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Disproval of Claimed Unusually Stable Primary Ozonides of 1,4-Dichloro-2-butenes

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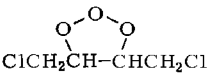
Beweise gegen postulierte ungewöhnlich stabile Primärozonide von 1,4-Dichlor-2-butenen

Ozonolysen von *cis*- und *trans*-1,4-Dichlor-2-buten (**1**) in Methanol ergaben ca. äquimolare Anteile an 2-Chlor-1-methoxyethanol (**6a**) und 2-Chlor-1-methoxyethylhydroperoxid (**7a**) als Hauptprodukte sowie eine geringe Menge 2,2'-Dichlor-1-hydroxy-1'-methoxydiethylperoxid (**8a**). Ozonolyse von **1** in [D$_4$]Methanol ergab die entsprechenden deuterierten Produkte **6c** – **8c**. Die postulierte Existenz$^{1)}$ von ungewöhnlich stabilen Primärozoniden **2** wird widerlegt.

In a recent paper$^{1)}$ it was reported, that the ozonolysis of *cis*- and *trans*-1,4-dichloro-2-butene (**1**) in methanol or in [D$_4$]methanol at – 10°C afforded mixtures of the "unusually stable" stereoisomeric primary ozonides **2**. In support of this contention, the following arguments have been advanced: ^{1}H NMR signals at δ = 4.68 and 4.80 assigned to the methine protons of *cis*- and *trans*-**2**, conversion of **2** into **3** upon treatment of the reaction mixtures with isopropylmagnesium bromide, and formation of **4** and **5** upon prolonged standing of reaction mixtures in methanol at 24°C. Apparent discrepancies between claims and experimental evidence provided incentives for a reinvestigation.

$ClCH_2CH{=}CHCH_2Cl$

1



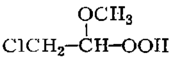
2

$ClCH_2CH(OH)CH(OH)CH_2Cl$

3

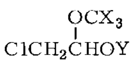
$ClCH_2CH(OCH_3)_2$

4



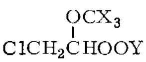
$ClCH_2{-}\overset{OCH_3}{CH}{-}OOH$

5



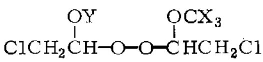
$ClCH_2\overset{OCX_3}{C}HOY$

6



$ClCH_2\overset{OCX_3}{C}HOOY$

7



$ClCH_2\overset{OY}{C}H{-}O{-}O{-}\overset{OCX_3}{C}HCH_2Cl$

8

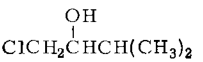
a: X = Y = H; **b**: X = D, Y = H; **c**: X = Y = D

$ClCH_2CH{=}O$

9

$ClCH_2CO_2CH_3$

10



$ClCH_2\overset{OH}{C}HCH(CH_3)_2$

11

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In the present study *cis*- and *trans*-**1** have been ozonized individually both in methanol and *cis*-**1** also in [D_4]methanol. Ozonolysis was in each case carried out to complete conversion of **1**[2]. The temperature was $-15\,^{\circ}C$ at the start and it was continuously lowered to $-50\,^{\circ}C$. After termination of the ozone treatment, the crude mixtures were allowed to warm up to $-10\,^{\circ}C$ and were then immediately analyzed by ^1H NMR spectroscopy.

Ozonolysis of *cis*-**1** in [D_4]methanol afforded reaction products, which exhibited the ^1H NMR spectrum of Fig. 1. The signals centered at δ = 3.45 and 4.65 are due to the CH_2- and CH-groups, respectively, of the hemiacetal **6c**, as shown by comparison with authentic **6c** in CD_3OD. The latter has been obtained in 88% yield by admixture of **9** with CD_3OD and subsequent removal of excess CD_3OD by azeotropic distillation with added dichloromethane. The signals centered at δ = 3.54, 3.68 and 4.79 of Fig. 1 are due to **7c**. The latter has been isolated in 53% yield, albeit as **7b** due to H/D-exchange during chromatographic separation. The signals centered at δ = 5.00 and 5.34[3] of Fig. 1 appeared with low intensities in the spectra of freshly ozonized solutions (Fig. 1, bottom). The intensities increased moderately upon prolonged standing[4] and very significantly upon removal of CD_3OD, i. e. upon concentration of the ozonized solutions (Fig. 1, top). These signals are due to the $CH(OCD_3)$ and CH(OD) groups, respectively, of **8c**. Each of these signals represents the overlapping X-parts of two ABX-systems, which arise from the two diastereomers of **8c**. By reaction of **7b** with **9** in CD_3OD at ambient temperatures, **8c** has been independently prepared.

