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2-Chloro-1,3,5-trithiane and 2-Chloro-1,3-dithiane. Their Ionic Dissociation and Reactions with Nucleophiles

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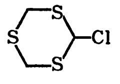
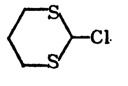
2-Chloro-1,3,5-trithiane and 2-chloro-1,3-dithiane have been prepared by chlorination of the corresponding polythianes with *N*-chlorosuccinimide. These chlorides afford various substitution products when treated with nucleophiles, whereas nuclear substitution of the aromatic ring occurs when the chlorides are treated with phenol or *N*,*N*-dimethylaniline. ^{1}H NMR spectra of these chlorides show remarkable solvent dependence which is explained by assuming ionic dissociation of the chlorides to produce polythianyl cation and chloride anion. Free energies of activation for the dissociation in various solvents indicate that the dissociation of 2-chloro-1,3,5-trithiane is more sluggish than that of 2-chloro-1,3-dithiane. The results are attributed to the difference in availability of electrons on the sulfur atoms in two systems.

Derivatives of 1,3,5-trithiane and 1,3-dithiane have been found to show interesting stereoselectivities in reactions.[2–5] 2-Benzoyloxy-1,3,5-trithiane derivatives exhibited strong preference for the axial attack of nucleophiles and solvent-dependence of the stereoselectivity was partially attributed to the intermediacy of ion pairs.[3] Chloride ion, being a more effective leaving group than benzoate ion, may modify the reactivity and stereoselectivity of the trithiane and dithiane derivatives. And, if the reactivity is enhanced, there is a chance that an unusual phenomenon is observed.

Thus, 2-chloro-1,3,5-trithiane (**1**) and 2-chloro-1,3-dithiane (**2**) were prepared and their reactivities were examined. This paper describes the results of such studies together with a study on anomeric effect in these compounds as an extension of previous works[6–8] with the polythiane derivatives.



(**1**)



(**2**)

Experimental

NMR Measurement. The ^{1}H NMR spectra were recorded on a Hitachi R 20B spectrometer, operating at 60 MHz, with a temperature variation accessory. Temperature was read by the chemical shift differences between protons of methanol for lower temperatures and by those of ethylene glycol protons for higher temperatures than 34 °C. ^{13}C NMR spectra were obtained on a Varian CFT-20 spectrometer with a temperature variation accessory.

Kinetic Parameters. The rate constants of the exchange processes at the coalescence temperature were obtained by applying the following equation[9]

$$k_c = \frac{\pi}{\sqrt{2}}\sqrt{6J_{AB}^2+\nu_{AB}^2}$$

where J_{AB} is the coupling constant of the AB protons in positions 4 and 6 and ν_{AB} the chemical shift difference of those protons. The coalescence of the AB type signals was observed for compound **2** by irradiating the signals due to protons in position 5. Free energies of activation were obtained by the usual method.

Chlorination. To a suspension or solution of 0.5 g of 1,3,5-trithiane or 1,3-dithiane in 10 ml of benzene, which had been dried over sodium, powdered *N*-chlorosuccinimide (1.1 equivalents) was added during a 15 min period at 20 °C with stirring under a nitrogen atmosphere. Stirring was continued for 15 min after completion of the addition. The reaction mixture was filtered to remove insoluble materials, contact with moisture being avoided as completely as possible. Since attempted isolation of the resulting chlorides failed because of their high reactivities, the filtrate was directly submitted to some reactions. Spectra of chlorides in other solvents were obtained after evaporation of the filtrate *in vacuo* followed by dissolving the residue in appropriate solvents.

Benzenethiolysis. The benzene solution was treated with 2—3 equivalents of benzenethiol at room temperature for 2—3 hr and the resulted mixture was evaporated *in vacuo*. Recrystallization from hexane gave 2-phenylthio-1,3,5-trithiane (**3**), mp 122—123 °C (lit. 123.0—123.5 °C)[6] and 2-phenylthio-1,3-dithiane (**4**), mp 58—59 °C (lit. 59 °C),[10] in 80 and 90% yields, respectively.

