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Non-symmetric substituted ureas locked in (*E*,*Z*) conformation: an unusual anion binding *via* supramolecular assembly

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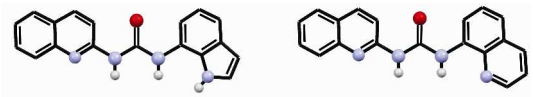
Two new asymmetric ureidic receptors L^1 (1-(1H-indol-7-yl)-3-(quinolin-2-yl)urea) and L^2 (1-(quinolin-2-yl)-3-(quinolin-8-yl)urea) have been synthesised and their affinity towards different anions tested in DMSO-d_6. L^1 adopts both in solution and in the solid state an (*E*,*Z*) conformation. A moderate affinity for acetate has been observed with L^1 while no interaction has been observed with L^2. The different behaviour has been ascribed to the presence/absence of the indole group. In the case of L^1 the indole group causes the formation of a peculiar supramolecular architecture with two molecules of the receptor binding the anions in (*E*,*Z*) conformation via H-bonds. L^2 also adopts an (*E*,*Z*) conformation in the solid state. However, the absence of the indole in L^2 hampers the formation of the supramolecular assembly with the partecipation of anionic species.

A popular area of supramolecular chemistry in which hydrogen bonds play a key role is anion recognition performed by neutral receptors containing ureidic, amidic, indolic etc. NH groups able to act as hydrogen bond donors towards anionic substrates.[1-4] Moreover, in biological systems, the integrity of a huge number of biomolecular structures, information storage and transfer processes, replication and catalysis are strongly dependent on the formation of specific patterns of complementary inter- and intramolecular hydrogen bonds.[5] For this reason designing, developing and understanding new systems able to self-assemble only by means of hydrogen bonds formation is one of the challenges of modern supramolecular chemistry.[6] When designing an anion receptor many factors must be taken into account such as the number and typology of the hydrogen bond donor groups, the complementarity in shape and dimension between the binding domain of the receptor and the anionic substrate, and the nature of the receptors in terms of formation of intra- or inter-molecular hydrogen bonds (that could prevent the availability of the donor groups for anion coordination).

Following our interest in anion recognition involving indole as hydrogen bond donor group[7] we designed and succesfully synthesised two new ureidic asymmetric derivatives: L^1 which contains a quinoline and an indole moieity, and L^2 featuring two quinoline moieties.



Scheme 1 Pictorial draw of the receptors studied in the paper (● = N; ● = O)

Both were synthesised starting from 2-isocyanatoquinoline obtained by Curtius rearrangement from quinoline-carbonyl azide[8] and 7-aminoindole and 8-aminoquinoline, respectively, in dry toluene. In the case of L^1 the resulting precipitate was washed with DCM and then with MeOH to get the pure product in 29% yield. In the case of L^2 the pure product was simply obtained by filtration from the reaction mixture as a white solid in 63% yield (see ESI†). Crystals suitable for X-ray diffraction analysis were obtained for both substituted urea derivatives L^1 and L^2. L^1 was crystallised by slow evaporation from a 1:1 (v/v) mixture of DCM and MeOH resulting in a solvate phase ($L^1\alpha$)[9]. A further crystallization experiment from MeOH/THF 2:1 (v/v) in the presence of tetrabutylammonium acetate, resulted in a new phase of the receptor L^1 ($L^1\beta$)[9]. Crystals of L^2 were grown by slow evaporation from DMSO. A summary of the basic crystal data are given in the ESI†.

The two phases $L^1\alpha$ (trigonal, *R*-3, Z' = 1) and $L^1\beta$ (orthorombic, $Pna2_1$, Z' = 2) (Table S1), adopt an (*E*,*Z*) conformation (Fig. 1a) with the formation of an intramolecular hydrogen bond between one of the NHs of the urea moiety and the nitrogen of the quinoline group (N(3)···N(1) distances, are 2.658(4) Å for $L^1\alpha$ and respectively 2.653(6) Å and 2.682(6) Å for $L^1\beta$[10]) in agreement with the literature data on solid state regarding pyridyl urea derivatives.[11-13] Moreover (Fig. 1a), the presence of the indole group allows the formation of an additional intramolecular hydrogen bond between the NH of the indole and the ureidic carbonyl group (N4···O1 distances are 2.686(4) Å for $L^1\alpha$ and respectively 2.687(5) Å and 2.703(5) Å for $L^1\beta$[9]).

