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Reaction of Aromatic *N*-Oxides with Dipolarophiles. X.[1a] Role of Charge-Transfer Complexes in 1,3-Dipolar Cycloaddition of Pyridine *N*-Oxides to Phenyl Isocyanate[1b,c]

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In the 1,3-dipolar cycloaddition reaction of 3-methylpyridine *N*-oxide with phenyl isocyanate, spectroscopic evidence indicates that phenyl isocyanate forms charge-transfer complexes with both pyridine *N*-oxide and aromatic solvents such as pyridine. In connection with the charge-transfer complex formation, the solvent effect on the site selectivity was investigated. The most prominent solvent effect was observed in the reaction using 3-methylpyridine as a solvent. The equilibrium constants for the interaction of 3-methylpyridine *N*-oxide with phenyl isocyanate in several solvents were found to be quite large, indicating that the reaction mixtures favor complex formation. The proton nuclear magnetic resonance (^{1}H-NMR) spectra of the mixtures show a high field shift of the methyl signal of 3-methylpyridine *N*-oxide due to charge-transfer complexation. Based on these results, the structure and role of the complexes are discussed.

Keywords——charge-transfer complex; 1,3-dipolar cycloaddition; pyridine *N*-oxide; phenyl isocyanate; site selectivity; visible absorption spectra; equilibrium constant; frontier molecular orbital; kinetics

Introduction

One of the most important recent theoretical developments in connection with cycloaddition has been the application of the frontier molecular orbital (FMO) approach.[2] This method has been used successfully to account for the cycloaddition characteristics (reactivity and peri- and regioselectivities) by considering the interaction of the highest occupied molecular orbital (HOMO) of the donor and the lowest unoccupied molecular orbital (LUMO) of the acceptor.

On the other hand, 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, and the FMO theory has been used successfully in explaining the formation of charge-transfer complexes.[3]

In the previous papers,[1c,4] we showed that the 1,3-dipolar cycloaddition of pyridine *N*-oxides (**1**) to phenyl isocyanates takes place by a concerted process on the basis of the observed stereoselectivity, the lack of solvent dependence, the low activation enthalpy and the strongly negative entropy. Calculation based on MINDO/3 approximation[5] suggested that the reaction falls into the category of a neutral-type reaction in Sustmann's classification for cycloadditions.[6] The calculation also indicated that the reactivity may result from both the FMO interaction and the relatively high degree of coulombic attraction arising from the highly polarized structures of both addends, and the aromaticity of pyridine *N*-oxides (**1**) may play a major role in determination of the reactivity.[4]

We have observed that the reaction often proceeds with the appearance of charge-transfer (CT) bands beyond 450 nm.[1c] This paper deals with the role of charge-transfer complexes in the cycloaddition reaction of pyridine *N*-oxides (**1**) with phenyl isocyanate (**2**).

Results

Site Selectivity in 1,3-Dipolar Cycloaddition of 3-Methylpyridine *N*-Oxide (1b) with Phenyl Isocyanate (2)

As described in a previous paper,[1c] the rates of the cycloadditions of pyridine *N*-oxides with phenyl isocyanate (**2**) were not affected by change in the polarity of the solvents, ruling out an intermediate involving a significant degree of charge separation. However, the solvent effect on the site selectivity in connection with the role of the charge-transfer complex still remains obscure. Therefore, we have studied the cycloaddition behavior of unsymmetrical pyridine *N*-oxides toward phenyl isocyanate (**2**) choosing 3-methylpyridine *N*-oxide (**1b**) as a model compound.

For an unsymmetrically substituted pyridine *N*-oxide such as 3-methylpyridine *N*-oxide (**1b**), two different orientations of addition (site selectivity) are possible, as shown in Chart 1. If only steric control is operative, the adduct (A) formed by attack at atoms O and C_6 should be formed predominantly. However, the observed product ratios in some solvents were not consistent with this assumption.

