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Stoichiometric molecular imprinting using polymerisable urea and squaramide receptors for the solid phase extraction of organo-arsenic compound roxarsone

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The design, preparation and evaluation of molecularly imprinted polymers for roxarsone (4-hydroxy-3-nitrophenylarsonic acid), an organo-arsenic swine and poultry feed additive, using bi-substituted ureas and squaramide receptors as the functional monomers, are demonstrated. Pre-polymerisation studies of the template–monomer complexation performed by ^{1}H NMR experiments show that squaramide-based monomers provide association equilibrium constant values higher than urea-based monomers. Equilibrium rebinding experiments in methanol show that two squaramide-based materials have good molecular recognition properties towards roxarsone, with high affinity (K_{eq} = 16.85×10^3 L mol^{-1} and 14.65×10^3 L mol^{-1}, respectively), high imprinting factors (4.73 and 3.64 respectively) and good selectivity towards two roxarsone-related compounds, acetarsone (3-acetamido-4-hydroxyphenylarsonic acid) and nitarsone (4-nitrophenylarsonic acid). Polymer MIP-SQ2 was successfully used to setup an experimental protocol for the direct solid phase extraction of roxarsone from surface water samples. The method gives clean HPLC traces, with recoveries between 91% and 95% at concentration levels of 5.0, 10, and 25 mg L^{-1}. Sample preconcentration down to 1 μg L^{-1}, with good recoveries between 87% and 97%, are shown, confirming that it is possible to employ the developed materials to efficiently preconcentrate roxarsone in water samples.

Introduction

Roxarsone (4-hydroxy-3-nitrophenylarsonic acid, ROX) is an aryl-arsonate feed additive used until recently in swine and poultry husbandry to promote weight increase and to act as a wide-spectrum coccidiostat drug.[1-4] The use of roxarsone leads to significant risks for public health, since the compound itself, as well as its degradation products, may contaminate soil and surface water supplies through the uncontrolled use of poultry litter as a fertilizer additive.[5-9] Although several adsorbents, such as mixed metal oxides,[10-12] metal-organic frameworks,[13] graphene[14] or carbon nanotubes[15] have been proposed for removal of roxarsone from aqueous environments, most of them showed limited adsorption capacities and lack of selectivity for the target compound. Consequently, the design of advanced functional materials with good adsorption capacity and selectivity towards roxarsone is of particular relevance.

Molecular imprinting is a technique that enables the generation of specific binding sites within the matrix of a synthetic organic polymer, in analogy with binding sites found in nature's own specific receptors, namely enzymes and antibodies.[16] Usually, the generation of such imprinted sites within the polymer matrix is achieved by exploiting non-covalent interactions between the template of interest and a complementary functional monomer at the pre-polymerisation stage. As a consequence, the strength of template-monomer interaction is a critical issue in the binding site formation process.[17] In literature, oxyanions have been reported to strongly interact with substituted ureas and squaramides,[18-21] and tailor-made functional monomers based on such molecular structures have been described for molecular imprinting of carboxylates,[22,23] sulfopeptides[24] and phosphopeptides.[25-28] The organo-arsenate anion shows marked structural similarities with organo-phosphate and organo-sulfate anions, thus in this paper we investigated the feasibility of roxarsone-imprinted polymers prepared by using tailor-made functional monomers based on bi-substituted ureas and squaramides. We studied the binding properties of the prepared materials towards the target molecule and their selectivity towards two closely related organo-arsenates, acetarsone (3-acetamido-4-hydroxyphenyl arsonic acid, ACE) and nitarsone (4-nitrophenylarsonic acid, NIT), and the imprinted polymer with the best binding properties was used to demonstrate the feasibility of a molecularly imprinted solid phase extraction (MISPE) of roxarsone from surface waters.

Experimental

Materials

Acetarsone (ACE), deuterated dimethylsulfoxide (DMSO-6$_d$), ethylene dimethacrylate (EDMA), nitarsone (NIT), roxarsone (ROX), tetrabutylammonium benzoate, tetrabutylammonium

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hydroxide (1.0 M methanolic solution, TBAOH) were purchased from Sigma-Aldrich (Gillingham, United Kingdom). 2,2'-azobis(2,4-dimethyl)valeronitrile (ABDV) was from Wako Chemicals (Neuss, Germany). Polymerisation inhibitors in EDMA were removed by filtration through activated basic alumina. Methanol and all other chemicals were purchased from VWR International (Milan, Italy). All the solvents were of HPLC grade, whereas all chemicals were of analytical grade. The water used was ultra-purified in Purelab Prima System from Elga (Marlow, UK).

