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Protonation and anion binding properties of aromatic bis-urea derivatives – apprehending the proton transfer

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Abstract

A series of aromatic bis-urea derivatives was prepared and their proton dissociation, as well as anion binding properties in DMSO were investigated. To this end, UV-Vis and ^{1}H NMR spectroscopies and computational methods were employed. The synthesised molecules differed in the relative position of the urea moieties (*ortho*- and *meta*-derivatives) and in the functional groups (–H, –CH_3, –OCH_3, –NO_2) in the *para*-position of the pendant phenyl groups. Remarkably high acidities of the compounds (log $K_1^H \approx 14$), were ascribed primarily to the stabilising effect of the aromatic subunits. Quantum-chemical calculations corroborated the conclusions drawn from experimental data and provided information from the structural point of view. Knowledge regarding protonation properties proved to be essential for reliable quantitative determination of anion binding affinities. Studied receptors were selective for acetate and dihydrogen phosphate among several anions. Formation of their complexes of 1:1 and 1:2 (ligand:anion) stoichiometries was quantitatively characterised. Proton transfer was taken into account in the course of data analysis, which was especially important in the case of AcO^-. *Ortho*-receptors were proven to be more efficient acetate binders, achieving coordination with all four NH-groups. The *meta*-analogues preferred dihydrogen phosphate, which acted as both hydrogen bond donor and acceptor. Cooperative binding was detected in the case of 1:2 $H_2PO_4^-$ complexes which was assigned to formation of interanionic hydrogen bonds.

1. Introduction

As the field of anion coordination chemistry has evolved, new levels of complexity of the related systems have been explored, which increased the urge for thorough research of all processes related to anion coordination.[1–9] In this field, urea derivatives have been among the most studied receptors, and numerous studies of their complexation with diverse anionic species have been reported.[10–18] In pursuit of higher affinity and selectivity, original concepts have been examined with the goal of achieving the desired receptor properties.[19–22]. A prerequisite facilitating the anion receptor development is comprehensive understanding of the thermodynamics underlying anion binding, leading to apprehension of structure-reactivity correlation, assessment of the individual contributions to the complex stability, better insight into the solvent effect on the corresponding equilibria, *etc*.[23–26] Consequently, the synthetic and other experimental efforts can be steered in the right direction.

In order to gather reliable thermodynamic information about the anion binding processes it is of great importance to identify and characterise the coupled reactions. In the case of anion receptors bearing urea, and especially thiourea moieties, one of the most commonly encountered side-reactions is deprotonation of the NH-group, accompanied by protonation of the anion, *i.e*. receptor to anion proton transfer.[27–34] This process is especially favourable in aprotic organic solvents of lower polarity due to drastic increase in basicity of the commonly used anions (*e.g.* fluoride, carboxylates, or dihydrogen phosphate) with respect to aqueous medium. Although proton transfer has been recognized as an important process, particularly if fluoride or carboxylate anions are used as guests, it has rarely been

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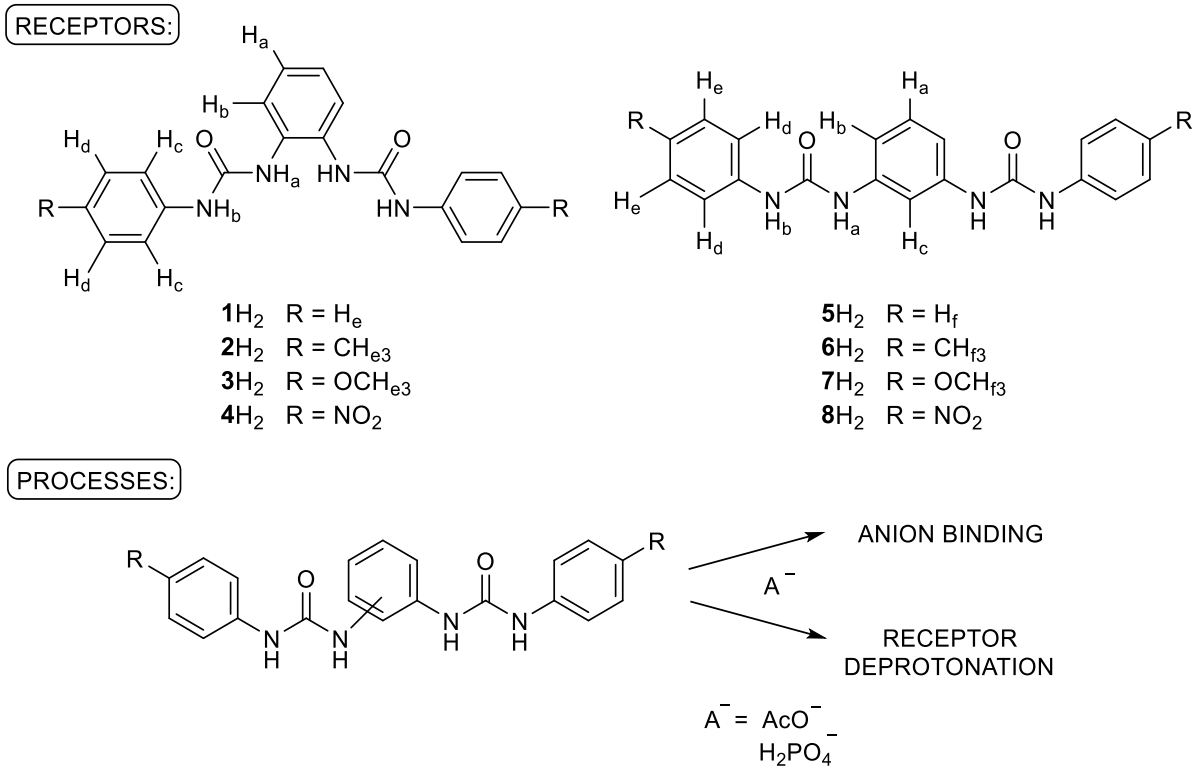
included quantitatively in an adequate manner. This is in great part due to complexity of the established equilibria in such solutions, which makes the analysis of the related titration data rather complicated. Namely, for the full characterisation of such systems detailed information on both ligand and anion protonation properties is essential. Further on, the occurrence of such complex system of chemical equilibria can be evasive if standard experimental procedures are applied.[34]

Herein, we present a systematic study on proton dissociation of aromatic bis-urea derivatives (**1**H_2-**8**H_2, Scheme 1) and their anion binding properties, taking into account that these two processes are inherently coupled. To this end, both experimental (UV-Vis, ^{1}H NMR) and theoretical methods were applied and recently reported data acid-base properties of phosphoric and acetic acid in DMSO were implemented.



Scheme 1. Structures of the studied aromatic urea-based anion receptors and the reactions investigated.

2. Results and discussion

2.1. Protonation

The proton dissociation of the prepared urea derivatives (**1**H_2-**8**H_2**)** in DMSO was characterised by competitive spectrophotometric and ^{1}H NMR titrations using 1,8-diazabicycloundec-7-ene (DBU) as a base. DBU was chosen due to low spectral overlap with the urea derivatives, suitable basicity (expected from the data available in acetonitrile (log K^H = 24.34)[35] and the fact that its interaction with the studied ligand (other than deprotonation) is not expected. The protonation of DBU was not previously studied in DMSO, and for that reason the corresponding equilibrium constant was determined spectrophotometrically by titrating bromothymol blue ($BTBH_2$, log K_1^H = 11.3)[36] with DBU (Figure 1). Significant dependence of UV-Vis spectra of bromothymol blue solution on the concentration of DBU was observed, caused by deprotonation of $BTBH^-$ (characteristic peak at 638 nm appeared). The non-linear regression analysis of the obtained titration data allowed the determination of the equilibrium constant for the protonation of DBU, rendering the value log K^H = 13.13(7). The lack of spectral changes

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at n(DBU) / n($BTBH_2$) < 1 (Figure 1) was due to the fact that $BTBH_2$ is a diprotic acid, with quantitative dissociation of the first proton in DMSO. Thus, changes in the spectrum were observed only after complete neutralisation of the "free" hydrogen ion, *i.e.* upon the second dissociation step.

