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Nuclear Magnetic Resonance for the Pathway of the Reaction of *N*-Sulfinylanilines with Ethylene Oxide

Fukiko YAMADA, Tomihiro NISHIYAMA, Motokazu KINUGASA
and Masayoshi NAKATANI

Department of Applied Chemistry, Faculty of Engineering, Kansai University, Senriyama, Suita, Osaka

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The reaction of *N*-sulfinylanilines (I) with either ethylene carbonate or alkene oxides have been well studied in recent years. For example, Tsuge and his co-workers[1] reported that, in the presence of catalytic amounts of lithium halide, I reacted with ethylene carbonate at temperatures above 140°C to form the corresponding *N,N'*-diarylpiperazines (V). Etlis *et al.*[2] confirmed that, in the presence of NEt_4-Br, I reacted with alkene oxide at 95—100°C in sealed ampules to give 2-oxo-3-aryl-1,2,3-oxathiazolidines (III). Recently Deyrup and Moyer[3] have prepared several derivatives of III by reactions of β-amino alcohol with thionyl chloride in the presence of a base; the general structure of these compounds was determined by means of their NMR spectra. In these circumstances, we thought it desirable to study how the reaction of I with ethylene oxide (II) takes place in the absence of a catalyst and at a low temperature. In this paper, the reaction of I with II and the NMR data of the resulting products will be reported. The reaction scheme will also be discussed.

Experimental

The NMR spectra were obtained at 60 MHz with a Japan Electron Optics, Model JNM 3H-60, spectrometer. The chemical shifts were described in ppm downfield from the internal TMS (δ). The IR spectra were recorded on a Hitachi, Model EPI-2, grating spectrophotometer. The molecular-weight determination was made by a vapor-pressure osmometer, Hewlett Packard 302.

Materials. *N*-Sulfinylaniline (Ia), *N*-sulfinyl-*p*-toluidine (Ib), and *N*-sulfinyl-*p*-chloroaniline (Ic) were prepared and purified by the reported method.[4] II was of a commercially-available, pure grade and was dried by using a potassium hydroxide tube just before use. All the reagents used were of an analytical grade.

The Reaction of I with II. In a three-necked, 100-m*l* flask, 30 g of I was placed, the flask was then kept at a constant temperature. A constant flow of II (4.5 *l*/hr) was introduced into the reaction mixture throughout the reaction. The progress of the reaction was periodically checked by measuring the NMR spectrum of the reaction mixture. After the reaction had been completed and the excess II had been evaporated, a red-brown sirup remained. For the isolation of pure compounds from the mixture, the following two procedures were employed.

Procedure A. Fractionation of the Products. The above mixture (10—20 g) was chromatographed on 100 g of silica gel, using methylene chloride and methanol as eluents. Each eluate was examined by means of its NMR spectrum. The eluates which showed the same NMR spectra were combined and then evaporated *in vacuo*. The combined solutions (1, 2, and 3) were classified as follows: the initial eluate (1) was almost entirely composed of compound III, the middle one (2) contained mainly a resinous compound, IV, and the third one (3) gave small amounts of *N*-(2-hydroxyethyl)anilines (1—2 wt%). 2-Oxo-3-phenyl-1,2,3-oxathiazolidine (IIIa, 12 wt% yield) or 2-oxo-3-*p*-tolyl-1,2,3-oxathiazolidine (IIIb, 12 wt% yield) was obtained from the reaction of II with Ia or Ib. 2-Oxo-3-*p*-chloro-

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[1] O. Tsuge, S. Mataka, N. Tashiro and F. Mashiba, This Bulletin, **40**, 2709 (1967).

[2] V. S. Etlis, A. P. Sineokov and M. E. Sergeeva, *Khim. Geterotskil. Soedin*, 682 (1966).

[3] J. A. Deyrup and C. L. Moyer, *J. Org. Chem.*, **34**, 175 (1969).

[4] A. Michaelis and R. Herz, *Ber.*, **23**, 3480 (1890).

phenyl-1,2,3-oxathiazolidine (IIIc) was not isolated from the reaction of Ic. IIIa and IIIb were purified by recrystallization from methylene chloride and *n*-hexane. The analytical results and melting points of IIIa and IIIb coincided with those of the compounds previously reported.[2] The resinous compounds, IVa, IVb, and IVc, were purified by rechromatography on silica gel. IVa: 78 wt% yield, mol wt 579, Found: C, 55.83; H, 6.26; N, 6.79; S, 11.01%. IVb: 71 wt% yield, mol wt 403, Found: S, 13.41%. IVc: 85 wt% yield, mol wt 485, Found: S, 12.31%.

