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Reaction of Aromatic *N*-Oxides with Dipolarophiles.¹⁾ XII. Stereoselective *exo* Cycloaddition of 3,5-Lutidine *N*-Oxide with *N*-Substituted Maleimides and a Frontier Molecular Orbital and Mechanistic Study

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Pericyclic reactions of 3,5-lutidine *N*-oxide with *N*-phenylmaleimides were investigated. The primary cycloadducts are thermally labile and undergo 1,5-sigmatropic rearrangement to give the 2,3-dihydropyridine derivatives. The proton nuclear magnetic resonance structural assignment of the 1,5-sigmatropy products implies that the primary cycloaddition proceeds through an *exo* transition state. The reaction behavior is discussed in terms of frontier molecular orbital theory, based on MINDO/3 and CNDO/2 calculations and kinetic data. It was concluded that the reaction falls into the category of a 'normal-type' cycloaddition and the *exo* cycloaddition is brought about by the unfavorable secondary orbital interaction.

Keywords—1,3-dipolar cycloaddition; 3,5-lutidine *N*-oxide; *N*-phenylmaleimide; kinetics; frontier molecular orbital; *exo* cycloaddition; 1,5-sigmatropy; substituent effect

Introduction

1,3-Dipolar cycloaddition is a valuable tool for the construction of five-membered heterocyclic ring systems.²⁾ The classical approach to the reaction was revised by Sustmann³⁾ and Houk⁴⁾ from the frontier molecular orbital (FMO) theoretical point of view.⁵⁾ In our continuing studies on the 1,3-dipolar cycloaddition reaction of aromatic *N*-oxides with dipolarophiles,⁶⁾ we have examined the cycloaddition of pyridine *N*-oxides with phenyl isocyanates and showed that the observed cycloaddition behavior can be rationalized in terms of the following controlling factors: (1) highest occupied molecular orbital (HOMO)–lowest unoccupied molecular orbital (LUMO) interaction, (2) secondary orbital interaction, (3) aromaticity, (4) charge-transfer (CT) complexation. From the frontier molecular orbital viewpoint based on the CNDO/2,⁷⁾ MINDO/2,⁸⁾ and MINDO/3⁹⁾ calculation data, we have sought a new and more reactive synthon applicable to the 1,3-dipolar cycloaddition of aromatic *N*-oxides. In this connection, we previously communicated the reaction of *N*-phenylmaleimides (II) with 3,5-dimethylpyridine *N*-oxide (3,5-lutidine *N*-oxide) (I) to afford 2,3-dihydropyridine-type cycloadducts (III) arising from 1,5-sigmatropy of the primary *exo* cycloadducts.¹⁰⁾

We now discuss the reaction in detail with newly obtained data in order to clarify the overall nature of the reaction.

Results and Discussion

The CNDO/2 method has been used with success to predict the cycloaddition reactivity

TABLE I. FMO Energy Levels^{a)} of the Addends (I and IIa—k)

Compd.	MINDO/3		CNDO/2	
	HOMO	LUMO	HOMO	LUMO
Pyridine <i>N</i> -oxide	-8.762	0.546	-10.549	2.246
Lutidine <i>N</i> -oxide (I)	-8.662	0.596	-10.420	2.396
<i>N</i> -Substituted maleimides				
H	-10.485	-0.470		
-MeOC₆H₄- (IIb)			-13.416	0.882
-MeC₆H₄- (IIe)			-13.614	0.873
Ph- (IIa)			-13.861	0.837
-ClC₆H₄- (IIh)			-13.563	0.634
-NO₂C₆H₄- (IIk)			-13.245	0.448
PhN=C=O	-8.552	0.915		

a) eV.

of various types of 1,3-dipoles and dipolarophiles. In this study, therefore, CNDO/2 calculations were performed to estimate the relative reactivity of pyridine *N*-oxides with *N*-substituted maleimides. The molecular geometries of the parent molecules of pyridine *N*-oxide and maleimide were determined by a semiempirical self-consistent field molecular orbital method based on the MINDO/3 approximation combined with geometrical optimization by the Fletcher-Powell method.⁹⁾ The resulting geometries were then used for the CNDO/2 calculations of substituted molecules. The optimized geometry and dipole moment of pyridine *N*-oxide are in agreement with the observed values determined by X-ray crystallographic analyses.¹¹⁾ The calculation data are summarized in Table I.

