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1,3-Dipolar Cycloadditions to Bicyclic Olefins. III. The Effects of Aromatic Solvents on the exo/endo Product Ratios for the 1,3-Dipolar Cycloadditions of Nitrile Oxides to Norbornadienes[1,2)]

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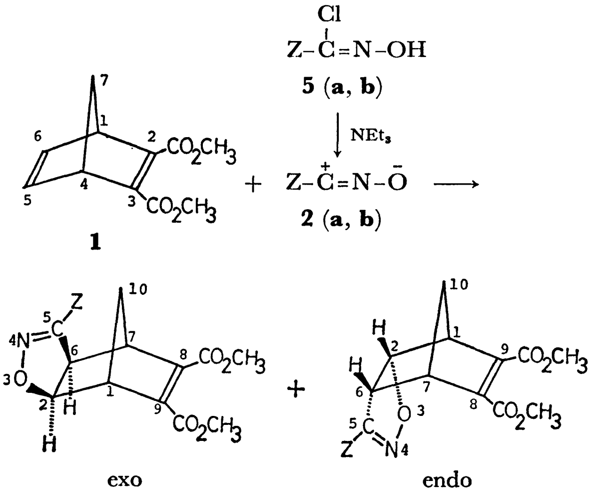
When no hydrogen-bonded complex is formed between the precursors (α-chloro-α-hydroxyiminoacetophenone (**5a**) and α-chloro-α-hydroxyiminoacetone (**5b**)) of nitrile oxides (phenylglyoxylonitrile oxide (**2a**) and methylglyoxylonitrile oxide (**2b**)) and norbornadienes(2,3-bis(methoxycarbonyl)norbornadiene (**1**) and norbornadiene (**6**)) in solvents, the exo/endo product ratios for the cycloadditions of **2a** and **2b** to **1** or **6** increase or decrease with increasing temperature. When the hydrogen-bonded complex between **5a** and **1** is formed in a solvent cage, however, the ratio keeps a constant value until the temperature is elevated up to a certain temperature, at which the ratio jumps up. After the jumping, the ratio has another constant value, regardless of the temperature. Similar results are obtained in the cycloaddition of **2b** to **1** in the aromatic solvents used.

The 1,3-dipolar cycloaddition of phenylglyoxylonitrile oxide (**2a**) to 2,3-bis(methoxycarbonyl)norbornadiene (**1**) gives both the exo and endo adducts (**3a** and **4a**).[3)] When non-aromatic solvents are used, the exo/endo product ratio increases with an increase in the temperature (Fig. 1).[2)] However, when aromatic solvents are used, strange phenomena are observed, as is shown in Fig. 2; that is, the plot of the exo/endo product ratio *vs.* the temperature gives horizontal lines, but jumps up at a certain temperature. After the jumping, the ratio takes another constant value, regardless of the temperature. In this paper, a tentative explanation for the phenomena will be given.



1 **5 (a, b)** **2 (a, b)** **3(a, b)** **4(a, b)**

a; Z=C_6H_5CO, **b**; Z=CH_3CO

Results

The Relationship between the exo/endo Product Ratio and the Temperature. (i) The cycloaddition of **2a** to **1**: The results shown in Fig. 2 were obtained when the cycloaddition was carried out as follows: a dilute solution of triethylamine was slowly stirred into a solution of a mixture of **1** and α-chloro-α-hydroxyiminoacetophenone (**5a**), which is the precursor of **2a** (see

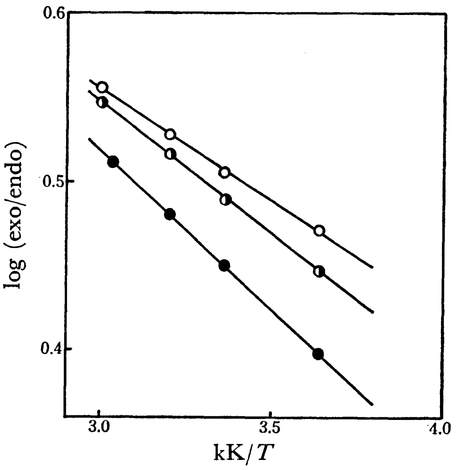


Fig. 1. The linear relationship between $1/T$ and the exo/endo product ratio for the cycloaddition of **2a** to **1** in non-aromatic solvents.
○: THF, ◑: $CHCl_3$, ●: acetone.

