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A density functional study towards the preferential binding of anions to urea and thiourea

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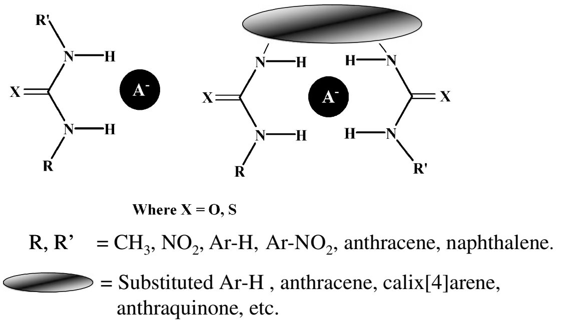
Abstract—A DFT study predicted the trend towards binding of anions with simple urea/thiourea receptor units, which has been found to be in good agreement with experimentally observed results. Our results provide a trend for the interaction of anions of different shapes with urea/thiourea receptor molecules, which do not always follow the basicity scale of anions.

Anion sensing has been of interest to chemists for many years, and the detection of simple anions in biological systems is highly desirable.[1] One successful approach for preparing anion hosts has been to add hydrogen bond donors to an organic scaffold to yield receptors that interact with anions through hydrogen bonding. In this regard, identification of host structures that can exhibit maximum binding to a specific anion is not a trivial task. Hosts containing a variety of donor (D) groups, D–H, have been investigated. Examples include ureas/thioureas,[2,3] amines,[4] amides,[5] thioamides,[6] sulfonamides,[7] indole,[8] pyrroles,[9] imidazolium and guanidium cations.[10] Urea and thiourea based receptors have been used more extensively for anion detection. Presumably, because of their diprotic donor groups and easy synthetic manipulations. In general, the commonly used anions, such as F^-, CH_3COO^-, $H_2PO_4^-$, ClO_4^-, Cl^-, Br^- and I^- with urea and thiourea based receptors do not follow the trend of basicity for these anions.[2] The normal trend of basicity for these anions would be $CH_3COO^- > F^- > H_2PO_4^- > NO_3^- > Cl^- > Br^- > ClO_4^- \sim I^-$ (Supplementary data, Table 1).[11,3c] Interestingly, urea and thiourea based receptors preferred to interact with fluoride more strongly in the presence of oxyanions, which is contrary to the basicity scale. Nitrate and chloride ions have a large basicity difference, however, they show similar selectivity, when studied together.[2i,a,3b] In the designed process, the receptors for recognition of halides and oxyanions are based on synthetic feasibility and selection of anions for interactions are largely intuitive and empirical. Reports on the prediction of selectivity trends of anions with specific receptor units are scarce.[12] In this regard, the preferential interaction of halides and commonly employed oxyanions with urea/thiourea based receptors has received little theoretical attention.

Herein, we report a density functional study of the above mentioned anions binding with simple urea/thiourea units at B3LYP/6-311+G** level of theory and a survey of the experimental results available for these anions with urea/thiourea based receptors in the literature.[2,3] The predicted results fit well with mono- as well as bis-urea/thiourea receptors attached to different basic skeletons (Scheme 1).



Scheme 1. Schematic representation of mono- and bis-urea/thiourea binding with anions.

Keywords: Anion sensor; DFT calculation; Urea/thiourea; Selectivity.

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Electronic binding energies, ΔE, computed for complexes formed between hydrogen bond donors and acceptors provide a useful scale to assess the relative strengths of these interactions. To probe the relative strength of these anions with urea/thiourea moieties, B3LYP/6-311+G** calculations were performed.[13] The complex geometries were fully optimized at this level of theory. It is important to note that these anions have different shapes and as a result, the nature of the interactions are different. Optimal hydrogen bonding interactions between a donor (D–H) and an anion (A) receptor require N–H···A bonds.[14] This requirement is not achieved by the urea moiety when binding with a single spherical anion to form a six-membered chelate ring.

