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Trace analysis of phenolic xenoestrogens in water samples by stir bar sorptive extraction with in situ derivatization and thermal desorption–gas chromatography–mass spectrometry

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Abstract

A method for the simultaneous measurement of trace amounts of phenolic xenoestrogens, such as 2,4-dichlorophenol (2,4-DCP), 4-*tert*-butylphenol (BP), 4-*tert*-octylphenol (OP), 4-nonylphenol (NP), pentachlorophenol (PCP) and bisphenol A (BPA), in water samples was developed using stir bar sorptive extraction (SBSE) with in situ derivatization followed by thermal desorption (TD)–gas chromatography–mass spectrometry (GC–MS) analysis. The conditions for derivatization with acetic acid anhydride were investigated. A polydimethylsiloxane (PDMS)-coated stir bar and derivatization reagents were added to 10 ml of water sample and stirring was commenced for 10–180 min at room temperature (25 °C) in a headspace vial. Then, the extract was analyzed by TD–GC–MS. The optimum time for SBSE with in situ derivatization was 90 min. The detection limits of 2,4-DCP, BP, OP, NP, PCP and BPA were 2, 1, 0.5, 5, 2 and 2 pg ml^{-1}, respectively. The method showed good linearity over the concentration ranges of 10, 5, 2, 20, 10 and 10–1000 pg ml^{-1} for 2,4-DCP, BP, OP, NP, PCP and BPA, respectively, and the correlation coefficients were higher than 0.99. The average recoveries of those compounds in river water samples were equal to or higher than 93.9% (R.S.D. <7.2%) with correction using the added surrogate standards. This simple, accurate, sensitive and selective method can be used in the determination of trace amounts of phenolic xenoestrogens in river water samples.

Keywords: Water analysis; Stir bar sorptive extraction; Derivatization, GC; Phenolic xenoestrogens

1. Introduction

Many non-steroidal anthropogenic chemicals are known to mimic the effects of 17β-estradiol, a natural estrogen. Xenoestrogens with markedly different chemical structures have been identified in vitro [1–5] and in some cases in vivo [6–10]. Many xenoestrogens including those investigated in this work possess a phenolic group. Because of their widespread application as industrial chemicals, often in the form of an aqueous solution, phenolic xenoestrogens are expected to end up primarily in the aquatic environment via river and sewage, in contrast to phytoestrogens. Recent work has shown that although normally only female fish produce vitellogenin, an increase in plasma vitellogenin levels was detected in wild male fish thriving in rivers polluted by phenolic xenoestrogens [11–15]. Accordingly, it is highly possible that these compounds may leach into the environment. In the present study, we focus on the combined determination of such phenolic xenoestrogens as 2,4-dichlorophenol (2,4-DCP), 4-*tert*-butylphenol (BP), 4-*tert*-octylphenol (OP), 4-nonylphenol (NP), pentachlorophenol (PCP) and bisphenol A (BPA).

Highly reliable methods are required for the detection of trace compounds with estrogenic activity. Many analytical methods for the determination of phenolic xenoestrogens in water samples have been reported including liquid chromatography (LC) with electrochemical detection (ED) [16], fluorescence detection (FD) [17] and mass spectrometry

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(MS) [18]. However, the LC method has low resolution and the sample matrix is frequently affected. On the other hand, gas chromatography–mass spectrometry (GC–MS) was initially used for the determination of phenol compounds even though derivatization was required [19,20]. The derivatization leads to sharper peaks and hence to better separation of and higher sensitivity for the phenols. However, the derivatization faces the risk of contamination and hence an overestimation of phenolic xenoestrogen concentration. In order to overcome this problem, in situ derivatization already has been developed by various reports, which involves the simple addition of a reagent to a liquid sample.