Reaction with Imidazole. The benzene solution of the chloride was treated with 2 equivalents of imidazole and the mixture was allowed to stand overnight. The whole was washed with water, and the benzene layer dried over magnesium sulfate. Chromatography on silica gel afforded 2-(1-imidazolyl)-1,3,5-trithiane (**5**), mp 174.5—175.5 °C, and 2-(1-imidazolyl)-1,3-dithiane (**6**), mp 139.5—140.5 °C, in 75 and 90% yields, respectively.

5. Found: C, 35.22; H, 3.99; N, 13.79; S, 47.10%. Calcd for $C_6H_8N_2S_3$: C, 35.27; H, 3.95; N, 13.71; S, 47.07%. ^{1}H NMR (δ CDCl$_3$); 4.17 and 4.25 (4H, q, J=15.5 Hz), 6.27 (1H, s), 7.14 (1H, m), 7.27 (1H, m), 7.86 (1H, m).

6. Found: C, 45.42; H, 5.41; N, 15.00; S, 34.68%. Calcd for $C_7H_{10}N_2S_2$: C, 45.13; H, 5.41; N, 15.04; S, 34.42%. ^{1}H NMR (δ, CDCl$_3$): 1.8—2.3 (2H, m), 2.8—3.0 (4H, m), 5.98 (1H, s), 7.14 (1H, m), 7.35 (1H, m), 7.94 (1H, m).

Reaction with Succinimide. To a reaction mixture obtained by treating polythianes with *N*-chlorosuccinimide as above, was added 3—5 equivalents of triethylamine and the whole was allowed to stand overnight. The mixture was washed with water and the benzene layer separated. The solution was dried over magnesium sulfate and evaporated *in vacuo*. Chromatography of the residue on silica gel afforded 2-(*N*-succinimidyl)-1,3-5,trithiane (**7**), mp 148—149 °C, and 2-(*N*-succinimidyl)-1,3-dithiane (**8**), mp 101—101.5 °C, in 70 and 75% yields, respectively.

7. Found: C, 35.78; H, 3.95; N, 5.65; S, 40.74%. Calcd for $C_7H_9NO_2S_3$ C, 35.74; H, 3.86; N, 5.95; S, 40.83%. ^{1}H NMR (δ, CDCl$_3$): 2.79 (4H, s), 4.02 and 4.76 (4H, q, J=14 Hz), 6.24 (1H, s).

8. Found: C, 44.08; H, 4.94; N, 6.43; S, 29.45%. Calcd for $C_8H_{17}NO_2S_2$: C, 44.22; H, 5.10; N, 6.45; S, 29.51%. ^{1}H NMR (δ, CDCl$_3$): 1.8—2.3 (2H, m), 2.6—3.0 (2H, m), 2.74 (4H, m), 3.24—3.7 (2H, m), 6.06 (1H, s).

Reaction with Phenol. The benzene solution of the crude chloride was mixed with 7 ml of phenol at 41 °C and allowed to stand at room temperature overnight. The volatile materials were removed by distillation *in vacuo* and the residue was recrystallized from chloroform or acetone to give 2-(*p*-hydroxyphenyl)-1,3,5-trithiane (**9**), mp 183—184 °C, and 2-(*p*-hydroxyphenyl)-1,3-dithiane (**10**), mp 149—150 °C, in 50 and 75% yields, respectively.

9. Found; C, 46.87; H, 4.58%. Calcd for $C_9H_{10}OS_3$: C, 46.93; H, 4.38%. ^1H NMR (δ, $CDCl_3$): 4.00 and 4.51 (4H, q, J=15.5 Hz), *ca.* 4.8 (1H, s), 5.22 (1H, s), 6.82 and 7.31 (4H, q, J=9 Hz).

