Deltamides and croconamides: expanding the range of dual H-bond donors for selective anion recognition

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Abstract: Dual H-bond donors are widely used as recognition motifs in anion receptors. We report the synthesis of a library of dual H-bond receptors, incorporating the deltic and croconic acid derivatives, termed deltamides and croconamides, and a comparison of their anion binding affinities (for monovalent species) and Brønsted acidities to those of the well-established urea and squaramide dual H-bond donor motifs. For dual H-bond cores with identical substituents, the trend in Brønsted acidity is croconamides > squaramides >deltamides > ureas, with the croconamides found to be 10-15 pK_a units more acidic than the corresponding ureas. In contrast to the trends displayed by ureas, deltamides and squaramides, *N,N'*-dialkyl croconamides displayed higher binding affinity to chloride than the *N,N'*-diaryl derivatives, which was attributed to partial deprotonation of the *N,N'*-diaryl derivatives at neutral pH. A number of differences in anion binding selectivity were observed upon comparison of the dual H-bond cores. Whereas the squaramides display similar affinity for both chloride and acetate ions, the ureas have significantly higher affinity for acetate than chloride ions and the deltamides display higher affinity for dihydrogenphosphate ions than other oxoanions or halides. These inherent differences in binding affinity could be exploited in the design of anion receptors with improved ability to discriminate between monovalent anions.

Introduction

The development of molecular receptors capable of the selective recognition, sensing or transport of anionic species has numerous potential applications, and this has led to an increasing interest in anion receptor chemistry over the past two decades.[1] While several types of interactions including electrostatic interactions, coordination bonds with metal ions and, more recently, halogen bonds have been employed for anion recognition, hydrogen bonds remain a key motif for binding to anions.[1a,2] Dual hydrogen bond donors such as (thio)ureas and squaramides (Figure 1) are of particular interest in this regard, as they can form two hydrogen bonds to an anionic guest and provide an excellent geometric match for Y-shaped anions such as carboxylates.[3] Dual hydrogen bond donors have also been shown to have superior hydrogen bond donicity to monodentate hydrogen bond donors of similar acidity,[4] providing improved anion binding capacity, together with a decreased propensity for the receptor to be deprotonated by basic anions. This latter property is of particular importance in the development of new anion binding motifs, since if a hydrogen bond donor is too acidic, it is no longer effective at binding to anions at neutral pH.[5] Finding dual hydrogen bonding motifs with the right balance between hydrogen bond donicity and Brønsted acidity should provide improved anion receptors and allow them to be tailored towards specific anions.

Squaramides, which are derivatives of the cyclic oxocarbon family,[6] are widely recognized as having higher hydrogen bond donicity than the analogous ureas (Figure 1), leading to higher binding affinities for halide ions.[7-9] This increase in affinity is attributed to an increase in the aromaticity of the squaramide ring upon anion binding[10] and the ability to delocalize charge density across both carbonyl groups.[9] However, this also results in higher Brønsted acidity, resulting in an increased propensity for squaramide containing anion receptors to deprotonate in the presence of basic anions such as acetate, leading to reduced receptor selectivity.[7]

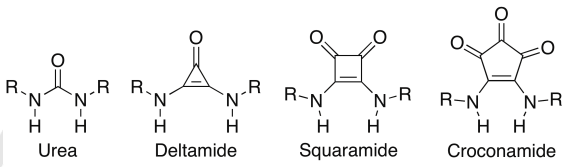

Figure 1. Structures of dual hydrogen bond donors for anion recognition.

The increased aromatic character of the squaramide ring upon either hydrogen bonding or deprotonation is reflected in the high Brønsted acidity of the parent squaric acid (pK_{a1} = 0.55).[11] The cyclic oxocarbon family also contains the three-carbon deltic acid and five-carbon croconic acid, which have similar properties to squaric acid but differ in their acidity (pK_{a1} = 2.57 and 0.68, respectively).[11] Whereas deltic acid (and the corresponding dianion) are reported to be more strongly aromatic than squaric acid, it has been suggested that croconic acid and its dianion are not aromatic.[12] We envisaged that these differences might impact upon both the hydrogen bond donicity and Brønsted acidity of the analogous amides: the deltamides and croconamides (Figure 1), and impact their anion binding abilities. While anion recognition by ureas and squaramides (including most of the compounds **UR1-6** and **SQ1-6**, Chart 1) has been extensively investigated,[3,7,9,13,14] there is only a single recent report of anion

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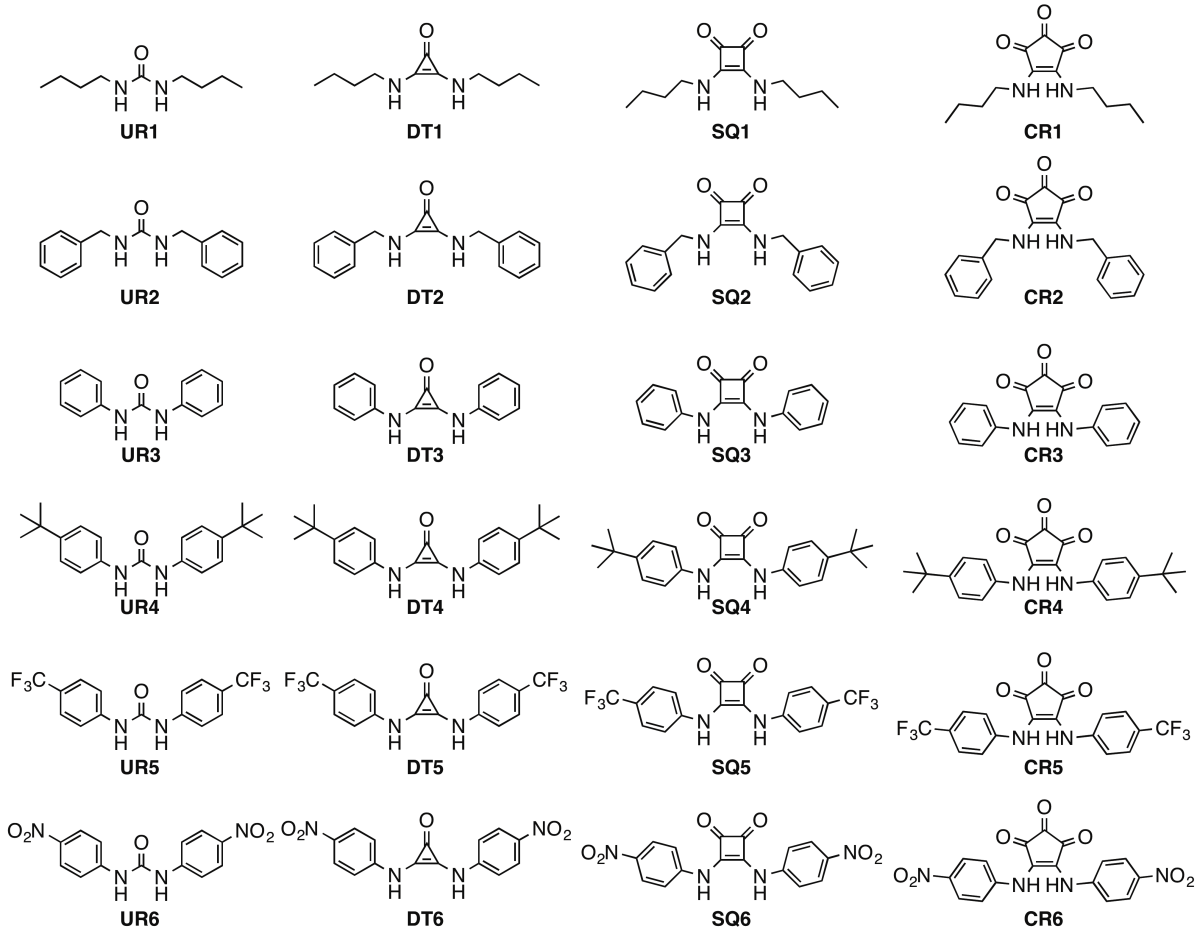


