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CALIX[4]ARENE UREA DERIVATIVES: THE PATHWAY FROM FUNDAMENTAL STUDIES TO THE SELECTIVE REMOVAL OF FLUORIDES AND PHOSPHATES FROM WATER

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Graphical Abstract:

HIGHLIGHTS

- Selectivity vs hosting capacity of receptors first addressed in carrier mediated ion extraction processes.
- The impact of fundamental studies in searching for applications.
- Counter-ion effect on the fluoride/phosphate removal from water by Molecular Simulation

ABSTRACT

Wet processes of phosphoric acids produce untreated wastewater containing large amounts of fluoride leading to serious environmental problems. This paper reports fundamental studies on two lower rim functionalised calix[4]arene based receptors namely **1**, 5, 11, 17, 23 tetra-tert-butyl, 25, 27 bis [diethylphenylurea]ethoxy, **2**, 26, 28 dihydroxycalix[4]arene, **2** and their ionic interactions. It is shown that these receptors only interact with fluoride and phosphate in acetonitrile. Their receptive properties are higher for phosphate (2:1 anion:receptor complex) relative to fluoride (1:1 complex). However thermodynamics shows that

these receptors are more selective for fluoride relative to phosphate in the formation of the 1:1 complex. The pathway from fundamental studies to the use of these receptors for removing these anions from water has been tested. The receptive properties of **1** for phosphate are held when the extraction involves aqueous solutions containing individual ions. However in mixtures containing both anions, the kinetics of the process and the selectivity of **1** for fluoride predominate and as a result, fluoride is better extracted than phosphate. The counter-ion effect on the removal process is assessed from Molecular Simulation studies. The removal of fluoride from phosphate is discussed taking into account existing technologies.

Key words: Fluoride, Phosphate, Extraction, Selectivity, Hosting Capacity.

1. INTRODUCTION

The phosphate fertilizer industry produces hazardous and acidic waste. Effluents are characterised by high concentrations of fluoride (F^-) and phosphates. About two hundred million people around the World [1] are affected by fluorosis [2,3]. Health problems associated with the presence of F^- in water have been extensively discussed [4, 5]. Technologies for removing F^- from water have been reported including their scope and limitations [4]. It was concluded that all technologies available have some limitations and therefore there is not a universal technology for this purpose. The presence of phosphates in fluorinated water add more complexity to the removal process. Technological approaches for removing these two anions from water often involve several steps or materials used are non-selective or the proposed approach is very costly [6-13]. Selective supramolecular receptors for their removal have not been explored. Danil de Namor [14] has discussed the problems associated with the presence of F^- in water and the need for new removal technologies. It is known that a large discharge of F^- is produced by untreated wastewater [15].

We have previously reported calix[4]pyrrole based materials for removing F^- from water [16-19]. While calixpyrroles are mostly known as anion selective receptors, calixarenes have been mainly used as cation complexing agents [20]. However in both cases their binding properties are dependent on the functional groups attached to these receptors.

A number of calix[4]arene derivatives have been explored for the removal of phosphates and chromates [21,22] as well as for the removal of phosphates and hydrogen sulphate [23] from water but we are not aware of the use of calix[4] based macrocycles for the remediation of phosphates and F^- from water. Upper and lower rim calix[4]arene urea derivatives have been the subject of numerous investigations mainly concerned with their ability to form dimeric capsules as well as topologically new molecules [24-28]. Other contributions are their use as anion complexing agents [29-33]. This paper reports i) synthesis and characterisation of two new calix[4]arene derivatives, namely **5**, **11**, **17**, **23** tetra-*tert*-butyl, **25**, **27** bis[diethylphenylurea]ethoxy, **26**, **28** dihydroxycalix[4]arene, **1** and **25**, **27** bis[diethylphenylurea]ethoxy, **26**, **28** dihydroxycalix[4]arene, **2** .ii) structural, electrochemical and thermodynamic characterisation on their complexation with phosphate and F^- iii) the extraction properties of **1** for F^- and phosphates (individually and mixed) in water.

Scheme 1

2. EXPERIMENTAL

2.1 Chemicals

For chemicals, their source and purification see Supplementary Material.

2.2 Synthesis of **1** and **2** and Characterisation [34-37]

Scheme 2 shows the synthetic route for the preparation of **1**. The same procedure was followed for **2** prior de-*tert*-butylation of the *p*-substituted calix[4]arene. Synthetic details and characterisation are given as Supplementary Material.

Scheme 2

2.3 NMR studies

¹H NMR and ¹³C NMR studies were performed on a 500 MHz Bruker AVANCE NMR spectrometer.

The complexation of **1** and **2** towards cations (alkali, alkaline-earth, transition and heavy metals) and anions (halides, nitrate, phosphate, sulphate) in the appropriate solvents were investigated using ¹H NMR. Complexation was checked by adding cation or anion salt solution (1.0×10^{-3} - 3.0×10^{-2} mol.dm⁻³) into the NMR tube containing the ligand in CD₃CN (1.0×10^{-4} - 3.0×10^{-3} mol.dm⁻³). Proton chemical shifts of free and complex ligand were measured. For ¹H NMR titrations, gradual additions of anionic species in CD₃CN were made into a NMR tube containing **1** dissolved in CD₃CN, then the ¹H NMR spectrum was acquired. Chemical shifts of complexed receptor were compared to those of free ligand.

