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Fluoride binding by an anionic receptor: tuning the acidity of amide NH groups for basic anion hydrogen bonding and recognition

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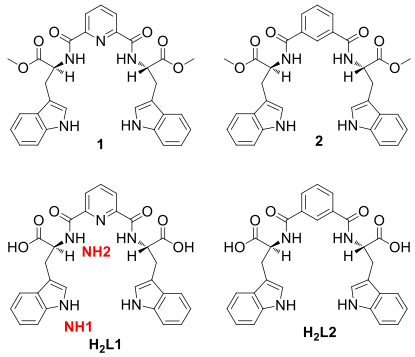
Here we report a family of bis-amide receptors for anion binding that contain carboxylic acid groups vicinal to the amide function. Deprotonation of the carboxylic acids decreases the acidity of amide NHs, switching on the anion binding ability of the deprotonated receptors with selectivity for fluoride complexation. The proposed systems represent a unique example of anionic receptors able to bind anions via H-bonding.

Anion recognition and sensing have attracted considerable attention in the past 20 years due to the involvement of anionic species in environmental, industrial and biological fields.[1-5] A common approach is to exploit the formation of H-bonds between anions and H-bond donors, such as amide or urea NHs whose donating properties can be increased in the presence of an appropriate electron withdrawing group in the molecular skeleton of the receptor. Much work has been devoted to recognition and sensing of fluoride[6, 7] that, due to its intrinsic features can easily interact with H-bond donor containing receptors forming stable adducts. However, its high basicity in organic solvents[8] may cause the deprotonation of H-bond donor groups often causing a dramatic colour change of the solutions.[9-12]Pioneering work by Fabbrizzi, Gale and Gunnlaugsson highlighted that, without careful UV-Vis and NMR spectroscopic studies and a comparison with the behaviour of strong bases such as OH^-, deprotonation processes can be easily confused with binding.[13-16]It is well established that in solution, neutral receptor deprotonation promoted by fluoride could often lead to the formation of the bifluoride HF_2^-. In this regard, one of the methods adopted to discriminate between a deprotonation and an effective binding *via* H-bond formation is to follow the formation of $[HF_2^-]$ by ^{1}H-NMR or ^{19}F-NMR.[17] On the other hand, rational design of systems featuring electron-donating groups suitably placed in the molecular skeleton of the receptor unit, could, in theory, decrease the acidity of the H-bond sites preventing their deprotonation and favouring H-bonding interactions with basic anions and their selective recognition. In this sense, although the introduction of acidic groups such as OH, SH or COOH might promote further acid-base equilibria, their conjugate bases might work well as electron-donating groups towards vicinal H-bonding sites. To the best of our knowledge, this approach has not yet been explored for systems designed for pure H-bond interactions, such as urea- or amide-based anion receptors. Few examples of macrocycles bearing appended carboxylic acid moieties, have been reported in the literature,[18, 19] however, in these cases, the host-guest recognition event depends on hydrophobic interactions.

We have recently reported on anion recognition properties of pyridine-2,6-dicarboxamide and isophthalamide derivatives substituted with methyl esters of L-tryptophan (Scheme 1).[20]



Scheme 1. Receptors considered in this paper.

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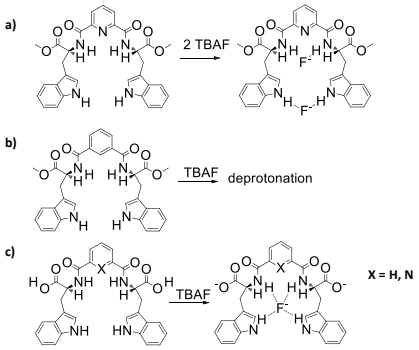
Electronic Supplementary Information (ESI) available: [general methods, synthetic details for the synthesis of **H_2L1** and **H_2L2**, stack plots for the ^{1}H-NMR titrations of **H_2L1** with OH^-, AcO^-, BzO^-, $HPpi^{3-}$, Cl^-, stack plots of the ^{19}F-NMR titrations of **H_2L2** with TBAF, crystallization conditions, details of the crystal data, structure refinement and crystal packing description for the three crystal structures.
]. See DOI: 10.1039/x0xx00000x

Receptor **1** worked as a hetero-ditopic dicompartimental receptor for halides (Scheme 2a), receptor **2** only formed 1:1 adducts and deprotonated in the presence of fluoride (Scheme 2b). Based on these results we decided to explore a new design, testing the response of these receptors towards several anionic species when the methyl ester function was replaced by a carboxylic acid group. We wished to evaluate the influence of the deprotonation of carboxylic moieties on the acidity of the amide NHs groups and hence the anion-binding ability of the corresponding carboxylate species (Scheme 2c).



Scheme 2 Proposed binding/deprotonation mode for receptors **1** (a), **2** (b), **H_2L1** and **H_2L2** (c) with fluoride.