Similarly to the two phases $L^1\alpha$ and $L^1\beta$, the crystal structure of L^2 (monoclinic, $P2_1/c$, Z' = 2) shows an intramolecular hydrogen bond (Fig. 1 c) involving one of the ureidic NH group and the nitrogen of the quinoline group (N(4)···N(2) and (N(6)···N(8) distances are respectively 2.697(2) Å and 2.694(2) Å), resulting in an (*E*,*Z*) conformation (Fig. 1d).

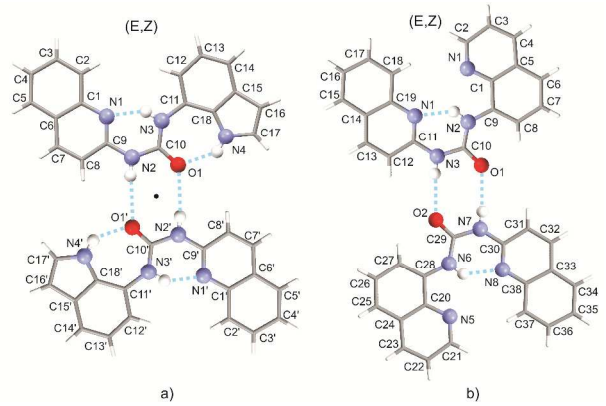


Figure 1 Ureidic dimer and relevant intra and inter-molecular interactions for $\mathbf{L^1\alpha}$ (a) as representative for the pair ($\mathbf{L^1\alpha}$ and $\mathbf{L^1\beta}$) and $\mathbf{L^2}$(b) in the (*E,Z*) conformation. The numbering scheme is also reported. Centre of inversion is indicated as • (symmetry code: -x+5/3, -y+1/3, -z-2/3).

A further common feature in the three structures is represented by the adoption of a similar supramolecular synthon[14] (Fig 1a and b) consisting of a dimer (centrosymmetric for $\mathbf{L^1\alpha}$ and pseudo-centrosymmetric for $\mathbf{L^1\beta}$ and $\mathbf{L^2}$) connected via hydrogen bonds involving the donor ureidic carbonyl group of one molecule and the ureidic NH group not involved into intramolecular hydrogen bonds of an adjacent molecule (N(2)···O(1) distances are 2.845(4) Å for $\mathbf{L^1\alpha}$, N(102)···O(201) and N(202)···O(101) distances are respectively 2.997(5) Å and 2.848(5) Å for $\mathbf{L^1\beta}$ and N(3)···O(2) and N(7)···O(1) distances are 2.830(2) and 2.888(2) Å for $\mathbf{L^2}$). This is not surprising if the similar shape/conformation and the common set of hydrogen bond donor and acceptor are taken into account.

A crystal packing comparison of the three structures $\mathbf{L^1\alpha}$, $\mathbf{L^1\beta}$ and $\mathbf{L^2}$, carried out using the XPac program[15,16], reveals that this common supramolecular synthon is precursor of a higher dimensional common molecular arrangement (experimental details of the analysis are provided in ESI†). The analysis reveals a 1-D similarity (dissimilarity index χ = 8.2)[15b] defined as Supramolecular Construct[15a] (SC A). This consists of a row of ureidic dimers which respectively propagates along the *001* direction for $\mathbf{L^1\alpha}$ (lattice vector = 7.098 Å), the *0-10* direction for $\mathbf{L^1\beta}$ (lattice vector = 7.131 Å) and the 100 direction for $\mathbf{L^2}$ (lattice vector = 8.041 Å).). Apart the N-H···O dimers discussed above (Figure 1), no significant interactions are involved in connecting the SC A (Figure 2) which is mainly the result of the close packing. The only exception is represented by $\mathbf{L^1\beta}$, in which π-π interactions respectively involving the ureidic and quinolinic moieties of adjacent dimers, contribute in connecting this molecular arrangement (the shortest Cen-Cen distances are respectively 3.63 Å and 3.80 Å).