An alternative hydrogen bonding is possible with oxyanions, such as CH_3COO^-, $H_2PO_4^-$, NO_3^- and ClO_4^-. Each –N–H donor group can bind to a different oxygen atom in an anion, yielding an eight-membered chelate ring. Furthermore, the two nitrogen atoms in urea are pyramidal in the computed geometries giving rise to two conformers for the free ligand. In the C_s symmetric *syn* conformer, the nitrogen atoms are pyramidal in the same direction. In the C_2 symmetric *anti* conformer, the nitrogen atoms are pyramidal in opposite directions. A recent study indicated that the C_s symmetric *syn* conformer of urea binds better with halides and oxy anions than the *anti* conformer.[15a] In the present study, the C_s symmetric *syn* conformer of urea was considered for interactions with anions. The interaction of the *syn* urea conformer with anions maintained its identity in complexed forms. In the case of thiourea, the *anti* conformer was used for the study.[16] In the complexed state with anions, the nitrogens in the thiourea unit tend towards planarity in each case studied here.

The results in Figure 1 and Table 1 confirm that the urea/thiourea units form stable complexes with anions through hydrogen bonding interactions. Halides interact with two N–H donor groups with bent N–H···X angles, where $X = F^-$, Cl^- and Br^- (Fig. 1 and Table 1). The oxyanion complexes form symmetric N–H···O bonds and exhibit a more optimal N–H···O angle yielding an eight-membered chelate ring.[15,3b] The Y-shaped geometries formed in oxyanion cases have been observed in some of the crystal structures determined for these anions.[3b] The calculated results verify that F^- forms the strongest complex with the urea/thiourea receptors among the anions studied. In the oxyanion series, acetate forms the strongest complex with the urea/thiourea receptors studied here. Thiourea showed much stronger interactions with anions than urea (Fig. 1).[3a] The preferences for F^- and $CHCOO^-$ ions compared to other anions are clearly distinctive. However, the computed binding energies for NO_3^- and Cl^- ions with urea/thiourea units were largely comparable.[2a,15a] The order of selectivity predicted at B3LYP/6-311+G** level with urea/thiourea are $F^- > CH_3COO^- > H_2PO_4^- > Cl^- \sim NO_3^- > Br^- > ClO_4^-$. Further, to examine the selectivities obtained with the DFT calculations, additional calculations were performed at HF and MP2 levels using the 6-311+G** basis set. The selectivity trends were found to be similar with DFT results (Supplementary data, Table 2). This selectivity trend follows the observed preferences for these anions with mono-urea/thiourea receptors (Scheme 1).[2] Importantly, the presence of bis-urea/thiourea receptors does not alter this

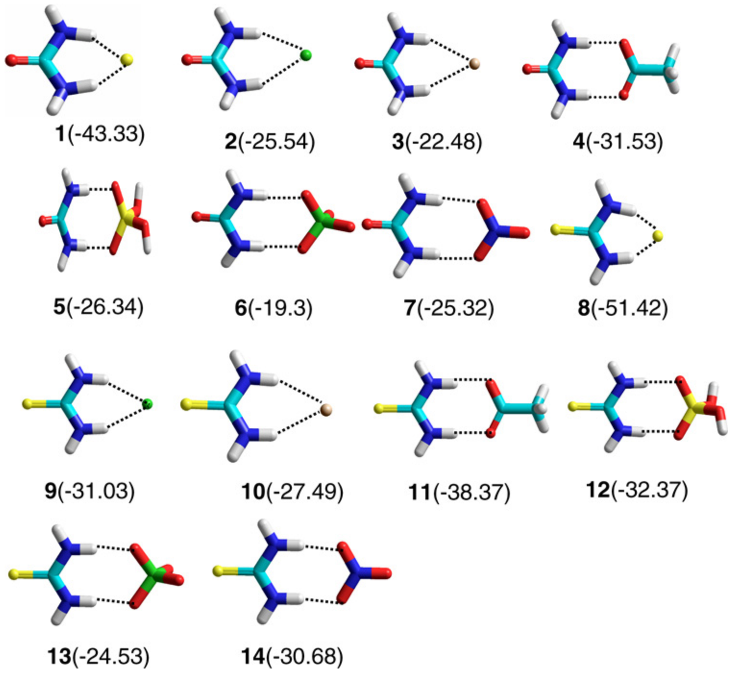

Figure 1. Optimized geometries of the complexes and their binding energy values (kcal/mol) at B3LYP/6-311+G** level of theory. Urea: **1**F^-, **2**Cl^-, **3**Br^-, **4**CH_3COO^-, **5**$H_2PO_4^-$, 6ClO_4^-, **7**NO_3^-; thiourea: **8**F^-, **9**Cl^-, **10**Br^-, **11**CH_3COO^-, **12**$H_2PO_4^-$, **13**ClO_4^-, **14**NO_3^-. The calculated binding energy is the energy difference $\Delta E = E_{elec}(\text{complex}) - E_{elec}(\text{anion}) - E_{elec}(\text{urea/thiourea})$.

