Synthesis and anion recognition studies of new ureylbenzamide-based receptors

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ABSTRACT
A new group of ureylbenzamide-based receptors (1–4) has been synthesized; its binding affinity and capacity to form supramolecular complexes in solution with different anions have been investigated. For designing these receptors, it was considered a combination of the positions of the urea and amide groups (ortho and meta), and the chromophore groups naphthyl and nitrophenyl, yielding four receptors. The position and chromophore structure affected the acidity of the urea and amide hydrogens in the order 4 > 3 > 2 > 1. All the spectroscopic studies showed a significant change of 1 and 2 compared with 3 and 4 in the presence of different TBAX salts in acetonitrile. The 1H-NMR spectra show a preferential interaction of the anions with the urea group in receptors 1 and 2 due to the less steric hindrance, while there is a cooperative interaction of amide group in receptors 3 and 4 due to the closeness of both groups.

Introduction
In recent years, research in supramolecular chemistry has experienced tremendous growth under the significant roles played by common anions in the biological and environmental world, and therefore, the development of effective methods for detecting anions is very important (1–6). Due to many possible applications, neutral receptor molecules for different anions have attracted much attention (7–10). Moreover, among the anion analytes of biological and environmental importance, fluoride is one of the most significant due to its crucial role in dental health, since most of the drinking water comes from processing plants that add fluorides before sending by the water systems to be consumed. Hence, damages both the environment when discarded and reach rivers and seas, and it is also involved in dental and bone health when fluoride is consumed (11).

Despite all efforts, attempts to increase the receptor’s affinity and specificity for fluoride ion have mostly led to a complexity of design and synthesis, and therefore there is a challenge to make an effective sensor that is sensitive and has a high association constant for fluoride ion (12–15). Ureas and thioureas are neutral receptors providing H-bond donors, which bind to anions by hydrogen bonding interactions regardless of solution pH (16, 17). A molecule with one or more preorganised urea or thiourea groups can provide H-bond donors for an anion which increases its capability to form supramolecular complexes (18–23). Other functional groups capable to...
establish electrostatic interactions with anions as iminum, guanidinium or pyridinium, have been included in the urea receptors structure to improve the strength of the interaction and the stability of the complexes (24, 25). Several receptors with additional H-bond donor groups as hydroxyl and amino, which induce a cooperative effect have been reported (14, 26).

On the other hand, it is well known that amide groups are excellent H-bond donors and may form supramolecular complexes with different anions (27, 28). This ability is exploited in the design of anion receptors with both amide and urea groups because a cooperative effect in the anion recognition (29–33).

In this work four receptors containing the urea and benzamide groups were prepared (Figure 1), a cooperative effect between these two groups was expected and the different relative position between urea and amide group (ortho and meta) were designed to modulate the urea and amide hydrogens acidity. The analytical response to study the supramolecular anions recognition was determined by the chromophore attached to the urea group (nitrophenyl and napthyl).

**Experimental**

**Materials and equipment**

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. 1H NMR spectra were recorded using a Bruker 400 MHz NMR spectrometer at a probe temperature of 30 °C with TMS as internal standard. Electronic impact mass spectra were obtained by direct insertion in an Agilent 5975C mass spectrometer, and the intensities were reported as a relative percentage to the base peak after the corresponding m/z value. FAB mass spectra and HRMS were recorded in a MStation JMS-700 JEOL. Fluorescence emission spectra were obtained using a Varian spectrophotometer. UV–Vis absorption spectra were obtained using a Cary 300 spectrophotometer.

**Procedure for the spectrophotometric titrations**

The effect of anions upon the absorbance of receptors 1 and 3 was examined by adding 6 μL of a 5 × 10⁻³ M TBAX solution to a known volume (3 mL) of a 5 × 10⁻⁵ M receptor solution. The effect of anions upon the absorbance of receptors 2 and 4 was examined by adding 6 μL of a 2.5 × 10⁻³ M TBAX solution to a known volume (3 mL) of a 2.5 × 10⁻⁵ M receptor solution.

