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ORIGINAL PAPER

Electrochemical reduction of the iodinated contrast medium iomeprol: iodine mass balance and identification of transformation products

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Abstract Potentiostatic-controlled electrochemical reduction of iomeprol was used to deiodinate iomeprol (IMP), a representative of the iodinated X-ray contrast media. The reduction process was followed by product analysis with liquid chromatography-electrospray ionization-tandem mass spectrometry and ion chromatography-inductively coupled plasma-mass spectrometry. The identification is mainly based on the interpretation of the mass fragmentation. The product analysis showed a rather selective deiodination process with the successive occurrence of IMP-I, IMP-2I, IMP-3I, and a transformation product (TP), respectively. The TP was formed from IMP-3I by a further cleavage of an amide bond and release of a (C = O)CHOH group from the side chain of IMP. The iodine mass balance on the basis of IMP and iodide showed a gap of about 26% at the beginning of the electrolysis process which could be completely closed by taking the intermediates IMP-I and IMP-2I into consideration. This means that the major intermediates and the TPs were considered and that the reduction process is a rather selective one to remove organically bound iodine from X-ray contrast media. An attractive application area would be the electrochemical deiodination of X-ray contrast media in urine of patients or hospital effluents.

Keywords Electrolysis · Cathodic dehalogenation · Iodine mass balance · Mass-spectrometric fragmentation

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Introduction

Iomeprol (IMP) belongs to the therapeutic class of iodinated X-ray contrast media (XCM), a class of diagnostics for radiographic contrast which are pharmaceutically inactive. XCM are derivatives of 2,4,6-triiodobenzoic acid mostly with amide-bound polar side chains in the 1,3, and 5 positions of the aromatic ring and are characterized by their high water solubility and stability against human metabolism and to some extent biodegradation. They are administered in high doses up to 200 g per patient for imaging of organs or blood vessels. The total amount used worldwide is estimated to be 3,500 t per year [1]. After their application XCM are rapidly eliminated via urine and feces in their original—nonmetabolized—form and are transported via sewage to sewage treatment plants. XCM have been shown to be ubiquitously distributed in sewage. They are not significantly removed during conventional and advanced sewage treatment processes and therefore enter receiving waters and have been found in drinking water as well [1–3]. For example, effluent concentrations with maximum values of iopromide of 21 μg/L (Germany), or maximum concentrations of 0.9 μg/L for IMP and about 100 μg/L for diatrizoate have been found in rivers [4] and lakes [5]. In some cases XCM have been detected in raw drinking water and in tap water below the microgram per liter range [6, 7]. Under special conditions iopromide

was biotransformed in water—soil systems [8]. The transformation products, however, still exhibited an unchanged iodinated aromatic ring and only changes in the side chains occurred.

According to the precautionary principle, the environmental input of such persistent and hence long-living, mobile compounds such as XCM should be limited. XCM also considerably contribute to adsorbable organic halogen (AOX) compounds in wastewater, which is an important parameter of wastewater regulation. Therefore, new approaches for water treatment are of interest to eliminate XCM before they can enter the aquatic environment.

In water treatment, oxidation of XCM with ozone was not able to remove the bound iodine and did not appear to be efficient owing to low reaction rates [2, 9]. Photocatalytic degradation with TiO_2 is suggested to remove XCM under partial deiodination in water treatment [10]. Reverse-osmosis membranes with a nominal molecular mass cutoff of about 150 Da could remove several XCM from secondary effluents [11]. A promising approach is the treatment of iopromide with zero-valent iron particles, which showed at low pH the occurrence of iodide and therefore the possibility of reductive deiodination [2].

In recent years, electrochemical degradation of aqueous-phase solvents has received growing attention. Several halogenated compounds such as trichloroethene [12], tetrachloromethane [13], dichlorophenols [14], and chlorinated and brominated haloacetic acids [15] have been successfully dehalogenated with different types of electrode materials and reactors (e.g. mixed metal oxide coated titanium, porous copper, palladium catalyzed titanium, nickel and gold electrodes). Nickel and copper cathode materials were superior to a variety of other metals for dehalogenation of tetrachloromethane [13]. The reductive dehalogenation of alkyl iodides at carbon cathodes in organic solvents is of particular interest in organic synthesis of cycloalkanes [16]. For the reductive deiodination of alkyl iodides at palladized silver electrodes a one-electron step has been proposed with the formation of iodide and a free alkyl radical, which is further reduced in a second step [17, 18].

