Substituent Effect of Dipole and Dipolarophile in the Reaction of Nitrones with *N*-(Substituted phenyl)maleimides

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The reactions of *C*-(*p*-substituted phenyl)-*N*-(*p*-substituted phenyl)nitrones with *N*-(*p*-substituted phenyl)maleimides were carried out in THF to give both *trans*- and *cis*-isoxazolidines. The formation ratios of *trans*- to *cis*-isoxazolidines (I_T/I_C) were determined by the NMR spectra of the cycloadduct mixtures. Though the values of I_T/I_C varied with the electronic characters of the substituents, R_1, R_2, and R_3, they were always found to be larger than unity.

In an earlier paper[1] from this laboratory we have reported on the configuration of the cycloadduct of nitrone with *N*-phenylmaleimide. In order to investigate the substituent effect of dipole and dipolarophile in the reactions of nitrones and *N*-phenylmaleimides, we have studied the reactions of nitrones having the substituents R_1 in *C*-phenyl and R_2 in *N*-phenyl groups both at the *p*-positions, with *N*-phenylmaleimide having the substituent R_3 at the *p*-position. We have found that the ratios of *trans*- to *cis*-isoxazolidines in the

Table 1. The melting points, analytical data, and ratios, I_T/I_C, of *trans*- to *cis*-isoxazolidines

Run No.	R_1	R_2	R_3	Mp[a] °C	Anal (Calcd), %			I_T/I_C
					C	H	N	
1-A[1]	H	H	H	197—199 (*cis*)	—	—	—	1.7
				153—155 (*trans*)	—	—	—	
1-B	H	H	NO_2	213—214	66.61	4.14	10.22	2.1
				194—195.5	66.50	4.18	10.19	
					(66.50	4.13	10.21)	
1-C	H	H	OCH_3	215	71.90	4.99	6.96	1.5
				191—192	71.99	4.98	6.90	
					(71.98	5.03	7.00)	
2-A	NO_2	H	H	226—228 (decomp.)	66.67	4.33	10.26	2.6
				204—207 (decomp.)	66.57	4.13	10.17	
					(66.50	4.13	10.12)	
2-B	OCH_3	H	H	193—195	72.20	5.09	7.23	1.4
				148—150	71.66	5.08	7.22	
					(71.98	5.03	7.00)	
3-A	H	CH_3	H	188—189	75.00	5.24	7.16	2.9
				170—171	74.76	5.26	7.14	
					(74.94	5.24	7.29)	
3-B	H	CH_3	NO_2	—	—	—	—	3.0
3-C	H	CH_3	OCH_3	207—208	72.41	5.36	6.63	2.4
				179	72.32	5.36	6.66	
					(72.45	5.35	6.76)	
4-A	H	*t*-Bu	H	196—197.5	76.28	6.14	6.28	2.5
				166—167	75.77	6.09	6.63	
					(76.03	6.15	6.57)	
4-B	H	*t*-Bu	NO_2	198—199	68.20	5.33	8.91	3.9
				180—182	68.13	5.43	8.91	
					(68.78	5.34	8.92)	
4-C	H	*t*-Bu	OCH_3	195—196	74.36	6.24	6.22	2.1
				179—181	73.27	6.25	6.32	
					(73.66	6.18	6.14)	
5-A	H	Cl	H	175—176 (*trans*)	68.76	4.76	6.83	3.1
					(68.23	4.23	6.92)	
5-B	H	Cl	NO_2	158—159 (*trans*)	62.00	3.91	9.35	1.6
					(61.43	3.58	9.56)	
5-C	H	Cl	OCH_3	—	—	—	—	3.6

a) Upper line for *cis*-isomer, lower line for *trans*-isomer.

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[1] Y. Iwakura, K. Uno, and T. Hongu, This Bulletin, **42**, 2282 (1969).

cycloadduct mixtures varied with the electronic character of the substituents, R_1, R_2, and R_3. The ratios of *trans*- to *cis*-isoxazolidines were determined directly by the NMR spectra of the cycloadduct mixtures. Detailed results are described in the present paper.

Results and Discussion

The reactions of *C*-phenyl-*N*-(*p*-substituted phenyl) nitrones with *N*-(*p*-substituted phenyl)maleimides were carried out in anhydrous THF to give cycloadducts in quantitative yields. In agreement with earlier work,1) the formations of *trans*- and *cis*-isoxazolidines were observed. The melting points and analytical data of *trans*- and *cis*-isoxazolidines obtained are summarized in Table 1 with the ratios of *trans*- to *cis*-isoxazolidines in the cycloadduct mixtures.