**Procedure for the fluorimetric titrations**

The effect of anions upon the emission of 1 was examined by adding 3 μL of a 5 × 10⁻³ M TBAX solution to a known volume (3 mL) of a 2.5 × 10⁻⁵ M receptor solution. The effect of anions upon the emission of 3 was examined by adding 6 μL of a 5 × 10⁻³ M TBAX solution to a known volume (3 mL) of a 5 × 10⁻⁵ M receptor solution. The addition was limited to 0.120 mL, so that the dilution remained insignificant.

**Synthesis**

*N-Benzyl-3-nitrobenzamide (6).* Benzylamine (0.754 mmol) was added slowly to a stirred mixture of 3-nitrobenzoyl chloride (5) (140 mg, 0.754 mmol) and triethylamine (0.15 mL) in dry THF under Ar atmosphere. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with distilled water and then was extracted with CH₂Cl₂. The organic layer was dried over anhydrous Na₂SO₄ and evaporated to afford a solid product. The product was suspended in diethyl ether and the solvent was removed in vacuo and temperature to give an analytically pure solid compound. 61% yield. Mp 90–92 °C. FTIR: 3306, 2921, 2850, 1719, 1606 cm⁻¹. 

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**Figure 1.** Ureylbenzamide receptors 1–4.
1709, 1643, 1603, 1504, 1451 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.60 (t, J = 2.0 Hz, 1H), 8.34 (ddd, J = 8.2, 2.2, 1.1 Hz, 1H), 8.17 (ddd, J = 7.8, 1.7, 1.1 Hz, 1H), 7.63 (t, J = 8.1 Hz, 1H), 7.34 (m, 5H), 6.82 (t, J = 5.7 Hz, 1H), 4.65 (d, J = 5.7 Hz, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ 164.0, 137.7, 136.1, 133.5, 130.1, 129.1, 128.8, 128.2, 128.1, 126.3, 122.0, 44.6. MS (EI) m/z: 256 (M⁺), 129.1, 128.8, 128.2, 128.1, 126.3, 122.0, 44.6. MS (EI) m/z: 128.7, 127.8, 127.5, 117.9, 116.4, 113.8, 44.0. MS (FAB⁺): calculated for C₂₅H₂₂N₃O₂ 396.1712, found 396.1709.

3-Amino-N-benzylbenzamide (7). A mixture of 6 (0.192 g, 0.749 mmol) and Pd/C 10% (40 mg) was stirred under H₂ atmosphere. The reaction mixture was stirred overnight at room temperature and heat to obtain a pale yellow solid. 75% yield. Mp 218–220 °C. FTIR (ATR): 3280, 1680, 1626, 1508 cm⁻¹. ¹H NMR (DMF-d₇, 400 MHz): δ 10.29 (s, 1H), 9.63 (s, 1H), 9.24 (t, J = 5.8 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.16 (m, 1H), 7.93 (m, 1H), 7.72–7.65 (m, 9H), 7.1 (t, J = 7.3 Hz, 1H), 4.51 (d, J = 5.8 Hz, 2H). ¹³C NMR (DMF-d₇, 100 MHz): δ 168.3, 153.5, 139.7, 139.4, 134.3, 133.8, 132.0, 131.3, 128.4, 128.2, 127.8, 127.7, 127.2, 126.9, 125.9, 125.7, 125.6, 124.1, 122.7, 121.8, 121.2, 120.6, 42.6. MS (EI) m/z: 395 (M⁺, 1), 252 (10), 226 (30), 142 (80), 91 (100). MS (FAB⁺): calculated for C₁₂H₁₀N₂O₃ 391.1412, found 391.1412.

N-Benzyl-3-(3-(naphthalen-1-yl)ureido)benzamide (3). Pale yellow solid. 75% yield. Mp 196–198 °C. FTIR (ATR): 3280, 1680, 1626, 1508 cm⁻¹. ¹H NMR (DMF-d₇, 400 MHz): δ 10.29 (s, 1H), 9.63 (s, 1H), 9.24 (t, J = 5.8 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.16 (m, 1H), 7.93 (m, 1H), 7.72–7.65 (m, 9H), 7.1 (t, J = 7.3 Hz, 1H), 4.51 (d, J = 5.8 Hz, 2H). ¹³C NMR (DMF-d₇, 100 MHz): δ 168.3, 153.5, 139.7, 139.4, 134.3, 133.8, 132.0, 131.3, 128.4, 128.2, 127.8, 127.7, 127.2, 126.9, 125.9, 125.7, 125.6, 124.1, 122.7, 121.8, 121.2, 120.6, 42.6. MS (EI) m/z: 395 (M⁺, 1), 252 (10), 226 (30), 142 (80), 91 (100). MS (FAB⁺): calculated for C₁₂H₁₀N₂O₃ 391.1412, found 391.1412.

