Reaction of Aromatic *N*-Oxides with Dipolarophiles. XIV. Inverse-Type Cycloaddition of Pyridine *N*-Oxides with 1,4-Epoxy-1,4-dihydronaphthalene and Its Mechanistic Aspects

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In connection with the stereoselective *exo* cycloaddition in the 1,3-dipolar reaction of 3,5-lutidine *N*-oxide and *N*-arylmaleimides, the inverse-type cycloaddition of some pyridine *N*-oxides with 1,4-epoxy-1,4-dihydronaphthalene was investigated. In these reactions, the aromatized furopyridine-type compounds formed from the 1,5-sigmatropic rearrangement products of the primary cycloadducts were isolated. During the course of the reaction, coloration due to charge-transfer complex formation was observed. The reaction obeyed a second-order rate law and showed little solvent effect. The observed reactivity and stereochemistry are discussed in terms of frontier molecular orbital (FMO) considerations.

Keywords 1,3-dipolar cycloaddition; MNDO frontier molecular orbital; charge-transfer complex; reactivity; pyridine *N*-oxide; 1,4-epoxy-1,4-dihydronaphthalene; solvent effect; activation parameter

Cycloaddition of aromatic *N*-oxides with acetylenes and cumulenes has been extensively investigated[1] and the reaction behavior has been rationalized in terms of frontier molecular orbital (FMO) theory.[2] In the previous paper,[3] we reported that 1,3-dipolar cycloaddition of 3,5-dimethylpyridine (3,5-lutidine) *N*-oxide with *N*-substituted maleimides afforded the *endo* 1,5-sigmatropic rearrangement products, which arose from the thermodynamically less stable *exo* primary cycloadducts. The cycloaddition falls into the category of normal electron-demand cycloaddition[4] and the *exo* selectivity was interpreted in terms of unfavorable secondary-orbital interactions[2b] between the FMO of both addends.

These results afforded valuable information on the stereochemistry of 1,3-dipolar cycloadditions of aromatic *N*-oxides with olefins, about which little is known, in contrast to the extensive data available on the reactions of aliphatic *N*-oxides (nitrones) and Diels–Alder reactions.

As a continuation of the investigation, we pursued inverse electron-demand 1,3-dipolar cycloadditions[4] and searched for suitable dienophiles which would behave as donors toward pyridine *N*-oxides.

This paper describes the results of 1,3-dipolar cycloaddition of several electron-deficient pyridine *N*-oxides (I) with 1,4-epoxy-1,4-dihydronaphthalene (IIa) which has no additional orbitals that can be involved in secondary nonbonding interactions.

Results

Theoretical Expectations for Cycloaddition Reactivities of Pyridine *N*-Oxides (I) and 1,4-Epoxy-1,4-dihydronaphthalene (IIa) To evaluate the cycloaddition reactivities of I and IIa, we performed modified neglect of diatomic overlap (MNDO)[5] calculations with complete optimization of structure. Input data of IIa were determined by empirical molecular mechanics calculation for π-systems (MMPI)[6] using a crude geometry of IIa composed of standard bond lengths, angles and dihedral angles.[7] The calculation predicts the highest occupied molecular orbital (HOMO) and the next highest occupied molecular orbital (NHOMO) energies of 9.33 and 10.08 eV, respectively, resulting from the destabilizing effect of 1,3-n,π-interactions (through-space interactions).[8] The HOMO energy is 0.85 eV higher than that of ethylene. The degree of destabilization seems to be underestimated relative to the experimental value as judged from the values of related compounds.[9] The presence of through-space interactions between the bridged oxygen and the ethylenic and aromatic π-systems was confirmed by inspection of the calculated bond-orders.

The molecular geometry of the parent molecule of pyridine *N*-oxide was determined by means of MNDO optimization. The optimized geometry and dipole moment of pyridine *N*-oxide are in agreement with the observed values determined by X-ray crystallographic analyses.[10] The resulting geometry was then used for the calculations of substituted molecules, *i.e.*, 3,5-dichloropyridine *N*-oxide (Ib), 3-chloropyridine *N*-oxide (Id), 3-carboxypyridine (nicotinic acid) *N*-oxide (Ie), and 3-ethoxycarbonylpyridine *N*-oxide (If). The MNDO calculation of pyridine *N*-oxides (Ia—e) and IIa were performed. The FMO energy levels and heats of formation obtained are summarized in Table I.

The lowest unoccupied molecular orbital (LUMO) of Ib is located largely on positions 2 and 3, with a node close to the N atom. The next lowest unoccupied molecular orbital (NLUMO), lies only 0.12 eV above the LUMO and consequently might play a crucial role in cycloaddition.

It has been shown that the values of the coefficients do not have a marked effect on the rates of cycloaddition reactions and it was suggested that this may arise from

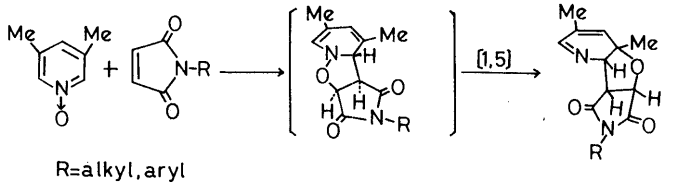


Chart 1

TABLE I. FMO Energy Levels and Heats of Formation[a]

Compd. No.	HOMO[b]	LUMO[b]	NLUMO[b]	Heats of formation[c]
Ia	−9.211	−1.174	−1.019	58.83
Ib	−9.351	−1.272	−1.148	34.85
Id	−9.075	−0.909	−0.799	39.34
Ie	−9.048	−1.241	−0.775	−39.87
IIa	−9.333	0.063		41.84

a) Calculated by MNDO. Pyridine *N*-oxide: HOMO −8.769 eV, LUMO −0.474 eV, heat of formation 44.66 kcal/mol. *b*) eV. *c*) kcal/mol.