Chart 1. Structures of the ureas, deltamides, squaramides and croconamides

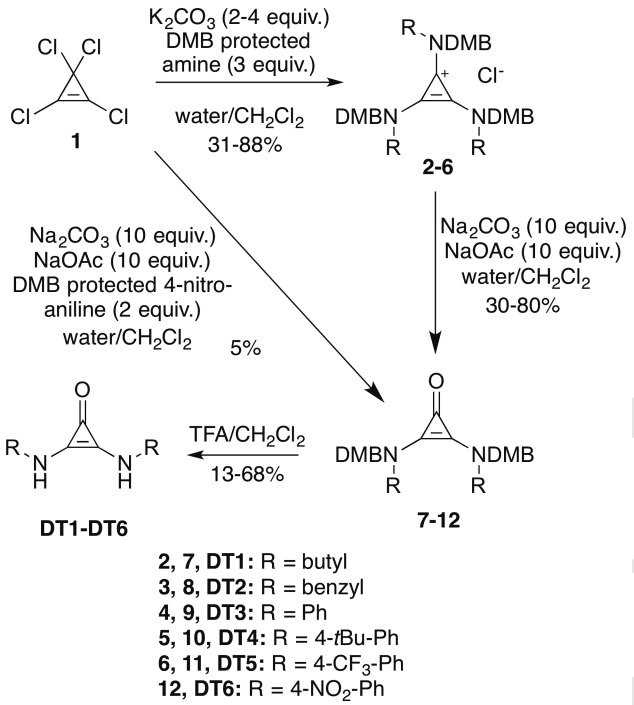
binding by the croconamides[15] and the analogous *N*,*N*'-disubstituted deltamides have not previously been reported. In order to compare the binding properties for monovalent anions of ureas, deltamides, squaramides, and croconamides we synthesized a systematic library of symmetrical croconamides **CR1-CR6** and deltamides **DT1-DT6**, bearing both alkyl and aryl substituents (Chart 1). The aryl substituents were chosen to include *p*-*tert*-butylphenyl derivatives for increased solubility in organic solvents and *p*-nitrophenyl and *p*-trifluoromethylphenyl groups, as these are commonly used to enhance anion binding affinities for both urea and squaramide derivatives. The *p*-nitrophenyl derivatives also allow the use of UV-visible spectroscopy to monitor anion binding.[9] For comparison, we also synthesized and evaluated the known squaramide derivatives **SQ1**,[16] **SQ2**[17] and **SQ4**,[18] for which little anion binding data has been previously reported.

Results and Discussion

Synthesis.

Squaramides **SQ1**, **SQ2**, and **SQ4** were synthesized *via* condensation of diethyl squarate with two equivalents of butylamine, benzylamine, and *p*-*tert*-butylaniline, respectively, as reported previously.[16-18] The aryl-substituted croconamides **CR3-CR6** were similarly prepared from dimethyl croconate,[19] upon condensation with aniline, *p*-*tert*-butylaniline, *p*-trifluoromethylaniline, and *p*-nitroaniline, respectively. Condensations with aniline and *p*-*tert*-butylaniline proceeded within 24 hours and at room temperature whereas longer reaction times (up to 48 hours) and elevated temperatures (up to 90°C) were required for condensation of the electron deficient *p*-trifluoromethylaniline and *p*-nitroaniline. In contrast, attempts to synthesise the butyl-substituted croconamide **CR1** from dimethylcroconate and two equivalents of *n*-butylamine initially gave a mixture of mono-, di-, and tri-functionalised derivatives of croconic acid dimethyl ester (see ESI, Figure S2).[20] This was

attributed to the increased nucleophilicity of the primary amine as compared to aniline. Reduction of the reaction temperature to 5°C and shortening of the reaction time to 30 minutes resulted in the formation of the desired disubstituted croconamide **CR1**. The synthesis of the benzyl substituted croconamide **CR2** from dimethylcroconate and two equivalents of benzylamine proceeded within two hours and at room temperature. Crystals of **CR4** suitable for X-ray crystallography were obtained upon slow evaporation of an acetonitrile solution. In the solid state, **CR4** adopts a *syn*/*syn* conformation (see ESI Figure S89), similar to that recently observed for the *N*,*N'*-[3,5-bis(trifluoromethyl)phenyl]-croconamide.[15]



Scheme 1. Synthesis of deltamides **DT1-DT6**.

The deltamides were synthesised *via* an alternative approach, using a modification of the method recently reported by Lambert *et al.* for the synthesis of the deltic guanidinium macrostere.[21] Deltamides **DT1-DT6** were prepared starting from commercially available tetrachlorocyclopropene **1** (Scheme 1). For **DT1-DT5**, threefold nucleophilic substitution of **1** with the appropriate 2,4-dimethoxybenzyl (DMB) protected anilines or aliphatic amines in the presence of potassium carbonate afforded the corresponding cyclopropenium chloride salts **2-6**. Subsequent hydrolysis of the trisubstituted species in the presence of excess sodium acetate and sodium carbonate gave the corresponding cyclopropenones **7-11** which were then treated with trifluoroacetic acid (TFA) to remove the DMB-protecting groups, affording deltamides **DT1-DT5** in moderate overall yields. Reaction of **1** with DMB-protected *p*-nitroaniline under these conditions did not proceed even at elevated temperatures. However, when the reaction was performed at elevated temperatures and in the presence of excess sodium acetate and sodium carbonate, a low yield (5%) of the corresponding cyclopropenone **12** could be isolated. Removal of the DMB protecting groups with TFA proceeded smoothly to give the bis(*p*-nitrophenyl)deltamide **DT6**.

With the exception of **DT1**, all of the prepared deltamides were found to be stable when either stored under vacuum, at -20°C under argon, or as DMSO solutions. **DT1** was successfully synthesized and characterized by ^{1}H NMR, ^{13}C NMR, and high resolution mass spectrometry (HRMS) and its purity was confirmed by liquid chromatography-mass spectrometry (LCMS). However, DMSO and chloroform solutions of **DT1** decompose within few hours to give complex mixtures of ring-opened products (Figure S1).[22]

Crystals of **DT3** and **DT4** suitable for single crystal X-Ray analysis were obtained by slow evaporation of their respective dimethyl sulfoxide (DMSO) solutions. (For full structure determination details see the ESI.) In both cases, the deltamides adopt the *anti/anti*-conformation required for dual H-bond donation to anions. While the crystal structure of **DT3** is solvent free (Figure 2, top), the **DT4** structure incorporates a DMSO molecule. Interestingly, the DMSO forms a hydrogen bond with only one of the two available amide protons (N···O distance of 2.837(2) Å) (Figure 2, bottom). This observation is in contrast to the solid-state structures of a range of symmetrically substituted squaramides such as **SQ3**, **SQ5** or a 3,5-bis(*tert*-butyl) substituted squaramide, all of which were found to bind to the DMSO oxygen in the solid state through both amide hydrogen atoms.[5,8]

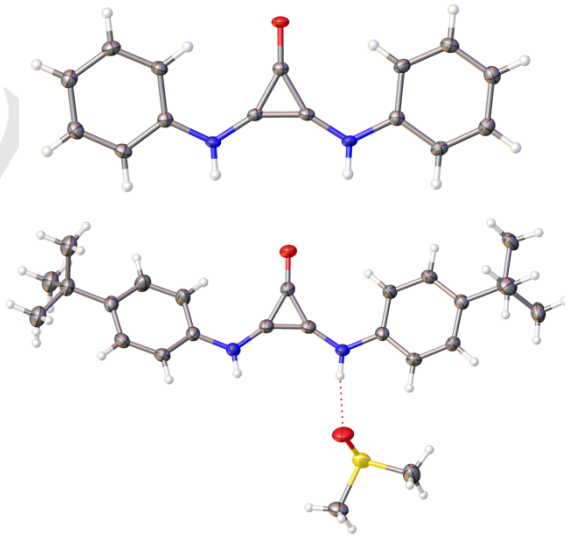


Figure 2. Single crystal X-ray diffraction determined depictions of **DT3** (top) and **DT4·DMSO** (bottom) with displacement ellipsoids shown at the 50% probability level. C=grey, O=red, N=blue, S=yellow, H=white, Hydrogen bonds=dashed lines. The N···O distance is 2.837(2) Å..

Anion Binding Studies.

With the deltamides and croconamides in hand, we proceeded to evaluate their anion binding abilities in d_6-DMSO and d_3-MeCN, to allow comparison to previously reported data for the squaramide and urea derivatives. Initial screening for anion

binding was performed by adding ten equivalents of the tetrabutylammonium salts of a range of halide (Cl^-, Br^-, I^-) and monovalent oxoanions (HSO_4^-, $H_2PO_4^-$, NO_3^-, ReO_4^-, ClO_4^-, TsO^-, BzO^-, AcO^-) to d_6-DMSO solutions of receptors **CR1-CR5** and **DT2-DT5**, respectively. For **CR1-CR5**, only the addition of chloride gave rise to significant downfield shifts of the croconamide NH protons indicating the formation of hydrogen bonds between the receptors and chloride. Addition of $H_2PO_4^-$, BzO^-, and AcO^- led to the disappearance of the NH signals and a distinct color change from yellow to red, suggesting that these anions deprotonate **CR1-CR5**. This was confirmed by UV-visible spectroscopy, where upon addition of 10 equiv. of $H_2PO_4^-$ to **CR5** the absorbance at 420 nm increased, together with the disappearance of the two absorption bands at 383 and 470 nm. Almost identical spectra were obtained upon addition of 10 equiv. of hydroxide, confirming the deprotonation event (Figure 3).

