[Chem. Pharm. Bull. 34(2) 572—581 (1986)]

Reaction of Aromatic *N*-Oxides with Dipolarophiles. IX.[1a] Formation of 1:2 Cycloadduct of 2-Alkylpyridine *N*-Oxides and Phenyl Isocyanates and a Frontier Molecular Orbital Study

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(Received July 8, 1985)

A series of 1:2 cycloadducts of a new type was obtained from the reaction of 2-alkylpyridine *N*-oxides with phenyl isocyanates. The reaction mechanisms are discussed in terms of frontier molecular orbital theory based on CNDO/2 and MINDO/2 calculations and kinetic data. The small solvent effect and activation parameters ($E_a = 14$ kcal/mol, $\Delta S = -46$ e.u.) observed for the reaction of 2-alkylpyridine *N*-oxides with phenyl isocyanates indicate that the cycloaddition proceeds *via* concerted pathways involving little charge separation in the transition state.

Keywords——1,3-dipolar cycloaddition; 2-alkylpyridine *N*-oxide; phenyl isocyanate; kinetics; frontier molecular orbital; 1:2 cycloadduct; solvent effect; sigmatropic rearrangement

Introduction

Recent studies[1] in our laboratory have been directed toward obtaining a better understanding of the mechanistic aspects of the 1,3-dipolar cycloaddition reaction of pyridine *N*-oxides with phenyl isocyanates. As mentioned in detail in the previous papers,[1] we have shown that the 1,3-dipolar cycloaddition proceeds by a concerted mechanism on the basis of the stereoselectivity, the lack of solvent-dependence and the strongly negative activation entropy. We also identified some controlling factors in the reaction, such as secondary-orbital interaction, the aromaticity of the pyridine *N*-oxides and charge-transfer complex formation.

We previously communicated the isolation of a single 1:2 adduct (**3**) from the reaction of 2,3-dimethylpyridine *N*-oxide (**1**) with phenyl isocyanate (**2**), as shown in Chart 1.[2] Here, we discuss this result in detail, present additional data, and compare the results with those obtained in our previous studies.[1]

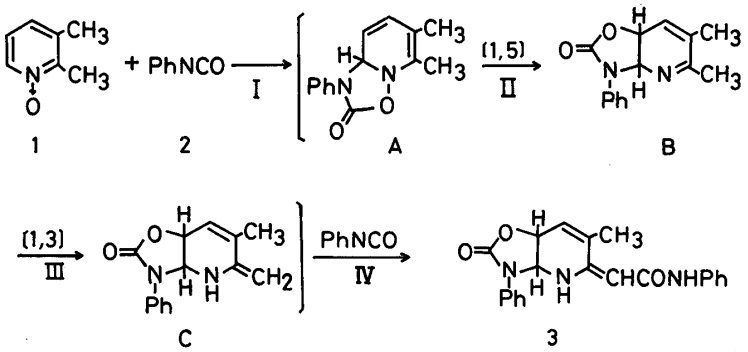


Chart 1

Results and Discussion

From calculations on pyridine *N*-oxides based on the MINDO/3[3] and CNDO/2[4] methods, we consider that introduction of an electron-donating group at the 2-position of the pyridine nucleus rather than the 3-position causes a destabilization of the frontier molecular orbital (FMO) energy level, because there is a node close to the C_3-atom of pyridine *N*-oxide. The CNDO/2 calculation indicates a 0.3-eV rise of the highest occupied molecular orbital (HOMO) for 2,3-dimethylpyridine *N*-oxide (**1**) as compared with that for unsubstituted pyridine *N*-oxide (**4**), suggesting that **1** will show high reactivity toward phenyl isocyanate in comparison with **4**.

First of all, the 1,3-dipolar reaction of 2,3-dimethylpyridine *N*-oxide (**1**) with phenyl isocyanate (**2**) was reinvestigated in detail using dimethylformamide (DMF) as a solvent. The effects of the reaction temperature and duration on the reaction of **1** with **2** are summarized in Table I.

In the previous communication,[2] we did not deal with the structure of the 1 : 2 adduct (**3**) in detail. As the reaction involves the formation of an acrylamide moiety, two geometrically isomeric products are possible, *i.e.*, with the phenylcarbamoyl moiety being *cis* and *trans* with respect to the ring N–H [the *cis*-form (D) and *trans*-form (E)] (Fig. 1).

