Studies of the *cis-trans* Isomerization of 3-Aryl-1,2,3-oxathiazolidine-2-oxides

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The isomerization of the *cis*- or *trans*-3-aryl-1,2,3-oxathiazolidine-2-oxides was investigated under various conditions. The isomerization proceeded in carbon tetrachloride, chloroform, and benzyl chloride solutions at a low temperature. On the other hand, in other organic solvents, such as benzene, acetone, pyridine, *N*,*N*-dimethylformamide, and chlorobenzene, isomerization did not occur. The results can be explained by the mechanism which yields the open-chain halosulfamic acid anion by the attack of a halogen ion on the 5-position. The anion can close to *cis*- or *trans*-oxathiazolidine.

In recent years, a number of studies have been reported on the *cis-trans* isomerization of some heterocyclic compounds. For example, the *cis-trans* isomerization of 3-*t*-butyl-1,2,3-oxathiazolidine-2-oxides in the presence of tetrabutylammonium bromide results in the inversion of sulfoxide, with the preservation of the stereochemistry at the 4- and 5-carbons.[1]

Cyclic sulfoxides have also been inverted by photochemical means or by treatment with hydrogen chloride.[2,3] Cyclic sulfites have been equilibrated thermally.[4]

In a previous paper, we reported that the reaction of *N*-sulfinylanilines with propylene oxide or epichlorohydrin in the presence of catalysts led to 3-aryl-5-methyl- or 3-aryl-5-chloromethyl-1,2,3-oxathiazolidine-2-oxide respectively.[5] These oxathiazolidines exist in the *cis* and *trans* configurations between the S=O group and the methyl or chloromethyl group in the 5-position, and it is possible to determine the substituent geometry of the isomeric pairs by means of NMR spectroscopy.

This paper will describe the *cis-trans* isomerization of oxathiazolidines under various reaction conditions and a possible isomerization mechanism.

Experimental

Measurements. The NMR spectra were recorded at 60 MHz with a Japan Electron Optics JNM-3H-60 spectrometer. The chemical shifts (δ) were described in ppm downfield from the internal TMS. The change in the % age composition of the isomers was followed by the NMR method. A constant-temperature water or oil bath was employed; it was equipped with an immersion heating element that made possible a temperature control of ± 0.2 °C.

Materials. The oxathiazolidines, 3-aryl-5-methyl-1,2,3-oxathiazolidine-2-oxides (R=H **1b**, *o*-CH_3 **2b**, *m*-CH_3 **3b**, *p*-CH_3 **4a**, *o*-Cl **5a**, *m*-Cl **6b**, and *p*-Cl **7b**) and 3-aryl-5-chloromethyl-1,2,3-oxathiazolidine-2-oxides (R=H **8a**, *o*-CH_3 **9a**, *m*-CH_3 **10b**, *p*-CH_3 **11a**, *o*-Cl **12a**, *m*-Cl **13b**, and *p*-Cl **14a**) were prepared by a previously reported method.[5] *Cis* and *trans* isomers are represented by the notations of **a** and **b** respectively. All the reagents used were of an analytical grade.

Results and Discussion

Isomerization. Experiments on the isomerization of oxathiazolidines in chloroform were carried out as follows. A definite amount of oxathiazolidine was dissolved in chloroform (2.0 mol/l). This solution was then divided into test tubes and sealed. The sealed tubes were then shaken at a constant temperature, the progress of the isomerization being periodically checked by measuring the NMR spectrum. The isomerization rate of each oxathiazolidine can be obtained from the integrated data of the *cis* and *trans* 5-methyl or methine proton signals in its NMR spectrum. In the isomerization of the **6b** oxathiazolidine in chloroform, the changes in the NMR spectra with the reaction time are shown in Fig. 1. The NMR spectrum of **6b** exhibits a methyl proton signal at 1.65 ppm (d, J=6.0 Hz), one methylene signal, Ha, at 3.31 ppm (dd, t observed, J *trans*=8.5 Hz), another methylene signal, Hb, at 3.93 ppm (q, J *cis*=5.2 Hz), a methine signal at 5.26—5.68 ppm (m), and a ring proton signal at 6.8—7.34 ppm (m). In the early stages of this isomerization, new peaks appeared at 1.79 ppm (d, J=6.0 Hz), 3.78 ppm (d, J=6.3 Hz), 3.80 ppm (d, J=7.8 Hz), and 4.85—5.23 ppm (m). These new peaks gradually increased with the reaction time, and after about 2 hr the mixture reached equilibrium. These new peaks are the same as those of *cis* 3-(*m*-chlorophenyl)-5-methyl-1,2,3-oxathiazolidine-2-oxide **6a** reported previously.[5] Plots of the conversion *versus* the reaction time for the oxathiazolidines are shown in Fig. 2. These results indicate that the equilibrium

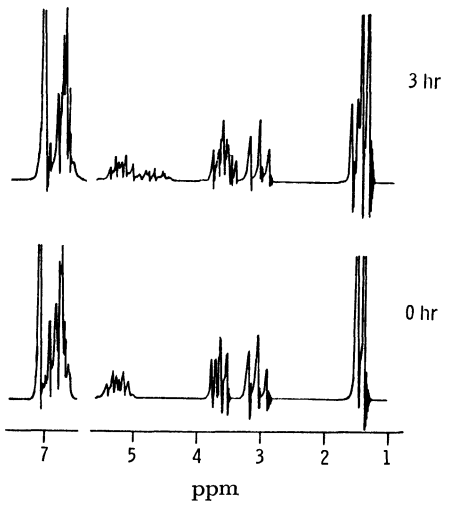


Fig. 1. Changes of the NMR spectra of **6b** with reaction time at 30 °C.