For **CR6**, binding to anions was not observed in either d_6-DMSO or d_3-MeCN. Signals attributable to the croconamide NH protons were not observed in the NMR spectra in either solvent, and the UV-vis spectra indicated that this compound exists in its deprotonated form in both DMSO and MeCN solution (Figure S5). Similar behavior has previously been observed for the analogous *p*-nitrophenyl squaramide **SQ6**.[18]

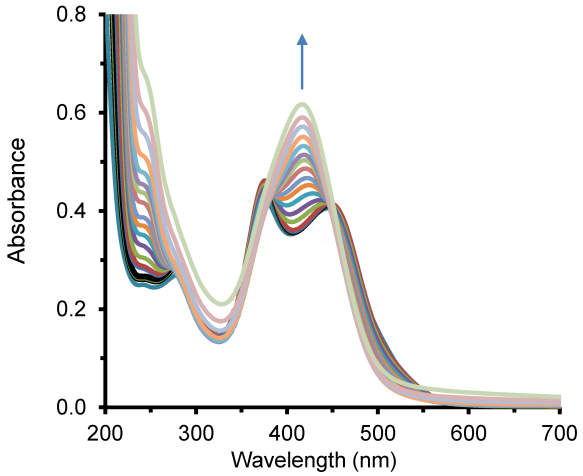


Figure 3. Representative UV-Vis spectra recorded over the course of a titration of CR5 (20 μM) with TBAOH (0 to 10 equiv.) in MeCN/water (9:1, v/v) at 298 K. [OH^-]=0, 4, 8, 12, 16, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 180, 200 μM.

Subsequent titrations of **CR1-CR5** with TBACl were performed and the data analyzed using bindfit (v0.5)[23] and HypNMR.[24] In all cases, the best fit with the highest reproducibility was to a 1:1 binding model (Figure S29-S33) to give the association constants in Table 1. Unexpectedly, alkyl derivatives **CR1** and **CR2** were found to have higher affinities for chloride than the aryl derivatives **CR3-CR5**, and for the aryl derivatives, the addition of the electron withdrawing *p*-CF_3 group to **CR5** resulted in a decrease in affinity in comparison to that observed for phenyl derivative **CR3**. This trend is opposite that normally observed for urea and squaramide derivatives, where it is well-established that addition of aryl substituents bearing electron withdrawing groups increases affinity for a range of anions.[3,8]

Table 1. Apparent Association Constants (K_a, M^{-1}) of Deltamides and Croconamides for Anions in d_6-DMSO[a]

	Cl^-	$H_2PO_4^-$	AcO^-	BzO^-
CR1	230	–[c]	–[c]	–[c]
CR2	110	–[c]	–[c]	–[c]
CR3	42	–[c]	–[c]	–[c]
CR4	20	–[c]	–[c]	–[c]
CR5	19	–[c]	–[c]	–[c]
CR6	–[c]	–[c]	–[c]	–[c]
DT2	<5	110	11	6
DT3	9	$>10^4$	2300	730
DT4	6	8700	1200	500
DT5	12	$>10^4$	6500	4300
DT6[b]	<100[d]	–[c]	–[c]	–[c]

[a] Determined by ^{1}H NMR spectroscopy in DMSO-d_6 (0.5% water) at 300 K unless otherwise noted. Anions were added as their tetrabutylammonium (TBA) salts. Values rounded to a maximum of two significant figures. Estimated errors in K_a <15%. [b] Binding studies performed by UV-vis spectroscopy in DMSO (0.5% water) at 298 K. [c] Addition of the anion caused the receptor to deprotonate. [d] Changes in spectra too small to fit to a binding model.

Given the propensity for the croconamides to deprotonate upon addition of basic anions in DMSO, we also evaluated their binding behavior in MeCN, since deprotonation of hydrogen bond donors by anions is less likely in this solvent.[25] In d_3-MeCN, downfield shifts of the signals attributable to the NH protons were observed upon addition of all halide anions (Cl^-, Br^-, and I^-) as well as NO_3^-, TsO^-, and HSO_4^- and the titration data were fitted to 1:1 binding models (as above) to provide association constants for these anions (Table 2). However, the addition of $H_2PO_4^-$, BzO^-, and AcO^- again led to the deprotonation of receptors **CR1-CR5** (as observed for these anions in DMSO). In d_3-MeCN, **CR1-CR5** were observed to bind halides with complex stability decreasing across the series $Cl^- > Br^- > I^-$, reflecting a correlation between binding affinity and higher charge density of the anion. For the oxoanions, complex stability decreases along the series $TsO^- > HSO_4^- > NO_3^-$, reflecting the intrinsic basicity of these oxoanions. For both halides and oxoanions these trends parallel those previously observed for both ureas and squaramides.[9] However, in contrast to both ureas and squaramides, the alkyl croconamides have higher binding affinities for a given anion than the aryl derivatives, as was observed in d_6-DMSO.

Table 2. Apparent Association Constants (K_a, M^{-1}) of Deltamides and Croconamides for Anions in MeCN[a]

Receptor		Association Constant K_a (M^{-1})								
		Cl^-	Br^-	I^-	$H_2PO_4^-$	BzO^-	AcO^-	NO_3^-	TsO^-	HSO_4^-
Deltamides	**DT4**	630	120	27	$>10^4$	$>10^4$	6500	48	900	590
	DT6[b]	2100	970	280	2.8×10^7	2.4×10^5	2.5×10^6	—[c]	3900	5.0×10^4
Croconamides	**CR1**	$>10^4$	5300	230	—[d]	—[d]	—[d]	300	1500	390
	CR2	$>10^4$	5700	—[e]	—[d]	—[d]	—[d]	560	1900	680
	CR3	$>10^4$	550	—[e]	—[d]	—[d]	—[d]	—[e]	—[e]	60
	CR4	1400	140	6	—[d]	—[d]	—[d]	13	32	21
	CR5	2100	280	22	—[d]	—[d]	—[d]	31	110	43
	CR6[b]	—[f]	—[f]	—[f]	—[f]	—[f]	—[f]	—[f]	—[f]	—[f]

[a] Apparent association constants (K_a/M^{-1}) determined by ^1H NMR spectroscopy in MeCN-d_3 (0.5% water) at 300 K unless otherwise noted. Anions were added as their tetrabutylammonium (TBA) salts. Values rounded to a maximum of two significant figures. Estimated errors in K_a <15%. [b] Binding studies performed by UV-vis spectroscopy in MeCN (0.5% water) at 298 K. [c] Changes in UV-vis absorbance too small to obtain the association constant. [d] Addition of the anion resulted in deprotonation of the receptor. [e] K_a could not be determined due to broadening of the NH proton signal. [f] Receptor exists in its deprotonated form at neutral pH in MeCN.

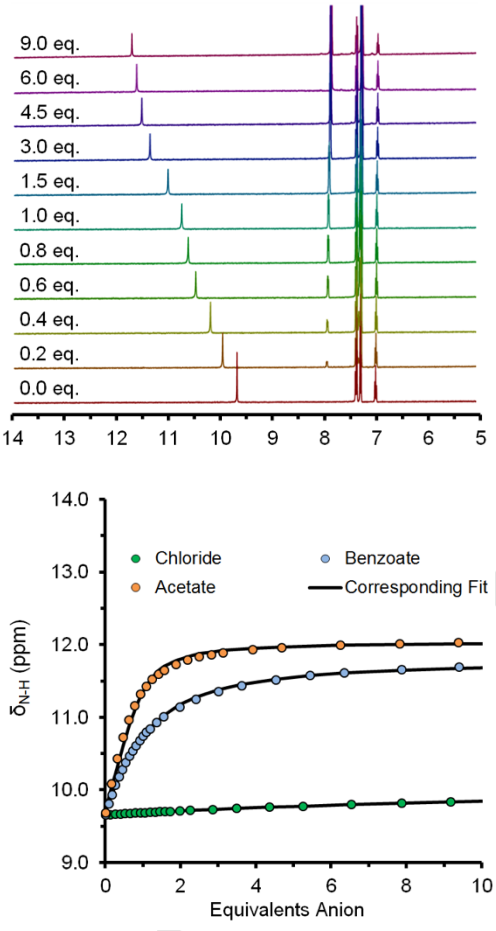


Figure 4. ^1H NMR spectroscopic binding studies of **DT3**. (Top) Representative stack plot of the ^1H NMR spectrum of receptor **DT3** (2.5 mM) upon titration with TBA benzoate in DMSO-d_6 (0.5% water) at 300 K. (Bottom) Fitting curves for the titration data of **DT3** with chloride, benzoate, and acetate. The titration data was fitted to a 1:1 binding model.