Fukui's "principle of growing frontier electron density along the reaction path"[2a] and that the dominant interaction plays an important role in reactivity determination, which may arise from Fukui's other "principle of narrowing interfrontier level separation".[2a] The importance of these proposals has been supported by much experimental evidence.[11]

As can be seen in Table I and Fig. 1, the calculated energy of the frontier orbitals of 3,5-dichloropyridine *N*-oxide (Ib) is considerably lower in energy than those of the parent pyridine *N*-oxide. Thus, the calculation data indicate that 1,4-epoxy-1,4-dihydronaphthalene (IIa) should behave as a good donor with I. The dominant MO interaction is between the LUMO (NLUMO) of I and the HOMO (NHOMO) of IIa, the alternatives being larger in energy separation.

Cycloaddition Reaction of Quinoline *N*-Oxide (Iz) with IIa As far as we know, there is only one report concerning the 1,3-dipolar cycloaddition of IIa with aromatic *N*-oxides. In 1964, Wittig and Steinhoff isolated the cycloadduct (IIIz) of IIa and Iz and its cleaved product.[12] However, they did not refer to the stereochemistry of the cycloaddition and did not clarify whether the product is the primary cycloadduct or the 1,5-sigmatropic rearrangement product.

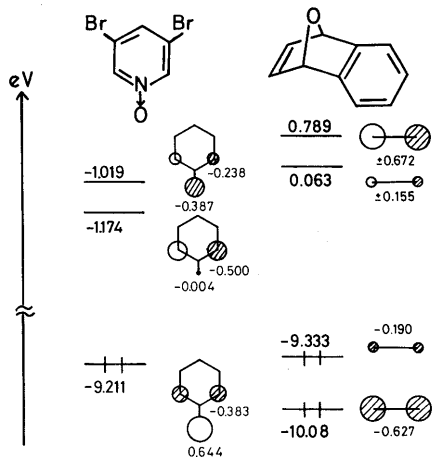


Fig. 1. MNDO Calculations of 3,5-Dichloropyridine *N*-Oxide (Ib) and 1,4-Epoxy-1,4-dihydronaphthalene (IIa)

First of all, we reexamined the 1,3-dipolar reaction of IIa with Iz. The cycloaddition proceeded smoothly in refluxing benzene to afford the cycloadduct (IIIz) in 40% yield. The carbon 13 nuclear magnetic resonance (^{13}C-NMR) spectrum of IIIz showed the presence of five sp^3 carbons, suggesting that IIIz was not the 1,5-sigmatropic rearrangement product but the primary cycloadduct. Inspection of the 400 MHz proton nuclear magnetic resonance (^{1}H-NMR) spectrum of IIIz indicates that the coupling constant among H(9) and H(9a) protons is 7.90 Hz, corresponding to an *endo* isomer. As regards the *endo*/*exo* nature of IIa, the cycloaddition occurred at the Pz- lobe developed in the *exo* direction. From these data, the cycloadduct IIIz can be defined as the *endo*–*exo* primary cycloadduct (see Chart 2). The spectral data used for structure determination of IIIz are summarized in the experimental section.

Cycloaddition of 3,5-Dibromo- and 3,5-Dichloropyridine *N*-Oxide (Ia and Ib) with IIa Based on the cycloaddition behavior of Iz, we next carried out the cycloaddition of Ia with IIa. Heating a solution of Ia and IIa in refluxing benzene for 2 h gave a crystalline mass (IVa). The elemental analysis data agreed well with the constitution of a 1 : 1 adduct. The mass spectrum (MS) of IVa showed the presence of one bromine atom, indicating that dehydrobromination had occurred after the cycloaddition. Treatment of IVa with Na_2CO_3 in dimethyl sulfoxide-d_6 (DMSO-d_6) solution gave Va (the free form of IVa). The ^{1}H-NMR spectrum of IVa showed a very simple spectral pattern reflecting the aromatization of the dihydropyridine moiety. The H_α proton of the pyridine nucleus showed typical *ortho* coupling constant (J=8.0 Hz) suggesting that the bromine atom of Ia underwent 1,2-shift ($\beta \rightarrow \gamma$) to give IVa. On the

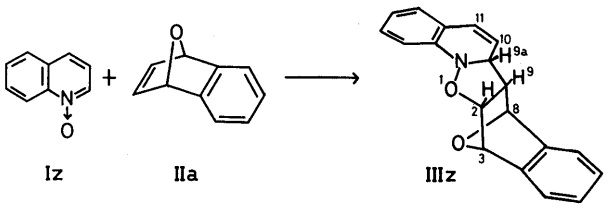


Chart 2

TABLE II. Reaction of Pyridine *N*-Oxides (I) with 1,4-Epoxy-1,4-dihydronaphthalene (IIa)

Starting material		Reaction conditions			Product		
Compd. No.	R	Solv.	Temp. (°C)	Time (h)	Compd. No.	R	Yield (%)
Ia	3,5-DiBr	Benzene	60	2	IVa	γ-Br	36.4
Ia	3,5-DiBr	Benzene	Reflux	2	IVa	γ-Br	42.9
Ia	3,5-DiBr	Toluene	Reflux	2	IVa	γ-Br	30.5
Ia	3,5-DiBr	Benzene[a]	Reflux	2	VIa	β-Br	32.0
Ib	3,5-DiCl	Benzene	60	2	IVb	γ-Cl	18.8
Ib	3,5-DiCl	Benzene	Reflux	2	IVb	γ-Cl	29.2
Ib	3,5-DiCl	Toluene	Reflux	2	IVb	γ-Cl	30.3
Ib	3,5-DiCl	Benzene[a]	Reflux	2	VIb	β-Cl	23.5
Ic	3-Br	Toluene	Reflux	24	IVc	H	20.0
Ic	3-Br	Toluene[a]	Reflux	12	VIc	H	35.8
Id	3-Cl	Toluene	Reflux	24	IVd	H	23.6
Id	3-Cl	Toluene[a]	Reflux	12	VId	H	37.8
Ie	3-COOH	DMF	130	24	VIc	H	12.5
If	3-COOEt	Toluene	Reflux	34	IVf	β-COOEt	20.0

a) In the presence of Et_3N.