Chart 1. Molecular structures of aryl-arsonates roxarsone (ROX, template), acetarsone (ACE), nitarsone (NIT) and urea- (UR1-UR2) and squaramide-based (SQ1-SQ3) functional monomers.

Functional monomers 1-(4-vinylphenyl)-3-(3,5-bis(trifluoro methyl)phenyl)urea (UR1), 1-(4-vinylphenyl)-3-(4-nitrophenyl) urea (UR2), 3,4-bis((4-vinylphenyl)amino)-cyclobut-3-ene-1,2-dione (SQ1), 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-((4-vinylphenyl)amino)cyclobut-3-ene-1,2-dione (SQ2) and 3-((4-nitrophenyl)amino)-4-((4-vinylphenyl)amino)cyclobut-3-ene-1,2-dione (SQ3) depicted in chart 1 were synthesised as previously described.[22,23] Roxarsone tetrabutylammonium salt (ROX-TBA) was prepared by mixing TBAOH and ROX, molar ratio 2:1, in dry methanol. The solvent was evaporated under reduced pressure until a constant weight was reached and the ammonium salt was recovered quantitatively. Stock solutions of roxarsone, nitarsone and acetarsone were prepared by dissolving 25.0 mg of solid in 5.0 mL of methanol and stored in the dark at -20 °C until use.

Surface water samples were taken in Spring 2019 from an irrigation channel near Torino (Italy) in a single sampling, pooled, filtered on 0.22 μm cellulose acetate filters, and stored in silanised glass bottles in the dark at 4 °C. Total arsenic (organic + inorganic) was estimated to be <60 ng mL^{-1} by ICP-MS.[29]

^{1}H NMR titration of functional monomers

The association equilibrium constants (K_a) between roxarsone and the functional monomers were measured by ^{1}H NMR titration in DMSO-d$_6$. Increasing amounts (5-300 μL) of a 20 mmol L^{-1} solution of ROX-TBA in DMSO-d$_6$ were added in NMR tubes containing 300 μL of a 2 mmol L^{-1} solution of monomer in DMSO-d$_6$, adjusting the final volume to 600 μL with DMSO-d$_6$. The ^{1}H NMR spectra were recorded on a Bruker ECX 400 MHz spectrometer (Coventry, UK) at 25°C. Chemical shifts are referred to the solvent reference signal. The complexation-induced shift (Δδ) of the squaramide vinyl protons were measured and titration curves were drawn by plotting Δδ vs ROX-TBA molar concentration. The titration data averaged from three repeated measurements were fitted to a binding isotherm by non-linear least square regression,[30] from which the K_a was calculated.

Polymers synthesis

In 10-mL screw-cap glass vials containing the template molecule, ROX-TBA (0.5 mmol, 373 mg), the functional monomers (1 mmol, UR1 374 mg, UR2 283 mg, SQ1 316 mg, SQ2 426 mg, SQ3 333 mg) and the cross-linker EDMA (20 mmol, 3.77 mL) were added to 1.5 mL of DMSO. Pre-polymerisation mixtures were sonicated until complete dissolution and the free-radical initiator ABDV (1% wt. of total monomer, 10.2 mg) was added. Then, vials were purged with a flow of dry argon for 10 min, and polymerisation was started by placing the vials in a thermostated oven set at 50°C. After 24 h vials were smashed, and the polymers monoliths were recovered with a steel spatula, ground in a ball-mill and wet-sieved to 25-38 μm particle size. The particulate was packed in 5 mL polypropylene SPE cartridges and exhaustively washed with methanol/acetic acid 9:1 (v/v) until polymers were deemed free from roxarsone by HPLC analysis of the eluates. Then, the particulate was washed repeatedly with acetone, dried in the oven at 50 °C and then stored at room temperature. Control polymers (CP) were prepared and treated in the same manner, using tetrabutylammonium benzoate as template.

