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Fluorinated tripodal receptors for potentiometric chloride detection in biological fluids

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ABSTRACT

Fluorinated tripodal compounds were recently reported to be efficient transmembrane transporters for a series of inorganic anions. In particular, this class of receptors has been shown to be suitable for the effective complexation of chloride, nitrate, bicarbonate and sulfate anions via hydrogen bonding. The potentiometric properties of urea and thiourea-based fluorinated tripodal receptors are explored here for the first time, in light of the need for reliable sensors for chloride monitoring in undiluted biological fluids. The ion selective electrode (ISE) membranes with tren-based tris-urea bis(CF_3) tripodal compound (ionophore I) were found to exhibit the best selectivity for chloride over major lipophilic anions such as salicylate ($\log K^{pot}_{Cl^-/Sal^-} = +1.0$) and thiocyanate ($\log K^{pot}_{Cl^-/SCN^-} = +0.1$). Ionophore I-based ISEs were successfully applied for chloride determination in undiluted human serum as well as artificial serum sample, the slope of the linear calibration at the relevant background of interfering ions being close to Nernstian (49.8 ± 1.7 mV). The results of potentiometric measurements were confirmed by argentometric titration. Moreover, the ionophore I-based ISE membrane was shown to exhibit a very good long-term stability of potentiometric performance over the period of 10 weeks. Nuclear magnetic resonance (NMR) titrations, potentiometric sandwich membrane experiments and density functional theory (DFT) computational studies were performed to determine the binding constants and suggest 1:1 complexation stoichiometry for the ionophore I with chloride as well as salicylate.

1. Introduction

Chloride is one of the most critical targets in biological fluids as its concentration, along with that of some other ions such as sodium, potassium, calcium, magnesium and lithium, is used for rapid patient care decisions (Dimeski et al., 2010). Accordingly, approaches to monitor these critical care species require development of sensors and devices for real-time monitoring with very high precision and accuracy.

Few methodologies are used in clinical laboratories for chloride determination, such as for example colorimetric, coulometric-amperometric and potentiometric procedures for serum analysis (Frost and Meyerhoff, 2015; Panteghini et al., 1986). Undeniably, potentiometric sensors offer one of the most convenient non-destructive way of determining ionic species due to their low cost, simple fabrication and miniaturization and low-energy consumption (Bakker and Telting-Diaz, 2002; Bobacka et al., 2008).

There exist two main types of anion-selective membranes for the potentiometric detection with ion-selective electrodes (ISEs). The first type, historically the most explored one, is the ISE membrane based on crystalline materials such as the AgCl-based solid-state electrode. However, the latter is not suitable for the analysis of biological samples since it suffers from protein adsorption to the AgCl surface (Bratov et al., 2004; Hulanicki and Michalska, 1995). The second type of membranes is based on polymeric matrices doped with ionophore and/or ion exchanger. The ISEs based on polymeric membranes have recently become an attractive tool for the direct monitoring of chloride in clinical analysis (Burtis and Bruns, 2014; Frost and Meyerhoff, 2015; Oesch et al., 1986; Yoon et al., 1998), however only few of the receptors reported so far possess adequate performance for practical application owing to challenges arising when analyzing biological fluids.

There are several issues in the development of the receptors adequate for the analysis of biological samples: i) leaching of active membrane components; ii) low biocompatibility of the membrane

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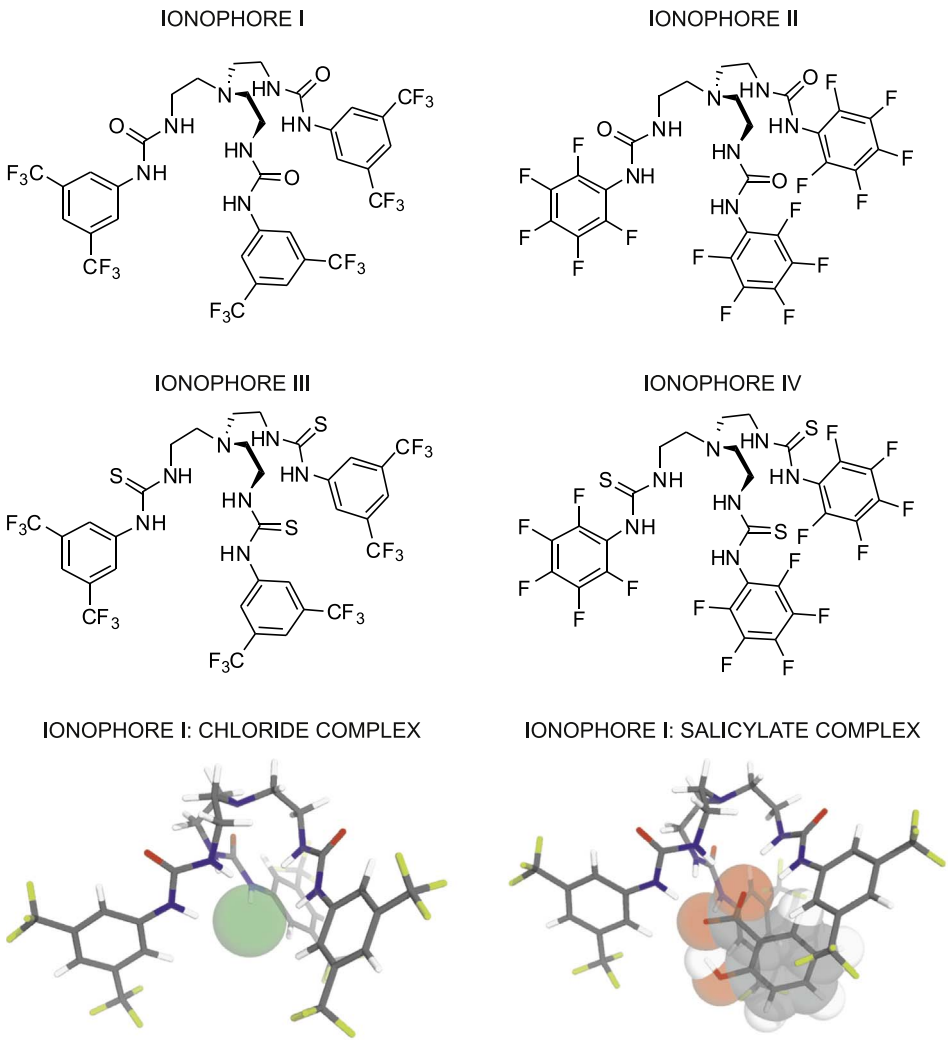

