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Reaction of Aromatic *N*-Oxides with Dipolarophiles. VI.[1] Further Studies on the 1,3-Dipolar Cycloaddition Reaction of Pyridine *N*-Oxides with Phenyl Isocyanates[2]

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To provide additional evidence for the concerted mechanism postulated for the 1,3-dipolar cycloaddition reaction of pyridine *N*-oxides with phenyl isocyanates, kinetic studies on the cycloaddition reactions were conducted in a variety of solvents.

The cycloaddition showed low sensitivity to the ionizing power of the medium, indicating that it proceeds by a mechanism which involves very little change in charge separation between the ground state and the transition state. The observed cycloadditivity and site selectivity are discussed in terms of the following controlling factors based on MINDO/3 calculations: HOMO-LUMO control, secondary orbital interaction, steric interaction, dipole–dipole interaction and charge-transfer complexation.

Keywords——1,3-dipolar cycloaddition; pyridine *N*-oxide; phenyl isocyanate; kinetics; frontier molecular orbital; solvent effect

Pericyclic reactions are of interest from both a theoretical and a synthetic viewpoint and have received considerable attention in the past.[3] Among them, 1,3-dipolar cycloaddition is an important general method for the formation of five-membered rings. The scope of this reaction has been investigated, particularly by Huisgen and co-workers.[4] In general, the main features of 1,3-dipolar cycloaddition indicate the involvement of a nonionic concerted mechanism.

In our continuing studies on the 1,3-dipolar cycloaddition reaction of pyridine *N*-oxides with phenyl isocyanates, we noticed that certain experimental results concerning the observed site selectivity were in striking contrast to expectations based upon conventional electronic and steric theories. In addition, some of the experimental observations gave us the impression that there are cases where the concerted mechanism does not operate or requires serious modification. The mechanism of the reaction is considered to involve a pericyclic transition state.[3] However, the evidence is largely indirect, and is based on reaction data in different solvents.

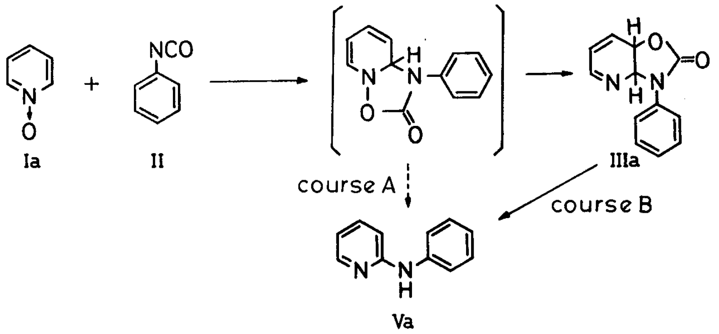


Chart 1

In order to clarify further the cycloaddition behavior already observed, we decided to reexamine the cycloaddition of pyridine *N*-oxides with phenyl isocyanates from a kinetic viewpoint. The results are discussed here in detail in comparison with previous work based on frontier molecular orbital (FMO) theory.[5)]

Results

Product and Kinetic Studies

As reported in the previous papers,[6)] the primary cycloadducts are thermally labile and undergo 1,5-sigmatropic rearrangement to give the 2,3-dihydropyridine derivatives even at room temperature. The 2,3-dihydro derivatives are also thermally unstable, decomposing to 2-anilinopyridine derivatives upon heating above 150 °C. Based on the above results, the relative amounts of the products were determined by gas chromatography with benzophenone as an internal standard. The yields of the cycloaddition products are shown in Table I.

The ratio of 5-methyl-2,3-dihydropyridine derivative (IIIb) to 3-methyl-2,3-dihydro derivative (IVb) was *ca.* 1.2 : 1.0. On the other hand, in the reaction of 3-methoxypyridine *N*-oxide (Ic), the 3-methoxy-2,3-dihydropyridine derivative (IVc) was formed preferentially, and transformed to 2,3-dihydro-2-oxo-3-phenyloxazolo[4,5-*b*]pyridine (VIIc) by elimination of methanol.

