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# Why Iron? A Spin-Polarized Conceptual Density Functional Theory Study on Metal-Binding Specificity of Porphyrin

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Heme is a key cofactor of hemoproteins in which porphyrin is often found to be preferentially metalated by the iron cation. In our previous work [Feng, X. T.; Yu, J. G.; Lei, M.; Fang, W. H.; Liu, S. B. *J. Phys. Chem. B* 2009, 113, 13381], conceptual density functional theory (CDFT) descriptors have been applied to understand the metal-binding specificity of porphyrin. We found that the iron–porphyrin complex significantly differs in many aspects from porphyrin complexes with other metal cations except Ru, for which similar behaviors for the reactivity descriptors were discovered. In this study, we employ the spin-polarized version of CDFT to investigate the reactivity for a series of (pyridine)<sub>n</sub>–M(II)–porphyrin complexes—where M = Mg, Ca, Cr, Mn, Co, Ni, Cu, Zn, Ru, and Cd, and *n* = 0, 1, and 2—to further appreciate the metal-binding specificity of porphyrin. Both global and local descriptors were examined within this framework. We found that, within the spin resolution, not only chemical reactivity descriptors from CDFT of the iron complex are markedly different from that of other metal complexes, but we also discovered substantial differences in reactivity descriptors between Fe and Ru complexes. These results confirm that spin properties play a highly important role in physiological functions of hemoproteins. Quantitative reactivity relationships have been revealed between global and local spin-polarized reactivity descriptors. These results contribute to our better understanding of the metal binding specificity and reactivity for heme-containing enzymes and other metalloproteins alike.

## 1. Introduction

Heme, a key cofactor of hemoproteins, is a metal-binding porphyrin consisting of a heterocyclic organic ring made from four pyrrole subunits linked via methine bridges (Scheme 1) and participates in a variety of life-essential processes and reactions,<sup>1–3</sup> including electron transfer<sup>4</sup> (e.g., cytochrome c), transport of gaseous molecules<sup>5</sup> (e.g., hemoglobin), and catalysis<sup>6</sup> (e.g., cytochrome P450). It is often found that porphyrin in hemoproteins preferentially binds with the iron cation in its inner cavity under physiological conditions, demonstrating the unique metal-binding specificity for this transition metal ion. When in its resting or functioning state, up to two axial ligands are required to bond with the metal cation in the metal–porphyrin complex to carry out the catalytic process (Scheme 1). The most common axial residues in hemoproteins are histidine and cysteine. The quest to appreciate the metal-binding specificity of porphyrin is to answer why the iron ion is preferred over other metal ions in hemoproteins in physiological conditions. Is it because of the metal ion size or thermodynamic or electronic properties?

In our previous work,<sup>7</sup> conceptual density functional theory (CDFT) has been applied to understand the metal-binding specificity of porphyrin, and it was found that both metal-binding

structural and electronic properties of the metal cation play important roles in differentiating the metal-binding specificity. Differences in metal-binding specificity of metal–porphyrin complexes can result from different causes. For example, no Ca–porphyrin or Cd–porphyrin complex exists in Nature because Ca(II) and Cd(II) cations are too big to fit into the inner cavity of the porphyrin ring. For other complexes such as Zn(II) and Mn(II), it was concluded that electronic properties, as, for example, shown from the second-order perturbation theory analysis of the Fock matrix in the NBO basis and chemical reactivity descriptors such as hardness, electrophilicity, and dual descriptors that dictate their metal-binding specificity. It has also been revealed that the iron complex differs from other metal ion complexes in bonding and reactivity properties (i.e., charge distribution, stability, and nucleophilicity) when two axial bonds are formed, enhancing and facilitating the role of the iron cation as the center of the catalytic process and thus implying that the number and nature of the axial ligands also play an important role in the catalytic process. Another main conclusion of our previous work is that Fe(II) and Ru(II) complexes show similar reactivity from the CDFT perspective. This result agrees with the fact that Ru complexes<sup>8,9</sup> have been widely utilized in artificial photosynthesis systems, displaying extraordinary properties in both photoexcitation and electron transfer. There is still one question though: why does Nature prefer iron, not ruthenium? Although this may be related to the scarcity of the latter in Nature, it can also be anticipated that spin states and multiplicity should play an important role. As such, the

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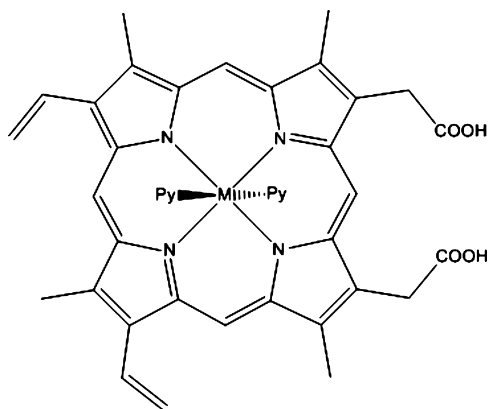
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**SCHEME 1: (Pyridine)<sub>n</sub>–Metal–Porphyrin Systems Investigated in This Work, with M = Mg, Ca, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ru, and Cd and *n* = 0, 1, and 2**



investigation of this matter in spin-resolved conceptual DFT is the aim of the present work.

