Fragmentation and Isomerization Reactions of Phenyl Substituted 2-Oxo-1,3,2-dioxathianes (Trimethylene Sulfites)

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The preparation and Grob-like fragmentation of several phenyl substituted 2-oxo-1,3,2-dioxathianes (trimethylene sulfites) have been examined. Preparation of the 4,4,6-triphenyl derivatives gives a chair S=O equatorial isomer which fragments readily in polar solvents to produce benzaldehyde and 1,1-diphenylethylene. Isomerization to an unreactive twist boat isomer occurs as a minor reaction in solution and in the solid state on prolonged storage. Activation parameters and substituent effects on the fragmentation reaction are consistent with an ionic mechanism. The diphenyl derivatives react only in the presence of boron trifluoride etherate giving mainly isomerization to the stable chair, S=O axial form; fragmentation is a minor pathway.

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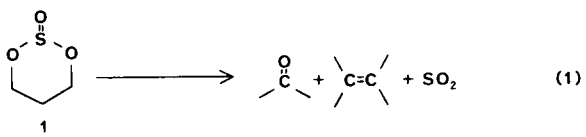
Introduction.

The 2-oxo-1,3,2-dioxathiane (trimethylene sulfite, **1**) ring system has been the subject of numerous stereochemical investigations. Of particular interest have been the conformation of the six membered ring and the position occupied by the exocyclic oxygen. Usually the most stable stereochemical arrangement is the chair form with the oxygen in an axial position (chair/axial) [1]. In the preparation of trimethylene sulfites by the reaction of 1,3-diols with thionyl chloride the less stable chair/-equatorial form is often the major product [2]. In a few cases, particularly those with bulky groups *trans* to one another at C-4 and C-6, twist-boat forms have been isolated [3].

Despite the extensive stereochemical work, relatively little is known about the chemical reactivities of trimethylene sulfites. The few reports which have appeared have dealt with either oxidation to a sulfate [4] or nucleophilic displacement at carbon [5] or sulfur [6]. As part of our studies of the chemistry and photochemistry of sulfite esters we had occasion to prepare a series of phenyl substituted trimethylene sulfites and have observed a fragmentation reaction which produces alkenes and carbonyl compounds (eq. 1). In this report we wish to describe the results of our investigation of this reaction.



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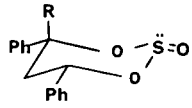
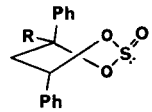
Results and Discussion

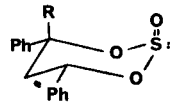
Phenyl substituted trimethylene sulfites **2a, 2b** and **3a** were prepared by reaction of the corresponding 1,3-diols with thionyl chloride. The *meso* diphenyl diol gave the



2a, R=H
3a, R=Ph



2b, R=H
3b, R=Ph



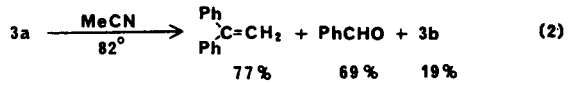
2c, R=H
3c, R=Ph

chair/equatorial isomer **2a** and the *d,l*-isomer gave a non-chair form **2b** as has been described by Buchanan *et al.* [3]. The triphenyl diol gave a product which was also assigned a chair-equatorial stereochemistry **3a** on the following basis. The ^{1}H nmr coupling constants of the benzylic proton (3.8 Hz and 11.6 Hz) are consistent with a chair conformation and the chemical shift (5.38 ppm) indicates that the exocyclic oxygen occupies an equatorial position, since an axial oxygen is known to be strongly deshielding giving a chemical shift of *ca.* 6 ppm. The S=O stretching frequency (1220 cm^{-1}) is also consistent with the proposed structure and is in fact identical to that of **2a**. On prolonged storage (several months), conversion to a stereoisomer occurred. The ^{1}H nmr coupling constants of the benzylic proton changes to 6.7 and 10.7 Hz, consistent with dihedral angles near 30 and 150 degrees [7]. This indicates that the isomer is not a chair form, but is instead a twist boat **3b**. The chemical shift of the benzylic proton changed only slightly (to 5.42 ppm) again ruling out the chair/axial form **3c**. The stability of the twist boat form is not surprising considering the *trans*-4,6-diphenyl substitution pattern similar to that found in **2b**.

