(-)-$	Carbonyl group bonded to nitrogen

Figure 1. The most common functional groups

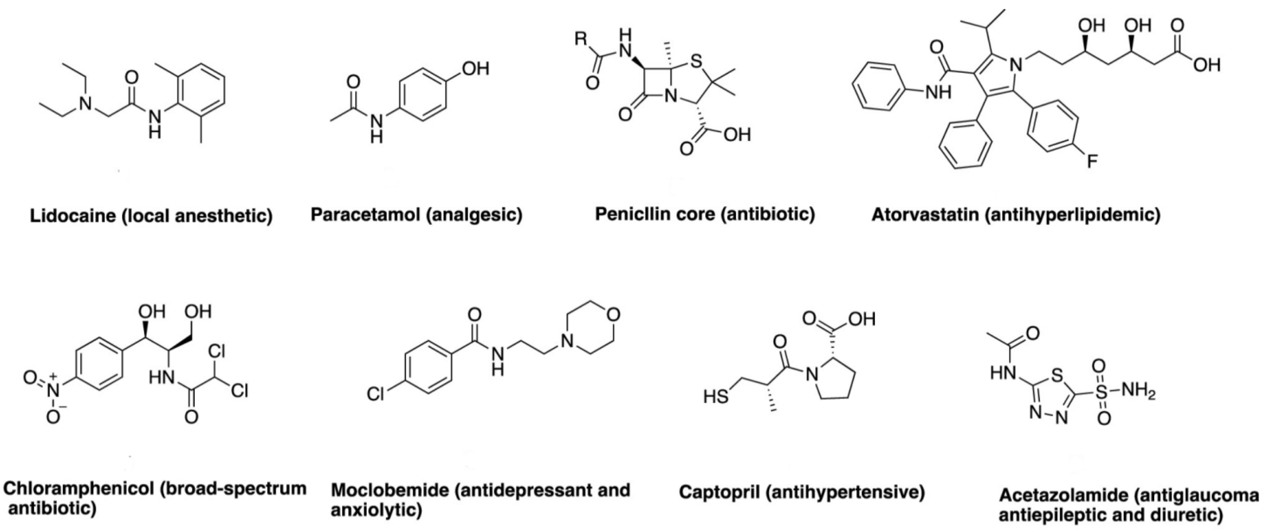


Figure 2. Amide-Based Drug Structures and Functions

Given their significance, educational games and other classroom activities have been devised to create a more engaging and interactive learning experience for students when it comes to understanding functional groups [7-14].

Amides, as an organic functional group, are characterized by the presence of carbon, oxygen, and nitrogen atoms. These functional groups exhibit a distinct atomic arrangement, with nitrogen forming a bond with the carbonyl carbon, which is double-bonded to an oxygen atom (Figure 1). The significance of the amide functionality within the field of molecular sciences cannot be emphasized enough. Most notably, this structural motif serves as the foundational linkage in the structural framework of peptides, proteins, and an extensive array of other biomolecules [15].

In the domain of medicine, amide-forming reactions are considered among the most prevalent processes in the pharmaceutical industry (Figure 2) [16]. The importance of the amide bond has been increasingly recognized in drug design and development as our understanding of its properties has advanced over the past century. Many widely used drugs, such as lidocaine, paracetamol, the penicillins represented by the core structure, atorvastatin, chloramphenicol, moclobemide, captopril, and acetazolamide, among others, feature an amide functional group as an integral part of their pharmacophore or auxophore (Figure 2) [17].

Approximately a quarter of all approved drugs, and a substantial majority of drug candidates, encompass at least one amide bond in their molecular architecture. The amide functional group, whether in its secondary or tertiary configuration, is the most prevalent among bioactive molecules, present in 40.3% of all compounds. It is closely followed in prevalence by the ether group (38.3%) and the tertiary amine (29.7%). Other common functional groups include fluoro (22.6%), chloro (19.5%), secondary amine (19.4%), and alcohol (14.3%) [18]. In Figure 3 [18], the rankings of the 15 most common functional groups for each time period are displayed. The amide group has maintained its leading position consistently, underscoring its enduring status. Understanding the interactions between amides and biological targets constitutes a fundamental aspect of drug discovery endeavors [19]. Amides are also widely employed in the creation of coordination complexes for various applications [20-22].