2.4 Conductometric studies

The cell constant was determined as described elsewhere [38]. Concentration ranges of ligands and ionic species were 8×10^{-4} – 1×10^{-3} and 5×10^{-5} – 1×10^{-4} mol.dm⁻³ respectively.

2.5 Calorimetric titrations

The NANO ITC (isothermal titration calorimeter) was used to determine the stability constant, log K_s and enthalpy of complexation, Δ_cH, of **1** and **2** with ionic species in MeCN at 298.15 K. The reliability of the instrument was checked by using a standard reaction as described elsewhere [39].

For calorimetric titrations of **1** and **2** with anions in MeCN, a solution of the ionic species (1×10^{-2} – 2×10^{-2} mol.dm⁻³) was titrated incrementally into the sample cell containing the ligand (1 cm³, 1×10^{-3} – 5×10^{-3} mol.dm⁻³) in the same solvent. Individual peaks in the thermogram were integrated by the instrument software and presented in a Wiseman plot. Corrections for heats of dilution were made.

2.6 Molecular modelling studies

Molecular simulation studies were carried out using the MOE 2015.10 software [40]. Energy minimisation of complexes and ligands was carried out using the AMBER10:EHT force field [41,42]. Initially 3D structures of **1** and **2** were built using the Builder module of MOE 2015.10 software and Low

Mode Molecular Dynamics simulation [43] was used to find the lowest energy conformation. Ions were built separately and complexed to ligands followed by energy minimisation of the complex.

2.7 Extraction of anions by **1**

The determination of optimum pH, mass of material and uptake capacity of **1** for removing anionic species from aqueous solutions as well as the kinetics and the effect of temperature on the removal process are described in the Supplementary Material.

2.8 Recycling of the receptor

This was carried out by treating the loaded receptor with HCl 0.1 mol.dm⁻³

3. RESULTS AND DISCUSSION

3.1 Structural Characterisation of **1** and **2**

Receptors **1** and **2** were characterised by 1D (¹H and ¹³C) and 2D (HSQC, HMBC and COSY) NMR Spectroscopy, microanalysis and Mass Spectrometry (see Supplementary Material).

3.2 Complexing properties of **1** and **2** with ions

The complexing properties of **1** and **2** in acetonitrile (dipolar aprotic solvent) and methanol (protic) were assessed by ¹H NMR, conductometry and calorimetry.

3.2.1 ¹H NMR measurements

No significant chemical shift changes of **1** were observed upon addition of cation salts. Among anions, **1** interacts selectively with F⁻ and H₂PO₄⁻ as tetra-n-butylammonium salts in CD₃CN. For F⁻, downfield chemical shift changes relative to the free ligand were observed for the equatorial proton 1' (0.17 ppm), protons 5'''/9''' (0.25 ppm) while the hydroxyl (H-1) and the NH protons (2''' and 3''') could not be calculated due to broadness of the NH (urea group) and the OH signals (lower rim). These findings are indicative of a strong interaction between this anion and these functional groups through hydrogen bond formation in CD₃CN. As for H₂PO₄⁻, interactions were significant to an extent that it was not possible to follow the chemical shift changes in protons 1, 2'''-3'''. Downfield chemical shifts for the equatorial proton 1' (0.11 ppm) and 5''' and 9''' (0.22 ppm) were lower than those observed for F⁻ and **1** in this solvent.

To gain more insight into the nature of these interactions, ¹H NMR titrations were carried out with the interacting ions. Thus chemical shift changes for H-5''' and H-9''' were chosen given that the NH protons of urea functional groups could not be traced in the ¹H NMR spectrum. Regarding the titration of **1** with F⁻ in CD₃CN, chemical shift changes of the H-5'''/9''' proton resonances of **1** are plotted against anion/ligand molar ratios (Fig.1).

Fig. 1

Significant downfield changes are observed which are more pronounced upon increasing the amount of F⁻ added until a concentration ratio of 1 is reached and then no further changes are observed. These results indicate formation of a 1:1 (**1**: F⁻) complex in CD₃CN. A different picture emerges from the titration of **1** with phosphate in CD₃CN (Fig. 2).

Fig. 2

No significant shift changes are observed for these protons until the concentration ratio of 1 is reached. Further addition of phosphate leads to significant downfield chemical shift changes in the H-5'''/H-9''' protons of the phenyl urea ring until the anion: receptor ratio reaches 2 where no further changes were observed. This outcome indicates that **1** has a greater capacity for phosphate relative to F⁻. The uptake of two anions per ligand requires a rearrangement of the receptor arms in order to limit the closeness of approach of ions and in this way avoids repulsive forces.

No complexation of **1** with ions in CD₃OD was observed, demonstrating once again the solvent effect on ion-calixarene complexation processes. To explain these data, ¹H NMR measurements in CD₃CN and CD₃OD were carried out and chemical shift changes relative to CDCl₃ were calculated. Significant de-shielding effects were observed for the aromatic protons (H-3/5 = 0.20 ppm) and (H-3''/5'' = 0.20 ppm) in CD₃CN relative to CDCl₃ while hardly any changes were observed in CD₃OD relative to the reference solvent. A similar effect was found for the calix(4)arene tetraester and was attributed to interaction of acetonitrile with the hydrophobic cavity of the ligand [44-46]. Moreover Danil-de-Namor and co-workers [47, 48] isolated a calix(4)arene derivative from DMF and from MeCN and X-ray diffraction studies were performed. Recrystallization from MeCN led to the formation of an adduct with the solvent sitting in the hydrophobic cavity of the ligand and in this way exerting an 'allosteric effect' on the hydrophilic cavity by which the latter is better pre-organised to interact with cations.

