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# Electrochemical assessment of a tripodal thiourea-based anion receptor at the liquid|liquid interface†

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Thiourea-based receptors for anions have been widely studied due to their ability to transport anions across phospholipid bilayers. The binding affinity of a tripodal thiourea-based receptor for anions was assessed at the aqueous|organic interface using electrochemical measurements. A 1:1 stoichiometry was determined for the complexation of most anions, with a higher stoichiometry found in the presence of excess $Cl^-$ and $Br^-$ anions. High stability constants were estimated for the formation of the complexes at the aqueous|1,2-dichlorobenzene (DCB) interface. When compared with an organic solvent of higher polarity, nitrobenzene (NB), the high stability constants observed in DCB are believed to be due to the less competitive environment of the less polar solvent. Protonation of the receptor at the bridgehead tertiary amine was also inferred from the potential-dependent voltammetric measurements that are not related to anion:receptor complexation. The inherent advantages of the electrochemical method with the use of low polarity solvents are expected to provide new insights into the binding and transport of newly-developed neutral receptors.



## Introduction

Anion transfer reactions play a substantial role in the maintenance of life. In biological systems, regulating the flux of anions such as chloride, sulphate and phosphate across the cellular phospholipid membrane is a vital molecular process.[1] Any retardation to the transport of these anions can affect the physiological functions of organisms. For example, the fatal genetic disease, cystic fibrosis, is attributed to a malfunctioning of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a chloride channel.[2] In an industrial context, processes that include monitoring, sensing, detecting and/or extraction of ions involve ion transfer and complexation across a membrane or an interface. For example, the detection and extraction of some anionic pollutants (*e.g.* nitrates, anionic dyes, *etc.*) is a significant industrial practice for safe water streams.[3]

Over the last decades, supramolecular chemists have developed a range of synthetic receptors which are capable of strong binding to cations,[4,5] whereas synthetic receptors that mimic natural anion receptors are much less abundant. Some anion receptors with different binding motifs and shapes have been developed for the purposes of detection, transportion and extraction.[6,7] Thioureas are one of the molecular classes that show high anion–ligand complex stability and selectivity. A thiourea has two highly polar N–H groups, which form the basis of strong anion:thiourea complexation *via* hydrogen bonding interactions.[8]

Pascal and co-workers[9] reported the first synthetic anion receptor utilising amide NH···anion interactions, which showed an affinity for fluoride in dimethyl sulfoxide DMSO-$d_6$, as assessed by $^1$H and $^{19}$F NMR spectroscopic studies. Anion receptors based on urea/thiourea moieties were later investigated by Wilcox and co-workers.[10] Using UV-visible spectroscopic titrations, the urea-based anion receptor was found to form stable complexes with anions in chloroform, favouring oxyanions as they are capable of forming two hydrogen bonds with the urea/thiourea moieties.

Three major factors were recognised to affect the stability and selectivity of the thiourea-based complexes. First, increasing the number of the NH moieties in the receptor gives more hydrogen bond donor sites, which is translated into higher binding affinity for anions. For example, a tripodal thiourea[11] was found to form more stable complexes with anions when

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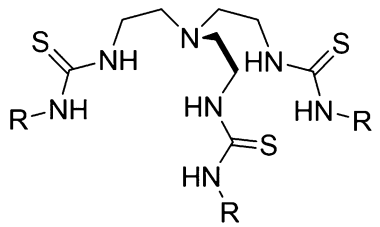


**1** (R = $(CH_2)_4CH_3$)

Fig. 1 Structure of the tripodal thiourea receptor, tri(2-aminoethyl)amine linked with three *n*-pentyl groups.

compared with a comparable monopodal thiourea molecule[12] in the same solvent. Second, the acidity of the NH protons plays a substantial role in selectivity. Generally, a more acidic NH moiety results in a stronger NH···anion interaction. However, perturbation of this effect may occur due to, for example, solvent effects[13] and shape complementarity.[14] Third, structure and geometry of the receptor can impact the stability and selectivity of the complex. Particularly, the geometry of the cavity-like receptors can encapsulate some anions more effectively than others, which in turns influences the selectivity and stability of the thiourea-based complexes.[14–16]

Gale and co-workers[15] have synthesised and studied multiple urea or thiourea containing receptors. One such compound was a tripodal thiourea with three *n*-pentyl groups (**1**, Fig. 1). Receptor **1** has six NH moieties that can be arranged in a cavity-like structure. The six NH moieties ensure higher binding affinity for anions. In addition, cavity-like structures offer flexibility and the ability to accommodate a range of anions. However, Gale and co-workers showed that the tripodal structure encapsulates spherical anions (*i.e.* $Cl^-$) more effectively than anions with planar structure (*i.e.* nitrate).[14] Indeed, receptor **1** was found to offer high affinity for $Cl^-$ ($K_a = 8 \times 10^5\ M^{-1}$) in acetonitrile, while binding of nitrate was more than three orders of magnitude weaker, as assessed by UV-vis titrations. In agreement with its binding selectivity, this tripodal receptor showed exceptional transport selectivity for $Cl^-$ against $NO_3^-$ (5-fold)[14] and also against $H^+/OH^-$ (39-fold).[15] $^1$H NMR titrations of receptor **1** against $Cl^-$ also showed efficient binding in 99.5 : 0.5 DMSO–$H_2O$ ($K_a = 648\ M^{-1}$),[17] but to the best of our knowledge the binding of $Cl^-$ by this receptor has never been studied in low polarity solvents.

Tris–thiourea **1** can also act as an ionophore, *i.e.* transporting chloride through phospholipid bilayers. This tripodal transporter has shown selective transport of chloride against nitrate, unusual selectivity that arises from its aforementioned preference for spherical anions.[14] Different types of chloride transport mechanisms by small ionophores have been described.[15] In a symport mechanism, a cation is co-transported with chloride in the same direction, whereas in an antiport mechanism, a different anion is transported in the opposite direction. Chloride can also be transported on its own, a uniport process, which results in electrogenic transport. Compound **1** has been described as being able to perform both $Cl^-$ uniport and $Cl^-/NO_3^-$ antiport (with nitrate transport as a limiting step) in large unilamellar vesicles,[14,15] as well as $Cl^-/I^-$ antiport in Fischer rat thyroid cells.[17]

Herein, an electrochemical approach has been employed to assess the complexation of multiple anions by the tripodal thiourea **1** at an interface between two immiscible solvents. The electrochemical method is expected to provide more insights into this class of receptors, assessing their binding affinity in a very low competitive solvent environment as well as their protonation/deprotonation behaviour at an interface of two immiscible solutions.

