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Ozone Degradation of Iodinated Pharmaceutical Compounds

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25   **Abstract**

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27   This study investigates the aqueous degradation of four iodinated X-ray contrast media (ICM)

28   compounds (diatrizoate, iomeprol, iopromide and iopamidol) by ozone and combined ozone

29   and hydrogen peroxide. In laboratory scale experiments, second order kinetic rate constants

30   for the reactions of the ICM compounds with molecular ozone and hydroxyl radicals, and

31   overall at pH 7.5, were determined. For the four ICM compounds the degradation rate

32   constants with molecular ozone were low and in the range of 1-20 $M^{-1} s^{-1}$, while the rate

33   constants with hydroxyl radicals were in the range of 1×10^9 - 3×10^9 $M^{-1} s^{-1}$. Diatrizoate had

34   the lowest rate constant of the four compounds with respect to molecular ozone reactions. At

35   pH 7.5, the extent of compound degradation was proportional to the applied ozone dose and

36   inversely related to the initial compound concentration at a given ozone dose. At this pH

37   approximately 90% of the degradation could be attributed to hydroxyl radical reactions.

38   Enhancement of the radical mechanism by the addition of hydrogen peroxide during

39   ozonation led to complete removal of the non-ionic compounds, and > 80% removal of

40   diatrizoate, at relatively low oxidant mass ratios ($H_2O_2/O_3 < 0.25$). A similar enhancement in

41   compound degradation was evident with the presence of small concentrations of humic

42   substances (~ 4-5 mg l^{-1}). Ozone oxidation led to major cleavage of the ICM compounds and

43   the release of inorganic iodine; the proportion of iodine release was similar among the non-

44   ionic ICM compounds but much greater for diatrizoate.

45

46   **CE Database Subject Headings:** Ozone, hydrogen peroxide, kinetics, halogen organic

47   compounds

Introduction

In the last decade it has been discovered that some municipal wastewater plant effluents contain high concentrations of adsorbable organo halogen (AOX) compounds, which can be differentiated as AOCl, AOBr, and AOI in respect to chlorine, bromine and iodine; among them, the AOI compounds contributes a large part to the total AOX. Based on the consumption of halogenated pharmaceuticals, iodinated X-ray contrast media (triiodinated benzene derivatives) (ICM) are the main contributors to the burden of total AOX compounds in clinical wastewater (Gartiser et al., 1996); ICM substances are used typically for medical diagnostic purposes. The observation that AOI concentrations in municipal treatment plant effluent receiving hospital wastewater are higher during week days rather than at the weekend, also indicates that ICM compounds are responsible for high AOI (Putschew et al., 2001). The global consumption of ICM is approximately 3500 tons annually. In Germany, a total of about 500 tons of all approved ICM compounds is used annually, with iopromide accounting for 130 tons (Steger-Hartmann et al., 1999). In one medical examination alone, 100 g of ICM (~ 30 g AOI equivalent) can be consumed (Putschew et al., 2001). In the aqueous environment, several iodinated compounds have been measured at μg l^{-1} levels, including groundwater, wastewater treatment plant effluents, rivers, creeks, and even drinking water (Hirsch et al., 2000; Putschew et al., 2000; Ternes and Hirsch, 2000).

Most individual compounds of ICM are derivatives of 2,4,6-triiodobenzoic acid, possessing polar carboxylic and hydroxyl moieties in their branch chain. These can be divided into two main categories: 1) ionic compounds containing a free carboxylic moiety (e.g. diatrizoate); 2) non-ionic compounds (NI-ICM) in which all carboxylic moieties are amide derivatives (Ternes and Hirsch, 2000). These compounds are released from the human body via urine and excrement after several hours of being applied, without being metabolised.

72   Since ICM are designed to have high polarity (e.g. $\log K_{ow} = -2.33$ (Octanol-Water Partition

73   Coefficient) for iopromide), water solubility, persistency, chemical and biological stability, to

74   ensure their effectiveness during X-ray examination and to prevent undesirable toxicological

75   effects caused by degradation products, there is no significant removal of ICM by

76   conventional municipal wastewater treatment processes (Kalsch, 1999; Ternes and Hirsch,

77   2000). For example, solid-phase adsorption has been confirmed to be ineffective (Steger-

78   Hartmann et al., 1999). While the ICM compounds themselves are not considered to

79   represent a significant risk to human health, there is greater concern about the eco-toxicity

80   (eg. mutagenicity) of metabolite/transformation products of ICM, whose presence is

81   suspected but of which very little is known (Kalsch, 1999; Putschew et al., 2000; Seitz et al.,

82   2006). Therefore, the need to identify effective treatment methods is a necessary precaution

83   while evidence concerning their toxicity, and that of their metabolite/transformation products,

84   is accumulated.

85   Among the potential technologies for treating ICM, ozone and advanced oxidation

86   processes (AOPs) are of interest since they are capable of transforming the compounds into

87   reaction products with less, or no, toxicological effect, rather than simply separating them

88   from the flow (e.g. by adsorption or membrane processes). AOPs comprise technologies that

89   generate hydroxyl radical (·OH) species which are powerful oxidants (next highest oxidation

90   potential after fluorine, at 2.86 V (Martins, 1998)) that can achieve effective degradation of a

91   wide range of organic contaminants in polluted water and air (Bolton et al., 1996). These

92   technologies are increasingly used in water and wastewater treatment plants (Capelo et al.,

93   2004; Murray and Parsons, 2004a and 2004b; Schrank et al., 2004).

94   Ozone is widely used in water and wastewater treatment due to its high oxidation

95   potential and avoidance of significant reaction products of toxicological concern (Paraskeva

96   and Graham, 2002). When applied in aqueous solution, substrate reactions occur partly by

97   direct (selective) interaction with molecular ozone, and partly by indirect (indiscriminate)

98   interactions with ·OH radicals, produced by the decomposition of ozone. Under aqueous

99   conditions typical of natural waters and wastewaters both direct and indirect reactions will

100   proceed simultaneously, and the contribution made by indirect reactions (via radical attack)

101   increases with increasing pH (Hoigné and Bader, 1983). The extent of radical reaction,

102   whether through the use of ozone at elevated pH or by applying an AOP (e.g.

103   ozone/hydrogen peroxide), depends in large measure on the nature of the water quality, and

104   specifically on the presence of scavenging or inhibiting species, such as natural organic

105   matter (e.g. humic substances - HS) and alkalinity.

106   HS, such as humic acid, are widely present in natural and waste waters at

107   concentrations ranging from several mg l^{-1} to tens of mg l^{-1} (Graham et al., 2003), and may

108   contribute up to 50% of the total aqueous organic content (Latifoglu and Gurol, 2003). As a

109   complex mixture of compounds, the role of HS has been studied in the ozonation process and

110   previous studies have confirmed their importance as initiators, promoters and scavengers of

111   hydroxyl radicals (Xiong and Graham, 1992; Graham et al., 2003). It is clear that the nature

112   of the ozone reactions with HS are very complex but that, in general, at relatively low HS

113   concentrations the interactions can enhance the degradation of organic substrates, while at

114   higher concentrations the degradation efficiency can be reduced significantly.