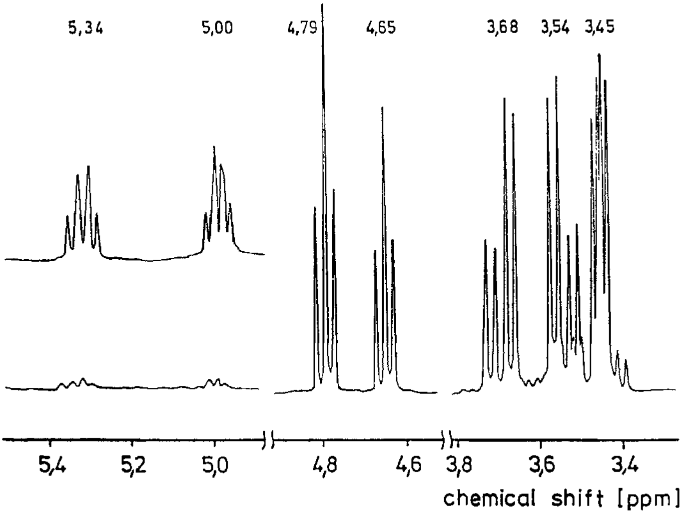
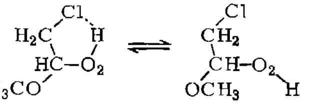


Figure 1. Signals in the 250 MHz Spectrum of a Reaction Mixture from the Ozonolysis of **1** in CD_3OD

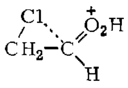
Ozonolysis of *cis*- and *trans*-**1** in methanol afforded reaction mixtures which exhibited the same ^1H NMR patterns in the region of 4.5 – 5.5 as those depicted in Fig. 1[5]. These signals could be assigned to the CH-groups of **6a** – **8a** by admixture of each of these compounds and concomitant enhancement of the corresponding signals. Furthermore, **7a** has been isolated as a colorless liquid in 60% yield[6], and **8a** has been isolated as a viscous liquid in 64% yield. The structure of **7a** has been further established by its reduction with dimethyl sulfide in $CDCl_3$ to give a mixture of **6a** and of **9**. The structure of **8a** has been further supported by independent preparation from **7a** and **9** in methanol as well as by HCl-catalyzed decomposition to give approximately equimolar amounts of **4** and **10**[7].

Treatment of a crude ozonolysis product of **1** in methanol with HCl/methanol gave equimolar amounts of **4** and **10**[7] in virtually quantitative yields, as evidenced by ^1H NMR analysis in the presence of 1,1,2,2-tetrachloroethane as internal standard. This added further proof to our conclusion, that **6a** and **7a** are the single major products from the ozonolysis of **1** in methanol. Treatment of the crude ozonolysis mixture with isopropylmagnesium bromide by the procedure given in ref.[1] afforded a liquid product. According to GLC-analysis it contained ca. 46% of **11** and a myriad of peaks of less than 4% intensity, each, however, none of the diastereomers of the diol **3**, as shown by coinjection of authentic *meso*-**3** and *racem.* **3**. Compound **11** has been isolated by prep. GLC.

