Measurement of partial atomic charges by least-squares refinement of variable electron density crystallographic models.

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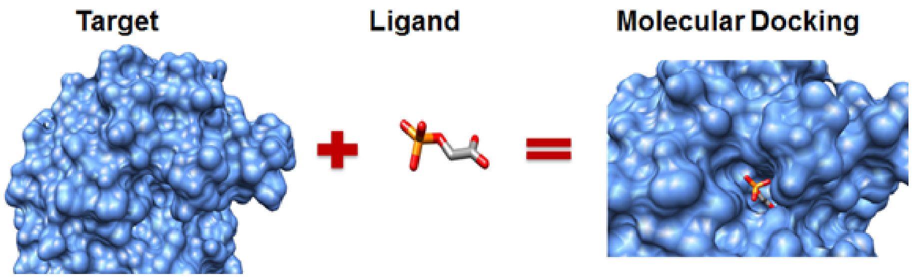
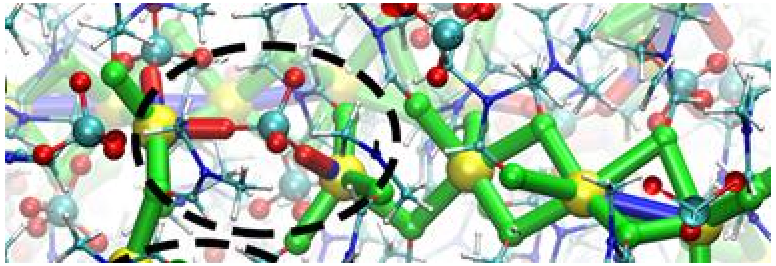
Determination of partial atomic charges for molecular simulation

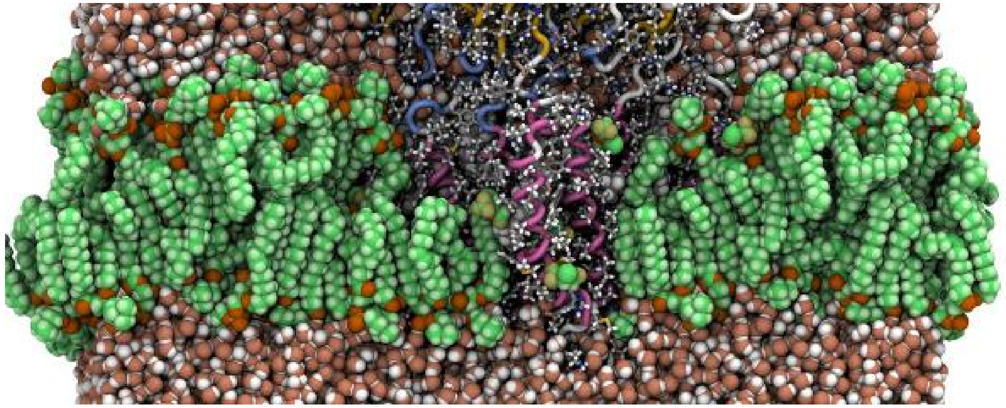
- Drug Design (source: autodock)



- Molecular dynamics simulation
    - Materials (source, Zdilla group)



    - Biology (Source, Klein group, Temple)

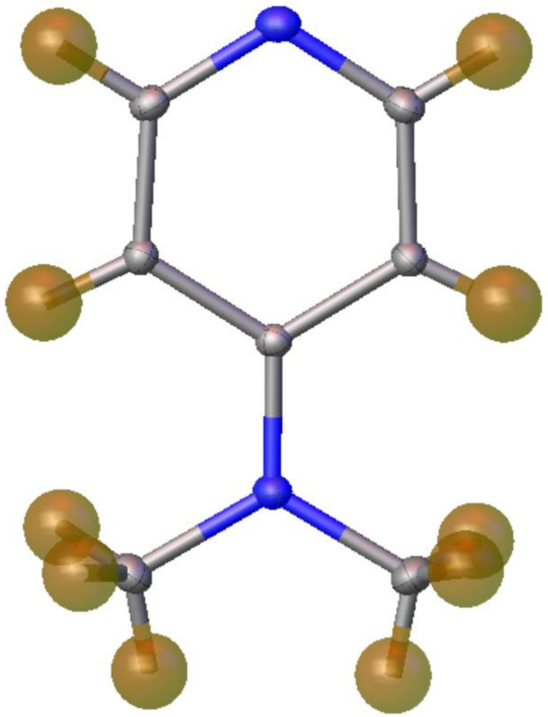


How are partial atomic charges determined and verified

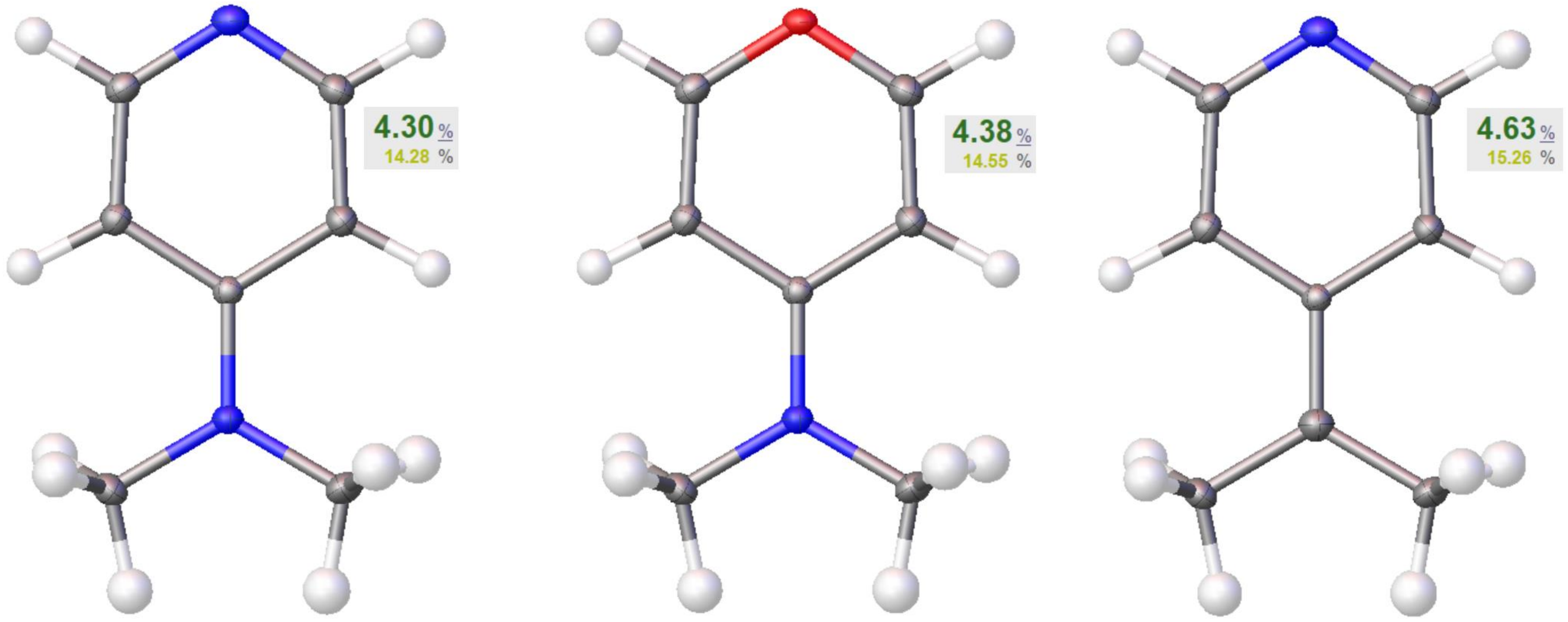
- Theoretical methods describe electronic structure
  - DFT (B3LYP)
  - MP2
- Various approaches to determine atomic charges
  - CHELPG (calculation of charge at surface points)
  - NBO (natural bonding orbitals: orbital description of electron density surrounding an atom)
  - Mulliken Charges (use of atomic orbital basis sets and coefficients describing the population of those basis sets)
  - Lowdin Charges
- Verified by comparison of physical properties
  - Melting point
  - Boiling Point
  - Dipole Moment
- Direct experimental approach to measure individual atomic charges is desired.

X-ray crystallography can see sub-electron charge densities.

Visible H atoms



One-electron misassignments



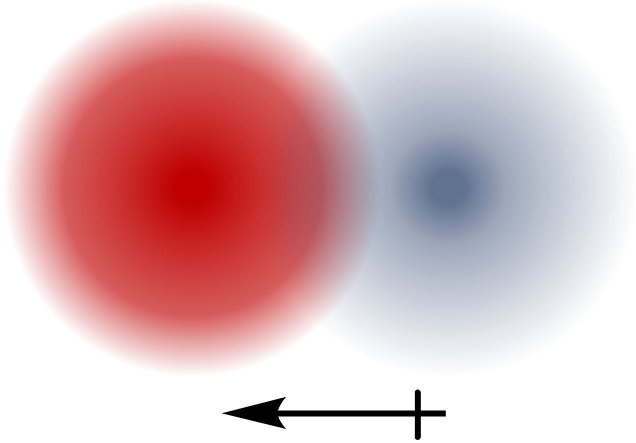
A simpler approach

- Use spherical atomic models
- “Polarize” bonds by refining occupancy rather than distorting orbitals
- Occ*Z = polarized electron count
- Z – Occ*Z = charge.

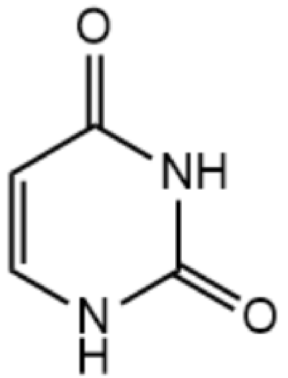
- Spherical Dirac atoms

- Overlapped atoms (normal X-ray model)

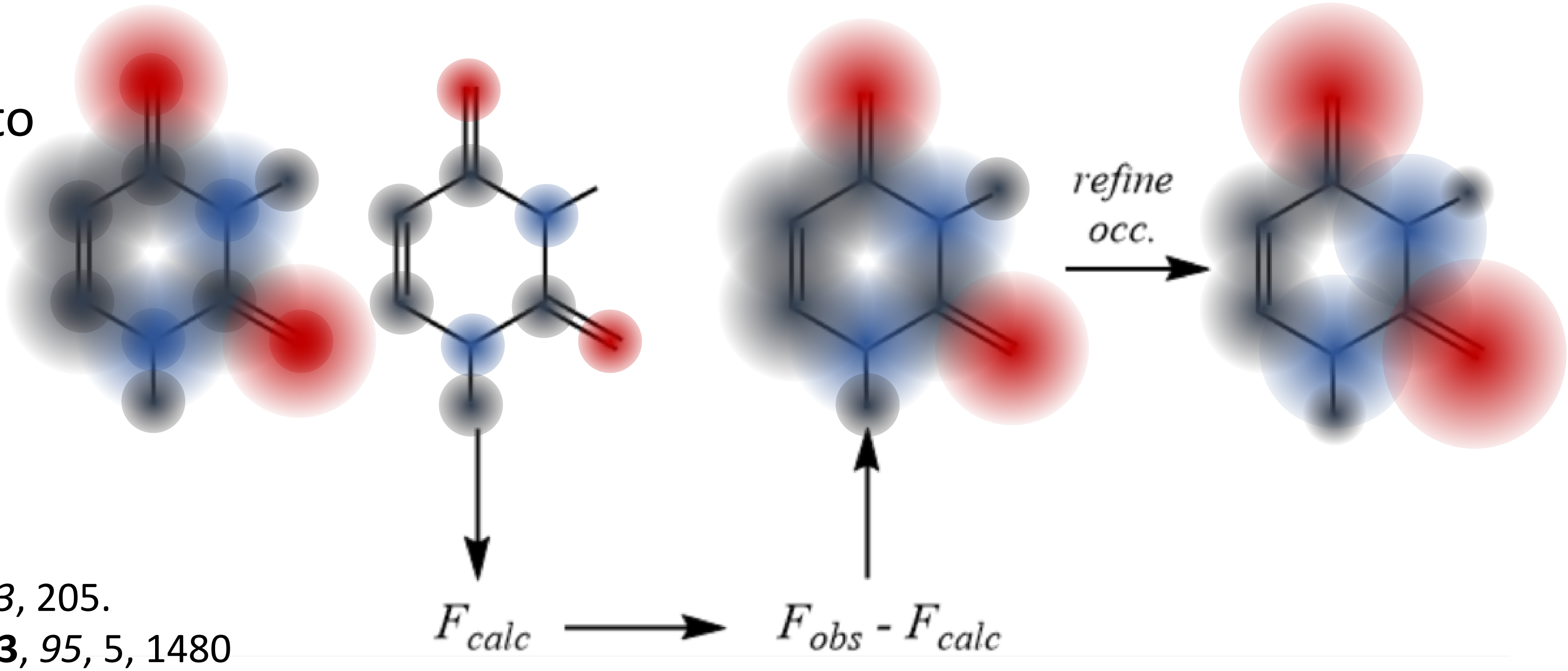
- Refined occupancy (polar sphereical atom model



Could XRD see bond polarization?



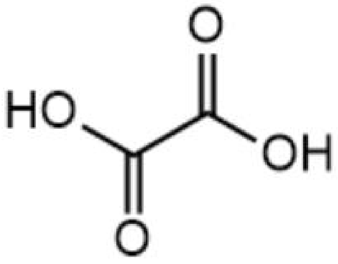
- Valence-shell structure factor refinement
  - Subtract FT of core electrons from data to generate an Fmap.
  - FS the difference map to get valence electron density.
- Refine using valence-only structure factors

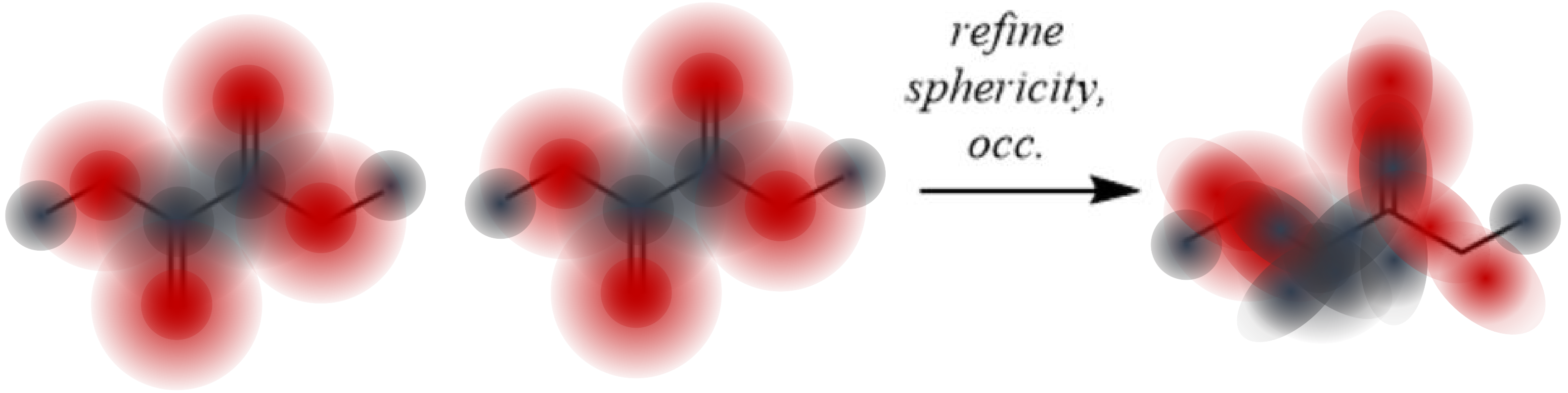


Stewart, R. F. J. *Chem. Phys*. **1970**, *53*, 205.
Corfield et al. *J. Am. Chem. Soc.* **1973**, *95*, 5, 1480

Could XRD see bond orbital distortion?