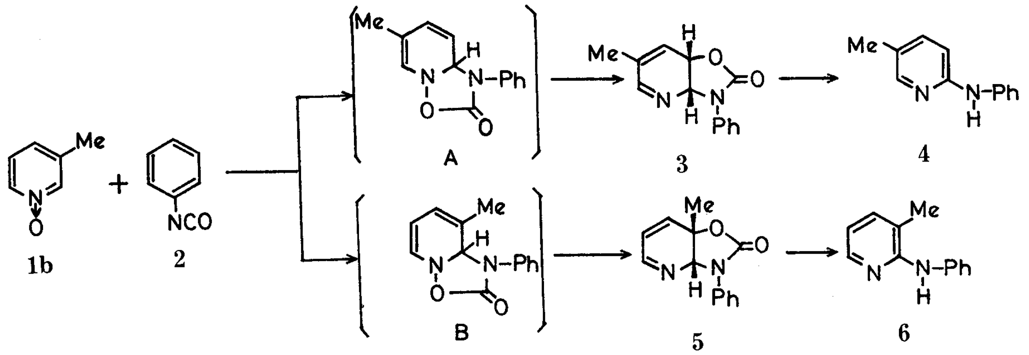


Chart 1

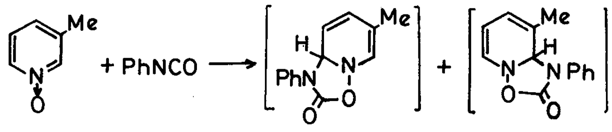
The primary cycloadducts (A and B) are thermally labile and undergo 1,5-sigmatropic rearrangement to give the 2,3-dihydropyridine derivatives (**3** and **5**) which are also thermally unstable, decomposing into 2-anilinopyridine derivatives (**4** and **6**) with extrusion of carbon dioxide upon heating above 150 °C. Therefore, the relative amounts of the cycloadducts were determined by measuring the amounts of the final products (**4** and **6**) by gas chromatography, using benzophenone as an internal standard. The results are shown in Table I.

As shown in Table I, the ratio of 5-methyl-1,2-dihydropyridine derivative (A) to 3-methyl-1,2-dihydropyridine derivative (B) was strikingly altered by changing of solvent. In sulfolane, the adducts were formed in approximately equal amounts (ratio = 1.0). On the other hand, when 3-methylpyridine was used as the solvent, the adduct (A) formed by attack at atoms O and C_6 was produced predominantly (ratio = 3.0).

In cycloaddition of cyclopentadiene with methyl crotonate, the amount of *endo*-adduct increases by more than 20% on going from a nonpolar solvent such as decalin to a polar solvent, *e.g.*, acetic acid. This phenomenon has been explained in terms of the dipole–dipole interaction, and the ratios have been used as a scale of solvent polarity, commonly referred to as omega value.[7]

Instead of omega values, we used E_T values[8] as a scale of solvent-ionizing power since

Table I. Site Selectivity in 1,3-Dipolar Cycloaddition of 3-Methylpyridine *N*-Oxide with Phenyl Isocyanate in Various Solvents



1b **2** A B

Solvent	A/B	Solvent	A/B
Pyridine	2.27	Nitrobenzene	1.50
2-Methylpyridine	1.67	Acetophenone	2.00
3-Methylpyridine	2.86	Methyl benzoate	1.79
4-Methylpyridine	2.19	Sulfolane	1.01
2,6-Dimethylpyridine	1.77	1,4-Dioxane	1.21
N,*N*-Dimethylaniline	2.00	Triethylamine	1.17
Anisole	1.19	Triethylenediamine	0.39
p-Methylanisole	1.55	Dimethylformamide	1.22
Toluene	1.12	Dimethylsulfoxide	1.06

they have been found to show a linear relationship with the omega values and to be available with a wider variety of solvents than the other known scales.

However, based on the E_T values, we could not find any correlation between the ratio of the products and the polarity of the solvent. This result implies that another factor may be operative in determination of the site selectivity. Broadly speaking, it appears that electron-deficient aromatic solvents commonly show a similar effect on the product distribution.

Visible Absorption Spectra of the Reaction Mixture

When a solution of pyridine *N*-oxide (**1a**) was mixed with a solution of phenyl isocyanate (**2**), the solution became light yellow-brown. The color did not discharge upon heating above 100 °C and remained during the reaction period. The visible spectra of mixtures of some pyridine *N*-oxides and phenyl isocyanate (**2**) in benzene solution are shown in Fig. 1.

The spectra showed essentially the same pattern, having a maximum in the vicinity of 450 nm. The complexes always exhibit a spectrum (called a charge-transfer spectrum) which is not the same as the sum of the spectra of the two individual molecules, suggesting that the complexes may exist only in solution in equilibrium with their components.

