Chemical Reactivity of the Imidazole: A Semblance of Pyridine and Pyrrole?

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ABSTRACT
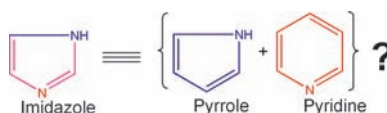
It has been suggested that pyridine and pyrrole could be patterns for imidazole reactivity studies due to the amine (—NH—) and aza (—N=) nitrogen atoms. The analyses of the local and global electronic indexes prove and quantify that imidazole has an intermediate analogy between pyrrole and pyridine.

Addition and substitution reactions of imidazole (**iz**) and its derivatives continue to attract considerable attention as they play an important role in the preparation of biologically active compounds and new materials.[1] Patterns of **iz** reactivity for Lewis and Brönsted reagent attacks are obtained from pyridine (**py**) and pyrrole (**pi**) due to the presence of aza (—N=) and amine (—NH—) nitrogen atoms in the rings.[1a] The sample is followed in the acid−base reactions, where **iz** behaves amphoterically like a combination of **py** and **pi** (Scheme 1).

Although **iz** and **pi** are π-excessive heterocycles (π donors), **iz**'s do not give rise to η^5 (π)-complexes with transition metals or their salts as **pi** does; **iz** behaves as a π-deficient ligand (π-acceptor) like **py**, and its aza nitrogen atoms form mainly $\eta^1(\sigma, N_{py})$-complexes as **py** does (Scheme 2).[2]

Electrophilic reagents attack **iz** and **pi** at the C-2 carbon atom principally, while **py** is attacked preferably at the N-1 nitrogen atom as **iz** and its C-3 and C-5 carbon atoms. Nucleophilic reagents prefer C-2, C-4, and C-6 carbon atoms of **py** (Scheme 3).[1a,3]

Therefore, even though the reactivity of the **iz** seems to be qualitatively comparable with the reactivity of **py** and/ or **pi**, two fundamental questions appear: how analogous are the aza (pyridine-like) and amine (pyrrole-like) nitrogen atoms in **iz**, **pi**, and **py** and how equivalent is the **iz** with the **pi** and **py** rings.

The answers to these questions should involve global and local analysis. In this case, the global reactivity indexes are the electronegativity χ and the chemical hardness η, and the principle is the global hard/soft acids/bases principle (HSAB) of Pearson; "hard acids/basis prefer to bind with hard bases/acids, $\eta_A \approx \eta_B$".[4] The local reactivity indexes are the local softness, $s_A(\mathbf{r})$, $s_B(\mathbf{r})$, ... and the principle is the local HSAB principle of Méndez and Gázquez;

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(1) (a) Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K. *Comprehensive Heterocyclic Chemistry III; Five-membered Rings with Two Heteroatoms, Each with Their Fused Carbocyclic Derivatives*, Vol. 4; Joule, J., Ed.; Elsevier: Oxford: U.K., 2008. (b) Dupont, J.; de Souza, R.; Suarez, P. *Chem. Rev.* **2002**, *102*, 3667. (c) Higasio, Y. S.; Shoji, T. *Appl. Catal., A* **2001**, *221*, 197.

(2) Dubois, M. R. *Coord. Chem. Rev.* **1998**, *174*, 191.
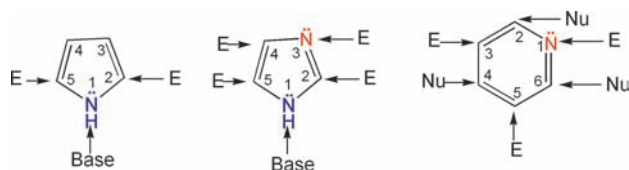
(3) In general, **pi** is not susceptible to nucleophilic attack and the position C-2 of **iz** is usually electrophilic. See ref 1a and Guadarrama-Morales, O.; Méndez, F.; Miranda, L. D. *Tetrahedron Lett.* **2007**, *48*, 4515.

