Generation of Orbitals that Control Molecular Reactivity: Projected Reactive Orbital Approach

Hajime Hirao*,† and Tomohiko Ohwada*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received: June 7, 2005; In Final Form: June 30, 2005

A method that generalizes the notion of frontier orbital (FO) theory is introduced. The method is based on the projected reactive orbitals (PROs). Although PROs have been shown to describe local reactivity better than FOs in high-symmetry systems, the PRO method needs an arbitrary choice of a reference atomic orbital (AO), causing ambiguity of the method and poor applicability to low-symmetry molecules. To overcome these difficulties, we examined three different kinds of methods for uniquely determining the reference AO, one of which (Method 1) was reported by other authors (Kurita, Y.; Takayama, C. *J. Phys. Chem. A* **1997**, *101*, 5593−5595). We specifically applied the methods to the prediction of basicities of heteroaromatic amines. The study showed that the newly developed reactivity-index maximization method (Method 3) yields the most reasonable PRO.

1. Introduciton

The frontier orbital (FO) theory,[1−3] which suggests that the stabilization of a reacting system through electron delocalization is determined by specific molecular orbitals (MOs) called the HOMO and LUMO (FOs), is useful in a wide range of reactivity problems. Indeed, the theory enables one to interpret and predict chemical reactivities and selectivities and is thus widely used in connection with accurate quantum chemistry. The simplicity of the FO theory is one of the factors behind its spread among experimentalists, who often require theory to give not only accuracy, but also pictorial means with which to explain chemical phenomena. Nevertheless, canonical MOs, which diagonalize the Lagrange multiplier matrix in the Roothaan−Hall equation,[4,5] are generally delocalized or scattered over the entire molecule; therefore, an FO of a large molecule is very often far from the chemists' common local reactivity concept of a functional group. This means that information on reactivity of a specific site is not always derived from the FOs. In addition, since MO energy levels become closer in energy as the size of a molecule increases, MOs other than the FOs must be considered while carrying out an orbital analysis, but are neglected for simplicity. A reasonable solution to this problem has been suggested based on superdelocalizability,[6] but this is calculated only for one reaction site.[7] Furthermore, the orbital phases cannot be considered in such a method,[7] despite the well-known importance of the orbital-symmetry relationship in the orbital concept.[8−11] Development of novel orbital methods free from these problems, which can usefully contribute to experimental chemists, is hence of utmost significance.

The *reactive orbital* concept seems to be the best solution to these problems.[12−15] It generates an orbital localized on a given reaction center, it takes into account all of the MOs without relegation, and it keeps the orbital-phase information. It should be noted here that extreme orbital localization results in nothing else but inactive bonding or nonbonding orbitals suited to description of chemical bonds; such orbitals are not necessarily the reactive orbitals that would control a reaction. A reactive orbital is obtained in the original definition by first determining an appropriate *reference atomic orbital* (*AO*),[12,16] represented by a few atomic orbitals (AOs) on the reaction center. The reference AO can be regarded as the orbital of a molecule used to form a new chemical bond with a reagent. The reference AO is then projected onto the occupied or unoccupied MO space to obtain a *projected reactive orbital* (*PRO*), which is, unlike a canonical MO, localized on a reaction center. It is not difficult to define such an AO in cases where a molecule possesses a high symmetry and the minimal basis set is used, because the selection of a reference AO can be made intuitively (but arbitrarily). For general applications of the method to molecules without ambiguity, however, a reasonable procedure for determining the reference AO is necessary. Despite this need, not much work along this line has been done so far; the practical information about the core of the PRO method is obviously insufficient. We find in the literature only one method dealing with this problem by Kurita and Takayama, who proposed to define a unique reference AO that gives the extreme value to the energy of the resultant reactive orbital.[7] Thus, aiming at obtaining more systematic knowledge about methods for determining a reference AO, we herein explore the further possibility of the PRO method.

2. Computational Details

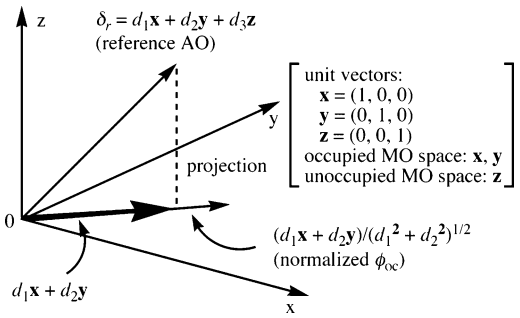
2.1. Model System and MO Calculations. We performed calculations on the same molecules as those in ref 7, i.e., heteroaromatic amines, which are frequently used in synthesizing drugs and agrochemicals. It should be noted that the HOMOs of these molecules are not lone-pair MOs but π-type MOs. To perform a PRO analysis, a reference AO should be specifically determined, which is not an intuitive task any more in such a complex system.