The electrochemical approach provides a simple and facile method to study the thermodynamic parameters of complex formation at an interface between two immiscible electrolyte solutions (ITIES). Shioya *et al.*[18] reported the first electrochemical study at the ITIES of anion-binding in 1998, whereas cation-binding studies were first reported significantly earlier.[19] Interfacial complexation is a specific type of a charge transfer reaction across the ITIES, known as facilitated ion transfer by a ligand.[19] Cyclic voltammetry can readily indicate whether a ligand can facilitate the transfer of a given ion or not. In addition, parameters including Gibbs energy of transfer, association (binding) constant and stoichiometric ratio between the ion and the ligand can be obtained.[20,21] The advantages of the electrochemical approach over other common methods are discussed briefly below.

First, a significant characteristic of the electrochemical approach is that it provides information on the binding of an isolated ion (no counterion) to a ligand, unlike other common techniques (*e.g.* NMR and UV-visible spectroscopy titrations) which in low polarity solvents generally involve the complexation of the salt as a whole. The electrochemical measurement therefore accesses thermodynamic and kinetic information relating to the "naked" anion–ligand complex, rather than the salt or ion pair.

Second, in some cases, estimation of the association constant of a complex by a spectroscopic titration can be confounded by other, interfering, equilibria. Deprotonation of the receptor or intermediate exchange on the NMR timescale may result in significant peak broadening[22] or complete disappearance of the peak during an NMR titration.[23] Likewise, fluorescence emissions can be quenched under similar conditions due to deprotonation of the receptor.[24] In the electrochemical approach, interfacial processes are driven by an applied potential and hence deprotonation, should it happen, is likely to occur as a separate voltammetric event that does not involve anion complexation. This implies that association constants can still be estimated for receptors with slowed exchange kinetics or where deprotonation also occurs.

Third, the electrochemical approach allows the anion complexation assays to be performed in a variety of solvents (polar and nonpolar), provided that the solvent is immiscible with water and can dissociate an electrolyte. Solvents can be selected that offer a less competitive environment: for instance, a neutral receptor, that binds anions through hydrogen-bonding interactions (*e.g.* thiourea), is less able to compete with a polar protic solvation shell that surrounds the target anion, but can compete with an apolar, aprotic solvent.[1] Thus, the choice of a solvent with low polarity may be favoured to maximise the affinity of an ion to a hydrogen-bonding-based receptor.

 

Fourth, in the transport context, the electrochemical approach is designed for electrogenic (electrophoretic) transport. That is because the electrochemical signal (*i.e.* current) is only obtained in the event of a net flux of charge across the interface. This provides a simple method, which is an alternative to conventional vesicle-based assays, to identify electrogenic transporters. In addition, the anion-complexing ligand acts as a carrier that follows a uniport mechanism; no counterbalancing ions move with the complex. A uniport mechanism also avoids one of the drawbacks of many assays of anion antiport, which occurs when transport of the target anion is not the rate-limiting step. This leads to underestimation of the transport abilities of a given anionophore.[14] It is worth noting that, in the electrochemical approach, if the ligand facilitates the transfer of more than one ion, the potential of transfer of each ion would depend on its Gibbs energy of transfer resulting in a distinct voltammetric (current) peak for each ion transfer, which would allow the study of each event separately.

Fifth, the aqueous|organic interface has been used broadly as a primitive model of a biological lipid membrane in contact with water, studying the partition coefficients of ions and drugs as well as assessing their transfer across such an interface.[25–27] The aqueous|organic interface can also be modified with phospholipid molecules to better resemble a biological membrane.[28] Traditionally, aprotic solvents such as nitrobenzene, 1,2-dichloroethane and *n*-octanol are used in these studies. There is still a need for new solvents which can better mimic the biological membrane.[29] The use of such low polarity solvents can be advantageous in mimicking the lipophilic interior of the membrane.

Finally, the electrochemical approach can be performed under different pH conditions and a greater variety of anions can be studied. This also allows the study of the protonation/deprotonation behaviour of the receptor at a variety of acidic/alkaline liquid|liquid interfaces. Therefore, the electrochemical approach at the ITIES can be advantageous as a mechanistic study as well as in potentiometric sensing, ion extraction processes and as a mimic of biological membranes.

Note, however, that the electrochemical measurement is "blind" to symport of an ion pair and antiport of ions of the same charge,[15] should they occur at the liquid–liquid interface, because a net transfer of charge is the basis of the electrochemical measurement.

Charge transfer reactions at the ITIES are controlled by an applied potential from an external source, *i.e.* the potentiostat. The potential for the transfer of an ion from one phase into another is dictated by its formal Gibbs energy of transfer, which depends on the nature of the ion and the solvents. Addition of a ligand can facilitate the transfer of the ion by lowering its solvation energy in the organic phase, hence reducing its Gibbs energy of transfer and producing a potential shift in the voltammetric measurements. The potential shift depends on the affinity of the ligand for the target ion. For Scheme 1, where the concentration of the anion is much higher than that of the ligand ($x \gg y$), the reversible half-wave potential of the facilitated ion transfer reaction ($\Delta_o^w\phi^{1/2}$) is related to the concentration of the anionic species ($c_{A^-}$) (eqn (1)):[20,30,31]

$$\Delta_o^w\phi^{1/2} = \Delta_o^w\phi_{A^-}^{o'} + \frac{RT}{2F}\ln\left(\frac{D_L}{D_{LA^-}}\right) - \frac{RT}{zF}\ln(K_a c_{A^-}) \qquad (1)$$

where $\Delta_o^w\phi_{A^-}^{o'}$ is the formal transfer potential of the anion from the aqueous phase to the organic phase, $R$ is the universal gas constant, $T$ is the temperature, $z$ is the charge number and $F$ is the Faraday constant. $K_a$ is the association constant of the anion for the receptor and $c_{A^-}$ is the anion concentration in the aqueous phase. $D_L$ and $D_{LA^-}$ are the diffusion coefficients of the ligand and the anion–ligand complex, respectively. Frequently the approximation $D_L \approx D_{LA^-}$ is valid, since the ligand molecule is much bigger than the anion. Therefore, determining the shift in $\Delta_o^w\phi^{1/2}$ while varying $c_{A^-}$ yields a linear relation with the gradient equal to $\frac{RT}{zF}$, in the case of a 1 : 1 stoichiometry. Furthermore, the intercept of the linear fit can be used to estimate the $K_a$ value.