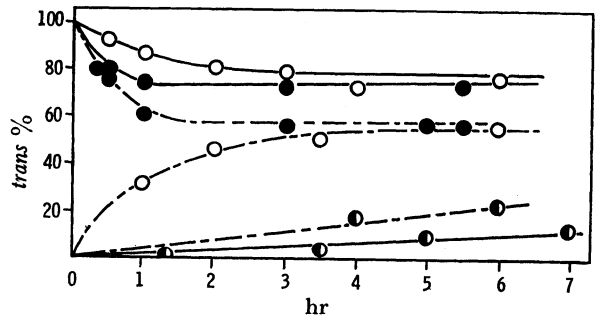


Fig. 2. Time conversion curves at 30 °C in the isomerization of the oxathiazolidines in chloroform (2.0 mol/l).

$R'=CH_3$	$R'=CH_2Cl$
—○— R=*p*-Cl	--○-- R=*p*-Cl
—◐— R=*p*-CH_3	--◐-- R=*p*-CH_3
—●— R=*m*-Cl	--●-- R=*m*-Cl

constant is influenced by the two kinds of substituents, R and R', and that the constants of the 5-chloromethyl-substituted oxathiazolidines are larger than those of the 5-methyl group.

Solvent Effects. The isomerizations of oxathiazolidines at 30 °C in various solvents, such as carbon tetrachloride, chloroform, benzyl chloride, acetone, pyridine, benzene, chlorobenzene, and *N,N*-dimethylformamide, were carried out in sealed tubes. From the results obtained, it was found that the isomerization rates of the oxathiazolidines depend upon the nature of the organic solvent. Figure 3 shows plots of the *trans* content *versus* the reaction time of **6b** in various organic solvents (2.0 mol/l). As is shown in Fig. 3, the isomerization proceeded in carbon tetrachloride, chloroform, and benzyl chloride solutions. On the other hand, in other organic solvents, such as benzene, acetone, pyridine, *N,N*-dimethylformamide, and chlorobenzene, the isomerization did not occur. These facts may indicate, therefore, that the solvents containing active halogen atoms markedly affect the isomerization of the *cis* or *trans* oxathiazolidines. In the case of chlorobenzene, the chlorine atom is stabilized by resonance with the benzene ring. The oxathiazolidine ring interacts with a chlorine atom of the solvent, and then the *cis-trans* isomerization occurs.

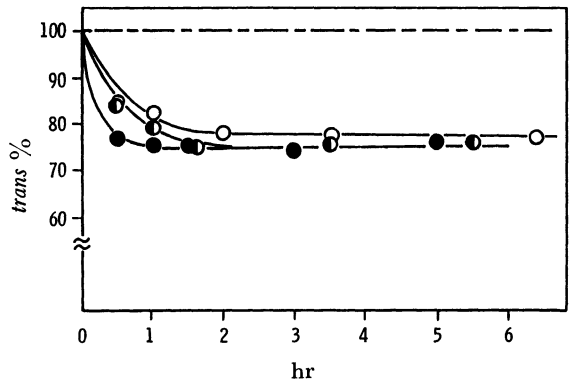
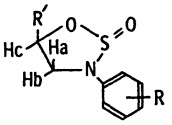


Fig. 3. Time conversion curves in various solvents in the isomerization of **6b**.

—○— $C_6H_5CH_2Cl$
—●— CCl_4
—◐— $CHCl_3$
------ C_6H_6, $(CH_3)_2CO$, C_5H_5N, and DMF

Table 1. Equilibrium constants for *cis* and *trans* oxathiazolidines in chloroform in the presence of NEt_4Br at 40 °C



Compd. No.	R	R'	Starting config	*K*
1b	H	CH_3	*trans*	0.47
	H	CH_3	*trans*	0.47[a]
2b	*o*-CH_3	CH_3	*trans*	0.69
4a	*p*-CH_3	CH_3	*cis*	1.53
5a	*o*-Cl	CH_3	*cis*	1.02
6b	*m*-Cl	CH_3	*trans*	0.37
7b	*p*-Cl	CH_3	*trans*	0.40
	p-Cl	CH_3	*trans*	0.39[a]
8a	H	CH_2Cl	*cis*	1.46
10b	*m*-CH_3	CH_2Cl	*trans*	0.68
11a	*p*-CH_3	CH_2Cl	*cis*	1.36
12a	*o*-Cl	CH_2Cl	*cis*	1.20
13b	*m*-Cl	CH_2Cl	*trans*	0.69

a) solvent: *N,N*-dimethylformamide, catalyst: LiCl.

