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OXIDATION BY CHLORINE DIOXIDE OF METHIONINE AND CYSTEINE DERIVATIVES TO SULFOXIDES

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Methionine and cysteine derivatives were oxidized asymmetrically by chlorine dioxide to sulfinyl derivatives.

Key words: chlorine dioxide, *S*-containing amino acids, methionine, cysteine, oxidation.

Methionine sulfoxide is an amino acid of plant origin that is present in garlic [1], onion [2], nuts [3], carrots [4], apples [5, 6], and bananas [7]. Cysteine sulfoxide is widely distributed in nature and is responsible for the characteristic odor and taste of garlic and onion [8, 9].

Methionine and cysteine sulfoxides can be prepared by oxidation of the corresponding *S*-containing amino acids. Oxidation of methionine and cysteine derivatives by various oxidants is known to form sulfoxides and sulfones [10-12]. Compounds of this class have been used in organic synthesis as ligands to prepare complexes of transition metals [13].

Herein the oxidation of optically active *S*-containing amino acids L-methionine (**1**) and cysteine derivatives [*S*-methyl-L-cysteine (**2**), *S*-benzyl-L-cysteine (**3**), *S*-trityl-L-cysteine (**4**)] by chlorine dioxide (ClO_2) to sulfoxides is reported.

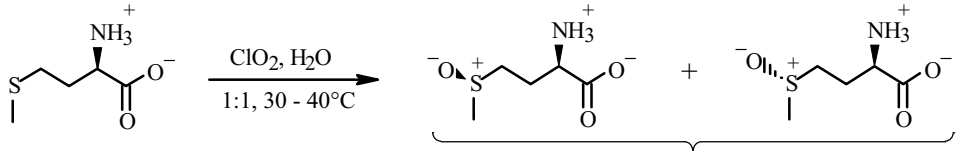
We established earlier that chlorine dioxide is a selective oxidant. Its reactivity can be regulated by changing the reaction conditions (ratio of reagents, temperature, time, solvent) [14].

Oxidation of **1**-**3** by aqueous ClO_2 at 30-40°C and a 1:1 substrate:oxidant mole ratio forms the corresponding sulfoxides in 95-97% yield. The structures of the products were elucidated by IR and NMR spectroscopy.

IR spectra of the oxidation products retained absorption bands characteristic of the carboxylic (1540-1650 cm^{-1}) and amino (1550-1485) groups. The appearance of an absorption band at 1040-1060 (S=O) indicated that sulfoxides were formed.

Oxidation of sulfides containing a chiral C atom to sulfoxides can be accompanied by a certain diastereoselectivity because of the formation of a new chiral center at the S atom.

Resonances corresponding to methylenes (multiplets at 2.40-2.43 ppm and 3.00-3.15) and amino acids (4.67-4.78) were observed in the PMR spectrum of **5**. Methyl protons resonated as two singlets (2.74 and 2.75), indicative of the formation by oxidation of enantiomerically pure methionine (**1**) as two diastereomers because the chirality at the α-C atom was retained and a new chiral center was formed at the S atom. According to NMR spectroscopy, the ratio of diastereomers was 1:1. Fractional crystallization from water:methanol mixtures with a gradually increasing methanol content in aqueous solution isolated two fractions from the mixture of diastereomers that were insoluble in methanol with $[\alpha]_D^{20}$ +60° (**5′**) and soluble in methanol with $[\alpha]_D^{20}$ –68° (**5″** (Scheme 1). It is known that the levorotary sulfoxide is soluble in methanol whereas the dextrorotary sulfoxide is poorly soluble [15].



