[4π + 2σ]-TYPE CYCLOADDITION REACTIONS OF NAPHTHO[*b*]-CYCLOPROPENE WITH *C,N*-DIPHENYLNITRONES TO FORM DIHYDRO-NAPHTHOXAZINES

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Abstract——Reactions of naphtho[*b*]cyclopropene with *C,N*-diphenylnitrone derivatives afforded dihydronaphthoxazine derivatives. The reaction is considered to proceed through a [4π + 2σ]-type cycloaddition process *via* a zwitter ionic intermediate generated by a rupture of the C-C σ-bond of the three-membered ring of naphtho[*b*]cyclopropene caused by a nucleophilic attack of the nitrone.

Much attention has been focussed on the chemistry of cyclopropene derivatives fused with aromatic systems such as benzocyclopropene or naphtho[*b*]cyclopropene, which have considerable bond length alternation in the aromatic rings and consequently reduce their aromtic stabilization.[1]

Cycloaddition reactions of these cyclopropene derivatives are known to proceed through two independent paths; one is a [4π + 2π]-type cycloaddition path and the other is a [4π + 2σ]-type cycloaddition path. In the former case, the aromatic rings must lose their aromatic characters, and in the latter case, the σ-bond of the three-membered ring must be ruptured.[2] The authors have reported the first example of the [4π + 2σ]-type cycloaddition reaction of benzocyclopropene with diphenylisobenzofuran or anthracene derivatives.[3] Recently, it was made clear that this type of reactions proceed with heterocumulenes such as isocyanates or 1,3-dipolar reagents.[4] However, the detailed reaction mechanism of the [4π + 2σ]-type cycloaddition reaction or the factors which determine the cycloaddition paths remain unsolved.

As a series of our research on the reactivities of cyclopropene derivatives fused with aromatic systems, we investigated cycloadditon reactions of naphtho[*b*]cyclopropene (1) with substituted *C,N*-diphenylnitrone derivatives (2). Here, the results are discussed.

Naphtho[*b*]cyclopropene (1) was heated with two molar equivalent of *C,N*-diphenylnitrone (2a) in chloroform at 60 ℃ for 40 h. The resulting mixture was chromatographed on silica gel to afford colorless needles of dihydronaphthoxazine (3a) in 75 % yield. No recovery of 1 was found at all. Analogous reactions of 1 with *C*-(*p*-methoxyphenyl)-*N*-phenylnitrone (2b), *C*-(*p*-chlorophenyl)-*N*-phenylnitrone (2c), and *C*-(*p*-cyanophenyl)-*N*-phenylnitrone (2d), gave the corresponding dihydronaphthoxazine derivatives (3b, 3c, and 3d), in 69, 53, and 59 % yields, respectively.

The structure of 3 was determined on the basis of its spectral, especially NMR spectral properties. A singlet peak at about 5.8 ppm and two doublet peaks at about 5.4 and 5.5 ppm with a large geminal coupling constant (J=16 Hz) in ^{1}H NMR as well as the existence of only two aliphatic signals at about 68 and 70 ppm in ^{13}C NMR support the structure 3. The formation of a possible regional isomer (4) and a three-membered ring structure (5) were excluded. The structure (3) was finally supported by the good agreement of its spectral properties with those of the analogous compounds.[3,4]

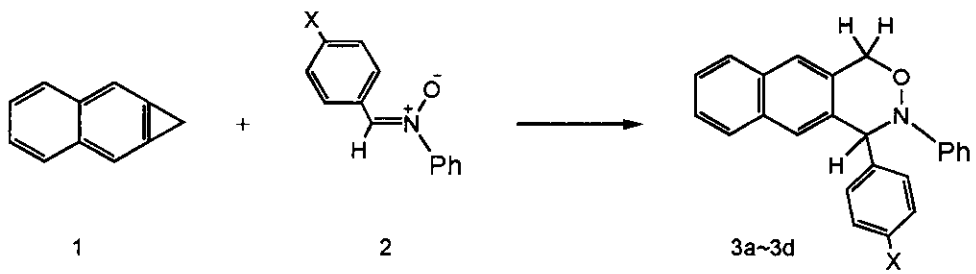


Figure 1.

