Application of the cobaltabisdicarbollide anion to the development of ion selective PVC membrane electrodes for tuberculosis drug analysis†

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Received (in Cambridge, UK) 31st July 2008, Accepted 10th October 2008
First published as an Advance Article on the web 7th November 2008
DOI: 10.1039/b813285b

The cobaltabisdicarbollide anion is used as a new material able to generate an ion-pair complex used for PVC membrane ion selective electrodes.

Potentiometry (*i.e.*, ion-selective electrodes (ISEs)) is a cost-effective analytical method for rapidly determining numerous analytes. ISEs have found widespread application in the fields of clinical diagnostics and environmental monitoring.[1,2] Probably the most common type of ISE used today is that typically composed of a polymer matrix, usually poly(vinyl chloride) (PVC), a plasticizer, an ion-complexing agent (ionophore), and lipophilic ionic additives (*i.e.* either alkylammonium salts for anion sensing or tetraphenylborates for cation sensing).[3,4] A modified form of this membrane uses an ion-pair typically tetraphenylborate and the cation to be measured as the electroactive substance.[5] ISEs made this way with $[BPh_4]^-$ as the ion-pair generator have been developed for drugs analysis.[6]

Carboranes, boranes and metallacarboranes are deltrahedra in which most or all of their vertexes are boron atoms. Very stable examples are $[CB_{11}H_{12}]^-$, $[B_{12}H_{12}]^{2-}$ and $[Co(C_2B_9H_{11})_2]^-$, $[\mathbf{1}]^-$. It has been demonstrated that $[CB_{11}H_{12}]^-$ is superior in performance to the very much used tetraphenylborates as an ISE membrane lipophilic anion additive. $[\mathbf{1}]^-$ has been used to produce very stable polypyrrole solid contacts in ISEs,[7,8] as a doping agent in intelligent membranes for ion capture,[10] and also as a lipophilic anionic additive.[9] Closo-boranes are lipophilic, have a bulky size (nearly 1 nm in diameter) and sufficient charge delocalization to produce very weak ion pairs.[11] Notwithstanding this, Cc–H···H–B and B–H···H–N dihydrogen bonds, and Cc–H···O hydrogen bonds, in which Cc stands for the cluster carbon atom, are commonly encountered in crystal structures as found in an inspection of the Cambridge Structural Database (CSD). In contrast, short contacts are not so frequent with tetraphenylborates. With recent trends in ion sensing moving toward miniaturization,[12] it becomes apparent that the lifetime of these sensors will ultimately be dictated by the membrane residence time of the active sensing components. Loss of ion exchangers results in a decrease in sensor sensitivity. This could be circumvented by covalently anchoring the ion exchanger to the polymer matrix,[13] but this is costly. In this communication, we propose to use $[Co(C_2B_9H_{11})_2]^-$ as the electroactive ion-pair maker. This anion, see Fig. 1a, is lipophilic, and because it is also a weakly coordinating anion[14,15] it has a lower charge density[16] than the other two boranes indicated above; more importantly, it is able to self-assemble through Cc–H···H–B dihydrogen bonds, and to be non-covalently bonded to the plasticizer through Cc–H···O hydrogen bonds. Moreover it can have weak B–H···H–N dihydrogen bonds with the electroactive cation. The opportunity to generate a self-assembled network based on the characteristics of $[\mathbf{1}]^-$ led us to produce simple ISEs in which $[\mathbf{1}]^-$ is the ion-pair generator and to check its possibilities with non-previously ISE monitored heterocycle based antibiotics that could be protonated to produce HN bonds intended for B–H···H–N dihydrogen bonds. One further goal aiming to show the prospects of $[\mathbf{1}]^-$ was to show the chances to convert an interference for one ISE into the target ion of the second, both ISEs based on $[\mathbf{1}]^-$. To this aim, we chose to monitor two common antibiotics for tuberculosis (TB).[17] This is a common and deadly infectious disease caused by mycobacteria. The standard and short treatment for active tuberculosis is based on isoniazid, rifampicin, pyrazinamide and ethambutol. The molecular structures of isoniazid (INH) and pyrazinamide (PZA) are shown in Fig. 1b and c, respectively. Some reported methods for pharmaceutical analysis require a long sample pre-treatment and expensive apparatus.[18–21] In contrast, ISEs represent a simple and rapid technique but they need to be selective. Therefore, the improvement of the selectivity opens the way to further investigations. Here we report the first examples of potentiometric plastic-membrane sensors for TB antibiotics. By combining $[\mathbf{1}]^-$ and the protonated form of the antibiotic, an ion-pair complex is obtained which is used to prepare the ion selective PVC membrane electrodes.