In addition, on the basis of experience in electrochemical dehalogenation techniques, one can expect that the cleavage of the carbon—iodine bond requires less energy than the cleavage of carbon—bromine and carbon—chlorine bonds [19]. The removal of organically bound iodine is a key process to remove AOX compounds and to make the transformation products more biodegradable and less bioaccumulative. The iodide released, on the one hand, is an essential element for humans and, on the other hand, provides only a small contribution to the iodide background of natural waters (1–500 μg/L).

The motivation of this work was to study electrochemical reduction of the iodinated compound IMP and to follow the process by identification of the transformation products. For this purpose liquid chromatography (LC)—electrospray ionization (ESI)—tandem mass spectrometry (MS-MS) and ion chromatography (IC)—inductively coupled plasma (ICP)—mass spectrometry (MS) were used to detect organic and inorganic products to balance iodine during the reduction process.

Experimental

Chemicals for electrolysis and analysis

Sodium perchlorate was purchased from Fluka, potassium iodide, potassium hydrogen phthalate, acetic acid (glacial 100%), and hydrochloric acid (65%) were from Merck, all of high purity. Methanol for high-performance LC (HPLC; gradient grade) was from VWR. IMP was provided by Altana (Constance, Germany) as a pure crystalline compound. HPLC—diode array detection analysis did not show additional peaks of impurities at levels higher than 1% of the original compound.

Electrolysis: electrochemical conditions for iomeprol reduction

The potentiostatic electrolyses were performed at −1 V in a laboratory reactor (modified EG&G PARC flat cell, Princeton Applied Research) with an M263A potentiostat (EG&G). The setup is shown in Fig. 1. A reticulated nickel foam electrode was used as the cathode (working electrode) and a platinum net was used as the anode (counter electrode). The potential of the working electrode was controlled by a three-electrode technique employing a Ag/$AgCl/KCl_{aq}$ (3 M) reference electrode. The cathode compartment (380 mL) and the anode compartment (100 mL) were separated by a cation-exchange membrane (Nafion NE 450). The nickel electrode was produced by a nickel coating on a reticulated polyurethane foam with 40 pores per inch (NiTech). A sheet with an area of 358 cm^2 and a mean thickness of 2 mm was fanfolded and placed in the cathode compartment. The nickel electrode had to be activated on each day by etching it with dilute HCl and rinsing it with deionized water. The IMP degradation also worked with a carbon felt electrode, but was not investigated further. The IMP concentration applied was 0.1 mmol/L. A sodium perchlorate solution (0.1 M) was used as the supporting electrolyte. For degradation of IMP in urine, a pure urine sample from a co-worker was spiked with an IMP standard and subjected to electrolysis without further additives. Samples of 1 mL were taken using a pipette directly from the electrolysis cell and stored in capped vials at 4 °C.

LC-ESI-MS-MS for identification and quantitation of IMP and its transformation products

IMP and its transformation products were analyzed directly in twofold-diluted to 100-fold-diluted aqueous samples without further pretreatment by a LC-ESI-MS-MS/UV system consisting of an Agilent 1100 HPLC instrument equipped with a diode-array detector and coupled to a triple-quadrupole MS API 3000 instrument (Applied Biosystems Sciex) with an ESI source (TurboIon Spray, Applied Biosystems Sciex).

The separation was performed on a Synergy Polar RP 80A (Phenomenex), 250 mm×4.6 mm column with 4-µm particles. The gradient elution started at 95% solvent A (water with 0.05% acetic acid), 5% solvent B (methanol with 0.05% acetic acid) for 5 min under isocratic conditions, was then rised to 30% solvent B within 25 min at a flow rate of 1.0 mL/min. The column temperature was 30 °C, and the injection volume was 50 µL. The wavelengths 236, 245 and 254 nm at a band width of 10 nm were used for UV detection.

