Surface plasmon resonance sensor based on Bi-monomer System (BMS) molecularly imprinted polymer for detection of 17β-estradiol in aqueous media

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Abstract. In this work, a hydrophilic and high sensitivity sensor was fabricated based on BMS (MAA : HEMA = 3 : 1, molar ratio) molecularly imprinted polymers (MIPs) film for 17β-estradiol (E2) detection in aqueous media combined with surface plasmon resonance (SPR) technique. In-situ UV polymerization method was used to synthesize the MIPs film on the gold surface which was modified with dodecyl mercaptan. Afterwards, the MIPs film was characterized by infrared spectroscopy (IR), scanning electron microscope (SEM) and contact angle measurements. The results showed that the MIPs film was successfully prepared on the surface of the sensor chip with good hydrophilicity and permeability. The analysis of SPR spectroscopy indicated that the MIPs film displayed greater selectivity to E2 than other competitors and non-imprinted polymers (NIPs) film and showed better adsorption performance than one kind of monomer for the same E2 concentration. The response of E2 sensor ranged from 2.5×10⁻¹⁶ to 2.5×10⁻⁸ mol/L with an ultra-low detection limit of 9.14×10⁻¹₈ mol/L in PBS buffer (pH 7.4). In addition, this sensor performed good reusability and stability. Finally, the sensor was successfully applied to detect E2 in tap water and human urine and had wide detection ranges and low detection limits in backgrounds.

1. Introduction
17β-estradiol (E2) is a steroid estrogen, a natural hormone material in animals and humans which plays a major role in maintaining the secondary physiological characteristics and normal physiological activities.[1] The level of E2 ranges from pg·mL⁻¹ to ng·mL⁻¹ in blood and urine.[2] Besides, E2 can enter the human body from the outer environment by drinking water or other ways and interfere with normal physiological processes.[3,4] So, the E2 monitoring systems with ultra-high sensitivity are important for clinical endocrinological investigations and environmental water monitoring. At present, various methods such as immunoassay,[5,6] chromatography,[7,8] electrochemical methods[9-11] and fluorescence methods[12] have been used to measure estradiol. However, all of these methods have some problems, for example, need complex sample pretreatments, time-consuming and expensive. So, it is necessary to develop faster and simpler methods.

The molecularly imprinted polymers (MIPs) technology is an analytical science, based on bionics, which simulates the interaction between antigens and antibodies in nature and has been developed for decades. MIPs possess several advantages over other detection approaches including their tailor-made recognition sites for the target analytes, low cost, simple preparation and applicability in harsh
chemical media. So, the MIPs technology has been widely used in various fields in recent years. Xiao, L. et al introduced a novel molecularly imprinted polymers grafted paper-based method for detection of E2 and the LOD reached 0.25 μg·L⁻¹ in milk and human urine samples.\cite{13} Dedi, F. et al developed a new electrochemical sensor based on molecularly imprinted polymeric microspheres and multi-walled carbon nanotube/gold nanoparticles modified carbon screen-printed electrodes for the detection of E2.\cite{14} Finally, Ning, F. J. et al introduced a novel nanosized substrate imprinted polymer on a magnetic graphene oxide surface for selective recognition and fast removal of E2.\cite{15} However, the sensitivity of these methods is not sufficient for ultra-low E2 content in some polluted water environment.

In 1993, Hayden, O. et al was first to use two different functional monomers to prepare MIPs.\cite{16} Subsequently, different research groups began to use a variety of functional monomers to prepare MIPs. For example, Chen, X. et al used two monomers, methacrylic acid and 4-vinylpyridine, to prepare rhein (4,5-dihydroxyanthraquinone-2-carboxylic acid) MIPs, and its sensitivity on the target molecule was higher than that obtained by using either methacrylic acid or 4-vinylpyridine.\cite{17} Hoai, N. T. et al and Cai, X. Q. et al. also prepared MIPs using two functional monomers and achieved good results for the detection of copper and lead ions.\cite{18,19} Therefore, MIPs relied on multi-monomers for preparation are more valuable for some target molecules.

