



Journal Name

COMMUNICATION

A halogen-bonding foldamer molecular film for selective reagentless anion sensing in water

Received 00th January 20xx,
Accepted 00th January 20xx

Robert Hein, Arseni Borissov, Martin D. Smith, Paul D. Beer* and Jason J. Davis*

DOI: 10.1039/x0xx00000x

www.rsc.org/

We describe self-assembled monolayers of novel halogen-bonding and hydrogen-bonding foldamer receptors capable of selectively recruiting perrhenate, iodide and thiocyanate in water. Unprecedented anion sensing via impedance-derived capacitance spectroscopy enables sensitive and selective anion detection without the need for a redox probe. Importantly, the sensing of any anion should be possible using this novel electrochemical approach.

Although enormously important, anion recognition and, in particular, sensing in pure water remains both challenging and underdeveloped.^{1,2} Recently we demonstrated that halogen bonding (XB) water-soluble anion receptors can complement or outperform more traditional receptors based on hydrogen bonding (HB) or simple electrostatic interactions.^{3–6} However, XB-mediated anion sensing in water remains rare.⁴ The detection of large, charge-diffuse anions such as perrhenate (ReO_4^-), is particularly challenging, yet of major interest, since both ReO_4^- and TcO_4^- are used as radiopharmaceuticals⁷ and TcO_4^- is a major hazardous pollutant originating from nuclear power generation.⁸

Sensing via electrochemical techniques is typically rapid, sensitive, environmentally flexible and scalable. Of these, electrochemical impedance spectroscopy (EIS), in which a small amplitude alternating current with varying frequencies is applied to the electrode at a constant potential, is a particularly sensitive means of reporting on steric, electrostatic or dielectric changes associated with an electrode-confined target capture event. It requires no synthetic integration of a reporting group (e.g. ferrocene) and leads to minimal perturbations of the electrode interface. Although EIS based sensing of large biomolecules has gained much attention^{9–14}, impedimetric ion sensing^{15–22}, particularly sensing of anions,

remains largely unexplored.^{19–22} In its standard form EIS assays require the pre-doping of the solution with an excess of signal amplifying redox probe, usually $\text{Fe}(\text{CN})_6^{3-/4-}$ or $\text{Ru}(\text{NH}_3)_6^{2+/3+}$. The use of high background concentrations of such multiply charged complexes, some of which may adsorb, is a major drawback when seeking to sensitively monitor low levels of specific ion binding. The omission of such transducers enables a more facile analysis of real-world samples and additionally allows for electrode potentials to be chosen with more flexibility.

In the absence of a redox transducer the change in interfacial capacitance can be used as a transducer of ion binding as preliminarily demonstrated for cation sensing.^{16,17} Selective anion sensing, via this strategy is, to the best of our knowledge, unprecedented.

Based on our previously reported tetratriazole-foldamer²³ we synthesised novel preorganised, water-soluble foldamers **1.XB/HB** and **2.XB/HB** (Fig. 1, ‡) capable of anion recognition in water. It should be noted that anion binding in pure water utilising such neutral, acyclic receptors is extremely rare.² The synthesis via multiple click reactions is described in the Supporting Information S2. Incorporation of a disulfide anchor group into **1.XB/HB** facilitates SAM formation via exposure of clean gold disk electrodes to solutions of **1.XB/HB** (in ACN/ H_2O 1:1) overnight to produce **1.XB/HB_{SAM}** (Fig. 2).

X-ray photoelectron spectroscopy (XPS) of **1.XB/HB_{SAM}** revealed the presence of iodine in the film only for **1.XB_{SAM}** with otherwise identical elemental composition for both SAMs **1.XB/HB_{SAM}** and excellent agreement with theoretical predictions (Fig. S5–10 and Tables S1–3).