As can be seen in Table I, the 1,3-dipolar reaction of 3,5-lutidine *N*-oxide (I) with *N*-substituted maleimides (II) falls into the category of a normal-type reaction in Sustmann's classification,³⁾ wherein the dominant interaction occurs between the HOMO of I and the LUMO of II, indicating that a dipolarophile bearing an electron-accepting substituent would show a high reactivity toward 3,5-lutidine *N*-oxide (I).

In the reaction of pyridine *N*-oxides with phenyl isocyanates previously reported from our laboratory, we could not establish the stereochemistry of the cycloaddition transition state from the structure of the reaction products, because the dipolarophiles have a linear

Chart 1

TABLE IIa. Cycloadducts from the 1,3-Dipolar Reaction of 3,5-Dimethylpyridine *N*-Oxide with *N*-Substituted Maleimides^{a)}

Adduct ^{b)}	R	mp (°C)	Yield (%)	IR (cm ⁻¹) ^{c)} C=O
IIIa	C ₆ H ₅ -	172.5—173.5	40.2	1715
IIIb	<i>p</i> -MeOC ₆ H ₄ -	187—188	36.5	1700
IIIc	<i>o</i> -MeC ₆ H ₄ -	185—186	56.2	1710—1715
IIId	<i>m</i> -MeC ₆ H ₄ -	179—180	40.2	1715
IIIe	<i>p</i> -MeC ₆ H ₄ -	187—188	38.7	1715
IIIf	<i>o</i> -ClC ₆ H ₄ -	162—163	42.8	1715—1720
IIIg	<i>m</i> -ClC ₆ H ₄ -	175	40.5	1710
IIIh	<i>p</i> -ClC ₆ H ₄ -	209	25.2	1710
IIIi	<i>o</i> -NO ₂ C ₆ H ₄ -	207—208	46.3	1730—1735
IIIj	<i>m</i> -NO ₂ C ₆ H ₄ -	231—232	44.9	1720
IIIk	<i>p</i> -NO ₂ C ₆ H ₄ -	186—187	34.7	1715—1720
IIIl	<i>n</i> -C ₄ H ₉ -	119—120	37.5	1710
IIIm	CH ₃ -	184—185	32.8	1682
III n	α -Naphthyl	231—232	30.0	1715—1720

a) Refluxed for 10 h. b) Colorless needles. c) KBr.

TABLE IIb. Analytical and Mass Spectral Data for the Cycloadducts (IIIa—n)

