1,3-Dipolar Cycloadditions of *N*-(*p*-Substituted benzylidene) *p*-Substituted Benzylamine *N*-Oxides with *trans*-Bis(*p*-substituted benzoyl)ethylenes and the Substituent Effects on the Reaction Rates

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1,3-Dipolar cycloadditions of *N*-(*p*-substituted benzylidene) *p*-substituted benzylamine *N*-oxides with *trans*-bis(*p*-substituted benzoyl)ethylenes gave the *trans*- and the *cis*-2,3-bis(*p*-substituted phenyl)-4,5-bis(*p*-substituted benzoyl)isoxazolidines. The configurations of the resulting isoxazolidines were determined by NMR spectra. The formation ratios of the *trans*- to *cis*-adducts were determined by liquid chromatography. The second-order rate constants in xylene at 60 °C were obtained by high speed liquid chromatographic analysis. The rates varied with the σ values of the substituents R_1 on the *N*-benzylidene benzylamine *N*-oxides and R_3 on the dibenzoylethylenes, and linear relationships between log *k* and σ have been established. These results indicate that the HOMO(*N*-oxide)–LUMO(dibenzoylethylene) interaction predominates. The ρ-values for R_1 and R_3 were respectively; $\rho=-0.41\pm0.01$, $\rho=+0.60\pm0.02$.

Several 1,3-dipolar cycloadditions of nitrones have been studied.[1–4] The reactions of *N*-benzylidene benzylamine-*N*-oxide with *trans*- or *cis*-dibenzoylethylene has been reported to give 2,3-diphenyl-4,5-dibenzoylisoxazolidine, quantitatively.[5] However the configurations of the resulting isoxazolidines have not been established.

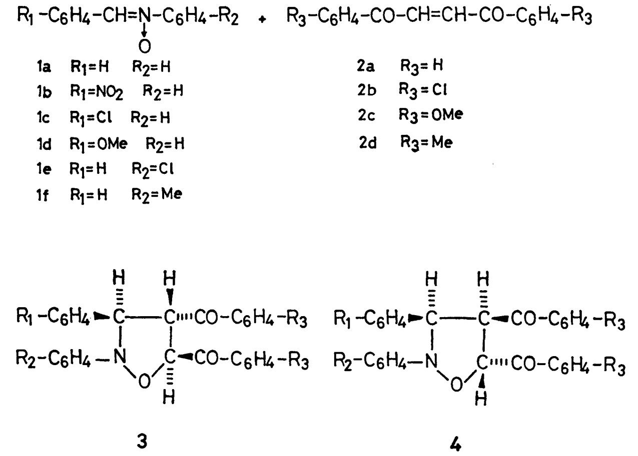
In the reaction of a 1,3-dipole and a dipolarophile, the eight stereoisomers are affected by the following three factors: the orientation of the addition, the direction of the cycloaddition, that is, either *exo* or *endo* and the reaction mechanism, either one or two-step. However, there have been few reported cases in which stereoisomers were obtained by the two-step mechanism. In the system here, the C_{2h}-symmetry of the *trans*-dibenzoylethylene prevented the formation of the stereoisomers caused by the two orientations. If these reactions proceed by a concerted mechanism, only two stereoisomers caused by *exo*- and *endo*-additions, the *trans*- and *cis*-isoxazolidines are expected.

This paper will report the configurations of the resulting isoxazolidines and some reactions of *N*-(*p*-substituted benzylidene) *p*-substituted benzylamine *N*-oxides with *trans*-bis(*p*-substituted benzoyl)ethylenes. The formation ratios of *trans*- to *cis*-forms were investigated to determine the substituent effect or the steric effect.

There have been some quantitative reports in the literatures[6–8] on the effect of substituents on the reaction rates. This paper describes the substituent effects on the reaction rate, and a semiquantitative treatment of the correlation between log *k* and σ using the second-order perturbation theory.

