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POSSIBLE REACTION PATHWAYS FOR THE FORMATION OF 3-CHLORO-4-(DICHLORO METHYL)-5-HYDROXY-2(5H)-FURANONE (MX).

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ABSTRACT

Three compounds, 3,4,5-trimethoxybenzaldehyde (I), 1-dichloromethyl-3,4,5-trimethoxy-benzene (II) and 3,4,5-trimethoxyphenylacetic acid (III) were treated with aqueous chlorine at pH 2. Aqueous chlorination of the three compounds increased the formation of MX (3-chloro-4-dichloromethyl-5(2H)-hydroxy-furanone) and *E*-MX (*E* 2-chloro-3-dichloromethyl-4-oxo-butenoic acid) in the order I > II > III. By ^{1}H-NMR spectroscopy and gas chromatography it was shown that II hydrolizes readily to I in water. It is known that III is converted to II in chlorination reactions. We suggest that the (formed) aldehyde group remains intact during the formation of MX and *E*-MX from these three compounds. They could thus form MX and *E*-MX, via similar mechanisms. This suggested mechanism may also occur when phenolic precursor structures present in humic material are treated with chlorine in the process of drinking water production.

INTRODUCTION

The strong mutagen 3-chloro-4-dichloromethyl-5-hydroxy-2(5H)-furanone, (MX) is formed during chlorine disinfection of drinking water[1-3]. MX is the strongest mutagen identified in chlorine treated drinking waters[3], tested in the Ames-test[4]. Although MX is present only in trace quantities, ususally a few ng/L,

it contributes with 15-57 % to the total mutagenicity of these waters[5]. It is formed in the reactions between chlorine and the humic material present, probably aromatic units, in the raw water[6-8]. The aromatic structure of natural humic material has been studied by chemical degradation[8-10]. These studies show the precence of various phenolic units. Proton-NMR studies show that aldehyde groups as well as acid groups are present[11]. Several phenolic model compounds also produce MX, *E*-MX and related compounds by aqueous chlorination[12-14]. The less mutagenic isomer *E*-MX, *E*-(2-chloro-3-dichloromethyl-4-oxobutenoic acid), has always been found with MX. *E*-MX is also formed by aqueous chlorination of the same phenolic model compounds that MX is formed from and usually in higher concentrations[3,13-14]. The yields of MX and *E*-MX by chlorine treatment of some phenolic compounds are higher than from natural waters, but at most we found 0.3 % when the chlorination was performed at acid pH[13]. Therefore it is very difficult to establish definite mechanisms of formation. However, one mechanism was presented by Folke Österberg[15] and another mechanism was presented by Ruud Peters[14]. Peters suggest that *E*-MX is formed first and then MX is formed by isomerisation of *E*-MX. We discuss some aspects on the suggested mechanisms and present our experimental data on the chlorination of 3,4,5-trimethoxybenzaldehyde, 1-dichloromethyl-3,4,5-trimethoxybenzene and 3,4,5-trimethoxyphenylacetic acid (Fig. 1). Our results show that 1-dichloromethyl-3,4,5-trimethoxybenzene forms 3,4,5-trimethoxybenzaldehyde by hydrolysis in water. From the literature[16,17] it is known that phenylacetic acid can form a dichloromethyl group of the α-carbon by aqueous chlorination. A possible mechanism of MX and *E*-MX formation is suggested for 3,4,5-trimethoxybenzaldehyde.

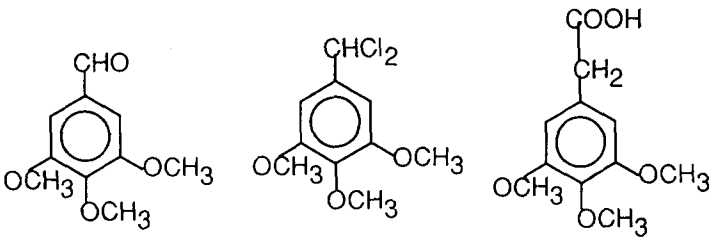

Fig. 1 Structures of the studied compounds.