The NMR spectra of the cycloadduct mixture (run 4-B) obtained without any purification are shown in Fig. 1. Signals of each isomers were assigned as shown in the figure according to the previous paper.1)

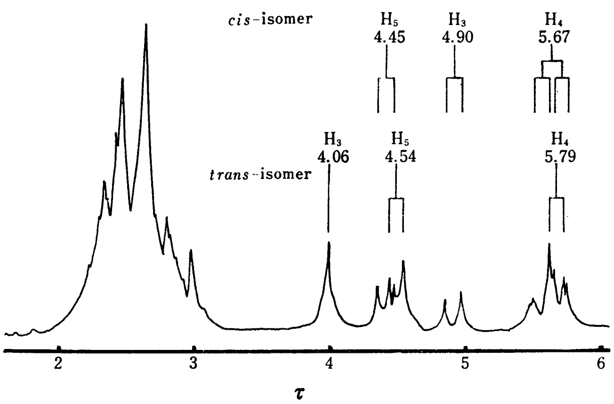
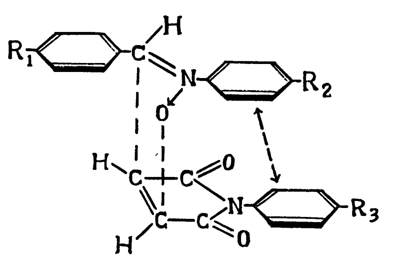


Fig. 1. The NMR spectra of cycloadduct mixture (run 4-B) in DMSO-d_6.

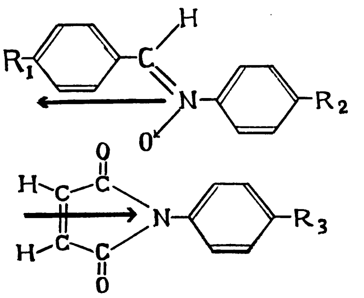
As shown in Fig. 1, proton signals at *C*-3 of isoxazolidine rings appear to be a singlet and doublet according to *trans*- and *cis*-isoxazolidines, respectively, without any overlap. Accordingly, the ratio of *trans*- to *cis*-isoxazolidines (I_T/I_C) can be directly obtained from the NMR spectral comparison, and the values of I_T/I_C thus obtained are summarized in Table 1.

The value of I_T/I_C for every 1,3-dipolar cycloaddition reaction was found to be>1, indicating that the formation of *trans*-isoxazolidine is more favorable than *cis*-isomer. Assuming the reaction of nitrone with *N*-phenylmaleimide by one step mechanism,2) $I_T/I_C>1$ reveals that addition reaction of nitrone with *N*-phenylmaleimide would proceed favorably through the above transition state as shown in Scheme 1.



Scheme 1

For establishing such a favorable transition state of the addition reaction in the present investigation, it is necessary that the dipole moments of both reaction species, dipole and dipolarophile, should orient to the arrow-signed direction as shown in Scheme 2.



Scheme 2

If the substituent R_1 of nitrone is an electron withdrawing group, the greater dipole moment is anticipated, *i.e.*, the formation of *trans*-isoxazolidine would be predominant. Eventually higher value of I_T/I_C is obtained.

Figure 2 shows the relation between the electronic characters of R_1 and the values of I_T/I_C from Table 1. An approximately linear relation appeared to exist between the Hammett σ value of R_1 and the value of log I_T/I_C. Increasing the negativities of the substituents R_1, the greater values of I_T/I_C were obtained. Such experimental facts seem to support strongly above mentioned assumptions.

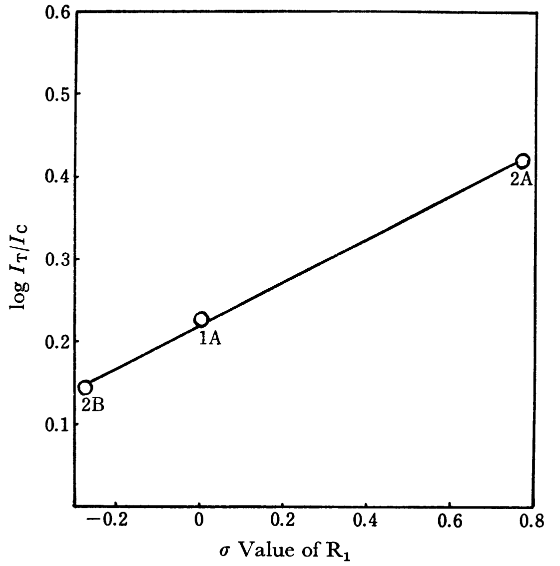


Fig. 2. The relation between the Hammett σ value of R_1 and the log I_T/I_C.
R_2=H; R_3=H.

