Aroylthioureas: new organic ionophores for heavy-metal ion selective electrodes †

Elena Otazo-Sánchez,*‡[a,b] Leonel Pérez-Marín,[b,c] Osvaldo Estévez-Hernández,[b] Susana Rojas-Lima[a] and Julián Alonso-Chamarro[d]

[a] *Centro de Investigaciones Químicas (CIQ), Universidad Autónoma del Estado de Hidalgo, México*
[b] *Instituto de Materiales y Reactivos (IMRE), Universidad de la Habana, 10400 La Habana, Cuba*
[c] *Instituto Tecnológico de Toluca, Metepec, 52140 Estado de México, México*
[d] *Grup de Sensors y Biosensors, Facultat de Ciènces, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, España*

Thiourea derivatives (46 aroylthioureas) having different substituents close to the sulfur atom were synthesized and their ionophore potential in ion selective electrodes (ISEs) was examined. Structural considerations were taken into account based on the corresponding heavy-metal ISE parameters. As ionophores, some 1-furoyl-3-substituted thioureas (series 2) gave the best results in Pb(II), Hg(II) and Cd(II) ISEs. The strong intramolecular hydrogen bond in series 2 allows ligand interaction only through the C=S group. Substituents on the furan and phenyl rings give rise to low solubility in the membrane plasticizer. 3-Alkyl substituted furoylthioureas improve solubility but enhance oxidative processes with chain length. New X-ray diffraction (XRD) structures and theoretical DFT calculations were considered in the analysis of the substituent influence on the selectivity of ISEs. These new ionophores have advantages because of their stability, simple synthesis and easy modification of the sulfur binding ability resulting from substitution.

Introduction

Ionic and molecular recognition materials are subjects of interest due to their wide application. One such application concerns the development of chemical sensors which simplify the systematic control and prevention of water pollution and the protection of the environment.

The requirements of very low detection limits (LDL) and lower limits of linear response (LLLR), the reproducibility, the Nernstian response of the calibration curve (slope value = $59.16/Z_a$ mV decade^{-1}), the lifetime and the problem of high selectivity properties ($K_{A,B}^{pot}$) limit the suitability of the recent liquid and solid state membrane-based ISEs developed for environmental sensing. Liquid-membrane ion selective electrodes have many advantages.[1] The membranes are currently prepared with PVC, the plasticizer (mediator) and the immobilized-recognition-compound (so-called ionophore or carrier) directly deposited onto a conductive epoxy resin–graphite composite, without internal reference solution.[2] The construction of PVC membrane electrodes is easy to implement, inexpensive and reliable.[3] These electrodes show good stability and their response is acceptable for analytical applications.

Many recognition compounds have been tested as ionophores in ion selective electrodes. Their structures are cyclic[4,5] or acyclic.[6–8] Some ionophores are commercially available[9] and others have been reported in recent years.[1d]

The principal membrane component is the ion recognition substance whose structural compatibility with ions was the focus of study in the early years in order to provide the basis for a good sensitive and selective ISE. So far, the kinetics and thermodynamics of the process occurring in the membrane have been taken into account. A complicated multivariate mechanism is operative. The stability of the formed complex, the partition coefficient and the ion mobility depend on the media and they are important factors to be taken into account. The reversible ion–complex formation and the relative stability of the complex between the plasticizer and water, the solubility ratio of the ionophore and its complex between both media, the ion transport through the membrane, and the interface process define the final behaviour and suitability of ISEs. Only a few chemical sensors have been developed for monitoring the heavy-metal ions in water.[1d] Early reports of Pb^{2+} and Cd^{2+} ionophores present bis-amide and bis-thioamide functional groups[10] in a so-called podand molecule (two arms) which chelates the ion.
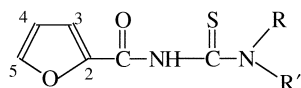
Thioureas are well known as good ligands for metal ions and this property can be used in cation-selective membranes. In contrast, they have been reported as neutral ionophores in anion-selective electrodes.[11] The sulfur atom in the thioureido CS group is expected to be more nucleophilic than the corresponding CS group in thioamides. Some studies have been done on their complexation properties[12] and more recently with platinum-group metals.[13]

We first reported **2f** as a good ionophore for Pb(II) ISE.[14a] Compounds **2a** and **1e** were then reported for Pb(II)[15] and Cd(II)[16] ISEs, respectively. Our goal was achieved when we reported Hg(II) ISEs with ionophores **2b**[17a] and 1,3-diphenyl-thiourea.[17b] Both showed good responses/selectivities and detected Hg(II) as Hg^{2+} and Hg(OH)$^+$, depending on the pH of the solution. These are important features, as there have been no reports of good membrane Hg(II) ISEs. Moreover, the response mechanism and the complexation between Hg^{2+} and Hg(OH)$^+$ with the membrane have been demonstrated.[17c]

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Here we report a general structure based analysis of the behaviour of 46 aroylthioureas (series 1–4) in ISEs. In these simple structures, the presence of three different heteroatoms (N, S, O) could result in different types of complex formation with transition and heavy-metal ions. The presence of various substituents remote from, or near to the CS group causes differences in the complex stability and mediator solubility, changing the behaviour of the constructed heavy-metal ISEs.