Compd.	Formula	Anal. Calcd (Found)			MS <i>m/z</i> (M ⁺)
		C	H	N	
IIIa	C ₁₇ H ₁₆ N ₂ O ₃	68.91 (68.80)	5.44 (5.51)	9.45 (9.40)	296
IIIb	C ₁₈ H ₁₈ N ₂ O ₄	66.25 (65.98)	5.56 (5.46)	8.56 (8.66)	326
IIIc	C ₁₈ H ₁₈ N ₂ O ₃	69.67 (69.33)	5.80 (5.84)	9.00 (8.98)	310
IIId	C ₁₈ H ₁₈ N ₂ O ₃	69.67 (69.76)	5.80 (5.90)	9.00 (9.07)	310
IIIe	C ₁₈ H ₁₈ N ₂ O ₃	69.67 (69.75)	5.80 (6.11)	9.00 (9.13)	310
IIIf	C ₁₇ H ₁₅ ClN ₂ O ₃	61.72 (61.83)	4.54 (4.53)	8.47 (8.45)	330
IIIg	C ₁₇ H ₁₅ ClN ₂ O ₃	61.72 (61.59)	4.54 (4.47)	8.47 (8.93)	330
IIIh	C ₁₇ H ₁₅ ClN ₂ O ₃	61.72 (62.03)	4.54 (4.77)	8.47 (8.57)	330
IIIi	C ₁₇ H ₁₅ N ₃ O ₅	59.82 (59.98)	4.43 (4.61)	12.31 (12.34)	341
IIIj	C ₁₇ H ₁₅ N ₃ O ₅	59.82 (59.85)	4.43 (4.58)	12.31 (12.35)	341
IIIk	C ₁₇ H ₂₅ N ₃ O ₅	59.82 (60.21)	4.43 (4.51)	12.31 (12.32)	341
IIIl	C ₁₅ H ₂₀ N ₂ O ₃	65.20 (65.44)	7.29 (7.36)	10.14 (10.23)	276
III m	C ₁₂ H ₁₄ N ₂ O ₃	61.53 (61.13)	6.02 (5.98)	11.96 (12.11)	234
III n	C ₂₁ H ₁₈ N ₂ O ₃	72.83 (72.96)	5.20 (5.43)	8.09 (8.14)	346

structure and both the transition states (*exo* and *endo* addition) give the same product. On the other hand, in the reaction of pyridine *N*-oxides with substituted maleimides (II), it may be possible to discuss the stereochemistry of the transition state because of the rigid ring structures of both addends.

Refluxing a mixture of 3,5-lutidine *N*-oxide (I) and a slight excess of the *N*-substituted maleimides (IIa—n) in toluene for 10 h resulted in the formation of crystalline products (IIIa—n, respectively). The spectral data, physical constants and elemental analyses of the cycloadducts (IIIa—n) are summarized in Tables IIa—c.

The infrared (IR) spectra of III showed characteristic bands at 1690—1720 cm⁻¹, suggesting the presence of an unconjugated imido carbonyl group. The mass spectra (MS) of III exhibited molecular peaks corresponding to the 1 : 1 cycloadducts. Four *sp*³ carbons were

TABLE IIc. ¹H-NMR Spectral Data for the Cycloadducts (IIIa—n)