In this work, we investigated the interfacial complexation of the anions $Cl^-$, $Br^-$, $CH_3COO^-$, $SO_4^{2-}$, $HPO_4^{2-}$ and $H_2PO_4^-$ with the tripodal thiourea **1** at the aqueous|1,2-dichlorobenzene (DCB) interface, using cyclic voltammetry and differential pulse voltammetry techniques. The stoichiometry and association constants, were estimated from the voltammetric measurements. The effect of the organic solvent was also explored by replacing DCB with nitrobenzene (NB). This study is the first electrochemical study to assess the binding behaviour of a tripodal thiourea. Receptor **1** has been chosen as it is reported to be an electrogenic carrier of anions.[15] Moreover, it shows strong binding and good transport selectivity for spherical anions, such as chloride. Receptor **1** is soluble in organic solvents such as acetonitrile and DMSO but, to the best of our knowledge, the binding of chloride by this receptor has never been studied in very low polarity solvents like DCB. Finally **1** also shows anion transport activity in Fischer rat thyroid (FRT) cells, a cell line widely employed to investigate epithelial ion transport.[17]

## Experimental

Sodium chloride (NaCl, ≥99%), tetramethylammonium chloride (TMACl, 99%), sodium bromide (NaBr, +99%), sodium phosphate monobasic monohydrate ($NaH_2PO_4{\cdot}H_2O$, 98–102%), sodium

| Ag | AgCl | 1 mM BTPPACl<br>**Ref. water** | 10 mM BTPPATFPB<br>*y* mM receptor **1**<br>**DCB** | *x* mM $M^+A^-$<br>**Water** | AgCl | Ag |
|---|---|---|---|---|---|---|

Scheme 1 Composition of the ITIES cell employed for the facilitated transfer of anions by the tripodal thiourea **1**. $M^+$ and $A^-$ represent the cation and the anion of the salt, respectively.

phosphate dibasic anhydrous ($Na_2HPO_4$, 99%), lithium acetate dihydrate ($CH_3COOLi{\cdot}2H_2O$, BioXtra), bis(triphenylphosphoranylidene)ammonium chloride (BTPPACl, 97%), 1,2-dichlorobenzene (DCB, anhydrous 99%) and nitrobenzene (NB, 99%) were purchased from Sigma-Aldrich and used as received. Sodium sulphate anhydrous ($Na_2SO_4$, ≥99%), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaTFPB, 97%), *N*,*N*′-di(*n*-butyl)thiourea (98%) and hydrochloric acid (HCl, ~37%) were purchased from Alfa Aesar. Tetramethylammonium bromide (TMABr, 98%) and tetramethylammonium acetate (TMAAc, 97%) were purchased from Fluorochem. Tetramethylammonium sulphate ($TMA_2SO_4$, >98%) was purchased from TCI. Sodium hydroxide (NaOH, ≥98%) was purchased from Fluka. The organic phase supporting electrolyte, bis(triphenylphosphoranylidene)ammonium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BTPPATFPB), was prepared by a metathesis reaction of BTPPACl and NaTFPB following a previously reported method.[32] Receptor **1** was prepared following an approach we have previously described, detailed in the ESI.† Ultra-pure water (resistivity of 18 MΩ cm, Milli-Q) was used for the preparation of aqueous solutions.

The electrochemical measurements were performed in a four-electrode setup with current ($I$) recorded as a function of the Galvani potential difference measured at the water phase with respect to the organic phase ($\Delta\phi$). The electrochemical cell consists of a platinum gauze counter electrode (CE) and a silver/silver chloride (Ag/AgCl) reference electrode (RE) in each liquid phase. The cell has three arms: two capillary arms for the REs and a third arm allowing direct access to the lower phase for a CE without disruption of the liquid|liquid interface. The interfacial area is equal to 0.64 cm.$^2$ The general cell composition is shown in Scheme 1. The electrochemical measurements were carried out with a potentiostat (Metrohm Autolab B.V., PGSTAT100, Netherlands). Both cyclic voltammetry and differential pulse voltammetry techniques were used to assess the facilitated anion transfer by **1** at ITIES. The pH of NaCl solutions were adjusted with HCl and NaOH solutions. The pH of the solutions was measured by Mettler Toledo SevenExcellence S470 pH/Conductivity Benchtop Meter.

## Results and discussion

The general composition of the 4-electrode cell is detailed in Scheme 1. Cyclic voltammetry was employed to assess the complexation of the anion to **1** at the liquid|liquid interface. In order to elucidate the role of the tripodal thiourea **1**, the first measurement was performed in its absence (Fig. 2a), *i.e.* $y = 0$ with reference to Scheme 1. Upon the polarisation of the water|DCB interface in the presence of the supporting electrolytes ($x$ in Scheme 1) 20 mM $NaCl_{(aq)}$|10 mM $BTPPATFPB_{(DCB)}$, a large potential window (with only capacitive currents ≈0 μA) was observed, with limits set by $Na^+$ and $Cl^-$ ion transfers at the positive and negative limits of the cyclic voltammogram (CV), respectively. These limits are set by the Gibbs energy of transfer of each ion, and the nearly-zero current in between indicates that no other charge transfer processes are taking place at the interface within this polarisation window.[33] Hence, the facilitated transfer of $Cl^-$ ion by a relevant ligand can be studied in this system.

In the presence of 1 mM receptor **1** in DCB, two reversible peaks (Wave 1 and Wave 2) and one irreversible peak (Wave 3) were observed within the potential window of the CV (Fig. 2a). This demonstrates that, at these conditions and potential range, more than one interfacial charge transfer process takes place in the presence of receptor **1**. Furthermore, the magnitudes of peaks 1 and 2 were found to depend proportionally on the concentration of receptor **1**, meaning their peak currents were limited by its concentration (Fig. S1, ESI†). In order to determine whether any of the waves were related to a $Cl^-$—**1** complexation, the half-wave potential of every wave was measured while varying the concentration of NaCl. It was noticed that the half-wave potential of Wave 1 (≈−0.2 V, at 20 mM) shifts positively upon increasing the concentration of $Cl^-$ in the

