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Spectroscopic study of 2-, 4- and 5-substituents on pK_a values of imidazole heterocycles prone to intramolecular proton-electrons transfer

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ABSTRACT

New 2-(1H-imidazol-2-yl)phenols (**L1Et**–**L8*t*BuPt**) bearing a phenolic proton in the vicinity of the imidazole base were prepared and characterized. Experimental studies of the dependence of their protonation/deprotonation equilibrium on substituent identities and intramolecular hydrogen bonding tendencies were carried out using electronic absorption spectroscopy at varying pH values. In order to make comparison, 2-(anthracen-10-yl)-4,5-diphenyl-1H-imidazole (**L9Anthr**) bearing no phenolic proton and 4,5-diphenyl-2-(4,5-diphenyl-1H-imidazol-2-yl)-1H-imidazole (**L10BisIm**) bearing two symmetrical imidazole base fragments were also prepared and experimentally investigated. DFT calculations were carried out to study frontier orbitals of the investigated molecules. While electron-releasing substituents produced increase in protonation–deprotonation pK_as for the hydroxyl group, values for the imidazole base were mainly affected by polarization of the imidazole ring aromaticity across the 2-imidazole carbon and the 4,5-imidazole carbons axis of the imidazole ring. It was concluded that electron-releasing substituents on the phenol ring and/or electron-withdrawing substituents on 4,5-imidazole carbons negatively affects donor strengths/coordination chemistries of 2-(1H-imidazol-2-yl)phenols, and vice versa. Change of substituents on the phenol ring significantly altered the donor strength of the imidazole base. The understanding of pK_a variation on account of electronic effects of substituents in this work should aid the understanding of biochemical properties and substituent environments of imidazole-containing biomacromolecules.

1. Introduction

For the past many decades, interest in the understanding of factors controlling the mechanisms of reactions of biological and medicinal interests has been sustained [1–5]. Coupled proton-electron transfer is a subject of significant current interest [6–9] and physicochemical data such as ionization constant values (often derived as pK_as) are routinely employed in characterizing biomolecules such as metalloenzymes, amino acids, etc. The pK_a of a drug is one of the most important parameters employed to explain its physicochemical behaviour and acid-base properties, and to study pharmaceutical pre-formulations [10]. Changes in pK_a values in biological macromolecules are often investigated to establish modes of interactions between an acid or base fragment and its neighbouring functional groups [11]. However, in the presence of supramolecular folding that exists in biological macromolecules, investigation of behaviours of pH sensitive functions is hindered. Small, well-characterized, organic molecules provide access to understanding of phenomena observed in the macrostructures. Spectroscopic determination of ionization constant of weak acids or bases is of widespread application and considered suitable even at extremes of pH, poor solute solubilities and for species prone to conformational photo-tautomerism [11–13]. Aqueous–organic mixtures are often employed for various pH buffers in ionization constant determinations [10].

Moieties such as adenine, guanine, histidine, etc., contain imidazole functions and are involved in intramolecular and intermolecular chemistries of biological macromolecules under pH specific conditions [14–18]. Imidazole base of histidine is recognized to be an interesting ligand in the bioinorganic chemistry of most heamoptoteins of which investigation of basicity and steric effects gives understanding of the role of the leaving group in controlling mechanisms [9,19]. In previous studies on histidine, it is believed that pK_a values assigned to the imidazole ring (p$K_a \approx 6$) is distinguishable from values ascribed to carboxy (p$K_a \approx 2$) or amino (p$K_a \approx 9$) functionalities [1,2,11]. However, pK_a values of some

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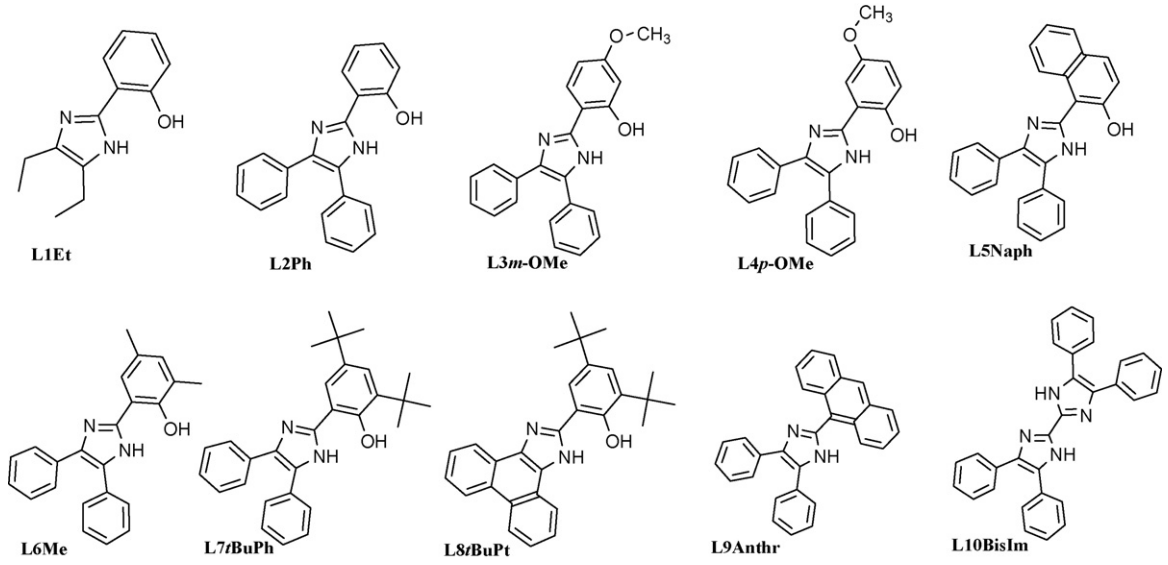