HPLC analysis

The HPLC apparatus was an Agilent 1100 (Milan, Italy), consisting of a binary solvent delivery pump provided with a 20 μL manual injection system and a UV-Vis detector. HPLC analysis of were performed on a Kinetex C$_8$ column (100Å, 5 μm, 3x100 mm) from Phenomenex (Milan, Italy). The mobile phase was made of 94:5:1 (v/v/v) mixture of water/methanol/acetic acid. The flow rate was set at 1.0 mL min^{-1}, and the detection wavelength was 245 nm. In isocratic mode, the elution time was 4.1, 5.1 and 2.9 min for ROX, NIT and ACE, respectively. Analyte standard solutions at concentrations between 1.0 and 100 μg mL^{-1} were prepared in water/methanol 9:1 (v/v) immediately before use. The standards were analysed three times consecutively and average peak areas were plotted against concentration. The calibration plot was drawn by using a weighted linear regression (weight = 1/conc). The limits of detection and quantification (ROX: LOD=1.03 μg mL^{-1}, LOQ=3.13 μg mL^{-1}; NIT: LOD=1.30 μg mL^{-1}, LOQ=3.92 μg mL^{-1}; ACE: LOD=1.16 μg mL^{-1}, LOQ=3.92 μg mL^{-1}) were calculated as LOD = 3 S$_y$/b and LOQ = 10 S$_y$/b, respectively, where S$_y$ is the standard error of the response and b is the slope of the calibration plot.

Equilibrium batch rebinding

Approximately 10 mg of each polymer were accurately weighed in 4 mL flat bottom amber glass vials. Then, 0.50 mL of methanol solutions containing increasing amounts of analyte ranging from 2.5 to 75 μg were added and sonicated for 10 min. The vials were incubated overnight at room temperature under continuous agitation on a horizontal rocking table. The solutions were then filtered through 0.22 μm nylon membranes, and the free amounts of ligand were measured by HPLC. Each experimental point was assessed as the average of three repeated measures. The binding isotherms were calculated by using SigmaPlot 12 (Systat Software Inc., Richmond, CA, USA).

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Non-linear least square fitting was applied to the averaged experimental data, by using a Langmuir isotherm model:

$$B = \frac{B_{max} K_{eq} F}{1 + K_{eq} F}$$

where B is the amount of analyte bound to the polymer, F the free analyte, K_{eq} the binding constant and B_{max} the binding site density. To assure robust results, weighted (1/y) Pearson VII limit minimisation was chosen. To avoid being trapped in local minima which would give incorrect results, the fitting was carried out several times using different initial guess values for the isotherm parameters.

The imprinting factor (*IF*) was calculated as:

$$IF = \frac{(K_{eq})_{MIP}}{(K_{eq})_{NIP}}$$

The binding selectivity (α) was calculated as:

$$\alpha = \frac{(K_{eq})_{analog}}{(K_{eq})_{template}}$$

MISPE of roxarsone in surface water

All experiments were conducted in 10 mL polypropylene SPE cartridges (Phenomenex, Milan, Italy), packed with 50 mg of the MIP-SQ2. All measurements were carried out in triplicate and recoveries were calculated as the averages of the repeated measures to estimate the method repeatability. Aqueous solutions of roxarsone were prepared from methanol standard solution by direct dilution with surface water. Before each experiment, cartridges were washed with 5×1 mL of triethylamine 1% (v/v) in water and conditioned with 5×1 mL of water.

Aqueous solutions of roxarsone were diluted 1:1 (v/v) in citrate buffer 50 mmol L^{-1} pH 4.0 and loaded onto the cartridges by applying gentle vacuum. After sample loading, air was passed through the cartridges for 5 min. Then, cartridges were washed with 1 mL of citrate buffer 50 mmol L^{-1} pH 4.0 and eluted with 2×1 mL of triethylamine 1% (v/v) in water. The eluates were immediately dried under a stream of nitrogen at 40 °C and reconstituted in 0.5 mL of mobile phase for HPLC analysis.

Results and discussion

Binding of roxarsone to functional monomers

In recent years, several of the tailor-made functional monomers considered in this work have been successfully used to obtain imprinted polymers with molecular recognition properties towards oxyanions. Squaramides SQ1-SQ3 have been described to imprint carboxylates,[23] while the urea UR1 has been extensively used to imprint phosphorylated peptides.[25-26] Considering that the arsenate moiety on roxarsone shows structural similarity with the phosphate substituent present on phosphotyrosine, we hypothesised that UR1-UR2 and SQ1-SQ3

could also be suitable for preparing roxarsone-imprinted polymers based on the formation of stable complexes held together by directional N–H···O bonds between the acidic N–H structure of the functional monomer and the anionic oxygen of the template molecule.