Department of Chemistry, University of Oxford, South Parks Road, Oxford OX1 3QZ, U. K. E-mail: paul.beer@chem.ox.ac.uk, jason.davis@chem.ox.ac.uk

† Electronic Supplementary Information (ESI) available: Details on methods and synthetic procedures as well as further characterization of the interface and sensor performance. See DOI: 10.1039/x0xx00000x

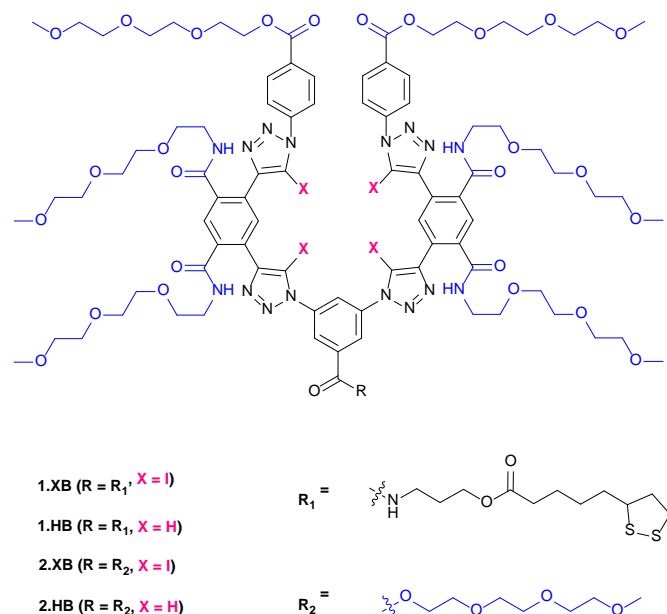


Fig. 1 Chemical structures of halogen and hydrogen bonding anion receptors **1.XB/HB** and **2.XB/HB**.

The thickness of the SAMs was determined by ellipsometry as 3.22 ± 0.21 nm and 3.51 ± 0.40 nm, respectively, consistent with the formation of a monolayer. The presence of the PEG-groups in **1.XB/HB**_{SAM} induces formation of hydrophilic, hydrated SAMs, as supported by water contact angles of 60° and 55° (Fig. S11), in good agreement with prior observations at PEG-SAMs.²⁴

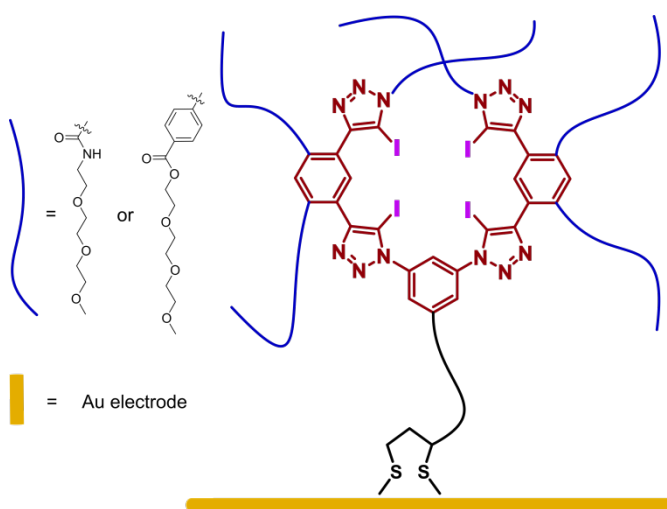


Fig. 2 Schematic representation of **1.XB**_{SAM} on a gold electrode. Surface immobilization is achieved via a multivalent disulfide anchor (black) to immobilize the foldamer anion binding motif (red/purple) onto the electrode. Hydration of the film as well as preorganisation of the triazole binding motifs is induced by PEG groups (blue).

All electrochemical experiments were carried out in pure aqueous solution containing 100 mM NaCl as supporting electrolyte. Sodium chloride was chosen as electrolyte because it does not interact with the foldamer and is present in similar concentrations in biologically and environmentally relevant samples. As expected, the foldamer SAMs are not electroactive (Fig. S12) and are densely packed with a molecular surface

coverage of $(8.85 \pm 1.70) \times 10^{-11}$ mol/cm² and $(6.40 \pm 1.60) \times 10^{-11}$ mol/cm² for **1.XB**_{SAM} and **1.HB**_{SAM}, respectively (as determined by reductive stripping voltammetry, Fig. S13). This corresponds to a molecular footprint of approx. 2 nm², which is in good agreement with the size of **1.XB/HB** and is indicative of well-packed, ordered SAMs. This was further confirmed by a lack of Faradaic activity in the presence of 10 mM Fe(CN)₆^{3-/4-} (Fig. S14) where the films block access of the redox probe to the electrode.