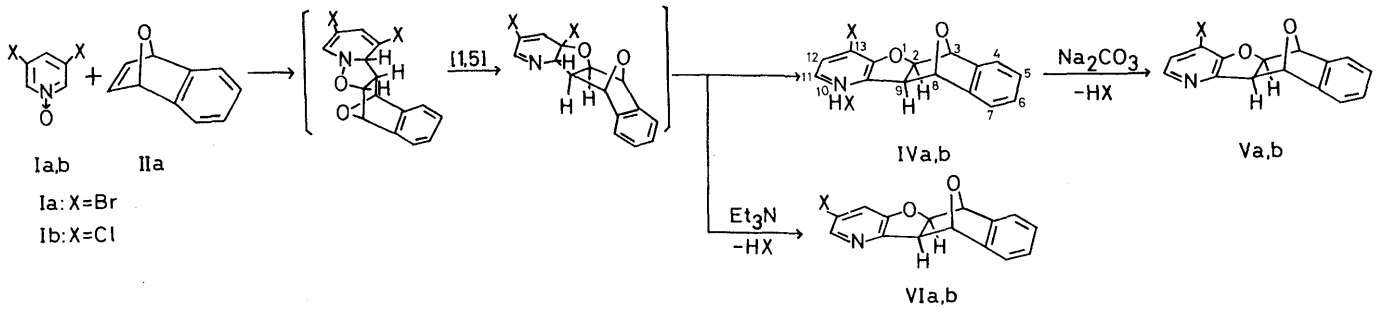


Chart 3

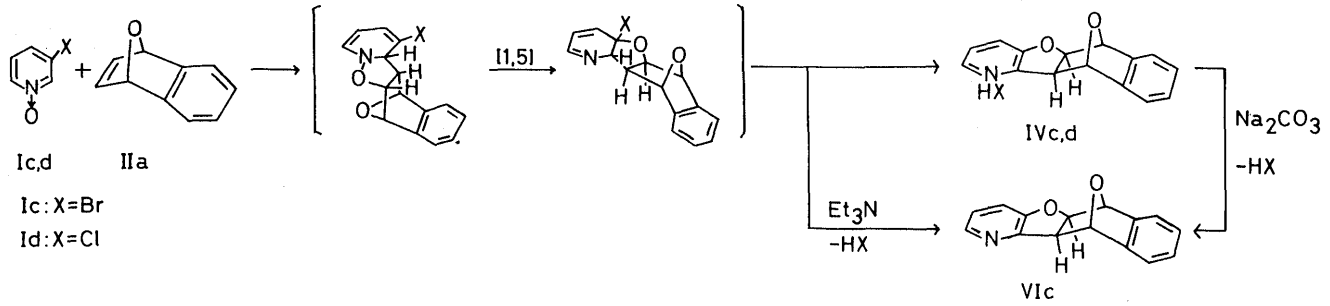


Chart 4

TABLE III. Rate Constants and Activation Parameters for the Reaction of 3,5-Dibromopyridine *N*-Oxide (Ia) with 1,4-Epoxy-1,4-dihydronaphthalene (IIa)

Temp. (°C)	Solvent	Molar ratio (Ia : IIa)	k (l/mol·s)	ΔE (kcal/mol)	$\Delta S^{\neq}$ (e.u.)	Charge-transfer complex (Color)
60	C_6H_6	1 : 1	1.09×10^{-4}			Red
65	C_6H_6	1 : 1	1.23×10^{-4}	13.6	−47	Red
70	C_6H_6	1 : 1	1.71×10^{-4}			Red
70	C_6H_6	1 : 2	1.60×10^{-4}			Red
70	C_6H_6	1 : 5	1.25×10^{-4}			Red
70	C_6H_6	1 : 7	9.96×10^{-5}			Red
75	C_6H_6	1 : 1	2.18×10^{-4}			Red
70	C_6H_5Br	1 : 1	1.58×10^{-4}			Red
70	AcOEt	1 : 1	1.57×10^{-4}			Red
70	$C_6H_5NO_2$	1 : 1	1.69×10^{-4}			Green
70	DMSO	1 : 1	3.78×10^{-5}			Unobsd.
70	DMF	1 : 1	4.55×10^{-5}			Unobsd.

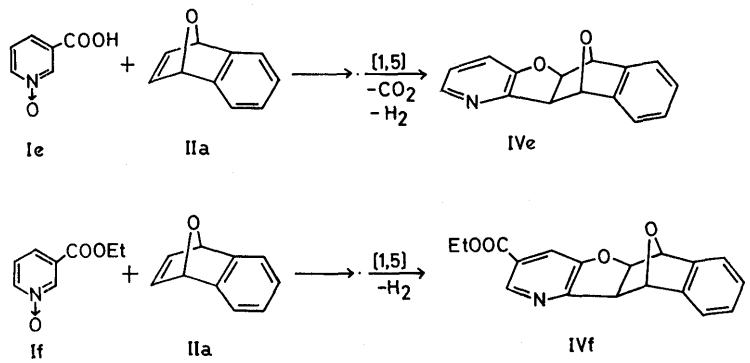


Chart 5

other hand, the same reaction was carried out in the presence of triethylamine to give the normal product VIa, which showed a characteristic *meta* coupling constant (J = 1.8 Hz).

