Chapter

Introductory Chapter: Azoles, Their Importance, and Applications

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1. Introduction

Heterocyclic compounds constitute an important and very broad class of organic molecules that are found to play a vital role in our daily life. The presence of the various heterocyclic frameworks in natural products and their widespread applications in the areas of material science, medicinal chemistry, agrochemicals, etc. emphasizes their extraordinary significance in diverse fields. Among the heterocyclic frameworks, structurally diverse azoles have been found to play an extremely significant role. Azoles represent a broad, very interesting, and perspective class of five-membered heterocyclic aromatic compounds whose framework contains from one and up to five nitrogen atom(s) and can also contain at least one S or O atom as a part of the azole conjugated ring (N,S and N,O subclasses of azoles, respectively) [1]. The parent azole compounds, as exemplified by imidazole, pyrazole, 1,2,3-triazole, tetrazole, and pentazole, are aromatic structures with two double bonds (**Figure 1**).

There have been synthesized various successively reduced analogs, such as azolines and azolidines, with just one double bond. Only one lone pair of electrons from each heteroatom in the azole ring participates in the aromatic bonding. The numbering of ring atoms in azoles starts with the heteroatom that does not participate in the double bond and proceeds toward the other heteroatom (**Figure 1**). Since the beginning of their studies and applications, major advances in the chemistry of pyrazoles, imidazoles, triazoles, tetrazoles, and their fused heterocyclic derivatives have been performed [2–6]. These azoles are also widely found as core structures in a large variety of natural and artificially synthesized compounds possessing important agrochemical and pharmaceutical properties [7–11]. The well-known ability of these heterocyclic cores to serve both as biomimetics and reactive pharmacophores encourages their applications in numerous drugs [12–17].

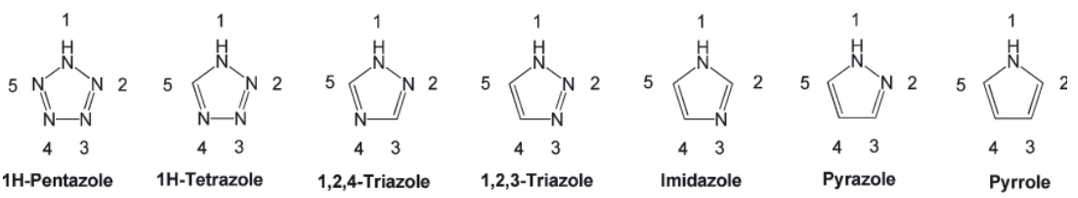

Figure 1.
Structural formulae of unsubstituted neutral azoles (only includes nitrogen). Reprinted (adapted) with permission from ref. [2]. Copyright (2011) American Chemical Society.

2. Coordination Chemistry of Azoles

Also, among other applications, which will be briefly touched in this chapter, azoles are known to play a significant role in coordination chemistry [18–22]. Thus, 1,2,3-triazoles (cf. **Figure 1**) have been known since the end of the 19th century, when 2-phenylbenzotriazole 1-oxide was described [23]. As early as 1937, the binding ability of the triazole ring was studied [24], although the first crystallographically characterized coordination compound was reported only in 1976 [25]. The isomeric to 1,2,3-triazoles 1,2,4-triazole ring was first mentioned in the end of the 19th century, in 1885 [18, 26]. Its ability to bind metal ions was established a few decades later [27] and the first crystal structure of one of the adducts was published already in 1962 [28]. In 1886, the term *tetrazole* was proposed for a five-membered heteroarene with four nitrogens [18], and in first decade of the 20th century, 1910, the potential binding of this heterocycle to metal ions was reported [18]. The first tetrazole complex characterized by X-ray diffraction study was reported in 1971 by Mason [10]. It should be noticed that although the chemistry of these three principal azoles has been studied for more than a century, their coordination behavior earlier was not the subject of extensive investigation [18, 27, 29]: structural reports of triazole- and tetrazole-based coordination compounds became increasingly common in the research literature only since the early 1980s [30]. The excellent 2011 review by Aromi et al. [18] clearly demonstrated the high versatility and suitability of the 1,2,3-triazole, 1,2,4-triazole, and tetrazole rings for the design and construction of outstanding coordination materials with attractive physicochemical properties. The straightforward preparation of such azole-containing ligands together with their synthetic flexibility allowed the syntheses of numerous outstanding systems such as coordination polymers and MOFs (metalloorganic frameworks), metal complexes, and coordination compounds with spin-crossover properties. It should be emphasized that these areas indeed represent current hot topics of investigation. Moreover, these N-donor ligands have found applications in many other fields of applied coordination chemistry, such as biological chemistry, nanomaterials, anion recognition, and nonlinear optics [18].