N-Benzyl-2-(3-(4-nitrophenyl)ureido)benzamide (4). Pale yellow solid. 75% yield. Mp 218–220 °C. FTIR (ATR): 3277, 1696, 1618, 1596, 1560, 1495 cm⁻¹. ¹H NMR (DMF-d₇, 400 MHz): δ 10.17 (s, 1H), 10.5 (s, 1H), 9.35 (t, J = 5.8 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 9.2 Hz, 2H), 7.78 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 9.2 Hz, 2H), 7.49 (td, J = 7.8, 1.0 Hz, 1H), 7.35–7.20 (m, 5H), 7.11 (t, J = 7.6 Hz, 1H). ¹³C NMR (DMF-d₇, 100 MHz): δ 168.3, 151.9, 146.7, 141.1, 140.4, 139.4, 139.2, 131.8, 128.4, 128.0, 127.2, 126.9, 125.1, 121.8, 120.8, 117.3, 42.6. MS (EI) m/z: 390 (M⁺, 1), 252 (100), 91 (60). MS (FAB⁺): 391 [M+H⁺]. HRMS (FAB⁺): calculated for C₂₁H₁₄N₄O₄ 391.1406, found 391.1412.

Molecular modelling

3D molecular modelling and optimisation of geometries of the proposed sensor structures and its complexes were carried out by DFT, method B3LYP and the 6–31+G (d, p) base using Gaussian 09 computational programme (34).

Results and discussion

Synthesis

The synthetic routes for compounds 1–4 are shown in Scheme 1. First, m-nitrobenzoyl chloride was treated with benzylamine obtaining the benzamide 6. Then, the nitro-reduction of 6 under hydrogen atmosphere gave the 3-aminobenzamide 7, and finally the addition of the naphthyl or nitrophenyl isocyanate lead to the products 1 and 2. In the other route, isatoic anhydride was treated with benzylamine to obtain the 2-aminobenzamide 9. Then, the
latest compound was treated with naphthyl or nitrophenyl isocyanate to afford the receptors 3 and 4.

Receptors 1–4 were characterised by infrared spectroscopy (IR), nuclear magnetic resonance (NMR) and electronic impact mass spectrometry MS(EI), and their chemical composition was verified by high-resolution mass spectrometry (HRMS). Receptors 1–4 IR spectra showed the vibration corresponding to the urea and amide N-H stretching between 3260 and 3300 cm\(^{-1}\). Also, the two stretching vibrations for urea and amide carbonyls were found at 1640–1700 and 1618–1630 cm\(^{-1}\), respectively.

In the \(^1\)H NMR spectra obtained in DMSO-\(d_6\), the typical signal patterns for a meta and ortho substituted aromatic ring for receptors 1–2 and 3–4, respectively, were observed. Also, the signals for the chromophore groups, naphthyl in 1 and 3, or nitrophenyl in 2 and 4, were detected and correctly assigned (Figures S1–S4). As was expected, the chemical shift of the amide and urea N-H hydrogens was affected by the relative position and the structural nature of the chromophore due to resonance and inductive effects (see Table S1). In the meta receptors (1 and 2) the chromophore has no effect over the amide hydrogen (H\(_g\)) chemical shift. The major effect was observed over the urea hydrogen H\(_g\) directly attached to the chromophore. The signal moved 0.88 ppm downfield by the presence of the nitrophenyl group. In the ortho receptors H\(_g\) hydrogen was slightly shifted, 0.18 and 0.30 ppm for 3 and 4, respectively. Now, the urea signals H\(_g\) were the most shifted to downfield due to the resonance effect in the benzamide ring. The H\(_g\) signals also were considerably affected by an inductive effect in 3 combined with a resonance effect in 4.