The second-order rate constants of the reactions in several solvents at various temperatures were obtained by following the disappearance of the peak of pyridine *N*-oxides by gas chromatography. The second-order rate constants (k_2) are summarized in Table II. The rates

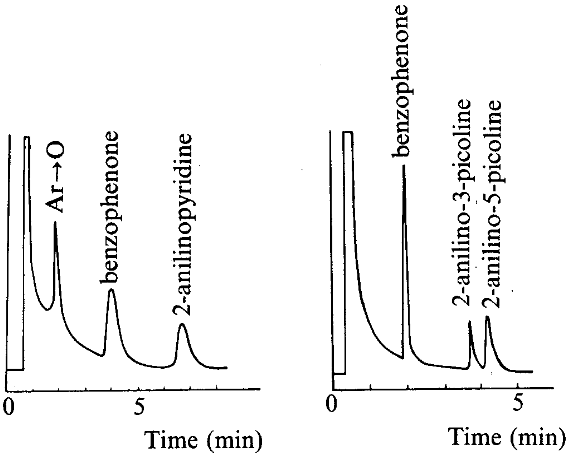


Fig. 1. Gas Chromatographic Analyses for 1,3-Dipolar Cycloadditions of Ia and Ib with Phenyl Isocyanate

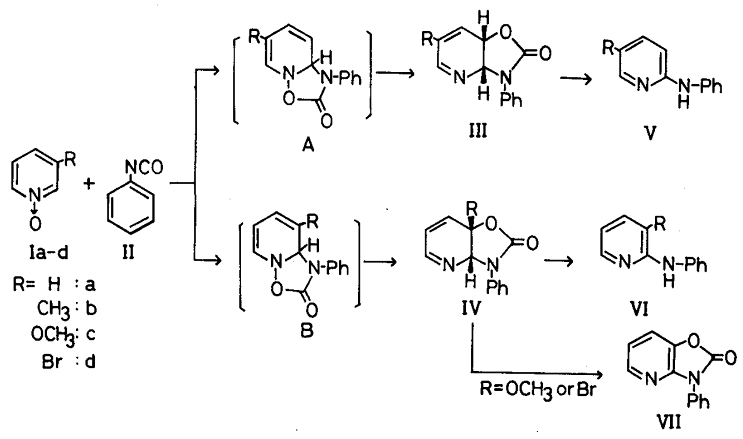


Chart 2

Table I. Yields of Cycloadducts in the Reaction of Substituted Pyridine *N*-Oxides with Phenyl Isocyanate in Different Solvents

Compd.	R	Solvent	Yield (%)	
			A	B
Ia[a]	H	DMF[d]	79	
Ib[b]	Me	DMF[d]	42	35
		DMSO[d]	38	36
		Toluene[d]	37	33
Ic	OMe	DMF	4	34
Id[c]	Br	DMF	5	60

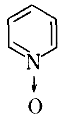
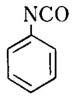
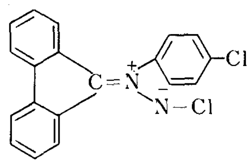
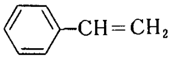
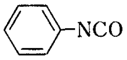
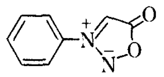
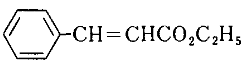
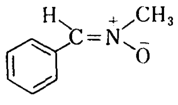
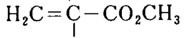
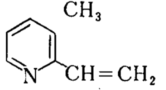
[a] See ref. 4*a*. [b] See ref. 5*a*, *c*. [c] See ref. 5*e*. [d] Analyzed by GLC.

Table II. Second-Order Rate Constants for 1,3-Dipolar Cycloaddition of Ia and II at Various Temperature

Solvent	E_T(kcal mol^{-1})	Temp. (°C)	$k_2 \times 10^5$ (mol$^{-1}\cdot$s^{-1})[a]
DMF	43.8	100	5.36
Nitrobenzene	42.0	80	0.62
		90	1.70
		100	3.02
		110	6.16
Bromobenzene	37.5	100	2.89
Toluene	33.9	100	4.82

[a] Average error, *ca.* ±6%.

