Fukui Function as a Descriptor of the Imidazolium Protonated Cation Resonance Hybrid Structure

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ABSTRACT
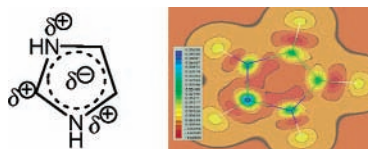
The Lewis structures that contribute to the imidazolium protonated cation resonance hybrid can be explained in a unified way in terms of the Fukui function (density functional descriptor) and the local hard and soft acids and bases principle. The results obtained open the possibility of analyzing the resonance contributors and the resonance hybrid in terms of the electronic density.

Proton transfer, as a result of the tautomeric shift in the imidazole ring, is thought to be responsible for the pharmacological activity of molecules such as histamine.[1] According to the resonance theory,[2] the imidazolium protonated cation (IPC) can be represented by the classical resonance hybrid depicted in structure **I** (Scheme 1).[3] In general, structures **II**

Scheme 1
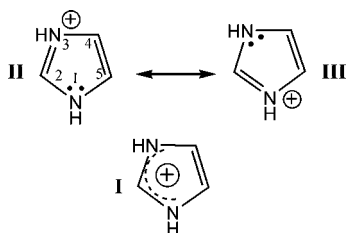
and **III** are the only ones considered to contribute to structure **I**, in which the positive charge is isolated on the 3-N and 1-N atoms, respectively.

However, as we will show, structure **I** does not accurately represent the IPC resonance hybrid, since it lacks the resonance structure that includes the positive charge in the 2-C atom, which does not have an octate of electrons (structure **IV**, Scheme 2), and it does not represent the contribution of the ring aromatic character due to the lone pair shift in structures **V−VII**. Clearly, these structures are not classical for the IPC, because they involve imidazolium ylide structures. Nonetheless, one unusual feature of the chemistry of imidazoles is the ease with which the proton can be removed from 2-C atom in neutral or basic conditions, yielding the slow formation of imidazolium ylides.[4]

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Scheme 2
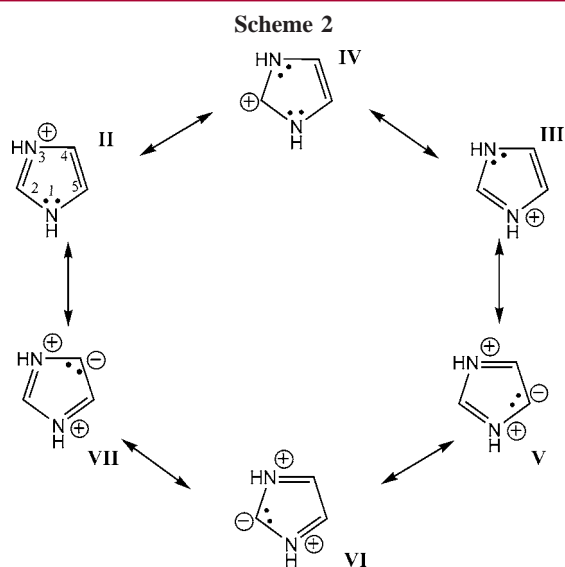
In general, resonance theory is applied as a qualitative method using chemical intuition.[2] In this letter, we use for the first time the Fukui function,[5] which has a formal definition in the density functional theory (DFT),[6] to explain in a unified way the resonance structures **II–VII**, suggesting a new resonance hybrid structure of the IPC. The evaluation of the charge position in the IPC (Scheme 2) is based on the principle that "the regions of a molecule where the Fukui function is large are chemically softer than the regions where the Fukui function is small, and by invoking the hard and soft acids and bases principle (HSAB) in a local sense, one may establish the behavior of the different sites with respect to hard or soft reagents".[7] The Fukui function represents the change of the electronic density $\rho(r)$ in a given point with respect to the change in the number of electrons N: $f(r) = (\partial\rho(r)/\partial N)_{v(r)}$, and it can be evaluated for nucleophilic, electrophilic, and radical attacks [$f^+(r)$, $f^-(r)$, $f^o(r)$ respectively].[5] For the IPC, the species considered were neutral, monocationic, and dicationic with N + 1, N, and N − 1 electrons, respectively. The electronic density for the monocation was studied using ab initio calculations at the B3LYP/6-31G(d,p) level with GAUSSIAN98.[8] Neutral and dication electronic densities were calculated as before, at the UB3LYP/6-31G(d,p) level, and showed no spin contamination for the doublet open shell structures. All of them were evaluated in the geometry of the equilibrium state of the monocation. For the nucleophilic attack, Figure 1 shows the largest values of $f^+(r)$ for the 2-C and the 1,3-N atoms. They are associated with the softer regions of the IPC, which are able to stabilize an uptake of electronic charge and are especially reactive toward electron-rich reactants. Therefore, the best representa-
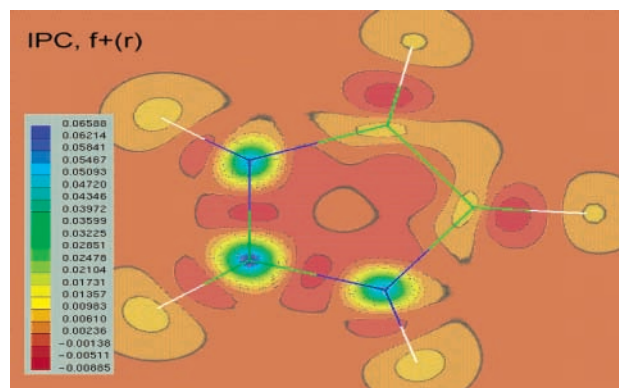