¹ H-NMR (in CDCl ₃) ppm	
IIIa	1.33 (3H, s, C _{7a} -Me), 1.88 (3H, d, <i>J</i> =2 Hz, C ₆ -Me), 4.01 (1H, t, <i>J</i> =8 Hz, C ₃ -H), 4.35 (1H, dd, <i>J</i> =8, 2 Hz, C _{3a} -H), 4.86 (1H, d, <i>J</i> =8 Hz, C ₂ -H), 5.88 (1H, t, <i>J</i> =2 Hz, C ₇ -H), 6.93—7.66 (5H, m, -Ar), 7.80 (1H, t, <i>J</i> =2 Hz, C ₅ -H)
IIIb	1.31 (3H, s, C _{7a} -Me), 1.84 (3H, d, <i>J</i> =1.5 Hz, C ₆ -Me), 3.82 (1H, s, -OMe), 4.05 (1H, dd, <i>J</i> =9.6, 7.2 Hz, C ₃ -H), 4.37 (1H, dd, <i>J</i> =9.6, 1.5 Hz, C _{3a} -H), 4.91 (1H, d, <i>J</i> =7.2 Hz, C ₂ -H), 5.91 (1H, t, <i>J</i> =1.5 Hz, C ₇ -H), 6.83—7.22 (4H, m, -Ar), 7.83 (1H, t, <i>J</i> =1.5 Hz, C ₅ -H)
IIIc	1.38 (3H, s, C _{7a} -Me), 1.95 (3H, d, <i>J</i> =1.8 Hz, C ₆ -Me), 2.14 and 2.21 (3H, s, -Ar-Me), ^{a)} 3.99—4.50 (2H, m, C ₃ -H, C _{3a} -H), 4.87—5.06 (1H, m, C ₂ -H), 6.02 (1H, m, C ₇ -H), 6.97—7.35 (4H, m, -Ar), 7.85—8.98 (1H, m, C ₅ -H)
IIId	1.37 (3H, s, C _{7a} -Me), 1.90 (3H, d, <i>J</i> =1.8 Hz, C ₄ -Me), 2.39 (3H, s, -Ar-Me), 4.09 (1H, dd, <i>J</i> =9.6, 7.6 Hz, C ₂ -H), 4.42 (1H, dd, <i>J</i> =9.6, 2.4 Hz, C _{3a} -H), 4.95 (1H, d, <i>J</i> =7.6 Hz, C ₂ -H), 5.96 (1H, dd, <i>J</i> =2.4, 1.8 Hz, C ₇ -H), 6.95—7.39 (4H, m, Ar), 7.87 (1H, t, <i>J</i> =2.4 Hz, C ₅ -H)
IIIe	1.31 (3H, s, C _{7a} -Me), 1.83 (3H, d, <i>J</i> =2 Hz, C ₆ -Me), 2.35 (3H, s, -Ar-Me), 4.02 (1H, dd, <i>J</i> =9, 8 Hz, C ₃ -H), 4.35 (1H, dd, <i>J</i> =9, 2 Hz, C _{3a} -H), 4.88 (1H, d, <i>J</i> =8 Hz, C ₂ -H), 5.88 (1H, t, <i>J</i> =2 Hz, C ₇ -H), 6.90—7.35 (4H, m, Ar), 7.79 (1H, t, <i>J</i> =2 Hz, C ₅ -H) ^{b)}
IIIf	1.38 (3H, s, C _{7a} -Me), 1.96 (3H, d, <i>J</i> =1.8 Hz, C ₆ -Me), 4.04—4.48 (2H, m, C ₃ -H and C _{3a} -H), 4.86—5.11 (1H, m, C ₂ -H), 5.97 (1H, m, C ₇ -H), 7.08—7.56 (4H, m, -Ar), 7.85—7.93 (1H, m, C ₅ -H)
IIIg	1.34 (3H, s, C _{7a} -Me), 1.87 (3H, d, <i>J</i> =1.5 Hz, C ₆ -Me), 4.09 (1H, dd, <i>J</i> =8.9, 7.5 Hz, C ₃ -H), 4.38 (1H, dd, <i>J</i> =8.9, 1.5 Hz, C _{3a} -H), 4.94 (1H, d, <i>J</i> =7.5 Hz, C ₂ -H), 5.94 (1H, t, <i>J</i> =1.5 Hz, C ₇ -H), 7.10—7.45 (4H, m, -Ar), 7.81 (1H, t, <i>J</i> =1.5 Hz, C ₅ -H)
