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A density functional study towards substituent effects on anion sensing with urea receptors

Amrita Ghosh · D. Amilan Jose · Amitava Das · Bishwajit Ganguly

Abstract Effects of substituents on anion binding in different urea based receptors have been examined using density functional (B3LYP/6-311+G**) level of theory. The complexes formed by a variety of substituted urea with a halide anion (fluoride) and an oxy-anion (acetate) have been calculated. The stronger complexes were predicted for receptors with fluoride ion than that of acetate ion, however, in water the preference was found to be reversed. The pK_a calculations showed the preferred sites of deprotonation for positional isomers, while interacting with anions. The position of the substituent in the receptor, however, could change the preferred sites of deprotonation compared to the site predicted with pK_a values.

Keywords Anion binding · Density functional study · Receptor · Substituent effect · Urea

Introduction

The development of simple receptors with suitable chromophoric units capable of recognizing biologically relevant anions like fluoride, chloride, phosphate and carboxylate has attracted considerable interest [1–10]. In this regard, urea based hydrogen bond donors and related derivatives have been the focus of attention in recent years. Urea is one of the most attractive anion receptor functionality owing to their ability to participate in hydrogen-bonded adduct formation and broad range of applications in several chemical disciplines [11–23]. Urea functionality has two relatively strong hydrogen-bonding sites and participate in H-bonding either through two –N(H) hydrogen atoms or through –C(O) oxygen atom. Thus, urea derivatives functionalized with various chromogenic or signaling unit(s) have been synthesized for the recognition studies [13, 15–17, 19, 22–51]. Binding affinity of various urea-based receptors towards an anionic analyte mainly governed by pendant unit attached to the urea moiety [37–51]. Literature reports reveal that for simple phenyl urea receptors, acidity of the urea –N(H) hydrogens is affected by the presence of certain substituent in the phenyl rings [52–56]. However, systematic study to modulate the acidity of the urea –N(H) hydrogen and thereby the binding affinity for anions through the substituent effect is scarce in the literature [56].

To gain a better insight, we have studied the relative binding affinities of urea and its various symmetric and asymmetric urea derivatives *ca.* monophenyl urea, diphenyl urea, *o*-nitro, *m*-nitro, *p*-nitro, *p*-trifluoromethane, *p*-methyl and di-*p*-nitro substituted phenyl urea **1**–**9** (Scheme 1) with fluoride and acetate ions using density functional level of theory (DFT). The calculated results provide an understanding of the relative acidity of two/one urea –N(H) hydrogen(s) in symmetric/ asymmetric derivatives and their relative affinities towards these anions. Further, the studies also provide the information towards the deprotonation possibility—which, however, is of general interest to experimental chemists [54–56].

A. Ghosh · D. A. Jose · A. Das (✉) · B. Ganguly (✉)
Central Salt and Marine Chemicals Research Institute (CSIR),
Bhavnagar 364002 Gujarat, India
e-mail: amitava@csmcri.org
e-mail: ganguly@csmcri.org

Computational details

All the calculations were performed using the Gaussian 03 E01 [57]. The geometries were fully optimized using

	R	R$_1$
1	H	H
2	Phenyl	H
3	Phenyl	Phenyl
4	Toluene	Phenyl
5	p-CF$_3$-Benzene	Phenyl
6	o-NO$_2$ Benzene	Phenyl
7	m-NO$_2$ Benzene	Phenyl
8	p-NO$_2$ Benzene	Phenyl
9	p-NO$_2$ Benzene	p-NO$_2$ Benzene
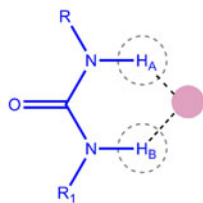
Scheme 1 Different urea receptors (**1–9**) employed in this study

B3LYP/6–311+G** level of theory. Harmonic force constants were computed at the optimized geometries to characterize the stationary points as minima. The interaction energy is simply obtained by the energy of the complex subtracted by the sum of energies of constituents. The interaction is very strong due to charged hydrogen bonds; thus, the basis set superposition error (BSSE) is expected to be negligible compared with the magnitude of the total interaction energies [48, 49, 58]. To calculate the pK_a values of molecules, we have considered the thermodynamic cycle shown below.