10. Found: C, 56.49; H, 5.60; S, 29.92%. Calcd for $C_{10}H_{12}OS_2$: C, 56.57; H, 5.70; S, 30.20%. ^1H NMR (δ, $CDCl_3$): 1.7—2.3 (2H, m), 2.85—3.1 (4H, m), 5.11 (1H, s), *ca.* 5.2 (1H, s), 6.76 and 7.32 (4H, q, J=8.5 Hz).

Reaction with N,N-*Dimethylaniline.* The benzene solution of crude **2** was mixed with 2.5 ml of *N*,*N*-dimethylaniline and the mixture was allowed to stand at room temperature overnight. The volatile materials were distilled off *in vacuo* and the residue was recrystallized from acetone to give 2-(*p*-*N*,*N*-dimethylaminophenyl)-1,3-dithiane (**11**), mp 115.5—116.5 °C, in 30% yield. Found: C, 59.99; H, 6.86; N, 5.95; S, 26.89%. Calcd for $C_{12}H_{17}NS_2$: C, 60.21; H, 7.16; N, 5.85; S, 26.78%. ^1H NMR (δ, $CDCl_3$): 1.7—2.3 (2H, m), 2.85—3.1 (4H, m), 2.92 (6H, s), 5.11 (1H, s), 6.77 and 7.32 (4H, q, J=8.5 Hz).

Results

Preparation and Conformation of Chloropolythianes. Chlorinations of 1,3,5-trithiane and 1,3-dithiane were carried out with the use of *N*-chlorosuccinimide in benzene under the conditions of α-chlorination of sulfides.[11] Since **1** and **2** were found to react readily with the atmospheric moisture, the reaction mixture was used after filtration of succinimide for spectral measurement and for reactions. The purity of **1** and **2** was checked by ^1H NMR spectra and found to be 90—95%. The yield was estimated to be 90—95% from the ^1H NMR spectra. The following ^1H NMR data were recorded at room temperature (δ, C_6H_6): **1**, 5.52 (1H, s), 2.91 and 4.56 (4H, q, J=15.0 Hz); **2**, 5.76 (1H, s), 2.64 (4H, m), 1.58 (2H, m).

The ^1H NMR spectra of these chlorides were obtained at −80 °C to avoid possible complexity of various origins. A carbon disulfide solution of **1** exhibited signals at δ 6.21 (1H, s) and 5.08 and 3.72 (4H, q, J=15 Hz), whereas that of **2** complex signals (Fig. 1) and a singlet at δ 6.02 (1H, position 2). The coupling constants and chemical shifts involving the protons in 4 and 6 positions obtained by the first order analysis are given in Table 1. The spectra of **1** and **2** in carbon disulfide at −30 °C were essentially the same with those at −80 °C.

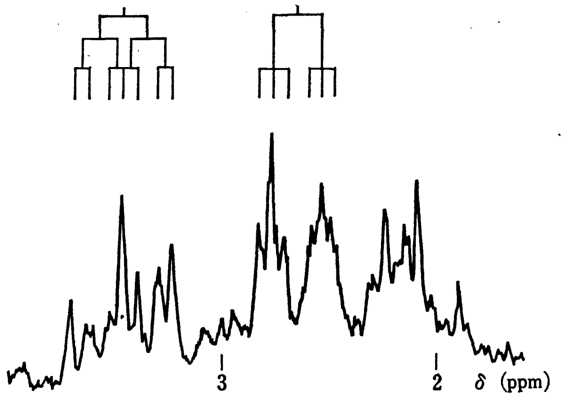
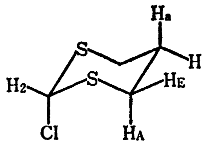


Fig. 1. First-order analysis of ^1H NMR signals due to 4,6-protons of **2** in carbon disulfide at −80 °C.

Table 1. ^1H NMR data of **2** in carbon disulfide at −80 °C, as analyzed in Fig. 1.