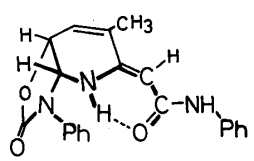
The infrared (IR) spectrum of **3** showed a characteristic carbonyl absorption at 1715 cm^{-1}. An associated secondary amine absorption at 2700—3300 cm^{-1} and a weak carbonyl absorption at 1640 cm^{-1} suggest the presence of an intramolecular hydrogen bonding between the hydrogen atom of the ring N–H and the oxygen atom of the C=O group, which reflects the *cis*-form (D) of **3**.

In general, the thermal decarboxylation of a 2,3-dihydropyridine-type 1 : 1 adduct (type B) was observed at higher reaction temperature in the reaction of pyridine *N*-oxides with

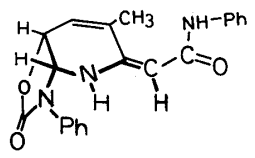
Table I. Relationship between Reaction Temperature, Duration and Yield in the Reaction of **1** with **2** in DMF

Conditions		Molar ratio	Yield of **3** (%)[a]
Temp. (°C)	Duration (h)		
110	2	1:2	9
110	3.5	1:2	11
110	7	1:2	20
110	7	1:1	10
110	10	1:2	17
140	2	1:2	17
140	3.5	1:2	27
140	7	1:2	20
140	10	1:2	18
140	10	1:25	60

a) Calcd. on the basis of **1**.



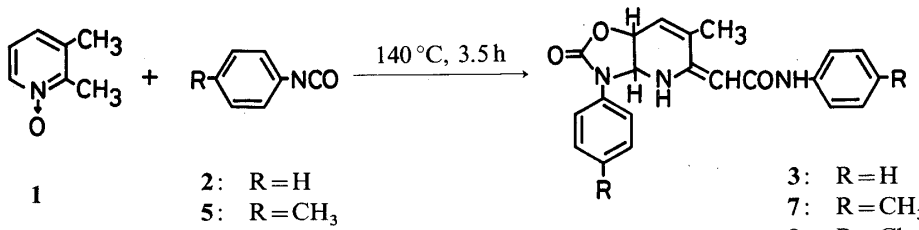
D *cis*



E *trans*

Fig. 1. Possible Geometrical Isomers of the 1 : 2 Cycloadduct from the Reaction of **1** with **2**

TABLE II. Reaction of **1** with *p*-Substituted Phenyl Isocyanates (**2**, **5**, **6**)



1

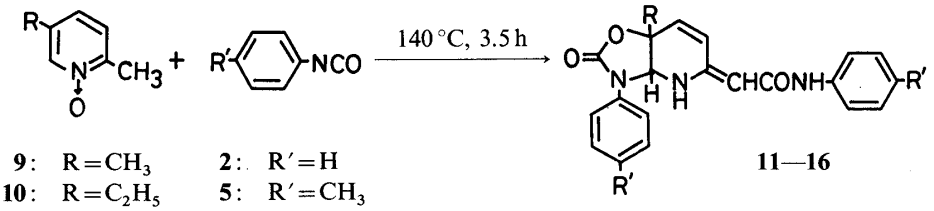
2: R=H
5: R=CH_3
6: R=Cl

3: R=H
7: R=CH_3
8: R=Cl

Starting materials[a]	R	Solvent	Product	
			Compd. No.	Yield (%)[b]
1+**2**	H	DMF	**3**	27
1+**2**	H	Xylene	**3**	40
1+**5**	CH_3	DMF	**7**	25
1+**5**	CH_3	Xylene	**7**	36
1+**6**	Cl	DMF	**8**	26
1+**6**	Cl	Xylene	**8**	38

a) Molar ratio 1:2. *b*) Calcd. on the basis of **1**.