3-Methylpyridine showed the most prominent effect (ratio = 2.86). The spectrum exhibited two maxima at 380 and 450 nm as shown in Fig. 2 (curve a). The latter can be ascribed to the charge-transfer complex of 3-methylpyridine *N*-oxide (**1b**) and phenyl isocyanate (**2**). The newly appeared absorption at 380 nm may be due to charge-transfer phenomena between the solvent and phenyl isocyanate (**2**), which can be observed directly in the visible absorption spectrum of a solution of phenyl isocyanate (**2**) in 3-methylpyridine (curve b). It is noteworthy that phenyl isocyanate (**2**) is able to form charge-transfer complexes with both 3-methylpyridine *N*-oxide (**1b**) and 3-methylpyridine.

In order to obtain some information about the degree of stabilization of the charge-transfer complex, we determined the equilibrium constants in typical solvents. The equilibrium constants were determined by use of the Lang's self-consistent field (SCF) method[9] in which the calculations are repeated until self-consistency is reached. The calculation data are summarized in Table II. The values of the equilibrium constants are very large, indicating that, at least at the given temperature, the equilibrium is largely shifted in favor of formation of the charge-transfer complex. The constant for sulfolane is considerably larger than those of

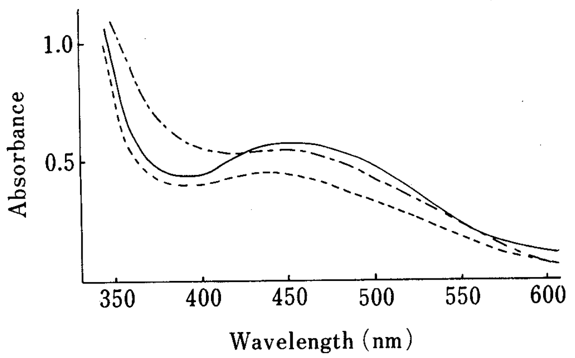
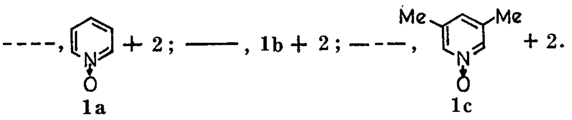


Fig. 1. Visible Absorption Spectra of Mixtures of Some Pyridine N-Oxides and Phenyl Isocyanate in Benzene



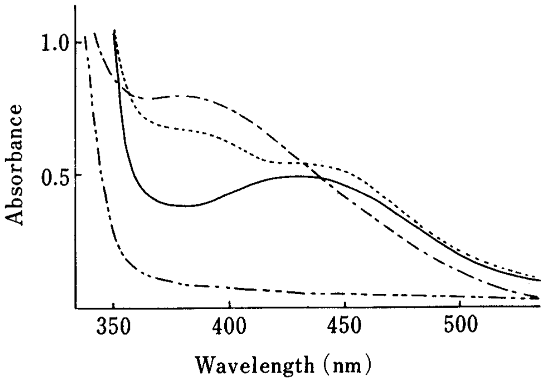


Fig. 2. Visible Absorption Spectra of Mixtures of Phenyl Isocyanate and 3-Methylpyridine N-Oxide in 3-Methylpyridine and Sulfolane Solutions

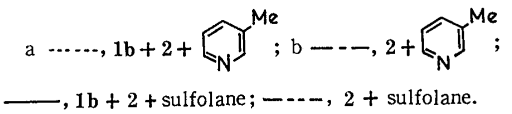


TABLE II. Rate Constants for 1,3-Dipolar Reaction of 3-Methylpyridine N-Oxide with Phenyl Isocyanate in Several Solvents and Equilibrium Constants of Its Reaction Mixture

Solvent	Rate constants[a] $k_2 \times 10^5$ ($s^{-1} \cdot mol^{-1}$)	Equilibrium constants[b] K (M^{-1})
3-Methylpyridine	3.06	17.0
Sulfolane	19.1	45.0
Triethylamine	0.093	

a) k_2 measured at 110 °C. *b*) K measured at room temp.

other solvents, implying that the mode of complexation in aromatic solvents might be different from that in nonaromatic solvents.[10)]

Proton Nuclear Magnetic Resonance (^{1}H-NMR) Spectral Behavior of the Charge-Transfer Complexes