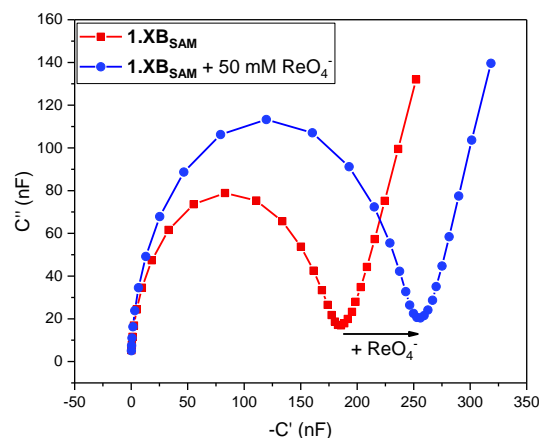


Fig. 3 Capacitive Nyquist plots of **1.XB**_{SAM} in the absence and presence of 50 mM ReO₄⁻. Measurements were performed at OCP (≈ 0 V) in the presence of 100 mM electrolyte (x NaCl + y NaReO₄, x + y = 100 mM).

EIS at open-circuit potential (OCP, ≈ 0 V) in the absence of any redox probe leads to the expected impedimetric signatures devoid of any characteristic charge-transfer features (Fig. S15A) and the impedance is largely unresponsive to all analytes (anions) used herein (Fig. S15A and Fig. S16). However, if capacitive analysis is carried out the resulting capacitive Nyquist and Bode plots (Fig. 3 and Fig. S17) are clearly responsive to the presence of analyte. The film capacitance C , which is a sensitive function of anion concentration, can be obtained as the x-intercept of the hemispherical region in the capacitive Nyquist plots or from data fitting to a $R_s[C(R_TQ)]$ equivalent circuit where R_s is the solution resistance, C the film capacitance, R_T a translational resistive term arising from ionic ingress²⁵ and Q a constant phase element (Fig. S15). The film capacitance of **1.XB/HB**_{SAM} in the absence of any target anion was determined as 4.85 ± 0.36 μ F/cm² and 4.83 ± 0.72 μ F/cm², respectively. As can be seen in Fig. S18, there is only a small effect of the electrolyte concentration on C , indicating that, as expected, the measured capacitance is dominated by the SAM and not the electrolyte/solution. Utilising a simple Helmholtz model (plate capacitor, eq. 1) and the ellipsometrically determined film thickness, d , the dielectric constant ϵ_r of **1.XB/HB**_{SAM} in the absence of target analyte can be calculated as 17.6 and 19.2, respectively.[§]

$$C = \frac{\epsilon_0 \epsilon_r A}{d} \quad (1)$$

Although the detailed physicochemical origins of the capacitance change in the presence of a target anion are currently under investigation, we directly attribute the increase in capacitance of XB and HB foldamer SAM upon anion binding to an increased film dielectric constant (eq. 1). This change is fully consistent with the introduction of a charged guest species and a concomitant hydration of the hydrophobic core (i.e. binding site) of the SAM. It is important to note that this change arises from a specific binding event; exposure of non-receptive interfaces (e.g. alkanethiol SAMs) to target anions under the same conditions induces negligible change in the capacitance (<2%). This is further corroborated by the fact that the two structurally identical films **1.XB**/**HB**_{SAM} display a significantly different response to target anions which can only arise from the change in the *specific* binding site, proving that the anion indeed binds to the specifically engineered receptors rather than otherwise associating/interacting with the interface.