- Valence-shell structure factor refinement
  - Fix 1s, 2s orbitals
  - Refine size of *p* orbitals
  - Refine atomic occupancy
- Requires careful treatement of theoretical quantum models
- Challenge: orbital stretching correlates with vibrational parameters. Need vibrational parameters from neutron data.

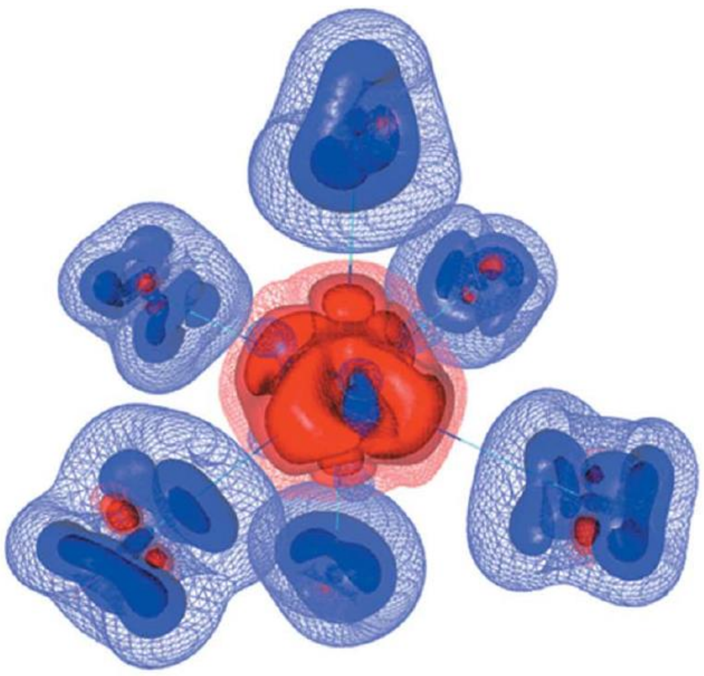


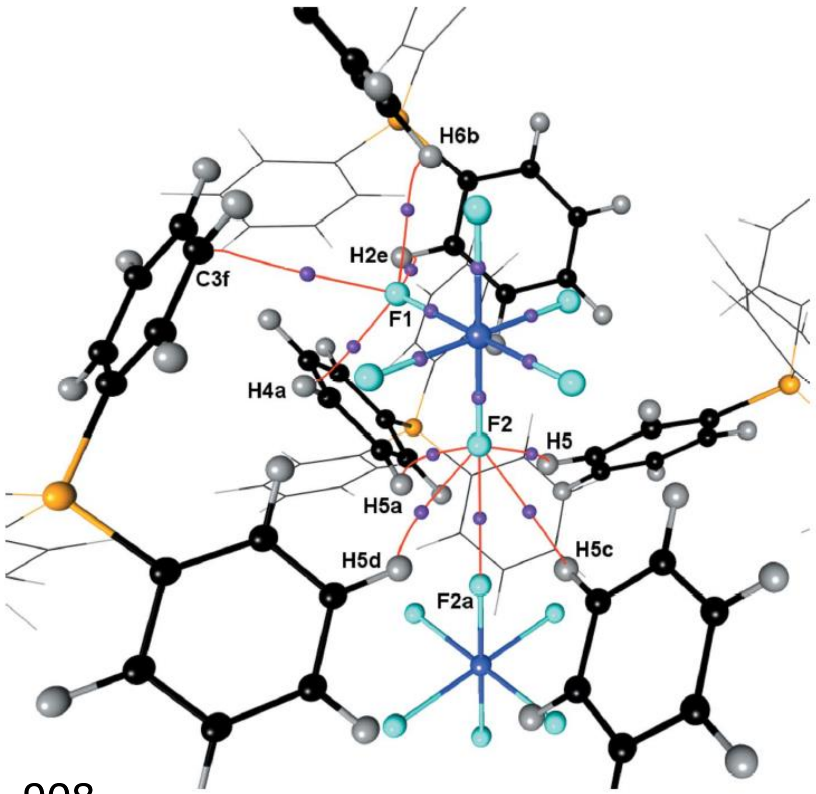


Coppens et al., *Science*. **1970**, *167*, 1126.

Could XRD see valence electronic structure?

- What has been done in the past:
  - Subtract FT of core electrons from data to generate an Fmap.
  - FS the difference map to get valence electron density.
- Powerful, but requires specialization sophistication





Gianopoulos et al., IUCrJ (2019). 6, 895–908

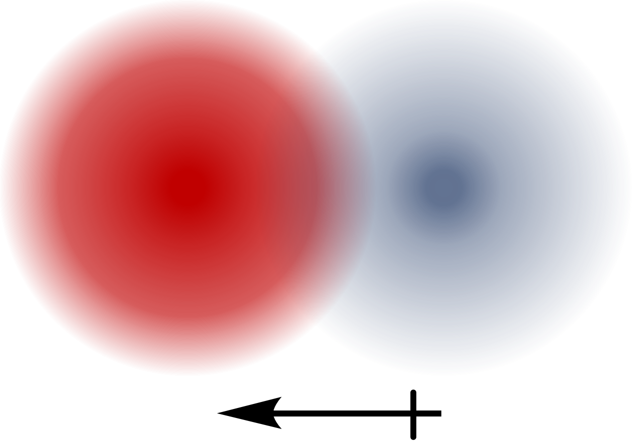
A simpler approach

- Can we take advantage of superior modern technology to simplify the process
  - Better, more sensitive detectors
  - Software that makes occupancy refinement simple and shows unnacounted for electron density automatically.
  - Use thermal parameters to account for orbital smearing

- Spherical Dirac atoms

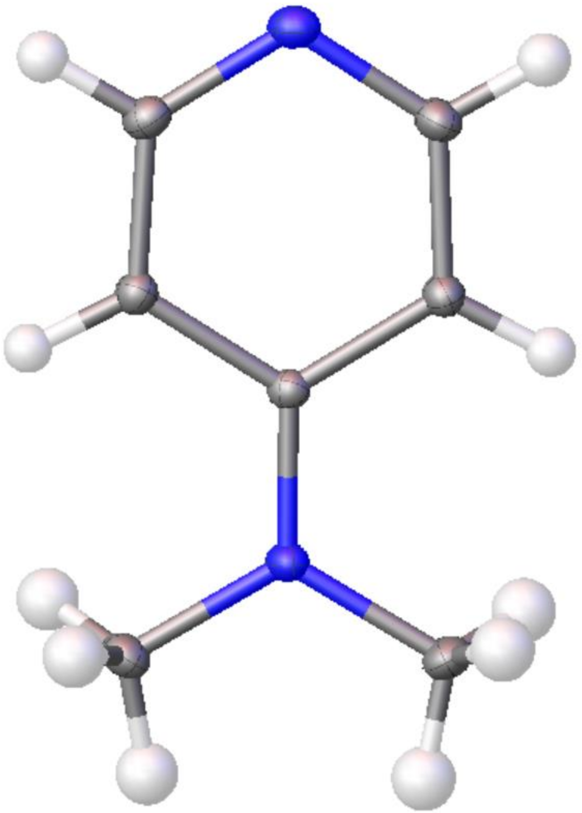
- Overlapped atoms (normal X-ray model)

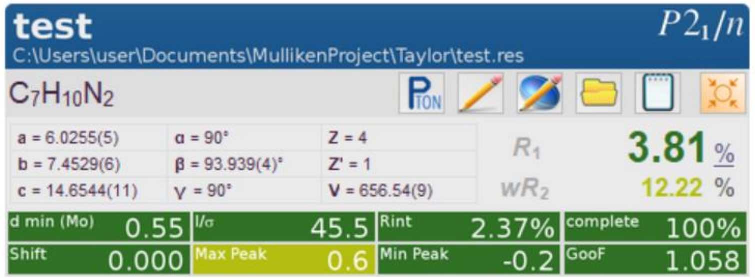
- Refined occupancy (polar sphereical atom model



First Test: *p*-dimethylaminopyridine

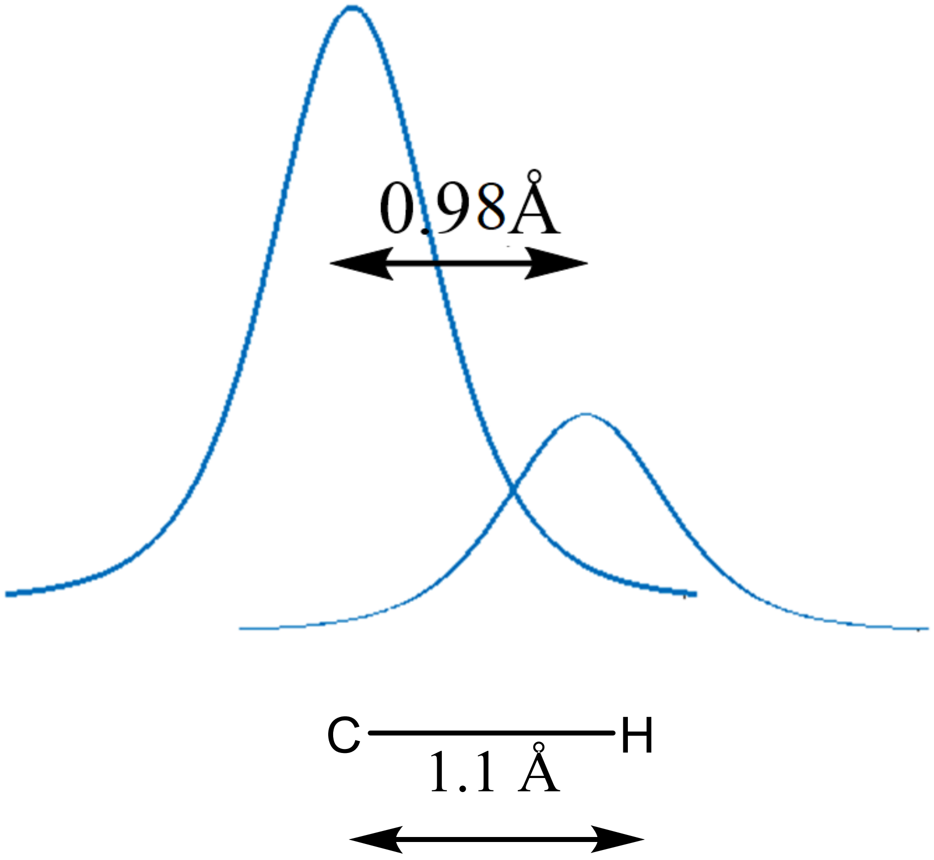
- Plan:
  - Refine a structural model for an excellent data set
  - Fix atom locations and refine atomic occupancies
- Presumptions and potential pitfalls
  - Presumably, higher resolution is better
  - Want an isotropic crystal
  - Want low temperature (we can do 100 K)
  - Do we want to lengthen the C-H bonds?
  - Do we want to fix thermal parameters of non-H atoms?
  - Do we want to refine hydrogen thermal parameters?





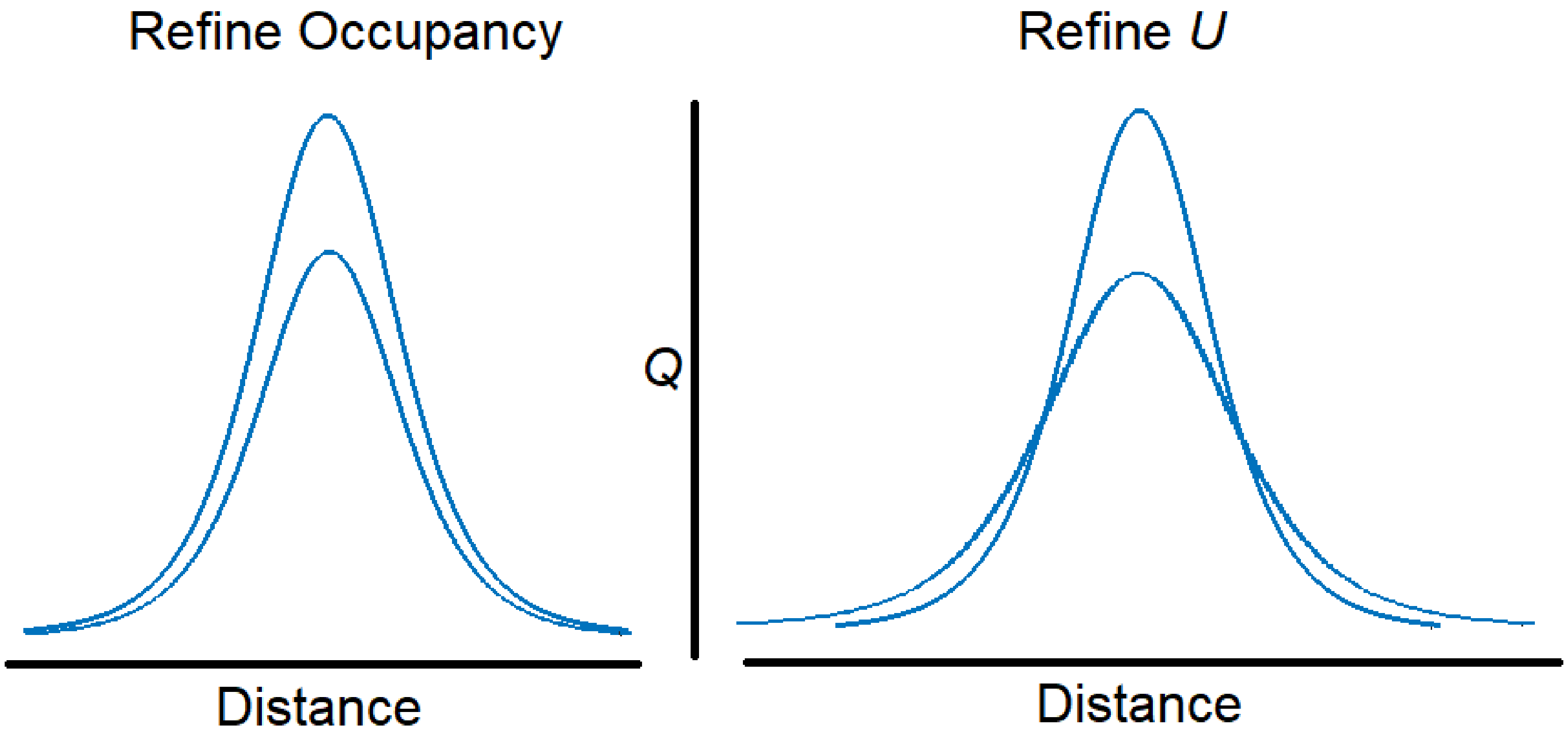
Do we want to lengthen C-H bonds?