Precedure B. Thermal Decomposition. The mixture described above was maintained at 160°C for about 1 hr under reduced pressure, and then it was extracted with benzene. The benzene extract was evaporated to give V as a solid. This was recrystallized from benzene to give colorless needles. *N,N'*-Diphenylpiperazine (Va, 73 wt% yield), *N,N'*-di-*p*-tolylpiperazine (Vb, 56 wt% yield), and *N,N'*-di-*p*-chlorophenylpiperazine (Vc, 78 wt% yield) were obtained from the corresponding reaction mixture by Procedure B. The analytical results and melting points of Va, Vb, and Vc coincide with those of the compounds previously reported.[1]

Results and Discussion

The Reaction Process. In the case of the reaction of Ia with II, the changes in the NMR spectra with the reaction time are shown in Fig. 1. The two-proton and three-proton multiplets due to the ring protons of Ia appear in the regions of 8.0—8.2 and 7.6—7.7 ppm respectively. These signals changed with the reaction time. Of these signals, the three-proton signal changed most remarkably as a result of the overlapping of the ring-proton signal of the reaction product. The two-proton signal gradually decreased, and it disappeared when the reaction was over. However, the two-proton signal does not overlap with any other signal. Therefore, the conversion of Ia can be determined by means of the data of the integrated two-proton

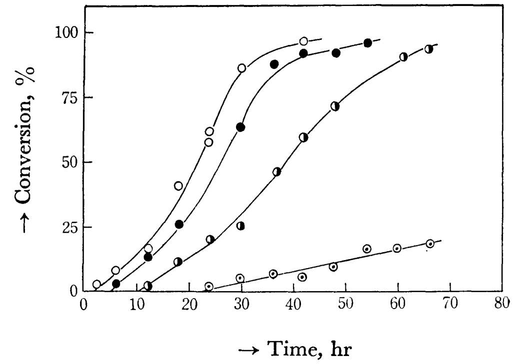


Fig. 2. Time-conversion curves at various temperatures in the reaction of Ia with II.
—○—: the reaction at 15°C
—●—: the reaction at 25°C
—◑—: the reaction at 40°C
—⊙—: the reaction at 65°C

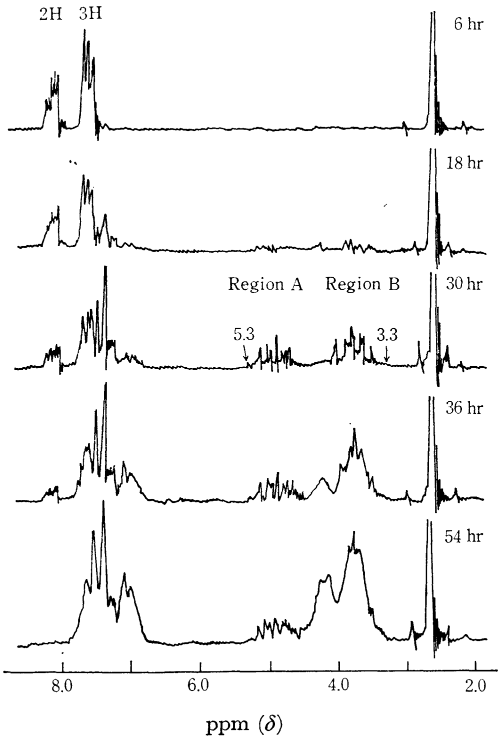


Fig. 1. Changes of the NMR spectra with reaction time at 25°C.

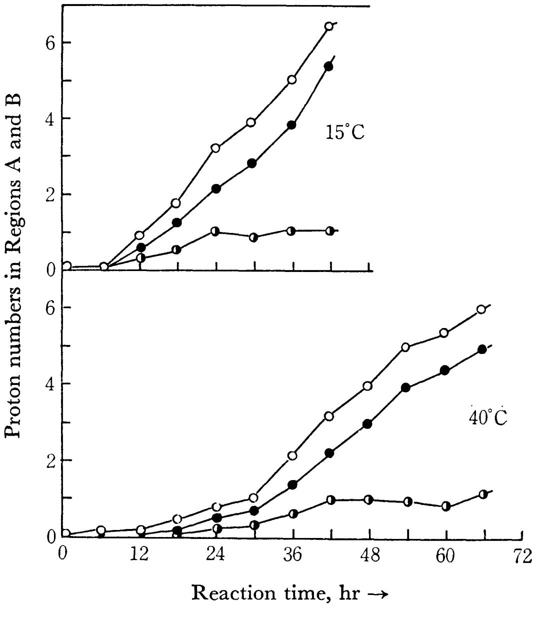


Fig. 3. Plots of the proton numbers in Regions A and B *vs.* reaction time in the reaction of Ia with II.
◑: Proton numbers in Region A; ●: Proton numbers in Region B; ○: Total proton numbers in Region (A+B).