¹H NMR studies of **2** and ionic species showed an analogous behaviour to that for **1** in that no interaction was observed with any cation in CD₃CN. Amongst the choice of anions, **2** only interacts with F⁻ and H₂PO₄⁻. The specific resonances for protons 2'''-NH, 3'''-NH and 1-OH of the complex could not be calculated due to the broadness of the NH signals of the urea group and the OH signal of the lower rim. In the case of F⁻ it was not possible to follow the chemical shifts of most proton resonances due to the effect of the environment which led to an unreadable spectrum. As for the H₂PO₄⁻ anion, downfield chemical shift changes were found for the equatorial (1' = 0.12 ppm), 1''' (0.11 ppm) and 5'''/9''' (0.28 ppm) protons. The interactions again were significant to an extent that it was not possible to follow the chemical shifts changes in protons 2'''-NH, 3'''-NH and 1-OH. In a similar way for **1**, no interaction was found between **2** and these anions in CD₃OD. ¹H NMR measurements of **2** in CD₃CN and CD₃OD, were performed and the chemical shift changes relative to CDCl₃ were calculated. While hardly any chemical shift changes were observed in moving from the reference solvent to CD₃OD, a remarkable downfield chemical shift change was observed in the aromatic proton 4 (0.54 ppm) in CD₃CN relative to CDCl₃. Quite clearly the absence of *t*-butyl groups in the *para* position makes this aromatic proton more exposed to interact with the solvent and as a result of pre-organisation of the hydrophilic cavity, anion-ligand interactions occur.

3.2.2 Conductometric titrations

To corroborate the composition of the complex and to assess qualitatively the strength of anion-receptor interaction conductometric titrations were carried out. Representative curves (molar conductance, Λ_m , against ligand : anion ratios) for the titration of F⁻ and H₂PO₄⁻ and **1** in acetonitrile (Fig. 3) corroborate the stoichiometry of the complexes obtained from ¹H NMR titration, in that this

ligand hosts a unit of F^- while two units of $H_2PO_4^-$ are taken up by **1** in this solvent. The same pattern was observed for these ions and **2** in acetonitrile.

Fig.3

In addition complexes of moderate stability are formed with the usual pattern of a decrease in conductance from A to B and almost constant values from B to C. Based on these results we proceeded with direct calorimetric titrations of these systems to have a quantitative assessment of the strength of complexation and to identify whether these processes are enthalpy or entropy controlled [20]

3.2.3 Thermodynamic parameters of complexation of **1** and anions in acetonitrile at 298.15

Titration calorimetry was implemented to compute the stability constant, K_s (expressed as $\log K_s$) and enthalpy, $\Delta_c H$ and thus derive the thermodynamic parameters of complexation for the systems under investigation. Results are listed in Table 1.

For fluoride these are referred to the process,

For dihydrogen phosphate, data refer to the following processes

From stability constant data, the standard Gibbs energies of complexation were calculated (eqn. 4). K_s values are referred to the standard state of 1 mol dm⁻³ (units are cancelled).

$$\Delta_c G^\circ = -RT \ln K_s \quad \text{eqn.4}$$

In this equation, R and T are the gas constant and temperature (Kelvin) respectively. The entropy of complexation was calculated from eqn.5

$$\Delta_c G^\circ = \Delta_c H^\circ - T\Delta_c S^\circ \quad \text{eqn.5}$$

For interpretation of thermodynamic data of **1** with F^- , single-ion values for transferring the anion from water (protic) to MeCN (dipolar aprotic)[43] are considered. Thus $\Delta_t S^\circ [F^-] (H_2O \rightarrow MeCN) = -134 \text{ J.K}^{-1}.\text{mol}^{-1}$ (data based on the Ph_4AsBPh_4 convention) [50,51] is large and negative. In the complexation process, the reverse situation occurs, in that F^- is transferred from MeCN to a protic host (the urea groups of **1**) and this process is entropically favoured. On the other hand, **1** interacts with MeCN as shown by the downfield shifts observed for the aromatic protons of **1** in moving from $CDCl_3$ to CD_3CN . The de-solvation of the receptor upon complexation will also lead to a favourable entropy. Both processes appear to overcome the unfavourable entropy resulting from conversion of two components (receptor and anion) into a single one (complex). A similar situation occurs with the enthalpy, in that the $\Delta_t H^\circ F^- (H_2O \rightarrow MeCN) = 30 \text{ kJ.mol}^{-1}$ (data based on the Ph_4AsBPh_4) is enthalpically unfavoured, while the opposite is observed in Table 1. In addition, energy will be required for the de-solvation of the receptor (endothermic process). The complexation process involving the host-ion binding is expected to be exothermic. These individual processes are likely to contribute to the

$\Delta_c H^\circ$ of F^- and **1** in MeCN. As a result, the process is slightly exothermic. Consequently both parameters contribute favourably to $\Delta_c G^\circ$ but the process is entropically controlled. For phosphate, thermodynamic data fits into a 1:2 (ligand:anion) model where K_{s1} is enthalpically controlled and entropically unfavoured while K_{s2} is entropically controlled and enthalpically unfavoured. Molecular simulation studies (Fig.4) show that the conformation of lowest energy (greater stability) is that in which the first dihydrogen phosphate anion enters interaction with the pendent arm containing the urea functionality through hydrogen bond formation.