The ESI voltage was 4.5 kV, and the dry gas temperature was 450 °C. The mass analyzer was operated at unit-mass resolution in the positive mode with a declustering potential of 75 V and a collision energy between 30 and 60 eV for mass fragmentation (N_2 as collision gas). IMP was measured in the multiple reaction monitoring mode using the mass transitions *m/z* 778 → *m/z* 687 and *m/z* 778 → *m/z* 559 (collision energy 30 eV). Transformation products of the electrolysis were first observed by UV detection. The molecular mass $[M + H]^+$ was assigned by a quadrupole 1 scan and then the mass fragmentation pattern was recorded by a product ion scan using the $[M + H]^+$ ions as precursor masses.

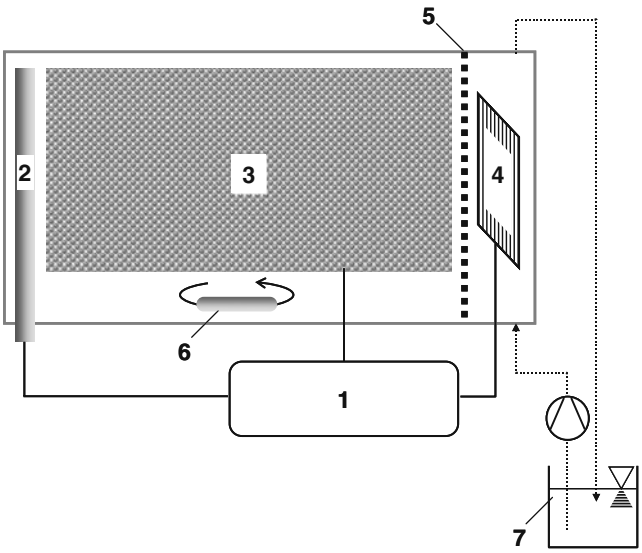

Fig. 1 Setup used for the electrochemical reduction of iomeprol (IMP): *1* potentiostat, *2* reference electrode, *3* nickel foam working electrode, *4* platinum net as the counter electrode, *5* cation-exchange membrane (Nafion), *6* magnetic stir bar, *7* anolyte reservoir connected to a recirculating pump and to the anode compartment

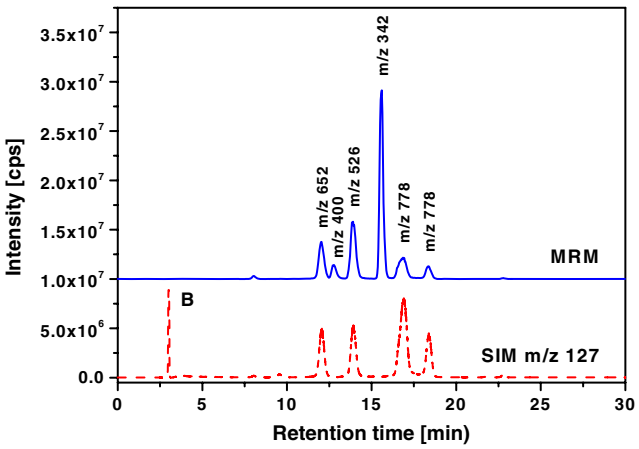

Fig. 2 Multiple-ion monitoring (*MRM*) and selected-ion monitoring (*SIM*) chromatograms of IMP and its electrolytic transformation products; IMP (*m/z* 778); *B* blank; MRM transitions *m/z* 778 → *m/z* 687, *m/z* 652 → *m/z* 561, *m/z* 526 → *m/z* 435, *m/z* 400 → *m/z* 309, *m/z* 342 → *m/z* 251, SIM *m/z* 127

Quantitation was based on external calibration with an IMP standard in aqueous solution between 10 and 1,200 µg/L.

Iodide released during ionization from iodoorganic compounds was measured by LC-ESI-MS-MS under the same conditions as described above but in the negative mode with a declustering potential of 80 V and single-ion monitoring at *m/z* 127 according to the method described in [20].

IC-ICP-MS conditions for iodide and total iodine measurement

The iodine content of the organic and inorganic products was measured by IC-ICP-MS using a Sykam metal-free S 1000 LC system coupled to an Elan 6000 ICP-MS instrument (PerkinElmer Sciex; according to the method described in [21]).