The ^{1}H-NMR spectra of the complexes in several solvents show features that provide information about the structure of the charge-transfer complexes. In the ^{1}H-NMR spectrum of the mixture of 3-methylpyridine N-oxide (**1b**) and phenyl isocyanate (**2**) in $CDCl_3$, the methyl signal resonates at moderately higher field (2.13 ppm) than in the case of 3-methylpyridine N-oxide (**1b**) itself (2.35 ppm) (Fig. 3a). The shielding of the methyl group may be explained in terms of the face-to-face structure of the complex in which the methyl group is lying over the aromatic ring. On the other hand, the mixture of 3-methylpyridine and phenyl isocyanate (**2**) did not show a high-field shift of the methyl signal of 3-methylpyridine (Fig. 3b) although the characteristic charge-transfer absorption band was recognized in the visible absorption spectrum (Fig. 2, curve b). This result indicates that the complex of 3-methylpyridine and phenyl isocyanate (**2**) does not have such an ordered structure as in the above case, but has a simple structure arising from the electrostatic attraction.

The spectrum of the mixture of the three components (3-methylpyridine N-oxide (**1b**), phenyl isocyanate (**2**) and 3-methylpyridine) showed interesting spectral characteristics. Addition of 3-methylpyridine N-oxide (**1b**) to a mixture of phenyl isocyanate (**2**) and 3-

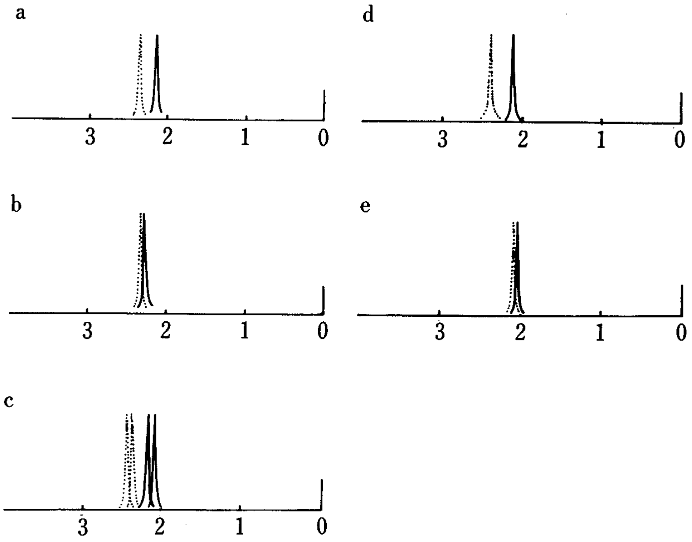


Fig. 3. Shifts of Methyl Proton Signals of Pyridine *N*-Oxides Due to Charge-Transfer Complexation with Phenyl Isocyanate in $CDCl_3$

a) 3-methylpyridine *N*-oxide and phenyl isocyanate. b) phenyl isocyanate and 3-methylpyridine. c) 3-methylpyridine *N*-oxide, phenyl isocyanate and 3-methylpyridine. d) 3,5-dimethylpyridine *N*-oxide and phenyl isocyanate. e) 3-methyl-2-phenylpyridine *N*-oxide and phenyl isocyanate.

methylpyridine caused a high-field shift of the methyl signals of 3-methylpyridine and 3-methylpyridine *N*-oxide (**1b**) (Fig. 3c).

This result may be consistent with the formation of a new type of complex between the two addends and 3-methylpyridine, the planes of the aromatic rings (3-methylpyridine *N*-oxide (**1b**) and 3-methylpyridine) being parallel to the phenyl isocyanate molecule. In such a complex, the hydrogen atoms of the methyl groups must be situated in a region of moderate shielding above and below the plane of the phenyl ring. A similar result was observed in 3,5-dimethylpyridine *N*-oxide (**1c**) (Fig. 3d).

The ability to form a planar structure seems to be important, and this assumption is supported by the fact that 3-methyl-2-phenylpyridine *N*-oxide (**1d**), in which the two aromatic rings cannot be coplanar,[11)] did not form a complex with phenyl isocyanate (**2**) as evidenced by its ^{1}H-NMR and visible absorption spectra (Fig. 3e).

