Hydrophilic Redox Buffers for Textile-Based Potentiometric Sensors

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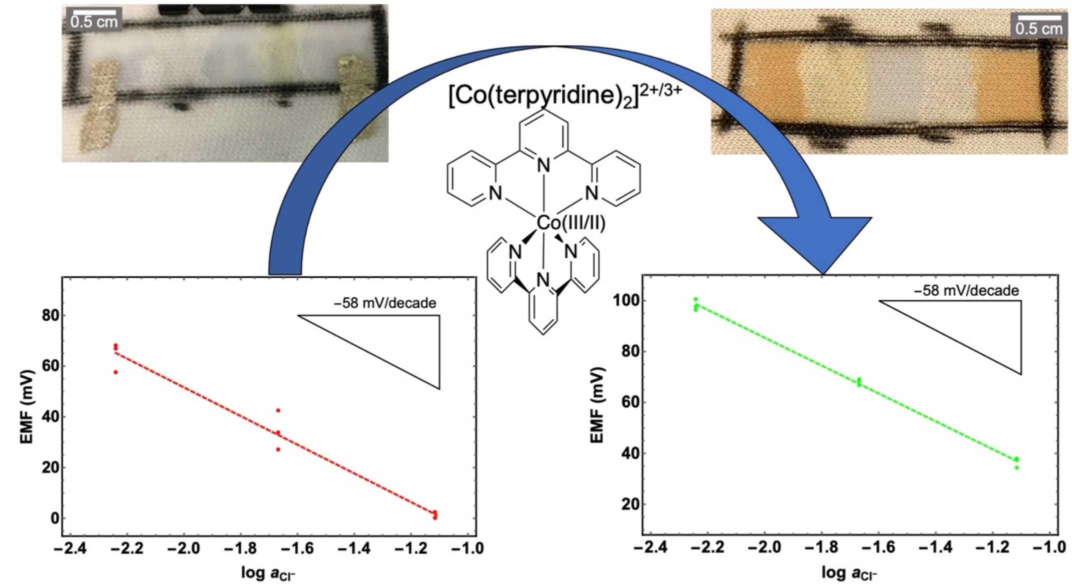
TOC Figure



Abstract

One of the barriers to the more widespread use of ion-selective electrodes (ISEs) in resource-limited areas is the need for frequent recalibration of such devices. The incorporation of a redox buffer to minimize the effect of redox-active impurities in the system has previously been shown to significantly improve reproducibility. To date, however, there have been no examples of redox buffers compatible with anion-sensing polymeric sensing membranes that can be incorporated into the inner filling solution of an ISE. Here, we introduce a novel hydrophilic redox buffer, cobalt(II/III) bis(terpyridine), and show the improvement of the standard deviation of E^0 of chloride sensors from 2.7 to 0.3 mV upon introduction of the redox buffer into the inner filing solution of conventional, rod-shaped electrodes. The redox buffer is also compatible with a textile-based sensing platform, which was shown by incorporation into a textile-based platform with embedded ion-sensing and reference membranes. As only a surprisingly small number of hydrophilic redox buffers have been reported in the literature, the cobalt(II/III) bis(terpyridine) redox buffer may also find applications outside of the field of ISEs.

Keywords:

- Ion-selective electrodes
- Calibration-free
- Potentiometric sensors
- Textile-based sensors
- Redox buffer

1. INTRODUCTION

There is a need for ion-selective electrodes (ISEs) that can be used in mobile settings with limited resources.[1,2] A major focus of work in this area has been on the miniaturization of ISEs, with variations in the degree of incorporation of either the sample holder, reference electrode, or ion-sensing electrode into an underlying support substrate. Examples include paper- and textile-based sampling with conventional sensing and reference electrodes,[3–6] paper- and thread-based strip-type ISEs dipped into sample solutions[7–10] sandwich-type ISEs in which a sensing membrane is held in place between two pieces of filter paper,[11–13] and paper- or textile-based devices with membranes integrated into the underlying support substrate.[14–16]

A much-desired characteristic of ISEs for such applications is high ease-of-use and, in particular, the elimination of frequent or individual calibrations, which require additional equipment and trained users. While the term "calibration-free" does not have an agreed-upon definition, it is generally evaluated in terms of the standard deviation (SD) of the standard potential, E^0, which is defined as the potential that is measured with such a device at a primary ion activity of 1.[17–19] For example, for diagnostic tests, the U.S. Food and Drug Administration mandates a maximum acceptable error for Na^+ of ± 4 mM within the range of 80-200 mM, which translates to a 0.7 mV acceptable standard deviation for a sodium ISE,[20] whereas manufacturers of clinical mainframe analyzers, which are recalibrated very frequently, strive for substantially narrower confidence intervals.