The spin-polarized CDFT (SP-CDFT), first proposed by Galván, Vela, and Gázquez in 1988,<sup>10–13</sup> provides a general DFT framework for the discussion of chemical reactivity for the systems or processes where spin density is considered as the fundamental variable. Within this framework, many response functions and equations have been introduced for the description of the chemical reactivity for spin-polarized systems;<sup>14–16</sup> these include the spin potential, the spin hardness, and the generalized Fukui functions. Derived from SP-CDFT, some other descriptors have also been suggested. An important example is the so-called spin-philicity, introduced by Pérez et al.,<sup>17</sup> which has been shown to be an effective descriptor for molecules<sup>18–21</sup> and reactions.<sup>22–27</sup> In this work, we utilize SP-CDFT to explore the metal-binding selectivity and specificity of porphyrin metalated by a series of divalent metal ions. We are in particular interested in the different behavior of Fe(II) and Ru(II) complexes. We will show that within the spin resolution, a significant difference between the two metal complexes is observed, confirming the uniqueness of the metal-binding specificity from the iron-porphyrin complex.

## 2. Theoretical Background

In CDFT,<sup>28–34</sup> also called density functional reactivity theory or chemical DFT, a number of global and local reactivity descriptors have been introduced and recently applied to a number of problems.<sup>35–49</sup> These reactivity indices include chemical potential  $\mu$  (electronegativity  $\chi \equiv -\mu$ ), hardness  $\eta$ , softness  $S$ , Fukui function  $f(\mathbf{r})$ , and electrophilicity  $\omega$ . For an  $N$ -electron system with external potential  $\nu$  and total energy  $E$ , these indices can be defined as follows:

$$\mu = \left( \frac{\partial E}{\partial N} \right)_\nu = -\chi \approx -(I + A)/2 \quad (1)$$

$$\eta = \left( \frac{\partial^2 E}{\partial N^2} \right)_\nu = \left( \frac{\partial \mu}{\partial N} \right)_\nu = I - A = 1/S \quad (2)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (3)$$

with  $I$  and  $A$  as the (vertical) first ionization potential and electron affinity, respectively, which can be approximated by

the HOMO and LUMO energies via  $I \approx -\epsilon_{\text{HOMO}}$  and  $A \approx -\epsilon_{\text{LUMO}}$ .<sup>50–53</sup>

For open shell systems, both the charge density,  $\rho = \rho_\alpha + \rho_\beta$ , and spin density,  $\rho_S = \rho_\alpha - \rho_\beta$ , are treated as the basic and independent variables, rendering the so-called spin-polarized CDFT (SP-CDFT). The SP-CDFT approach provides a general treatment for processes involving both electron transfer and spin polarization. Since in SP-CDFT there are two independent variables of the electron density,  $N$  (total number of electrons) and  $N_S$  (total number of spin electrons), the energy change associated with the electron change at the condition of a fixed external potential can be dealt with in two different ways: one with a changing  $N$  at fixed  $N_S$  and the other with changing  $N_S$  at fixed  $N$ . Each of these applies to a special case of the electron number change and real chemical changes are only well described by considering both cases. The changes in the total energy can be proceeded in the standard Euler equation manner, giving two Lagrange multipliers,  $\mu_N$  and  $\mu_S$ ,

$$\mu_N = \left( \frac{\partial E}{\partial N} \right)_{N_S, \nu, \mathbf{B}} \quad (4)$$

and

$$\mu_S = \left( \frac{\partial E}{\partial N_S} \right)_{N, \nu, \mathbf{B}} \quad (5)$$

where  $\nu$  is the external potential and  $\mathbf{B}$  is the external magnetic field.  $\mu_N$  is equivalent to the chemical potential  $\mu$  in the spin-restricted case, and  $\mu_S$  measures the tendency to undergo spin transfer, at constant  $N$ , which can further be approximated by:

$$\mu_S^+ \approx \frac{(\epsilon_{\text{LUMO}}^\alpha - \epsilon_{\text{HOMO}}^\beta)}{2} \quad (6)$$

and

$$\mu_S^- \approx \frac{(\epsilon_{\text{HOMO}}^\alpha - \epsilon_{\text{LUMO}}^\beta)}{2} \quad (7)$$

Equations 6 and 7 correspond to the two possible ways of spin transfer, one from  $\beta$  spin to  $\alpha$  spin and the other from  $\alpha$  spin to  $\beta$  spin. A larger value of  $\mu_S^+$  means that the system is less likely to increase the spin number because of the bigger HOMO/LUMO gap. Similarly, we can define the spin-hardness, viewed as the response of the spin potential relative to changes in the spin number,

$$\eta_{SS}^+ = \left( \frac{\partial^2 E}{\partial N_S^2} \right)_{N, \nu, \mathbf{B}} = \left( \frac{\partial \mu_S}{\partial N_S} \right)_{N, \nu, \mathbf{B}} \approx \frac{(\mu_S^{*-} - \mu_S^+)}{2} \quad (8)$$

where  $\mu_S^+$  is the spin potential of the ground state and  $\mu_S^{*-}$  stands for the spin potential for the  $N_S + 2$  state. For example, if the ground state  $N_S$  is singlet,  $N_S + 2$  will be triplet. Note that unlike the spin-restricted counterpart, where  $\eta$  is always positive, this is no longer the case for  $\eta_{SS}^+$ ; indeed, it is always negative because the spin potential of the  $N_S + 2$  state is smaller than that of the ground state.