Similar cycloaddition behavior was also observed in the case of 3,5-dichloropyridine *N*-oxide (Ib). The spectral data are summarized in the experimental section.

Cycloaddition of 3-Bromopyridine *N*-Oxide (Ic) and 3-Chloropyridine *N*-Oxide (Id) with IIa As predicted, Ic and Id showed moderate reactivity toward IIa. The reactions were carried out in refluxing toluene and required prolonged heating. The yields were lower than in the cases of Ia

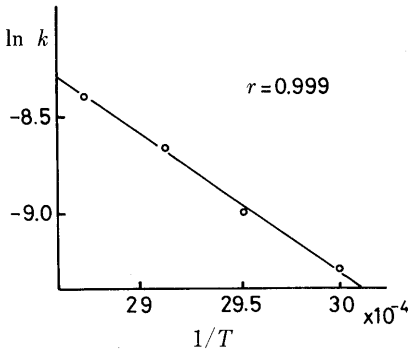


Fig. 2. Arrhenius Plot for the Reaction of 3,5-Dibromopyridine *N*-Oxide (Ia) with 1,4-Epoxy-1,4-dihydronaphthalene (IIa)

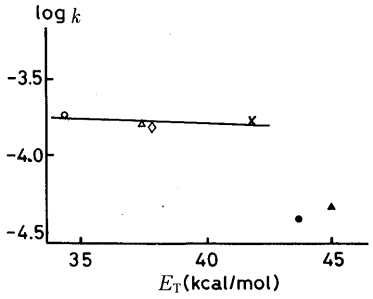


Fig. 3. Solvent Effect for the Reaction of 3,5-Dibromopyridine *N*-Oxide (Ia) with 1,4-Epoxy-1,4-dihydronaphthalene (IIa)

○, benzene; △, bromobenzene; ◇, AcoEt; ×, nitrobenzene; ●, DMF; ▲, DMSO.

and Ib. As observed in the case of Ia (Ib), the products (IVc,d) were isolated as the corresponding pyridinium hydrobromide or hydrochloride, indicating that the primary cycloaddition had occurred at the O and C_2 positions followed by 1,5-sigmatropic rearrangement and aromatization to give IVc,d.

Cycloaddition of Nicotine *N*-Oxide Derivatives (Ie,f) with IIa Nicotine *N*-oxide (Ie) and its ethyl ester (If) showed low reactivities toward IIa. The results are listed in Table II and in the experimental section. In the case of Ie, the cycloaddition occurred at atoms O and C_2. On the other hand, in the case of If, the cycloaddition occurred at atoms O and C_6.

Kinetic Studies The second-order rate constants of the reaction of Ia with IIa were obtained by following the disappearance of the peak of Ia by high-performance liquid chromatography (HPLC) with 4-methoxyacetophenone as an internal standard. The second-order rate constants (k_2) are summarized in Table III.

The rates of the reaction of Ia with IIa in dry benzene are shown in Fig. 2. From the data, the activation parameters were calculated (see Table III). The activation energy for the reaction was found to be 13.6 kcal/mol, lower than those for the average 1,3-dipolar cycloaddition of aromatic *N*-oxides with dipolarophiles (19—20 kcal/mol)[3] and comparable to those for the 1,3-dipolar cycloaddition of nitrones (15 kcal/mol),[13] while the entropy of activation, −47 e.u., is considerably lower than those reported for the typical 1,3-dipolar reaction (*ca.* −30 e.u.), suggesting a highly ordered transition state.

The E_T values of Reichardt *et al.*,[14] based on the bands of solvatochromism of pyridinium *N*-phenolbetaines, were used as a scale of solvent ionizing power in studying the effect of solvent on the rate of reaction. As illustrated in Fig. 3, plots of log k_2 *vs.* E_T values show a linear relationship except for dipolar aprotic solvents (dimethylformamide (DMF) and DMSO). The magnitude of the slope has been used as a measure of the sensitivity of a reaction to the ionizing power of the medium. The value is only -1.70×10^{-4}, the sensitivity to ionizing power being very low as compared with those of typical concerted reactions. The small response to variation of the polarity of the solvent rules out an intermediate involving any significant degree of charge separation such as an ion-pair intermediate. A small reverse solvent effect might be due to the fact that I has a large dipole moment whereas the product does not and the large deviation for the dipolar aprotic solvents (DMF and DMSO) may be due to specific solvation, in which a large desolvation energy might be required in going from the ground state to the excited state.

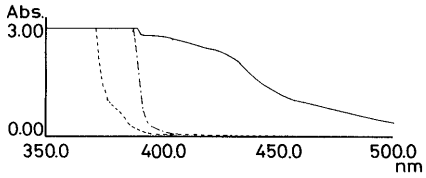


Fig. 4. Charge-Transfer Complexation of 3,5-Dibromopyridine *N*-Oxide (Ia) with 1,4-Epoxy-1,4-dihydronaphthalene (IIa)

—·—, 3,5-diBrPNO; ----, epoxynaphthalene; ——, 3,5-diBrPNO + epoxynaphthalene.

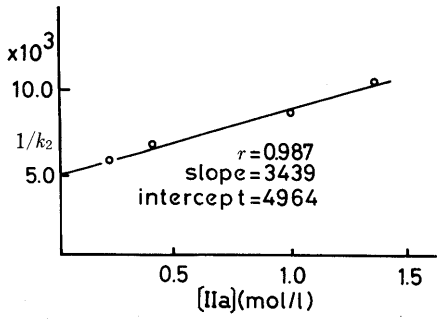
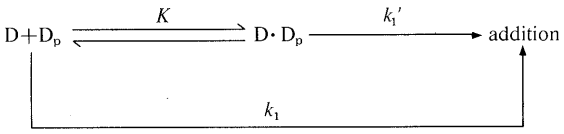


Fig. 5. Relationship of $1/k$ with Dipolarophile Concentration in the Reaction of 3,5-Dibromopyridine *N*-Oxide (Ia) with 1,4-Epoxy-1,4-dihydronaphthalene (IIa)



D, dipole; D_p, dipolarophile; $D \cdot D_p$, charge-transfer complex; k_1, k_1', rate constants; K, equilibrium constant.

$$1/k_2 = 1/k_1 + K \cdot [D_p]/k_1$$

Chart 6

Visible Absorption Spectra of the Reaction Mixture and Charge-Transfer Complex Formation When a solution of Ia in dry benzene was mixed with a solution of IIa, the solution became red. The color did not discharge upon heating at 60 °C and remained during the reaction period. The visible absorption spectra of mixtures of some pyridine *N*-oxides and IIa in benzene solution are shown in Fig. 4.

