A Simple MO Treatment on the Nucleophilic Substitution Reactions of Six-membered Aza-aromatic Compounds

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Nucleophilic substitution reactions of monoaza- and diaza-naphthalenes and -phenanthrenes were discussed on the basis of an HMO calculation taking the nature of the reagent into consideration. Results were compared with the orientation of some nucleophilic substitution reactions, *i.e.* Chichibabin amination, phenylation by phenyllithium, and methylation by methylsulfinylmethanide ion. The nature of the reagent was explicitly taken into account as the difference in the coulomb integrals and the reagent-dependent orientation of these reactions were explained theoretically.

In recent decades, molecular orbital theory has been applied to many organic reactions and, in most instances, succeeded in interpreting the reactions. In the field of heteroaromatic chemistry, many applications of MO theory were also reported.[1] In an earlier stage the reactivity indices were calculated and shown to reproduce the orientations of substitution reactions.[2-5] However, several heteroaromatic compounds exhibit different orientations depending on the nature of nucleophiles (or electrophiles), which prevents the use of common reactivity indices throughout all kinds of nucleophilic (or electrophilic) reactions. For example, quinoline, a typical of the six-membered aza-aromatics, reacts with amide anion in liquid ammonia to produce 2-aminoquinoline,[6] while it is methylated to produce 4-methylquinoline by methylsulfinylmethanide ion (dimsyl anion) in DMSO.[7] Both reactions are caused by the attack of nucleophile, being usually classified as nucleophilic substitution reactions. The results are embarrassing when the reactions were predicted in terms of reactivity indices. On the other hand, the reactivity indices themselves are also inconsistent, predicting the different sites of reaction depending upon the kinds of the indices. Brown[8] has classified the reactivity indices from the theoretical consideration on the transition states of the reactions and has given a general guideline to select the proper index as follows: When the reagent or the substrate is reactive, orientation of the reaction is determined by localization energy (L_r) or superdelocalizability (S_r), while the orientation is determined by electron density (q_r) or polarizability (π_{rr}) in the case contrary. The classification is rationalized afterwords by several authors by considering the orbital energies of the reagents (and also of the substrates). Klopman[9] has developed a generalized poly-electronic perturbation theory (GE theory) in which the energies of the unoccupied MO's of electrophile (acceptor) and of the occupied MO's of nucleophile (donor) were both taken into accounts and succeeded in explaining the different orientation of the nucleophilic substitution reactions of pyridinium salts. Simonetta[10] has proposed a π-electronic model for the transition state of aromatic substitution reaction in which the AO's of the tetra-valent carbon and the leaving and the substituting groups were treated analogous to the case of hyperconjugation in order to separate the π-orbitals from the σ-orbitals. The reactivity is discussed on the basis of the π-part of MO's alone. Chalvet and Daudel[11-13] have developed a theory for the treatment of the transition state of aromatic substitution, in which, again, π-MO's of the interacting system were solely considered to predict the orientation of the reaction as a function of the HOMO-energies of the attacking nucleophile.

In practice, substituted benzenes are resistant to nucleophilic aromatic substitutions and react only at the ipso position of the nucleophilically activated halogen or alkoxyl substituent. On the contrary, nucleophilic substitution reaction is quite common with so-called π-electron-deficient aza-aromatic compounds,[6,7,14-22] and the orientations of the reactions are dependent on the nature of the attacking nucleophiles. The present authors have reported the nucleophilic substitutions of several monoaza- and diaza-naphthalenes, -phenanthrenes, and -anthracenes,[23-25] and found remarkable differences in orientations depending upon the nature of the nucleophiles. In this paper, the different orientation observed in some nucleophilic reactions will be discussed according to the above mentioned theory developed by Chalvet and Daudel.