The thermodynamic cycle yields the aqueous pK_a for the acid B-H, which is shown in Eq. 1 [59]. The gas phase free energy of protonation is calculated at the same level of theory used for the calculation of solvation free energy. The free energy of solvation in water has been calculated using self-consistent reaction field (SCRF) methods using the conductor-like polarizable continuum model (CPCM) [60–63].
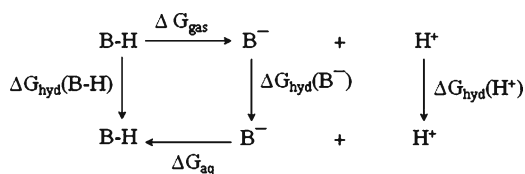
$$\Delta G_{aq} = \Delta G_{gas} + \Delta G_{hyd}(B^-) + \Delta G_{hyd}(H^+) - \Delta G_{hyd}(B-H);$$
At a given temperature T, the pK_a is then given by, [64]

$$\mathrm{p}Ka = [G(B^-_{gas}) - G(BH_{gas}) + \Delta G_{hyd}(B^-) \\ - \Delta G_{hyd}(BH) - 269.0]/1.3644. \qquad (1)$$

A dielectric constant (ε) of 78.4 (water) was used in solvation calculations and the solvation-free energy of the proton taken from the experimental $\Delta G_{hyd}(H^+)$ is equal to -264.61 kcal mol^{-1}. The calculation of G$_{gas}$ uses a reference state of 1 atm and the calculations of ΔG_{hyd} use a reference state of 1 M. Converting the ΔG_{gas} reference state (24.46 L

at 298.15 K) from 1 atm to 1 M is accomplished using Eq. 2:

$$\Delta G_{gas}(1\ M) = \Delta G_{gas}(1\ atm) + RT\ln(24.46). \qquad (2)$$

Single point solvent calculations were performed using B3LYP/6–311+G** optimized geometries of receptors **1–9** and their corresponding complexes with anions employing CPCM [60–63]. The free energies of solvation for fluoride and acetate ions have been reproduced using the B3LYP/6–311 +G** level and are in very good agreement with the reported experimental values, which are discussed below. Further, the reliability of B3LYP method in this study comes through its reproducibility of electron affinity data of the F atom [65].

Results and discussion

We selected simple urea molecules **1–9** to examine the effect of the presence of electron donating and withdrawing substituents on anion binding affinities by DFT calculations. Urea molecules (**1–9**) are well known to form a 1:1 adduct with anionic analytes like halides and oxyanions [11–56]. Anions bind with the urea –N(H) hydrogen atoms by the ion-dipole interaction and the magnitude of the positive dipole primarily determines the anion binding strength. Urea molecules with different **R** and **R$_1$** groups (Scheme 1) are expected to influence the positive dipole of each urea –N(H) hydrogen atoms in the urea-based receptor molecules and therefore their relative binding affinities. To investigate the relative strength of these different substituted urea derivatives, we have performed B3LYP/6–311+G** calculations to obtain the optimized geometries of the urea derivatives **1–9** and their corresponding 1:1 adducts with F$^-$ and CH$_3$COO$^-$ (Scheme 1) using Gaussian suite program [57].

Crystal structures reported for some urea derivatives revealed a planar conformation [66]. However, results of theoretical calculations reported on urea molecule tend to suggest that this molecule prefer to adopt a nonplanar conformation and this was in agreement with microwave studies [67–73]. Non-planar conformation for urea was also evident when the geometry for this molecule was optimized at B3LYP/6–311+G** level of theory. The nitrogen atoms were found to be pyramidalized by 7°. The most stable C_{2v} urea conformation was considered in this study [72, 73]. However, the phenyl substituted urea derivatives (**3–9**, Scheme 1) were found to be planar when the geometry for these molecules were optimized at the same level of theory. The structures for **1**, **3**, and **9** were in good agreement with the reported crystal structures [74–77].