The spectra have a maximum in the vicinity of 450 nm, characteristic of a charge-transfer spectrum, which is not the same as the sum of the spectra of the two individual molecules. Use of dipolar aprotic solvents did not yield the charge-transfer spectrum.

In order to clarify the existence of the charge-transfer complex, we evaluated the equilibrium constant for the reaction of Ia with IIa. As shown in Fig. 5, the second-order rate constants for the reaction decrease as the dienophile concentration increases, suggesting that the adduct may be formed not only from the 1,3-dipole-dipolarophile complex but also from the direct cycloaddition of the free 1,3-dipole with the dipolarophile (Chart 6). By use of the treatment of Andrews and Keefer,[15] plots of $1/k_2$ *vs.* dipolarophile concentration should give a straight line of slope $1/k_1'$ and an intercept of $1/k_1'K$. Figure 5 presents such a graphical interpretation of the data for the reactions of Ia with IIa at 60 °C. From the linear plot, values of k_1', k_1 and K have been calculated. The equilibrium constant (0.692) is comparable to that for the reaction of anthracenes and maleic anhydrides.[15]

Discussion

As described above, the reaction of the halogenopyridine *N*-oxides (Ia—d) with IIa falls into the category of an "inverse-type" reaction in Sustmann's classification[4] for cycloadditions, wherein the dominant interaction is the one between the LUMO (NLUMO) of Ia—d and the HOMO of IIa. Because the LUMO of Ia—d has a node close to the O atom, the NLUMO's of Ia—d play a leading role in the cycloaddition.

The LUMO of nicotine *N*-oxide (Ie) is approximately the same as that of 3,5-dichloropyridine *N*-oxide (Ib), and qualitative similarities in reactivity between the two compounds are expected. However, Ie showed considerably low reactivity with IIa although both the LUMO (−1.2406 eV) and NLUMO (−0.7752 eV) of Ie have sufficient coefficients at the O, C_2 and C_6 atoms.

In order to understand this discrepancy, the stabilization energies due to frontier molecular orbital (FMO) interactions were evaluated according to the perturbation theory.[16] The stabilization energies (ΔE) of the dominant interactions were calculated assuming the approach of addends in parallel planes separated at 1.5 Å. The calculation indicates that the stabilization energy for the reaction of Ie is slightly larger than Ib indicating that Ie should show high cycloaddition reactivity toward IIa. Contrary to the prediction, the reaction of Ie or If with IIa required severe reaction conditions and the yields were low as compared with the cases of Ia and Ib. Judged from the fact that the reaction of If with IIa proceeded under milder reaction conditions, the observed low reactivity of nicotine *N*-oxide (Ie) is considered to be a result of stabilization of the ground-state of the reaction system by strong charge-transfer complex formation or by stabilization of the 1,3-dipole by intermolecular hydrogen bonding of the oxygen atom of the $\geq N\rightarrow O$ group and the hydrogen atom of the COOH substituent.[3,15]

As regards the site selectivity for the reaction of 3-halogenopyridine *N*-oxides (Ic, d), the interaction of NLUMO of Id and HOMO of IIa is considered to play an important role: the interaction between NLUMO of Ib and HOMO of IIa is larger than the one between LUMO of Id and HOMO of IIa. Even if the interaction of Ib with IIa is of "neutral" type, the same conclusion is obtained.

In a recent rationalization of cycloaddition reactivity and its mechanistic phenomena, it has been proposed tha charge transfer is of importance in stabilizing the transition states of cycloadditions, for which the FMO theory has been used successfully in explaining the formation of charge-transfer complexes by considering the interactions of the HOMO of the donor and the LUMO of the acceptor. In this connection, Fukui and the coworkers clarified that the inverse-type cycloaddition is energetically unfavorable because of accumulation of electron density in the central part of the intermolecular region owing to the symmetric FMO coefficients, so that the cycloaddition will presumably be less concerted or will occur through complex formation such as charge-transfer complex formation before affording the cycloadduct.[17] This proposal was recently supported by experimental evidence indicating that the orientation of the molecular complex plays an important role in determining both the reactivity and stereochemistry. In Diels–Alder reaction, one of the authors supported this proposal using model reactions of cyclopentadienones with various electron-rich dienophiles involving medium-membered conjugated cyclic polyenes.[18] More recently, in field of 1,3-dipolar cycloaddition, we clarified the possible role of a charge-transfer complex in determining the site selectivity for the "neutral-type" reaction of 3-methylpyridine (pic-

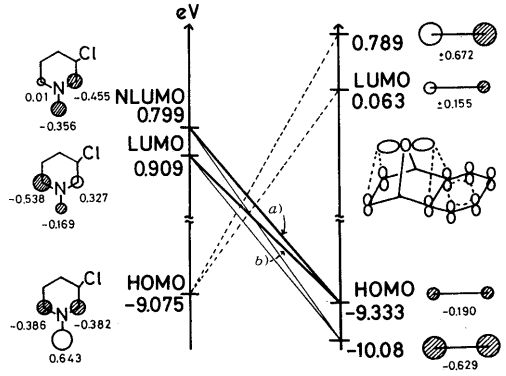


Fig. 6. Dominant FMO Interactions and Stabilization Energies in the Reaction of 3-Chloropyridine *N*-Oxide (Id) with 1,4-Epoxy-1,4-dihydronaphthalene (IIa)

a) $\Delta E_{(\text{homo}-\text{nlumo})} = -2.73$ eV. *b)* $\Delta E_{(\text{homo}-\text{lumo})} = -2.01$ eV.