TABLE III. Reaction of 2,5-Disubstituted Pyridine *N*-Oxides (**9**, **10**) with Phenyl Isocyanates (**2**, **5**, **6**)



9: R=CH_3
10: R=C_2H_5

2: R′=H
5: R′=CH_3
6: R′=Cl

11—**16**

Starting[a] materials	R	R′	Solvent	Product	
				Compd. No.	Yield (%)[b]
9+**2**	CH_3	H	DMF	**11**	25
9+**2**	CH_3	H	Xylene	**11**	37
9+**5**	CH_3	CH_3	DMF	**12**	26
9+**5**	CH_3	CH_3	Xylene	**12**	35
9+**6**	CH_3	Cl	DMF	**13**	28
9+**6**	CH_3	Cl	Xylene	**13**	36
10+**2**	C_2H_5	H	DMF	**14**	25
10+**2**	C_2H_5	H	Xylene	**14**	35
10+**5**	C_2H_5	CH_3	DMF	**15**	28
10+**5**	C_2H_5	CH_3	Xylene	**15**	35
10+**6**	C_2H_5	Cl	DMF	**16**	31
10+**6**	C_2H_5	Cl	Xylene	**16**	38

a) Molar ratio 1:2. *b*) Calcd. on the basis of *N*-oxides.

phenyl isocyanates,[1] whereas, in this case, no decarboxylation product was obtained. The reaction at 140 °C for 3.5 h in DMF gave the optimum result, and **3** was isolated in 27.5% yield. The use of a large excess of **2** over **1** (*e.g.* 25 eq) improved the yield of **3** to *ca.* 60%.

TABLE IV. Analytical Data for Products (**3**, **7**, **8**, **11**—**16**)

Compd. No.	mp (°C)	Appearance	Formula	Analysis (%) Calcd (Found)		
				C	H	N
3	227—229	Colorless prisms	$C_{21}H_{19}N_3O_3$	69.79	5.30	11.63
				(69.81	5.38	11.78)
7	217—219	Colorless prisms	$C_{23}H_{23}N_2O_3$	70.93	5.95	10.79
				(70.79	6.12	10.75)
8	251—253	Colorless prisms	$C_{21}H_{17}Cl_2N_3O_3$	58.60	3.95	11.16
				(58.41	3.90	11.07)
11	259—260	Colorless prisms	$C_{21}H_{19}N_3O_3$	69.79	5.30	11.63
				(69.85	5.19	11.46)
12	236—238	Colorless prisms	$C_{23}H_{23}N_3O_3$	70.93	5.95	10.79
				(70.87	5.91	10.74)
13	260—262	Colorless prisms	$C_{21}H_{17}Cl_2N_3O_3$	58.60	3.95	11.16
				(58.50	3.82	11.05)
14	226—228	Colorless prisms	$C_{22}H_{21}N_3O_3$	70.38	5.64	11.19
				(70.45	5.43	10.94)
15	220—222	Colorless needles	$C_{24}H_{25}N_3O_3$	71.44	6.25	10.41
				(71.53	6.20	10.37)
16	245—247	Colorless needles	$C_{22}H_{19}Cl_2N_3O_3$	59.46	4.28	10.81
				(59.32	4.19	10.76)

In the reaction of 2,5-dimethylpyridine *N*-oxide (**9**) or 5-ethyl-2-methylpyridine *N*-oxide (**10**) with **2**, **5** and **6**, similar results were obtained. The reaction conditions and yields are summarized in Table III. The analytical and spectral data are listed in Tables IV and V.

Qualitatively speaking, the *para*-substituent ($-CH_3$ or Cl) of phenyl isocyanates did not have a marked effect on the cycloaddition reactivity, as shown in Tables II and III.

Huisgen *et al.*[5] proposed that the typical 1,3-dipolar cycloaddition reaction proceeds by a concerted mechanism showing a small solvent effect on the rate of reaction. In the reaction of pyridine *N*-oxides with phenyl isocyanates, 1 : 2 adducts were obtained in somewhat better yield in xylene than in DMF, which suggests that the reaction proceeds by a nonionic mechanism (Tables II and III).

The 1 : 2 adduct (**3**) obtained from the reaction of **1** with **2** was converted to pyridinol (**17**) by refluxing in ethanolic potassium hydroxide. It is noteworthy that direct heating of the 1 : 2 adducts (**3**, **7**, **8**) also gave the corresponding pyridinols (**17**—**19**) (Tables VI and VII, and Chart 2). In contrast, isolation of the corresponding pyridinols from the 1 : 2 adducts (**11**—**16**) obtained from the reaction of 2,5-dialkylpyridine *N*-oxides (**9** and **10**) was unsuccessfull. These results appear to indicate that the formation reaction of pyridinols (**17**—**19**) may be brought about by the gain of aromaticity of the pyridine ring with extrusion of phenyl isocyanate.