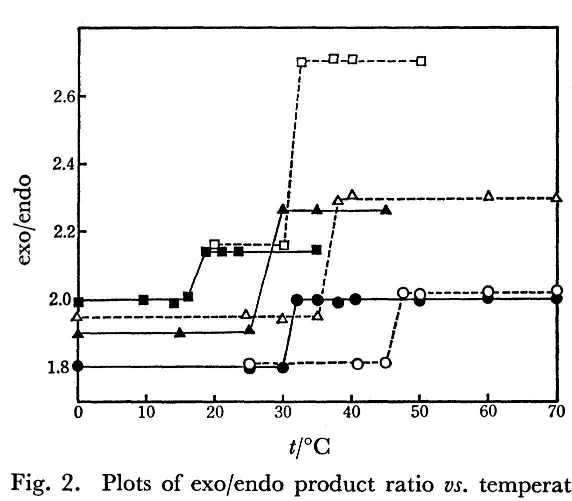


Fig. 2. Plots of exo/endo product ratio *vs.* temperature for the cycloaddition of **2a** to **1** in aromatic solvents.
●: Toluene, ○: benzene, ▲: anisole, △: chlorobenzene, □: nitrobenzene, ■: *o*-xylene.

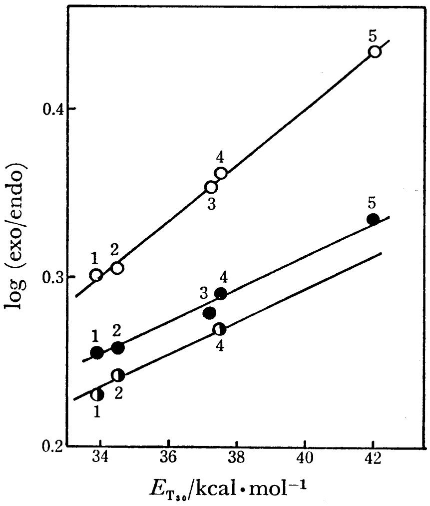


Fig. 3. Height of horizontal line *vs.* $E_{T_{30}}$ (25 °C) value. ○: exo/endo product ratio after the jumping for the cycloaddition of **2a** to **1**, ●: exo/endo product ratio before the jumping for the cycloaddition of **2a** to **1**, ◑: exo/endo product ratio for the cycloaddition of **2b** to **1**, 1: toluene 2: benzene, 3: anisole, 4: chlorobenzene, 5: nitrobenzene.

Method A in the Experimental section). The plots in Fig. 2 are characterized as follows.

a) The height of the horizontal lines in Fig. 2 can be linearly related to the E_T value[4] of the solvent, as is shown in Fig. 3.

b) The jumping temperature stands to the molar volume[5] of the solvent in a linear relation, as is shown in Fig. 4.

(ii) The cycloaddition of **2b** to **1**: The cycloaddition was carried out in the manner described above. Figure 5 shows the results. When benzene was used, the exo/endo product ratio jumped up at about 40 °C. When toluene or chlorobenzene was used, however, the jumping did not occur. Also, in this case the height of the horizontal lines increased with an increase in the E_T value of the solvent (Fig. 3).[6]

(iii) The cycloaddition of **2a** to norbornadiene (**6**): The cycloaddition was carried out in benzene in a manner similar to that described above. The exo/endo product ratio decreased with an increase in the temperature (Fig. 6).

(iv) The cycloaddition of "free **2a**" to **1**: After having been generated in the reaction system, the dipole which we called "free **2a**" was allowed to react with **1** in toluene (Method B in the Experimental section). In this case, the exo/endo product ratio increased with an increase in the temperature (Fig. 7).