Results and Discussion

1,3-Dipolar cycloadditions of *N*-(*p*-substituted benzylidene) *p*-substituted benzylamine *N*-oxides (**1a**—**f**) (DPN) with *trans*-bis(*p*-substituted benzoyl)ethylenes (**2a**—**c**) (DBE) were conducted in anhydrous benzene to give a mixture of two stereoisomeric isoxazolidines, quantitatively. The configurations of these were determined to be as expected the *trans*- and *cis*-2,3-bis(*p*-substituted phenyl)-4,5-bis(*p*-substituted benzoyl)isoxazolidines, that is, **3** and **4** in Scheme 1. Thin-layer and high speed liquid chromatography have shown that the reaction mixture had no components other than the two stereoisomers. Column chromatography successfully isolated them from the reaction mixture.



$$R_1\text{-}C_6H_4\text{-}CH{=}\underset{\downarrow\atop O}{N}\text{-}C_6H_4\text{-}R_2 + R_3\text{-}C_6H_4\text{-}CO\text{-}CH{=}CH\text{-}CO\text{-}C_6H_4\text{-}R_3$$

	R_1	R_2
1a	H	H
1b	NO_2	H
1c	Cl	H
1d	OMe	H
1e	H	Cl
1f	H	Me

	R_3
2a	H
2b	Cl
2c	OMe
2d	Me

Scheme 1.

The structures of **3** and **4** were determined by NMR spectra. For example, the NMR spectra of the *trans*- and *cis*-2,3-diphenyl-4,5-dibenzoylisoxazolidines which were produced by the reaction of *N*-benzylidene benzylamine *N*-oxide (**1a**) and dibenzoylethylene (**2a**) are shown in Fig. 1. In the spectrum of the *trans*-adduct (a), the peaks at $\delta=5.05$(d), 5.38(d-d) and 6.01(d) are C_3–H, C_4–H, and C_5–H, respectively. The decoupling signal of C_5–H turned the double-doublet peak of C_4–H to a doublet one. This result confirms these assignments. Coupling constants, C_3–H—C_4–H ($J_{3,4}$) and C_4–H—C_5–H($J_{4,5}$) were as follows; $J_{3,4}=6.0$ Hz, $J_{4,5}=3.4$ Hz. In the spectrum of the *cis*-adduct(b), the peaks C_3–H, C_4–H and C_5–H are situated at $\delta=5.44$(d), 5.82(d-d) and 6.32(d), respectively. The coupling constants are $J_{3,4}=7.5$ and $J_{4,5}=5.6$. In saturated or unsaturated rings, the *cis*-forms coupling constant is generally larger than that of the *trans*-form,[9,10] thus these stereoisomers were concluded to have the above configurations since

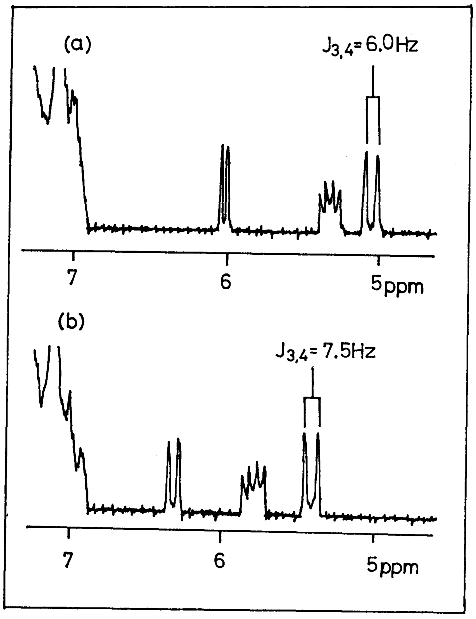
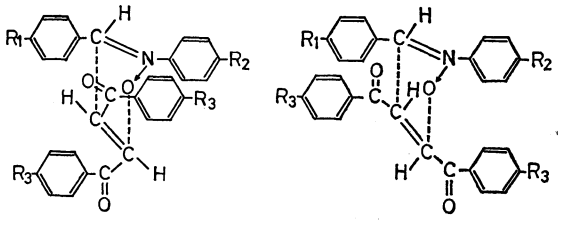


Fig. 1. NMR spectra of *trans*-(**3**) and *cis*-(**4**) isoxazolidine. (a); *trans* (b); *cis* (in DMSO-d_6, 60 MHz).