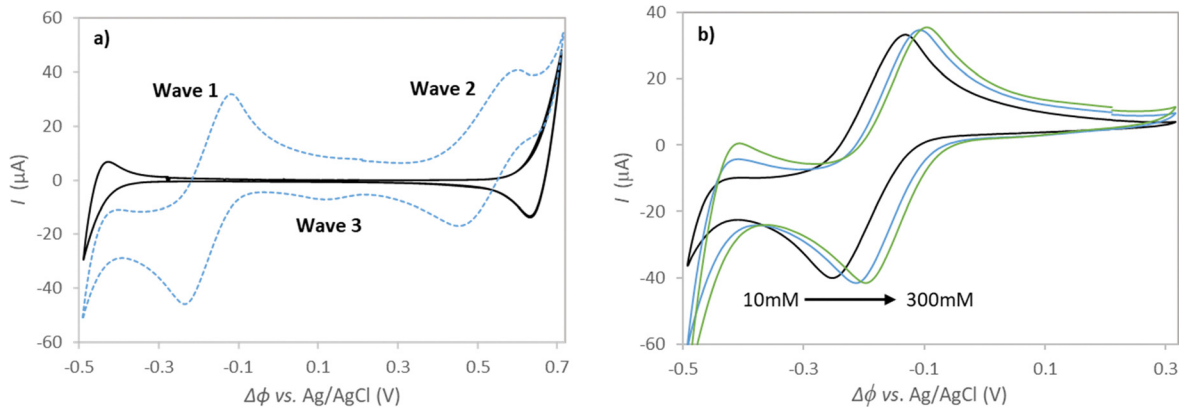


Fig. 2 CVs of Scheme 1 (a) in the presence of only the supporting electrolytes, $x$ = 20 mM $NaCl_{(aq)}$|10 mM $BTPPATFPB_{(DCB)}$ (black solid line) and after the addition of receptor $\mathbf{1}_{(DCB)}$ ($y$ = 1 mM, blue dashed line). The three new peaks are assigned as Wave 1, Wave 2 and Wave 3 (b) and upon varying the concentration of NaCl; 10 (black line), 100 (blue line) and 300 mM (green line) in the presence of receptor **1** (1 mM). CVs were calibrated in accordance with the formal transfer potential of $TMA^+$ at the water|DCB interface.[34] Scan rate = 30 mV $s^{-1}$.

 

aqueous phase (Fig. 2b). This is consistent with the formation of interfacial complexes between the aqueous anions and the receptor in the organic phase.[35]

A linear fit of the Randles–Ševčík equation (see ESI,† eqn (S1)) was extrapolated, with the peak current proportional to the square root of the scan rate (Fig. S2, ESI†). This is indicative of a diffusion-controlled facilitated ion transfer process, and hence in the case of an excess of anion, the transfer is limited by the diffusion of the receptor towards the interface or by that of the complex away from it.[21] Thus, the diffusion coefficient ($D$) of receptor **1** in DCB was calculated from the linear fit to be $(3.2 \pm 0.2) \times 10^{-6}$ cm$^2$ s$^{-1}$, which is in the range of common neutral receptors (*e.g.* valinomycin[30,36] and crown ethers[37,38] which are bigger than and relatively similar to **1** in size, respectively) in non-aqueous solutions.

In order to determine the stoichiometry and association constant ($K_a$) of the complex, the reversible half-wave potential of the facilitated $Cl^-$ transfer reaction ($\Delta^w_o\phi^{1/2}$) was monitored while changing the concentration of the $Cl^-$ species ($c_{Cl^-}$), as in eqn (1). Fig. 3a shows the plot of the shift in the $\Delta^w_o\phi^{1/2}$ as a function of $\log(c_{Cl^-})$ (more details in the ESI†). The plot provided a linear fit with the gradient equal to 55.7 mV decade$^{-1}$. This value corresponds to a 1 : 1 stoichiometry of the $Cl^-$—**1** complex. Notably, voltammetric measurements at slower scan rate (10 mV s$^{-1}$) revealed a concentration-dependent stoichiometry. That is, a gradient value for the linear fit consistent with a 1 : 1 stoichiometry is seen for lower aqueous concentrations; however, more concentrated aqueous solutions (>0.2 M, equivalent to a concentration ratio of 400 : 1 ($Cl^-_{(aq)}$ : **1**$_{(DCB)}$)) exhibited a lower gradient value for the linear fit (35.5 mV decade$^{-1}$) (Fig. 3b), which could be interpreted as a transition to a 2 : 1 stoichiometry $(Cl^-)_2$—**1** complex.

Using proton NMR titrations, Spooner *et al.*[17] used a 1 : 1 binding model to obtain the association constant of $Cl^-$ to receptor **1** in 0.5% $H_2O$/DMSO-$d_6$. Other tripodal thiourea derivatives were also reported to form 1 : 1 complexes with $Cl^-$.[11,39,40] On the other hand, Jowett *et al.* reported that developments in binding isotherm fitting methodology provided a better fit to the 2 : 1 anion : receptor binding model, when assessing tripodal thioureas linked to phenyl groups.[41] However, in the current study a deviation from a 1 : 1 stoichiometry was only observed for high aqueous concentrations.

Analysis of the linear fit was extended to extract the association (binding) constant ($K_a$) from the intercept term. For the $Cl^-$—**1** complex in DCB, the $K_a$ was estimated to be equal to $(1.2 \pm 0.4) \times 10^9$ M$^{-1}$. This high $K_a$ value implies that receptor **1** possesses a high affinity for $Cl^-$, as demonstrated by $^1$H NMR[17] and UV-visible[14] spectroscopy titrations. An accurate comparison with other thiourea derivatives is not possible at this stage as their $K_a$ values are reported for different conditions (different solvents). To put the value obtained in context, $K_a$ values from $^1$H NMR spectroscopy titrations for tetraalkylammonium chloride binding to different tripodal thioureas in $H_2O$/DMSO-$d_6$ are reported to be $\leq 10^3$ M$^{-1}$.[11,17,39,40] Shioya *et al.*[18] studied two bis-thiourea molecules using the electrochemical approach at ITIES, and found them to bind $Cl^-$ in 1,2-dichloroethane (DCE) with $K_a$ values estimated to be $\leq 10^3$ M$^{-1}$. Perhaps the highest reported $K_a$ value is for a cholapod receptor in DCE estimated to be $\sim 10^{12}$ M$^{-1}$ by an electrochemical approach.[42] A key difference between those studies and the current work is the solvent environment where the complexation takes place varies. Indeed, the characteristics of the solvent must be taken into account as it may influence the hydrogen-bonding interactions responsible for the complexation in neutral thioureas.[43] Thus, the effect of the solvent DCB on the stability of the complex will be revisited and discussed with an experimental study (*vide infra*).