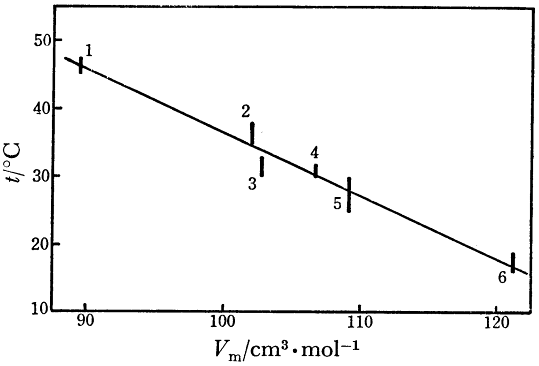


Fig. 4. Jumping temperatures *vs.* molar volumes of solvents (25 °C).
1: Benezene, 2: chlorobenzene, 3: nitrobenzene, 4: toluene, 5: anisole, 6: *o*-xylene.

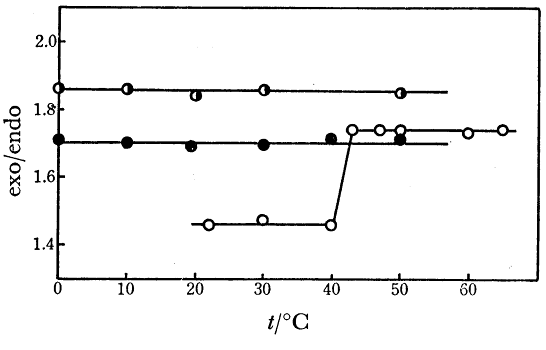


Fig. 5. Plots of exo/endo product ratio *vs.* temperature for the reaction of **2b** with **1**.
○: Benzene, ●: toluene, ◑: chlorobenzene.

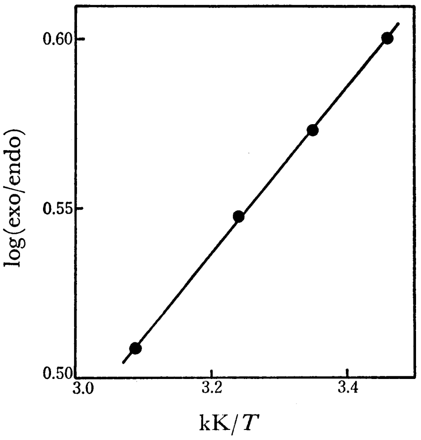


Fig. 6. Plots of exo/endo product ratio *vs.* temperature for the reaction of **2a** with **6**.

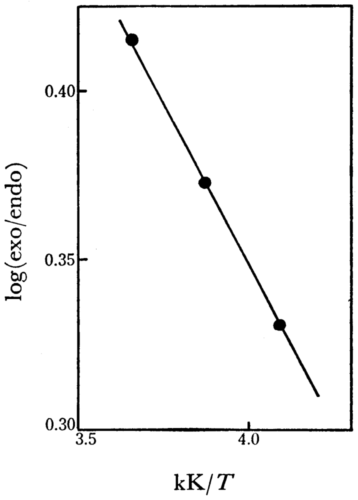


Fig. 7. Plots of exo/endo product ratio *vs.* temperature for the cycloaddition of "free **2a**" to **1** in toluene.

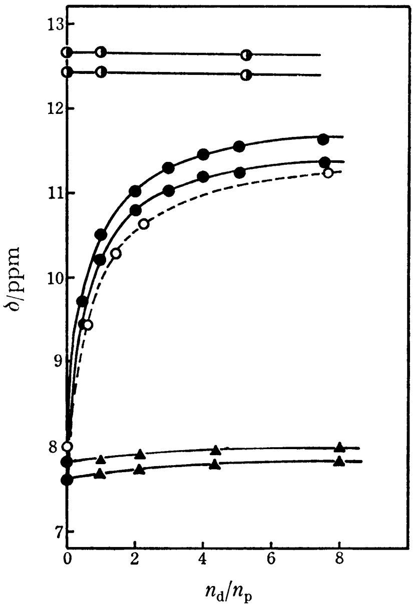


Fig. 8. Chemical sflifts of OH protons of **5a** and **5b** *vs.* n_d/n_p.
n_d=mole number of **1**(or **6**), n_p=mole number of **5a**(or **5b**), ◑: **1** to **5a**(in acetone), ●: **1** to **5a**(in benzene-d_6) ○: **1** to **5b**(in benzene-d_6), ▲: **6** to **5a** (in benzene-d_6).