Under the condition of a fixed external potential and total number of electrons, we can investigate the total energy change as a function of the spin number change through the following Taylor series,

$$\Delta E_{N,v} = \mu_S \Delta N_S + \frac{1}{2} \eta_{SS} \Delta N_S^2 \quad (9)$$

With the maximum increase or decrease in spin multiplicity,  $\Delta N_S^\pm = -\mu_S^\pm / \eta_{SS}$ , the maximum energy change,  $\Delta E_{\max}^\pm$ , is given by

$$\Delta E_{\max}^\pm = -\frac{(\mu_S^\pm)^2}{2\eta_{SS}} = \omega_S^\pm > 0 \quad (10)$$

where  $\omega_S^+$  and  $\omega_S^-$  denote the spin-philicity and spin-donicity, respectively, serving as the estimation of system's capability to change its spin multiplicity. Since values of  $\Delta E$  are always positive, the  $\omega_S^\pm$  descriptor will always be positive. Therefore, the lower the  $\omega_S^\pm$  value, the easier the system changes spin multiplicity. Notice that these descriptors do not involve electron transfer because the total number of electrons is held fixed in eq 9. They thus describe the process of spin reorganization as a consequence of spin polarization in the global system and probe the spin reactivity without the involvement of the electron transfer.

To describe regioselectivity tendencies of individual atoms in molecules, Fukui function<sup>54</sup> and dual descriptor<sup>55,56</sup> were employed. Yang and Mortier<sup>57</sup> have proposed that for systems with a gain of electrons the condensed Fukui index,  $f_k^+ = q_k(N+1) - q_k(N)$ , in the finite difference approximation is a measure of nucleophilic attack, where  $q_k(N)$  is the gross atomic charge for atom  $k$  with  $N$  electrons, obtained from a population analysis (such as NBO analysis). For systems that can donate electrons, the condensed Fukui index is susceptible to electrophilic attack with  $f_k^- = q_k(N) - q_k(N-1)$ . For radical attack reactions,  $f_k^0 = (1/2)(f_k^+ + f_k^-)$ , where  $q_k(N+1)$ ,  $q_k(N)$ , and  $q_k(N-1)$  are the gross NBO population on atom  $k$  in a molecule with  $N+1$  (anion state),  $N$  (neutral state), and  $N-1$  (cation state) electrons, respectively. Morell, Grand, and Toro-Labbe proposed the first dual descriptor using the cross-term third-order derivative  $f^{(2)}(r) = (\partial f(r)/\partial N)_v = (\delta \eta / \delta v(r))_N$ . Under the finite difference approximation, one gets  $f^{(2)}(r) = f^+(r) - f^-(r)$ . The dual descriptor,  $f^{(2)}(r)$ , will be positive in electrophilic regions where  $\rho_{\text{LUMO}}(r)$  is large and will be negative in nucleophilic regions where  $\rho_{\text{HOMO}}(r)$  dominates.

These local reactivity indices can also be introduced within the framework of SP-CDFT. There are two kinds of spin Fukui functions defined as

$$f_{NS}(r) = \left( \frac{\partial \rho(r)}{\partial N_S} \right)_{N,v,B} = \left( \frac{\delta \mu_S}{\delta v(r)} \right)_{N,N_S,B} \quad (11)$$

and

$$f_{SS}(r) = \left( \frac{\partial \rho_S(r)}{\partial N_S} \right)_{N,v,B} = -\frac{1}{\mu_B} \left( \frac{\delta \mu_S}{\delta B(r)} \right)_{N,N_S,v} \quad (12)$$

respectively. The first measures the response of the total electron density  $\rho(r)$  to a change in spin multiplicity, whereas the second

involves the change in the spin density  $\rho_S(r)$  in response to the spin multiplicity change. These local functions are discontinuous with respect to  $N_S$  and can also be condensed to a region (usually an atom)  $k$ . Using the frozen core approximation,  $f_{SS,k}^+$  and  $f_{SS,k}^-$  can be obtained as follows

$$f_{SS,k}^+ \approx \frac{1}{2} [|\Phi_{\text{LUMO},\alpha,k}|^2 + |\Phi_{\text{HOMO},\beta,k}|^2] \quad (13)$$

$$f_{SS,k}^- \approx \frac{1}{2} [|\Phi_{\text{HOMO},\alpha,k}|^2 + |\Phi_{\text{LUMO},\beta,k}|^2] \quad (14)$$

whereas  $f_{NS,k}^+$  and  $f_{NS,k}^-$  can be approximated by

$$f_{NS,k}^+ \approx \frac{1}{2} [|\Phi_{\text{LUMO},\alpha,k}|^2 - |\Phi_{\text{HOMO},\beta,k}|^2] \quad (15)$$

$$f_{NS,k}^- \approx \frac{1}{2} [|\Phi_{\text{HOMO},\alpha,k}|^2 - |\Phi_{\text{LUMO},\beta,k}|^2] \quad (16)$$

where  $\Phi_{\text{HOMO},\alpha,k}$ ,  $\Phi_{\text{HOMO},\beta,k}$ ,  $\Phi_{\text{LUMO},\alpha,k}$ , and  $\Phi_{\text{LUMO},\beta,k}$  are HOMO and LUMO orbitals for  $\alpha$  and  $\beta$  electrons, respectively. A region  $k$  in a molecule with a larger  $f_{SS,k}^+$  implies a region that is more likely to increase or decrease its spin density. When approximated by eqs 13 and 14,  $f_{SS,k}^\pm$  should always be positive and normalized. If  $f_{NS,k}^+ > 0$ , the region  $k$  gains electrons as the total spin number is increased/decreased, and if  $f_{NS,k}^+ < 0$ , the region is more likely to lose electrons. These local descriptors can be termed “spin reactivity indices” describing the tendency of molecular areas to gain or lose electrons or spin electrons when the total spin number of the system is changed.