H_2L1 and **H_2L2** were synthesized following a modified literature procedure (see ESI, for synthetic details).[21] To clarify the binding mode of the receptors, we decided to study the complexation process by ^{1}H- and ^{19}F-NMR spectroscopy in DMSO-d_6.

Firstly, we studied the acid-base properties of **H_2L1** in presence of increasing aliquots of TBAOH in DMSO-d_6 (see ESI, Fig. S1A). Upon addition of 0.4 eq. of OH^- the carboxylic acid proton resonance at 12.8 ppm disappears. This could be ascribed to the chemical exchange that broadens the resonance and causes coalescence. Upon addition of increasing amounts of TBAOH, the two NH signals at 10.7 ppm and 9.3 ppm (NH1 and NH2, Scheme 1) experiment, at first, a downfield and upfield shift, respectively. When further amounts of TBAOH are added, the NH protons signals become broad and eventually disappear in the presence of about 2.5 eq. of TBAOH, suggesting a full deprotonation of the receptor. The results relative to the ^{1}H-NMR titration of **H_2L1** and TBAF in DMSO-d_6 are reported in Figs. 1 (S1B for an expanded spectrum) and S2 (ESI). During the first part of the titration (up to 2 equivalents of F^- added, Fig. 1), we observe three distinct events: 1) the signal of the COOH protons disappears after the first addition of F^- (0.5 eq.), 2) the signal of the NH1 protons shifts downfield, 3) the signal of the NH2 protons shifts upfield. When 4 eq. of TBAF are present in solution a triplet at around 16 ppm appears confirming the presence of HF_2^- in solution. When a further amount of TBAF is added, we observe a pronounced downfield shift of the NH1 signal probably attributed to the adduct formation of **L1**$^{2-}$ with fluoride while the triplet attributed to HF_2^- is still present.

This behaviour was confirmed by titrating **H_2L1** with TBAF, after preliminary deprotonation of carboxylic groups with TBAOH. The comparison between the titrations of **H_2L1** with TBAOH and TBAF (ESI, Fig. S2) highlights that the first part of the titration is almost identical in both cases.

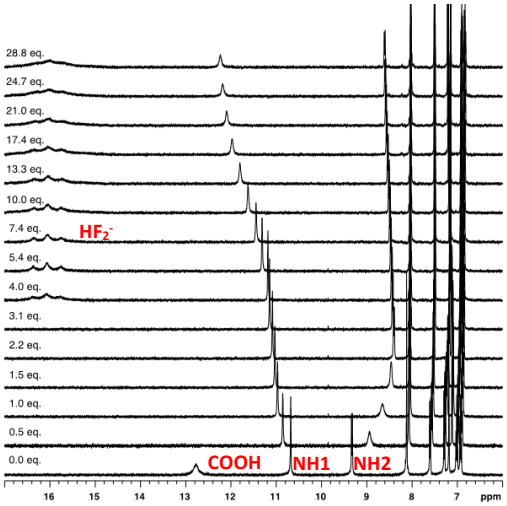


Figure 1. Stack plot of ^{1}H-NMR spectra recorded after the addition of increasing amounts of TBAF to **H_2L1** (0.005 M) in DMSO-d_6.

This behaviour can be explained considering the full deprotonation of the carboxylic acid groups in the presence of 2 eq of OH^- or F^-. In the case of the titration with F^-, the addition of 4 equivalents of the anion species determines the formation of 2 equivalents of HF_2^- (due to the formation of the complex $HF{\cdot}F^-$) which causes the appearance of a triplet at around 16 ppm. In the presence of an excess of TBAF we observed a marked variation of both NH shifts, more evident for NH1, that, however, does not reach a plateau even in the presence of about 30 eq. of fluoride. This behaviour suggests that after the initial deprotonation of **H_2L1**, the resulting **L1**$^{2-}$ species interacts with fluoride *via* H-bond with both indole and amide NHs. In other words, the deprotonation of **H_2L1** triggered by a strong base is able to switch on the ability of **L1**$^{2-}$ to bind fluoride. We then performed a ^{1}H-NMR titration of the receptor **H_2L1** with $TBAHF_2$ in DMSO-d_6 (ESI, Fig.S4). After the initial disappearance of the carboxylic protons signal, we observed a downfield shift of the NH1 signal of about 0.1 ppm and an upfield shift of 1 ppm of the NH2 signal. Upon increasing the amount of $TBAHF_2$ added, we do not observe a further shift of NH1 (as observed in the case of the ^{1}H-NMR titration of **H_2L1** with TBAF) while a new broad peak ascribable to HF_2^- appears in the spectrum. Interestingly, the signal of the HF_2^- shifts downfield and increases in intensity during the titration, suggesting that the free HF_2^- is in fast exchange on the chemical shift time scale with the complexed HF_2^-. In the presence of TBA salts of AcO^-, BzO^-, $HPpi^{3-}$, Cl^- we only observed the deprotonation (except for the titration with TBACl) of the receptor without any further interaction with the anions (Figs. S5-S8, S11, ESI). A similar behaviour was also observed in DMSO in the case of **H_2L2** (Fig S9-S10 for the ^{19}F-NMR experiments, ESI).