Fig 4.

As a result the process is enthalpically favourable (exothermic) and takes place with a loss of entropy resulting from the interaction of two separate entities (anion and receptor) to give a single unit (anionic complex). The molecular simulation model suggests that interaction also takes place between the second phosphate anion and **1** and occurs in the remaining pendent arm of the receptor. It seems reasonable to consider that the entrance of a second anion requires the pendent arms to increase the distance between them so as to avoid repulsive forces originated by the presence of two anions within the same receptor and may lead to a breakage of the hydrogen bonds between the unsubstituted hydroxylphenols [52]. This process requires energy. Subsequently the exothermicity of the process will decrease significantly relative to the fluoride-**1** system. This interpretation is supported by the data shown in Table 1. Therefore the process is enthalpically stable but entropy controlled. Complexation thermodynamics of **2** and anions in acetonitrile (Table 1) reflects a similar pattern to that observed for the **1**- F^- system in acetonitrile. However the complex stability of **2**- F^- is lower than that of the former receptor. This is expected given that removal of *p*-*tert*-butyl groups in moving from **1** to **2** decreases the rigidity of the receptor and therefore the stability of the complex. The more favourable entropic contribution for **1** relative to **2** must be attributed to the higher de-solvation of F^- in its interaction with **1** relative to **2**. It is indeed the entropy contribution which leads to a higher stability of **1** and F^- given that the enthalpy contribution is approximately the same for both ligands and F^- in this solvent. Complexes of **1** and **2** with phosphate in MeCN show similar stabilities (hence Gibbs energy) but differ significantly in the enthalpy and entropy contributions as a result of an entropy-enthalpy compensation effect [53]. Thus while the **1**- $H_2PO_4^-$ is enthalpically favoured and takes place with an entropy loss, the opposite is shown for **2**- $H_2PO_4^-$. It is the greater flexibility of the latter receptor which leads to a more favourable entropy and a lower enthalpic stability than that found for **1** and this anion in the formation of 1:1 and 1:2 complexes in acetonitrile. In both cases these processes are enthalpically and entropically favoured but entropy controlled.

In summary the thermodynamic data demonstrate the role of the receptor rigidity in controlling the higher stability of **1 relative to **2** for the fluoride ion.**

3.4 APPLICATIONS

3.4.1 Extraction experiments

Based on the above results the extraction ability of **1** (representative receptor) for the removal of F^- and $H_2PO_4^-$ from water was investigated. Given that **1** is not water soluble, the ligand in the solid state was used for extracting these anions. Thus the following factors were considered.

Fig. 5

The pH effect on the uptake of phosphate from water by **1** is shown in Fig. 5 where the maximum percentage of phosphate extracted from water by **1** occurs at pH = 6.8. Taking into account the dissociation constants of H₃PO₄ in water at 298.15 K [54] ($pK_{a1}=2.15$, $pK_{a2}=7.20$, $pK_{a3}=12.38$), it follows that at this pH, H₂PO₄⁻ predominates in solution. As the amount of HPO₄²⁻ increases the % E decreases. Therefore a pH of 6.8 was used for extracting phosphate from water. Fig. 6 shows that the % of anion extracted increases as **the mass of the material** increases, due to the increase of binding sites with increasing the amount of material until the receptor is saturated. Thus 51 % of fluoride is extracted by using 6.6 g of **1** per dm³ of solution, while the amount of phosphate extracted for the same solid: solution ratio was 82 %.

Fig. 6

The uptake capacity of anions per unit of mass of material (mmol/g) was calculated by eqn 9

$$Q_{eq} = \frac{C_i - C_{eq} \times V}{m} \quad \text{eqn.9}$$

where, Q_{eq} , C_i , C_{eq} , V , and m denote uptake capacity (mmol/g), initial concentration of anion salt in water (mmol/dm³), equilibrium concentration of anion in water (mmol/dm³), volume of solution (cm³) and mass of material (g) respectively. Thus the **removal capacity of 1** (amount of fluoride taken up per gram of material) is 0.75 mmol/g for fluoride, while for phosphate it is 1.27 mmol/g, approximately twice the capacity for fluoride. These results are linked to the fact that **1** takes 2 phosphate ions per unit of ligand relative to fluoride (1 ion per unit of ligand) and demonstrate the impact of thermodynamics (fundamental studies) on the application of these receptors either as decontaminating agents or indeed for designing ion selective electrodes. These findings lead to an important issue to address which is the distinction between **selectivity** and **hosting ability of the receptor** for assessing which of these features predominate in the extraction process when the two anions are present in aqueous solution and this is discussed below. Another point to stress is **the counter-ion effect** on the removal process. While thermodynamic data of complexation are independent of the counter-ion (salt fully dissociated as extensively discussed elsewhere [20]), this is not the case in the extraction process where electro-neutrality requires anion and cation extracted by the solid neutral material. In **real water samples**, cations such as sodium are likely to serve as counter-ions instead of Bu₄N⁺. The lowest energy conformation of **1** was -102.54 kcal/mol and for **2** was -79.73 kcal/mol, showing that **1** has the lowest energy. Minimum energies using the AMBER10:EHT Force field for compounds plus ligand and counter-ion (Table 2) and images of the complexes formed (Fig. 4) show a clear preference in **1** for Bu₄N⁺ over Na⁺ in di-hydrogenphosphate and sodium over tetra-n-butylammonium for fluoride. For **2** it is again Bu₄N⁺ over Na⁺ in di-hydrogenphosphate but in this case it is Bu₄N⁺ over Na⁺ in fluoride.