For the deltamides **DT2-DT5**, an anion screen in d_6-DMSO (as described above) showed negligible shifts of the signals attributable to the NH protons upon addition of Br^-, I^-, HSO_4^-, NO_3^-, ReO_4^-, or ClO_4^-, with very small downfield shifts observed upon addition of Cl^-, and significant downfield shifts observed upon the addition of $H_2PO_4^-$, BzO^-, and AcO^-, indicating the formation of hydrogen bonds to these anions. Subsequent titrations with Cl^-, $H_2PO_4^-$, BzO^-, and AcO^- were performed and in all cases the binding data was best fit to a 1:1 binding model (Table 1 and Figure 4).[26,27] For **DT2-DT5**, binding to Cl^- was found to be very weak (K_a < 12 M^{-1} in all cases), but stronger binding was observed to the oxoanions with binding affinities decreasing across the series $H_2PO_4^-$ > AcO^- > BzO^-. This trend does not correlate with the basicity of the anions, in direct contrast to previous observations for the urea and squaramide compound series,[9,28] nor does it correlate with the recently reported hydrogen bond acceptor parameter series, in which carboxylates are shown to be stronger hydrogen bond acceptors than $^-O_2P(OR)_2$.[29]

In general, the series **DT2-DT5** follows the expected trend of aryl substituents on the deltamide nitrogen atoms resulting in increased binding affinity for all anions in comparison to alkyl substituents and the introduction of electron withdrawing groups onto the deltamide substituents results in increased anion affinity, as has been previously observed for ureas and squaramides.[8]

The low solubility of the deltamides in MeCN prevented a detailed evaluation of the binding affinities of **DT2**, **DT3** or **DT5** in this solvent, but **DT4** was sufficiently soluble to allow NMR titrations to be performed in d_3-MeCN with a wide range of anions, with subsequent determination of association constants by fitting to a 1:1 binding model (Table 2). In this solvent, the binding trend for the halide ions shows complex stability decreasing across the series Cl^- > Br^- > I^-, while for the oxoanions, complex stability decreases along the series $H_2PO_4^-$ > AcO^- ≈ BzO^- > TsO^- ≈ HSO_4^- >> NO_3^-, with Cl^- having a similar affinity to HSO_4^-. For **DT6**, anion binding affinity was determined in more dilute solution using

UV-vis spectroscopic titrations.[30] Addition of anions resulted in a red-shift of the absorbance band at 385 nm, with a clear isosbestic point indicating the presence of only two species in solution, consistent with the formation of 1:1 complexes (Figure 5, top). A similar trend in anion binding affinities was observed for **DT6** under these conditions to that observed above for **DT4** by NMR titration (Table 2). Notably, no deprotonation of this receptor was observed in MeCN. However, in DMSO, addition of $H_2PO_4^-$, AcO^- and BzO^- led to deprotonation of this receptor, as evidenced by a decrease in the absorbance band at 406 nm and concomitant increase in absorbance at 538 nm (Figure 5, bottom), which was accompanied by a colour change of the receptor solution from yellow to red. The addition of OH^- led to similar changes in the spectra, confirming that these were a result of deprotonation (Figure S70). This is comparable to the behavior of the corresponding *p*-nitrophenyl urea derivative, previously reported by Fabbrizzi and coworkers.[31]

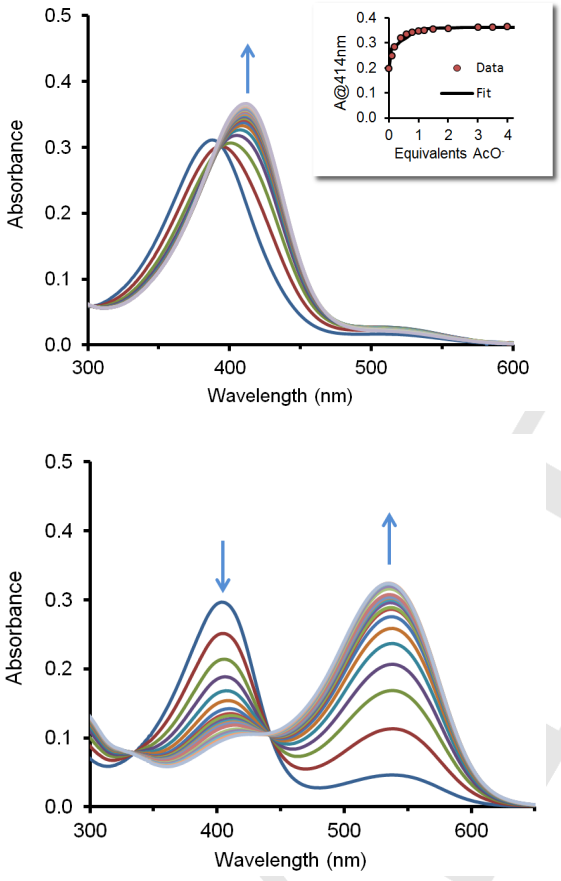


Figure 5. UV-Vis Spectroscopic Binding Studies of **DT6**. (Top) Representative UV-Vis spectra recorded over the course of a titration of **DT6** (20 μM) with TBA acetate in MeCN (0.5% water) at 298 K. [AcO^-] = 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 30, 34, 40, 50, 60, 70, 80, 100 μM. Inset: Fitting curve for the titration data at 414 nm to a 1:1 binding model. (Bottom) Representative UV-Vis spectra recorded over the course of a titration of **DT6** (20 μM) with TBA acetate in DMSO (0.5% water) at 298 K. [AcO^-] = 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 40, 50, 60, 80, 100 μM.

Crystals of the **DT4** and **DT5** complexes with benzoate suitable for single crystal X-Ray analysis were obtained by slow evaporation of DMSO solutions of **DT4** and **DT5**, respectively in the presence of tetrabutylammonium benzoate (TBABzO). As shown in Figure 6, in the **DT5**-benzoate structure a **DT5** molecule forms a 1:1 complex with a benzoate anion through two hydrogen bonds. The asymmetric interaction between the two at least in part reflects the difference between the 2.238(3) Å carboxylate oxygen-oxygen separation and the 3.582(2) Å amine nitrogen-nitrogen separation. In contrast, as Fig. 7 indicates, in the **DT4**-benzoate crystal structure the benzoate bridges two (of three; see ESI material) crystallographically independent deltamide molecules, with one carboxylate oxygen participating in a hydrogen bond interaction with the amide proton of one deltamide and the other carboxylate oxygen likewise linked to the amide of the second deltamide. A water molecule provides a second hydrogen bond bridge between the two deltamides.

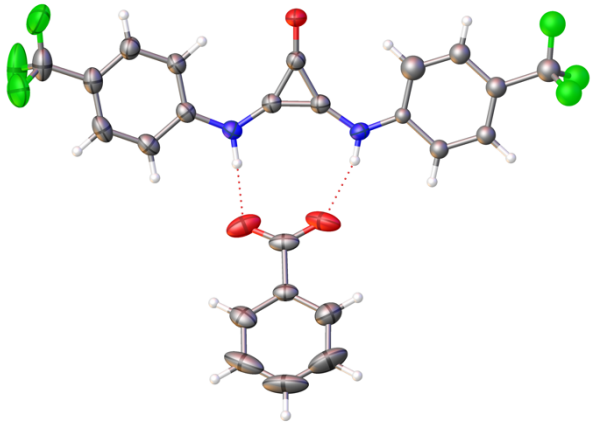


Figure 6. Single crystal X-ray diffraction determined depictions of the **DT5**·benzoate complex, with displacement ellipsoids shown at the 50% probability level. The tetrabutylammonium counterion and rotational disorder of the *p*-CF3 groups (see the ESI material) are omitted for clarity. C=grey, O=red, N=blue, F=bright green, H=white, Hydrogen bonds=dashed lines. The N···O distances are 2.715(2) and 2.736(2) Å.

The structures of the **DT4** and **DT5** complexes demonstrate binding mode flexibility that reflects both packing interactions and the difference in separation between the carboxylate oxygens and amine nitrogens. The DFT-optimized structures of **DT5** and the 1:1 **DT5** complexes with OAc^- and $H_2PO_4^-$ indicate that the $H_2PO_4^-$ ion is a better geometric match for the deltamide unit (Figure 8), requiring less alteration of the free **DT5** structure upon binding. This provides a possible explanation for the unusual binding trends observed for the deltamides with respect to these oxoanions, since any change to the structure required for binding to an anion would incur a 'reorganisation' energy penalty.