115   In this paper we describe the reactivity of a specific group of ICM compounds,

116   including one ionic compound, diatrizoate, and three NI-ICM compounds, iopromide,

117   iopamidol and iomeprol, with ozone, and specifically with molecular ozone and hydroxyl

118   radicals. The laboratory tests involved the determination of second order rate constants, and

119   an investigation of the role of HS in solution and the potential benefits of adding hydrogen

120   peroxide to the ozonation reaction.

121

122   **Experimental Methods**

123   *Materials*

124   Due to their wide use and large global consumption, four ICM compounds were

125   chosen to study in this work. Diatrizoate acid dihydrates (solid) and iopromide were

126   purchased from Schering AG (Berlin, Germany) with high purity. Iomeprol and iopamidol

127   were purchased from Bracco (UK), as 51.03% and 75.5% aqueous solutions (250 and 370 mg

128   I ml^{-1}), respectively, containing trometamol and hydrochloric acid (at low concentrations).

129   All organic compounds were used without any further purification. The chemical structures

130   of these compounds are illustrated in Fig. 1; the pK_a (acid dissociation constant) of diatrizoic

131   acid is 3.4, and in the range of 10.2-10.6 for iopromide, iopamidol and iomeprol. Aqueous

132   solutions of organic compounds were prepared in Milli-Q high purity water (> 18.2 MΩ) up

133   to the concentration of 1000 mg l^{-1} as stock, and stored at 4 ˚C, ready for use. Organic

134   solvents were HPLC (high performance liquid chromatography) grade and obtained from

135   VWR (UK).

136   In order to investigate the behaviour of the ICM with different oxidant species and at

137   different pH values, pH buffer solutions were used. Thus, pH 2 stock buffer solution was

138   prepared by dissolving 10 g of analytical grade sodium dihydrogen phosphate and 7 ml

139   analytical grade phosphoric acid (d = 1.7 g ml^{-1}, 85%) in 1 litre Milli-Q high purity water

140 (Xiong and Graham, 1992). Higher pH buffer solutions were obtained by adding different

141 quantities of 2 M sodium hydroxide solution to the stock pH 2 buffer.

142   Hydrogen peroxide was obtained as a 35% solution (Acros Organics, UK), and

143 diluted to 750 mg l^{-1} as stock solution ready to use. Humic acid sodium salt (Aldrich, UK)

144 was employed in later tests as a model material representing HS.

145

146   *Analytical methods*

147   Determination of the ICM compounds in aqueous solution was carried out by HPLC

148 coupled with ultraviolet (UV) detection. A 150×4.6 mm, 5 µm C_{18} column was used at room

149 temperature (21 ˚C) with a gradient programme and isocratic flow rate of 1.0 ml min^{-1} of

150 eluent as follows: where A = Milli-Q water + 0.05% trichloroacetic acid (w v^{-1}) and B =

151 methanol + 0.05% trichloroacetic acid (w v^{-1}), from 5% B to 8% B in 10 min, to 40% B after

152 45 min, hold for 10 min, back to 5% B after 55 min, and then hold 20 min for equilibration.

153 The UV detector wavelength was set at 238 nm (Turpeinen and Pomoell, 1986). The

154 ozonation byproduct, iodate (IO_3^-), was measured by HPLC, coupled with an Ion-Pak (Anion)

155 column, using an isocratic programme (water + 1.7 mM $NaHCO_3$ + 1.8 mM Na_2CO_3), and

156 UV detection at 205 nm;

157   The total organic carbon (TOC) of ozonated solutions was measured using a TOC

158 analyzer (Shimadzu TOC-Vws), calibrated by Milli-Q high purity water and potassium

159 hydrogen phthalate solutions (10 mg l^{-1} presented as TOC). Sample analysis of TOC was

160 carried out in duplicate in most cases to minimize system errors, and all duplicated

161 experiments showed good reproducibility corresponding to a standard deviation of less than

162 5%.

163

164   *Ozonation method*

165   Ozone was produced from pure medical grade oxygen using a LABO (II) ozone

166   generator (Ozotech UK). Stock aqueous ozone solutions were prepared by bubbling ozone

167   into buffered Milli-Q high purity water to the required concentration. The concentration of

168   aqueous ozone was determined by UV spectrometry at 258 nm (molar extinction coefficient

169   is $2950 \ l \ mol^{-1} \ cm^{-1}$); this method has been widely used for pure ozone solutions or inorganic-

170   buffered ozone solutions. The ozonation experiments were initiated by mixing appropriate

171   quantities of aqueous ozone solution with solutions of concentrated ICM compounds. After

172   ozonation, the residual concentration of ozone was measured by the standard indigo method,

173   instead of the UV method in order to avoid the possible interference from other dissolved

174   organic compounds; in solution, ozone rapidly decolorizes indigo ($k > 10^7 \ M^{-1} \ s^{-1}$), and the

175   decrease in UV absorbance of the indigo solution is linear with increasing concentration of

176   ozone (Bader and Hoigné, 1981). All experiments were performed at a constant

177   temperature 21 ± 1 ˚C.

178

179   *Kinetic reaction rate modelling*

180   **Kinetic rate constant of ozone consumption (k_{O_3})**

181   The direct reaction of molecular ozone with an ICM compound can be expressed by

182   Eq. 1:

183         $$ICM + \beta \cdot O_3 \rightarrow PRODUCTS \qquad\qquad (1)$$

184   where β represents the molar stoichiometry of the reactants.

185   At pH 2, the ICM compounds are undissociated (in the case of diatrizoate, the

186   compound is mainly undissociated, since the $pK_a \sim 3.4$) and the decomposition of molecular

187 ozone is assumed to be slow. Thus, the ozonation reaction can be assumed to be second order

188 with respect to molecular ozone and ICM, and the rate equation can be expressed as:

189 $$-d[O_3]/dt = k_{O_3}[O_3][ICM] \qquad (2)$$

190 If the experiments are conducted in conditions where the ICM compound is in relative

191 excess compared to ozone, the reaction rate will be pseudo-first order. The explicit ozone

192 decay equation can be obtained by the integral of Eq. 2, as follows:

193 $$\ln[O_3]_t = \ln[O_3]_0 - k_{O_3}[ICM]_0 \cdot t = \ln[O_3]_0 - k'_{O_3} \cdot t \qquad (3)$$

194 where k'_{O_3} is the apparent rate constant, and $k'_{O_3} = k_{O_3}[ICM]_0$.