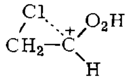
On the basis of the results presented above, we conclude that the ozonolysis of **1** in methanol or in [D_4]methanol at −10°C or even at lower temperatures affords approximately equal amounts of fragments **7** and **9**. The reactive fragment **9** undergoes subsequent reactions with methanol and to a lesser degree with **7**[8] to yield **6** and **8**, respectively. Our results are, thus, at variance with the previously reported claims in the following points: (i) The arguments presented for the existence of stable primary ozonides in [D_4]methanol or methanol have been refuted, for the ^1H NMR signals previously assigned to the two isomers of **2** (*viz.* δ = 4.68 and 4.80) are due to **6c** (δ = 4.65) and **7c** (δ = 4.79), respectively, and the formation of **3** upon treatment with Grignard reagent could not be confirmed. (ii) The assignment of an ^1H NMR signal at δ = 4.96 to the methine proton of **7a** is erroneous, for it is due to the previously not identified peroxide **8**. In view of this, it is questionable, whether **7a** had indeed been isolated as a "pure" compound, as it was claimed. (iii) The ^1H NMR spectra of the fresh ozonolysis products have provided no evidence for the initial formation of isomeric methoxy hydroperoxides like **12** and **13**, as it had been suggested[1], based on the above mentioned erroneous assignment of the signal at δ = 4.96. In consideration of these results, much of the reasoning which had been advanced about the influence of chlorine substituents on the non-concerted formation of primary ozonides and on the stabilization of protonated zwitterions **14**–**16** by charge delocalization appears rather futile.



12 **13**



14



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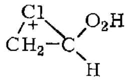

16

Experimental Part

^1H NMR: 60 MHz spectra with Bruker WP-60; 250 MHz with Bruker WM-250. – ^{13}C NMR: Bruker WH-300. – IR-spectra: Beckman 4260. – Analytical GLC: Shimadzu GC 6 A. – PGC: Perkin Elmer F 21.

*Ozonolysis of cis-***1** *in CD_3OD:* A solution of 1.09 g (8.7 mmol) of *cis*-**1** in 3.0 g of [D_4]methanol was treated with a stream of ozone in oxygen (1.5 mmol O_3/liter). The temperature was −15°C at the start, and it was lowered to −50°C during the course of the reaction. When the solution turned blue, the ozone treatment was terminated, and it was flushed with nitrogen. A sample of the crude product was analyzed by 250 MHz ^1H NMR spectroscopy at −10°C, to give the spectrum shown in Fig. 1. Subsequently, samples of **6c** and of **7b** have been sequentially added and the ^1H NMR spectra were again recorded to show increases of the signals assigned to **6c** and **7c**, respectively. – In a second ozonolysis experiment, the reaction mixture was allowed to warm up to room temperature and was subsequently separated by flash chromatography[9] (column 3 × 50 cm, 190 g silicagel, pentane/ether 8 : 1 and 5 : 1 in amounts of 3.5 and 1.5 l, respectively) to give **7b**.

2-Chloro-1-(trideuteriomethoxy)ethyl Hydroperoxide (**7b**): Colorless liquid, yield 600 mg (53%). – ^{1}H NMR (250 MHz, CD$_3$OD, TMS): ABX system with $\delta_A = 3.54$, $\delta_B = 3.68$, $\delta_X = 4.79$; $J_{AB} = 11.6$, $J_{AX} = 5.5$, $J_{BX} = 5.2$ Hz. – ^{1}H NMR (250 MHz, CDCl$_3$, TMS): $\delta_A = 3.60$, $\delta_B = 3.74$, $\delta_X = 4.87$; $J_{AB} = 11.8$, $J_{AX} = 5.1$, $J_{BX} = 5.9$ Hz; $\delta = 8.33$ (s; OOH). – IR (film): 3365, 2975, 2895, 2255, 2225, 2130, 2075, 1434, 1401, 1365, 1212, 1117, 1075, 998, 975, 804, 766 cm^{-1}.

Preparation of **6c**: A solution of 600 mg (7.6 mmol) of **9** in 1.25 ml of [D$_4$]methanol was kept at room temp. for 48 hours. This solution showed only the ^{1}H NMR signals of **6c** (CD$_3$OD, TMS): ABX-system with $\delta_A = 3.47$, $\delta_B = 3.43$, $\delta_X = 4.65$; $J_{AB} = 11.4$, $J_{AX} = 5.2$, $J_{BX} = 4.9$ Hz. Then 15 ml of dichloromethane was added and the mixture was concentrated in a rotary evaporator at room temp./60 Torr. The liquid residue (1.1 g) was shown by 250 MHz ^{1}H NMR spectroscopy to consist of a mixture of 88% **6c** (CDCl$_3$, TMS): $\delta = 4.73$ (t, $J = 3.8$ Hz; 1H), 3.59 (d, $J = 3.8$ Hz; 2H), and of 12% **9**: $\delta = 4.06$ (d, $J = 1.7$ Hz; 2H), 9.64 (t, $J = 1.7$ Hz; 1H).