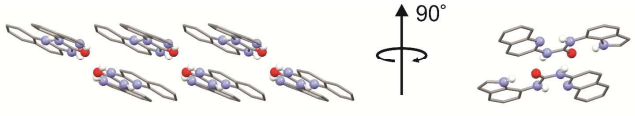


Figure 2 Representation of the SC A along its direction of propagation viewed along two perpendicular direction.

The SCs A are then differently assembled in the three structures, generating major departures in the resulting crystal packing (Figure 3). The analysis also reveals in the structure of $\mathbf{L^1\alpha}$ the presence of 1-D channels built by indolic units and developing along the *001* direction. Furthermore the analysis reveals that no hydrogen bond donor or acceptor site are available in the cavity. These channels are consistent with the fact that $\mathbf{L^1\alpha}$ crystallised including solvent molecules (MeOH)[17] in the crystal packing (see also ESI†).

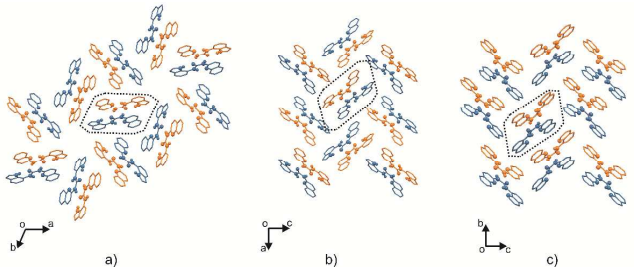


Figure 3. Crystal packing representation of the three structures $\mathbf{L^1\alpha}$, $\mathbf{L^1\beta}$ and $\mathbf{L^2}$. a) $\mathbf{L^1\alpha}$ viewed along the *001* direction; b) $\mathbf{L^1\beta}$ viewed along the *010* direction; c) $\mathbf{L^2}$ viewed along the *100* direction. The molecules are colour coded according to the orientation of the ureidic C-O vector: blue pointing towards the viewer, orange pointing away from the viewer. An instance of the SC A viewed along its direction of propagation is also indicated by black dashed lines.

We investigated whether the two receptors could assume in solution the same conformation observed in the solid state and which was their behaviour in the presence of anionic substrates.

In $CDCl_3$ solution $\mathbf{L^1}$ adopts the same (*E,Z*) conformation observed in the solid state as confirmed by ^{1}H-NMR chemical shift assigned by ^{1}H-^{1}H TOCSY experiments. In particular the H3A signal, involved in a strong intramolecular hydrogen bond, is observed at 12.97 ppm, the H4A signal is observed at 10.20 ppm and the H2A one is observed at 7.86 ppm. The chemical shift of the H2A signal is concentration dependent in the concentration range of 20-0.25 mM (see Figure 4) in agreeement with its involvement in an intermolecular hydrogen bond forming a duplex as observed in the solid state, while the H3A and the H4A signals are concentration independent being locked by intramolecular hydrogen bonds. A nonlinear regression analysis[18] of the ^{1}H-NMR data yielded to a dimerization constant of 430± 37 M^{-1} (see ESI†).

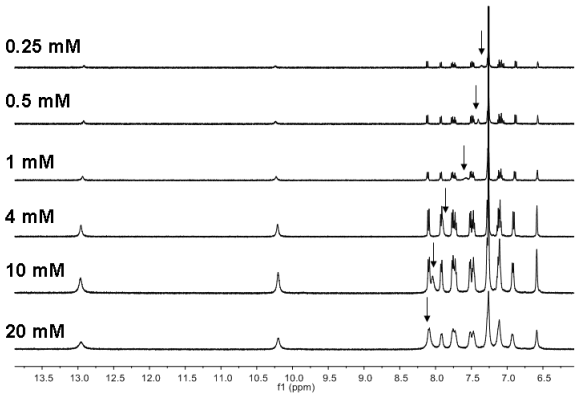


Figure 4 ^{1}H-NMR stack plot of solutions of $\mathbf{L^1}$ in $CDCl_3$ at 298 K at decreasing concentrations. The arrows indicate the H2A signal moving towards higher fields upon dilution.