The magnitudes of dipole moments of *N*-phenylmaleimides may depend on the electronic characters of R_3 in *p*-substituted *N*-phenylmaleimides. There are also fairly good relationships between the Hammett σ values and the values of log I_T/I_C as shown in Fig. 3.

In the series of the substitutents (R_2=H, CH_3, and

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2) R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968).

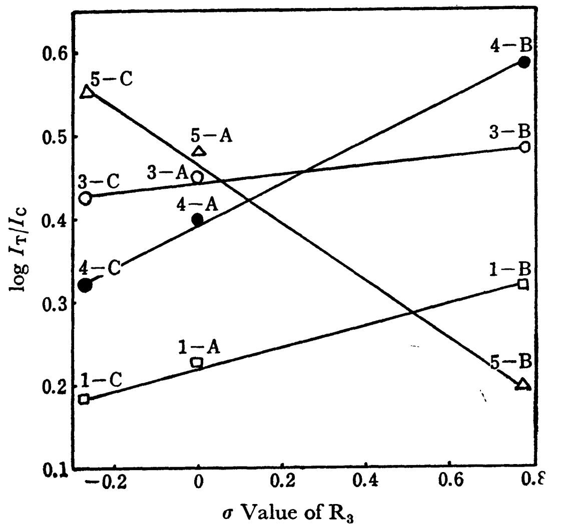


Fig. 3. The relation between the Hammett γ values of R_3 and the log I_T/I_C.
R_1=H; R_2: △=Cl, ○=CH_3, ●=t-Bu, □=H.

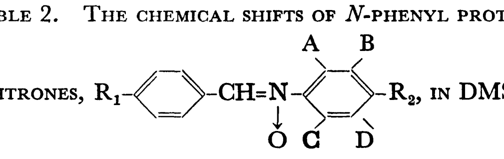
t-Bu) on N-phenyl group of nitrone, the greater electronegativities of the substituents, the greater values of I_T/I_C were obtained. These results may also appear to be consistent with that the dipole-dipole interaction between dipole and dipolarophile would influence on the formation ratios of *trans*- to *cis*-isoxazolidines. But when R_2 is Cl, the results are reversed, *i.e.*, with increase in the electro-negativities of R_3, the smaller values of I_T/I_C were obtained.

If the above mentioned assumptions are reasonable, we may draw a conclusion tentatively that the dipole moment of nitrone having the substituent, R_2=Cl, should orient to the reverse direction to those of nitrones having the substituents, R_2=H, CH_3, and t-Bu. Considering that Cl is an electron-withdrawing group, such a possible dipole orientation of a nitrone having Cl as R_2 can not be denied. We can point out one more additional possible consideration as an influencing factor on the configurations of *trans*- and *cis*-isoxazolidines in the present work. As shown in Scheme 1, at the transition state in 1,3-dipolar cycloaddition of nitrone with N-phenylmaleimide N-phenyl group of nitrone exists near enough to N-phenyl group of N-phenylmaleimide. In this event, the affinity between N-phenyl group of nitrone and N-phenyl group of N-phenylmaleimide may affect on the values of I_T/I_C. This explanation is in accordance with the fact that $I_T/I_C>1$ was always obtained as shown in Table 1. The τ values of the protons of N-phenyl group of nitrone having Cl as R_2, shifted to lower values than those of other nitrones as shown in Table 2. Such a fact may indicate clearly that the electron density of N-phenyl group of nitrone having Cl as R_2, is being much lowered. Accordingly, the affinity between N-phenyl group of N-phenylmaleimide having electron-donating R_3 and N-phenyl group of nitrone would exert to give the results as indicated in Fig. 3.

The relations between the Hammett σ values of R_2 and the values of log I_T/I_C are shown in Fig. 4.

In the series of the reaction of nitrone with N-phenylmaleimide having NO_2 as R_3, the greater electronegativities of R_2, the greater values of I_T/I_C were obtained but not linearly. But as shown in Fig. 4, in the case of R_2=H and CH_3, the results obtained were different, *i.e.*, nitrone having no substituent on N-phenyl group gave the smallest value of I_T/I_C. Nitrones having either electron donating or withdrawing group on N-phenyl group gave the greater values of I_T/I_C.

