Theoretical Study of Reactivities in Electrophilic Aromatic Substitution Reactions: Reactive Hybrid Orbital Analysis

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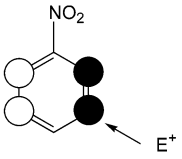
Orbital interactions in electrophilic aromatic substitution reactions of anisol, nitrobenzene, and some other analogues were studied. A single frontier orbital (FO), i.e., the HOMO of substituted benzenes, particularly of nitrobenzene, does not account for the regioselectivities of the reaction. We first applied configuration analysis to identify the relative importance of orbital interactions between an electrophile (H^+ in this work) and the substituted benzenes. We herein define the *reactive hybrid orbital* (RHO) method for measuring the reactivity of each carbon atom of substituted benzene. An RHO is made by combining all occupied molecular orbitals properly so that the reactivity index for a reaction center, which is similar to superdelocalizability, is maximized. The RHO reactivity indices, λ_{oc}, ρ_{oc}, and ρ'_{oc}, were shown to predict correctly the experimentally observed regioselectivity and reactivity in the electrophilic aromatic substitution reactions of anisol, nitrobenzene, and other monosubstituted benzenes. Moreover, it was shown that the RHO values for carbon atoms in a polycyclic aromatic hydrocarbon are in good agreement with experimentally determined partial rate factors.

Introduction

Electrophilic aromatic substitution is one of the most thoroughly studied reactions in organic chemistry.[1−20] It was to this class of reactions that the frontier orbital (FO) theory was applied for the first time by Fukui et al.[21,22] Since then, the FO theory has gained general acceptance by the chemical community and has been utilized to interpret reactivities and selectivities of chemical reactions.[23] Nevertheless, the FO theory does not predict meta selectivity in the electrophilic substitution of nitrobenzene.[1a,11b] That is, the highest occupied molecular orbital (HOMO) of nitrobenzene has equivalent amplitudes on the ortho and meta positions as shown below, and thus the FO theory predicts that substitution would occur at both positions.



Therefore, most textbooks of organic chemistry and physical organic chemistry avoid the use of FO theory in this case and attempt to interpret this regioselectivity in terms of stabilization of the intermediate cationic σ-complexes, rather than in terms of orbital interactions.[1]

The frontier orbitals are canonical MOs, and they are, in general, delocalized over a whole molecule.[24] Local characteristics of chemical reactions are not well represented by using such delocalized MOs. This difficulty has been resolved by employing some localized reactive orbitals, such as interaction frontier orbitals (IFOs)[25] and projected reactive orbitals (PROs),[26] which have been developed by Fujimoto et al. These orbitals include all the MOs relevant to the interaction of a reactant with a putative reagent, making it possible to see what part of the reactant participates actively in electron delocalization and what changes in bonds will be brought about in the reaction.[25,26] Accordingly, it is inappropriate to analyze molecular reactivities in terms of a single FO and it is therefore not surprising that the FO theory fails to predict selectivity of some chemical reactions.

Although the IFO method can afford a means of extracting orbital interactions compactly in terms of paired orbitals of the reagent and reactant moieties by analyzing the wave function of an interacting system,[25] the PRO method [26] developed for a reactant molecule in an isolated state is more suitable for practical purposes, e.g., prediction of reactivities and selectivities of chemical reactions. In the PRO method, the reference function is defined as the AO contributions of the reaction center out of the HOMO or IFO of a minimum molecule of the relevant functional groups, and the function has been commonly applied to molecules bearing substituents for obtaining reactive orbitals.[26] Unfortunately, this scheme limited the objects of analysis by means of the PRO method to molecules having very similar structures.[26] Therefore, in this paper, we propose a novel method to obtain a reactive orbital without use of a reference function. The present method provides a reactive IFO-like orbital that is well localized around a reaction center and its energy level is high; therefore electron delocalization toward a reagent can most efficiently take place through the orbital, which we will call the reactive hybrid orbital (RHO).

The purpose of this paper is therefore 2-fold: (1) to clarify the fundamental orbital interactions in electronic aromatic substitution reactions and (2) to introduce a practical method for obtaining a reactive orbital to estimate local reactivity of molecules. The reactivity indices obtained here measure the

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power of a reaction center to donate electrons toward an unoccupied reactive orbital of a reagent.

It should also be noted that construction of reliable reactivity indices is, in a practical sense, an important task in basic organic chemistry, as well as in applied chemistry such as medicinal chemistry, where trustworthy quantitative structure−activity relationships (QSAR) are essential to the success of computer-assisted drug designs.[27] In particular, the electronic factor discussed in this paper is considered to be one of the most fundamental and significant components determining SAR.[27]

Calculations

Energetically stable geometries of anisol and nitrobenzene were located on potential energy surfaces at the RHF/6-31G* level using the *Gaussian 98* program.[28] Vibrational frequency analyses were also performed to confirm that obtained structures correspond to energy minima. The wave functions and MOs calculated at the RHF/6-31G*//RHF/6-31G* or RHF/3-21G//RHF/6-31G* level were then analyzed to get a deeper understanding of interactions between reagent and reactant, as explained in detail in the next section. Orbital representations were created with MOLEKEL 4.2, using a contour value of 0.055.[29]