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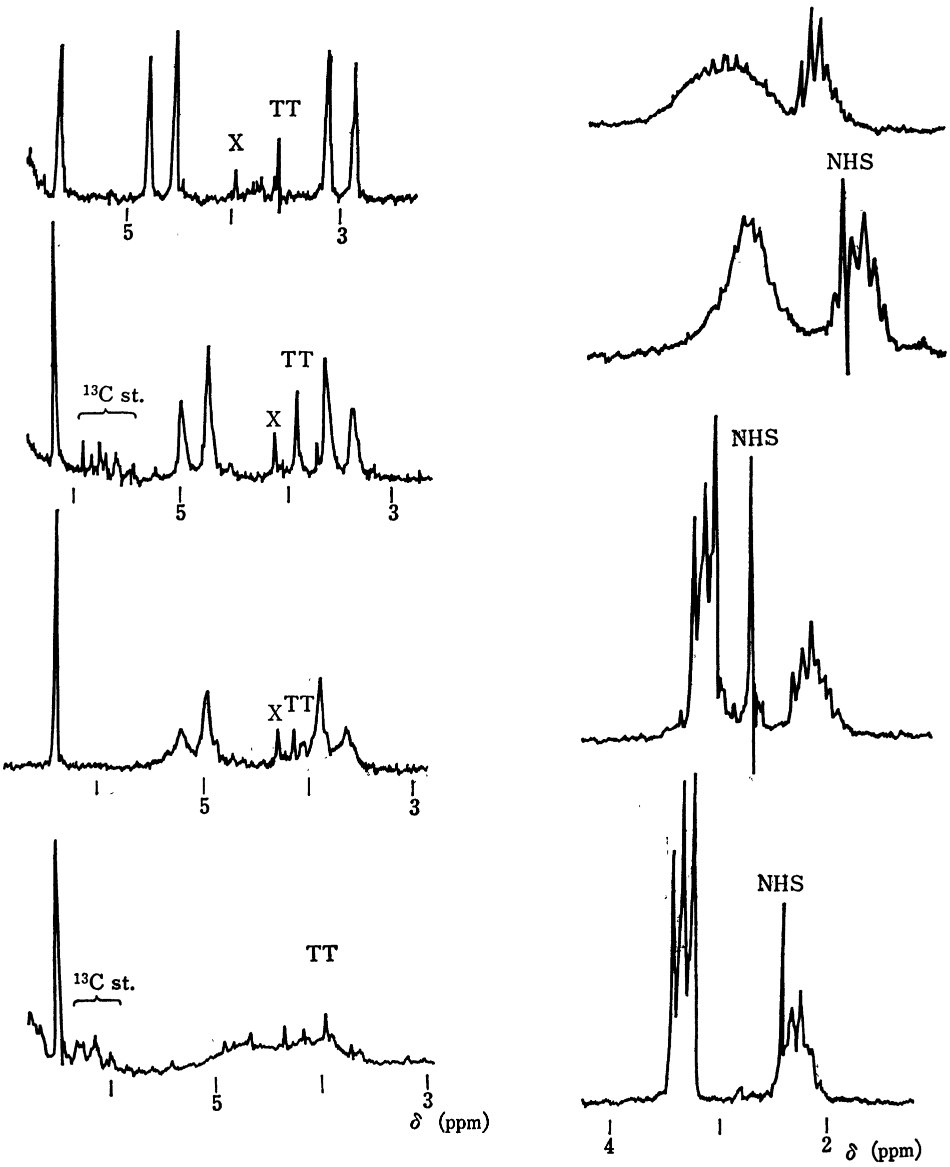
Coupling constants		Chemical Shifts	
Assignment	Hz	Assignment	δ
J_{aE}	3	H_E	2.66
J_{eE}	3	H_A	3.49
J_{aA}	10.5∼11		
J_{eA}	3.5		
J_{AE}	14		

Solvent and Temperature Dependence of NMR Spectra. ^1H NMR spectra of **1** and **2** were remarkably affected by the solvent. Some of the typical results are shown in Fig. 2. With sulfur dioxide solutions of **2**, the following NMR data were obtained at −50 °C: ^1H NMR (ppm from external TMS), 2.27 (2H, m),

