1,3-Dipolar Cycloadditions to Bicyclic Olefins. II. The Effects of Non-aromatic Polar Solvents on the *exo*/*endo* Product Ratios in 1,3-Dipolar Cycloadditions to Norbornadienes[1, 2]

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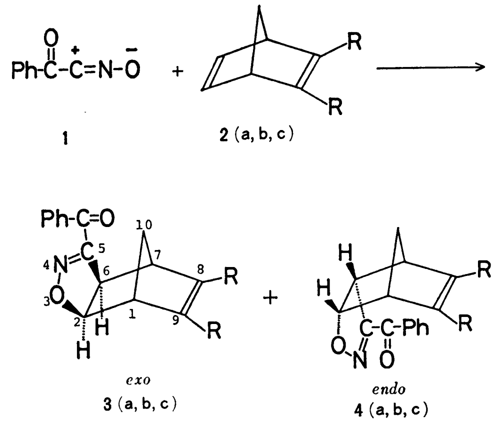
The *exo*/*endo* product ratios for three types of 1,3-dipolar cycloadditions of phenylglyoxylonitrile oxide(**1**) to 2,3-bis(methoxycarbonyl)norbornadiene(**2a**), norbornadiene, and 2,3-dicyanonorbornadiene decrease with increasing E_T value of the non-aromatic polar solvent used. The *exo*/*endo* ratio in the reaction of **1** with **2a** is larger than unity, but the value of $\Delta H^{\neq}_{exo}-\Delta H^{\neq}_{endo}$ is nevertheless positive. This phenomenon is attributed to the relatively large positive value of $\Delta S^{\neq}_{exo}-\Delta S^{\neq}_{endo}$, that is, $\Delta G^{\neq}_{exo}-\Delta G^{\neq}_{endo}<0$ at ordinary temperatures. On the basis of these results, the conditions, under which the *exo*/*endo* ratio in the reaction of **1** with **2a** is smaller than unity, were determined. The results can be reasonably explained by the assumption that the dipole moment of the *endo*-form in the transition state is greater than that of the *exo*-form.

In a previous paper, it was reported that various 1,3-dipolar cycloadditions to norbornadienes gave exo-adducts together with small amounts of endo-adducts.[2] Now, the *exo*/*endo* product ratios for the Diels-Alder reactions of cyclopentadiene with dienophiles, such as methyl acrylate, methyl methacrylate, and methyl *trans*-crotonate, decrease with increasing Ω value of the solvent used.[3] This fact suggests that the stereoselectivity of the 1,3-dipolar cycloadditions to norbornadienes may also depend on the solvent, because the 1,3-dipolar cycloadditions are mechanisms analogous to Diels-Alder reactions. Therefore, the effects of the solvents on the stereoselectivity of the cyloadditions of phenylglyoxylonitrile oxide (**1**) to 2,3-bis(methoxycarbonyl)norbornadiene (**2a**), norbornadiene (**2b**), and 2,3-dicyanonorbornadiene (**2c**), which have been shown to be kinetically controlled,[2] were studied and it was found that the *exo*/*endo* product ratios decrease with increasing E_T value[4] of the non-aromatic polar solvent. In addition, it was found that these ratios depend on the reaction temperature.



1 2 (a, b, c)

exo 3 (a, b, c) *endo* 4 (a, b, c)

a: R=CO$_2$CH$_3$, **b**: R=H, **c**: R=CN

Experimental

Solvents. THF was dried over NaOH for one week and distilled over LiAlH$_4$; bp 66 °C. Ethyl acetate was dried over CaCl$_2$ for a few days and distilled; 77 °C. Chloroform was shaken together with concd sufuric acid, washed with distilled water, dried over CaCl$_2$, and distilled; bp 61 °C. Dichloromethane was dried over CaCl$_2$ and distilled; bp 40 °C. Acetone was dried over MgSO$_4$ and distilled; 56.5 °C. 2-Propanol was dried over CaO and distilled; bp 82.5 °C. Ethanol was refluxed over CaO for 12 h and distilled; bp 78.5 °C. Methanol was prepared by distilling commercial methanol over CaO; bp 64.5 °C.

