Talanta 128 (2014) 500–504

Contents lists available at ScienceDirect

Talanta

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

Separation of Gd–humic complexes and Gd-based magnetic resonance imaging contrast agent in river water with QAE-Sephadex A-25 for the fractionation analysis

Hiroaki Matsumiya [a,*], Hiroto Inoue [b], Masataka Hiraide [b]

[a] Division of Environmental Research, EcoTopia Science Institute, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603, Japan
[b] Department of Molecular Design and Engineering, Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603, Japan

ARTICLE INFO

Article history:
Received 2 May 2014
Received in revised form
5 June 2014
Accepted 6 June 2014
Available online 14 June 2014

Keywords:
Humic substance
Gd-based MRI contrast agent
Speciation analysis
Fractionation analysis
River water
Inductively coupled plasma-mass spectrometry

ABSTRACT

Gadolinium complexed with naturally occurring, negatively charged humic substances (humic and fulvic acids) was collected from 500 mL of sample solution onto a column packed with 150 mg of a strongly basic anion-exchanger (QAE-Sephadex A-25). A Gd-based magnetic resonance imaging contrast agent (diethylenetriamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetato aquo gadolinium(III), Gd–DTPA^{2-}) was simultaneously collected on the same column. The Gd–DTPA complex was desorbed by anion-exchange with 50 mM tetramethylammonium sulfate, leaving the Gd–humic complexes on the column. The Gd–humic complexes were subsequently dissociated with 1 M nitric acid to desorb the humic fraction of Gd. The two-step desorption with small volumes of the eluting agents allowed the 100-fold preconcentration for the fractionation analysis of Gd at low ng L^{-1} levels by inductively coupled plasma-mass spectrometry (ICP-MS). On the other hand, Gd(III) neither complexed with humic substances nor DTPA, *i.e.*, free species, was not sorbed on the column. The free Gd in the effluent was preconcentrated 100-fold by a conventional solid-phase extraction with an iminodiacetic acid-type chelating resin and determined by ICP-MS. The proposed analytical fractionation method was applied to river water samples.

1. Introduction

Gadolinium(III) has found great use as a contrast agent in magnetic resonance imaging (MRI) because of the unique magnetic properties, which accelerate spin relaxation of the water protons to enhance the MRI contrast of fine body structures [1,2]. However, free Gd(III) ions (*e.g.*, simple hydrated ion) are toxic due to their inhibition of Ca(II)-regulated signaling in the cells; hence Gd(III) is administrated into the body in the form of a stable and hydrophilic complex to facilitate the rapid and complete excretion without being metabolized [1]. For example, a Gd(III) complex of diethylenetriamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetic acid (Gd–DTPA) is marketed as Magnevist, which is the first approved and widespread for use in MRI diagnostics [1,2]. Typically, *ca.* 1 g of Gd is applied to an MRI patient with each dose and *ca.* 25 g of Gd is consumed per week in a hospital applying MRI [3]. An annual consumption of Gd in a university hospital was reported to increase to 4.2 kg in proportion to the replacement of X-ray imaging techniques by MRI in the mid-1990s [4]. Such large consumption of Gd may cause great discharge of anthropogenic Gd into the environment, eventually increasing its concentration to anomalously high levels.

Since the first report by Bau and Dulski in 1996 [5], anomalously high concentrations of Gd, or positive Gd anomalies, have been reported for wastewater and surface waters, especially in urban areas [6–11]. Some reports also describe the insufficient removal of Gd-based contrast agents during wastewater treatment due to the high solubility in water [12,13]. Based on these reports, attempts have been made to apply the positive Gd anomaly as an indicator in hydrological studies [14,15]. However, most of these reports, including the first report by Bau and Dulski, relied on the determination of total dissolved Gd, typically by 50- to 200-fold preconcentration followed by inductively coupled plasma-mass spectrometry (ICP-MS), though a better understanding of the positive Gd anomaly requires the speciation analysis. The preconcentration procedures employed were based on the strong complexation of Gd with chelating agents (*e.g.*, ethylhexyl phosphates). In addition, ICP-MS is inherently incapable of speciation analysis. Therefore, the conventional methods cannot distinguish between anthropogenic and naturally-occurring dissolved species of Gd. A recent report describes the speciation analysis of Gd in river and lake waters by high-performance liquid chromatography