- We typically model X-H bonds as ~0.1 Å short (e^- polarized into the bond)
- C-H bonds very slightly polar, H atoms slightly positive.
- Force realistic X-H distance?



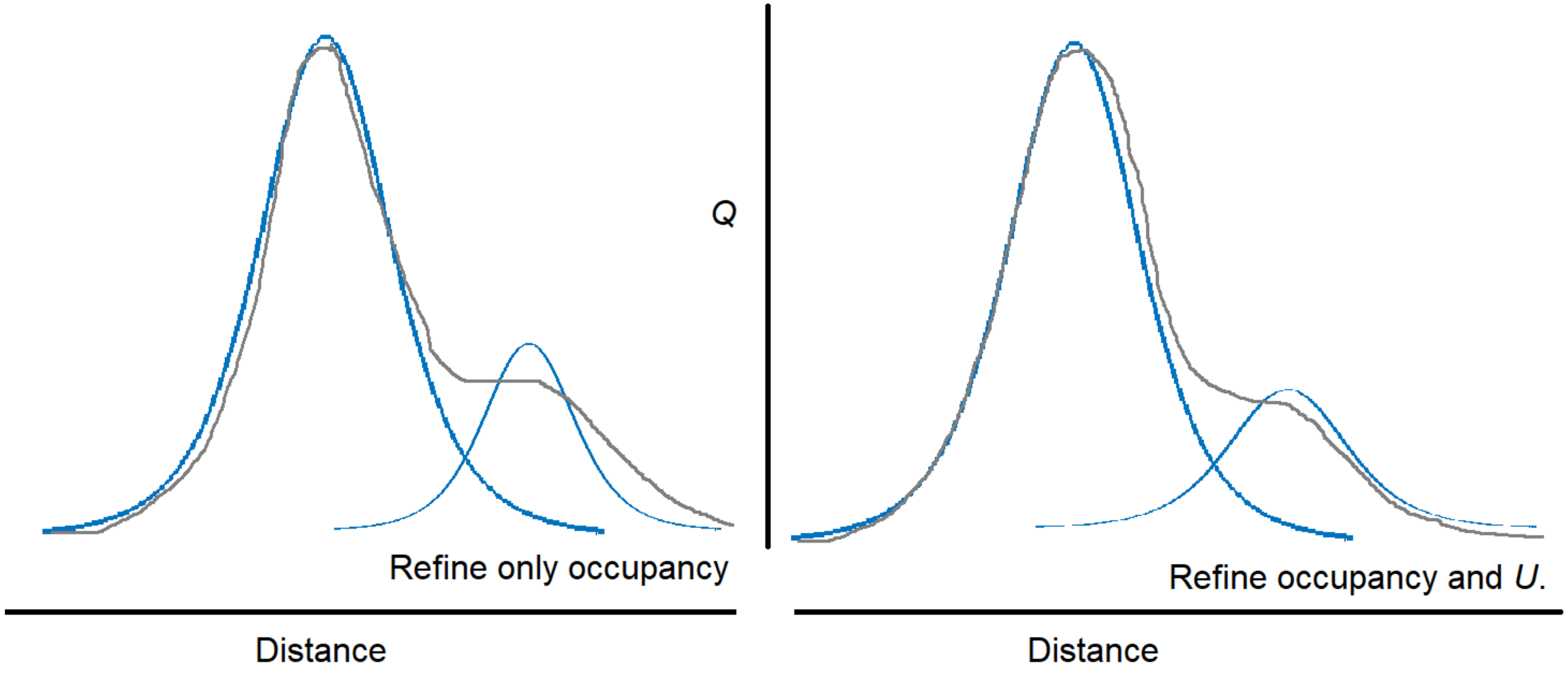
Fix thermal parameters of non-H atoms?

- Two ways to fit the electron density curve
  - Occupancy (increases height and width)
  - *U* (decreases height and increases width)



Fix thermal parameters of hydrogen atoms?

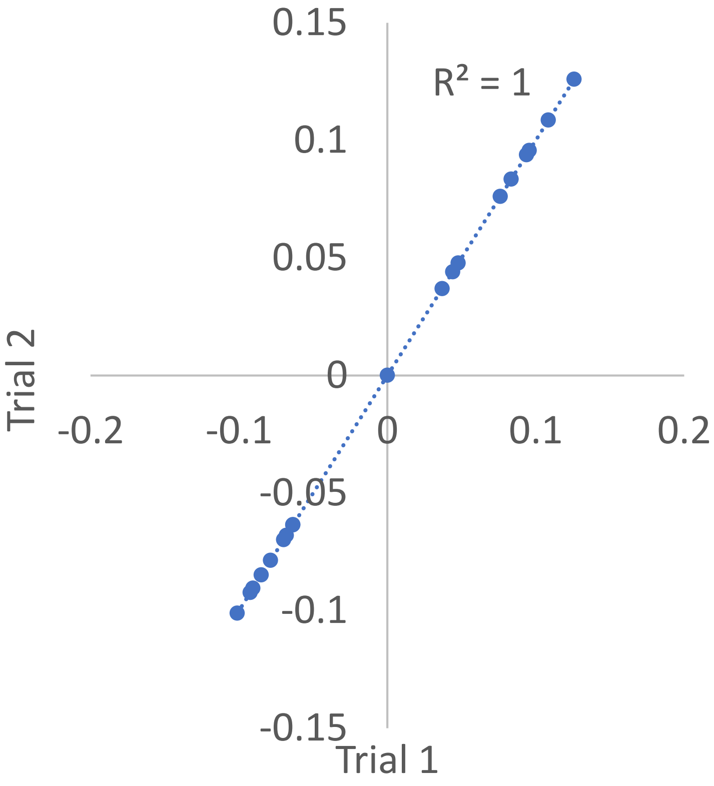
- Refining H thermal parameter could better fit the electron density curve, but could cause correlation.

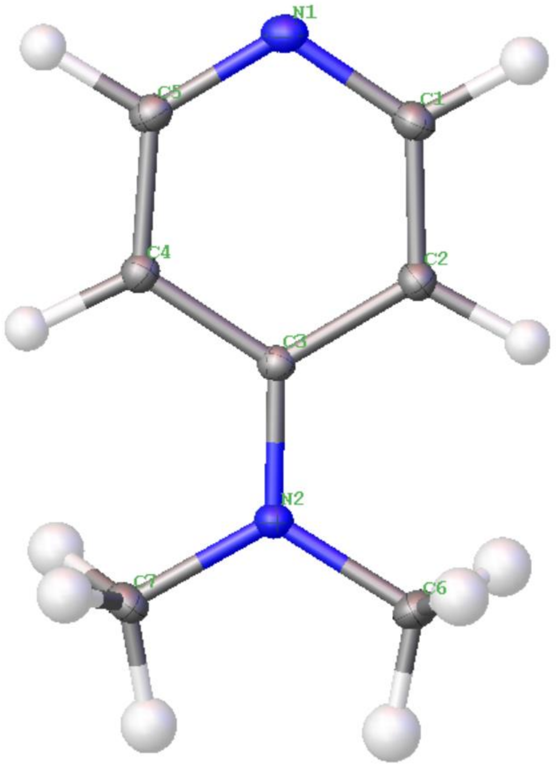


Reproducibility test – same crystal

- All atoms fixed
- Resolution = 0.55 Å
- C-H bonds lengthened to 1.1 Å
- Non-H *U*'s refined (anisotropically)
- H *U*'s refined (isotropically)
- Experiment done twice from scratch
- Reproducible
- Occupancy/thermal parameters not correlating

Atom	Solve11Aa
C1	-0.097641294
C2	-0.154443136
C3	-0.047393511
C4	-0.130108158
C5	-0.042781395
C6	-0.08192369
C7	-0.033010993
N1	-0.027963623
N2	-0.081559235
H1	0.101911907
H2	0.094235162
H4	0.032244691
H5	0.080904531
H6A	0.082269959
H6B	0.118489225
H6C	0.059512811
H7A	-0.007615718
H7B	0.102073735
H7C	0.032800977

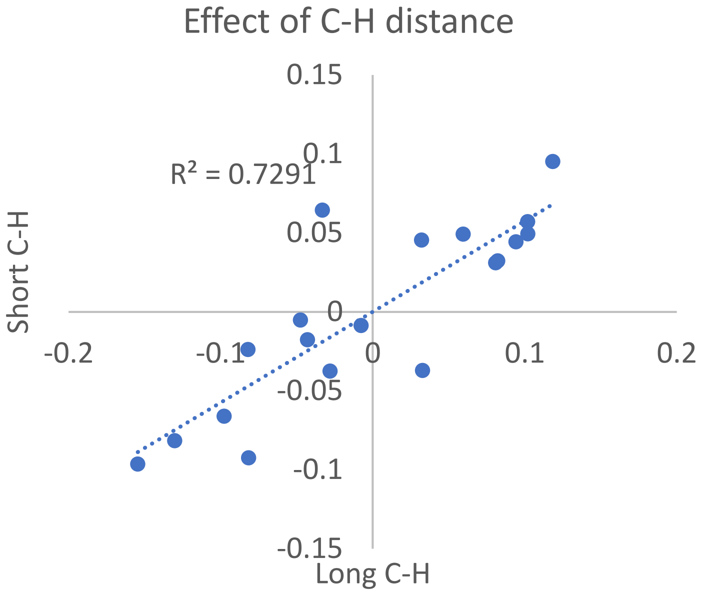


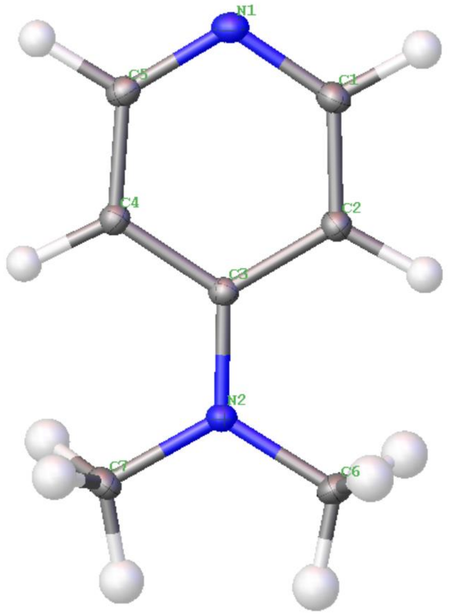


Reproducibility tests: Short vs. Long C-H

- All atoms fixed
- Resolution = 0.55 Å
- Non-H *U*'s refined (anisotropically)
- H *U*'s tied to connected atom
- Lenghtened hydrogens (vertical) compared to shorter (0.9) hydrogens (horizontal)
- Same trend with some scatter.
- Overall C-H charges move closer to 0
- Nitrogen charges become more negative

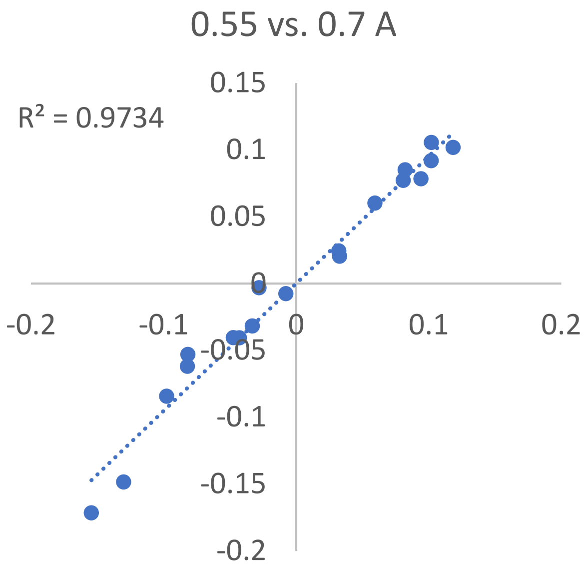
Atom	Long C-H	Short C-H
C1	-0.097641294	-0.066170798
C2	-0.154443136	-0.096486252
C3	-0.047393511	-0.005298331
C4	-0.130108158	-0.081690861
C5	-0.042781395	-0.017738537
C6	-0.08192369	-0.023898251
C7	-0.033010993	0.064270203
N1	-0.027963623	-0.037674433
N2	-0.081559235	-0.092558289
H1	0.101911907	0.057050463
H2	0.094235162	0.044227791
H4	0.032244691	0.045365124
H5	0.080904531	0.030922004
H6A	0.082269959	0.03219018
H6B	0.118489225	0.095095755
H6C	0.059512811	0.049109263
H7A	-0.007615718	-0.00879406
H7B	0.102073735	0.049330691
H7C	0.032800977	-0.03724751