Moreover, variable temperature ^{1}H-NMR experiments confirmed the presence of a duplex in solution in these experimental conditions as, once again, the H2A signal moves upfield by increasing the temperature ($1.50\cdot10^{-2}$ ppm K^{-1}) while the signal of H3A involved in an intramolecular hydrogen bond shows a much lower shift with temperature ($5.27\cdot10^{-2}$ ppm K^{-1}); in the range 294-321 K;[19] the H4A signal resulted unaffected (see ESI†).

Anion binding studies were performed by means of ^{1}H-NMR titrations in $CDCl_3$ in the presence of acetate, benzoate and chloride (as their tetrabutylammonium salts). Interestingly, upon addition of 0.4 equivalents of acetate or benzoate all the NH signals broaden and the H8A signal starts to move downfield. In particular, in the presence of an excess of acetate (around 3 equivalents) the NH signals can be observed again as sharp signals as shown in the stack plot in Figure 5.

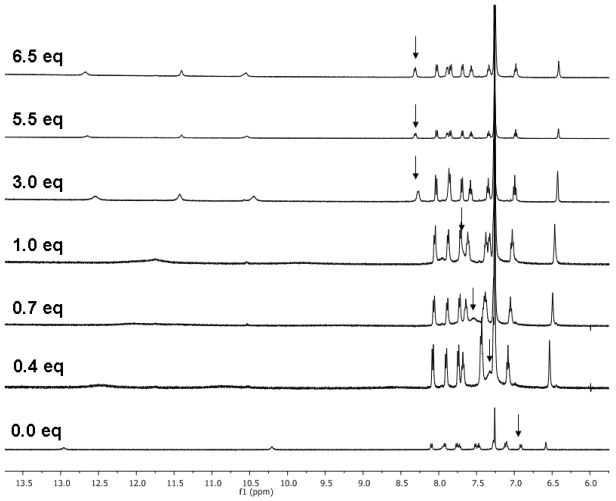


Figure 5 ^{1}H-NMR stack plot of a $CDCl_3$ solution of $\mathbf{L^1}$ (0.005 M) upon addition of tetrabutylammonium acetate (0.075 M) in $CDCl_3$ at 298 K. The arrows indicate the H8A signal.

In particular the signal for H3A is not affected by the presence of the anionic substrate, indicating that this proton is still involved in the intramolecular hydrogen bond N3−H3A···N1, while the H2A, H4A, and H8A signals move downfield (about 1.5 ppm, 2.7 ppm, and 1.4 ppm, respectively). These results suggest that upon addition of acetate the duplex is no longer present in solution and the anion is bound to each monomer by means of three hydrogen bonds, two from the NH moieties (one ureidic and one indolic) and one from the CH group of the quinoline.

A similar behaviour was observed in the presence of benzoate while in the case of chloride the broaden of the NH signals was less dramatic (Figure 6).

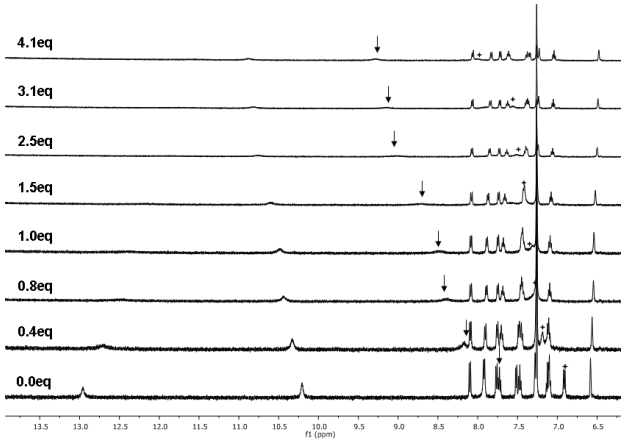


Figure 6 ^{1}H-NMR stack plot of a $CDCl_3$ solution of $\mathbf{L^1}$ (0.005 M) upon addition of tetrabutylammonium chloride (0.075 M) in $CDCl_3$. The arrows indicate the H8A (upfield) and the H2A (downfield) signals.

The broadening of the NH signals prevented us from determining the affinity costants of $\mathbf{L^1}$ for the anionic substrates. For this reason we moved to DMSO-d_6, a solvent more suitable for these type of studies.