* Corresponding author. Tel.: +81 52 789 3591; fax: +81 52 789 3241.
E-mail address: h-matsu@numse.nagoya-u.ac.jp (H. Matsumiya).

http://dx.doi.org/10.1016/j.talanta.2014.06.005
0039-9140/

followed by ICP-MS [16]. A 10-fold preconcentration was performed by evaporation for the reliable determination at low ng L^{-1} levels.

The present study was undertaken to develop a separation and preconcentration method for the speciation analysis of Gd by ICP-MS, taking into account humic and fulvic acids. These humic substances have not been considered in the above-mentioned previous reports. Humic and fulvic acids are the major and ubiquitous components of dissolved organic matter in natural waters, formed by chemical and microbial degradation of biological tissues [17,18]. Such naturally occurring humic substances contain a number of carboxylic and phenolic groups and behave as negatively charged polyelectrolytes having complexation ability. A variety of metal ions can react with them to form water-soluble humic complexes. Recently, fundamental studies on the complexation of Gd and humic acid in model solutions have been done by ultrafiltration and capillary electrophoresis followed by ICP-MS from a viewpoint of radioactive waste treatment [19,20]. In the present study, the analytical fractionation of Gd–humic and DTPA complexes was examined, taking the latter as an example of Gd-based contrast agents.

Our research group has studied the use of Sephadex A-25 anion-exchangers (hydrophilic macroreticular cross-linked dextran beads modified with ternary or quaternary ammonium groups) to collect metal–humic complexes for speciation analysis [21–23]. Negatively charged humic complexes were rapidly and strongly sorbed on the A-25 beads, leaving free metal cations in the solution. Because the MRI contrast agent Gd–DTPA is a divalent anion, an attempt has been made in the present study to collect both Gd–humic and DTPA complexes on the A-25 beads. Free Gd cations, if present, should not be retained on the beads. The collected Gd–DTPA was selectively desorbed by anion-exchange with a sulfate solution. The remaining Gd–humic complexes were subsequently dissociated with nitric acid to desorb the humic fraction of Gd. The two-step desorption with small volumes of the eluting agents offered the 100-fold preconcentration for the analytical fractionation and determination of Gd–humic and DTPA complexes at low ng L^{-1} levels by ICP-MS. The proposed method was applied to river water samples collected in urban and remote areas.

2. Experimental

2.1. Apparatus and reagents

A Seiko (Chiba, Japan) SPQ-6500 ICP-mass spectrometer was used for the determination of Gd under the following plasma conditions: RF power, 0.9 kW; sampling depth, 12 mm; and argon flow rates (L min^{-1}), 17 for outer, 0.7 for intermediate, and 1.0 for carrier. The isotope measured was ^{158}Gd. A Jasco (Tokyo, Japan) V-630BIO spectrophotometer was used with a 1-cm quartz cell for the determination of humic substances at 400 nm.