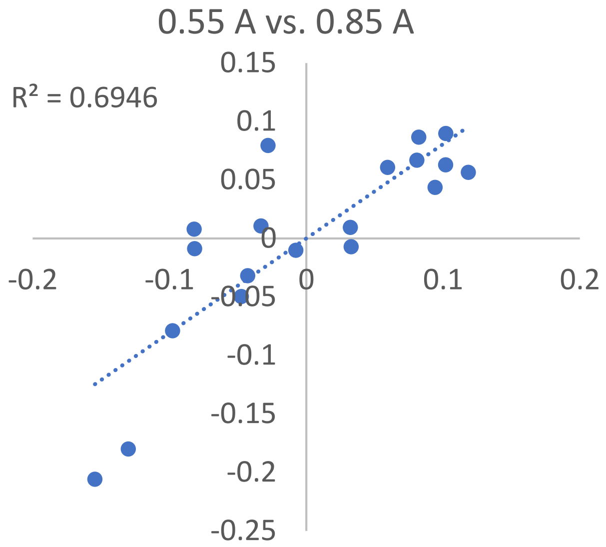


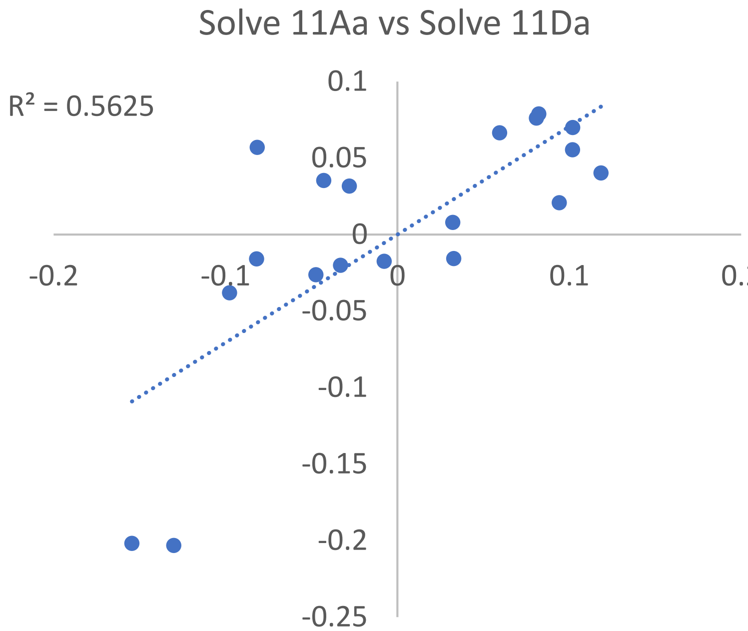


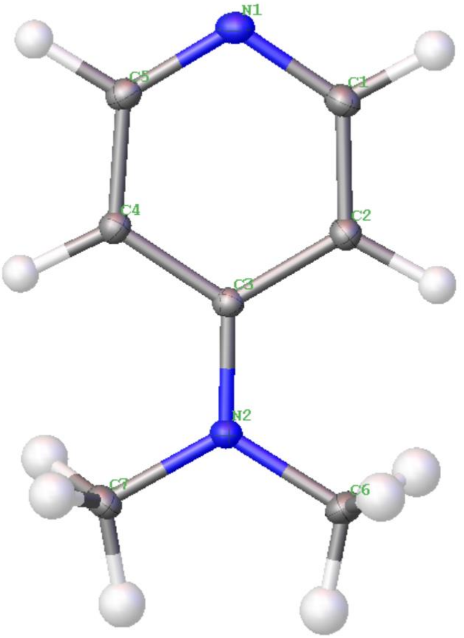
Reproducibility tests, Resolution effects

- One sample
- All atoms fixed
- Resolution varied
- C-H bonds lengthened to 1.1 Å
- Non-H *U*'s refined (anisotropically)
- H *U*'s refined



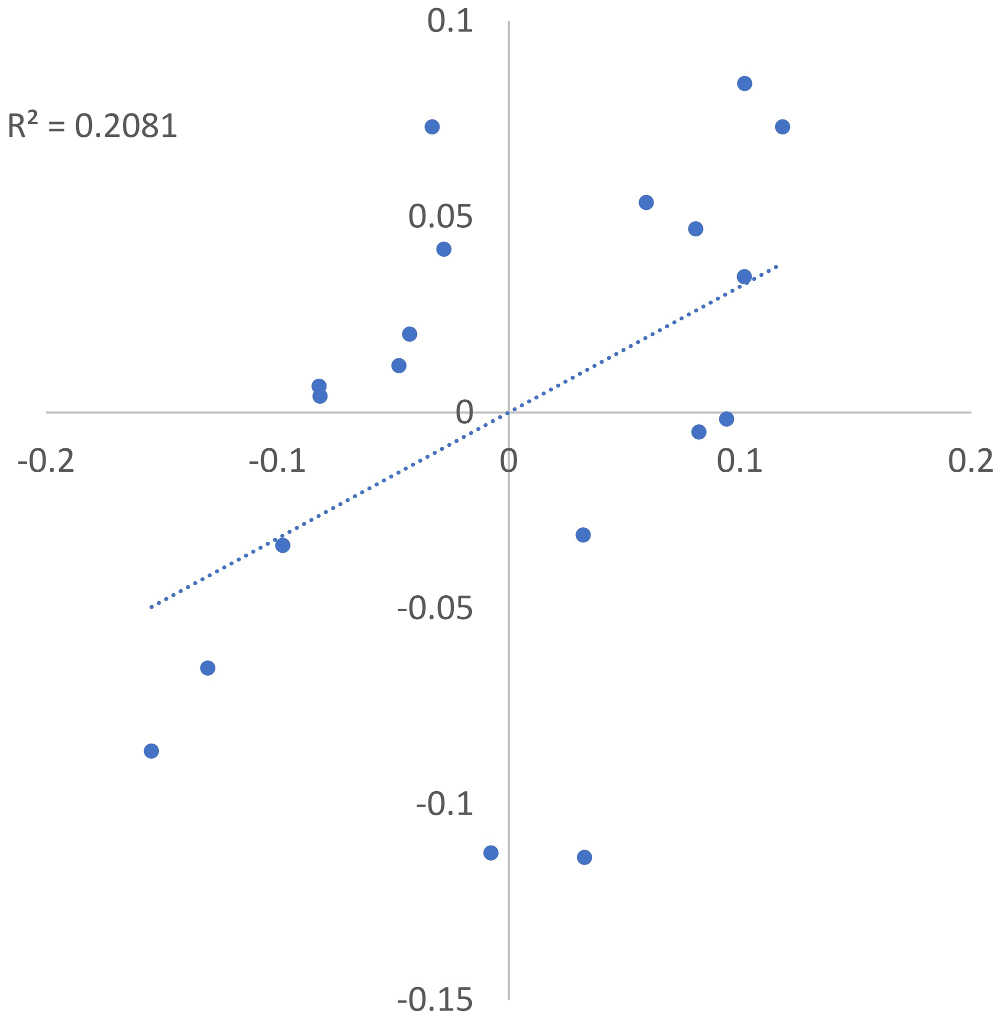


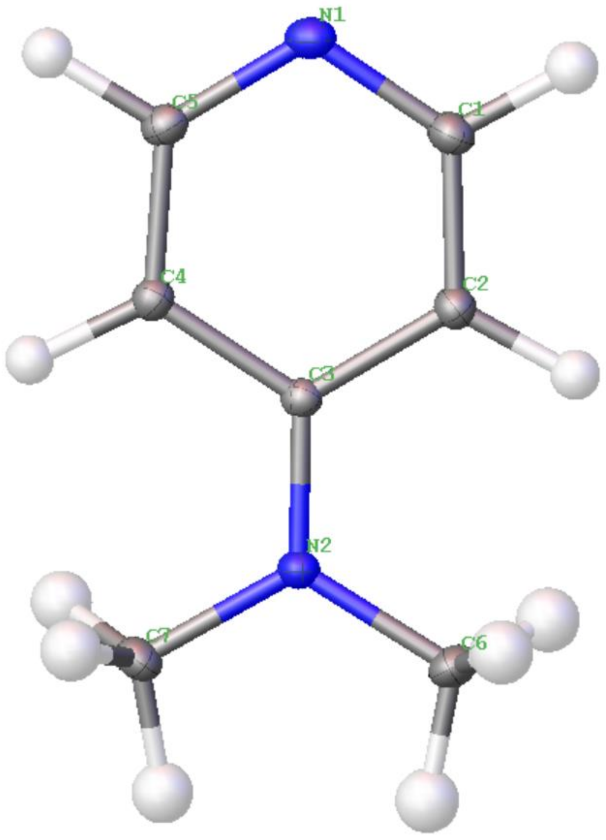




Reproducibility tests, fix or float H *U*

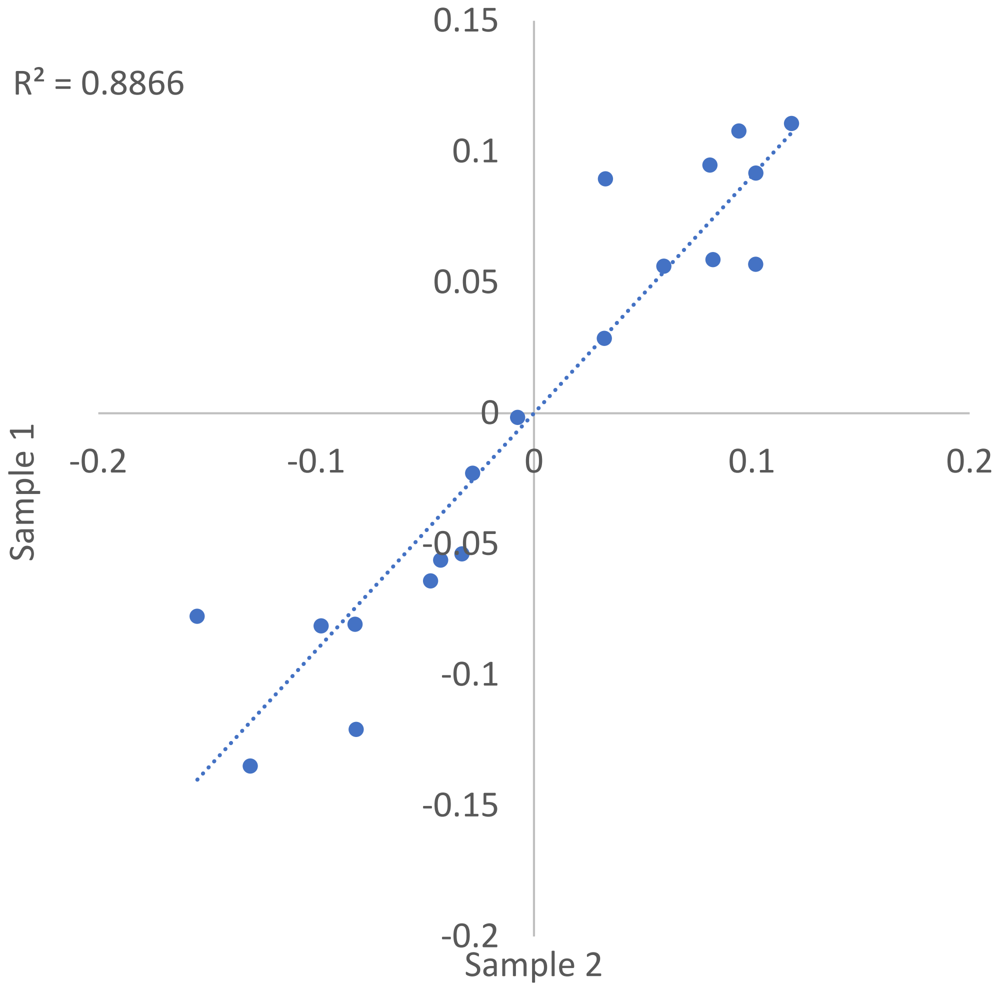
- One sample
- All atoms fixed
- Resolution = 0.55 Å
- C-H bonds lengthened to 1.1 Å
- Non-H *U*'s refined (anisotropically)
- H *U*'s refined vs *U's* fixed
- H *U* refinement appears to introduce random scatter

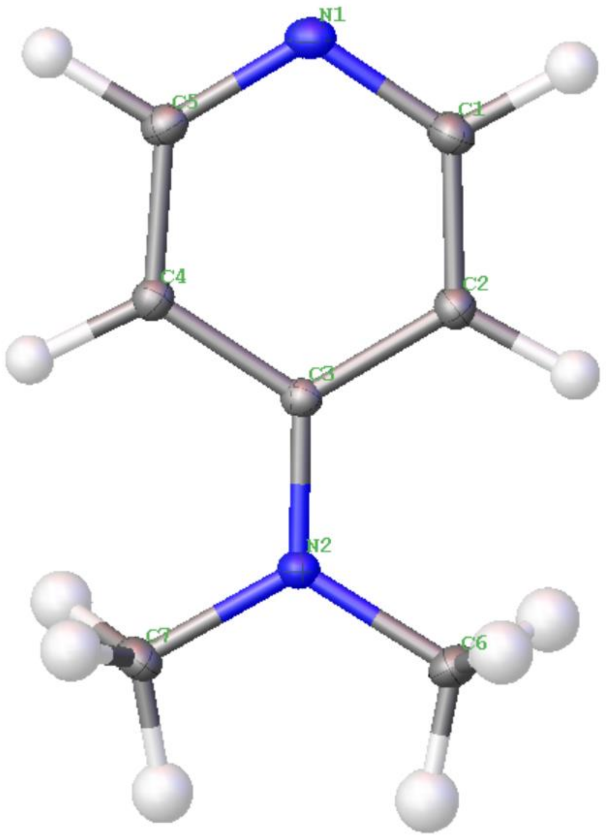




Reproducibility tests, two samples, floating H *U*

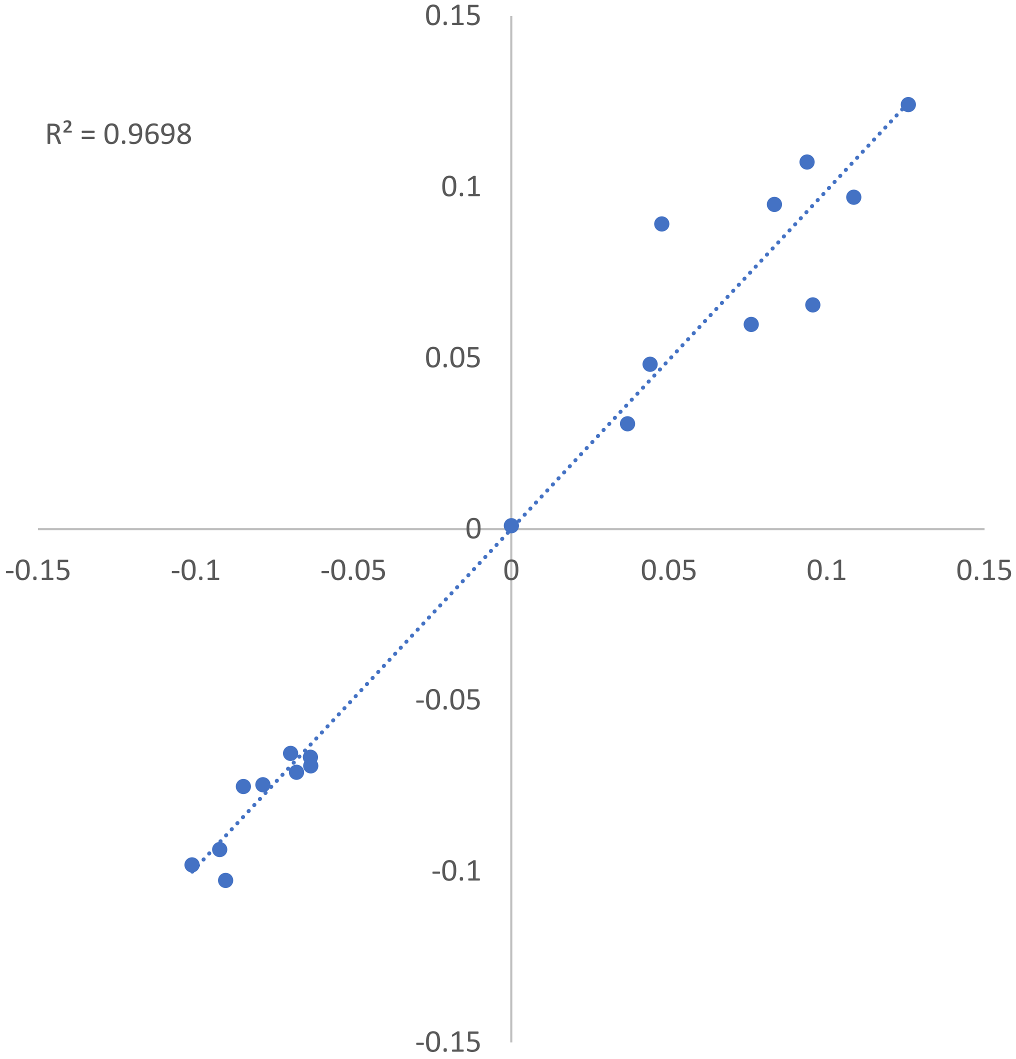
- Compare two crystals
- All atoms fixed
- Resolution = 0.55 Å
- C-H bonds lengthened to 1.1 Å
- Non-H *U*'s refined (anisotropically)
- H *U*'s refined (isotropically)
- Reasonably reproducible