The SPR detector is an optical sensor that measures surface changes of target substances. It has features of high sensitivity, label-free, fast response and real-time monitoring. The MIPs technology combined with SPR to detect bovine serum albumins,\cite{20} pesticides,\cite{21} pharmaceuticals\cite{22} and hormones\cite{23,24} has achieved very good results. In this work, we continuously optimize the performance of MIPs by changing composition of the BMS (HEMA and MAA). The results revealed that the MIPs film fabricated with BMS on the surface of SPR sensor chip showed higher sensitivity and better water compatibility for the detection of E2 in PBS buffer than that of single monomer. Furthermore, the SPR sensor displays excellent selectivity and stability in actual sample testing of tap water and human urine. This approach provides a reference path for improvement and implementation of efficient MIPs performance.

2. Experimental

2.1. Materials

Methacrylate (MAA), hydroxyethyl methacrylate (HEMA), 4-vinylpyridine (4-VP), acrylic acid (AA), acrylamide (AAm) and benzophenone (BP) were obtained from Tianjin Fuchen Chemical Reagent Factory (Tianjin, China). 17β-estradiol (98%), testosterone (98%), progesterone (98%), estrone (98%), 1-dodecyl mercaptan (98%) were purchased from J&K Scientific Ltd (Beijing, China). Ethylene glycol dimethacrylate (EGDMA) was purchased from Aladdin Regent Company (Shanghai, China).NaH₂PO₄·2H₂O, Na₃H₂PO₄·12H₂O, H₂SO₄ were purchased from Beijing chemical plant (Beijing, China). NaCl, acetonitrile, ethanol and acetic acid were bought from Tong Guang Fine Chemicals Company (Beijing, China). MAA, HEMA and EGDMA were distilled under reduced pressure before use. Phosphate buffered saline (PBS) solution was prepared from 150 mM NaCl and 10 mM phosphate. The pH value was adjusted using HCl and NaOH.

2.2. Apparatus

The Contact Angle Meter (Powereach, JC2000C, Shanghai Zhongchen Digital Technical Apparatus Co., China) was used to measure the contact angle of the MIPs films by adding a drop of water on the surface of MIPs films. The UV-vis spectrometer (U-3310, Hitachi, Japan) was used to study the interaction between monomers and template. A Nicolet 6700 FT-IR spectrometer (Thermo Scientific, U.S.A.) with a photoelastic modulation module (PEM) was used to characterize functional group composition of the MIP and NIP films. Scanning Electron Microscopy (Zeiss SUPRATM 55 SAPPHIRE, Germany) was used to characterize surface morphology of MIPs films. UV irradiation was carried out using a LED light source (λ=365 nm, irradiation power of 3 W/cm²) to form MIPs.
films. In addition, the SPR setup (home-built) based on Kretschmann configuration with 632.8 nm laser source was used to study the performance of MIPs films. The SPR substrate consisted of a glass slide (LaSFN9, refractive index=1.845) with a metal layer (Au 50nm in thickness).

2.3. Surface modification of the SPR chip
A glass slide (LaSFN9) coated with a gold layer (50nm) was immersed into an ethanol solution of 1.0 mmol/L dodecyl mercaptan for 24hrs, at room temperature in order to form a self-assembled monolayer (SAM). The SAM on gold surface allowed subsequent growth of polymer films. Afterwards, the chip was washed several times with pure ethanol and dried under stream of nitrogen.

2.4. In-situ synthesis of the MIPs films
E2 (13.6 mg, 25 mM), MAA (13.0 μL, 75mM) and HEMA (6.0 μL, 25 mM) were dissolved in 2 mL acetonitrile at room temperature for 3hrs to obtain the pre-complex of template and BMS. The cross-linker EGDMA (142.5 μL, 375 mM) and photoinitiator BP (40 mg, 0.02 g mL⁻¹) were then added to the pre-polymerization solution followed by ultrasonication for 5 min. Then the solution was bubbled by nitrogen for 5 min. After that, the reaction solution was allowed to enter the reaction cell. Finally, the in-situ polymerization was carried out via UV photoinitation and monitored using SPR. Second layer, the outer layer, was made by the same protocol except that the EGDMA volume of 171 μL and BP of 30 mg was used. The NIPs films were prepared using the same methodology but in the absence of E2. The basic optimization experiments on the MIPs films can be found in our previous research.[25]