Figure 2.

The reaction of 1 and *C,N*-diphenylnitrone (2a) in benzene was very slow compared to that in chloroform. Thus, after heating at 60 ℃ for 40 h (the same conditions as the case of chloroform), only 9 % of 3a was yielded and 70 % of 1 was recovered unchanged. Considering the larger ion stabilizing capability of chloroform compairing to benzene,[5] this is thought to suggest that the reaction proceeded through an ionic intermediate.

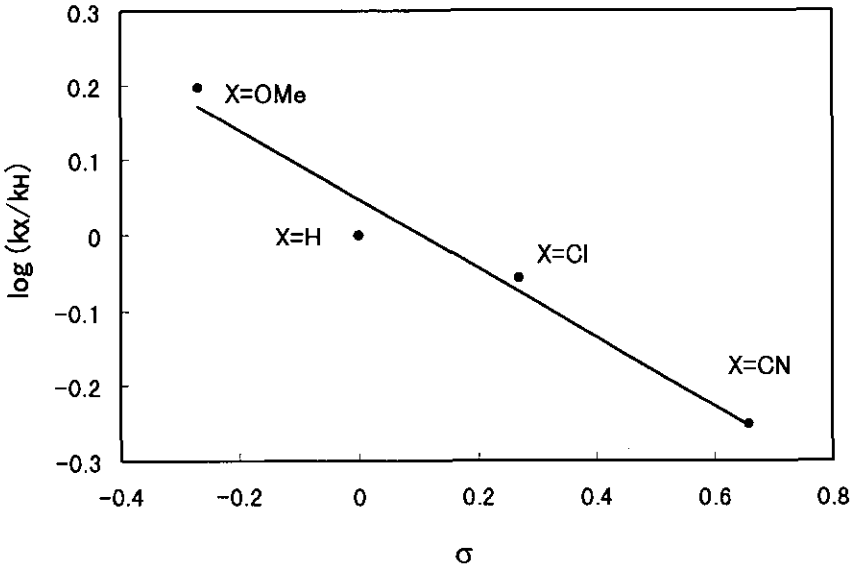


Figure 3. Plot of Hammett's sigma values (σ) versus logarithms of relative rate ratios ($\log(k_X/k_H)$).

The relative rate ratios (k_X/k_H) of the reaction of 1 with various nitrone derivatives (2a to 2d) were measured in a similar way to our previous method.[6] The ratios were 1.00 : 1.60 : 0.88 : 0.56 for 2a : 2b : 2c : 2d. A fairly good linear relation was observed between the logarithms of the relative rate ratios ($\log (k_X/k_H)$) and Hammett's sigma values (σ).[7] The ρ value was calculated as -0.46, suggesting that the reaction was accelerated by the introduction of electron-donating substituents in the phenyl group attached at the nitrone-carbon atom.

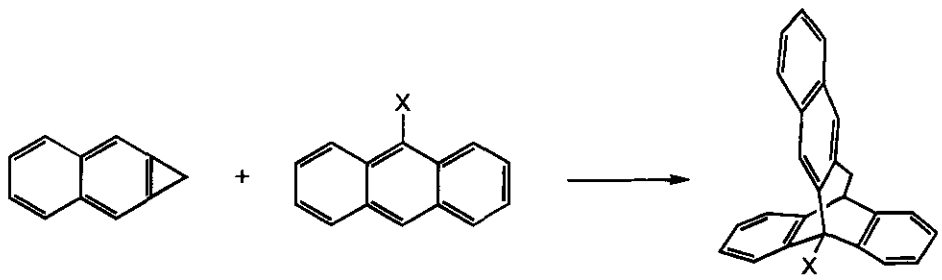


Figure 4.

The analogous linearity between the relative rate ratios and Hammett's sigma values (σ) was found in the reaction of 1 and anthracene derivatives (7) with various substituents at 9 position.