In conclusion, the receptors acidity order was 4 > 3 > 2 > 1, and this property had a significant influence in the anions recognition. Likewise, the solvent affected the chemical shifts of the signals, in a mixture CD\(_3\)CN:DMSO-\(d_6\) (9:1) they move to up field because of the minor competitiveness of the mixture.

Receptors 1–4 were analysed by MS(EI), and the molecular ions M\(^+\) at 395 amu for 1 and 3, and 390 amu for 2 and 4, were detected. MS(FAB\(^+\)) analysis provided the corresponding [M+H]\(^+\) ions at 396 amu for 1 and 3, and at 391 amu for 2 and 4. The HRMS analysis confirmed the chemical composition for all compounds.

**Study of anions recognition by electronic absorption**

Figure S5 shows the UV–Vis spectra for receptor 1–4. The receptors 1 and 3 have a broad absorption band at 296 nm due to the amino conjugated naphthyl group. The receptors 2 and 4 present a broad absorption bands slightly shifted to 338 and 332 nm, respectively, owing to the nitrophenyl group. These bands correspond to an auxocrome π–π* electronic transitions.

It was possible to evaluate the supramolecular interaction of receptors by UV–Vis in acetonitrile and DMSO by titration with tetrabutylammonium salts, TBAX, where X = AcO (A), BzO (B), H\(_2\)PO\(_4\) (HP), F, Cl(C) and Br. The results showed significant changes in the absorption bands of receptor 2, followed by 1 and 4 (Figures S6, S7 and S10). Interestingly, the receptor 3 did not show changes with any anion at any concentration (Figure S9). Figure 2 shows the UV–Vis spectra obtained by titration of 2 with TBAA.

The absorption band at 337 nm shifted to 368 nm and two isosbestic points at 270 and 348 nm are present. These results indicate the supramolecular interaction between receptor 2 and acetate anion. Similar results with TBAB and TBAF were observed. Also, it was observed a weaker interaction with the rest of the anions (Figure S7). The effect of the anion over the receptor 2 absorbance was in the order AcO\(^-\) > BzO\(^-\) ≈ F\(^-\) >> Cl\(^-\) > H\(_2\)PO\(_4\)\(^-\) ≈ Br\(^-\) (Figures 2(b) and S8). The absorbance curves fitted with a typical 1:1 interaction model.

The receptor 1 showed response towards these TBAX salts, with exception of TBABr. During the titration, the absorption band at 296 nm shifted to 305 nm with a hyperchromic effect caused by the interaction with the anions. Two isosbestic points at 278 and 296 nm were observed.

![Scheme 1. Synthesis of ureylbenzamide receptors 1–4.](image-url)
complexes with values in the order of $10^6$ for TBAA and $10^5$ for TBAB and TBAF, as well decrease two or three orders as the geometry changes and the size of the anion increases. This receptor has affinity for trigonal anions due to the well-known Y interaction with the urea group. For halides, the binding constant decreases as the size increases. The association constant values were lower with receptors 1 and 4, in the order of $10^4$ and $10^3$, even with fluoride, acetate and benzoate salts. The conclusion at this point was that the relative position between the amide and urea groups was determinant in the anion recognition and the complexes stability due to this steric factor. Also, the shape, size and basicity of the anions have a great influence in the recognition process and the complexes stability.

To explain the behaviour observed with receptor 3 in the titrations with TBAX salts, the structure of the free receptor and the complex with fluoride were optimised by theoretical calculations first with the PM6 semiempirical method and then using the density functional theory and the non-local correlation B3LYP with a 6–31+G(d,p) basis in the gas phase (14, 17–19, 22).

Two aspects that stand out in the geometry of the free receptor are the intramolecular hydrogen bond between the amide carbonyl group and the urea hydrogen Hf, and the coplanarity of the naphthyl-urea-benzamide moieties (Figure 3(a)). In the complex, the fluoride ion interacts with the two urea hydrogens and the amide carbonyl rotates allowing the interaction with the N-H hydrogen. The coplanarity in the molecule is lost, and the naphthyl group is almost in a perpendicular position respect to the urea and benzamide moieties (Figure 3(b)). These conformational changes are responsible for the lack of signal in the titrations of receptor 3 with the TBAX salts by UV–Vis, because of the electronic conjugation from the naphthyl group to the urea is avoided.