A standard Gd solution (1.0 mg mL^{-1} in 1 M HNO_3) was purchased from Wako Jun-yaku (Osaka, Japan) and diluted to appropriate concentrations with 0.1 M nitric acid. A Gd–DTPA solution (1.0 mgGd mL^{-1}) was prepared by dissolving gadolinium(III) dihydrogen diethylenetriamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetate hydrate (Sigma-Aldrich, St. Louis, MO, USA) in water and it was diluted to appropriate concentrations with water before use; the concentration was checked by ICP-MS. A humic acid solution (0.10 mg mL^{-1}) was prepared as follows: powder of a standard humic acid (2S101H, Suwannee river II, International Humic Substance Society, St. Paul, MN, USA) was dissolved in 0.1 M potassium hydroxide solution. The solution was diluted to 0.10 mg mL^{-1} with water while adjusting the pH to 7.0 with 0.1 M nitric acid. A fulvic acid solution (0.50 mg mL^{-1}) was prepared by dissolving powder of a standard fulvic acid (2S101F, Suwannee river II, International Humic Substance Society) in water. Stock solutions of Gd–DTPA, humic acid, and fulvic acid were stored in a dark place at 4 °C. Synthetic river water (Na 5.2, K 1.0, Mg 1.8, Ca 4.6, Cl 9.2, SO_4 6.8, and NO_3 7.1 μg mL^{-1} [24]) was prepared as follows: 50 mg of sodium chloride, 100 mg of sodium sulfate, 20 mg of potassium chloride, 200 mg of calcium nitrate tetrahydrate, and 150 mg of magnesium chloride hexahydrate were dissolved in 100 mL of water. An aliquot of the solution was diluted 100-fold with water while adjusting the pH to 7.0 by adding a 2-hydroxy-3-morpholinopropanesulfonic acid (Dojin Kagaku Kenkyujo, Kumamoto, Japan)-tetramethylammonium hydroxide (TMAH, ultra-pure grade, Tama Kagaku Kogyo, Kawasaki, Japan) buffer to give a concentration of 1.0 mM.

A strongly basic anion-exchanger, QAE-Sephadex A-25 (0.05–0.1 mm particles, having diethyl(2-hydroxypropyl)aminoethyl groups, chloride-form), was purchased from Sigma-Aldrich and swollen in water before use. A 50 mM tetramethylammonium sulfate solution was prepared by neutralizing 64% (w/w) sulfuric acid (Wako Jun-yaku) with 25% (w/w) tetramethylammonium hydroxide (ultra-pure grade, Tama Kagaku Kogyo) and diluting the solution with water.

An Empore disk cartridge (Teflon fiber disk containing an iminodiacetic acid-type chelating resin, 10 mm in diam.) was purchased from 3 M Bioanalytical Technologies (St. Paul, MN, USA) and used for the solid-phase extraction of free Gd species. The cartridge was washed successively with ethanol, water, 1 M nitric acid, and water, and it was conditioned with 1 M ammonium acetate solution before use.

All reagents used were of reagent grade, unless otherwise stated. Water was purified with a Millipore (Billerica, MA, USA) Milli-Q Integral 5 A-10 system.

2.2. Fractionation analysis (see Fig. 1)

2.2.1. Gd–humic and DTPA complexes

A 500-mL volume of sample solution was introduced onto a column packed with 150 mg of QAE-Sephadex A-25 (7 mm i.d. × 15 mm high) using a peristaltic pump at a flow rate of 25 mL min^{-1} to collect Gd–humic and DTPA complexes. A 4.0-mL volume of 50 mM tetramethylammonium sulfate solution was added onto the column to desorb the DTPA complex selectively; the eluate was reserved for the analysis by ICP-MS. Subsequently, 2.0 mL of 1 M nitric acid was added onto the same column to desorb the remaining Gd (the fraction of humic complexes). Each eluate was diluted to 5.0 mL with water for the determination of Gd by ICP-MS. A calibration graph was prepared using 0.1 M nitric acid containing Gd at pg mL^{-1} to low ng mL^{-1} levels.

2.2.2. Free Gd species

After introducing 500 mL of sample solution onto the A-25 column (*vide supra*), the effluent (containing free Gd species) was again introduced onto an Empore disk cartridge at a flow rate of 10 mL min^{-1} for the solid-phase extraction. After washing the cartridge with 5 mL of 1 M ammonium acetate, the Gd on the cartridge was eluted with 2.0 mL of 3 M nitric acid. The elution was repeated once more. The combined eluates were diluted to 5.0 mL with water for the determination of Gd by ICP-MS. A calibration graph was prepared as described above.