A mixture of acetic acid and PBS (pH 7.4) buffer (v/v = 1/9) was used as a washing solution to remove the template molecules from the MIPs films. The SPR chip was rinsed for about 10 min at flow rate of about 1.0 mL min⁻¹ using aforementioned mixture at room temperature. After that, the SPR chip was washed with pure PBS buffer (pH 7.4). The preparation process of the MIPs film is shown in Scheme1.
2.5. Procedure of analysis

Real time detection of E2 was performed using an SPR system. All the sample solutions of E2, testosterone, progesterone and estrone were prepared using PBS buffer (pH 7.4). SPR measurements were conducted at 25°C at a fixed flow rate of approximately 1.0 mL/min. PBS was continuously passed through the SPR chip until a steady baseline was obtained (around 6 min). The rebinding of E2 was observed by injecting a series of samples with E2 in PBS (pH 7.4) at concentrations ranging from $2.5 \times 10^{-16}$ to $2.5 \times 10^{-8}$ mol/L. Each sample was monitored for 20 min by SPR. The reflectivity changes ($\Delta R$) were monitored in the process and the changes of $\Delta R$ were obtained from three measurements ($n = 3$).

3. Results and Discussion

3.1. Monomer selection

In this work, MAA was used as a dominant functional monomer for preparation of MIPs films. On one hand, hydrogen bonding between E2 and MAA can form a stable pre-complex which is key to prepare effective MIPs\cite{25}. On the other hand, the MAA was used as “universal” functional monomer with special advantages over other monomers.\cite{26,27}

We know that the performance of MIPs prepared from one kind of monomer is limited\cite{17-19} which may be related to its simple structure. Therefore, we need to improve the structure of MIPs to meet further testing requirements. In order to make a suitable BMS, four different functional monomers (HEMA, 4-VP, AAm and AA) were respectively mixed with the main monomer MAA, where MAA accounted for 75% of the total monomer system and the other monomer was 25% (molar percentage). We obtained different MIPs films under the same conditions. The contact angles of the MIPs films were measured by using one drop of double distilled water on the surface. The precise figure was captured immediately as shown in figure 1. It can be seen from the results that the MIPs films prepared with 75% MAA and 25% HEMA monomers has better hydrophilicity which favors the survival of MIPs films and detection of E2 in the aqueous phase. Therefore, MAA and HEMA were chosen for BMS to further improve the performance of the MIPs films.
Figure 1. Contact angle values of the MIPs film prepared with 75% MAA and (A) 25% HEMA; (B) 25% AA; (C) 25% AAm; (D) 25% 4-VP.

3.2. Effect of inner BMS composition on binding capacity

Previously, the inner layer was mainly used to construct molecular recognition sites\textsuperscript{[28]}. Hence, its composition and structure should have a great influence on binding capacity of the MIPs film. Therefore, this study involved the effect of different molar ratios of MAA and HEMA (only the inner film) on binding response of the MIPs film. Different MIPs films were prepared with different compositions of the BMS from 0% HEMA to 100% HEMA (molar percentage of MAA and HEMA) while the total amount of BMS was kept unchanged. The obtained MIPs films had the same thickness and were eluted by the same process. Subsequently, PBS buffer (pH 7.4) containing 2.5×10\textsuperscript{-6} mol/L E2 was separately bound with different MIPs films for 20 min (n=3 times). The reflectivity changes (ΔR) were monitored in the process and the binding kinetics of E2 (2.5×10\textsuperscript{-6} mol/L) were shown in figure 2A. Figure 2B showed that with increased ratio of HEMA from 0 to 25% in BMS, the values of ΔR increased; while as the ratio was increased continuously from 50% to 100%, the ΔR value decreased. So, ΔR was maximum to the same E2 concentration when the MIPs film was prepared from 75% MAA and 25% HEMA.

Figure 2. (A) Binding kinetics and (B) reflectivity changes of the MIPs films prepared by different proportions of BMS (HEMA = 0 - 100%) using 2.5 × 10\textsuperscript{-6} mol/L E2 in PBS at pH = 7.4 (n=3 times, RSD=3.40-8.30%).
The above phenomenon may be related to the number of holes formed with specific recognition sites. The aforementioned MIPs films were characterized by scanning electron microscopy (SEM) as seen in figure 3. With the addition of co-monomer HEMA in BMS from 0 to 25%, the holes on the surface of the MIPs film increased (figure 3a-c). However, with continuous increase in proportion of HEMA from 50% to 100% (figure 3d and 3e), the holes were gradually reduced. The holes provided channels that helped the template molecules pass through the film consequently binding the imprinted sites. So the binding capacity of MIPs films to E2 in the aqueous phase increased gradually from 0 to 25% HEMA in BMS and reduced from 50% to 100%, that is, the reflectivity change ($\Delta R$) of E2 imprinted surface was largest when the MIPs film was prepared by 25% HEMA and 75% MAA.

