

Chemical hardness and orbital overlap in substituted aromatics



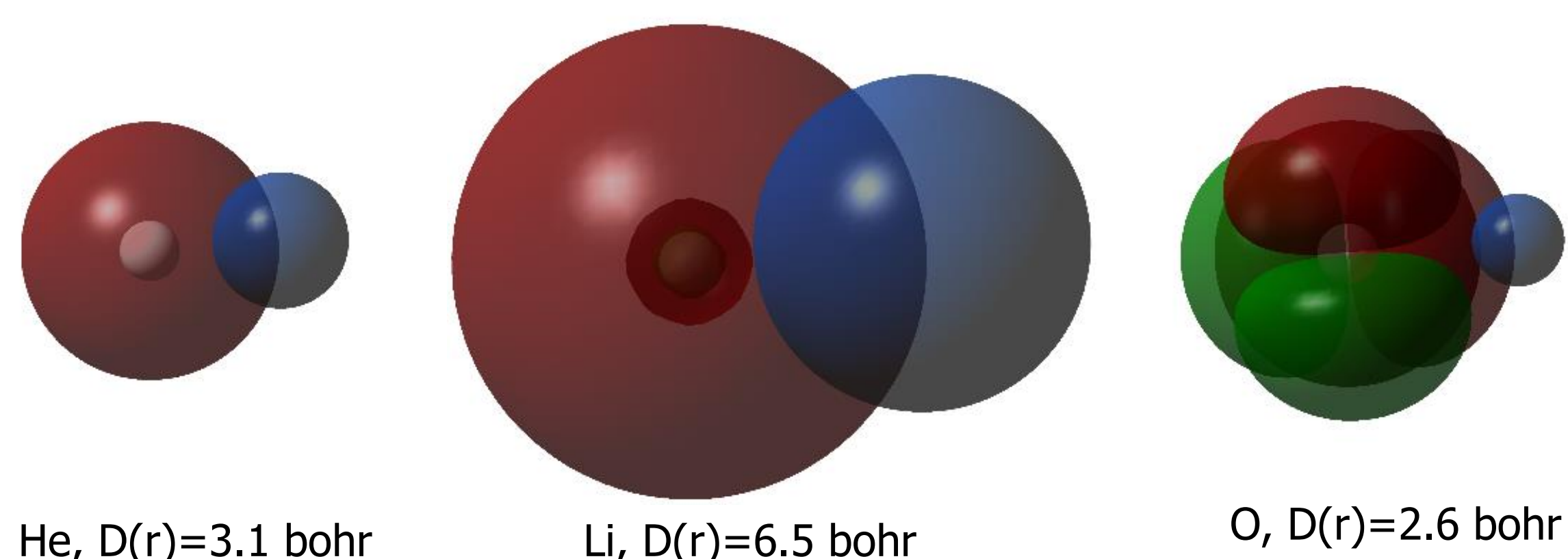
Nicholas Henderson, Arshad Mehmood, Benjamin Janesko
Texas Christian University, Fort Worth, TX 76129