While most research into improving the reproducibility of ISEs is performed with conventional, rod-shaped ISEs, there is a growing amount of work on the development of miniaturized ISEs with improved reproducibilities. One such method involves the short-circuiting of multiple ISEs to a single reference electrode.[21] While first used successfully for rod-shaped solid-contact K^+ ISEs, this method was also used for miniaturized, carbon-fiber based Na^+ ISEs and lowered the E^0 SD from 37.6 to 1.45 mV (n=4) for sampling in aqueous solutions.[22] Improvements in reproducibility were also achieved through careful optimization of the fabrication methods of strip-type paper-based ISEs prepared from a filter paper coated with carbon nanotubes and poly(3-octylthiophene) as a solid contact, along with plasticized poly(vinyl chloride) (PVC) ion-selective membranes.[8,23,24] For example, the SD of the potential of 3 K^+-selective devices in the same solution was lowered from approximately 10 mV to approximately 2 mV by using cyclohexanone rather than tetrahydrofuran (THF) as the solvent for membrane cocktails and performing a single step for the application of both the carbon nanotubes and the poly(3-octylthiophene) onto the filter paper.

Another method for improving the reproducibility of low-cost miniaturized ISEs is based on the use of a molecular redox buffer to control the potential at the interface of the inner filling solution and the electron conducting inner electrode. Redox buffers contain both the reduced and oxidized form of a redox couple and resist changes in the EMF of a solution, just as a traditional pH buffer resists changes in pH. They have been used for thermal energy harvesting[25] and are well-known for their critical roles in nature, at scales as small as those of biological cells to geochemical dimensions. However, surprisingly little work has been devoted to develop redox buffers other than the commonly used $[Fe(CN)_6]^{3-}/[Fe(CN)_6]^{4-}$ and thiol/disulfide buffers. Consequently, recent work with ISEs comprising redox buffers has had only little precedence to work from.

Early examples include the use of Co(II/III) tris(phenanthroline), cobalt(II/III) tris(4,4′-dinonyl-2,2′-bipyridyl) as well as 7,7,8,8,-tetracyanoquinodimethane and the corresponding anion radical to make solid-contact ISEs [26–29] In all these cases, the use of the redox buffers improved the reproducibility of E^0. Incorporation of cobalt(II)porphyrin and cobalt(III)corrole, which do not form a redox pair, into the transduction layer of paper-based K^+ ISEs was reported to result in an improvement in the E^0 SD in, although it has also been suggested that the presence of low level redox-active impurities in the reagents may have been responsible for this finding.[30,31] Ferrocyanide and ferricyanide, in a ratio of 6.9 to 1, were doped into the transduction layer of screen-printed K^+ ISEs.[32] The hydrophilic ferrocyanide/ferricyanide redox couple was also incorporated into a hydrogel that served as inner filling solution of cation-selective electrodes, resulting in an E^0 SD of 1.1 mV for plasticized PVC membranes.[33]

We expand here the scope of applications of redox buffers to anion sensing with fully integrated paper- and textile-based ISEs.[14,16] For their practical use, redox buffers must contain chemically stable, reduced and oxidized species, which requires a relatively small standard redox potential. In addition, a redox couple used as component of the inner filling solution of an anion-selective ISE must also be hydrophilic, and it cannot comprise a redox-active anionic species, or else it would be likely to interfere with anion sensing through distribution into the anion-selective membrane. To date, redox buffers fulfilling these criteria have not been reported.

2. EXPERIMENTAL METHODS

2.1. Materials

Reagents were purchased from the following sources: inhibitor-free anhydrous THF, methanol, tridodecylmethylammonium chloride, $CoCl_2•6H_2O$, Br_2, and KCl from

Sigma (St. Louis, MO, USA); high molecular weight PVC and *o*-nitrophenyl octyl ether (*o*-NPOE) from Fluka (Buchs, Switzerland); 2,2′:6′,2″-terpyridine and the ionic liquid 1-methyl-3-dodecylmidazolium bis(trifluoromethylsulfonyl)imide (referred to here as $[C_{12}mim^+][C1C1N^-]$) and 1-methyl-3-octylmidazolium bis(trifluoromethylsulfonyl)imide ($[C_8mim^+][C1C1N^-]$) from Fisher Scientific (Pittsburg, PA, USA), D_2O from Cambridge Isotope Laboratories (Andover, MA, USA), Au wire from Alfa Aesar (Ward Hill, MA, USA), and Polx1200 polyester continuous knit filament cleanroom wipes from Berkshire Corporation (Great Barrington, MA, USA). In-house deionized water was purified to a resistivity of 18.2 MΩ/cm with a Milli-Q PLUS reagent-grade water system (Millipore, Bedford, MA, USA) and used for all experiments involving water.