Fig. 7

Furthermore the fact that the receptor in the solid state is able to extract selectively these ions as observed in MeCN may indicate that the conformation of **1** in the solid state may not differ significantly from that in acetonitrile.

The **effect of the temperature** on the extraction process was investigated.

Fig.8

Fig. 8 shows an increase in the removal capacity of the material by increasing temperature, in both cases, these processes are endothermic. Given the limitations of the van't Hoff equation [20] only apparent enthalpy values of 5.3 and 3.3 kJ/mol for fluoride and phosphate respectively were calculated.

Extraction experiments were not specifically designed to obtain detailed **kinetic information** on the process, and there was not a lot of data over the region in which the extraction went from zero to maximum. Nevertheless, the rate of uptake of these species was independent of the stirring rate and gave information about the timescale of the process. It was assumed that this is a first order reaction where the rate of uptake of these ionic species is proportional to the distance from equilibrium. Data were fitted to an exponential. The best fit line corresponds to a half-life of 12.79 min for fluoride and 10.72 min for dihydrogen phosphate while the rates of extraction were 0.05 and 0.06 s⁻¹ respectively.

The results obtained by equilibrating the material with aqueous solutions containing both anions (6.8.10⁻⁵mol.dm⁻³each) showed that the uptake of fluoride (41 %) was higher than that of phosphate (33 %). The trend obtained follows the selective behaviour of this receptor for fluoride relative to phosphate which is the pattern followed in the formation of 1:1 complexes (see Table 1). This is again in accord with the kinetics of the process. As discussed above the extraction of fluoride by this material is faster relative to phosphate

3.3 Comparison with other technologies

No previous work has been reported on the use of macrocycles for removing fluorides from phosphates when both are in solution. These have been investigated separately. The two technologies available are those reported by Gouider *et.al* [6] and by Yousefi *et.al* [7] The former involves an integrated approach consisting of co-precipitation of fluoride and phosphate from aqueous medium by lime (twelve hours) followed by a two phase biological treatment for removing the remaining phosphorous which requires a number of steps, taking a period of 160 days. The treatment reported by Yousefi uses nano-filtration which is expensive due to the energetic requirements and cost of membranes which is higher than those used in reverse osmosis. We are strongly of the view that the use of an easily recyclable and selective material offers advantages for the removal of fluorides from phosphates and should be further explored.

3. FINAL CONCLUSIONS

This paper demonstrates that a systematic investigation on the receptor-ion binding properties through fundamental studies is a crucial step to rationalise the extracting properties of these receptors for ions. Indeed availability of thermodynamic and kinetic information lead to the conclusion that the

selectivity rather than the **hosting capacity** of the receptor for a given ion controls the higher extraction observed for fluoride relative to phosphate when the two anions are present in solution. Molecular simulation studies disclose the effect of the counter-ion on the extraction process suggesting that Na^+ (commonly found in water) rather than Bu_4N^+ enhances the extraction of fluoride from water. In addition the fact that through a pH switching mechanism the receptor can be recycled calls upon the need to proceed with further investigations. In fact at pH 1 the material can be recycled several times with a decrease in capacity not higher than 5 %.

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REFERENCES

- [1] A. Amairaj, A. Pius, Health risk from fluoride exposure of a population in selected areas of Tamil Nadu South India, *Food Science and Human Wellness* 2 (2013) 75-86.
- [2] N. Kakumanu, S. D. Rao, Skeletal fluorosis due to excessive tea drinking, *N Engl. J. Med.* 368 (2013) 1140.
- [3] D.T. Waugh, W. Potter, H. Limeback, M. Godfrey, Risk assessment of fluoride intake from tea in the Republic of Ireland and its implications for public health and water fluoridation, *Int. J. Environ. Res. Public Health* 13 (2016) 1-22
- [4] P. C. Podgorny, L. McLaren, Public perceptions and scientific evidence for perceived harms/risks of community water fluoridation: An examination of online comments of pertaining to fluoridation cessation in Calgary in 2011, *Can. J. Public Health* 106 (2015) e413-e425.
- [5] S. Peckham, N. Awofeso, Water fluoridation: a critical review of the physiological effects of ingested fluoride as a public health intervention, *Sci. World J* 2014 (2014) 1-10.
- [6] M.Gouider, N. Mlaik, M. Feki, S. Sayadi, Integrated physicochemical and biological treatment process for fluoride and phosphorus removal from fertilizer plant wastewater, *Water Environ. Res.* 83 (2011) 731-738.
- [7] N. Yousefi, A. Fatehizadeh, K. Ghadiri, N. Mirzaei, S. D. Ashrafi, A. H. Mahvi, Application of nanofilter in removal of phosphate, fluoride and nitrite from groundwater, *Desalin Water Treat.* 57 (2016) 11782-11788.
- [8] B. Warmadewanthi, J.C. Liu, Selective separation of phosphate and fluoride from semiconductor wastewater, *Water Sci. Technol.* 59 (2009) 2047-2053
- [9] B. D. Turner, P. J. Binning, S. W. Sloan, Impact of phosphate on fluoride removal by calcite, *Environ. Eng. Sci.* 27 (2010) 643-650
- [10] D. Dolar, K. Košutić, B. Vučić, RO/NF treatment of wastewater from fertilizer factory—Removal of fluoride and phosphate, *Desalination*, 265 (2011), 237-241
- [11] H. Deng, X. Yu, Adsorption of fluoride, arsenate and phosphate in aqueous solution by Cerium Impregnated fibrous protein, *Chem. Eng. J.* 184 (2012) 205-212
- [12] T. Nur, M.A.H. Johir, P. Loganathan, S. Vigneswaran, J. Kandasamy, Effectiveness of purolite A500PS and A520E ion exchange resins on the removal of nitrate and phosphate from synthetic water, *Desalination and Water Treatment* 47(2012) 50 -58.
- [13] T. Kanno, J. Horiuchi, Simultaneous removal behaviour of phosphate and fluoride ions in the presence of scallop shell, *J. Chem. Eng. Japan*, 48 (2015) 276-280