In DMSO-d_6, probably because of its higher solvating power, the formation of the duplex was not observed as confirmed by dilution and variable temperature experiments. However, on the basis of the ^{1}H chemical shift values observed (10.12(H2A) , 10.89 (H4A) and 11.67 (H3A) ppm) in comperison with those observed for the two ureidic and the indolic N-H groups in the symmetric 1,3-bis(1H-indol-7-yl)urea,[7c,20] (8.63 and 10.77 ppm, respectively) the presence of the two aforementioned intramolecular H-bonds, namely, N3−H3A···N1 and N4−H4A···O1, can be inferred. This conclusion is further supported by both two-dimensional NOESY[21] and selective one-dimensional DPFGSE-noesy1d[22] experiments (200 ms mixing time). On the basis of the NOESY cross-peaks relative intensity, an upper limit of 2.7 Å has been applied to restrain the corresponding inter-proton distances together with the gromos-53a6 force field[23] parameters. One hundred structures were independently calculated using a simulated annealing protocol[24] with the software Dynamo.[25] Additional inter-atomic distance restraints were also introduced to simulate the two mentioned intramolecular H-bonds. Violations from the experimental NOEs have never been observed. The 20 structure with the lowest potential energy were then selected and used for the analysis. Figure 7 shows the average structure together with the quantitative estimation of the different NOE enhancements (obtained analyzing the one-dimensional noesy results with the so-called PANIC method).[26] It is interesting to note that H2A and H4A protons resulted to have almost the same distance from H3A, as reflected by comparable NOE enhancements. However, H2A provided a relatively higher NOE-enhancement to H8A, as well as H3A to H12A. In the resulting molecular structure the two aromatic rings do not lie on the same plane but are differently tilted with respect to the carbonyl group, and H2A and H4A are located on opposite sides of the molecule. Overall, the statistical analysis showed that the most populated conformer is characterized by the two

dihedral angles N1–N2–C10–O1 and N4–N3–C10–O1 equal to -106° and +15°, respectively. The (*E*,*Z*) conformation of the free receptor is thus maintened in solution both in $CDCl_3$ and in DMSO-d_6.

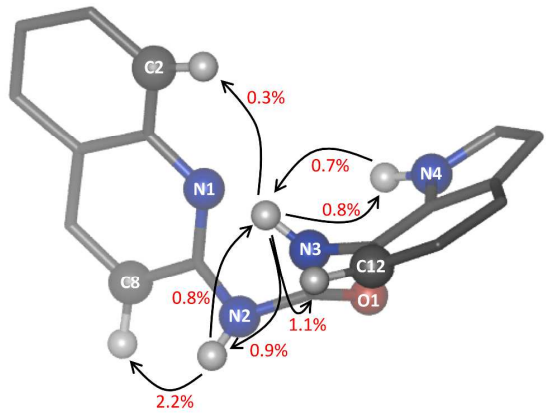


Figure 7 The most populated conformation adopted in solution by $\mathbf{L^1}$ calculated on the basis of the experimental NOEs in DMSO-d_6 is reported together with the quantitative estimation of the NOE enhancements. The protons not mentioned in the discussion are omitted for clarity.

Anion-binding studies were performed by means of ^{1}H-NMR titrations in DMSO-d_6. In this experimental conditions no broadening of the NH signals was observed, as expected. The EQNMR program[27] was used to calculate stability constants from the ^{1}H-NMR titration curves obtained (see ESI†) fitting the data to a 1:1 binding model. As shown in Table 2 moderately high stability constants were observed for the adducts formation between $\mathbf{L^1}$ and the anions considered with the highest value of K_a = 1203 M^{-1} for acetate. However, the affinity of $\mathbf{L^1}$ towards anions is lower than that observed with symmetric bis-indolylureas[7c] and symmetric and asymmetric carbazolylureas.[7b]

This is probably due to the fact that only two of the three NHs available in L^1 are effectively interacting with the anionic substrate. During ^{1}H-NMR titrations, in fact, we noticed that of the three NH groups of $\mathbf{L^1}$ only two (namely the H2 and the H4A) were shifted downfield upon addition of anions as shown in Figure 8 in the case of acetate.