Inspired by our recent work to understand metal specificity of porphyrin using conceptual DFT descriptors, in which, among other things, we found that spin polarization plays an important role in determining the metal-binding ability of the metal–porphyrin complex, we will now use spin-polarized CDFT indices such as spin potential  $\mu_S$ ; spin hardness  $\eta_{SS}$ ; spin-philicity and -phobility,  $\omega_S$ ; and spin Fukui functions,  $f_{SS}(r)$  and  $f_{NS}(r)$ ; to study spin-related regioselectivity properties of porphyrin before and after its metal binding. This work is aimed at an in-depth understanding of porphyrin's metal-binding specificity and preference over the iron cation in hemoglobin, cytochrome P450 proteins, and other enzymes in nature.

### 3. Computational Details

Following our earlier work, we choose 11 divalent metal cations in this study for the porphyrin-M(II) complex, with  $M = \text{Fe, Mg, Ca, Cr, Mn, Co, Ni, Cu, Zn, Ru, and Cd}$ . To study the impact of the axial ligands on the structural and electronic properties of the complex, we used the six-membered pyridine ring (Py). We will consider cases with zero, one, and two pyridines axially bonded to the metal cation as the axial-binding models, (pyridine)<sub>*n*</sub>–M(II)–porphyrin complexes, with  $n = 0, 1$ , and  $2$ . These binding models will be denoted p0, p1, and p2, respectively. Scheme 1 shows p2 as an example.

All calculations were performed using the DFT B3LYP<sup>58–60</sup> functional and a compound basis set, where the 6-31G basis set was used for the elements C and H, and the 6-311+G(d) basis was used for N, O, and M (where  $M = \text{Mg, Ca, Cr, Mn, Co, Ni, Cu, Zn}$ ).<sup>61,62</sup> This generic basis set<sup>63</sup> has previously proven to be effective<sup>64,65</sup> by being both efficient and reliable in predicting structural and reactive properties for heme-like



systems. For Ru and Cd for which no Pople-type basis set is available, we used the ECP Stuttgart basis set. For each system, we first performed a tight structural optimization, followed by a frequency calculation to confirm that the optimized structure was indeed a minimum on the potential energy surface. Single-point frequency calculations and NBO analyses were carried out with tight SCF convergence and ultrafine grids in the structural optimizations. For metal ions with different spin states, each multiplicity was examined and the spin state with the lowest energy was then chosen for subsequent studies. The effectiveness of the present approach in dealing with spin multiplicity under the framework of DFT has been addressed earlier.<sup>66–68</sup> Spin reactivity indices were calculated according to the formulation in the above section after the optimized structure with the lowest energy spin multiplicity had been obtained. All calculations were performed using the Gaussian 03 package.<sup>69</sup>

#### 4. Result and Discussion

The computed global SP-CDFT-based reactivity descriptors, including the spin potential  $\mu_S^+$  of the ground state, the spin potential  $\mu_S^{*-}$  of the  $N_S + 2$  excited state, the spin hardness  $\eta_{SS}^+$ , and the spin philicity  $\omega_S^+$  for the (pyridine)<sub>n</sub>–metal–porphyrin complexes (Scheme 1) with 11 different divalent cations and varying numbers of axial pyridine groups ( $n = 0, 1$ , and 2) are given in Table 1. As can be seen, the values of spin potentials  $\mu_S^+$  and  $\mu_S^{*-}$ , spin hardnesses  $\eta_{SS}^+$ , and spin philicities  $\omega_S^+$  decrease as the number of axial pyridine groups increases from 0 to 2. This indicates that after the coordination of the metal–porphyrin complex with pyridine, its capability of increasing its spin multiplicity in general also increases, a distinct feature commonly seen in hemoproteins when undergoing redox reactions in the active site. In comparison with other metal complexes with the same number of pyridine groups, the Fe-porphyrin complex stands up and often possesses the smallest value for each of the SP-CDFT quantities in most cases, indicating that the Fe system is most likely to increase the total spin number. For example, in the p0 case,  $\omega_S^+$  of the Fe-porphyrin complex is 0.81 eV, the smallest among the eleven complexes;  $\eta_{SS}^+$  is  $-1.34$  eV, also the smallest among the series. For p1 and p2 series, the small values of  $\mu_S^+$  and  $\eta_{SS}^+$  of the Fe-porphyrin complex also result in small values for the spin philicity. Also in these cases, it is consistently the smallest except for two cases, the p1–Co–porphyrin and the p2–Cr–porphyrin, suggesting that these species can take up spin more easily than others within the series. When looking at  $\mu_S^+$  for  $n = 0$ , we observe that the Ru–porphyrin complex possesses the highest tendency to raise  $N_S$  (smallest  $\mu_S^+$  value). This is not necessarily in contradiction with its spin-philicity, because the spin potential represents the slope of the curve at the integer  $N_S$  point, whereas the spin-philicity probes the maximum tendency of energy change with respect to the optimal spin number change. The latter descriptor also includes the contribution from the spin hardness,  $\eta_{SS}^+$ , which can be seen as the response of the spin potential to the change in the spin number  $N_S$ . These results from SP-CDFT are markedly different from those obtained from the spin-restricted CDFT results, where we found that global conceptual DFT indices behaved similarly for both Fe–porphyrin and Ru–porphyrin complexes. Put together, these results show that to answer the question of why Nature selects iron rather than ruthenium, besides their abundance difference: in metalation with porphyrin in hemoproteins one has to resort to the spin polarized version of CDFT, since spin states play an important in catalytic reactions of the enzymes.