Preparation of **8c**: A solution of 188 mg (2.40 mmol) of **9** and 160 mg (1.25 mmol) of **7b** in 0.2 ml of [D$_4$]methanol was kept at room temp. for 24 h and then analyzed by 250 MHz ^{1}H NMR. The spectra showed, besides the signals of **6c** and **7c**, those of **8c** (CD$_3$OD, TMS): $\delta = 3.50 - 3.70$ (m; 4H), 4.99 and 5.01 (overlapping X-parts of two ABX-systems; 1H), 5.32 and 5.35 (overlapping X-parts of two ABX-systems; 1H). The ratio of **6c**, **7c**, and **8c** was 48:20:32.

*Ozonolysis of trans-***1** *in Methanol*

a) *Isolation of* **7a**: A solution of 2.01 g (16.0 mmol) of *trans*-**1** in 6.5 ml of methanol was ozonized with the procedure described above for the ozonolysis of *cis*-**1** in CD$_3$OD. ^{1}H NMR analysis at –10°C (250 MHz, CDCl$_3$, TMS) showed the same pattern of signals in the region of 4.5 – 5.5 ppm as that depicted in Fig. 1 (NMR analysis of crude ozonolysis products of *cis*-**1** in methanol gave the same NMR spectra). – Sequential admixture of **6a**, **7a**, and **8a** to the product mixture resulted in increased signals of the corresponding patterns *viz.* at $\delta = 4.74$ for **6a**, 4.87 for **7a** and 4.99 and 5.01 as well as 5.43 and 5.45 for **8a**. – For the isolation of **7a** half of the above crude product mixture was separated by flash chromatography[9] (conditions as for **7b**). Isolated **7a** was distilled at room temp. and 10^{-4} Torr, yield 600 mg (60%).

2-Chloro-1-methoxyethyl Hydroperoxide (**7a**): Colorless liquid, yield 600 mg (60%). – ^{1}H NMR (250 MHz, CDCl$_3$, TMS): $\delta = 3.57$ (s; 3H), ABX-system with $\delta_A = 3.60$, $\delta_B = 3.74$, $\delta_X = 4.87$; $J_{AB} = 11.8$, $J_{AX} = 5.3$, $J_{BX} = 5.7$ Hz; 8.31 (s; 1H)[10]. – ^{13}C NMR (75.46 MHz, CDCl$_3$, TMS): $\delta = 106.31$ (dq, $J = 166$ and 4 Hz), 56.80 (qd, $J = 144$ and 4 Hz), 41.33 (td, $J = 153$ and 2 Hz). – IR (film): 3370, 2970, 2940, 2839, 1432, 1400, 1360, 1181, 1112, 1060, 1010, 978, 809, 767 cm^{-1}.

$C_3H_7ClO_3$ (126.5) Calcd. C 28.48 H 5.58 Cl 28.02 Found C 28.46 H 5.52 Cl 27.98

Reduction of **7a** *with Dimethyl Sulfide:* To 28.5 mg (0.45 mmol) of dimethyl sulfide a solution of 14.0 mg (0.11 mmol) of **7a** in 0.5 ml of CDCl$_3$ has been added dropwise. ^{1}H NMR analysis (60 MHz, CDCl$_3$, TMS) showed the signals of **6a** ($\delta = 3.49$, s; 3.60, d, $J = 3.7$ Hz; 4.74, t, $J = 3.7$ Hz), of **9** ($\delta = 4.06$, d, $J = 1.7$ Hz; 9.64, t, $J = 1.7$ Hz), and of dimethyl sulfoxide ($\delta = 2.62$, s). The intensities of the signals of **6a**, **9**, and dimethyl sulfoxide had a ratio of 0.75:0.25:1.

b) *Isolation of* **8a**: A solution of 1.18 g (9.4 mmol) of *trans*-**1** in 1.75 ml of methanol was ozonized as described above. The crude reaction product was allowed to warm up to room temp. and the solvent was distilled off by gradually lowering the pressure to 10^{-2} Torr at room temperature. Subsequently, the product was kept at 45°C/10^{-2} Torr for 5 h. The viscous residue consisted of pure **8a**, yield 1.25 g (64%).