$7.5(J_{cis}) > 6.0(J_{trans})$. The observation that the *trans*-adduct, which is favored sterically, was the major product also supported these identifications. The NMR spectra of the other reaction products showed similar signal patterns.

DBE has C_{2h}-symmetry at the center of C=C double bond, so that two orientations of the addition give the same product. But there are two directions of the interaction between two components. *trans*-Isoxazolidine was formed through the *exo*-form transition state, and *cis*-isoxazolidine through the *endo*-form (Scheme 2).



exo-addition *endo*-addition

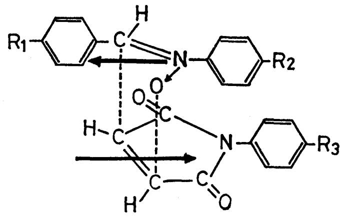
Scheme 2.

Melting points and the analytical data of the resulting isoxazolidines are summarized in Table 1. The formation ratios of the *trans*-forms to the *cis*-forms are also shown. They were determined by high speed liquid chromatography.

TABLE 1. THE MELTING POINTS AND THE ANALYTICAL DATA OF THE RESULTING ISOXAZOLIDINES AND THE FORMATION RATIOS

Run	Mp (°C)	Analytical data[a)] (Calcd) C%	H%	N%	3/4
1a+**2a**	151.0—152.0	80.40	5.42	2.98	
	108.5—108.7	80.02	5.44	3.42	4.2
		(80.37	5.31	3.23)	
1b+**2a**	160.0—163.0	73.23	4.86	5.47	
	158.5—159.5	72.72	4.70	5.65	4.7
		(72.80	4.60	5.86)	
1c+**2a**	155.5—156.5	74.39	4.71	2.97	
	120.0—121.0	74.06	4.76	3.01	5.0
		(74.43	4.74	2.99)	
1f+**2a**	127 (dec)	80.06	5.82	2.95	
	117.3—117.5	80.30	5.76	3.03	3.0
		(80.51	5.63	3.14)	
1a+**2b**	141.0—143.5	69.28	4.21	2.81	
	127.0—127.5	69.47	4.21	2.83	4.0
		(69.33	4.21	2.79)	
1b+**2b**	—		—		4.5
1c+**2b**	213.0—214.5	65.14	4.02	2.42	
	156.5—158.0	64.80	3.80	2.60	4.7
		(64.88	3.76	2.61)	
1d+**2b**	145 (dec)	67.24	4.39	2.55	
	147.5—148.5	67.83	4.40	2.53	4.5
		(67.68	4.35	2.63)	
1e+**2b**	188.5—191.0	64.91	3.37	2.63	
	125.5—126.5	64.67	3.74	2.83	5.2
		(64.88	3.76	2.61	
1f+**2b**	121.5—123.0	70.12	4.74	2.55	
	129.5—130.0	69.85	4.49	2.71	3.9
		(69.77	4.49	2.71)	
1a+**2c**	—		—		4.4
1b+**2c**	143.5—145.0	68.68	4.91	5.03	
	139.0—141.5	68.90	4.91	5.12	6.3
		(69.14	5.20	5.20)	
1c+**2c**	122.0—124.0	70.38	5.00	2.61	
	125.0—126.0	70.32	4.95	2.66	4.5
		(70.52	4.96	2.65)	

a) The upper line is for the *cis*-form, and the lower line is for the *trans*-form.



Scheme 3.