![Figure 3](image-url)

Figure 3. SEM images of MIPs films prepared by varying concentrations of MAA : HEMA (a) (100 : 0)%,(b) (87.5 : 12.5)%, (c) (75 : 25)%, (d) (50 : 50)%, (e) (0 : 100)% (f) the NIPs film prepared with 25% HEMA and 75% MAA.

Additionally, hydrophilicity of the MIPs films prepared with BMS in different ratios was characterized and the results were displayed in figure 4. The contact angle value of the MIPs film prepared by 75% MAA and 25% HEMA was minimal, which means better hydrophilicity of the MIPs film compared to other ratios of the BMS. This may also have a certain relationship with higher binding capacity of the MIPs film prepared from 75% MAA and 25% HEMA to E2 in the aqueous phase. From these, we concluded that addition of HEMA monomer in MIPs film can change morphology and property of films, thus changing performance of the MIPs film. But only by adding the right amount of co-monomer HEMA can the MIPs film have better capability compared to that prepared from single monomer MAA. This conclusion can be applied to other similar studies. In this research, the MIPs film prepared from the BMS of 25% HEMA and 75% MAA had the best binding capacity to E2 than the MIPs films with other ratios. Therefore, the MIPs film prepared by 25% HEMA and 75% MAA was chosen for the next experimental study.
3.3. Contact angle measurements

The contact angle values of bare gold, dodecyl mercaptan modified Au surface and the MIPs film prepared from the BMS (75% MAA and 25% HEMA) were obtained as 84.38°, 104.32° and 38.55° respectively. It can be seen clearly that dodecyl mercaptan modified Au surface became more hydrophobic compared with bare gold as shown in figure 5a and b. This indicated that dodecyl mercaptan with hydrophobic alkyl chain was successfully formed on the chip surface. The contact angle value of the chip surface modified by the MIPs film was reduced to 38.55°(figure 5c). The change in contact angle indicated the successful fabrication MIPs film on the chip surface with better water compatibility.

3.4. SEM analysis

The surface morphology of the MIPs and NIPs films was characterized by scanning electron microscopy (SEM). See figure 3c, the surface of the MIPs film roughed with many nano-size cavities (a diameter of 50-250 nm) evenly distributed on the MIPs film. However, because there were no template molecules left in the recognition cavity in the NIPs film, the surface of the film was tight without any holes (figure 3f). The thickness of the MIPs film was approximately 100 nm as shown in figure 6b. The SEM images suggested that the films were successfully fabricated on the SPR sensor chip surface.
3.5. IR spectra

Figure 7 shows the IR spectrum (2500-750 cm\(^{-1}\)) of the MIPs film and NIPs film on the SPR sensor chips. It can be observed that the peak at 1735 cm\(^{-1}\) is the characteristic peak of C=O stretching vibration. The peaks near 1261 cm\(^{-1}\) and 1176 cm\(^{-1}\) represent antisymmetric and symmetric vibrations of C-O-C group, respectively. These results also demonstrated that the MIPs and NIPs film had been synthesized on the SPR sensor chip surface separately.