No.	R	R′
1a	- CH₂ CH₂ CH₂ CH₂ CH₂- (piperidyl)	
1b	-CH₂CH₃	-CH₂CH₃
1c	-nC₄H₉	-nC₄H₉
1d	-C₆H₅	-C₆H₅
1e	-C₆H₅	-CH₂C₆H₅
1f	-C₆H₅	-CH₂CH₃
1g	-C₆H₅	-CH₃

Series 1
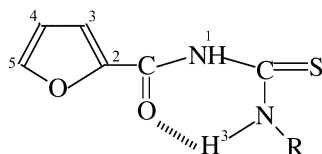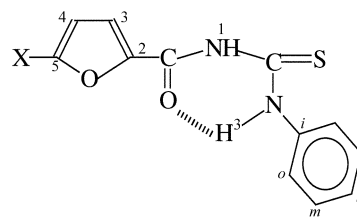

No.	R	No.	R
2a	-CH₂CH₂OH	2n	-C₆H₄N(CH₃)₂-p
2b	-C₆H₁₁	2o	-C₆H₄OC₂H₅-p
2c	-CH₂C₄H₃O	2p	-C₆H₄OCH₃-p
2d	-CH₂C₆H₅	2q	-C₆H₄OCH₃-m
2e	-C₁₂H₂₅	2r	-C₆H₄CH₃-p
2f	-C₆H₅	2s	-C₆H₄CH₃-m
2g	-C₆H₄CH₃-o	2t	-C₆H₄Cl-p
2h	-C₆H₄NO₂-o	2u	-C₆H₄Cl-m
2i	-C₁₀H₇	2v	-C₆H₄Cl-o
2j	-2-C₅H₅N	2w	-C₆H₄Br-p
2k	-C₆H₄CF₃-m	2x	-C₆H₄Br-m
2l	-C₆H₄CN-p	2y	-C₆H₄NO₂-p
2m	-C₆H₄C₁₄H₂₉-p	2z	-C₆H₄NO₂-m

Series 2

No.	X
3a	CH₃
3b	Br
3c	Cl
3d	I
3e	NO₂

Series 3

No.	X
4a	H
4b	p-CH₃
4c	p-Br
4d	p-OCH₃
4e	p-Cl
4f	m-Cl
4g	p-NO₂
4h	m-NO₂

Series 4
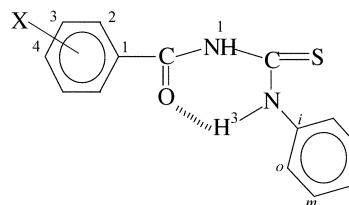

Ar′-COOH ⟶ Ar′-CO-Cl ⟶ Ar′-CO-N=C=S

Scheme 1

Results and discussion

The ionophores presented have the advantages of quick and easy synthesis and purification,[18] and the potential for dramatic steric and electronic variation in the region of the sulfur atom. Therefore, it is relatively simple to modify a convenient property (see Scheme 1). The stability of these compounds is such that they can be used for analytical purposes. We have classified them into four series: 1) 3,3-disubstituted furoylthioureas, 2) 3-monosubstituted furoylthioureas, 3) 1-(5-substituted)-furoyl-3-phenylthioureas and
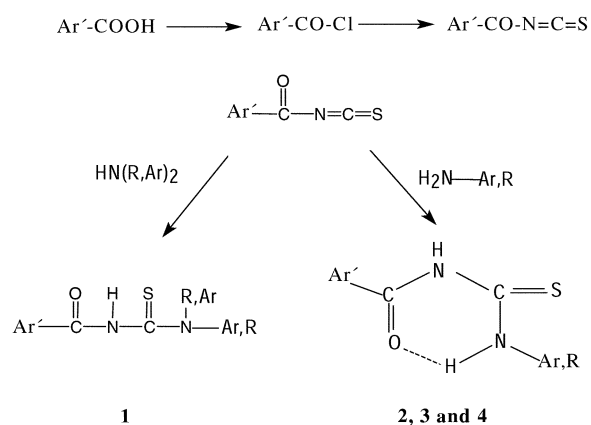
4) 1-(*meta* and *para* substituted)-benzoyl-3-phenylthioureas. Synthesized 1-furoyl- and 1-benzoylthioureas contain hydrophobic substituents and some lipophilic groups, which prevent the solubility of ionophores in the aqueous solutions tested. Best yields were obtained with primary and secondary aromatic amines (60–95%). Very low yields were obtained for aliphatic amines (30–70%), especially secondary ones, due to their higher nucleophilic character. In this case, competitive side-reaction at the C=O group was decreased by lowering the
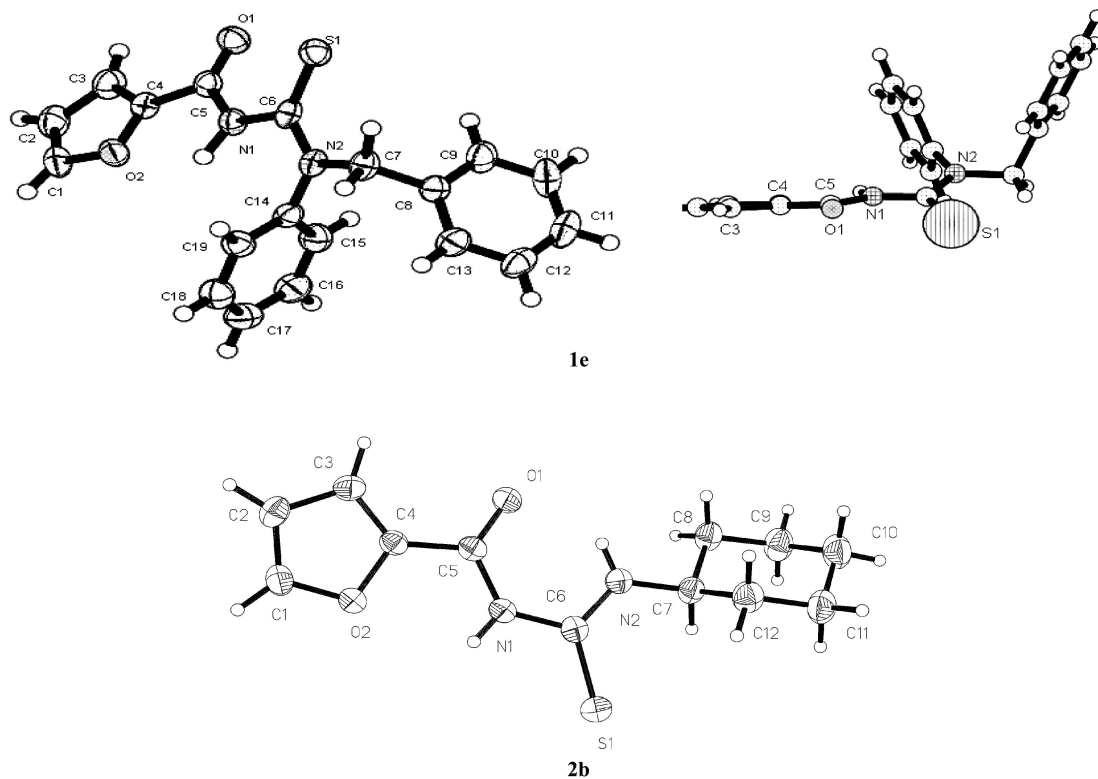
1e