Materials. Dipolarophiles, **2a**[5] and **2c**,[2] were prepared by methods descrived in the literature. Norbornadiene was purchased and distilled before use. α-Chloro-α-hydroxyiminoacetophenone (**9**), which is a precursor of **1**, was prepared by a method described in the literature.[6] All of the cycloadducts (**3a, 3b, 3c, 4a, 4b**, and **4c**) produced by the cycloadditions of **1** to **2a, 2b**, and **2c** have been characterized in previous work.[2]

General Procedure for 1,3-Dipolar Cycloadditions. a) The reaction of **1** with **2a**: A mixture of **9** (460 mg, 2.50 mmol) and **2a** (520 mg, 2.50 mmol) was dissolved in an appropriate solvent (40 cm^3). Then, the solution was maintained at a given temperature (Which was controlled to within ±0.1 °C). A solution of triethylamine (330 mg, 3.26 mmol) in the same solvent (10 cm^3) as that used above was added dropwise over 1 h. After additional stirring for 1 h, the triethylammonium chloride obtained was removed by filtration. The filtrate was evaporated under reduced pressure to give a mixture of the *exo*- and *endo*-adducts. This mixture was submitted to a measurement of the *exo*/*endo* product ratio by the NMR technique (*vide infra*). (When the ammonium salt was soluble in the solvent, the solvent was evaporated and then the cycloadducts were extracted with benzene.)

b) The reactions of **1** with **2b** and **2c**: Two molar equivalents of **2b** or **2c** with respect to **1** were taken. In the case of the reaction of **1** with **2b**, a small amount of bisadducts was produced in addition to a mixture of the *exo*- and *endo*-monoadducts. The monoadducts were separated from the bisadducts using column chromatography on silica gel.

Measurement of the exo/endo *Product Ratios.* Quantitative analysis of the *exo*/*endo* product ratios was carried out using NMR spectra (recorded on a Hitachi NMR R-24A spectrometer at 60 MHz.) The ratios were determined by measuring the area ratios of the signals of the *endo*- and *exo*-protons attached on each 2-carbon atom of the *exo*- and *endo*-adducts. These signals were well separated and, moreover, no other signals appeared in the vicinity of these signals.[2]

In order to minimize the error in the measurement of the area integrals, concentrated solutions containing the *exo*- and *endo*- adducts (in 40% CDCl$_3$ solutions) were prepared. The ratio values are subject to an uncertainty of ±0.02.

Results and Discussion

The Linear Relationship between the exo/endo *Product Ratios and the* E_T *Value of the Solvent.* The *exo/endo* product ratios in all three systems were dependent on the kind of the solvent, in the manner shown in Fig. 1. This figure indicates the following.

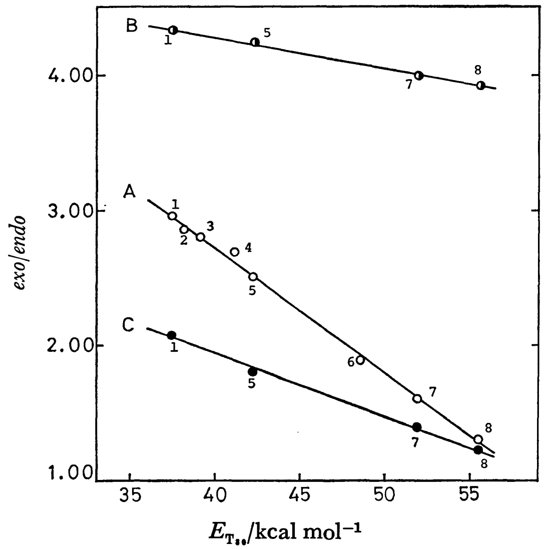


Fig. 1. The linear relationship between the *exo/endo* product ratios (at 0 °C) and $E_{\mathrm{T}_{30}}$ value of the solvent.
A: Reaction of **1** with **2a**, B: reaction of **1** with **2b**, C: reaction of **1** with **2c**, 1; THF, 2; EtOAc, 3; $CHCl_3$, 4; CH_2Cl_2, 5; acetone 6; 2-propanol, 7; EtOH, 8; MeOH.

a) All the *exo/endo* product ratios are greater than unity.

b) The *exo/endo* ratios in each system decrease linearly with increasing E_T value[4] of the solvent.

c) The *exo/endo* ratios for the three systems are in decreasing order, **2b**, **2a**, and **2c**.