2.2. Redox buffer preparation

$Co(II)(terpyridine)_2Cl_2$ was prepared from $CoCl_2 \bullet H_2O$ and terpyridine using a modified literature procedure.[34] Oxidation to Co(III) was performed with Br_2 as oxidant.[35] Details of the synthesis and characterization are provided as Supplementary Information.

2.3. Precursor Solutions for the Preparation of Sensor and Reference Membranes

All sensing membranes were prepared following literature protocols.[14] Precursor solutions for Cl^- ion sensing membranes were prepared by dissolving 60.0 mg PVC, 120.0 mg *o*-NPOE, and 10.0 mg tridodecylmethylammonium chloride in 1.0 mL THF. Precursor solutions for reference membranes were prepared by dissolving 30.0 mg $[C_{12}mim^+][C_1C_1N^-]$, 60.0 mg PVC, and 60.0 mg *o*-NPOE in 1 mL THF.

2.4. Fabrication of Conventional ISEs

Membranes were prepared by pouring 1.25 mL of THF solutions containing the membrane components into a flat-bottomed glass Petri dish (diameter 25 mm), covering the dishes with cardboard, and allowing the THF to evaporate overnight. Circular membranes (diameter 12 mm) were cut out of a master membrane the following day using a cork borer and then mounted into custom-made ISE bodies,[36] with an aqueous inner filling solution containing 2.5 mM $[Co(II)(terp)_2]Cl_2$, 2.5 mM $[Co(III)(terp)_2]Cl_3$, and 1 mM KCl in contact with a Au wire as inner reference. For electrodes with an ionic-liquid-based reference membrane, the inner filling solution was saturated with the ionic liquid. Either a double-junction type external reference electrode (DX200, Mettler Toledo, Switzerland; 3.0 M KCl saturated with AgCl as inner filling solution and 1.0 M LiOAc as bridge electrolyte) or a capillary reference electrode (AgCl/Ag, 3.0 M KCl inner filling solution),[37] as specified in the text, was used for measurements with this type of electrodes.

2.5. Fabrication of Textile-Based Electrodes

Textile-based devices were fabricated using a previously reported method.[16] Microfluidic zone barriers were hand drawn in matching patterns on both sides of the textile using a wax-based Sharpie Peel-Off China Marker. This was followed by curing for 10 min at 100 °C. For initial experiments, a dumbbell-shaped wax pattern was drawn, with separate reference and sample zones as well as a central contact area, as introduced by Lan and co-workers.[38] For electrodes with embedded membranes, solutions of the membrane components were applied to the textiles using a micropipette. Three cycles, consisting each of deposition of a 7 μL aliquot of the appropriate solution on the front and the back of the textile, were completed for all devices, with a 10-min waiting period between cycles. The Au wire used as an electrical contact in these devices was inserted through interyarn gaps into the textile (see Fig. S4B).

2.6. Potentiometric Measurements

Electrode potentials were measured using an EMF 16 voltmeter (input impedance 10 TΩ) controlled by EMF Suite 1.03 software (Lawson Labs, Malvern PA, USA). For textile-based devices, a Au wire was inserted in each side of the device through gaps in the textile. Alligator clips were used to connect the device to the voltmeter, and all devices were placed on top of a sheet of PVC and held in place with binder clips for stability. For each device, 25 µL each of the aqueous sample and reference solution were simultaneously deposited into the respective zones. It took approximately 30 s for the solutions to fully wet the textile; the recorded response is the average EMF over the following 30 s. All devices were used once only, and each sample was measured in triplicate. Activity coefficients were calculated according to a two-parameter Debye-Hückel approximation,[39] and EMF values were corrected for liquid-junction potentials with the Henderson equation.[40]

3. RESULTS AND DISCUSSION

3.1. Selection of the Redox Buffer

In our search for a hydrophilic redox buffer compatible with anion sensing, we considered commercially available buffers as well as several other metal and organometallic complexes but identified fundamental issues with most of them. Commonly used commercially available redox buffers include ZoBell's solution ($Fe(CN)_6^{3-/4-}$), which is incompatible with anion sensing because of the negative charge of the redox buffer species, quinhydrone, which is not stable over time, and Light's solution

