

A PDB Search for the Anion-Quadrupole

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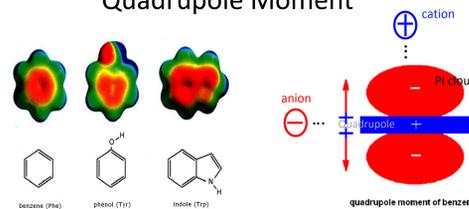
UT Dept. of Chemistry

Electrostatic potential surfaces and Quadrupole Moment

Figure 1:

Right) Schematic of the quadrupole moment vs. the Cation- π interaction.

Left) Electrostatic potential surface of benzene, phenol, and indole (red negative, blue positive) with C) their corresponding chemical structures. Left Panel, Courtesy of Dougherty (Science, 271:163; 1996).



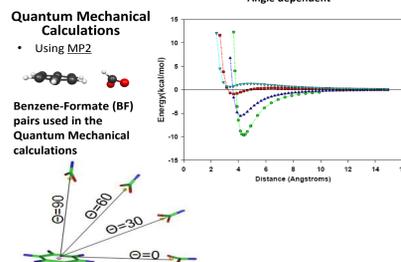
Notes:
Benzene mimics PHE
Phenol mimics TYR
Indole mimics TRP

RED : Negative
BLUE : Positive

Figure 2:

Shown are the results of the quantum mechanical calculations. Favorable energies increase for smaller angles with respect to the plane of the aromatic ring. MP2 level theory was used as well as benzene and formate pairs to mock phenylalanine and aspartate/glutamate sidechains.

Interaction energies: favorable or not?



Abstract

A statistical search and analysis of 4515 proteins from the protein database (PDB) is done to verify the biological significance of a potential, not yet established, noncovalent interaction called the **anion-quadrupole** interaction. It is thought that the quadrupole moment, associated with the plane of an aromatic ring, can create a strong enough positive charge to interact favorably with nearby anions. We have already established through quantum mechanical calculations that the potential strength of this interaction is significant (-2 to -7 kcal/mol). This PDB search quantifies the presence and describes common features of these interactions. This work will help in future molecular studies which are currently lacking in any knowledge of the anion-quadrupole interaction. Specifically, this interaction may play a vital role in protein folding, ligand/drug interactions and even DNA backbone interactions.

Introduction

Noncovalent interactions (ionic, hydrophobic, hydrogen bonds, Van der Waals, etc.) play a key role in many molecular events. The dual-dipole moment (quadrupole moment) occurring at the plane of an aromatic ring can potentially contribute to another noncovalent interaction, appropriately named the anion-quadrupole. Figure 1 shows how the dual dipoles of a benzene molecule can render the planar-ring region positively charged. This allows for it to then form a noncovalent interaction with any nearby anionic group. Additionally, a cation can interact with the negatively charged pi cloud region of benzene. This cation- π interaction has been previously described by Dougherty and Gallavan.

From the schematic diagram in figure 1, it becomes evident that an electrostatic interaction will be most favorable when an anion is in alignment with the aromatic ring. This would increase polarization effects which contribute to the overall interaction.

To test this, the quantum mechanical energies of benzene-formate pairs, which mock PHE-ASP/GLU pairs, were calculated at various angles with respect to the aromatic ring (Figure 2). These preliminary results do indeed show an angle dependency occurring with the anion-quadrupole interaction.

The next step was to search the PDB to:

- 1.) quantify the presence of this interaction in nature
- 2.) see if this interaction behaved as expected in biologically relevant structures.

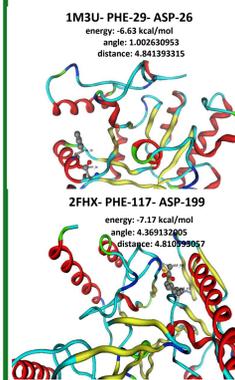


Figure 7:

Two cartoons of an anion-quadrupole interaction. 2FHX and 1M3U are the protein names. They are followed by the type of residue and residue number. The Angle, Energy, and Distance for each interaction is given.

Results

The PDB files of the 4515 proteins were first parsed through using an in-house C++ program, STAAR (Statistical Analysis of Aromatic Rings). See Figure 1 for the full workflow of the project. It selects all of the potential anion-quadrupole interactions by applying a strict filter. PHE-ASP/GLU pairs with less than a 7 angstrom distance between each residue were selected for further analysis. Additional PERL scripts and Excel formulas aided in extraction of the desired geometric data. Energies were calculated with the Kitaura-Morokuma decomposition method using GAMESS. Figure 3 shows the results of the energy calculations being compared with the angles.

