

# Employing systematic charge density studies to probe anion binding behavior in supramolecular chemistry of urea and thiourea

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Anion receptor chemistry has a broad range of applications including catalysis by promoting enzymatic reactions, sensing environmental pollutants and designing small, drug-like molecules that can facilitate transport of anions across lipid bilayers for cystic fibrosis and anticancer therapies<sup>1</sup>. Thioureas and ureas are frequently used for anion complexation because of their strong hydrogen bond donor ability for binding both spherical (F<sup>-</sup>, Cl<sup>-</sup>) and Y-shaped oxoanions (CH<sub>3</sub>COO<sup>-</sup>). While the structural properties of ureas in the solid state have been widely studied, including their co-crystal structures with hydrogen bond acceptor molecules, the properties of analogous thioureas have been less explored. There are a number of differences between ureas and thioureas that could be expected to alter the solid-state structures of their analogous compounds. Thiourea N-H bonds are more acidic than those in ureas, making thioureas stronger H-bond donors, despite sulfur being a less effective hydrogen bond donor than oxygen.

To probe the effect that structural modifications have on hydrogen bonding interactions, a systematic charge density study approach was employed. The receptors were designed and structural modifications systematically introduced in order to gain a deeper understanding of the effects of anion basicity and receptor configuration on guest binding. By altering the bound anion across a series, whilst maintaining a common receptor scaffold, the influence of the anion on the nature of the interaction can be probed<sup>2</sup>.

Greater electron density at BCPs with increasing anion basicity (Cl<sup>-</sup> > CH<sub>3</sub>COO<sup>-</sup> > F<sup>-</sup>) suggests that stronger interactions are observed for more basic anionic guests. The exponential relationship between the value of the electron density at the BCP and H...A distance enables classification of the observed hydrogen bonds into two distinct regions: strong N-H...CH<sub>3</sub>COO<sup>-</sup>/F<sup>-</sup> and weak N-H/C-H...Cl<sup>-</sup>. This correlation agrees with trends observed by solution NMR studies<sup>3</sup>. Pairwise comparison of a common anion bound to receptors with differing positions and levels of substitution of an electron withdrawing group at the periphery of the receptor (*para* vs. *meta* and *para* vs. *3,5-dinitro* respectively) shows a clear variation in the atomic charges and electronic potential distribution<sup>3,4</sup>. Interestingly, the effect of the loss of one electron withdrawing group i.e. an asymmetric receptor, is less pronounced than that of changing the central anion binding group from urea to thiourea<sup>5</sup>. These considerable differences in the electronic distribution across the family help to account for the varying ability and application of urea and thiourea molecules as anion-receptors. Depending on whether the purpose of the anion-receptor interaction requires maximised association i.e. tightly bound whatever the situation, or a more easily reversible hydrogen bonding interaction i.e. for transport and release, the structure can be tailored to suit the purpose. This is a crucial requirement from the supramolecular chemists' point of view and can be assessed and quantified by charge density analysis.

## References:

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