IIIh	1.35 (3H, s, C _{7a} -Me), 1.82 (3H, d, <i>J</i> =2 Hz, C ₆ -Me), 4.03 (1H, dd, <i>J</i> =9, 7 Hz, C ₃ -H), 4.33 (1H, dd, <i>J</i> =9, 2 Hz, C _{3a} -H), 4.89 (1H, d, <i>J</i> =7 Hz, C ₂ -H), 5.88 (1H, t, <i>J</i> =2 Hz, C ₇ -H), 7.10—7.60 (4H, m, -Ar), 7.80 (1H, t, <i>J</i> =2 Hz, C ₅ -H)
IIIi	1.35 (3H, s, C _{7a} -Me), 1.91 (3H, d, <i>J</i> =1.2 Hz, C ₆ -Me), 4.01—4.50 (2H, m, C ₃ -H and C _{3a} -H), 4.95—5.10 (1H, m, C ₂ -H), 5.98 (1H, m, C ₇ -H), 7.25—8.27 (5H, m, -Ar and C ₅ -H)
IIIj	1.39 (3H, s, C _{7a} -Me), 1.93 (3H, d, <i>J</i> =1 Hz, C ₆ -Me), 4.17 (1H, dd, <i>J</i> =9, 7.2 Hz, C ₃ -H), 4.43 (1H, dd, <i>J</i> =9, 2 Hz, C _{3a} -H), 5.03 (1H, d, <i>J</i> =7.2 Hz, C ₂ -H), 5.99 (1H, dd, <i>J</i> =2, 1 Hz, C ₇ -H), 7.05—8.40 (4H, m, -Ar), 7.88 (1H, t, <i>J</i> =2 Hz, C ₅ -H)
IIIk	1.36 (3H, s, C _{7a} -Me), 1.87 (3H, d, <i>J</i> =2 Hz, C ₆ -Me), 4.16 (1H, dd, <i>J</i> =8.8, 7.2 Hz, C ₃ -H), 4.40 (1H, dd, <i>J</i> =8.8, 2 Hz, C _{3a} -H), 4.99 (1H, d, <i>J</i> =7.2 Hz, C ₂ -H), 5.96 (1H, t, <i>J</i> =2 Hz, C ₇ -H), 7.40—8.43 (4H, m, -Ar), 7.82 (1H, t, <i>J</i> =2 Hz, C ₅ -H)
IIIl	0.95 (3H, t, <i>J</i> =6.6 Hz, aliphatic Me), 1.35 (3H, s, C _{7a} -Me), 1.10—1.70 (4H, m, -CH ₂ CH ₂ -), 1.90 (3H, d, <i>J</i> =2 Hz, C ₆ -Me), 3.46 (2H, t, <i>J</i> =7.2 Hz, N-CH ₂ -), 3.99 (1H, dd, <i>J</i> =8.4, 7.2 Hz, C ₃ -H), 4.34 (1H, dd, <i>J</i> =8.4, 2 Hz, C _{3a} -H), 4.82 (1H, d, <i>J</i> =7.2 Hz, C ₂ -H), 5.89 (1H, t, <i>J</i> =2 Hz, C ₇ -H), 7.79 (1H, t, <i>J</i> =2 Hz, C ₅ -H)
IIIIm	1.47 (3H, s, Me), 2.02 (3H, d, <i>J</i> =1.2 Hz, Me), 3.09 (3H, s, N-Me), 4.13 (1H, dd, <i>J</i> =9.6, 7.2 Hz, C ₃ -H), 4.46 (1H, dd, <i>J</i> =9.6, 2.4 Hz, C _{3a} -H), 4.97 (1H, d, <i>J</i> =7.2 Hz, C ₂ -H), 6.02 (1H, dd, <i>J</i> =2.4, 1.2 Hz, C ₇ -H), 7.94 (1H, t, <i>J</i> =2.4 Hz, C ₅ -H)
IIIIn	1.39 (3H, s, Me), 1.96 (3H, brs, Me), 4.0—4.6 (2H, m, C ₃ and C _{3a} -H), 4.85—5.30 (1H, m, C ₂ -H), 6.04 (1H, dd, <i>J</i> =1.5 Hz, C ₇ -H), 7.1—8.2 (8H, m, Ar and C ₅ -H) ^{c)}

