

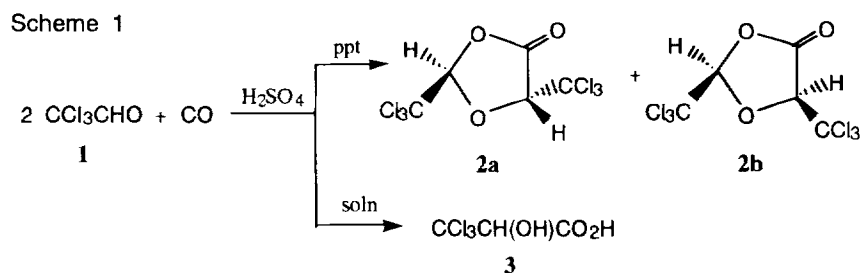
Carbonylation of Trichloroacetaldehyde (Chloral) in Concentrated Sulfuric Acid: Stereocontrolled Synthesis of *cis*- and *trans*-2,5-Bis(trichloromethyl)-1,3-dioxolan-4-one

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Abstract: Carbonylation of trichloroacetaldehyde(chloral) in concentrated sulfuric acid readily gave 2,5-bis(trichloromethyl)-1,3-dioxolan-4-ones (*cis* and *trans*) and 3,3,3-trichloro-2-hydroxypropanoic acid. The *cis* isomer was isolated for the first time, and confirmed by X-ray structural analysis. The *cis/trans* ratio of dioxolanones largely depended upon the concentration of sulfuric acid. Highly diastereoselective formation of the dioxolanones was achieved with 99wt% sulfuric acid (*cis* : *trans* = 95 : 5) or with 90wt% sulfuric acid (0 : 100).

Carbonylation of olefins and alcohols in strongly acidic media to give acids and esters is known as Koch-Haaf reaction.¹ Aldehydes such as formaldehyde or acetaldehyde also react to afford α -hydroxycarboxylic acids.^{2,3} In contrast, some chlorinated derivatives of acetaldehyde are reported to undergo a cyclization reaction incorporating carbon monoxide and two molecules of the acetaldehydes to give 2,5-disubstituted 1,3-dioxolan-4-ones.^{4,5} The similar preparation of a dioxolanone derivative from trichloroacetaldehyde (chloral, **1**) in concentrated or fuming sulfuric acid has been known for a long time,⁶ but the precise structure of the dioxolanone was determined as a *trans*-isomer only about a decade ago.⁷ The dioxolanone derivative prepared by acid-catalyzed acetalization of chloral with 3-chloro-2-hydroxypropanoic acid was also the *trans* isomer.⁸ Thus, there has been no report so far made on the formation of the *cis*-isomer nor on the stereocontrol of the product formation. Here we describe the first isolation of the *cis*-isomer and highly stereoselective preparation of *cis*- and *trans*-dioxolanones through the carbonylation of chloral in sulfuric acid.



Results and Discussion

The reaction of aldehyde **1** with carbon monoxide (50 atm) in concentrated sulfuric acid (99-90wt%) at 47 °C gave white precipitates, which contained two components. Recrystallization preferentially afforded one

component, that is, *trans*-2,5-bis(trichloromethyl)-1,3-dioxolan-4-one (**2a**). From the mother liquor was isolated by means of chromatography a white crystal, which exhibited the spectra similar to those of **2a** and was supposed as the *cis*-isomer **2b**. Its structure was correctly determined by X-ray crystallography⁹ as shown in Fig. 1. Compared with the structure of the *trans*-isomer **2a**, which has a nearly planar five-membered ring,⁷ the ring in **2b** is slightly bent,¹¹ the oxygen atom at the 1-position (O2 in Fig. 1) being forced out of the plane of the five-membered ring due to severe steric repulsion of the two trichloromethyl groups.