EXPERIMENTAL

Preparation of 1-dichloromethyl-3,4,5-trimethoxybenzene. 1-dichloromethyl-3,4,5-trimethoxybenzene was prepared from 3,4,5-trimethoxybenzaldehyde (Aldrich-Chemie, Germany) by chlorination with PCl_5 at room temperature with dichloromethane as solvent and according to similar methods reported for the production of cinnamylidenchloride[18]. The compound was recrystallised five times from diisopropyl ether.

ether. Analytical data are as follows: ^{1}H-NMR($CDCl_3$) 6.7 (s, 2H), 6.6 (s, 1H), 3.9 (s, 9H). IR(KBr):3040-2860m, 2280s, 1600-625 many and strong bands. MS: M^+calc 250.0163, M^+found 250.0086, 215, 182. According to gas chromatographic (GC) analysis **II** was 90-95 % pure and contained 5-8 % I.

Chlorination of compounds and analysis of MX and *E*-MX. 50 mg of each 3,4,5-trimethoxybenzaldehyde (**I**), 1-dichloromethyl-3,4,5-trimethoxybenzene (**II**) and 3,4,5-trimethoxyphenyl acetic acid (**III**) (Aldrich-Chemie, Germany) were reacted with freshly prepared hypochlorite/hypochlorous acid in one liter 0.1 M phosphate buffer, pH 2.1 ± 0.1 until the chlorine residual was ≤ 0.15 mg/L (about 24 h). The reaction took place at ambient temperature in the dark. The work-up procedure was as described before[13]. The extracts were analyzed for MX and *E*-MX by gas chromatography/mass spectrometry in the selected ion monitoring mode after methylation[1,13].

^{1}H-NMR and gas chromatography (GC). 1-dichloromethyl-3,4,5-trimethoxybenzene was dissolved in a few mL of t-butanol before 0.1 M phosphate buffer (pH 2) was added. Samples were withdrawn at intervals and extracted with diethyl ether, dried with Na_2SO_4, the solvent was evaporated and the residue dissolved in $CDCl_3$ with 1 % tetramethylsilane as internal standard. **II** was dissolved in $CDCl_3$. Proton NMR spectra were recorded on a 60 MHz apparatus (JEOL PMX 60si) and changes in the shifts at 6.6 (dichloromethyl-group) and 9.8 (aldehyde-group) were monitored. GC analysis was used for quantification of the NMR results (Varian Model 3700 equipped with a FID detector; HP-1 25 m, 0.20 i.d.).

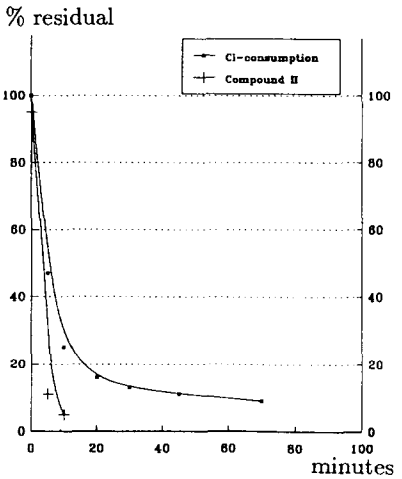

Fig. 2 Chlorine consumption and hydrolysis of **II**.

RESULTS AND DISCUSSION

All three compounds formed substantial amounts of MX and *E*-MX (Table I). The experiment was performed three times and the reported yields are mean values of the three determinations. We have reported

Table I Formation of MX and *E*-MX from I, II and III by aqueous chlorination at pH 2.

Compound	Chlorine dose mol/mol compd.	MX mmol/mol	*E*-MX
I	2:1	1.33	10.53
	4:1	0.86	6.34
II	2:1	1.10	6.20
	4:1	1.20	3.77
III	2:1	0.20	1.06
	4:1	0.67	1.88

on the formation of MX and *E*-MX from **I** earlier[13], but the formation from **II** and **III** has not yet been reported to our knowledge. The dichloromethyl-group of **II** seems to hydrolyze immediately (93 % within 6 min.) to an aldehyde group at pH 2 as determined from the gas chromatograms and the integrals of the NMR-spectrum, i.e. **II** converts to **I**. The rate of chlorine consumption of **II** was also very rapid, almost 80 % in ten minutes (Fig. 2). Compounds like **III** (i.e. having an electron-withdrawing group adjacent to the α-carbon) are known to react with chlorine to form a dichloromethyl-group from the α-carbon [16,17] and therefore **III** can form **II** (and eventually **I**). Thus the MX and *E*-MX formation from all three compounds may occur via common intermediates. From Table I it can be seen that **III**, **II** and **I** form MX and *E*-MX (taken together) in increasing amounts, when chlorine treated; i.e. in the order of increasing amount of aldehyde-group.