An IonPac AS9 (Dionex, 250 mm×4 mm) anion-exchange column was used for isocratic elution with a 30 mM ammonium carbonate solution at a flow rate of 1 mL/min. The injection volume was 25 µL. A retention time of 13.3 min resulted for iodide. The iomeprol and iodate were eluted almost nonretained at 1.8 min.

The ICP settings were 1.3 kW power, 15 L/min plasma flow, and 0.7 L/min nebulizer flow. Iodine was measured at *m/z* 127 with a dwell time of 25 ms with the detector in the analog mode. Quantitation was based on external calibration with KI solutions.

Dissolved organic carbon

All dissolved organic carbon measurements were performed with a TOC-5000 (Shimadzu) total organic carbon analyzer on the basis of external calibration with a potassium hydrogen phthalate standard solution (concentration range 1–10 mg/L).

Results and discussion

Electrolytical degradation

IMP was completely degraded in aqueous solution within 2 h of potentiostatic electrolysis on a reticulated nickel foam electrode in the cathode compartment at −1 V.

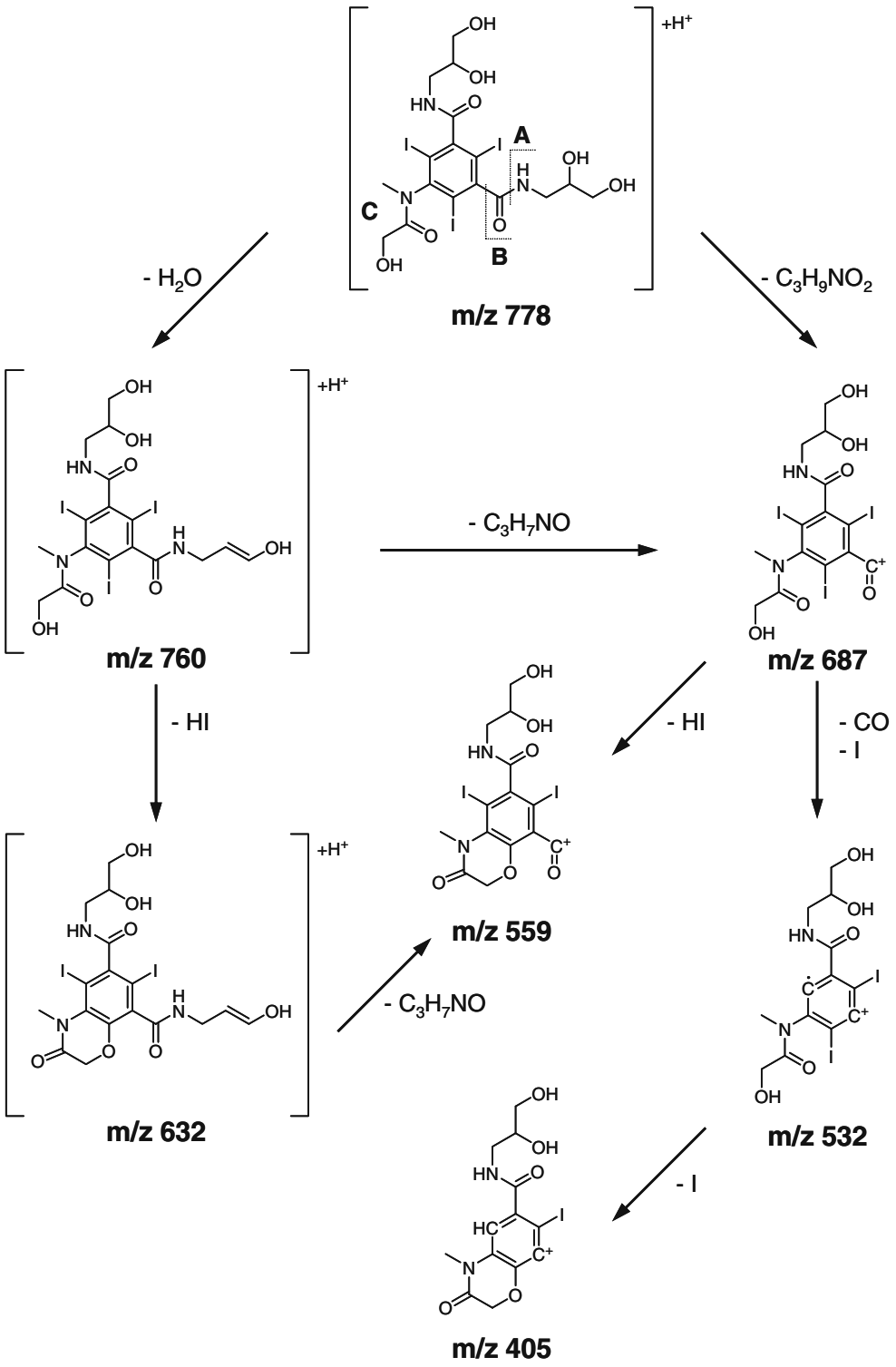

Fig. 3 Tentative mass-spectrometric fragmentation pathway of IMP (positive ionization)

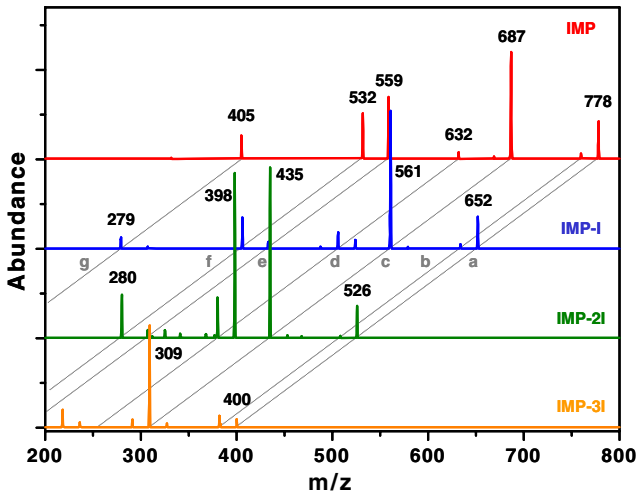

Fig. 4 Mass fragmentation of IMP and its three deiodination products. The *grey lines* reveal the common fragmentation pattern. *a* $[M + H]^+$, *b* $-H_2O$, *c* -A-H, *d* $-H_2O$-HI, *e* -A-H-HI, *f* -B-H-I, *g* -B-H-2I