2.3. Determination of humic substances

A 500-mL volume of sample solution was gently stirred with heating at 80 °C to evaporate to *ca.* 5 mL without boiling. The solution was diluted to 10 mL with water, while adjusting the pH

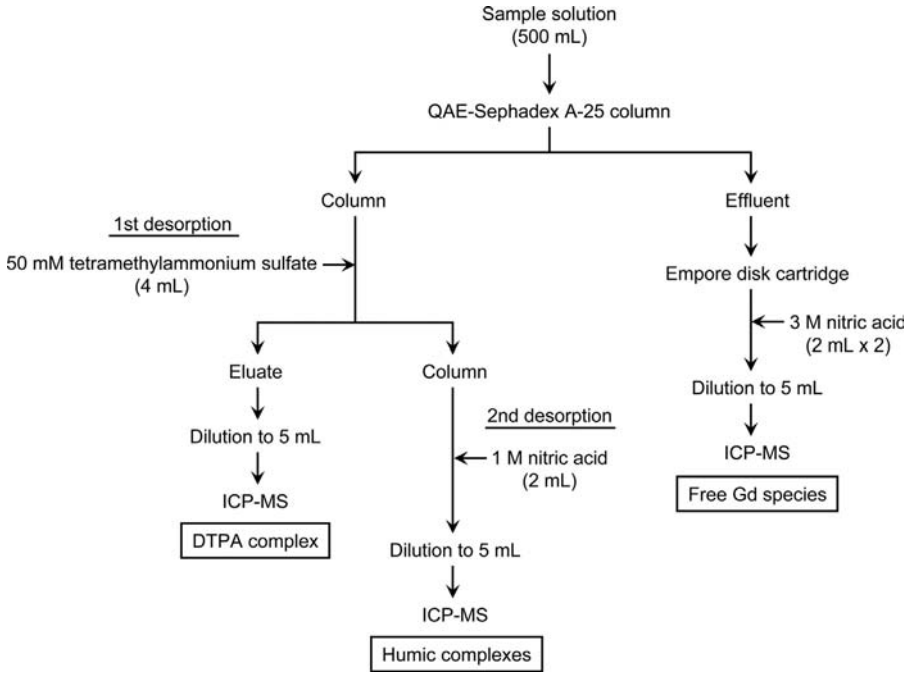

Fig. 1. Fractionation procedure.

to 13 with 5 M potassium hydroxide to increase the absorptivity, and the absorbance was measured at 400 nm to determine humic substances [25].

3. Results and discussion

3.1. Sorption of Gd species

Because the sorbent used was an anion-exchanger, free Gd species (*e.g.*, simple hydrated cation) should not be retained on the A-25 column. First, this was confirmed as follows. A 5.0-ng amount of Gd(III) ion was added to 500 mL of synthetic river water without humic substances and the solution was introduced onto the A-25 column. The effluent was analyzed by solid-phase extraction followed by ICP-MS to determine the Gd passing through the column. To determine the Gd retained on the A-25 column, 2.0 mL of 1 M nitric acid was added onto the column and the eluate was analyzed by ICP-MS. The Gd passing through the column was 4.9 ng and no Gd was detected in the eluate, indicating no retention of free Gd species on the A-25 column.

The sorption of Gd–humic complexes was investigated. Different amounts of humic and/or fulvic acids were added to 500 mL of synthetic river water containing 5.0 ng of Gd. The solution was stirred for at least 30 min for the equilibration. Upon the introduction of the sample solution, the top half of the column was colored dark brown, indicating the sorption of humic substances. The desorption was done twice by the dissociation of the Gd–humic complexes, with 2.0 mL each of 1 M nitric acid, to ensure the complete desorption. As given in Table 1, smaller amounts of humic substances led to the incomplete sorption of Gd. The sum of the Gd found in the effluent and eluate (4.8–5.1 ng) was almost equal to the amount of the Gd added (5.0 ng), indicating no loss of Gd during the sorption and desorption. As described above, free Gd was not retained on the A-25 column. Therefore, the incomplete sorption of Gd can be explained by the incomplete complexation with humic substances. The increase in the amounts of humic substances resulted in the quantitative recovery of Gd in the eluate, indicating the complete complexation, sorption, and desorption of Gd. However, the recovery was decreased again when the sample solution contained 5.0 mg of humic acid and 10 mg of fulvic acid. The whole column was colored dark brown before the full introduction of the sample solution, indicating the saturation of the column with humic substances. Therefore, the decreased recovery may be ascribed to the incomplete sorption of Gd–humic complexes, not to the incomplete complexation.