Such analytical procedures as liquid–liquid extraction (LLE) [20–22] and solid-phase extraction (SPE) [16–19,23–25] have been developed for the determination of phenolic xenoestrogens. However, LLE requires large volumes of organic solvents and additional clean-up steps, and although SPE requires small volumes of organic solvents, the manual version, needed for the concentration of large sample volumes, still takes 8–10 h. Recently, solid-phase microextraction (SPME)–GC–MS has been successfully used for the determination of NP, BPA and 17α-ethinylestradiol with quantification limits below 0.6, 0.9 and 0.06 ng ml^{-1}, respectively [26]. However, the sensitivity of the above methods is still considered to be low. Because SPME with polydimethylsiloxane (PDMS) is by nature an equilibration technique that is based on the partitioning of an analyte between the stationary phase and the aqueous sample, the enrichment factors are dependent on the distribution coefficients of the analyte in the two phases. As a consequence, the limited enrichment on the SPME fiber is mainly due to the volume of the PDMS phase (typically 0.5 μl or less). Increasing the amount of PDMS relative to the aqueous matrix will markedly increase the enrichment of the analyte. Recently, a new sorptive extraction technique that uses a stir bar coated with 50–300 μl of PDMS was developed [27]. The technique is known as stir bar sorptive extraction (SBSE) and its main advantage is its wide application range that includes volatile aromatics, halogenated solvents, polyaromatic hydrocarbons, polychlorinated biphenyls (PCBs), pesticides, preservatives, pharmaceuticals, odor compounds and organotin compounds [28–35]. Moreover, analytical method for the determination of endocrine disrupting chemicals, such as aldrin, dieldrin, 4,4′-DDE and 4,4′-DDT was reported [36]. In addition, we already reported the determination of OP and NP in top and river water samples [37] and body fluid samples [38] by SBSE without derivatization method. On the other hand, SBSE with in situ derivatization has been successfully used in the determination of phenolic compounds in various samples [39–41]. In addition, we already performed the determination of BPA in water and body fluid samples by SBSE with in situ derivatization [42]. However, to our knowledge, simultaneous analysis of phenolic xenoestrogens by SBSE with in situ derivatization has not been reported.

The aim of this study is to determine trace amounts of phenolic xenoestrogens in water samples by SBSE with in situ derivatization, followed by thermal desorption (TD)–GC–MS. The developed method was applied to river water samples.

2. Experimental

2.1. Materials and reagents

2,4-Dichlorophenol, 4-*tert*-butylphenol, 4-*tert*-octylphenol, 4-nonylphenol (mixture), pentachlorophenol and bisphenol A of environmental analytical grade and acetic acid anhydride for trace analysis were purchased from Kanto Chemical Inc. (Tokyo, Japan). Deuterium 4-*tert*-butylphenol (a mixture in which the hydrogen of BP was replaced with 11–14 deuterium) (BP-d), deuterium 4-*tert*-octylphenol (a mixture in which the hydrogen of OP was replaced with 1–12 deuterium) (OP-d), and 4-(1-methyl) octylphenol-d_5 (m-OP-d_5) surrogate standards were purchased from Hayashi Pure Chemical Inc. (Osaka, Japan). 2,4-Dichlorophenol-d_4 (2,4-DCP-d_4), $^{13}C_6$-pentachlorophenol ($^{13}C_6$-PCP) and $^{13}C_{12}$-bisphenol A ($^{13}C_{12}$-BPA) surrogate standards were purchased from Cambridge Isotope Laboratories Inc. (MA, USA). The chemical structures are shown in Fig. 1. Other reagents and solvents were of pesticide or analytical grade and purchased from Wako Pure Chemical Inc. (Osaka, Japan). The water purification system used was Milli-Q gradient A 10 with an EDS polisher (Millipore, Bedford, MA, USA). The EDS polisher was a new filter purchased from Millipore, Japan.

2.2. Standard solutions

Concentrated solutions (1.0 mg ml^{-1} in methanol) of the compounds were prepared as required by the addition of purified water and a specific amount of surro-

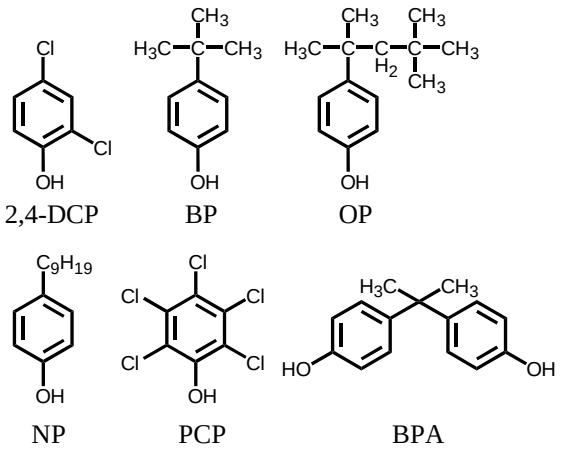

Fig. 1. Chemical structures of 2,4-DCP, BP, OP, NP, PCP and BPA.

gate standard. Six-point calibrations (10–1000 pg ml^{-1} for 2,4-DCP; 5–1000 pg ml^{-1} for BP; 2–1000 pg ml^{-1} for OP; 20–1000 pg ml^{-1} for NP; 10–1000 pg ml^{-1} for PCP; and 10–1000 pg ml^{-1} for BPA) were performed daily for all samples with the surrogate standards.