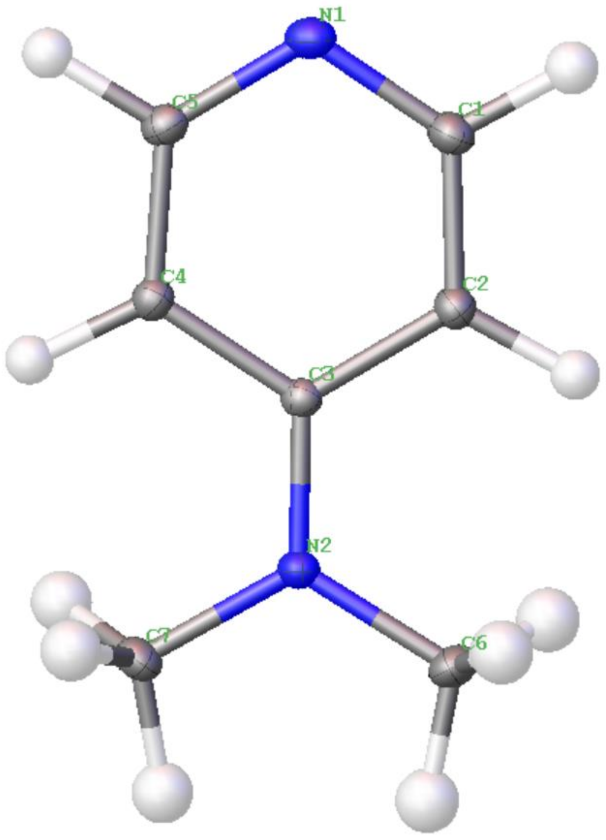




Reproducibility tests, two samples – Fixed H *U*

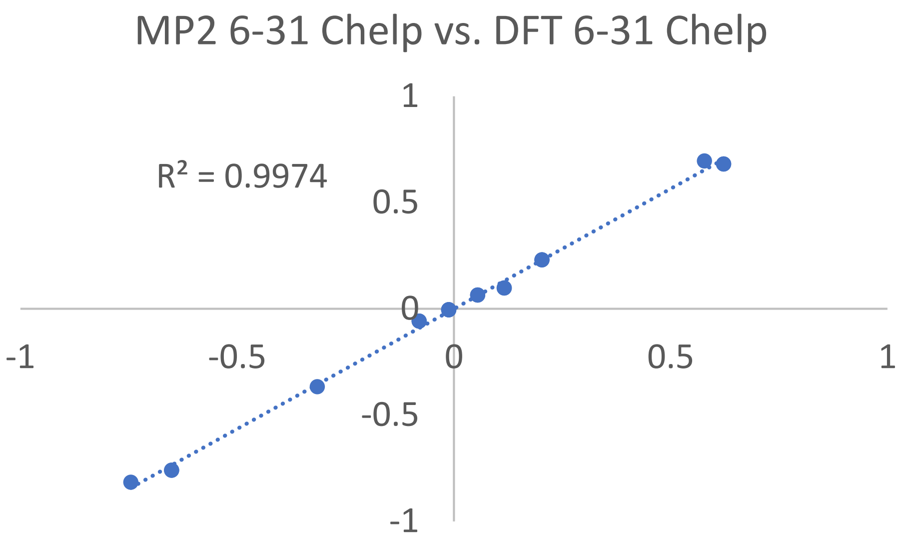
- Compare two crystals
- All atoms fixed
- Resolution = 0.55 Å
- C-H bonds lengthened to 1.1 Å
- Non-H *U*'s refined (anisotropically)
- H *U*'s tied to neighbor
- Improved reproducibliity

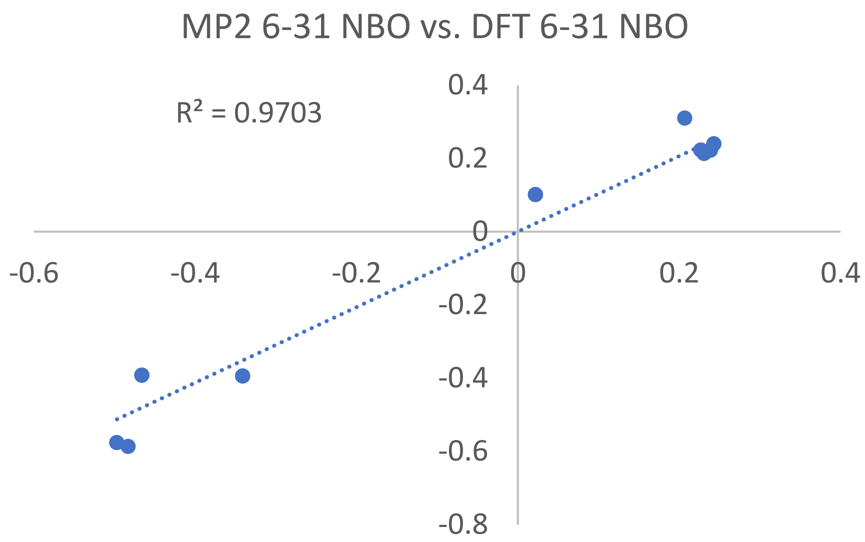


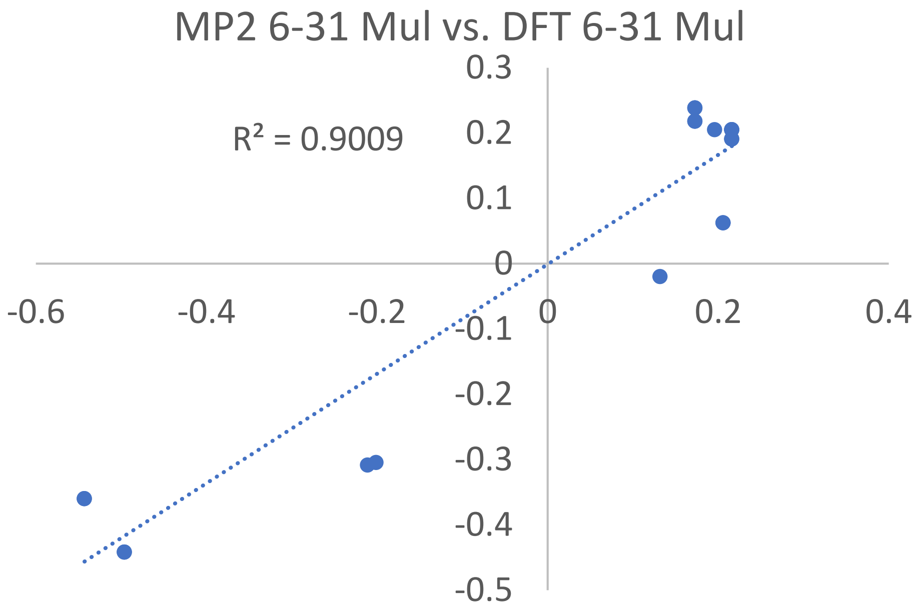


Theoretical calculations

- Compared MP2 and DFT (6-31g*).
- Considered
  - CHELPG (surface charge)
  - NBO (natural bond orbital)
  - Mulliken (atomic orbital basis set polarization)