The sorption of Gd–DTPA was examined using 500 mL of synthetic river water containing 5.0 ngGd of Gd–DTPA without humic substances. The desorption was done twice with 2.0 mL

Table 1
Sorption and desorption of 5.0 ng of Gd in the presence of humic substances.

Sample solution (500 mL, pH 7)[a]		Gd found (ng)			
Humic acid added (mg)	Fulvic acid added (mg)	In effluent[b]		In eluate[c]	
		Run 1	Run 2	Run 1	Run 2
0.05	0	1.9	1.7	3.0	3.3
0.10	0	0.9	0.9	4.2	4.2
0.25	0	ND[d]	ND	5.1	5.1
0.50	0	–	–	4.8	–
0	0.10	1.8	1.5	3.3	3.4
0	0.25	0.8	0.5	4.2	4.4
0	0.50	ND	ND	4.8	4.9
0	1.0	–	–	4.9	–
0.05	0.10	1.1	1.2	3.8	3.9
0.10	0.25	ND	ND	4.9	5.1
0.50	2.5	–	–	4.8	–
2.0	5.0	–	–	4.9	–
5.0	10	–	–	3.3	–

[a] Na 5.2, K 1.0, Mg 1.8, Ca 4.6, Cl 9.2, SO_4 6.8, and NO_3 7.1 μg mL^{-1}.
[b] Determined by solid-phase extraction followed by ICP-MS.
[c] Desorbed with 1 M nitric acid and determined by ICP-MS.
[d] Not detected (< 0.01 ng).

each of 1 M nitric acid. The Gd in the combined eluates was 5.0 ng, indicating the complete sorption and desorption.

3.2. Desorption of Gd species

As described above, both Gd–humic and DTPA complexes were desorbed by the addition of 1 M nitric acid, which led to the unselective desorption and thus made the speciation analysis impossible. Highly polyvalent humic complexes should be sorbed on the A-25 column more strongly than Gd–DTPA; hence an attempt was made to selectively desorb Gd–DTPA by anion-exchange with a sulfate solution. After the sorption of Gd–DTPA without humic substances, different volumes and concentrations of sulfate solution were applied for the desorption. As given in Table 2, 4.0 mL of 50 mM sulfate solution was adequate for the complete desorption.

The desorption of Gd complexed with humic substances was investigated as follows. A 5.0-ng amount of Gd was mixed with 0.5 mg of humic acid or 2.5 mg of fulvic acid in 500 mL of synthetic river water. The amounts of humic and fulvic acids were large enough for the complete complexation of Gd. The solution was introduced onto the A-25 column for the sorption. The desorption was done with 4.0 mL of 50 mM sulfate solution followed by 2.0 mL of 1 M nitric acid. As given in Table 3, Gd complexed with humic substances was not recovered at the first desorption (by anion-exchange with 50 mM sulfate solution), whereas it was almost completely recovered at the second desorption (by the dissociation of Gd–humic complexes with 1 M nitric acid). Almost the complete recovery was reproducible, even though the addition of 1 M nitric acid was not repeated. The results given in Tables 2 and 3 indicate that the analytical fractionation can be made by the two-step desorption with 50 mM sulfate solution followed by 1 M nitric acid.

3.3. Analytical fractionation of Gd–humic and DTPA complexes

A series of synthetic samples were prepared and introduced onto the A-25 column. The desorption of Gd was done with 50 mM sulfate solution followed by 1 M nitric acid. The results are given in Table 4. For Group A samples, to which Gd–DTPA had been added along with Gd ion but without humic substances, the amounts of Gd recovered at the first desorption (with 50 mM sulfate solution) were almost equal to those of Gd–DTPA added. As expected, no Gd was detected at the second desorption (with 1 M nitric acid); only the humic fraction of Gd should be recovered at this stage. For Group B samples, which contained small amounts of humic substances, the Gd recovered at the second desorption was near 80% of Gd ion added. This can be explained by the incomplete formation of Gd–humic complexes because the Gd passing through the column (determined by the analysis of the effluent) was near 20% of Gd ion added. For Groups C–F, the amounts of Gd recovered at the first and second desorptions were both consistent with those of Gd added as Gd–DTPA and Gd ion, respectively. This indicates that Gd–DTPA was selectively recovered at the first desorption as well as that Gd ion was completely complexed with humic substances and recovered at the second desorption. For Group G samples, which contained large amounts of humic substances, the recovery of Gd was decreased at both the first and second desorptions, most probably because the saturation of the column with humic substances caused the incomplete sorption of Gd–humic and DTPA complexes.