Results and Discussion

Configuration Analysis of the Interaction between Electrophile and Benzenes. In textbooks, orbital interactions are usually described in terms of canonical molecular orbitals.[1] Thus, we utilized those orbitals initially to analyze the orbital interactions in electrophilic aromatic substitution. To identify how importantly each MO participates in the orbital interaction with an electrophile (H^+ in this analysis), configuration analysis[30] has been performed. The analysis expands the wave function of the combined system of a reagent and a reactant in terms of possible electronic configurations of two fragments denoted here by q,

$$\Psi = C_0\Psi_0 + \sum_q C_q\Psi_q \qquad (1)$$

where Ψ_0 indicates the electron configuration in which the two fragments retain their original electron configurations in an isolated state, and Ψ_q represents an electron-transferred configuration between the two fragments or an electron-excited configuration within the same fragment. To show that not only the HOMO, but also other π-type occupied MOs participate significantly in electron delocalization in aromatic substitutions, we take a simple model system, wherein a proton as an electrophile is located 1.5 Å above the carbon atoms of the ortho, meta, or para positions of the geometry-optimized benzenes.[31] In Figure 1, the π-type canonical MOs of anisol and nitrobenzene are shown. Basically, coefficients C_q for the electron-transferred configurations in which a single electron is shifted from occupied π MOs of the benzenes to unoccupied MOs of an electrophile (H^+) have nonzero values, whereas the contributions from other configurations are negligible.[30] Table 1 shows the coefficients for one-electron-transferred configurations, in which an electron is shifted from an occupied π-type MO of the anisol or nitrobenzene fragment to the LUMO of the H^+ fragment.

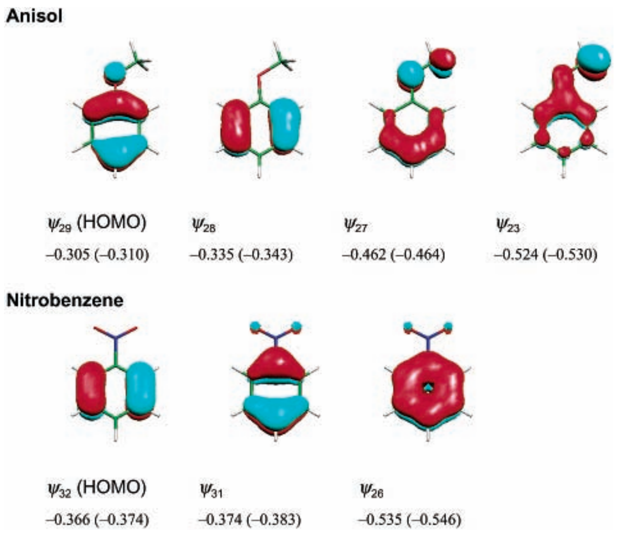


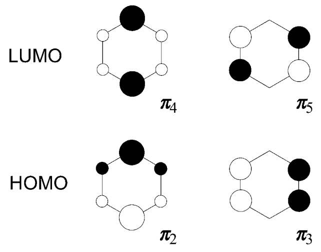
Figure 1. π-type canonical MOs (RHF/6-31G*//RHF/6-31G*) and their energy levels (in hartrees) calculated at the RHF/6-31G*//RHF/6-31G* and RHF/3-21G//RHF/6-31G* (in parentheses) levels for anisol and nitrobenzene.

TABLE 1: Absolute Values of Coefficients of the One-Electron-Transferred Electron Configurations from the MOs in Anisol, Nitrobenzene, or Benzene to the LUMO of H^+ Calculated at the RHF/6-31G*//RHF/6-31G* and RHF/3-21G//RHF/6-31G* (in Parentheses) Levels

$\lvert C_{i\to l}\rvert$	l (LUMO of H^+)		
i (π MO)	ortho	meta	para
	Anisol[a]		
ψ_{29} (π_2-type)[b]	0.231 (0.236)	0.234 (0.233)	0.413 (0.412)
ψ_{28} (π_3-type)	0.342 (0.345)	0.313 (0.314)	0.036 (0.038)
ψ_{27}	0.100 (0.093)	0.158 (0.161)	0.157 (0.163)
ψ_{23}	0.090 (0.101)	0.081 (0.095)	0.067 (0.080)
	Nitrobenzene		
ψ_{32} (π_3-type)[b]	0.370 (0.373)	0.349 (0.351)	0.000 (0.000)
ψ_{31} (π_2-type)	0.152 (0.154)	0.203 (0.205)	0.415 (0.419)
ψ_{26}	0.153 (0.158)	0.144 (0.150)	0.146 (0.151)
	Benzene[c]		
ψ_{21} (π_2)[b]	0.196 (0.197)	0.196 (0.197)	0.421 (0.424)
ψ_{20} (π_3)[b]	0.356 (0.359)	0.356 (0.359)	0.000 (0.000)
ψ_{17}	0.155 (0.160)	0.155 (0.160)	0.155 (0.160)

[a] The values for the ortho and meta positions on the same side as the methoxy group. [b] The HOMO. [c] For benzene, the position over which the amplitude of the π_2 MO was the largest was considered to be the para position.