Scheme 1

Scheme 2

$\eta^5\pi$-complex $\quad\quad$ $\eta^1(\sigma,N_{Py})$-complexes
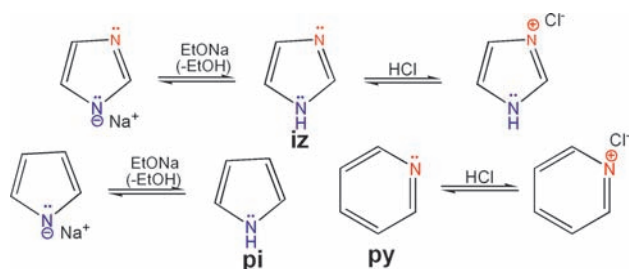
Scheme 3

"the interaction between two molecules will occur through their atoms of nearly equal softness, $s_A(\mathbf{r}) \approx s_B(\mathbf{r})$".[5] Both principles were proved by minimization of the grand canonical potential[4c,5a] and have been widely used for the prediction and understanding of the reactivity for several systems.[6]

Analyses of the global reactivity indexes derived from calculations at the B3LYP/6-311+G(2d,2p) level of theory

Scheme 4

$\Delta\eta = 0.3$ eV, $\quad$ ΔNICS(0) = -0.69 ppm, ΔNICS(1) = -0.36 ppm

$\Delta E = -7.71$ kcal mol^{-1}, $\quad$ $\Delta H° = -7.51$ kcal mol^{-1}, $\quad$ $\Delta G° = -7.41$ kcal mol^{-1}

using Gaussian03[7] show that **iz** exhibits intermediate electronegativity and hardness values between **pi** and **py**; χ**py** (4.34 eV) > χ**iz** (4.05 eV) > χ**pi**(3.66 eV) and η**py** (5.37 eV) > η**iz** (4.94 eV) > η**pi**(4.62 eV). According to the global HSAB principle, soft species would attack the **pi** ring, hard species would attack the **iz** ring, and harder species would attack the **py** ring, in agreement with the experimental evidence.[1a] The cooperative effect of the aza and amine nitrogen atoms in the **iz** can be explained if we consider the **iz** formation by the exchange reaction of one carbon atom in the **pi** ring for one aza nitrogen atom of **py** (Scheme 4). According to the maximum hardness principle (MHP),[8] the reaction is permitted because the change of reagents to products is accompanied with an increase of the hardness from reagents to products ($\Delta\eta = 0.3$ eV). Calculation of the thermodynamic parameters verifies that the exchange reaction is spontaneous ($\Delta G° = -7.41$ kcal mol^{-1}) and exothermic ($\Delta H° = -7.51$ kcal mol^{-1}). The increase in hardness takes place with an increase in the aromaticity (ΔNICS(0) = -0.69 ppm and ΔNICS(1) = -0.36 ppm)[9] from reagents to products.

In addition, the calculated dipole momentum values follow the trend μ**iz** (3.88 D) > μ**py** (2.30 D) > μ**pi**(1.07 D); the values indicate low polarity for the amino-type nitrogen atom in the **pi** ring and higher polarity for the aza-type nitrogen atom in the **py** ring; the polarity is increased in the **iz** ring by the coexistence of both nitrogen atoms in the five member ring.[10]

The local softness $s_A(\mathbf{r})$ is obtained from the local fukui function[11] $f_A(\mathbf{r})$ and the global softnes S_A (inverse of η_A): $s_A(\mathbf{r}) = S_A f_A(\mathbf{r})$. Figure 1 gives us the $f_A(\mathbf{r})$ hypersurface diagrams for electrophilic $f^-_A(\mathbf{r})$ and nucleophilic $f^+_A(\mathbf{r})$ attacks and provides us maps of the reactive sites of each ring under soft species interactions.[12] It can be observed that the higher value for electrophilic attack in **py** is located

(4) (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (b) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512. (c) Chattaraj, P. K.; Lee, H.; Parr, R. G. *J. Am. Chem. Soc.* **1991**, *113*, 1855. (d) Parr, R. G.: Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford: New York, 1989.

(5) (a) Gázquez, J. L.; Méndez, F. *J. Phys. Chem.* **1994**, *98*, 4591. (b) Méndez, F.; Gázquez, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9298. (c) Ayers, P. W; Parr, R. G. *J. Am. Chem. Soc.* **2000**, *122*, 2010. (d) Chattaraj, P. K *J. Phys. Chem.* **2001**, *105*, 511.

(6) (a) Mendez, F.; Galván, M.; Garritz, A.; Vela, A.; Gázquez, J. L. *THEOCHEM* **1992**, *211*, 81. (b) Popa, M. V. *Rev. Mex. Fis.* **2007**, *53*, 241. (c) Gregus, Z.; Roos, G.; Geerlings, P.; Nemeti, B. *Toxicol. Sci.* **2009**, *110*, 282. (d) Ramírez, R.; García-Martínez, C.; Méndez, F. *J. Phys. Chem. A* **2009**, *113*, 10753. (e) Pal, S.; Chandrakumar, K. R. S. *J. Am. Chem. Soc.* **2000**, *122*, 4145. (f) Geerlings, P.; De Proft, F.; Langenaeker, W. *Chem. Rev.* **2003**, *103*, 1793.