The Effect of Catalysts. Catalytic isomerizations at 40 °C were carried out by a procedure similar to that used in the absence of catalysts. The results under the influence of lithium chloride (LiCl) and tetraethylammonium bromide (NEt_4Br) are given in Table 1 in terms of the equilibrium constants. In all the cases, equilibrium was reached within 20 min. The results indicate that the *trans* isomer is more stable than the *cis* isomer. This is also brought out clearly by a comparison of the values of the equilibrium constants shown in Table 1.

In an *N,N*-dimethylformamide solution, the isomerization did not occur in the absence of a catalyst, but it proceeded rapidly in the presence of LiCl.

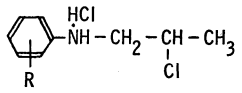
It is well known that the chloride ion equilibrates cyclic sulfoxides[6] and alkoxysulfonium salts.[7] It can, therefore, be thought that the halogen ion is related to the isomerization of oxathiazolidines.

The present isomerization is further illustrated by the action of dry HCl. When a sample of oxathiazolidine in a benzene solution was exposed to a trace amount of dry HCl at room temperature, equilibrium was reached within 5 min in all cases. For example, when a sample of the pure *trans* oxathiazolidine, **6b**, was exposed to dry HCl, the equilibrium composition was 74% *trans* and 26% *cis*, based on the integration of the NMR signal of the methyl protons. After the reaction

Table 2. *cis-trans* Isomerization ratio by the action of dry HCl

Compd. No.	Before reaction *trans* : *cis*	After reaction *trans* : *cis*
4a	0 : 100	68 : 32
6b	100 : 0	74 : 26
7b	94 : 6	74 : 26
14a	0 : 100	62 : 38

Table 3. Reactions of oxathiazolidines with dry HCl



Reaction of dry HCl with	Mp °C	Yield %	% C	% H	% N	% Cl
4a	132—134	79	54.81 (54.54)	6.93 (6.81)	6.41 (6.36)	31.83 (32.27)[a]
6b	104—106	78	44.93 (44.90)	5.10 (4.98)	5.89 (5.82)	44.21 (44.28)
7b	123—127	72	45.25	5.17	5.86	43.85

a) Calcd value.

Table 4. Isomerization for *cis* and *trans* oxathiazolidines at higher temperature

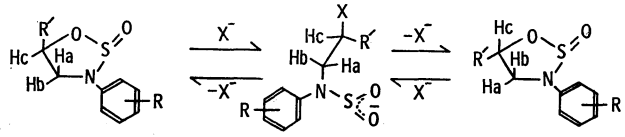
Compd. No.	Solvent	Conditions °C	Time hr	*trans* %	*cis* %
1b	—	100	8	100	0
	—	120	10	66	34
	C_6H_6	100	15	100	0
	C_6H_6	120	13	68	32
	CH_3CN	120	15	100	0
	$(CH_3)_2NCHO$	120	16	67	33
4a	—	100	8	0	100
	CH_3CN	120	4.5	55	45
6b	—	100	7	100	0
8a	—	100	8	0	100
	—	120	12	22	78
	C_6H_6	100	15	0	100
	C_6H_6	120	12	0	100
	CH_3CN	100	3	56	44
	C_5H_5N	100	3	57	43
	$(CH_3)_2NCHO$	100	3	56	44
10b	—	100	14	100	0
	CH_3CN	120	6	100	0
13b	—	100	7	100	0

mixture had reached equilibrium, the temperature was raised to 80 °C. More dry HCl was passed through until a precipitate appeared. The precipitate was subsequently filtered and recrystallized with chloroform to give a colorless crystal (mp 104—106 °C; 78%), which was identified as *N*-(β-chloropropyl)-*m*-chloroaniline hydrochloride. These results are summarized in Tables 2 and 3.

Effect of Temperature. The effects of the temperature and of the solvents are given in Table 4. In all of the oxathiazolidines, the isomerization did not occur below about 100 °C. As is shown in Table 4, the isomerization proceeded at about 120 °C.

For the isomerizations of the *trans* oxathiazolidines, **1b** and **10b**, the polar solvents have no appreciable effect. On the other hand, in the *cis* oxathiazolidines, **4a** and **9a**, the isomerization occurs rapidly. Therefore, it is clear that the isomerization is affected by the starting *cis*- or *trans*-form rather than by the R and R′ substituent at higher temperatures.

Possible Isomerization Mechanism. On the basis of the results mentioned above and other considerations,[1] a possible reaction mechanism for the isomerization can be described as follows:



cis-form anion *trans*-form

X: halogen

The above open-chain halosulfamic acid anion may be expected to be formed by the attack of the halogen ion, which is produced from the solvent or the catalyst. Then, this anion can become close to *cis*- or *trans*-oxathiazolidine.

A similar mechanism involving a bromosulfite anion has been proposed in the reaction of oxirans with sulfur dioxide in the presence of NEt_4Br.[8]

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