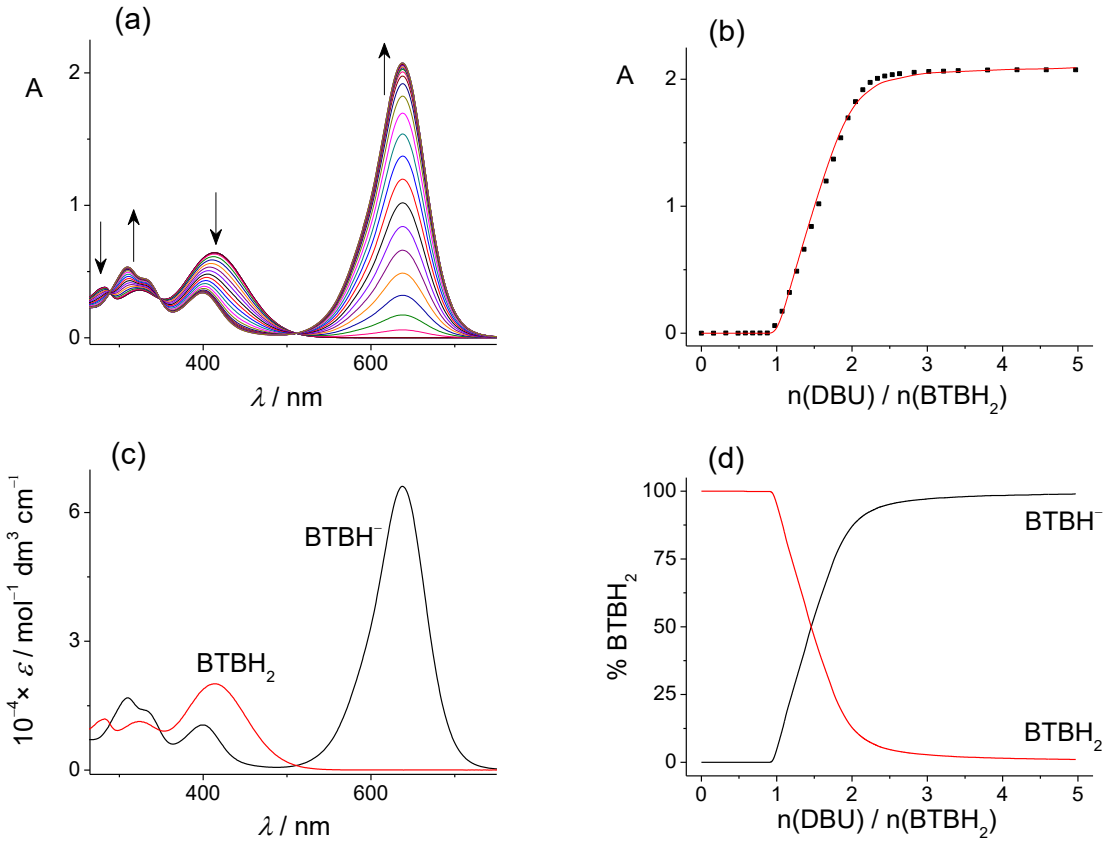

Figure 1. a) Spectrophotometric titration of $BTBH_2$ (c = 3.19 × 10^{-5} mol dm^{-3}) with DBU (c = 2.37 × 10^{-3} mol dm^{-3}) in DMSO at (25.0 ± 0.1) °C; l = 1 cm, V_0 = 2.28 mL. Spectra are corrected for dilution. b) Dependence of absorbance at 638 nm on n(DBU) / n($BTBH_2$) molar ratio. ■ experimental, ─ calculated. c) Characteristic UV-Vis spectra of $BTBH_2$ and its deprotonated form. d) Distribution of protonation species of bromothymol blue during the titration of a $BTBH_2$ solution with DBU.

Having characterised protonation properties of DBU we were able to use it as a base for the investigations of the urea-based ligands. By adding DBU to the solution of the ligands, significant changes in the ^{1}H NMR and UV-Vis spectra were observed. In the case of NMR titrations, all proton signals exhibited detectable changes in the chemical shift (Figure 2 and Figures S25-S31 in the Supporting Information). This was most pronounced for singlets ascribed to urea NH-protons, for which the downfield shift was complemented with a severe broadening and decrease in intensity. Such finding is in line with the assumption that proton transfer to DBU takes place, indicating that the studied ureas are indeed prone to proton dissociation. However, the signals of protons involved in dissociation equilibria were not suitable for quantitative analysis and only the signals of aromatic signals were taken into account in the fitting procedures. Data analysis was done by means of HypNMR program in a multivariate fashion, taking into account as many proton signals as possible (Tables S1-S7 in the Supporting Information).

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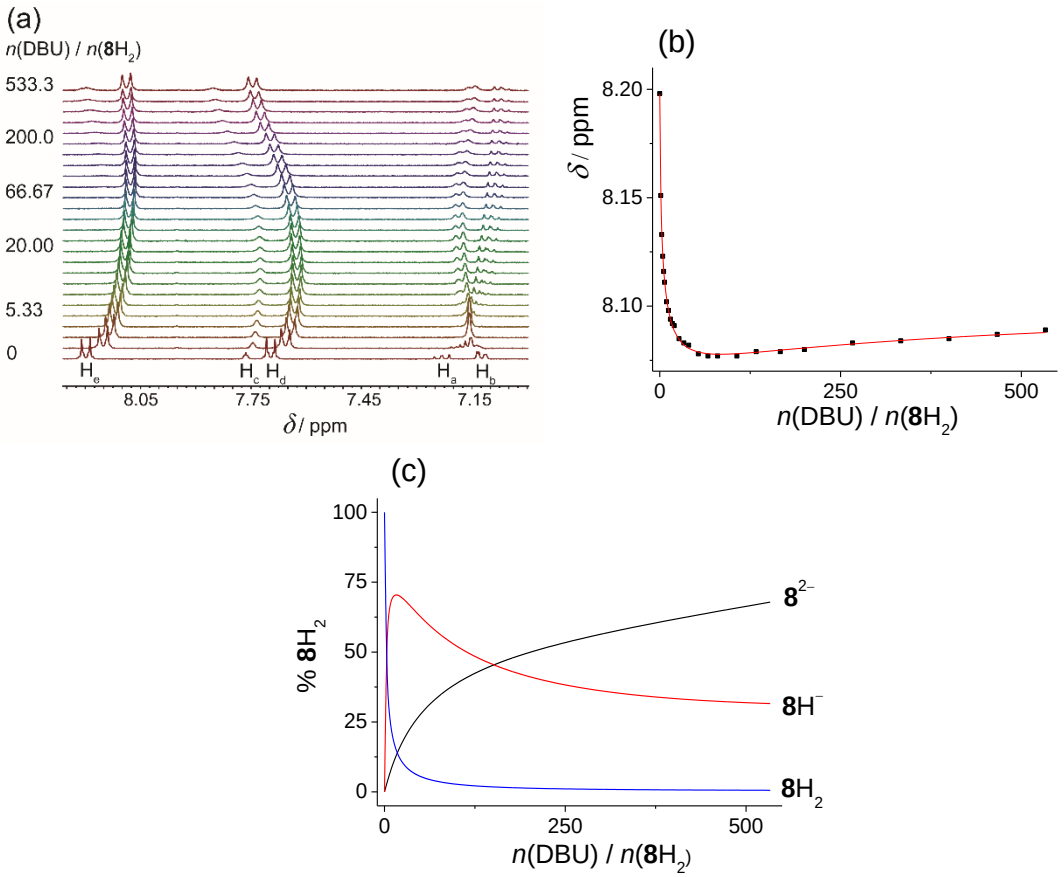

Figure 2. a) ^{1}H NMR titration of **8**H$_2$ (c = 5.86 × 10^{-4} mol dm^{-3}) with DBU (c = 4.10 × 10^{-1} mol dm^{-3}) in DMSO-d_6 at (25.0 ± 0.1) °C, V_0 = 0.525 mL. b) Dependence of H$_e$ proton chemical shift on n(DBU) / n(**8**H$_2$) molar ratio. ■ experimental, ─ calculated. c) Distribution of protonation species of **8**H$_2$ during the titration of **8**H$_2$ solution with DBU.

A satisfactory fit of the ^{1}H NMR titration curves could be achieved only by assuming two-step deprotonation of the ligand molecules, yielding protonation equilibrium constants given in Table 1. UV-Vis titrations of *ortho*-compounds (Figures S32-S34 in the Supporting Information) afforded first protonation constants, whereas the K_2^H was fixed at the value determined by NMR to achieve convergence. The values of K_1^H attained by the two methods were in good agreement. In the case of *meta*-derivatives only ^{1}H NMR titrations were employed for quantitative characterisation of protonation equilibrium constants, whereas the UV-Vis data could only be used for calculation of the characteristic spectra of the protonation species. More details regarding the data processing are provided in the Experimental part (Section 4.3.5).

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Table 1. Protonation constants of the studied compounds in DMSO at 25 °C.

	log K_1^H		log K_2^H
	^{1}H NMR[a]	UV-Vis[b]	^{1}H NMR[a]
1H_2	14.36(4)	14.32(6)	13.1(2)
2H_2	14.50(5)	14.68(5)	13.5(2)
3H_2	14.40(5)	14.48(2)	13.2(2)
5H_2	14.98(2)		14.8(1)
6H_2	14.78(5)		14.5(2)
7H_2	14.80(3)		14.4(2)
8H_2	15.27(3)		13.86(6)

[a] Uncertainties are given in parentheses as standard deviation of the fit

[b] Uncertainties are given in parentheses as standard error of the mean (N = 3)