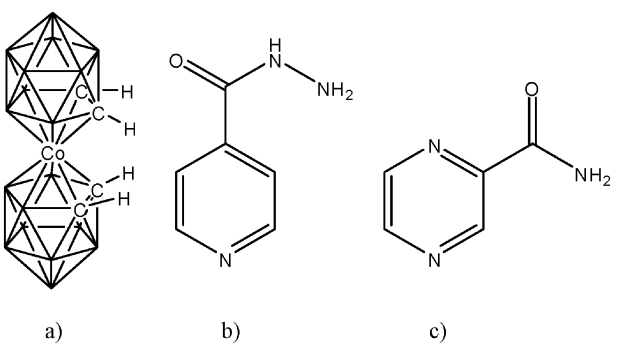

Fig. 1 Molecular structures of (a) $[Co(C_2B_9H_{11})_2]^-$($[\mathbf{1}]^-$), (b) isoniazid (INH), and (c) pyrazinamide (PZA). For $[\mathbf{1}]^-$, non-specified vertexes correspond to BH.

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† Electronic supplementary information (ESI) available: Experimental section, synthesis and characterization of electroactive materials, electrode characteristics, and selectivity coefficients. See DOI: 10.1039/b813285b

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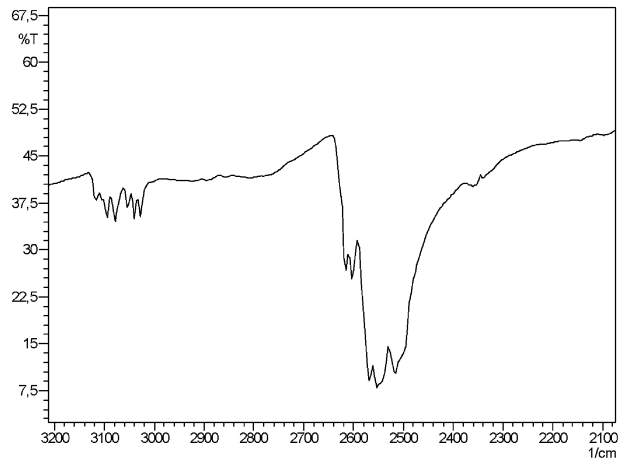

Fig. 2 FTIR spectrum of H[H-PZA]$_2$ between 3250–2200 cm^{-1}. Frequencies near 3200–3100 cm^{-1} are due to CC–H and C_{aryl}–H; those near 2500 cm^{-1} are due to B–H.