Amides are classified as primary, secondary, and tertiary amides. Given their widespread use as fundamental building blocks in the chemical sciences, it is important to have a clear understanding of these amide classifications.

Established in 1919, the International Union of Pure and Applied Chemistry (IUPAC) is the globally recognized authority for chemical nomenclature and terminology. IUPAC has a rich history of providing nomenclature for both organic and inorganic compounds, which is documented in various publications, including the IUPAC Colour Books (Gold, Green, Blue, Purple, Orange, White, and Red). The "Blue Book," known as the Nomenclature of Organic Chemistry, offers recommendations on organic chemical naming, while the "Gold Book" known as the Compendium of Chemical Terminology provides internationally accepted definitions for chemical terms. The "Green Book" compiles terms and symbols in physical chemistry, while the "Orange Book," named the Compendium of Analytical Nomenclature, offers definitions for analytical chemistry terms. The "Purple Book" focuses on polymer nomenclature, and the "Red Book," referred to as the Nomenclature of Inorganic Chemistry, provides recommendations for inorganic chemical naming. Lastly, the "White Book" contains definitions relevant to biochemical research. This standardized naming system aims to ensure consistent and globally accepted terminology, avoiding confusion resulting from varying naming practices among scientists.

In this study, we identify discrepancies in amide classification rules within the historical IUPAC Blue Books and highlight the lack of acceptance of IUPAC's amide classifications within the scientific community.