The ability of the compounds to dissociate two protons is not surprising, since the two urea groups are relatively far apart and somewhat independent of each other. Consequently, differences between log K_1^H and log K_2^H are almost insignificant in the case of *meta*-derivatives **5**H_2-**7**H_2. For the *ortho*-analogues the difference in log K values is approximately 1, due to a stronger effect of the excess negative charge formed upon first deprotonation step. The possibility that such behaviour was caused by intramolecular hydrogen bond between the two urea groups was dismissed by employing computational methods. We performed detailed conformational searches for compounds **1**H_2 and **5**H_2, as representatives of both ligand classes (*ortho*- and *meta*-), starting with several geometries for each compound (Scheme 2). Modelling was performed in DMSO (zero, one or two explicit solvent molecules were included), and the calculations were conducted on neutral, mono-, and dianionic forms of the unsubstituted bis-ureas. None of the reasonably stable conformers of *ortho*-compound featured intramolecular –NH···O=C hydrogen bond (denoted as *"in-out-2"* conformer). Apparently, the hydrogen bond between the two urea moieties is sterically hindered, and instead, the hydrogen bonding potential of the urea moieties was saturated by solvent molecules. As a result, in excess DMSO the most stable conformation of the *ortho*-compound (regardless of the protonation state) is the one with NH-groups oriented towards each other (denoted as *"out-out"* conformer) (Scheme 2). In contrast, the *meta*-derivative showed almost no preference between the *"out-out"* and *"in-out"* conformers. In this case carbonyl oxygen atoms can interact with two different aromatic hydrogen atoms (H_b and H_c) which results in two conformers differing in carbonyl oxygen orientation, but exhibiting rather similar energies. The changes in NMR spectra observed upon deprotonation affirmed the importance of intramolecular hydrogen bonds involving aromatic hydrogen atoms. In the case of *meta*-derivatives, both protons adjacent to urea groups (H_b and H_c) experienced deshielding upon deprotonation (Figure 2 and Figures S28-S31 in the Supporting Information), which can be ascribed to enhancement of their hydrogen bonds with carbonyl atom as it accommodates excess of negative charge. All other hydrogen nuclei featured an upfield shift, which is in line with the increase in electron density in the phenyl ring upon proton dissociation. As shown in the following section, preorganisation governed by intramolecular CH···O= hydrogen bonds had significant impact on the anion complexation properties of the studied receptors.

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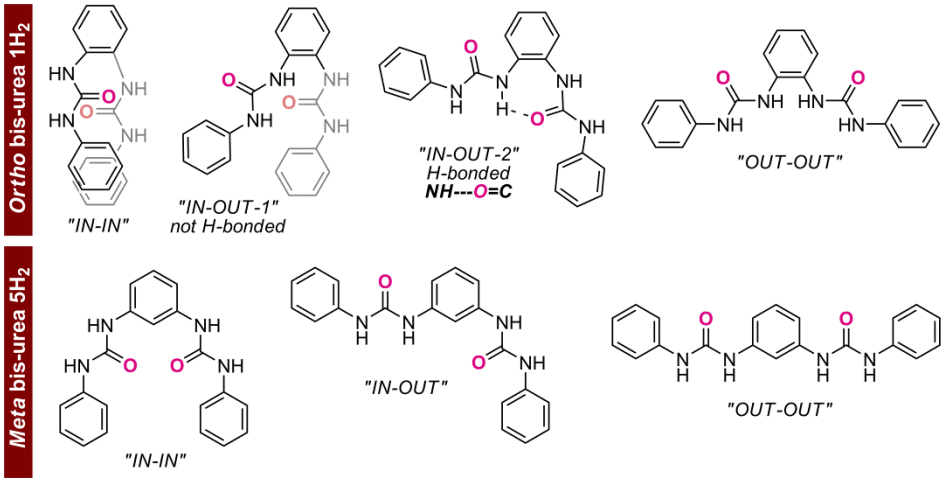
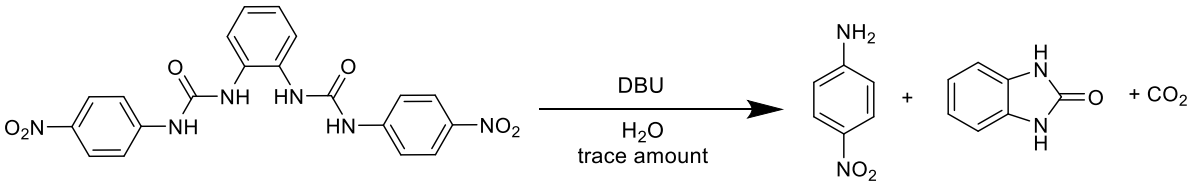


Scheme 2. Possible conformers for compounds **1**H_2 and **5**H_2 which have been used as starting points for calculations.

We also note that computational results for both **1**H_2 and **5**H_2 in presence of explicit DMSO molecules indicate that a hydrogen atom from the NH-group close to the central phenyl moiety is more prone to leave the molecule first, followed by deprotonation of the NH-group in the other urea moiety that is further away from the central benzene ring.

The effect of methyl or methoxy group in the *para*-position of the pendant benzene rings on the protonation properties was not considerable. The ligands comprising these substituents exhibited rather similar dissociation affinity as the unsubstituted derivative, among both *ortho*- and *meta*-compounds. On the other hand, introduction of electron withdrawing NO_2-functional group greatly affected the properties of the bis-urea receptors. In the case of **4**H_2 (nitro-substituted *ortho*-derivative) we detected time dependence of the ^{1}H NMR and UV-Vis spectra upon addition of DBU. As proton signals of starting compound decayed two new sets appeared indicating a process different from deprotonation. Reaction was tested on preparative scale and products were isolated using column chromatography and identified by NMR (Scheme 3). It was confirmed that this was due to decomposition of the ligand (Scheme 3).



Scheme 3. Reaction of **4**H_2 with DBU in DMSO.

Compound **8**H_2 (*meta*-analogue of **4**H_2) proved to be stable upon addition of DBU and the titration revealed that the first proton dissociation is considerably more favourable compared to other bis-ureas (Table 1). In contrast, formation of dianionic species was in this case significantly less favourable, reflecting a 26-fold difference between K_1^H and K_2^H.

It should be stressed out that, to the best of our knowledge, compounds **1**H_2-**8**H_2 exhibit the most pronounced acidity in DMSO, among the urea derivatives studied so far. This affirmed the remarkable stabilisation of anionic form afforded by charge delocalisation through benzene rings, further assisted by intramolecular hydrogen bonds. On average, the dissociation constant of the studied ligands is approximately 12 orders of magnitude greater than the one determined for simple urea and 5 orders larger with respect to phenylurea in the same solvent.[37] This aspect of our results is especially important

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since the K^H values reported for urea and phenyl urea some 30 years ago are commonly used as a frame of reference for assessment of urea acidity, even for more elaborate derivatives comprising several aromatic moieties.[38] With this respect, our results strongly suggest that the possibility of proton transfer in the course of anion binding studies should be treated with much more scrutiny.

2.2. Anion binding

The binding affinity of the prepared receptors towards various weakly basic anions (chloride, nitrate, perchlorate) in DMSO was examined (Figures S59-S79 in the Supporting Information) by means of UV-Vis spectroscopy and no significant spectral changes occurred. On the other hand, the addition of acetate (AcO^-) and dihydrogen phosphate (DHP) causes significant spectral changes (Figure 3 and 6, Figures S35-S40, and S47-S58 in the Supporting Information). The processes responsible for this finding have been thoroughly investigated by means of ^{1}H NMR and UV-Vis titrations. One of the reactions expected to occur in the course of these titrations is proton transfer. If one takes into account the information given in the previous section regarding protonation properties of the ligands ($\log K_1^H \approx 14$) and previously reported data on acid-base properties of anions, it becomes evident that proton transfer is especially prominent in the case of acetate ($\log K_H = 12.82$).[39]

Respectively, we analysed the data using a model including the following reactions: **a)** formation of receptor:anion complexes, **b)** dissociation of the ligands, **c)** protonation of anion, **d)** homoassociation and dimerisation (of neutral species in the case of acetic acid, and anion in the case of DHP) The equilibrium constants for the "side-reactions" (b-d) were kept fixed in the course of titration data processing, whereas the anion complex stability constants were varied. Both anions were found to form 1:1 and 1:2 (ligand:anion) complexes. More details regarding the data analysis are provided in the Experimental part (Section 4.3.6). Since urea derivatives are often prone to form dimers or higher aggregates, we checked the possibility of host aggregation by recording their ^{1}H NMR spectra in a wide concentration range (Figures S80-S81 in the Supporting Information) and found no indication of aggregate formation for any of the investigated ligands. The ion pairing reactions were not considered in the data analysis since the TBA salts which were used for the addition of anions were not expected to form ion pairs, and we detected no indication of this reaction.

2.2.1. Acetate

The best fit of the data regarding UV-Vis titrations of the studied compounds with TBAOAc was attained by assuming formation of complexes comprising one and two anions in addition to partial deprotonation of the receptors. The latter was accounted for by including the protonation of acetate and ligand in the fitting model (Figure 3 and Figures S35-S40 in the Supporting Information). The calculated equilibrium constants are listed in Table 2.