Theoretical

In order to predict the orientations of the substitution reactions on the heteroaromatic compounds, the relative MO energies of the transition states leading to variously oriented substituted products were estimated by a method similar to the unified treatment of transition state proposed by Chalvet *et al.* In this theory, a transition state is treated as a heteroaromatic π-system (substrate) with extension of delocalization by reagent, and the MO Φ of the transition state is formed in terms of the linear combination of the reagent atomic orbital (or group orbital) γ and the substrate molecular orbitals ϕ^σ and ϕ^π.

$$\Phi = \lambda\gamma + \sum C_i\phi_i^\sigma + \sum C_j\phi_j^\pi$$
$$= \lambda\gamma + \sum C_m\chi_m^\sigma + \sum C_n\chi_n^\pi$$

As the reagent (X) attacks the periphery of the π-electron cloud of the substrate aromatic molecule, the overlap between the ϕ^σ and γ will be small and can be neglected. Thus,

$$\langle\gamma|\phi^\sigma\rangle = \langle\gamma|\chi_r^\sigma\rangle = 0$$

and

$$\langle\gamma|\boldsymbol{h}|\phi^{\sigma}\rangle = \langle\gamma|\boldsymbol{h}|\chi_{\mathrm{r}}^{\sigma}\rangle = 0$$

where r refers to the site of the nucleophilic (or electrophilic) attack in the substrate molecule. This means that the relative energies of the transition state can be estimated by considering solely the following π-MO's.

$$\Phi^{\pi} = \lambda\gamma + \sum C_{\mathrm{n}}\chi_{\mathrm{n}}^{\pi}$$

The calculation of the Φ^{π}'s can be carried out within the framework of the Hückel MO approximation if the following integrals are properly evaluated.

$$\alpha_{\mathrm{x}} = \langle\gamma|\boldsymbol{h}|\gamma\rangle$$

$$\beta_{\mathrm{rx}} = \langle\gamma|\boldsymbol{h}|\chi_{\mathrm{r}}^{\pi}\rangle$$

These integrals can be evaluated by the following way. The perturbation energy caused by the interaction with the reagent has been shown to increase monotonously as the increase of β_{rx} without significant crossings of the energies within the range of $\beta_{\mathrm{rx}}=0$—2.0.[12] Thus the resonance integrals β_{rx} are simply evaluated to be 0.5 after Chalvet *et al.*

The coulomb integrals α_{x} are evaluated with reference to the Mulliken's electronegativities[26,27] of the attacking nucleophiles. Discussions in this paper are confined to the following three reactions; (i) phenylation with phenyllithium, (ii) methylation by dimsyl anion, and (iii) Chichibabin amination. The phenylation with phenyllithium is assumed to be induced by the initial attack of phenyl carbanion. The anion has been proved to be a sigma anion carrying the unshared electron pair in an sp^2 non-bonding AO. The anion is stabilized by the aromatic sextet of electrons as is in the parent hydrocarbon. Methylation of the six-membered aza-aromatic compounds by dimsyl anion is rather complex in the mechanistic point of view, involving an initial addition of the nucleophile and subsequent elimination in some cases. However, the orientation of the reaction is determined by the initial attack of dimsyl anion towards the heteroaromatic nucleus. The transition state energies of this initial process can be properly evaluated by the method mentioned above. The dimsyl anion is a carbanion in conjugation with sulfinyl group, and its anionic center is supposed to be planar. Thus, the unshared electron pair of this anion should occupy a p-AO. Chichibabin amination reactions are carried out in liquid ammonia, and the effective nucleophile is amide anion. The anion is generally supposed to take an angular conformation. However, the hybridization state of its nitrogen atom is not known in details, since the exact geometry of the anion has not been determined. Anyhow the nitrogen atom has a non-bonding AO of which s-character is ranging from 0 to 50%. In other words, the AO has an intermediate character between pure p and sp-hybridized.

Ionization potentials I, electron affinities A, and Mulliken's electronegativities χ_{M} for these AO's are given, together with the estimated α_{x} values, in Table 1. Ionization potentials, electron affinities, and other properties have been correlated with coulomb integrals by many authors.[26,28-31] Nevertheless, coulomb and other integrals for HMO calculations have been assigned in a qualitative manner with reference to these properties

Table 1. The electronegativities and the coulomb integrals of carbon and nitrogen atoms of various valence states

Atom	AO	I/eV	A/eV	χ_{M}	h_{x}
C(sp^2)	2p(π)	11.16	0.03	5.60	−0.5
	tr(σ)	15.62	1.95	8.79	+2.0
N[a]	2p	13.94	0.84	7.39	
N(sp^2)	2p	14.12	1.78	7.95	+1.5
N(sp)	2p	14.11	2.14	8.13	

a) Unhybridized N atom.