Table 2. ^1H NMR data and thermodynamic parameters for the ionic dissociation of **1** and **2**

Compound	Solvent	J_{AB}(Hz)	$\Delta\nu_{AB}$(Hz)	T_c(°C)	k_c(s^{-1})	$\Delta G_c^{\ddagger}$(kc al/mol)
1	C_6H_6	15	98	>80	1.9×10^2	>17.1
	o-$Cl_2C_6H_4$	15	78	106	1.9×10^2	18.5
	$CDCl_3$	14.5	74	>60[a)]	$1.7_5\times10^2$	>16.2
	$C_6H_5NO_2$	14	72	40	1.8×10^2	15.1
	$(CH_3)_2SO$	—	—	<20	—	<14.2[b)]
2	CS_2	14	51	33±3	$1.3_0\times10^2$	15.0
	C_6H_6	—	—	≤ 0	—	≤13.5[b)]

a) From the line-broadening, the coalescence temperature was roughly estimated to be 85 °C. Then $\Delta G_c^{\ddagger}$ becomes *ca.* 17 kcal/mol. b) These values are derived by using coupling constants and chemical shifts in other solvents: the data used for **1** are those obtained with *o*-dichlorobenzene solution.



a) **1** at 35 °C. From top to bottom: in C_6H_6, in o-$Cl_2C_6H_4$, in $CDCl_3$, and in $C_6H_5NO_2$. Signals marked X and TT are due to impurities and 1,3,5-trithiane, respectively, and ^{13}C st signals are carbon-13 satellites of the solvents.

b) **2** at 32 °C, except for sulfur dioxide solution (at −40 °C). From top to bottom: in CS_2, in C_6D_6, in $CDCl_3$, and in SO_2. The signals marked NHS are due to succinimide.

Fig. 2. Solvent dependence of ^{1}H NMR spectra.

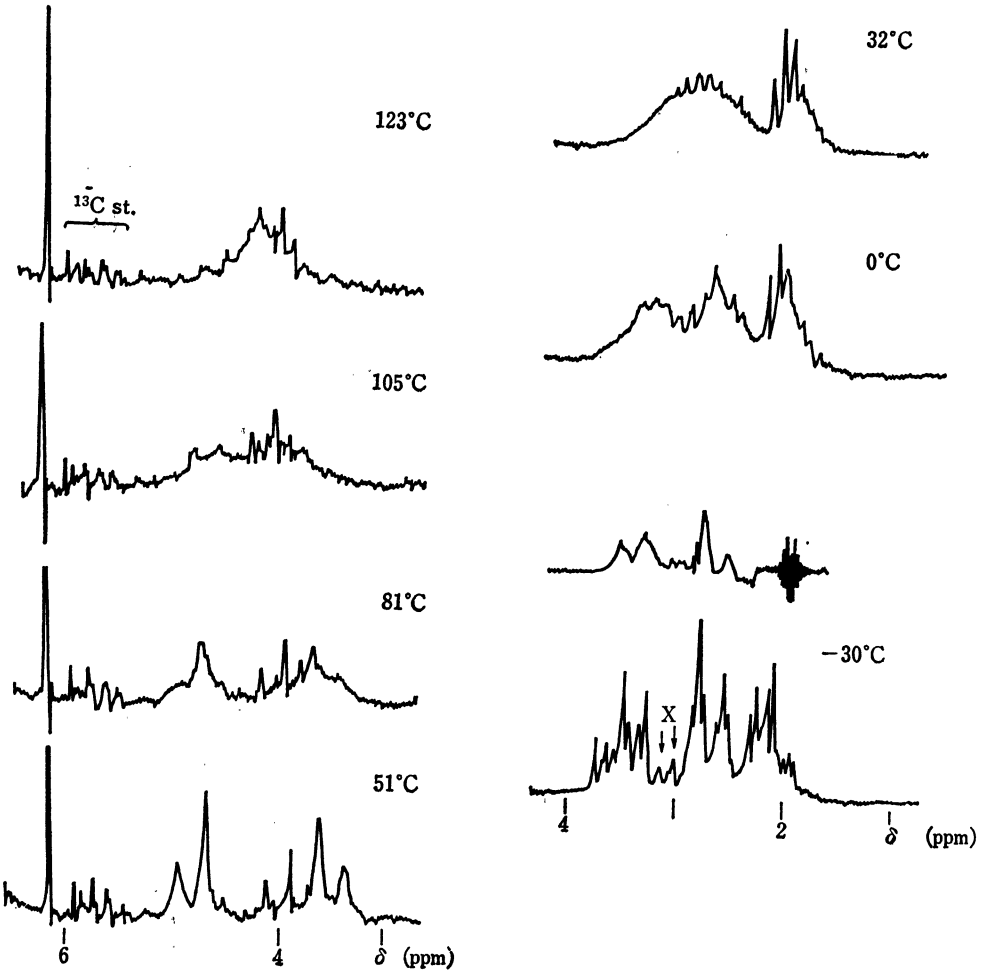
3.30 (4H, m), 10.65 (1H, s); ^{13}C NMR (ppm from external TMS), 16.0 (5-C), 30.5 (4, 6-C), 184.5 (2-C). The ^{13}C NMR spectra were essentially the same within the temperature range of −50∼0 °C.