These results suggest that the charge-transfer complexes in question do not have a random structure but a highly ordered one resembling crystal structure,[12)] in which the molecules are stacked in parallel planes.

Discussion

Molecular-orbital theory suggests that electrons from one of the two original molecules jump into higher vacant orbitals of the other, and the electron transfers leading to charge-transfer complex formation and to transition-state intermediate formation in cycloaddition reactions very probably require similar structural arrangements, in which the two interacting molecules lie in parallel planes.[13)]

We have previously indicated that the transition state of 1,3-dipolar cycloaddition might be stabilized by the secondary orbital interaction.[1c)] The MINDO/3[5)] coefficients and energies of the FMO's and net charges are listed in Fig. 4.

The second lowest unoccupied molecular orbital (NLUMO), for 3-methylpyridine *N*-oxide (**1b**), lies only 0.3 eV higher than the LUMO and consequently might also be expected to contribute to a considerable extent to the frontier orbital energy term. The LUMO's of 3-methylpyridine *N*-oxide (**1b**) and phenyl isocyanate (**2**) have a nodal property at the O atom and at the N atom, respectively, indicating that the stabilization is derived from an inverse-type interaction among the HOMO of phenyl isocyanate (**2**) and the NLUMO of 3-methylpyridine *N*-oxide (**1b**) in addition to the normal-type interaction.[6)]

The formation of the cycloadduct involving the sterically unfavorable cycloaddition

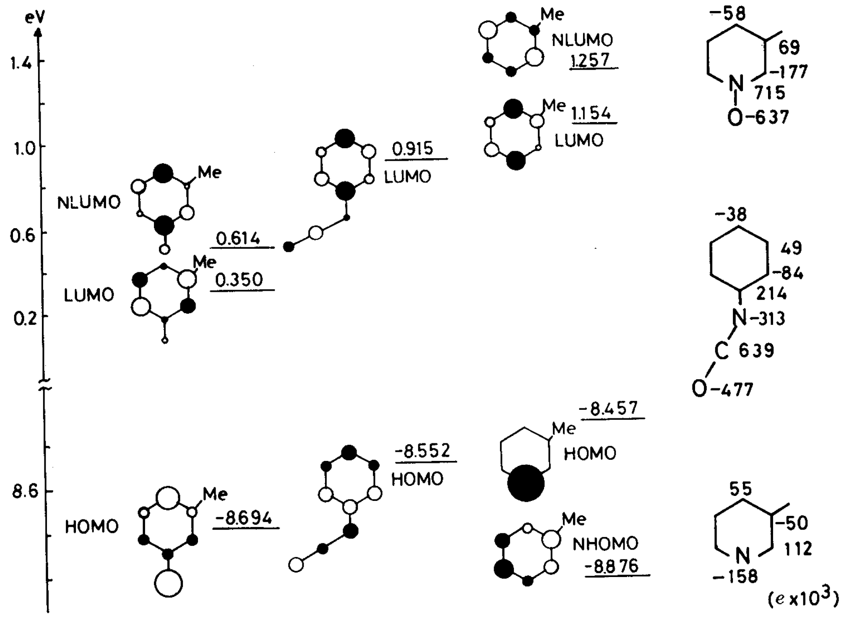


Fig. 4. FMO Energy Levels, Coefficients and Net Charges of 3-Methylpyridine *N*-Oxide, Phenyl Isocyanate and 3-Methylpyridine

(attack at atoms O and C_2) may also be accounted for by the effective secondary orbital interaction involving the inverse-type interaction.[1c)]

The perturbation calculation data[4)] indicate that, in the early stages of the reaction, coulombic attractions are operative rather than FMO interactions, as reflected by the highly polarized structure of the addends, and the resultant molecular complexes may be further stabilized by FMO interaction involving the secondary orbital interaction, resulting in the formation of a highly ordered complex.

An inspection of a Dreiding model of the possible transition state[1c)] indicates that the methyl protons of 3-methylpyridine *N*-oxide (**1b**) lie over the π-electron system of the ring (at the periphery of the ring). In this model, when the two molecules come together within the sum of their van der Waals radii so that the maximum overlap of the interacting orbitals may be attained, the methyl protons are situated close to the region 3.0 Å from the center of the phenyl ring and 3.5 Å over the plane of the ring. The theoretical prediction[14)] based on the above geometry agrees well with the observed anisotropy.