1 **5**

Scheme 1

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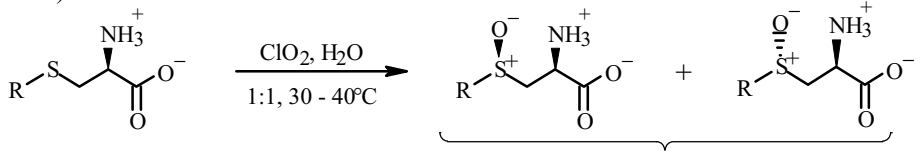
The dextrorotary sulfoxide obtained from L-methionine had the (*S*)-configuration around the asymmetric S atom whereas the levorotary sulfoxide had the (*R*)-configuration [16].

The resonances of the methyl protons were doubled in the PMR spectrum of oxidized methylcysteine **6** (2.83 and 2.84 ppm) (Scheme 2), analogously to the PMR specrum of **5**. The ratio of diastereomers according to the PMR spectra was 1:1. The PMR spectrum of **7** contained resonances for the amino acid and for aromatic protons. Two singlets (1:1 ratio) for methylene protons of the benzyl group were found at 3.66 and 3.69 ppm. This was also indicative of the formation of two diastereomers (Scheme 2).



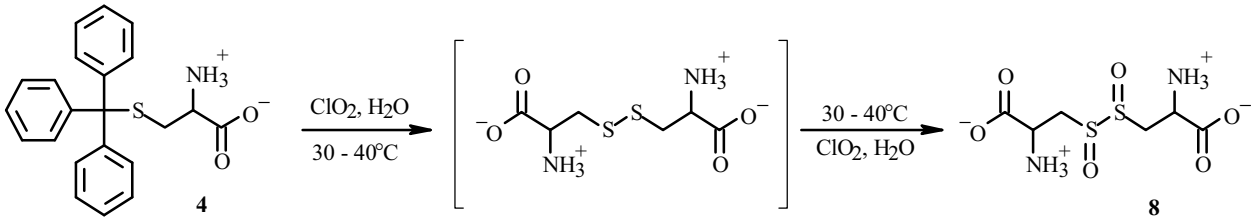
2, 3 **6, 7**

2, 6: R = CH_3; **3, 7:** R = Bn

Scheme 2

Thus, oxidation of S-containing optically active amino acids by aqueous ClO_2 produced sulfoxides (95-97% yield) that were a mixture of two diastereomers in almost equal amounts.

The behavior of *S*-trityl-L-cysteine (**4**) was unique. Oxidation of it by various oxidants caused cleavage of the *S*-trityl group and formation of triphenylmethyl cation and an intermediate complex, from which cystine disulfide was formed [16]. In our hands, oxidation of **4** by aqueous ClO_2 at 30-40°C at a 1:1 substrate:oxidant mole ratio probably also formed the disulfide that was then oxidized to the corresponding disulfoxide **8** in 95% yield (Scheme 3).



4 **8**

Scheme 3

The PMR spectrum of **8** did not exhibit resonances for the trityl protons and did contain resonances for methylene and methine protons as multiplets.

The triphenylmethyl cation was probably chlorinated to form triphenylchloromethane [17].

EXPERIMENTAL

IR spectra in KBr disks were recorded on a Specord M 80 spectrometer at 400-4000 cm^{-1}. NMR spectra in D_2O were recorded on a Bruker DRX-400 spectrometer (operating frequency 400 MHz) with HMDS internal standard.

We used commercially available *S*-methyl-L-cysteine, *S*-benzyl-L-cysteine, *S*-trityl-L-cysteine, and L-methionine (98-99% pure) without further purification. Ethanol and methanol were purified by distillation. The course of reactions was monitored by TLC on Silufol plates with elution by *n*-butanol:acetic acid:water (6:2:2). Compounds were detected by treatment with alcoholic ninhydrin (10 g ninhydrin, 90 g 95% ethanol).

S-containing amino acids were oxidized by ClO_2 prepared commercially as an aqueous solution (5-7 g/L) at OAO MBP Syktyvkar LPK. The amount of ClO_2 required for the reaction was calculated by taking into account the ClO_2 concentration in solution. The ClO_2 concentration in all instances was determined by the literature method [18].