The same calculations were made for receptors 1, 2 and 4, and their respective complexes with fluoride (see Figures S12–S14). The coplanarity of the chromophore-urea-benzamide system present in the three receptors is conserved in their respective complexes with fluoride, and as a consequence there is an effect over electronic transitions for the system by the coordination of the anion.

The major response with this receptor was observed with TBAF (Figure S6 and S11).

The receptor 4 showed response with TBAA, TBAB, TBAHP and TBAF. The absorption band is slightly shifted from 332 to 346 nm and it has a hypochromic behaviour, which indicates the interaction with the anions. There are two isosbestic points at 276 and 353 nm. The major response with this receptor was observed with TBAA (Figures S7 and S11).

In Table 1 are listed the association constants for the complexes calculated from the absorbance data using the Hypspec programme (35–37).

The results are consistent with the experimental observations, the biggest constants correspond to receptor 2

![Figure 2.](image)

**Figure 2.** (colour online) (a) UV–Vis spectra obtained in the titration of 2 with TBAA in acetonitrile. [2] = 2.5 × 10⁻⁵ M. (b) Normalised absorbance profiles obtained by the titration of 2 with different TBAX salts, λ = 368 nm.

<table>
<thead>
<tr>
<th>Salt</th>
<th>Receptor 1 ( \log K_f )</th>
<th>A/R ratio</th>
<th>Receptor 2 ( \log K_f )</th>
<th>A/R ratio</th>
<th>Receptor 4 ( \log K_f )</th>
<th>A/R ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBAA</td>
<td>4.55 ± 0.005</td>
<td>1:1</td>
<td>6.06 ± 0.05</td>
<td>1:1</td>
<td>4.35 ± 0.002</td>
<td>1:1</td>
</tr>
<tr>
<td>TBAB</td>
<td>3.55 ± 0.01</td>
<td>1:1</td>
<td>5.28 ± 0.004</td>
<td>1:1</td>
<td>3.85 ± 0.005</td>
<td>1:1</td>
</tr>
<tr>
<td>TBAF</td>
<td>4.17 ± 0.005</td>
<td>1:1</td>
<td>5.72 ± 0.002</td>
<td>1:1</td>
<td>4.22 ± 0.02</td>
<td>1:1</td>
</tr>
<tr>
<td>TBAHP</td>
<td>3.68 ± 0.01</td>
<td>1:1</td>
<td>3.43 ± 0.03</td>
<td>1:1</td>
<td>4.31 ± 0.02</td>
<td>1:1</td>
</tr>
<tr>
<td>TBAC</td>
<td>3.60 ± 0.004</td>
<td>1:1</td>
<td>4.24 ± 0.004</td>
<td>1:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBABr</td>
<td>3.74 ± 0.01</td>
<td>1:1</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
showed broad fluorescence bands due to the presence of the naphthyl fluorophore attached to the urea group. Interestingly, the receptor 1 is more fluorescent than 3, this indicates more electron delocalisation from the urea towards the naphthyl group in this receptor, while in 3 the inductive effect of the benzamide system is predominant lowering the electron delocalisation. As was expected, the fluorescence in receptors 2 and 4 is quenched because of the presence of a nitro group in the chromophore.

The quantum yields \( \Phi_F \) at \( 1 \times 10^{-6} \) M were determined following the Equation (1).

\[
\Phi_F = \Phi_R \times \frac{\text{Int}}{A \cdot n^2} \cdot n^2_R
\]

Figure 4. (colour online) (a) UV–Vis spectra obtained in the titration of 2 with TBAF in DMSO. [2] = 2.5 \times 10^{-5} M.
Note: Inset: Absorbance profile at 355 nm.

Figure 3. (colour online) Receptor 3 (a) and complex 3−F\(^-\) (b) optimised geometries calculated by DFT.

The interaction of receptors 1–4 with TBAX salts was analysed using DMSO as solvent. Interestingly, only with receptor 2 spectroscopic changes were observed in the presence of TBAA, TBAB and TBAF. In Figure 4 are shown the spectra obtained with TBAF, where the absorbance at 355 nm diminishes and slightly shift to red colour and a new band appears at 485 nm after the addition of one TBAF molar equivalent. Also, two isosbestic points are present at 288 and 380 nm. In addition, the solution turns from colourless to red colour. The presence of this new band gave evidence of the urea group deprotonation by fluoride due to high receptor acidity (13,16,30,31).