CHART 1: Degenerate HOMOs and LUMOs of Benzene



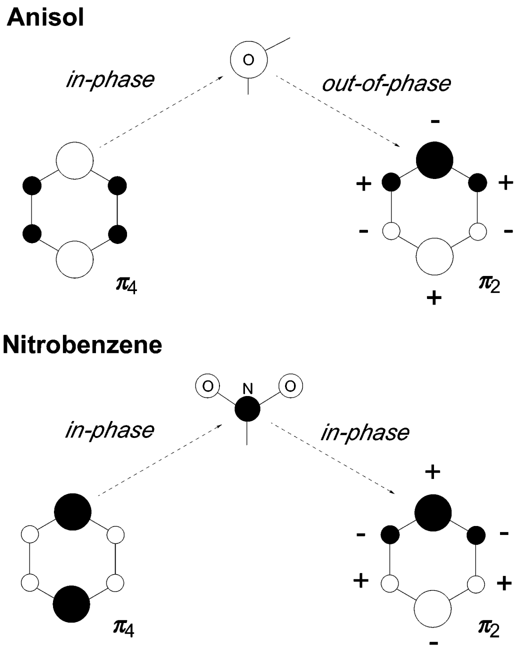
Upon perturbation of the π MOs of benzene, illustrated in Chart 1, by a substituent, the degeneracy of π_2 and π_3 is removed. As a consequence, π_2 becomes the HOMO in the case of anisol and π_3 becomes the HOMO in the case of nitrobenzene (Figure 1). As can be seen in Table 1, not only the HOMO but also the other π-type orbitals participate in the orbital interactions. In particular, in the cases of ortho and meta substitutions of anisol and para substitution of nitrobenzene, the contribution of the HOMO−1 to the interaction is larger than that of the HOMO. In Table 2, the most important occupied MOs in

TABLE 2: Summary of Orbital Interactions in Anisol and Nitrobenzene

	the most important MO in orbital interactions[a]	the MO determining regioselectivity[b]
	Anisol	
ortho	HOMO−1	HOMO
meta	HOMO−1	HOMO
para	HOMO	HOMO
	Nitrobenzene	
ortho	HOMO	HOMO−1
meta	HOMO	HOMO−1
para	HOMO−1	HOMO−1

[a] Identified by configuration analysis. See Table 1 and the text for detail. [b] Interpreted by the orbital mixing rule. See ref 32.

SCHEME 1: Orbital-Mixing Patterns in Anisol and Nitrobenzene[a]



[a] As a result of orbital mixing, the amplitude of the π_2-type MO in the + region is increased, whereas that in the − region is reduced.

interactions with an electrophile, as identified by analysis of the wave function, are summarized. It has been found that both in anisol and in nitrobenzene, the π_3-type MO plays the most significant role in the orbital interactions for ortho and meta substitutions, irrespective of the height of the energy level relative to the π_2-type MO. In para attack, however, the π_2-type MO takes part most significantly in the orbital interaction with an electrophile. For reference, we also tabulated the C_q values for benzene (Table 1). In benzene, all the positions are equivalent and it is meaningless to assign any position as ortho, meta, or para; however, because our main purpose here is to understand orbital interactions in benzenes, we defined these positions in benzene on the basis of MO amplitudes (see Table 1). In the case of benzene, we see that the π_3 MO interacts more strongly with an electrophile than the π_2 does in ortho and para attacks. The results suggest that, in general, the π_3-type MO plays the most important role in the orbital interaction in ortho and meta substitutions, whereas in para substitution, the π_2-type MO plays the most significant role.

Furthermore, the origin of the regioselectivity might be ascribed to orbital mixing between the π_2 and π_4 MOs of benzenes (see Chart 1) through intervention of the orbital of the substituent.[32] The mixing relation among the coefficients of π_2, π_4, and the fragment orbital of a substituent is determined by the relative heights of the energy levels of these orbitals. In Scheme 1, orbital mixing of the fragment orbitals in anisol and nitrobenzene is summarized. In the case of anisol, the energy level of the occupied orbital of the substituent fragment (−OH) is lower than that of π_2 of benzene, whereas in the case of nitrobenzene, the energy level of the unoccupied orbital of the substituent fragment (−NO_2) is between those of π_2 and π_4.

As a result, the amplitude of the HOMO (π_2-type) increases around the ortho and para positions in anisol, whereas that around the meta position is reduced, compared with π_2 of benzene. The HOMO−1 (π_3-type) remains almost unaffected in anisol. In contrast, although the HOMO (π_3-type) is unaffected by −NO_2 in nitrobenzene, the amplitude of HOMO−1 (π_2-type) is reduced around the ortho and para positions and is enhanced around the meta position. The change in amplitude of π_2 MOs by the perturbation can be detected in the orbital amplitudes shown in Figure 1. Therefore, the MOs giving rise to the difference in relative reactivity between the ortho and meta positions of anisol and nitrobenzene are different from those that participate most strongly in orbital interactions, as summarized in Table 2. On the other hand, the absolute reactivity of each position is determined by the electron-donating ability from several π-type orbitals. Hence, it is unreasonable and impossible to attempt to explain the reactivity of aromatic substitution solely in terms of the FO; rather, the multiple π orbitals of benzenes are apparently relevant to the reactivities. Orbital mixing would modify the components of a reactive orbital that is built from π-type canonical MOs, thereby leading to a difference in reactivity depending on the reaction site.

Definition of Reactive Hybrid Orbital and Interpretation of Regioselectivities of Electrophilic Aromatic Substitution. Our next step was to develop a method for obtaining a reactive orbital for practical use. Like a situation where a hybrid atomic orbital is used, it is clearer to see orbital interactions in terms of a single hybrid MO rather than in terms of all of the relevant canonical MOs, under the conditions that the original forms of the canonical MOs are unchanged. Furthermore, the composition of the hybrid MO should be informative as the configuration analysis, i.e., relative importance of the contribution of canonical MOs being well-characterized. In addition, the hybrid MO should be consistent with local characteristics of chemical interactions. It was shown that the IFO method gives a practical way of deriving those hybrid MOs fulfilling these requirements, starting from the canonical MOs of the reactant and reagent fragment molecules.[25] However, a method that gives hybrid MOs without using the reagent MOs seems more useful in a practical sense for comparing reactivities of the reactant molecules. Thus, we develop such a method for obtaining a well-behaved reactive orbital called the reactive hybrid orbital (RHO). When an electron-donating orbital ϕ_{oc} is represented by a linear combination of canonical occupied MOs as

$$\phi_{oc} = \left(\sum_{i}^{oc} d_i \psi_i\right) \Big/ \left(\sum_{i}^{oc} d_i^2\right)^{1/2} \tag{2}$$

the energy level of the orbital can be evaluated by

$$\lambda_{oc} = \left(\sum_{i}^{oc} d_i^2 \epsilon_i\right) \Big/ \left(\sum_{i}^{oc} d_i^2\right) \tag{3}$$

where ϵ_i is the energy level of the canonical MO ψ_i obtained by solving a Hartree−Fock−Roothaan equation. The orbital ϕ_{oc} is then represented by a linear combination of atomic orbitals