Behavior of the Precursors of Nitrile Oxides in Solutions. (i) NMR chemical shifts of the precursors: When mixtures of **1** and **5a** in appropriate molar ratios were dissolved in acetone, the δ value[7] of the hydroxylic proton of **5a** did not change, regardless of the n_d/n_p ratio, as is shown in Fig. 8, where n_d is the number of moles of the dipolarophile and n_p is the number of moles of the precursor. In benzene-d_6, however, the δ value changed with the n_d/n_p ratio, as is shown in Fig. 8: The δ value increased rapidly as the value of n_d/n_p changed from 0 to 1. After n_d/n_p had reached 1, the δ value increased gradually with the increase in the n_d/n_p. For the precursor (α-chloro-α-hydroxyiminoacetone (**5b**)) of **2b** also, a similar phenomenon was observed (Fig. 8).[7] These results suggest that a 1: 1 hydrogen-bonded complex is formed between **1** and **5a** (or **5b**) in benzene-d_6. When mixtures of **6** and **5a** in appropriate molar ratios were dissolved in benzene-d_6, the δ value of the hydroxylic proton of **5a** scarcely changed (Fig. 8). This result implies that no hydrogen-bonded complex is formed between **6** and **5a** in benzene-d_6.

Table 1. Solubilities of **5a** and **5b** (mg/cm^3, 25 °C)

Solvent	**5a**	**5b**
Benzene	9.8	17
Toluene	7.7	15
Anisole	89	
Chlorobenzene	8.9	13
Nitrobenzene	80	
o-Xylene	7.3	
Norbornadiene	19	
BMCND[a)]	500	790
THF	1250	
Acetone	870	
Methyl acetate	620	
Ethanol	740	

a) 2,3-Bis(methoxycarbonyl)norbornadiene.

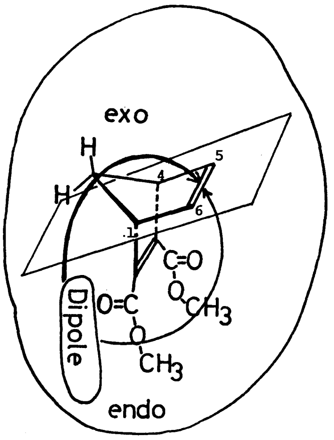
(ii) Solubility of the precursors: The precursors, **5a** and **5b**, are very soluble in non-aromatic solvents and in **1**, but they are only slightly soluble in aromatic solvents and in **1** (Table 1). Moreover, the following phenomena were observed: when 0.25 mmol of **5a** was added to 0.5 cm^3 of benzene-d_6, a large portion of the **5a** remained insoluble. The addition of 0.25 mmol of **1** to this suspension gave a clear solution. Such a phenomenon was also observed for the other aromatic solvents used. For **5b** also, a similar phenomenon was observed. These results support the formation of the hydrogen-bonded complex of **1** with **5a** (or **5b**) in aromatic solvents.

Discussion

When no hydrogen-bonded complex is formed between the precursors of nitrile oxides and norbornadiene in solvents, the exo/endo product ratios for the reactions of the nitrile oxides and norbornadienes increase or decrease with an increase in the temperature. The reason for the increase or decrease of the ratios has been reported previously.[2] When the hydrogen-bonded complexes between the precursors of nitrile oxides and the norbornadiene, **1**, are formed in solvent cages, however, stepped lines are obtained, as is shown in Figs. 2 and 5. We will now give a tentative explanation for these phenomena.