In a proposed transition state model, the secondary orbital interaction may contribute to stabilization of the transition state, cancelling out the destabilization due to the steric repulsion between the hydrogen of the methyl group and the phenyl ring of the isocyanate, wherein the conformation of the phenyl ring is considered to affect the stabilization of the transition state resulting in changes of the product ratio.

In the parallel approach, the $2p_z$ orbitals of $N=C=O$ are considered to be nearly parallel with those of the phenyl ring and there is interference between the hydrogens of the methyl group and the phenyl ring of the isocyanate. However, this interference may be eliminated by rotation of the phenyl ring about the bond that links the $N=C=O$ to the ring. The rotation is considered to be restricted by the complex formation. Therefore, the apparent planarity of the dipolarophile is enhanced and the freedom of motion is restricted. In this situation, the cycloaddition might occur at the less hindered site.

Thus, we can safely say that the observed site selectivity may be affected by the charge-transfer complexation, and significant changes of the product ratio in aromatic solvents such as 3-methylpyridine may occur, depending on the stability of the ternary molecular complex.

Finally, mention should be made of the cycloaddition reactivity due to charge-transfer complex formation. The ratio of the rate of cycloaddition in 3-methylpyridine to that in sulfolane is 1 : 6.3 (Table II). The rate of addition in sulfolane solution seems greater than can be accounted for merely on the basis of the small normal influence[1c)] of solvent polarity, indicating that the rate enhancement may be attributable to the formation of a polar complex. Theoretical studies[3)] provide insight into the cycloaddition behavior in sulfolane. The perturbation equations derived from a charge-transfer complex model for pericyclic reaction transition states indicate that when two molecules are brought closer together the energies of the charge-transfer configurations drop by a considerable amount due to the increase in coulombic attraction between the positively charged donor and the negatively charged acceptor, in which the ground state configuration and charge-transfer configuration move closer in energy, and interact more strongly. Thus the ground state surface is stabilized, and the activation energy for reaction is decreased.

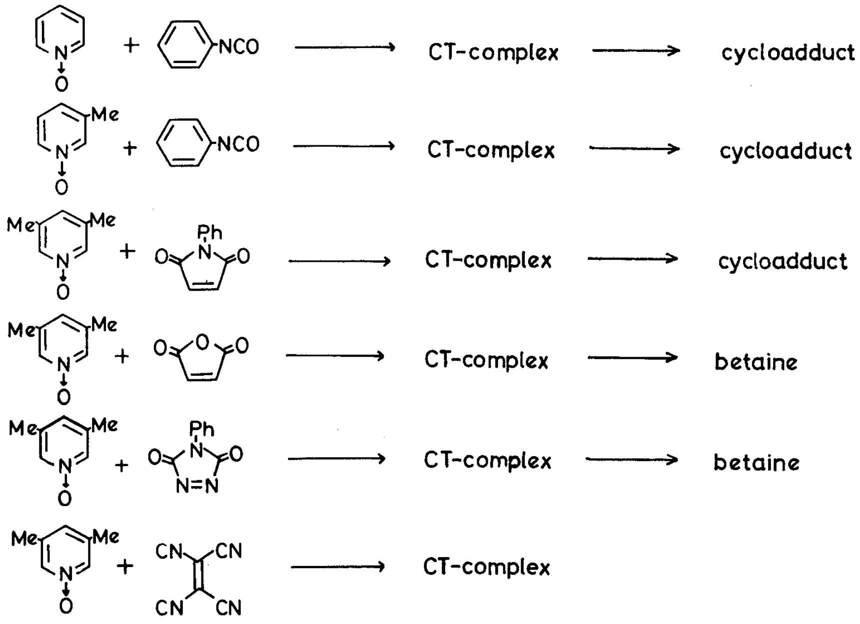


Chart 2

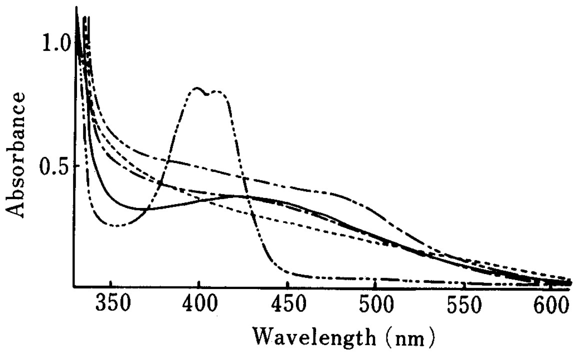
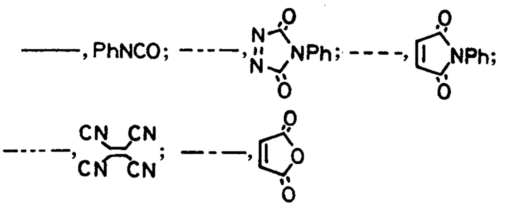