* Address correspondence to these authors. E-mail: hiraoh@yfaat.ch.huji.ac.il, ohwada@mol.f.u-tokyo.ac.jp.

† Present address: Department of Organic Chemistry and The Lise Meitner-Minerva Center for Computational Quantum Chemistry, The Hebrew University of Jerusalem.

10.1021/jp0530294 CCC: $30.25
Published on Web 08/02/2005

SCHEME 1: A 3D Image of the Projection of a Reference AO onto the 2D Occupied MO Space



We performed geometry optimizations on these molecules at the HF/6-31G* level by using Gaussian 98.[17] The obtained HF/6-31G* canonical MOs were used to obtain reactive orbitals explained below. Reference AOs and PROs were visualized by Molden.[18]

2.2. Projected Reactive Orbital (PRO) Method. The starting point of the PRO method (also called the localized frontier orbital (LFO) method) is the assumption that we already have an appropriate reference AO δ_r, which is usually expressed by the combination of a few AOs χ_μ on the reaction center r:[12,13]

$$\delta_r = \sum_{\mu}^{\text{nao}} C_\mu \chi_\mu \tag{1}$$

where nao is the number of basis AOs used for the expansion of δ_r with a set of coefficients $\{C_\mu\}$. The predefined δ_r is projected onto the occupied MO space or the unoccupied MO space to obtain an occupied reactive orbital ϕ_{oc} or an unoccupied reactive orbital ϕ_{unoc}, respectively.[12−15] We henceforth limit our discussion to an occupied reactive orbital for simplicity, but an unoccupied reactive orbital is obtained similarly. Specifically, after rewriting δ_r as a linear combination of MOs ψ_i (LCMO) (eq 2), a normalized occupied PRO ϕ_{oc} is represented by using the LCMO coefficients as eq 3.[12−15]

$$\delta_r = \sum_{i}^{\text{oc}} d_{ir}\psi_i + \sum_{j}^{\text{unoc}} d_{jr}\psi_j \tag{2}$$

$$\phi_{oc} = (\sum_{i}^{\text{oc}} d_{ir}\psi_i)/(\sum_{i}^{\text{oc}} d_{ir}^2)^{1/2} \tag{3}$$

where "oc" and "unoc" mean that the sums run over all the occupied MOs and all the unoccupied MOs, respectively. Scheme 1 illustrates this projection procedure schematically in the simple three-dimensional vector space, in which any vector from the origin can be represented by specifying the respective components (d_1, d_2, and d_3) of the orthonormal unit vectors **x**, **y**, and **z**. Let us assume here that the *xy*-plane is the occupied MO space, while the *z*-axis is the unoccupied MO space. In this example, the numbers of the occupied MOs and the unoccupied MOs are thus 2 and 1, respectively. A vector close to the reference AO (vector here) δ_r in the occupied MO space is obtained by projection of δ_r onto the *xy*-plane. By normalizing this two-dimensional vector, we obtain the occupied reactive orbital (vector) ϕ_{oc}. As a result, δ_r is resolved into the occupied MO component, thereby allowing us to evaluate the electron-donating power of the reaction center. This 3D picture can be extended to more complex MO systems, in which each orthonormal MO (total number: N) can be considered as a unit vector, and the N-dimensional MO space can be divided into the occupied and unoccupied MO spaces.

The energy level of ϕ_{oc} is calculated by

$$\lambda_{oc} = (\sum_{i}^{\text{oc}} d_{ir}^2 \epsilon_i)/(\sum_{i}^{\text{oc}} d_{ir}^2) \tag{4}$$

where ϵ_i is the energy of MO ψ_i. This value evaluates the electron-donating ability of a reaction center. Normalized δ_r can also be written as[13]

$$\delta_r = a\phi_{oc} + (1 - a^2)^{1/2}\phi_{unoc} \tag{5}$$

The quantity $2a^2$ ($0 \le a^2 \le 1$) counts the number of electrons occupying δ_r; therefore, a^2 is regarded as the localization of electrons within ϕ_{oc} at δ_r. This value has an analogous meaning to the Fukui function of the structural unit.[13] The reactivity is determined in the orbital concept mainly by orbital distribution of the reaction center and the level of orbital energy: in an approximate sense, the former is proportional to the stabilization energy, while the latter is inversely proportional. Thus, we may define a superdelocalizability-like *reactivity index* as