3.6. Binding evaluation of MIPs film coated sensor chip

In order to evaluate binding capacity of the MIPs film, a series of E2 solutions (2.5×10\(^{-16}\) mol/L to 2.5×10\(^{-8}\) mol/L) prepared with PBS buffer (pH 7.4) were sequentially injected into the cell and each sample was bound with the MIPs film for 20 min to reach equilibrium, followed by pure PBS buffer for 5 min (figure 8B). The detection process was recorded by SPR in real time and for each sample, the resonance angle of the E2 imprinted film was obtained in PBS buffer of pH=7.4 (as seen in figure 8A). Figure 8C showed the calibration curve for the detection of E2 in PBS pH 7.4. The reflectivity changes (\(\Delta R\)) versus the concentrations of E2 was obtained as \(y=0.71495x+13.24121\), \(R^2=0.99343\) in the range from 2.5×10\(^{-16}\) to 2.5×10\(^{-8}\) mol/L. Each point of the calibration graph corresponded to the mean value obtained from three times measurements. The limit of detection (LOD) was estimated to be 9.14×10\(^{-18}\) (S/N=3). The LOD was determined as the concentration of E2 at which the response was three times the standard deviation of the reflectivity baseline while taking the error bars into account.
Figure 8. (A) Angular reflectivity spectra of the MIPs film: (a) After washing, rebinding of E2 at concentrations of (b) \(2.5 \times 10^{-16}\) mol/L, (c) \(2.5 \times 10^{-14}\) mol/L, (d) \(2.5 \times 10^{-12}\) mol/L, (e) \(2.5 \times 10^{-10}\) mol/L and (f) \(2.5 \times 10^{-8}\) mol/L. Inset: Magnification of the resonance angles. (B) Rebinding kinetics of E2 (\(2.5 \times 10^{-16}\) to \(2.5 \times 10^{-8}\) mol/L). (C) Calibration curve of E2 (\(2.5 \times 10^{-16}\) to \(2.5 \times 10^{-8}\) mol/L) detected in PBS buffer at pH = 7.4 (n=3 times, RSD=2.8-9.7%).

3.7. Selective analysis of the MIPs film-coated sensor chip

In order to study the selectivity of the MIPs film, estrone, testosterone and progesterone were chosen as competitors. The concentration of each sample was \(2.5 \times 10^{-6}\) mol/L in PBS buffer solution (pH 7.4). Each molecular analogue solution was monitored three times on the same sensor chip and the results were shown in figure 9. It indicated that the MIPs film had higher adsorption capacity for E2 (\(\Delta R = 0.029\)) in comparison to estrone (\(\Delta R = 0.004\)), testosterone (\(\Delta R = 0.003\)) and progesterone (\(\Delta R = 0.005\)). The reason is the holes formed by the E2 imprinted film were exactly the same as the structure of the E2 molecule causing better adsorption of E2 to the recognition sites. Other three analogues are similar to E2 in the structure but not identical and the difference in their recognition sites results in the physical adsorption, not specific adsorption. Thus, the NIPs film was also prepared and the respective response (\(\Delta R\)) towards E2, estrone, testosterone and progesterone was obtained as 0.55%, 0.41%, 0.39% and 0.52%. Moreover, the selectivity coefficient \(\gamma\) is described by the following equation: \(\gamma = \Delta R_{template}/\Delta R_{competitor}\) and the \(\gamma\) values of the MIPs and NIPs film were calculated and shown in Table 1. Consequently, excellent selectivity of MIPs film was indicated.

Figure 9. (A) Comparison of SPR reflectivity changes (\(\Delta R\)) for MIPs and NIPs film after adsorption of \(2.5 \times 10^{-6}\) mol·L\(^{-1}\) E2 and competitors (n=3 times, RSD=1.75-3.45%). (B) The structures of E2, estrone, testosterone and progesterone.

Table 1. The selectivity coefficient \(\gamma\) of the MIPs and NIPs film.
3.8. Reproducibility and stability of the sensor chip

In order to evaluate the reproducibility of the sensor chip, adsorption-desorption cycles were repeated five times by 2.5×10⁻⁶ mol/L E₂ sample on the same chip (figure 10A). The chip was washed with only PBS (pH 7.4) after each adsorption. From figure 9B, the reflectivity changes (ΔR) of each adsorption cycle in series were 100%, 99.74%, 97.86%, 92.80% and 92.80% compared to the initial adsorption which demonstrated that the sensor had a good reproducibility during E₂ adsorption-desorption cycles. Additionally, the stability of the sensor coated with the E₂ MIPs film was also investigated. After 56 days stored in dry conditions at room temperature, the value of the reflectivity changes was 76.63% of the original value. The result shown in figure 11 indicated that the sensor had a very long working life and excellent stability.

|          | γ estrone | γ testosterone | γ progesterone |
|----------|-----------|----------------|---------------|
| MIPs     | 7.25      | 8.79           | 5.80          |
| NIPs     | 1.34      | 1.41           | 1.06          |

Figure 10. (A) Reproducibility of the MIPs film: a. adsorption of E₂ (2.5×10⁻⁶ mol/L in PBS pH = 7.4), b. desorption (pure PBS pH = 7.4). (B) The reflectivity change (ΔR) of adsorption in each cycle.