($Fe(NH_4)(SO_4)_2$), which requires acidic conditions. Considering their standard redox potential, we also considered metal chloride salts such as $CuCl_2$/CuCl and $CrCl_3$/$CrCl_2$. However, CuCl has a poor solubility in water (K_{sp} of 1.72×10^{-7}), and Cr^{2+} is easily oxidized under ambient conditions, preventing their possible use.[41] A range of $Fe^{3+/2+}$ complexes with bi- and tridentate ligands were considered, but either the chemical stability of the complexes is insufficient, or their redox potential is shifted too positive.[42] Based on published characteristics, the complexes most promising as redox buffers appeared to be Co(II/II) tris(bipyridine) and Co(II/III) tris(phenanthroline). However, while the respective Co(III) are very stable chemically, the Co(II) complexes formed with these bidentate ligands have comparatively small stabilities.[43,44] Therefore, we decided to work with Co(II/II) bis(terpyridine), the tridentate terpyridine (see Figure 1) providing a higher complex stability. Details for the syntheses of the chloride salts of Co(III) and Co(II) bis(terpyridine) are provided in the Supplementary Information, along with a cyclic voltammogram of this redox buffer.[42,45] With its redox potential at ±90 mV versus AgCl/Ag, this the Co(II/III) bis(terpyridine) is well-suited as redox buffer.

This system eliminates the interface of AgCl and an internal filling solution as well as the AgCl/Ag interface. The phase boundary potential at the former interface is sensitive to any species that reacts with silver ions, which might be a reason why AgCl/Ag based paper- and textile-based devices have not exhibited a higher device-to-device reproducibility. Moreover, while macro-sized AgCl/Ag reference electrodes are well known to exhibit an excellent performance, paper- and textile-based devices are typically prepared with commercial AgCl/Ag inks that have a composition not disclosed by the manufacturer, which might be another cause for limited reproducibility. Therefore, we hypothesized that the new redox buffer might improve the reproducibility of the reference half-cell potential.

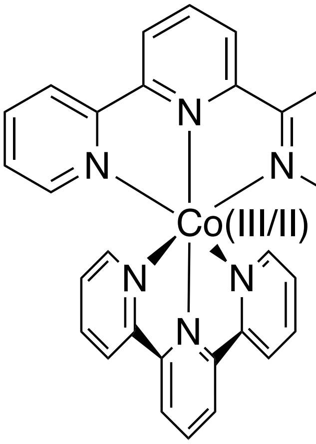


Figure 1. Structural formula of cobalt(II/III) bis(terpyridine).

In contrast to previously introduced hydrophobic redox buffers that have been incorporated into an ion-selective membrane,[26–28] the present hydrophilic redox buffer is designed to be incorporated into the inner filling solution of an ISE to control the potential at the electron conductor/inner filling solution interface. The potential at the interface of the electron conductor and inner filling solution depends on the ratio of the reduced and oxidized species present in the solution, as predicted by the Nernst equation, $E = E^0 - 58.2\ \mathrm{mV} \log\frac{c_{red}}{c_{ox}}$, where c_{red} and c_{ox} represent the concentration of the reduced and oxidized species, respectively, and E^0 is the standard redox potential.[26] To confirm this relationship, solutions with c_{red}/c_{ox} ratios of 1:1, 1:5, and 5:1 were prepared, each with a total concentration of the Co(III/II) complexes of 5 mM. A Au wire was used as the working electrode and a capillary reference electrode[37] (AgCl/Ag, 3.0 M KCl inner filling solution) was used to accommodate the small sample volumes (1.0 mL). The EMF of each solution was found to depend on log c_{red}/c_{ox}, with a slope of -56.9 ± 0.6 mV/decade (n=3) (Fig.

2C). This value agrees with the Nernst equation and confirms that the phase boundary potential at the interface of the Au wire and the solution is indeed determined by the redox buffer, serving its intended purpose.