a) The methyl group of *o*-Me-C₆H₄- was observed as a split peak. This may result from restricted rotation about the N-Ar bond. b) The high-resolution ¹H-NMR (400 MHz) spectrum indicates that the C₇ proton is coupled with the C₆-methyl proton (*J*=1.46 Hz) and with the C₅ proton (*J*=2.2 Hz); which is again coupled with the C_{3a} proton (*J*=2.2 Hz). c) The data can be interpreted in terms of a 1:1 mixture of conformational isomers.

observed in the carbon-13 nuclear magnetic resonance (¹³C-NMR) spectrum of III,¹²⁾ suggesting that the product (III) is not the primary adduct (three *sp*³ carbons) but the rearranged product (see Chart 1). Further, the proton nuclear magnetic resonance (¹H-NMR) spectra of III exhibited ABX patterns due to three *cis*-oriented methine protons (*J*_{2,3}=7—8 Hz, *J*_{3,3a}=8—9 Hz).¹³⁾

The ¹H-NMR spectra of the products exhibited essentially the same spectral patterns attributable to an ABX spin system. The coupling constants were evaluated by first-order analysis assuming it to be an AMX system. In the case of the cycloadduct from I and *N*-(*o*-

Chart 2

TABLE III. Solvent Effect and Activation Parameters for 1,3-Dipolar Reaction of I with IIa in Bromobenzene

Temp. (°C)	Solvent (E_T) ^{a)}	$k \times 10^6$ ($M^{-1} \cdot s^{-1}$)	ΔE (kcal/mol)	$\Delta S^\ddagger$ (e.u.)
100	Toluene	(33.9)	1.95	
100	Bromobenzene	(37.5)	3.07	
100	Acetophenone	(41.3)	2.96	
100	Sulfolane	(44.0)	2.93	
110	Bromobenzene		4.96	
120	Bromobenzene	11.0	20.0	−35
130	Bromobenzene	21.4		

a) See ref. 16.

TABLE IV. Activation Parameters for Typical 1,3-Dipolar Cycloaddition Reactions

Reaction ^{a)}	ΔE (kcal/mol)	$\Delta S^\ddagger$ (e.u.)
3,5-Lutidine <i>N</i> -oxide + <i>N</i> -phenylmaleimide ^{b)}	20.0	−35
Pyridine <i>N</i> -oxide + phenyl isocyanate ^{c)}	20.0	−30
<i>C,C</i> -Biphenylene- <i>N</i> (α)-(<i>p</i> -chlorophenyl)- <i>N</i> (β)-cyanoazomethine imine +		
ethyl acrylate	12.5	−35
styrene	15.6	−31
phenyl isocyanate	12.1	−33
<i>N</i> -Phenyl- <i>C</i> -methylsydnone +		
ethyl cinnamate	18.3	−32
dimethyl acetylenedicarboxylate	14.7	−31
<i>C</i> -Phenyl- <i>N</i> -methylnitron +		
methyl methacrylate	15.7	−32
2-vinylpyridine	18.3	−30

a) See ref. 2a. b) This study. c) See ref. 5a.

tolyl) maleimide or *N*-naphthylmaleimide, a distorted ABX pattern was observed. This may be caused by restricted rotation about the N–Ar bond, which can be recognized by the presence of a temperature effect (Chart 2).

From these data, we can safely say that IIIa–n are *endo* 2,3-dihydropyridine-type cycloadducts formed from the primary *exo*[4 + 2] π cycloadducts by 1,5-sigmatropic rearrangement (Chart 1).

In order to examine the cycloaddition behavior of 3,5-lutidine *N*-oxide (I) towards *N*-substituted maleimides (II), kinetic measurements¹⁴⁾ were carried out. The second-order rate

Fig. 1. Plots of k vs. E_T Values for the Reaction of I with IIa
 $\rho = 0.016$.

TABLE V. Substituent Effect in 1,3-Dipolar Cycloaddition of I with II

<i>p</i> -Substituent	σ_p^+	$k \times 10^6$ ($M^{-1} \cdot s^{-1}$)
OMe	-0.12	9.65
Me	-0.311	10.3
H	0.0	10.9
Cl	0.114	8.88
NO ₂	0.790	13.1

The correlation coefficient (r) excluding Cl is 0.992. Slope (ρ) = 0.0859.