In general, there seems to be an exchange process for both compounds and the process is faster in more polar solvents.

On raising the temperature, we observe spectra to become simplified (see Fig. 3), although decomposition takes place to some extent and lines due to impurities appear. The spectra at low temperatures are roughly reproducible when the temperature is lowered again. The results suggest that the exchange process becomes fast at the higher temperature. The coalescence temperatures (T_c), exchange rate constants at T_c (k_c) and the free energies of activation at T_c ($\Delta G_c^{\neq}$) obtained with various solvents are given in Table 2.

The process is unimolecular because the spectra were little affected by concentration in the range of 0.08—0.65 M. The process is not quenched by addition of potassium carbonate to remove a minute amount of hydrogen chloride which is produced by hydrolysis of **1** or **2** by moisture.

Reactions. Since the chlorides **1** and **2** were not stable, these were treated with nucleophiles and the products were analyzed and characterized. As expected, reaction with benzenethiol led to the formation of 2-phenylthio derivatives and those with imidazole and succininimide afforded the corresponding 1-

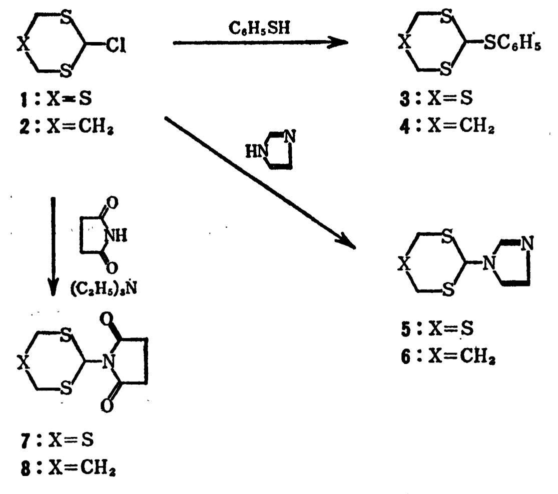


a) **1** in *o*-dichlorobenzene. Signals marked X and TT are due to impurities and 1,3,5-trithiane, respectively, and those marked ^{13}C st are carbon-13 satellites of the solvent.

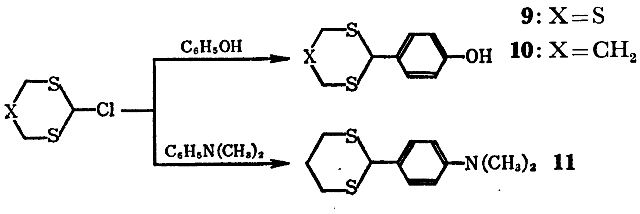
b) **2** in carbon disulfide. Signals marked X are due to impurities. The second spectrum from the bottom is obtained by irradiating signals due to 5-methylene protons at −30 °C.