$$\rho_{oc} = -a^2/\lambda_{oc} \tag{6}$$

These theoretical values based on a PRO can be used to evaluate the chemical reactivity of a specific site in a molecule. From the above discussion, however, we can see that the appropriate determination of a reference AO is the essence of the PRO method, while it is not necessarily clear how we should determine δ_r. This ambiguity is likely to cause several practical problems, e.g., (a) intuitively determined δ_r would sometimes not give a PRO describing reactivity, and (b) δ_r and its resulting PRO are different from user to user, which prevents fair comparison and routine use of the method. These are the reasons why we pursue better methods for determining a unique reference AO in this paper.

2.3. Equations for Determining a Reference AO. *2.3.1. Method 1* (λ_{oc} *Maximization*). We call the method of Kurita et al.[7] "Method 1", which is explained in detail in ref 7. In brief, Method 1 determines $\{C_\mu\}$ in eq 1 under the condition that λ_{oc} has a maximum value. They showed that such C_μ values are analytically obtained by solving a matrix equation. In addition to the λ_{oc} values reported in ref 7, we calculated a^2 and ρ_{oc} values on the basis of the obtained PROs by this method.

2.3.2. Method 2 (a^2 *Maximization*). We shall next derive an equation for obtaining C_μ values, which maximize a^2. Since each AO can be expressed as LCMO:

$$\chi_\mu = \sum_{i}^{\text{oc}} D_\mu^{\,i}\psi_i + \sum_{j}^{\text{unoc}} D_\mu^{\,j}\psi_j \tag{7}$$

d_{ir} and a^2 can be represented as follows.

$$d_{ir} = \sum_{\mu} C_\mu D_\mu^{\,i} \tag{8}$$

$$a^2 = \sum_{i}^{\text{oc}} d_{ir}^2 = \sum_{i}^{\text{oc}} (\sum_{\mu} C_\mu D_\mu^{\,i})^2 \tag{9}$$

Assuming that the reference AO is normalized:

$$\langle \delta_r | \delta_r \rangle = \sum_i^{\mathrm{oc}} {d_{ir}}^2 + \sum_j^{\mathrm{unoc}} {d_{jr}}^2$$
$$= \sum_i^{\mathrm{oc}} (\sum_\mu C_\mu {D_\mu}^i)^2 + \sum_j^{\mathrm{unoc}} (\sum_\mu C_\mu {D_\mu}^j)^2$$
$$= 1 \qquad (10)$$

we maximize the following functional L, with respect to the coefficients C_μ:

$$L = \sum_i^{\mathrm{oc}} (\sum_\mu C_\mu {D_\mu}^i)^2 - \omega \{ \sum_i^{\mathrm{oc}} (\sum_\mu C_\mu {D_\mu}^i)^2 + \sum_j^{\mathrm{unoc}} (\sum_\mu C_\mu {D_\mu}^j)^2 - 1 \} \qquad (11)$$

where ω is a Lagrange multiplier. We set the first variation in L equal to zero.

$$\delta L = \sum_i^{\mathrm{oc}} (2 \sum_\mu C_\mu {D_\mu}^i) \delta C_\nu {D_\nu}^i - \omega \{ \sum_i^{\mathrm{oc}} (2 \sum_\mu C_\mu {D_\mu}^i) \delta C_\nu {D_\nu}^i + \sum_j^{\mathrm{unoc}} (2 \sum_\mu C_\mu {D_\mu}^j) \delta C_\nu {D_\nu}^j \}$$
$$= 2 \delta C_\nu [\sum_i^{\mathrm{oc}} (\sum_\mu C_\mu {D_\mu}^i) {D_\nu}^i - \omega \{ \sum_i^{\mathrm{oc}} (\sum_\mu C_\mu {D_\mu}^i) {D_\nu}^i + \sum_j^{\mathrm{unoc}} (\sum_\mu C_\mu {D_\mu}^j) {D_\nu}^j \}]$$
$$= 2 \delta C_\nu \sum_\mu [\sum_i^{\mathrm{oc}} ({D_\mu}^i {D_\nu}^i) C_\mu - \omega \{ \sum_i^{\mathrm{oc}} ({D_\mu}^i {D_\nu}^i) + \sum_j^{\mathrm{unoc}} ({D_\mu}^j {D_\nu}^j) \} C_\mu]$$
$$= 0 \qquad (12)$$