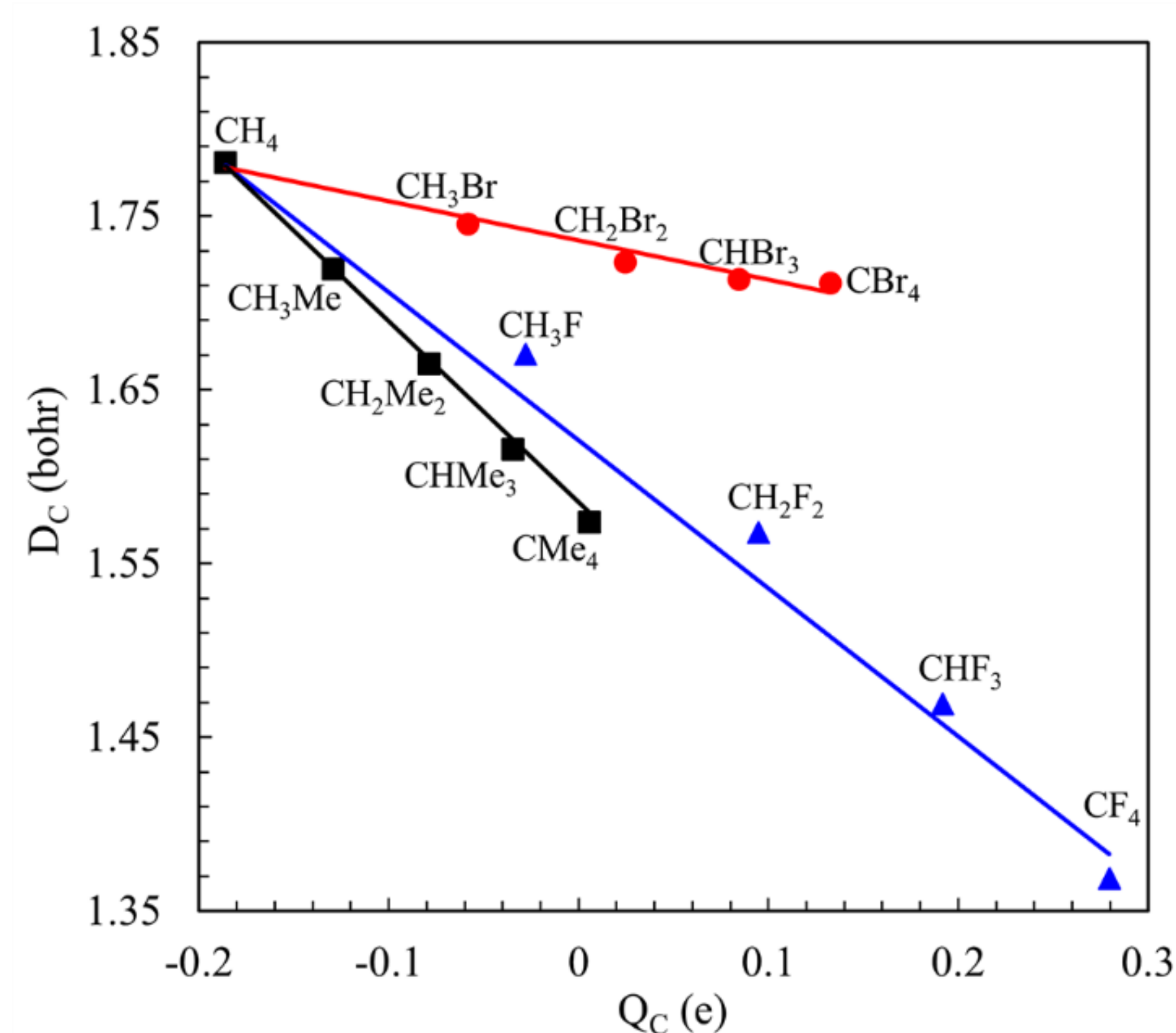
Abstract

Hard-soft acid base theory is often used to explain the selectivity of chemical reactions, under the assumption that hard (soft) nucleophiles prefer to react with hard (soft) electrophiles. Computationally, quantifying the relative hardness and softness of different sites in a molecule remains challenging. Our "orbital overlap distance function" allows us to quantify which regions in a molecule contain compact vs. diffuse molecular orbitals. Here we explore the idea that compact molecular orbitals correspond to chemically hard regions, and that diffuse and polarizable orbitals correspond to chemically soft regions. We combine the orbital overlap distance with electrostatic potentials to quantify the hardness and electrophilicity of different sites in heterocyclic aromatic compounds. Results are compared to known experimental trends in aromatic reactivity.