In order to obtain some evidence for the rationalization of a series of pericyclic reactions involved in the formation reaction of the 1 : 2 adduct, we next performed a kinetic study on the reaction of **1** with **2**. The pseudo-first-order rate constants in DMF at various temperatures were obtained by following the decrease of the peak area of **1** by gas chromatography. The second-order rate constants of the reaction of **1** with **2** were calculated in the usual manner and are summarized in Table VIII. From the data, the activation parameters were calculated. The activation energy for the reaction was found to be 14 kcal/mol, which is similar to those for typical 1,3-dipolar cycloadditions.[5a] On the other hand, the activation entropy, -46 e.u., was considerably smaller than the values reported for

TABLE V. Spectral Data for 1:2 Cycloadducts (**3**, **7**, **8**, **11**—**16**)

Compd. No.	NMR (DMSO-d_6, 60 MHz) C_6-CH_3 (3H, s)	=CHCO– (1H, s)	C_{7a}-H (1H, m)	C_{3a}-H C_7-H	N_4-H (1H, d, $J_{4,3a}$ = 3 Hz)	–CONH– (1H, s)	Others	IR (cm^{-1}) –CONH–	N_4-H	–CONH–	C=O	MS (*m/e*) M^+
3	1.95	5.20	5.28 —5.46	5.80 —6.15	9.37	9.58	6.70—7.60 (10H, m, aromatic CH)	3300	2700—3300	1640	1715	361
7	2.07	5.24	5.30 —5.47	5.80 —6.10	9.42	9.60	6.80—7.57 (8H, m, aromatic CH)	3340	2700—3300	1650	1730	389
8	2.01	5.20	5.30 —5.46	5.80 —6.15	9.35	9.61	6.78—7.60 (8H, m, aromatic CH)	3300	2700—3300	1642	1715	429, 433 Relative intensity 3:1

Compd. No.	NMR (DMSO-d_6, 60 MHz) C_{7a}-CH_3 (3H, s)	=CHCO– (1H, s)	C_{3a}-H (1H, d, $J_{3a,4}$ = 3.5 Hz)	C_6-H C_7-H	N_4-H (1H, d, $J_{4,3a}$ = 3.5 Hz)	–CONH– (1H, s)	Others	IR (cm^{-1}) –CONH–	N_4-H	–CONH–	C=O	MS (*m/e*) M^+
11	1.65	4.92	5.72	6.05	9.03	9.55	6.81—7.55 (10H, m, aromatic CH)	3300	2700—3300	1645	1715	361
12	1.63	4.91	5.71	6.11	9.10	9.56	6.80—7.50 (8H, m, aromatic CH)	3340	2700—3300	1642	1720	389
13	1.63	4.90	5.72	6.07	9.05	9.55	6.75—7.60 (8H, m, aromatic CH)	3320	2700—3300	1645	1720	429, 433 Relative intensity 3:1

Compd. No.	NMR (DMSO-d_6, 60 MHz) $-CH_2CH_3$ (3H, t, $J=7$ Hz)	$-CH_2CH_3$ (2H, q, $J=7$ Hz)	$=CHCO-$ (1H, s)	C_{3a}-H (1H, d, $J_{3a,4}=3.5$ Hz)	C_6-H (1H, d, $J_{6,7}=10$ Hz)	C_7-H (1H, d, $J_{7,6}=10$ Hz)	N_4-H (1H, d, $J_{4,3a}=3.5$ Hz)	–CONH– (1H, s)	Others
14	1.00	1.97	4.95	5.80	6.00	6.25	9.09	9.60	6.70—7.63 (10H, m, aromatic CH)
15	0.97	1.99	4.94	5.77	6.01	6.25	9.06	9.55	6.90—7.70 (8H, m, aromatic CH)
16	0.98	1.98	4.95	5.83	6.04	6.27	9.05	9.58	6.81—7.55 (8H, m, aromatic CH)