The Effect of Temperature on the exo/endo *Product Ratio.* A linear relationship between $1/T$ and the *exo/endo* ratio was observed for the reactions of **1** with **2a** and **2b** carried out in acetone, chloroform, or THF (Fig. 2).

From the results shown in Fig. 2, the differences in activation parameters were calculated (Table 1). Table 1 shows the following.

a) In the reaction of **1** with **2a**,

$$\Delta H^{\ddagger}_{exo} - \Delta H^{\ddagger}_{endo} > 0 \qquad (1)$$

and

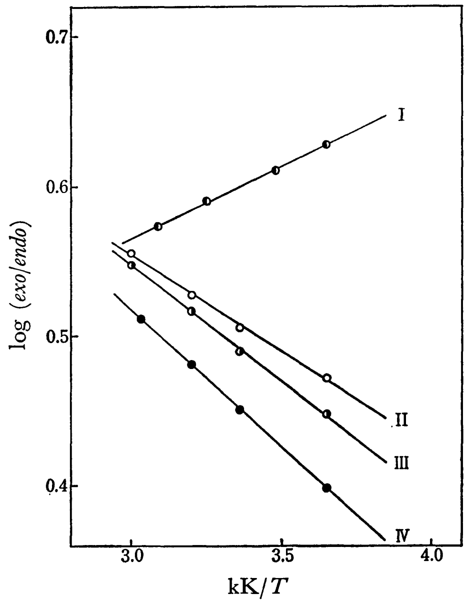


Fig. 2. The linear relationship between $1/T$ and the *exo/endo* product ratio.
I: Reaction of **1** with **2b** in acetone, II: reaction of **1** with **2a** in THF, III: reaction of **1** with **2a** in $CHCl_3$, IV: reaction of **1** with **2a** in acetone.

$$\Delta S^{\ddagger}_{exo} - \Delta S^{\ddagger}_{endo} > 0, \qquad (2)$$

and in the reaction of **1** with **2b**,

$$\Delta H^{\ddagger}_{exo} - \Delta H^{\ddagger}_{endo} < 0 \qquad (3)$$

and

$$\Delta S^{\ddagger}_{exo} - \Delta S^{\ddagger}_{endo} > 0. \qquad (4)$$

If judged only from expression (1) without respect to expression (2), the *exo/endo* ratio should be smaller than unity. Actually, however, the ratio is greater than unity as shown in Fig. 1. This phenonmenon implies that the entropy term of the reaction greatly contributes to the difference in the free energies of activation, that is, the value of $\Delta G^{\ddagger}_{exo} - \Delta G^{\ddagger}_{endo}$ is negative at ordinary temperatures (Table 1).

Expressions of (3) and (4) explain the fact that the *exo/endo* ratio is greater than unity.

b) The value of $\Delta G^{\ddagger}_{exo} - \Delta G^{\ddagger}_{endo}$ for the reaction of **1** with **2a** decreases with increasing E_T value of the solvent.

Conditions Which Give an exo/endo *Product Ratio Smaller than Unity.* The results shown in Fig. 1 suggest that the yield of the *endo*-adduct of the reaction of **1** with **2a** should surpass that of the exo-adduct, if a solvent having a larger E_T value than 58.6 is used as the

TABLE 1. DIFFERENCES IN ACTIVATION PARAMETERS IN THE REACTION OF **1** WITH **2a** AND **2b***) (1 cal=4.184 J)

Diene	Solvent	$E_{\mathrm{T}_{30}}$ / kcal mol^{-1}	$\Delta\Delta H^{\ddagger}$ / cal mol^{-1}	$\Delta\Delta S^{\ddagger}$ / cal K^{-1} mol^{-1}	$\Delta\Delta G^{\ddagger}$ / cal mol^{-1} (at 25 °C)
2a	CH_3COCH_3	42.2	+856	+4.88	−599
2a	$CHCl_3$	39.1	+703	+4.63	−677
2a	THF	37.4	+603	+4.34	−691
2b	CH_3COCH_3	42.2	−439	+1.26	−815

*) $\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}_{\mathrm{exo}} - \Delta H^{\ddagger}_{\mathrm{endo}}$, $\Delta\Delta S^{\ddagger} = \Delta S^{\ddagger}_{\mathrm{exo}} - \Delta S^{\ddagger}_{\mathrm{endo}}$, $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_{\mathrm{exo}} - \Delta G^{\ddagger}_{\mathrm{endo}}$.