In the titration of 2 with TBAA in DMSO the absorption band shifted from 355 to 375 nm with two isosbestic points at 278 and 365 nm; with TBAB the absorption band slightly shifted to higher wavelength, the isosbestic points were at 290 and 370 nm. The band at 485 nm was observed in the titration of 2 with both salts, but the absorbance was insignificant compared to TBAF (Figure S15). These results are important because they demonstrated the strong supramolecular interaction between receptor 2 with TBAX salts even in a very competitive media as DMSO solvent.

**Study of anions recognition by molecular fluorescence**

The fluorescence spectra were obtained for receptors 1–4 in acetonitrile and are shown in Figure S16. Receptors 1 and 3 showed broad fluorescence bands due to the presence of the naphthyl fluorophore attached to the urea group. Interestingly, the receptor 1 is more fluorescent than 3, this indicates more electron delocalisation from the urea towards the naphthyl group in this receptor, while in 3 the inductive effect of the benzamide system is predominant lowering the electron delocalisation. As was expected, the fluorescence in receptors 2 and 4 is quenched because of the presence of a nitro group in the chromophore.

The quantum yields \( \Phi_F \) at \( 1 \times 10^{-6} \) M were determined following the Equation (1).

\[
\Phi_F = \Phi_R \times \frac{\text{Int}}{A \cdot n^2} \cdot n^2_R
\]

where \( \Phi_F \) is the sample quantum yield, \( \text{Int} \) is the area under the emission peak (at given wavelength scale), \( A \) is the absorbance at the excitation wavelength and \( n \) is the refractive index of the sample. The subscript \( R \) denotes the respective values of the reference substance. Antracene was used as reference substance. The quantum yield values of the receptors are in accordance with the experimental tendency, \( 1 > 3 >> 2 > 4 \). The photophysical parameters of receptors 1–4 in acetonitrile are listed in Table S3.

The receptor 1 interaction with TBAA, TBAB, TBAF and TBAHP salts was studied by molecular fluorescence. In general, the fluorescence intensity diminished as the TBAX salt was added indicating the interaction with the anions (Figures 5 and S17). The fluorescence profiles showed an affinity order as follows TBAA > TBAB > TBAF > TBAHP.

Also, the interaction of receptor 3 with TBAX salts was evaluated by fluorescence. The effect of the interaction with the anion over the fluorescence intensity was lower compared with receptor 1 (Figures 6 and S18). The fluorescence profiles showed an affinity order as follows TBAF > TBAA > TBAB > TBAHP. The difference in the response of receptor 3 is attributed to the combination of
the steric hindrance in this receptor and the size and shape of the anions (fluoride is a small spherical anion).

In Table 2 are listed the association constants for the complexes calculated from the emission data using the Hypspec programme.

The results are consistent with the experimental observations, the biggest values correspond to the complexes with TBAA and TBAB followed by TBAF and TBAHP. Interestingly, the binding constants magnitude are similar for each anion with both receptors. The relative position between the amide and urea groups with the same chromophore affected the analytical response, but apparently, according with binding constants the strength of the interaction is equal.

**NMR studies**

$^1$H NMR titrations in CD$_3$CN:DMSO-$d_6$ (9:1) were performed with receptors 1–4 to establish their interaction site with the different anions. Specifically, we were interested in the cooperative interaction of amide group in the recognition process. In the titration of receptor 1 with TBAA, both urea hydrogen Hf and Hg signals move to downfield 1.04 and 0.95 ppm, respectively, after the addition of 2 M equivalents of the salt (Figure 7). The amide hydrogen signal He remains at the same chemical shift. This result indicates the expected typical Y interaction between the carboxylate and urea groups through a double hydrogen bonding. Considering the high basicity of fluoride anion, the titration of receptor 1 with TBAF was achieved. The spectra showed that the urea hydrogen Hf and Hg signals move to downfield 1.24 and 1.06 ppm, respectively, but again the He signal remains constant (Figure S19). The interaction occurs only with the urea group and it is stronger than with TBAA, there is no evidence of an acid-base reaction despite the fluoride basicity.