Table 2. The chemical shifts of N-phenyl protons of nitrones,



$R_1-C_6H_4-CH=N(\rightarrow O)-C_6H_4-R_2$, in DMSO-$d_6$

R_1	R_2	Position of protons		
		-CH=	A	B
H	H	2.00	1.91	2.50
H	CH_3	1.54	2.16	2.66
H	t-Bu	1.68	2.28	2.68
H	Cl	1.46	2.01	2.39

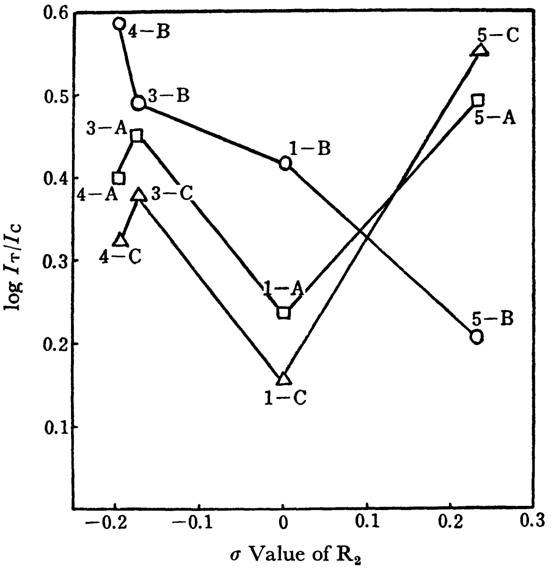


Fig. 4. The relation between the Hammett σ values of R_2 and the log I_T/I_C.
R_1=H; R_3: □=H, ○=NO_2, △=OCH_3

As we have already pointed out on the explanations of Figs. 2 and 3, the value of I_T/I_C may be influenced by following two factors: (1) dipole orientation of the dipole and dipolarophile; (2) affinity between N-phenyl group of nitrone and N-phenyl group of N-phenylmaleimide. When affinity between N-phenyl group on nitrone and N-phenyl group of N-phenylmaleimide is small, (1) will be a main factor governing the value of I_T/I_C. The results shown in Fig. 4 may not be inconsistent with this explanation. In Fig. 4, if the Hammett σ value of R_2 is positive, (2) might be assumed as a governing factor for the I_T/I_C, but if the σ value of R_2 is negative, (1) will become important. When (1) is a predominant factor governing the value of I_T/I_C, p-substituent of N-phenyl group of nitrone would come near to N-phenyl group of phenylmaleimide. It will be reasonably explained that the decrease of the value of I_T/I_C, in the case of t-Bu, is due to the steric hindrance of bulky group.

We have proceeded explanations on the results obtained in the present work, on the basis of one step addition mechanism. Further studies are under progress.

Experimental

Materials. A typical example of *C*-phenyl-*N*-(*p*-*t*-butylphenyl)nitrone was prepared in the following manner. Nitration of *t*-butylbenzene was carried out by the procedure of Ketcham.[3] The oily product, *p*-nitro-*t*-butylbenzene was obtained in 80% yield (bp, 108.5—110°C/5 mmHg), identified by the IR spectrum. Then *p*-nitro-*t*-butylbenzene was reduced to hydroxylamine by zinc dust in 65% yield by the usual manner, mp 89.5—90°C.

Found: C, 72.57; H, 8.89; N, 8.32%.

Calcd for $C_{10}H_{15}ON$: C, 72.69; H, 9.15; N, 8.48%.

The mixture of equimolar amounts of *p*-*t*-butylphenylhydroxylamine and benzaldehyde in ethanol was refluxed for three hrs. Recrystallization three times from *n*-hexane afforded white needles, *C*-phenyl-*N*-(*p*-*t*-butylphenyl)-nitrone (mp, 117—119°C) in 71% yield.

Found: C, 80.31; H, 7.39; N, 5.40%.

Calcd for $C_{17}H_{19}ON$: C, 80.57; H, 7.56; N, 5.53%.

Other nitrones, were prepared in over 70% yields by the procedure of Wheeler *et al.*[4] Their melting points were as follows: R_1=H, R_2=H, 112—113°C (lit, 114°C);[4] R_1=H, R_2=CH_3, 123°C (lit. 123°C);[4] R_1=H, R_2=Cl, 174—175°C (lit, 174°C)[5], 181°C)[4]. *N*-phenylmaleimides, R_3, were synthesized by the procedure of Searle.[6] Their melting points were as follows: R_3=H, 90—91°C (lit, 90—91°C);[6] R_3=NO_2, 167°C (lit, 167—168°C);[6] R_3=OCH_3, 146°C. The last product was a new compound and gave following analytical data.

Found: C, 64.98; H, 4.46; N, 6.89%. Calcd for $C_{11}H_9O_3N$: C, 65.69; H, 4.46; N, 6.89%.

NMR Spectra. The NMR spectra were measured in DMSO-d_6 solution (concentration: about 10% solution of the sample by weight) at room temperature with Japan Electron Optics C-60 spectrometer (60 MHz). Tetramethylsilane was used as an internal reference.

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[5] K. Kubota, M. Yamakawa, and Y. Mori, This Bulletin, **36**, 1552 (1963).

[6] N. E. Searle, U. S. 2444536 (1948).