(7) Frisch, M. J. et al. Gaussian 03, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004. Full reference for Gaussian 03 program is provided in the Supporting Information.

(8) Pearson, R. G. *J. Chem. Educ.* **1987**, *64*, 571. (b) Zhou, Z.; Parr, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 1371. (c) Parr, R. G.; Chattaraj, P. K. *J. Am. Chem. Soc.* **1991**, *112*, 5720. (d) Pearson, R. G. *Chemical Hardness*; Wiley-VCH: Weinheim, Germany, 1997. (e) Gázquez, J. L.; Martínez, A.; Méndez, F. *J. Phys. Chem.* **1993**, *97*, 4059.

(9) The **iz**, **pi**, **py**, and benzene NICS values were taken from Chen, Z.; Wannere, Ch. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P.; von, R. *Chem. Rev.* **2005**, *105*, 3842.

(10) The **iz** ring has very high solubility in water and is less soluble in nonpolar solvents.

(11) Parr, R. G.; Yang, W. *J. Am. Chem. Soc.* **1984**, *106*, 4049.

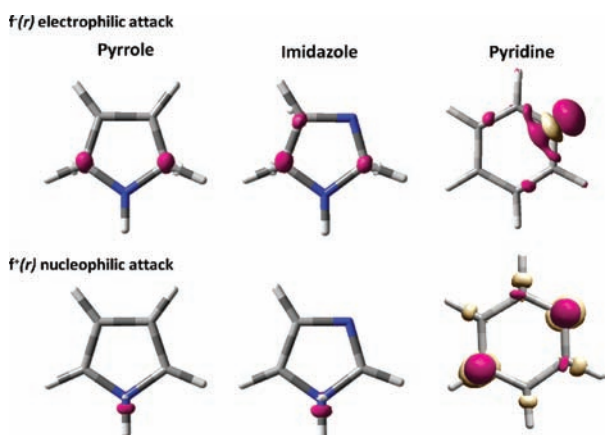(12) Red colors correspond to positive values.

Figure 1

in the N-1 nitrogen and C-3 and C-5 carbon atoms and that for nucleophilic attack in the C-2, C-4 and C-6 carbon atoms and N-1 nitrogen atom. These results suggest an unprecedented nucleophilic attack at the pyridine nitrogen atom that was obtained experimentally eight years ago by Gibson et al.[13] From Figure 1, we can observe the topological similitude between **iz** and **pi**, and the higher values for an electrophilic attack are located in the carbon atoms of the rings. The nitrogen atoms have no contribution for the soft electrophilic attack! According to the local HSAB principle, the soft carbon atoms of **iz** will be more reactive with soft species. The trick is that the carbon atoms of **iz** cannot react since they are bonded to hydrogen atoms, the N-3 nitrogen atom being the unique unoccupied site in the **iz** able to perform the σ interaction. Our theoretical result was confirmed three years ago by the experimental study of Ruiz and Perandones.[14] They obtained crystal structures of compounds where the hard Mn^{2+} cation ($\eta = 9.02\,eV$)[5d] was bonded to the hard N-3 nitrogen atom of **iz** and the soft Au^+ cation ($\eta = 5.6\,eV$)[5d] was bonded to the soft C-2 atom of **iz**. It is interesting to observe that the higher values for a nucleophilic attack are located in the region of the N−H bond for **iz** and **pi** (Figure 1).[3]

We calculate the local softness, condensed to the individual nitrogen atoms in the molecules **iz**, **pi**, and **py** using the condensed fukui function[15] $s^-_N = Sf^-_N$. For electrophilic attack, the condensed softness follows the trend $s^-_{N-1(py)}$ ($0.033\,eV^{-1}$) $> s^-_{N-3(iz)}$ ($0.016\,eV^{-1}$) $> s^-_{N-1(iz)}$ ($0.008\,eV^{-1}$) $> s^-_{N-1(pi)}$ ($0.000\,eV^{-1}$). Therefore, **py** has a softer N-1 nitrogen atom than **iz**, while **pi** has a harder N-1 atom than **iz**.
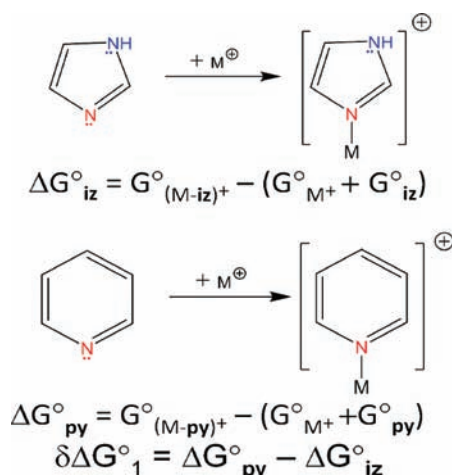
In order to assess the condensed softness trend and to understand the preferred interactions of each nitrogen atom in the rings with hard/soft electrophiles, we studied the coordination reactions between the Li^+, Na^+, and K^+