Compd. No.	IR (cm^{-1}) –CONH–	N_4-H	–CONH–	C=O	MS (*m/e*) M^+
14	3300	2700—3300	1640	1715	375
15	3260	2700—3300	1640	1735	403
16	3340	2700—3300	1642	1730	443, 447 Relative intensity 3 : 1

TABLE VI. Pyrolysis of 1:2 Adducts (**3**, **7**, **8**)

Starting material	Heating temp. (°C)	Product Compd. No.	Product Yield (%)	mp (°C)	Appearance	Formula	Analysis (%) Calcd (Found) C	H	N
3	230—235	**17**	49	242—245	Colorless needles	$C_{14}H_{14}N_2O_2$	69.46 (69.54	5.83 5.72	11.56 11.59)
7	220—225	**18**	45	230—233	Colorless needles	$C_{15}H_{16}N_2O_2$	70.31 (70.15	6.25 6.18	10.93 10.82)
8	255—260	**19**	51	268—271	Colorless needles	$C_{14}H_{13}ClN_2O_2$	60.76 (60.90	4.70 4.58	10.13 10.02)

TABLE VII. Spectral Data for Pyridinols (**17**, **18**, **19**)

Compd. No.	NMR (DMSO-d_6, 60 MHz) $-CH_3$ (3H, s)	$-CH_2-$ (2H, s)	C_4-H, aromatic CH	C_5-H (1H, d, $J_{6,4}=2.6$ Hz)	$-CONH-$ (1H, s)	$-OH$ (1H, s)	IR (cm^{-1}) NH	C=O	OH	MS (*m/e*) M^+
17	2.22	3.72	6.80—7.62 (6H, m)	7.76	9.50	9.95	3225	1655	2200—3400	242
18	2.21	3.73	6.83—7.60 (5H, m)	7.78	9.51	9.97	3250	1660	2200—3400	255
19	2.21	3.70	6.83—7.61 (5H, m)	7.74	9.50	9.91	3230	1660	2200—3400	276, 278 Relative intensity 3:1

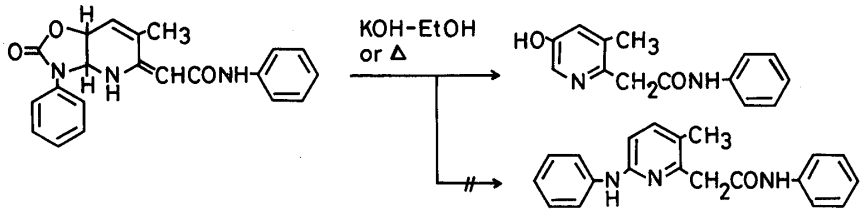


Chart 2

TABLE VIII. Second-Order Rate Constants at Various Temperatures in the Reaction of **1** with **2**

Temp. (°C)	$1/T$ (°K)	k_2 (l/mol s)	$\log k_2$	$r^{a)}$
80	2.83×10^{-3}	1.25×10^{-5}	−4.90	0.997
90	2.75×10^{-3}	2.35×10^{-5}	−4.63	0.998
100	2.68×10^{-3}	4.52×10^{-5}	−4.34	0.998
110	2.61×10^{-3}	6.12×10^{-5}	−4.21	0.996

a) Correlation coefficient.

typical 1,3-dipolar reactions,[5a)] which suggests that the reaction proceeds *via* a highly ordered transition state. From the data mentioned above, we may conclude that this reaction proceeds *via* a typical concerted mechanism.

Next, we will discuss the reaction mechanism in detail by dividing the whole reaction into

four steps from the FMO theoretical point of view. (Chart 1)

As described in the previous paper,[1a] the first step (I) of the reaction is the concerted cycloaddition of **2** to **1**. Generally, a cycloaddition reaction is very sensitive to steric interference,[5b] so **2** very probably attacks **1** from the less hindered site to give a 1,6-dihydropyridine type cycloadduct (A). The second-order rate constant for this reaction is almost equal to that for the reaction of **4** with **2**[1c] indicating that the rate-determining step of this reaction is the cycloaddition of **2** to **1**.