in most instances, and such integrals are also employed to formulate the Hückel determinant of the substrate heteroaromatic molecules in this investigation. Thus, the α_{x}'s are also evaluated by taking the following factors into account. Firstly, as the β_{rx} is *a priori* assigned to be 0.5 which corresponds to a rather weak interaction, the effect of electronegativity should be a little exaggerated in the α_{x} integrals to compensate the smaller β_{rx}. Secondly, the coulomb integrals for anionic centers should be shallower than those for the neutral atoms of similar electronic states. Thirdly, the electronegativities of the anionic centers of the reagents increase in the order; dimsyl anion<amide anion<phenyl anion, even though there exists some ambiguity in the χ_{M} value of the nitrogen atom in amide anion. Thence, h_{C}(dimsyl)<h_{N}(amide)<h_{C}-(phenyl). In conclusion, the integrals given in Table 1 were employed in the calculations. These values are carefully adjusted so as to be consistent with other integrals in the substrate heteroaromatic molecules.

Results and Discussion

By performing the MO calculations described in the theoretical part, total π-energies of the models for the transition states were obtained. The total π-energy E_{π}(r) is dependent on the site (r) of reaction in a molecule concerned, and the one with the lowest π-energy corresponds to the transition state for the most feasible reaction path, which should be realized in practice. The relative π-energies for the various reaction sites in the heteroaromatic molecules 1 to 13 are shown graphically in Fig. 1(a)—(n) as a function of the coulomb integral ($\alpha_{\mathrm{x}}=\alpha+h_{\mathrm{x}}\beta$) of the attacking nucleophiles. In these figures, the "transition state" with the lowest π-energy at $h_{\mathrm{x}}=-3$ is chosen as the reference(s) and the energy difference E_{π}(r)−E_{π}(s) in β unit are plotted as a function of h_{x}. Then, the relative "transition state" energy for the site chosen as the reference is given by the straight line E_{π}(s)=0 (which superposed on the abscissa). When the energy curves for other "transition states" do not intersect the abscissa, the relative energies of them are always higher than E_{π}(s), and the heteroaromatic molecule is expected to react at the same site (s) irrespective of the nature of the attacking nucleophiles. When the energy curve(s) of other "transition states" crosses the abscissa, the lowest energy one is replaced as the change in h_{x}. Therefore, the site of the nucleophilic attack is predicted to be altered as the change in the