The interaction of receptor 2 with TBAA was analysed under the same experimental conditions. Both urea hydrogen Hf and Hg signals move to downfield 1.05 and 1.02 ppm,
The tetrahedral geometry of $\text{H}_2\text{PO}_4^-$ induces a different fashion in the interaction, where the Hf hydrogen does not participate. The three signals behave broadening in the complex and the multiplicity for the methylene signal completely changes from a doublet to a singlet at one molar equivalent added, the integration of three signals correspond to one hydrogen each one.

The titration of receptor 4 with TBAA induced the broadening and chemical shift of urea hydrogens (0.54 and 0.20 ppm for $\text{H}_f$ and $\text{H}_g$, respectively), the amide signal becomes broad but no significant chemical shift was observed (Figure S24). The integration of the three signals corresponds to one hydrogen each one. In addition, the doublet signal for methylene hydrogens becomes to a singlet. Then, there is a supramolecular interaction with the carboxylate through the three hydrogens in a non-equivalent strength. With the TBAB a slightly chemical shift and broadening of urea and amide hydrogen signals were observed (Figure S25). The signal for methylene hydrogens remains as a doublet. Here, the steric hindrance of benzoate diminished the supramolecular interaction. The TBAF salt caused the complete absence of the urea and amide hydrogen signals since the first aliquot added (Figure S26). The doublet signal for methylene hydrogens becomes a singlet, and the rest of signals remain constant. These changes indicate the deprotonation due to the basicity of fluoride and the high acidity of the receptor.

respectively, after the addition of 2 M equivalents of the salt (Figure 8). The rest of signals remain constant during the titration, indicating that the supramolecular interaction occurs only with the urea group.

The titration of receptor 3 with TBAA showed a slight shift to downfield of the urea ($\text{H}_f$ and $\text{H}_g$) and amide ($\text{H}_e$) hydrogens signals of 0.13, 0.21 and 0.14 ppm, respectively, after 2 M equivalents of salt added (Figure S20). A similar behaviour was observed in the titration with TBAB. The signals for $\text{H}_f$, $\text{H}_g$, and $\text{H}_e$ move downfield in 0.13, 0.20 and 0.12 ppm (Figure S21). These results indicate the interaction of carboxylate group with the three hydrogens. Considering the chemical shifts of the signals, the supramolecular interaction may not be as strong as occurs with the receptor 1, and the interaction with the urea hydrogens is not equal. On the other hand, in the titration with TBAF the signals of urea and amide hydrogens completely disappear with the addition of one molar equivalent of the salt, and the doublet signal corresponding to the methylene hydrogens ($\text{H}_h$) becomes to a singlet (Figure S22). This spectral change may indicate the deprotonation of the receptor by an acid–base reaction, but there is not present the typical signal of the $\text{HF}_2^-$ at downfield and the integration of each signal corresponds to one hydrogen. Then, a supramolecular interaction is established between these two species. Interestingly, the TBAHP salt induced the chemical shift of the signals for $\text{H}_g$ (0.57 ppm) and $\text{H}_e$ (0.37 ppm), but signal for $\text{H}_f$ remains constant (Figure S23). The tetrahedral geometry of $\text{H}_2\text{PO}_4^-$ induces to a different fashion in the interaction, where the $\text{H}_f$ hydrogen does not participate. The three signals behave broadening in the complex and the multiplicity for the methylene signal completely changes from a doublet to a singlet at one molar equivalent added, the integration of three signals correspond to one hydrogen each one.