**TABLE 1: Global Reactivity Descriptors from Spin-Polarized Conceptual DFT Including Spin Potentials of Ground State and  $N_S + 2$  State ( $\mu_S^+$  and  $\mu_S^{*-}$ ), Spin Hardness ( $\eta_{SS}^+$ ), and Spin-Philicity ( $\omega_S^+$ ) for Pyridine–Metal(II)–Porphyrin Complexes<sup>a</sup>**

py No.	metal ion	2S + 1	$\mu_S^+$	$\mu_S^{*-}$	$\eta_{SS}^+$	$\omega_S^+$
0	Mg	1	1.45	0.74	−0.53	2.01
	Ca	1	1.43	0.68	−0.54	1.90
	Cr	5	1.50	0.53	−0.48	2.32
	Mn	6	1.47	0.75	−0.53	2.03
	Fe	3	1.47	<b>−0.27</b>	<b>−1.34</b>	<b>0.81</b>
	Co	2	1.48	0.87	−0.49	2.23
	Ni	1	1.49	0.87	−0.50	2.24
	Cu	2	1.47	0.80	−0.51	2.12
	Zn	1	1.47	0.84	−0.49	2.18
	Ru	3	1.30	0.34	−0.46	1.83
	Cd	1	1.46	0.73	−0.54	2.00
1	average		1.45	0.66	−0.58	1.97
	Mg	1	1.43	0.68	−0.54	1.90
	Ca	1	1.42	0.84	−0.47	2.15
	Cr	5	1.49	0.81	−0.52	2.14
	Mn	6	1.46	0.72	−0.54	1.97
	Fe	3	<b>1.24</b>	<b>0.35</b>	<b>−0.59</b>	<b>1.29</b>
	Co	2	1.49	−0.27	−1.36	0.82
	Ni	3	1.47	0.76	−0.53	2.04
	Cu	2	1.46	0.73	−0.53	2.00
	Zn	1	1.44	0.85	−0.48	2.18
	Ru	1	1.42	0.72	−0.51	1.96
2	Cd	1	1.41	0.85	−0.46	2.16
	average		1.43	0.64	−0.59	1.87
	Mg	1	1.38	0.61	−0.54	1.77
	Cr	3	0.63	−0.11	−0.57	0.35
	Mn	6	1.43	0.65	−0.55	1.85
	Fe	1	1.45	<b>−0.13</b>	<b>−1.17</b>	<b>0.90</b>
	Co	2	1.48	0.78	−0.53	2.08
	Ni	3	1.40	0.63	−0.54	1.80
	Cu	2	1.45	0.71	−0.54	1.95
	Zn	1	1.42	0.86	−0.46	2.17
	Ru	1	1.38	0.63	−0.53	1.80
	average		1.34	0.51	−0.60	1.63

<sup>a</sup> All values are in eV.

The peculiarity of the Fe–porphyrin system is further demonstrated in other properties. For example, the spin potential  $\mu_S^{*-}$  of the p0–Fe system, that is,  $\mu_S^{*-}$  of its  $N_S + 2$  state (i.e., quintet), is  $-0.27$  eV, the only case of a negative value for the p0 series (Table 1), indicating that the  $N_S + 2$  state of the p0–Fe system is more stable than other metal species of the same nature. Its counterpart for the multiplicity increasing process,  $\mu_S^{*+}$  of the p0–Fe system, that is,  $\mu_S^{*+}$  of its  $N_S + 2$  state is found to be  $+1.45$  eV (not shown). Combining its negative  $\mu_S^{*-}$  and positive  $\mu_S^{*+}$  for the  $N_S + 2$  state, we find that the p0–Fe system is unique in relative stability, compared to other systems in p0 series, which have both positive  $\mu_S^{*-}$  and  $\mu_S^{*+}$  values. This large difference between the two states indicates that the higher spin state of the p0–Fe system could be a stable or intermediate state, accessible during the catalytic reactions in physiological conditions. To confirm this, we also computed the dual descriptor of p0–Fe\* and found that it is considerably larger than that of the ground state triplet, with  $f_M^{*(2)} = 0.693$  and  $f_M^{(2)} = 0.052$ , respectively, meaning that the higher spin state of p0–Fe is much more electrophilic than the ground state. Note that  $\mu_S^{*-}$  of p1–Co, p2–Cr, and p2–Fe are also negative, and that their  $\mu_S^{*+}$  (not shown in Table 1) are positive. Their dual descriptors, however, behave differently, with  $f_{p1-Co}^{*(2)} = 0.457$ ,  $f_{p2-Cr}^{*(2)} = 0.153$ ,  $f_{p2-Fe}^{*(2)} = 0.236$  (all positive) for the  $N_S + 2$  state and  $f_{p1-Co}^{(2)} = -0.146$ ,  $f_{p2-Cr}^{(2)} = -0.022$ ,  $f_{p2-Fe}^{(2)} = -0.289$  (all negative), for the  $N_S$  ground state, respectively. Compared to