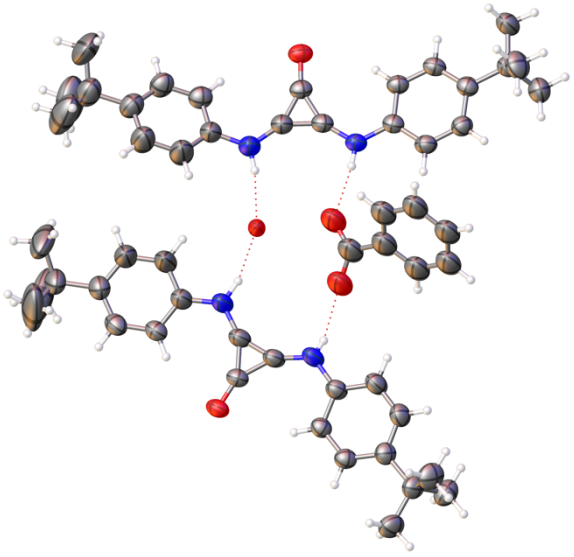


Figure 7. Single crystal X-ray diffraction determined depiction of the solid state **DT4**·benzoate complex, with displacement ellipsoids at the 50% probability level. Two crystallographically independent **DT4** molecules are bridged by hydrogen bond interactions with a benzoate anion and a water molecule. A hydrogen bond interaction between the bridging water molecule and the benzoate anion is expected, however the water hydrogen sites were not located. A third crystallographically independent **DT4** molecule which does not participate in a hydrogen bonding interaction with the benzoate anion (see ESI material) and the tetrabutylammonium counterion are omitted for clarity. Disorder of the benzoate anion and the water molecule is also not shown (see ESI material). C=grey, O=red, N=blue, H=white, Hydrogen bonds=dashed lines.

pK_a determination. To gain further insight into the anion binding behavior of the croconamides and deltamides and place this in context with regards to that of the ureas and squaramides, we evaluated the Brønsted acidity of all four compound classes, either through direct measurement of experimental pK_a values or *via* computation (Table 3). Where possible, experimental pK_a values were determined by pH-spectrophotometric titrations in a mixture of acetonitrile-water (9/1, v/v) and in the presence of $TBAPF_6$ (0.1 M) as described previously for squaramide (**SQ3** and **SQ5**, among others), thiosquaramide, urea (**UR5**), and sulfonamide based anion receptors.[5,7] Additionally, and in cases where experimental values could not be obtained, theoretical pK_a values in MeCN were calculated using density functional theory (DFT) at the G3(MP2,CC)-(+)[32] level in conjunction with the SMD implicit solvation model[33] (see ESI for full details).[34] In general, the experimentally and computationally determined pK_a values are in reasonable agreement (within 1.3 pK_a units) and allow for a comparison of the acidity of the four different receptor classes as well as for a comparison within one class.

For deltamides **DT1-DT5**, no deprotonation was observed in the pH-spectrophotometric titrations. This behavior is similar to that reported previously for **UR5**[7] indicating that the pK_a values of deltamide based receptors **DT1-DT5** as well as the value for **UR5** lie outside the range covered by the described pH-spectrophotometric method, which is limited to compounds with pK_a<14.[7] This is consistent with the pK_a values of **DT1-DT5** obtained computationally, which range from 13.9 to 22.4. In contrast, the pK_a for **DT6** was established experimentally as 12.0, indicating the increased acidity of the deltamide protons when the strongly electron withdrawing *p*-nitrophenyl substituent is appended to the nitrogen atom.

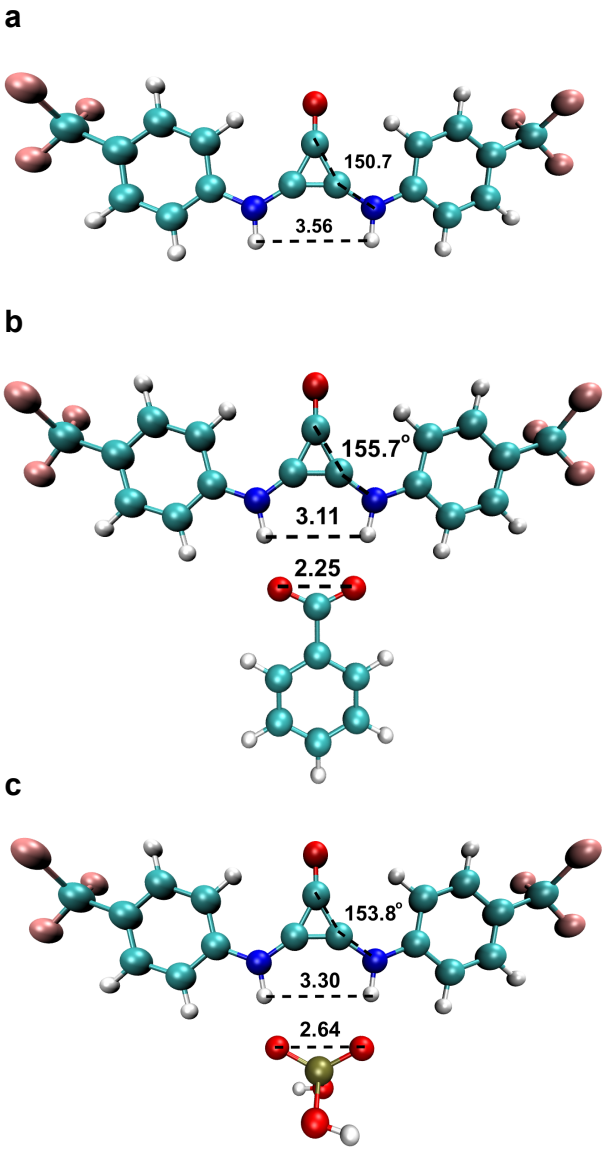


Figure 8. M06-2X/6-31+G(d) optimized molecular structure of **DT5**, **DT5**•benzoate, and **DT5**·dihydrogenphosphate complex in DMSO. H-H and O-O bond distances (Å) and C-C-N bond angles (°) are indicated. C=cyan, O=red, N=blue, F=pink, P=bronze, H=white.

Deprotonation of the croconamides was more readily observed experimentally. In the course of the pH-spectrophotometric titrations, **CR1** and **CR2** were found to undergo a single deprotonation event characterized by a decrease in absorbance at ~397 nm with an increase at approx. 430 nm (Figure 9). An absorbance peak at approx. 360 nm did not change significantly

Table 3. Experimental and Calculated pK_a Values for Ureas **UR1-UR6**, Deltamides **DT1-DT6**, Squaramides **SQ1-SQ6**, and Croconamides **CR1-CR6**.

	pK_a			pK_a	
	Exp.[a]	Calc.[b]		Exp.[a]	Calc.[b]
UR1	n.d.[c]	26.3	SQ1	—[h]	16.7
UR2	n.d.[c]	24.3	SQ2	n.d.[c]	14.6
UR3	18.7[d], 19.5[e]	18.3	SQ3	11.7[i], 12.5[j]	—[k]
UR4	n.d.[c]	18.7	SQ4	n.d.[c]	12.9
UR5	—[f]	15.3	SQ5	9.8[i]	10.4
UR6	n.d.[c]	14.8	SQ6	n.d.[c]	10.0
DT1	—[g]	22.4	CR1	10.2	11.2
DT2	—[h]	20.8	CR2	9.3	10.4
DT3	—[h]	15.8	CR3	8.4	7.1
DT4	—[h]	16.3	CR4	8.6	7.8
DT5	—[h]	13.9	CR5	7.3	6.8
DT6	12.0	12.9	CR6	—[l]	5.9

[a]Experimental values determined using the pH-spectrophotometric method described above in MeCN/water mixture (9/1, v/v; in the presence of 0.1 M $TBAPF_6$ unless otherwise stated. Errors estimated as ±0.5 pK_a units. [b]Calculated values determined in pure MeCN. Errors in calculated pK_a values [±1 pKa unit].[34] [c]The pK_a value has not been determined or reported in the literature. [d]Data from reference 37. Measured in dry DMSO at 25°C using the Bordwell overlapping indicator method;[36] error ±0.1 pK_a units. [e]Data taken from reference 38. Measured in DMSO at 25°C using the Bordwell overlapping indicator method;[36] error not reported. [f]No deprotonation observed using the pH-spectrophotometric method described above as reported in reference 7. [g]Receptor not stable (see above). [h]Present work. No deprotonation observed using the pH-spectrophotometric method described above. [i]Data taken from reference 5. [j]Data taken from reference 39. Measured in DMSO at 25°C using the Bordwell overlapping indicator method;[36] error ±0.1 pK_a units. [k]Reference pK_a for pK_a calculations performed in this work. [l]Not determined due to instability of receptor under acidic conditions.

throughout the titrations. However, for the aryl-substituted croconamides **CR3**, **CR4** and **CR5**, a more complex titration profile was observed. This is most obvious for the *p*-trifluoromethylphenyl derivative **CR5**, although all compounds follow the same trend. At low pH, **CR5** has a broad absorbance band (λ_{max} 416 nm) with a shoulder evident at approx. 374 nm. An absorbance of much lower intensity is also evident at 500 nm. As the pH is increased, the shoulder at 374 nm grows in intensity and an absorbance band grows at 454 nm, with a concomitant decrease in absorbance at 416 nm. As the pH is increased further (pH >9) the absorbance at 374 nm decreases in intensity while the absorbance band at 454 nm is blue-shifted to 422 nm. However, for this second transition, clear isosbestic points were not obtained, suggesting the presence of multiple species in solution. We postulate that the second transition may be the second deprotonation event for the aryl-substituted croconamides (**CR3-CR5**), which appear to be highly acidic, as indicated by their ready deprotonation by weakly basic anions such as $H_2PO_4^-$. This is consistent with the highly acidic nature of the parent croconic acid, for which the reported values of pK_{a1} and pK_{a2} are 0.80 and 2.24, respectively.[11] However, this could also reflect hydration or decomposition of the croconamide core under these conditions.[35] The experimentally obtained pK_a values of **CR1-CR5** corresponding to the first deprotonation event range from 7.3 to 10.2 and are summarized in Table 3. These values are in good agreement with the calculated values also shown in Table 3. In the case of **CR6**, the pK_a could not be determined experimentally, as the receptor was unstable in acidic conditions (pH < 5.5) as determined by changes in both the UV-vis spectrum and NMR spectra (Figure S88).