Since δC_ν is arbitrary, the term within the square bracket should be zero.

$$\sum_\mu \sum_i^{\mathrm{oc}} ({D_\mu}^i {D_\nu}^i) C_\mu = \omega \sum_\mu \{ \sum_i^{\mathrm{oc}} ({D_\mu}^i {D_\nu}^i) + \sum_j^{\mathrm{unoc}} ({D_\mu}^j {D_\nu}^j) \} C_\mu \qquad (13)$$

By introducing matrixes **P**, **Q**, and **R**:

$$(\mathbf{P})_{\mu\nu} = \sum_i^{\mathrm{oc}} {D_\mu}^i {D_\nu}^i \qquad (14)$$

$$(\mathbf{Q})_{\mu\nu} = \sum_j^{\mathrm{unoc}} {D_\mu}^j {D_\nu}^j \qquad (15)$$

$$\mathbf{R} = \mathbf{P} + \mathbf{Q} \qquad (16)$$

we obtain the final equation to be solved.

$$\mathbf{PC} = \mathbf{RCw} \qquad (17)$$

where **C** is a nao × nao square matrix of the expansion coefficients $\{C_\mu\}$, and **w** is a diagonal matrix of localizability a^2. Because **P** does not depend on **C** unlike the Fock matrix in the Roothaan−Hall equation, we can obtain the solution by only one diagonalization.

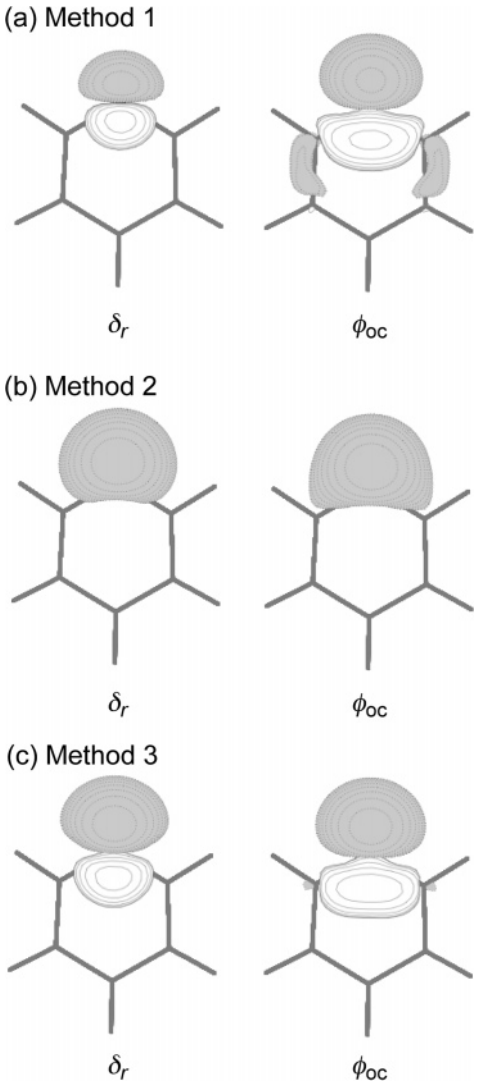


Figure 1. Normalized reference AOs and PROs of pyridine.

2.3.3. Method 3 (ρ_{oc} *Maximization*). We also examined a method that maximizes the reactivity index (eq 6). Because we could not obtain an analytical equation, we maximized ρ_{oc} by minimizing $1/\rho_{oc}$ (variables: $\{C_\mu\}$) using the Davidon−Fletcher−Powell (DFP) method.[19,20] The calculation time needed to solve a problem by Method 3 is almost the same as those for the above two analytical methods (a few seconds). Therefore, the numerical solution to the problem is not a disadvantage. We need an initial guess of $\{C_\mu\}$ in Method 3, which can be, for example, 1.0 only for the coefficient of a nitrogen inner p-type AO approximately pointing in the lone-pair direction, and 0.0 for those of other AOs.