The Orbital Overlap Distance

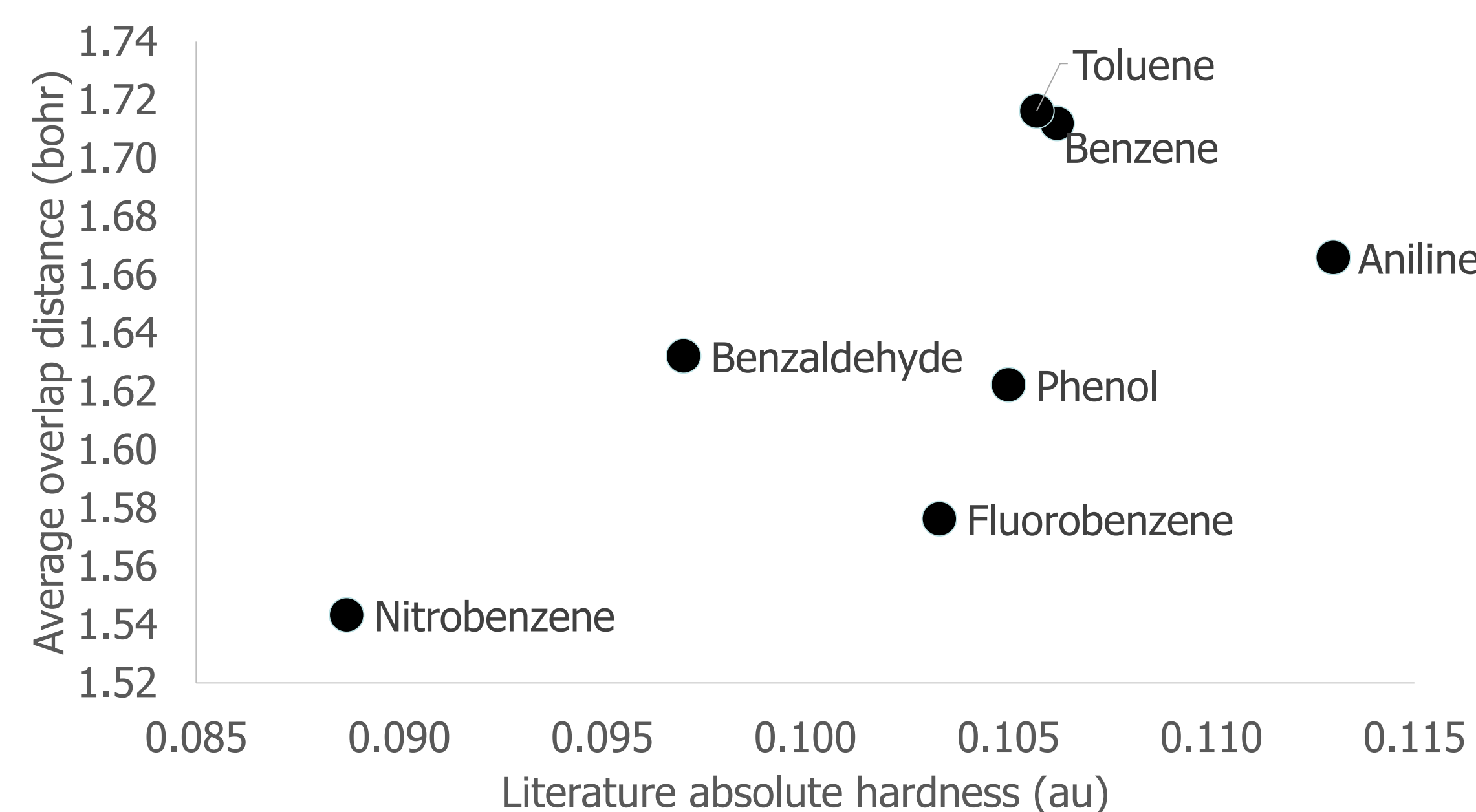


- Compute atom or molecule's occupied orbitals (red + green) using DFT
- Place a test function (blue) at each point \mathbf{r}
- Overlap distance $D(\mathbf{r})$ is the width of the test function that best overlaps the occupied orbitals
- Compact orbitals have small $D(r)$, diffuse and weakly bound orbitals have large $D(r)$
- Plot $D(r)$ on density isosurfaces, or average $D(r)$ over individual atoms in a molecule



Computed partial charge Q and average overlap distance D of central carbon atom. More positive carbons hold the remaining electrons more tightly, giving smaller D . The different trendlines highlight the molecules' different chemistry