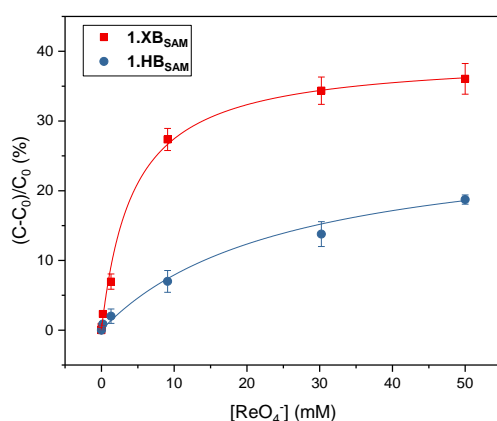


Fig. 4 Normalized capacitance increase of **1.XB**/**HB**_{SAM} at OCP (≈ 0 V) in the presence of increasing amounts of ReO_4^- . Fits were obtained according to a Langmuir adsorption model (eq. 2). Error bars represent one standard deviation across three independent electrodes.

A more detailed analysis of **1.XB**_{SAM} film capacitance confirms a response which is greatest for perrhenate (Fig. 4) but also significant for iodide or thiocyanate (Fig. S19A). The respective isotherms were fitted to a simple Langmuir adsorption model (eq. 2, Table 1 and S4) where θ is the fractional occupancy of the receptive sites and K the binding constant between the receptor and the anion. In all cases a good fit ($R^2 > 0.974$) was obtained and the binding constants determined to be 231, 362 and 170 M^{-1} for perrhenate, iodide and thiocyanate, respectively (Table 1). Addition of these anions to **1.HB**_{SAM} also induces an increase in capacitance (Fig. 4 and S19B), albeit with a significantly smaller response for all anions, in particular at low concentrations. This is a reflection of the lower affinity of all anions to **1.HB**_{SAM}, with $K = 11$, 66 and 61 M^{-1} for perrhenate, iodide and thiocyanate, respectively ($R^2 > 0.991$, Table 1 and S4). This decreased affinity is in agreement with anion binding constants of **2.XB**/**HB** in solution (vide infra). At high anion concentrations the responses of **1.XB**/**HB**_{SAM} converge, in good agreement with the Langmuir adsorption

model (binding site saturation). Slight deviations from an ideal Langmuir isotherm for iodide might be attributed to its electroactivity at moderate potentials.^{§§} Interestingly, the maximum increase in capacitance (at saturation) differs for these monovalent anions indicating that the change in capacitance (due to change in ϵ_r) has a significant non-electrostatic component. For example, a large increase in capacitance of up to 35% (change of ϵ_r from 17.6 to 23.8) is observed for perrhenate at **1.XB**_{SAM} whereby iodide and thiocyanate induce a much smaller change (≈ 15%).

$$\theta = \frac{K[\text{Anion}]}{1 + K[\text{Anion}]} \quad (2)$$

The limit of detection (LOD) of the **1.XB**_{SAM} sensor was determined to be 28, 14, and 42 μM for perrhenate, iodide and thiocyanate, respectively, indicating highest sensitivity for iodide. The **1.HB**_{SAM} sensor was predictably and significantly less sensitive with respective LOD values of 80, 47 and 113 μM for perrhenate, iodide and thiocyanate (Table 1 and Supporting Information S4), highlighting the superiority of the halogen-bonding interface.

Table 1 Limits of detection and binding constants of various anions to **1.XB**/**HB**_{SAM}.

Anion	1.XB _{SAM}		1.HB _{SAM}	
	K^a (M^{-1})	LOD ^b (μM)	K^a (M^{-1})	LOD ^b (μM)
ReO_4^-	231	28	11	80
I^-	362	14	66	47
SCN^-	170	42	61	113
ClO_4^-	/	/	/	/
Br^-	/	/	/	/
NO_3^-	/	/	/	/

^a Determined from fitting to Langmuir model (eq. 2, Fig. 5). ^b For further details see Supporting Information S4. / – no binding (negligible increase in C). Estimated errors for K and LOD: <20%.