Table III. Activation Parameters for 1,3-Dipolar Cycloaddition Reactions

	Reactions[a]		E_a (kcal/mol)	$\Delta S^{\neq}$ (e.u.)
(1)			20	−30
(2)		+ $CH_2=CHCOCH_3$	12.5	−35
(3)		+ 	12.6	−31
(4)		+ 	12.1	−33
(5)		+ $H_3CO_2CC\equiv CCO_2CH_3$	14.7	−31
(6)		+ 	18.3	−32
(7)		+  $H_2C=C(CH_3)-CO_2CH_3$	15.7	−32
(8)		+ 	18.3	−29

[a] Reactions (2)—(8), see ref. 4*a*.

of the reaction of pyridine *N*-oxide (Ia) with phenyl isocyanate (II) in nitrobenzene 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 20 kcal/mol, slightly higher than that for the average 1,3-dipolar reaction, while the entropy of activation, -30 e.u., lies within the range reported for the typical 1,3-dipolar reaction and suggests a highly ordered transition state.

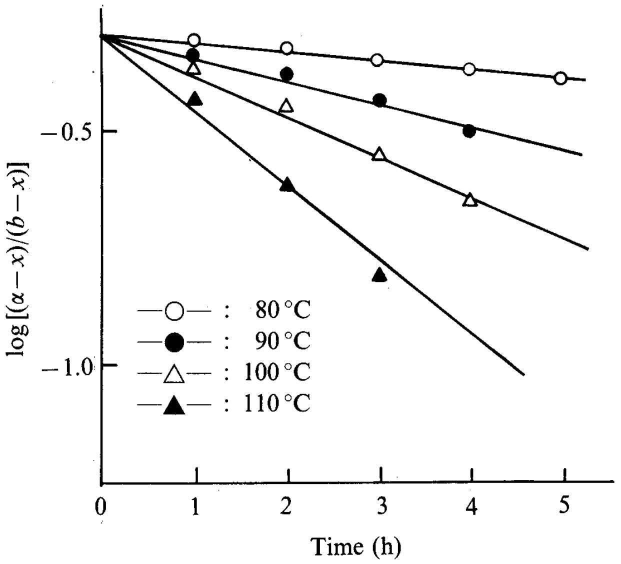


Fig. 2. Rate Plot for 1,3-Dipolar Cycloaddition of Ia with Phenyl Isocyanate in Various Temperatures in Nitrobenzene

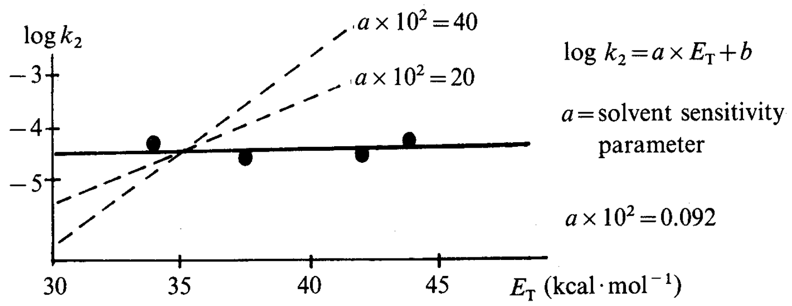


Fig. 3. Plot of $\log k_2$ *vs.* E_T for the Rearrangement

TABLE IV. Sensitivity of Various Reactions to Solvent Ionizing Power (E_T Value)

Reaction No.	Reaction	Solvent sensitivity parameter, $a^{a)} \times 10^2$
(1)	*O*-(2-Dimethylaminoethyl) *S*-methyl dithiocarbonate$^{b)}$	40.4$^{c)}$
(2)	*p*-Methoxyneophyl *p*-toluenesulfonate$^{b)}$	17.9$^{c)}$
(3)	*endo*[4+2]π cycloadduct of phencyclone and *N*-(ethoxycarbonyl)azepine$^{d)}$	6.62$^{c)}$
(4)	Allyl *p*-cresyl ether$^{d)}$	4.34$^{c)}$
(5)	Cycloaddition of cyclooctatetraene with cyclopentadienone derivative	$-0.01^{e)}$
(6)	1,3-Dipolar cycloaddition of pyridine *N*-oxide with phenyl isocyanate	0.09

a) $\log K_2 = aE_T + b$. *b*) Solvolysis. *c*) See ref. 8*a*.
d) [3,3]-Sigmatropic rearrangement. *e*) See ref. 8*b*.