- [14] A. F. Danil de Namor, The Fluoride Dilemma. Thermodynamics of anion recognition by calixpyrroles, *J. Therm. Anal. Calorim.* 87(2007) 7-14.
- [15] B. Grzmil, J. Wronkowski, Removal of phosphates and fluorides from industrial wastewater, *Desalination* 189 (2006) 261-268.
- [16] A. F. Danil de Namor, M. Shehab, Selective recognition of halide anions by calix[4]pyrrole: a detailed thermodynamic study, *J. Phys. Chem. B* 10 (2003) 6462-6468.
- [17] A. F. Danil de Namor, M. Shehab, Recognition of a biologically and environmentally important anion (dihydrogen phosphate) by calix[4]pyrrole: thermodynamic aspects, *J. Phys. Chem. B* 108 (2004) 7324-7330.
- [18] A.F. Danil de Namor, M. Shehab, Double-cavity calix[4]pyrrole derivative with enhanced capacity for the fluoride anion, *J. Phys. Chem.* 109 (2005) 17440-17444.
- [19] A. F. Danil de Namor, M. Shehab, R. Khalife, I. Abbas, Modified calix[4]pyrrole receptor: solution thermodynamics of anion complexation and a preliminary account on the phosphate extraction ability of its oligomer, *J. Phys. Chem. B* 111 (2007) 12177-12184.
- [20] A. F. Danil de Namor, R. M. Cleverley, M. L. Zapata Ormachea, Thermodynamics of calixarene chemistry, *Chem. Rev.* 98 (1998) 2495-2526.
- [21] Ş. Ertul, M. Bayrakci, M. Yilmaz, Removal of chromate and phosphate anion from aqueous solutions using calix[4]arene receptors containing proton switchable units, *J. Hazard. Mater.* 181 (2010) 1059-1065.
- [22] Ş. Yigiter, M. Bayrakci, Ş. Ertul, M. Yilmaz, Synthesis of novel silica gel immobilized-calix [4] arene amide ionophores and their anion binding abilities toward phosphate and chromate anions, *J. Appl. Polym. Sci.* 124 (2011) 3831-3839.
- [23] B. Kendi, H. N. Naziroglu, M. Yilmaz, A. Sirit, Synthesis and anion binding properties of diamide derivatives of p-tert-Butylcalix[4]arene, *J. Macromol. Science Part A*, 47 (2010) 225-229.
- [24] K. D. Shimizu, J. Rebek, Synthesis and assembly of self-complementary calix[4]arenes, *Proc. Natl. Acad. Sci.* 92 (1995) 12403-12407.
- [25] P. M. Marcos, C. S. Proenga, F. A. Teixeira, J. R. Ascenso, R. J. Bernardino, P. J. Cragg, Synthesis, NMR and DFT conformational studies of homooxacalixarene (cyano propyl) oxy derivatives, precursors to urea –terminated compounds, *Tetrahedron* 69 (2013) 7430-7437.
- [26] C. Perez-Casas, H. Höpfl, A. K. Yatsimirsky, Structures of urea/thiourea 1,3 di-substituted thiacalixarenes and corresponding monofunctional receptors and their anion recognition properties, *J. Incl. Phenom. Macrocycl. Chem.* 68 (2010) 387-398.

