Journal Name

COMMUNICATION

Tuning the acid properties of amide NH groups for basic anion H-bonding and recognition†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Riccardo Montis,[a§*] Andrea Bencini,[b] Simon Coles,[c] Luca Conti,[b] Luca Fusaro,[d] Claudia Giorgi,[b] Peter Horton,[c] Vito Lippolis,[a] Lucy Mapp[c,e] and Claudia Caltagirone[a*]

Here we report a family of bis-amide receptors for anion binding, featuring carboxylic acid functions. When compared with methylesther analogs, after deprotonation of carboxylic groups the resulting conjugate bases act as electron-donating groups, decreasing the acidity of amide NHs, and resulting in receptors highly selective for fluoride anion species.

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.[1-6] One of the main approaches to the design of receptors for anion binding dictates the presence in their structures of a pseudo-cavity featuring strong H-bond donors, such as amide or urea NHs, able to interact with the guest species. The strength of the interaction can be tuned by carefully placing an appropriate electron withdrawing group in the molecular skeleton of the receptor.

In particular, a lot of work has been devoted to fluoride recognition and sensing.[7-9] Because of its intrinsic features (high charge density, small ionic radius) fluoride can easily interact with H-bond donors containing receptors forming stable adducts. However, due to its high basicity in organic solvents,[10] it can easily cause the deprotonation of hydrogen bond donor groups. The deprotonation event is often accompanied by a dramatic colour change of the solutions, making these kind of systems suitable for colorimetric recognition.[11-16] Pioneering papers by Fabbrizzi and Gale pointed out that it can be quite easy to confuse a deprotonation process with a binding process without attentive UV-Vis and NMR spectroscopic studies and a comparison with the behaviour of strong bases such as OH^-.[17-20] It is well established that in solution neutral receptors deprotonation promoted by fluoride could often lead to the formation of the stable self-complex HF_2^- between HF and F^- species. In this regard, one of the methods adopted to discriminate between a deprotonation and an effective binding *via* hydrogen-bond formation is to follow the formation of $[HF_2^-]$ by ^{1}H-NMR or ^{19}F-NMR.[21]

On the other hand, a 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. However, this approach has not been taken into account so far and urea- or amide-based anion receptors containing OH, SH or COOH groups are not common.[22, 23]

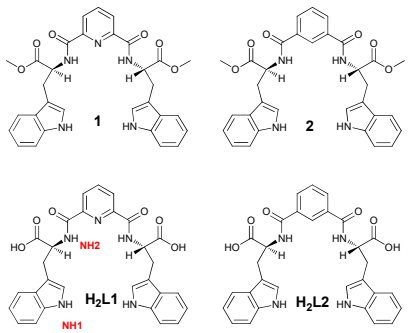
We have recently reported on anion recognition properties of pyridine-2,6-dicarboxamide and isophthalamide derivatives substituted with methyl esthers of L-tryptophan (Scheme 1).[24] Receptors **1** proved to be a hetero-ditopic dicompartimental receptor for halides, with slightly higher affinity towards fluoride anions. Receptor **2** only formed 1:1 adducts and deprotonated in the presence of fluoride.

Based on these results we decided to explore a new design, testing the response of these receptor towards several anion species when the methyl ester function is replaced by a carboxylic group. We wanted 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. With this purpose we developed the two new pyridine-2,6-dicarboxamide and isophthalamide derivatives containing L-tryptophan moieties, namely **H_2L1**, and **H_2L2**, reported in Scheme 1.