The E_T values of Dimroth,[7] 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 rearrangement, because they were obtained with a wider variety of solvents than the other known scales. As illustrated in Fig. 3, plots of $\log k_2$ against E_T values for the reaction show a linear relationship ($\log k_2 = aE_T + b$). Values of the least-squares slope *a* for various reactions[8] whose mechanisms are well established are summarized in Table IV. As shown in Table IV, the ionic reactions have large *a* values, indicating that the reactions occur through a highly polarized transition state such as an ion pair. The value for 3,3-sigmatropic rearrangement ranges from 4.00×10^{-2} to 7.00×10^{-2}. On the other hand, the *a* values in the present case are very small and comparable to the value in the case of reaction No. 5, a typical example of a concerted cycloaddition reaction. The small response to variation of the polarity of the solvent rules out an intermediate involving any significant degree of charge separation.

Molecular Orbital Calculation

For quantitative application of frontier molecular orbital theory to pericyclic reactions, Houk *et al.* recommended the use of the experimental eigenvalues and they evaluated the orbital energies of a wide variety of unsaturated compounds by the empirical estimation using the known values of the ionization potentials and electron affinities of the parent molecules.[9] In their extensive studies on 1,3-dipolar cycloaddition, Houk *et al.* estimated the frontier molecular orbital of the parent cumulenes.[9c]

However, many of them were obtained by extrapolation and often conflict with the values reported elsewhere. Therefore, we have used the frontier coefficient magnitudes and frontier orbital energies from MINDO/3 calculations[10] as a basis to discuss the cycloaddition behavior of pyridine *N*-oxides toward phenyl isocyanates.

The molecular geometries of the parent molecules were determined by means of semiempirical SCF MO calculations based on the MINDO/3 approximation combined with geometrical optimization by the Fletcher–Powell method.[10] The resulting geometries were then used for the calculations of substituted molecules. The calculated optimum geometry and dipole moment of pyridine *N*-oxide are in agreement with the observed values determined by X-ray crystallographic analyses.[11]

The calculated N–O bond length is considerably shorter than that in trimethylamine *N*-oxide (1.388 Å), indicating the contribution of charge transfer[11] from the O atom to the ring system.

Isocyanic acid is predicted to be linear in accordance with the partially optimized structure of phenyl isocyanate. The linear form is more stable than the bent form. The dipole moment of the colinear structure of phenyl isocyanate is larger than the experimental value by 0.57 Debye. The MINDO/3 calculated bond angle of 180° is almost certainly an overestimate of the true value. The experimental structure of phenyl isocyanate has been determined based on dielectric data showing that the moment of NCO is directed at about 42° with respect to the Ph–N bond in aromatic isocyanates.[12] Indeed, the nonlinear structure required to reproduce the experimental value of dipole moment has the C–N–C bond angle of 135°. For the purpose of further calculations and discussions, we assume the bond angle to be 135°.

The calculated energies of the frontier orbitals of pyridine *N*-oxide [−8.76 (HOMO), 0.439 LUMO) and 0.546 eV (NLUMO)] are higher in energy than those of parent nitrone [−9.77 (HOMO) and −1.05 eV (LUMO)].[9c] Thus, the calculations indicate that the pyridine *N*-oxide should behave as a good donor against general olefins.

Isocyanic acid ($H{-}N{=}C{=}O$) resembles ketene and has degenerate HOMO's and LUMO's, 0.5 eV lower in energy than those of ketene. In phenyl isocyanate, attachment of the aryl group stabilizes the out-of-plane orbital more than the in-plane orbital, which compresses the frontier orbital energies and the coefficient at the site of attachment in isocyanate.