2-Chloro-1-(2-chloro-1-methoxyethyldioxy)ethanol = 2-Chloro-1-hydroxyethyl 2-Chloro-1-methoxyethyl Peroxide (**8a**): Colorless, viscous liquid, yield 1.25 g (64%). – ^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 3.60, 3.61 (s; each; OCH_3), 3.85 (m, broad; OH), 3.50 – 3.70 (m, overlapping AB-parts of four ABX-patterns; CH_2), 4.99 (apparent q due to overlapping X-parts of two ABX-patterns and coinciding inner lines; J_{AX} = J_{BX} ca. 5 Hz; 1 H)[11], 5.45 (m due to overlapping X-parts of two ABX-patterns and to coupling with the OH group; 1 H)[12]. – IR (film): 3410, 2965, 2937, 2837, 1432, 1334, 1180, 1113, 1008, 974, 832, 770 cm^{-1}.

$C_5H_{10}Cl_2O_4$ (205.0) Calcd. C 29.29 H 4.91 Cl 34.58 Found C 29.15 H 4.80 Cl 34.52

Preparation of **8a**: A solution of 20 mg (0.16 mmol) of **7a**, 17 mg (0.22 mmol) of **9**, and 10 mg of methanol in 0.5 ml of $CDCl_3$ was kept at room temp. for 7 days. To this solution, 15 mg of 1,1,2,2-tetrachloroethane was added and the solution was analyzed by 60 MHz ^{1}H NMR spectroscopy. It showed the presence of 93% of **8a** based on **7a** as the reagent which was used in a deficient amount: δ = 5.00 and 4.98 as well as 5.43 and 5.46.

Acid-catalyzed Decomposition of **8a**: To a solution of 213 mg (1.04 mmol) of **8a** in 0.5 ml of $CDCl_3$ at 0°C 0.13 ml of a 7.5 M solution of anhydrous hydrogen chloride in dry methanol was added with stirring. The mixture was heated at 40°C for 16 h and at 60°C for 12 h in a closed flask. To the cooled mixture 183 mg (1.1 mmol) of 1,1,2,2-tetrachloroethane was added and the solution was analyzed by 60 MHz ^{1}H NMR spectroscopy ($CDCl_3$, TMS). It showed the presence of **4** (δ = 4.53, t, J = 5.5 Hz, 1 H; 3.51, d, J = 5.5 Hz, 2 H; 3.42, s, 6 H) and **10** (δ = 4.08, s, 2 H; 3.81, s, 3 H) in molar equivalents of 1.05 and 0.89 based on the starting material **8a**.

Acid-catalyzed Reaction of Ozonolysis Mixtures: A solution of 1.02 g (8.2 mmol) of *trans*-**1** in 1.5 ml of methanol has been ozonized as described above. At –20°C 1.1 ml of a 7.5 M solution of anhydrous hydrogen chloride in methanol was added. The mixture warmed up to room temp. within 18 h and was then heated to 60°C for 6 h. To the solution, cooled to 0°C, 1.38 g (8.2 mmol) of 1,1,2,2-tetrachloroethane was added and the solution was analyzed by 60 MHz ^{1}H NMR spectroscopy ($CDCl_3$, TMS). It showed the presence of **4** (δ = 4.53, t, J = 5.5 Hz, 1 H; 3.51, d, J = 5.5 Hz, 2 H; 3.42, s, 6 H) and **10** (δ = 4.08, s, 2 H; 3.81, s, 3 H) in molar equivalents of 1.03 and 0.97 based on the starting olefin **1**.