Table 1. Spectral properties of III and IV

Compound No.	IR (S=O) cm^{-1}	NMR data, δ, ppm in CH_2Cl_2			
		methylene		aromatic ring	CH_3
		$-\overset{\vert}{N}-CH_2-$	$-O-CH_2-$		
IIIa	1172	m 3.3—4.1	m 4.3—5.2	m 6.9—7.6	
IIIb	1169	m 3.4—4.1	m 4.4—5.1	q 7.1	s 2.4
IVa	1195	m 3.2—4.5 (6.6H)*		m 6.7—7.7	
IVb	1190	m 3.3—4.5 (8.5H)*		m 6.6—7.5	s 2.4
IVc	1133	m 3.0—4.8 (9.3H)*		m 6.5—7.8	

( )*: proton numbers

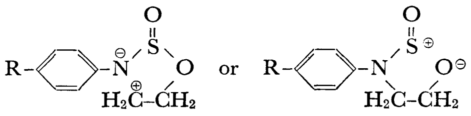
spectrum. The methylene-proton signal of II exhibits a singlet peak at 2.68 ppm. In the earlier stage of the reaction, new signals were observed in the region of 3.3—5.3 ppm and gradually increased with the reaction time. These signals consist of two parts; one (Region A) is in the region of 4.6—5.3 ppm, and the other (Region B) in the region of 3.3—4.3 ppm. The proton numbers of the signal in the A or B region can be evaluated by comparing the data of the integrated signal with those of the signals due to the phenyl protons, which are unchanged by the reaction. Plots of the conversion *versus* the reaction time and of the proton numbers in the A or B region against the time are shown in Figs. 2 and 3 respectively. The NMR data of III and IV are shown in Table 1, and the chemical shifts in the A and B regions are shown in Table 2.

Table 2. NMR data (δ) of the regions A and B

Reaction of II with	Region A	Region B
Ia	4.6—5.3	3.3—4.3
Ib	4.5—5.4	3.2—4.5
Ic	4.7—5.4	3.3—4.7

By comparing the NMR data of IIIa and IVa with those in the A and B regions, the signals in the regions can be assigned to the methylene groups of the oxathiazolidine ring produced by the reaction. The methylene proton numbers in the B region increased with the reaction time up to about 7 (Fig. 3). These facts may indicate, therefore, that the expansion of the oxathiazolidine ring is caused by the insertion of either II or IIIa into the ring.

Probable Mechanism. On the basis of the results presented above, the probable reaction pathway is that shown in Chart 1. The reaction proceeds gradually after an induction period (Figs. 2 and 3). The intermediate A may be expected to be formed in this induction period.



Intermediate A

The authors wish to thank Miss H. Nishikawa, the micro analytical laboratory of this department and the staff of the Research Laboratories, Fujisawa Pharmaceutical Co., Ltd. for the elementary analyses.

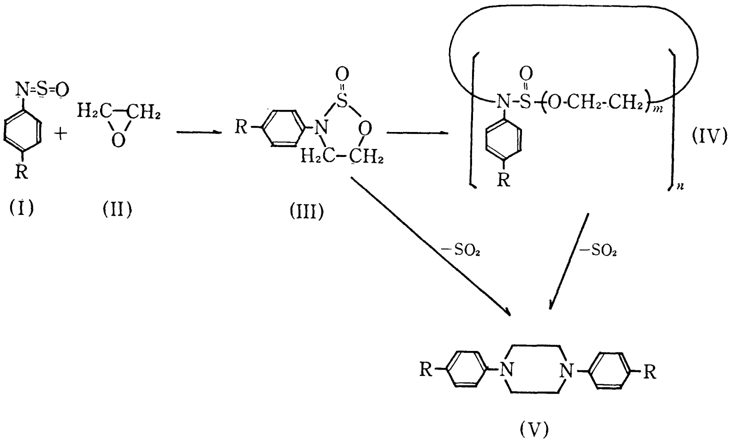


Chart 1

Ia, IIIa, IVa and Va; R=H
Ib, IIIb, IVb and Vb; R=CH_3
Ic, IIIc, IVc and Vc; R=Cl