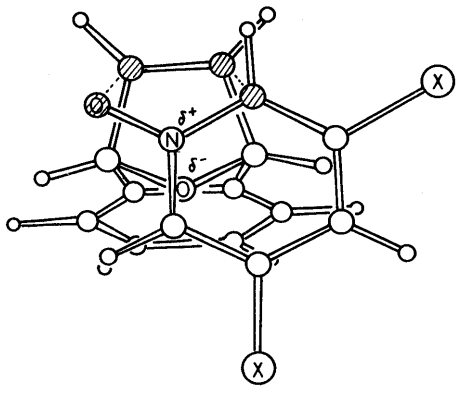


Fig. 7. Possible Coulombic Interaction in the Reaction of Pyridine *N*-Oxides (I) with 1,4-Epoxy-1,4-dihydronaphthalene (IIa)

oline) *N*-oxide with phenyl isocyanates.[19]

In the reactions studied here, spectroscopic evidence for the presence of the complex was obtained, supporting Fukui's proposal. During the course of the reaction, coloration due to charge transfer complexation was observed. The value of the equilibrium constant for the reaction of Ia with IIa is comparable to those for the reactions of anthracenes with maleic anhydrides. The small response to the change of solvent polarity for aprotic solvents rules out formation of an ionic intermediate. These facts suggest that the 1,3-dipolar cycloaddition proceeds, at least in part, *via* a charge-transfer complex, whose orientation must determine both the site selectivity and stereochemistry of the primary cycloadduct.

Finally, mention should be made of the stereochemistry of the primary cycloadduct (IIIz) of I and IIa. Unfortunately, we could isolate neither the primary cycloadduct nor the 1,5-sigmatropic rearrangemant product. So, the stereochemistry of the 1,3-dipolar cycloaddition is still obscure. However, taking into consideration the stereochemical outcome observed for the reaction of quinoline *N*-oxide (Iz) with II, we believe that the cycloaddition proceeds *via* an *endo* transition state.

The electron transfers leading to charge-transfer complex formation and to transition-state intermediate formation in cycloadditions very probably require similar structural arrangements, in which the two interacting π-systems lie in nearly parallel planes. In such a situation, as depicted in Fig. 7, we can suppose that the *endo* approach of I toward the opposite site of the double bond of IIa is severely hindered by the phenyl ring of IIa and the *exo*-site attack[20] to IIa might be energetically favorable.

In the reaction system, IIa does not have any π-orbital available for secondary nonbonding interaction. Inspection of the HOMO of IIa indicates that the HOMO electron density is largely localized at the ethylene moiety and the small coefficient at the bridged oxygen atom indicating that the contribution of the nonbonding interaction is very small. On the other hand, the MNDO net atomic charges (NC) of the bridged oxygen atom of IIa (NC = -0.302) and the nitrogen atom of the 1,3-dipole (NC = 0.267 in Ib) are large enough to give rise to a strong stabilization owing to the coulombic attraction between I and II.

In summary, the results of this report have shown that the observed reactivity and site selectivity for the 1,3-dipolar cycloaddition reaction of Ia—f wiht IIa can be rationalized in terms of FMO interactions involving the NHOMO and NLUMO. Taking into consideration the absence of secondary nonbonding interaction in our systems, the *endo* selectivity of the cycloaddition is considered to result from the orientation of the molecular complex created prior to cycloaddition.

Experimental

All melting points are uncorrected. ^{1}H-NMR spectra were taken with Hitachi R-600 (60 MHz) and JEOL GX-400 (400 MHz) spectrometers for *ca.* 10% (w/v) solution with tetramethylsilane (TMS) as an internal standard; chemical shifts are expressed in δ values. Infrared (IR) spectra were recorded on a Hitachi 270-30 infrared spectrophotometer equipped with a double-bladed grating. Visible absorption spectra were taken with a Hitachi 150-20 spectrometer. MS were taken with a JEOL JMS-DX303HF double-focussing spectrometer operating at an ionization potential of 75 eV. A Hitachi 655A-12 HPLC equipped with an ultraviolet detector was used to measure the reaction rates.

Molecular orbital calculations were performed on a FACOM M-360 computer in the Computer Center of Kumamoto University. Graphic analysis of the MO calculation data and least-squares calculations were performed on Fujitsu FM-16β FDII and FM R-60HD personal computers.

Materials 3,5-Dibromopyridine *N*-oxide (Ia), 3,5-dichloropyridine *N*-oxide (Ib), 3-bromopyridine *N*-oxide (Ic), 3-chloropyridine *N*-oxide (Id) and quinoline *N*-oxide (Iz) were prepared according to the established methods.[10] Nicotinic acid *N*-oxide (Ie), 3-ethoxycarbonylpyridine *N*-oxide (If), and 1,4-epoxy-1,4-dihydronaphthalene (IIa) were commercially available from Tokyo Kasei Ltd. and were used without further purification.