195 Experiments were performed in Milli-Q high purity water with phosphate buffer to

196 pH 2 to avoid hydroxyl radical formation from decomposition chain reactions. The second

197 order rate constants were determined under conditions where the ICM was in excess (mole

198 ratio [ICM]:[O$_3$] > 10). The tests were undertaken in 250 ml flasks (single-reactor) with the

199 reaction initiated by addition of small quantities of concentrated ozone stock solutions (16 mg

200 l^{-1}) to solutions containing the ICM compound. After mixing for 5 seconds by magnetic

201 stirrer, sampling was performed at fixed time intervals, and residual ozone concentrations

202 were measured by the indigo method. Several experiments with different initial ICM

203 compound concentrations were performed under identical conditions. The results were

204 evaluated by plotting the logarithm of the residual ozone versus time, and determining the

205 apparent rate constant (k'_{O_3}) from the gradient of the line of best fit. From the linear

206 variation of k'_{O_3} with the initial ICM compound concentration, the rate of ozone consumption

207 (k_{O_3}) can be determined from the gradient of the line.

208

209   **Degradation rate constant of ICM compounds with molecular ozone (k_{ICM/O_3})**

210   The degradation of ICM compounds with molecular ozone can be expressed by Eq. 4:

211      $$-\mathrm{d}[ICM]/\mathrm{d}t = k_{ICM/O_3}[O_3][ICM] \qquad (4)$$

212 where k_{ICM/O_3} is the reaction rate constant.

213   The value of the rate constant (k_{ICM/O_3}) for each compound was determined at pH 2

214 where it was assumed that each compound is undissociated and that hydroxyl radical species

215 were effectively absent. In addition, the rate constant for dissociated diatrizoate with

216 molecular ozone was determined at pH 7.5 in the presence of *tert*-BuOH as hydroxyl radical

217 scavenger. The rate constant can be obtained from the integration of Eq. 4, as follows:

218      $$\ln([ICM]_t/[ICM]_0) = -k_{ICM/O_3}\int_0^t [O_3]dt \qquad (5)$$

219 where the term $\int_0^t [O_3]dt$ represents the time-integrated concentration of ozone. The value of

220 the second order rate constant (k_{ICM/O_3}) can be found from the gradient of a plot of log

221 reduction of ICM compound against the time-integrated ozone concentration.

222

223   **Competition kinetics method**

224   A competition kinetics method was used to determine the ICM compound degradation

225 rate under conditions where the determination of residual ozone is impractical owing to its

226 rapid decomposition (ie. pH 7.5). This method requires a reference compound with a known

227 degradation rate constant that can be readily analyzed with the individual ICM compound

228 under study. The herbicide, atrazine, was employed as the reference compound since it has

229 been extensively studied and was expected to demonstrate a similar reaction mechanism and

230 rate constant with ozone ($k_{pH2} = 2.250$ and $k_{pH7.5} = 12.244$ M^{-1} s^{-1} (Xiong and Graham,

231   1992)). Experiments were performed using a series of 25 ml conical flasks (multi-reactor)

232   containing equal concentrations of ICM compounds and reference compound at pH 7.5. The

233   reaction was initiated by adding different sub-stoichiometric amounts of aqueous ozone

234   solution to the ICM compound solutions. After 2 hours of reaction with continuous stirring,

235   during which all the dissolved ozone was consumed, the residual concentrations of ICM

236   compounds and atrazine were measured by HPLC. From these results the compound

237   degradation rate constant was obtained according to Eq. 6:

238    $$\ln([ICM]_0 / [ICM]_t) = k_{ICM} / k_{Atrazine} \ln([Atrazine]_0 / [Atrazine]_t) \qquad (6)$$

239

240   **Stoichiometric factor (β)**

241   As explained above, the direct reaction of molecular ozone with ICM compounds can

242   be expressed by Eq. 1, therefore, $k_{O_3} = \beta \times k_{ICM/O_3}$, and the stoichiometric factor is given by:

243    $$\beta = k_{O_3} \big/ k_{ICM/O_3} \qquad (7)$$

244   where β is the stoichiometric factor corresponding to the number of ozone molecules

245   consumed per molecule of ICM degraded.

246

247   **Reaction kinetics with ·OH radicals**

248   A similar competition kinetics method was used to determine the second order rate

249   constants for the reaction between the ICM compounds and hydroxyl radicals ($k_{ICM/\cdot OH}$),

250   produced from the decomposition of ozone. The rate constants can be determined by

251   following the removal of an ·OH-probe compound, which can give indirectly the

252   concentration of ·OH radicals in the ozonation process (Elovitz and von Gunten, 1999).

253   During ozonation an ideal ·OH-probe compound reacts only with ·OH radicals and not with

254 molecular ozone or its secondary oxidants and other reaction species. Hence, by measuring

255 the decomposition of the ·OH-probe compound, the ·OH concentration could be calculated

256 indirectly. In our experiments, p-chlorobenzoic acid (pCBA) was used as the ·OH-probe

257 compound because of its very low reactivity with molecular ozone ($k_{pCBA/O_3} < 0.15$ M^{-1} s^{-1}),

258 but extremely rapid reaction with ·OH ($k_{pCBA/·OH} = 5 \times 10^9$ M^{-1} s^{-1}); pCBA is highly

259 dissociated at pH 6.0 - 9.0, with a pK_a of 3.99 (Elovitz and von Gunten, 1999).

260   The ozonation method was developed from that described by Elovitz and von Gunten

261 (1999), and a heterogeneous gas ozone bubbling system was employed, in which the

262 concentration of ozone can be controlled at a required level by adjusting the ozone generator

263 conditions. The method makes use of a parameter, R_{ct}, which represents the ratio of the ·OH-

264 exposure to the molecular ozone-exposure that can be calculated as a function of reaction

265 time. The value of R_{ct} ($= [·OH]/[O_3]$) has been shown to be constant for the majority of

266 ozonation reactions for a given pH value (Elovitz and von Gunten, 1999). Thus, by

267 controlling the concentration of ozone, the concentration of hydroxyl radicals is also

268 controlled since R_{ct} is constant at a given pH. As indicated above, the probe compound

269 (pCBA) has a very low reactivity with ozone and therefore the kinetics of the reaction with

270 ·OH can be expressed by Eq. 8:

271       $$-\mathrm{d}[pCBA]/\mathrm{d}t = k_{pCBA/·OH}[pCBA][·OH] \tag{8}$$

272   Integration of Eq. 8 gives the following expression in terms of the ·OH concentration:

273       $$\ln([pCBA]_t/[pCBA]_0) = -k_{pCBA/·OH}[·OH]\cdot t \tag{9}$$

274   Hence, the reduction in concentration of the probe compound at any time provides an

275 indirect measurement of the ·OH-exposure for the reaction period. The parameter, R_{ct}, is

276   defined by Eq. 10:

$$R_{ct} = \int [\cdot OH] dt \Big/ \int [O_3] dt = [\cdot OH]/[O_3] \qquad (10)$$

278   Substitution of Eq. 10 into Eq. 9 gives:

$$\ln([pCBA]_t / [pCBA]_0) = -k_{pCBA/\cdot OH} R_{ct} [O_3] \cdot t \qquad (11)$$

280   Eq. 11 suggests that the ratio of ·OH-exposure to ozone-exposure (R_{ct}) could be

281   calculated from the variation of the concentrations of pCBA and ozone. Therefore, R_{ct} can be

282   found from the gradient of a plot of the log-reduction of pCBA (left-hand side of Eq. 11)

283   against reaction time, because in the experiment the ozone concentration is kept constant and

284    $k_{pCBA/\cdot OH}$ is a known constant value of 5×10^9 $M^{-1} s^{-1}$ (Elovitz and von Gunten, 1999).