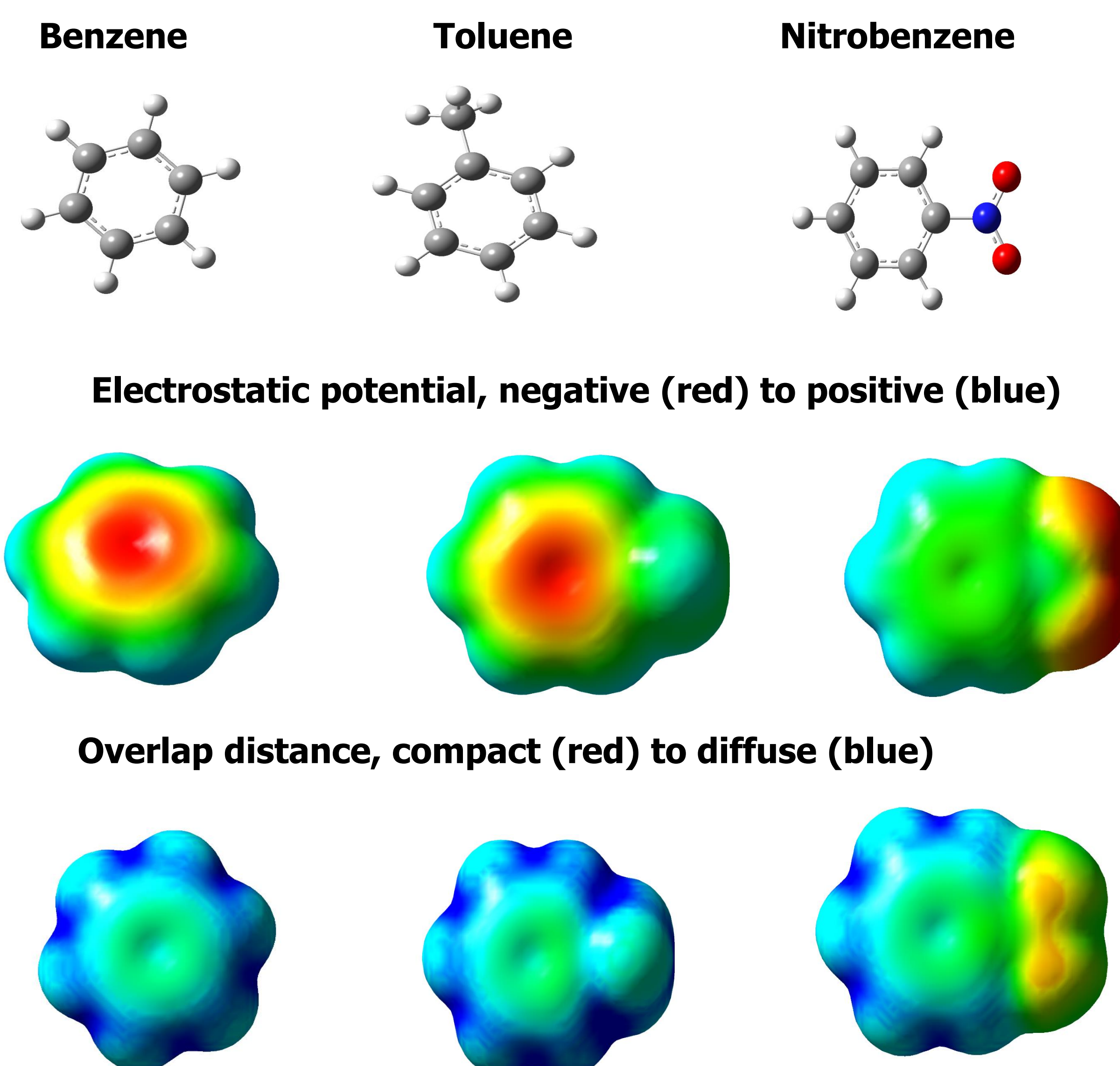
Global hardness vs average overlap distance