Receptor **1** was further explored to investigate its binding affinity for other anions; including $Br^-$, $CH_3COO^-$ and $SO_4^{2-}$. Voltammetric measurements showed facilitated transfer of these anionic species at the water|DCB interface in the presence of receptor **1** in DCB (Fig. 4). The stoichiometry and association constant for each anion are listed in Table 1. The stoichiometry of the $Br^-$—**1** complex was found to follow that of the $Cl^-$—**1** complex, that is 1 : 1 stoichiometry at low concentrations but a deviation towards 2 : 1 stoichiometry occurs at higher concentrations. On the other hand, the oxyanions $CH_3COO^-$ and $SO_4^{2-}$ maintained a 1 : 1 complex stoichiometry over all the attempted concentration ranges, consistent with earlier (single phase) observations for multiple tripodal thioureas.[11,39,40]

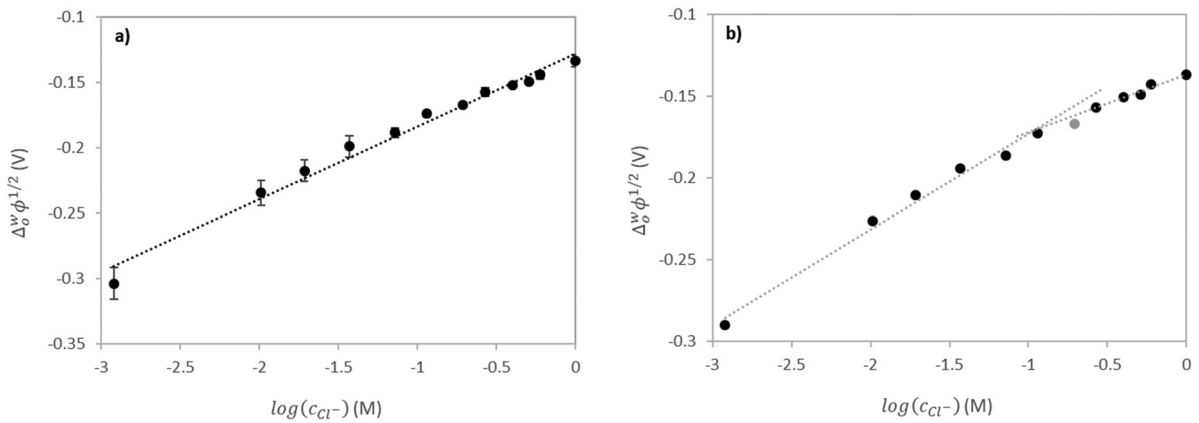


Fig. 3 Plots of the shift in the $\Delta^w_o\phi^{1/2}$ as a function of $\log(c_{Cl^-})$, extracted from the voltammetric measurements of Scheme 1 at (a) different scan rates (10, 30 and 50 mV s$^{-1}$) and (b) at 10 mV s$^{-1}$.

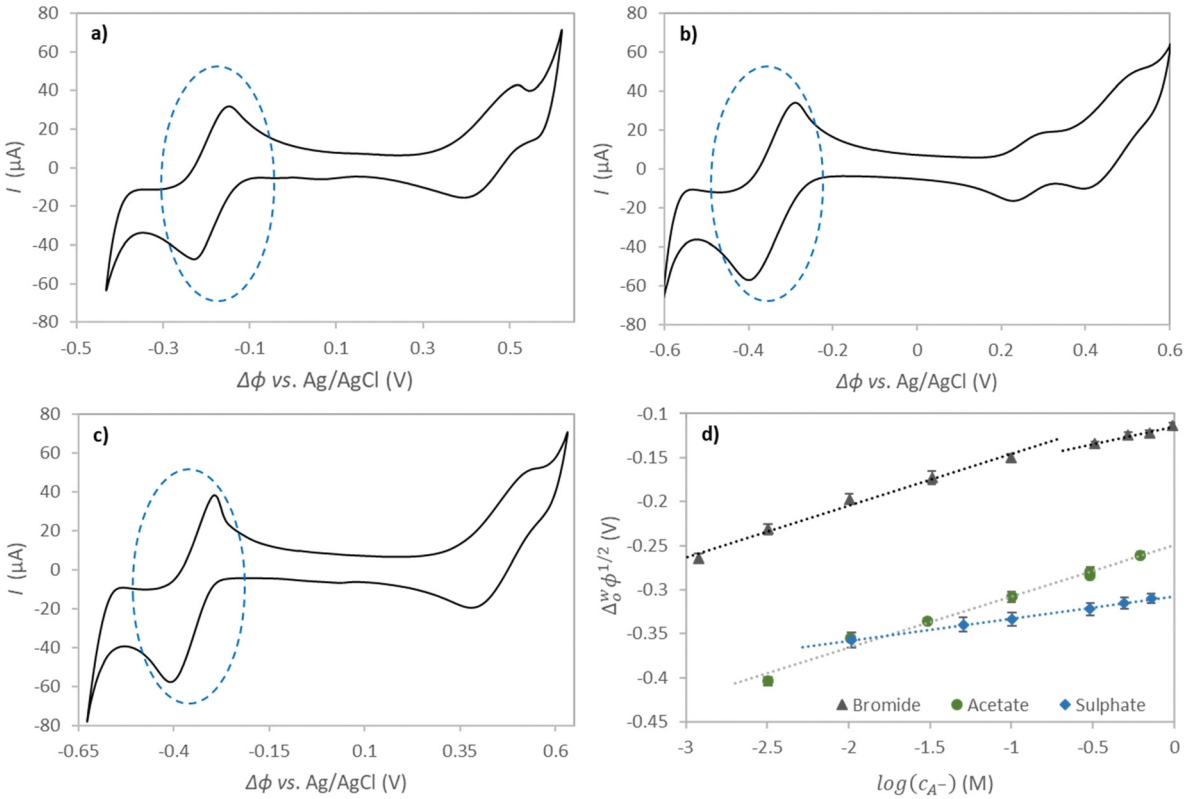


Fig. 4 CVs of Scheme 1 in the presence of 0.5 mM receptor $\mathbf{1}_{(DCB)}$ with (a) 20 mM $NaBr_{(aq)}$ (b) 20 mM (pH 6.7) $CH_3COOLi_{(aq)}$ and (c) 20 mM $Na_2SO_{4(aq)}$, with peaks attributed to complex transfer highlighted in blue. CVs were calibrated in accordance with the formal transfer potential of $TMA^+$ at the water|DCB interface.[34] Scan rate = 30 mV $s^{-1}$. (d) Plots of the shift in the $\Delta_o^w\phi^{1/2}$ as a function of log($c_{A^-}$). The gradient of the linear fit of the divalent sulphate anion (25.2 ± 0.8 mV $decade^{-1}$) maintains half the value of that for the monovalent anions, bromide (59.0 ± 3.8 mV $decade^{-1}$) and acetate (58.4 ± 3.1 mV $decade^{-1}$).