3. Azoles in Polymers

It is also of high interest to mention recent progress in azine- and azole-type N-heteroaromatic compounds for applications in structural engineering of high-mobility polymeric semiconductors [31]. The most fast developing area of polymeric semiconductors is production of novel semiconductors by employing the highly tunable donor–acceptor structural motifs. This approach revolutionized the whole strategy of the semiconducting polymers design. Furthermore, the appeal of replacing benzene or thiophene moieties with various sp^2-hybridized N-heteroaromatics, such as azine or azole heterocycles, directed design efforts toward developing materials with n-type or ambipolar charge transport behaviors. The nitrogen atoms introduced in polymer molecules allow to adjust molecular orbital energies, enhancing electron injection by lowering frontier molecular orbital energy levels. Moreover, they allow to reduce the steric effects which, in turn, results in maximizing electronic coupling. In this work an overview of recent progress in syntheses and characterization of azine- or azole-type N-heteroaromatics to be used in structural engineering of high-mobility polymeric semiconductors was given [31]. Various synthetic routes for creating these N-heteroaromatic building blocks and corresponding polymers were reviewed. These routes may inspire new developments in molecular engineering. Also, important structural features were

discussed including the new semiconductor polymer electronic structures and conformational preferences. This review also discussed the correlations between the molecular structures of these N-heteroaromatic compounds and the device performances. To summarize, the semiconducting polymers containing N-heteroaromatic rings should be considered as primary candidates for functional design of compounds for specific applications in modern organic electronics.

Moreover, recently the latest achievements and problems associated with self-healing and shape memory metallopolymers (MP) such as metal complexes based on the polymers containing azole donor fragments among others (phenol, carboxylic acid, pyridine, histidine, and urethane) were reviewed [32]. Particular attention was paid to the principles of action of the shape memory MPs. MPs are in general of considerable interest due to their applications as functional materials for sensors, soft electronic devices, transistors, conductors, nanogenerators, bone tissue engineering, etc.

4. Azoles as Energetic Compounds

Of course, of a very high interest are applications of azoles and their derivatives as energetic compounds: thus, various azole-based energetic salts – tetrazole-based, triazole-based, imidazole and pyrazole-based – were reviewed by Gao and Shreeve in 2011 [2], and recently current synthesis and properties of energetic pentazolate and its derivatives were reviewed by Wozniak and Piercey [33]. The pentazolate, or cyclo-N_5^-, received increased attention in last two decades. Being the compound without carbons and hydrogens, the pentazolate anion is well known to release large amounts of energy upon decomposition simultaneously liberating environmentally friendly N_2 gas. Due to these extremely appealing qualities, the pentazolate anion and derivatives are essential in the development of novel high-energy-density materials. The review by Wozniak and Piercey considered the following aspects: (i) historical significance of cyclo-N_5^-; (ii) its precursors; (iii) synthesis routes of obtaining cyclo-N_5^- with a focus on arylpentazole precursors; (iv) factors affecting the stability of cyclo-N_5^-; (v) energetic performances of currently used energetic cyclo-N_5^--containing compounds; and (vi) future possible experimental research.