Table 1. Equilibrium constants (K_a/M^{-1}) for the reactions of $\mathbf{L^1}$ and $\mathbf{L^2}$ with the tetrabutylammonium anion salts considered (HCO_3^- was used as tetraethylammonium salt) in DMSO-d_6 at 300 K. All errors estimated to be ≤10% (except for chloride for which the error is estimated to be 21%) (see ESI †).

Anion	$\mathbf{L^1}$	$\mathbf{L^2}$
F^-	deprot.	deprot.
Cl^-	12	no interaction
CH_3COO^-	1203	no interaction
$C_6H_5COO^-$	634	no interaction
HCO_3^-	282	no interaction
$H_2PO_4^-$	n.d	no interaction

The N3–H3A resulted unaffected by the addition of all the anions considered, indicating its involvement in the intramolecular hydrogen bond with N1. As observed in $CDCl_3$, also in DMSO-d_6 the C8–H8A is also affected by the presence of anions.

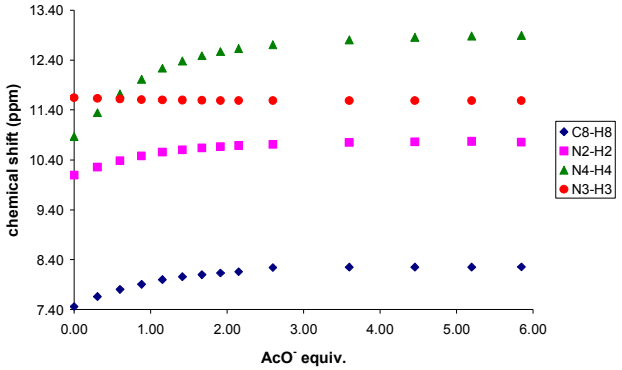


Figure 8 ^{1}H-NMR titration curves of $\mathbf{L^1}$ (0.005 M) with tetrabutylammonium acetate (0.075 M) in DMSO-d_6.

Similar titration curves were obtained with the other anions (see ESI†).

As we observed the most interesting results with acetate we decided to perform a detailed NMR study of $\mathbf{L^1}$ in the presence of this anion in order to understand the conformational changes experienced by the receptor and the nature of the complex.

Following the same procedure adopted in the absence of the anion, the most populated conformer for $\mathbf{L^1}$ in the presence of one equivalent of acetate was computed on the basis of the ^{1}H-NMR noesy experiments. It is interesting to note that the 2D-NOESY cross-peaks pattern resulted to be comparable to that obtained in the absence of acetate, indicating that the conformational changes induced by the anion are not dramatic. Violations of the experimental NOEs have never been observed in all of these three cases and the N3−H3A···N1 intramolecular H-bond was always present. In particular, three different possible complexes have been hypothesised, all of which are, at least in principle, compatible with the 1:1 binding model derived from the titration curves (Figure 10). First, one acetate molecule might coordinate to the H2A, the H4A and the H8A hydrogens of the same $\mathbf{L^1}$ molecule (Figure 9a). Second, two acetate molecules could coordinate to two $\mathbf{L^1}$s, thus forming a duplex, by bridging analogous N-H groups, i.e. one of the acetates coordinating both the H2As and the H8As, while the other both the H4As (Figure 9b). Lastly, the duplex could be formed by two acetate molecules coordinating different N-H groups from two $\mathbf{L^1}$s (Figure 9c).

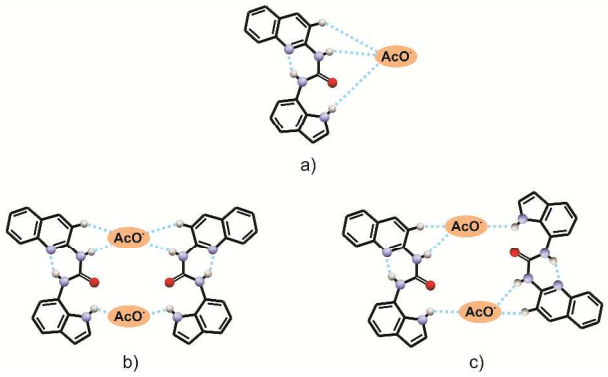


Figure 9 Proposed coordination modes of $\mathbf{L^1}$ with acetate.