2b

Fig. 1 ORTEP structures obtained for **2b** and **1e**.

reaction temperature to −15 °C. A total of 46 aroylthioureas (18 of which are new compounds) were synthesized and all were characterized. Characterization data are given in the supplementary information. †

XRD Structures

Structures **1e** and **2b** were obtained by monocrystal XRD. ORTEP structure diagrams are shown in Fig. 1. The crystallographic and structural data are given in Tables S1 to S13 of the Supplementary Information. For the representative compound **2b**, the intramolecular hydrogen bond is clearly demonstrated, as was earlier reported for series 2–4.[19] Dihedral angles in the system CO–NH–CS–NH are close to 0° in **2b** in a fixed *E,Z* conformation with CO and CS groups in an "S"-shaped arrangement. The furan ring is about 30° out of plane in relation to the CO group, in an *anti* (*OO-trans*) conformation. A quasi-planar structure is observed. Compound **2b** shows the thioureido group in an equatorial position of the cyclohexyl ring, as expected.

Unlike **2b**, **1e** shows a nearly planar structure only at the furoylthioureido group (Fig. 1). The furan ring is only 5° out of plane with respect to the CO group. In addition, they are in an *anti* (*OO-trans*) conformation. The dihedral angles in the CO–NH–CS–NH system are nearly 0° in a *Z,Z* conformation, resulting in a "U"-shaped arrangement with respect to the CO and CS groups. The CS group is 22.5° out of plane. Both phenyl and benzyl groups are almost orthogonal with the thioureido near-plane (see Fig. 1). The *R* value of **1e** is higher than that of **2b**. It is assumed that the reason for this is the quality (the R_{int} value is rather high) and weakness of the crystal.

The structure of **1e** has recently been calculated by DFT methods.[20] The calculated structural parameters do not agree with those reported here by XRD, with the exception of the observed "U"-shaped arrangement of the CO and CS groups. The main differences are observed with the dihedral angles. The theoretical structure locates the phenyl group in a *Z* position almost in the plane of the N–CS group. In contrast, XRD shows this group in an *E* position, at 84.4° to the N–CS plane.

Therefore, it will be necessary to recalculate the orbital data based on the experimental data reported here for this compound.

From the published data[19] and the XRD structure of **2b**, we can generalize that series 2, 3 and 4 present a strong intramolecular hydrogen bond, in a nearly planar rigid *E,Z* structure. The theoretical structures calculated for **2f**[21] and **2a**[20] agree with this fact, therefore, the reported orbital data are reliable. Consideration of the frontier orbitals suggests that coordination with soft heavy-metal ions should only be through the sulfur atom with no chelate formation taking place. Unlike series 2, in series 1 chelate formation is more feasible.

Sensor behaviour: Nernstian response and selectivity

In ISEs, the criterion for ionophore suitability to a specific ion sensor is based on its linear (Nernstian) response towards the analyte ion in a range of concentrations. This range and the calibration parameters are determined from a graphic potential (*E*/mV) *vs.* activity (*α*/M) of the analyte ion. Frequently, the electrode does not give any response, or, it might show an erratic (non-linear) response. In some cases, even when there is a linear response, an invalid slope value for an ion is obtained (slope value $\neq 59.16/Z_a$ mV decade^{-1}). In those cases, it is assumed to be an inadequate ionophore for the detection of the ion. Fig. 2 shows representative electrochemical behaviour for **2f** in a Pb^{2+} ISE.[14] In Fig. 2 the LLLR and LDL are graphically represented.

Table 1 shows the general primary results obtained from the studied thioureas in ISEs. Table 2(*a*), (*b*) contains the calibration parameters and selectivity coefficients obtained for them. As shown in Table 2(*a*), only **1e**, **1f**, **2a**, **2b**, **2f** and **2m** gave reversible and Nernstian responses in the respective constructed sensors.

When a Nernstian response is obtained for a sensor, a second challenge might be solved: selectivity. Fig. 3, 4 and 5 show graphically the selectivity coefficients obtained for the ISEs. Many methods have been developed[22] to determine the potentiometric selectivity coefficients $K_{A,B}^{pot}$. They measure changes of potential in the presence of two ions

Table 1 Summary of ionophore behaviour suitability in studied thioureas[a]