Fig. 2. Plots of k vs. σ_p^+ for the Reaction of I with II
 $\rho = 0.086$.

constants of the reaction of I with IIa in several solvents at various temperatures were obtained by following the disappearance of I by high-performance liquid phase chromatography (HPLC) using methyl *o*- or *p*-nitrobenzoate as an internal standard.

The energy of activation (ΔE) for the reaction of I with IIa is 20 kcal/mol,¹⁵⁾ moderately higher than the average for 1,3-dipolar reactions, while the entropy of activation, $\Delta S^\ddagger = -35$ e.u., lying within the range reported for the typical 1,3-dipolar cycloaddition, suggests a highly ordered transition state.^{2a)}

Next, the solvent effect was investigated. As a scale of solvent ionizing power for clarification of the degree of charge separation in the transition state, the E_T values of Reichardt¹⁶⁾ have been successfully employed in studying the effect of solvent on the rate of reaction. As illustrated in Fig. 1, plots of $\log k$ against E_T values show a linear relationship with a very small slope (only 1.56×10^{-2}), comparable to those of typical concerted reactions.^{6a,17)} The small response to variation of solvent ionizing power rules out an intermediate involving any significant degree of charge separation.

The substituent effect of the *N*-phenylmaleimides (II) on the reaction rates were also examined by plotting the logarithm of $\log k(x)$ against σ_p^+ .¹⁸⁾ The plots show a linear correlation. The magnitude of the slope, the ρ -value, is assumed to be an indication of the narrowness of the HOMO-LUMO energy gap. The ρ -value is very small (1.20×10^{-1}), indicating that the FMO energy separation is relatively large, and the positive value indicates that the reaction falls into the category of normal-type cycloaddition. The results hitherto

Fig. 3. Steric Interactions for the *endo* Cycloaddition

Fig. 4. Frontier Orbitals and Secondary Interactions for the Cycloaddition of I with II

Fig. 5. Hydrogen Bonding between I and II

TABLE VI. Frontier Orbital Energies and Coefficients for 3,5-Lutidine *N*-Oxide and Protonated 3,5-Lutidine *N*-Oxide Calculated by the MINDO/3 Method

	ArN→O	ArN→O⋯H ⁺ ^{a)}
FMO energy level (eV)		
LUMO	0.60	−4.11
HOMO	−8.66	−13.73
HOMO coefficient		
O	−0.590	−0.430
N	0.298	0.428
C ₂	0.363	0.156
Net charge		
O	−0.639	−0.446
N	0.723	0.596
C ₂	−0.201	0.123

^{a)} The donor–acceptor hydrogen-bond distance (NH⋯O) is assumed to be 2.0 Å.

mentioned are fully in accordance with the concerted reaction behavior.

At first glance, it seems reasonable to attribute the *exo* addition to steric repulsion between the pyridine moiety of the 1,3-dipole and the *N*-aryl group of the dipolarophile, in which the *N*-aryl ring and the imide ring can not be coplanar (they lie in a nearly perpendicular disposition) (Fig. 3). However, this assumption is not acceptable because the dipolarophile bearing the *N*-methyl or *N*-(*n*-butyl) substituent shows a similar cycloaddition behavior to give the *endo* 1,5-sigmatropy product *via* *exo* cycloaddition. These facts indicate that electronic factors may be operative in stabilization of the transition state.

The frontier orbital interactions for *exo* and *endo* transition states are depicted in Fig. 4. As can be seen in Fig. 4, the secondary interactions of the frontier orbitals in the *endo*-transition state are antibonding, indicating that the reaction passing through the *exo*-transition state is more favorable than that passing through the *endo* one.