**TABLE 2: Selected Local Descriptors from SP-CDFT Such As Spin-Polarized Fukui Function  $f_{SS,k}^+$  and  $f_{NS,k}^+$  for p0-, p1-, and p2-Metal(II)-Porphyrin Complexes, Where k is M (metal cation), N-Pph (Nitrogen Atom on the Porphyrin Ring), and C-Pph (Bridging/Meso Carbon Atoms on the Porphyrin Ring)**

py No.	metal ion	$f_{SS,k}^+$			$f_{NS,k}^+$		
		M	N-Pph	C-Pph	M	N-Pph	C-Pph
0	Mg	0.001	0.042	0.063	0.000	0.029	0.006
	Ca	0.021	0.088	0.057	-0.006	-0.023	0.011
	Cr	0.048	0.043	0.063	0.048	0.041	0.003
	Mn	0.013	0.044	0.063	0.012	0.033	0.005
	Fe	<b>0.224</b>	0.042	0.057	<b>-0.185</b>	0.039	0.011
	Co	0.019	0.040	0.062	0.017	0.039	0.002
	Ni	0.021	0.041	0.064	0.020	0.039	0.004
	Cu	0.007	0.040	0.064	0.006	0.036	0.005
	Zn	0.004	0.039	0.064	0.002	0.036	0.005
	Ru	0.264	0.082	0.046	-0.057	0.028	0.015
	Cd	0.010	0.059	0.060	-0.004	0.007	0.009
	average	0.057	0.051	0.060	-0.013	0.028	0.007
1	Mg	0.361	0.142	0.056	-0.329	-0.066	0.013
	Ca	0.051	0.104	0.050	-0.046	-0.047	0.006
	Cr	0.081	0.046	0.062	0.064	0.041	0.003
	Mn	0.202	0.095	0.060	-0.089	0.002	0.009
	Fe	<b>0.765</b>	0.052	0.040	<b>-0.690</b>	0.035	0.024
	Co	0.089	0.047	0.064	-0.003	0.035	0.004
	Ni	0.264	0.071	0.062	-0.150	0.020	0.006
	Cu	0.226	0.108	0.058	-0.184	-0.027	0.011
	Zn	0.397	0.143	0.054	-0.275	-0.037	0.011
	Ru	0.263	0.060	0.038	-0.214	0.029	0.020
	Cd	0.055	0.116	0.056	0.029	-0.025	0.013
	average	0.250	0.089	0.054	-0.171	-0.004	0.011
2	Mg	0.180	0.158	0.054	-0.162	-0.089	0.014
	Cr	0.180	0.053	0.057	-0.112	0.029	0.007
	Mn	0.308	0.165	0.054	-0.252	-0.084	0.013
	Fe	<b>0.764</b>	0.052	0.039	<b>-0.620</b>	0.027	0.027
	Co	0.585	0.175	0.055	-0.489	-0.092	0.013
	Ni	0.594	0.181	0.054	-0.503	-0.103	0.014
	Cu	0.251	0.141	0.055	-0.189	-0.056	0.013
	Zn	0.358	0.154	0.054	-0.275	-0.060	0.014
	Ru	0.425	0.071	0.040	-0.119	0.041	0.022
	average	0.405	0.128	0.051	-0.302	-0.043	0.015

p0-Fe, these three systems exhibit the tendency to be electrophilic in the excited state with the  $N_S + 2$  multiplicity, but the former shows unique reactivity: both  $N_S$  and  $N_S + 2$  states are electrophilic.

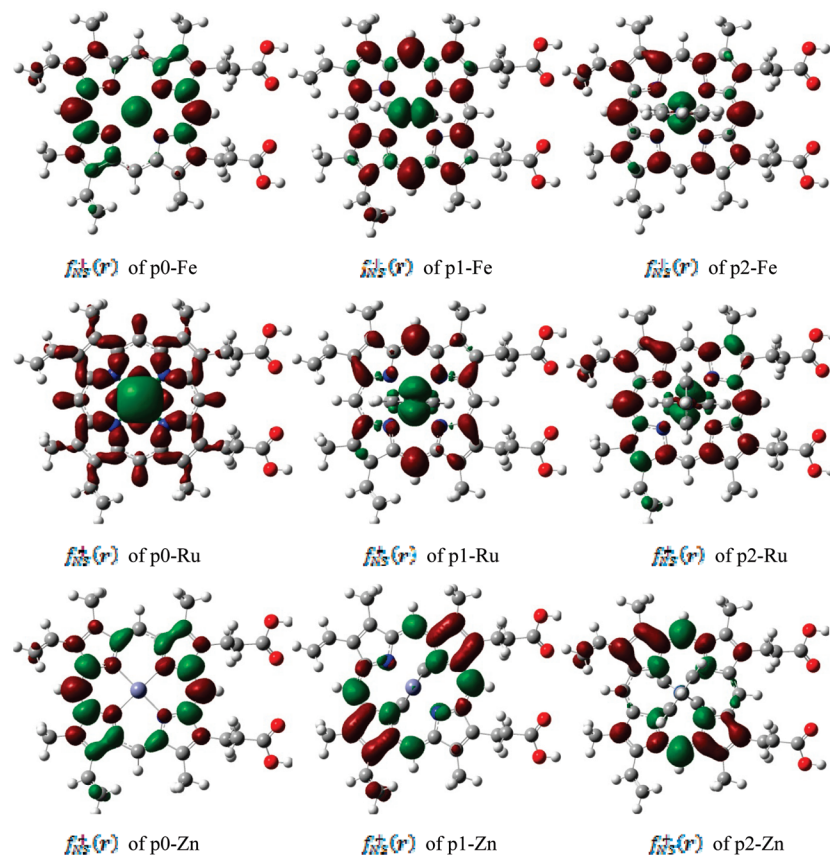
Next, we investigate the behavior of local descriptors from SP-CDFT, given in Table 2, where the condensed spin polarized Fukui functions,  $f_{SS}^+$  and  $f_{NS}^+$  are given for three atoms, the metal cation M in the porphyrin inner cavity, the nitrogen atom, N-Pph, bonded with the metal ion, and the carbon atom, C-Pph, at the meso position of the porphyrin ring. The spin uptake process mainly takes place at the site having the largest value of  $f_{SS}^+$ . We find that in the p0 cases, both the Fe and Ru systems have the markedly larger values for this quantity than both the other metal ions as well as the nitrogen and carbon atoms, suggesting that the metal cation of these two complexes are the center of electron oxidation and the most involved in the spin uptake, in agreement with the experimental findings. For the p1 and p2 systems, which are involved in the catalytic reactions of hemoproteins functions, however, the  $f_{SS}^+$  value of Fe and Ru becomes very different, showing that Fe is much more preferred than other metal ions as the metal oxidation site among the series. This uniqueness of regioselectivity in metal oxidation (or electron donation) tendency distinguishes the Fe complex from others (including Ru) in this study, exhibiting the preferred metal binding specificity of porphyrin with the iron cation.

