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Selenoureas for anion binding as molecular logic gates.

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The first example of molecular logic gate based on selenoureas/ anions host-guest interaction, that performs a ternary logic operation using a ¹H-NMR easy to read response output is described here. Selenoureas are very versatile receptors for anion binding, capable of forming at room temperature in solution both mono- and bi-coordinated adducts.

Classic molecular logic gates are based on molecules which are able to perform a logic operation when one (or more) chemical process acts as input and one (or more) easily detectable analytical signal acts as output. The first pioneering works in this field were reported by Aviram¹ and de Silva² almost 30 years ago. In particular, de Silva et al., realised that the binary notation, zeros and ones, and the principles of Boolean language, could be applied to chemical systems and they reported the first molecular logic AND gate using protons and sodium ions as chemical inputs and fluorescence as optical output.² Since then, many examples of molecular logic gates have been developed and the complexity of the realized logic functions has dramatically increased.³⁻⁸ Most of the described molecular logic gates are based on fluorescent chemosensors because the "OFF" or "ON" fluorescent status can be straightforwardly translated into the "0" or "1" Boolean operations. Nevertheless, Keinan et al. demonstrated that chemical shift and peak integration in ¹H-NMR spectra can be efficiently used as measurable parameters to develop an infochemical device able to perform three different operations, i) text encoding, ii) encryption of 21-digit binary numbers and their addition and subtraction, and iii) encryption

of 21-digit decimal numbers.⁹ Jurczak proposed a novel strategy for the classification of guest chirality based on the combination of artificial neural networks and anion-receptor chemistry using ¹H-NMR spectroscopy.¹⁰

Urea and thiourea moieties have been widely used for the design of artificial receptors for anion binding and sensing.¹¹⁻¹³ Recently, we proposed for the first time selenoureas as a new binding motif for anion recognition and sensing.¹⁴ Normally, ureas and thioureas act, at least in solution, as bidentate ligands for anions forming eight-membered ring with oxoanions or six-membered rings with spherical anions such as halides,^{15, 16} while, to the best of our knowledge, stable monocoordinated adducts are unknown. Following our interest in the development of selenourea-based receptors for anion binding, we designed and synthesised a new family of aromatic selenoureas L1-L3 and we compared their anion binding properties with those of the corresponding thioureas (L4-L6) and ureas (L7-L9) using ¹H-NMR spectroscopy in DMSO- d_6 (Fig. 1). We wanted to explore the possibility for selenoureas of forming mono-coordinated adducts in solution along with classic bi-coordinated ones and, therefore, the possibility to construct molecular logic gates based on the nature of the adduct formed, as illustrated hereinafter.



The synthesis of the selenoureas L1-L3 is based on the reaction of phenyl isoselenocyanate (for L1) or 1-naphtyl isoselenocyanate (for L2 and L3) with aniline (for L1 and L2) and 1-naphtylamine (for L3) in a 1:1 mixture of dry DCM and EtOH under inert atmosphere in the dark at room temperature to give the desired product in good yields (84%, 79%, and 55%, for L1, L2, and L3, respectively, see ESI for synthetic details).

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The synthesis of the isoselenocyanates was previously reported by Fernández-Bolaños et al.¹⁷ Receptors **L4-L9** were already described in the literature.¹⁸⁻²²

In order to evaluate the anion binding modes of L1-L3, as well as those of the other receptors, 1D-NMR titrations in DMSO- d_6 were performed with chloride, dihydrogenphosphate, acetate, and benzoate as their tetrabutylammonium salts. Resonances due to the selenourea NHs protons were found to shift from 10-11 ppm to higher frequencies as a consequence of the anion coordination event. Additionally, the appearance of multiple resonances in the range 10-12 ppm and of new resonances both in the aromatic range and at lower frequencies (5-6 ppm), was observed in a number of instances, suggesting the presence of more than one adduct species in solution. In order to rationalize this behaviour and to assign the new resonances, both 1D and 2D-NMR experiments were carried out in DMSO- d_6 , starting from the case of the structurally asymmetric L2 and acetate as guest anion species. This prototypical study case was chosen because during the titration, for a relatively wide range of anion added equivalents, four ¹H singlets were simultaneously present in the 10-12 ppm range together with two new singlets in the 5-6 ppm range (Fig.2a, Fig. S1 for a complete stack plot).