The fragmentation of **3a** occurred readily in polar solvents (reactivity: methanol > acetonitrile >> tetrahydrofuran > cyclohexane) to produce 1,1-diphenylethylene and benzaldehyde (eq. 2). No styrene could be detected by ^{1}H nmr spectroscopy, indicating that the reaction is highly regioselective. Treatment of twist boat isomer **3b** under conditions identical to those in eq. 2 gave no detectable fragmentation.

The progress of the fragmentation of **3a** in acetonitrile

could be monitored by measuring the appearance of the aldehyde singlet at 9.6 ppm.

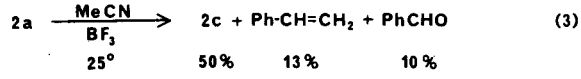


(2)

Maximum conversions were approximately 60%, the remainder of the starting material being converted to unreactive **3b**. The decomposition of **3a** followed first order kinetics for more than two half lives. Rate constants were measured at 40.7°, 50.0°, 60.5°, and 70.0° and an Arrhenius plot of the data gave the following activation parameters: Ea = 21.1 kcal/mol, $\Delta H^{\neq}$ = 20.4 kcal/mol and $\Delta S^{\neq}$ = -14.0 eu.

To further explore the nature of the reaction, three *para* substituted derivatives were prepared as shown in Scheme 1. The stereochemistry of the product sulfites was strongly influenced by the nature of the substituent, and both the substituent and stereochemistry influenced the reactivity. Chloro and methyl derivatives **6** and **7a** gave initial products which could be assigned chair/equatorial configurations by analogy with **3a** (see the Table). Fragmentation rate constants were measured for both and are recorded in the Table. The *para* chlorine retarded the rate slightly whereas the methyl substituent activated the ring toward fragmentation [8]. Preparation of the methoxy derivative, **8**, gave a twist boat product which failed to fragment in acetonitrile. Addition of boron trifluoride etherate catalyzed the fragmentation of **8** but was ineffective with **3b** again illustrating the activation provided by electron donating groups. The relative rate constants for the uncatalyzed fragmentation of the chair/equatorial isomers showed a good correlation with Okamoto-Brown substituent constants (σ^{+}) yielding a reaction constant ρ = -5.4.

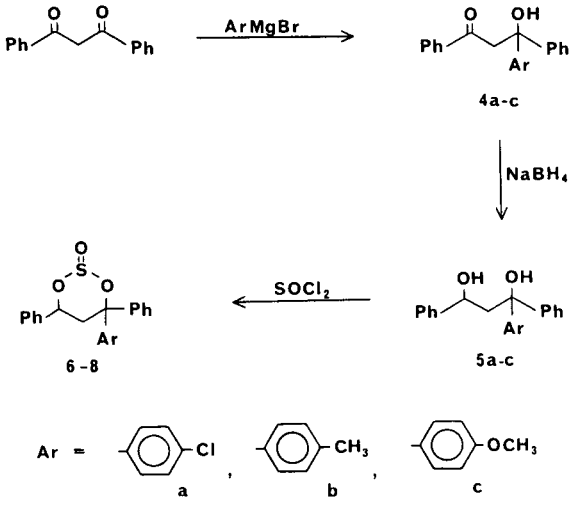
The behavior of the diphenyl chair/equatorial derivative **2a** provided an interesting contrast with the triphenyl derivative. It was completely unreactive in refluxing acetonitrile, but addition of boron trifluoride etherate (25°, 18 hours) gave isomerization to the more stable chair/axial form, **2c**. Fragmentation was only a minor pathway (eq. 3). Nearly identical results were obtained after similar treatment of **2b**.



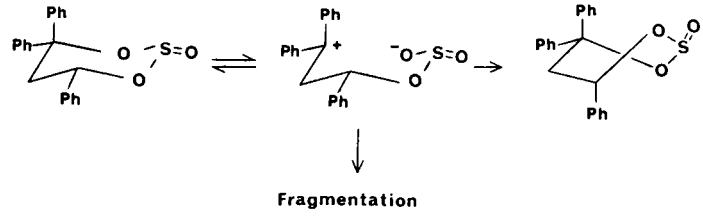
(3)

The regioselectivity of the reaction along with the solvent and substituent effects are consistent with a stepwise mechanism *via* an ionic intermediate which can either fragment or recombine to give the twist boat isomer (Scheme 2). The activation energy is similar to many reported for solvolysis reactions [9] and the entropy of activation is consistent with a transition state in which ordering of solvent molecules occurs to accommodate the developing charges [10].