To elucidate the electronic effect of various substituents and their positional effect on the relative binding affinity of the urea functionality towards anions, we have carried out

calculations on respective 1:1 adducts of F⁻ and urea derivatives, **1–9**. Geometries for these adducts were fully optimized at the B3LYP/6–311+G** level of theory (Fig. 1) with electron withdrawing substituents like phenyl, −NO₂ and −CF₃ and electron donating substituent like −CH₃ group. Two –N(H) hydrogen atoms of the urea moiety bind with F⁻ to yield a six-membered chelate ring with bent N—H....F⁻ angles. The calculated results suggest that the H-bond donor ability can be attuned through substitution at the pendant benzene rings (Fig. 1). Electron withdrawing groups (−NO₂ and −CF₃) appreciably strengthen the N—H....F⁻ interaction energy and thereby shorten the intermolecular distance between the F⁻ and the H-bond acceptor unit (Fig. 1 and Table 1). This is due to the greater positive charge development on –N(H) hydrogen atoms of the urea functionality. Effect of substitution with an electron donating group like −CH₃ (**4**) does not show any significant effect on the binding affinity of the receptors towards F⁻. Among different nitro-derivative of receptors (**6–9**), bis-substituted one (**9**) forms the strongest 1:1 adduct as compared to the other mono-nitro derivatives (**6–8**) (Fig. 1). The calculated binding energy for **9** with F⁻ was found to be 79.8 kcal mol⁻¹ (Fig. 1). Recently, Fabbrizzi et al. [55] have shown that the bis-nitro urea derivative (**9**) forms a strong adduct with F⁻ and on addition of another equivalent of F⁻ deprotonates the –N(H) proton [54–56, 74–77]. Optimized structures for adducts **1...F⁻**, **3...F⁻** and **9...F⁻**, derived from respective symmetrical urea deriva-

tives revealed that intermolecular distances between two –N(H) hydrogen atoms and the F⁻ were equal. However, intermolecular H-bond distances between two –N(H) hydrogen atoms and the F⁻ for unsymmetrical derivatives, ca. **2**, **4–8** were found to be different (Fig. 1). H...F⁻ distance for –N(H) hydrogen, closer to the electron withdrawing substituent were found to be relatively shorter than the other –N(H) hydrogen atom while forming an 1:1 adduct.

The shorter H…F⁻ interatomic distances would be more susceptible towards deprotonation in presence of excess F⁻ [54–56, 78]. The effect of electron–donating substituent on the sites of deprotonation seemed to be opposite as one of the two –N(H) hydrogen atoms that was closer to the electron–donating functionality showed slightly longer interatomic distance with the fluoride ion (Fig. 1). Therefore, optimized geometries tend to suggest that the sites of deprotonation of one of the two –N(H) hydrogen atoms of urea derivatives could be tuned through remote substituent effect.

Positional isomers **6**, **7** and **8** did not show similar binding affinity towards the fluoride ion. The order of binding affinity followed the trend **8 > 7 > 6**; **6** with nitro functionality in the 2-position (ortho) was found to make a weaker 1:1 adduct with fluoride ion as compared to the other two positional isomers. The strong intramolecular hydrogen bonding between the –N(H) hydrogen atom and the nitro group of the pendant phenyl ring [54–56] in **6** was