285   The degradation of each ICM compound can be described by an overall kinetic

286   equation involving the second order reactions of the compound with both ozone and ·OH.

287   The kinetic equations are:

$$-d[ICM]/dt = k_{ICM/\cdot OH}[\cdot OH][ICM] + k_{ICM/O_3}[O_3][ICM] \qquad (12)$$

$$= k_{ICM/\cdot OH} R_{ct}[O_3][ICM] + k_{ICM/O_3}[O_3][ICM] \qquad (13)$$

$$= (k_{ICM/\cdot OH} R_{ct} + k_{ICM/O_3})[O_3][ICM] \qquad (14)$$

291   Integration of Eq. 14 yields the following equation which can be used to determine

292   the rate constants:

$$\ln([ICM]_t / [ICM]_0) = -(k_{ICM/\cdot OH} R_{ct} + k_{ICM/O_3})[O_3] \cdot t \qquad (15)$$

294   where $k_{ICM/\cdot OH}$ and k_{ICM/O_3} are the second-order rate constants for the reaction of each ICM

295   compound with ·OH radicals and molecular ozone, respectively.

13

296   On the basis of Eq. 15, experiments were undertaken to determine the value of

297    $k_{ICM/\cdot OH}$ for each ICM compound. A custom-made 500 ml glass reaction vessel equipped

298   with an ozone gas bubbling system was employed for the tests and the reactions were

299   undertaken as follows. An aqueous ozone solution of the required concentration (measured

300   by UV spectrophotometer at 258 nm) was prepared by bubbling ozone gas for 10 min into

301   Milli-Q high purity water, buffered to pH 7.5 with phosphoric acid. The reaction was initiated

302   by adding small quantities of concentrated ICM compound and pCBA solution, and after 5

303   seconds of mixing, samples (1 ml) were taken from the vessel in fixed time intervals, and

304   mixed with 0.5 ml $K_2S_2O_3$ to quench the residual ozone. The residual concentrations of ICM

305   compound and pCBA were determined by HPLC. At a given pH and temperature, the value

306   of R_{ct} is determined from the change is pCBA (Eq. 11) and hence, from Eq. 15, the value of

307    $k_{ICM/\cdot OH}$ can be calculated from the plot of log removal of ICM compound versus the reaction

308   time.

309

310   **Results and discussion**

311   *Kinetic rate constants of ICM compounds*

312   The kinetic rate constants for the ICM compounds were determined from the

313   ozonation experiments undertaken at either pH 2 or 7.5 and by the various methods described

314   above; the values of the rate constants are given in Table 1. Most of the experiments were

315   duplicated and standard deviations were less than 10%.

316   In general, the overall compound degradation rate constant at a given pH value will

317   reflect the form of the compound (ie. degree of dissociation) and the proportion of molecular

318   ozone and hydroxyl radical species present during the reaction. The results in Table 1 show

319   that the reaction rates of the four ICM compounds with molecular ozone are relatively low,

320   and that the de-protonated form of diatrizoic acid, diatrizoate, was more reactive with

321   molecular ozone than the acid. Also, the non-ionic ICM compounds were found to be more

322   reactive than diatrizoate with molecular ozone. Even at pH 7.5, where the reaction rates are

323   higher, the compound degradation rate constants are relatively low (≤ 30 $M^{-1}s^{-1}$), which are

324   consistent with the findings of other studies that have reported a poor overall removal extent

325   of ICM compounds with ozonation (e.g. (Seitz et al., 2006)). The greater degradation rates at

326   pH 7.5, compared to those under acid conditions, reflect the significant contribution of

327   hydroxyl radical attack at pH 7.5; the corresponding reaction rate constants for hydroxyl

328   radical attack are extremely high ($\sim 1.0 \times 10^{9}$) and approximately equivalent for the four ICM

329   compounds (see Table 1).

330   Reactions involving molecular ozone are highly selective and demonstrate similar rate

331   constants with specific compound moieties. For instance, the (deprotonated) phenolic moiety

332   is very reactive with ozone, with rate constants $\sim 10^{9}$ $M^{-1}s^{-1}$ (Deborde et al., 2005), while for

333   aromatic amino groups the reaction rate constants are much lower at $\sim 10^{6}$ $M^{-1}s^{-1}$ (Huber et

334   al., 2003). In the case of the ICM compounds relatively low degradation rate constants (< 30

335    $M^{-1}s^{-1}$) were obtained, which can be explained by the absence of ozone active groups, and all

336   the reactive positions in the aromatic/benzoic acid rings are occupied by weakly active

337   groups, such as the iodine atom. Similarly low rate constants were found in previous studies

338   for phenoxyalkyl acid derivative herbicides (Xiong and Graham, 1992). The relatively low

339   kinetic rate constants with molecular ozone indicate that under aqueous conditions typical of

340   water and wastewater treatment (ie. pH $\sim$ 7), direct ozone reactions will play a secondary role,

341   and the principal degradation mechanism will be via hydroxyl radical attack (this is discussed

342 later – Fig. 4). Thus, reaction rate constants for the ICM compounds with ·OH radicals have

343 been determined in our experiments. The rate constants were found to be very high and in the

344 range of $1-3\times10^9$ $M^{-1}s^{-1}$; however, although these are very high they are also relatively low

345 compared with other pharmaceutical chemicals (Huber et al., 2003). The degradation rate

346 constant, $k_{ICM/·OH}$, for iomeprol is similar to that found by Huber et al. (2003) (ie.

347 $3.3\pm0.6\times10^9$ M^{-1} s^{-1}) for oxidation by O_3/H_2O_2 and γ-radiolysis methods (Huber et al.,

348 2003).