(LCAO) as

$$\phi_{\mathrm{oc}} = \sum_{\mu} C_{\mu}\chi_{\mu} \tag{4}$$

If we extract only the terms containing the AOs on the atom of the reaction center (denoted here by A) from eq 4:

$$\phi'_{\mathrm{oc}} = \sum_{\mu \in A} C_{\mu}\chi_{\mu} \tag{5}$$

then we can define a site electron density f_{oc} and an index ρ_{oc}, respectively, as

$$f_{\mathrm{oc}} = \langle \phi_{\mathrm{oc}} | \phi'_{\mathrm{oc}} \rangle \tag{6}$$

and

$$\rho_{\mathrm{oc}} = -f_{\mathrm{oc}}/\lambda_{\mathrm{oc}} \tag{7}$$

The value $2f_{\mathrm{oc}}$ corresponds to the electrons in ϕ_{oc} belonging to atom A, and the formula of ρ_{oc} is similar to that of superdelocalizability based on the Hückel approximation.[33] We obtained a set of d_i values in eq 2, which gives the maximum value of ρ_{oc}, by minimizing $1/\rho_{\mathrm{oc}}$ numerically with the Davidon–Fletcher–Powell method.[34] The orbital ϕ_{oc} represented by eq 2 with the optimized d_i values is specifically called an occupied RHO. The reactivity of the electron-donating center can also be evaluated on the basis of the RHO obtained above by

$$\rho'_{\mathrm{oc}} = -f'_{\mathrm{oc}}/\lambda_{\mathrm{oc}} \tag{8}$$

where f'_{oc} is defined as

$$f'_{\mathrm{oc}} = \langle \phi'_{\mathrm{oc}} | \phi'_{\mathrm{oc}} \rangle \tag{9}$$

Note that $2f'_{\mathrm{oc}}$, unlike 2 f_{oc}, does not count electrons in the internuclear region which are used for bonding with the adjacent atoms, e.g., the π-bonding region in the case of the aromatic π orbitals. Thus ρ'_{oc} is more similar to superdelocalizability than ρ_{oc} is.[35] The occupied RHO is a high-lying orbital (i.e., a negatively small λ_{oc} value), but it is localized on the reaction center (i.e., a large f_{oc} value).

Although the RHO method owes some of the fundamental ideas to the projected reactive orbital (PRO) method,[26] they are essentially different from each other. For clarity, it seems worth explaining the difference between the two methods. In the PRO method, a reference function δ_{r} of a reactant, which is assumed to represent most approximately a *transient bond* with a reagent, is defined prior to calculations. However, determination of the reference function needs a somewhat arbitrary selection of AOs. Furthermore, projection of a reference function represented by a few AOs only on a reaction center extracted from the HOMO or IFO of a molecule results in a low-energy PRO as compared with an interaction frontier orbital.[26] Though the set $\{d_i\}$ of eq 2 was determined by projection of a reference function δ_{r} in the PRO method, we directly optimize $\{d_i\}$ in the RHO method; therefore an RHO can be calculated without the concept of a reference function. By using the present method, a reactive orbital can be uniquely obtained even in complicated cases where a split valence basis set such as 6-31G* or 3-21G(*) is used. It should also be noted that a related method, which determines δ_{r} that gives the maximum value of λ_{oc}, was proposed by Kurita and Takayama.[36] Their method localizes a reactive orbital by imposing a limitation on δ_{r} within an AO space of a molecule. The reference function δ_{r} cannot contain d-type AOs in generating a reactive orbital for the formation of new chemical bonds with electrophiles.[36] Also, localization of a reactive orbital calculated by their method, particularly for a conjugated or aromatic system is insufficient, despite the limitation mentioned above. This is because their method focuses on the energy level of a reactive orbital and pays less attention to the localizability of the orbital. Although their method made some improvement over the original PRO method in that it offered a procedure for determining a reference function in a unique, analytical manner, the meaning of a reference function became less clear. These seem to indicate inadequacy of the concept of a reference function; hence development of a method for deriving a reactive orbital without the concept is important.