2.3. Water samples

River water was sampled from three sites (upstream, midstream and downstream) of Tama River, Tokyo, Japan. All samples were stored at −20 °C prior to use.

2.4. Instrumentation

Stir bars coated with 500 μm thick (24 μl) PDMS were obtained from Gerstel (Mullheim an der Ruhr, Germany). Prior to use, the stir bars were conditioned for 4 h at 300 °C in a flow of helium. The stir bars could be used more than 50 times with appropriate re-conditioning. For the extraction, 20 ml headspace vials from Agilent Technologies (Palo Alto, CA, USA) were used. TD–GC–MS analysis was performed using a Gerstel TDS 2 thermodesorption system equipped with a Gerstel TDS-A autosampler and a Gerstel CIS 4 programmable temperature vaporization (PTV) inlet (Gerstel) and an Agilent 6890 gas chromatograph with a 5973 mass-selective detector (Agilent Technologies).

2.5. TD–GC–MS conditions

The temperature of TDS 2 was programmed to increase from 20 °C (held for 1 min) to 280 °C (held for 5 min) at a rate of 60 °C min^{-1}. The desorbed compounds were cryofocused in the CIS 4 at −150 °C. After desorption, the temperature of CIS 4 was programmed to increase from −150 to 300 °C (held for 10 min) at a rate of 12 °C s^{-1} to inject the trapped compounds into the analytical column. The injection was performed in the splitless mode. The separation was accomplished on a DB-5MS fused silica column (30 m × 0.25 mm i.d., 0.25 μm film thickness, Agilent Technologies). The oven temperature was programmed to increase from 60 to 300 °C (held for 4 min) at a rate of 15 °C min^{-1}. Helium was used as the carrier gas at a flow rate of 1.2 ml min^{-1}. The mass spectrometer was operated in the selected ion-monitoring (SIM) mode with electron impact ionization (ionization voltage: 70 eV). Fifteen ions were monitored for SIM (*m/z* 162, 164 for 2,4-DCP; *m/z* 135, 150 for BP; *m/z* 135, 177 for OP; *m/z* 135, 177 for NP; *m/z* 266, 268 for PCP; *m/z* 213, 228 for BPA; *m/z* 169 for 2,4-DCP-d_4; *m/z* 145 for BP-d; *m/z* 140 for OP-d; *m/z* 162 for m-OP-d_5; *m/z* 276 for $^{13}C_6$-PCP; and *m/z* 225 for $^{13}C_{12}$-BPA; the underlined number is the *m/z* of the ion used for determination). The monitoring time was programmed from 6 to 9 min for 2,4-DCP, 2,4-DCP-d_4, BP and BP-d, and from 9 to 12 min for OP, OP-d, NP, m-OP-d_5, PCP and $^{13}C_6$-PCP, and from 12 to 15 min for BPA and $^{13}C_{12}$-BPA.

In the quantitative procedure, standard solutions of the compounds were prepared by dissolving the compounds in purified water to cover the calibration range. Quantitative analysis was performed in the SIM mode in order to maximize sensitivity. The concentrations were calculated relative to the surrogate standards added to the sample prior to analysis. Six-point calibrations (10–1000 pg ml^{-1} for 2,4-DCP; 5–1000 pg ml^{-1} for BP; 2–1000 pg ml^{-1} for OP; 20–1000 pg ml^{-1} for NP; 10–1000 pg ml^{-1} for PCP; and 10–1000 pg ml^{-1} for BPA) were performed daily for all samples. Although a blank run of the stir bar was always performed after an analysis, memory effects were never detected.