(13) Clentsmith, G. K. B; Gibson, V. C.; Hitchcock, P. B.; Kimberly, B. S; Rees, C. W. *Chem. Commun.* **2002**, 1498.
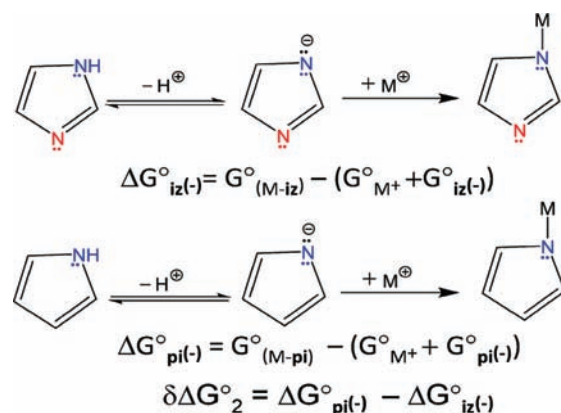
(14) Ruiz, J.; Perandones, B. F. *J. Am. Chem. Soc.* **2007**, *129*, 9298.

(15) The s^-_k and f^-_k values were calculated using the Mulliken population analysis and a finite-difference approximation (Tables S7−S9 in the Supporting Information). For definition of condensed Fukui functions, see: Yang, W.; Mortier, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 5708.

Scheme 5

$$\Delta G^\circ_{iz} = G^\circ_{(M-iz)^+} - (G^\circ_{M^+} + G^\circ_{iz})$$

$$\Delta G^\circ_{py} = G^\circ_{(M-py)^+} - (G^\circ_{M^+} + G^\circ_{py})$$
$$\delta\Delta G^\circ_1 = \Delta G^\circ_{py} - \Delta G^\circ_{iz}$$

Scheme 6

$$\Delta G^\circ_{iz(-)} = G^\circ_{(M-iz)} - (G^\circ_{M^+} + G^\circ_{iz(-)})$$

$$\Delta G^\circ_{pi(-)} = G^\circ_{(M-pi)} - (G^\circ_{M^+} + G^\circ_{pi(-)})$$
$$\delta\Delta G^\circ_2 = \Delta G^\circ_{pi(-)} - \Delta G^\circ_{iz(-)}$$

cations and the N-3/N-1 nitrogen atoms of **iz**/**py** and N-3/N-1 nitrogen atoms of the imidazolate/pyrrolate anions respectively (Schemes 5 and 6).

Table 1 shows the calculated ΔG° and $\delta\Delta G^\circ_1$ values for the coordination reactions between alkaline cations and the N-3 and N-1 nitrogen atoms of **iz** and **py** respectively. As we can observe, the interaction energy decreases from Li^+ to K^+ for both aza nitrogen atoms in **iz** and **py**, and the strongest interaction occurs with the Li^+ cation. However, the $\delta\Delta G^\circ_1$ values show that N-3 nitrogen atom of **iz** has a higher interaction energy with the harder cation (Li^+) than the N-1 nitrogen atom of **py**, while for the softer cation (K^+) the N-1 nitrogen atom of **py** shows a higher interaction than the N-3 nitrogen atom of **iz**.[16] The more negative

(16) Our calculated hardness values for the alkaline cations were in agreement with the known experimental hardness trend: ηLi^+ ($35.21\,eV$) $> \eta Na^+$ ($21.10\,eV$) $> \eta K^+$ ($13.60\,eV$); see ref 4d.

(17) Huang, H.; Rodgers, M. T. *J. Phys. Chem. A* **2002**, *106*, 4277.