Fig. 1 The optimized geometries of **1–9** with fluoride ion and their binding energies (in kcal mol⁻¹) at the B3LYP/6–311 +G** level. Calculated binding energies using water as solvent are given in parentheses. The interatomic distances are expressed in angstrom (Å)
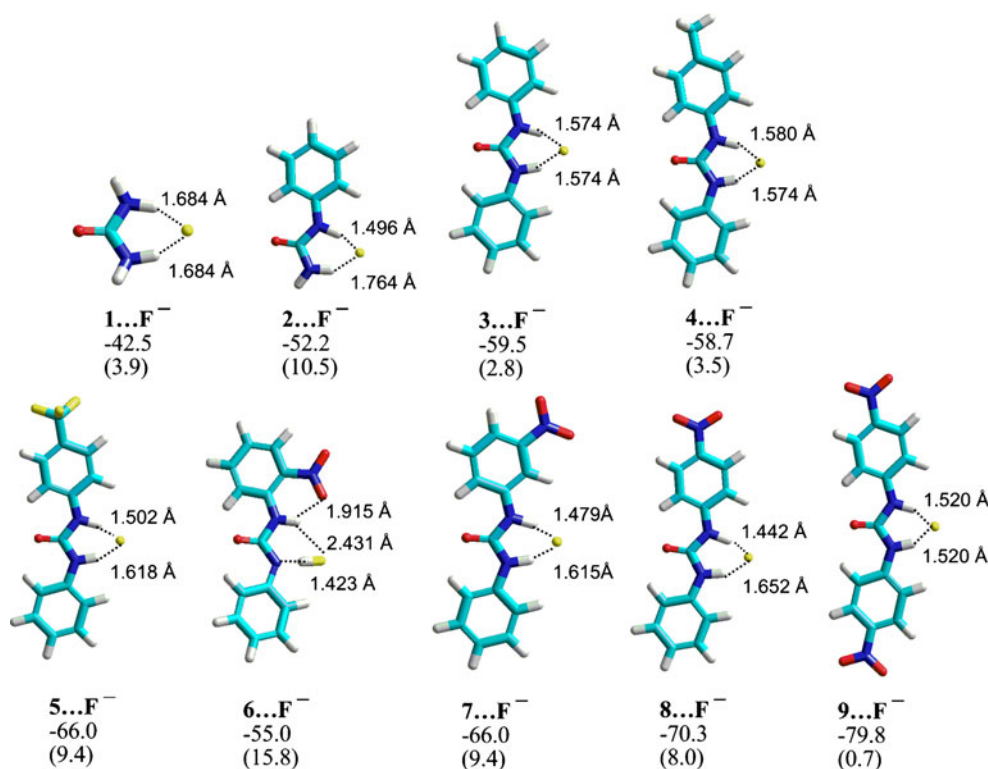
Table 1 Optimized intermolecular distances (Å) of complexes **1– 9**

Structure	N----H_A	H_A----F^-	N---H_B	H_B----F^-
1	1.046	1.684	1.046	1.684
2	1.076	1.496	1.035	1.764
3	1.058	1.574	1.058	1.579
4	1.058	1.580	1.059	1.574
5	1.051	1.502	1.073	1.618
6	1.423	2.431	--------	1.041
7	1.079	1.479	1.052	1.615
8	1.089	1.442	1.046	1.652
9	1.069	1.520	1.069	1.520

found to make this hydrogen less available for interaction with the fluoride ion. As a result, the binding affinity was largely dependent on the interaction with the other –N(H) hydrogen atom. The calculated interatomic distances were relatively more unsymmetrical in this case (Fig. 1); the shorter –N-H...F^- distance was observed for the –N(H) hydrogen that was away from the nitro substituent. Thus, one could expect that the site of deprotonation would be different for this isomer **6** than that of **7** and **8** (Fig. 1). Further, our calculated results are in good agreement with the earlier experimental reports, which revealed that the *para*-nitro-substituted urea receptors exhibited higher binding constant as compared to the urea with pendant phenyl ring substituted with electron donating group [8, 29, 52–56, 75].

To examine the influence of solvent on the binding affinity of fluoride ion with receptors **1–9**, additional calculations were performed in water employing single-point solvent calculations with the optimized geometries of receptors **1–9** and their complexes using CPCM continuum model. The calculated binding energies were found to be poor for F^- with **1–9** (Fig. 1). The higher solvation free energy for fluoride ion in water (-105.1 kcal mol^{-1}) reduces its interaction with the receptor molecules. The large solvation free energy of F^- (-104.8 kcal mol^{-1}) was well reproduced (-105.1 kcal mol^{-1}) using conductor-like polarized continuum model (CPCM) at B3LYP/6–311+G** level of theory [78]. Therefore, sensing fluoride ion in protic media is a great challenge for experimentalists [1, 78–84]. Lewis acidic receptors, which can covalently interact with the fluoride anions in aqueous medium are being explored for this purpose [85].