Searching the PDB:

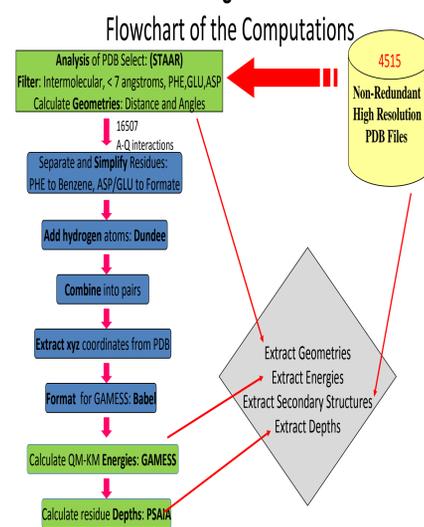
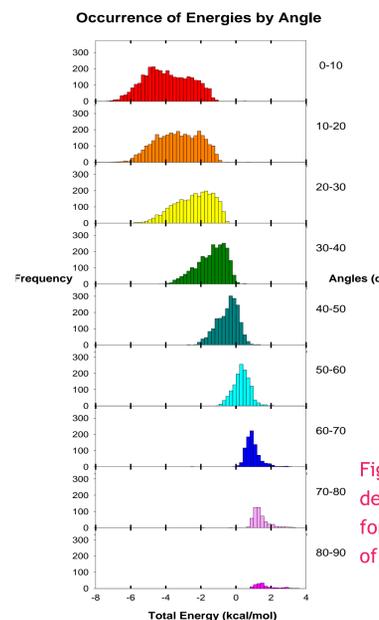


Figure 1: A flowchart depicting the workflow.



The depths of the pairs were calculated using PSAIA. This is shown in Figure 4. To check for any preferences, a count of GLU vs. ASP residues was also done (Figure 5). Finally, the mechanical forcefield energies were compared to the quantum mechanical energies to see how good current forcefields could reproduce the anion-quadrupole (Figure 6). Figure 7 is provided to visually show how 2 anion-quadrupoles exist in a protein structure.

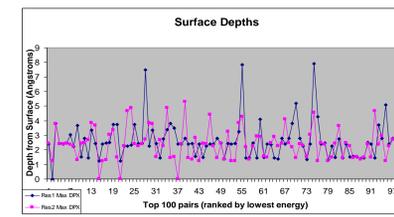


Figure 4:

Surface depths of the top 100 energies. The blue line tracks the PHE and the pink line tracks the GLU/ASP of the pair. They appear to be buried.

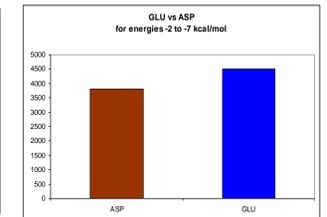


Figure 5:

Checking for a GLU or ASP preference in the sampled pairs. There appears to be none.

144 proteins, functional groups only, correlation CHARMM22 / MP2 Correlation = 0.81, similar to what has been published for cation/ π

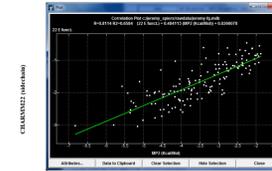
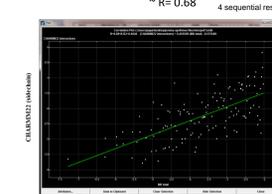


Figure 6:

Comparisons of forcefield energies (CHARMM22) with the quantum energies. The top panel is comparing CHARMM22 with the MP2 values. The bottom panel is comparing CHARMM22 with the Kitaura-Morokuma (KM) values.

Side chains, correlation between CHARMM22 and MK ~ R = 0.68 4 sequential residues removed



Forcefield parameters are 'ok' for reproducing A-Q interactions (R=0.68). Functional groups are better reproduced (R = 0.81).

Conclusion

Anion-quadrupoles appear to be abundant in the PDB. There is indeed an angle dependency for the anion-quadrupole interaction. The best energies occur at low angles with respect to the plain of the ring and also seem to be buried from the surface of the protein. There does not appear to be a preference for GLU vs. ASP. Finally, current forcefields do okay but are still deficient in reproducing the effects of an anion-quadrupole interaction.

Future work on this project would include expanding the STAAR program to include other aromatic groups (TYR, TRP) as well as non protein residue-residue interactions (DNA backbone, ligands, etc.).

References:

1. Dougherty, DA (1996) "Cation- π Interactions in Chemistry and Biology: A New View of Benzene, Phe, Tyr and Trp." Science 271: 161-168.

Figure 3: Energies are binned by in increments of 10 degrees with respect to the geometry of the benzene-formate pair. It is shown that there is a higher abundance of favorable interactions occurring at lower angle.