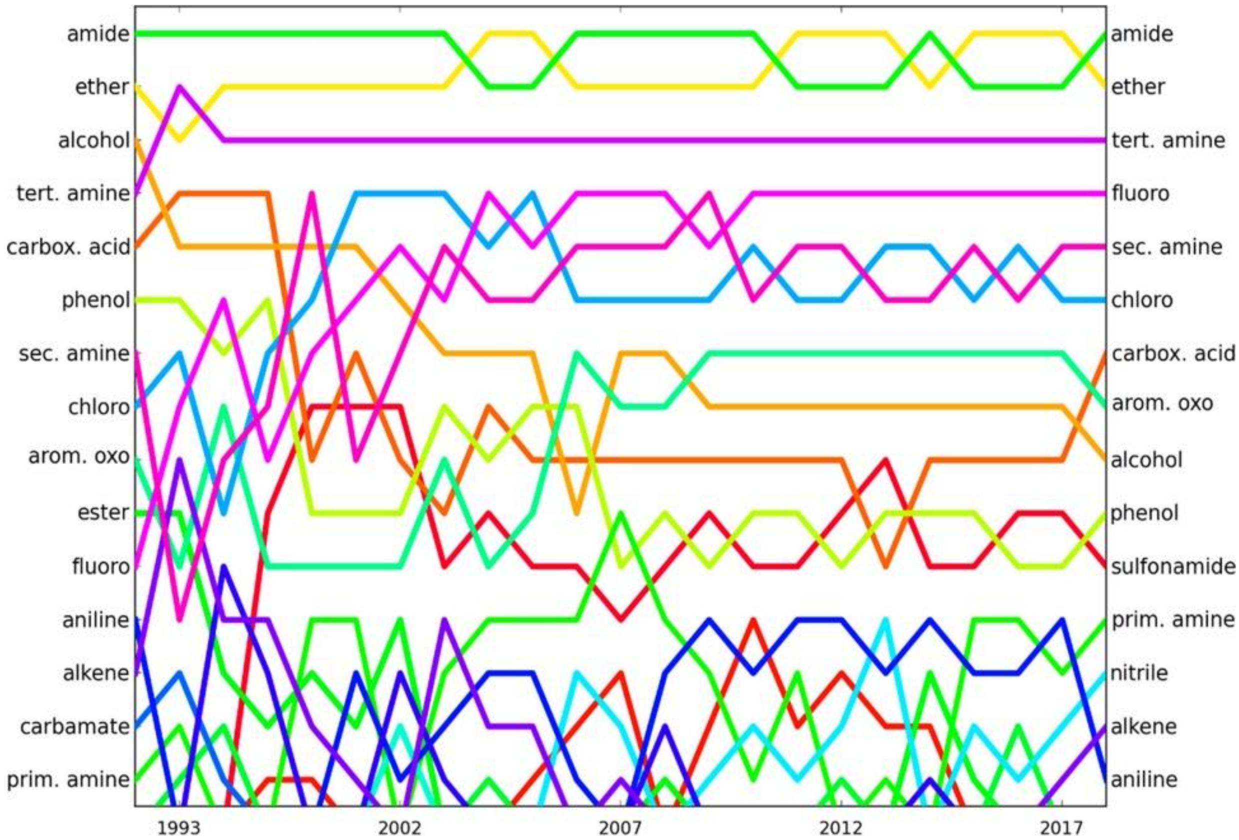


Figure 3. Evolution of the popularity ranking of functional groups over time

2. Study and Results

Our investigation draws upon a range of sources, including chemistry textbooks, peer-reviewed journal articles, and online chemistry tutoring websites, to substantiate the assertion that IUPAC's recommendations regarding amide classifications are not consistently adhered to. Our findings underscore the need for IUPAC to reconsider these recommendations in order to prevent potential confusion among students and scientists.

In a typical chemistry textbook [23], amides are classified as follows (Figure 4) [23]: “The N atom of an amide may be bonded to other hydrogen atoms or alkyl groups. Amides are classified as 1°, 2°, or 3° depending on the number of carbon atoms bonded directly to the nitrogen atom.” 1°, 2°, and 3° mean primary amide, secondary amide, and tertiary amide, respectively.

Similar classifications of amides based on the number of carbon atoms bonded directly to the nitrogen atom can be found in many chemistry textbooks from reputable publishers [24-28].

While chemistry textbooks often introduce a three-way classification for amides, indicating that the degree of substitution on the amide nitrogen determines whether it is primary (RCONH), secondary (RCONHR), or tertiary (RCONR), IUPAC's stance on amide classification varies over time, leading to potential confusion. For example, in the 1979 edition of IUPAC’s Blue Book [29], rule C 821.1 states that “Compounds containing one, two, or three acyl groups attached to nitrogen bear the generic name "amide." When only one acyl group is attached to a nitrogen atom, the generic name "primary amide" may be used; when two acyl groups are so attached, the generic name "secondary amide" may be used; and when three acyl groups are so attached, the generic name "tertiary amide" may be used.” IUPAC categorizes amides according to the count of acyl groups (with the general formula RCO), not alkyl groups. Furthermore, the footnote to rule C-824 discusses R1-CO-NHR_2 and R1-CO-NR_2R_3 and states, “These compounds have been called, respectively, secondary and tertiary amides, but this usage is not recommended.”

In 1993, IUPAC published "A Guide to IUPAC Nomenclature of Organic Compounds," [30] which served as a partial revision of the 1979 Blue Book. Notably, this 1993 publication entirely omits the amide classification previously discussed. This edition states that “Although unsubstituted monoacyl derivatives of ammonia can be called 'primary amides', classification of mono-, di-, and triacyl derivatives of ammonia as primary, secondary, and tertiary amides in analogy with amines cannot be encouraged because of the common usage of the term 'tertiary amide' to describe a disubstituted primary amide with the general structure R-CO-NR'R".”

The 2013 edition of the Blue Book revisits the definitions for amide classification provided in the 1979 edition. The only difference is that in the 1979 edition, IUPAC states that R1-CO-NHR_2 and R1-CO-NR_2R_3 should not be classified as secondary and tertiary amides; however, in the 2013 edition, it does not have that statement but rather repeats amide classifications should be done based on only number of acyl groups on the nitrogen atom. Rule P-66.1.0 states, “Compounds having one, two, or three acyl groups on a single nitrogen atom are generically included and may be designated as primary, secondary, and tertiary amides, respectively.” This edition reiterates that the number of acyl groups connected to the single nitrogen atom determines the classification of amides.