Table 1. Interaction Energy Values ($\Delta G°$) for Coordination Reactions of Aza Nitrogen Atoms in Pyridine and Imidazole with Alkaline Metals and Their Difference ($\delta\Delta G°_1$) Obtained by the Equation $\delta\Delta G°_2 = \Delta G°_{py} - \Delta G°_{iz}$ (Values Are in kcal mol^{-1})

M^+	$\Delta G°_{py}$	$\Delta G°_{iz}$	$\delta\Delta G°_1$
Li$^+$	−38.70	−44.13	5.37
		(−44.26 ± 2.4)[a]	
		(−42.33)[b]	
Na$^+$	−24.82	−29.90	5.08
		(−27.08 ± 1.6)[a]	
		(−28.23)[b]	
K$^+$	−21.43	−19.73	−1.70
		(−19.96 ± 1.7)[a]	
		(−19.86)[b]	

[a] Experimental gas-phase values.[17] [b] Calculated gas-phase values. MP2(full)/6-311+G(2d,2p)//MP2(full)/6-31G*.[17].

value of $\delta\Delta G°_1$ reflects that the N-1 nitrogen atom in **py** is softer than the N-3 nitrogen atom in **iz**.

An excellent agreement between theory and experiment is found for the Li$^+$ and K$^+$ interacting systems, whereas the theoretical interaction energy to the Na$^+$ system is 1.3 kcal mol^{-1} higher than the experimental value. The results obtained indicate that the B3LYP functional is reliable for the analysis done.

The opposite case is presented in the analysis of the N-3 and N-1 nitrogen atoms of **iz** and **pi** respectively (Table 2).

The imidazolate **iz**(−) and pyrrolate **pi**(−) anions were considered in the interaction with the alkaline cations since they are the species used in coordination chemistry.[2] The interaction energy of the nitrogen atoms of **iz**(−) and **pi**(−) anions increase from the softer atom (K$^+$) to the harder cation (Li$^+$). The $\delta\Delta G°_2$ values show that the nitrogen atom of **pi**(−) has the higher interaction energy with the alkaline cations than the nitrogen atom of **iz**(−). However, the difference decreases from Li$^+$ to K$^+$ suggesting that for a softer cation than K$^+$ (cf. Rb$^+$ and Cs$^+$) the differences will decrease to zero or positive values. The calculated $\delta\Delta G°_2$ values point out that the pyrrolate nitrogen atom is

(18) The $\delta\Delta G°_1$ and $\delta\Delta G°_2$ values indicate that the condensed values obtained from the Mulliken population analysis and the finite-difference approximation are reliable for the analysis.

Table 2. Interaction Energy Values ($\Delta G°$) for Coordination Reactions of Amine Nitrogen Atoms in Pyrrolate and Imidazolate (1-N: −) with Alkaline Metals and Their Difference ($\delta\Delta G°_2$) by the Equation $\delta\Delta G°_2 = \Delta G°_{pi(-)} - \Delta G°_{iz(-)}$ (Values Are in kcal mol^{-1})

M^+	$\Delta G°_{pi(-)}$	$\Delta G°_{iz(-)}$	$\delta\Delta G°_2$
Li$^+$	−144.06	−138.34	−5.73
Na$^+$	−121.42	−116.44	−4.98
K$^+$	−102.19	−98.88	−3.30

harder than its homologous form in imidazolate, and this is compatible with the N-1 nitrogen atom of **pi** being harder than the case of **iz** obtained from the condensed softness.[18]

Therefore, our analysis at a global and a local level prove and quantify that **py** is the harder ring and has a softer N-1 nitrogen atom than **iz**, while **pi** is the softer ring and has a harder N-1 atom than **iz**. Soft, hard, and harder species would attack the **pi**, **iz**, and **py** rings respectively. The reactivity of the nitrogen atoms of the rings for a soft electrophilic attack follows the trend N-1(**py**) > N-3(**iz**) > N-1(**iz**) > N-1(**pi**). However, the softer C-2, C-4, and C-5 carbon atoms of **iz** are more reactive than its N-3 and N-1 nitrogen atoms for a soft electrophilic attack. Furthermore, there is a closer topological similitude between the **iz** and **pi** chemical soft reactivity than **py**.

In conclusion the semblance of **iz** with **pi** and **py** depends on the hard/soft character of the interacting species: (a) **iz-py** semblance for atomic hard species and/or global soft species, and b) **iz−pi** semblance for atomic soft species and/or global hard species in agreement with the experimental evidence.[1a]

Supporting Information Available. Complete ref 7, Cartesian coordinates, electronic and zero-point energies, and thermochemical data for fully optimized geometries of pyridine, imidazole, pyrrole are included. This material is available free of charge via the Internet at http://pubs.acs.org.