Treatment of Ozonolysis Products with Isopropylmagnesium Bromide: A solution of 6.24 g (50.0 mmol) of *cis*-**1** in 5 ml of CD_3OD was treated with 30 mmol of ozone at –40°C. The solution was flushed with nitrogen and subsequently concentrated at 0.05 Torr and temperatures of –10°C at the start and –80°C at the end. To the residue a solution of 0.2 mol of isopropylmagnesium bromide in ether was added dropwise at –80°C and the mixture was kept stirring at –80°C for 2 days. Then it was refluxed for 2 h, subsequently hydrolyzed with a solution of 35.0 g of ammonium chloride in 150 ml of water at ca. 0°C and carefully neutralized with 1 N H_2SO_4 at ambient temperature. The aqueous phase was extracted with ether, the extracts were combined with the ether phase and dried over sodium sulfate. After removal of ether in a rotary evaporator at room temp./40 Torr, there remained 6.2 g of a liquid residue. According to GLC-analysis (glass column 0.3 × 300 cm, 2.5% Nitrilesiliconoil on Chromosorb G; 60 – 160°C at 4°C/min) it contained ca. 46% of **11** (t_R = 14 min) and a myriad of peaks of less than 4% intensity, each. The presence of diols **3** has been excluded by coinjection of authentic compounds[13] *meso*-**3** (t_R = 37 min) and *racem.* **3** (t_R = 44 min), since the chromatogram of the product mixture showed no peaks in these areas. – From the residue, **11** was isolated by PGC (glass column 0.8 × 300 cm, 5% Nitrilesiliconoil on Chromosorb G; 60 – 160°C at 5°C/min).

1-Chloro-3-methyl-2-butanol (**11**): Colorless liquid. – ^{1}H NMR (60 MHz, $CDCl_3$, TMS): δ = 0.95 (d, J = 6.6 Hz; 3 H), 0.99 (d, J = 6.6 Hz; 3 H), 1.79 (m; 1 H), 2.33 (broad s; 1 H), 3.79 – 3.34 (m; 3 H).

[1] *E. Tempesti, M. Fornaroli, L. Giuffrè, E. Montoneri,* and *G. Airoldi,* J. Chem. Soc., Perkin Trans. 1 **1983**, 1319.

[2] In previous work[1] ozonolysis of **1** has been carried out to 40 – 50% conversion only. By monitoring of the reaction with ^1H NMR analyses we have ascertained, that complete conversion of **1** gave qualitatively the same results as partial conversion.

[3] This signal has not been assigned by *Tempesti* et al., although it was present in their published spectra, too.

[4] An increase of the signal at δ ca. 5.0 upon standing of the reaction mixtures had already been reported by *Tempesti* et al., and it has been associated with the conversion of the primary ozonides **2** into **4**, **12**, and **13**.

[5] The pattern in the region of 3.4 – 3.8 ppm was considerably more complicated than in Fig. 1 due to overlap of OCH_3 signals.

[6] The previous authors have mentioned "deviations or anomalies" in the assignments of spectral data for **7a** and have ascribed this to "the relative stability of pure hydroperoxide containing electron releasing groups". We have found **7a** to be stable at room temperature.

[7] For similar reactions see *K. Griesbaum* and *J. Neumeister,* Chem. Ber. **115**, 2697 (1982), and *M. Meister,* Dissertation, Univ. Karlsruhe 1984.

[8] Reactions of methoxy hydroperoxides with aldehydes to form peroxyhemiacetals have recently been observed by us in a number of instances: *K. Griesbaum, H. Keul, S. Agarwal,* and *G. Zwick,* Chem. Ber. **116**, 409 (1983), and *M. Meister, G. Zwick,* and *K. Griesbaum,* Can. J. Chem. **61**, 2385 (1983).

[9] *W. C. Still, M. Kuhn,* and *A. Mitra,* J. Org. Chem. **43**, 2923 (1978).

[10] These assignments have been confirmed by simulation of the spectrum based on the experimental data for the AB-part of the ABX-system.

[11] In the 60 MHz spectrum this signal appeared as two overlapping triplets. This, in conjunction with an erroneous assignment of this signal at δ = 4.96, made the previous authors propose the initial formation of the isomers **12** and **13**.

[12] In the 250 MHz spectrum of the crude product mixture in $CDCl_3$ this signal appears like two triplets with overlapping outer lines, centered at δ = 5.40 and 5.43 with J ca. 5 Hz each.

[13] Prepared according to *L. N. Owen,* J. Chem. Soc. **1949**, 243.

[131/84]

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