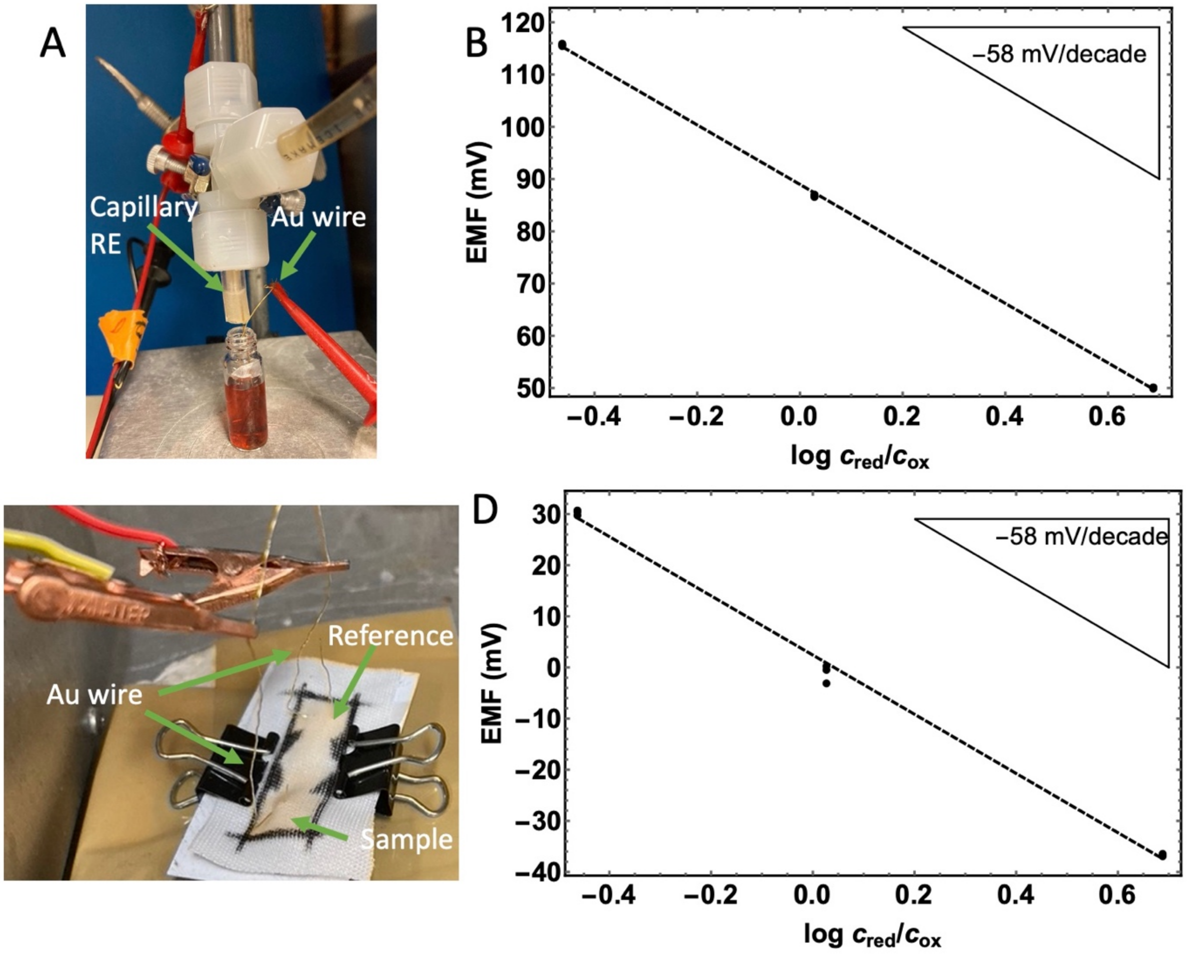


Figure 2. Photograph of conventional setup for measuring the EMF dependence on the ratio of Co(II)(terpyridine)$_2$ and Co(III)(terpyridine)$_2$ (A) and the corresponding potentiometric response (B). Photograph of a textile-based sampling setup for measuring EMF dependence (C) along with the corresponding potentiometric response (D). See Figure S4 of the Supplementary Information for larger photographs.

3.2. Conventional Electrodes with Inner Filling Solutions Comprising Redox Buffer

Upon confirmation of the ability of the redox buffer to control the phase boundary potential at the interface to the inner metal contact, the redox buffer was incorporated into the inner filling solution of electrodes with sensing membranes prepared with plasticized PVC as polymer matrix and tridodecylmethylammonium chloride as anion exchanger. To prepare the first set of electrodes, such an anion exchange membrane was affixed to a Tygon tube (manufactured from plasticized PVC), with an inner filling solution of 2.5 mM each of $Co(II)(terpyridine)_2Cl_2$ and $Co(III)(terpyridine)_2Cl_3$ as well as 1 mM KCl. A Au wire was immersed into this solution as electron conductor. With this setup, the phase boundary potential at the Au wire/inner filling solution interface is well controlled by the redox buffer, and the only sample-dependent phase boundary potential of the entire electrochemical cell is the one between the sample and the ion-sensing membrane. Therefore, at room temperature, the electrodes are expected to respond to the activity of Cl^- in the sample solutions according to the Nernst equation: $EMF = E^0 - 58.2\ \mathrm{mV} \log \mathrm{a}_{\mathrm{Cl}^-}$.[17] The working range of chloride sensors integrated into Polx1200-based devices was determined previously to be 0.2 to 100 mM. Therefore, we tested in this work 6.25 to 100 mM KCl solutions as samples. Electrodes of this kind gave an experimental response slope of –59.9 ± 0.1 mV/decade, consistent with theory, and an E^0 of 12.9 ± 0.3 mV (n=5) (see Fig. 3). In contrast, electrodes with an inner filling solution of 1 mM KCl and a Ag/AgCl wire as transducer gave a SD of E^0 of 2.7 mV (n=5). The significant improvement in the SD of E^0 upon introduction of the redox buffer confirms the ability of the redox buffer to control the potential at the interface of the electron conductor and the inner filling solution.