Scheme 1. Molecular frameworks investigated in this work.

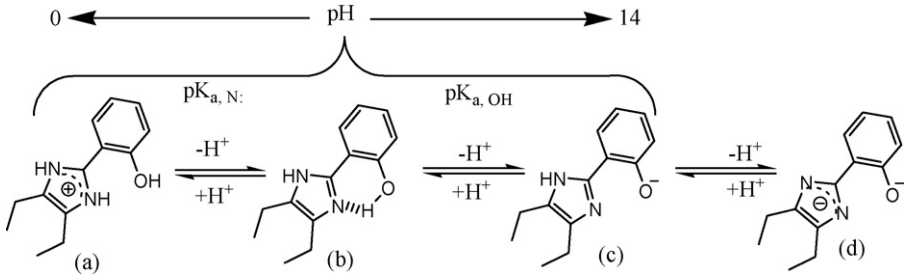
imidazole bases have been reported to be inaccessible within the pH scale range [20]. On account of protonation–deprotonation reactions, spectroscopic behaviour of imidazole base chromophores have attracted considerable attention towards potential pH sensory and fluorescence switching applications [21–29]. Proper understanding of donor–acceptor properties of imidazole bases in the presence of different neighbouring functionalities is still lacking. As discussed in our previous report on ^{1}H NMR comparison [30], protonation and deprotonation schemes have been concluded for an oxazole system which the authors wrongly thought to be an imidazole ligand [29]. Progress has been made in the understanding Excited State Intramolecular Proton-electron Transfer (ESIPT) phenomenon of 2-(imidazol-2-yl)phenols [31–35]. However, such studies have been largely restricted to 2-(1H-benzo[*d*]imidazol-2-yl)phenols with scarce knowledge of substituent and solute media effects. In preceding experiments recently published on a series of ligands and their corresponding zinc complexes involving some of the compound in the present studies, the role of substituents and solvents media in preventing ESIPT was presented and changing solvent polarities from tetrahydrofuran (THF, dielectric constant ≈7) to dimethylformamide (DMF, dielectric constant ≈38) yielded little or no change on absorption peak positions (i.e. 0–2 nm shifts). However, observed shifts in photoluminescence maxima (spread over 1–57 nm) for the reported imidazole-phenol ligands as a result solvent variation (from THF to DMF) indicated that significant change in polarities for polar solvents produced significant modification of excited state electronic characteristics while having insignificant effects on the ground state electronic structures [36]. Calculational reports also largely restricted to 2-(1H-benzo[*d*]imidazol-2-yl)phenols are known [37,38]. The B3LYP/6–311 + G* basis set has been successfully employed as a reliable method in DFT calculations of imidazole organic systems [39]. Investigation of the consequence of intramolecular proton–base interactions on physicochemical parameter such as ionization constants of the proton donor as well as the acceptor is unknown.

Owing to importance of imidazole bases, attention has been drawn to investigation of small molecules containing imidazole nucleus, and such studies are yet few. Moreover, works involving a series of imidazole bases with differing substituent environment is also scarce. Particularly, studies of substituent environments on ionization constants of imidazoles prone to intramolecular proton–electron transfer have not been reported. Herein, we present our results on syntheses and spectroscopic investigation of ionization constants for a series of 2-aryl-1H-imidazoles. Two imidazole molecules that lack intramolecular proton–electron transfer capacities have been included for comparison. Calculated properties based on optimized geometries of the molecules as well as experimental ^{1}H NMR and FTIR data of active protons were discussed in attempt to rationalize observed variations in ionization constants (Scheme 1).

2. Experimental

2.1. General considerations

All manipulations of oxidation-prone reactions were performed under nitrogen atmosphere using standard Schlenk techniques. All starting materials were obtained commercially as reagent grades and used without further purification. **L1Et**, **L2Ph**, **L3*m*-**



Scheme 2. Possible protonation states for base and active proton components. (a), (b) and (c) were observed within pH 0–14.