The probable sites of deprotonation of these receptors with anions can be predicted by pk_a calculations. We have performed the pk_a calculations for **1**, **4**, **6** and **8**, respectively. The pk_a calculations were performed with B3LYP/6–311+G** level of theory. Urea can be considered as a case study to compare the calculated pk_a with the available experimental data. As described in the computa-

tional section, the pk_a calculated for urea **1** was found to be 24.2 in good agreement with the experimental results [86–88]. The relative acidity calculated for the –N(H) hydrogen atoms of the urea group in **4**, **6** and **8** are shown in Table 1. For the unsymmetrical receptor **4**, –N(H) hydrogen atom of urea moiety attached to phenyl ring is more acidic than the –N(H) hydrogen atom attached to tolyl ring, which is expected due to a better electron donating ability of the tolyl functionality than the typical phenyl group. The influence of nitro group at *para* position in **8** showed much lower pk_a values for –N(H) hydrogen atoms compared to the parent urea molecule (Table 2). The –N(H) hydrogen atom attached to nitro-phenyl moiety in **8** was found to be more acidic than the one attached to phenyl group (Table 2). Therefore, the preferred site of –NH deprotonation should be from nitro-phenyl side in both **6** and **8**, respectively. This result is in agreement for receptor **8**; however, the predicted site of deprotonation for **6** from pk_a calculation differs from the anion binding study results (Fig. 1). The binding of F^- with **6** showed the deprotonation from the phenyl side and corroborated by the results determined spectrophotometrically [89, 90]. Therefore, it appears that the relative position of substituent on the receptor molecule can also determine the deprotonation site, which cannot be qualitatively conceived by standard methods.

Urea is also known to be an efficient receptor for oxy-anions like acetate, as it can form two N–H...O bonds with two geminal oxygen atoms of the acetate ion [91]. Thus, we have optimized these substituted urea derivatives with the acetate ion. In general, the binding affinity of acetate derivatives with these receptors was found to be weaker than that of F^- ion (Figs. 1 and 2). This is one of the examples, where the basicity trend does not influence the binding affinity of anions with receptor molecules [91]. The trend of binding energy for receptor molecules **1–9** with acetate ion was in general found to be similar to that of F^- ion.

Acetate also forms shorter –N(H)...O bond with more acidic urea hydrogen atoms. Interestingly, in the case of compound **6**, the intramolecular hydrogen bond between the –N(H) hydrogen and $-NO_2$ group was completely

Table 2 B3LYP/6–311+G** calculated pka for **1**, **4**, **6**, and **8**

Compound		pk_a
Simple Urea (**1**)	Deprotonation at -N(H)	24.22
Phenyl-toluene urea (**4**)	Deprotonation at phenyl-N(H)	23.02
	Deprotonation at Tolyl-N(H)	23.38
Phenyl-(o-NO_2 benzene) urea (**6**)	Deprotonation at phenyl-N(H)	22.12
	Deprotonation at nitro-N(H)	21.73
Phenyl-(p-NO_2 benzene) urea (**8**)	Deprotonation at phenyl-N(H)	18.88
	Deprotonation at nitro-N(H)	16.73