Our results indicate that the aldehyde group is of importance for the formation of both MX and *E*-MX from these compounds. Several aldehydes have been reported to produce MX and *E*-MX after chlorine treatment[13,14]. Homovanillic acid, which is also known to produce MX and *E*-MX[13] upon chlorination, may form an aldehyde group. Amino-groups are known to produce aldehyde groups when chlorine treated at relatively low doses[19]. Thus aldehyde groups can potentially be formed during chlorination of humic water and humic and fulvic acids, in addition to the ones possibly present in the native material. In water purification plants the water is chlorine disinfected at neutral pH, which would enhance the hydrolysis of formed dichloromethyl-groups to aldehyde-groups in the raw water. All three compounds formed more *E*-MX than MX. This is also found when humic water, humic and fulvic acids are treated with aqueous chlorine[7]. Peters[14] found that *E*-MX was formed in approx. four times higher amounts than MX, when he chlorinated 3,5-dihydroxybenzaldehyde. He suggests that the formation of MX would proceed via a mechanism adopted from the reaction of chlorine with resorcinol[20,21] leading to the formation of *E*-MX and eventually to MX by isomerisation. Fig. 3 a.

However, it has been shown that *E*-MX does not isomerise to MX practically at all at pH 6 or 8[21]. In fact, MX isomerises slowly to *E*-MX (and partly breaks down) at neutral pH. Peters shows that *E*-MX can isomerize to MX, but the work is actually performed at pH 2. The isomerisation at acid pH has been observed by others as well[22]. The mechanism Peters proposes includes the formation of one molecule of