A solution of 1 and two molar equivalents of 7 in chloroform were heated at 70 ℃ for 50 h. Separation of the reaction mixture with silica gel column chromatography using hexane-ethyl acetate 9:1 as a developing solvent gave 8 (yields: 8a, 26 %; 8b, 63 %; 8c, 28 %; 8d, 12 %). The structure of 8 was determined by comparison of their spectral, mainly NMR spectral properties with those of the analogous compounds.[3]

The relation between the relative rate ratios (1.00 : 1.60 : 1.03 : 0.67 for 8a : 8b : 8c : 8d) and Hammett's sigma values (σ) is as follows.[8]

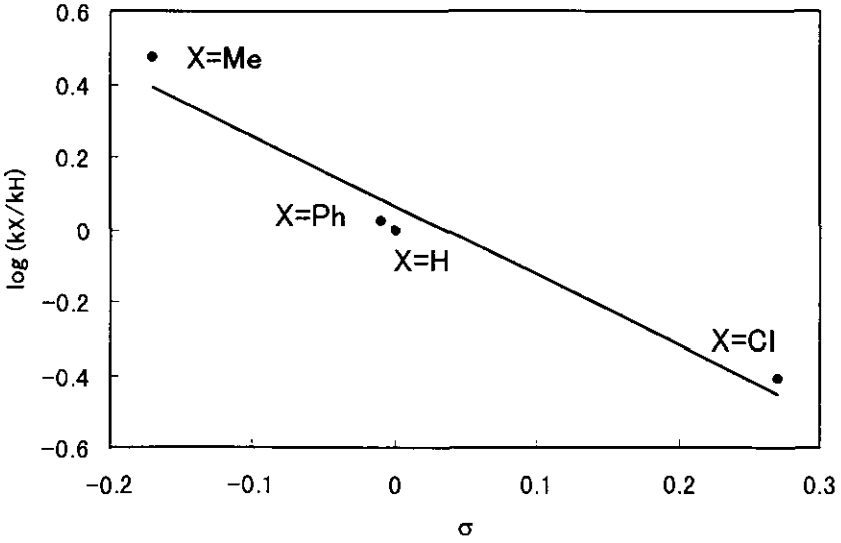
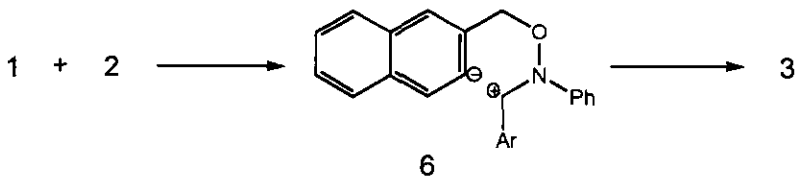


Figure 5. Plot of Hammett's sigma values (σ) versus logarithms of relative rate ratios (log (k_X/k_H)).



6

Figure 6.

Considering the above mentioned profile of the reactions that solvent benzene retards the reaction comparing to chloroform,[5] that the oxigen atom of nitrones charges negatively, and that the charge of sp^3-carbon atom on the three-membered ring is positively,[9] the reaction is considered to proceed through an ionic multistep mechanism. Finally the reaction mechanism is proposed as follows.[10] The negatively charged oxygen atom of nitrone attacks on the sp^3-carbon atom of 1 to form a zwitter ionic intermediate (6), which then cyclizes to give 3.[11]

EXPERIMENTAL

IR spectra were taken with a JASCO FT/IR 5300 spectrophotometer. MS spectra were measured with a Hitachi M-2000 spectrometer. NMR spectra were measured with Hitachi R-90, Varian XL-200, or Varian GEMINI 2000 spectrometers with tetramethylsilane as an internal standard. Melting points were recorded on a Yanagimoto Micro Melting Point Apparatus and are uncorrected. Wakogel C-200 and Wakogel B5-F were used for column and thin layerchromatography, respectively. The solvents were purified according to the standard procedures. Naphtho[*b*]cyclopropene and several nitrone derivatives were prepared by a method described in the literatures.[1]

Only typical reactions are mentioned below.