349

350 ***Removal of ICM under various ozone conditions***

351 The ICM compound degradation rate was studied at pH 7.5 to investigate the effect of

352 ozone dose and initial concentration of ICM compounds. In general, the removal of ICM

353 compounds by ozone is only moderate, with diatrizoate showing the least reactivity with

354 ozone. Thus, for an ozone dose of 16 mg l^{-1} and a reaction time of 30 min (complete

355 consumption of ozone), only 26% of 10 mg l^{-1} diatrizoate was degraded, and for the other

356 three compounds the oxidation efficiency ranged from 52 to 77%.

357 Fig. 2 shows the influence of ozone dose on the removal of ICM compounds (initial

358 concentration: 10 mg l^{-1}), based on a 30 min reaction period. Clearly, greater removal

359 efficiencies are achieved with higher ozone dosages, as would be expected from the second-

360 order rate equation (Eq. 12), and the non-linear variation partly reflects the complementary

361 reactions between reaction intermediate products with ozone. Fig. 3 shows the effect of initial

362 concentration of ICM compound on removal efficiency for a given applied ozone

363 concentration of 16 mg l^{-1}. It can be seen that the degree of compound removal was inversely

364 related to the initial compound concentration. Whilst this behaviour may only be accounted

365   for/validated by detailed modelling, owing to the complexity of the ozone/radical interactions

366   with the compound, the overall trend is intuitively plausible; that is, for a given quantity of

367   ozone available for reaction, the extent of compound degradation (%) is inversely related to
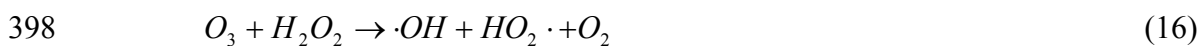
368   its initial concentration.

369   The results of the ozone tests are similar to those obtained in the study by Ternes et al.

370   (2003), which also showed incomplete degradation of ICM compounds with initial ozone

371   dosages ranging from 5 and 15 mg l^{-1}, and that an increase in removal efficiency with

372   increasing ozone dose. Diatrizoate was found to be especially recalcitrant and had the lowest

373   removal rate of the ICM compounds studied (Ternes et al., 2003).

374   From the earlier kinetics studies, the compound decomposition rates were observed to

375   be much higher at near-neutral pH conditions (pH 7.5) than those in acid conditions (pH 2)

376   owing to the presence of hydroxyl radical chain reactions. These reactions mechanisms were

377   examined by undertaking tests in the presence of *tert*-BuOH, which is a powerful hydroxyl

378   radical scavenger and relatively un-reactive with molecular ozone; the reaction rate constant

379   of *tert*-BuOH with molecular ozone is extremely small (0.003 $M^{-1}s^{-1}$) compared to that with

380   hydroxyl radicals (7.6×10^8 $M^{-1}s^{-1}$) (Staehelin and Hoigné, 1982). Thus, if the role of

381   hydroxyl radicals is a significant one, it would be expected that the degradation efficiency of

382   ICM compounds would be greatly reduced in the presence of *tert*-BuOH. An excess of *tert*-

383   BuOH (100 mg l^{-1}) was used in the experiments in order to maximum the radical scavenging.

384   Fig. 4 summarises the results and shows the great difference in compound removal efficiency

385   in the presence/absence of *tert*-butanol. It is clear that the decomposition of ICM compounds

386   at pH 7.5 is overwhelmingly caused by reactions with ·OH radicals, equivalent to

387   approximately 90% of the total degradation (Fig. 4).

388

389   *Ozonation of ICM compounds in the presence of hydrogen peroxide*

390   In the previous tests, it is clear that ICM compound degradation is not rapid or

391   complete under the ozonation conditions studied, and hydroxyl radicals have been confirmed

392   to be the principal oxidant. Many previous studies have demonstrated the effectiveness of

393   combining ozone with hydrogen peroxide to enhance the oxidation of refractory organics;

394   this is based on the ability of hydrogen peroxide to initiate the decomposition of ozone (at

395   mass ratios of H_2O_2:$O_3 < 1$:1) leading to greater formation of hydroxyl radicals than with

396   ozone alone, or with elevated hydroxide ion concentrations (Staehelin and Hoigné, 1982).

397   The simplified mechanisms are shown in the following Eqs. 16-17:

398          $$O_3 + H_2O_2 \rightarrow \cdot OH + HO_2 \cdot + O_2 \qquad\qquad (16)$$

399          $$O_3 + HO_2 \cdot \rightarrow \cdot OH + 2O_2 \qquad\qquad (17)$$

400   Hydrogen peroxide can also act as a radical scavenger at higher relative

401   concentrations so the applied dosage needs to be optimised (Lee et al., 2003). In this phase of

402   the experimental work, the potential enhancement of ICM compound degradation by

403   combined ozone and hydrogen peroxide was studied. The method involved making an

404   aqueous ozone solution to the required concentration (by bubbling gaseous ozone into 250 ml

405   Milli-Q water for approximately 10 min), to which concentrated hydrogen peroxide was

406   added, followed in turn by the addition of the ICM compound to the reaction vessel to

407   initiated the oxidation reaction.

408   The combination of ozone and hydrogen peroxide process was confirmed to be very

409   effective for ICM compound degradation. Fig. 5 shows the removal efficiency of each

410   compound in the presence of hydrogen peroxide ranging from 0 to 15 mg l^{-1}, based on 30 min

411 of reaction. For 10 mg l^{-1} of each of the NI-ICM compounds, a complete degradation was

412 achieved by the addition of only 1 mg l^{-1} H_2O_2 in combination with 16 mg l^{-1} ozone. For the

413 case of 10 mg l^{-1} diatrizoate, the removal efficiency increased rapidly with H_2O_2

414 concentration, from ~25% in the absence of H_2O_2, to nearly 90% with 4-5 mg l^{-1} H_2O_2; a

415 small further increase in diatrizoate removal to a maximum of 97% was achieved as the H_2O_2

416 concentration increased to 15 mg l^{-1}. It is clear that a relatively low H_2O_2 dose could result in

417 a significant improvement to the ozonation treatment. Thus, although the optimal H_2O_2/O_3

418 mass ratio for some water treatment applications has identified as 0.4-0.5, lower ratios

419 (0.0625 for NI-ICM; 0.25 for diatrizoate) have been observed in our tests; however, it should

420 be remembered that our tests were carried out in blank waters. The importance of other

421 reactive species will be considered in the next stage of our tests.

422

423   ***Ozonation of ICM in the presence of HS***

424   In this study, the influence of HS on ICM compound degradation by ozone was

425 investigated using humic acid as a model material. At an initial ICM compound concentration

426 of 10 mg l^{-1} and 16 mg l^{-1} of O_3 it was found in the previous tests (Fig. 3) that, in the absence

427 of HS, the degradation of ICM compounds (30 min reaction time) ranged between poor (~

428 25% for diatrizoate) to substantial (~ 75% for iopamidol). However, the presence of relatively

429 small concentrations of HS ($\leq$ 5 mg l^{-1}) was found to significantly enhance the ozone

430 degradation of the ICM compounds, and particularly for the NI-ICM compounds (Fig. 6). In

431 Fig. 6, it can be seen that the maximum degradation efficiency was achieved with

432 approximately 4-5 mg l^{-1} of HS, and this gave complete removal of the NI-ICM compounds.