Due to the asymmetric structure of L2 the two signals observed at ~10 ppm in the free receptor are due to the two selenourea NHs protons. After the coalescence regime at the beginning of the titration, up to six different singlets attributable to NHs protons were observed (Fig. 2a) which could be categorized into three couples of resonances on the basis of their frequency: high (>10.5 ppm), intermediate (9.5-10.5 ppm) and low (4.5-6.0 ppm) (Fig. S2). g-COSY, TOCSY and ROESY were carried out on L2 in DMSO- d_6 in the presence of 2.5 equivalents of acetate (in this condition all the six singlets were well-resolved, see ESI and Fig S2 for a detailed description) with the aim of identifying all the species present in solution. From the results of these experiments we concluded that three different adduct species were present in solution: a bi-coordinated and two different monocoordinated adducts of L2 with acetate as shown in Fig. 2. Attribution of the NHs signals for the two mono-coordinated adducts, which are marked in red and blue in Figure 2, is inherently ambiguous, but it is important to stress here that the presence of the bi-coordinated adduct is clearly demonstrated by the presence of resonances above 11 ppm, while the presence of mono-coordinated species is unambiguously supported by resonances in the 4.5-6.0 ppm range. Among the two signals assigned to each monocoordinated adduct, the one at higher frequency (10-10.5 ppm) is attributed to the selenourea NH proton coordinating the anion, the one at the lower frequency is attributed to the non-coordinating NH (see ESI, Fig. S3).

This interpretation is also strongly supported by a previous study reported by Roberts *et al.*²³ on the interaction of simple urea, thiourea, 1,1-dimethylurea and 1,1-dimethylthiourea with acetate. It was demonstrated that the resonance frequency of the urea protons depended on their localization in space with respect to the chalcogen, with *cis* NH protons

characterized by a remarkably lower frequency than *trans* NH protons.



Fig. 2 a) ¹H-NMR spectra of free **L2**, upon addition of 0.5 equivalents of TBAACO (tetrabutylammonium acetate), and in the presence of 2.5 equivalents of TBAACO in DMSO-*d*₆; b) structures of the proposed mono and bi-coordinated adducts. Colour code: purple indicates bi-coordinated adduct, red and light blue indicate mono-coordinated adducts and the corresponding ¹H-NMR signals.

At room temperature, rotation around C-N bonds was fast enough to observe only a single time averaged resonance but, by decreasing the temperature, the two separate signals were visible in the spectrum, after the coalescence regime was overcome.²³ It was also demonstrated that by moving from oxygen to sulfur, the coalescence temperature increased as well as the frequency separation between cis and trans NH proton signals.²³ Our results seem to be consistent with this evidence and show that the trends (coalescence temperature and frequency separation) on changing the chalcogen continue also by moving further along the 16 group down to selenium. In fact, even increasing the temperature up to 330 K to speed up the rotation around the C-N bonds, we did not reach the coalescence regime for L2 (it should also be noted that our substituents in the selenourea moiety are bulkier than Robert methyls).