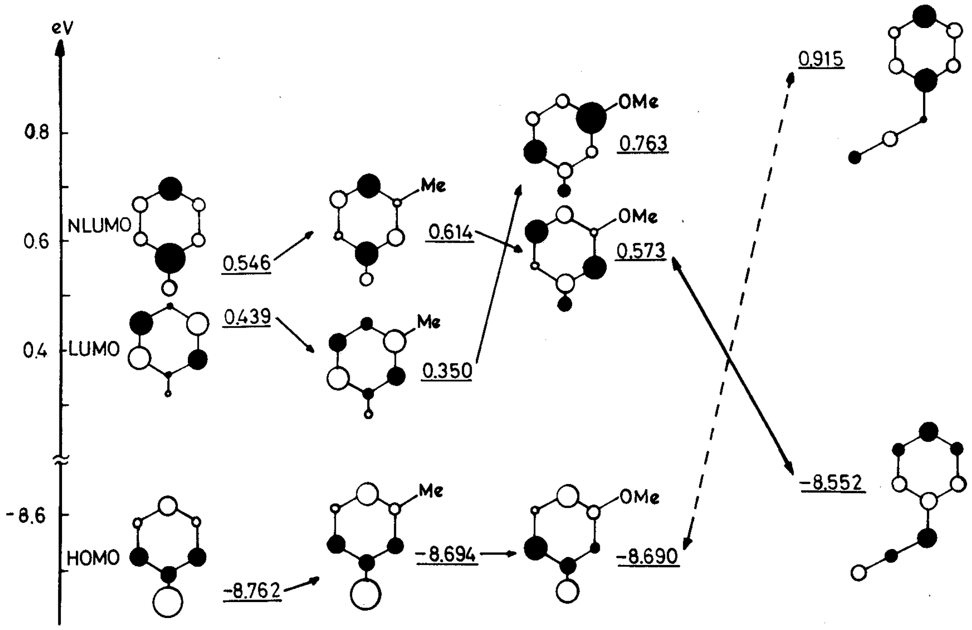


Fig. 4. FMO Energy Levels and Coefficients by the MINDO/3 MO Method

As can be seen in Fig. 4, the frontier molecular orbital energy difference (HOMO–LUMO) of pyridine *N*-oxide is situated among the FMO energy levels of phenyl isocyanate, indicating that pyridine *N*-oxide participates in a neutral-type cycloaddition where both interactions play an important role in determining the reactivity for the cycloaddition.

The highest occupied molecular orbital (HOMO) of pyridine *N*-oxide is located largely on the nitrogen atom.

Discussion

One of the most important recent theoretical developments in connection with cycloaddition has been the application of the frontier orbital approach. This method has been used successfully to account for reaction rates and peri- and regioselectivity by considering the interaction of the HOMO of the donor and the lowest unoccupied molecular orbital (LUMO) of the acceptor.

The direction of the addition is in agreement with prediction made on the basis of the perturbation theory: bonding always occurs between the C atom of the isocyanate and the O atom of the pyridine *N*-oxide where the largest coefficients of interacting frontier orbitals are found and coulombic attraction is also greatest due to the electron-localized heterocumulene nature of both addends.

For an unsymmetrical molecule such as 3-substituted pyridine *N*-oxide, two different orientations of addition (site selectivity) are possible, as shown in Chart 2.

If only steric control is operative, the adduct formed by attack at atoms O and C_6 should be formed predominantly. The observed product ratio is not compatible with this assumption. This trend is prominent in the cases of 3-methoxy- and 3-bromopyridine *N*-oxides.

Inspection of the calculation data provided a clue to the anomaly. Both the energy and the form of the HOMO are affected to a smaller extent than those of the LUMO because the former has a node close to the C_3 and C_5 atoms. The LUMO orbital is localized at the positions of the C_3 and C_5 atoms, and consequently substitution by donor group at positions 3 and 5 destabilizes the LUMO orbital. The second lowest unoccupied molecular orbital