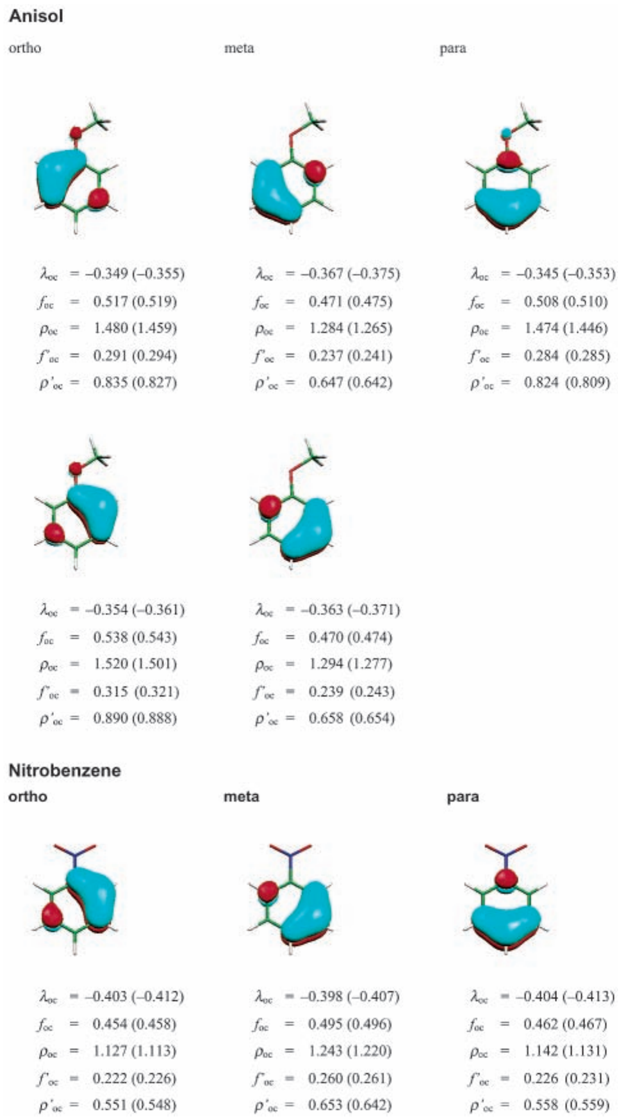


Figure 2. Contour plot of the RHO at each point calculated at the RHF/6-31G*//RHF/6-31G* level. RHO values, λ_{oc}, f_{oc}, ρ_{oc}, f'_{oc} and ρ'_{oc} calculated at the RHF/6-31G*//RHF/6-31G* and RHF/3-21G//RHF/6-31G* (in parentheses) levels are also shown.

In Figure 2, the RHOs for ortho, meta, and para attacks in anisol and nitrobenzene are depicted. In all cases, the RHOs have the largest amplitude around the reaction center, but they are not localized completely on the reaction center. They also have amplitudes around the adjacent two carbons and have an *out-of-phase* amplitude around the carbon at the 4-position with respect to the reaction center. This suggests that the AOs on multiple carbon atoms of the benzene system, in addition to the reaction center, participate in the aromatic reaction.

TABLE 3: Absolute Values of LCMO Coefficients of the RHOs in the Ortho, Meta, and Para Positions in Anisol, Nitrobenzene, and Benzene Calculated at the RHF/6-31G*//RHF/6-31G* and RHF/3-21G//RHF/6-31G* (in Parentheses) Levels

π MO[a]	LCMO coefficient of RHO		
	ortho	meta	para
	Anisol[b]		
ψ_{29} (π_2-type)[c]	0.495 (0.500)	0.508 (0.504)	0.871 (0.862)
ψ_{28} (π_3-type)	0.771 (0.769)	0.700 (0.698)	0.082 (0.089)
ψ_{27}	0.275 (0.246)	0.435 (0.425)	0.436 (0.439)
ψ_{23}	0.279 (0.298)	0.246 (0.277)	0.211 (0.237)
	Nitrobenzene		
ψ_{32} (π_3-type)[c]	0.811 (0.811)	0.771 (0.771)	0.000 (0.000)
ψ_{31} (π_2-type)	0.361 (0.361)	0.475 (0.475)	0.901 (0.902)
ψ_{26}	0.450 (0.448)	0.422 (0.423)	0.434 (0.431)
	Benzene[d]		
ψ_{21} (π_2)[c]	0.451 (0.451)	0.451 (0.451)	0.902 (0.902)
ψ_{20} (π_3)[c]	0.781 (0.782)	0.781 (0.782)	0.000 (0.000)
ψ_{17}	0.432 (0.431)	0.432 (0.431)	0.432 (0.431)

[a] See Figure 1. [b] The values for the ortho and meta positions on the same side as the methoxy group. [c] The HOMO. [d] For benzene, the position over which the amplitude of the π_2 MO was the largest was considered to be the para position.

Table 3 summarizes the LCMO coefficients of the RHOs in the ortho, meta, and para positions. In anisol, the HOMO (π_2-type) is the major component of the RHO only in the case of para attack. On the other hand, in nitrobenzene, the HOMO (π_3-type) is the most important in the cases of ortho and meta attacks. In both compounds, ortho and meta attacks of an electrophile are facilitated mainly by electron delocalization from the π_3-type MOs, whereas para attacks are facilitated by that from the π_2-type MOs. In addition, the LCMO coefficient of π_3 of benzene is the largest in ortho and meta substitutions and that of π_2 is largest in para substitution. From these results, it can be understood that the RHOs showed trends in the relative importance of canonical MOs similar to the results of configuration analysis. Therefore, it appears that the complicated orbital interactions shown in Table 1 are condensed compactly and appropriately to a single hybrid MO, i.e., the RHO, which takes part in electron delocalization toward an electrophile.

Calculated RHO parameters, i.e., λ_{oc}, f_{oc}, ρ_{oc}, f'_{oc}, and ρ'_{oc} defined above for these compounds, are also presented in Figure 2. In anisol, the RHO energy level λ_{oc} is lower and ρ_{oc} is larger in the ortho and para positions than those in the meta position, predicting that electrophilic substitution will occur in the ortho and para positions. On the other hand, in nitrobenzene, the values predict meta regioselectivity. These predictions are consistent with experimental results.[1] In the case of benzene, the values are identical in all positions. Interestingly, it was also predicted that anisol is more reactive in the para position than benzene but less reactive in the meta position, which is consistent with the signs of the σ_p^+ and σ_m constants for anisol.[27]

Reactivities of Monosubstituted Benzenes and Policyclic Aromatic Hydrocarbons. Now let us apply the RHO method to monosubstituted benzenes (Table 4), experimentally examined. In Table 4, we summarize the results of RHO calculations (RHF/6-31G*) and logarithms of the partial rate factors (log(PRF)) for mercuration,[3d] nitration,[3c,e,4,37] and chlorination[3f] of some monosubstituted benzenes. One sees that the RHO indices are on the whole in good agreement with the reaction rates. In Figure 3, λ_{oc} values are plotted against log(PRF) values, demonstrating that λ_{oc} is closely correlated with log(PRF).