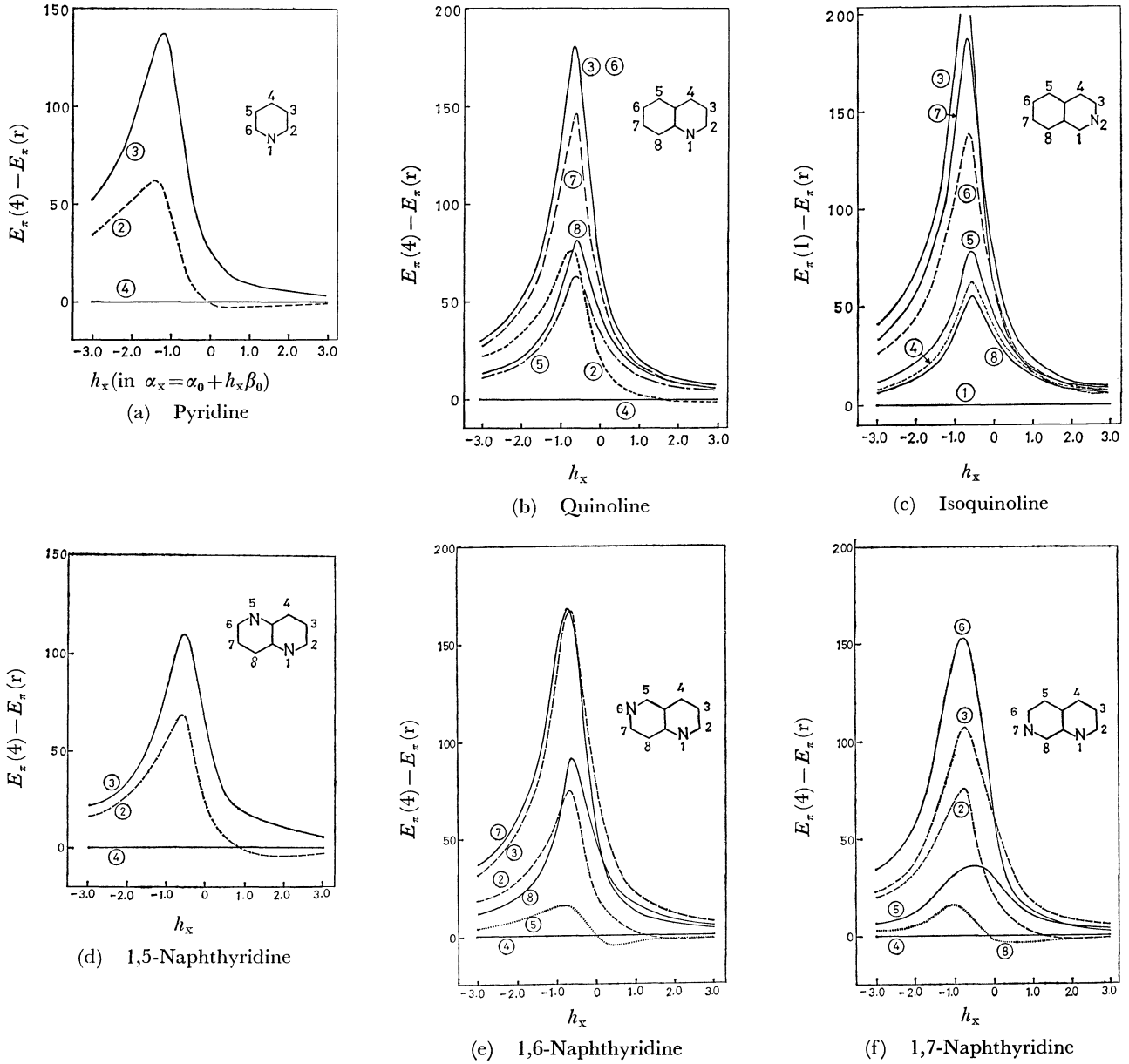
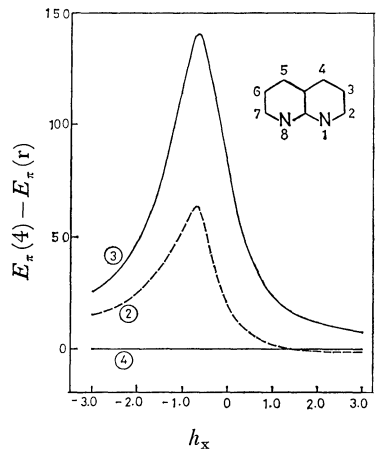


Fig. 1. Relative π-energies for the transition states of various reaction sites (in β units $\times 10^3$).

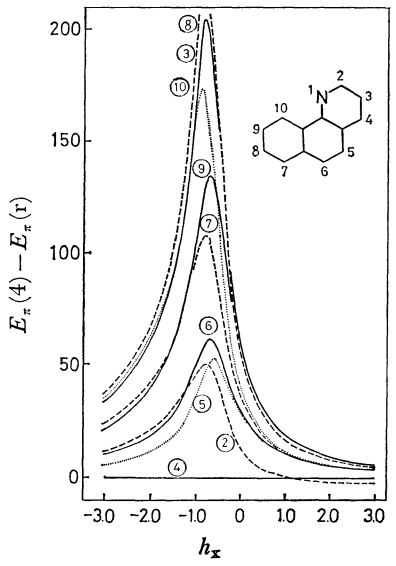
nucleophilicity of the reagent.

Of all the heterocycles investigated, isoquinoline (**3**), 5-azaphenanthrene (**10**), 4,6-diazaphenanthrene (**12**), acridine (**13**), and 1,10-diazaanthracene (**14**) belong to the former cases. Nucleophilic substitution reactions of these nitrogen heterocycles have been extensively investigated by several authors. Since the first report on pyridine and related substances by Chichibabin and Zeide,[6] the amination by alkali amide in liquid ammonia has been applied to a variety of the six-membered aza-aromatic compounds and called Chichibabin reaction. This modification of amination on a series of naphthyridines have been studied in details by Paudler and Kress,[17] and further extended to the benzo analogs of naphthyridines by the present authors.[23-25] The reaction on 1,5-naphthyridine had been reported to give the 2-amino derivative initially,[17] but the 4-amino derivative was identified as the product of the amination recently.[18,23]