Hydrolysis of IMP due to an increasing pH in the cathode compartment and diffusion/migration of IMP and its products to the anode compartment during the experiment were checked and could be excluded. The dissolved organic carbon concentration remained, however, relatively constant, indicating the formation of transformation products without any mineralization of the carbon skeleton of IMP. Electrolysis experiments at a lower IMP concentration (0.001 mmol/L) showed the same course of IMP degradation and product formation but on a shorter time-scale of about 10 min. The energy consumption for the complete deiodination of IMP (0.1 mM) in deionized water could be estimated to be 2 Wh/g IMP, unaccounted for the electrical efficiency of the potentiostat. This is a rather low energy consumption compared with that for the dechlorination of 2,4-dichlorophenol (20 Wh/g dichlorophenol) or pentachlorophenol (80 Wh/g pentachlorophenol) [22]. In pure urine the complete degradation of IMP (0.1 mM) needed about 2 h and required much more energy, about 47 Wh/g IMP. The subsequent experiments to elucidate the degradation pathway and to balance iodine were performed in pure aqueous solutions.

Identification of transformation products

Four transformation products of IMP could be observed by HPLC-UV detection and HPLC-MS during the electrolysis. The *m/z* values of the molecular ions $[M + H]^+$ of the LC-ESI-MS analysis exhibit mostly a mass difference of $\Delta m/z$=126 and therefore indicate a sequence of reduction reactions by the formal substitution of iodine (127 amu) by hydrogen (*m/z* 778 → *m/z* 652 → *m/z* 526 → *m/z* 400; Fig. 2).

