

Probing the nature of Halogen-Aromatic Interactions by empirical potential

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INTRODUCTION

Non-covalent weak interactions such as Halogen Bonds have shown to be a very powerful tool in drug design. Actually, they can be the leading figure in several protein-ligand systems¹. However, their nature is not simple to be described by Molecular Mechanics. In this line, there are a few empirical potentials being developed to improve the force fields accuracy. Nevertheless, these potentials do not consider the cases when the electrostatic factor is not favored². In this work, the interaction of benzene and s-triazine is a model to understand the nature of halogen-aromatic interactions as well as to reveal how the empirical potentials can be developed to attend these systems.

METHODS

The parallel between quantum and molecular mechanics was carried out by PES calculations with DFT-D3 and UFF methods. The s-triazine is reported in Fig 1. The NBO analysis was used to evaluate the electronic and steric contributions for the interaction.

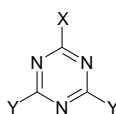


Figure 1. s-Triazine structure (X=Br, Y=H,NO₂).

RESULTS AND DISCUSSION

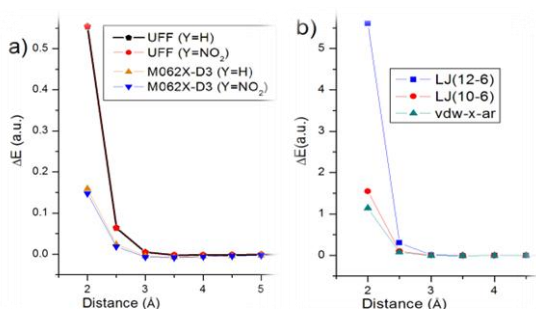


Figure 2. s-Triazine-Benzene interaction results: a) Uff versus m062x-d3/6-31+ and b) The new

potential (vdw-x-ar) plotted in comparison with Lennard-Jones potentials when Y=H.

Fig 2a shows the dissemblance between m062x-d3 and Uff PES. The crucial points lie at low range interactions. At 2.0Å, $\Delta E_{M062x} = -100.03$ kcal.mol⁻¹ and $\Delta E_{UFF} = -347.8$ kcal.mol⁻¹. When Y=NO₂, the positive charges on σ -hole are intensified, increasing the electrostatic repulsion with the centroid of benzene ring. However, when ΔE_{UFF} remains almost the same ($\Delta E_{UFF} = -347.64$ kcal.mol⁻¹), the DFT method detects a significant energy stabilization ($\Delta E_{M062x} = -92.6$ kcal.mol⁻¹). This feature can happen due to the orbital contribution to these interactions through $\pi_{C-C} \rightarrow \sigma^*_{C-Br}$ transitions, which can be noticed, for instance, at 3.0Å and 2.0Å with energies equal to 0.63 and 15.72kcal.mol⁻¹ respectively, when Y=H.

$$E_{vdw-x-ar}(r) = \gamma \left\{ \frac{r_e - (\delta/6 \cos \theta)}{r} - 2 \frac{r_e}{r + [(1+\delta)2^{1+\delta}/25r] \cos \theta} \right\} \quad (1)$$

Results from the new developed potential (1) are shown in Fig 2b. Besides the low range energy minimization, the new equation can predict the variation of σ -hole charge (δ) and its position regarding the interaction axis.

CONCLUSIONS

Directly, this work shows that in some cases, the Halogen Bonds do not depend only on attractive electrostatic interactions due to the σ -hole. Although, the σ -hole charge can be directly related to the σ^*_{C-Br} energy level, that can also be affected by electron withdrawing groups. The orbital contribution must be taken in account and applied to empirical potentials.

ACKNOWLEDGMENTS

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¹ R. Wilcken et al., J. Med. Chem., 56, 1363-1388, (2013).

² L. A. Santos et al., J. Phys. Chem. A, 118, 5808-5817, (2014).

³ L. Du et al., J. Comp. Chem., 34, 2032-2040, (2013).