Importantly, exposure of **1.XB**/**HB**_{SAM} to other anions such as bromide, perchlorate or nitrate at concentrations > 10 mM did not result in any significant change in the capacitance indicating that both XB and HB foldamer SAMs only selectively bind the charge-diffuse anions iodide, perrhenate and thiocyanate over other similar anions such as bromide or perchlorate. A comparative solution phase binding analysis of the water soluble **2.XB**/**HB** receptors was carried out in water by isothermal titration calorimetry (ITC, Tables S5-6)[‡], where a higher binding affinity for all tested anions, but lower guest selectivity, was observed. Furthermore, **2.XB** forms 2:1 host-guest complexes in solution. Altered enthalpic and entropic contributions, together with steric constraints on 2:1 binding, reduce anion affinity to the foldamer SAMs but enable better discrimination between halide guests than is possible in solution. For example, while both bromide and iodide strongly bind to **2.XB**/**HB** in solution (Table S5-6), films of **1.XB**/**HB**_{SAM} are able to discriminate these very similar halides (see Table 1 and Supporting Information S4).

Significantly, due to reversibility of the non-covalent host-guest interaction, the capacitive response of these films is not only selective but also reversible, enabling sensor re-use (Fig.

S20) and potentially continuous, real-time monitoring of anions under flow conditions.

In contrast to standard Faradaic EIS where the electrode potential is restricted to the formal potential and solution phase conditions (solubility) suitable for the redox probe (e.g. $\text{Fe}(\text{CN})_6^{3-/4-}$) the herein presented non-Faradaic capacitive method can be performed at a freely chosen electrode potential and in principle in any solvent. The former is relevant for sensing of analytes such as iodide (achieved herein) whose moderate oxidation potential would overlap with the most commonly used $\text{Fe}(\text{CN})_6^{3-/4-}$ in Faradaic EIS. Not only does the free choice of electrode potential allow measurement conditions that are more compatible with the analyte or interface of choice but could potentially enable modulation of (an)ion binding strength and selectivity through specific surface polarisation. In cases where receptor surface density is high (as it is here, see Fig. S21) initial levels of impedance can also be high and thereafter unresponsive to target.

In summary, we have prepared and characterized a well-defined self-assembled receptive interface capable of selective and sensitive sensing of the environmentally and biologically relevant anions ReO_4^- , I^- and SCN^- .^{7,8,26} To the best of our knowledge, this work is the first example of 1) impedimetric/capacitive sensing of ReO_4^- , I^- and SCN^- ; 2) a XB receptive interface and 3) non-Faradaic capacitive anion sensing. It is noteworthy that the methods employed herein are applicable to the analysis of host-guest recognition within molecular films without the synthetic need to integrate a redox or optical transducer or to pre-dope the analyte solution with an excess of redox probe. Importantly, the sensing of any anion should be possible with this novel approach, if the appropriate anion receptor is employed. Furthermore, we believe that this methodology is not only highly relevant for anion sensing applications in real-life samples, but can also serve as a powerful tool to investigate host-guest interactions at interfaces by avoiding drawbacks commonly associated with Faradaic techniques. We are currently seeking to apply this strategy for a variety of ion sensing applications, in particular the sensing of ion-pairs or zwitterionic species (challenging using Faradaic methods).

AB is grateful to the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine (EP/L015838/1) for a studentship. We would like to thank Dr. Candan Catli, Dr. Robert Jacobs and Dr. Philip Holdway for assistance with surface analysis and Dr. Andrew Piper for helpful comments.

Conflicts of interest

There are no conflicts to declare

Notes and references

‡ Synthesis and detailed solution-phase anion binding studies of 2.XB/HB and similar receptors have been reported separately.²⁷

§ As expected for such a polar, hydrophilic film, these dielectric constants are much larger than for a simple alkylated film.

§§ While all measurements were performed at OCP (usually between -50 to +50 mV) and iodide oxidation only occurs at 0.5 V the onset of faradaic activity at lower potentials might be observed at high iodide concentrations. It should be noted that the OCP of the system might change upon addition of target anion, however this change is not always monotonic nor analytically useful.