We also performed a ^{19}F-NMR titration of **H_2L1** with TBAF in DMSO-d_6 (Fig.2). The stack plot of the titration shows that the signal of the HF_2^- appears at around -157 ppm and shows an upshift to -148 ppm up to 4 equivs of F^- added; when an excess of TBAF is present in solution the signal of F^- appears at around -100 ppm.

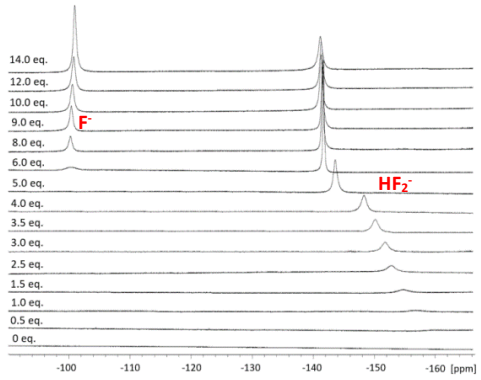


Figure 2. Stack plot of ^{19}F-NMR spectra recorded after the addition of increasing amounts of TBAF to **H_2L1** (0.012 M) in DMSO-d_6.

This supports the hypothesis of the initial deprotonation of the carboxylates of **H_2L1** with the subsequent formation of HF_2^- in solution. Furthermore, the upshift of the signal of the HF_2^- species confirms that the deprotonated $\mathbf{L_1}^{2-}$ initially interacts with the HF_2^- species, being the shift due to a fast exchange on the chemical shift time scale between a free and a complexed HF_2^-. At around 6 equivalents the resonance of HF_2^- is stable at approximately -142 ppm and its intensity does not increase.

Table 1. Measured overall stability constants (Log β) and calculated stepwise association constants (Log K) for the adducts of the receptors with fluoride in H_2O/EtOH (1:1 v/v) at 298 K (I = 0.1 M).

Equilibrium	Log β	
	H_2L1	**H_2L2**
$L^{2-} + 2H^+ + F^- \rightleftharpoons [H_2LF]^-$	16.1(1)	15.8(1)
$L^{2-} + 3H^+ + F^- \rightleftharpoons [H_3LF]$	21.5(1)	-
$L^{2-} + 4H^+ + 2F^- \rightleftharpoons [H_4LF_2]$	28.4(1)	-
	Log K	
$H_2L + F^- \rightleftharpoons [H_2LF]^-$	3.2(1)	3.3(1)
$H_3L^+ + F^- \rightleftharpoons [H_3LF]$	4.0(1)	-
$H_3L^+ + HF_2^- \rightleftharpoons [H_4LF_2]$	3.8(1)	-

Simultaneously, we observed the appearance of the signal of the F^- that increases in intensity. These results are also confirmed by titrating a solution of TBAF with increasing amount of **H_2L1** (see also Fig. S3, ESI).

The acid-base properties of **H_2L1** and **H_2L2** and their coordination properties towards fluoride were also studied in a more competitive solvent mixture, i.e. H_2O/EtOH (1:1 v/v) by means of potentiometric measurements. The scarce solubility of the ligands in pure water prevents their study in this medium. The protonation constants and the distribution diagrams of species formed by **H_2L1** and **H_2L2** are reported in ESI, Table S1 and Fig. S12.

Fluoride interacts with the receptors to form 1:1 adducts under pH 8 (stability constants of the adducts for fluoride are reported in Table 1; the distribution diagram is shown in Fig. S13). For both receptors, the formation of a $[H_2\mathbf{L}F]^-$ complex with fluoride is detected in solution, and, in the case of $\mathbf{L1}^{2-}$, a $[H_3\mathbf{L1}F]$ and $[H_4\mathbf{L1}F_2]$ adducts are also observed. Interestingly, the formation of $[H_4\mathbf{L1}F_2]$ adduct necessarily involves the interaction between the $[H_3\mathbf{L1}]^+$ charged receptor and the HF_2^- anion (Table 1, Figs S13, ESI).

Finally, we investigated the anion binding ability of **H_2L1** and **H_2L2** in the solid-state, crystallizing the two receptors in the presence of the TBA salts of AcO^-, BzO^-, $HPPi^{3-}$, Cl^- and F^-.