The mass spectra of iodinated compounds often show a strong signal at *m/z* 127 in the negative mode. This is iodide which can be cleaved from the iodoorganic compounds mainly by electrolytic processes at the tip of the ESI needle and probably also by collision-induced fragmentation in the source region of the mass spectrometer [20]. Therefore selected-ion monitoring of *m/z* 127 indicates the presence or absence of iodine in the compounds of specific peaks (Fig. 2). The presence of iodine in IMP (*m/z* 778) and the products with *m/z* 652 (IMP-I) and *m/z* 526 (IMP-2I) as well as the absence of iodine in products with *m/z* 400 (IMP-3I) and *m/z* 342 further support the idea of the subsequent deiodination processes.

The mass fragmentation spectrum of IMP is dominated by the loss of iodine (I with $\Delta m/z$=127 and HI with $\Delta m/z$=128) and water ($\Delta m/z$=18) as well as by fragmentation of the amide bonds in the two symmetrical side chains of the molecule (A+H, $\Delta m/z$=91; Fig. 3) with further loss of CO ($\Delta m/z$=28) and iodine, resulting in a fragment at *m/z* 532. No fragmentation of side chain C is observed. The loss of HI can be explained by the rearrangement of side chain C with internal formation of a six-membered ring (Fig. 3; *m/z* 632). Another possibility to explain the loss of HI would be the rearrangement of side chain B with formation of a seven-membered ring.

The characteristics of the fragmentation of the deiodinated IMP products are quite similar to those of IMP, but accordingly shifted to lower masses (Fig. 4). The mass of highest abundance (basepeak) in all spectra of the transformation products is always the fragment ion formed by the loss of side chain A + H ($\Delta m/z$=91). Fragments due to the loss of A + H + HI ($\Delta m/z$=559) and B + H + I ($\Delta m/z$=532) occur at much lower intensity in the products IMP-I and IMP-2I (Fig. 4). In the product IMP-3I these fragments are consequently absent since no iodine is left in the

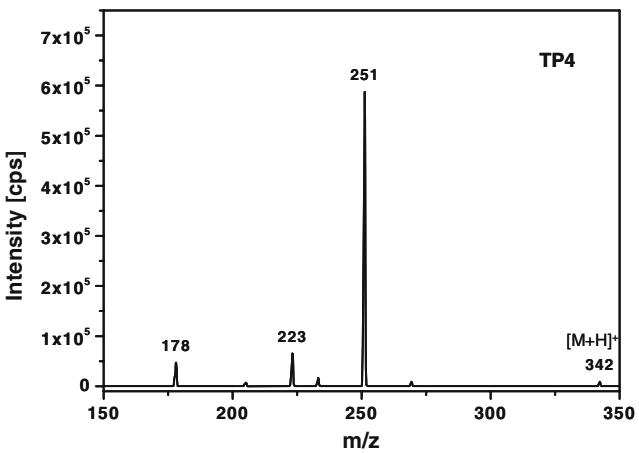

Fig. 5 Mass fragmentation of the completely deiodinated transformation product TP4 (*m/z* 342)

molecule. A further interesting fragmentation is the loss of HI ($\Delta m/z$=128) and HI + H_2O ($\Delta m/z$=146 amu), which is of low intensity for IMP and IMP-I, but almost the basepeak for IMP-2I and is absent for IMP-3I (Fig. 4). Thus, the position of the remaining iodine in the transformation product IMP-2I is characterized by the preferential loss of HI in mass fragmentation. Since the HI loss can be attributed to the interaction of both side chains C and B and their ring formation, the exact position of the iodine in IMP-2I without single labeled iodine substituents cannot be elucidated on the basis of MS alone.

A further transformation product (TP4) of the electrochemical reduction of IMP occurred at *m*/*z* 342. The compound no longer contains any iodine and is further characterized by mass fragments due to the losses of side chains A and B (fragments at *m*/z 251 and *m*/*z* 223; Fig. 5). Therefore, the formation of TP4 from the completely deiodinated compound (*m*/*z* 400) occurred by electrochemical reduction at side chain C with loss of C(=O) = CHOH. In Fig. 6 the reactions of the electrochemical deiodination of IMP and the formation of TP4 are summarized. The sequence shown for the reductive iodine cleavage is only