The reactions of nitrones with *N*-phenylmaleimides have been reported.[11,12] In this system the formation ratios varied in the range 1.5—3.9, depending on the electronic characters of the substituents on the nitrones and maleimides. This result suggests that the two reactant species orient in such a way that the interaction of the two dipole moments is favored (Scheme 3). Between log (I_t/I_c) and the Hammett σ values of the substituents on the nitrones and maleimides a linear relationship has been established.

DBE has three planar configurations. Two of these have C_{2h}-symmetry, and the unsymmetric one is hindered sterically between a vinyl hydrogen and an *o*-hydrogen in the benzene ring. By this reasoning the dipole moment will have an insignificant influence on the formation ratios, and consequently the steric effect will be the predominant factor when the two components are approaching and the π-orbitals begin to interact. The steric effect in the reaction of DPN with DBE would be expected to be greater than that in the reaction of DPN with *N*-phenylmaleimide. In this system the formation ratios are in the range 3.0—6.3, which are a little greater than the formation ratios of the maleimides. This result suggests that the *endo*-type addition is more hindered by the steric effect. In the reactions of DPNs with three DBEs, the values of the formation ratios are not so dissimilar, for example, the ratios of the reactions of **1a** with **2a**, **2b**, and **2c** are 4.2, 4.0, and 4.4, respectively, and the ratios of the reactions of **1c** with **2a**, **2b**, and **2c** are 5.0, 4.7, and 4.5, respectively.

The generation of C-T complexes between two benzene rings could be regarded as a factor governing the formation ratios. In *exo*- and *endo*-additions, the benzene ring of DPN makes about 90° with that of DBE when the two approach and interact in the most stable planar configurations, and about 30° in a less stable configuration. The generation of C-T complexes produces a fluorescence spectrum, but since this was not observed, this factor does not seem to have a predominating effect on the formation ratios.

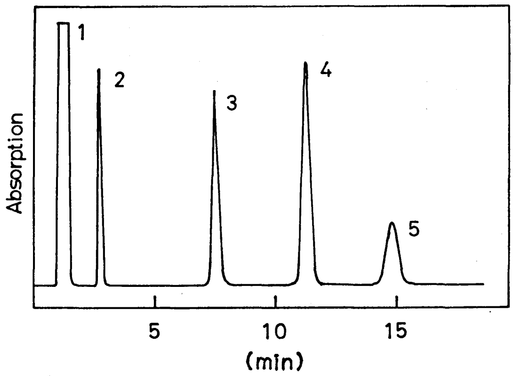


Fig. 2. The HLC chart of the reaction mixture of **1a** and **2a**.

In order to study the effects of substituents on the reaction rates, the rate constants of the reactions of **1a**—**d** with **2a**—**d** were determined by high speed liquid chromatography (HLC). Figure 2 shows an HLC chart of the reaction mixture of *N*-benzylidene benzylamine *N*-oxide (**1a**) and dibenzoylethylene (**2a**) at the middle stage of the reaction. The peaks 1, 2, and 4 are of xylene (solvent), nitrobenzene (standard) and DBE, respectively. Before reaction, there were only these three peaks, and as the reaction proceeded, peaks, 3 and 5 appeared and became larger. They are considered to be the *trans*- and *cis*-isoxazolidines. The R_f-values of *trans*-isoxazolidine is usually larger than that of *cis*-one, and the ratio of *trans*- to *cis*-isoxazolidine is greater than 1 due to the steric effect. From these facts, peak 3 is assigned as the *trans*-isomer, and peak 5 as the *cis*-isoxazolidine. The NMR spectra of the products further supported the assignments. In all cases, the peak of DPN was not found in the HLC chart because of a strong attachment to the packing material. In some cases the relative positions of the peaks of DBE and *cis*-isoxazolidine were reversed. In the plots of $1/C$ ("C" is the concentration of DPN or DBE, and the mol-concentrations of DPN and DBE were equal to each other throughout the reaction) *vs.* the reaction time, a linear relationship was established. Therefore, the cycloaddition proved to have a second-order rate constant, first-order with respect to each reactant species.