Fig. 3. Temperature dependence of ^{1}H NMR spectra.

imidazolyl and succinimidyl derivatives respectively.

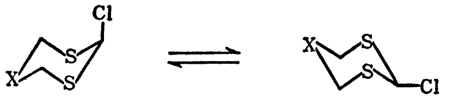


Of interest were the reactions with aromatic compounds which are rich in electron densities. Reactions with phenol and *N*,*N*-dimethylaniline in benzene afforded nuclear substitution products: polythianyl group entered in the *para* position of the electron-donating groups.



Discussion

Observed solvent and temperature effect on the ^{1}H NMR spectra might be explained by the normal ring inversion leading to an equilibrium (Eq. 1) between equatorial and axial isomers of the chloro compounds. Thus it is necessary to discuss the conformation of these compounds.



(1)

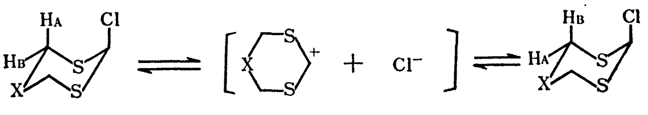
Inspection of the ^{1}H NMR spectral data of **1** and **2** in carbon disulfide at −80 °C reveals that there is only one stable conformer for each compound under the conditions: although the temperature of −80 °C is usually low enough to freeze the ring inversion of the trithiane ring,[12] no signals attributable to another conformer are found. The complex spectrum of **2** is the reflection of freezing of the inversion of the dithiane ring. The conformer can either be equatorial or axial, in principle. However, for the following reasons, the conformer will best be assigned to the axial.

Firstly, it is known that strong anomeric effect operates in trithianes.[6,7] 2-Benzoyloxy-1,3,5-trithiane exists as an axial conformer exclusively. The chloro group, being more effective in giving anomeric effect than the benzoyloxy,[13] must destablize the equatorial form to a greater extent. Secondly, assuming the axial conformer explains the ^{1}H NMR data better.[14] In 1,3,5-trithianes, an equatorial proton in 2-position, where a substituent is borne, is known to give a signal height of 0.8—1.2 if an average height of the AB quartet signals due to protons in 4- and 6-positions is taken as unity. The relative height of a signal due to an axial form, on the other hand, is 1.4—1.6. This owes to the presence of the long-range W-letter coupling by which the equatorial proton gives a broader signal. The observed relative signal height of 0.8 for the 2-proton of **1** is consistent with the conformation which has the proton equatorially and the chloro group axially. It is also known that, in 1,3,5-trithiane series, if a substituent in 2-position is axially oriented, the axial protons in 4- and 6-positions are deshielded by the anisotropy effect of the axial bond and the difference in chemical shifts of the AB protons in 4- and 6-positions amounts to 1.20 ppm or more. On the other hand, the equatorial substituent gives little effect to the chemical shifts of 4- and 6-protons. As a result, the difference in chemical shifts of AB protons in the equatorial conformer is less than 0.65 ppm. The observed difference of 1.36 ppm must be an indication that the conformation is axial.

^{1}H NMR spectrum of **2** showed complex signals but could be analyzed by the first order approximation. It must have been impossible to analyze by a conventional method if the two conformers coexisted. The chemical shifts of the axial and equatorial protons in 4- and 6-positions listed in Table 1 are consistent with the presence of the axial conformer, the difference being 0.83 ppm. It is also more plausible to assume the overwhelming presence of the axial isomer from the analogy of the trithiane compound **1**.