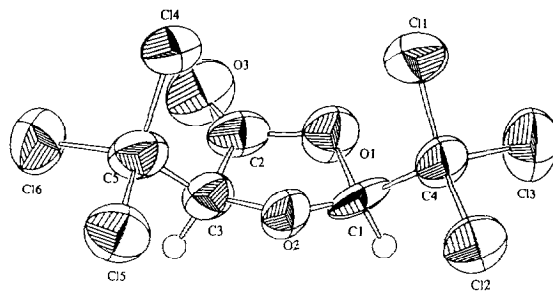


Figure 1. ORTEP drawing of **2b** with 50% probability thermal ellipsoids. Some selected bond distances(Å) and bond angles(degree) are as follows:

Selected Bond Distances		Selected Bond Angles			
O1-C1	1.46(1)	O1-C1-O2	107(1)	C1-O2-C3	108(1)
O1-C2	1.37(2)	O2-C3-C2	103(1)	O1-C2-C3	108(1)
O2-C1	1.37(2)	C1-O1-C2	106(1)	O1-C2-O3	118(1)
O2-C3	1.41(1)	C3-C2-O3	133(1)	O1-C1-C4	110(1)
O3-C2	1.18(1)	O2-C1-C4	113(1)	C2-C3-C5	113(1)
C1-C4	1.49(2)	O2-C3-C5	110(1)	Cl1-C4-C1	111.7(10)
C2-C3	1.50(2)	Cl2-C4-C1	107.3(9)	Cl3-C4-C1	109(1)
C3-C5	1.50(2)	Cl4-C5-C3	112(1)	Cl5-C5-C3	107.2(10)
Cl1-C4	1.76(1)	Cl6-C5-C3	108.4(10)		
Cl2-C4	1.75(1)				
Cl3-C4	1.74(1)				
Cl4-C5	1.75(1)				
Cl5-C5	1.77(1)				
Cl6-C5	1.75(1)				

In addition to these dioxolanones, there was obtained 3,3,3-trichloro-2-hydroxypropanoic acid (**3**) from the solution part of the reaction mixture (Scheme 1).¹² The composition of these products remarkably changed upon variation in reaction conditions as shown in Table 1. Higher concentration of **1** increased the ratio of the dioxolanones to the acid **3** (entries 4 and 3). Particularly dramatic change was observed in the *cis/trans* ratio of dioxolanones as well as in the reaction rate. The reaction in 99wt% sulfuric acid was very fast, and gave predominantly the *cis*-isomer **2b** (the *cis/trans* ratio = 95 : 5). As the acid concentration was lowered, the reaction became slower, and in 90wt% sulfuric acid the produced dioxolanone was 100% *trans*-isomer **2a**. Thus, it is now possible to prepare either of the stereo-isomers of the dioxolanone derivative **2**, by selecting the reaction conditions.

The preferential formation of the *cis*-isomer **2b** in highly concentrated sulfuric acid could be interpreted in the following way. Olah *et al* have demonstrated that the *anti*-form (with respect to the R-C-O-H sequence) predominates as the structure of protonated aldehydes, based on the NMR study on these species in highly acidic

Table 1. Carbonylation of Chloral in Concentrated Sulfuric Acid^a

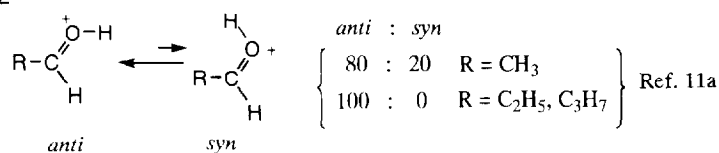
entry	H ₂ SO ₄ /wt%	time / min	conv. of 1 /%	dioxolanones	3 yield /% ^c
				2a : 2b (yield /%) ^b	
1 ^d	99	14	94.3	5 : 95 (47.8)	17.5
2	97	24	93.7	50 : 50 (49.4)	26.8
3	95	60	96.9	68 : 32 (60.0)	25.4
4 ^e	95	90	97.5	69 : 31 (81.0)	8.3
5	90	420	97.8	100 : 0 (64.6)	14.6

^a Conditions: sulfuric acid, 28 mL; chloral hydrate, 5.0 mmol; CO, 50 atm; temperature, 47 °C.