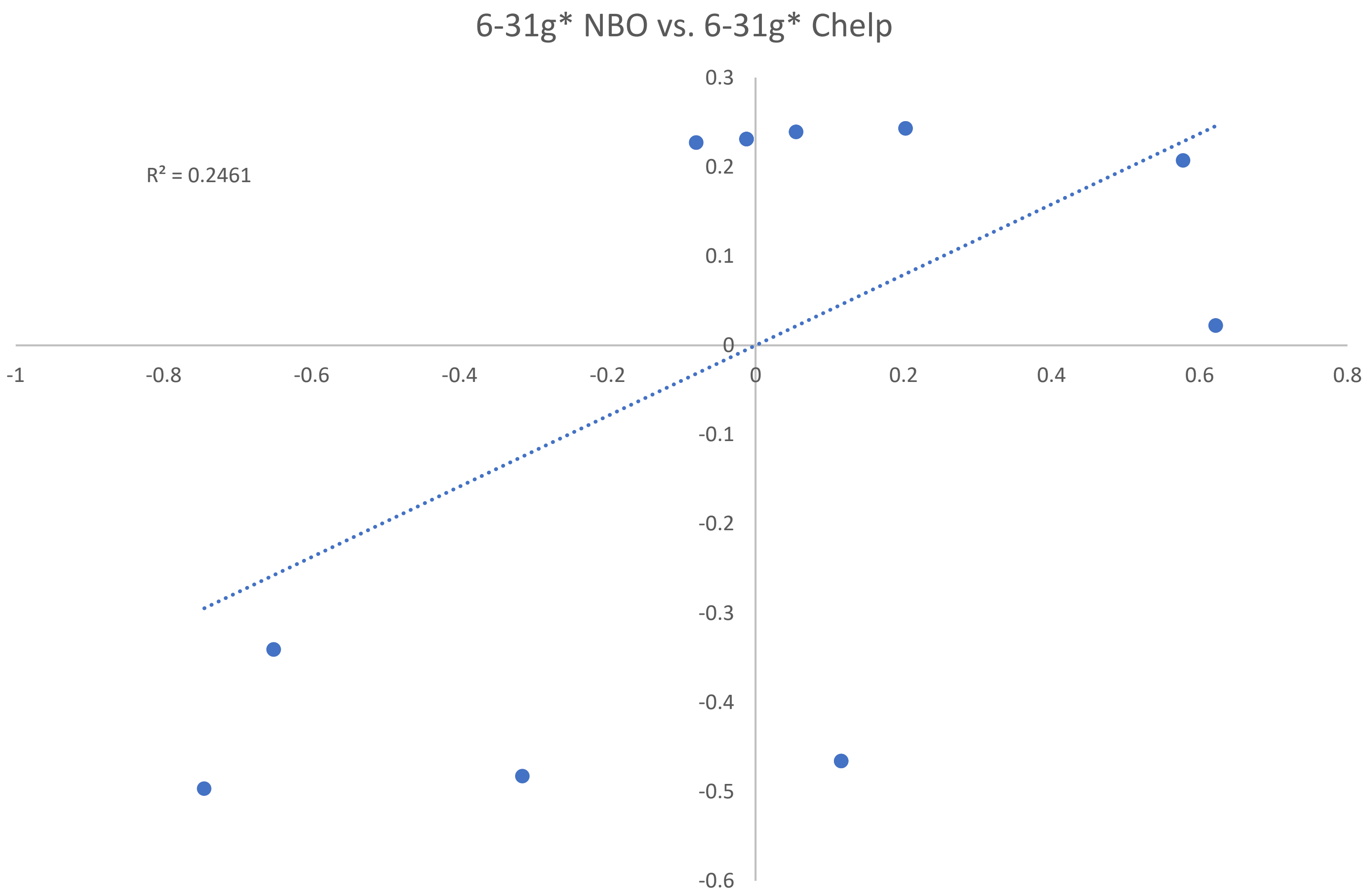




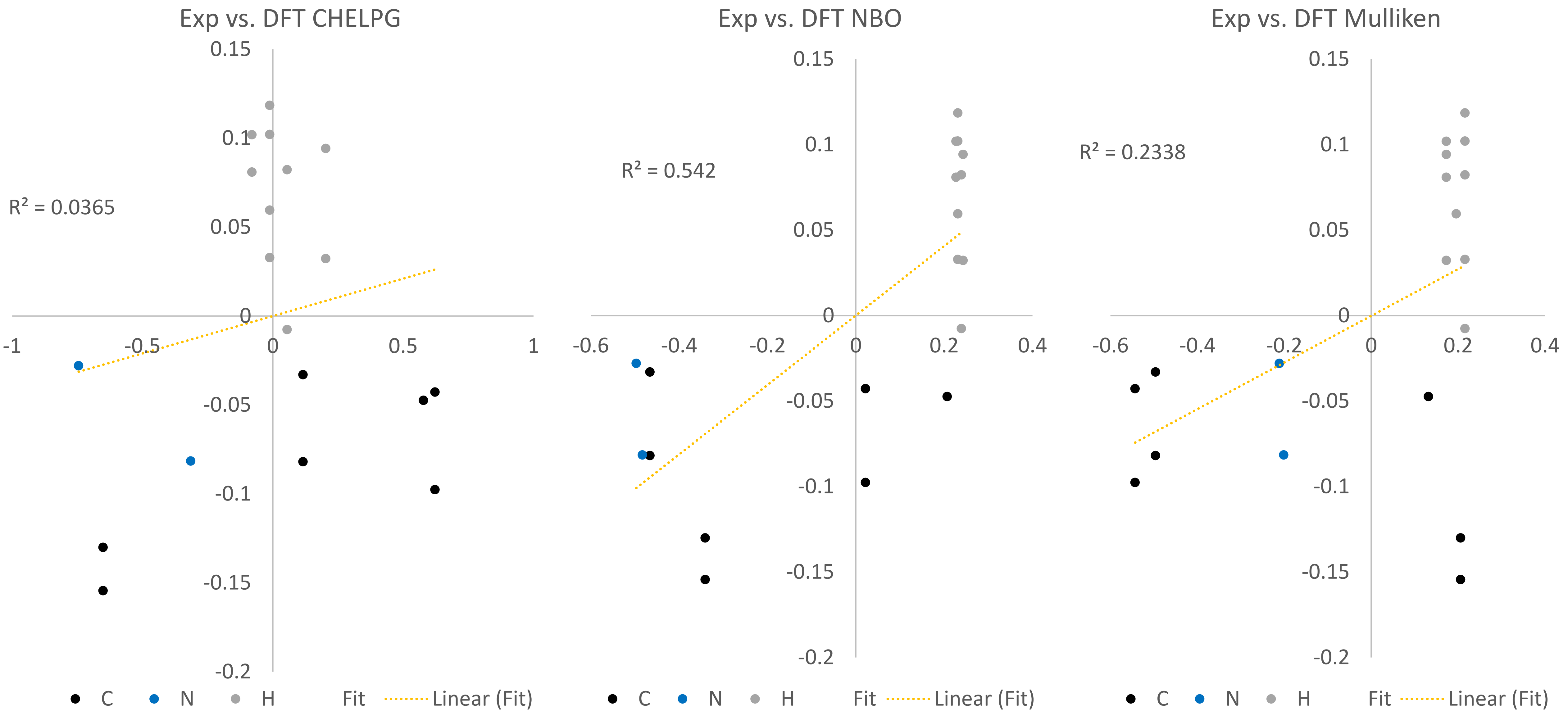


Theoretical methods vs. theoretical method

- Different theoretical methods disagree with one another

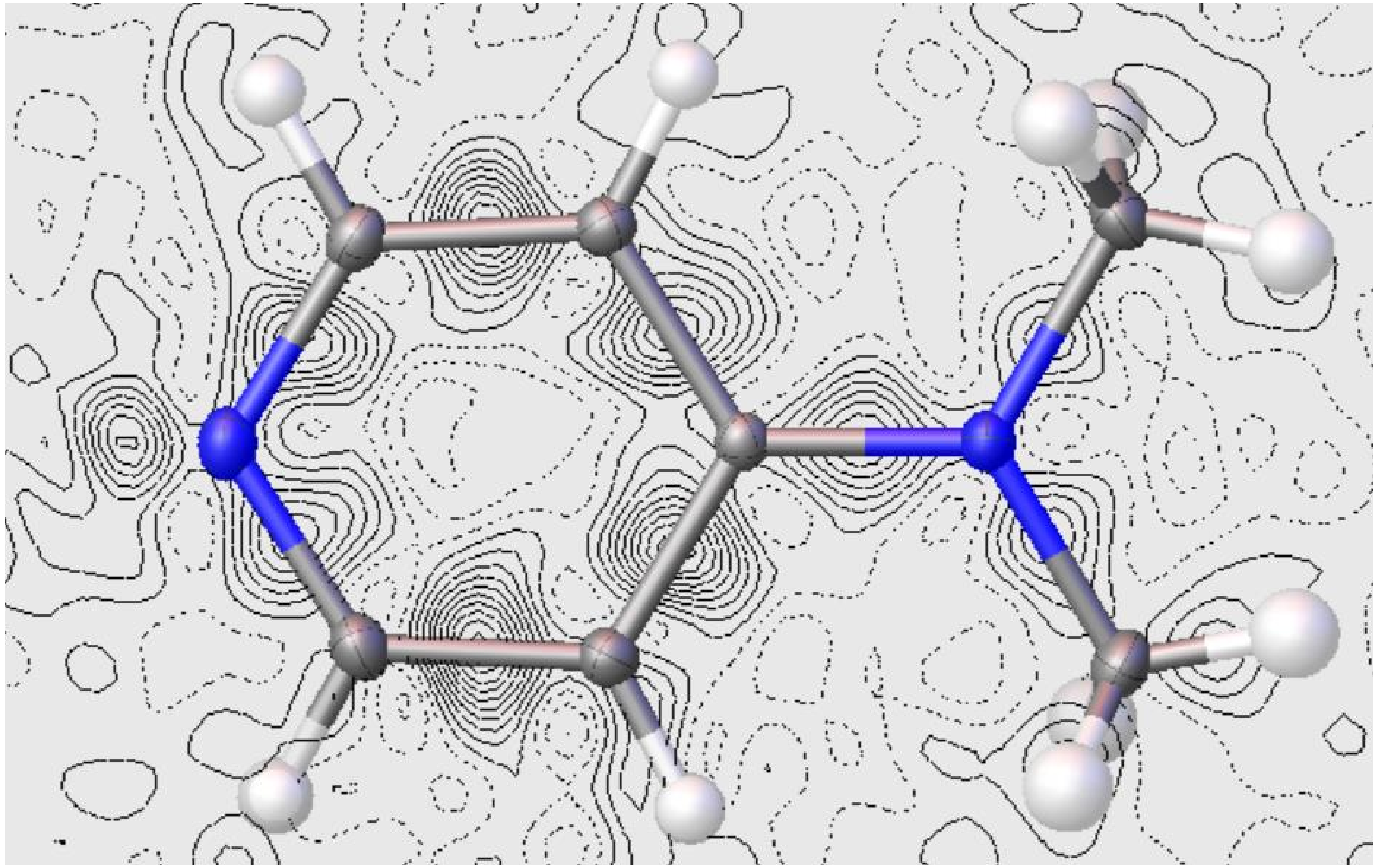


Experiment Vs. Theory



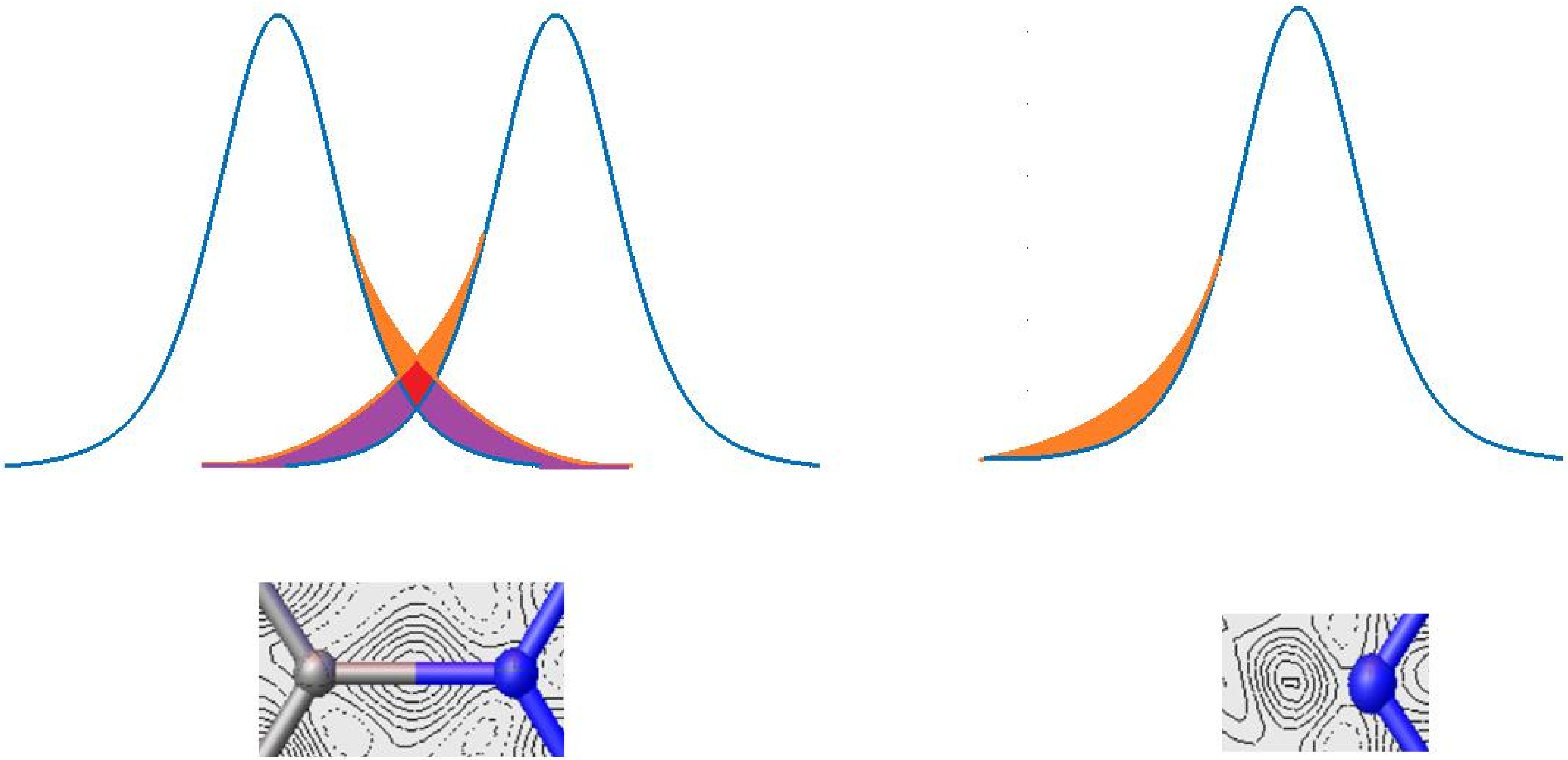
Why are the nitrogens low in charge?

- The use of spherical atoms results in residual electron density peaks
  - In bonds
  - "lone pairs"



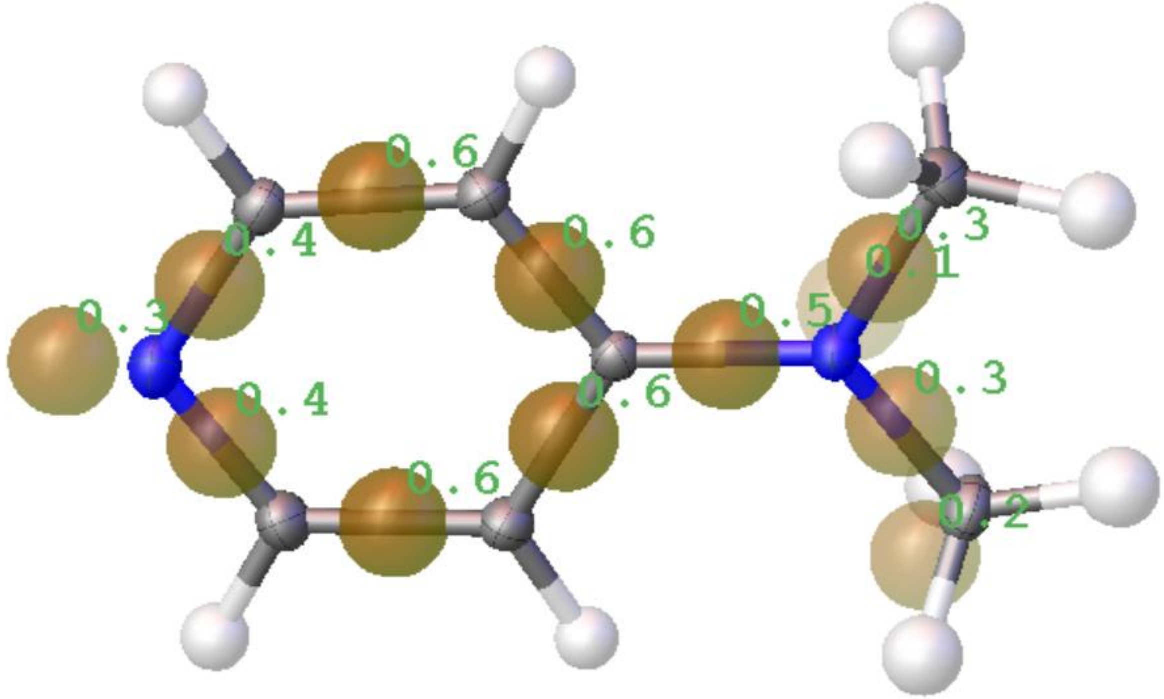
This introduces a low-electron bias on “terminal” atoms with lone pairs.

- Bonding residuals can be ignored because the overlap of adjacent atoms compensates for each other
- Lone pair residuals cannot be ignored because they are not integrated at all.