General Method for Oxidation of *S*-Containing Amino Acids. A weighed portion of *S*-containing amino acid (1 mmol) was added with stirring to a 150-mL three-necked flask equipped with a thermometer and reflux condenser and containing aqueous ClO_2 (1 mmol) heated to 30°C. Stirring was continued until the reaction was finished (1 h, TLC monitoring) at 30°C. The water was distilled at reduced pressure. The oxidized product was purified by recrystallization from ethanol.

The following compounds were prepared by this method:

L-Methionine Sulfoxide (5). Yield 97%. IR spectrum (KBr, ν, cm^{-1}): 1030 (S=O), 1520 (N–H), 1595 (C=O). PMR spectrum (400 MHz, D_2O, δ, ppm): 2.40-2.43 (m, 2H, $C\underline{H}_2CH$), 2.74 and 2.75 (2s, 3H, CH_3), 3.00-3.15 (m, 2H, SCH_2), 4.14-4.18 (m, 1H, CH), 4.67-4.78 (m, 3H, NH_2, OH).

***S*-Methyl-L-cysteine Sulfoxide (6).** Yield 97%. IR spectrum (KBr, ν, cm^{-1}): 1650 (C=O), 1510 (N–H), 1035 (S=O). PMR spectrum (400 MHz, D_2O, δ, ppm): 2.83 and 2.84 (2s, 3H, CH_3), 3.19-3.57 (m, 2H, CH_2), 4.41-4.46 (m, 1H, CH), 4.71-4.91 (m, 3H, NH_2, OH).

***S*-Benzyl-L-cysteine Sulfoxide (7).** Yield 95%. IR spectrum (KBr, ν, cm^{-1}): 1648 (C=O), 1500 (N–H), 1046 (S=O). PMR spectrum (400 MHz, D_2O, δ, ppm): 2.18-2.34 (m, 2H, $C\underline{H}_2CH$), 3.06 (m, 1H, CH), 3.66 and 3.69 (2s, 2H, $C\underline{H}_2C_6H_5$), 4.99-5.10 (m, 3H, NH_2, OH), 6.55-6.69 (m, 5H, C_6H_5).

Dialaninedisulfoxide (8). Yield 95%. IR spectrum (KBr, ν, cm^{-1}): 1648 (C=O), 1496 (N–H), 1048 (S=O). PMR spectrum (400 MHz, D_2O, δ, ppm): 2.82-2.95 (m, 4H, 2 CH_2), 3.87-3.89 (m, 2H, 2 CH), 4.95-5.16 (m, 6H, 2 NH_2, 2 OH).

Method for Separating Diastereoisomers of *S*-Containing Amino Acids by Recrystallization. A weighed portion of methionine sulfoxide was recrystallized from methanol (40 mL, 80%). The compound obtained after recrystallization was dissolved in water (10 mL). Methanol was added to make the solution 60, 75, 85, and 91% in methanol by addition to the filtrate from each precipitation.

The following compounds were obtained by this method:

L-Methionine sulfoxide (5′), mp 178°C (dec.), $[\alpha]_D^{20}$ +60° (*c* 2.0, H_2O). PMR spectrum (400 MHz, D_2O, δ, ppm): 2.29-2.39 (m, 2H, $C\underline{H}_2CH$), 2.74 (s, 3H, CH_3), 3.00-3.14 (m, 2H, CH_2S), 3.86-3.92 (m, 1H, CH), 4.78 (s, 3H, NH_2, OH).

L-Methionine sulfoxide (5″), mp 238°C (dec.), $[\alpha]_D^{20}$ –68° (*c* 7.3, H_2O). PMR spectrum (400 MHz, D_2O, δ, ppm): 2.35-2.37 (m, 2H, $C\underline{H}_2CH$), 2.75 (s, 3H, CH_3), 3.00-3.15 (m, 2H, CH_2S), 4.04-4.08 (m, 1H, CH), 4.77 (s, 3H, NH_2, OH).

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