- [27] Y. Rudzevich, A. Bogdan, M. O. Vysotsky, V. Böhmer, Tetraurea calix[4]arenes: From dimeric capsules to topological novel molecules, in: J. Vicens, J. Harrowfield (Eds.), *Calixarenes in the Nanoworld*, Springer, France, 2007, pp. 21-46.
- [28] P. Ballester, G. Gil-Ramírez, Self-assembly of dimeric tetraurea calix[4]pyrrole capsules, *Proc. Natl. Acad. Sci.* 106 (2009) 10455-10459.
- [29] X. Wang, Z. Zhao, B. Chen, X. Li, M. Liu, Microwave assisted synthesis of bidentate chiral unsymmetrical urea derivatives of *p*-tert-butyl calix[4]arene and their anion recognition properties, *J Chem. Res.* 39 (2015) 251-310.
- [30] I. Vatsouro, E. Alt, M. Vysotsky, V. Böhmer, Guest exchange in dimeric capsules formed by tetra-urea calix[4]arenes, *Org. Biomol. Chem.* 6 (2008) 998-1003.
- [31] K.C. Nam, J. C. Chun, S. O. Kang, S. W. Ko, Upper rim urea derivative of calix[4]arene: anion selective neutral receptor, *Bull. Korean Chem. Soc.* 20 (1999) 1108-1110.
- [32] J. Budka, P. Lhoták, V. Michlová, I. Stibor, Urea derivatives of calix[4]arene 1,3-alternate: an anion receptor with profound negative allosteric effect, *Tetrahedron Lett.* 42 (2001) 1583-1586.
- [33] Y. S. Yang, S. W. Ko, I. H. Song, B. J. Ryu, K. C. Nam, Synthesis and anion binding properties of the bridged urea derivatives of calix[4]arene, *Bull. Korean Chem. Soc.* 24 (2003) 681-683.
- [34] R. V. Rodik, V. I. Boyko, V. I. Kalchenko, Calixarenes in biotechnology and biomedical research, in: A. Rahman, M. I. Choudhary, A. B. Reitz (Eds.), *Frontiers in Medicinal Chemistry*, Bentham Science Publishers, Ukraine, 2016, pp 206-231.
- [35] W. C. Zhang, Synthesis of 4-tert-butylcalix[4]arenes bearing two schiff-base units at the lower rim, *Synthesis* 9 (1997) 1073-1076.
- [36] A. F. Danil de Namor, L. E. Pulcha-Salazar, M. A. Llosa-Tanco, D. Kowalska, J. Villanueva-Salas, R. A. Schulz, Solution and co-ordination enthalpies (solid state) of lithium and sodium macrocycle (ethyl *p*-tert-butylcalix(4)arene tetraethanoate, cryptand 222 and crown ethers) systems, *J. Chem. Soc. Faraday Trans.* 94 (1998) 3111-3115.
- [37] C. D. Gutsche, L. G. Lin, Calixarene 12: the synthesis of functionalized calixarene, *Tetrahedron* 42 (1986) 1633-1640.
- [38] A. F. Danil de Namor, A. El Gamouz, S. Alharthi, N. Al Hakawati, J. R. Varcoe, A ditopic calix[4]pyrrole amide derivative: highlighting the importance of fundamental studies and the use of NaPh4B as additive in the design and applications of mercury(ii) ion selective electrodes., *J. Mater. Chem. A* 3 (2015) 13016-13030.

- [39] L. E. Briggner, I. Wadsö, Test and calibration processes for microcalorimeters, with special reference to heat conduction instruments used with aqueous systems, *J. Biochem. Biophys. Methods* 22 (1991) 101-118.
- [40] Molecular Operating Environment (MOE), 2013.08, Chemical Computing Group ULC, 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7, 2017.
https://www.chemcomp.com/MOE-Molecular_Operating_Environment.htm.
- [41] D.A. Case, T. Darden, T. Cheatham, C. Simmerling, J. Wang, R. Duke, R. Luo, M. Crowley, R.C. Walker, W. Zhang, K. Merz, B. Wang, S. Hayik, A. Roitberg, G. Seabra, I. Kolossváry, K. Wong, F. Paesani, J. VanÅcek, A. Kollman, Assisted Model Building with Energy Refinement (AMBER 10), University of California, 2008. <http://ambermd.org/index17.html>.
- [42] P. R. Gerber, K. Müller, MAB: a generally applicable molecular force field for structure modelling in medicinal chemistry, *J. Comput. Aided Mol. Des.* 9 (1995) 251–268.
- [43] I. Kolossváry, W.C. Guida, Low mode search. an efficient, automated computational method for conformational analysis: application to cyclic and acyclic alkanes and cyclic peptides, *J. Am. Chem. Soc.* 118 (1996) 5011–5019.
- [44] C. D. Gutsche, *Calixarenes Revisited*, Royal Society of Chemistry, Cambridge, 1998.
- [45] A.S. de Araujo, O. E. Piro, E.E.Castellano, A.F. Danil de Namor, Combined crystallographic and solution molecular dynamics study of allosteric effects in ester and ketone *p-tert*-butylcalix[4]arene derivatives and their complexes with acetonitrile, Cd(II) and Pb(II), *J. Phys. Chem. A* 112 (2008) 11885-11894.
- [46] A. F. Danil de Namor, E. E. Castellano, L. E. Pulcha Salazar, O. E. Piro, O. Jafou, Thermodynamics of cation (alkali-metal) complexation by 5,11,17,23-tetra-*tert*-butyl[25,26,27,28-tetrakis(2-pyridylmethyl)oxy]-calix(4)arene and the crystal structure–superstructure of its 1:1 complex with sodium and acetonitrile, *Phys. Chem. Chem. Phys.* 1 (1999) 285-293.
- [47] A. F. Danil de Namor, S. Chahine, E. E. Castellano, O. E. Piro, Solvent control on the selective, nonselective, and absent response of a partially substituted lower rim calix(4)arene derivative for soft metal cations (mercury(II) and silver(I)). Structural and thermodynamic studies, *J. Phys. Chem. A.* 109 (2005) 6743-6751.
- [48] A. F. Danil de Namor, S. Chahine, D. Kowalska, E. E. Castellano, O. E. Piro, Selective interaction of lower rim calix[4]arene derivatives and bivalent cations in solution. crystallographic evidence of the versatile behavior of acetonitrile in lead(II) and cadmium(II) complexes, *J. Am. Chem. Soc.* 124 (2002) 12824-12836.