Figure 1. Contour plot of the nucleophilic Fukui function (obtained by electronic density cubes differences). The highest and lowest values are indicated in the scale by the blue and red colors, respectively. The blue, green, and white lines indicate the nitrogen, carbon, and hydrogen atoms, respectively.

tion of the IPC for nucleophilic attack can be obtained from the resonance structures **II–IV**.
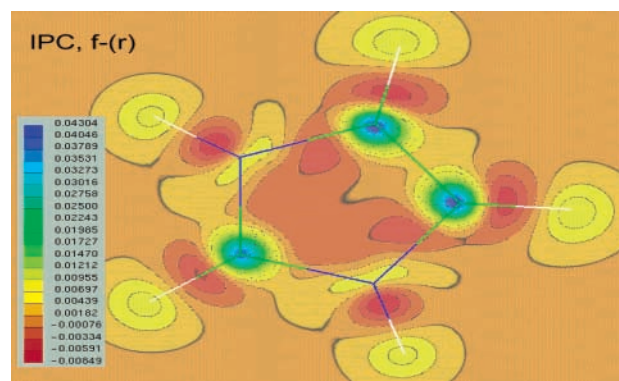

Figure 2. Contour plot of the electrophilic Fukui function.

For the electrophilic attack, Figure 2 indicates that the largest values of $f^-(r)$ are located in the 2-C, 4-C, and 5-C atoms. They are associated with the softer regions of the IPC, by giving up electronic charge, and are especially reactive toward electron-poor reactants; thus, the best representation of the IPC for electrophilic attack can be obtained from the resonance structures **V–VII**.

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(7) (a) Gázquez, J. L.; Méndez, F. *J. Phys. Chem.* **1994**, *98*, 4591−4593. (b) Méndez, F.; Gázquez, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9298−9301. (c) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533−3539.

(8) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

The radical attack, represented as the average contribution of $f^+(r)$ and $f^-(r)$, is depicted in Figure 3. $f^0(r)$ reaches a
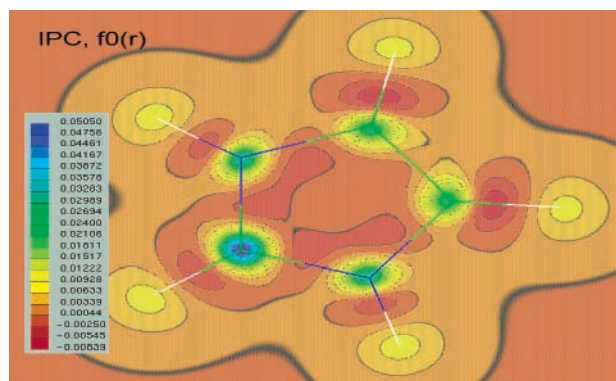

Figure 3. Contour plot of the average Fukui function.

pronounced maximum in the 2-C atom, where this region, which is the softest, is the reactive site toward electron-rich/poor reactants. The 1,3-N atoms show a higher contribution of $f^0(r)$ than 4,5-C atoms. The former will be reactive toward electron-rich reactants, while the later will be reactive toward electron-poor reactants. Hence, $f^0(r)$ includes the total contribution of the resonance structures **II−VII** for nucleophilic and electrophilic attack (the resonance hybrid structure of the IPC). In all of these cases, the reactive atoms predicted from the Fukui functions are concomitant with the experimental evidence.[3,4,9]

The results of the analysis of the reactivity at the atomic level, using the condensed Fukui function,[10] are concomitant with the results obtained from the Fukui function. Table 1 shows the condensed Fukui function values for the IPC obtained from Mulliken charge analysis. We can observe that the 2-C atom has the highest value for all of the condensed Fukui functions, followed by the 1,3-N atoms in the nucleophilic and radical attacks, and by the 4,5-C atoms in the electrophilic attack.

The condensed Fukui functions, interpreted in terms of the local HSAB principle for soft−soft interactions, gave us an explanation of the structures **II−VII**. As a result of this analysis, we can suggest a new hybrid resonance structure **VIII** that includes the nucleophilic and electrophilic behavior of the IPC and the properties of the classical delocalized structure **I**. It is interesting to observe the ambiphilic character of the 2-C atom, which can act as an electrophilic/nucleophilic atom toward electron-rich/poor sites, respectively. This specific reactivity will depend on the species it will react with.[9,11]

VIII
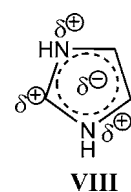
The results obtained in this work open the possibility of analyzing the resonance theory in terms of the electron density.

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Table 1. Condensed Fukui Functions for the IPC

atom	f^+	f^-	f^0
1-N	0.141	0.012	0.107
2-C	0.301	0.157	0.263
3-N	0.141	0.012	0.107
4-C	0.036	0.059	0.042
5-C	0.036	0.059	0.042