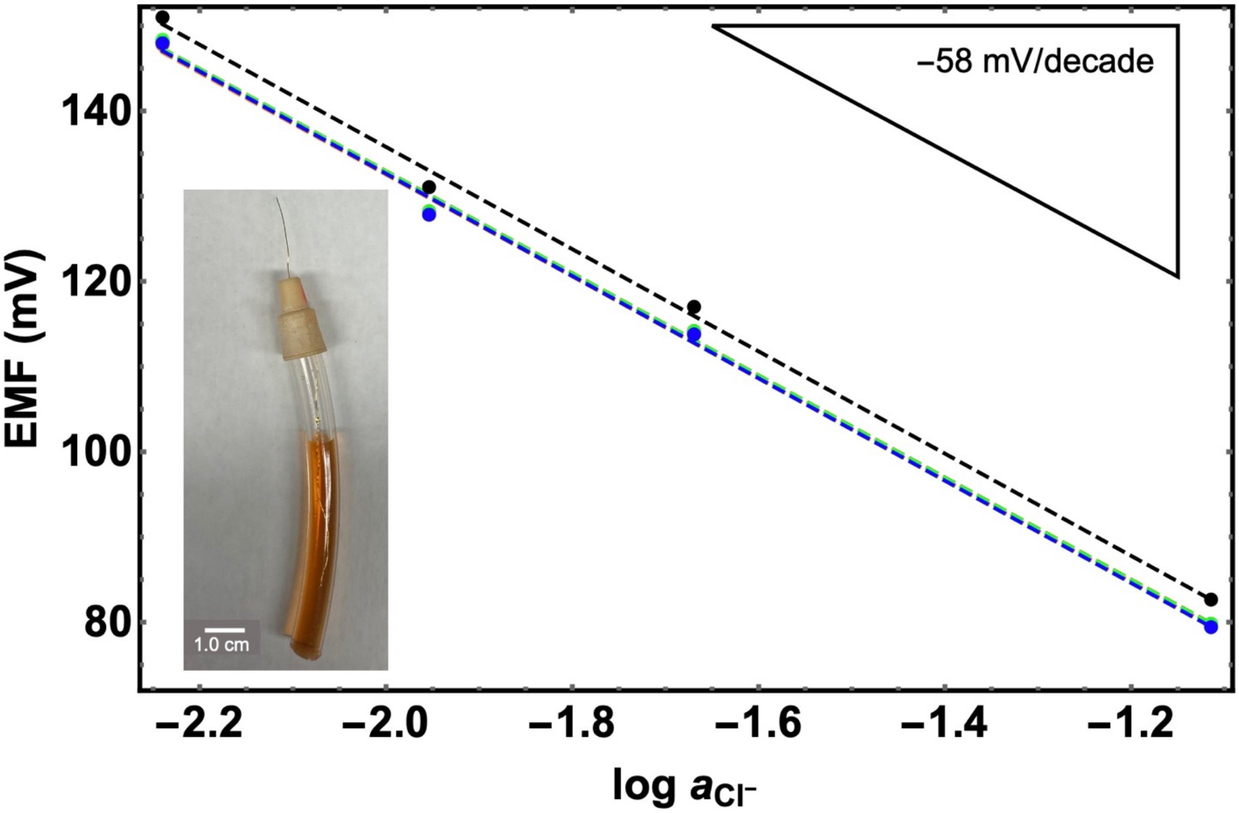


Figure 3. Potentiometric response of ISEs with a Cl⁻ ion-sensing membrane and a redox buffer containing inner filling solution (n=5) contained in a Tygon tube.