Table 2
Desorption of 5.0 ngGd of Gd–DTPA with different volumes and concentrations of sulfate solution[a].

Volume (mL)	Gd desorbed (ng)		
	With 10 mM sulfate	With 25 mM sulfate	With 50 mM sulfate
2.0	ND[b]	ND	ND
3.0	ND	1.8	3.3
4.0	ND	2.9	4.8, 4.9, 5.2

[a] Sample solution applied (500 mL, pH 7): Na 5.2, K 1.0, Mg 1.8, Ca 4.6, Cl 9.2, SO_4 6.8, and NO_3 7.1 μg mL^{-1}.
[b] Not detected (< 0.01 ng).

Table 3
Desorption of 5.0 ng of Gd complexed with humic substances.

Sample solution (500 mL, pH 7)[a]	Gd desorbed (ng)	
	At 1st desorption (with 50 mM sulfate solution)	At 2nd desorption (with 1 M nitric acid)
Humic acid 0.5 mg	ND, ND, ND[b]	4.8, 4.9, 5.0
Fulvic acid 2.5 mg	ND, ND, ND	4.8, 5.0, 5.2

[a] Na 5.2, K 1.0, Mg 1.8, Ca 4.6, Cl 9.2, SO_4 6.8, and NO_3 7.1 μg mL^{-1}.
[b] Not detected (< 0.01 ng).

Table 4
Fractionation of Gd–DTPA and humic complexes in synthetic samples.

Sample solution (500 mL, pH 7)[a]		Gd desorbed (ng)	
Gd–DTPA added (ngGd)	Gd ion added (ng)	At 1st desorption (with sulfate solution)	At 2nd desorption (with nitric acid)
Group A (without humic and fulvic acids)			
1.0	2.0	1.0	ND[b]
1.0	5.0	1.1	ND
2.0	1.0	2.1	ND
5.0	1.0	5.2	ND
Group B (humic acid 0.05 mg, fulvic acid 0.10 mg)			
1.0	2.0	0.93	1.6
1.0	5.0	1.0, 1.1	3.6, 3.8[c]
2.0	1.0	2.0	0.80
5.0	1.0	5.2	0.81
Group C (humic acid 0.10 mg, fulvic acid 0.25 mg)			
1.0	2.0	0.93	1.9
1.0	5.0	0.95	4.9
2.0	1.0	1.8	0.93
5.0	1.0	4.7	1.0
Group D (humic acid 0.25 mg, fulvic acid 1.0 mg)			
1.0	2.0	0.91	2.0
1.0	5.0	1.1	4.7
2.0	1.0	2.0	0.95
5.0	1.0	5.0	0.96
Group E (humic acid 0.50 mg, fulvic acid 2.5 mg)			
1.0	2.0	1.0	1.9
1.0	5.0	0.97	4.7
2.0	1.0	1.9	1.1
5.0	1.0	5.4	1.1
Group F (humic acid 2.0 mg, fulvic acid 5.0 mg)			
1.0	2.0	0.94	1.8
1.0	5.0	1.1	5.1
2.0	1.0	2.1	1.1
5.0	1.0	4.8	1.0
Group G (humic acid 5.0 mg, fulvic acid 10 mg)			
1.0	2.0	0.62	1.5
1.0	5.0	0.65	3.6
2.0	1.0	1.6	0.83
5.0	1.0	3.3	0.65

[a] Na 5.2, K 1.0, Mg 1.8, Ca 4.6, Cl 9.2, SO_4 6.8, and NO_3 7.1 μg mL^{-1}.
[b] Not detected (< 0.01 ng).
[c] 1.1 ng of Gd was found in the effluent (analyzed by solid-phase extraction followed by ICP-MS).