2.6. SBSE with in situ derivatization of phenolic xenoestrogens from river water samples

Ten milliliters of river water sample was placed in a headspace vial containing surrogate standard. Then, sodium carbonate (53.0 mg) and sodium hydrogen carbonate (42.0 mg) for pH adjustment (pH 10.5), and acetic acid anhydride (200 μl) as the derivatization reagent were added. The stir bar was added and the vial was crimped with a Teflon-coated silicone septum. SBSE was performed at room temperature for 10–180 min while stirring at 1000 rpm. After the extraction, the stir bar was easily removed with forceps (due to magnetic attraction), rinsed with purified water, dried with lint-free issue and placed in a glass thermal desorption tube. The thermal desorption tube was then placed in the thermal desorption unit. Then, the stir bar was thermally desorbed in the TD system, and this was followed by GC–MS.

3. Results and discussion

3.1. Derivatization of phenolic xenoestrogens

In the mass analysis of standard solutions using electron impact ionization (EI)-MS, *m/z* 162, 135, 135, 135, 266 and 213 were observed as the main peaks of 2,4-DCP, BP, OP, NP, PCP and BPA, respectively. For the surrogate standards, 2,4-DCP-d_4, m-OP-d_5, $^{13}C_6$-PCP and $^{13}C_{12}$-BPA, their main peaks were detected at *m/z* 165, 126, 272 and 225, respectively. However, the fragment ion peaks of the standard compounds and the main peaks of the surrogate standards were overlapped in the case of 2,4-DCP and PCP. Therefore, the monitoring ions of 2,4-DCP-d_4 and $^{13}C_6$-PCP were set at *m/z* 169 and 276, respectively. On the other hand, many fragment ion peaks were observed in the vicinity of *m/z* 145 and 140, respectively, for BP-d and OP-d surrogate standards. However, because *m/z* 135, which is the monitoring ion of BP and OP, was not observed, measurement could be performed satisfactorily by using BP-d and OP-d as surrogate standards (Fig. 2). The mass spectrometer was operated in the SIM mode. Fifteen ions were monitored (*m/z*