5. Azoles in Ionic Liquids

Furthermore, it is worthwhile to mention the review by Easton et al. [34] where azolate anions in ionic liquids (IL) were considered. Owing to their ease of synthesis, diffuse positive charge, and chemical stability, 1-alkyl-3-methylimidazolium cations are one of the most routinely utilized and historically important components in ionic liquid chemistry. However, the versatile chemistry of azoles to allow their use as an anionic component in ILs, as azolates, was investigated relatively scarcely. Azolate anions possess numerous desired properties for IL formation, such as diffuse ionic charge, tailorable asymmetry, and synthetic flexibility, with the added advantages of not relying on halogen atoms for electron withdrawing effects. The review explored the 122 known so far azolate-containing ionic liquids which were prepared from only 39 disparate azolate anions, with a goal to highlight not only their well pronounced utility as IL components, but also the ways in which their advantageous properties may be used by the broader scientific community for design of new tailored materials. In this context, it is also worthwhile to mention another work by Easton et al. [35] where a non-stoichiometric approach to control the solid-state behavior of protic ionic liquids (PILs) was demonstrated by direct

mixing of 4,5-dicyanoimidazole (HDCNim) with either 1-ethylimidazole (C2im) or 1-butylimidazole (C4im) in different mole fractions.

6. Azoles as Corrosion Inhibitors

Also, azoles and their derivatives find numerous applications as organic corrosion inhibitors as was reviewed by Xhanari and Finšgar [36] and Fateh et al. [37]. In the first review, the authors summarized the research performed during the last two decades regarding the use of very important organic corrosion inhibitors for Al and its alloys in alkaline (mainly NaOH and KOH) and chloride solutions. The focus of this review was on the type of corrosion inhibitors and on their inhibition effectiveness and mechanism. The most frequently used corrosion inhibitors were shown to be the mercapto compounds, azole derivatives, organic dyes, and different polymers. Weight loss and electrochemical techniques were among the most frequently used techniques for evaluation of the corrosion inhibition effectiveness of the studied compounds. The second review covered corrosion of Cu and its alloys in corrosive environments along with their corrosion inhibitors. The main corrosion inhibitor groups for copper were introduced and a review of adsorption models was provided. The most widely used corrosion inhibitors for protection of copper in salt and weak acidic environments were shown to be organic compounds from azole family, such as triazole, benzotriazole, and thiazole, and for strong acidic media imidazol and tetrazole were demonstrated to perform the best. Also, it is worthwhile to mention the 2008 work by Kuznetsov and Kazansky [6].

7. Azoles in Chemosensors

Next, it is interesting to mention the recent developments in 1,2,3-triazole-based chemosensors as very recently reviewed by Ahmed and Xiong [38]. This review summarized the latest developments in the field of chemosensors based on click-generated triazoles which were used for detection of a range of metal cations, anions, and neutral analytes. The detection of metal ions became a significant and perspective field of research due to their medicinal, biological, and environmental impacts. This resulted in significant increase in the number of articles published on this subject, which reported more reliable and sophisticated triazole-based chemosensors for a variety of analytes. The review considered the development of chemosensors reported between 2012 and 2020 due to their advantages over other chemosensors, including such criteria as ease of recognition, simple instrumentation, along with high selectivity and high sensitivity.

8. Conclusions and Perspectives

Various oxygen-containing azoles, as exemplified by oxadiazoles, oxazoles, and isoxazoles, have been also thoroughly studied for their diversified biological activities. Widely used as potent antifungal agents (fungicides) due to their valuable properties like broad spectrum of action, chemical stability, and oral bioavailability [39–42], various azole derivatives have also demonstrated many other promising biological properties including antidiabetic, immunosuppressant, antiinflammatory, antiviral, antitubercular, and anticancer activities [8, 12, 42–46].

As can be seen, azoles have always been considered as an extremely suitable scaffold for the design of various novel therapeutic agents and other extremely

versatile and useful compounds with potential applications in various areas such as materials, energetics, catalysis, etc. The intensive research work in the area of azoles, covering synthesis, characterization, and computational studies of their various novel derivatives is continuously ongoing [44, 47–52]. Thus, the area of azoles and their derivatives, their physico-chemical properties, and applications is of continuous high interest, and therefore this book will be a valuable addition to the knowledge which has been accumulated so far in this field.

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