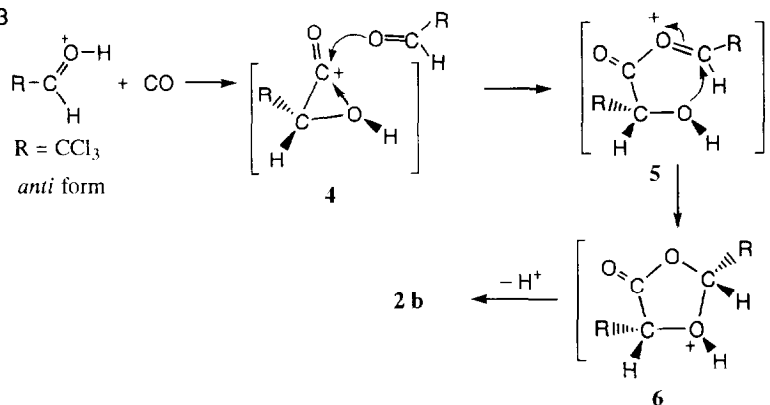
^b Determined by GLC. ^c Determined by HPLC. ^d Temperature was 42 °C. ^e Charged chloral hydrate was 18.2 mmol.

media such as HSO₃F-SbF₅ (Scheme 2).¹³ When carbon monoxide reacts with such protonated aldehyde of the *anti*-form, it is assumed that the *anti*-geometry is retained for the sequence R-C-O-H in the intermediate **4**, in which some electronic interaction exists between the acyl carbon and the hydroxyl oxygen (Scheme 3).¹⁴ In the next step, when the acyl carbon reacts with the second aldehyde molecule, the addition is expected to occur in the *anti*-fashion, just as in the protonation of aldehydes mentioned above, and the following cyclization (**5** to **6**) also favors the *anti*-geometry with regard to the two R-C-O-H sequences in the molecule. Thus, the preferential formation of the *cis*-isomer **2b** is achieved after deprotonation as shown in Scheme 3.

Scheme 2



Scheme 3



On the other hand, in less concentrated sulfuric acid, *e.g.*, 90wt% H₂SO₄, the intermediate such as **4** would be hydrolyzed to give α -hydroxycarboxylic acid **3**, which reacts with the second molecule of the aldehyde to give the dioxolanone having the thermodynamically more stable *trans*-geometry.

During the prolonged reaction time, isomerization from the *cis*-isomer to the *trans*-isomer does take place. For example, the *cis*/*trans* ratio of the dioxolanone produced by the reaction in 90wt% H₂SO₄ was 27 : 73 at

the early stage (23% conversion; 47 °C; 30 min), but the ratio changed to 0 : 100 after the reaction of 420 min when the reaction was completed. In the more concentrated acid, i.e., 95wt% H₂SO₄, the isomerization was much retarded, that is, the *cis/trans* ratio was 35 : 65 at 40% conversion of the reaction compared with 32 : 68 at 97% conversion. Apparently the water content of the acid is affecting the isomerization rate.

When dichloroacetaldehyde was used instead of trichloroacetaldehyde, the general trend in product distribution was quite similar. Thus, under the conditions similar to those in Table 1 (50 atm of CO, 25 °C, 10 mmol of the aldehyde, 98.0% conversion at 2 h),¹⁵ the reaction in 97wt% sulfuric acid afforded 2,5-bis(dichloromethyl)-1,3-dioxolan-4-one (64.8% yield) with the *cis/trans* ratio of 57 : 43 and 3,3-dichloro-2-hydroxypropanoic acid (9.2% yield).^{16,17} In less concentrated sulfuric acid (90wt%), the reaction was slower (78.2% conversion after 10 h at 25 °C) and the content of the *cis*-isomer decreased (*cis/trans* ratio = 20 : 80 with the total yield of 53.9%). The reaction was much accelerated in 99wt% sulfuric acid (94.0% conversion after 1 h), and the *cis* selectivity did increase (*cis/trans* ratio = 76 : 24) (54.3% total yield); however the selectivity was lower than that of the case of trichloroacetaldehyde probably due to the fast isomerization.

In summary, the present study indicated that the selective formation of the previously unknown *cis*-isomer of bis(trichloromethyl) dioxolanone can be achieved by choosing the highly acidic medium for the carbonylation reaction of the aldehyde **1** while the *trans*-isomer can be exclusively obtained as the product from thermodynamic control of the reaction.