3. Results and Discussion

3.1. Reference AOs and PROs. We used a combination of all s- and p-type valence AOs (total number: 8) on the basic nitrogen to expand δ_r (eq 1) in Method 1, which is completely the same as the procedure adopted by Kurita et al.[7] As they reported, if the d-type AOs were included in the expansion of δ_r, the equation could not be solved. On the other hand, in Methods 2 and 3, we did not encounter this difficulty; thus, we utilized all the s-, p-, and d-type basis AOs (total number: 15)

TABLE 1: Summary of pK_a Values and PRO Values[a]

			Method 1			Method 2			Method 3		
no.	molecule	pK_a[b]	λ_{oc}	a^2	ρ_{oc}	λ_{oc}	a^2	ρ_{oc}	λ_{oc}	a^2	ρ_{oc}
1	1,2,5-thiadiazole	−4.9	−0.536	0.708	1.321	−0.854	0.995	1.166	−0.563	0.936	1.662
2	1,2-benzisoxazole	−4.7	−0.544	0.692	1.271	−0.841	0.997	1.186	−0.564	0.932	1.651
3	isoxazole	−2.97	−0.540	0.698	1.293	−0.837	0.997	1.191	−0.560	0.930	1.662
4	2,1-benzisoxazole	−2.20	−0.534	0.693	1.298	−0.834	0.997	1.196	−0.554	0.929	1.678
5	isothiazole	−0.51	−0.508	0.682	1.343	−0.833	0.995	1.195	−0.536	0.933	1.740
6	benzoxazole	−0.13	−0.517	0.731	1.414	−0.792	0.996	1.256	−0.536	0.941	1.756
7	2,1-benzisothiazole	−0.05	−0.504	0.689	1.365	−0.831	0.995	1.197	−0.532	0.933	1.753
8	pyrazine	0.4	−0.511	0.666	1.303	−0.807	0.995	1.234	−0.533	0.947	1.775
9	1-methylindazole	0.42	−0.518	0.707	1.364	−0.808	0.996	1.233	−0.537	0.933	1.737
10	2-chloropyridine	0.7	−0.509	0.655	1.287	−0.825	0.993	1.204	−0.532	0.946	1.777
11	oxazole	0.8	−0.510	0.735	1.440	−0.787	0.996	1.264	−0.528	0.939	1.779
12	pyrimidine	1.1	−0.506	0.690	1.364	−0.793	0.995	1.254	−0.526	0.947	1.800
13	1,2,3-triazole (N_3)[c]	1.17	−0.516	0.727	1.410	−0.806	0.996	1.236	−0.531	0.930	1.754
14	benzothiazole	1.2	−0.510	0.685	1.345	−0.834	0.993	1.191	−0.533	0.939	1.761
15	1-methyl-1,2,3-triazole (N_3)[c]	1.25	−0.509	0.728	1.429	−0.799	0.996	1.247	−0.524	0.930	1.775
16	indazole	1.31	−0.522	0.716	1.371	−0.809	0.997	1.232	−0.540	0.934	1.730
17	2-methylindazole	2.02	−0.508	0.710	1.397	−0.802	0.997	1.242	−0.526	0.930	1.767
18	1-methylpyrazole	2.06	−0.507	0.714	1.407	−0.799	0.996	1.247	−0.525	0.930	1.773
19	pyridazine	2.1	−0.510	0.642	1.261	−0.802	0.996	1.242	−0.529	0.942	1.779
20	1,2,4-triazole (N_4)[c]	2.45	−0.507	0.744	1.468	−0.787	0.996	1.266	−0.523	0.938	1.793
21	pyrazole	2.52	−0.513	0.719	1.401	−0.802	0.996	1.242	−0.530	0.932	1.757
22	thiazole	2.53	−0.505	0.695	1.376	−0.831	0.994	1.196	−0.527	0.937	1.778
23	3-chloropyridine	2.8	−0.501	0.650	1.297	−0.806	0.994	1.234	−0.525	0.946	1.804
24	1-methyl-1,2,4-triazole (N_4)[c]	3.20	−0.502	0.745	1.485	−0.780	0.996	1.277	−0.517	0.938	1.814
25	4-chloropyridine	3.8	−0.500	0.656	1.312	−0.799	0.995	1.245	−0.522	0.947	1.812
26	pyridine	5.2	−0.485	0.652	1.345	−0.784	0.995	1.269	−0.507	0.945	1.864
27	benzimidazole	5.53	−0.490	0.729	1.487	−0.779	0.996	1.277	−0.508	0.936	1.843
28	1-methylbenzimidazole	5.57	−0.487	0.729	1.497	−0.776	0.996	1.282	−0.505	0.936	1.855
29	3-methylpyridine	5.7	−0.482	0.651	1.351	−0.782	0.995	1.273	−0.504	0.945	1.874
30	2-methylpyridine	6.0	−0.479	0.639	1.335	−0.781	0.995	1.274	−0.502	0.944	1.880
31	4-methylpyridine	6.0	−0.482	0.657	1.363	−0.781	0.995	1.274	−0.503	0.945	1.877
32	imidazole	6.95	−0.479	0.733	1.530	−0.773	0.995	1.288	−0.496	0.934	1.883
33	1-methylimidazole	7.33	−0.476	0.734	1.543	−0.769	0.996	1.295	−0.492	0.933	1.897