Keeping in mind the final goal of integrating this redox buffer into a planar design in which ionic-liquid-based reference membranes are used,[14,16,46] we also examined the compatibility of the proposed redox buffer with reference membranes. For this purpose, an ionic-liquid-based reference membrane was affixed to a Tygon tube with an aqueous inner filling solution comprising 2.5 mM each of Co(II)(terpyridine)$_2$Cl$_2$ and Co(III)(terpyridine)$_2$Cl$_3$, 1 mM KCl, and the ionic liquid at saturation concentration, as well as a Au wire as electron conductor. In this case, the phase boundary potential at the sample/reference membrane interface is controlled by the partitioning of the ionic liquid between the two phases and does not depend on the sample composition.[47] When measured with respect to a conventional reference electrode, the response slopes of this ionic-liquid-based reference electrode to any type of ion should be ideally 0 mV/decade. Electrodes of this kind resulted in a theoretically predicted slope of 0.4 ± 0.1 mV/decade and an E^0 of –16.6 ± 1.9 mV (n=4) when tested in sample solutions of 0.01 to 85 mM KCl (see Figure S5B). Analogous electrodes without the redox buffer but a chloride containing inner filling solution in contact to a Ag/AgCl wire as transducer exhibited a response of 0.2 ± 0.4 mV/decade and E^0 of 105.2 ± 10.0 mV (n=3) when tested in sample solutions of 0.01 to 85 mM KCl (see Figure S5A). As for the chloride ISEs too, introduction of a redox buffer improved the reproducibility, as seen in the reduction of the SD of E^0.

3.3. Textile-Based Devices with Redox Buffer

The suitability of the redox buffer for textile-based electrodes was also tested. As in conventional electrodes, initial experiments were designed to confirm the dependence of the potential at the Au/redox buffer solution interface on the ratio of reduced to oxidized species present. A dumbbell-shaped wax pattern was drawn onto rectangular pieces of a polyester textile to define separate sample and reference zones,[38] and a Au wire was woven through the textile as electron conductor (see Figure 2C). For potentiometric measurements, 20 µL of a reference solution of 1:1 c_{red}/c_{ox} was applied to the reference zone while 20 µL of a sample solution was applied to the sample zone. The three sample solutions contained either 1:1, 1:5, or 5:1 c_{red}/c_{ox}, with a constant total concentration of 5 mM Co(III/II) bis(terpyridine). In these devices, the only sample dependent phase boundary potential is that between the sample solution and the Au wire. The potentiometric response of electrodes of this kind is shown in Figure 2D; as these are single-use sensors, each data point represents a separate device. The EMF of each solution was found to depend on log c_{red}/c_{ox}, with a slope of –57.9 ± 2.3 mV/decade (Fig. 2D), confirming the ability of the redox buffer to control the potential when the redox buffer solution is in direct contact with the textile of textile-based sensor devices.

The compatibility of textile-based devices with polymeric reference and ion-sensing membranes embedded into the polyester textile was also assessed, as previous work has shown that miniaturization of ISEs can result in performance limitations.[14,48] Using the double-membrane design introduced previously for both paper and textile-based sensors (shown in Fig. 4A),[14,16] the reference solutions in contact with the Au wire contain 100 mM KCl, and 2.5 mM each of Co(II)(terpyridine)$_2$Cl$_2$ and Co(III)(terpyridine)$_2$Cl$_3$, while the sample solutions with varying amounts of KCl are only in contact with the sensing and the reference membrane but not the inner electrodes. Therefore, theory suggests that the only sample dependent phase boundary potential to be that between the sensing membrane and the sample, resulting in a slope of –58.2 mV/decade at 20 ºC. Indeed, devices of this kind gave a within error Nernstian slope of –58.5 ± 5.2 mV/decade (E^0 of –38.0 ± 10.7 mV), and a lower LOD of $10^{-3.0 \pm 0.6}$ M Cl^-.This LOD is very similar to LODs of similar Polx1200-based devices with embedded membranes and is relatively high.[16,48] However, it is low enough for samples of interest in clinical chemistry, and its value is not related to the properties of the redox buffer introduced here.

However, these experiments showed that the improved reproducibility in E^0 observed for conventional electrodes with an inner filling solution containing the hydrophilic Co(II/III) bis(terpyridine) buffer did not translate to textile-based devices comprising [C_{12}mim$^+$][$C_1C_1N^-$]-doped reference membranes. This is not a complication caused by the redox buffer. Instead, it results from a poorer reproducibility of the phase boundary potentials at the interfaces of the ionic-liquid-based reference membrane when combined with a textile device (see the Supplementary Information, pp S8–S13 for data). To address this issue, we fabricated and tested devices using reference membranes doped with the ionic liquid [C_8mim$^+$][$C_1C_1N^-$], rather than the [C_{12}mim$^+$][$C_1C_1N^-$] used originally. As reported previously,[49] this ionic liquid was washed 10 times with water, with the intent to remove impurities that may affect results. Devices of this kind gave a within error Nernstian slope of –54.7 ± 2.2 mV/decade (E^0 of –24.1 ± 3.8 mV), and a lower LOD of $10^{-3.0 \pm 0.5}$ M Cl^- (Figure 4B). This is a significant improvement over analogous textile-based devices using a 100 mM KCl inner-filling-solution and a AgCl/Ag ink transducer.[16] While we used in this work a Au wire woven through each reference zone (weaving of a wire into the textile is shown in Figure S4), this wire could be replaced by a printed carbon ink strip to facilitate mass manufacturing. The end user would only have to deposit a patient's sample and a drop of reference solution (supplied with a kit) onto the appropriate zones. It is also interesting to note the improved reproducibility in the higher concentration region, that is, above 1 mM (see Figure 4B).