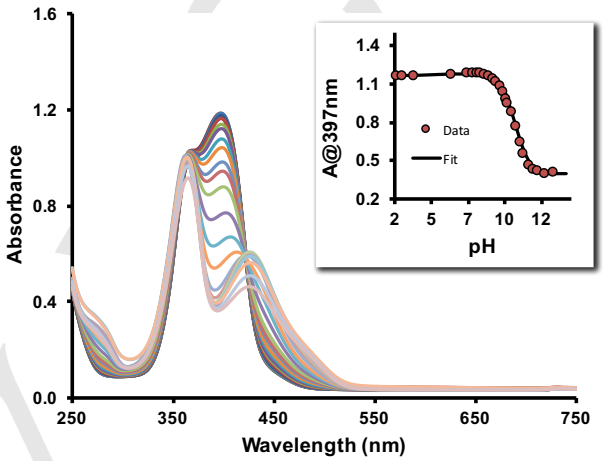


Figure 9. Absorption spectra taken over the course of a pH-spectrophotometric titration of **CR1** in acetonitrile/water solvent mixture (9:1, v/v; in the presence of 0.1 M $TBAPF_6$). (Inset): Four parameter sigmoid curve fit with the point of inflexion corresponding to the pK_a value of **CR1**.

While a direct comparison is not possible as a result of the different solvent systems used, both the experimental and computational pK_{a1} values determined for **CR5** (7.3 and 6.8) in this work are inconsistent with the previously reported pK_a for this compound in DMSO (10.8).[15] Our titration data, which shows two clear transitions between pH 4 and 12, suggests that the previously reported value is in fact that of the second deprotonation event (pK_{a2}) for this molecule. Our lower pK_{a1} value is more consistent with the observation that **CR5** is readily deprotonated upon addition of the relative weak base, $H_2PO_4^-$.

The ease with which the croconamides are deprotonated is further demonstrated by the isolation of the tetrabutylammonium salt of the bis(*o*-chlorophenyl) croconamide **CR7** upon slow evaporation of a MeCN solution of **CR7** in the presence of five equivalents of tetrabutylammonium sulfate (TBA_2SO_4). This resulted in the formation of single crystals suitable for X-ray diffraction analysis. The so obtained X-ray crystal structure shows a singly deprotonated **CR7** anion with a tetrabutylammonium counterion (TBA[**CR7**-H^+]) (see Fig. 10 and the ESI material); the structure does not contain sulfate. The C-N bond length between the five-membered ring carbon and the deprotonated nitrogen atom is 1.285(2) Å, while that of the opposite C-N bond is 1.349(2) Å. The C-O bond on the opposite side of the deprotonated nitrogen is slightly but significantly elongated with respect to the adjacent and the central C-O bond in the five-membered ring (1.239(2) Å c.f. 1.2262(19) Å and 1.2294(19) Å respectively). These observations

are in agreement with the two resonance structures of [**CR7**-H$^+$]$^-$ (Fig. 10). The deprotonated croconamide crystal structure affirms the conclusions drawn from the ^{1}H NMR binding studies and pH titrations. Croconamides appear to be prone to deprotonation even in the presence of only slightly basic anions such as sulfate.

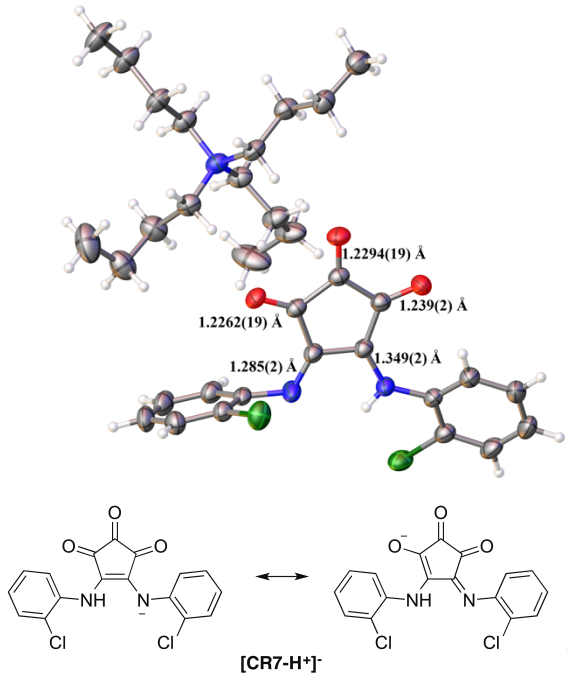


Figure 10. (Top) Single crystal X-ray diffraction determined depiction of [**CR7**-H$^+$]$^-$ and it's with TBA counterion. Displacement ellipsoids are shown at the 50% probability level; disorder found for 2-chlorophenyl residue has been omitted for clarity. C=grey, O=red, N=blue, Cl=purple, H=white. (Bottom) Mesomeric structures of [**CR7**-H$^+$]$^-$.

Comparison of dual H-bond motifs. Table 4 summarizes the apparent association constants K_a obtained as part of this work for deltamides **DT1-DT6**, squaramides **SQ1, SQ2**, and **SQ4**, and croconamides **CR1-CR6**, with chloride and acetate in DMSO (0.5% water, unless otherwise noted). Where possible, literature values are also given for ureas **UR1-UR6** and squaramides **SQ3**, **SQ5**, and **SQ6.** A number of differences are apparent between these dual H-bond motifs, with regards to anion binding affinities and selectivity. Some of these are partly explained by the differences in pK_a between the compound classes. For compounds bearing the same substituents, the trend for pK_a values is ureas > deltamides > squaramides > croconamides with the croconamides being 10 – 15 pK_a units more acidic than the corresponding ureas. Within each compound class the diaryl derivatives are 4 – 8 pK_a units more acidic than the dialkyl derivatives, with the addition of *p*-nitro or *p*-trifluoromethyl groups leading to decreased pK_a values compared to the unsubstituted phenyl derivatives.

Strikingly, the pK_a of the aryl croconamides is 6-8, indicating that they are partially deprotonated at neutral pH and explaining both the low observed binding affinities for chloride ions and their deprotonation by acetate. A similar trend in both binding affinity and proton acidity has previously been observed for the thiosquaramides.[5] However, the pK_as of the alkyl-substituted croconamides **CR1** and **CR2**, are similar to that of *N,N'*-diphenylsquaramide **SQ3** and this is reflected in the similar (and relatively high) binding affinities observed for chloride ions by **CR1** (K_a = 230 M^{-1}) and **SQ3** (K_a =260 M^{-1}) in d$_6$-DMSO. Both the alkyl croconamides (**CR1**, **CR2**) and the arylsquaramides (**SQ3-SQ6**) are deprotonated in DMSO solution upon addition of acetate.

One additional factor that may contribute to the different trend observed for the croconamide series in comparison to the ureas and squaramides is the energy penalty required for the molecules to adopt the conformation required for anion binding. In DMSO solution, the *anti/anti*- conformation required for anion binding is favoured as a result of hydrogen bonding to DMSO solvent molecules. In this conformation there is a tendency towards planarization for all compounds upon chloride binding, increasing the sp_2 character on the nitrogen atom and providing more favourable electrostatic interactions with the anion.[34] The cost of this 'reorganisation' energy penalty is higher for aryl croconamides than for alkyl croconamides (Table S2) as a result of increased steric interaction between the phenyl rings and the carbonyl groups and this may contribute to the lower binding affinities observed for the aryl croconamides.