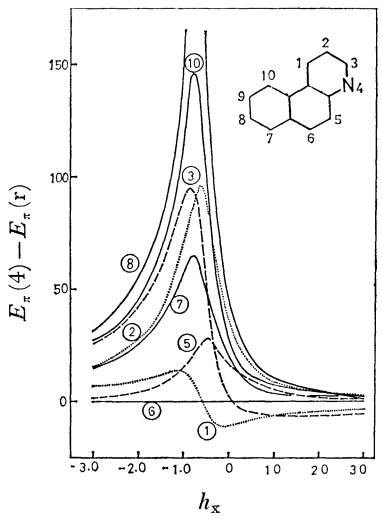
Phenylation by phenyllithium in ether or hydrocarbon medium is also a well-known reaction, and the substitution occurs predominantly on the carbon atom ortho to the ring nitrogen atom in almost all cases reported.[14-16,32] The present authors[25] have investigated on the orientation of the phenylation of 1,*x*-naphthyridines and shown that the main product is the 2-phenyl derivative in the reactions of all isomeric heterocycles. Methylation of these aza-aromatic compounds were first reported by Russel and Weiner.[7] They carried out the reaction on pyridine and several of its benzo analogs and, though pyridine is unreactive to dimsyl anion, showed that the ortho or para-substituted derivatives were produced *via* addition-elimination mechanism. The methylation was applied to diazanaphthalenes and diazaphenanthrenes by the present authors.[24,25] The products of these reactions were summarized in Table 2 together with the orientations predicted from Fig. 1 by assuming the coulomb



