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Condensed Fukui function predicts innate C–H radical functionalization sites on multi-nitrogen containing fused arenes†

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The condensed Fukui function could be correlated with the reported innate C–H radical functionalization sites on some heterocycles. This computational method was further extended to predict the innate C–H functionalization sites on multi-nitrogen containing fused arenes, and the calculated results were validated by experimental outcomes.

Due to the peculiar electronic character of many nitrogen-containing arenes, harsh reaction conditions or guided functionalization are often required for a successful modification.[1] These methods either reduce functional group tolerance or add synthetic steps. To avoid these problems, philosophically, it is intriguing to follow and make use of the native reactivity of these heterocycles. However, only recently has this philosophy been reincarnated by the radical-generating sulfinates. According to recent progress made by Baran *et al.*, innate C–H functionalization has become a powerful strategy for heteroarene functionalization.[2] Along this line, Baran *et al.* further established empirical rules for the prediction of innate C–H radical functionalization site on some nitrogen-containing heteroarenes.[3]

Multi-nitrogen containing fused arenes are important scaffolds in medicinal chemistry and drug discovery. Direct functionalization on these ring systems is very useful for diversification and proprietary purposes. On the basis of preliminary study, we found that the radical-generating sulfinate salt chemistry works well on such systems. However, NMR characterization of this type of product was often hampered by the high nitrogen content and fused structures. Furthermore, it is difficult to apply Baran's empirical rules on such complex systems to predict the innate C–H functionalization sites.

In past decades, the condensed Fukui function (eqn (1)) was utilized to rationalize and predict the reactivities of various organic reaction systems.[4] As shown in eqn (1), the condensed Fukui functions are calculated based on atomic charges obtained from electron density population analysis. Inspired by the previous studies, which indicated that the innate C–H functionalization of heterocycles was strongly related to their intrinsic electronic properties and reactivities,[3] we proposed that this inexpensive computational method could be used in parallel with Baran's empirical prediction rules to understand and predict the innate C–H functionalization. Thus, we proved that the condensed Fukui functions could be correlated with the innate C–H functionalization sites reported by Baran *et al.* More importantly, we performed experiments to verify that this inexpensive computational method could be extended to predict the innate C–H radical alkylation sites on multi-nitrogen containing fused arenes.

$$\begin{aligned}&\text{Nucleophilic attack}: f_{\mathrm{A}}{}^{+} = q_{N}^{\mathrm{A}} - q_{N+1}^{\mathrm{A}}\\&\text{Electrophilic attack}: f_{\mathrm{A}}{}^{-} = q_{N-1}^{\mathrm{A}} - q_{N}^{\mathrm{A}}\\&\text{Radical attack}: f_{\mathrm{A}}{}^{0} = (q_{N-1}^{\mathrm{A}} - q_{N+1}^{\mathrm{A}})/2\end{aligned} \tag{1}$$

The definition of condensed Fukui functions: q_N^{A} is the partial charge of atom A in the molecule with N electrons, while q_{N-1}^{A} and q_{N+1}^{A} are partial charges of atom A in the molecule with $N-1$ electrons and $N+1$ electrons, respectively.

Initially, we assessed the correlation between condensed Fukui functions and the previous experimental results of Baran *et al.* Seven representative molecules (**1** through **6**, and protonated **3**) were selected from the vast collection[3] and subjected to computation. For the first step, the molecules with N electrons were subjected to geometry optimization at B3LYP/6-31+G** level along with the solvent (DMSO) continuum model.[5] Concerning the atomic charge calculation for Fukui function analysis, previous studies[6] demonstrated that the Hirshfeld

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population analysis serves as a good candidate for condensed Fukui function calculation, since it constantly gives the positive Fukui function values and shows better accuracy in predicting the reactive sites. Thus, as the second step, the geometry optimized structures were modified to yield new molecules with $N+1$ and $N-1$ electrons, which were subjected to single point calculation to yield the Hirshfeld charges and then the three f_A values in eqn (1). We immediately found that the condensed Fukui function for radical attack (f_A^0 value)[7] could not be associated with the experimentally validated reaction sites. However, we were surprised to see that the condensed Fukui function of nucleophilic attack (f_A^+ value) correlated well with the reported reaction sites, as the reaction site had the largest f_A^+ value in all the molecules.[3] Higher f_A^+ values on selected molecules from Baran's work are illustrated in Fig. 1. For compound **1**, C5 with the highest f_A^+ value was characterized as the major isopropylation site, while C4 with the second highest f_A^+ value was also functionalized, albeit to a lesser extent. For compound **2**, the observed single isopropylation site again corresponded to C5 with the highest f_A^+ value. For compound **3**, the f_A^+ values of C2 and C3 were quite close, rendering the prediction rather difficult. Experimentally, the slightly higher C3 (0.087) was demonstrated to be more functionalized. On protonated **3**, the preferred isopropylation site was reverted dramatically according to Barran *et al.*, and our calculation agreed with this finding by a significant elevation of the f_A^+ value on C2. On bis-nitrogenated mono rings **4** and **5**, the calculation indicated a large gap between the first and the second highest f_A^+ values. As anticipated, for both compounds, experimentation found only single isopropylation on the site with the highest f_A^+ value. Compound **6** is a system of significant complexity. The condensed Fukui function predicted C9 as a major site for modification, and this has been proved by the reported results (90% isopropylation on C9). However, it should be noted that the minor isopropylation (10%) site was observed on C2, which could not be forecasted by the calculation. Generally, it was fair to conclude that our calculated f_A^+ value showed good agreement with the experimental isopropylation sites found by Baran *et al.*

Encouraged by the good consistency between the experimental and computational results, we further selected eight multi-nitrogen containing fused arenes (compounds **7–14**) that are frequently encountered scaffolds in medicinal chemistry, and calculated the corresponding condensed Fukui function. Solely based on Baran's empirical rules, it is not straightforward to predict the reaction site of these compounds. However, with the condensed Fukui function method, the f_A^+ values were rapidly obtained. Higher f_A^+ values are displayed for the eight substrates in Fig. 2.