After these findings, we moved on to evaluate the effect of the chalcogen on the binding modes by using the asymmetric receptors L2, L5, and L8 and acetate as anion (see ESI Figs. S1 and S4). In the case of L8, upon addition of increasing amounts of acetate, the usual progressive shift of the two NHs signals was previously reported,²¹ which clearly indicated the formation of a bi-coordinated adduct and the fast (on the NMR time scale) exchange rate between the adduct and the free receptor. In the case of L5 the behaviour appeared the same (Fig. S4) but the system immediately showed a coalescence regime, indicating that the exchange rate significantly decreased when compared to L8. As reported above, in the case of the L2 (Fig. S1), we observed the formation of both the bi- and mono-coordinated adducts in equilibrium with a slow exchange rate. In the light of the above-mentioned evidence from the literature (and the correlations we found with substituents' size in the receptors as reported hereinafter), the observed differences between L8, L5, and L2, could be reasonably explained considering the increasing size of the Van der Waals radius of the chalcogen, which could change the

Journal Name

rotation barrier around the C-N bonds following the order L2>L5>L8. The effect of the chalcogen on the binding modes was also confirmed in the case of the symmetric diphenyl-substituted L1, L5, and L7 (see ESI, Fig. S5).

We then evaluated the role of the anion size and geometry on the coordination modes of selenoureas **L1-L3** by comparing chloride, dihydrogenphosphate, acetate, and benzoate. Results obtained for the prototypical case of **L2** are summarised in Table 1 and in the stack plots in the ESI (Fig. S6). Results for **L1** and **L3** are shown in Figs. S9 and S10, respectively.

Table 1 Type of adducts observed for L2 with different anions in DMSO- d_6

Anion Cl-	Mono-coordination	Bi-coordination
H ₂ PO ₄	×	\checkmark
AcO	\checkmark	\checkmark
BzO	\checkmark	\checkmark

In the case of the relatively small and spherical chloride anion, the usual progressive shift of the two selenourea NHs to higher frequency was observed only at high anion equivalents added, indicating a low binding affinity. No coalescence regime was observed, while the resonance shift presumably reflected the fast exchange rate between the free receptor and the bicoordinated adduct.

In the case of dihydrogenphosphate, after a first coalescence regime the two signals reappeared in the spectrum but located at lower frequency than those of the free receptor. Upon addition of further increasing amounts of anion, the progressive shift of the two NHs was observed, up to frequency values higher than those observed for the free receptor. This peculiar behaviour can be explained with a fast exchange rate between the two possible mono-coordinated species and the bi-coordinated adduct. The absence of resonances in the 4.5-6.0 ppm range, characteristic of monocoordinated adducts, showed that the bi-coordinated species is the dominating one, to which dihydrogenphosphate anion can evolve very rapidly from any of the two mono-coordinated forms. This is absolutely reliable if one considers the tetrahedral geometry of the anion. The presence of four oxygen atoms pointing to different directions should be able to facilitate the second coordination event even if the receptor adopts a "distorted" non-planar conformation.

The observation of distinct resonances for both mono- and bicoordinated adducts in the case of the Y-shape anions acetate and benzoate reflected the slower exchange rate between the different species formed in solution. The bulky selenium atom in the receptor should limit rotations around the C-N bonds, thus limiting the accessible conformations. As a consequence, the complementarity between the directionality of the two NHs hydrogen bond donors and the Y-shape of these anions is more difficult to be achieved when selenoureas are compared to ureas and thioureas (see ESI, Fig. S7). The bulkier benzoate, indeed, formed only one of the two possible monocoordinated adducts with **L2** because of its increased steric hindrance, which determined the preferential coordination direction on the less cluttered phenyl side of the receptor. Finally, we evaluated the effect of the substituents size in the receptors on the anion binding ability of selenoureas L1-L3, by using acetate as prototypical anion. The results are summarised in Table 2 and in the stack plots in the ESI (Fig. S9 and S10).

|--|

Receptor	Mono-coordination	Bi-coordination
L1	\checkmark	\checkmark
L2	\checkmark	\checkmark
L3	\checkmark	×

Both in the case of the di-phenyl (L1) and phenyl-naphthyl (L2) substituted receptors, resonances corresponding to both mono- and bi-coordinated adducts were observed, with the difference in the total number of NH singlets simply due to the symmetry of the receptor itself (Fig. S8a and S8b). Differently, in the case of 1,3-dinaphtylselenourea L3 we observed only the mono-coordinated species (Fig. S8c). In the light of all the collected evidence, this difference is clearly due to the increased steric hindrance provided by the two aryl substituents, making the formation of the bi-coordinated adduct particularly unfavourable. We performed ¹H-NMR titrations also with receptors L4-L9 and all the anions considered and we observed only the formation of the bicoordinated adducts. It is worth noticing that we did not observed any relevant variation in the Uv-Vis and the fluorescent properties of receptors L1-L3 upon addition of the anions investigated.