Correspondingly, the most populated conformer obtained in each of the cases showed the same values for the N1−N2−C10−O1 and N4−N3−C10−O1 dihedral angles, ca. -136° and -67°, respectively. Thus, compared to the conformer obtained in the absence of anion (see Fig. 5), while the tilt angle of the quinoline moiety remains almost comparable (due to the presence of the aforementioned intramolecular H–bond), that of the indole changes dramatically. Figure 10 shows the average structure of $\mathbf{L^1}$ in the presence of one equivalent of acetate together with the quantitative estimation of the different NOE enhancements.

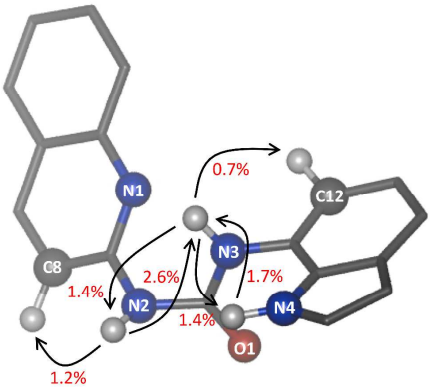


Figure 10 The most populated conformation adopted in solution by $\mathbf{L^1}$ in the presence of acetate calculated on the basis of the experimental NOEs in DMSO-d_6 is reported together with the quantitative estimation of the NOE enhancements. The protons not mentioned in the discussion are omitted for clarity.

Similarly to what was observed in the absence of the acetate, H2A and H4A have almost the same distance from H3A. However, in the presence of acetate, the inter–HN NOE enhancements are higher than the H2A–H8A and the H3A–H12A ones. These observations further confirmed the structural change induced by the presence of the acetate, which, as shown in Figure 10, resulted in all the three HNs being located on the same side of the molecule. Finally, a deeper analysis of the ^{1}H chemical shift values obtained in the absence and in the presence of the acetate, allowed for discriminating between the three proposed binding possibilities. Indeed, not only the chemical shift of the H2A, H4A and H8A protons changed, as said, but the H5A, H7A resonances also sligthly shifted, while all the other signals remained unaffected. First, this is clearly not compatible with the model of one acetate molecule coordinating a unique $\mathbf{L^1}$. The formation of a supramolecular assembly like those in Fig.10b and Fig.10c, on the other hand, provides a valid explanation. Infact, while the shifts for H2A, H4A and H8A can be explained considering the coordination of the anion, only the approaching of a second molecule of $\mathbf{L^1}$ involved in the supramolecular assembly, might affect the chemical shift of the H5A and H7A protons. The radial distribution functions were computed for all of the aromatic ring hydrogens of one $\mathbf{L^1}$ molecule with respect to all the carbons of the other (see ESI†). Definitely, among the two assemblies tentatively simulated, only the second one (see Fig. 9c) resulted to have the H5A and H7A protons as the closest atoms to the second $\mathbf{L^1}$ molecule. For the sake of clarity, Figure 11 shows the most representative calculated configuration for this supramolecular assembly.

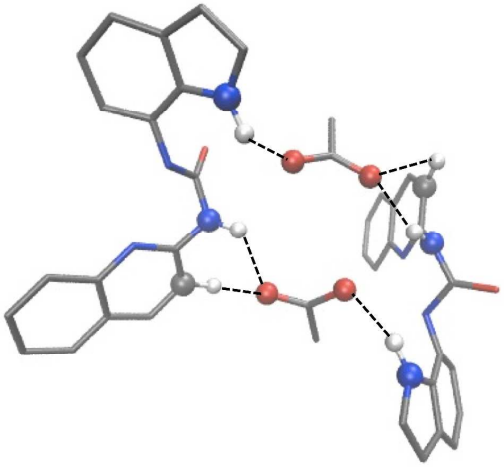


Figure 11 The most representative calculated configuration for two $\mathbf{L^1}$ and two interacting acetate molecules in the assembly formed in DMSO-d_6.

The proposed binding mode has never been observed, to the best of our knowledge, in indole containing ureas, both symmetric and asymmetric, with anions. [7, 28]

As shown in Table 1 fluoride causes deprotonation of the receptor with a colour change in the solution from colourless to yellow and a change in the fluorescence emission with the formation of a new luminescence band in the visible region (see Fig. 12). The addition of dihydrogenphosphate causes the loss of the signal of the H2A in the ^{1}H-NMR titration: this could be ascribed to a deprotonation or to a strong binding. However, the interaction with this anion is not accompained by a change of the photophysical properties of the system.