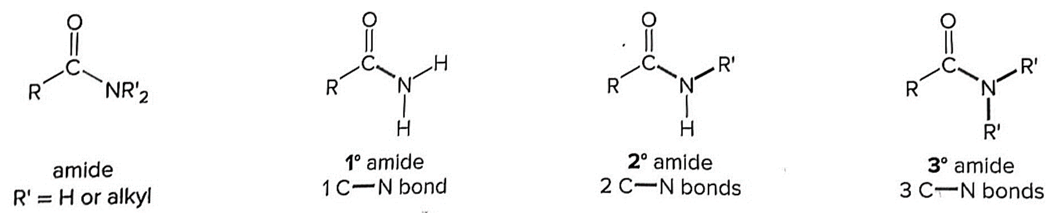


Figure 4. Classification of Amides as primary, secondary, and tertiary amides

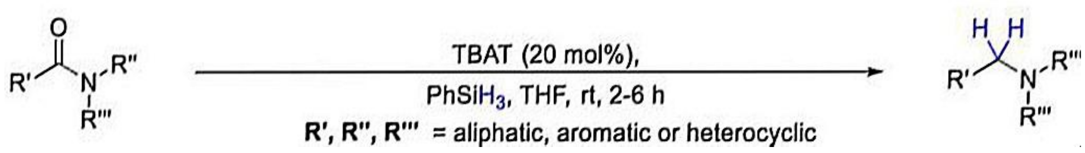


Figure 5. A tertiary amide in a reduction reaction

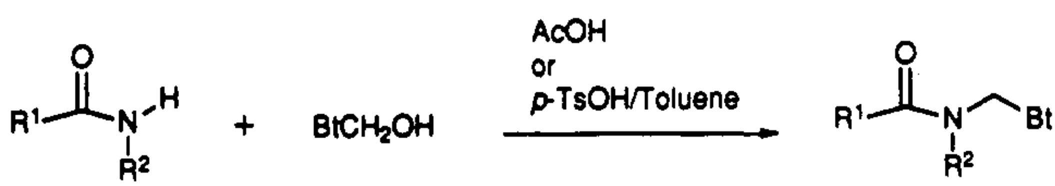


Figure 6. The conversion of secondary into tertiary amides

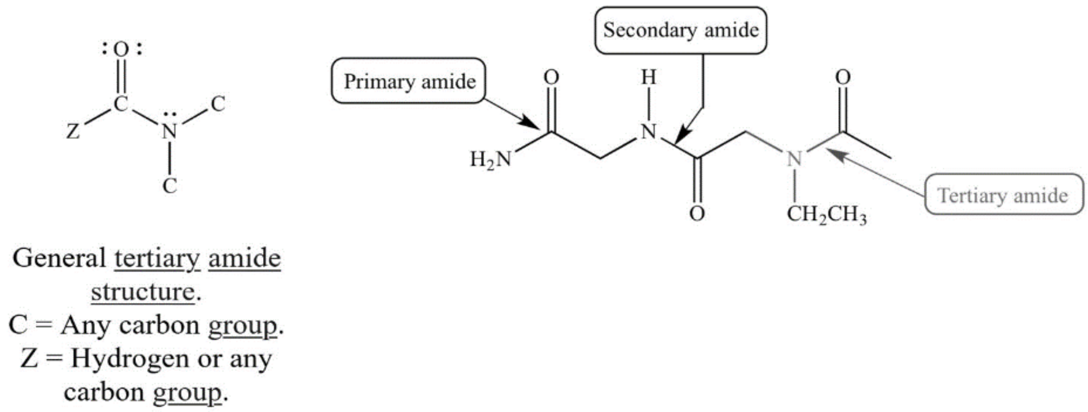


Figure 7. Amide Classification taken from UCLA Illustrated Glossary of Organic Chemistry

In 2022, IUPAC released an eBook, an updated edition based on the 2013 Blue Book [32]. Within this eBook, IUPAC omitted the classification of primary, secondary, and tertiary amides from Rule P-66.1.0. In this revised eBook edition, Rule P-66.1.0 now specifies, “Compounds having one, two, or three acyl groups on a single nitrogen atom are generically included.”

As observed, IUPAC's position on amide classification has fluctuated over time and lacks consistency. However, the scientific community has consistently classified amides based on the number of carbon bonds attached to the nitrogen atom. This consensus is evident not only in textbooks but also in peer-reviewed journal articles.

In a recent peer-reviewed article [33], it was reported that Tetrabutylammonium triphenyldifluorosilicate (TBAT) catalyzed the deoxygenative reduction of tertiary amides to amines. In the reaction scheme published in the article (Figure 5) the amide was classified as a tertiary amide, based on the number of atoms connected to the nitrogen, which does not follow IUPAC recommendations.

In another study [34], the conversion of secondary into tertiary amides using benzotriazole was examined. In the reaction scheme published in the article (Figure 6), the amides were classified as primary and tertiary amides, which does not follow IUPAC recommendations.

Comparable classifications of amides as secondary and tertiary amides, which diverge from IUPAC's recommended classification, are frequently found in numerous peer-reviewed journal articles [35-41].