Compound	Solubility in TEHP	Response/ion = slope value	Notes about ionophore
1a, **1g**	Yes	Not yet studied	Low yields of **1a**
1b, **1c**	Yes	No response: poisoned	Low yields, difficult to purify
1d	No	—	—
1e	Moderate	Nernst/Cd = 29.28 mV decade^{-1}	Very low selectivity
1f	Yes	No Nernst/Pb = 45 mV decade^{-1}	
2a	Yes	Nernst/Pb = 29.17 mV decade^{-1}	Very low selectivity
2b	Yes	Nernst/Hg: 58.72 mV decade^{-1} at pH = 7 28.32 mV decade^{-1} at pH = 4 Nernst/Pb = 28 mV decade^{-1} No Nernst/Ag = 45 mV decade^{-1}	Very high selectivity
2c, **2d**, **2e**[b]	No	—	Turns dark
2f	Yes	Nernst/Pb = 30 mV decade^{-1}	Good selectivity
2g, **2r**, **2s**	Yes	Not yet studied	—
2h, **2t–z**	No	—	—
2i	Yes	Undergoing study in optical sensors	Shows fluorescence
2j, **2n–q**	No	Not recommended	Present interferent functional groups
2k, **2l**	Yes	No response to any ion	—
2m[b]	Yes	Nernst/Pb = 28.7 mV decade^{-1}	Very high selectivity
3a, **3c**	Yes	Not yet studied	—
3b, **3d**, **3e**	No	—	—
4a	Moderate	No Nernst/Pb = 43 mV decade^{-1}	Lower solubility
4b	Yes	Not yet studied	—
4c, **4e–h**	No	—	—

[a] Solubility ≥20 mg in 100 g plasticizer TEHP. TEHP was the best solvent for these compounds. [b] Soluble in DOS and *o*-NPOE.
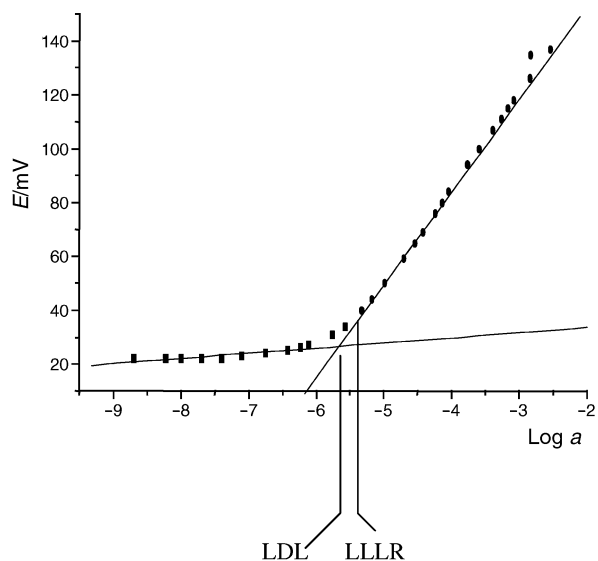

Fig. 2 Calibration curve for Pb^{2+} ISE constructed with **2f**. LLLR and LDL are represented.

simultaneously: the principal and the interfering ions. To facilitate the comprehension of the data, it should be mentioned that $K_{A,B}^{pot}$ (potentiometric selectivity coefficient) is calculated by the fixed interference method by eqn. (1), where a_A and a_B are the

$$K_{A,B}^{pot} = a_A/(a_B)^{z_A/z_B} \qquad (1)$$

activities, and Z_A and Z_B are the charges of the principal (A) and interfering (B) ions, respectively.

The quoted values of $K_{A,B}^{pot}$ were mostly determined by the fixed interference method. Other methods approved by IUPAC have also been tested and no significant differences in $K_{A,B}^{pot}$ values were observed.[17b] $K_{A,B}^{pot}$ indicates the extent of the selectivity of a given ion sensor towards the interfering ions. The reference value is taken for the specific principal ion (log $K_{A,B}^{pot} = 0$). Consequently, the values quoted in Table 2(*b*) reflect the bigger or smaller selectivity behaviour, between the ion sensed and the interfering ion, of a given ionophore.

Pb(II) ionophores

Good Pb(II) ISEs were obtained with ionophores **2f**[14a] and **2m**.[14b] The latter presents the best slope and calibration

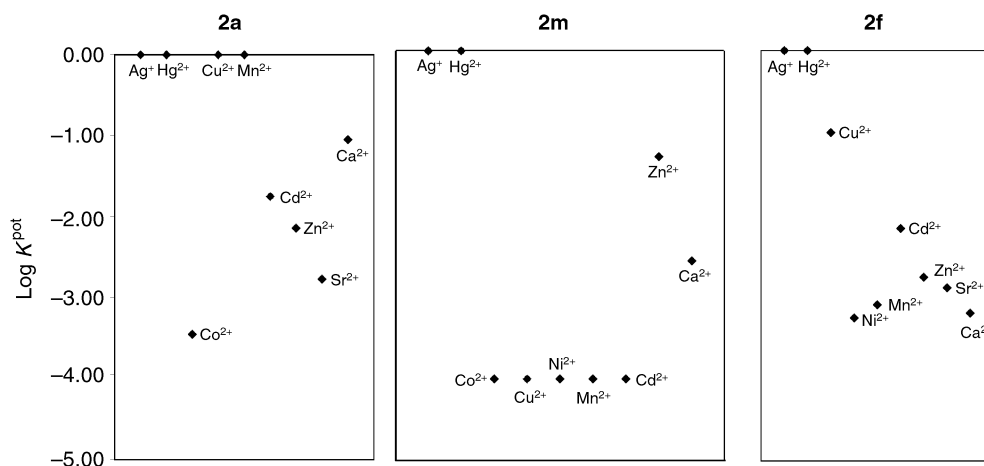**Fig. 3** Selectivity in Pb(II) sensors: potentiometric selectivity coefficient $K_{A,B}^{pot} = a_A/(a_B)^{Z_A/Z_B}$. log $K_{A,B}^{pot} \geq 0$, strong interference—the sensor responds mainly to the interfering ion; log $K_{A,B}^{pot}$ between -2 and -1, moderate interference; log $K_{A,B}^{pot} \leq -3$; no interference.