[a] *Dipartimento di Scienze Chimiche e Geologiche, Universita`degli Studi di Cagliari, S.S. 554 Bivio per Sestu, 09042 Monserrato (CA), Italy Email address: ccaltagirone@unica.it*
[b] *Dipartimento di Chimica 'Ugo Schiff' Via della Lastruccia, 3-13 50019 SESTO FIORENTINO (FI), Italy.*
[c] *Chemistry University of Southampton Highfield Southampton SO17 1BJ (UK).*
[d] *Université de Namur, rue de Bruxelles 61, B-5000 Namur, Belgique.*
[e] *Johnson Matthey, 250 Cambridge Science Park, Cambridge CB4 0WE (UK).*
[§] *Current address: School of Chemical Engineering and Analytical Science, The University of Manchester, The Mill, Sackville Street, Manchester M1 3AL (UK) Email address. riccardo.montis@manchester.ac.uk*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

H_2L1 and **H_2L2** were synthesised following a modified literature procedure (see ESI† for synthetic details).[25]
Protonation of the receptors and their coordination properties towards halides and phosphate anions were studied in H_2O/EtOH (50:50 v/v) by means of potentiometric measurements. The scarce solubility of the ligands in pure water prevents their study in this medium. Table S1 (see ESI†) reports the protonation constants of the receptors (the distribution diagrams of **H_2L1** and **H_2L2** protonated species are reported in ESI†, Fig. S1).



Scheme 1. Receptors considered in this paper.

The binding ability of the different protonated/deprotonated forms of the receptors towards halide anions, nitrate, phosphate and pyrophosphate (Ppi) anions, were analysed by means of potentiometric measurements in the same medium (H_2O/EtOH, 50:50 v/v) on changing the pH. Fluoride and Ppi interact with the receptors to form 1:1 adducts under pH 8 (overall stability constants of the adducts are reported in in ESI† Table S3 and S4; distribution diagrams are shown in Figs. S2 and S3). The other anions considered did not give any detectable interaction under the potentiometric experimental conditions. For both receptors, the formation of a $[H_2LF]^+$ complex with fluoride is detected in solution (a $[H_2LF]^-$ adduct is also formed in the case of $L1^{2-}$). Although the carboxylate groups of **$L1^{2-}$** and **$L2^{2-}$** are more basic than fluoride (Tables S1 and S2), we cannot rule out the the interaction between anionic forms of the receptors and F^- in these adducts. This hypothesis can gain confidence considering the higher basicity of fluoride in H_2O/EtOH (50:50 v/v) (logK = 4.2 for F^- protonation) than in pure water (LogK = 3.2).[26] Interestingly, in the case of **H_2L1** a $[H_4L1F_2]$ adduct is also formed at acidic pH values, which necessarily involves the interaction between the $[H_3L1]^+$ charged receptor and the HF_2^- anion (see ESI†, Table S4, Figs S4). To clarify the binding mode of the receptors, we decided to study the complexation process also by ^{1}H- and ^{19}F-NMR spectroscopy. Unfortunately, both receptors and their adducts showed a too low solubility at the concentrations normally used for NMR experiments in H_2O or EtOH and in their mixture preventing the studies in these solvents. The most efficient solvent to overcome the scarce solubility of ligands and/or adducts was DMSO-d_6. Assignment of the ^{1}H-NMR chemical shifts was made via 2-D NMR spectroscopy experiments for the two receptors.
Firstly, we studied the acid-base properties of **H_2L1** in presence of increasing aliquots of TBAOH in a solution of the receptor in DMSO-d_6 (see ESI†, Fig. S4). Upon addition of 0.4 eq. of OH^- the signal at 12.8 ppm attributed to the carboxylic protons disappears. This could be ascribed to the chemical exchange that broadens the signal and causes coalescence. The two NHs signals at 10.7 ppm and 9.3 ppm (NH1 and NH2, Scheme 1) shift at first downfield and upfield, respectively, upon addition of increasing amounts of TBAOH. When further amounts of TBAOH are added, the signals attributed to the NH protons 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 the ESI† (Figs. 1 and S5). During the first part of the titration (up to 2 equivalents of F^- added), we observe three distinct events: 1) the signal attributed to 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 we observe the appearance of a triplet at around 16 ppm which can be assigned to 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 formation of an adduct between **$L1^{2-}$** and the fluoride anion, while the triplet attributed to HF_2^- is still present.