Cycloaddition of Quinoline *N*-Oxide (Iz) with 1,4-Epoxy-1,4-dihydronaphthalene (IIa) A solution of quinoline *N*-oxide (Iz) hydrate (1.5 g, 7 mmol) in dry C_6H_6 was concentrated *in vacuo* to remove water. Then 3.5 ml of dry C_6H_6 and IIa (1.0 g, 7 mmol) were added to the residue. The mixture was refluxed for 7 h. After cooling, the solvent was removed *in vacuo*. Fractional recrystallization of the resultant crystalline mass from AcOEt gave IIIz (1.5 g, 24.7%). mp 171—172 °C (lit. 14, 172 °C). IR (KBr): 2960 (CH), 1595 (C=C) cm^{-1}. ^{1}H-NMR (in $CDCl_3$) δ: 2.83 (1H, dd, J = 7.90, 6.84 Hz, C_9-H), 4.10 (1H, dd, J = 5.37, 7.90 Hz, C_{9a}-H), 4.37 (1H, d, J = 6.84 Hz, C_2-H), 5.22 (1H, s, C_8-H), 5.40 (1H, s, C_3-H), 6.12 (1H, dd, J = 9.77, 5.37 Hz, C_{10}-H), 6.36 (1H, d, J = 9.77 Hz, C_{11}-H), 6.78—7.27 (8H, m, aromatic CH). High-MS *m/z*: 289.109 (M^+, Calcd $C_{19}H_{15}NO_2$: 289.110).

Cycloaddition of Pyridine *N*-Oxides (Ia—g) with 1,4-Epoxy-1,4-dihydronaphthalene (IIa) (General Procedure) A solution of I (1 mmol) and IIa (1 mmol) in 10 ml of solvent was heated under the conditions given in Table II. After cooling, the precipitates were collected by suction, and purified by recrystallization to give IV (see Table II).

IVa: mp 221—222 °C (EtOH, colorless needles). IR (KBr): 2985 (CH), 1480 (CH) cm^{-1}. ^{1}H-NMR (400 MHz, in DMSO-d_6) δ: 4.68 (1H, d, J = 7.33 Hz, C_9-H), 5.84 (1H, d, J = 7.33 Hz, C_2-H), 6.02 (1H, s, C_8-H), 6.11 (1H, s, C_3-H), 7.35—7.60 (4H, m, aromatic CH), 8.81 (1H, dd, J = 6.60, 8.06 Hz, C_{11}-H), 8.84 (1H, d, J = 8.06 Hz, C_{12}-H), 9.57 (1H, d, J = 6.60 Hz, N_{10}-H). MS *m/z*: 395, 397, 399 (M^+, relative intensity 1 : 2 : 1), 315, 317 ($M^+ - HBr$, relative intensity 1 : 1). *Anal.* Calcd for $C_{15}H_{11}Br_2NO_2$: C, 45.37; H, 2.72; N, 3.53. Found: C, 45.44; H, 2.89; N, 3.68.

IVb: mp 213 °C (EtOH, colorless needles). IR (KBr): 3000 (CH), 1455 (CH) cm^{-1}. ^{1}H-NMR (400 MHz, in DMSO-d_6) δ: 4.76 (1H, d, J = 7.33 Hz, C_9-H), 5.89 (1H, d, J = 7.33 Hz, C_2-H), 6.03 (1H, s, C_8-H), 6.09 (1H, s, C_3-H), 7.37—7.59 (4H, m, aromatic CH), 8.23 (1H, d, J = 8.25 Hz, C_{12}-H), 8.74 (1H, dd, J = 7.60, 8.25 Hz, C_{11}-H), 9.57 (1H, d, J = 7.60 Hz, N_{10}-H). MS *m/z*: 307, 309, 311 (M^+, relative intensity 3 : 6 : 1), 261, 263 ($M^+ -$ HCl, relative intensity 3 : 1). *Anal.* Calcd for $C_{15}H_{11}Cl_2NO_2$: C, 58.46; H, 3.60; N, 4.55. Found: C, 58.66; H, 3.71; N, 4.63.

IVc: mp 210—211 °C (EtOH, colorless needles). IR (KBr): 3040 (CH), 1585 (C=C), 1448 (CH) cm^{-1}. ^{1}H-NMR (400 MHz, in DMSO-d_6) δ: 4.73 (1H, d, J = 6.96 Hz, C_9-H), 5.74 (1H, d, J = 6.96 Hz, C_2-H), 5.97 (1H, s, C_8-H), 6.02 (1H, s, C_3-H), 7.33—7.39 (4H, m, aromatic CH), 8.13—8.56 (3H, m, C_{11-13}-H), 9.45 (1H, d, J = 6.57 Hz, N_{10}-H). MS *m/z*: 317, 319 (M^+, relative intensity 1 : 1), 237 ($M^+ -$ HBr). *Anal.* Calcd for $C_{15}H_{12}BrNO_2$: C, 56.63; H, 3.80; N, 4.40. Found: C, 56.61; H, 3.62; N, 4.55..

IVd: mp 208—209 °C (EtOH, colorless needles). IR (KBr): 3040 (CH), 1585 (C=C), 1445 (CH) cm^{-1}. ^{1}H-NMR (400 MHz, in DMSO-d_6) δ: 4.02 (1H, d, J = 6.78 Hz, C_9-H), 5.33 (1H, d, J = 6.78 Hz, C_2-H), 5.72 (1H, s, C_8-H), 5.79 (1H, s, C_3-H), 7.27—7.23 (7H, m, aromatic CH, C_{11-13}-H), 8.34 (1H, d, J = 4.40 Hz, N_{10}-H). MS *m/z*: 273, 275 (M^+, relative intensity 3 : 1), 237 ($M^+ -$ HCl). Treatment of IVd with Na_2CO_3 gave VIc.