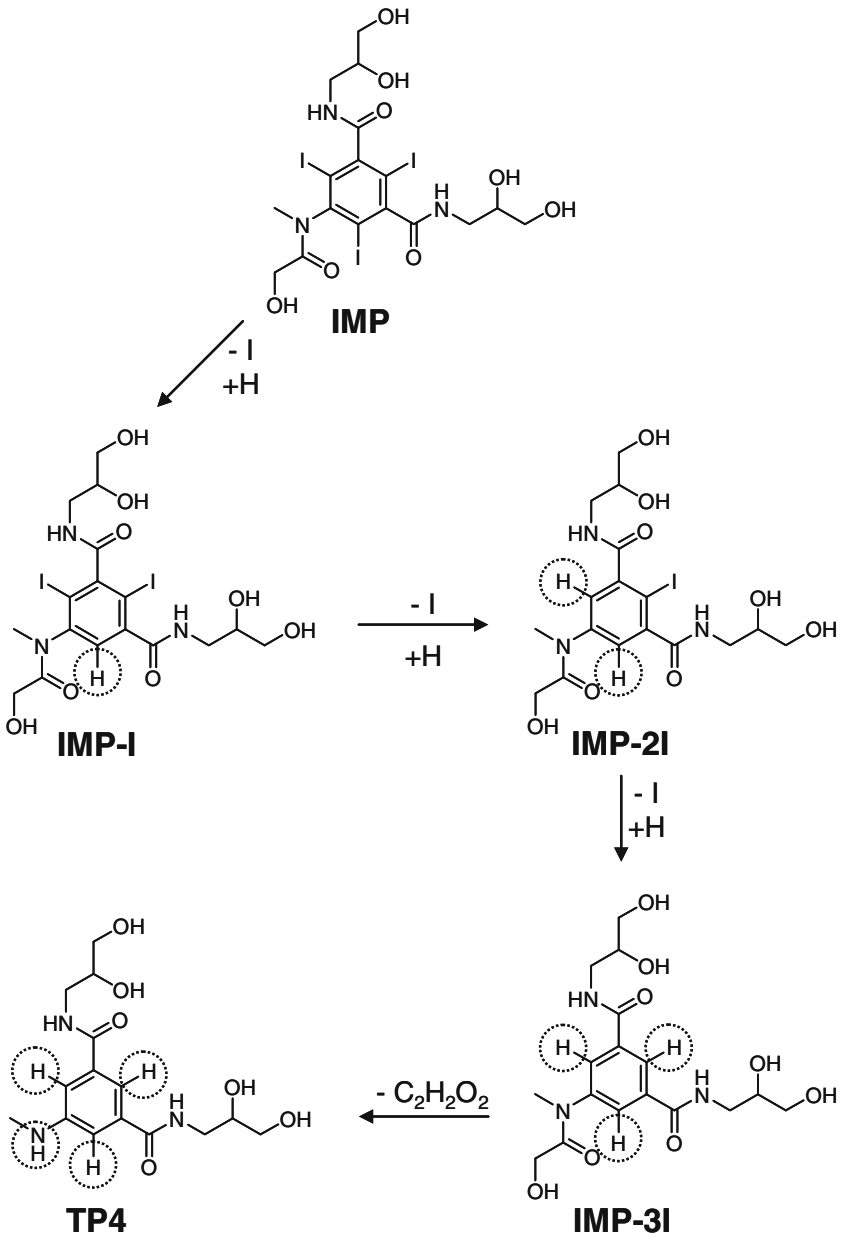

Fig. 6 Dehalogenation pathway for the electrochemical reduction of IMP. The *dotted circles* indicate sites where reduction occurred

one possibility out of three, but does not influence the result of a fully deiodinated IMP and TP4.

Reaction progress and iodine mass balance

The occurrence of the deiodinated reaction products during the progress of the electrochemical reduction can be seen in Fig. 7. It has to be noted that the maxima of the individual compounds were all normalized to 100%. The maximum concentrations of the reaction products IMP-I and IMP-2I were estimated to be in the range from 10 to 20% and the maximum concentration of IMP-3I was estimated to be below 5% of the initial concentration of IMP assuming the same response of the products as of IMP. With increasing degree of deiodination, the maxima of the deiodinated products are shifted to longer electrolysis times, indicating a decreasing reaction rate of the reductive deiodination process. This can be due to an increased requirement of the steric orientation or a decreased interaction with the electrode material with decreasing iodine content of the molecules. Principally, two types of iodine substituents are present. One iodine substituent is in the *ortho* position of both side chains B and two iodine substituents are between side chains B and C. The individual reduction potentials of the successive deiodination steps, however, could not be analyzed by cyclic voltammetry because of too small differences which are below the resolution of this technique.