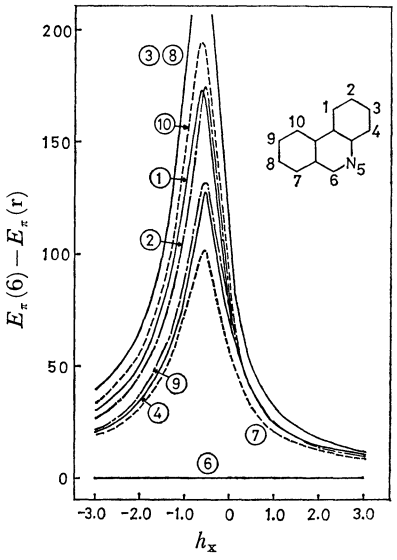
(g) 1,8-Naphthyridine



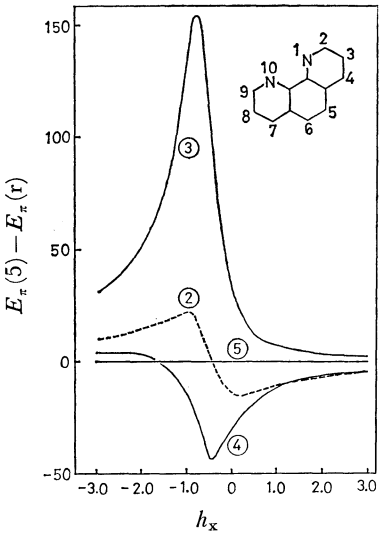
(h) 1-Azaphenanthrene



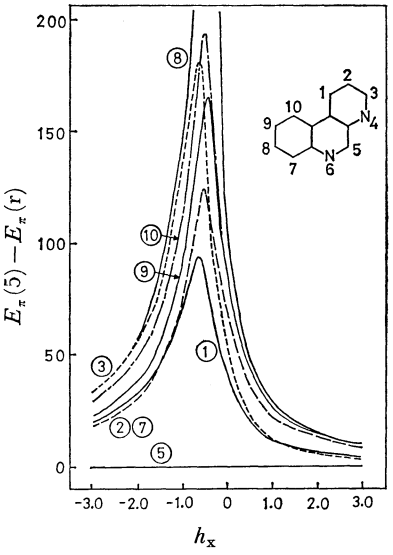
(i) 4-Azaphenanthrene



(j) 5-Azaphenanthrene



(k) 1,10-Diazaphenanthrene



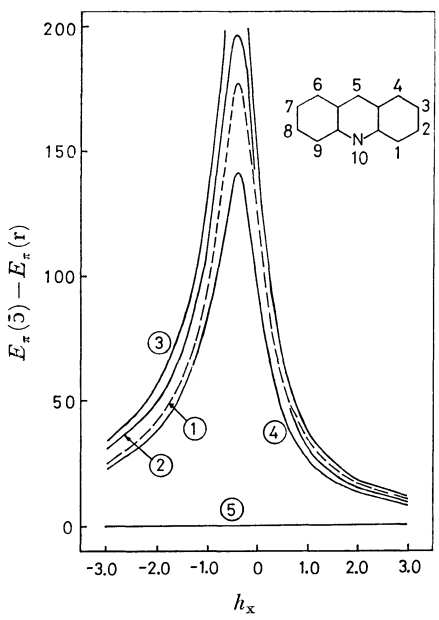
(l) 4,6-Diazaphenanthrene

Fig. 1

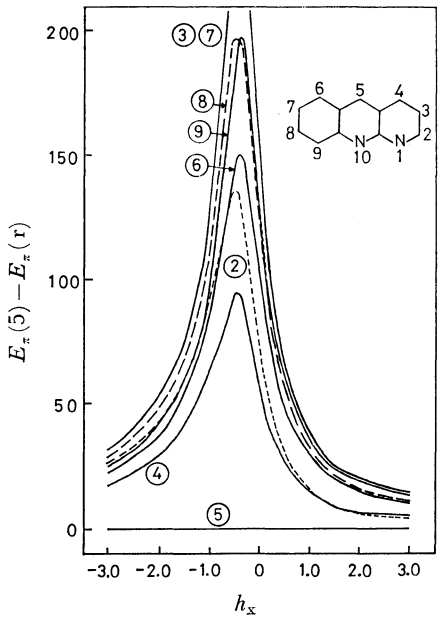
integrals of the reagents as given in Table 1.

The orientations of the compounds **3**, **10**, **12**, **13**, and **14** are invariable throughout all three kinds of nucleophilic reaction, and the prediction from Fig. 1 is shown to be consistent with the experimental results. With other heterocycles, the orientation alters with the change in reagents in accord with the crossing of the π-energy curve in Fig. 1. 1,5-Naphthyridine (**4**), for example, produce 2-phenyl-, 2- or 4-amino-, and 4,8-dimethyl-naphthyridines by the above mentioned reactions, and the difference in orientation is properly explained by the crossing of the transition state π-energy curve for the 2 (and 6)-position with abscissa which corresponds to that for the 4(and 8)-position. Thus, the reagent of which h_x is larger than 1 (crossing point) is predicted to attack toward 2 (and 6)-position. The compounds **1**, **2**, **5**, **6**, **7**, **8**, **9**, and **11** also have some similar crossings with abscissa in their "transition state" π-energy curve and expected to behave differently toward the attack of various nucleophiles in orientation. The difference in orientation is verified with all the compounds investigated experimentally (**2**, **5**, **6**, **7**, **8**, and **9**). Phenylation and amination have not yet been carried out on 1,10-diazaphenanthrene (**11**), lacking the evidence for the different orientation, and pyridine (**1**) is unreactive toward dimsyl anion even if it is expected to react at the 4-position.[33] After all the comparison with the experimental consequence illustrates that the method is quite trustworthy and widely applicable to the qualitative prediction of the orientation.

The results are compared with the orientations predicted from reactivity indices. Among various reactivity indices, electron density q_r, as well as superdelocalizability $S_r^{(-)}$ and frontier electron density $f_r^{(-)}$ for nucleophilic reactions, is suitable for this discussion, being given in Table 3. With the heterocycles of which reaction site toward nucleophile is



(m) Acridine



(n) 1,10-Diazaanthracene

Fig. 1.

TABLE 2. PRODUCTS OF SOME NUCLEOPHILIC SUBSTITUTION REACTIONS AS COMPARED WITH THOSE PREDICTED

Compound		Phenylation ($h_x=2.0$)	Amination ($h_x=1.5$)	Methylation ($h_x=-0.5$)
Pyridine (**1**)	th.	2>4	2>4	4>2
	exp.	(2)	(2)	unreact.
Quinoline (**2**)	th.	2>4	2>4	4>5
	exp.	(2)	(2)	(4)
Isoquinoline (**3**)	th.	1>3	1>8	1>8
	exp.	(1)	(1)	(1)
1,5-Naphthyridine (**4**)	th.	2>4	2>4	4>2
	exp.	(2)	(2), (4)[a]	(4, 8)[b]
1,6-Naphthyridine (**5**)	th.	2>5	2>5	4>5
	exp.	(2)	(2)	(4)
1,7-Naphthyridine (**6**)	th.	8≈2	8>2	4>8
	exp.	(2)	(8)	(4, 8)[b]
1,8-Naphthyridine (**7**)	th.	2>4	2>4	4>2
	exp.	(2)	(2)	(4, 5)[b]
1-Azaphenanthrene (**8**)	th.	2>4	2>4	4>2≈5
	exp.		(2)	(4) + (5) + (6) + (4, 6)[b]
4-Azaphenanthrene (**9**)	th.	3>1	3>1	6>1≈5
	exp.		(3)	(5) + (6)
5-Azaphenanthrene (**10**)	th.	6>7	6>7	6>7
				(6)
1,10-Diazaphenanthrene (**11**)	th.	2>4	2>4	4>5
	exp.			(4) + (4, 7)[b]
4,6-Diazaphenanthrene (**12**)	th.	5>3	5>3	5>1
	exp.		(5)	(5)
Acridine (**13**)	th.	5>4	5>4	5>4
	exp.		(5)	(5)
1,10-Diazaanthracene (**14**)	th.	5>2	5>2	5>4
	exp.		(5) + (2, 5)[b]	(5)