All anions studied yielded relatively high stability constants with receptor **1** in DCB (Table 1). The selectivity of **1** was assessed from the $K_a$ data, with the binding affinity trend in the order of $SO_4^{2-} > Cl^- > Br^- > CH_3COO^-$. Generally, anion binding constants in organic solvents follow the hydrophilicity order of the Hofmeister series: $Br^- < Cl^- < CH_3COO^- < SO_4^{2-}$. In this case, $CH_3COO^-$ deviates from the expected selectivity, showing the lowest affinity for the receptor. This observation agrees with the binding and transport selectivity that compound **1** has shown for spherical anions against planar anions, due to a better fit of the spherical geometry into the tripodal cavity.[14] The high affinity observed for $SO_4^{2-}$ suggests that the cavity of **1** is also suitable for anion with a tetrahedral geometry, which agrees with the exceptional ability that some tripodal thioureas have shown to transport $SO_4^{2-}$.[41]

Table 1 Stoichiometry and association constant data for anion transfer facilitated by receptor **1**

| Anion | Stoichiometry | $K_a$ ($M^{-1}$) |
|---|---|---|
| $Cl^-$ | 1 : 1[a] | $(1.2 \pm 0.4) \times 10^9$ |
| $Br^-$ | 1 : 1[a] | $(4.7 \pm 0.6) \times 10^7$ |
| $CH_3COO^-$ | 1 : 1 | $(1.9 \pm 0.1) \times 10^5$ |
| $SO_4^{2-}$ | 1 : 1 | $(2.0 \pm 0.5) \times 10^{14}$ |

[a] Deviation observed at high anion concentration in the aqueous phase.

In terms of anion transfer across an aqueous|organic interface, generally, the transfer reaction is influenced by the dehydration (solvation) energy of the anion, in which, the more hydrophilic anion requires higher potential ($\Delta\phi$), and hence higher Gibbs energy of transfer. Thus, the extraction reaction typically follows the hydrophobicity order of the Hofmeister series: $Br^- > Cl^- > CH_3COO^- > SO_4^{2-}$.[1,44] This is true for simple ion transfer. However, in the presence of a ligand, the extraction reaction would be dictated by the properties of the ligand and its interaction with the target anion, particularly its ability to replace the solvation shell of the aqueous anion.[31]

Complexation of phosphate anions (another anion with tetrahedral geometry) with receptor **1** at the water|DCB interface was also explored. Voltammetric measurements of a 1 M (pH 7) phosphate $buffer_{(aq)}$|10 mM $BTPPATFPB_{(DCB)}$ in the presence of 1 mM receptor $\mathbf{1}_{(DCB)}$ provided two reversible peaks within the potential window of the CV (Fig. 5a). The potential shift was probed from lower to higher phosphate buffer concentrations (Fig. 5b). It was observed that at lower concentrations, Wave 1 consisted of two reversible sub-waves (peak i ≈ 0.11 V and peak ii ≈ 0.24 V), and as the concentration increased they shifted positively until they merged into a single wave at higher concentrations of the buffer (vanishing of peak i and growth of peak ii). On the other hand, varying the phosphate concentration did not affect the potential of Wave 2. This implies that Wave 1 belongs to

 

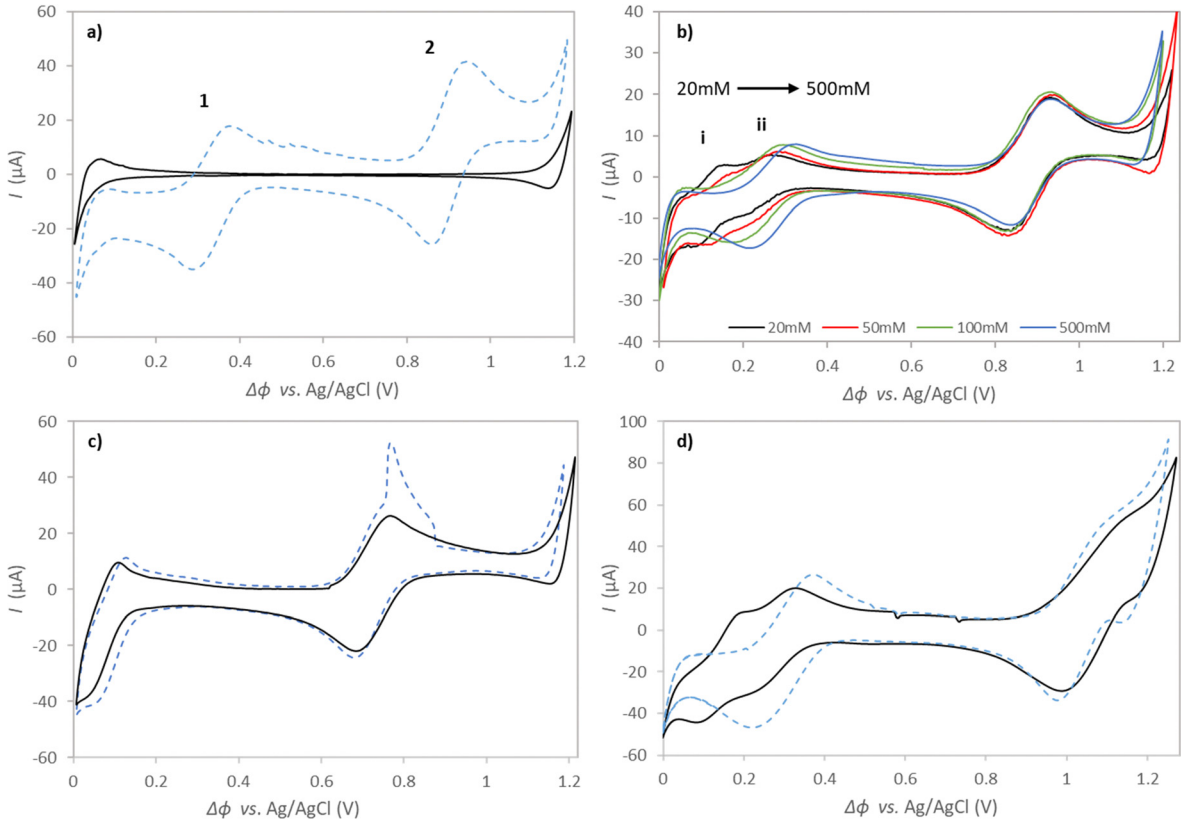


Fig. 5 CVs of Scheme 1 (a) in the presence of only the supporting electrolytes 1 M (pH 7) phosphate buffer$_{(aq)}$|10 mM BTPPATFPB$_{(DCB)}$ (black) and after the addition of 1 mM receptor **1**$_{(DCB)}$ (blue) (b) and upon varying the concentration of the buffer solution; 20 (black line), 50 (red line) 100 (green line) and 300 (blue line) mM (with 0.5 mM receptor **1**$_{(DCB)}$). CVs of the phosphate buffer solutions at pH (c) 4.8 and (d) 9 for 20 (black) and 100 mM (blue) solutions. Scan rate of a, c and d = 30 mV s$^{-1}$ b = 10 mV s$^{-1}$.

the phosphate—**1** complex formation at the interface. It is worth noting that *N*,*N*′-di(*n*-butyl)thiourea was assessed as a receptor for phosphate, however voltammetric measurements showed no clear sign of a facilitated phosphate ion transfer across the water|DCB interface (Fig. S6, ESI†), suggesting the tripodal structure of thiourea **1** gives a significant enhancement in affinity for anions. In addition, protonation/deprotonation of *N*,*N*′-di(*n*-butyl)thiourea was not observed within the potential window, suggesting that the bridgehead nitrogen atom is responsible for Wave 2, implying that the charge transfer at this potential is due to protonation of this nitrogen.