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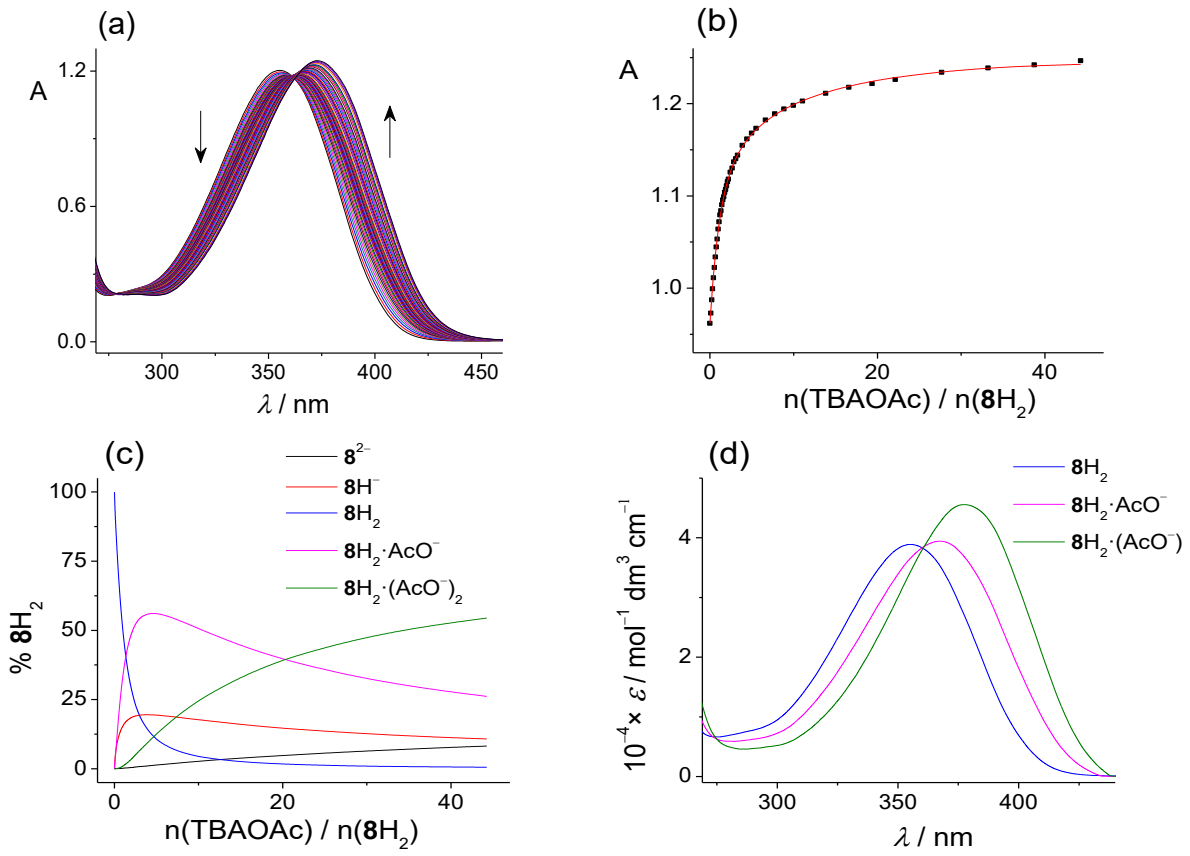

Figure 3. a) Spectrophotometric titration of **8**H_2 (c = 3.09 × 10^{-5} mol dm^{-3}) with TBAOAc (c = 7.94 × 10^{-3} mol dm^{-3}) in DMSO at (25.0 ± 0.1) °C; l = 1 cm, V_0 = 2.32 mL. Spectra are corrected for dilution. b) Dependence of absorbance at 373 nm on n(TBAOAc) / n(**8**H_2) molar ratio. ■ experimental, ─ calculated. c) Distribution of protonation species and acetate complexes of **8**H_2 during the titration of **8**H_2 solution with TBAOAc. d) Characteristic UV-Vis spectra of **8**H_2 and its acetate complexes.

The same model was applied to describe the NMR titration curves (Figure 4 and Figures S41-S46 in the Supporting Information), affording K_1 values which were in good agreement with the values calculated from the spectrophotometric data (Table 2). In these cases, the equilibrium constants for dianionic complexes were fixed at the value determined by the UV-Vis experiment. The signals ascribed to the NH-nuclei were again excluded from the quantitative data analysis.

Distribution diagrams constructed using the acquired equilibrium constants (Figure 3c and Figures S35c-S40c in the Supporting Information) clearly demonstrated the relevance of proton transfer reactions. For example, almost 20 % of the *meta*-ligands is present in anionic form when one equivalent of acetate is added. Even the percentage of fully deprotonated form reached considerable values (> 10 %) at high anion excess (> 50 equivalents).

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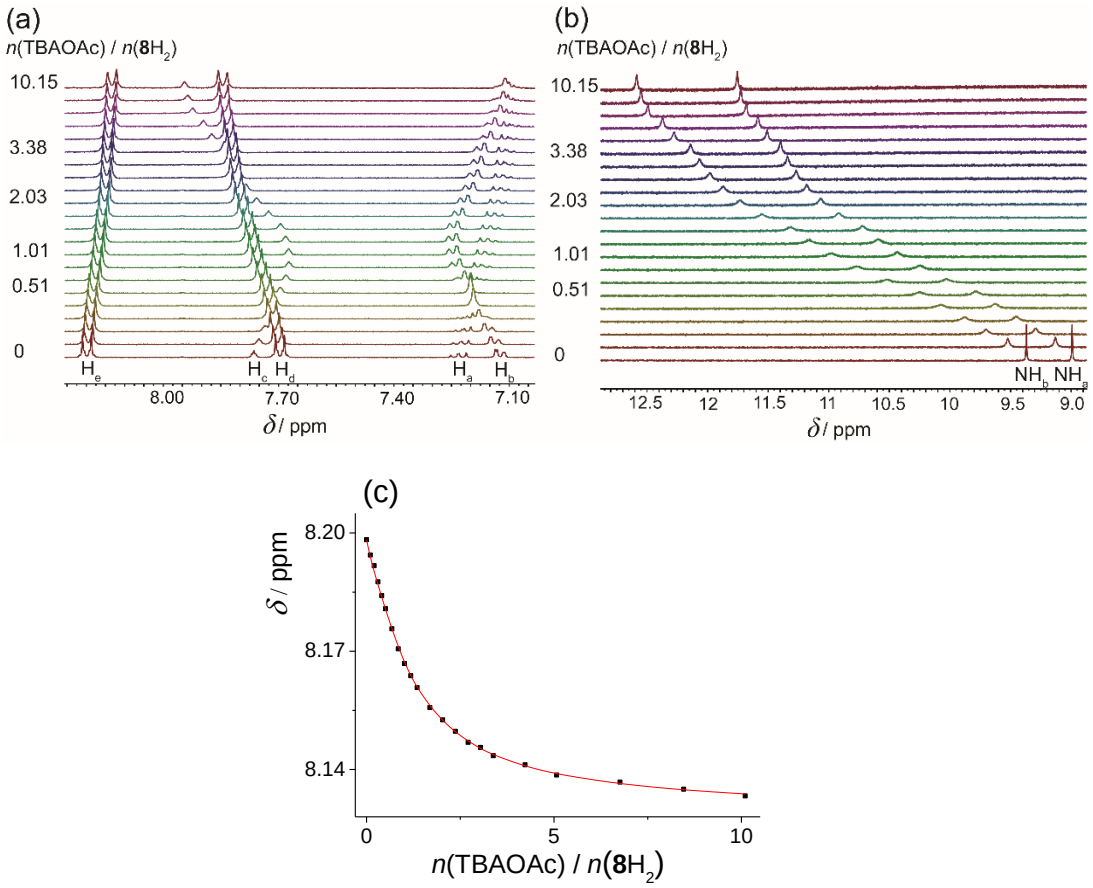

Figure 4. ^{1}H NMR titration of **8**H_2 (c = 5.86 × 10^{-4} mol dm^{-3}) with TBAOAc (c = 1.04 × 10^{-2} mol dm^{-3}) in DMSO-d_6 at (25.0 ± 0.1) °C, V_0 = 0.525 mL; a) aromatic and b) urea NH-proton signals. c) Dependence of H_e proton chemical shift on n(TBAOAc) / n(**8**H_2) molar ratio. ■ experimental, ─ calculated.

Ortho-ureas were found to form more stable 1:1 acetate complexes than their *meta*-analogues (Table 2). This could be ascribed to the fact that both urea groups of *ortho*-receptors easily interacted with the carboxylate anion forming four hydrogen bonds. Computational results and NOESY spectra (Figures S82-S90, Supporting Information) were in agreement with these assumptions. In the most stable conformations of the **1**H_2 AcO^- complex (Tables S32-S33 in the Supporting Information), the receptor offered all four NH-protons for interaction with acetate (Figure 5). On the other hand, we propose that in the case of *meta*-analogues the urea moieties acted as individual binding sites. Computational analysis of **5**H_2·AcO^- complex suggested that acetate interacts only with one urea and relative energies of the corresponding conformers were found within a rather narrow energy window (0.4 kcal mol^{-1}). In the NOESY spectra of **5**H2 and **8**H_2 solutions and solutions containing predominantly their acetate complexes the interactions NOE interactions were retained, suggesting that the conformational changes upon complexation were not very significant.