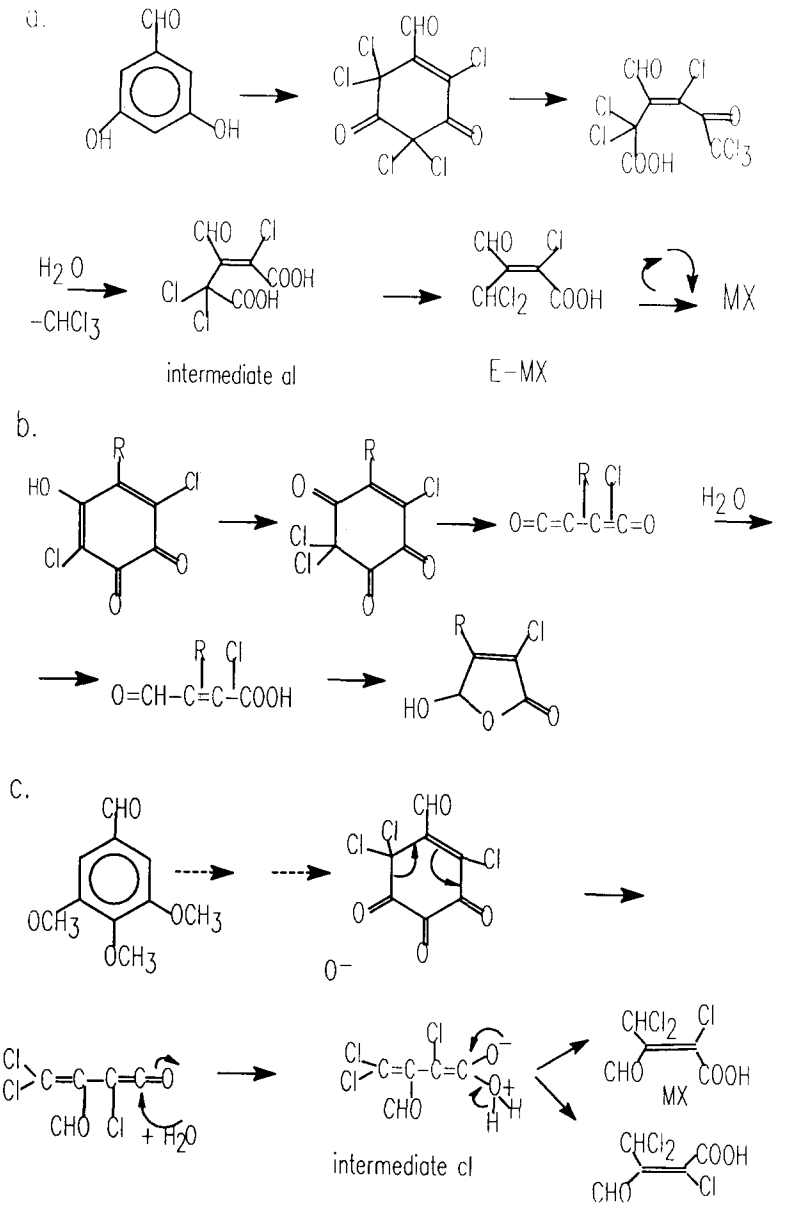

Fig. 3. Suggested mechanisms for the formation of MX and *E*-MX.

a. According to Peters (ref. 14).

b. According to Österberg (ref. 15)

c. a modified version of a. and b.

chloroform for one molecule of *E*-MX/MX. The formation of $CHCl_3$ from resorcinol is enhanced by alkaline pH[21], whereas MX concentrations are highest when chlorination is performed at acid conditions[3,13]. Thus this conceivable MX formation mechanism cannot be the main route to $CHCl_3$-formation.

To see if MX could be formed directly from intermediate aI (the mechanism suggested by Peters) we calculated the energy levels (MME) of the rotamers of intermediate aI in Fig. 3 a and the energy barrier between them with a molecule modelling computer program (ChemX). There was a small difference between the rotamers with the one forming MX on a lower level. The energy barrier between the two rotamers is considerable, but only about one fourth of a single double bond. The double bond is loosened because of the extensive conjugation of the molecule and it may be that the formation of *both* rotamers can occur leading eventually to the formation of *E*-MX and to a lesser extent MX, mainly via the mechanism proposed by Peters[14].

The mechanism of MX formation presented by Österberg[15] is reasonable from the point of view of organic and lignin chemistry. Fig. 3 b. We produced the MX precursor in Österberg's model without the hydroxy-group in the C6-position, but with a dichloromethylgroup as R. In water this group hydrolysed to an aldehyde group as easily as **II** did (data not shown). If the R-group in the mechanism of Österberg was a dichloromethyl-group initially (or formed during the reactions) it seems that it would hydrolyze to an aldehyde group, giving rise to a fragment different from MX. To explain the formation of MX (and *E*-MX) from **I** (and **II** and **III**) we suggest a modified mechanism from the two aforementioned. Fig. 3 c. It starts with the formation of a quinoid structure and the incorporation of chlorine into the aromatic ring like the other two mechanisms discussed. The aldehyde group remains intact througout the reaction like in the suggestion made by Peters[14]. Because of the single bond between the C2 and C3 in intermediate cI both MX and *E*-MX can be formed via this mechanism but the formation of *E*-MX could be slightly favoured because of steric reasons. It should be emphasized that the formation mechanisms discussed refers to the small proportion of the chlorination reactions leading to the formation of MX/*E*-MX.

In conclusion, we suggest that aldehyde groups (or potential ones) in the aromatic rings of natural humic material are important for the formation of MX and *E*-MX by chlorination. The aldehyde-group remains intact during the reaction. We also suggest that the formation of both MX and *E*-MX from **III** and **II** proceeds via the pathway suggested by us for 3,4,5-trimehtoxyaldehyde. The formation of MX from 3,5-dihydroxyaldehyde may proceed via the mechanism suggested by Peters[14]. However, it seems more probable that isomers of the intermediates are formed rather than isomerization of *E*-MX to MX at neutral pH.

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