Fig. 5. Charge-Transfer Spectra of Mixtures of Pyridine N-Oxide and Various Dipolarophiles



These results suggest that whether the cycloaddition does occur or not depends upon the relative stabilities of the ground state and transition state. Indeed, it was experimentally observed that the cycloaddition of pyridine N-oxides proceeded in the case of phenyl isocyanates or N-phenylmaleimides, whereas in the case of 4-phenyl-1,2,4-triazoline-3,5-dione or tetracyanoethylene, charge transfer might be sufficiently great that the reaction course might be altered to result in a stepwise reaction (substitution reaction) or formation of a stable charge-transfer complex which could not transform to the corresponding cycloadduct[15] (see Chart 2 and Fig. 5).

Experimental

All melting points are uncorrected. The ^{1}H-NMR spectra were taken with Hitachi R-600 and JEOL JNM-C-60H spectrometers in *ca.* 10% (w/v) solution with tetramethylsilane (TMS) as an internal standard; chemical shifts are expressed in δ values.

Infrared (IR) absorption spectra were recorded on a JASCO DS-301 IR spectrophotometer equipped with a grating. Mass spectra were taken with a JEOL JMS-01SG double-focusing spectrometer operating at an ionization potential of 75 eV. Ultraviolet (UV) and visible absorption spectra were determined with a Hitachi 150-20 spectrophotometer.

All the calculations were performed on FACOM M-200 and M-382 computers in the Computer Center of Kyushu University.

Preparation of Materials——Pyridine *N*-oxide (**1a**),[16] 3-methylpyridine *N*-oxide (**1b**),[17] 3,5-dimethylpyridine *N*-oxide (**1c**),[18] and 3-methyl-2-phenylpyridine *N*-oxide (**1d**)[19] were prepared according to the previously established methods.

Phenyl isocyanate was obtained from commercial suppliers and was used without further purification.

General Procedure for Cycloaddition. Cycloaddition Reactions of Pyridine *N*-Oxides with Phenyl Isocyanate——A solution of **1** and an excess amount of phenyl isocyanate in a solvent 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 relative amounts of the products from the reaction of 3-methylpyridine *N*-oxide (**1b**) with phenyl isocyanate (**2**) were determined by gas-liquid chromatography (GLC) using authentic samples of 2-anilino-3-methylpyridine and 2-anilino-5-methylpyridine. The product ratios are listed in Table I.

Kinetics——A solution of 3-methylpyridine *N*-oxide (0.01 mol) and phenyl isocyanate (0.02 mol) in the given solvent was prepared. The solution was pipetted into a test tube. The tube was sealed with a ground glass stopper and then immersed in a constant temperature bath. The rate was followed at a given temperature by measuring the decrease of the peak area of the 3-methylpyridine *N*-oxide using benzophenone as an internal standard. The data are summarized in Table II.

Measurement of Visible Absorption Spectra——Solutions of pyridine *N*-oxides (0.002 mol) and phenyl isocyanate (0.002 mol) in a given solvent were used for the measurement. The results are summarized in Figs. 1 and 2.

Determination of the Equilibrium Constants of Charge-Transfer Complex Formation——Solutions of 3-methylpyridine *N*-oxide (0.2 mol) containing various amounts (0.2—2.0 mol) of phenyl isocyanate were prepared. After equilibration, the visible absorption spectra were measured. From the data, the equilibrium constant were calculated according to Lang's method.[9] The data are summarized in Table II.

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11) The methyl protons of 3-methyl-2-phenylpyridine *N*-oxide resonate at 2.08 ppm, at 0.24 higher field than those of 3-methylpyridine *N*-oxide. This fact suggests that the phenyl ring of the former lies in a perpendicular disposition with respect to the pyridine ring.

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