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Table 2. Stability constants of acetate complexes with studied urea receptors in DMSO at 25 °C.

	log K_1		log K_2
	UV-Vis[a]	^{1}H NMR[b]	UV-Vis[a]
1H_2	5.33(4)	5.1(1)	3.35(9)
2H_2	4.96(4)	5.2(1)	3.83(9)
3H_2	4.92(6)	4.91(9)	3.52(9)
5H_2	3.92(2)	3.90(4)	2.60(3)
6H_2	3.82(4)	4.0(1)	2.55(3)
7H_2	3.83(3)	3.94(5)	2.63(9)
8H_2	4.61(4)	4.73(5)	3.26(9)

[a] Uncertainties are given in parentheses as standard error of the mean (N = 3)
[b] Uncertainties are given in parentheses as standard deviation of the fit

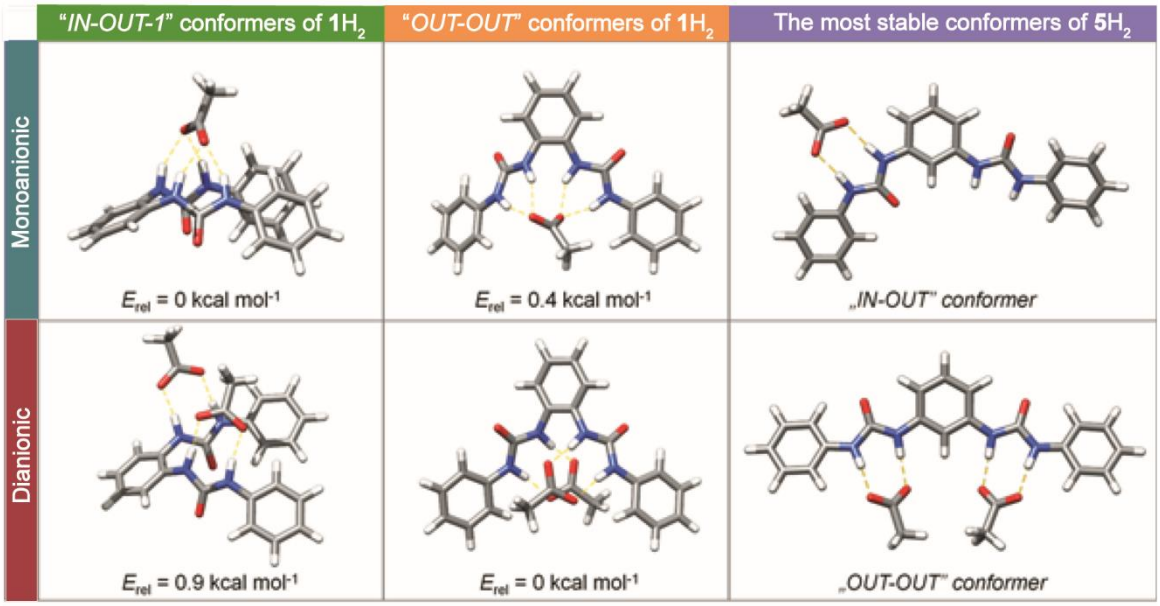

Figure 5. The most stable conformers of monoanionic and dianionic acetate complexes of **1**H_2 and **5**H_2. Energies for the **1**H_2 conformers are reported relative to the most stable conformer.

The formation of dianionic complexes was expected, given the fact that both urea moieties can act as individual binding sites. The relatively high stability of the complexes of 1:2 stoichiometry (ligand:anion) in the case of *ortho*-receptors is somewhat surprising as one might foresee some unfavourable steric effect. However, computational results indicated that the complexation of two AcO^- anions by the *ortho*-receptors attaining the "*out-out*" or even "*in-out-1*" conformation is in fact not sterically hindered.

In general, we detected only minor influence of the pendant benzene ring substituent in the *para*-position on the anion binding properties. The unsubstituted ligands exhibited somewhat higher affinity towards complexation in comparison to receptors containing electron-donating substituent. On the other hand, ligand **8**H_2, comprising electron-withdrawing nitro group formed most stable acetate complex among *meta*-derivatives. This finding is in line with previous reports on similar receptor series

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examining the impact of NO_2-functionality on the complex stability, and it is usually explained by better donating affinity of the NH-groups due to electron withdrawing effect of NO_2-group.[19,30]

2.2.2. Dihydrogen phosphate

As mentioned above, dihydrogen phosphate was also studied as a suitable guest for the prepared host molecules. This anion is significantly less basic (log K_H = 10.80) than acetate (log K_H = 12.82),[39] and the percentages of the anionic forms of the ligands in the course of the titrations were very low (< 5 %). Still, we adopted the fitting scheme analogous to the one used for acetate (Figures 6 and 7, Figures S47-S58 in the Supporting Information), and thus obtained equilibrium constants are given in Table 3.

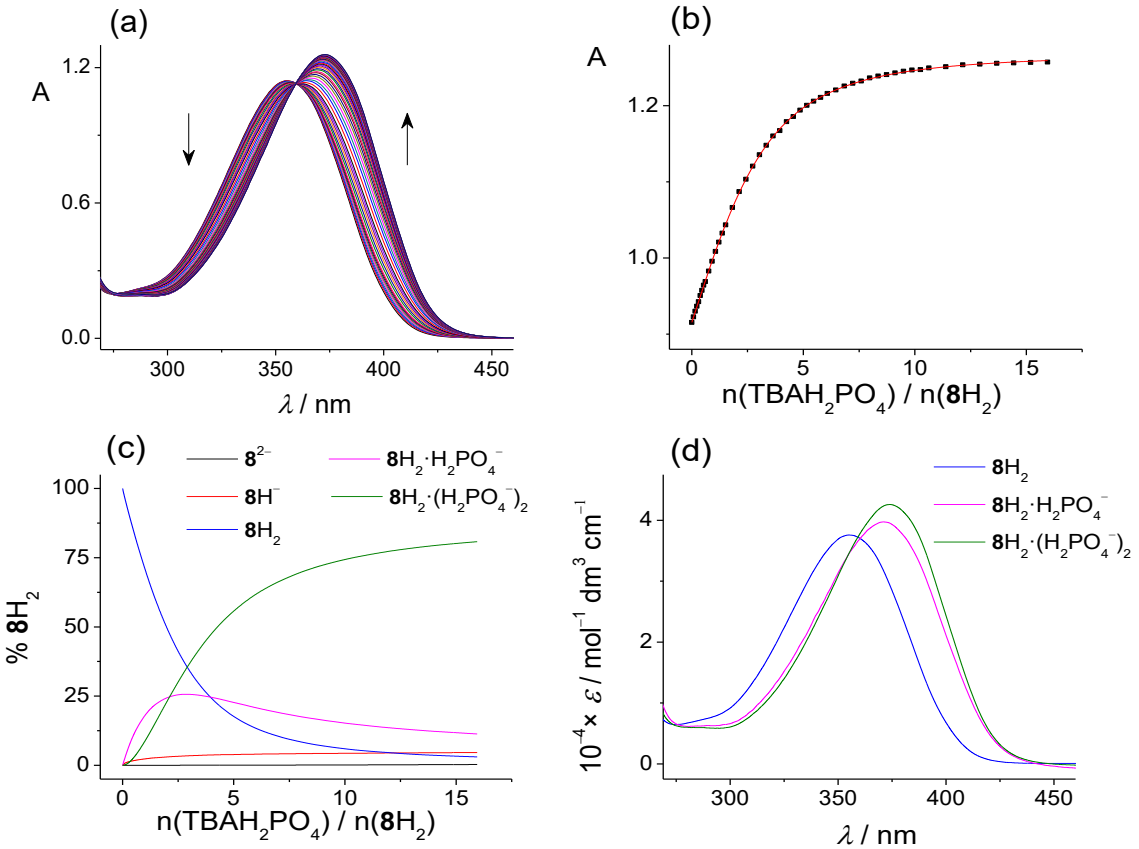

Figure 6. a) Spectrophotometric titration of **8**H_2 (c = 3.04 × 10^{-5} mol dm^{-3}) with $TBAH_2PO_4$ (c = 1.07 × 10^{-3} mol dm^{-3}) in DMSO at (25.0 ± 0.1) °C; l = 1 cm, V_0 = 2.32 mL. Spectra are corrected for dilution. b) Dependence of absorbance at 373 nm on $n(TBAH_2PO_4)$ / n(**8**H_2) molar ratio. ■ experimental, ─ calculated. c) Distribution of protonation species and dihydrogen phosphate complexes of **8**H_2 during the titration of **8**H_2 solution with $TBAH_2PO_4$. d) Characteristic UV-Vis spectra of **8**H_2 and its dihydrogen phosphate complexes.