In contrast, both urea and deltamide series of compounds bind chloride only weakly (K_a <75 M^{-1}) in d$_6$-DMSO and binding affinities follow the trend aryl > alkyl with the introduction of electron withdrawing groups onto the aromatic substituents providing a significant boost in binding affinity for the urea series, but not for the deltamides. Since the deltamides are more acidic than the corresponding ureas, this difference can not be explained by differences in pK_a and is more likely a result of geometric factors, with the dual H-bond donors in the deltamides spaced further apart than they are in the corresponding ureas. Indeed, computational calculations suggest that complexation to chloride incurs a significantly higher energy penalty in deltamides.[34] Similarly, binding affinities for acetate are similar for both **UR3** and **DT3**, but **DT3** is approx. 2.5 pK_a units more acidic than **UR3**, so would be expected to bind acetate more strongly if acidity of the NH donor was the primary consideration.

The binding affinities for the *p*-nitrophenyl derivatives **UR6**, **DT6**, and **SQ6** in MeCN are provided in Table 5. No binding was observed for **CR6** under these conditions, as the receptor exists predominantly in its deprotonated form. However, the differences in binding affinities between the other dual H-bond donors are readily observed in this less polar solvent. While all three receptors display similar binding affinities for acetate (log K_a = 6.4-6.6), chloride binding affinities vary by three orders of magnitude, with **SQ6** > **UR6** > **DT6**. **DT6** is therefore better able to discriminate acetate from chloride than either **SQ6** or **UR6**. **DT6** also displays significantly higher affinity for $H_2PO_4^-$ than either **SQ6** or **UR6**, binding to this anion with a higher affinity than it displays for acetate (**DT6**: log K_a 7.45 for $H_2PO_4^-$, log K_a 6.40 for AcO^-); this trend is opposite to that displayed by either **UR6** or **SQ6** and does not correlate with anion basicity. Thus, both deltamides and ureas favor binding to oxoanions whereas the

squaramides display similar affinities to both carboxylates and chloride. In addition, the deltamides have a subtly different selectivity profile to the ureas as a result of the greater distance between the hydrogen bond donor atoms.

Table 4. Apparent Association Constants for Ureas **UR1-UR6**, Deltamides **DT1-DT6**, Squaramides **SQ1-SQ6**, and Croconamides **CR1-CR6** with chloride and acetate in DMSO[a]

	K_a (M^{-1})			K_a (M^{-1})	
	Cl^-	AcO^-		Cl^-	AcO^-
UR1	< 10[b]	—[c]	SQ1	56	2200
UR2	—[c]	—[c]	SQ2	57	2000[k]
UR3	31[d]	2100[e]	SQ3	260[d]	—[c]
UR4	—[c]	—[c]	SQ4	300	—[j]
UR5	75[d]	—[c]	SQ5	460[d]	—[c]
UR6	120[f]	>10^4 [g]	SQ6	—[m,i]	—[l]
DT1	—[h]	—[h]	CR1	230	—[j]
DT2	< 5	11	CR2	110	—[j]
DT3	9	2300	CR3	42	—[j]
DT4	6	6500	CR4	20	—[j]
DT5	12	1200	CR5	19, 10[m]	—[j]
DT6	<100[i]	—[j]	CR6	—[l]	—[l]

[a]Apparent association constants (K_a/M^{-1}) determined by ^{1}H NMR spectroscopy in DMSO-d_6 (0.5% water) at 300 K unless otherwise noted. Anions were added as their tetrabutylammonium (TBA) salts unless otherwise noted. Values rounded to a maximum of two significant figures. Estimated errors in K_a <15% unless otherwise noted. [b]Value reported in reference 40 for the **UR1** analogue 1-butyl-3-isopentylurea as determined by ^{1}H NMR spectroscopy in DMSO-d_6 (0.5% water) at 298 K (estimated error <15%). [c]K_a not reported in the literature. [d]Value from reference 8. K_a in DMSO-d_6 (0.5% water) at 298 K (estimated error in K_a <15%). [e]Value from reference 41. K_a in DMSO-d_6 (0.5% water) at 298 K (error in K_a ±18%). [f]Value from reference 42. K_a in DMSO-d_6 (0.5% water) at 298 K (error in K_a ±2%). [g]Value from reference 42. K_a in DMSO-d_6 (0.5% water) at 298 K. Acetate was added as its tetramethylammonium salt. [h]Receptor not stable. [i]The absorbance changes observed during UV-vis spectroscopic titrations of **DT6** with chloride in DMSO-d_6 (0.5% water) at 298 K were too small to obtain an accurate value for K_a. [j]Addition of the anion caused the receptor to deprotonate. [k]Value from reference 17. K_a in DMSO-d_6 at 295 K (error in K_a <5%). Acetate was added as its tetramethylammonium salt. [l]The receptor exists in its deprotonated form in DMSO. [m]Value from reference 15. K_a in dry DMSO-d_6 at 295 K (error in K_a <1%).

Table 5. Apparent Association Constants (logK_a) for *p*-nitrophenyl Derivatives in MeCN at 25 °C, Determined by UV-vis Titration.

Anion	UR6[a]	DT6	SQ6 [a]	CR6
Cl^-	4.55	3.32	6.05	Deprot.
Br^-	3.22	2.99	4.70	Deprot.
I^-	<2	2.44	3.51	Deprot.
NO_3^-	3.65	<2	3.68	Deprot.
HSO_4^-	4.26	4.70	4.02	Deprot.
TsO^-	n.d.	3.59	n.d.	Deprot.
$H_2PO_4^-$	5.37	7.45	5.42	Deprot.
AcO^-	6.61	6.40	6.5	Deprot.
BzO^-		5.38		Deprot.

[a] Values from reference 9.

Conclusions

A library of compounds incorporating dual H-bond motifs in the form of croconamides and the hitherto unreported deltamides has been prepared and their anion binding behavior and Brønsted acidity has been evaluated and compared to that of the known dual H-bond motifs, the ureas and squaramides. The croconamides were found to be considerably more acidic than the corresponding squaramides, and displayed an unusual trend in chloride binding affinities, with the *N,N'*-dialkylcroconamides having higher affinities than the *N,N'*-diaryl derivatives. This was attributed to a combination of the *N,N'*-diaryl derivatives existing partially in deprotonated form at neutral pH, therefore reducing their ability to bind to anions, and the higher 'reorganisation energy' penalty for aryl- vs alkyl-croconamides . In contrast, the deltamides are less acidic than the squaramides, but more acidic than the ureas. Within the deltamide series, the anion affinity trend is analogous to that observed previously for both ureas and squaramides, with the *N,N'*-diaryl derivatives displaying higher affinity than the *N,N'*-dialkyl derivatives, and the introduction of electron withdrawing groups to the aryl substituents resulting in increased anion affinity. Hence binding affinity within a series reflects the inherent acidity of the amide protons.

Some interesting differences in anion binding selectivities emerge when different dual H-bond cores with the same substituents are compared. The deltamides display lower anion binding affinities for chloride than the corresponding ureas and squaramides, whereas the affinity of all three dual H-bond cores for acetate ions is similar. In contrast to the ureas and squaramides, where anion binding affinity correlates with anion basicity, the deltamides also display higher affinity for $H_2PO_4^-$ than for carboxylates and other oxoanions. This can be attributed to the differences in structure between these three cores, which position the amide protons at different distances and different angles with respect to one another. Hence the geometric match between the receptor and anion appears to be a significant factor in determining anion selectivity.

These differences in binding selectivity for the different dual H-bond donor cores could be exploited through their incorporation into more complex molecular scaffolds containing multiple dual hydrogen bond donors, where, in addition to matching anion geometry through scaffold design, the inherent selectivity of the dual H-bond donor motifs can now be tuned to match the anion of interest, while the strength of the interaction for a given core can be tuned through appropriate substitution of the amide nitrogen atoms. This will assist in the design of future anion receptors that bind to their targets using hydrogen-bonding.

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Keywords: anion recognition • hydrogen bonding • deltamide • croconamide • squaramide

[1] (a) P. A. Gale, E. N. W Howe, X. Wu, *Chem* **2016**, *1*, 351-422; (b) T. S. Snowden, E. V. Anslyn, *Curr. Opin. Chem. Biol.* **1999**, *3*, 740-746; (c) T. Gunnlaugsson, M. Glynn, G. M. Tocci, P. E. Kruger, F. M. Pfeffer, *Coord. Chem. Rev.* **2006**, *250*, 3094-3117; (d) E. A. Katayev, Y. A. Ustynyuk, J. L. Sessler, *Coord. Chem. Rev.* **2006**, *250*, 3004-3037; (e) E. J. O'Neil, B. D. Smith, *Coord. Chem. Rev.* **2006**, *250*, 3068-3080; (f) S. Kubik, *Chem. Soc. Rev.* **2010**, *39*, 3648-3663; (g) A. Caballero, F. Zapata, P. D. Beer, *Coord. Chem. Rev.* **2013**, *257*, 2434-2455; (h) R. B. P. Elmes, K. A. Jolliffe, *Chem. Commun.* **2015**, *51*, 4951-4968; (i) M. J. Langton, C. J. Serpell, P. D. Beer, *Angew. Chem. Int. Ed.* **2016**, *55*, 1974-1987.