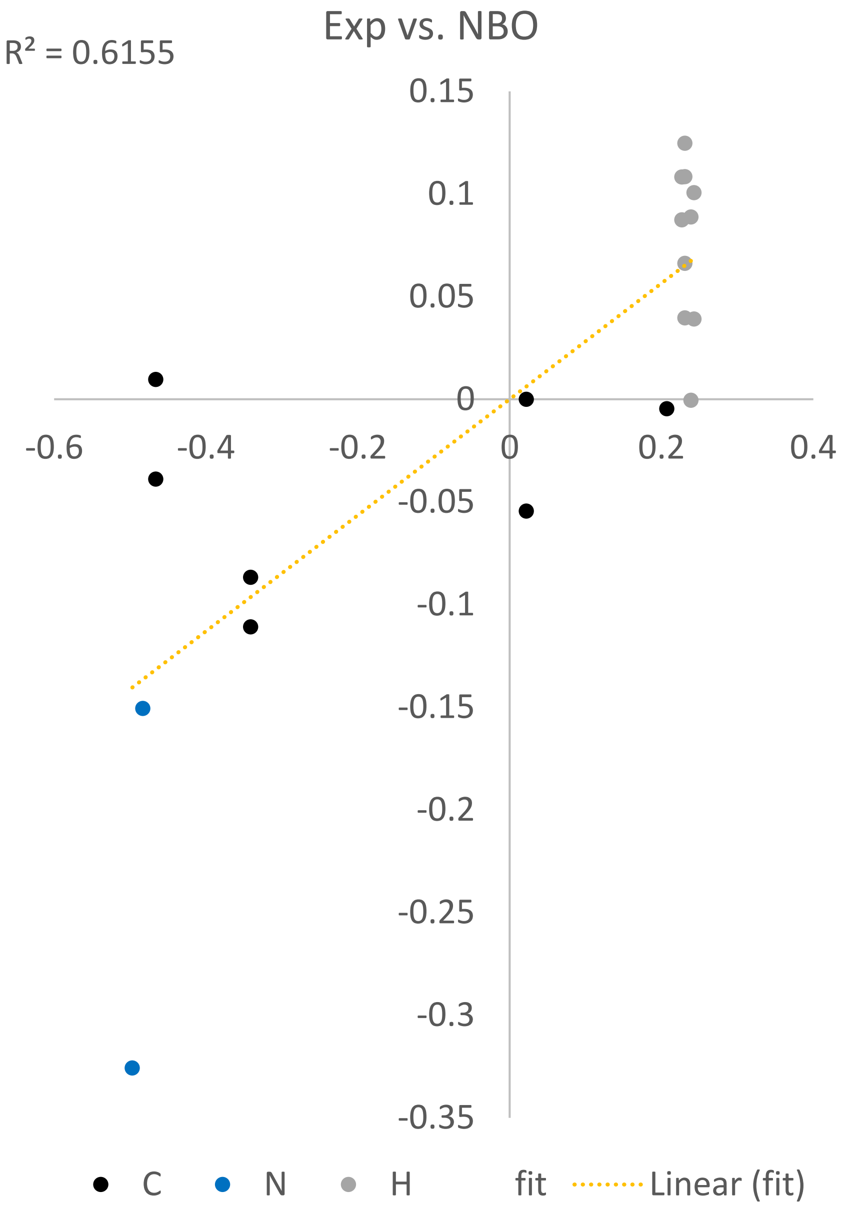


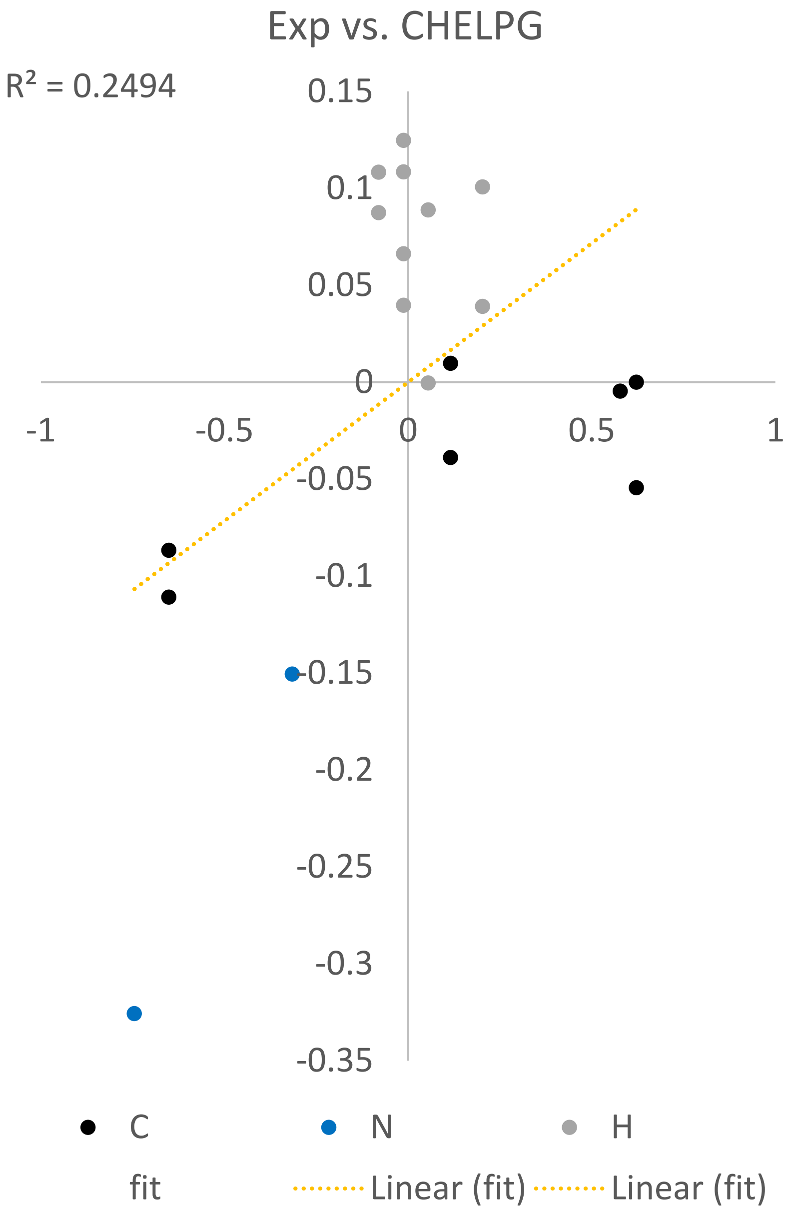
Modern ShelX GUIs make it easy to quantify (Q-peaks)

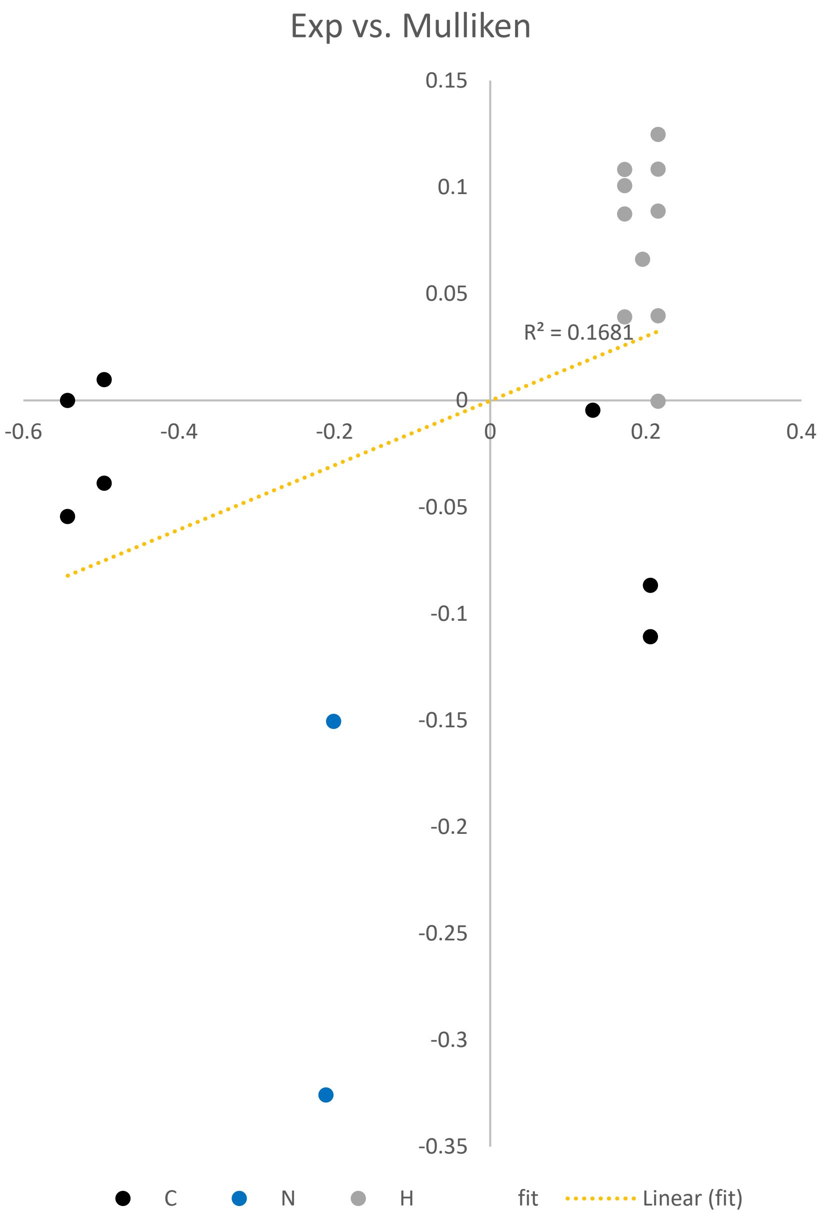
- Q peaks are $e^-/Å^3$ (a hydrogen is about 0.9 $Å^3$)
- Lone pair Q peak represents an approximation of the missing charge from a terminal atom.



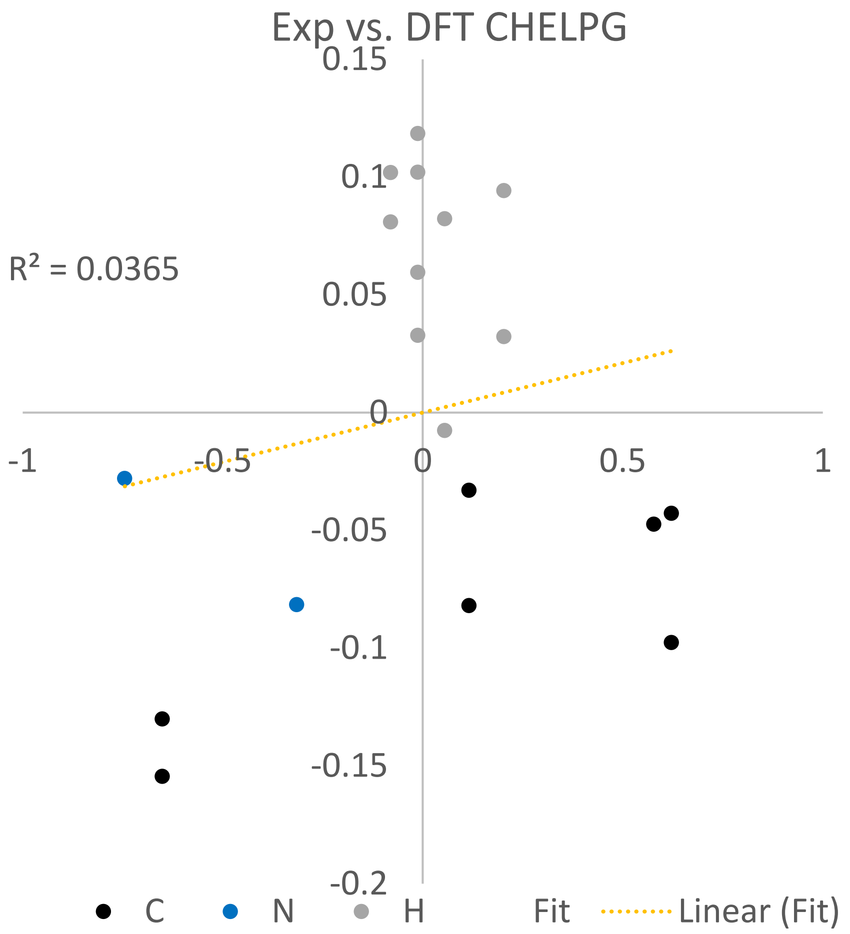
Experiment Vs. Theory (with lone pair correction)

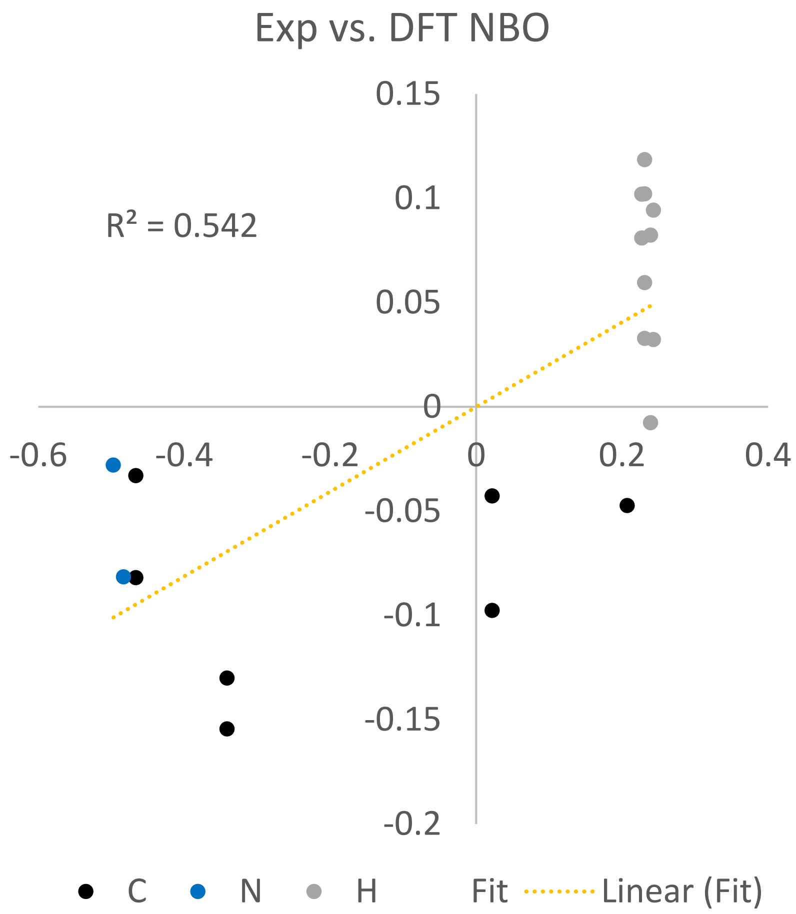


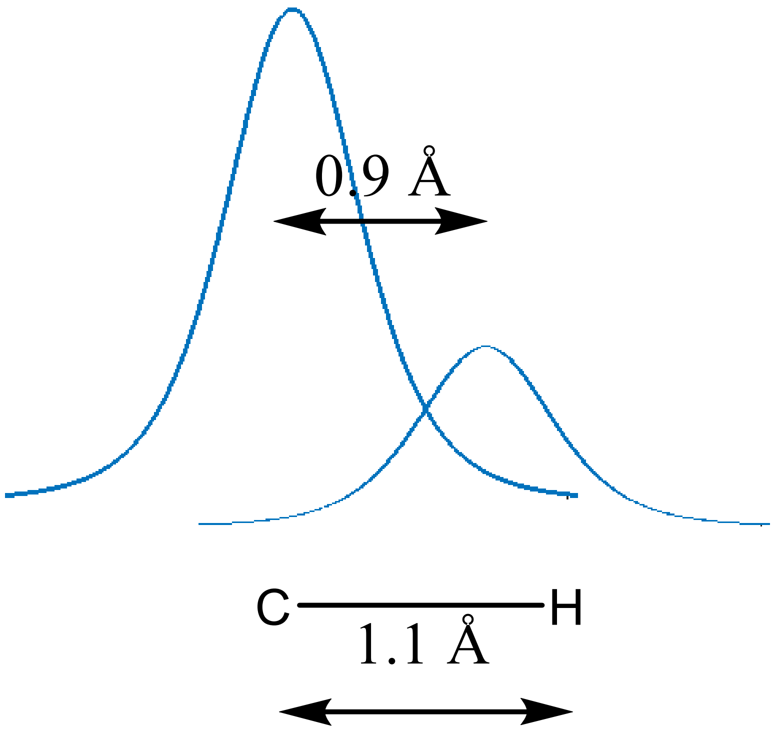




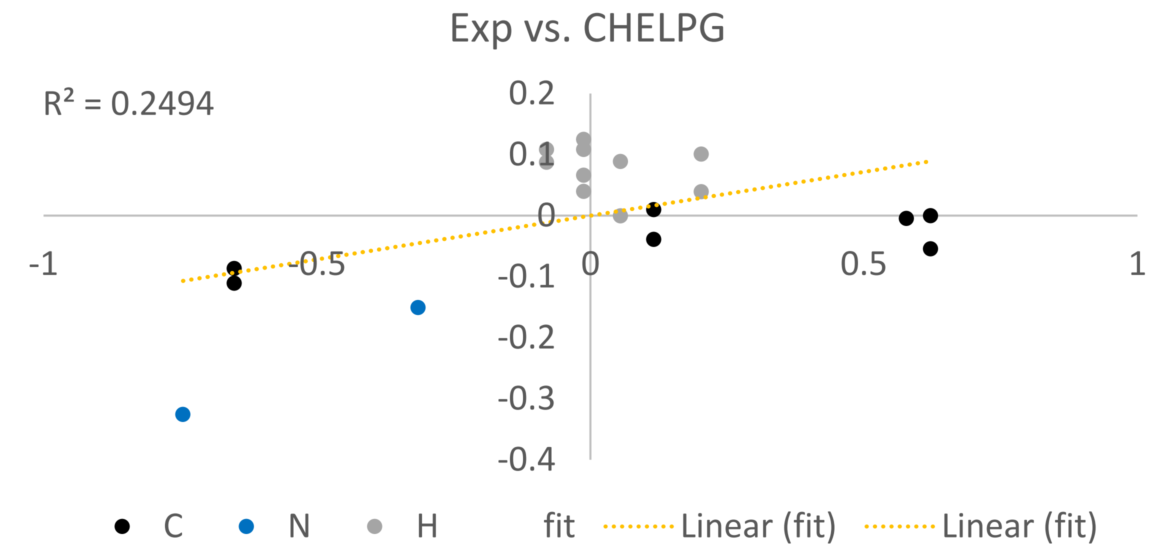
Shorten the bonds?