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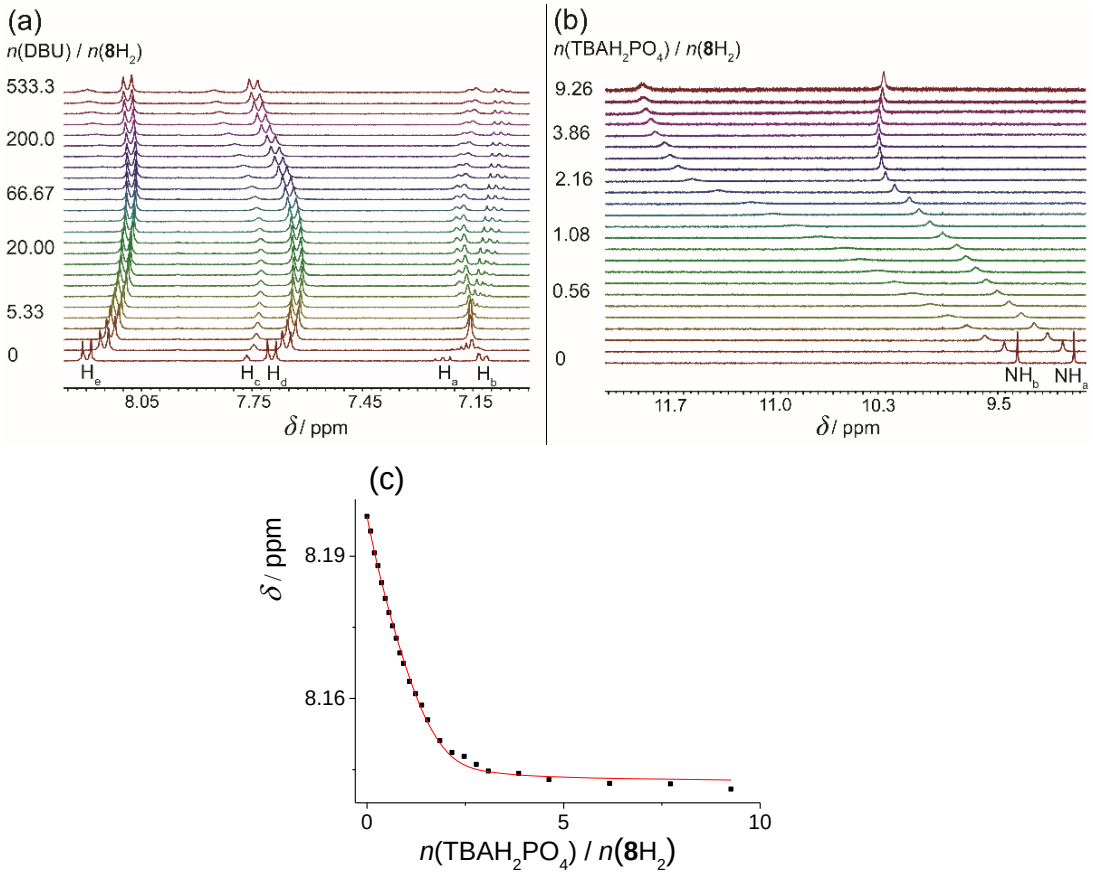

Figure 7. ^{1}H NMR titration of **8**H$_2$ (c = 5.86 × 10^{-4} mol dm^{-3}) with TBAH$_2$PO$_4$ (c = 9.49 × 10^{-3} mol dm^{-3}) in DMSO-d_6 at (25.0 ± 0.1) °C, V_0 = 0.525 mL; a) aromatic and b) urea NH-proton signals. c) Dependence of H$_e$ proton chemical shift on n(TBAH$_2$PO$_4$) / n(**8**H$_2$) molar ratio. ■ experimental, ─ calculated.

Table 3. Stability constants of dihydrogen phosphate complexes with studied urea receptors in DMSO at 25 °C.

	log K_1		log K_2
	UV-Vis[a]	^{1}H NMR[b]	UV-Vis[a]
1H$_2$	5.21(8)	5.13(3)	3.7(1)
2H$_2$	4.90(6)	5.01(6)	3.56(8)
3H$_2$	4.80(4)	4.79(4)	2.84(4)
5H$_2$	4.65(8)	4.63(7)	3.4(1)
6H$_2$	4.38(9)	4.60(9)	3.42(5)
7H$_2$	4.47(5)	4.49(9)	3.35(9)
8H$_2$	4.17(5)	4.36(8)	4.37(5)

[a] Uncertainties are given in parentheses as standard error of the mean (N = 3)

[b] Uncertainties are given in parentheses as standard deviation of the fit

Again, two types of complexes, comprising one or two anions have been detected. In the case of *ortho*-receptors, similar stabilities of DHP complexes were found as in the case of acetate analogues. On the other hand, *meta*-receptors proved to be more efficient binders for DHP with respect to acetate,

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featuring almost ten times greater stability constants for DHP complexes. This finding pointed out that cooperative interactions existed in the case of DHP complexes of *meta*-receptors, which was clarified by *in silico* results. As already elaborated, coordination of anion by all four NH-moieties is not geometrically favourable in the case of *meta*-ligands. However, dihydrogen phosphate can act both as an hydrogen bond donor and acceptor. As a donor, it can engage in a PO–H···O=C interaction with the carbonyl oxygen atom of one urea group. Acting as an acceptor, it can form two NH···O=C hydrogen bonds with the ligand. Such array of interactions is sterically and energetically favourable for the *in-out* conformer of **5**H_2, leading to its highest stability among all examined conformers (Figure 8).

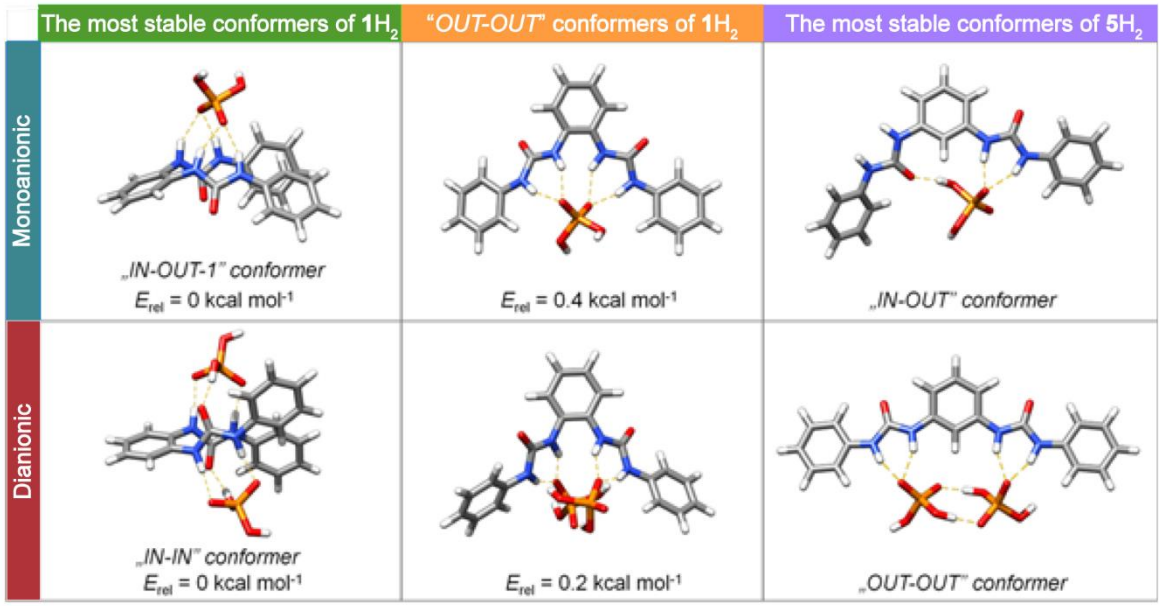

Figure 8. The most stable conformers of 1:1 and 1:2 dihydrogen phosphate anions (DHP) complexes of **1**H_2 and **5**H_2. Energies for the **1**H_2 conformers are reported relative to the most stable conformer.

Binding of the second dihydrogen phosphate was also much more favourable in the case of *meta*-derivatives, especially in the case of compound **8**H_2. For this receptor the successive stability constant of dianionic DHP complex was greater than the one characterising the monoanionic complex. This can be ascribed to strong stabilising influence of the PO–H···O=P hydrogen bonds formed between two anions within the complex, apart from the common NH···O=P interactions. In the conformational space of dianionic DHP complexes of **5**H_2 the structure in which such pairing between two anions is achieved proved to be > 10 kcal mol^{-1} more stable in comparison to other obtained minima.

Further on, the dramatic changes in the chemical shifts related to H_b and H_c protons observed during the titrations with $TBAH_2PO_4$ (Figure 7 and Figures S53-S58 in the Supporting Information) were in agreement with the assumptions given above and the structural insights provided by quantum-chemical calculations. The significant downfield shift of the H_c proton is caused by destabilisation of the associated intramolecular CH_c···O=C hydrogen bond, while the opposite was observed for H_b. This is even more pronounced in the case of dianionic complex formation, since **5**H_2·$(H_2PO_4^-)_2$ complex preferred the "*out-out*" conformation. This results in disruption of the intermolecular hydrogen bond involving H_c proton, encouraging the CH_b···O=C interaction. Such behaviour was not detected in the case of AcO^- which indicated that the conformational changes induced by complexation were much less significant.