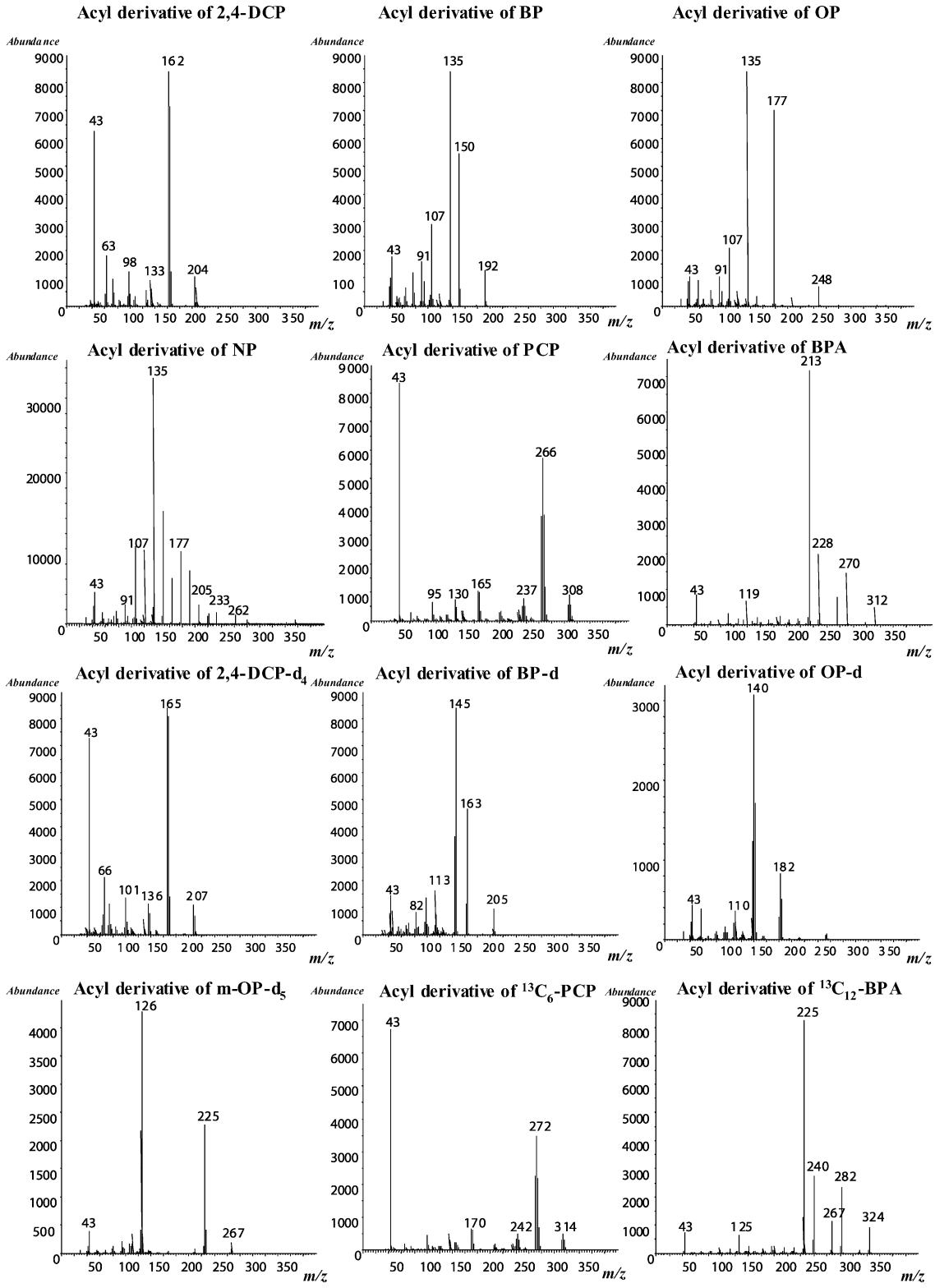

Fig. 2. Mass spectra of acyl derivatives of 2,4-DCP, BP, OP, NP, PCP, BPA, 2,4-DCP-d_4, BP-d, OP-d, m-OP-d_5, $^{13}C_6$-PCP and $^{13}C_{12}$-BPA.

Table 1
The $\log K_{o/w}$ and theoretical recoveries of phenolic xenoestrogens and their acyl derivatives by SBSE

Compound	$\log K_{o/w}$[a]	Theoretical recovery (%)
2,4-DCP	2.80	60.2
2,4-DCP acetate	2.88	64.5
BP	3.28	82.0
BP acetate	3.74	93.0
OP	4.41	98.4
OP acetate	5.53	99.9
NP	5.38	99.8
NP acetate	6.28	100.0
PCP	4.74	99.2
PCP acetate	4.81	99.3
BPA	3.50	88.4
BPA diacetate	4.48	98.6

[a] The $\log K_{o/w}$ values for all compounds as calculated from "the log *P* predictor" and "SRC KowWin", as well as calculated recoveries.

162, 164 for 2,4-DCP; *m/z* 135, 150 for BP; *m/z* 135, 177 for OP; *m/z* 135, 177 for NP; *m/z* 266, 268 for PCP; *m/z* 213, 228 for BPA; *m/z* 169 for 2,4-DCP-d_4; *m/z* 145 for BP-d; *m/z* 140 for OP-d; *m/z* 162 for m-OP-d_5; *m/z* 276 for $^{13}C_6$-PCP; and *m/z* 225 for $^{13}C_{12}$-BPA; the underlined number is the *m/z* of the ion used for determination).

3.2. Theoretical recovery of SBSE

Table 1 shows $\log K_{o/w}$ and the theoretical recoveries of the compounds investigated in this work. The $K_{o/w}$ values were calculated from the log *P* predictor, which is available from Interactive Analysis Inc. (Bedford, MA, USA), and the KowWin program, which is available from Syracuse Research Corporation (SRC, USA).Theoretical recoveries are calculated by the following equation:

$$\text{theoretical recovery} = \frac{K_{o/w}/\beta}{1 + K_{o/w}/\beta} = \frac{1}{\beta/K_{o/w} + 1}$$

where $\beta = V_w/V_{PDMS}$, V_{PDMS} the volume of PDMS and V_w the volume of water. The theoretical recoveries of SBSE were calculated based on a 10 ml sample volume and a stir bar with a phase thickness of 500 μm (24 μl of PDMS). The results revealed that the theoretical recoveries of phenolic xenoestrogens were increased by the derivatization. The chromatogram of phenolic xenoestrogen standard solution (100 pg ml^{-1}) subjected to SBSE with in situ derivatization was compared with that subjected to SBSE without derivatization, and an increase in sensitivity was observed in the former (Fig. 3).