The splitting of Wave 1 at lower concentrations is attributed to distinct transfer of the various protonation states of the phosphate anion. Hence, voltammetric measurements were performed for both pH 4.8 and 9 phosphate buffer solutions, where the major phosphate species are the monobasic $H_2PO_4^-$ and dibasic $HPO_4^{2-}$ forms, respectively.[45] For pH 4.8, Wave 1 was found to be very close to the negative potential limit, while for pH 9 the wave was further from the negative limit, with a split at low concentration (20 mM) before transforming into a distinct single wave at higher concentrations (Fig. 5c and d), resembling that for pH 7 buffer solutions (Fig. 5a). Thus, it can be concluded from Wave 1 that receptor **1** indeed facilitates the transfer of phosphate anions, though the transfer of the divalent anion is more probable in a competitive environment. It is worth noting that, a peak splitting of Wave 1 due to two different stoichiometric complexations (*i.e.* $(HPO_4^{2-})$—**1** and $(HPO_4^{2-})_2$—**1** complex) cannot be excluded here. Due to the mobile protonation equilibria and overlap of the facilitated ion transfer peaks, stoichiometry and $K_a$ data were not assessed by this method.

The emergence of the feature identified in Fig. 5 as Wave 2 at more positive potentials (*e.g.* at 0.5 V in Fig. 2a) in all the CVs of the studied anions at the water|DCB interface was investigated. It was clear from the previous CVs of phosphate ions that varying the pH of the buffer solution shifted the potential of Wave 2 with respect to the positive limit (Fig. 5c and d). The effect of the aqueous solution acidity on Wave 2 was probed with 20 mM NaCl$_{(aq)}$ solutions. Fig. 6a shows the CVs of the NaCl solutions prepared at pH 3, 7 and 11. It was observed that Wave 2 shifted positively under alkaline conditions, while in the acidic pH solution it shifted negatively, relative to its original shift in neutral conditions. This behaviour may indicate that Wave 2 results from interfacial acid/base reactions, which may suggest protonation/deprotonation of the tripodal thiourea molecule.

Some studies of one phase solutions such as DMSO[46] and acetonitrile,[47] using $^1$H NMR and UV-visible spectroscopy showed that the NH moieties of the thiourea groups can deprotonate in the presence of basic anionic species.[48] Hence, the deprotonation

in the one-phase medium is an anion-induced reaction, either an abstraction of proton; prior to hydrogen-bonding interaction as in case of more basic anions (*e.g.* $OH^-$, $F^-$, acetate)[23,49] and/or after the anion complexes with the receptor, as an excess of it (in both cases, anions with low[24] and high[49] basicity) can lead to deprotonation of the receptor. However, in this electrochemical approach with the anion and receptor present in two different phases, the emergence of Wave 2 was observed to be independent of Wave 1 (which has been ascribed to complex formation) for all the anions. That is, upon the polarisation of the water|DCB interface, in presence of receptor **1**, at a shorter potential range (0.1 to 0.68 V) that excluded the region of Wave 1, Wave 2 appeared in the CV (Fig. 6b). This observation indicates that Wave 2 is a potential dependent event that is not related to complex formation (Wave 1). Furthermore, the negative shift of Wave 2 with lower pH values of the aqueous phase resembles that of a facilitated proton transfer from the aqueous phase into the organic phase by a ligand in the organic phase.[50,51] Thus, Wave 2 can be attributed to protonation of the tripodal thiourea receptor. Some studies (potentiometric,[52] structural[53] and theoretical calculations[39]) showed that the bridgehead nitrogen of tripodal urea/thiourea molecules can be possibly protonated in acidic conditions. In this regard, receptor **1** can be considered to have two binding sites; while the acidic –NH moieties complex with the basic aqueous anions, the tertiary amine acts as a base binding a proton from the aqueous phase. However, a thorough understanding of the protonation reaction in the current study can be deduced when taking into account the p$K_a$ of the receptor.

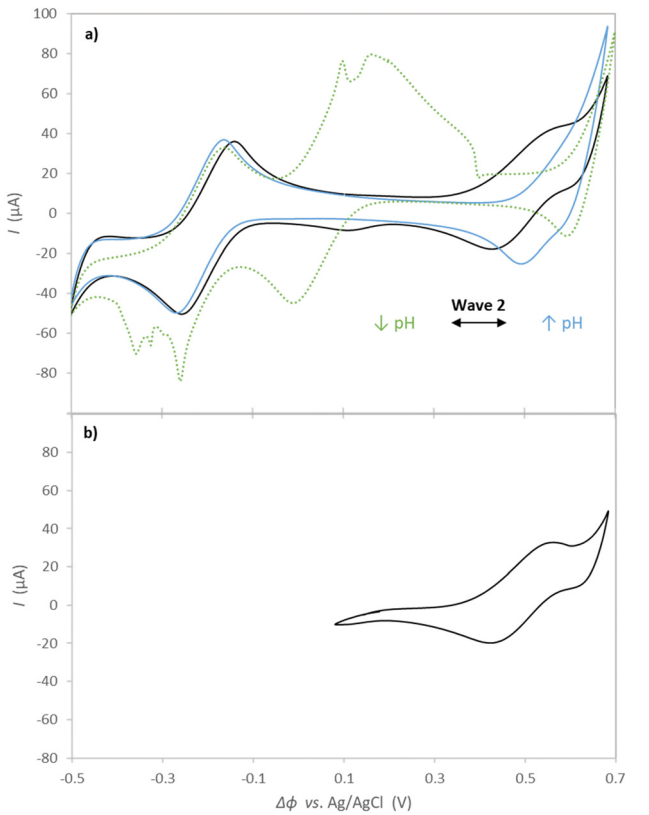


Fig. 6 CVs of Scheme 1 in the presence of 20 mM $NaCl_{(aq)}$|10 mM $BTPPATFPB_{(DCB)}$ and 1 mM receptor $\mathbf{1}_{(DCB)}$ at (a) pH 3 (blue), 7 (black) and 11 (green). (b) Same cell conditions at pH 7 with a shorter applied potential range, in the range of Wave 2. CVs were calibrated in accordance with the formal transfer potential of $TMA^+$ at the water|DCB interface.[34] Scan rate = 30 mV $s^{-1}$.