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It should be noted that the compounds **1**H_2 and **4**H_2 have been included in a previous study reported by Gale *et al.*,[11,13,19,22,30] and their anion binding (1:1 complex stoichiometry) was characterised by ^{1}H NMR titrations in DMSO containing 0.5 % water. Most recently, Gunnlaugsson *et al.* investigated anion binding of meta derivative **7**H_2, characterising both mono- and dianionic complexes with AcO^- and DHP.[15] In these studies stability constants determined by NMR spectroscopy were somewhat lower than those determined by us. This is most likely caused by the fact that significantly higher ligand concentrations were used and proton transfer was not accounted for. Consequently, the refinement yielded conditional constants which are concentration dependent. It is not surprising that the proton transfer was not detected in previous studies of compounds belonging to the ligand class studied in this work since: **a)** acidity of urea-group has generally been considered very low and the effect of the aromatic subunits on its properties was underestimated, **b)** titration data could be easily fitted to simple binding models in spite of proton transfer occurring in the system, which was clearly shown by Yatsimirsky *et al*,[34] **c)** the relevance of this reaction is less pronounced at higher ligand concentrations

Finally, we devote some more attention to the cooperativity manifested as the enhanced stability of 1:2 DHP complexes. This characteristic, owing its existence to interanionic hydrogen bonds, has been recognised in several examples during the last decade,[18,40–43] including complex of an analogue of **1** comprising a cyclohexane linker.[12] However, the thermodynamics of the effect was thoroughly explored only recently,[39] which led to exploitation of attractive interaction between dihydrogen phosphates to afford interesting self-assembled systems with advantageous properties.[44–46] In this context, our results present a valuable contribution, providing an insight in the spatial arrangement of the donor moieties required for optimal interaction between the two DHP units. It is our strong belief that hydrogen bonds between phosphate moieties could be exploited as a valuable interaction affording exciting new supramolecular systems in the future.

3. Conclusion

The presented research provided a systematic study of anion binding by urea-based receptors, acknowledging the importance of ligand to anion proton transfer. Quantitative examination of the protonation properties revealed that in DMSO these two processes are inherently coupled. Striking effect of the aromatic rings attached to urea subunits was detected, *i.e.* their presence remarkably increased the acidity of the NH-protons.

In the context of anion coordination, the studied receptors were found to be selective for dihydrogen phosphate and acetate, forming complexes with either one or two anions, whereas the binding of other, less basic, anions was not detected under the experimental conditions used. By careful consideration of the experimental data in synergy with computational results, we were able to identify the interactions responsible for the stabilisation of the anion complexes. In addition to "conventional" hydrogen bonds between anion and receptor with urea NH-groups acting as donors, hydrogen bond accepting potential of carbonyl oxygen atom was found to be of pivotal importance in the case of 1:1 DHP complexes enhancing their stabilities. Further on, formation of hydrogen bonds between two bound dihydrogen phosphate anions gave rise to cooperative binding, resulting in unusually high stability of dianionic complexes of DHP.

We hope that our results will encourage researchers focused on anion binding to take the possibility of proton transfer into account in their future research. Arguably, this work provides guidelines for the implementation of such approach, as the methodology developed can be applied to a variety of receptor classes. We also envision that information regarding structure-reactivity relationship and an array of involved interactions (especially in the case of DHP) will inspire new advances in anion receptor chemistry.

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4. Experimental section

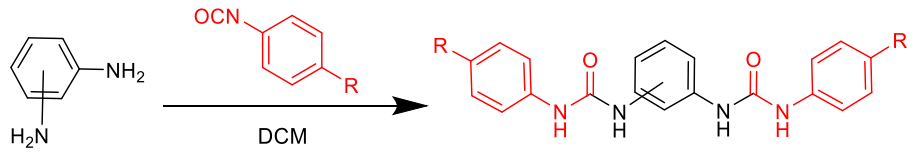
4.1. General

All solvents and reagents are commercially available from Aldrich and were used as received without further purification, unless stated otherwise. Water content in DMSO used for spectrophotometry was < 0.06 %, determined by Karl-Fischer titration.[39]

4.2. Synthesis

Bis-urea derivatives **1**H_2-**8**H_2 were prepared by reaction of *ortho*- or *meta*-phenylenediamine with two equivalents of *para*-substituted phenyl isocyanates in DCM (Scheme 4). Compounds **1**H_2, **4**H_2, **5**H_2 and **8**H_2 were prepared by slight modification of previously published procedures (see Supporting Information).[11] Procedures for the synthesis of novel bis-urea derivatives **2**H_2, **3**H_2, and **6**H_2 , as well as **7**H_2 for which a new synthetic path was devised can be found in the Supporting Information, together with the characterisation data (see Figures S1-S24 in the Supporting Information). These single-step synthetic paths involving simple purification procedures afforded excellent yields. It should be mentioned that in the case of **7**H_2 the overall yield was significantly improved (52 % to 90 %).

^{1}H and ^{13}C NMR spectra of all products were recorded on Bruker Ascend 400 MHz at rt using TMS as a reference in proton spectra and middle signal of DMSO (39.52) in carbon spectra (chemical shifts are reported in ppm). Fourier-transform infrared attenuated total reflectance (FT-IR-ATR) measurements were performed with a PerkinElmer Spectrum Two instrument equipped with a diamond crystal Quest ATR Accessory. HRMS spectra of novel compounds (**2**H_2, **3**H_2, and **6**H_2) were obtained on a Bruker Microflex MALDI/TOF instrument.



Scheme 4. Synthesis of bis-urea derivatives **1**H_2-**8**H_2.

4.3. Physicochemical measurements

4.3.1. Materials

The solvents (dimethyl sulfoxide (DMSO, Sigma-Aldrich, spectrophotometric grade) and deuterated dimethyl sulfoxide (DMSO-d_6, Sigma-Aldrich, >99.8 %)) were used as received. The salts used were tetrabutylammonium dihydrogen phosphate ($TBAH_2PO_4$, Sigma–Aldrich, >97 %), tetrabutylammonium acetate (TBAOAc, Sigma–Aldrich, >97 %), tetraethylammonium chloride (TEACl, Sigma–Aldrich, >98 %), tetrabutylammonium perchlorate ($TBAClO_4$, Sigma–Aldrich, >98 %) and tetrabutylammonium nitrate ($TBANO_3$, Sigma–Aldrich, >99 %). Bromothymol blue ($BTBH_2$, Kemika, >95 %), and 1,8-diazabicycloundec-7-ene (DBU, Sigma–Aldrich > 99.0 %).

Bromothymol blue and DBU solutions were standardised prior to use by means of potentiometric titrations performed in the following way: a known amount of titrant was dissolved in water and titrated with the standardised solution of hydrochloric acid (in the case of DBU) or sodium hydroxide (in the case of $BTBH_2$). The concentration was calculated using the inflection point of the obtained titration curves.

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4.3.2. Spectrophotometry

Spectrophotometric titrations were carried out at (25.0 ± 0.1) °C by means of a Varian Cary 5 spectrophotometer equipped with a thermostatting device. The titrant solution was added in stepwise fashion directly into the measuring quartz cell (Hellma, Suprasil QX, l = 1 cm) using calibrated syringes (Hamilton). The spectral changes were recorded after each addition. Absorbances were sampled at 1 nm intervals with an integration time of 0.2 s. All titrations were done in triplicate. Spectrophotometric data were processed by nonlinear regression analysis using the HypSpec program.[47]

4.3.3. NMR titrations

NMR spectra were recorded using a Bruker Avance III HD 400 MHz/54 mm Ascend spectrometer. The temperature was kept constant at 25 °C. Chemical shifts are reported in ppm and referenced to residual solvent signal. Calibrated syringes (Hamilton) were used for the addition of titrant and titrand solutions. All NMR titration data were processed by nonlinear regression analysis using the HypNMR program.[48] In all cases the fitting procedure was performed in a multivariate fashion, and all proton signals which exhibited significant changes and could be monitored throughout the titration were included in the data processing. Tables S1-S21 (Supporting Information) contain the calculated characteristic chemical shifts for the species in equilibria, indicating which proton signals were used in the data analyses. Concentration dependence of ^{1}H NMR spectra of all investigated receptors other than **4**H_2 in DMSO-d_6 at 25 °C was acquired to dismiss the possibility of ligand aggregation. The concentration was varied by stepwise addition of receptors stock solutions ($c \approx 1.2 \times 10^{-2}$ mol dm^{-3}) to DMSO-d_6 in covering the range $1.2 \times 10^{-4} < c$(receptors) / mol dm$^{-3} < 1.2 \times 10^{-2}$.

4.3.4. Protonation constant of DBU

Protonation constant of DBU in DMSO was determined by means of spectrophotometric titrations which were carried out by adding solution of DBU ($c \approx 2.4 \times 10^{-3}$ mol dm^{-3}) to solution of bromothymol blue ($c \approx 3.2 \times 10^{-5}$ mol dm^{-3}, V_0 = 2.28 mL) in DMSO at 25 °C. In the course of analysis of the data, protonation constant of bromothymol blue was kept fixed at the literature value (log K^{H} = 11.3).[36] Characteristic spectrum of the protonated form of bromothymol blue was fixed using the spectrum of $BTBH_2$ solution acquired prior to the addition of DBU.

4.3.5. Protonation constants of bis-urea receptors

Protonation constants of **1**H_2-**3**H_2 and **5**H_2-**8**H_2 were determined by means of ^{1}H NMR titrations. Solution of DBU ($c \approx 6.5 \times 10^{-2}$ mol dm^{-3} in the case of *ortho*-derivatives and $c \approx 4.0 \times 10^{-1}$ mol dm^{-3} in the case of *meta*-derivatives) was added to solutions of investigated receptors ($c \approx 6.0 \times 10^{-4}$ mol dm^{-3}, V_0 = 0.525 mL) in DMSO-d_6 at 25 °C. When *meta*-derivatives were, time between addition of DBU solutions to receptor solutions and acquisition of ^{1}H NMR spectra was approximately 10 minutes which was the time needed for reaching chemical equilibrium. In the data fitting procedure, protonation constant of DBU was kept fixed at the value determined spectrophotometrically and ^{1}H NMR chemical shifts of protons characteristic for protonated forms of receptors were kept fixed at the values acquired prior to the addition of DBU.