3.3. Optimum time for SBSE with in situ derivatization

One important parameter affecting SBSE was the extraction time. To determine the optimum extraction time, 1.0 ng ml^{-1} standard solutions of phenolic xenoestrogens were used. The extraction time profiles (equilibration curves) of the compounds in 10 ml standard solutions using SBSE with in situ derivatization are shown in Fig. 4. All compounds reached equilibrium after approximately 90 min.

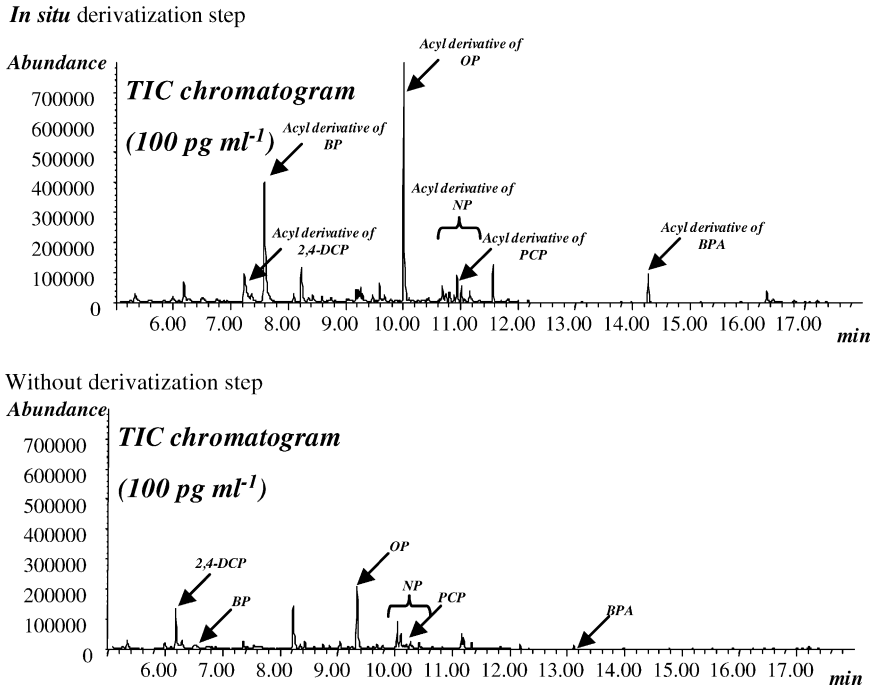

Fig. 3. Comparison of chromatogram of phenolic xenoestrogens subjected to SBSE with in situ derivatization with that subjected to SBSE without derivatization. For SBSE with in situ derivatization: a PDMS-coated stir bar and derivatization reagents were added to 10 ml of phenolic xenoestrogen standard solutions (100 pg ml^{-1}) and stirring was commenced for 90 min at room temperature (25 °C) in a glass vial. The extract was then analyzed by TD–GC–MS. For SBSE without derivatization: the same procedure was performed except that no derivatization reagents were added.

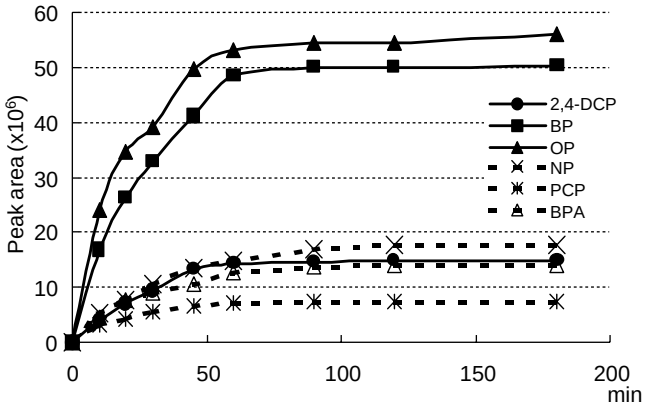

Fig. 4. Extraction time profiles of phenolic xenoestrogens in water samples using stir bar. A PDMS-coated stir bar and derivatization reagents were added to 10 ml of standard solutions (1.0 ng ml^{-1}) and stirring was commenced for 10–180 min at room temperature (25 °C) in a glass vial. The extract was then analyzed by TD–GC–MS.

Therefore, this condition was used for the determination of phenolic xenoestrogens in water samples.