The next step (II) is the 1,5-sigmatropic rearrangement of A to the 5,6-dihydropyridine type cycloadduct (B) as depicted in Fig. 2. We previously reported that the ease of rearrangement of the primary adduct could be rationalized on the basis of MINDO/3 calculation on the model reaction of pyridine *N*-oxide with isocyanic acid. The calculation indicated that the rearranged compound is more stable than the primary one by 27 kcal/mol in terms of heat of formation (ΔH_f).[1b]

The third step of the reaction (III) is the isomerization of B to the enamine-type compound (C). It is well known that suprafacial [1,3]-sigmatropic hydrogen shift does not occur under thermal conditions. However, in this case, the lobe of the hydrogen on the 2-Me group is in phase with the lone pair on the ring nitrogen. Therefore, the suprafacial [1,3]-sigmatropic hydrogen shift is allowed.[6] Inspection of the FMO's of a model compound G depicted in Fig. 3 indicates that the LUMO orbital is localized at the $2p_z$-orbitals of the hetero diene moiety and the 1_s orbitals of the α-methyl hydrogen atoms in which the LUMO coefficient of the C_2-methyl proton is rather large (0.112), so that the situation is very favorable for migration to the nitrogen atom.[6]

Ahlbrecht *et al.*[7] studied the equilibrium PhMeCHCH=NMe⇌PhMeC=CHNHMe and showed that K_s varied between 0.46 and 3 in a wide range of solvents. Curtin *et al.*[8] suggested that, in the equilibrium between diphenylamine and diphenylacetaldehyde imine, the imine form is the kinetically favored product in ether or in an alcohol solvent, and it rearranges to the more stable enamine form in the hydroxylic solvents. These considerations indicate that the imino form might exist in the reaction mixture to a considerable extent.

The fourth step (IV) is the [2+2] cycloaddition of **2** to C, wherein **2**, in turn, behaves as a 4π-addend.[9] For analysis of this step of the reaction, we extracted the electron systems which participate in the reaction directly. The results of the MO calculation of model compounds, F, G, H and **2** based on MINDO/2[10] are summarized in Fig. 3. As can be seen in Fig. 3, a marked rise of HOMO and the lowest unoccupied molecular orbital (LUMO) was observed in the case of H in comparison with F or G. The results indicate that the enamine type compound (H) is considerably more reactive than F and G.

The regioselectivity of this step can be rationalized in terms of the magnitude of the coefficients of FMO. According to the perturbation equation, the larger lobe overlaps with the larger one, and the smaller ones overlap each other. Therefore, the nitrogen atom of **2** attacks the C_2 atom of the pyridine nucleus of the enamine type compound (C) and the carbon atom of NCO attacks the exocyclic carbon atom. The cycloaddition of **2** to C also proceeds concertedly as depicted in Figs. 2 and 3.

The resultant 1:2 adduct containing a four-membered ring undergoes electrocyclic ring cleavage assisted by the favorable FMO interaction among the electron-rich enol group and the electron-deficient C–N bond as shown in Chart 3. Effenberger and Gleiter[11] reported