Reaction of Naphtho[b]cyclopropene (1) with C,N-Diphenylnitrone (2a). A solution of 1 (144.4 mg, 1.03 mmol) and 2a (403.3 mg, 2.04 mmol) in chloroform (12 ml) was heated at 60 ℃ for 40 h. After evaporation of the solvent, the residue was column chromatographed on silica gel and recrystallized from ethyl acetate-chloroform to give colorless crystals (3a) (250 mg, 75 %).

3a: Colorless needles. mp 197-198 ℃. MS m/z (rel intensity): 337.2 (M^+, 6), 319.2 (100), 302.2 (5), 289.0 (8), 240.1 (22), 189.1 (5). IR (KBr): 3061, 2920, 1597, 1493, 1323, 750 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 5.40 (d, 1H, J=16 Hz), 5.46 (d, 1H, J=16 Hz), 5.84 (s, 1H), 6.96 (t, 1H, J=8.0 Hz), 7.07 (d, 2H, J=8.0 Hz), 7.12-7.18 (m, 5H), 7.21 (dd, 2H, J=8.0, 8.0 Hz), 7.40 (dd, 1H, J=8.0, 8.0 Hz), 7.45 (t, 1H, J=8.0 Hz), 7.51 (s, 1H), 7.65 (s, 1H), 7.69 (d, 1H, J=8.0 Hz), 7.81 (d, 1H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ ppm: 68.6, 70.8, 118.7, 122.5, 123.2, 125.7, 126.0, 127.2, 127.3, 127.5, 127.7, 127.8, 128.5, 128.5, 130.0, 130.0, 132.0, 132.3, 134.6, 139.9, 148.7. Anal. Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N , 4.15. Found: C, 85.44; H, 5.21; N, 4.09.

3b: Colorless needles. mp 188-189 ℃. MS m/z (rel intensity): 367.3 (M^+, 4), 349.5 (100), 304.2 (15). IR (KBr): 3059, 2951, 1597, 1493, 1259, 1028, 748 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 3.72 (s, OCH_3), 5.41 (d, 1H, J=16 Hz), 5.43 (d, 1H, J=16 Hz), 5.79 (s, 1H), 6.68 (d, 2H, J=9.3 Hz), 6.97 (t, 1H, J=8.0 Hz), 7.03 (d, 2H, J=9.3 Hz), 7.07 (d, 2H, J=8.0 Hz), 7.23 (dd, 2H, J=8.0, 8.0 Hz), 7.40 (dd, 1H, J=8.0, 8.0 Hz), 7.45 (dd, 1H, J=8.0, 8.0 Hz), 7.50 (s, 1H), 7.64 (s, 1H), 7.69 (d, 1H, J=8.0 Hz), 7.81 (d, 1H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ ppm: 55.1, 68.2, 70.8, 113.1, 118.8, 122.4, 122.5, 123.1, 125.6, 125.9, 127.1, 127.3, 127.7, 128.5, 131.1,

132.1, 132.2, 132.3, 135.1, 148.8, 158.9.

3c: Colorless needles. mp 182-183 ℃. MS m/z (rel intensity): 371.1 (M^+, 3), 353.4 (100), 317.0(9). IR (KBr): 3057, 2942, 1595, 1491, 1091, 750 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 5.38 (d, 1H, J=16 Hz), 5.44 (d, 1H, J=16 Hz), 5.80 (s, 1H),6.98 (t, 1H, J=8.0 Hz), 7.05 (d, 2H, J=8.0 Hz), 7.06 (d, 2H, J=8.9 Hz), 7.12 (d, 2H, J=8.9 Hz), 7.23 (dd, 2H, J=8.0, 8.0 Hz), 7.41 (dd, 1H, J=8.0, 8.0 Hz), 7.46 (dd, 1H, J=8.0, 8.0 Hz), 7.48 (s, 1H), 7.65 (s, 1H), 7.69 (d, 1H, J=8.0 Hz), 7.81 (d, 1H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ ppm: 67.9, 70.8, 118.6, 118.6, 122.7, 123.3, 125.8, 126.2, 127.1, 127.3, 127.7, 128.0, 128.6, 131.3, 131.9, 132.3, 132.3, 133.5, 134.1, 138.3, 148.5.