TABLE 4: Comparison of the RHO Values (RHF/6-31G*) and Partial Rate Factors (PRFs) for Aromatic Substitution Reactions[a]

substituent	λ_{oc}	ρ_{oc}	ρ'_{oc}	log(PRF)		
				mercuration	nitration	chlorination
H	−0.362	1.346	0.704	0.0	0.0	0.0
p-OCH$_3$	−0.345	1.474	0.824	3.36	-	7.67
p-Me	−0.354	1.392	0.743	1.37	1.69	2.91
p-^{t}Bu	−0.354	1.385	0.736	1.24	1.76	2.60
p-Ph	−0.357	1.361	0.719	0.81	1.27	2.78
m-^{t}Bu	−0.358	1.351	0.705	0.53	0.58	0.73
m-Me	−0.360	1.339	0.694	0.35	0.32	0.69
p-F	−0.367	1.368	0.741	0.47	−0.11	0.64
p-Cl	−0.374	1.301	0.682	−0.44	−0.89	−0.42
m-F	−0.378	1.254	0.636	−1.41	-	−2.44
m-Cl	−0.381	1.266	0.652	−1.22	−3.08	−2.85
m-NO$_2$	−0.398	1.243	0.653	-	−6.79	-
p-NO$_2$	−0.404	1.142	0.558	-	−8.14	-

[a] Experimental values taken from refs 3c and 4. See also refs 3d−f.

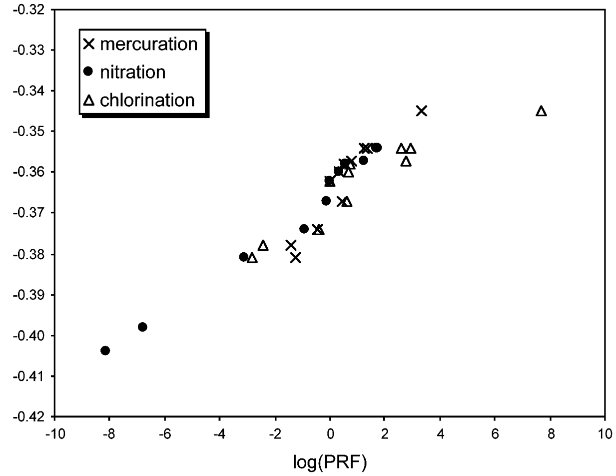


Figure 3. Relationship between the RHO energy level λ_{oc} and logarithms of the partial rate factors (log(PRF)) for mercuration, nitration, and chrorination of monosubstituted benzenes.

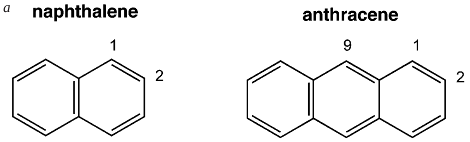
We next apply the RHO method to larger systems. It was pointed out that the FO theory often fails for large systems such as polycyclic aromatic ones.[24] The RHO values (RHF/6-31G*) for carbon atoms for benzene, naphthalene, and anthracene were calculated and compared with the magnitude of the experimentally determined partial rate factors for protiodetritiation (Table 5).[5b] The RHO indices are consistent with not only regioselectivity but also the difference in reactivity among molecules of different sizes. The number of occupied π orbitals increases with the increase in the size of a molecule. Additionally, the energy gap between these π orbitals are reduced as compared with those in benzene. These lead to the increase in the relative importance of MOs other than the FO (HOMO), which is taken into consideration in the present method. Table 6 presents the LCMO coefficients of RHOs. The α regioselectivity in electrophilic aromatic substitution in naphthalene was successfully predicted by FO theory.[21] In fact, the present analysis showed that the HOMO plays the most important role in the α attack (Table 5). Furthermore, it is interesting to note that other low-lying MOs also play active roles in α attack, and in β attack, the HOMO−1 plays a more important role than the HOMO does.

Before concluding, we discuss the relevance of our new approach to the critiques of FO theory.[11b,24] The FO theory accounted for the orientation of substitution rather than relative rates of substitution in different alternant hydrocarbons. As

TABLE 5: Comparison of the RHO Values Calculated at the RHF/6-31G*//RHF/6-31G* Level and Partial Rate Factors (PRFs) of Protiodetritiation of Benzene, Naphthalene, and Anthracene in CF_3CO_2H at 70 °C[a]

hydrocarbon	position	λ_{oc}	ρ_{oc}	ρ'_{oc}	log (PRF)[b]
benzene	1	−0.362	1.346	0.704	0.00
naphthalene	1	−0.351	1.379	0.738	3.07
	2	−0.355	1.363	0.723	2.18
anthracene	1	−0.348	1.378	0.740	3.90
	2	−0.351	1.372	0.734	3.05
	9	−0.327	1.464	0.814	7.10

[a]



[b] Data taken from ref 5b. See also refs 9a and 9b.