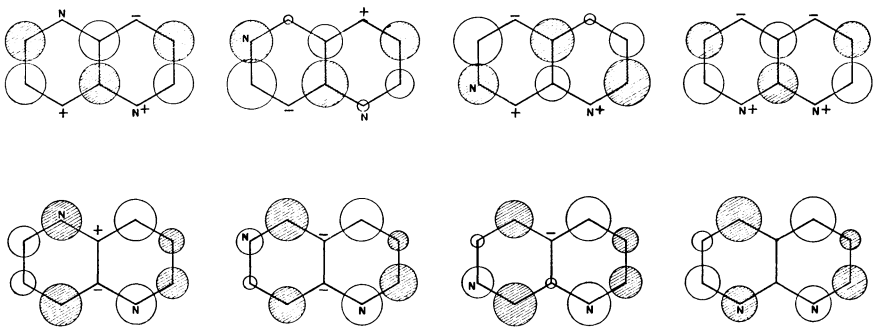
a) Different product was reported by several authors.[17,18,23] b) Disubstituted derivative.

Table 3. Reactivity indices for the nucleophilic reactions of aza-aromatic compounds

Compound	r	q_r	$S_r^{(-)}$	$f_r^{(-)}$	Compound	r	q_r	$S_r^{(-)}$	$f_r^{(-)}$
Pyridine (**1**)	2, 6	**0.943**	**0.983**	0.271	4-Azaphenanthrene (**9**)	1	0.942	**1.152**	0.265
	3, 5	0.992	0.853	0.107		2	0.999	0.906	0.154
	4	0.951	0.978	**0.627**		3	**0.926**	1.083	0.094
Quinoline (**2**)	2	**0.917**	1.146	0.258		5	1.008	0.998	0.275
	3	1.001	0.881	0.102		6	0.978	1.090	**0.314**
	4	0.932	**1.257**	**0.457**		7	0.995	1.000	0.148
	5	0.989	1.058	0.296		8	0.999	0.864	0.001
	6	0.999	0.884	0.099		9	0.996	0.916	0.157
	7	0.984	0.938	0.145		10	0.999	0.943	0.035
	8	1.007	1.002	0.263	5-Azaphenanthrene (**10**)	1	0.996	0.962	0.099
Isoquinoline (**3**)	1	**0.918**	**1.259**	**0.480**		2	0.999	0.909	0.139
	3	0.968	0.944	0.046		3	0.993	0.884	0.016
	4	0.991	1.039	0.338		4	1.004	0.991	0.191
	5	1.000	1.005	0.296		6	**0.891**	**1.390**	**0.484**
	6	0.984	0.937	0.177		7	0.979	1.072	0.225
	7	0.997	0.884	0.095		8	0.999	0.864	0.001
	8	0.986	1.058	0.352		9	0.980	0.987	0.212
1,5-Naphthyridine (**4**)	2, 6	**0.915**	1.178	0.203		10	1.001	0.943	0.068
	3, 7	0.985	0.953	0.116	1,10-Diazaphenanthrene (**11**)	2, 9	**0.927**	**1.115**	0.249
	4, 8	0.939	**1.293**	**0.360**		3, 8	0.993	0.900	0.001
1,6-Naphthyridine (**5**)	2	**0.901**	1.228	0.285		4, 7	0.940	1.194	0.262
	3	1.000	0.887	0.079		5, 6	0.994	1.035	**0.296**
	4	0.919	1.338	**0.446**	4,6-Diazaphenanthrene (**12**)	1	0.942	1.178	0.176
	5	0.907	**1.339**	0.398		2	0.979	1.014	0.181
	7	0.951	1.003	0.070		3	0.923	1.099	0.054
	8	1.002	1.045	0.264		5	**0.898**	**1.434**	**0.419**
1,7-Naphthyridine (**6**)	2	**0.912**	1.173	0.208		7	1.000	1.022	0.147
	3	0.985	0.953	0.133		8	0.992	0.888	0.005
	4	0.933	1.291	**0.394**		9	0.995	0.938	0.124
	5	0.980	1.115	0.286		10	0.995	0.968	0.051
	6	0.966	0.950	0.323	Acridine (**13**)	1, 9	1.015	1.068	0.137
	8	0.925	**1.296**	0.369		2, 8	0.974	1.075	0.126
1,8-Naphthyridine (**7**)	2, 7	**0.903**	1.235	0.251		3, 7	1.004	0.924	0.065
	3, 6	1.002	0.884	0.078		4, 6	0.981	1.222	0.191
	4, 5	0.992	**1.342**	**0.392**		5	**0.896**	**1.926**	**0.502**
1-Azaphenanthrene (**8**)	2	**0.928**	1.112	0.293	1,10-Diazaanthracene (**14**)	2	0.887	1.477	0.207
	3	0.998	0.874	0.026		3	1.007	0.920	0.053
	4	0.941	**1.188**	**0.396**		4	0.910	1.606	0.270
	5	0.997	1.020	0.303		5	**0.880**	**2.138**	**0.489**
	6	0.997	1.013	0.246		6	0.977	1.273	0.170
	7	0.999	0.981	0.112		7	1.004	0.929	0.053
	8	0.994	0.883	0.008		8	0.970	1.128	0.121
	9	1.000	0.897	0.147		9	1.017	1.070	0.107
	10	0.992	0.963	0.016					