3d: Colorless needles. mp 183-185 ℃. MS m/z (rel intensity): 362.1 (M^+, 7), 345.4 (100), 314.1 (8). IR (KBr): 3056, 2959, 2226, 1597, 1491, 750 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 5.38 (d, 1H, J=16 Hz), 5.48 (d, 1H, J=16 Hz), 5.88 (s, 1H), 6.99 (t, 1H, J=8.0 Hz), 7.04 (d, 2H, J=8.0 Hz), 7.23 (dd, 2H, J=8.0, 8.0 Hz), 7.24 (d, 2H, J=8.6 Hz), 7.43 (d, 2H, J=8.6 Hz), 7.44 (dd, 1H, J=8.0, 8.0 Hz z), 7.48 (dd, 1H, J=8.0, 8.0 Hz), 7.48 (s, 1H), 7.67 (s, 1H), 7.70 (d, 1H, J=8.0 Hz), 7.82 (d, 1H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ ppm: 67.8, 70.6, 111.3, 118.2, 118.6, 122.9, 123.4, 125.9, 126.3, 127.1, 127.3, 127.5, 128.7, 130.5, 131.5, 132.2, 132.4, 132.9, 144.8, 148.0.

Reaction of Naphtho[b]cyclopropene (1) with Anthracene (7a). A solution of 1 (280 mg, 2.00 mmol) and 7a (712 mg, 4.00 mmol) in chloroform (20 ml) was heated at 70 ℃ for 40 h. After evaporation of the solvent, the residue was column chromatographed on silica gel using hexane-ethyl acetate (9:1) as a developing solvent to give yellow crystals 8a (163mg, 26 %).

8a: Yellow needles. mp 225-226 ℃. MS m/z (rel intensity): 318 (M^+, 100), 302 (12). IR (KBr): 3023, 2916, 762, 747 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 3.47 (d, 1H, J=4.5 Hz), 4.32 (t, 1H, J=4.5 Hz), 5.03 (s, 1H), 6.5-7.8 (m, 14H). ^{13}C NMR ($CDCl_3$) δ ppm: 37.2, 45.6, 55.3, 124.8, 125.2, 125.3, 125.8, 126.4, 126.6, 126.7, 126.9, 130.8, 132.0, 132.6, 133.1, 139.1, 140.5, 143.3. Anal. Calcd for $C_{25}H_{18}$: C, 94.30; H, 5.70. Found: C, 94.26; H, 5.70.

8b: Yellow needles. mp 263-264 ℃. MS m/z (rel intensity): 332 (M^+, 100), 317 (97). IR (KBr): 3024, 2917, 770, 747 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 2.50(s, Me), 3.52 (d, 1H, J=4.3 Hz), 4.31 (t, 1H, J=4.3 Hz), 7.0-7.9 (m, 14H). ^{13}C NMR ($CDCl_3$) δ ppm: 21.2, 38.8, 45.2, 46.0, 121.5, 1 22.8, 125.1, 125.4, 125.6, 126.0, 126.4, 126.6, 127.5, 130.6, 131.7, 132.3, 134.2, 141.2, 141.6, 145.5. Anal. Calcd for $C_{26}H_{20}$: C, 93.94; H, 6.06. Found: C, 93.68; H, 5.94.

8c: Orange oil. MS m/z (rel intensity): 394 (M^+, 100), 344 (22). ^1H NMR ($CDCl_3$) δ ppm: 3.52 (d, 2H, J=3.0 Hz), 4.42 (t, 1H, J=4.8 Hz), 6.95-8.48 (m, 19H). ^{13}C NMR ($CDCl_3$) δ ppm: 38.8, 44.6, 45.7, 125.1, 125.3, 125.6, 126.0, 126.6, 126.8, 127.3, 127.4, 127.5, 127.7, 128.0, 128.6, 134.6, 137.0, 138.4, 139.1, 140.2, 140.7, 145.1.