TABLE 6: Absolute Values of LCMO Coefficients of the RHOs on Carbon Atoms in Policyclic Aromatic Hydrocarbons Calculated at the RHF/6-31G*//RHF/6-31G* Level

	naphthalene		anthracene		
MO	C1	C2	C1	C2	C9
HOMO	0.725	0.505	0.578	0.486	0.775
HOMO−1	0.009	0.619	0.015	0.504	-
HOMO−2	0.533	0.268	0.586	0.358	-
HOMO−3	0.320	0.475	0.353	0.174	0.475
HOMO−4	-	-	0.240	0.464	0.308
HOMO−5	-	-	-	-	-
HOMO−6	-	-	-	-	-
HOMO−7	0.297	0.251	0.311	0.330	-
HOMO−8	-	-	-	-	-
HOMO−9	-	-	-	-	-
HOMO−10	-	-	0.206	0.164	0.282

shown above, we found a good correlation of the calculated RHO indices to the magnitude of the experimental partial rate factors for polyaromatic molecules. This suggests that our approach could be extended to comparison with divergent molecules. The FO theory does not always predict regioselectivies; nitrobenzene is a representative example, as discussed in this paper. Our approach has also been shown to overcome this problem by taking into account all relevant MOs properly. Finally, we analyze reactivities in terms of a single hybrid MO, rather than in terms of the relevant MOs separately. Thus, we can obtain outcomes of calculation in the simplest format, which has been the major reason for the success of the FO theory.[24]

Conclusion

It has been shown that in many cases of electrophilic aromatic substitution, the FO does not always play the most important role, indicating that the importance of the HOMO should not be exaggerated, and other MOs should also be taken into consideration. In anisol, ortho, meta, and para substitutions are facilitated mainly by electron delocalization from the HOMO−1, HOMO−1, and HOMO, respectively, whereas in nitrobenzene, they are facilitated by the HOMO, HOMO, and HOMO−1, respectively. As a result of orbital mixing, the amplitude of the HOMO of anisol and that of the HOMO−1 of nitrobenzene are changed, as compared with π_2 of benzene, leading to regioselectivity. Thus, the reactivity of the ortho, meta, and para positions of substituted benzenes can be evaluated only by taking into account all the relevant MOs that should participate in interactions with an attacking electrophile. It has also been demonstrated that the orbital interactions can be reasonably described not by a single FO but by a single reactive orbital named the RHO, which is constructed by combination of several MOs to provide the maximum reactivity index ρ_{oc} of a reaction center. It is worth noting that in the field of QSAR, descriptors for substituent effects have been inadequate.[38] This may be because the FOs have predominantly been utilized to describe such effects. Thus, the difficulties might be overcome by employing RHOs instead of FOs.

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References and Notes

(1) (a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A, Structure and Mechanisms*, 4th ed.; Kluwer Academic: New York, 2000; Chapter 10. (b) Isaacs, N. *Physical Organic Chemistry*, 2nd ed.; Longman: Singapore, 1995; Chapter 10.

(2) Roberts, J. D.; Sanford, J. K.; Sixma, F. L. J.; Cerfontain, H.; Zagt, R. *J. Am. Chem. Soc.* **1954**, *76*, 4525.

(3) (a) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1957**, *79*, 1913. (b) Stock, L. M.; Brown, H. C. *J. Am. Chem. Soc.* **1962**, *84*, 1668. (c) Brown, H. C.; Stock, L. M. *J. Am. Chem. Soc.* **1962**, *84*, 3298. (d) Brown, H. C.; Goldman, G. *J. Am. Chem. Soc.* **1962**, *84*, 1650. (e) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979. (f) Stock, L. M.; Baker, F. W. *J. Am. Chem. Soc.* **1962**, *84*, 1661.

(4) Mésure, A. D.; Tillett, J. G. *J. Chem. Soc. (B)* **1966**, 669.

(5) (a) Taylor, R. In *Comprehensive Chemical Kinetics*; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1972; Vol. 13. (b) Ansell, H. V.; Hirshler, M. M.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1977**, 353.

(6) Olah, G. A. *Acc. Chem. Res.* **1971**, *4*, 240.

(7) Hubig, S. M.; Kochi, J. K. *J. Am. Chem. Soc.* **2000**, *122*, 8279.

(8) Holman, R. W.; Eary, T.; Whittle, E.; Gross, M. L. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2187.

(9) (a) Streitwieser, A., Jr.; Lewis, A.; Schwager, I.; Fish, R. W.; Labana, S. *J. Am. Chem. Soc.* **1970**, *92*, 6525. (b) Streitwieser, A., Jr.; Mowery, P. C.; Jesaitis, R. G.; Lewis, A. *J. Am. Chem. Soc.* **1970**, *92*, 6529. (c) Wang, D. Z.; Streitwieser. A. *Theor. Chem. Acc.* **1999**, *102*, 78.

(10) De la Mare, P. B. D. *J. Chem. Soc.* **1954**, 4450.

(11) (a) Dewar, M. J. S.; Maitlis, P. M. *J. Chem. Soc.* **1957**, 2521. (b) Dewar, M. J. S. *J. Mol. Struct.* (*THEOCHEM*) **1989**, *200*, 301.

(12) (a) Langenaeker, W.; Demel, K.; Geerlings, P. *J. Mol. Struct.* (*THEOCHEM*) **1991**, *234*, 329. (b) Langenaeker, W.; De Proft, F.; Geerlings, P. *J. Phys. Chem.* **1995**, *99*, 6424. (c) Vos, A. M.; Nulens, K. H. L.; De Proft, F.; Schoonheydt, R. A.; Geerlings, P. *J. Phys. Chem. B* **2002**, *106*, 2026.