At the moment the dipole is generated by the elimination of hydrogen chloride from the precursor, which is a component of the hydrogen-bonded complex in a solvent cage, it must be present near the polar ester groups. Then, it would be transferred to the exo or endo side of the C_5–C_6 double bond of **1**, taking some kind of rotation. The solvent cage can be divided into the exo and endo spaces by the plane containing the four carbon atoms (C_1, C_4, C_5, and C_6) (see the figure). Here, we assume that the exo/endo product ratio depends on the ease of approach of the dipole to the exo and endo sides and that the ease of approach depends on the size of the exo and endo spaces. If the exo and endo spaces are large enough for the dipole to take any pathway of transfer and any mode of rotation, the exo/endo product ratio will become the value obtained when the cycloaddition is carried out in a gas phase. If the solvent cage is small, however, the pathway of the transfer and the mode of rotation of the dipole may be limited. The endo space must be smaller than the exo space, because the ester groups in the endo space would attract the polar solvent. Hence, as the E_T value of the solvent becomes larger, the endo space may decrease more greatly than the exo space. This means that the exo/endo product ratio increases with an increase in the E_T value of the solvent (Fig. 3).

The sizes of the exo and endo spaces of the solvent cage would increase gradually with an increase in the temperature, and the former more rapidly than the



latter. Until the exo space reaches a certain size which is large enough for the dipole to take other pathways of translation and modes of rotation, the exo/endo product ratio keeps a constant value, and then it jumps up suddenly at this size. Since the size of the solvent cage increases with an increase in the molar volume of the solvent, the jumping temperatures will lower with an increase in the molar volume of the solvent, as is shown in Fig. 4.

Experimental

Solvents. Benzene was refluxed for 10 h over sodium and then carefully distilled; bp 80 °C. Toluene was refluxed for 10 h over sodium and distilled; bp 111 °C. Chlorobenzene was dried over $MgSO_4$ and distilled; bp 131—132 °C. Anisole was dried over sodium and then distilled; bp 155—156 °C. Nitrobenzene was dried over $MgSO_4$ and then distilled; bp 210—211 °C. *o*-Xylene was dried over sodium and then distilled; bp 144 °C.

Materials. The norbornadiene, **1**, was prepared by a method described in the literature.[9] Norbornadiene was purchased and distilled before use. The precursors of the nitrile oxides, **5a**[10] (mp, 131—132 °C) and **5b**[11] (mp, 104—105 °C), were also prepared by methods described in the literature.

Products. The cycloadducts obtained in the reaction of **2a** with **6** and the cycloadducts, **3a** and **4a**, have been characterized in a previous paper.[3]

The cycloadducts, 5-acetyl-8,9-bis(methoxycarbonyl)-2,6-exo-3-oxa-4-azatricyclo[5.2.1.$0^{2,6}$]deca-4,8-diene(**3b**), 5-acetyl-8,9-bis(methoxycarbonyl)-2,6-*endo*-3-oxa-4-azatricyclo-[5.2.1.$0^{2,6}$]deca-4,8-diene (**4b**), were isolated using column chromatography on silica gel and chracterized.

3b: Colorless viscous oil; IR (neat) 1720 (ester C=O), 1690 (C=O), and 1625 cm^{-1} (C=N); NMR ($CDCl_3$) $\delta=1.53$ and 1.87 (2H, ABq, $J=10.5$ Hz, 10-CH_2), 2.44 (3H, s, $COCH_3$), 3.76 (3H, s), 3.79 (3H, s), 3.5—3.9 (3H, m, 1-H, 7-H, and 2-H_{endo}), 5.15 ppm (1H, d, $J=8$ Hz, 6-H_{endo}). 2,4-Dinitrophenylhydrazone of **3b**: mp 169—171 °C.

Found: C, 50.71; H, 3.78; N, 14.98%. Calcd for $C_{20}H_{19}N_5O_9$: C, 50.74; H, 4.05; N, 14.80%.