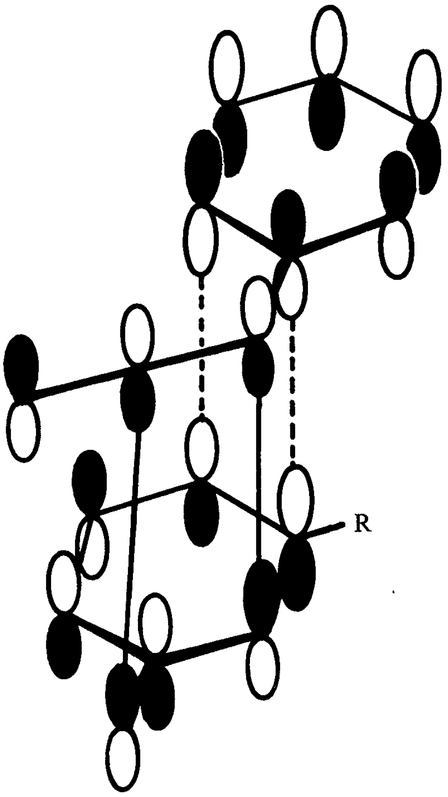


Fig. 5. Transition State of Ic and II in *endo* Addition

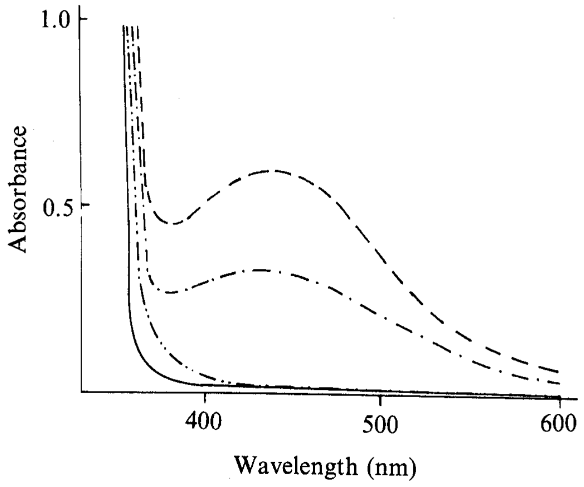


Fig. 6. Visible Absorption Spectrum of the Reaction Mixture of Pyridine *N*-Oxides and Phenyl Isocyanate

(A) The sum of the absorptions of individual benzene solutions, 3-picoline *N*-oxide and phenyl isocyanate (——).

(B) Absorption of a combined solution of 3-picoline *N*-oxide and phenyl isocyanate (– – – –).

(C) The sum of the absorptions of individual benzene solutions, 3,5-lutidine *N*-oxide and phenyl isocyanate (– - – -).

(D) Absorption of a combined solution of 3,5-lutidine *N*-oxide and phenyl isocyanate (—–—).

(NLUMO), shown in Fig. 3 for the unsubstituted molecule, lies only 0.1 eV higher than the LUMO and consequently might also be expected to contribute to considerable extent to the frontier orbital energy term. It is noteworthy that substitution of a methoxy group at C_3 of pyridine *N*-oxide causes a crossover in which C_2 coefficient of LUMO becomes larger than that of C_6.

The LUMO's of 3-picoline *N*-oxide and phenyl isocyanate have a nodal property at the O atom and at the N atom respectively, indicating that the stabilization is mainly derived from the interaction among the HOMO of the phenyl isocyanate and the NLUMO of 3-picoline *N*-oxide. In the case of 3-methoxypyridine *N*-oxide, the LUMO has a node at the C_6 atom, which is very favorable for the formation of the cycloadduct attacked at the O and C_2 atoms. This interaction may be stabilized by the secondary orbital interaction as illustrated in Fig. 5. Thus, the steric effect could be overpowered by the FMO controlling effects.

In a recent rationalization of reactivity and mechanistic phenomena observed in cycloadditions, it has been proposed that 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 *et al.* pointed out 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,$^{13)}$ so that the cycloaddition will presumably be less concerted or will occur *via* complex formation (*e.g.* charge–transfer complex) before affording the final product. This proposal was recently supported by experimental evidence indicating that the orientation of the molecular complex plays a leading role in determining both the reactivity and stereochemistry of the addition.$^{14)}$

In the reaction studied here, spectroscopic evidence for the presence of the complex was obtained. When phenyl isocyanate was added to 3-picoline *N*-oxide in benzene solution, there was a marked intensification of the yellow color and the visible absorption spectrum of the mixture was not that which results from the addition of the spectra of pure samples of the two solutes. This fact indicates that the 1,3-dipolar cycloaddition proceeds *via* a charge–transfer complex, whose orientation must determine both the regiochemistry and stereochemistry of the adduct.[14)]

Another factor which must be taken into consideration in the discussion of reactivity is the coulombic attraction. The calculation on the basis of the perturbation equation derived by Klopman and Salem[15)] indicates that the stabilization energy due to coulombic interaction reaches one-fourth of the FMO interaction energy for the reaction conducted in dimethylformamide (DMF).

Within the distance used for the perturbation calculation, electrostatic forces between the polar reactant molecules can have a significant role in determining the orientation in the transition state. The energy change due to dipole–dipole interaction is expressed by the equation $\Delta E = 14.4 \cdot \mu a \cdot \mu b / r$, where ΔE is in kcal/mol, μ is the dipole moment in Debye units, and r is the distance of separation in angstroms.[16)] The orientation in which the dipoles line up in an antiparallel manner is favored. The directions of the dipole moments of the addends were determined from SCF calculations.[17)] The difference in energy between the parallel and the antiparallel is large, and was estimated to be 34 kcal/mol at 2.0 Å.