Table 1. Geometric parameters of ureas **1**–**7** and thioureas **8**–**14** with different anion complexes

Structure	H···X (Å)	D···X (Å)	D—H···X (deg)	H···O—A (deg)
Urea				
1	1.685, 1.684	2.654, 2.653	152.0, 152.0	—
2	2.329, 2.326	3.292, 3.289	155.5, 155.9	—
3	2.514, 2.513	3.480, 3.479	157.0, 157.1	—
4	1.839, 1.839	2.872, 2.872	178.2, 178.1	117.2, 117.3
5	1.887, 1.893	2.912, 2.917	176.6, 176.3	116.1, 115.4
6	1.979, 1.977	2.996, 2.995	177.2, 178.5	123.3, 122.9
7	1.913, 1.913	2.937, 2.936	177.9, 177.8	121.6, 121.8
Thiourea				
8	1.635, 1.633	2.598, 2.597	149.7, 149.8	—
9	2.269, 2.268	3.225, 3.224	154.0, 154.0	—
10	2.454, 2.454	3.413, 3.413	155.3, 155.3	—
11	1.774, 1.773	2.813, 2.813	178.6, 178.6	117.5, 117.5
12	1.831, 1.829	2.861, 2.860	178.6, 178.5	115.1, 115.2
13	1.925, 1.925	2.945, 2.945	178.5, 178.6	123.3, 123.3
14	1.855, 1.854	2.883, 2.882	178.7, 178.8	121.8, 121.6

selectivity pattern when attached to the basic skeletons shown in Scheme 1. These results suggest that the interactions are electrostatic in nature, but cannot be related to the intrinsic basicity of anions. Recently, attempts have been made to relate the basicities of oxyanions and their binding affinity to urea receptors using the partial negative charge located on each oxygen atom of the anion.[3b,c] Our charge analysis for oxyanions at B3LYP/6-311+G** level did not support these results (Supplementary data, Figs. 1 and 2). For example, the O-atoms of the phosphate anion bear more negative charge than those of acetate, though phosphate generally exhibits a lower association constant than that of acetate.[2] The lower binding energy for the phosphate anion with urea/thiourea units compared to acetate presumably arises due to the strain induced upon complexation. The calculated O–P–O angle (126.2°) of the phosphate anion reduces to (122.0°) upon binding with the receptor moieties. On the other hand, the O–C–O angle remains unchanged upon complexation with urea/thiourea receptors. Therefore, the acetate anion geometry is more suited for binding to urea/thiourea receptors compared to phosphate and their binding stabilities are consequently, more geometrical than electrostatic in nature. The computed gas-phase selectivity trend for halides and oxyanions is in good agreement with experimentally determined selectivity patterns, however, we have noticed a few exceptions in the predicted trend for these anions.[2b,3d] Macrocycles and compounds with greater flexibility in the basic skeletons can alter the selectivity trends for some of these anions.[2j,n] In addition, the solvent has a role to play in the selectivity process.[2u,17,15]

In summary, we have predicted a selectivity trend for halides, tetrahedral and nitrate oxyanions with urea/thiourea units. The calculated trend is found to be in good agreement with mono- and bis-urea/thiourea receptor experimental results. The selectivity trend does not always follow the basicity scale for the studied anions. The charge density pattern may not necessarily be a sole deciding factor for the preferential interaction with the receptors, optimal geometric arrangement of –N–H donors and acceptors is also important to achieve the maximum stability. Further, these calculated results will help in the design of receptors for anions of choice in conjunction with strategies available in the literature.[12,15]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.120.

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