Table 2. The second-order rate constant k and log k of the reaction of **1** with **2** (in xylene, at 60 °C)

R_3		R_1			
		NO_2	Cl	H	MeO
Cl	$k\times10^3$	1.8	2.9	4.6	4.8
	log k	−2.74	−2.54	−2.34	−2.32
H	$k\times10^3$	1.3	2.5	3.3	3.4
	log k	−2.89	−2.60	−2.48	−2.47
Me	$k\times10^3$	1.1	2.2	2.6	2.5
	log k	−2.96	−2.66	−2.59	−2.60
MeO	$k\times10^3$	1.0	1.8	2.1	3.2
	log k	−3.00	−2.74	−2.68	−2.49

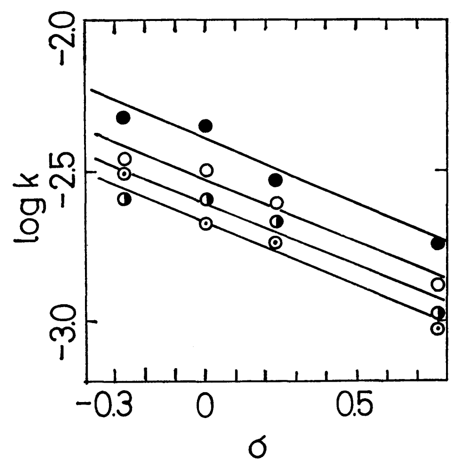


Fig. 3. The relation between the Hammett σ value of R_1 and log k.
● Cl-DBE, ○ H-DBE, ◑ Me-DBE, ⊙ MeO-DBE.

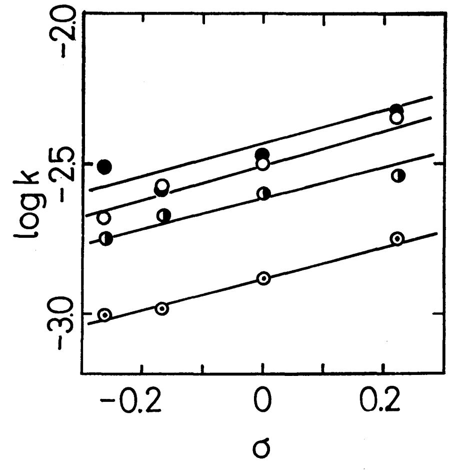


Fig. 4. The relation between the Hammett σ value of R_3 and log k.
● MeO-DPN, ○ H-DPN, ◑ Cl-DPN, ⊙ NO_2-DPN.

The second-order rate constants k and $\log k$ are shown in Table 2. Figure 3 demonstrates the dependence of the σ value of R_1 on $\log k$, and that the increasing negativity of R_1 brings about a decrease in rate. Plots of $\log k$ *vs.* the σ values of R_3 are shown in Fig. 4, which indicates the linear increase in rate when the negativity of R_3 is increased in every DPN. Thus the reaction rates are influenced by the energy difference, E_I(HOMO(1,3-dipole)–LUMO(dipolarophile)) more than E_{II}(HOMO(dipolarophile)–LUMO(1,3-dipole)). Therefore, these reactions belong to the Sustmann Type I.[8)]

According to the perturbation theory, the interaction energy (ΔE) of the HOMO–LUMO combination is approximated as follows when a reaction belongs to the Sustmann Type I.[2,13,14)]

$$\Delta E = \frac{(C_aC_d'\beta_{ad}+C_cC_e'\beta_{ce})^2}{E_I}, \qquad (1)$$

where C and C' are the coefficients of the atomic orbitals of HOMO and LUMO, respectively, and β is the resonance integral. Assuming that the two resonance integrals are equal, $\beta_{ad}=\beta_{ce}=\beta$, and setting $(C_aC_d'+C_cC_e')^2=A$, Eq. 1 is turned into the following simple equation:

$$\Delta E = \frac{A\beta^2}{E_I}. \qquad (2)$$

Since $\log k$ is proportional to ΔE, thus

$$\log k = m\frac{A\beta^2}{E_I} + q \text{ (``}m\text{'' and ``}q\text{'' are constants).} \qquad (3)$$