Since raising the temperature did not give any sign of the presence of the equatorial isomer but causes sudden broadening of the signals in NMR spectra, the conformational equilibrium may be taken to be one-sided in favor of the axial isomer. That essentially the same ^{1}H NMR spectra were obtained at −80 °C and at −30 °C is a support for the presence of one isomer only because the ring inversion of 1,3,5-trithianes usually causes coalescence of signals at about −60∼−40 °C. Since the equatorial isomer is not detected by the present technique, the free energy difference between the axial and the equatorial conformations must be over 1.7 kcal/mol at −50 °C.

Then it becomes necessary that the cause for the line-broadening of the ^{1}H NMR signals be sought in other processes than the ring inversion (Eq. 1). The exchange is not a kind of ionic process catalyzed by proton since the addition of potassium carbonate to the system did not affect the rate. Yet, the solvent effect that the rate of exchange is larger in polar solvents strongly suggests the process is of ionic nature. Two possibilities arise to account for the phenomenon. The first is the dissociation of the chloride into the polythianyl cation (**12**) and chloride ion (Eq. 2) and the second is that into the chloropolythianide anion (**13**) and proton (Eq. 3). The second possibility cannot be ruled out without convincing evidence because the anion (**13**) must be stable due to delocalization of the negative charge over chlorine and two sulfur atoms.[15]



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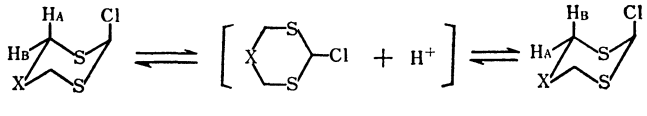

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(3)

NMR spectra of the ionic species, if we could generate it to, at least, a significant extent, should shed light on this problem. Sulfur dioxide was chosen as a solvent, because it is strongly ionizing. Both the ^{1}H NMR and ^{13}C NMR spectra of **2** at −50 °C exhibited a signal at a very low field, 10.65 and 184.5 ppm from external TMS, respectively. The results unambiguously indicate that the dissociation according to Eq. 2 takes place in sulfur dioxide solution at −50 °C. As to the extent of the dissociation, we feel it is almost complete because the spectra are essentially the same although the temperature was varied between −50 °C and 0 °C and the features of the ^{1}H NMR spectra are very similar to those reported for 1,3-dithian-2-yl tetrafluoroborate in nitromethane-d_3.[16] The situation is reminiscent of the case of triphenylmethyl chloride[17] which is known to show first-order kinetics for chloride exchange in benzene solution.[18]

The conclusion drawn from the spectral data is also supported by the chemical properties. Substitution of aromatic rings of high electron density with an easily ionizing halides such as triphenylmethyl chloride is known.[19] Formation of phenol and dimethylaniline derivatives (**9**—**11**) can therefore be taken as an indication that the polythianyl chloride dissociates easily according to Eq. 2.

As auxiliary evidence, the behavior of polythianes bearing a methoxycarbonyl group may be cited. Although the methoxycarbonyl group is a more anion-stabilizing group than the chloro group, the barriers to proton exchange of 2-methoxycarbonyl-1,3-dithiane and -1,3,5-trithaine were too large to be detected by the dynamic NMR technique.

The kinetic data of the benzene solutions in Table 2 indicate that the free energies of activation for the ionic dissociation of **1** is smaller than those of **2**. It generally appears that the more polar solvent is needed to effect the dissociation of **1** to a similar extent with **2**. The results are in harmony with the facts that anomeric effect is larger in 1,3-dithanes than in 1,3,5-trithianes[6-8] and benzenethiolysis of 2-benzoyloxy-1,3-dithiane is much faster than that of 2-benzoyloxy-1,3,5-trithiane.[10] Since the level of highest occupied molecular orbital of the trithiane system is more effectively lowered than the dithiane system because of the delocalization over the three sulfur atoms,[20] stabilization of the cation in question will be less effective. It seems a general tendency that the phenomenon concerned with the donation of electrons from sulfur atoms is more favored in the 1,3-dithiane system than in the 1,3,5-trithiane system. To the contraty, a phenomenon concerned with acceptance of electrons to these systems is expected to be more facilitated in the latter than in the former, although the comparison has not been made.

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