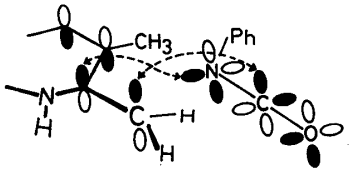


Fig. 2. Orbital Interaction of the [2+2] Cycloaddition

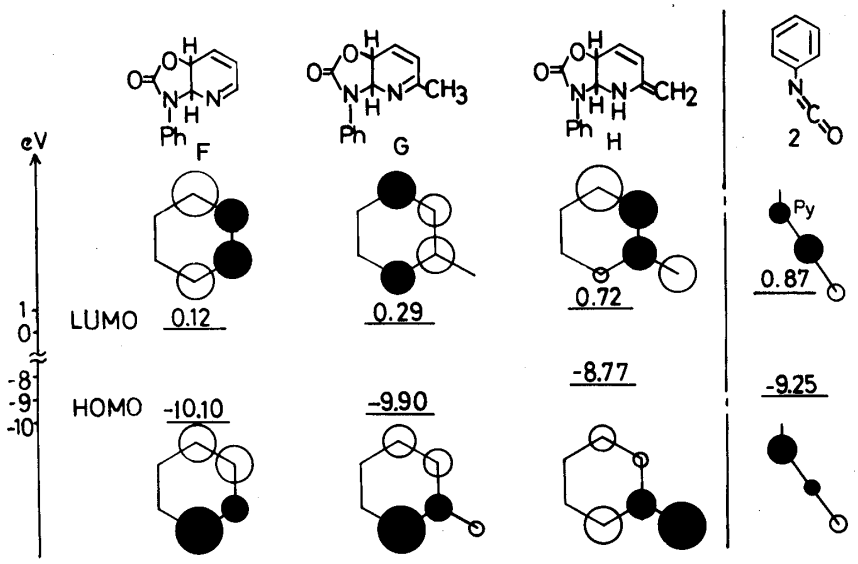


Fig. 3. MINDO/2 FMO Energy Levels and Coefficients for Model Compounds (F, G, H and **2**)

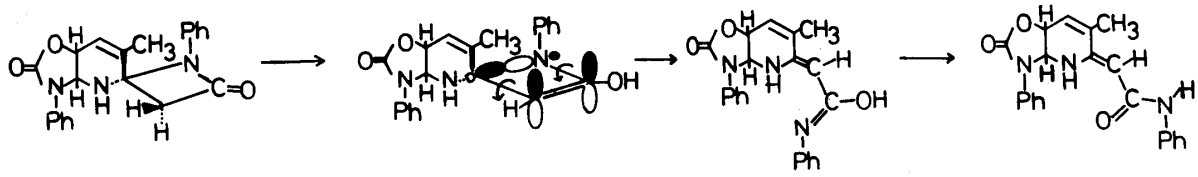


Chart 3

that the cycloadduct of 5,6-dihydropyran and tosyl isocyanate was readily converted to the corresponding acrylamide on refluxing in benzene. In our case, it can be considered that the ring opening of the 1 : 2-adduct may proceed more smoothly than in the case described above because of the more severe reaction conditions.

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% solutions with tetramethylsilane as an internal standard; chemical shifts are expressed in δ values. Infrared (IR) spectra were recorded on a JASCO IR-G infrared spectrophotometer equipped with a grating. Mass spectra (MS) were taken with a JEOL JMS-01SG double-focussing 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% Fluoxylate K Uniport HP (60—80 mesh, 3 mm × 2.5 m). Molecular orbital calculations were performed on a FACOM M-382 computer in the Computer Center of Kyushu University.

Cycloaddition Reactions of 2-Alkylpyridine *N*-Oxides (1, 9, 10) with Phenyl Isocyanates (2, 5, 6). General Procedure for Cycloaddition——A solution of the *N*-oxide (0.01 mol) and the isocyanate (0.02 mol) in the given solvent (8.2 ml) was heated at a given temperature. After the reaction, the solvent was evaporated off under reduced pressure. The residue was treated with Et_2O. The precipitated crystalline mass was collected by suction and recrystallized from acetone to give the 1 : 2 adduct (see Tables I—V).

Pyrolysis of 1 : 2 Adducts (3, 7, 8). General Procedure——The 1 : 2 adduct was heated at 5 °C higher temperature than its melting point for 2 h. The product was purified by column chromatography on silica gel with $CHCl_3$–AcOEt (1 : 2) as an eluent. The first fraction gave the pyridinol (see Tables VI and VII).

Hydrolysis of 3——A mixture of 1.0 g (2.77×10^{-3} mol) of **3** and 10 ml of 2.5% KOH–EtOH was refluxed for 1 h. The solvent was removed *in vacuo* and then 10 ml of H_2O was added to the residue. The alkaline solution was neutralized with 10% HCl. The precipitated crystals were collected and recrystallized from acetone to give **17** as colorless needles, mp 245—247 °C, in 95% yield (Table VII).

Kinetics——A solution of **1** (1.25×10^{-3} mol), **2** (3.13×10^{-2} mol) and benzophenone (2.49×10^{-4} mol) in 5 ml

of DMF in a ground glass stoppered tube was immersed in a thermostated oil bath (Tokyo Rika Kikai HB 200B) controlled to ± 0.05 °C. The rate was followed at a given temperature by measuring the decrease of the peak area of **1** by gas liquid chromatography.

Acknowledgement This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture. Thanks are also due to Mr. T. Kitasaki and Mr. H. Sato for technical assistance and to the members of the Analytical Department of this faculty for microanalyses.

References and Notes

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