(13) Von Szentpály, L. *Chem. Phys. Lett.* **1981**, *77*, 352.

(14) (a) Politzer, P.; Abrahmsen, L.; Sjoberg, P. *J. Am. Chem. Soc.* **1984**, *106*, 855. (b) Politzer, P.; Jayasuriya, K.; Sjoberg, P.; Laurence, P. R. *J. Am. Chem. Soc.* **1985**, *107*, 1174.

(15) Epiotis, N. D.; Shaik, S. *J. Am. Chem. Soc.* **1978**, *100*, 29.

(16) (a) Hehre, W. J.; Hiberty, P. C. *J. Am. Chem. Soc.* **1974**, *96*, 7163. (b) McKelvey, J. M.; Alexandratos, S.; Streitwieser, A., Jr.; Abboud, J. L. M.; Hehre, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 244.

(17) Zhou, Z.; Parr, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 5720.

(18) Osamura, Y.; Terada, K.; Kobayashi, Y.; Okazaki, R.; Ishiyama, Y. *J. Mol. Struct.* (*THEOCHEM*) **1999**, *461*−*462*, 399.

(19) Fuster, F.; Sevin, A.; Silvi, B. *J. Phys. Chem. A* **2000**, *104*, 852.

(20) Pankratov, A. N. *J. Mol. Struct.* (*THEOCHEM*) **2000**, *507*, 239.

(21) Fukui, K.; Yonezawa, T.; Shingu, H. *J. Chem. Phys.* **1952**, *20*, 722.

(22) Fukui, K.; Fujimoto, H. *Frontier Orbitals and Reaction Paths*; World Scientific: Singapore, 1997.

(23) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976.

(24) Anh, M. T.; Maurel, F. *New J. Chem.* **1997**, *21*, 861.

(25) (a) Fukui, K.; Koga, N.; Fujimoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 196. (b) Fujimoto, H. *Acc. Chem. Res.* **1987**, *20*, 448.

(26) (a) Fujimoto, H.; Mizutani, Y.; Iwase, K. *J. Phys. Chem.* **1986**, *90*, 2768. (b) Fujimoto, H.; H.; Satoh, S. *J. Phys. Chem.* **1994**, *98*, 1436. (c) Fujimoto, H.; Sakata, K.; Fukui, K. *Int. J. Quantum Chem.* **1996**, *60*,

401. (d) Hirao, H.; Omoto, K.; Fujimoto, H. *J. Phys. Chem. A* **1999**, *103*, 5807. (e) Hirao, H.; Fujimoto, H. *J. Phys. Chem. A* **2000**, *104*, 6649.

(27) Hansch, C.; Leo, A. *Exploring QSAR* (*Fundamentals and Applications in Chemistry and Biology*); American Chemical Society: Washington, DC, 1995.

(28) 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.

(29) (a) Flukiger, P.; Luthi, H. P.; Portmann, S.; Weber, J. *MOLEKEL 4.2*; Swiss Center for Scientific Computing: Manno, Switzerland, 2000−2002.

(30) (a) Fujimoto, H.; Kato, S.; Yamabe, S.; Fukui, K. *J. Chem. Phys.* **1974**, *60*, 572. (b) Lopez, R.; Menendez, M. I.; Suarez, D.; Sordo, T. L.; Sordo, J. A. *Comput. Phys. Commun.* **1993**, *76*, 235.

(31) In the attack by such a hard electrophile as H^+, the electrostatic contribution relative to the charge-transfer one to stabilization of a transition state should be large. However, the primary purpose of the analysis here is to clarify the origin of the latter that is also an important driving force of a reaction between reactant and reagent. We believe that the conclusion drawn by taking the simple model reflects the fundamental aspect of orbital interactions in aromatic systems, to which many kinds of reagents have been shown to attack. For study of substituent effects of aromatic compounds in terms of molecular electrostatic potentials, see for example ref 14 and: Gadre, S. R.; Suresh, C. H. *J. Org. Chem.* **1997**, *62*, 2625. For discussions from the HSAB viewpoint, see, for example, refs 12 and 17.

(32) (a) Inagaki, S.; Fukui, K. *Chem. Lett.* **1974**, 509. (b) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4054.

(33) Fukui, K.; Yonezawa, T.; Nagata, C. *Bull. Chem. Soc. Jpn.* **1954**, *27*, 423.

(34) (a) Fletcher, R.; Powell, M. J. D. *Comput. J.* **1963**, *6*, 163. (b) Reddy, P. J.; Zimmermann, H. J.; Hussain, A. *J. Comput. Appl. Math.* **1975**, *1*, 255.

(35) The orbital ϕ_{oc} obtained by maximizing ρ'_{oc} resulted in a similar orbital to ϕ_{oc} gained by maximizing ρ_{oc}. However, if this procedure (maximization of ρ'_{unoc}) was followed in the unoccupied MO space to obtain an unoccupied RHO ϕ_{unoc}, imbalance in amplitude of ϕ_{unoc} occurred in many cases. Therefore, we decided to adopt the procedure that maximizes ρ_{oc} or ρ_{unoc} for calculating an RHO.

(36) Kurita, Y.; Takayama, C. *J. Phys. Chem. A* **1997**, *101*, 5593.

(37) $HNO_3-CH_3NO_2$ or HNO_3-Ac_2O and at 0 °C or 25 °C (substituents except $-NO_2$, see ref 3e) and $HNO_3-H_2SO_4$, 25 °C (in the case of NO_2, see ref 4).

(38) Karelson, M.; Lobanov, V. S.; Katritzky, A. R. *Chem. Rev.* **1996**, *96*, 1042.