The results obtained can be summarised in a truth table (Table 3) where the input are i) the nature of the chalcogen (0, 1, 2 for oxygen, sulphur and selenium, respectively), ii) the steric hindrance of the aryl substituents at the urea moiety (0, 1, and 2 for diphenyl, phenyl-naphtyl, and di-naphtyl, respectively), and iii) the geometry of the anion (0, 1, 2, 3, for spherical chloride, tetrahedral dihydrogenphosphate, Y-shape acetate, and bulky Y-shape benzoate, respectively), while the output are the type of adducts formed identified on the base of ¹H-NMR signals (0, 1, 2, for only mono-coordinated, both monoand bi-coordinated, and only bi-coordinated, respectively). It is clear, that only selenoureas are able to give multiple response depending on the anion and on the aryl substituents considered. The output type in Table 3 can be easily determined using the flowchart in Fig. 3, which also provides the basis to implement the automatic NMR spectral analysis for the interactions of the receptors and anions investigated in the paper.

In conclusion, we showed that when compared to ureas and thioureas, selenoureas appear to be more versatile receptors for anion binding, capable of forming at room temperature in solution both mono- and bi-coordinated adducts depending on the geometry of the bound anion and the steric hindrance exerted by the chalcogen itself and the substituents on the urea moiety. This is reflected also on the increase of the NMR coalescence temperature that facilitate the easy detection of the mono-coordinated adduct in solution at room temperature. As a consequence, on using i) the steric ChemCommargins

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hindrance of the aryl substituents in selenoureas, and ii) the geometry of the anion guest as inputs, a molecular logic gate can be easily developed following ¹H-NMR signals of the adducts formed as chemical outputs.

Table 3 Truth table based on the interactions between receptors and anions investigated in this work.

Input		
Substituents ^b	Anion shape ^c	
0, 1, 2	0,1, 2,3	2
0, 1, 2	0,1, 2,3	2
0	0	2
0	1	2
0	2	1
0	3	1
1	0	2
1	1	2
1	2	1
1	3	0
2	0	2
2	1	2
2	2	0
	Substituents ^b 0, 1, 2 0, 1, 2 0 0 0 0 1 1 1 1 2 2 2 2	Substituents ^b Anion shape ^c 0, 1, 2 0,1, 2,3 0, 1, 2 0,1, 2,3 0 0 0 1 0 2 0 3 1 0 1 2 1 3 2 0 3 1 1 2 1 3 2 0 2 1 2 2

^aTernary input: 0, oxygen; 1, sulfur; 2, selenium.

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^bTernary input: 0, di-phenyl; 1, phenyl-naphthyl; 2, di-naphthyl. ^cQuaternary input: 0, spherical; 1, tetrahedral; 2, small Yshaped; 3, bulky Y-shaped.

^dTernary output: 0, only mono-coordination; 1, both mono- and bi-coordination; 2, only bi-coordination.



Figure 3 Explicative flowchart to implement automatic spectra analysis of the receptors $\mbox{L1-L3}$ in the presence of Cl[°], H_2PO4[°], CH₃COO[°] and Ph-COO[°].

The investigated series of selenoureas/anions thus, represents, to the best of our knowledge, the first example of molecular logic gate using the urea– based receptors for anions, that performs a ternary logic operation based on a ¹H-NMR easy to read response.

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22.