IVf: mp 182—183 °C. (C_6H_6, colorless needles). IR (KBr): 1720 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, in DMSO-d_6) δ: 1.40 (3H, t, J = 7.14 Hz, CH_2-CH_3), 3.77 (1H, d, J = 6.78 Hz, C_9-H), 4.39 (2H, q, J = 7.14 Hz, CH_2-CH_3), 5.13 (1H, d, J = 6.78 Hz, C_2-H), 5.60 (1H, s, C_8-H), 5.61 (1H, s, C_3-H), 7.22—7.40 (4H, m, aromatic CH), 7.61 (1H, d, J = 1.46 Hz, C_{13}-H), 8.77 (1H, d, J = 1.46 Hz, C_{11}-H). MS *m/z*: 309 (M^+), 280 ($M^+ -$ Et). *Anal.* Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 70.12; H, 4.96; N, 4.63.

Treatment of IVa,b with Sodium Carbonate A solution of IVa (IVb) (0.5 mmol) in 0.3 ml of DMSO-d_6 was treated with 0.5 mmol of Na_2CO_3. The mixture was sonicated at 25 °C for 10 min and then Na_2CO_3 was filtered off under argon. The formation of Va(Vb) was confirmed by the ^{1}H-NMR spectrum.

Va: ^{1}H-NMR (400 MHz, in DMSO-d_6) δ: 4.66 (1H, d, J = 6.96 Hz, C_9-H), 5.75 (1H,d, J = 6.96 Hz, C_2-H), 6.06 (1H, s, C_8-H), 6.08 (1H, s, C_3-H), 7.39—7.62 (4H, m, aromatic CH), 8.02 (1H, d, J = 8.43 Hz, C_{11}-H), 8.72

(1H, d, J=8.43 Hz, C_{12}-H).

Vb: ^{1}H-NMR (400 MHz, in DMSO-d_6) δ: 4.90 (1H, d, J=6.0 Hz, C_9-H), 5.97 (1H, d, J=6.0 Hz, C_2-H), 6.23 (2H, s, C_3-H, C_8-H), 7.47—7.85 (4H, m, aromatic CH), 8.24 (1H, d, J=8.7 Hz, C_{11}-H), 8.75 (1H, d, J=8.7 Hz, C_{12}-H).

Cycloaddition of Pyridine *N*-Oxides (Ia,b) with 1,4-Epoxy-1,4-dihydronaphthalene (IIa) in the Presence of Triethylamine (General Procedure) A solution of I (1 mmol), IIa (1 mmol) and triethylamine (2 mmol) in 10 ml of dry C_6H_6 was refluxed for 2 h. After cooling, the precipitates were filtered off by suction, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using C_6H_6–AcOEt (10 : 1) as an eluent to give VI, which was purified by recrystallization.

VIa: Yield 32%, mp 145—146 °C (C_6H_6, colorless prisms). IR (KBr): 1580 (C=C) cm^{-1}. ^{1}H-NMR (400 MHz, in $CDCl_3$) δ: 3.68 (1H, d, J=6.96 Hz, C_9-H), 5.11 (1H, d, J=6.96 Hz, C_2-H), 5.55 (1H, s, C_8-H), 5.58 (1H, s, C_3-H), 7.20—7.38 (4H, m, aromatic CH), 7.23 (1H, d, J=1.84 Hz, C_{13}-H), 8.17 (1H, d, J=1.84 Hz, C_{11}-H). MS m/z: 315, 317 (M^+, relative intensity 1 : 1), 236 ($M^+ - Br$). *Anal.* Calcd for $C_{15}H_{10}BrNO_2$: C, 56.99; H, 3.19; N, 4.43. Found: C, 57.14; H, 3.24; N, 4.32.

VIb: Yield 23.5%, mp 123—124 °C (C_6H_6, colorless prisms). IR (KBr): 1585 (C=C), 1462 (CH) cm^{-1}. ^{1}H-NMR (400 MHz, in $CDCl_3$) δ: 5.01 (1H, d, J=6.60 Hz, C_9-H), 5.38 (1H, d, J=6.60 Hz, C_2-H), 5.44 (1H, s, C_8-H), 5.48 (1H, s, C_3-H), 6.94 (1H, d, J=1.84 Hz, C_{13}-H), 7.13—7.28 (4H, m, aromatic CH), 7.96 (1H, d, J=1.84 Hz, C_{11}-H). MS m/z: 271, 273 (M^+, relative intensity 3 : 1), 236 ($M^+ - Cl$). *Anal.* Calcd for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.71; N, 5.16. Found: C, 66.53; H, 3.93; N, 5.26.

VIc: Yield 35.8% (in the case of Ic with IIa), 37.5% (in the case of Id with IIa), mp 115—116 °C (C_6H_6, colorless prisms). IR (KBr): 3005, 2970 (CH), 1605, 1575 (C=C), 1435 (CH) cm^{-1}. ^{1}H-NMR (400 MHz, in $CDCl_3$) δ: 3.72 (1H, d, J=6.96 Hz, C_9-H), 5.04 (1H, d, J=6.96 Hz, C_2-H), 5.57 (2H, s, C_3-H, C_8-H), 7.00—7.34 (6H, m, aromatic CH, C_{12}-H, C_{13}-H), 8.10 (1H, dd, J=1.83, 4.40 Hz, C_{11}-H). MS m/z: 237 (M^+). *Anal.* Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.91. Found: C, 75.89; H, 4.83; N, 6.01.

Kinetics A solution of Ia (1 mmol), IIa (1 mmol) and *p*-methoxyacetophenone (1 mmol), which was used as an internal standard, in 5 ml of a given solvent was placed in a ground glass stoppered tube and immersed in a thermostated oil bath (Advantec Toyo Ltd., LHB-20) controlled to ±0.05 °C. The rates were followed at a given temperature by measuring the decrease of the peak of Ia at 280 nm by HPLC using AcOEt–hexane (3 : 1) as an eluent.

Measurement of Visible Absorption Spectra Solutions of Ia (1 mmol/l) and IIa (1 mmol/l) in dry C_6H_6 were used for the measurement at 60 °C. The results are summarized in Figs. 2 and 3, and Table III.

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