TABLE 2. THE *exo/endo* PRODUCT RATIO IN THE REACTION OF **1** WITH **2a**[a)]

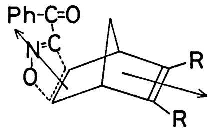
Medium	Solubility of **2a**	$E_{T_{30}}$ kcal mol^{-1}	$\frac{exo}{endo}$
MeOH	sol	55.5	1.31
MeOH-H_2O (7: 3)[b)]	sol	—	1.04
MeOH-H_2O (5; 5)[b)]	sol	—	0.725
water	insol	63.1	1.84
hexane	insol	30.9	1.88

a) Temp.: 0 °C, volume of medium: 40 cm^3, **1**: 2.50 mmol, **2a**: 2.50 mmol. b) Volume ratio.

reaction solvent. Such a solvent was prepared with the addition of water ($E_{T_{30}}$ value, 63.1) to mathanol ($E_{T_{30}}$ value, 55.5), since water does not dissolve **2a**.[7)] In a medium consisting of methanol and water (1: 1, volume ratio), the yield of the *endo*-adduct in the reaction surpassed that of the *exo*-adduct (Table 2).

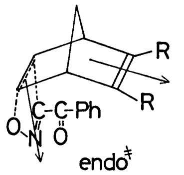
A Tentative Explanation for the Above Results. The explanation of Berson *et al.* for the *exo/endo* product ratio in the Diels-Alder reaction of cyclopentadiene with methyl acrylate[3)] was adopted here.

The permanent dipole moments of the *exo*- and *endo*-forms in the transition states, **5** and **6**, were assumed to be given approximately by the vectorial sum of the dipole moments of the two components, **7** and **8**. The values of the dipole moments of **8a**, **8b**, and **8c** can be estimated using the bond angles and the bond moments shown in the figure (*vide infra*). The bond angles and the bond moments for the transition states were assumed to be equel to those for the cycloadducts produced. The bond angles for the cycloadducts were determined from their molecular models and the values of the bond moments were extracted from the literature.[8—10)] The arrows shown for **5**—**8** are directed from the positive toward the negative end of each structure or component. The dihedral angles between the dipoles of the two components, **7** and **8**, were assumed to be 170° for the *exo*-form in the transition state and 55° for the *endo*-form using molecular models of the cycloadducts. The above estimate indicates that the resultant dipole moment of **6** is greater than that of **5**.



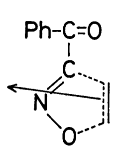
exo‡

5



endo‡

6



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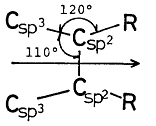

Bond moments

$\overset{+}{C}_{sp^3}$–$\overset{-}{C}_{sp^2}$ $\mu=0.68$ D
H–C_{sp^2} $\mu=0.63$ D
C–CO_2CH_3 $\mu=ca.$ 1.9 D
C_{sp^2}–CN $\mu=3.57$ D

8a: R = CO_2CH_3 ($\mu=4.2$ D)
8b: R = H ($\mu=0.3$ D)
8c: R = CN ($\mu=6.6$ D)

When the E_T value of the solvent becomes larger or the solute more polar, the free energy of solvation becomes smaller.[3,11)] As described above, the dipole moment of the *endo*-form in the transition state is greater than that of the *exo*-form. Therefore, the change from a small E_T value for the solvent to a large value results in a larger decrease in the free energy of solvation for the *endo*-form in the transition state as compared with that for the *exo*-form. Thus, as the E_T value of the solvent becomes larger, the rate of formation of the *endo*-adduct increases more greatly as compared with that of the *exo*-adduct. This explanation is reasonable on the basis of the present results.

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7) When this reaction was carried out in water, the *exo/endo* ratio was 1.84. This value resembles the value (1.88) of the *exo/endo* ratio for the reaction carried out in hexane which does not dissolve **2a**.

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