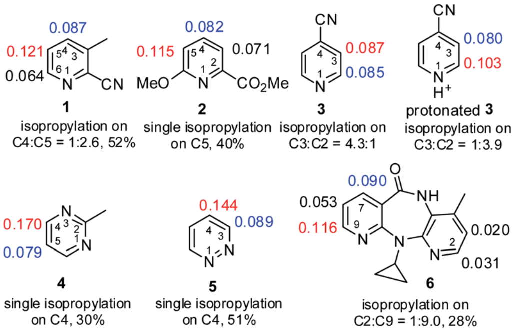


Fig. 1 Calculated f_A^+ of carbon atoms on representative nitrogen containing arenes (highest value in red, second highest in blue) and the reported radical alkylation sites with ratio or yield.

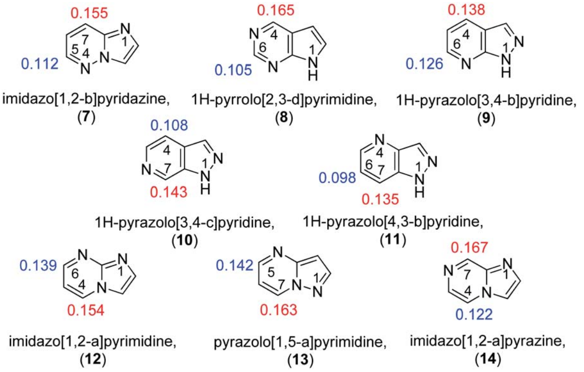
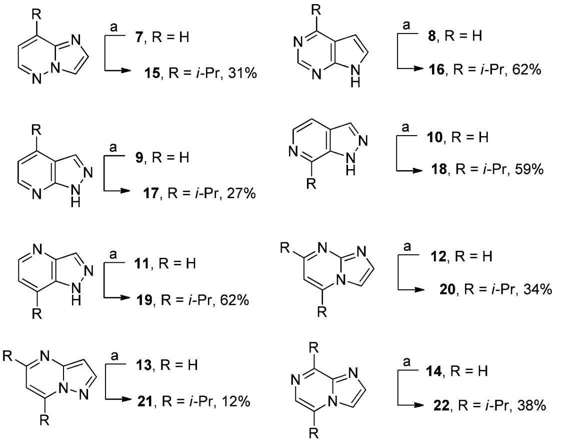


Fig. 2 Calculated f_A^+ of carbon atoms on multi-nitrogen containing fused arenes.

Meanwhile, to verify the computational results in Fig. 2, we devised radical isopropylation on compounds **7–14**. Although it is convenient to follow Baran's protocol ($Zn(i\text{-}PrSO_2)_2$, TBHP, DMSO, 50 °C),[3] such radical alkylation on multi-nitrogen containing arenes was surprisingly rare. The difficulties in product isolation and structure elucidation might account for this scarcity. Nevertheless, with careful experimentation, we were able to separate and characterize the major isopropylation products (**15–22**) on all eight starting materials. Due to multi-nitrogen substitutions present in the ring system, NMR analysis of the isopropylation sites became rather complicated and less reliable. We managed to obtain single crystals of compounds **16**, **18**, **20**, and **22**, and the corresponding XRD data[7] further corroborated the NMR analysis. The reagents and reaction conditions are shown in Scheme 1.



Scheme 1 Reagents and reaction conditions: (a) $Zn(i\text{-}PrSO_2)_2$, TBHP, DMSO, 50 °C.

As indicated in Fig. 2 and Scheme 1, compounds **7–11** were exclusively functionalized on the sites with the highest f_A^+ values to yield the mono isopropyl derivatives **15–19**. On compounds **12**, **13**, and **14**, double isopropylation products (**20**, **21** and **22**) were experimentally identified and the substitution positions were again consistent with the first and the second highest f_A^+ values of each starting material. From these examples, we also noticed that compound **9** with a small gap between the first and the second highest f_A^+ values yielded only mono isopropylated product **17**, while the large gap on compound **14** did not prevent the formation of double functionalization product **22**. It was, therefore, reasonable to suggest that the gap value was not significantly relevant to the number of isopropylation sites.

Nevertheless, from the above-described results, several general trends can be identified: (1) at least on typical mono- or multi-nitrogen containing single or fused rings, it was possible to use the f_A^+ values from the condensed Fukui function to predict the radical alkylation sites with Baran's synthetic method; (2) on multi-nitrogen containing fused arenes, if mono alkylation is observed on MS or NMR spectra, the reaction site would likely be the one with the highest f_A^+ value; (3) on multi-nitrogen containing fused arenes, if double alkylation is found experimentally, the sites with the top two f_A^+ values would probably be involved.

Conclusions

In conclusion, we utilized the inexpensive condensed Fukui function method to generate a map of f_A^+ values on typical mono- or multi-nitrogen containing single or fused rings. We also carried out radical alkylation on multi-nitrogen containing arenes with alkylsulfinate salts, and unambiguously characterized the products using MS, NMR and XRD methods. It was found that the experimental innate radical alkylation sites validated by Baran *et al.* and our group could be well correlated with the position of high f_A^+ values. Therefore, we believe that, in a limited, but highly important, subset of multi-nitrogen containing arenes, the condensed Fukui function method could assist the understanding of Baran's innate radical C–H functionalization.

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7 See ESI† for details.