Scheme 1



Scheme 2



More interesting is the remarkable dependence of reactivity on stereochemistry. The enhanced reactivity of the

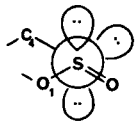
Table

Spectroscopic and Kinetic Data

Sulfite	X	ν S=O ($CHCl_3$)	J,J (Hz)	Stereochemistry [a]	K_{rel} (T, °C)
6	Cl	1220	3.3, 11.2 [b]	C/E	.73 (60)
3a	H	1220	3.8, 11.6	C/E	1
3b	H	1180	6.7, 10.7	T-B	0
7a	CH_3	1210	3.2, 11.4 [b]	C/E	27 (40)
8	OCH_3	1175	6.9, 10.5 [b]	T-B	0

[a] C/E = chair, equatorial, T-B = twist-boat. [b] Two overlapping doublets of doublets were observed.

chair-equatorial isomer can be attributed in part to differences in reactant free energies (typically a few kcal/mole [7]). It is likely that a stereoelectronic effect is also important. The cleavage of the C_4-O_3 bond in the chair-equatorial isomer may be enhanced by the antiperiplanar arrangement of the S=O group **9** which could increase the leaving group ability of the sulfite anion.



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The lower reactivity of the diphenyl derivatives could result from the reduced level of stabilization of the cationic center provided by the single phenyl group. The lack of the second phenyl group to stabilize the product alkene may also account for the reluctance of the diphenyl derivatives to fragment.

In summary, several phenyl substituted trimethylene sulfites have been prepared and their isomerization and fragmentation reactions have been examined. Evidence suggests that a zwitterionic intermediate is involved which forms most readily from a chair/equatorial sulfite stereoisomer. The triphenyl substituted twist-boat form was unreactive. Fragmentation is favored in the triphenyl case; isomerization is the major reaction in the diphenyl cases which only react in the presence of boron trifluoride etherate.

EXPERIMENTAL

General.

Melting points were determined with a Thomas-Hoover capillary melting apparatus and are corrected. The ^{1}H nmr spectra were recorded on a Varian T-60 spectrometer. Chemical shifts are reported on the δ scale, parts per million downfield from a tetramethylsilane internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrophotometer. The hplc analyses were performed with a Perkin-Elmer Series 10 Liquid Chromatograph using a Model LC-75 variable wavelength detector, a 5 μm C-18 column and eluting with 80% aqueous acetonitrile. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

All solvents were fractionally distilled and stored over molecular seives prior to use. Acetonitrile used for kinetic experiments was hplc grade and was fractionally distilled from phosphorus pentoxide before use.

The *meso* and *d,l* diastereomers of 1,3-diphenyl-1,3-propanediol [11], 1,1,3-triphenyl-1,3-propanediol [12] and sulfites **2a** and **2b** [3] were prepared using literature procedures.

cis-4,4,6-Triphenyl-2-oxo-1,3,2-dioxathiane (**3a**).

A solution of 1.2 g (0.010 mole) of thionyl chloride in 10 ml of benzene was added dropwise to a stirred solution of 2.7 g (0.0088 mole) of 1,1,3-triphenyl-1,3-propanediol and 1.5 g (0.019 mole) of pyridine in 90 ml of benzene at room temperature. The mixture was stirred for 2 hours then poured into an equal volume of cold water. The organic phase was separated and washed twice with 5% hydrochloric acid, once with 5% sodium bicarbonate, dried over magnesium sulfate and the solvent evaporated. Crystallization of the residue was induced by the addition of petroleum ether to give 2.6 g (84%) of **3a**, mp 115-117° dec; ^{1}H nmr (deuteriochloroform): δ 2.7-3.6 (m, 2H), 5.38 (dd, J = 3.8, 11.6 Hz, 1H) and 7.2-7.7 (m, 15H); ir (Nujol): 700, 720, 760, 840, 860, 1010 and 1220 cm^{-1}.