[a] λ_{oc} is in au and ρ_{oc} is in au^{-1}. [b] From ref 22 (see also ref 7). [c] The basic nitrogen examined in the analysis.

on the basic nitrogen atom for the expansion. By using these sets of AOs, we obtained reference AOs and PROs by the three methods. In Method 1, since the highest lying PRO was a π-type orbital, the second PRO was selected for evaluating the basicity of amines.[7] In Method 2, the most localized PRO was an s-type orbital of nitrogen, but the second one corresponded to the lone pair. Thus, here again, the second PRO was selected for analysis. Finally in Method 3, we obtained only one solution and did not need this kind of selection, because this method is a numerical one. Figure 1 compares the orbitals δ_r and ϕ_{oc} obtained by the three methods taking pyridine as an example. In each case, δ_r was completely localized on the nitrogen atom, just because δ_r is expanded only by nitrogen AOs. The PROs ϕ_{oc} values were obtained by projecting δ_r, and were delocalized toward adjacent atoms to some extent. We can visually understand from Figure 1 that these orbitals, which represent reactivity, were obtained without loss of the sp^2-like orbital-phase information. The PRO of Method 1 is more delocalized than that of the other two PROs due to the loose condition of localization. In Method 2, the orbitals were rather s-like. This is because the strict condition imposed to localize the orbital gathered low-lying AOs, which will not be delocalized toward other atoms upon projection. It is interesting to note that the PRO of Method 3, prepared from only an isolated pyridine molecule, is similar in shape to the interaction frontier orbital, which was obtained from the amine-H^+ interacting system.[21]

3.2. Performance of the Three PRO Methods. We applied the three PRO methods to the amine molecules. The results are summarized in Table 1.

In Figure 2, we show the correlation between the experimental pK_a values[22] and theoretically calculated PRO values. The λ_{oc} values obtained by Method 1 showed a fair correlation to pK_a as reported in ref 7 ($r^2 = 0.903$). However, the correlation between pK_a and ρ_{oc} was not good ($r^2 = 0.304$), which is ascribed to the scattered behavior of a^2 among molecules (Figure 2b). This occurs probably because the localization of the reactive orbital is achieved in this method only by the limited use of the AOs (valence s- and p-AOs on N) in the expansion of δ_r out of the total AOs in a molecule. Based on this assumption, we imposed a more strict condition to the localization of PROs in Method 2, where δ_r was expanded similarly by a limited number of AOs (all the AOs on N), and the resultant a^2 value was maximized as well. One notices that the a^2 values remained almost constant over the molecules in this method (Figure 2b), when looking at the plot for Method 2 in the equivalent scale width of a^2 to the plot for Method 1. The correlation of λ_{oc} and ρ_{oc} in Method 2 was, however, not good ($r^2 = 0.729$ for λ_{oc} and $r^2 = 0.712$ for ρ_{oc}). We can ascribe this result to the too low energies of the lone-pair PROs obtained by Method 2, which have a large s-character (Figure 1b), and is thus not reactive. These two results indicate that the effects of orbital energy and localization should be simultaneously considered to obtain a reasonable PRO. Indeed, Method 3, which maximizes the reactivity index and therefore takes into account the two effects simultaneously, showed the best correlations for both λ_{oc} ($r^2 = 0.955$) and ρ_{oc} ($r^2 = 0.931$) of the three methods. In particular, the correlation in the ρ_{oc} plot was remarkably improved in Method 3 over that in Method 1 (Figure 2c). For instance, Method 1 gave relatively small ρ_{oc} values to chloropyridines (10, 23, and 25), while Method 3 provided quite reasonable values. This could be ascribed to the extensively delocalized PROs of pyridines (Figure 1), which thus have small a^2 values.