Experimental Section

General Procedures. The carbonylation reaction was performed using a 50 mL magnetically stirred stainless-steel autoclave. The autoclave containing typically 0.83 g (5.0 mmol) of chloral hydrate dissolved in 28 mL of sulfuric acid was flushed three times with 20 atm of carbon monoxide, then pressurized up to 50 atm of carbon monoxide. The reaction was started by stirring in a thermostated oil bath. After completion of reaction judged from ceasing of gas take-up, the reaction mixture containing white precipitates was poured onto ice-water. The white solid was collected by filtration, dissolved in ether, and the solution was washed repeatedly with water, and dried over magnesium sulfate. After removing ether by evaporation, the white crude product was dried *in vacuo*. The yield and *cis/trans* ratio of the dioxolanones were determined by GLC (Hitachi 163; column, Apiezon Grease L, 1.2 m; temperature, 130 °C). The filtrate containing trichlorolactic acid (**3**) and unchanged chloral (**1**) was diluted and analyzed by HPLC (Shimadzu LC10AD; column, SCR-101H; eluent, aq. perchloric acid (pH, 2.1); temperature, 40 °C). NMR spectra were obtained using Varian VXR-200 spectrometer. IR measurement was performed with Shimadzu FTIR-8600. The concentration of commercial sulfuric acid was determined as 97.7wt% by alkaline titration of a quantitatively diluted solution. Sulfuric acid with higher or lower concentration was prepared within the error of ±0.1wt% by addition of fuming sulfuric acid containing 12% of SO₃ or by dilution with distilled water.

***trans*-2,5-Bis(trichloromethyl)-1,3-dioxolan-4-one (2a).** The white crude product consisted of mainly two components as judged from GLC (two peaks at *t_R* = 12.5 and 23.6 min) and from TLC (two spots at *R_f* = 0.69 and 0.46; hexane-benzene(1:1) / silica gel). Besides these two compounds, small amount (less than 2%) of dehydrochlorinated product of the dioxolanones was contained.¹⁸ Recrystallization of the crude product (e.g. 2.38 g in the case of entry 4 in Table 1) from hexane gave predominantly the *trans*-isomer (**2a**) (*t_R* = 12.5 min in GLC, *R_f* = 0.69 on TLC). The remaining mother liquor contained another component (**2b**). An

additional amount of **2a** was isolated from the mother liquor by column chromatography over silica gel eluted with hexane-benzene (1:1). Recrystallization of collected **2a** from hexane gave white needles (1.46 g, 4.52 mmol, 49.7% yield): mp 114-115 °C (lit.¹⁹ 115-116 °C); IR (KBr) 1806, 1198, 855, 799 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 6.07 (d, *J* = 1.6 Hz, 1H), 5.13 (d, *J* = 1.6 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃) δ 161.94, 104.06, 96.87, 93.76, 83.38. Anal. Calcd. for C₅H₂O₃Cl₆: C, 18.61; H, 0.62; Cl, 65.90. Found: C, 18.56; H, 0.73; Cl, 65.83.

cis-2,5-Bis(trichloromethyl)-1,3-dioxolan-4-one(2b). The fractions which were obtained after **2a** was eluted (vide supra) were combined and evaporated *in vacuo*. The residual solid was recrystallized from hexane to give a white crystal (0.650 g, 2.01 mmol, 22.1% yield). This white crystal was confirmed to be **2b** by X-ray structural analysis.⁹ mp 75-76 °C; IR (KBr) 1811, 1202, 853, 791 cm⁻¹; ¹H NMR (CDCl₃) δ 5.86 (d, *J* = 1.4 Hz, 1H), 5.10 (d, *J* = 1.4 Hz, 1H); ¹³C NMR (CDCl₃) δ 161.55, 102.07, 94.22, 92.21, 83.82. Anal. Calcd. for C₅H₂O₃Cl₆: C, 18.61; H, 0.62; Cl, 65.90. Found: C, 18.93; H, 0.72; Cl, 64.99.