Also displayed in Table 2 are the results for the other condensed spin-polarized Fukui function  $f_{NS,k}^+$  for the same atoms

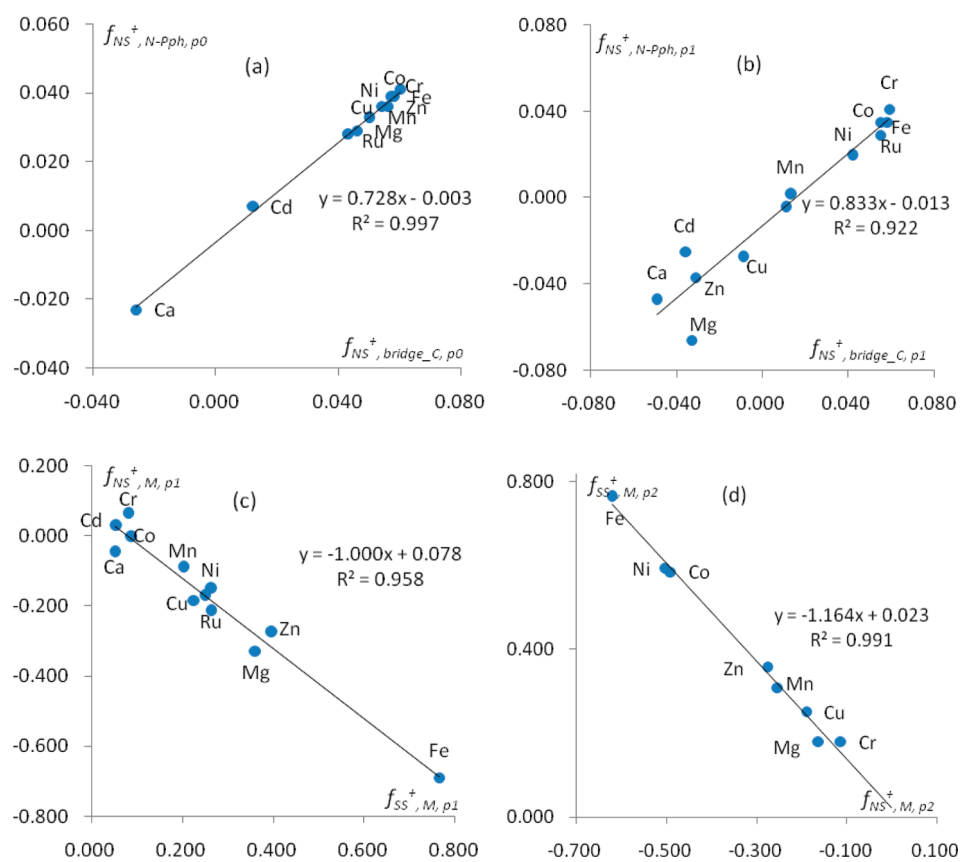
of the three systems. This quantity provides the information for the response of the total electron density condensed on atom k with respect to the increase of the total spin number. A negative  $f_{NS,k}^+$  indicates that the atom inclines to be oxidized (electron donation) once excited. This is because according to eq 15 a better electron donor has a larger HOMO spin density and thus a more negative  $f_{NS,k}^+$  according to the equation. From Table 2, we found out on average from p0 to p1 to p2, the  $f_{NS,k}^+$  value of metal cations  $-0.013$  for p0, to  $-0.171$  for p1, to  $-0.302$  for p2. This finding demonstrates that as more pyridine groups are bonded to the metal ion in the porphyrin complex, the metal ion itself becomes a better electron donor (or worse acceptor of electrons), consistent with other results from the conceptual density functional theory. Another prominent feature of the  $f_{NS,k}^+$  results in Table 2 is that in all three cases (p0, p1, and p2) the iron cation has the smallest  $f_{NS,k}^+$  value, indicating that the Fe center of the Fe-porphyrin complex possesses the largest electron donation capability. Recall that in our earlier work Ru and Fe were found to have similar reactivities within the nonspin-resolved CDFT framework. From both  $f_{SS,k}^+$  and  $f_{NS,k}^+$  results in Table 2, in addition to the global indices in Table 1, we can clearly see that in the spin resolution these two metal complexes are markedly different in reactivity properties.