Table 5
Analysis of 500-mL aliquot of filtered river water samples.

Gd–DTPA added (ngGd)	Gd found (ng)			Humic substances found[b] (mg)	pH
	In effluent[a]	In eluent			
		At 1st desorption (with sulfate solution)	At 2nd desorption (with nitric acid)		
Asuke (remote area)					
0	ND[c]	ND	3.6 ± 0.2[d]	0.43	7.0
0.50	–	0.48, 0.52	3.5, 3.7		
1.0	–	0.89, 0.91	3.6, 3.8		
Yamazaki (urban area)					
0	ND	0.82 ± 0.09[d]	3.6 ± 0.1[d]	0.55	7.1
0.50	–	1.3, 1.4	3.5, 3.6		
1.0	–	1.7, 1.8	3.5, 3.7		

[a] Determined by solid-phase extraction followed by ICP-MS.
[b] Determined by spectrophotometry using fulvic acid as a standard.
[c] Not detected (< 0.01 ng).
[d] Mean $\pm$ standard deviation, $n=4$.

3.4. Application to river water samples

The proposed method was applied to river water samples collected in remote and urban areas. After filtration with 0.45-μm Omnipore hydrophilic PTFE membrane filters, a 500-mL aliquot of the filtered sample was treated as described in Section 2.2. Another 500-mL aliquot of the filtered sample was also treated as described in Section 2.3. For the spectrophotometric determination, fulvic acid was used as a standard because fulvic acid was found to be a predominant species of aquatic humic substances [25].

Table 5 gives the analytical results. Nearly the same amount of humic substances was found in both the samples collected in remote and urban areas (Asuke and Yamazaki, respectively). After the full introduction of the samples, only the top half of the columns was colored dark brown, indicating no saturation with humic substances. No Gd was found in the effluent for both the Asuke and Yamazaki samples, suggesting that free Gd species existed at a negligible level. For the Asuke sample, Gd was not detected at the first desorption (with 50 mM sulfate solution), whereas it was detected at the second desorption (with 1 M nitric acid). For the Yamazaki sample, Gd was, in contrast, detected at both the first and second desorptions. The uncertainties, expressed as relative standard deviations, were within 11%. The first fraction, at least in part, may consist of the anthropogenic Gd possibly including Gd–DTPA. The second fraction contained Gd at the same level for both the Asuke and Yamazaki samples and it can be considered as the humic fraction of dissolved Gd species. The Gd–DTPA added to the filtered samples was almost completely recovered at the first desorption and no positive error was observed at the second desorption, indicating that the analytical fractionation was successful. The blanks through the whole procedure were not detectable (< 0.01 ng).

4. Conclusion

The present study was undertaken to develop a separation and preconcentration method for the fractionation analysis of Gd by ICP-MS, taking into account naturally occurring humic and fulvic acids. Although environmentally important, they have not been considered in the previous studies on the positive Gd anomaly so far. The proposed method can distinguish between Gd–humic complexes and other dissolved Gd species and it can offer the 100-fold preconcentration for the analytical fractionation and determination of Gd species at low ng L^{-1} levels in river water samples. The proposed method will be useful in gaining insight into the behavior and fate of Gd species in aquatic environments. Gadolinium-based MRI contrast agents other than Gd–DTPA may behave differently in the fractionation. For example, a Gd complex of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), which is another widespread contrast agent, is a monovalent anion. It may be retained on the A-25 column more weakly and thus possibly separated from Gd–DTPA chromatographically. If not retained, the Gd complexes should pass through the column. Nonionic contrast agents, *e.g.*, a Gd complex of 2,2′,2″-(10-((2R,3S)-1,3,4-trihydroxybutan-2-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (DO3A-butrol), can be expected to have such behavior. The unretained complexes, if present, should be found in the effluent. The behavior of different Gd-based contrast agents and its potential in the fractionation analysis will be the subject of future investigation.

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