We isolated single crystals suitable for x-ray analysis for **H_2L1** as the free receptor and in presence of $(TBA)_3HPPi$ and TBAF, resulting in structures **H_2L1**·H_2O, (**HL1**)TBA·0.86H_2O and (**L1**·HF)TBA_2·2.25H_2O, respectively (ESI, Tables S3 and S4 and Figs. S14-S17).

Differently to what was observed in **H_2L1**·H_2O and (**HL1**)TBA·0.86 H_2O, in (**L1**·HF)TBA_2·2.25 H_2O the dianionic receptors adopt an antiperiplanar conformation with the indole moieties located perpendicularly one above and one below the plane defined by the pyridine fragment and the two amidic groups (Figure 3), thus allowing HF to interact with the H-donor groups of the pseudo-cavity.

According to solution studies, F^- and HF_2^- are the only anions able to interact with **H_2L1** in solution. The presence of HF instead of F^- in (**L1**·HF)TBA_2·2.25H_2O might be explained assuming that the water present in the solvent used or adsorbed due to the intrinsic hygroscopicity of the TBAF salt might promote secondary acid-base equilibria during the crystallisation experiment, determining the protonation of the initially formed $\mathbf{L1}^{2-}$/F^- host-guest complex. However, this structure confirms the anion binding mode suggested by solution studies. The absence of any interactions between the guest and the indole moieties of the receptor might be explained considering a change of the conformation either due to the crystallization process or to the conversion of F- into HF.

In our study, we have demonstrated for the first time with the receptor systems **H_2L1** and **H_2L2**, that the introduction of appropriate donor groups such as –COOH in close proximity to H-bond donors, can reduce their acidity. This can be exploited to increase the binding selectivity towards basic anions such as fluoride in aprotic solvents (DMSO) avoiding the deprotonation of amide NHs moieties and favouring anion recognition via H-bond formation. In fact, when compared to their methyl ester analogous **1** and **2**, both **H_2L1** and **H_2L2** in their deprotonated carboxylate forms, $\mathbf{L1}^{2-}$ and $\mathbf{L2}^{2-}$, only bind fluoride-containing anionic species via H-bond formation.

Furthermore, while in the case of receptor **2** we observed the deprotonation of both amide and indole NHs in the presence of TBAF, in **H_2L2** the amide NHs acidity in $\mathbf{L2}^{2-}$ is reduced by the initial sacrificial deprotonation of the carboxylic groups.

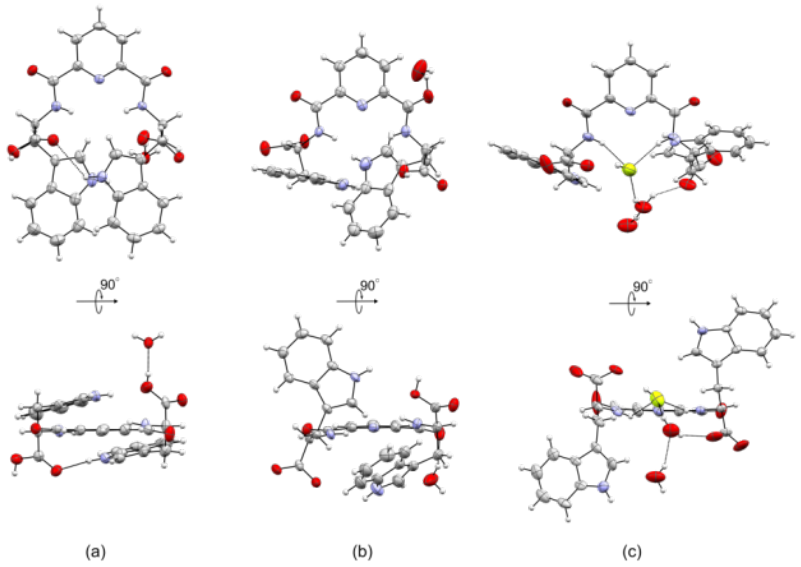


Figure 3. Conformations for **H_2L1**, **HL1**$^-$ and (**L1**·HF)$^{2-}$ in structures **H_2L1**·H_2O (a) , (**HL1**)TBA·0.86 H_2O (b), and (**L1**·HF)TBA_2·2.25 H_2O (c), viewed down two perpendicular directions. For the latter two compounds only one of the molecules present in the asymmetric unit is reported

As a consequence, fluoride is not able to deprotonate the NH groups and a host-guest interaction via H-bonding becomes possible. Finally, the design adopted for **H_2L1** and **H_2L2** has allowed, for the first time, selective anion binding by a receptor in its anionic form via H-bonding, contrary to what predictable on the basis of the Coulomb law.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ Crystallographic data for **H_2L1**, **(TBA)$^+$(HL1$^-$)** and **(TBA)$^+$(HL1$^-$)HF** have been deposited with the Cambridge Crystallographic Data Centre with CCDC1854630, 1854632 and 1854631 respectively. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ (fax +44 1223 336033) or email: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk.

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