8d: Orange oil. IR (KBr): 3057, 2920, 1454, 667 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 3.4 (d, 2H, J=4.0 Hz), 4.3 (t, 1H, J=4.0 Hz), 7.2-8.0 (m, 17H). ^{13}C NMR ($CDCl_3$) δ ppm: 39.0, 45.3, 48.9, 122.4, 124.4, 124.4, 124.6, 124.9, 125.2, 125.5, 125.6, 125.7, 125.9, 126.0, 126.4, 126.7, 127.1, 127.2, 127.5, 127.8, 127.9, 128.0, 129.0, 130.9, 138.2, 142.9.

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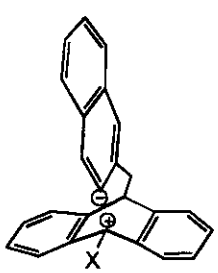
5. The following table shows that an ion stabilizing effect of chloroform is bigger than that of benzene.

Table 1. Several solvent constants of chloroform and benzene.

solvent	relative permittivity (ε)	anion solvation ability (A)	cation solvation ability (B)	polarity (A+B)
C_6H_6	2.28	0.15	0.59	0.74
$CHCl_3$	4.81	0.42	0.73	1.15

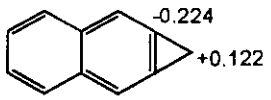
6. K. Saito, H. Ishihara, T. Murase, Y. Horie, and E. Maekawa, *Bull. Chem. Soc. Jpn.*, 1987, 60, 4317; K. Saito, S. Isobe, K. Ito, S. Kagabu, and K. Takahashi, *Chem. Lett.*, 1989, 1541; K. Ito and K. Saito, *Bull. Chem. Soc. Jpn.*, 1995, 68, 3539.
7. H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, 1957, 79, 1915.
8. The reaction of 1 and 7a in benzene gave the same product (8a) as the case of the solvent chloroform, but the yield was lower (10 %) than that in chloroform, suggesting that an ionic intermediate (9) analogous to that of the reaction with nitrones participates in this reaction.



9

Figure 7.

9. The electron densities of 1 and 2 were calculated as follows.
The sp^2 and the sp^3 carbons of the three-membered ring part of 1 are charged to negative and positive, respectively. The charges on the carbon, nitrogen, and oxygen atoms of the nitrones are summarized in the Table 2.



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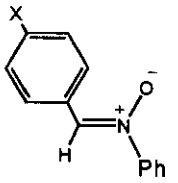

2

Figure 8.

Table 2. Electron density of **2** (Calcd. by PM3 method).

	X= OMe	X= H	X= Cl	X= CN
C	−0.525	−0.529	−0.531	−0.538
N	+1.059	+1.063	+1.066	+1.072
O	−0.635	−0.635	−0.635	−0.632

The MO calculations were carried out using an NEC PC-9801 RA 32-bit personal Computer with "PASOCON MOPAC/386" program which is based on the MOPAC (Ver. 4.0, QCPA No. 455) by Toray System Center.

10. A referee suggested a reaction mechanism to form 3 through the three-membered primary cycloadduct (5), which might be expected to be isolated. In spite of many efforts, isolation of 5 has never succeed. An investigation to make the reaction mechnism clear in detail is now in progress.
R. Neidlein and L. Tadesse, *Helv. Chim. Acta*, 1988, 71, 249; U. H. Brinker and H. Wuster, *Tetrahedron Lett.*, 1991, 32, 593.

11. Table 2 tells that the magnitudes of the negative charge on the oxygen atom of the nitrone seem not to be effected so much by the substituents "X" on the phenyl group. This means that it is hard to explain the substituent effects on the rate ratios by the terms of electron densities. The heat of formation of the zwitter ionic intermediates (6) was calculated. The order of the magnitude was 6a < 6b < 6c < 6d, which showed that the relative rate ratio was roughly reflected by the stability of the intermediates.

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