Finally, mention should be made of 1,5-sigmatropic rearrangement of the primary adducts. The facile rearrangement of the primary adducts was rationalized on the basis of MINDO/3 calculation on the model reaction of pyridine *N*-oxide with isocyanic acid, The calculation indicates that the heat of formation (ΔH_f) of the rearranged compound is 27 kcal/mol smaller in energy than that of the primary one, indicating the primary adduct to be thermodynamically less stable.[18)]

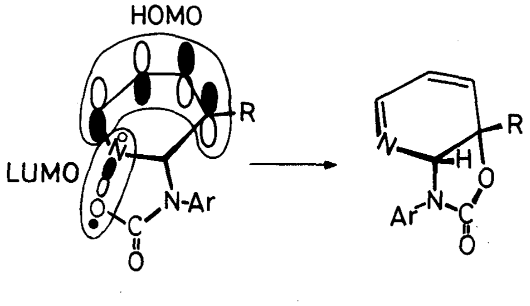


Chart 3

Experimental

All melting points are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken with JNM-MH-100 and JNM-C-60H spectrometers for *ca.* 10% (w/v) solution with tetramethylsilane as an internal standard; chemical shifts are expressed in δ values. Infrared (IR) spectra were recorded on a JASCO DS-301 infrared spectrophotometer equipped with a grating. Mass spectra (MS) were taken with a JEOL JMS-01SG double-forcusing spectrometer operating at an ionization potential of 75 eV. Gas chromatographic analyses were performed on a Yanagimoto G80 gas chromatograph equipped with a thermal conductivity detector and a column of 2% Fluoxlate K Uniport HP (60—80 mesh, 3 mm × 2.5 m).

All the calculations were performed on a FACOM M-200 computer in the Computer Center of Kyushu University.

Cycloaddition Reactions of 3-Methoxypyridine *N*-Oxide (Ic) with Phenyl Isocyanate. General Procedure of Cycloaddition——A solution of Ic and an excess amount of phenyl isocyanate in dimethyl formamide was heated at a given temperature until completion of reaction was confirmed by thin-layer chromatography (TLC). The solvent was evaporated off under reduced pressure. The residue was purified by column chromatography on silica gel with benzene. The first fraction gave VII (4%) as colorless needles: mp 151.5—152.5 °C (from MeOH); IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1760 (C=O), NMR.(in CDCl$_3$, 60 MHz): 7.75—6.80 (7H, m, C_6–H, C_7–H and phenyl), 7.97 (1H, dd, $J_{5,6}=5$ Hz, $J_{5,7}=2$ Hz, C_5–H). MS *m/e*: 212 (M^+), 168 (M^+-CO_2). *Anal.* Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.82; H, 3.67; N, 13.16.

The second fraction gave VIc (30%). Compound VIc was obtained as a colorless oil, bp 147—148 °C/1.5 mmHg; IR $\nu_{\max}^{\mathrm{neat}}$ cm^{-1}: 3420 (NH). NMR (in CDCl$_3$, 60 MHz): 3.77 (3H, s, –OCH$_3$), 7.65—6.47 (8H, m, C_4–H, C_5–H, NH and phenyl), 7.74 (1H, dd, $J_{6,4}=2$ Hz, $J_{6,5}=5$ Hz, C_6–H). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.24; H, 5.96; N, 14.26.

The products from Ia, Ib and Id were known compounds$^{5)}$ and the relative amounts were determined by gas liquid chromatography (GLC).

Kinetics——A solution of pyridine *N*-oxide (0.01 mol) and phenyl isocyanate (0.02 mol) in the given solvent was prepared. The solution was then pippeted into a test tube. The tube was sealed with a ground glass stopper and then immersed in a constant temperature oil bath (Tokyo Rika Kikai HB 200-B) controlled to ±0.05 °C. The rate was followed at a given temparature by measuring the decrease of the peak area of pyridine *N*-oxide using benzophenone as an internal standard. The data are summarized in Table II.

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