[2] For a recent review see N. Busschaert, C. Caltagirone, W. Van Rossom, P. A. Gale, *Chem. Rev.* **2015**, *115*, 8038-8155.

[3] V. Amendola, L. Fabbrizzi, L. Mosca, *Chem. Soc. Rev.* **2010**, *39*, 3889-3915.

[4] S. Tshepelvitsch, A. Trummal, K. Haav, K. Martin, I. Leito, *J. Phys. Chem. A* **2017**, *121*, 357-369.

[5] N. Busschaert, R. B. P. Elmes, D. D. Czech, X. Wu, I. L. Kirby, E. M. Peck, K. D. Hendzel, S. K. Shaw, B. Chan, B. D. Smith, K. A. Jolliffe, P. A. Gale, *Chem. Sci.* **2014**, 3617-3626.

[6] R. West, *Aldrichimica Acta* **1968,** *1*, 3-6.

[7] V. Amendola, L. Fabbrizzi and L. Mosca, F. P. Schmidtchen, *Chem. Eur. J.* **2011**, *17*, 5972-5981.

[8] N. Busschaert, I. L. Kirby, S. Young, S. J. Coles, P. N. Horton, M. E. Light, P. A. Gale, *Angew. Chem. Int. Ed.* **2012**, *51*, 4426-4430.

[9] V. Almendola, G. Bergamachi, M. Boiocchi, L. Fabbrizzi, M. Milani, *Chem. Eur. J.* **2010**, *16*, 4368-4380.

[10] D. Quiñonero, C. Garau, A. Frontera, P. Ballester, A. Costa, P. M. Deyà, *Chem. Eur. J.* **2002**, *8*, 433.

[11] L. M. Schwartz, R. I. Gelb, D. A. Laufer, Physical Chemistry of Oxocarbons, Chapter 3 in Oxocarbons, Ed. R. West, Academic Press, New York, **1980**, pp43-58.

[12] D. Quiñonero, A. Frontera, P. Ballester, P. M. Deyà, *Tetrahedron Lett.*, **2000**, *41*, 2001-2005.

[13] For recent reviews on anion recognition by ureas see: V. Blazek Bregovic, N. Basaric, K. Mlinaric-Majerski, *Coord. Chem. Rev*. **2015**, *295*, 80-124; A.-F. Li, J.-H. Wang, F. Wang, Y.-B. Jiang, *Chem. Soc. Rev*. **2010**, *39*, 3729-3745.

[14] For reviews on squaramides see J. Aleman, A. Parra, H. Jiang, K. A. Jorgensen, *Chem. Eur. J*. **2011**, *17*, 6890-6899; R. I. Storer, C. Aciro, L. H. Jones, *Chem. Soc. Rev.* **2011**, *40*, 2330-2346.

[15] A. Jeppesen, B. E. Nielsen, D. Larsen, O. M. Akselsen, T. I. Solling, T. Brock-Nannestad, M. Pittelkow, *Org. Biomol. Chem.* **2017**, *15*, 2784-2790.

[16] S. P. Kumar, P. M. C. Gloria, L. M. Goncalves, J. Gut, P. J. Rosenthal, R. Moreira, M. M. M. Santos, *Medchemcomm* **2012**, *3*, 489-493.

[17] R.; Prohens, S. Tomas, J. Morey, P. M. Deya, P. Ballester, A. Costa, *Tetrahedron Lett.* **1998**, *39*, 1063-1066.

[18] A. Rostami, A. Colin, X. Y. Li, M. G. Chudzinski, A. J. Lough, M. S. Taylor, *J. Org. Chem.* **2010**, *75*, 3983-3992.

[19] R. Malachowsky, S. Prebendowsky, *Ber. Deutsch. Chem. Ges.* **1938**, *71*, 2241-2247.

[20] R. Breslow, C. Werner, *Tetrahedron Lett*. **1999**, *40*, 2447.

[21] K. Mishiro, F. H. Hu, D. W. Paley, W. Min, T. H. Lambert, *Eur. J. Org. Chem.* **2016**, 1655-1659.

[22] K. J. Walst, R. Yunis, P. M. Bayley, D. R. Macfarlane, C. J. Ward, R. Wang, O. J. Curnow, *RSC Adv*. **2015**, *5*, 39565-39579; M. J. Taylor, P. W. J. Surman, G. R. Clark, *J. Chem. Soc*., *Chem. Commun*. **1994**, 2517.

[23] http://supramolecular.org (accessed 12th of April, 2017)

[24] P. Gans, A. Sabatini, A. Vacca, *Talanta* **1996**, *43*, 1739-1753.

[25] D. Esteban-Gómez, L. Fabbrizzi, M. Licchelli, *J. Org. Chem.* **2005**, *70*, 5717-5720.

[26] A 1:1 binding model was used as it gave the most consistent and reproducible association constants with the best fits, but analysis of the residuals[43] suggests that at higher anion concentrations, the 1:1 model is no longer valid for these compounds. However, attempts to fit the binding data to alternative models (e.g. 2:1) using both bindfit (v0.5) and HypNMR gave highly variable results.

[27] For titration of **DT5** with $H_2PO_4^-$ the changes in chemical shift of the signals for the NH protons could not be followed due to peak broadening. In this case, the association constant was determined by monitoring the changes in chemical shift of the aromatic proton signals.

[28] I. L. Kirby, M. Brightwell, M. B. Pitak, C. Wilson, S. J. Coles, P. A. Gale, *Phys. Chem. Chem. Phys.* **2014**, *16*, 10943-10958.

[29] S. J. Pike, J. J. Hutchinson, C. A. Hunter, *J. Am. Chem. Soc.*, **2017**, *139*, 6700-6706.

[30] Sufficient quantities of **DT6** to perform NMR titrations were not readily available.

[31] M. Boiocchi, L. Del Boca, D. Esteban-Gómez, L. Fabbrizzi, M. Licchelli, E. Monzani, *J. Am. Chem. Soc.*, **2004**, *126*, 16507-16514.

[32] D. J. Henry, M. B. Sullivan, L. Radom, *J. Chem. Phys.* **2003,** *118*, 4849-4860.

[33] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009,** *113*, 6378-6396.

[34] J. Ho, V. E. Zwicker, K. K. Y. Yuen, K. A. Jolliffe, *J. Org. Chem*., **2017**, *82*, 10732-10736.

[35] W. Städeli, R. Hollenstein, W. von Philipsborn, *Helv. Chim. Acta*., **1977**, *60*, 948-958.

[36] W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. Mccallum, G. J. Mccollum, N. R. Vanier, *J. Am. Chem. Soc.* **1975**, *97*, 7006-7014.

[37] G. Jakab, C. Tancon, Z. G. Zhang, K. M. Lippert, P. R. Schreiner, *Org. Lett.* **2012**, *14*, 1724-1727.

[38] F. G. Bordwell, D. J. Algrim, J. A. Harrelson, *J. Am. Chem. Soc.* **1988**, *110*, 5903-5904.

[39] X. Ni, X. Li, Z. Wang, J. P. Cheng, *Org. Lett.* **2014**, *16*, 1786-1789.

[40] N. J. Andrews, C. J. E. Haynes, M. E. Light, S. J. Moore, C. C. Tong, J. T. Davis, W. A. Harrell, P. A. Gale, *Chem. Sci.* **2011**, *2*, 256-260.

[41] S. A. Kadam, K. Martin, K. Haav, L. Toom, C. Mayeux, A. Pung, P. A. Gale, J. R. Hiscock, S. J. Brooks, I. L. Kirby, N. Busschaert, I. Leito, *Chem. Eur. J.* **2015**, *21*, 5145-5160.

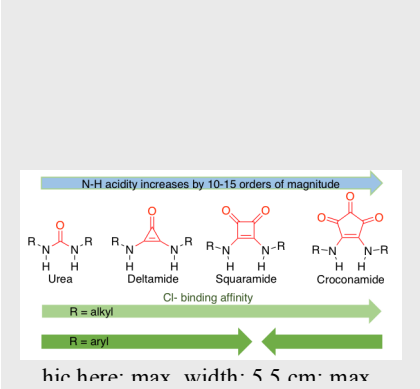
[42] L. Kirby, M. B. Pitak, M. Wenzel, C. Wilson, H. A. Sparkes, S. J. Coles, P. A. Gale, *CrystEngComm* **2013**, *15*, 9003-9010.

[43] P. Thordarson, *Chem. Soc. Rev.* **2011**, *40*, 1305-1323.

Layout 1:

FULL PAPER

Bite-angle and Brønsted acidity control anion binding affinity and selectivity by amides from the oxo-carbon family.



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