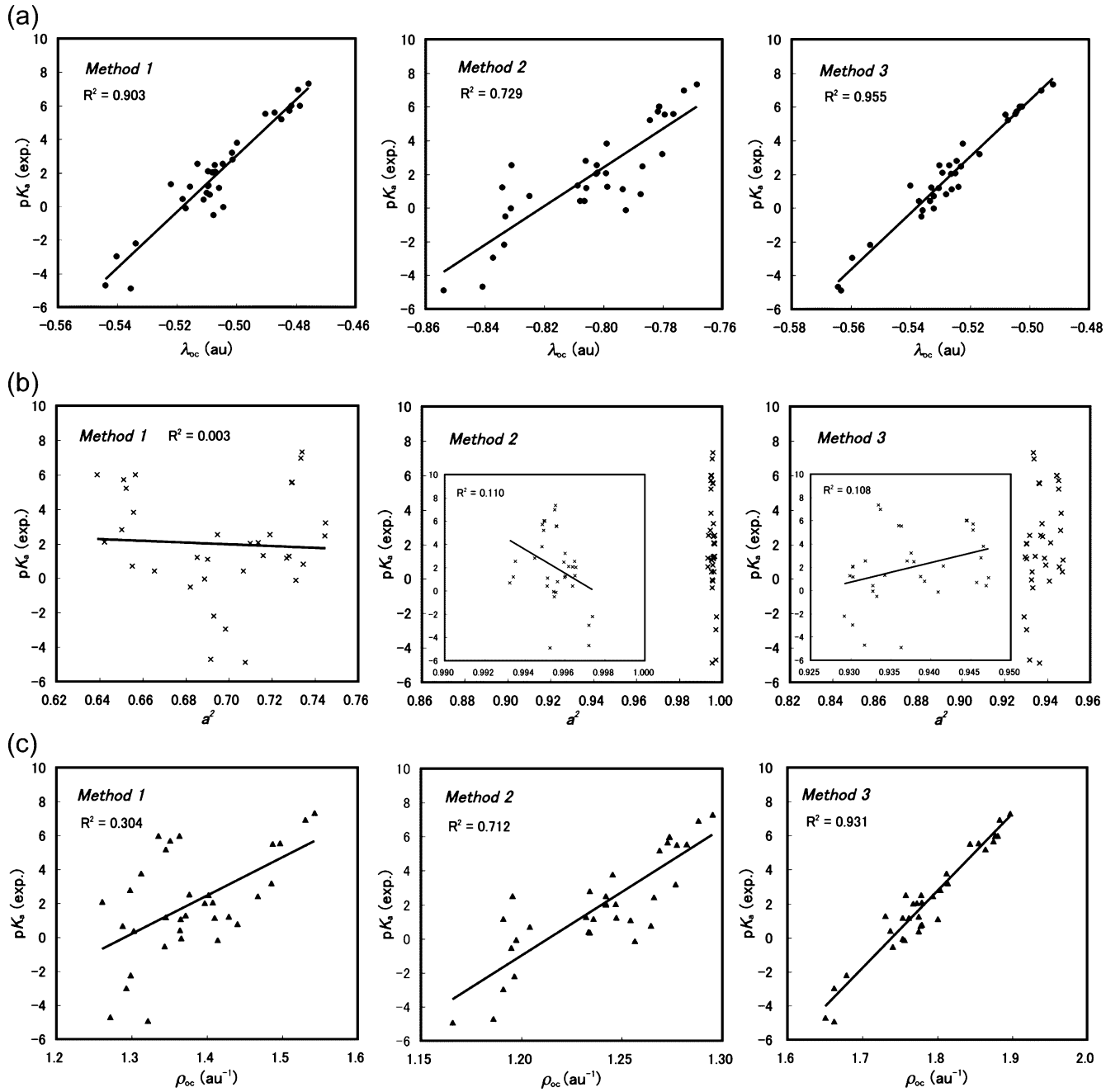


Figure 2. Correlation between (a) pK_a and λ_{oc}, (b) pK_a and a^2, and (c) pK_a and ρ_{oc}.

The above results clearly show that Method 3 predicts reactivity most reliably, followed by Method 1 and then Method 2. Because our basic concept in this study owes a great deal to ref 7, Method 3 can be regarded as an improved or modified PRO version of Method 1.[7] Method 2 however seems to possess only a poor ability to describe reactivity. These emphasize the importance of the simultaneous consideration of the effects of orbital energy and orbital localization in extracting the best-balanced *single reactive orbital* from the occupied or unoccupied MO space. In practice, as was done in Method 3, as well as in our reference-AO-free method (RHO method),[23−26] this can be achieved by maximizing the superdelocalizability-like reactivity index. The merit of these methods is the capability of preparing a putative interacting orbital not from an interacting system, but only from an isolated state. We believe that such reactive orbital methods are at least qualitatively useful and moreover highly suited to quick prediction and interpretation of molecular reactivities.