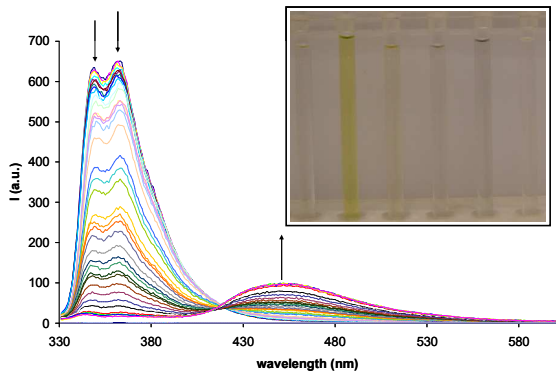


Figure 12 Changes in the fluorescence spectra of $\mathbf{L^1}$ ($1.27 \cdot 10^{-5}$ M) upon addition of increasing amounts of TBAF ($2.5 \cdot 0^{-2}$ M) in DMSO. Inset: Colour change of $\mathbf{L^1}$ (0.005 M) upon addition of five anion equivs. (0.075 M) in DMSO. From left to right: $\mathbf{L^1}$, F^-, AcO^-, Cl^-, BzO^-, HCO_3^- and $H_2PO_4^-$.

Experimental evidence suggests that $\mathbf{L^2}$ adopts a (*E*,*Z*) conformation in solution, too. Infact, we observed negligible changes (see ESI) in the ^{1}H-NMR spectrum of $\mathbf{L^2}$ in DMSO-d_6 upon addition of anions (except for fluoride that causes deprotonation without any change, however, in the absorption or emission properties of the system). Interestingly, the signal of one of the two ureidic NHs of the free $\mathbf{L^2}$ is far downfield (13.93 ppm) compared to the analogous $\mathbf{L^1}$ that falls at 11.64 ppm, and to the analogous symmetric bis-indolylurea that falls at 8.63 ppm[7c] suggesting that this NH is involved into an even stronger intramolecular hydrogen bond in solution compared to that observed for $\mathbf{L^1}$; moreover, its chemical shift is concentration independent as observed in the compound *N*,*N*′-2,di-pyridilurea (for this compound the urea NH signal falls at 12.80 ppm in $CDCl_3$; we could not perform a ^{1}H-NMR experiment on $\mathbf{L^2}$ in $CDCl_3$ due to the very low solubility of the molecule in this solvent).[29] All this is consistent with $\mathbf{L^2}$ assuming an (*E*,*Z*) conformation in solution with one ureidic NH being strongly intramolecularly hydrogen bonded as observed for $\mathbf{L^1}$. However, in this case, the absence of the indole group as hydrogen bond donor does not allow the interaction with anions as there would be only one hydrogen able to bind the guests via hydrogen bond. (Table 2).

In conclusion we have shown that when designing an anion receptor it is fundamental to consider the possibility of intra-molecular hydrogen bonds formation.

The indole moiety has demonstrated to be very useful for anion binding for the presence of the NH group that can act as an efficient hydrogen bond donor towards anionic substrates. In the case of $\mathbf{L^1}$, where an indole group has been replaced by a quinoline, the presence of an AD couple strongly stabilises the *anti* (*E*,*Z*) conformation even in the presence of anions. This favours the formation of a supramolecular architecture in solution in which two molecules of $\mathbf{L^1}$ cooperate to bind anions in an unusual fashion compared to that observed in similar symmetric and asymmetric indole-containing ureas. In contrast, $\mathbf{L^2}$ in which the indole moieties were replaced by quinolines, no interaction with anions is observed, thus confirming the crucial role played by indoles in designing neutral receptors for anion recognition.

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Notes and references

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†Electronic Supplementary Information (ESI) available: additional information as noted in the text including synthetic details for the preparation of $\mathbf{L^1}$ and $\mathbf{L^2}$, and X-ray crystallographic files in CIF format [CCDC n.]. See DOI: 10.1039/b000000x/

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