433 This maximum in the compound degradation represents the optimal HS concentration in

434 terms of its role as ·OH radical initiator and promoter. The optimal HS concentration

435 corresponds to a HS:ICM mass ratio of 0.57, which is comparable to the results obtained in

436 previous studies with other organic micropollutants (Ma and Graham, 1999; Graham et al.,

437 2003); the authors suggested that the optimal removal efficiency could be achieved at mass

438 ratios of 0.43 or higher. With mass ratios greater than the optimum, there is likely to be

439 increasing scavenging of ·OH radicals and a reduced compound reaction. The results shown

440 in Fig. 6 indicate that the degree of NI-ICM degradation decreased moderately at higher HS

441 concentrations up to 20 mg l^{-1}, but still remained high ($\sim \geq 80\%$), and was greater than for

442 ozonation without HS. For diatrizoate, the presence of HS concentrations greater than 5 mg l^{-1}

443 ^{1}, and particularly > 10 mg l^{-1}, led to significantly reduced compound degradation (10-15%).

444   The corresponding decay of ozone in solution was monitored during the compound

445 degradation tests (in the presence or absence of HS), and the results are shown in Fig. 7. It is

446 clear that ozone decay was accelerated by the presence of HS in solution, and that a relatively

447 low HS concentration of only 4 mg l^{-1} was able to cause a substantial increase in ozone

448 decomposition. It is also clear that a higher concentration of HS caused further increase in

449 ozone decay, compared to that in the absence (or low concentrations) of HS. From the

450 comparison of the degradation rates of ICM compounds (Fig. 6) and the decay rates of ozone

451 (Fig. 7) for identical concentrations of HS, it can be concluded that significant quantities of

452 hydroxyl radicals are generated and present at low humic levels (4-5 mg l^{-1}), while a radical

453 scavenging role is played at high humic levels (e.g. > 10 mg l^{-1}).

454   For diatrizoate, the maximum degradation by ozone in the presence of HS was only

455 40% (Fig. 6), thus, in order to increase this performance the combination of ozone and

456 hydrogen peroxide was studied. Ozonation tests were carried out with all four ICM

457 compounds in the presence of 4 mg l^{-1} HS and at two concentrations of hydrogen peroxide (5

458 and 10 mg l^{-1}). From the results summarised in Fig. 8, it can be seen that the addition of

459   hydrogen peroxide significantly enhanced the compound degradation. However, it is evident

460   that diatrizoate was still difficult to degrade completely under the applied conditions, even in

461   the presence of 10 mg l^{-1} H_2O_2, although the maximum reduction of ~ 85% was achieved in

462   about 30 min.

463

464   *TOC reduction*

465   The degradation of ICM compounds should be assessed as an overall oxidation

466   process, in which the principal objective is the mineralization of both parent compound and

467   daughter products. Thus, in this study the change in solution TOC was determined in order to

468   quantify the overall ozonation performance. The oxidation condition was considered

469   involving a 16 mg l^{-1} ozone dose and an initial ICM concentration of 10 mg l^{-1} (each

470   compound), and after 30 min oxidation the TOC values were evaluated and compared with

471   original values. However, it has been found that the reduction of TOC value and UV

472   absorbance was only 5.5% and 7.7%, respectively. The results indicated that the change in

473   TOC was negligible compared to the reduction in parent compound concentration. This

474   confirmed that mineralization was difficult to achieve within 30 min of ozonation and that the

475   reaction leads to the formation of intermediate products; the reaction mechanism is discussed

476   in the next section of the paper. Associated with the degradation of the parent compounds and

477   formation of intermediates was a corresponding reduction in the solution UV absorbance (λ =

478   254 nm), indicating the loss of aromaticity from the parent and intermediate compounds.

479

480   *Ozonation mechanism*

481   Previous studies of the ozonation of *p*-chlorophenol, trichlorophenol and

482   pentachlorophenol (Andreozzi and Marotta, 1999; Hong and Zeng, 2002; Graham et al., 2003)

483   have demonstrated that the carbon-chlorine bond can be broken during the ozone reaction,

484   releasing inorganic chlorine, and hence it was assumed in this study that an analogous release

485   of iodine could occur, in addition to the formation of iodinated aliphatic intermediates. The

486   cleaving of iodine from the aromatic ring leads to its release into the bulk solution in the form

487   of inorganic iodine, such as iodide. The oxidation of iodide by ozone is extremely fast with a

488   second order kinetic rate constant of $k = 1.2 \times 10^9$ $M^{-1} s^{-1}$ (Liu et al., 2001), and one oxygen

489   atom is transferred from molecular ozone to form the hypoiodite ion (IO^-). With additional

490   ozone, hypoiodite can be further oxidized to iodate, IO_3^-, which is relatively stable and can be

491   measured; the I^- to IO_3^- oxidation step was confirmed by a separate experiment involving the

492   ozonation of potassium iodide.

493   In a continuous ozone bubbling system (giving a constant aqueous ozone

494   concentration of 15 mg l^{-1}), 22 mg l^{-1} of iomeprol (sole compound in solution) was

495   completely oxidized within 10 min. During the reaction free inorganic iodine was measured

496   in the form of iodate, and the results are shown in Fig. 9 where the released iodine is

497   expressed as atomic I. It can be seen that the corresponding release of iodine at 10 min was

498   approximately 45% in molar terms (~5 mg/l as I), and subsequently reached 100% after 90

499   min of continuous ozonation. Given the combined effects of direct molecular ozone reactions

500   and the indiscriminate nature of hydroxyl radical attack during ozonation, iodine containing

501   intermediates will be formed initially, and inorganic iodine subsequently released from these

502   intermediates, as well as from the parent ICM compound. The existence of iodine containing

503   intermediates was indicated by HPLC analysis (detected at $\lambda = 225$ nm) and five product

504   compounds were prominent during the reaction (Fig. 10); although the chemical structure of

505   these compounds was not established, four of them were more polar than their parent

506   compound. Their maximum concentrations were achieved within 15 min of ozonation, and

507   then products 1-4 rapidly decreased, while product 5 reached a maximum later at 40 min and

508   then gradually declined.