Here, E_I, the energy difference, is supposed to be a function of the electronic character of the substituents, R_1 and R_3. Assuming that E_I is the first-order function of σ, and setting E_0 the standard value of E_I when the σ value of the substituent is zero, we have, $E_I=E_0+n\sigma$. Thus, substituting we have

$$\log k = \frac{mA\beta^2}{E_0+n\sigma} + q\text{(``}n\text{'' is a constant).} \qquad (4)$$

This equation shows that $\log k$ is the hyperbolic function of σ. When $n>0$, increasing σ decreases the value of $\log k$ since $\log k<0$ and $mA\beta^2>0$. This relation is shown in Fig. 5-1. When $n<0$, the relation is as shown in Fig. 5-2. In each case, a linear relationship between $\log k$ and σ was observed. σ varied in the narrow range, $-0.3<\sigma<0.8$, and $\log k$ in the range $-3.00<\log k<-2.32$. These results are very sililar to the solid lines in Figs. 5-1 and 5-2, respectively.

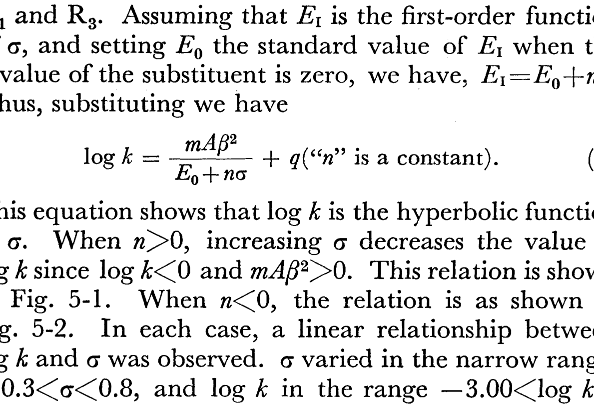


Fig. 5. The relation between $\log k$ and σ according to Eq. 4.

"n" is positive for the σ value of the substituent on a 1,3-dipole, and negative for that on a dipolarophile in Sustmann Type I reactions. In this way, $\log k$ is approximated to be the first-order function of σ in a very narrow range. Thus

$$\log k - q = \rho\sigma \text{ (``}\rho\text{'' is a constant).} \qquad (5)$$

From the experimental results, $\rho=-0.41\pm0.01$ for the σ value of the substituent R_1 and $\rho=+0.60\pm0.02$ for that of R_3 were obtained. Huisgen and coworkers have reported the linear correlation of $\log k$ ($\rho=0.77$) in the reaction of α-phenyl-*N*-methylnitrone with *p*-substituted styrene.[15)] In the reaction of symmetrical bis(*p*-substituted benzoyl)-ethylenes with *N*-(*p*-substituted benzylidene) *p*-substituted benzylamine *N*-oxide, similar correlations of $\log k$ were observed.

Experimental

N-*(*p-*Substituted benzylidene)* p-*Substituted Benzylamine* N-*Oxides(DPN).* All DPNs were prepared in the usual manner.[16)] Melting points and yields were as follows;

1a; mp; 111.0—112.0 °C yield; 40%
1b; mp; 182.0—183.0 °C yield; 34%
1c; mp; 149.0—150.0 °C yield; 45%
1d; mp; 134.5—136.0 °C yield; 27%
1e; mp; 169.0—171.0 °C yield; 63%
1f; mp; 122.0—123.5 °C yield; 24%

trans-*Bis(*p-*substituted benzoyl)ethylenes (DBE).* DBEs were prepared by the procedure of Conant and Lutz.[17—19)] It has been established that the products by this method are only of the *trans*-form. Melting points and yields were as follows;