3.4. Validation of SBSE with in situ derivatization and TD–GC–MS

The calculated limits of detection (LODs) of 2,4-DCP, BP, OP, NP, PCP and BPA in water samples by the in situ derivatization method were 2, 1, 0.5, 5, 2 and 2 pg ml^{-1}, respectively, for SBSE–TD–GC–MS detection with the ratio of the compound's signal to the background signal (S/N) of 3. In addition, the limits of quantification (LOQs) calculated when S/N >10 were 10, 5, 2, 20, 10 and 10 pg ml^{-1} for 2,4-DCP, BP, OP, NP, PCP and BPA, respectively. The peak area ratio with respect to each surrogate standard was plotted, and the response was found to be linear over the calibration range with a correlation coefficient (r^2) of 0.99. The results are summarized in Table 2. By our previous study, determination of OP and NP in river water samples by SBSE without derivatization has been reported [37]. The in situ derivatization method exhibited higher sensitivity than the method without derivatization. Moreover, a comparison of the SBSE method with the SPE method used in our previous study [16] was performed. The SBSE method was superior to the SPE method in terms of sensitivity. In addition, the SBSE method is applicable to a small amount of sample compared to the SPE method.

Table 2
Validation of SBSE with in situ derivatization and TD–GC–MS method

Compound	LOD[a] (pg ml^{-1})	LOQ[b] (pg ml^{-1})	Correlation coefficient (r^2)
2,4-DCP	2	10	0.999 (10–1000)[c]
BP	1	5	0.999 (5–1000)
OP	0.5	2	0.999 (2–1000)
NP	5	20	0.999 (20–1000)
PCP	2	10	0.998 (10–1000)
BPA	2	10	0.999 (10–1000)

[a] LOD: limit of detection (S/N = 3).
[b] LOQ: limit of quantification (S/N >10).
[c] Values in parentheses are the linear ranges of the calibration curves (pg ml^{-1}).

Table 3
Recoveries of phenolic xenoestrogens in spiked river water samples

Compound	Amount spiked			
	0.1 ng ml^{-1}		1.0 ng ml^{-1}	
	Recovery (%)	R.S.D. (%)[a]	Recovery (%)	R.S.D. (%)[a]
2,4-DCP	102.8	6.0	108.8	5.5
BP	102.1	7.2	107.1	3.6
OP	93.9	6.1	96.8	3.3
NP	113.0	5.9	112.3	5.3
PCP	107.8	6.0	101.8	3.9
BPA	103.0	5.3	99.3	4.3

[a] The recoveries and precision were also examined by replicate analysis ($n = 6$) of river water samples.

The recovery and precision of the method were assessed by replicate analysis ($n = 6$) of various samples fortified with surrogate standards at 0.1 and 1.0 ng ml^{-1}. The non-spiked and spiked samples were analyzed by SBSE with in situ derivatization and TD–GC–MS. The recoveries were calculated by subtracting the results for the non-spiked samples from those for the spiked samples. The results were obtained by using calibration graphs obtained from standard solutions with surrogate standards. The recovery was equal to or higher than 93.9% (R.S.D. <7.2%) for all river water samples (Table 3). Therefore, the method is applicable to the precise determination of trace amounts of phenolic xenoestrogens in river water samples.

3.5. Application of the analytical method

We measured the concentrations of phenolic xenoestrogens in three water samples (upstream, midstream and downstream) collected from Tama River, and the results are shown in Table 4. Typical chromatograms of downstream river water samples are shown in Fig. 5. 2,4-DCP, BP, OP, NP and BPA were detected in the river water samples. In addition,

Table 4
Concentrations of phenolic xenoestrogens in river water samples

Compound	Tama river (pg ml^{-1})		
	Upstream	Midstream	Downstream
2,4-DCP	29.8	68.2	81.4
BP	7.2	18.9	26.8
OP	N.D.	10.0	19.2
NP	37.6	48.5	57.9
PCP	N.D.	N.D.	N.D.
BPA	41.5	46.9	72.2

N.D. indicates 2,4-DCP, BP, OP, NP, PCP and BPA concentrations lower than 10, 5, 2, 20, 10 and 10 pg ml^{-1}, respectively.