- [49] A F. Danil de Namor, W. Aparicio-Aragon, N Nwogu, A. El Gamouz, O E. Piro, E.E. Castellano, Calixarene and resorcarene based receptors: from structural and thermodynamic studies to the synthesis of a new mercury(ii) selective material, *J. Phys. Chem. B* 115 (2011) 6922-6934.
- [50] G. T. Hefter, Solvation of fluoride ions.3. Review of fluoride solvation thermodynamics in non-aqueous and mixed solvents *Rev. Inorg. Chem.* 10 (1989) 185-223.
- [51] B. G. Cox, G. R. Hedwig, A. J. Parker, D. W. Watts, Solvation of ions. XIX. Thermodynamic properties for transfer of single ions between protic and dipolar aprotic solvents, *Aust. J. Chem.* 27 (1974) 477- 501.
- [52] A. F. Danil de Namor, S. Chahine, E. E. Castellano, O. E. Piro, Thermodynamics of host-guest interactions in lower rim functionalized calix[4]arenes and metal cations: the medium effect, *J. Phys. Chem. B* 108 (2004) 11384-11392.
- [53] E. Grunwald, E. Steel, Solvent reorganization and thermodynamic enthalpy-entropy compensation, *J Am. Chem. Soc.* 117(1995) 5687-5692.
- [54] D. W. Barnum, Predicting acid-base titration curves without calculations, *J Chem. Educ.* 76 (1999) 938-942.

LIST OF FIGURES

Schemes and Figures' captions

Scheme 1 Structure of receptors **1** and **2**

Scheme 2 Synthetic Route for the preparation of receptors **1** and **2**

1a = 5, 11, 17, 23 tetra-*tert*-butyl, 25, 27 bis[nitrilo]methoxy, 26, 28 dihydroxycalix[4]arene,[28]

1b =5,11,17,23 tetra-*tert*-butyl, 25, 27 bis[amino]ethoxy, 26, 28 dihydroxycalix[4]arene,[29]

1 = 5, 11, 17, 23 tetra-*tert*-butyl, 25, 27 bis [diethylphenylurea]ethoxy, 26, 28 dihydroxycalix[4]arene

2a = 25, 26, 27, 28 tetra-hydroxy-calix[4]arene [30-31]

2b =25, 27 bis[nitrilo]methoxy, 26, 28 dihydroxycalix[4]arene

2c= 25, 27 bis[amino]ethoxy, 26, 28 dihydroxycalix[4]arene

2 = 25, 27 bis[diethylphenylurea]ethoxy, 26, 28 dihydroxycalix[4]arene

Fig. 1 ^1H NMR titration of **1** with F in CD_3CN at 298 K

Fig. 2 ^1H NMR titration of **1** with phosphate species in CD_3CN at 298 K

Fig.3 Representative conductometric curves for the titration of fluoride (a) and dihydrogen phosphate (b) with **1** in acetonitrile at 298.15 K

Fig.4 3D structures showing simulated complexation between **1** with dihydrogen phosphate (a) and fluoride (b) anions; **2** with dihydrogen phosphate (c) and fluoride (d)

Fig. 5 Effect of pH on the extraction of phosphate from water by **1** at 298 K

Fig. 6 Effect of mass of **1** on %E of fluoride (a) and phosphate (b) from water at 298 K

Fig. 7 Determination of the capacity of **1** to uptake fluoride (a) and phosphate (b) from aqueous solution at 298 K

Fig.8 Effect of temperature on the uptake of fluoride (a) and phosphate (b) from aqueous solution by **1** at 298 K

Figures:

Scheme 1

Scheme 2

Fig. 1

Fig. 2

Fig. 3

(c)

(d)

Fig. 4

Fig. 5

Fig. 6

Fig. 7

Fig. 8

Tables:

Table 1 Thermodynamics of complexation of 1 and 2 with anions (as tetra-n-butylammonium counter ion) in acetonitrile at 298.15 K

Receptor 1

<i>Anion</i>	<i>Log K_s</i>	<i>Δ_cG° (kJ.mol⁻¹)</i>	<i>Δ_cH° (kJ.mol⁻¹)</i>	<i>Δ_cS° (J.mol⁻¹.K⁻¹)</i>
F ⁻	5.5 ± 0.3	-31.5 ± 0.5	-13.7 ± 0.3	59
H ₂ PO ₄ ⁻	3.7 ± 0.3	-20.9 ± 0.3	-44.3 ± 0.2	-78
	3.6 ± 0.4	-20.7 ± 0.6	135	135

Receptor 2

<i>Anion</i>	<i>Log K_s</i>	<i>Δ_cG° (kJ.mol⁻¹)</i>	<i>Δ_cH° (kJ.mol⁻¹)</i>	<i>Δ_cS° (J.mol⁻¹.K⁻¹)</i>
F ⁻	4.9 ± 0.3	-28.0 ± 0.3	-14.0 ± 0.2	47
H ₂ PO ₄ ⁻	3.9 ± 0.3	-21.9 ± 0.3	-8.3 ± 0.6	45
	3.7 ± 0.3	-20.9 ± 0.4	-3.7 ± 0.3	71

Table 2 Molecular modelling energies for anion complexes of 1 and 2 and different counter-ions.

Compound	Ligand	Counter-ion	Energy (kcal/mol)
2	2x H ₂ PO ₄ ⁻	Bu ₄ N ⁺	-268.28
2	2x H ₂ PO ₄ ⁻	Na ⁺	-241.26
1	2x H ₂ PO ₄ ⁻	Bu ₄ N ⁺	-233.91
1	2x H ₂ PO ₄ ⁻	Na ⁺	-183.18
1	F ⁻	Na ⁺	-107.98
2	F ⁻	Bu ₄ N ⁺	-100.04
1	F ⁻	Bu ₄ N ⁺	-99.98
2	F ⁻	Na ⁺	-96.94