Water Research 91 (2016) 244–250

Contents lists available at ScienceDirect

Water Research

journal homepage: www.elsevier.com/locate/watres

Investigating the stability of gadolinium based contrast agents towards UV radiation

Marvin Birka [a], Jörg Roscher [a], Michael Holtkamp [a], Michael Sperling [a, b], Uwe Karst [a, *]

[a] University of Münster, Institute of Inorganic and Analytical Chemistry, Corrensstraße 28/30, 48149 Münster, Germany
[b] European Virtual Institute for Speciation Analysis (EVISA), Mendelstraße 11, 48149 Münster, Germany

ARTICLE INFO

Article history:
Received 1 September 2015
Received in revised form
5 January 2016
Accepted 8 January 2016
Available online 11 January 2016

Keywords:
Xenobiotics
Contrast agents
Gadolinium
UV radiation
Speciation analysis

ABSTRACT

Since the 1980s, the broad application of gadolinium(Gd)-based contrast agents for magnetic resonance imaging (MRI) has led to significantly increased concentrations of Gd in the aqueous environment. Little is known about the stability of these highly polar xenobiotics under environmental conditions, in wastewater and in drinking water treatment. Therefore, the stability of frequently applied Gd-based MRI contrast agents towards UV radiation was investigated. The hyphenation of hydrophilic interaction liquid chromatography (HILIC) with inductively coupled plasma mass spectrometry (ICP-MS) and of HILIC with electrospray ionization mass spectrometry (ESI-MS) provided quantitative elemental information as well as structural information. The contrast agents Gd-DTPA, Gd-DOTA and Gd-BT-DO3A showed a high stability in irradiation experiments applying a wavelength range from 220 nm to 500 nm. Nevertheless, the degradation of Gd-BOPTA as well as the formation of Gd-containing transformation products was observed by means of HILIC-ICP-MS. Matrix-dependent irradiation experiments showed a degradation of Gd-BOPTA down to 3% of the initial amount in purified water after 300 min, whereas the degradation was slowed down in drinking water and surface water. Furthermore, it was observed that the sum of species continuously decreased with proceeding irradiation in all matrices. After irradiation in purified water for 300 min only 16% of the sum of species was left. This indicates a release of Gd(III) ions from the complex in course of irradiation. HILIC-ESI-MS measurements revealed that the transformation products mostly resulted from *O*-dealkylation and *N*-dealkylation reactions. In good correlation with retention times, the majority of transformation products were found to be more polar than Gd-BOPTA itself. Based on accurate masses, sum formulas were obtained and structures could be proposed.

1. Introduction

The anthropogenic input of xenobiotic compounds into the environment, including a broad variety of pharmaceuticals, has been observed in recent decades. Eventually, these contaminants can partially be detected in wastewater, surface water, ground water and drinking water (Richardson and Ternes, 2014; Kunkel and Radke, 2012). Since the 1980s, there is a significant input of anthropogenic gadolinium (Gd) into the water cycle originating from the frequent application of contrast agents containing this rare earth element (REE) (Bau and Dulski, 1996). Gd-based contrast agents are applied to support medical examinations with magnetic resonance imaging (MRI) because of the unique paramagnetic properties of the Gd(III) ion. Since free Gd(III) ions are toxic, they are administered to the patients as chelates with polyaminocarboxylates, which are eventually excreted fast and unmetabolized, mostly via the kidneys (Caravan et al., 1999; Idée et al., 2006). Fig. 1 shows the chemical structures of the most frequently administered Gd-based contrast agents for MRI.

As a result of this, large amounts of Gd are released into the wastewater and thereby into the environment, because the contrast agents are not being removed in wastewater treatment plants with common technology (Bau and Dulski, 1996; Lawrence et al., 2009; Verplanck et al., 2010). The anthropogenic Gd anomaly and its correlation with the application of contrast agents was

Abbreviations: AOP, Advanced oxidation process; ESI-MS, Electrospray ionization mass spectrometry; HILIC, Hydrophilic interaction liquid chromatography; ICP-MS, Inductively coupled plasma mass spectrometry; MRI, Magnetic resonance imaging; PE, Polyethylene; PMP, Polymethylpentene; PTFE, Polytetrafluoroethylene; REE, Rare earth element.

* Corresponding author. University of Münster, Institute of Inorganic and Analytical Chemistry, Corrensstraße 28/30, 48149 Münster, Germany.
E-mail address: uk@uni-muenster.de (U. Karst).

http://dx.doi.org/10.1016/j.watres.2016.01.012
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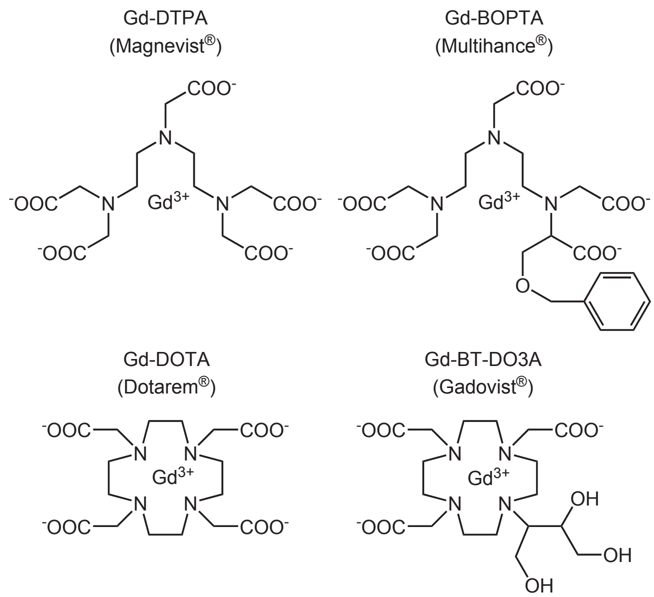