Fig. 2 The optimized geometries of **1–9** with acetate ion and the binding energies (kcal mol^{-1}) at the B3LYP/ 6–311+G** level. Calculated binding energies using water as solvent are provided in parentheses. The interatomic distances are expressed in angstrom (Å)
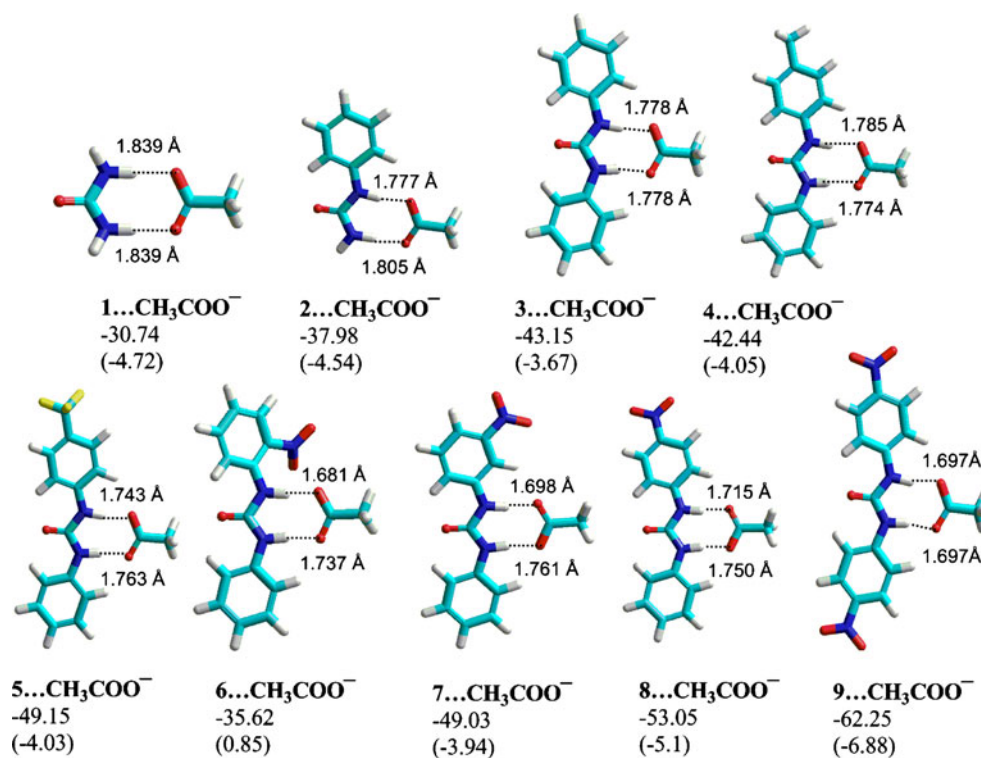
disturbed upon binding of the acetate ion and this observation was different from that of complex **6:F$^-$**. However, the order of binding affinity followed the trend for the positional nitro isomers **8 > 7 > 6**, similar to fluoride ion complex (Fig. 3).

The binding affinity of acetate anion with receptors **1–9** is weaker in aqueous phase compared to gas phase results. The lower binding affinity of acetate anion with **1–9** in water is due to the higher solvation energy of acetate anion (Fig. 3) [92]. B3LYP/6–311+G** level predicted the free energy of solvation (−75.7 kcal mol^{-1}) in good agreement with the reported experimental result (−77.0 kcal mol^{-1}) for acetate. However, the binding affinity of acetate ion with receptors **1–9** is stronger in water than that of F$^-$ (Fig. 3). It appears that the recognition of oxy-anions like acetate is also of considerable challenge for chemists in polar solvent like water [92]. These results show that the recognition of anions is largely dependent on surrounding medium besides the factors like basicity, co-operative binding responsible for the ion recognition process [78–84, 93–96]. Indeed, very few receptors which can achieve anion binding in water have been developed so far.

Even more exceptional are those which are able to bind fluoride and oxy-anions in water and nowadays a very appealing target as synthetic receptors.
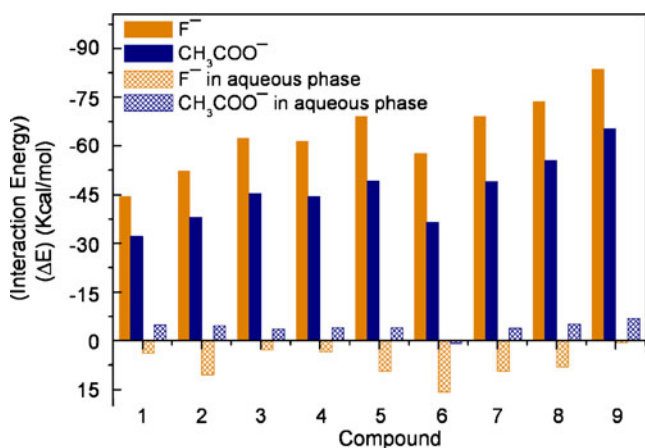
Conclusions

In this work, we have shown that the remote electronic effects can tune the binding affinity of anions with urea receptor molecules. However, the relative position of substituents is also playing an important role to control the binding affinity with such receptors. Electron withdrawing group(s) show(s) a marked influence on the site of –N(H) deprotonation in the unsymmetrically substituted receptor molecule, when exposed to the excess of anion. The sites of deprotonation are primarily dependent on the nature of the substituents and their relative positions in the receptor molecules. Further, studies reveal that the solvent medium is important for the selective binding of anions with the receptor molecules.

Fig. 3 Graphical representation for the interaction energy of the respective urea-anion complex

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