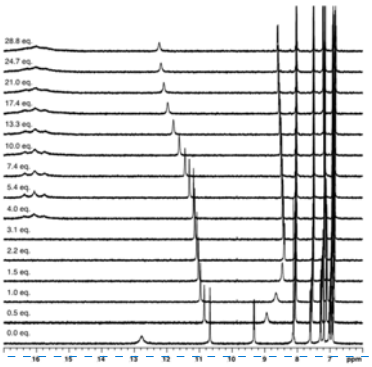


Figure 1 Stack plot of ^{1}H-NMR spectra recorded after the addition of increasing amounts of TBAF to a solution of **H_2L1** in DMSO-d_6.

The comparison between the titrations of **H_2L1** with TBAOH and TBAF (see ESI Figure S5) highlights that the first part of the titration is almost identical in both cases. This behaviour can be explained considering the full deprotonation of the carboxylic 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

Commentato [A1]: Claudia valuta tu se mettere questa frase, in ogni caso il fluoruro resta meno basico dei recettori deprotonati e non sappiamo come varia la basicità dei carbossilati passando dall'acqua all'acqua/EtOH

the anion species determines the formation of 2 equivalents of HF_2^- (due to the formation of the complex $HF{\cdot}F^-$) which determines the appearance of a triplet at around 16 ppm. In the presence of an excess of TBAF we observed a marked variation of both NHs 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 F^- *via* H-bond with both indole and amide NHs.

To confirm these hypothesis, we performed the ^{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 eq.s of F^- added; when an excess of TBAF is present in solution the signal of F^- appears at around -100 ppm. These evidences support 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^- specie confirms that the deprotonated **L1**$^{2-}$ initially interacts with the HF_2^- specie, 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 signal of the HF_2^- is stable at approximately -142 ppm and its intensity does not increase. 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 ESI†, Fig. S6).

We also performed a ^{1}H-NMR titration of the receptor **H_2L1** with $TBAHF_2$ in DMSO-d_6 (see Fig.3). After the initial deprotonation of the receptor, we observed a downfield shift of the signal of NH1 of about 0.1 ppm and an upfield shift of 1 ppm of the signal of NH2. 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. It is interesting to note that 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^-. With all the other anion tested (AcO^-, BzO^-, $HPpi^{3-}$, Cl^-, as their TBA salts) we only observed the deprotonation (except for the titration with TBACl) of the receptor without any further interaction with the anionic species (see ESI†, Figs. S7-S10, S13). A similar behaviour towards the considered anions was also observed in DMF in the case of **H_2L2** (see ESI†, Fig S11-S12 for the ^{19}F-NMR experiments).

We also investigated the anion binding ability of **H_2L1** and **H_2L2** at the solid-state using the TBA salts of AcO^-, BzO^-, $HPpi^{3-}$, Cl^- and F^-. Only in the cases of the crystallization of free receptor **H_2L1** and of **H_2L1** in presence of **(**$TBA)_3HPpi$ and TBAF, single crystals suitable for X-ray diffraction analysis were grown, which proved to be **H_2L1**$\cdot H_2O$, (**HL1**)TBA$\cdot 0.86H_2O$ and (**L1**$\cdot$HF)$TBA_2\cdot 2.25H_2O$, respectively.

Crystallization conditions, details of the crystal data, structure refinement and crystal packing description for the three new crystal structures are reported in the ESI† (see Tables S3 and S4 and Figs. S14-S17).

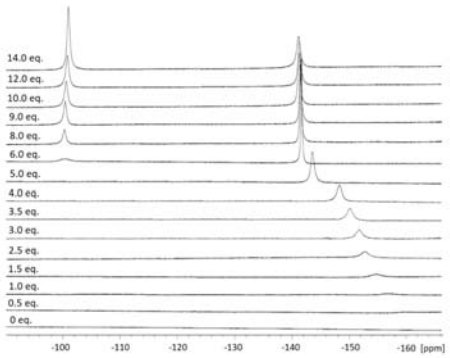


Figure 2 Stack plot of ^{19}F-NMR spectra recorded after the addition of increasing amounts of TBAF to a solution of **H_2L1** (0.012 M)in DMSO-d_6.