Fig. 1. (Top) Structures of the ionophores I-IV: (I) Tren tris-urea bis(CF_3) [$C_{33}H_{27}F_{18}N_7O_3$]; (II) Tren tris-urea pentafluoro [$C_{27}H_{18}F_{15}N_7O_3$]; (III) Tren tris-thiourea bis(CF_3) [$C_{33}H_{27}F_{18}N_7S_3$]; (IV) Tren tris-thiourea pentafluoro [$C_{27}H_{18}F_{15}N_7S_3$]. (Bottom) DFT (M06-2X/6−31+G(d)) optimized structures of the chloride and salicylate complexes of ionophore I without counter cation in vacuum; C (gray), H (white), N (blue), O (red), F (yellow-green), Cl (green). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

material with the sample and adsorption of proteins; iii) low selectivity of most receptors over interfering lipophilic anions such as salicylate, thiocyanate and bicarbonate commonly present in biological fluids (Bratov et al., 2004).

Certainly, salicylate is often the main interfering ion due to its lipophilicity, relatively high concentration and variable content in biological samples. For this reason, the determination of chloride in serum using ISEs often provides biased results owing to increased levels of salicylate in the samples from the patients who take aspirin (Yoon et al., 1998). Another challenge in potentiometric chloride detection concerns the upper detection limit of the ISEs since the high chloride concentration in clinical samples (*ca*., 100 mM in blood and serum) often causes strong complexation in the sensing phase, resulting in Donnan exclusion failure (Radu and Bakker, 2005).

While most chloride-selective ionophores reported in the past are organometallic compounds, some active membrane components reported recently are based on chloride complexation by hydrogen bonds (Sabek et al., 2015; Xiao et al., 1997; Zahran et al., 2010). Commonly used chloride-selective receptors with a metal center such as mercury, manganese or indium (Kondo et al., 1989; Park et al., 1991; Radu and Bakker, 2005; Rothmaier et al., 1996) often exhibit stability and/or toxicity issues (Sabek et al., 2015).

It is noted that most proposed receptors, both neutral and charged carriers, do not provide better selectivity and stability of chloride detection for clinical applications than traditional ion-exchanger based membrane (tridodecylmethylammonium chloride [TDMACl]) (Bratov et al., 2004). Consequently, the selectivity pattern of ISEs based on lipophilic quaternary ammonium salts (such as TDMACl) is fixed and follows the Hofmeister series since the selectivity of ion exchanger is mainly defined by the lipophilicity of the ion. The application of this type of chloride ISE is therefore limited to samples without significant concentrations of anions more lipophilic than chloride, and it would not be recommended for samples that contain salicylate or thiocyanate as in the case of blood or serum samples. Nevertheless, ISEs based on quaternary ammonium salts as active membrane component are still used commercially for chloride determination in biological samples despite the aforementioned limitations, owing to the lack of selective chloride receptors (Burtis and Bruns, 2014). To the best of our knowledge, only few studies published in the last two decades have reported on receptors with sufficiently improved potentiometric characteristics, close to those required for chloride detection in biological samples (Gupta et al., 2009; Sabek et al., 2015; Xiao et al., 1997; Zahran et al., 2010). However, even fewer studies demonstrated successful application of the investigated compounds for potentiometric chloride detection in undiluted non-spiked physiological samples (Sabek et al., 2015). Thus, further efforts are required to develop chloride selective ISEs with better selectivity, and adequate analytical performance and compatibility with biological fluids.