The electroactive ion-pair complexes were obtained by carefully mixing H[**1**] with the antibiotic in aqueous HCl. INH required a lower concentration of HCl than PZA to precipitate. Both precipitates were separated from the mother liquor by simple vacuum filtration, were washed with 0.1M aq HCl and were dried in vacuum at 0.1 torr. The chemical compositions of the compounds obtained were elucidated by ^{1}H-NMR by comparing the ratio of intensities between the Cc-*H* (4 in each unit of [**1**]) and the aromatic protons (4 in INH and 3 in PZA). The resulting salts were [H$_3$-INH][**1**]$_3$ and H[H-PZA]$_2$[**1**]$_3$. The ^{11}B and ^{13}C NMR, and the FTIR and MALDI-TOF supported these stoichiometries. Note that [H$_3$-INH][**1**]$_3$ is unusual as it implies that all three N in INH have been protonated. Up to now the only two crystal structures reported of protonated INH at the CSD, INAHZC01[22] and LUPMIS,[23] contain only two protonated N, although all three N participate in hydrogen bonding. The stoichiometry found for H[H-PZA]$_2$[**1**]$_3$ suggests a hydrogen bonding between two pyrazine units. This hydrogen bond is common and has been found in protonated pyrazines such as PYRZP02[24] and QEXBEB.[24] The relevance of hydrogen or dihydrogen bonding in these salts is evidenced in their IR spectra at the B–H and Cc–H or ArC–H stretching regions in which the signals show great fine structure (Fig. 2).

The isoniazid ISE membrane's composition was obtained dissolving 7.0% (w/w) [H$_3$-INH][**1**]$_3$, 63.0% (w/w) plasticizer and 30.0% (w/w) PVC in THF. The electrodes with the different plasticizers (o-nitro phenyl octyl ether, NPOE, di-octyl phthalate, DOP and di-butyl phthalate, DBP) were prepared and assembled as previously described.[25] As shown in Table 1 INH ISEs exhibited good results, high selectivity and excellent electrode properties. Even though the general compositions of the ion selective membranes were similar, the results indicated that the PVC membrane containing NPOE as plasticizer offered the best results with slope 52.37 mV/decade, linearity in the 1.00×10^{-4}–1.00×10^{-1}M concentration range, with 5.00×10^{-5} M as detection limit, and with a minimum lifetime (tested) of 45 days.

In Table 1 only the results obtained for INH based ISEs with NPOE and DOP, columns 2 and 4, are displayed. A more complete table, also including results with DBP is provided as ESI.† Of utmost relevance was the influence of an interfering ion. Table 2 shows the selectivity coefficients for ions of biological importance along with the PZA and sulfanilamide antibiotics. As shown in this table, the DOP membrane is the one that provides the best selectivity coefficients, near 10^{-4} both for PZA and sulfanilamide. The potentiometric selectivity coefficients ($K^{pot}_{A/B}$) were determined by the fixed interference method (FIM). The constant background concentration was 10^{-3} M for all interfering ions (Table 2).

Considering that the membrane electroactive species is the protonated antibiotic, measurements were done with a pH in the range 3.20–3.80. The uncommon membrane salt component [H$_3$-INH][**1**]$_3$ and the associated good response of the

Table 1 Electrode characteristics

Antibiotic	INH	PZA	INH	PZA
Plasticizer	NPOE	NPOE	DOP	DOP
Slope mV/decade	52.37	56.98	47.80	46.70
Correlation coefficient	0.9973	0.9971	0.9989	0.9975
Concentration range/M	1.00×10^{-4}–1.00×10^{-1}	5.00×10^{-4}–1.00×10^{-1}	1.00×10^{-4}–1.00×10^{-1}	5.00×10^{-5}–1.00×10^{-1}
Detection limit/M	5.00×10^{-5}	3.00×10^{-5}	5.80×10^{-5}	1.00×10^{-5}
Time response/s	<5	<5	<5	<5
Lifetime/day	>45	>45	>45	>45
pH	1.85–9.50	2.20–9.50	1.85–9.50	2.20–9.50

Table 2 Selectivity coefficients of electrode for various compounds

Interfering species	log $K^{pot}_{INH/B}$ NPOE	log $K^{pot}_{PZA/B}$ NPOE	log $K^{pot}_{INH/B}$ DOP	log $K^{pot}_{PZA/B}$ DOP
Na^+	−1.54	−3.36	−1.88	−5.19
K^+	−2.57	−5.32	−4.82	−6.39
Ca^{2+}	−4.28	−6.34	−5.20	<-7
Mg^{2+}	−4.47	−4.32	−4.98	<-7
INH	—	<-7	—	<-7
PZA	−2.87	—	−3.82	—
Sulfanilamide	−2.08	−6.02	−4.07	<-7