Table 2 Summary of experimental data obtained for thiourea-based heavy metal ISEs

(*a*) Calibration parameters

Ionophore	1,3-Diphenylthiourea	2f	1e	2a	2b	2m	1f	4a
Ion sensor	Hg^{2+} and $Hg(OH)^+$	Pb^{2+}	Cd^{2+}	Pb^{2+}	Hg^{2+} and $Hg(OH)^+$	Pb^{2+}	Pb^{2+}	Pb^{2+}
Slope[a]	30.8 and 58.6	30	29.28	29.17	28.32 and 58.72	28.7	45	43
LLLR[b]	2.0×10^{-6} and 6×10^{-6}	3.7×10^{-6}	2×10^{-4}	3.7×10^{-3}	7×10^{-6} and 4.15×10^{-6}	4.8×10^{-7}	1.99×10^{-4}	N.S.[e]
LDL[c]	2×10^{-6} and 4×10^{-6}	1.7×10^{-6}	8×10^{-5}	3.7×10^{-5}	5.0×10^{-6} and 3.4×10^{-6}	3.6×10^{-8}	6.3×10^{-5}	N.S.[e]
Lifetime	6 weeks	8 months	6 weeks	6 weeks	8 weeks	4 months	20 days	15 days
Plasticizer	TEHP	TEHP	TEHP	TEHP	TEHP	*o*-NPOE	TEHP	TEHP

(*b*) Selectivity parameters

Ionophore	Selectivity: log $K_{A,B}^{pot}$ for reliable sensors[d]					
	1,3-Diphenylthiourea	2b	2a	2f	2m	1e
Hg^+	0	0	0.00	0.00	0.00	0.00
Ag^+	−0.20	−1.44	0.00	0.00	0.00	−0.03
Co^{2+}	−4.57	−4.54	−3.45	N.S.[e]	−4.00	−1.84
Cu^{2+}	−4.10	−4.51	0.00	−1.00	−4.00	−1.75
Pb^{2+}	−4.27	−4.32	0	0	0	0.20
Mn^{2+}	−3.15	−4.55	0.00	−3.10	−4.00	N.S.[e]
Cd^{2+}	−4.87	−4.50	−1.75	−2.17	−4.00	0
Zn^{2+}	−4.58	−4.55	−2.14	−2.76	−1.29	N.S.[e]
Sr^{2+}	−4.70	−4.51	−2.77	−2.89	N.S.[e]	−1.97
Ca^{2+}	N.S.[e]	−4.57	−1.05	−3.20	−2.56	N.S.[e]
Ni^{2+}	N.S.[e]	N.S.[e]	N.S.[e]	−3.26	−4.00	N.S.[e]

[a] Slope = Sensitivity in linear response range of calibration curve. (Ideal value for M^{2+} ion = 29.6 mV decade⁻¹ and for M^+ = 59.1 mV decade⁻¹). [b] Lower limit of linear response. [c] Lower detection limit. [d] Potentiometric selectivity coefficient $K_{A,B}^{pot} = a_A/(a_B)^{Z_A/Z_B}$. log $K_{A,B}^{pot} \cong 0$, strong interference: the sensor responds mainly to the interfering ion; log $K_{A,B}^{pot}$ between −2 and −1, moderate interference; log $K_{A,B}^{pot} < −3$, no interference. [e] N.S. = not studied: no data reported.
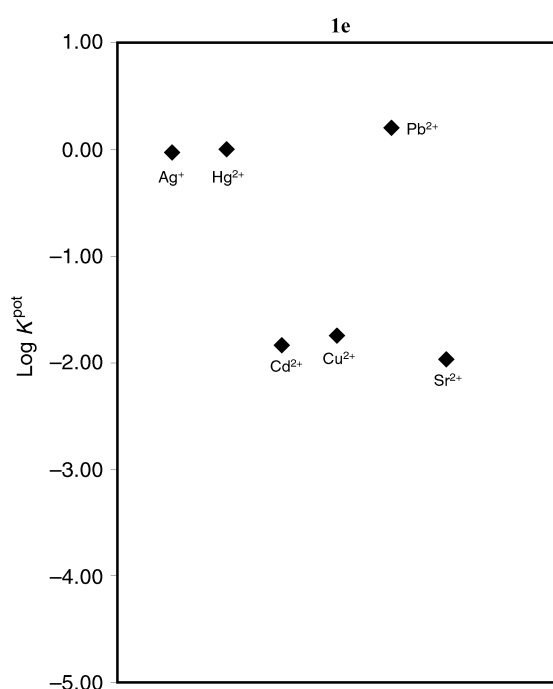

Fig. 4 Selectivity in the Cd(II) sensor: potentiometric selectivity coefficient $K_{A,B}^{pot} = a_A/(a_B)^{Z_A/Z_B}$. log $K_{A,B}^{pot} \geq 0$, strong interference—the sensor responds mainly to the interfering ion; log $K_{A,B}^{pot}$ between −2 and −1, moderate interference; log $K_{A,B}^{pot} \geq −3$; no interference.

parameters[23] (see Table 2(*a*)). Both sensors also have excellent lifetimes and good selectivity. Fig. 3 compares the selectivity of the three reported Pb(II) sensors. However, there is significant interference due to Hg^{2+} and Ag^+. As shown in Fig. 3, **2m** displays better selectivity than **2f**. It might be assumed that the most satisfactory parameters and selectivity are due to the presence of a lipophilic group $C_{14}H_{29}$ in the molecule. A **2m**

sensor was also constructed with a different plasticizer, *o*-nitrophenyl octyl ether (*o*-NPOE).

A mediocre Pb(II) ISE was made with **2a**. It exhibited a Nernstian response towards Pb^{2+} with a very low selectivity. A chelate interaction with most ions was proposed[20] to explain this poor selectivity. Due to the high stability of the chelates, the reversibility of the processes is very low and the lifetime, LDL, LLLR and selectivity of the ISEs are consequently very poor. Substituents with ion-complexing groups in the side chains are strongly not recommended. Compound **1f** gave a very poor Pb(II) sensor, with a very low lifetime. The selectivity was not studied.