Fig. 1. Chemical structures of frequently applied Gd-based contrast agents for MRI with the respective trademarks.

described first by Bau and Dulski in 1996, revealing an enrichment of Gd relative to the other REEs in samples from rivers and lakes (Bau and Dulski, 1996). Many following studies revealed Gd anomalies in surface waters, ground water, sea water and even in drinking water. It was shown that the phenomenon occurs worldwide in densely populated regions with a developed health care system giving people access to MRI examinations (Bau et al., 2006; Klaver et al., 2014; Nozaki et al., 2000; Kulaksiz and Bau, 2007; Tepe et al., 2014). However, the determination of total Gd concentrations and REE patterns, usually by means of inductively coupled plasma mass spectrometry (ICP-MS), does not provide any chemical information about the Gd species. Therefore, methods of speciation analysis are required in order to investigate the fate of individual contrast agents during wastewater treatment, in the environment as well as in drinking water purification processes. Künnemeyer et al. successfully employed the hyphenation of hydrophilic interaction liquid chromatography (HILIC) with ICP-MS for the detection and quantification of contrast agents in wastewater samples (Künnemeyer et al., 2009). HILIC was shown to be perfectly suitable for separating such highly polar metal complexes and ICP-MS provided a unique element-selective sensitivity. In a series of additional studies, HILIC-ICP-MS methods were employed for the determination of contrast agents in surface waters and even in drinking water. Thereby, the persistence of the complexes in the water cycle could be demonstrated (Birka et al., 2013; Lindner et al., 2013; 2015).

Nevertheless, little is known about their chemical behavior under environmental conditions or in technical processes of water treatment regarding degradation and the formation of transformation products. The effect of sunlight and especially UV radiation on Gd-based contrast agents has not been studied so far. Besides the reactivity in the aqueous environment, the impact of advanced oxidation processes (AOPs) has to be considered. AOPs are discussed to be suitable as additional step in wastewater treatment to decrease the input of xenobiotics through reactions with hydroxyl radicals and could involve UV irradiation (von Sonntag, 2008; De la Cruz et al., 2012). In 2013, Cyris et al. determined reaction rate constants for Gd chelates like Gd-DTPA in wastewater with ozone and hydroxyl radicals. Nearly no reactivity towards ozone was observed, while it was concluded that reactions with hydroxyl radicals took place (Cyris et al., 2013). Direct photolysis of xenobiotics through homolytic cleavage of bonds and reactive oxygen species is another approach to reduce the amount of xenobiotics (Arany et al., 2014; Keen et al., 2012). Furthermore, disinfection of drinking water by UV irradiation is a common technique possibly inducing the formation of transformation products (Richardson and Ternes, 2011).

Since the contrast agents incorporate a metal ion, the complex stability and the release of Gd(III) ions are of particular concern regarding the processes described above. In this paper, UV irradiation experiments with frequently applied contrast agents are presented to fundamentally assess their stability and transformation products being possibly generated. Additionally, the effect of different matrices on the degradation of Gd-BOPTA was studied. The employed analytical methods involve HILIC-ICP-MS providing quantitative information on Gd species and the hyphenation of HILIC with electrospray ionization-MS (ESI-MS) for complementary structural information.

2. Materials and methods

2.1. Chemicals and consumables

Nitric acid (65%, Suprapur), Gd standard for ICP-MS (1000 mg/L), and acetonitrile were purchased from Merck KGaA (Darmstadt, Germany). Rhodium (Rh) solution (1000 mg/L) from SCP Science (Baie D'Urfé, Canada) was used as standard for ICP-MS measurements. Formic acid and ammonium formate were obtained from Fluka Chemie GmbH (Buchs, Switzerland). The contrast agent standards were obtained as infusion solutions from the respective pharmaceutical companies: Dotarem (Gd-DOTA, 0.5 mol/L) by Guerbet (Sulzbach, Germany), Magnevist (Gd-DTPA, 0.5 mol/L) and Gadovist (Gd-BT-DO3A, 1.0 mol/L) by Bayer HealthCare AG (Berlin, Germany), and Multihance (Gd-BOPTA, 0.5 mol/L) by Nycomed (Konstanz, Germany). All chemicals were used in the highest quality available. Water was purified by an Aquatron Water Still purification system model A4000D (Barloworld Scientific, Nemours, France). Syringe filters with Polytetrafluoroethylene (PTFE) membranes (0.2 μm pore size) were purchased from VWR International (Darmstadt, Germany).

2.2. Preparation of contrast agent solutions for irradiation experiments

For initial irradiation experiments with the widely applied contrast agents Gd-DTPA, Gd-BOPTA, Gd-DOTA and Gd-BT-DO3A, the infusion solutions were diluted with purified water to a concentration of 0.5 mmol/L, each. The subsequent matrix-dependent experiments with Gd-BOPTA were carried out in purified water, unfiltered surface water, filtered surface water and drinking water. Additionally, meglumine was present in all solutions as counter ion originating from the infusion solution. The surface water was taken from the River Münster'sche Aa near the City of Münster, while the drinking water was directly obtained from the municipal water supply in Münster. Both samples were taken in vessels of polyethylene (PE). Approximately half of the surface water was filtered through a 0.2 μm PTFE syringe filter. The infusion solution of Gd-BOPTA was diluted with the different water samples to a final concentration of 0.5 mmol/L.

2.3. Preparation of standard solutions

The determination of total Gd concentrations with ICP-MS was carried out by external calibration in a range from 1 to 500 μg/L. Rh