4. Conclusion

In this paper, we dealt with an important question: How can we obtain the most reasonable orbital that represents molecular reactivity? We addressed this issue within the framework of the PRO method. We specifically focused on the problem of how to obtain a unique reference AO needed in the PRO analysis. We compared three different kinds of PRO methods, one of which was reported previously in ref 7, while the others were newly developed in this study. Encouragingly, it was found that our original reactivity-index maximization method (Method 3) shows the best predictability of basicities of heteroaromatic amines. In this method, a significant improvement over Method 1 was observed particularly in the predictability of the reactivity index ρ_{oc}.

Acknowledgment. H.H. is indebted to Prof. S. Shaik for enlightening comments. Some of the calculations were carried out at the Computer Center of the Institute for Molecular

Science. We thank this computational facility for generous allotments of computer time.

References and Notes

(1) Fukui, K.; Yonezawa, T.; Shingu, H. *J. Chem. Phys.* **1952**, *20*, 722−725.
(2) Fukui, K. *Science* **1987**, *218*, 747−754.
(3) Fukui, K.; Fujimoto, H. *Frontier Orbitals and Reaction Path*: *Selected Papers of Kenichi Fukui*; World Scientific: Singapore, 1997.
(4) Roothaan, C. C. J. *Rev. Mod. Phys.* **1951**, *23*, 69.
(5) Hall, G. G. *Proc. R. Soc.* (*London*) **1951**, *A205*, 542.
(6) Fukui, K.; Yonezawa, T.; Nagata, C. *Bull. Chem. Soc. Jpn.* **1954**, *27*, 423−427.
(7) Kurita, Y.; Takayama, C. *J. Phys. Chem. A* **1997**, *101*, 5593−5595.
(8) Fukui, K. In *Molecular Orbitals in Chemistry, Physics, and Biology*; Lowdin, P.-O., Pullman, B., Eds; Academic Press: New York, 1964; p 513.
(9) Fujimoto, H.; Sakata, K.; Fukui, K. *Int. J. Quantum Chem.* **1996**, *60*, 401.
(10) Woodward, R. B.; Hoffman, R. *J. Am. Chem. Soc.* **1965**, *87*, 395.
(11) Hoffmann, R.; Shaik, S.; Hiberty, P. C. *Acc. Chem. Res.* **2003**, *36*, 750−756.
(12) Fujimoto, H.; Mizutani, Y.; Iwase, K. *J. Phys. Chem.* **1986**, *90*, 2768−2772.
(13) Fujimoto, H.; Satoh, S. *J. Phys. Chem.* **1994**, *98*, 1436−1441.
(14) Hirao, H.; Omoto, K.; Fujimoto, H. *J. Phys. Chem. A* **1999**, *103*, 5807−5811.
(15) Hirao, H.; Fujimoto, H. *J. Phys. Chem. A* **2000**, *104*, 6649−6655.
(16) This AO is usually called a reference orbital function, but henceforth in this paper, we call it a reference AO to avoid confusion.
(17) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; 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. A.; 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*; Gaussian, Inc.: Pittsburgh, PA, 1998.
(18) Schaftenaar, G.; Noordik, J. H. *J. Comput.-Aided Mol. Des.* **2000**, *14*, 123−134.
(19) Davidon, W. C. *AEC Res. Dev. Rep.* **1959**, ANL-5990.
(20) Fletcher, R.; Powell, M. J. D. *Comput. J.* **1963**, *6*, 163−168.
(21) Fukui, K.; Koga, N.; Fujimoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 196−197.
(22) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon Press: New York, 1985.
(23) Hirao, H.; Ohwada, T. *J. Phys. Chem. A* **2003**, *107*, 2875−2881.
(24) Nakamura, S.; Hirao, H.; Ohwada, T. *J. Org. Chem.* **2004**, *69*, 4309−4316.
(25) Ohwada, T.; Hirao, H.; Ogawa, A. *J. Org. Chem.* **2004**, *69*, 7486-7494.
(26) Hirao, H.; Ohwada, T. *J. Phys. Chem. A* **2005**, *109*, 816−824.