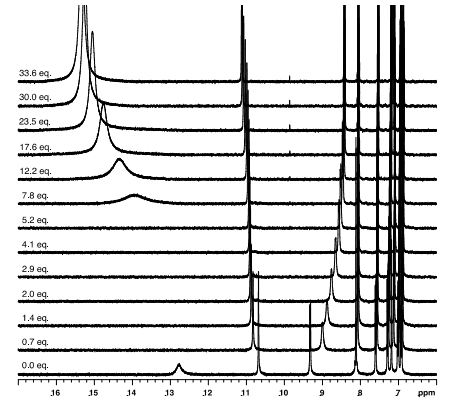


Figure 3 Stack plot of ^{1}H-NMR spectra recorded after the addition of increasing amounts of $TBAHF_2$ to a solution of **H_2L1** in DMSO-d_6.

As contrary to what observed in **H_2L1**$\cdot H_2O$ and (**HL1**)TBA$\cdot$0.86 H_2O, in (**L1**$\cdot$HF)$TBA_2\cdot$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 4), thus allowing HF to interact with the hydrogen donor groups.

According to solution studies, F^- and HF_2^- are the only anions able to interact with **H_2L1** in DMSO solutions. The presence of HF instead of F^- in (**L1**$\cdot$HF)$TBA_2\cdot$2.25 H_2O might be explained assuming that the water present in the solvent used or adsorbed due to the intrinsic hygroscopicity of the TBAF salt might promote secondary acid-base equilibria during the crystallisation experiment, determining the protonation of the initially formed **L1**$^{2-}$/F^- host-guest complex.

The great tendency of **H_2L1** and its salts to crystallize with water molecules is confirmed by all three compounds crystallographically characterized.

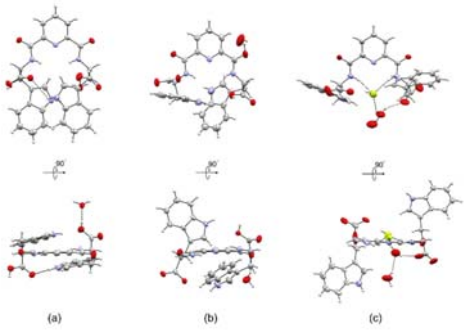


Figure 4. Ortep style representation of conformations for **H_2L1**, **HL1**$^-$ and (**L1**·HF)$^{2-}$ in structures **H_2L1·H_2O** (a) , **(HL1)TBA·0.86 H_2O** (b), and **(L1·HF)TBA2·2.25 H_2O** (c), viewed down two perpendicular directions. For the latter two compounds only one of the molecules present in the asymmetric unit is reported.

In conclusion, we have demonstrated for the first time with the receptor systems considered, **H_2L1** and **H_2L2**, that the introduction of appropriate donor groups such as –COOH in close proximity to H-bond donors, can tune their acidity reducing it. This can be exploited to increase the binding selectivity towards basic anions such as F^- in aprotic solvents (DMSO) avoiding the deprotonation of amide NHs moieties and favouring anion recognition *via* H-bond formation. In fact, as compared to **1** and **2**, which feature a weak –COOMe donor group in α position to the amide function, both **H_2L1** and **H_2L2** in their deprotonated carboxylate forms, **L1**$^{2-}$ and **L2**$^{2-}$, bind selectively only 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** thanks to the initial sacrificial deprotonation of the carboxylic groups, the amide NHs acidity in **L2**$^{2-}$ is reduced by the *in situ* formed –COO^- strong donors to the extent that fluoride is not able to deprotonate the NHs anymore and an host-guest interaction *via* H-bond becomes possible. Finally, the design adopted for **H_2L1** and **H_2L2** has allowed, for the first time, a selective anion binding by a receptor in its anionic form *via* H-bonding, contrary to what predictable on the basis of the Coulomb law.

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ Crystallographic data for **H_2L1·H_2O, (HL1)TBA·0.86H_2O and (L1·HF)TBA_2·2.25H_2O** 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.