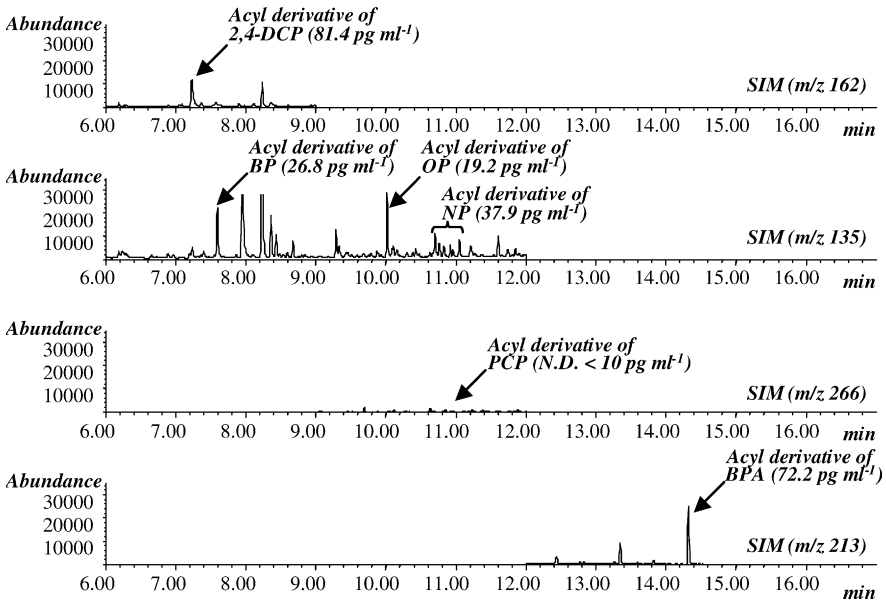

Fig. 5. Chromatograms of phenolic xenoestrogens in river water samples. A PDMS-coated stir bar, surrogate standards and derivatization reagents were added to 10 ml of river water sample and stirring was performed for 90 min at room temperature (25 °C) in a glass vial. The extract was then analyzed by TD–GC–MS.

the concentrations of the detected compounds were higher in the downstream samples than in the upstream samples. It was considered that the contamination came from the drainages for homes and industries.

The phenolic xenoestrogen levels in the river water samples were very low and could not be quantified by SPME–GC–MS [26]. However, the combination of SBSE with in situ derivatization and TD–GC–MS led to the successful determination of trace amounts of phenolic xenoestrogens in the river water samples.

One study reported morphological abnormalities in milt in approximately 30% of the male carp population downstream of sewage treatment plants in Tama River, Japan, during the period from 1997 to 1998 [43]. Subsequently, elevated levels of vitellogenin were observed in the male carp [44]. Therefore, this river is a good study area for assessing estrogenic activity in the aquatic environment in Japan. In addition, the determination of BP, OP, NP and BPA in Tama River water samples by LC–MS with off-line SPE was conducted [45], and concentrations of $<1\,pg\,ml^{-1}$ (BP), 10–80 $pg\,ml^{-1}$ (OP), 20–500 $pg\,ml^{-1}$ (NP) and 0.6–700 $pg\,ml^{-1}$ (BPA) were detected. However, the SPE method required a large sample volume (4–20 l) for realizing high sensitivity. In the present study, the combined use of SBSE with in situ derivatization and TD–GC–MS enable the successful determination of trace amounts of phenolic xenoestrogens in a small volume of water sample (10 ml).

4. Conclusions

The determination of trace amounts of 2,4-DCP, BP, OP, NP, PCP and BPA in water samples using SBSE with in situ derivatization followed by TD–GC–MS was investigated. The proposed method has many practical advantages such as a small sample volume (10 ml) and simplicity of extraction. It is also solvent-free and has high sensitivity. The LODs of 2,4-DCP, BP, OP, NP, PCP and BPA were 2, 1, 0.5, 5, 2 and 2 $pg\,ml^{-1}$, respectively. In addition, the LOQs were 10, 5, 2, 20, 10 and 10 $pg\,ml^{-1}$, respectively. The average recoveries were between 93.9 and 113.0% with acceptable precision (R.S.D. 3.3–7.2%) for the river water samples spiked with these compounds at concentrations of 0.1 and 1.0 $ng\,ml^{-1}$ and corrected by adding isotopically labeled surrogate standards. This simple, accurate and highly sensitive method is expected to have potential applications in various water samples.

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