Table 1. K_{a1} and K_{a2} values $\pm$ 1σ obtained from ^{1}H NMR titration of functional monomers with ROX-TBA in DMSO-d_6 solution. The experimental binding isotherm satisfies a statistical binding model with $K_{a1} = 4K_{a2}$.

functional monomer	K_{a1} (L mol^{-1})	K_{a2} (L mol^{-1})
UR1	899 ± 81	225 ± 20
UR2	936 ± 84	234 ± 21
SQ1	1815 ± 200	454 ± 91
SQ2	3074 ± 246	769 ± 63
SQ3	1698 ± 221	425 ± 55

To our knowledge no information about binding properties of these tailor-made monomers towards organic arsenates is presently available in literature. ^{1}H NMR titration experiments were initially performed to evaluate their ability to bind the target molecule. The association constants, reported in table 1, were calculated by the titration curves reported in figure 1. For all functional monomers the best fitting model resulted to be a statistical 2:1 binding ratio with $K_{a1} = 4K_{a2}$,[31] while the simper 1:1 model did not result in an accurate fitting. All the functional monomers considered in this work were found to complex with roxarsone with association constants in the range of 10^3 L mol^{-1}, although monomers provided with squaramide structure showed significantly higher values compared to the urea counterparts. These results confirm what has been already previously described for simpler anions like benzoate, dihydrogen phosphate, fluoride and iodide.[23]

Binding properties of imprinted polymers

Having an experimental proof that substituted ureas and squaramides exhibit a strong complexing behaviour towards roxarsone, it was decided to assess whether these functional monomers could be used as recognition elements in molecularly imprinted polymers. Considering the binding stoichiometry of 2:1 obtained by the ^{1}H NMR titrations in DMSO-d_6, five different imprinted polymers were prepared by solution polymerisation in the same porogen and with a corresponding functional monomer : template stoichiometry of 2:1. The choice of using ROX-TBA instead of free ROX as template was inspired by a previously reported successful imprinting protocol,[23] and by the necessity to warrant the complete template dissolution in the pre-polymerisation mixture. After a careful clean-up of the polymers to remove the template and any other residual monomers, rebinding experiments were performed to evaluate polymers binding properties and selectivity in methanol. It is worth highlighting that the decision not to use ROX-TBA as rebinding probe was due to preliminary rebinding experiments performed with that salt as ligand, which caused irreproducible results. Methanol was chosen because of its good solvent properties for ROX in its free acid form, and its compatibility with future extraction

bound roxarsone, μmol g^{-1}

Figure 2.
UR1, red
CP-UR2,

bound roxaesone, μmol g^{-1}

Figure 3.
(MIP-SQ
polymer
methano

protocols from complex samples of environmental or food origin.

The resulting binding isotherms reported in figures 2-3 were fitted with a Langmuir single binding site isotherm model, whose calculated fitting parameters are reported in table 2. All evaluated polymers show values of binding sites density in the order of magnitude of μmol g^{-1}, with higher values in the case of MIPs. However, all values measured are significantly lower than those previously reported in literature for MIPs prepared with the same functional monomers, possibly due to the use of the protonated form of the target analyte in the rebinding experiment.[23] All five MIPs show binding constants above 10^3 L mol^{-1} although urea-based polymers values are similar to CPs, thus indicating a lack of substantial molecular recognition effect and interactions with the ligand mainly related to non-specific binding. On the other hand, imprinted squaramide-based polymers show higher values of binding constants if compared to the corresponding CPs, demonstrating the presence of a considerable imprinting effect. These results highlight that imprinted polymers obtained by using ROX-TBA as template molecule recognise with increased difficulty the fully protonated form of ROX, and that only MIPs prepared with functional monomers based on a squaramide structure are able to assess a significant molecular recognition effect towards roxarsone in methanol, with imprinting factors of 1.92 (SQ1), 4.73 (SQ2) and 3.64 (SQ3). Moreover, polymers prepared with squaramides substituted with strong electron-withdrawing groups (SQ2, SQ3) demonstrate an enhanced molecular recognition effect if compared to SQ1, confirming what has been previously reported in literature.[23]

In order to explain these results, it is worth considering that throughout the imprinting process the non-covalent interactions of the template to functional monomers involve the deprotonated form of roxarsone added to the polymerisation mixture as ROX-TBA. On the other hand, when rebinding studies are performed in methanol, roxarsone is prevalently in its undissociated form. Consequently, the molecular recognition interaction may be based on a stable complex between the functional monomer and the undissociated acid. Therefore, it is plausible that difference in electrical charge and molecular shape between the ion pair ROX-TBA and the functional monomer in the imprinting process and neutral roxarsone and functional monomer in the rebinding process may induce a decrease in the strength of roxarsone – binding site complex, which ultimately results in a lower binding constants.