1. A. B. Aletti, D. M. Gillen and T. Gunnlaugsson, *Coordination Chemistry Reviews*, 2018, **354**, 98-120.
2. A. Bencini, V. Lippolis and B. Valtancoli, *Inorganica Chimica Acta*, 2014, **417**, 38-58.
3. N. Busschaert, C. Caltagirone, W. Van Rossom and P. A. Gale, *Chemical Reviews*, 2015, **115**, 8038-8155.
4. N. H. Evans and P. D. Beer, *Angewandte Chemie - International Edition*, 2014, **53**, 11716-11754.
5. P. A. Gale and C. Caltagirone, *Coordination Chemistry Reviews*, 2018, **354**, 2-27.
6. T. Gunnlaugsson, M. Glynn, G. M. Tocci, P. E. Kruger and F. M. Pfeffer, *Coordination Chemistry Reviews*, 2006, **250**, 3094-3117.
7. M. Cametti and K. Rissanen, *Chemical Communications*, 2009, 2809-2829.
8. M. Cametti and K. Rissanen, *Chemical Society Reviews*, 2013, **42**, 2016-2038.
9. Y. Zhou, J. F. Zhang and J. Yoon, *Chemical Reviews*, 2014, **114**, 5511-5571.
10. F. G. Bordwell, *Accounts of Chemical Research*, 1988, **21**, 456-463.
11. R. M. F. Batista, E. Oliveira, S. P. G. Costa, C. Lodeiro and M. M. M. Raposo, *Supramolecular Chemistry*, 2014, **26**, 71-80.
12. S. Guha and S. Saha, *Journal of the American Chemical Society*, 2010, **132**, 17674-17677.
13. D. Jiménez, R. Martínez-Máñez, F. Sancenón and J. Soto, *Tetrahedron Letters*, 2002, **43**, 2823-2825.
14. D. A. Jose, D. K. Kumar, B. Ganguly and A. Das, *Organic Letters*, 2004, **6**, 3445-3448.
15. M. Vázquez, L. Fabbrizzi, A. Taglietti, R. M. Pedrido, A. M. González-Noya and M. R. Bermejo, *Angewandte Chemie - International Edition*, 2004, **43**, 1962-1965.
16. G. Yan, H. Li, Y. R. Zhu, B. Shi, W. Qu, Q. Lin, H. Yao, Y. Zhang and T. Wei, *New Journal of Chemistry*, 2015, **39**, 8797-8801.
17. V. Amendola, M. Boiocchi, L. Fabbrizzi and A. Palchetti, *Chemistry - A European Journal*, 2005, **11**, 120-127.
18. M. Boiocchi, L. D. Boca, D. Esteban-Gómez, L. Fabbrizzi, M. Licchelli and E. Monzani, *Chemistry - A European Journal*, 2005, **11**, 3097-3104.
19. M. Boiocchi, L. Del Boca, D. E. Gómez, L. Fabbrizzi, M. Licchelli and E. Monzani, *Journal of the American Chemical Society*, 2004, **126**, 16507-16514.
20. L. S. Evans, P. A. Gale, M. E. Light and R. Quesada, *Chemical Communications*, 2006, 965-967.
21. M. Goursaud, P. De Bernardin, A. Dalla Cort, K. Bartik and G. Bruylants, *European Journal of Organic Chemistry*, 2012, 3570-3574.
22. J. M. Coterón, F. Hacket and H.-J. Schneider, *The Journal of Organic Chemistry*, 1996, **61**, 1429-1435.
23. Z. Rodriguez-Docampo, S. I. Pascu, S. Kubik and S. Otto, *Journal of the American Chemical Society*, 2006, **128**, 11206-11210.
24. C. Caltagirone, C. Bazzicalupi, A. Bencini, F. Isaia, A. Garau and V. Lippolis, *Supramolecular Chemistry*, 2012, **24**, 95-100.
25. J. You, X. Yu, C. Liu and R. Xie, *Synthetic Communications*, 1999, **29**, 2447-2455.
26. R. M Smith, A. E. Martell, NIST Stability Constants Database, version 4.0; National Institute of Standards and Technology: Washington, DC, 1997.