To provide further evidence of the disparity in reactivity between different metal systems, as well as the unique behavior of the Fe-porphyrin system in regioselectivity of spin-involved reactions, we present three-dimensional contour surfaces of spin polarized Fukui function,  $f_{NS,k}^+$  for p0, p1, and p2 metal-porphyrin complexes for Fe, Ru, and Zn ions, respectively (Figure 1). It is observed that for the Zn systems, the positive (red color) and negative (green color) regions from p0 to p1 to p2 are not very different, that almost all of the surfaces are distributed among the atoms on the porphyrin rings, and that no Fukui function contribution is seen on the Zn metal ion, indicating that (i) Zn ion is not the reactive site for the redox reaction and (ii) there is no significant reactivity change between p0 and p1 or p1 and p2 for the Zn-porphyrin complex. In the Fe-porphyrin systems, however, we find that from p0 to p1 and from p1 to p2, the negative (green) regions, representing the electron donation capability, gradually concentrates onto the Fe ion, with the green regions on the porphyrin rings progressively diminishing, suggesting that as more pyridine ligands are bonded to Fe, the metal ion itself becomes more of a nucleophile and is more capable of donating electrons, which is shown to be the case in experiments when it participates in redox reactions in hemoproteins. Looking at the Ru-complex series, we find that the trend of  $f_{NS,k}^+$  is opposite to the Fe-complex series. At p0, the Ru ion is the only electron-donor, but when p0 is changed to p1 after one pyridine is bonded and then to p2 with two axial pyridine ligands, the green regions become more and more delocalized, showing that the metal ion's electron-donating capacity is tremendously hindered by the pyridine binding to the metal ion. Since it is well-known that axial ligands of porphyrin are essential for the catalytic functions of hemoproteins in its physiological functions, we can see from Figure 1 that in the p2 case, the Fe ion differs from other metal ions by a concentration of the electron-donating capability (green color) solely onto the metal ion. This unique behavior from the  $f_{NS,k}^+$  Fukui function of the Fe-porphyrin complex thus provides strong evidence for the metal-binding specificity of porphyrin.

Note that the two Fukui functions,  $f_{SS,k}^+$  and  $f_{NS,k}^+$ , are inter-related, as are these functions on different atoms. A few linear relationships of these functions are shown in Figure 2. The first two correlations are between Fukui functions  $f_{NS,k}^+$  on nitrogen



**Figure 1.** The spin polarized Fukui function,  $f_{NS}^{+}(r)$ , of Fe, Ru, and Zn—porphyrin complexes in all three cases. The iso-surface value is 0.001 au. The color in red represents positive regions, and the color in green denotes negative regions.



**Figure 2.** Linear relationship between local spin polarized Fukui functions  $f_{SS}^{+}$  and  $f_{NS}^{+}$ .



and meso-carbon atoms,  $f_{NS,N-Pph}^+$  and  $f_{NS,bridge-C}^+$  in p0 and p1 systems with  $R^2 = 0.997$  and  $R^2 = 0.922$ , respectively. Figure 2 shows a strong linear relationships between the two Fukui functions on the metal ion,  $f_{SS,M}^+$  and  $f_{NS,M}^+$ , in p1 and p2 cases with  $R^2 = 0.958$  and  $R^2 = 0.991$ , respectively. These correlations can be explained in terms of eqs 13 and 15. If the relative contribution of one component of the two quantities on the right-hand side of these two equations is much larger than the other one, its dominance will dictate that the two equations are strongly correlated. The strong property correlations between N and C atoms illustrated in Figures 2a and 2b demonstrate that there exist intrinsic relationships of chemical reactivity properties among the atoms in the systems as a whole. In Figures 2a and 2b, Fe is in the top right corner. In Figure 2c Fe is on the lower right corner, and in Figure 2d Fe is located at the top left corner. These relationships confirm the main finding from this work. That is, iron is a special porphyrin binding metal ion. The iron cation in the Fe–porphyrin system is the preferred site for electron donation and local spin density change. Again, these results demonstrate the uniqueness and metal-binding specificity of porphyrin with the iron metal cation, much different from other metal complexes including ruthenium. Notice that in Figure 2d, Ru and Cd were removed because they were outliers, which may be because a different basis set was employed for them. However, the removal of these points does not change the conclusion drawn from the plot. It should also be remarked that the reactivity indices pertaining to the spin multiplicity decreasing process such as  $\mu_S^-$ ,  $\omega_S^-$ ,  $f_{SS,k}^-$ , and  $f_{NS,k}^-$ , etc., yields results and conclusions that are completely in line with the results discussed above.

## 5. Conclusions

Porphyrin metalated with a divalent metal cation, mostly Fe in Nature, is one of the key cofactors in hemoproteins. The explanation of the metal-binding specificity of porphyrin is still a matter of debate. On the basis of our early work on this subject, in this paper, we utilized the spin-polarized version of conceptual density functional theory to investigate the reactivity of a series of (pyridine)<sub>n</sub>–M(II)–porphyrin complexes with M = Mg, Ca, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ru, and Cd and  $n = 0, 1$ , and 2, and reveal the unique behavior of the Fe–porphyrin complexes with respect to a number of reactivity descriptors such as spin potential, spin hardness, spin-philicity, and spin-polarized Fukui functions.

We found that in agreement with the spin-restricted version of CDFT, both global and local reactivity descriptors exhibit considerable differences between Fe–porphyrin and other metal–porphyrin complexes. But different from our earlier work, results at the spin resolution showed a remarkable difference between Ru and Fe complexes. These results suggest that the specificity difference of porphyrin between Fe and Ru cations originates from the electronic (spin) properties and that to differentiate their behaviors one has to resort to spin resolved reactivity indices.

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