- 1 S. Kubik, *Chem. Soc. Rev.*, 2010, **39**, 3648-3663.
- 2 M. J. Langton, C. J. Serpell and P. D. Beer, *Angew. Chem. Int. Ed.*, 2016, **55**, 1974-1987.
- 3 M. J. Langton, S. W. Robinson, I. Marques, V. Félix and P. D. Beer, *Nat. Chem.*, 2014, **6**, 1039-1043.
- 4 J. Y. Lim and P. D. Beer, *Chem. Commun.*, 2015, **51**, 3686-3688.
- 5 S. P. Cornes, M. R. Sambrook and P. D. Beer, *Chem. Commun.*, 2017, **53**, 3866-3869.
- 6 M. J. Langton, I. Marques, S. W. Robinson, V. Félix and P. D. Beer, *Chem. Eur. J.*, 2016, **22**, 185-192.
- 7 W. A. Volkert and T. J. Hoffman, *Chem. Rev.*, 1999, **99**, 2269-2292.
- 8 E. A. Katayev, G. V. Kolesnikov and J. L. Sessler, *Chem. Soc. Rev.*, 2009, **38**, 1572-1586.
- 9 A. V. Patil, F. v. C. Bedatty Fernandes, P. R. Bueno and J. J. Davis, *Anal. Chem.*, 2014, **87**, 944-950.
- 10 Q. Xu and J. J. Davis, *Electroanalysis*, 2014, **26**, 1249-1258.
- 11 J. S. Daniels and N. Pourmand, *Electroanalysis*, 2007, **19**, 1239-1257.
- 12 F. C. Bedatty Fernandes, A. V. Patil, P. R. Bueno and J. J. Davis, *Anal. Chem.*, 2015, **87**, 12137-12144.
- 13 J. Piccoli, R. Hein, A. H. El-Sagheer, T. Brown, E. M. Cilli, P. R. Bueno and J. J. Davis, *Anal. Chem.*, 2018, **90**, 3005-3008.
- 14 X. Luo and J. J. Davis, *Chem. Soc. Rev.*, 2013, **42**, 5944-5962.
- 15 K. Morita, A. Yamaguchi and N. Teramae, *J. Electroanal. Chem.*, 2004, **563**, 249-255.
- 16 N. Wanichacheva, E. R. Soto, C. R. Lambert and W. G. McGimpsey, *Anal. Chem.*, 2006, **78**, 7132-7137.
- 17 S. Flink, F. C. Van Veggel and D. N. Reinhoudt, *J. Phys. Chem. B*, 1999, **103**, 6515-6520.
- 18 A. C. Ion, J.-C. Moutet, A. Pailleret, A. Popescu, E. Saint-Aman, E. Siebert and E. M. Ungureanu, *J. Electroanal. Chem.*, 1999, **464**, 24-30.
- 19 J. Wei, Z. Guo, X. Chen, D.-D. Han, X.-K. Wang and X.-J. Huang, *Anal. Chem.*, 2015, **87**, 1991-1998.
- 20 S. Zhang and L. Echegoyen, *J. Am. Chem. Soc.*, 2005, **127**, 2006-2011.
- 21 S. Zhang, A. Palkar and L. Echegoyen, *Langmuir*, 2006, **22**, 10732-10738.
- 22 F. Zhi, X. Lu, J. Yang, X. Wang, H. Shang, S. Zhang and Z. Xue, *J. Phys. Chem. C*, 2009, **113**, 13166-13172.
- 23 A. Borissov, J. Y. C. Lim, A. Brown, K. E. Christensen, A. L. Thompson, M. D. Smith and P. D. Beer, *Chem. Commun.*, 2017, **53**, 2483-2486.
- 24 B. Zhu, T. Eurell, R. Gunawan and D. Leckband, *J. Biomed. Mater. Res.*, 2001, **56**, 406-416.
- 25 J. Lehr, J. R. Weeks, A. Santos, G. T. Feliciano, M. I. G. Nicholson, J. J. Davis and P. R. Bueno, *Phys. Chem. Chem. Phys.*, 2017, **19**, 15098-15109.
- 26 F. Delange, *Thyroid*, 1994, **4**, 107-128.
- 27 A. Borissov, I. Marques, J. Y. C. Lim, V. Félix, M. D. Smith and P. D. Beer, *J. Am. Chem. Soc.*, 2019, **141**, 4119-4129.