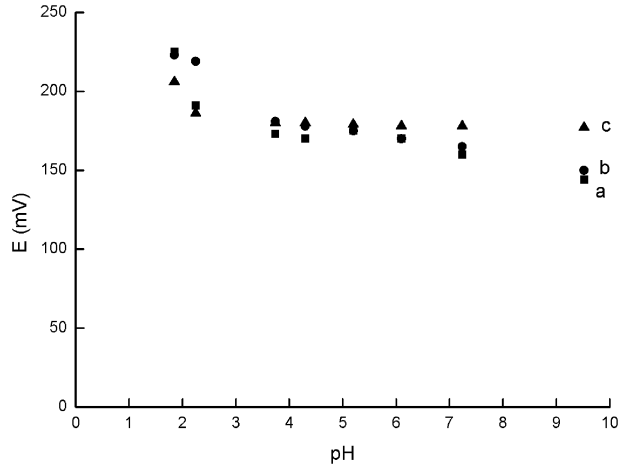

Fig. 3 Influence of pH on the electrode response for a solution of isoniazid 10^{-3} M. Plasticizer: NPOE (a); DOP (b); DBP (c).

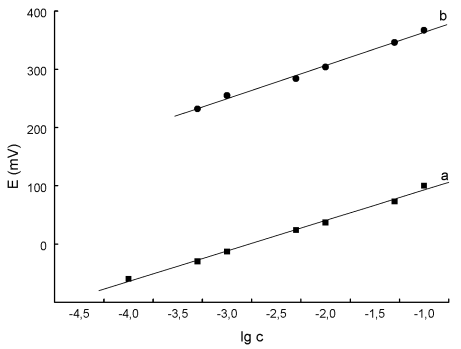

Fig. 4 Calibration curves of antibiotic selective electrodes based on ion-pair complex for: INH (a) and PZA (b).

ISE also indicated that it was very unlikely that the measured species was $[H_3\text{-INH}]^{3+}$, but other less protonated species of INH present in the associated equilibria within the membrane. This was made clear with the pH dependent study shown in Fig. 3, in which it is evidenced that the range of pHs at which the measures are linear is large between 2 and 10, especially for DBP. Fig. 4 shows the linear response of these electrodes to the concentration logarithm of the analyte.

As indicated in the introduction, one of the objectives was to show the ease with which the interfering ion may be converted into the principal one, and vice-versa. To this aim, membranes having $H[HPZA]_2[\mathbf{1}]_3$ as the electroactive component were made with compositions similar to those indicated for isoniazid. The responses are indicated in Table 1, columns 3 and 5. The interferences and selectivity coefficients are displayed in Table 2. No difference in behaviour to the isoniazid electrode is observed but the small selectivity coefficient for most of the tested ions is remarkable, and in particular for isoniazid and sulfanilamide with $K^{pot}_{PZA/B}$ smaller than 10^{-7}.

The simplicity with which a new set of sensors, *i.e.* sensitive for isoniazid or pyrazinamide, can be produced with a minimal change in the composition of the membrane but with a maximum change in the selectivity for a measured ion shows the potential of [**1**] as an ion-pair maker. It is our understanding that the hydrophobicity, the low charge density, the non-globular shape and the possibility to produce hydrogen and dihydrogen bonds either with the membrane structural components or the electroactive species all play relevant roles in such behaviour. We anticipate that [**1**] has considerable promise in the development of new ion-pair complexes as a membrane component for environmental and pharmaceutical analysis, and that it can be very attractive for ISE miniaturization.

This work was supported by CICYT (Project MAT2006-05339), Generalitat de Catalunya (2005/SGR/00709) and Ministerio de Educación y Ciencia (SAB2006-0127).

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