Cd(II) ionophores

We obtained a linear response for the ISE constructed with **1e**[16] towards Cd^{2+}. Pb^{2+} causes significant interference, as do Hg^{2+} and Ag^+. The log $K_{A,B}^{pot}$ values are represented graphically in Fig. 4. The introduction of another group (benzyl) at N(3) prevents the fixed intramolecular H-bonded configuration and causes a dramatic change in the behaviour of **1e** and **2f** in the ISEs. This fact suggests that the site of interaction with ions differs between both types of ionophore. It seems that the oxygen atom of CO has an important role in the coordination of Cd^{2+} by chelate formation in **1e** as has been proposed.[20] This Cd(II) ISE showed many important interferences. Hence, this is not a recommended ionophore due to its low selectivity. Note that a similar situation was observed for the **1f**-constructed Pb(II) ISE.

Hg(II) ionophores

The Hg(II) ion is not easily tested by means of ISEs. There are very few acceptable ionophores reported, and those have many disadvantages[1d] and a limited pH range for their use. In the literature, almost all ISEs studied respond non-linearly towards Hg(II) or have a very short lifetime.[5] This ion has poisoned the membrane in many of our studied ISEs due to the strong attraction to the sulfur atom. However, the new compound **2b** is able to meet this challenge.

Table 3 Summary of relevant orbital features calculated on structures **2f** and 1,3-diphenylthiourea

Parameter	1,3-Diphenylthiourea	**2f**
E_{LUMO}/eV	−2.326	−3.095
E_{HOMO}/eV	−4.943	−5.437
E_{HOMO-1}/eV	−5.310	−5.654
E_{HOMO-2}/eV	−5.933	−6.374
η^a	1.302	1.171
σ^b	0.768	−0.854
χ^c	3.634	4.266
Charge on S atom	−0.210	−0.189
Bond order S=C	1.67	1.689
%S coefficient on HOMOs	68.19 and 48.26	70.87 and 30.18
%O coefficient on HOMOs	—	0.33 and 0.17

[a] Hardness $\eta = \Delta E/2$. [b] Softness $\sigma = 1/\eta$. [c] Absolute electronegativity $\chi = (E_{HOMO} + E_{LUMO})/2$. Energy units, eV.
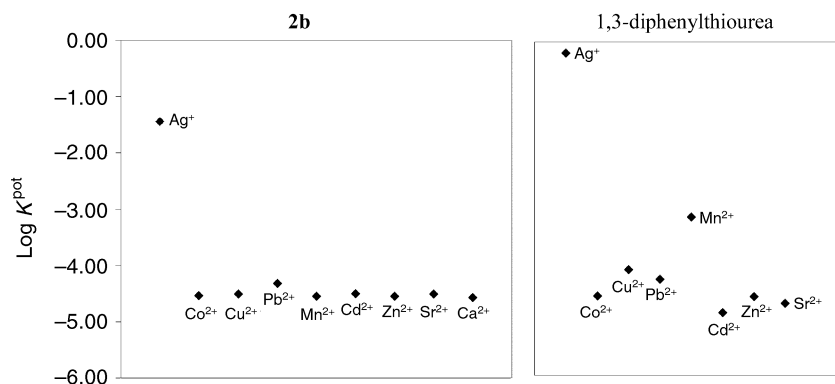
Fig. 5 Selectivity in Hg(II) sensors; potentiometric selectivity coefficient $K_{A,B}^{pot} = a_A/(a_B)^{Z_A/Z_B}$. log $K_{A,B}^{pot} \geq 0$, strong interference—the sensor responds mainly to the interfering ion; log $K_{A,B}^{pot}$ between −2 and −1, moderate interference; log $K_{A,B}^{pot} \geq -3$, no interference.

The change of the phenyl group in **2f** for a cyclohexyl in **2b**, resulted in an excellent sensor for Hg(II).[17a] It experiences no interferences from other ions and the lifetime is acceptable. This fact suggests that the nearby planar phenyl group participates in the coordination of **2f** with Hg(II) ions. The interaction centre is not only the S atom. The saturated cyclohexyl group raises the selectivity and lowers the reactivity towards the two detected Hg(II) species: Hg²⁺ and Hg(OH)⁺. The wider range of pH for the medium is also another advantage of this sensor.

In order to observe the influence of the furoyl group and the intramolecular hydrogen bond present in the most suitable series 2, ISEs were constructed with **4a** and the commercially available 1,3-diphenylthiourea. The benzoylthiourea **4a** was not soluble enough in any plasticizer used for the membrane preparation and the ISE showed poor results with very short lifetimes (see Tables 1 and 2). The furoyl group confers better membrane solubility on the structure than the benzoyl group does.

In contrast with **2f**, the reactivity of 1,3-diphenylthiourea towards heavy metal ions was reduced, resulting in another Hg(II) sensor with very high selectivity, except for the Ag⁺ ion.[17b] As seen in Fig. 5 for the two reported Hg(II) sensors, **2b** shows better selectivity than 1,3-diphenylthiourea. This is probably due to the higher solubility of **2b** in TEHP [tris-(2-ethylhexyl) phosphate].

Frontier orbital analysis

Table 3 shows the principal orbital parameters calculated for **2f** and 1,3-diphenylthiourea. In this paper, we reject the orbital data reported for **1e** due to the differences between calculated and XRD structures. Also, we have calculated the absolute electronegativity χ of both structures. 1,3-Diphenylthiourea and **2f** present a very similar picture as regards HOMO–HOMO-1 separation. They are so close that it may be assumed that both have almost the same weight in the nucleophilic response. The sulfur atom makes a large contribution to the HOMO and HOMO-1, very similar to 1,3-diphenylthiourea. The carbonyl oxygen atom participates hardly at all in the HOMOs of **2f**. The calculated χ is slightly greater in **2f**. The introduction of a furoyl group in the thioureido system increases the softness of the sulfur atom. Both facts might explain the greater reactivity of **2f** towards Hg(II) species than 1,3-diphenylthiourea.