The titration of receptor 4 with TBAA induced the broadening and chemical shift of urea hydrogens (0.54 and 0.20 ppm for $\text{H}_f$ and $\text{H}_g$, respectively), the amide signal becomes broad but no significant chemical shift was observed (Figure S24). The integration of the three signals corresponds to one hydrogen each one. In addition, the doublet signal for methylene hydrogens becomes to a singlet. Then, there is a supramolecular interaction with the carboxylate through the three hydrogens in a non-equivalent strength. With the TBAB a slightly chemical shift and broadening of urea and amide hydrogen signals were observed (Figure S25). The signal for methylene hydrogens remains as a doublet. Here, the steric hindrance of benzoate diminished the supramolecular interaction. The TBAF salt caused the complete absence of the urea and amide hydrogen signals since the first aliquot added (Figure S26). The doublet for methylene hydrogens becomes a singlet and the rest of signals remain constant. These changes indicate the deprotonation due to the basicity of fluoride and the high acidity of the receptor.
In the titration with TBAHP only the H$_f$ hydrogen slightly shifted to downfield as well as the amide hydrogen, while the H$_g$ signal remains constant (Figure S27). The signal for methylene hydrogens remains as a doublet. These results indicate the supramolecular interaction with the anion into a non-equivalent fashion with the urea group, and there is not an acid–base reaction due to the poor basicity or the steric hindrance present in this complex.

The NMR results demonstrate that in receptors where the urea and amide groups are meta position (1 and 2) there is no participation of the amide in the interaction with the anions. Therefore, the complexes with these receptors are less hindered and the Y interaction is favoured with the trigonal anions acetate and benzoate. In receptors with ortho position (3 and 4) the amide hydrogen is involving in the interaction due to the closeness of both groups. The magnitude of the chemicals shifts indicate a stronger interaction of receptors 1 and 2 with anions compared with 3 and 4. These differences may be attributed to the major steric hindrance present in receptor 3 and 4. Finally, the receptors 1 and 2 are less acidic than 3 and 4, which allows to establish intermolecular interactions (hydrogen bonding) with most of the anions. With receptors 3 and 4 the acid–base reaction becomes predominant as the basicity of the anion increases.

The structure of complex 4-AcO$^-$ was optimised by DFT considering the interaction with both amide and urea groups (a) and only the urea group (b) (Figure 9). The acetate interacts with H$_g$ through one oxygen atom and the interaction with H$_f$ and H$_e$ is with the other oxygen in the complex I. The distances H$_g$...O, H$_f$...O and H$_e$...O are 1.75, 1.80 and 1.85 Å, respectively. This result totally agrees with chemical shifts and signal broadenings in NMR spectra. In the structure II each urea hydrogen interacts with one oxygen atom and the H$_g$...O, H$_f$...O distances are 1.71 and 1.72 Å, respectively. Noteworthy, the complexation energy is 6.4 kcal/mol lower in structure I compared with II, indicating a major stability for this complex by the cooperative effect of the additional binding site.

**Conclusions**

The studies of receptors 1–4 with different TBAX salts using different analytical techniques revealed that the strength of the supramolecular interaction depends on
their molecular acidity and the steric hindrance. The electron withdrawing effect in the nitrophenyl group makes the urea hydrogens H\textsubscript{g} more acid in receptors 2 and 4 compared with 1 and 3. The inductive effect of amide group in the position ortho also has a great influence in both H\textsubscript{g} and H\textsubscript{g} but more in H\textsubscript{g} in receptor 3 and 4. The amide hydrogens H\textsubscript{g} are slightly more acid in 3 and 4 compared with 1 and 2. In consequence, the receptors 3 and 4 are more susceptible for deprotonation with the more basic anions as fluoride. Meanwhile, naphthyl group induces more steric hindrance than nitrophenyl, which reduces the possibility of interaction with the anions. In fact, it was impossible the detection of the interaction of receptor 3 by UV–Vis due to the steric factor. Those receptors where the amide and urea groups are in meta position presented higher spectroscopic changes compared with the ortho receptors, being more evident in receptor 2, which has nitrophenyl group as chromophore. The 1\textsuperscript{H} NMR studies demonstrate that the anion interacts preferentially with the urea group in the meta receptors, while there is a cooperative interaction of the amide hydrogens in the ortho receptors with the anions. The theoretical calculations demonstrate a thermodynamically favoured cooperative interaction of amide hydrogen in ortho receptors with anions. Finally, the geometry and size of the anions are determinant in the supramolecular interaction. The anions acetate and benzoate, both with trigonal geometry, and fluoride, with small spherical shape and higher basicity, interact more efficiently than chloride and bromide which are halides of higher size and less basicity, and dihydrogen phosphate, a tetrahedral anion with more steric hindrance.

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