Attempts to recrystallize **3a** resulted in substantial losses of material owing to fragmentation. An analytical sample was obtained by dissolving **3a** in warm carbon tetrachloride and precipitating it by the addition of petroleum ether.

Anal. Calcd. for $C_{21}H_{18}O_3S$: C, 71.98; H, 5.18. Found: C, 71.99; H, 5.53.

trans-4,4,6-Triphenyl-2-oxo-1,3,2-dioxathiane (**3b**).

After prolonged storage (several months) of **3a**, conversion to **3b** accompanied by some fragmentation occurred. Recrystallization from benzene gave pure **3b**, mp 186-187°; ^{1}H nmr (deuteriochloroform): δ 3.0-3.8 (m, 2H), 5.42 (dd, J = 6.7, 10.7 Hz, 1H) and 7.2-7.7 (m, 15H); ir (Nujol): 690, 740, 760, 800, 1000, 1175 and 1350 cm^{-1}.

Anal. Calcd. for $C_{21}H_{18}O_3S$: C, 71.98; H, 5.18. Found: C, 72.20; H, 5.34.

Hydroxyketones **4a-4c**.

The procedure of Cannone and Bilodeau [13] was used to prepare these compounds. Recrystallization was from ethanol.

Compound **4a** had mp 120-122°; ^{1}H nmr (deuteriochloroform): δ 3.85 (s, 2H), 5.37 (s, 1H), 7.0-7.7 (m, 12H) and 7.8-8.0 (m, 2H); ir (Nujol): 690, 760, 770, 830, 1000, 1015, 1220, 1670 and 3460 cm^{-1}.

Anal. Calcd. for $C_{21}H_{17}ClO_2$: C, 74.89; H, 5.09. Found: C, 74.50; H, 5.28.

Compound **4b** had mp 107-108°; ^{1}H nmr (deuteriochloroform): δ 2.32 (s, 3H), 3.93 (s, 2H), 5.40 (s, 1H), 7.0-7.7 (m, 12H) and 7.8-8.1 (m, 2H); ir (Nujol): 705, 755, 820, 940, 995, 1180, 1215, 1660 and 3450 cm^{-1}.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.42; H, 6.39.

Compound **4c** had mp 108-110°; ^{1}H nmr (deuteriochloroform): δ 3.72 (s, 3H), 3.85 (s, 2H), 5.5 (bs, 1H), 6.71 (d, J = 9 Hz, 2H), 7.1-7.6 (m, 10H) and 7.7-8.0 (m, 2H); ir (Nujol): 690, 705, 755, 770, 820, 840, 945, 1040, 1175, 1220, 1670 and 3470 cm^{-1}.

Anal. Calcd. for $C_{22}H_{20}O_3$: C, 79.49; H, 6.06. Found: C, 79.36; H, 6.04.

Diols **5a-5c**, General Procedure.

To a stirred solution of hydroxyketone **4** (0.010 mole) in 75 ml. of methanol was added 0.012 moles of sodium borohydride in small portions. The mixture was boiled for 2 hours, allowed to cool and the methanol was evaporated. The residue was partitioned between ether and 5% sodium hydroxide and the ether solution was separated, dried over magnesium sulfate and evaporated. The product was crystallized from ethanol.

Compound **5a** had mp 151-153°; ^{1}H nmr (deuteriochloroform): δ 2.5-3.0 (m, 3H), 4.6-5.1 (m, 2H) and 7.1-7.6 (m, 14H); ir (Nujol): 705, 765, 780, 830, 1010, 1060, 1090 and 3160 cm^{-1}.

Anal. Calcd. for $C_{21}H_{19}ClO_2$: C, 74.44; H, 5.65. Found: C, 74.14; H, 5.77.

Compound **5b** had mp 99-101°; ^{1}H nmr (deuteriochloroform): δ 2.28 and 2.37 (singlets, combined 3H), 2.5-2.7 (m, 2H), 3.2 (bs, 1H), 4.5-4.8 (m, 2H) and 6.9-7.6 (m, 14H); ir (Nujol): 690, 710, 760, 820, 865, 1060 and 3180 cm^{-1}.

Anal. Calcd. for $C_{22}H_{22}O_2$: C, 82.99; H, 6.96. Found: C, 83.22; H, 6.92.