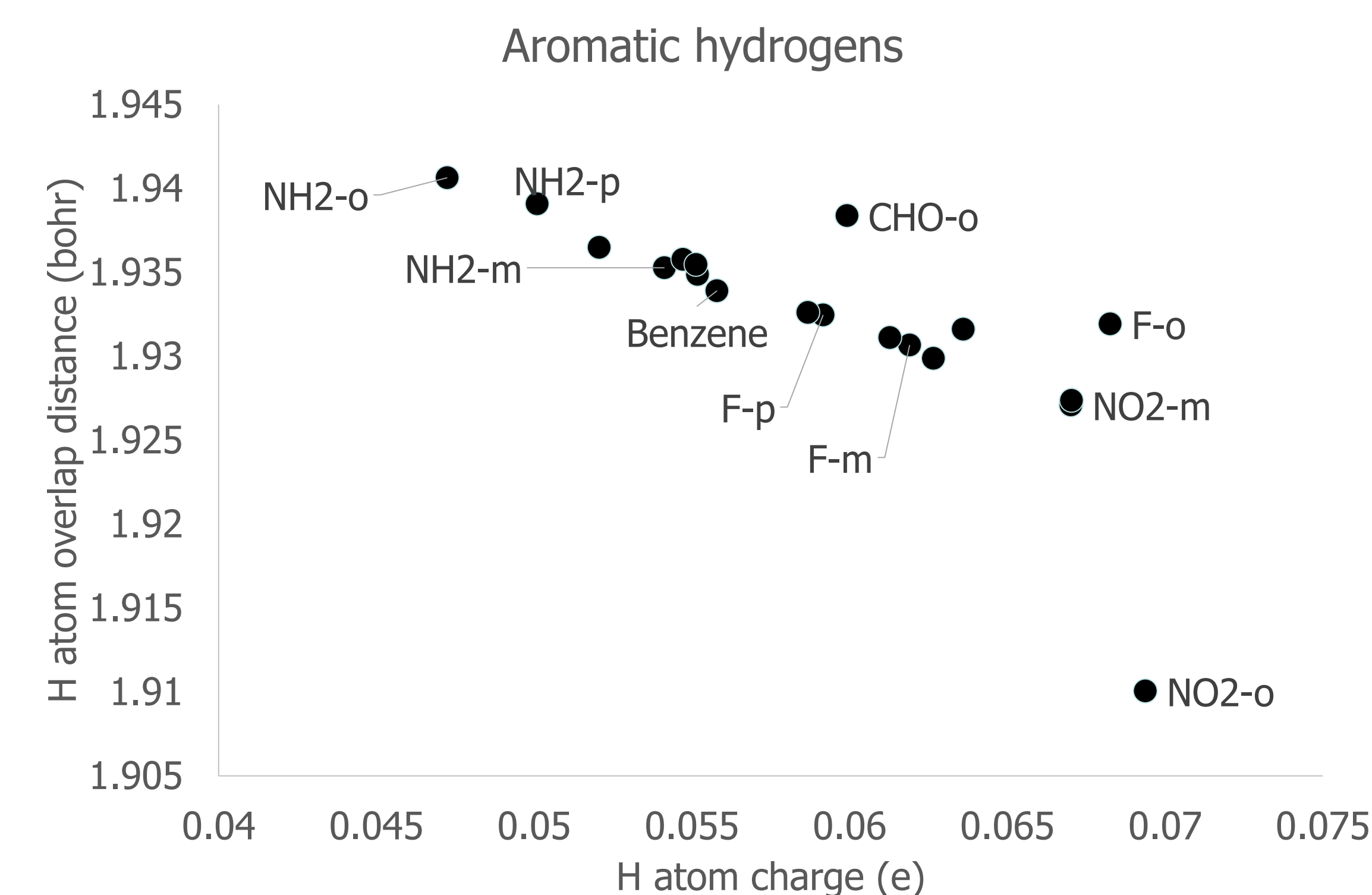
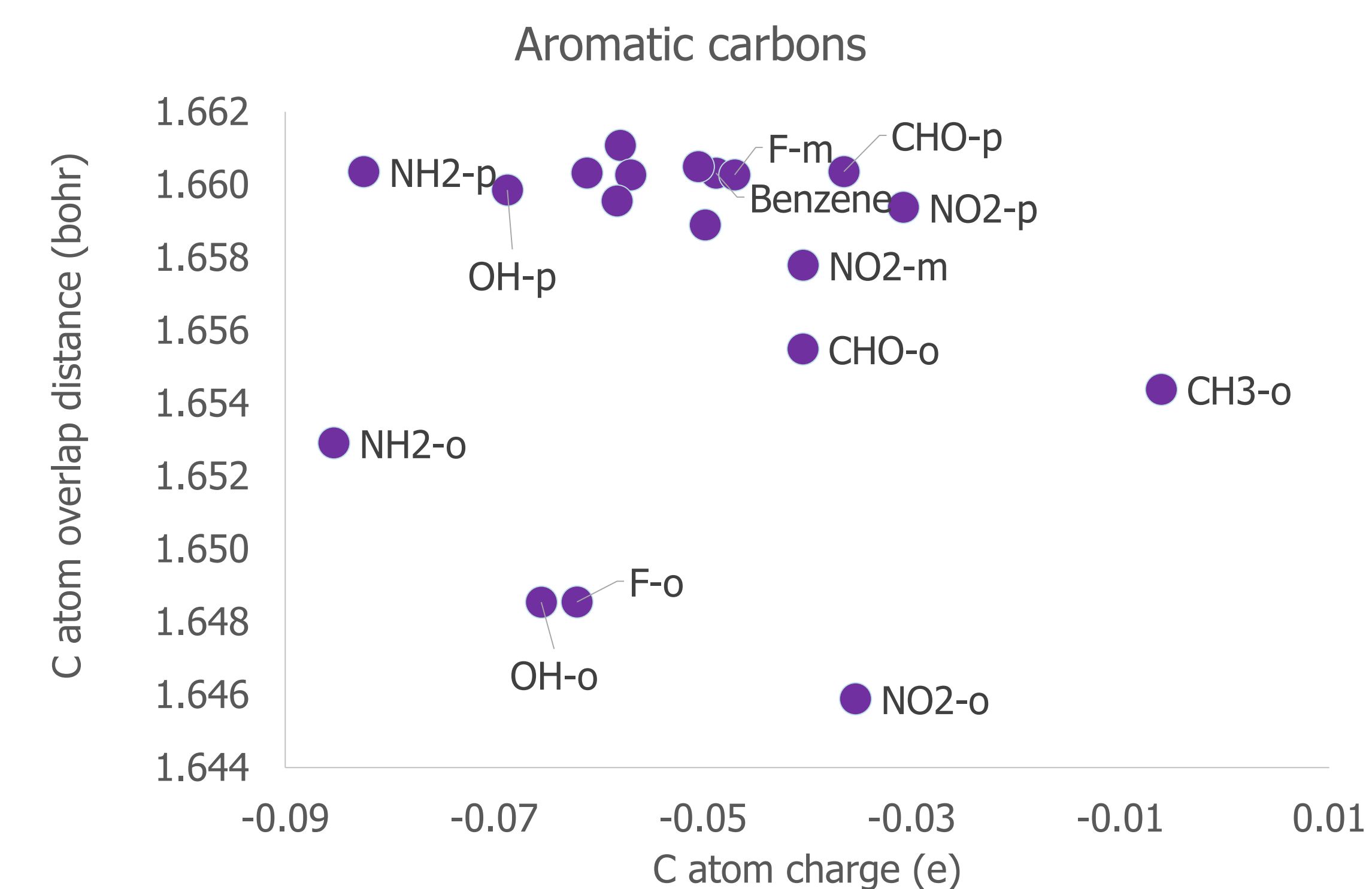
| Compound | Global Hardness | HOMO-LUMO gap | Molecule D | Aromatic carbon Q | Aromatic carbon D |
|---------------|-----------------|---------------|------------|-------------------|-------------------|
| Nitrobenzene | 0.089 | 0.178 | 1.543 | -0.025 | 1.640 |
| Benzaldehyde | 0.097 | 0.187 | 1.632 | -0.038 | 1.647 |
| Fluorobenzene | 0.103 | 0.239 | 1.576 | -0.033 | 1.639 |
| Benzene | 0.106 | 0.252 | 1.712 | -0.056 | 1.660 |
| Toluene | 0.106 | 0.242 | 1.716 | -0.050 | 1.650 |
| Phenol | 0.105 | 0.223 | 1.622 | -0.042 | 1.641 |
| Aniline | 0.113 | 0.203 | 1.666 | -0.053 | 1.645 |