Figure 11. (A) Rebinding kinetics of 2.5×10⁻¹⁰ mol/L E₂ in tap water after storage of 0 & 56 days. (B) The reflectivity changes (ΔR): rebinding of 2.5×10⁻¹⁰ mol·L⁻¹ E₂ in tap water after storage of 0 & 56 days.
3.9. Effect of pH on MIP binding
The effect of pH on the sensor response was investigated in PBS buffer containing $2.5 \times 10^{-8}$ mol/L E2, at room temperature. The pH values were adjusted (hydrochloric acid and sodium hydroxide: 0.1 mol/L) to 5.0, 6.0, 7.4, 8.0 and 9.0. It was found that the MIPs film displayed the lowest response at pH 6.0, as shown in figure 12. A relatively higher response to E2 was found at pH 7.4 and pH 5.0. The result may be related to the isoelectric point of the MIPs.[31]

![Figure 12. Reflectivity changes of the MIPs film for absorption of $2.5 \times 10^{-8}$ mol/L E2 in buffer solutions different pH (n=3 times, RSD=1.8-4.4%).](image)

3.10. Detection of E2 in actual samples
The performance of E2-MIPs film was tested by using tap water and human urine samples (See Table 2). The response of sensor coated with E2-MIPs film in actual samples represents high sensitivity. The results indicate that this biosensor can be successfully applied to E2 analysis in real environment and human body.

| Validation parameters | Tap water | Human urine |
|-----------------------|-----------|-------------|
| Linear range (mol \cdot L^{-1}) | $2.5 \times 10^{-16}$-2.5×$10^{-7}$ | $10^{-15}$-10^{-7} |
| Linearity ($R^2$) | 0.99583 | 0.99937 |
| Slope | -0.00261 | -0.00159 |
| Intercept | 0.04749 | 0.02694 |
| LOD (mol \cdot L^{-1}) | $1.41 \times 10^{-17}$ | $3.09 \times 10^{-17}$ |

4. Conclusions
In this paper, a hydrophilic and high sensitive sensor based on the MIPs film for 17β-estradiol (E2) detection in aqueous media was successfully prepared. The MIPs film was prepared by BMS with an optimal ratio (MAA : HEMA = 3 : 1, molar ratio), which had better binding properties and higher sensitivity than the MIPs film prepared by single monomer. Table 3 gives the reported analytical methods for determination of E2. The prepared E2-MIPs film showed good selectivity to E2 than that of other competitors and the NIPs film. Furthermore, the MIPs film can be regenerated easily by use of only PBS (pH 7.4) and maintain about 76.63% of the original value even after storage of 56 days in
dry conditions, at room temperature. Moreover, the MIPs film can work in actual samples, has a wide detection range and ultra-low detection limit for E2. The detection limits are $1.41 \times 10^{-17}$ mol/L in tap water and $3.09 \times 10^{-17}$ mol/L in human urine. In this article, the goal of optimizing MIPs performance is accomplished by adding proper amount of co-monomer HEMA to MAA to achieve tailored Bi-Monomer System. This approach provides a reference path for improvement and implementation of certain performance of MIPs.

Table 3. Comparison of different methods for detection of E2.

| Analytical methods                  | Environmental sample | Detection limit   | Ref. |
|-------------------------------------|----------------------|-------------------|------|
| SERS based immunoassay              | Human serum          | $2.40 \times 10^{-12}$ mol/L | 6    |
| GC-MC                               | Human serum          | $3.70 \times 10^{-12}$ mol/L | 7    |
| MIPs film based electrochemical     | Milk powder          | $2.76 \times 10^{-9}$ mol/L | 11   |
| Single monomer MIPs film based SPR  | Tap water            | $7.40 \times 10^{-15}$ mol/L | 25   |
|                                    | PBS buffer (pH 7.4)  | $1.15 \times 10^{-15}$ mol/L |      |
| BMS MIPs film based SPR             | Tap water            | $1.41 \times 10^{-17}$ mol/L | This study |
|                                    | PBS buffer (pH 7.4)  | $9.14 \times 10^{-18}$ mol/L |      |

Conflicts of interest
There are no conflicts to declare.

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