2a; mp; 106.5—108.0 °C (lit, 111 °C) yield; 30%
2b; mp; 170.5—171.5 °C (lit, 172 °C) yield; 13%
2c; mp; 166.0—166.5 °C (lit, 167.5—168.0 °C) yield; 16%
2d; mp; 147.0—148.0 °C (lit, 148 °C) yield; 18%

Reactions of DPNs with DBEs and Formation Ratios. All the reactions were carried out by the same method. For example, the reaction of *N*-benzylidene benzylamine *N*-oxide (**1a**) with *trans*-dibenzoylethylene (**2a**) was carried out as follows; **1a** (0.985 g(0.005 mol)) and **2a** (1.180 g(0.005 mol)) were dissolved in benzene (80 ml) and refluxed for about 3 h. The reaction was carried out in the dark, since **1a** is easily decomposed by sun-light. The reaction products, *trans*- and *cis*-isoxazolidines were isolated, respectively by column chromatography (200 mesh silica gel).

The formation ratios were determined by high speed liquid chromatography. The ε_{max} value of the *trans*-form was assumed to be equal to that of the *cis*-form. For example, the ε_{max} value of the *trans*-2,3-diphenyl-4,5-dibenzoylisoxazolidine and the *cis*-form were 32400 (247 nm) and 35300 (248 nm), respectively, consequently they can be assumed equal within an 8% difference. The HLC was performed using a stainless column (4 mmϕ × 50 cm) containing TSK-Gel LS310-P10 or Wakogel LC-ODS-10K. Chloroform and hexane were used as the eluent in various mixed ratios, depending on the samples and the gels. The flow rate was 2—4 ml/min. The eluate was analyzed by a UV detector in the range 254—270 nm region.

Kinetic Procedures. The rate constants were determined by HLC under the same conditions. A small amount of nitrobenzene (0.05 ml) was added to the reaction solvent as a standard for analysis before reaction. Nitrobenzene has an ε_{max} at 252 nm, and the ε_{max} is 10000, so that only a small amount is sufficient for the standard. Moreovre, since the R_f-value was found to be near to 1 under the experimental conditions, there was no possibility for peak overlap.

The area ratio(r) of DBE peak relative to that of nitrobenzene at zero time (r_0) was obtained first. At time t, the residual concentration of DBE (C) was calculated by comparison of the area ratio (r_t) with r_0. Plots of $1/C$ *vs.* the reaction time (second) gave good linear relations, from which the second-order rate constants were obtained. The UV spectra of DBEs were as follows:

2a; $\lambda_{max}=262$ nm $\varepsilon_{max}=20000$
2b; $\lambda_{max}=272$ nm $\varepsilon_{max}=20800$
2c; $\lambda_{max}=241$ nm $\varepsilon_{max}=18300$
2d; $\lambda_{max}=275$ nm $\varepsilon_{max}=18000$

The spectra of all DBEs were satuarated at a concentration of about 10^{-4} mol/l. The concentration of samples in the detector were considered far below it, since the concentration of DBE in the reaction mixture was 1/30 mol/l in each case, a sample size was under 1 μl, and the flow rate of the eluent was about 4 ml/min. In point of fact none of the peaks of DBEs was saturated. For all DBEs, good linearity was found between the areas of the peak and the concentration under 10^{-4} mol/l.

For example, the reaction of *N*-benzylidene benzylamine *N*-oxide (**1a**) with dibenzoylethylene (**2a**) was carried out as the following; **2a** (0.236 g(0.001 mol)) was dissolved in anhydrous xylene (30 ml) containing nitrobenzene (0.05 ml). After the reaction temperature was controlled at 60 °C (±0.1), **1a** (0.197 g(0.001 mol)) was added and stirred well. At intervals of about twenty minutes, the reaction mixture was analyzed by HLC.

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