509   In general, the mechanism of ICM degradation during ozonation can be described

510   schematically by Fig. 11. In further tests using a higher ozone concentration (20mg/l) the

511   degree of iodine release was compared during the first 10 min of reaction. It was found that

512   for the NI-ICM compounds (iomeprol and iopromide) similar amounts of iodine were

513   released from the parent compounds, whereas the iodine release for diatrizoate was much

514   greater (Fig. 12a), even though the loss of the parent compound was much less (Fig. 12b);

515   these tests were conducted under identical ozonation conditions. The results given in Fig. 12,

516   when expressed in molar terms, indicate that within 10 min of ozonation (continuous ozone

517   bubbling), approximately 100% iodine was released from the diatrizoate, while only ~40%

518   iodine was released from iopromide and iomeprol. From this, it appears that with diatrizoate

519   the primary oxidant attack position is at the Carbon-Iodine bond on the aromatic ring, while

520   for the NI-ICM compounds the much lower release of inorganic iodine suggests that the sites

521   of oxidant attack are more general, leading to the formation of iodine-containing byproducts

522   rather than exclusively iodine cleavage.

523

524   **Conclusions**

525   At present there is very little information available about the potential toxicity of ICM

526   compounds, but these compounds are a major contribution to high AOI levels in many waters

527   and are likely to be persistent. In addition, there is concern about the eco-toxicity of

528   metabolite/transformation products of ICM, whose presence is suspected but of which very

529   little is known. Therefore, the need to identify effective treatment methods is a necessary

530   precaution while evidence concerning their toxicity and that of their

531   metabolite/transformation products, is accumulated and evaluated.

532   Among the established oxidation methods applied in water and wastewater treatment,

533   ozone and ozone/H_2O_2 have the highest oxidation potential and are being considered as a

534   means of achieving higher water quality standards. In this study, ICM compounds have been

535   found to be relatively difficult to degrade by ozonation compared with other pharmaceutical

536   chemicals, but the degree of removal by ozone or ozone/H_2O_2 treatment may still be adequate

537   to meet environmental objectives. Second order kinetic rate constants for the reactions of

538   ICM compounds with molecular ozone and hydroxyl radicals have been determined using

539   various experimental methods; these can be used to predict treatment performance in practice

540   by comparison with equivalent rate values for other, more commonly found organic

541   contaminants. Diatrizoate was found to have a significantly lower reaction rate constant with

542   molecular ozone than the NI-ICM compounds (iomeprol, iopromide and iopamidol), but a

543   similar rate constant with hydroxyl radicals. Whilst hydroxyl radical attack is the dominant

544   reaction at near-neutral pH (7.5), the overall degradation performance for diatrizoate was low,

545   both in absolute terms and relative to the NI-ICM. The importance of hydroxyl radical attack

546   to the reactivity of each compound was evident from the greater oxidation performance

547   achieved with the addition of low concentrations of hydrogen peroxide during ozonation. In

548   addition, the presence of low concentrations of HS (4-5 mg l^{-1}) in solution substantially

549   enhanced ICM degradation by acting as radical promoter in the ozonation process. However,

550   greater HS concentrations reduced the removal efficiency, owing to the HS acting as a radical

551   scavenger and competing in reactions with the ozone. The reactions between the ICM

552   compounds and ozone were found to be capable of cleaving the carbon-iodine bonds and

553   releasing inorganic iodine into solution; this was measured in the form of iodate. Among the

554 ICM compounds, diatrizoate was found to release its iodine much more readily than the NI-

555 ICM, despite being less reactive overall with ozone; this suggests that there are significant

556 differences in the ozone reaction sites between diatrizoate and NI-ICM.

557

558 **Acknowledgement**

561

562

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639

640

642 **Table 1.** Kinetic rate constants of ICM compounds

Compound	Diatrizoic acid/Diatrizoate	Iomeprol	Iopromide	Iopamidol
k_{O_3} ($M^{-1}s^{-1}$)	48.65	NA	93.07	NA
k_{ICM/O_3} ($M^{-1}s^{-1}$)	1.77 ± 0.09 [1]a 3.67 ± 0.48 [1]b	14.01 ± 1.6 [1]	13.5 ± 0.7 [2]	18.0 ± 1.4 [2]
β	27.1	NA	6.9	NA
k_{ICM} ($M^{-1}s^{-1}$)	18.56 ± 1.62 [2]	23.70 ± 0.68 [2]	27.19 ± 2.69 [2]	31.35 ± 1.34 [2]
$k_{ICM/\cdot OH}$ ($M^{-1}s^{-1}$)	$3.0 \pm 0.5 \times 10^9$	$1.8 \pm 0.4 \times 10^9$	$2.2 \pm 0.7 \times 10^9$	$2.4 \pm 0.3 \times 10^9$
R_{ct} (pH 7.5)	5.0×10^{-9}			

643 [1]Integral method
644 [2]Competition method (pH 7.5)
645 a undissociated diatrizoic acid
646 b diatrizoate
647 NA: not available (ozone decay rate constant could not be determined owing to the presence
648 of trometamol and acid in stock solutions of iomeprol and iopamidol

Figure Legends

652	**Fig. 1.** Details of ICM compounds used in the study.

653	**Fig. 2**. Variation of compound removal with ozone dose (30 min ozonation; pH 7.5; $[ICM]_0 =$

654	10 mg l^{-1}).

655	**Fig. 3**. Variation of compound removal with initial ICM concentration (30 min ozonation; pH

656	7.5; $[O_3]_0 = 16$ mg l^{-1}).

657	**Fig. 4.** Extent of ICM compound degradation caused by molecular ozone and hydroxyl

658	radicals (pH 7.5; $[ICM]_0 = 10$ mg l^{-1}).

659	**Fig. 5.** Effect of hydrogen peroxide on ICM compound removal efficiency by ozone (30 min

660	ozonation; pH 7.5; $[O_3]_0 = 16$ mg l^{-1}; $[ICM]_0 = 10$ mg l^{-1}).

661	**Fig. 6**. Influence of HS on compound removal by ozone (30 min ozonation; pH 7.5; $[O_3]_0 =$

662	16 mg l^{-1}; $[ICM]_0 = 10$ mg l^{-1}).

663	**Fig. 7**. Variation of ozone decay with HS concentration (ICM mixture; 10 mg l^{-1} each

664	compound).