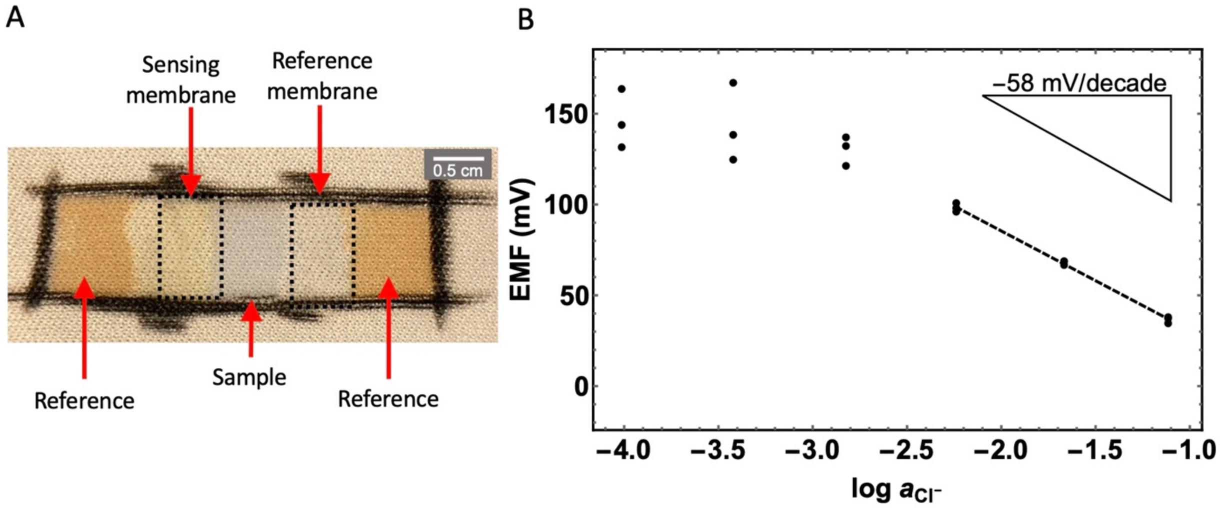


Figure 4. Photograph of a textile-based device with reference and sensing membrane (A) and potentiometric response to solutions of varying Cl^- activity (B).

Prospective users of Co(III/II) bis(terpyridine) should be aware of the twofold influence of adding KCl into this redox buffer. On one hand, for a double-membrane design as shown in Figure 4, the chloride activity controls the phase boundary potential at the interface of the chloride sensing membrane and the redox buffer reference solution. On the other hand, while the phase boundary potential at the Au/redox buffer interface is controlled by the ratio of Co(III) bis(terpyridine) and Co(II) bis(terpyridine), as confirmed by Figure 2, it is also affected by the KCl addition, apparently because the ionic strength of the solution influences the redox potential of the Co(III/II) bis(terpyridine) redox couple. However, because the composition of the redox buffer reference solution is independent of the sample composition, neither of these effects diminish the performance of devices with both sensing and reference membranes. The reader is directed to the Supplementary Information for a detailed discussion.

4. CONCLUSIONS

While redox buffers have long been used in chemical biology and as standards for redox probe calibration, there has been no hydrophilic redox buffer that can be used for the fabrication of anion-selective ISEs. To address the need for such a redox buffer, we introduce cobalt(II/III) bis(terpyridine). The complex is obtained through a single-step synthesis with minimal purification and is stable in both the reduced and oxidized forms. When incorporated into the inner filling solution of Cl^- ISEs with polymeric ion-exchanger membranes, the redox buffer reduces the E^0 SD from 2.7 to 0.3 mV. The complex is also shown to be compatible with ionic liquid-based reference membranes and textile-based platforms. Finally, greater reproducibility also translated to textile-based sensors with ion-sensing and reference membranes embedded within the material. This complex may also find use as an alternative to unstable calibration solutions and other applications of redox buffers.

CRediT authorship contribution statement

Eliza Herrero: Conceptualization; Methodology; Investigation; Data analysis; Validation; Writing - original draft, review & editing. **Takumi Goto**: Literature review of redox buffer species. **Philippe Bühlmann**: Supervision; Conceptualization; Funding acquisition; Resources; Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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