indifferent with varying h_x values (**3**, **10**, **12**, **13**, and **14**), their reactivity indices also foresee the same site for nucleophilic reactions. The predicted sites (indicated by bold letters in Table 3) are always consistent with those from the transition state π-energy curves in Fig. 1.

The reactivity indices for other compounds investigated are apparently inconsistent among them, predicting different sites of nucleophilic reaction for a compound. All of these compounds have crossings with abscissa in the transition state π-energy curves in Fig. 1, and the reagent dependent orientation has been rationalized. As expected by the frontier electron theory, frontier electron density is the most suitable index to predict the site of the attack by dimsyl anion of which HOMO energy is high ($h_x=-0.5$) and close to that of the LUMO of the heteroaromatic compounds reacting as substrates (Fig. 2). The orientations of the methylation agrees with those predicted from $f_r^{(-)}$'s in most instances. Hence, the methylation is frontier-controlled. Only one exception is the case of 1,10-diazaphenanthrene. The 5,6-bonds of azaphenanthrenes usually have higher double bond character than the other bonds in the same molecule, and the bond alter-



1,5-naphthyridine 1,6-naphthyridine 1,7-naphthyridine 1,8-naphthyridine

Fig. 2. The LUMO's and the next LUMO's of naphthyridines. In this figure, magnitudes of the AO coefficients (c_{ir}'s) are proportional to the radii of circles, and the hatched circles correspond to the coefficients with negative signs. Only the signs of c_{ir}'s are given when they are too small to be illustrated by circles.

nation is significant in the ring annelated by two benzene nuclei. Since both the reactivity indices (Table 3) and the transition state π-energy curves (Fig. 1) are calculated by assuming identical β-values to all C–C and C–N bonds in the rings, the results become less trustworthy by the increase in bond alternation. A variable β-calculation will improve them considerably.

On the other hand, the orientations of the amination and the phenylation are predicted by the electron densities. In these reactions, the HOMO's of the nucleophiles are estimated to be considerably lower than the LUMO's of substrates, being charge-controlled.[34]

Similar quantities for the delocalized π-model of the transition states were also obtained by the perturbational calculations on the PPP-SCF wave functions of these heterocycles.[35] However, the results agree with the experiments only fairly, and no further improvement is expected by the calculations on the basis of more sophisticated MO.

These calculations were carried out using the HITAC 8250 computer of Yokohama National University and the HITAC 8700 computer of the University of Tokyo Computer Center.

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