It has also been stated[20] that hydrogen-bonded carbonyl-thioureido systems (in **2a** and **2f**) exhibit independent behaviour of the OC–NH and SC–NH groups, regarding their bond order sequences.

Structure of the plasticizer

Solubility in the plasticizer is an important feature which influences the response of the sensor. Fig. 6 shows the structures of some frequently used plasticizers in membrane preparations. The most suitable for the solubility of the thioureas studied were TEHP, dibutyl phthalate (DBP) and o-NPOE. They contain big lipophilic chains and basic groups which interact with the more acidic NH-1 in aroylthioureas. Both facts make the compounds advantageous as plasticizers with these thioureas and support the ionophore behaviour. In general, the best results were obtained with TEHP, the most basic and lipophilic solvent. The interaction with the acidic NH promotes the solubility and enhances the nucleophilic character of the neighbouring sulfur atom.

An example is given in the comparison of the results between **2f** and **2m**. Lipophilic groups in **2m** raise the LLLR and LDL in comparison with **2f**. There is better solubility in other mediators, such as o-NPOE. This solvent also has inferior basic properties compared with TEHP. This might explain the lower reactivity and better selectivity of **2m** towards Cu²⁺ and Cd²⁺.

The solubility of these compounds was tested in all the plasticizers. It was seen that the plasticizer with the best capacity was TEHP, the one with the strongest interaction with the acidic NH and bigger lipophilic groups. Only the general
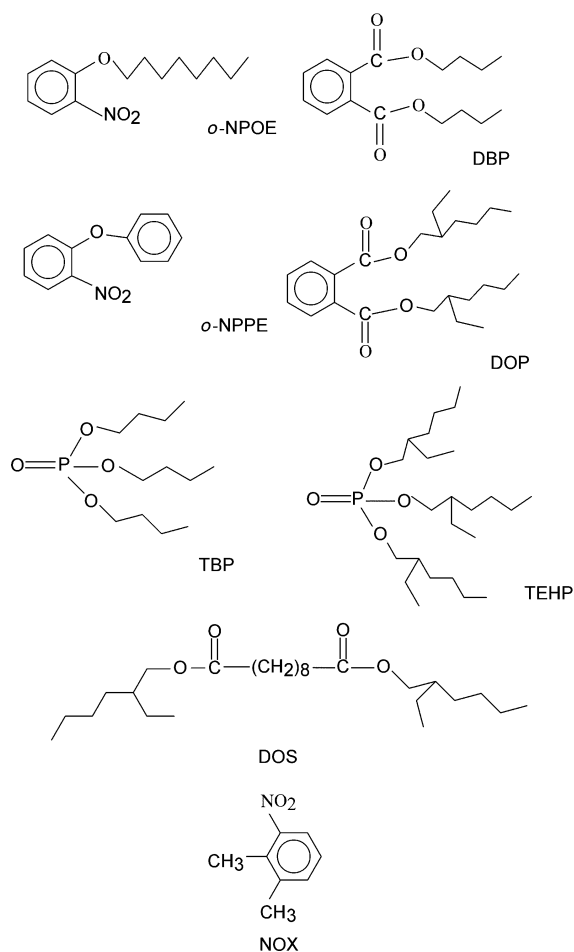
Fig. 6 Structures of plasticizers commonly used in membrane preparations.

solubility tests in TEHP are shown in Table 1. Many compounds of series 2, 3 and 4 were not soluble enough in many plasticizers. It was assumed that a solubility of ≥20 mg in 100 mg of plasticizer is more than suitable for the preparation of the membrane.

Conclusions

To gauge the usefulness for potentiometric sensors, forty six aroylthioureas were tested as ionophores. Regarding the structures of thioureas as heavy-metal ionophores for ISEs, the best choices for high selectivity and sensibility are the following: (a) 3-monosubstituted furoylthioureas (series 2) are strongly recommended. Their coordination strength and liposolubility can be easily modulated. (b) Series 3 and 4 are not suitable due to their low solubility in the plasticizers. Non-substituted 1-benzoyl-3-phenylthiourea shows poor reproducibility with no Nernstian responses, however, furoylthioureas do (series 2 and 4). (c) In all cases, long carbon chains are recommended as substituents in phenyl or furan rings, in order to raise liposolubility and to prevent the loss of the ionophore from the membrane. It is seen that the LDL and LLLD improve with this modification. (d) Series 1 showed poor selectivity due to chelate formation with metal ions. These compounds are not recommended as ionophores. For the same reason, functionalised side groups should be avoided to prevent chelate formation, which diminishes the lifetime of the sensor or poisons the membrane due to very stable complex formation. (e) Weakly reactive furoylthioureas, 3-cycloalkyl-substituted, or simply 1,3-diarylthioureas make the best sensors for Hg^{2+}. In both cases the substituent group lowers the nucleophilic character of the sulfur atom and raises the liposolubility. (f) Compounds **2e** and **2k**, the latter with strong electron-withdrawing groups and

good membrane solubility, might be tested. In the case of **2e** the plasticizer cannot be TEHP, but it was soluble enough in o-NPOE and bis(2-ethylhexyl) sebacate (DOS), which could have the advantage of a lower NH interaction. (g) 3-Aryl-substituted furoylthioureas of series 2 with quasi-planar fixed intramolecularly bonded structures gave long-lifetime sensors for Pb^{2+}. It is presumed that the phenyl group participates in the complex formation with Pb(II), but also with the interfering ions. Compounds of series 2 with bulky and electron-withdrawing substituents near the C=S group, which prevent interactions with the sulfur atom, should be synthesized and tested as sensors for softer ions. Compounds **2f**, **2m**, **2b** and 1,3-diphenylthiourea are the most recommended new ionophores for Pb^{2+} and Hg^{2+} sensors.