3,3,3-Trichloro-2-hydroxypropanoic acid (3,3,3-trichlorolactic acid) (3). The filtrate (200 mL) described in general procedures (vide supra) was treated with barium chloride. The precipitates were removed by filtration through Celite filter aid, and the filtrate was concentrated to 30 mL using a rotary evaporator and extracted with ether (3 × 50 mL). The combined organic layer was once washed with small amount of water, and dried over magnesium sulfate. Removal of the solvent gave an oily compound, which solidified upon further evacuation (*e.g.* 0.190 g in entry 4 in Table 1). Recrystallization from hexane-ether gave white prismatic crystals (0.165 g, 0.853 mmol, 17% yield; the HPLC analyzed value was 25%): mp 122-123 °C (lit.²⁰ 124 °C); IR(KBr) 3389, 3069, 1749, 1117, 831 cm⁻¹. Anal. Calcd. for C₃H₃O₃Cl₃: C, 18.63; H, 1.56; Cl, 54.99. Found: C, 18.76; H, 1.67; Cl, 54.85.

Acknowledgment

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9. Colorless crystals of **2b** are monoclinic, the space group is P2₁/c with $a = 10.762(8) \text{ \AA}$, $b = 6.115(5) \text{ \AA}$, $c = 17.102(6) \text{ \AA}$, $\beta = 97.82(4)^\circ$, $V = 1115(1) \text{ \AA}^3$, $Z = 4$, and $d_{\text{calc}} = 1.92 \text{ g/cm}^3$. Intensity data were collected on a Rigaku AFC7R diffractometer with graphite monochromated Cu-K α radiation. The structure was solved by direct methods using SHELXS86.¹⁰ The final residuals were $R = 0.084$ and $R_w = 0.099$ for 965 data with $I > 3.0\sigma(I)$. We were indebted to Dr. T. Nishinaga for carrying out the X-ray crystallography.
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11. The dihedral angle between the planes C1-O2-C3 and C1-O1-C2-C3 in Fig. 1 is approximately 24° .
12. The absolute configuration of the compounds in Schemes 1 and 3 are only tentative.
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15. In the reaction of dichloroacetaldehyde, ether was used as a co-solvent which was miscible with sulfuric acid. Without the solvent, an immediate polymerization occurred when the aldehyde was added to the acid.
16. The *cis*- and *trans*-isomers, which were separated by column chromatography, were assigned by analogy with the case of chloral based on R_f on TLC (0.40 and 0.19), t_R in GLC (7.9 and 9.0 min), and the NMR spectra (chemical shifts of *trans*-isomers were slightly down-field shifted: see Experimental Section, and the similar trend was observed also for 2-trichloromethyl-5-phenyl dioxolanone: Cort, L. A.; Stewart, R. A. *J. Chem. Soc. (C)* **1971**, 1386). Furthermore, the rate of dehydrochlorination of the *cis*-isomer was five-times faster than that of the *trans*-isomer. The *trans*-isomer was obtained as a colorless oil: bp $101^\circ\text{C}/1.0 \text{ mm}$; $^1\text{H NMR}$ (200 MHz, CDCl_3); δ 6.07 (dd, $J=1.5$ and 1.4 Hz , 1H), 6.00 (d, $J=2.0 \text{ Hz}$, 1H), 5.83 (d, $J=1.5 \text{ Hz}$, 1H), 4.99 (dd, $J=2.0$ and 1.4 Hz , 1H); $^{13}\text{C NMR}$ (50 MHz, CDCl_3); δ 165.50, 103.23, 78.91, 70.57, 68.68. The *cis*-isomer was also a colorless oil: bp $104^\circ\text{C}/0.90 \text{ mm}$; $^1\text{H NMR}$ (CDCl_3) δ 6.02 (d, $J=3.0 \text{ Hz}$, 1H), 5.79 (dd, $J=5.4$ and 0.7 Hz , 1H), 5.77 (d, $J=5.4 \text{ Hz}$, 1H), 4.87 (dd, $J=3.0$ and 0.7 Hz , 1H); $^{13}\text{C NMR}$ (CDCl_3) δ 164.94, 102.78, 78.85, 68.96, 67.61.
17. 3,3-Dichloro-2-hydroxypropanoic acid was obtained as white crystals by a similar procedure to the case of 3,3,3-trichloro-2-hydroxypropanoic acid (**3**): mp $76\text{--}77^\circ\text{C}$ (lit. $76\text{--}77^\circ\text{C}$): Reisse, E. *Ann. Chem.* **1890**, 257, 335.
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