Interestingly, the parent maleimide did not react with 3,5-lutidine *N*-oxide (I) under the conditions used in the case of *N*-phenyl maleimide (IIa). This anomaly may be explained by taking into consideration the stabilization by the hydrogen bonding between the oxygen atom of I and the acidic hydrogen (−CONHCO−) of the imido group. The hydrogen bonding should

cause a considerable decrease of the FMO energies of I and retardation of the reactivity. This assumption was confirmed by MINDO/3 calculations on a pair of model compounds (I and protonated 3,5-lutidine *N*-oxide). The calculations indicate that the hydrogen bonding stabilizes the frontier orbital energies and diminishes the frontier coefficient magnitudes and the net charges of the nitron moiety, and these changes are very unfavorable for the normal-type interaction (HOMO of I-LUMO of II) (see Table VI).

The involvement of charge-transfer complexes in cycloaddition has been suggested, and it has been proposed that charge transfer plays an important role in stabilizing the transition state.¹⁹⁾ In our previous paper,^{6c)} we clarified the influence of charge transfer on the site selectivity and the reactivity for 1,3-dipolar cycloaddition of 3-methylpyridine (picoline) *N*-oxide with phenyl isocyanates. In the reaction studied here, the reaction mixture of I and IIa (110 °C) showed a weak absorption beyond 550 nm (tailing), which is characteristic of a charge-transfer interaction. This finding suggests that charge-transfer complexation occurs only to a small extent, and this must be a consequence of the steric disadvantage¹⁹⁾ of nonplanar *N*-phenylmaleimide, in which the phenyl and the imido rings can not be coplanar.

Finally, mention should be made of 1,5-sigmatropy of the primary cycloadducts. MINDO/3 calculations on model cycloadducts of pyridine *N*-oxide with ethylene indicate that the heat of formation (ΔH_f) of the 1,5-sigmatropy product is 26.7 kcal/mol smaller than that of the primary one, suggesting the primary adduct to be thermodynamically less stable. The FMO view on the facility of the rearrangement is that the interaction of the LUMO of the σ bond with the HOMO of the diene is assisted by the low-lying LUMO of the N-O σ bond.

Chart 3

Experimental

All melting points are uncorrected. Nuclear magnetic resonance spectra were taken with Hitachi R-600, JNM-C-60H and GX-400 spectrometers (¹³C-NMR) for *ca.* 10% (w/v) solution with tetramethylsilane (TMS) as an internal standard; chemical shifts are expressed in δ values. IR spectra were recorded on a JASCO IR-G infrared spectrophotometer equipped with a grating. Mass spectra were taken with a JEOL JMS-OISG double-focussing spectrometer operating at an ionization potential of 75 eV. High performance liquid chromatographic analyses (HPLC) were performed on a JASCO FAMILIC 100N chromatograph equipped with a ultraviolet detector and a column of Fine Pak SIL C12.

Molecular orbital calculations were performed on a FACOM M-382 computer in the Computer Center of Kyushu University.

Cycloaddition of I with IIa (General Procedure)—A solution of I (0.01 mol) and IIa (0.01 mol) in toluene (10 ml) was refluxed for 10 h. The solvent was evaporated off under reduced pressure. The residue was chromatographed on silica gel (2.5 cm i.d. column, 60 g) with ethyl acetate to give IIIa as colorless needles. Recrystallization from ethyl acetate gave an analytically pure sample. The physical and spectral data are summarized in Tables IIa–c.

Kinetics—A solution of I (5.00×10^{-3} mol), II (5.00×10^{-2} mol) and benzophenone (2.49×10^{-4} mol) in 5 ml of bromobenzene was placed in a ground-glass stoppered tube and immersed in a thermostated oil bath (Tokyo Rika

Kikai, HB 200B) controlled to 0.05 °C. The rates were followed at a given temperature by measuring the decrease of I by HPLC. Methyl *o*-nitrobenzoate was used as an internal standard.

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References and Notes

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- 13) The calculated spectrum of the *exo* sigmatropy product is clearly inconsistent with the observed one for the *endo* isomer.
- 14) The previously reported data¹⁰⁾ for DMF and nitrobenzene solvents are erroneous because maleimides decompose in polar solvents on prolonged heating.
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