Experimental

Ionophores

Some thioureas of series 2–4 have been synthesized and reported in previous papers.[18] Identification data for such known thioureas and eighteen new ones are included in the electronic supplementary information.† Reagents for their synthesis were commercially available from Merck and Fluka (amines, furoic acid, and substituted benzoic acids) and were dried and used without further purification. NH_4SCN (Merck) was recrystallized from ethanol and kept under dry conditions. Furoyl chloride was obtained by reaction of dried furoic acid with freshly distilled $SOCl_2$ which was refluxed for 5–6 h. Excess of $SOCl_2$ was removed and furoyl chloride was distilled at normal pressure (fraction of bp 160–165 °C). Substituted furoyl chlorides and benzoyl chlorides were obtained similarly, and the excess of $SOCl_2$ removed without further distillation. Solvents (acetone, ethanol) were dried with Na_2SO_4, distilled and stored over molecular sieves. Melting points are uncorrected and were determined on a micro stage block. Elemental analyses were performed at the Instrumental Service of the Faculty of Sciences at the Autonomous University of Barcelona. FTIR spectra were recorded on a Philips Analytical PU9600 Fourier transform spectrometer. ^{1}H and ^{13}C NMR spectra were measured at 250 MHz an a Bruker AC-250F with an ASPECT 3000 computer at frequencies of 250 MHz (^{1}H) and 62.89 MHz (^{13}C) at 25 °C. Samples were dissolved in DMSO-d_6 at 5% (w/v) and TMS was used as internal reference. DEPT experiments were done with protonic pulses at 135° and 90°. Some assignments were made by HETCOR [13]C–[1]H. Detailed NMR data (including carbon types determined by DEPT experiments) are included in the supplementary information.†

General procedure for syntheses[18]

CAUTION:: many aroyl chlorides are lachrymators, especially, furoyl chloride. The crude products have a strong, foul smell. All procedures must be carried out in a well-ventilated hood. Under dry conditions, the aroyl chloride (30 mmol) was added to a solution of (30 mmol, 2.28 g) NH_4SCN in dried acetone (15 ml) with magnetic stirring, at room temperature over 10 min, after which a white precipitate of NH_4Cl appeared. Without filtration, 30 mmol of the appropriate aromatic amine in acetone (20 ml) were slowly added at room temperature (30 °C) with stirring. The recommended temperature for the addition of aliphatic primary amines is 0–5 °C and for secondary aliphatic amines −15 °C. When the mixture reached room temperature, it was refluxed for 10 min. After cooling, the reaction mixture was poured slowly into 400 ml ice–water with strong stirring. The aroylthiourea precipitated as a solid or an oily product. In the latter case, the mixture was left to stir overnight. The crude product was filtered off, dried and recrystallized (ethanol or DMF–ethanol 20 : 80), then washed with cool diethyl ether. The purity was tested by TLC (glass plates of 2.6 × 7.5 cm, 0.25 mm thick, Silica Gel G Nach Stahl −60). The

solvents used were benzene–chloroform (90 : 10) and chloroform–water (saturated). This method was used to prepare 46 aroylthioureas, which were recrystallized twice for analytical purposes. The ionophore 1,3-diphenylthiourea (Merck) was purified by double recrystallization from ethanol and dried over $CaCl_2$ for several days.

XRD measurements

The X-ray crystallographic studies for compounds **1e** and **2b**§ were done on a Bruker Smart 6000 diffractometer, $\lambda_{(Mo\ K\alpha)} = 0.71069$ Å, graphite monochromator, $T = 293$ K, $\omega/2\theta$, range $2 < \theta < 25°$. After optical alignment the cell parameters were determined by using the reflections collected on four sets of 20 frames each (program SMART[23]). Data were collected in the hemisphere mode. Data on a total of 1321 frames were used for data reduction (program SAINT-NT[24]). Corrections were made for Lorentz and polarization effects. Data were obtained by rotating φ successively by 0.3° using two different χ settings. The structure solution and refinement was performed with the program package SHELXTL-NT.[25] Non-hydrogen atoms were refined anisotropically by full-matrix least squares. Hydrogen atoms were positioned geometrically and refined using a "riding model".

Potentiometric measurements

These were made with a Cole Parmer digital potentiometer Model 59003–00, ±0.1 mV sensitivity. The reference electrode was an Orion Model 90–00–01, double-junction Ag/AgCl electrode. pH values were determined with a Cole Parmer Model 05772–20 simple junction glass electrode. LABNET Model V–20, 2–20 µl and BRAND 20–100 µl micropipettes were used.

Membrane and electrode preparations

The conventional method was employed[26,2c] for electrode preparation and calibration.

K^{pot} determinations

The fixed interference method was utilized. The detailed experimental methodology is fully described.[21]

Reagents and solutions for electrode preparation and potentiometric measurements

Standard solutions with pure water (0.1 µS cm^{-1}) and the appropriate analytical-reagent grade salts were prepared according to the literature.[9–16] Tris(2-ethylhexyl) phosphate (TEHP) was used as the solvent mediator in most cases. High molecular weight poly(vinyl chloride) (PVC) and tetrahydrofuran (THF) were purchased from Aldrich. The graphite–epoxy transductor was prepared with powdered graphite (1–2 µm) purchased from Aldrich, Araldite M4 and hardener (HR) HY5162 from Ciba-Geigy (Basel, Switzerland).

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§ CCDC reference numbers 160086 and 160087. See http://www.rsc.org/suppdata/p2/b1/b102029n for crystallographic files in .cif or other electronic format.

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