665	**Fig. 8**. Degradation of ICM (10 mg l^{-1}) by ozone and H_2O_2 ($[O_3]_0 = 16$ mg l^{-1}; HS 4 mg l^{-1}).
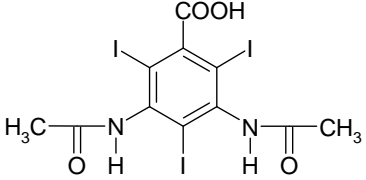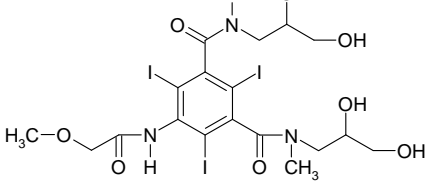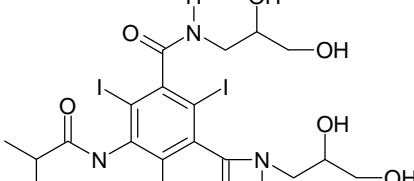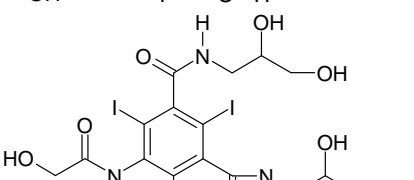
666	**Fig. 9.** Ozonation of iomeprol ($[ICM]_0 = 22$ mg l^{-1}) and resulting formation of iodine (as mg

667	l^{-1} of atomic I) (ozone gas bubbling system; aqueous $[O_3] = 15$ mg l^{-1}).

668	**Fig. 10.** Formation of principal reaction intermediates in the ozonation of iomeprol (HPLC

669	retention times given in parenthesis in legend).

670	**Fig. 11**. Schematic of ICM compound degradation pathways.

671	**Fig. 12.** Comparison of ICM reactions with ozone (ozone gas bubbling system; aqueous $[O_3]$

672	$= 20$ mg l^{-1}): (a) free iodine release rates (as mg l^{-1} of atomic I); (b) ICM compound
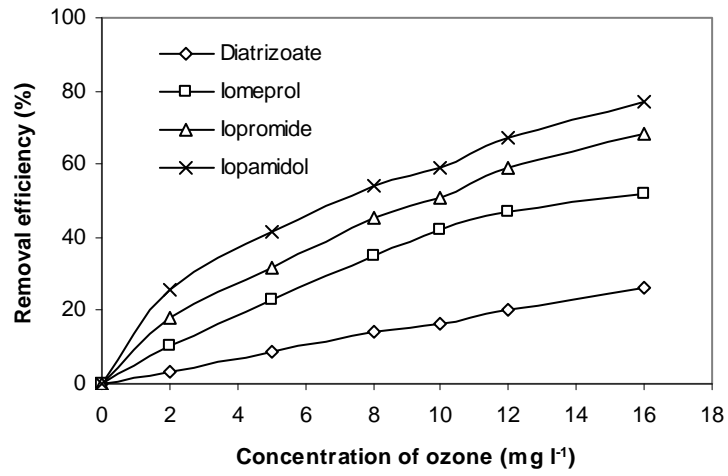
673	degradation ($[ICM]_0 = 20$ mg l^{-1}).

674

Substance	CAS-number	Chemical structure	Molecular weight	Description
Diatrizoate	131-49-7		613.92	Ionic X-ray diagnostic
Iopromide	73334-07-3		791.12	Non-ionic X-ray diagnostic
Iopamidol	60166-93-0		777.09	Non-ionic X-ray diagnostic
Iomeprol (Iomeron)	78649-41-9		777.09	Non-ionic X-ray diagnostic

Fig. 1.

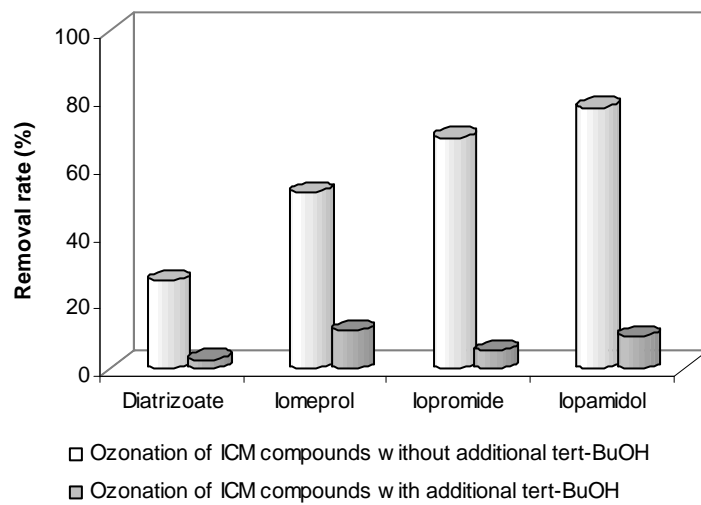679

680   **Fig. 2**.

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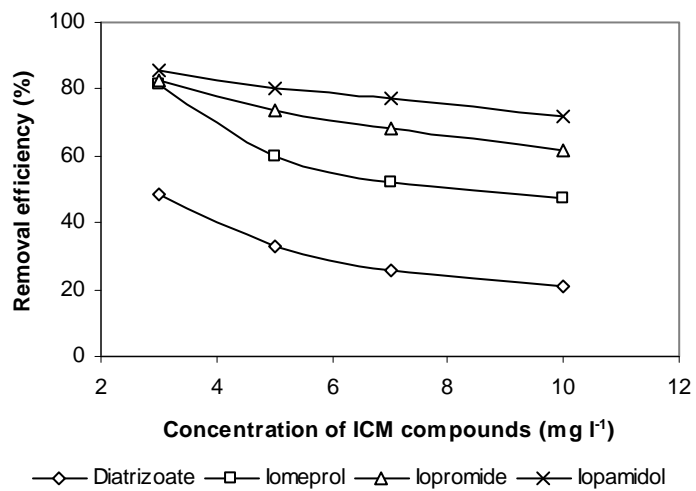
Fig. 3.

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Fig. 4.

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Fig. 5.

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696

697   **Fig. 6**.

698

699

Fig. 7.

700

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702

Diatrizoate, 16 mg l⁻¹ O₃, 4 mg l⁻¹ HS

Conc. of ICM compounds (mg l⁻¹)

Time (min)

Concentration of additional Hydrogen peroxide (mg l⁻¹)
◇ 0   □ 5   △ 10

703

Iomeprol, 16 mg l⁻¹ O₃, 4 mg l⁻¹ HS

Conc. of ICM compounds (mg l⁻¹)

Time (min)

Concentration of additional Hydrogen peroxide (mg l⁻¹)
◇ 0   □ 5   △ 10

704

Iopromide, 16 mg l⁻¹ O₃, 4 mg l⁻¹ HS

Conc. of ICM compounds (mg l⁻¹)

Time (min)

Concentration of additional Hydrogen peroxide (mg l⁻¹)
◇ 0   □ 5   △ 10

705

Iopamidol, 16 mg l⁻¹ O₃, 4 mg l⁻¹ HS

Fig. 8.

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Fig. 9.

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Fig. 10.

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Non-iodine containing products

ICM Compounds → I $\xrightarrow{O_3}$ IO- $\xrightarrow{O_3}$ IO$_2$- $\xrightarrow{O_3}$ IO$_3$-

O_3

Iodine containing products

718

719   **Fig. 11**.

720

721

(a)

722

723

724

725   **(b)**

726   **Fig. 12.**