4b: Mp 128—130 °C (from MeOH–H_2O); IR(KBr) 1730 (ester C=O), 1690 (C=O), and 1620 cm^{-1} (C=N); NMR ($CDCl_3$) $\delta=1.50$ and 1.90 (2H, ABq, $J=10$ Hz, 10-CH_2), 2.39 (3H, s, $COCH_3$), 3.5—4.0 (2H, m, 1-H and 7-H), 3.71 (3H, s), 3.75 (3H, s), 4.90 (1H, dd, $J=10$ and 4 Hz, 2-H_{exo}), 3.71 (3H, s), 3.75 (3H, s), 4.09 (1H, dd, $J=10$ and 4 Hz, 2-H_{exo}), and 5.56 ppm (1H, dd, $J=10$ and 4.5 Hz, 6-H_{exo}).

Found: C, 57.51; H, 5.03; N, 4.76%. Calcd for $C_{14}H_{15}NO_6$: C, 57.33; H, 5.16; N, 4.78%.

General Procedure for 1,3-Dipolar Cycloadditions. Method A (Cycloadditions Started from the Hydrogen-bonded Complex): A mixture of a norbornadiene (2.50 mmol) and a precursor of a nitrile oxide (2.50 mmol) was dissolved in an appropriate solvent (40 cm^3). Then, the temperature of the solution was maintained at a given temperature (which was controlled within ±0.1 °C). A solution of triethylamine (TEA) (330 mg, 3.26) in the same solvent (10 cm^3) as that used above was added, drop by drop, over a period of 1 h. After an additional 1 h of stirring at the same temperature, the resulting triethylammonium chloride was removed by filtration. The filtrate was evaporated under reduced pressure to give a mixture of the exo and endo adducts. This mixture was then submited to a measurement of the exo/enso product ratio.

For the cycloaddition of **2a** to **6**, two molar equivalents of **6** with respect to **2a** were used.

Method B (Cycloadditions of "Free 2a" to 1): Compound **5a** (520 mg, 2.50 mmol) was dissolved in 40 cm^3 of toluene. The temperature of this solution was maintained at a given temperature by means of a thermostat (±0.1 °C). Into the solution, a solution of TEA (330 mg, 3.26 mmol) dissolved in 5 cm^3 of toluene was added all at once, after which the soultion was stirred for 4 min at the same temperature, A solution of **1** dissolved in 5 cm^3 of the same solvent as that used avobe was then added to the above reaction mixture all at once, after which the solution was stirred for 1 h at the same temperature. The resulting triethylammonium chloride was removed by filtration. The evaporation of the solvent left a mixture of the exo and endo adducts.

Measuerment of the exo/endo Product Ratios. The NMR technique employed for measuring the exo/endo product ratios is described in the literature.[2]

The measurement of each exo/endo product ratio for the cycloadditions of **2a** and **2b** to **1** or **6** at a given temperature was repeated twice using the NMR technique. The difference between the average and the experimental data was within ±0.02. (Figs. 2, 5, 6, and 7.)

Measurement of Solubility of the Precursors, 5a and 5b. General procedure: An excess of the precursor of a nitrile oxide was added to an appropriate solvent of a constant volume. The solution was allowed to stand for about 12 h at 25 °C. Then, the insoluble material was removed by filtration. The filtrate was evporated to dryness under reduced pressure to give a residue. The weight of the residue was measured.

Measurement of the Chemical Shifts for OH Protons of 5a and 5b. General procedure: A mixture of a norbornadiene and **5a** (or **5b**) in an arbitary molar ratio was dissolved in a 0.5-cm^3 portion of benzene-d_6 (or acetone) containing a small amount of TMS in an NMR sample tube. Then, the chemical shift for the OH proton of the precusor of the nitrile oxide was measured. (The NMR spectra were recorded on a Hitachi NMR R-24A spectrometer at 60 MHz.)

The authors are indebted to Mr. Yoshimasa Kadoma for measuring the solubilities of **5a** and **5b**.

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6) For benzene, the exo/endo product ratio after the jumping was employed.

7) Both precursors, **5a** and **5b**, consist of two isomers, the *E*-form and the *Z*-form. Two sharp OH signals appear in the NMR spectrum of **5a**. This may be attibutable to a very slow chemical exchamge of the OH protons on the NMR time scale between the two isomers.[8] In the case of **5b**, only one broad singlet appears for the OH proton. This may be ascribed to a rapid chemical exchange of the OH protons between the two isomers.[8]

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