Electron withdrawing substituents give soft aromatics with compact aromatic carbons, electron donating substituents give harder aromatics with generally larger overlap distance

Plotted electrostatic potential and overlap distance



Substituent effects on o, m, p positions



- Partial charge and average overlap distance of aromatic C and H, seven monosubstituted benzenes
- Hydrogen and carbon atoms follow a consistent trend of partial charge vs. average overlap distance
- More positively charged atoms have more compact overlap distance
- Ortho positions are often outliers, consistent with direct interactions with substituent

Computational details

- B3LYP/6-31G DFT calculations, Gaussian development version
- Atomic charges and atom-averaged overlap distance from Hirshfeld population analysis
- Surface overlap distance from Multiwfn calculations
- A. Mehmood, S. I. Jones, P. Tao, BGJ, "An orbital-overlap complement to ligand and binding site electrostatic potential maps", J. Chem. Inf. Model. 2018, 58, 1836; A. Mehmood and BGJ, "An orbital-overlap complement to atomic partial charge", Angew. Chem. Int. Ed. 2017, 56, 6878; P. Mignon, S. Loverix, J. Steyaert, P. Geerlings, "Influence of the π - π interaction on the hydrogen bonding capacity of stacked DNA/RNA bases", Nucleic Acids Research. 2005, 33, 1782

Acknowledgements

Portions of this work were supported by NSF DMR-1505343