In addition, oscillations of the peak current were noticeable in the very acidic medium (pH 3). This is a similar scenario to Wave 2 of the acidic phosphate buffer solution (Fig. 5c). These oscillations were found to be reproducible over a series of successive cycles. The oscillations could be due to either interfacial desorption/adsorption of ion pairs at the interface[54,55] or the protonated receptor acting as a surfactant.[56,57]

In order to elucidate the effect of the organic solvent on the $K_a$ values, the organic phase DCB was replaced with nitrobenzene (NB). NB (like DMSO, a solvent frequently used in NMR titration experiments of anion binding) is a common aprotic solvent with large relative permittivity and dipole moment, unlike DCB which has a low relative permittivity and dipole moment.[43] Fig. 7a shows the CV of Scheme 1 with NB as the organic phase instead of DCB. In the presence of receptor **1**, a reversible peak for the facilitated transfer of $Cl^-$ was observed at *ca.* −0.12 V. The plot of the shift in the $\Delta_o^w\phi^{1/2}$ as a function of $\log(c_{A^-})$ provided a linear fit, with the gradient equal to 57.1 mV $decade^{-1}$, again corresponding to a 1 : 1 stoichiometry for the $Cl^-$—**1** complex (Fig. 7b). The $K_a$ value was estimated to be $(1.2 \pm 0.3) \times 10^5$ $M^{-1}$, which is comparable with the stability of $Cl^-$ complex for bis-thiourea derivative[58] ($(4.1 \pm 0.2) \times 10^4$ $M^{-1}$) and mono-thiourea derivative[59] ($(3.8 \pm 0.4) \times 10^4$ $M^{-1}$) in NB, estimated from electrochemical measurements. The higher $K_a$ value for receptor **1** characterises the enhanced affinity for $Cl^-$ due to the chelate effect and encapsulation.

Remarkably, the $K_a$ value in NB is 4–5 orders of magnitude lower than in DCB. The solvent effects on the $K_a$ value arise from the modulation of the anion:receptor interactions.[1,43] DCB, as an apolar aprotic solvent, would establish much weaker interactions with both the anion and the receptor than NB, which is a polar solvent with hydrogen bond donor properties. Thus, stronger solvation shells of the free species imply a higher desolvation penalty that the system has to pay, prior to formation of the hydrogen-bonding complex. As a result, the binding affinity of $Cl^-$ in NB is much less than that in DCB.

It is noteworthy that Wave 2 (see discussion of Fig. 5 and 6) is absent in the CV of the water|NB interface (compare Fig. 6a and 7a). It can be seen from Fig. 6a that the potential window of the water|NB interface (ranging from −0.35 V to +0.27 V) is significantly smaller than the water|DCB interface window, where Wave 2 is observed at around 0.5 V at pH 7 aqueous solution (Fig. 1a). Thus, the absence of Wave 2 is most likely due to the interfacial reaction occurring at higher potentials, outside the potential window of the water|NB interface, which may represent a weaker interaction in NB. This further confirms that the facilitated proton transfer reaction is a potential-dependent event not related to the anion:receptor complexation.

## Conclusion

In summary, the ability of receptor **1** to bind to a variety of anions has been assessed using cyclic voltammetry at the

 

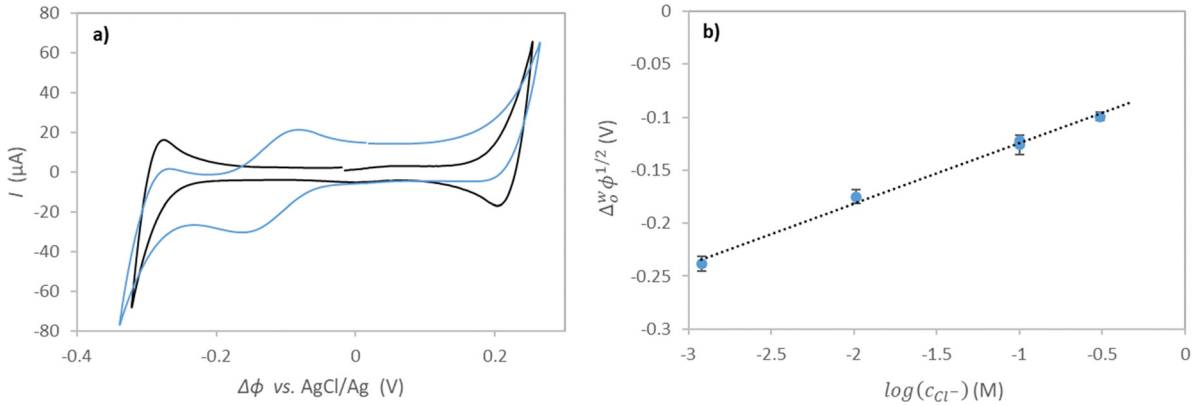


Fig. 7 CVs of Scheme 1 (a) in the presence of only the supporting electrolytes 20 mM $NaCl_{(aq)}$|10 mM $BTPPATFPB_{(NB)}$ in NB (black) and after the addition of 0.5 mM receptor $\mathbf{1}_{(NB)}$ (blue) Scan rate = 10 mV $s^{-1}$. (b) Plot of the shift in the $\Delta_o^w\phi^{1/2}$ as a function of $\log(c_{Cl^-})$, extracted from the voltammetric measurements.

aqueous|DCB interface. A 1 : 1 stoichiometry was found to describe the major binding mechanism. The anions tested were found to exhibit high association constants with **1** in DCB. The binding affinity trend, assessed from the $K_a$ data, is in the order of $SO_4^{2-} > Cl^- > Br^- > CH_3COO^-$, confirming the previously reported selectivity of this kind of tripodal receptors for spherical and tetrahedral anions against those with a planar geometry. Phosphate anions also showed strong binding to receptor **1**, although the affinities could not be quantified. In addition, it is inferred that the bridgehead N atom acts as a base, at a higher interfacial potential, binding a proton from the aqueous phase. As well as the water|DCB interface, the remarkable binding affinity of the thiourea molecule to the anions was examined at a more commonly studied interface, namely water|NB. The binding constant corresponding to the formation of the $Cl^-$—**1** complex in NB was found to be 4–5 orders of magnitude lower than that in DCB, in agreement with the typical solvent effects observed in binding constants determined by titration methods. Consequently, the high stability of the complexes in DCB is related to the poorer solvation of the anions (*i.e.* weaker interactions with both the anion and **1** in DCB). In summary, this electrochemical approach provides several advantages and the use of low polarity chlorinated solvents provided a better comparison with the lipophilic centre of a bilayer membrane. In addition, the large potential window of the water|DCB interface provided key insights, including the ability to observe the protonation of the tripodal thiourea receptor and the transport of ions in a variety of pH environments.

## Conflicts of interest

There are no conflicts to declare.

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