In addition to chemistry textbooks and a substantial corpus of peer-reviewed journal articles published in esteemed academic journals, it is noteworthy that university chemistry tutorial websites and online chemistry tutorial platforms also demonstrate a departure from IUPAC's rules concerning amide classifications. The University of California Los Angeles's Illustrated Glossary of Organic Chemistry website defines secondary amide as an amide in which the nitrogen atom is directly bonded to two carbon atoms, including the carbonyl group carbon and one additional carbon. Similarly, tertiary amide is defined as an amide in which the nitrogen atom is directly bonded to three carbon atoms, including the carbonyl group carbon and two additional carbon groups, as illustrated in Figure 7 [42].

Comparable amide classifications are evident on various university chemistry tutorial websites [43-44]. Notably, Khan Academy, a prominent online educational platform, also classifies amides differently from IUPAC's guidelines [45], aligning instead with the conventions found in textbooks, peer-reviewed journal articles, and university chemistry tutorial resources. This consistent departure from IUPAC's recommendations is similarly observed on numerous other online tutorial chemistry websites [46-49], underscoring their alignment with the classification schemes of amides prevalent in textbooks, peer-reviewed journal articles, and university chemistry tutorial resources.

3. Discussion

Organic chemistry connects the chemical structures of everyday substances with their practical properties. This knowledge is essential for distinguishing between plastics, understanding food additives, and linking drug names to active ingredients. Unlike other sciences that use widely understandable language, chemistry relies on complex symbols and formulas. Therefore, organic chemistry nomenclature is crucial in translating these symbols, making it a vital skill for students at all levels, although it is often a challenge. The amide functional group holds immense significance in the field of molecular sciences. It serves as the foundational linkage in the structural framework of peptides, proteins, and various biomolecules. In the realm of medicine, amide-forming reactions represent a cornerstone of the pharmaceutical industry. Over the past century, our understanding of the properties of the amide functional group has evolved, further underlining its crucial role in drug design and development.

IUPAC is globally recognized as the primary authority in chemical nomenclature and terminology. Nevertheless, its classification of amides has displayed inconsistency over time and lacks recognition and adherence within the scientific community. Over the years, IUPAC's approach to amide classification has displayed inconsistency, as observed across various editions of their guidelines. In the 1979 Blue Book edition, IUPAC introduced a classification system that labeled compounds with one, two, or three acyl groups attached to nitrogen as "amide," "primary amide," "secondary amide," and "tertiary amide," respectively. However, this approach underwent revision in the 1993 edition, where amide classification was entirely omitted, and the use of terms such as primary, secondary, and tertiary amides for mono-, di-, and triacyl derivatives of ammonia was discouraged. The 2013 edition reinstated the 1979 classification system, and in 2022, a newly updated eBook edition of the guidelines removed the specific classification of primary, secondary, and tertiary amides altogether. IUPAC recommends against classifying amides based on the number of carbon atoms or alkyl groups connected to the nitrogen atom. Nonetheless, our investigation, drawing evidence from textbooks, peer-reviewed articles, and online chemistry sources, indicates that amides continue to be consistently classified as primary, secondary, and tertiary amides, based on the number of carbon atoms connected to the nitrogen in the amide functional groups, in contrast to IUPAC's recommendations.

In light of the extensive examination of amide classification rules presented in this study, supported by substantial evidence from various sources including chemistry textbooks, peer-reviewed journal articles, and online resources, a resounding consensus within the scientific community emerges. This consensus consistently disregards IUPAC's fluctuating amide classification recommendations over time, firmly advocating for the classification of amides based on the number of carbon atoms bonded to the nitrogen atom. The compelling body of evidence presented here underscores the case for IUPAC to reevaluate and overhaul its existing amide classification guidelines. Given the robust and unequivocal nature of this evidence, we strongly recommend that IUPAC consider aligning its amide classification recommendations with the well-established and widely accepted practice of classifying amides based on the number of carbon atoms attached to the nitrogen atom, rather than the number of acyl groups connected to the nitrogen. IUPAC can easily implement this update in the latest ebook version of the Blue Book for current and future editions. Such alignment would not only alleviate potential confusion among students, researchers, and professionals but also enhance the practical relevance of IUPAC's nomenclature guidelines, ensuring their continued resonance with the conventions observed by the broader scientific community. This harmonious approach will pave the way for a more streamlined and universally accepted amide classification system.

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