Table 3. Binding constant (K_{eq}) and binding site density (B_{max}) $\pm$ 1σ, Pearson's correlation

The binding selectivity (α) towards roxarsone-related molecules, namely acetarsone and nitarsone, was evaluated for all imprinted polymers by measuring the binding isotherms reported in figures 4-5. Binding selectivity reported in table 3 show a sharp difference between the squaramide-based MIPs and the urea-based MIPs. In fact, the latter show a negligible selectivity. Instead, squaramide-based MIPs show a significant binding selectivity towards the template. Focusing the attention

to those MIPs characterised by a high imprinting factor (MIP-SQ2 and MIP-SQ3), it is worth noticing that binding selectivity seems to be influenced by the structural differences in the functional monomer, as no other differences can be easily identified between the polymers, in fact the presence of a nitro substituent (SQ3) makes the polymer selective for roxarsone only, with a limited recognition ($\alpha \leq 0.30$) for acetarsone and nitarsone, while the presence of trifluoromethyl substituents reduces this selectivity effect, making the MIP-SQ2 polymer unable to discriminate between template and nitarsone at all.

MISPE of roxarsone in aqueous samples

Polymer MIP-SQ2 presents the higher binding constant, therefore it was selected to setup a MISPE method for roxarsone in surface waters. Preliminary experiments were performed to assess its ability to recognize roxarsone in aqueous samples. As reported in figure 6 when 1 mL of surface water containing 50 mg L^{-1} of roxarsone and diluted 1:1 (v/v) with buffer is loaded onto the MISPE cartridge, the retention is fairly good when acidic buffers are used to load and wash the cartridge, with overall recoveries ranging from 91$\pm$3% (pH 4) to 84$\pm$3% (pH 6). Instead, the use of neutral or basic buffers cause a significant loss of analyte, with recovery tending to zero at pH = 9. When these results are compared to those obtained with a cartridge packed with the CP, the gain in terms of binding ability due to the imprinting effect is clear: the NIP cartridge does not retain roxarsone efficiently in acidic conditions, until the loss of analyte is quantitative in neutral or basic buffers.

Considering the effect of pH on cartridge loading and washing, it was therefore decided to recover roxarsone using a 1% (v/v) solution of triethylamine in water. Under these conditions the pH of the cartridge is approximately 13, guaranteeing the complete recover of the analyte in 2 mL of eluent. In these conditions, recoveries were determined (n=5) at three concentration levels and were found in the range between 91% and 95% (95$\pm$4% at 5.0 mg L^{-1}, 92$\pm$4% at 10 mg L^{-1}, and 91$\pm$3% at 25 mg L^{-1}). In these experimental conditions, the aqueous matrix caused no interference, and satisfactory sample clean-up and preconcentration were achieved, as can be seen in figure 7, where the chromatogram of surface water spiked with 5 mg L^{-1} of roxarsone shows a very clean chromatographic trace.

The possibility of detecting and quantifying small amounts of roxarsone in surface water samples was investigated by extracting increasing volumes of water (1, 2, 5, 10, 20, 50, and 100 mL) spiked with decreasing amounts of roxarsone (10, 5, 2, 1, 0.5, 0.2, and 0.1 μg). As can be seen from figure 8, in the dilution range considered, the analyte recovery was good, with values between 87% and 97% (1σ), confirming that it is possible to employ the developed materials to preconcentrate roxarsone down to 1 μg L^{-1} in water samples.

Conclusions

The feasibility of roxarsone-imprinted polymers prepared by using tailor-made functional monomers based on bis-substituted ureas and squaramides was investigated. Initial

absorbance 254 nm, mV

Figure 7.
roxarson

solution interaction experiments performed by ^{1}H NMR titrations show that both ureas- and squaramide-based functional monomers are able to complex roxarsone, while equilibrium rebinding experiments onto the imprinted polymers show binding constants in the order of magnitude higher than 10^3 L mol^{-1} for roxarsone and its analogues acetarsone and nitarsone. The squaramide-based functional monomer SQ2 showed to be well suited to prepare a molecularly imprinted polymer with high imprinting factor and binding affinity for roxarsone, and useful for the setup of a protocol of extraction which performances are comparable to the methods reported in the literature,[32] and is suitable to efficiently preconcentrate roxarsone down to 1 µg L^{-1} in water samples, a value that falls largely within the threshold level defined for arsenic in water by international organizations.[33]

Conflicts of interest

There are no conflicts to declare.

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