Compound **5c** had mp 138-140°; ^{1}H nmr (deuteriochloroform): δ 2.5-2.7 (m, 2H), 3.1 (bs, 1H), 3.70 and 3.78 (singlets, combined 3H), 4.4-4.7 (m, 2H), 6.73 (d, J = 9 Hz, 2H) and 7.0-7.6 (m, 12H); ir (Nujol): 695, 775, 830, 1020, 1060, 1240 and 3200 cm^{-1}.

Anal. Calcd. for $C_{22}H_{22}O_3$: C, 79.02; H, 6.63. Found: C, 79.26; H, 6.46.

Sulfites **6**, **7a** and **8**.

These compounds were prepared from diols **5a-5c** using the procedure described above for the preparation of **3a**.

Compound **6** had mp 116-117° dec; ^{1}H nmr (deuteriochloroform): δ 2.5-3.6 (m, 2H), 5.37 (dd, J = 3.3, 11.2 Hz, 1H) and 7.1-7.6 (m, 14H); ir (Nujol): 690, 720, 770, 840, 880, 1020 and 1190 cm^{-1}.

Anal. Calcd. for $C_{21}H_{17}ClO_3S$: C, 65.53; H, 4.45. Found: C, 65.47; H, 4.65.

Compound **7a** had mp 96-98° dec; ^{1}H nmr (deuteriochloroform): δ 2.25

and 2.37 (singlets, combined 3H), 2.6-3.5 (m, 2H), 5.2-5.6 (overlapping dd, J = 3.2, 11.4 and 3.8, 11.2 Hz, combined 1H) and 6.9-7.6 (m, 14H); ir (Nujol): 700, 720, 770, 790, 810, 840, 880, 1030 and 1190 cm^{-1}.

Anal. Calcd. for $C_{22}H_{20}O_3S$: C, 72.50; H, 5.53. Found: C, 72.12; H, 5.65.

Compound **8** had mp 141-142°; ^1H nmr (deuteriochloroform): δ 3.0-3.6 (m, 2H), 3.75 (s, 3H), 5.43 (dd, J = 6.9, 10.5 Hz, 1H), 6.83 (d, J = 10 Hz, 2H) and 7.2-7.6 (m, 12H); ir (Nujol): 700, 770, 800, 1175 and 1350 cm^{-1}.

Anal. Calcd. for $C_{22}H_{20}O_4S$: C, 69.45; H, 5.30. Found: C, 69.55; H, 5.48.

Fragmentation of **3a**.

A solution of 0.25 g (0.71 mmole) of **3a** in 3.5 ml of acetonitrile was heated at the reflux temperature for 2 hours. The ^1H nmr spectrum showed the complete disappearance of **3a** and the formation of 1,1-diphenylethylene (68%), benzaldehyde (65%) and **3b** (approximately 19%). Identity of the products was established by comparison of hplc retention times and ir and ^1H nmr spectra of products isolated by column chromatography (alumina, 0-5% ether/petroleum ether eluent) with those of authentic samples.

Fragmentation of **2a**.

To a solution of 0.29 g (1.1 mmole) of **2a** in 5.5 ml of acetonitrile was added 0.16 g (1.1 mmole) of boron trifluoride etherate. The mixture was stirred under a nitrogen atmosphere at room temperature for 18 hours. Analysis by ^1H nmr spectroscopy showed the presence of **2a** (50%), styrene (approximately 13%) and benzaldehyde (10%).

Kinetic Experiments.

A 0.133 molar solution of sulfite in purified, temperature equilibrated acetonitrile was prepared. Periodically, 0.5 ml aliquots were removed, quickly placed in an ice bath and immediately analyzed by ^1H nmr spectroscopy (0.067 molar *p*-dimethoxybenzene internal standard). All runs were performed in duplicate and all integrations were done in triplicate giving the following first order rate constants (x 10^4 s^{-1}): **3a** (40.7°): 0.29, 0.28; **3a** (50.0°): 0.89, 0.89; **3a** (60.5°): 1.9, 1.7; **3a** (70.2°): 6.5, 6.3; **6** (60.5°): 1.4, 1.2; **7a** (40.7°): 8.1, 7.2.

Acknowledgements.

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