The quantitative progress of the IMP reduction could be observed by the occurrence of iodide and by the iodine balance comprising iodine in IMP, in all the identified reaction products and in iodide. After about 45 min, half of the iodine was recovered as iodide, and after 180 min the iodide yield was already quantitative (Fig. 8). Considering

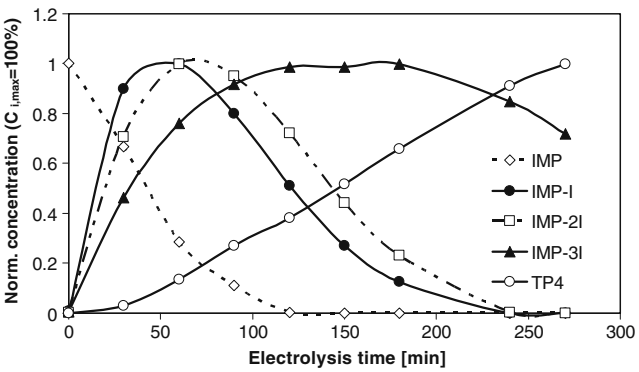

Fig. 7 Temporal progression of the normalized concentrations of the four transformation products during the electrochemical reduction of a 0.1 mM IMP solution

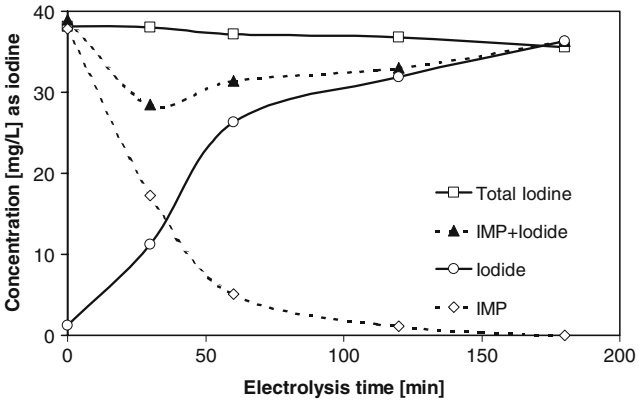

Fig. 8 Iodine mass balance comprising IMP, IMP-I, IMP-2I, and iodide for the electrochemical reduction of a 0.1 mM IMP solution

only the iodine in IMP and iodide, a gap in the iodine balance of 26 and 18% could be observed at the electrolysis times of 30 and 60 min, respectively. This gap can be filled predominantly by the first two reaction products IMP-I and IMP-2I, peaking at 50 and 70 min. This reveals that the major iodine-containing intermediates were identified. At an electrolysis time of 180 min, the concentrations of IMP-I and IMP-2I decreased considerably again, but IMP-3I showed its maximum concentration and hence an almost quantitative recovery of iodide and with it a complete deiodination of IMP was observed.

Conclusions and outlook

The potentiostatic-controlled electrochemical reduction of IMP was revealed to be a reliable process for the quantitative release of organically bound iodine of XCM as solvated iodide ions. Product analyses showed deiodinated IMP derivatives as intermediates and a completely deiodinated transformation product. The iodine mass balance revealed a quantitative recovery of iodide at the end of the electrochemical treatment. Owing to the common structure of all XCM it can be assumed that the cathodic dehalogenation is also applicable for the deiodination of other iodinated XCM. The process can be applied for the pretreatment of concentrated solutions or urine from patients to remove organically bound iodine before they are discharged to the sewage. The process of electrochemical reduction works without the addition of any reactive chemicals, and is also easy to operate for nonskilled personnel. Owing to a short turn-on time and the possibility to realize flow-through systems, the process is also useful for temporary use in hospitals with a short-term demand.

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