Spectrophotometric titrations of *ortho*-receptors with DBU were performed by adding solutions of DBU ($c \approx 1.0 \times 10^{-2}$ mol dm^{-3}) to solutions of **1**H_2–**4**H_2 ($c \approx 3.0 \times 10^{-5}$ mol dm^{-3}, V_0 = 2.32 mL) in DMSO at 25 °C. Spectra were recorded approximately 5 minutes after the addition of DBU solution, which was the time needed for chemical equilibrium to occur observed in no time dependence of UV-Vis spectral signals. Acquired UV-Vis titration curves were processed by fixing the protonation constant of DBU in DMSO at the value determined spectrophotometrically as well as the first protonation constant of receptors determined by ^{1}H NMR titrations. The second protonation constant was fitted. Characteristic spectra of protonated forms of receptors were kept fixed at the values

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determined by recording spectra without the addition of DBU. Characteristic spectra of protonated and deprotonated forms of DBU were fixed as well. Characteristic spectra of protonated form of DBU was obtained by adding solution of HCl in DMSO to the solution of DBU until no visible spectral changes resulting from protonation of DBU were observed. Characteristic spectra of deprotonated form of DBU was obtained by recording spectra of pure DBU in DMSO. Spectrophotometric titrations were used for quantitative analysis in the case of all *ortho*-receptors other than **4**H_2 due to observed chemical reaction with DBU.

In the case of *meta*-receptors, spectrophotometric titrations were used for determining characteristic spectra of deprotonated forms of receptors. Due to slow kinetics of deprotonation (proton transfer) reaction, *batch* titrations were performed. Solutions of *meta*-receptors and DBU of different *n*(*meta*-receptors) / *n*(DBU) molar ratios were prepared in plastic Eppendorf tubes and the spectra were recorded approximately 18 hours after the preparation of solutions. Concentrations of receptors during the titrations were kept fixed ($c \approx 3.0 \times 10^{-5}$ mol dm^{-3}) and the *n*(*meta*-receptors) / *n*(DBU) molar ratios at the end of titration were ≈ 55. Characteristic spectra of deprotonated forms were calculated by fixing protonation constants of *meta*-receptors at the values determined using ^{1}H NMR titrations as well as fixing the characteristic spectra of protonated form of receptors and characteristic spectra of protonated and deprotonated forms of DBU.

4.3.6. Anion complexation

Anion complexation properties of studied compounds (except **4**H_2) were investigated by performing spectrophotometric titrations of receptors with solutions of TBAOAc, $TBAH_2PO_4$, TEACl, $TBANO_3$ and $TBAClO_4$ in DMSO at 25 °C.

Solutions of TBAOAc ($c \approx 1.2 \times 10^{-3}$ mol dm^{-3} in the case of *ortho*-receptors and $c \approx 3.8 \times 10^{-3}$ mol dm^{-3} to $c \approx 7.9 \times 10^{-3}$ mol dm^{-3} in the case of *meta*-receptors) and $TBAH_2PO_4$ ($c \approx 1.1 \times 10^{-3}$ mol dm^{-3}) were added in stepwise manner to the solutions of investigated receptors ($c \approx 3.0 \times 10^{-3}$ mol dm^{-3}, $V_0 = 2.32$ mL). In the fitting procedures, protonation constants and characteristic spectra of deprotonated forms of receptors were kept fixed at the values determined by ^{1}H NMR titrations and spectrophotometric titrations with DBU respectively. Acid-base processes of acetic and phosphoric acid in DMSO (protonation, homoassociation and dimerisation) were accounted for and their equilibrium constants were kept fixed at the values recently reported by us: ($\log K^{H}$(AcOH) = 12.82, $\log K$(AcOH·AcO$^-$) = 2.45, $\log K^{d}$((AcOH)$_2$) = 1.45, $\log K^{H}$(H_3PO_4) = 10.80, $\log K^{d}$(($H_2PO_4^-$)$_2$) = 2.26, $\log K$(H_3PO_4·$H_2PO_4^-$) = 4.23, $\log K$(H_3PO_4·($H_2PO_4^-$)$_2$) = 2.92).[39] Spectrophotometric titrations regarding other studied anions were performed by adding solutions of TEACl, $TBANO_3$ and $TBAClO_4$ ($c \approx 7 \times 10^{-3}$ mol dm^{-3}) to receptor solutions ($c \approx 3.0 \times 10^{-3}$ mol dm^{-3}, $V_0 = 2.32$ mL) in DMSO at 25 °C until the *n*(salt) / *n*(receptor) molar ratio was around 100.

^{1}H NMR titrations of investigated receptors with TBAOAc and $TBAH_2PO_4$ were conducted by recording spectral changes of a solution of receptors ($c \approx 6.0 \times 10^{-4}$ mol dm^{-3}, $V_0 = 0.525$ mL) upon stepwise addition of a solution of TBAOAc ($c \approx 1.0 \times 10^{-2}$ mol dm^{-3}) or $TBAH_2PO_4$ ($c \approx 1.0 \times 10^{-2}$ mol dm^{-3}). ^{1}H NMR titration curves were processed by fixing the protonation constants of receptors as well as the characteristic spectra of deprotonated forms of receptors obtained by ^{1}H NMR titrations with DBU. Characteristic spectra of fully protonated form of receptors was kept fixed at the value determined by recording spectra prior to the salt addition. As in the case of spectrophotometric titrations with TBAOAc and $TBAH_2PO_4$, acid-base properties of acetic and phosphoric acid in DMSO were taken into account. Equilibrium constants for the formation of dianionic complexes with bis-urea receptors were kept fixed at the values determined spectrophotometrically, and the ones for monoanionic complexes were varied.

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4.4. Computational details.

Calculations were carried out using Gaussian09.[49] A density functional theory (DFT) approach with the wB97X-D exchange-correlation functional was applied to better account for the intramolecular dispersion interactions.[50] A relatively large basis set, 6-311++G(d,p), was used to minimize the intramolecular basis set superposition error.[51] For implicit solvation, a polarizable continuum model using the integral equation formalism (IEF-PCM)[52] was used to model dimethyl sulfoxide (DMSO, 46.83). Frequency calculations identified all stationary points as minima (zero imaginary frequencies).

Computational methods were employed in order to get a better insight in proton dissociation processes and anion binding, mainly from the structural viewpoint. Parent bis-urea compounds **1**H_2 and **5**H_2 as well as their mono- and dianions have been modelled using (*trans*,*trans*) conformation of the urea parts which is the accepted conformation for the *N*,*N'*-diarylureas with NH–C(=O)–NH core.[53][54] We note that *trans*/*cis* nomenclature is used for the conformations of *N*,*N'*-diarylurea bonds, based on the spatial relationship between *N*-aryl group and carbonyl oxygen atom. Taking advantage of this conformational preference, a detailed conformational searches of relative orientation of two (*trans*,*trans*) urea substituents on the central phenyl group have been performed for neutral diurea compounds as well as for their mono- and dianions (for details see the Supporting Information). Modelled anions have one deprotonated nitrogen *per* urea group. Since DMSO can serve both as a donor and acceptor of the hydrogen bond, it is expected that the solvent molecules interact with the urea functional groups. Thus, we performed calculations including either one or two discrete DMSO molecules, initially positioned in such a way to facilitate ligand-solvent interactions. This was achieved by directing the DMSO oxygen atom towards urea NH-groups, and/or pointing methyl groups of the solvent molecule towards carbonyl oxygen or deprotonated urea nitrogen. In general, higher stabilization was obtained if S=O groups were involved in interaction with NH-groups, than if methyl groups were pointing toward the keto C=O group of the urea moiety in neutral compounds.

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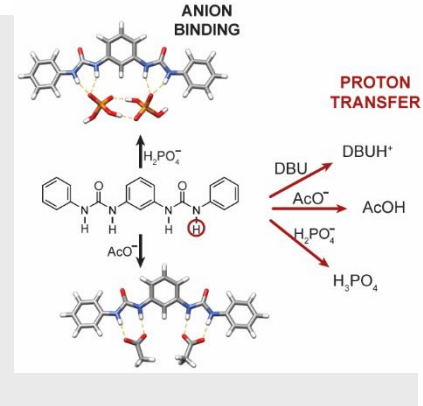
FULL PAPER

Aromatic ureas and basic anions - competition leading to partnership

Study of aromatic bis-urea derivatives in DMSO revealed their unexpectedly high acidity (p*K*a ≈ 14). Consequently, partial proton transfer occurs in their reaction with basic anions (AcO^- and $H_2PO_4^-$). This process was quantitatively accounted for in the course of anion binding studies. Reliable stability constants of anion complexes (1:1 and 1:2, receptor:anion) were determined. Factors defining the anion binding properties of the studied ligand series were thoroughly discussed.



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Protonation and anion binding properties of aromatic bis-urea derivatives – apprehending the proton transfer

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