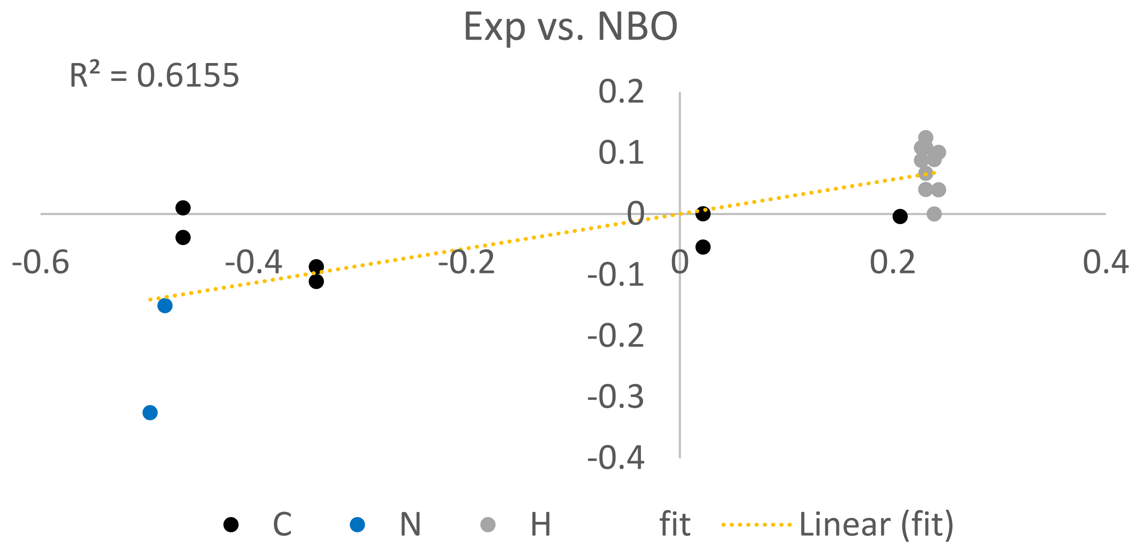


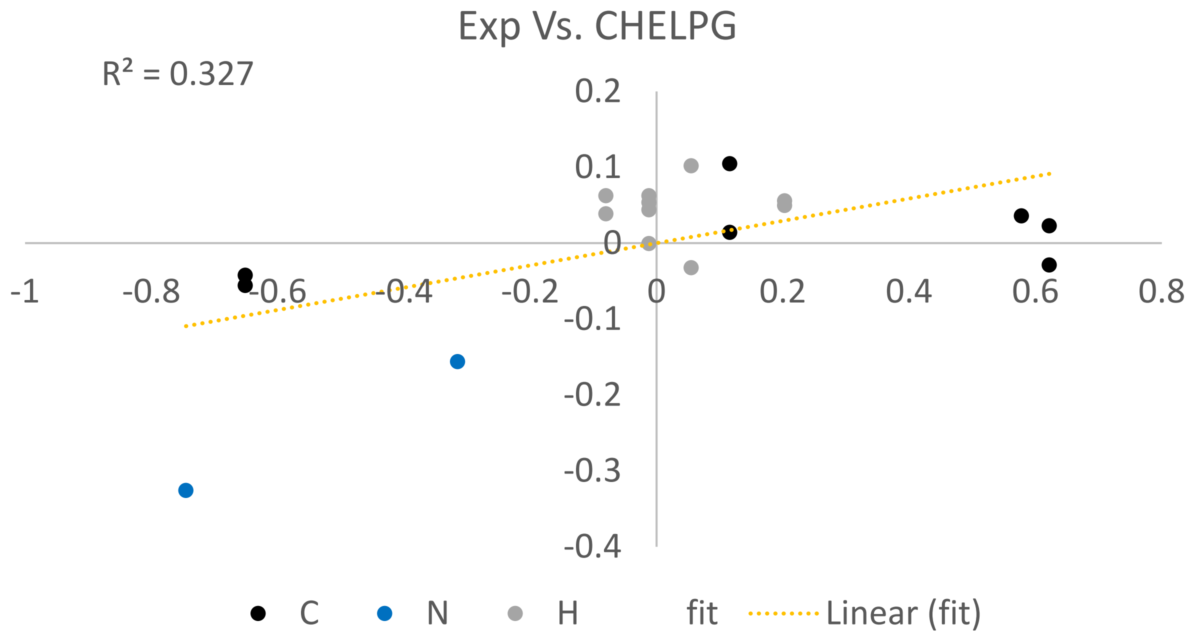


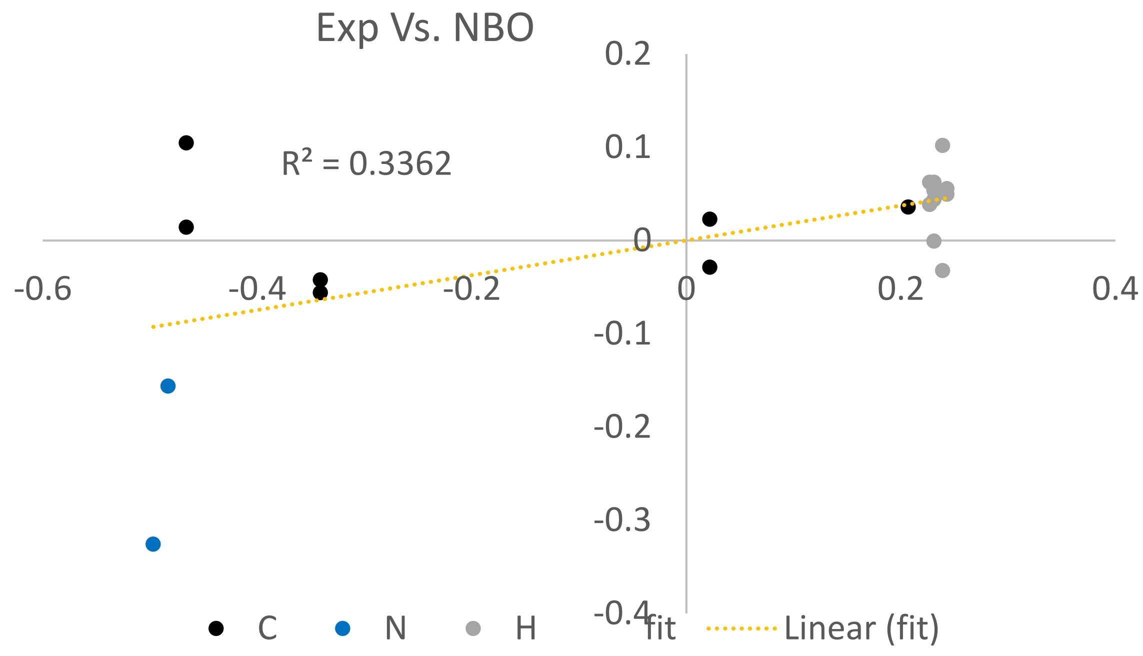


Experiment Vs. Theory (“long” vs. “short” C-H)





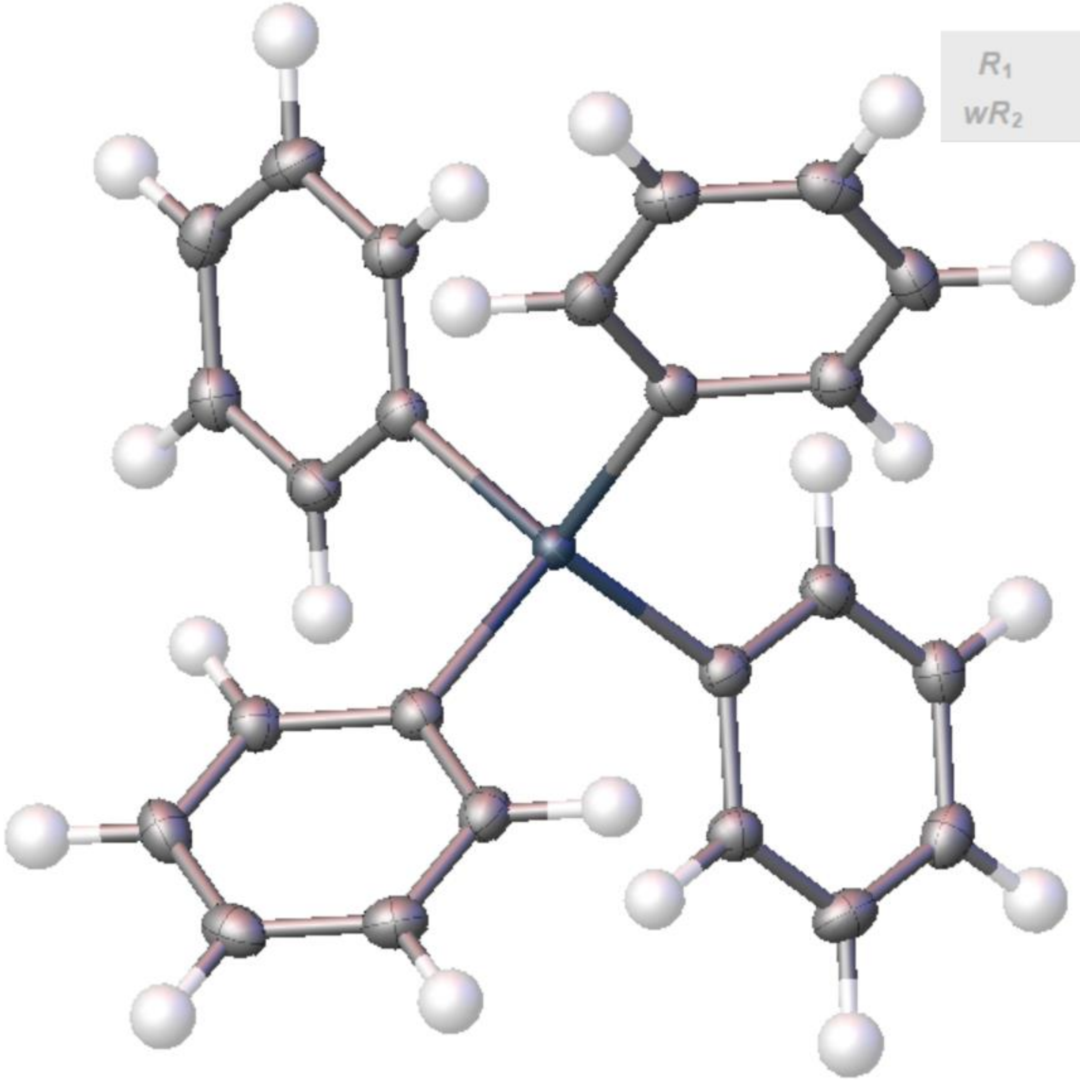




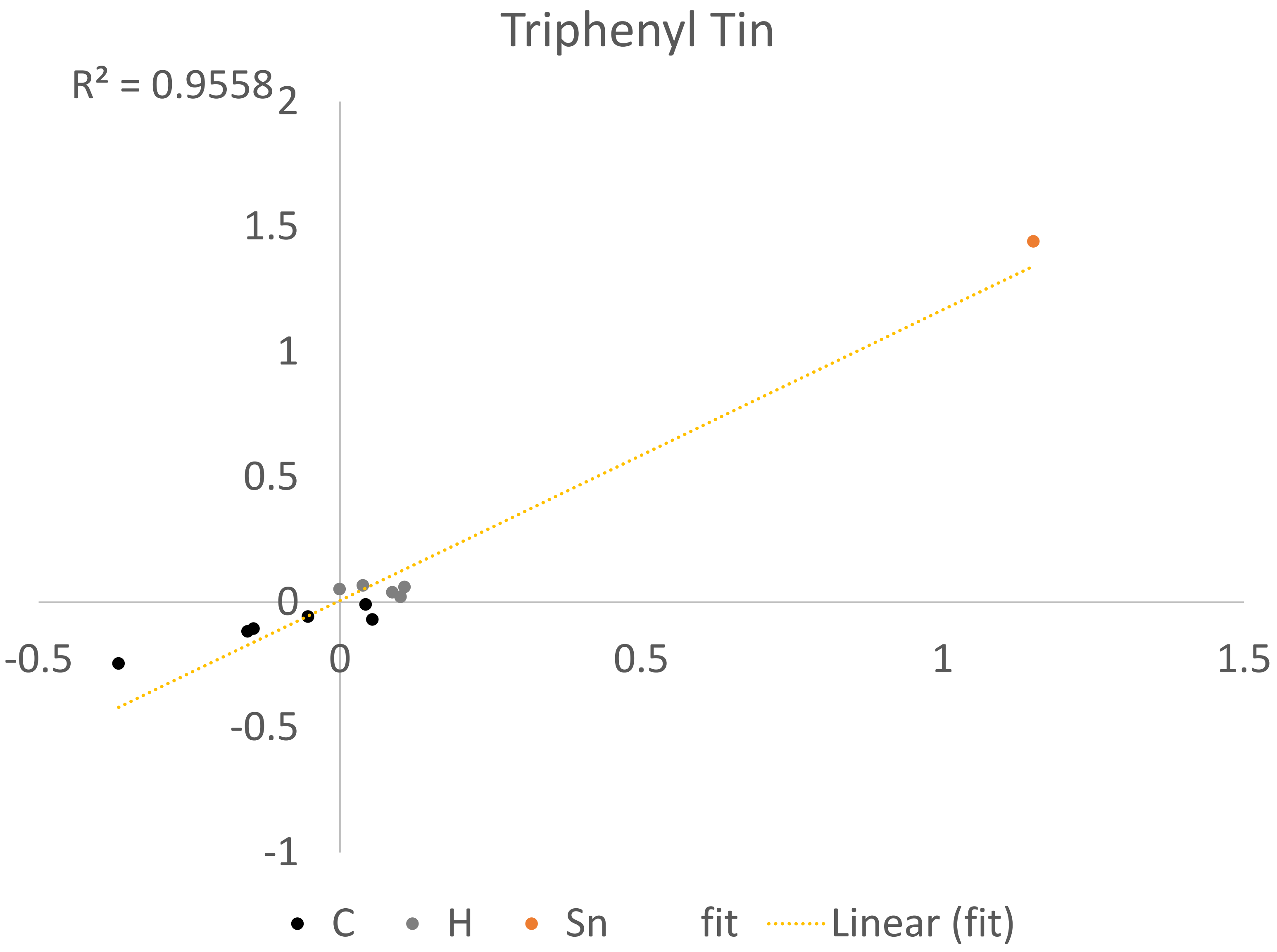
A molecule with very polar bonds and no terminal heteroatoms: Ph_4Sn

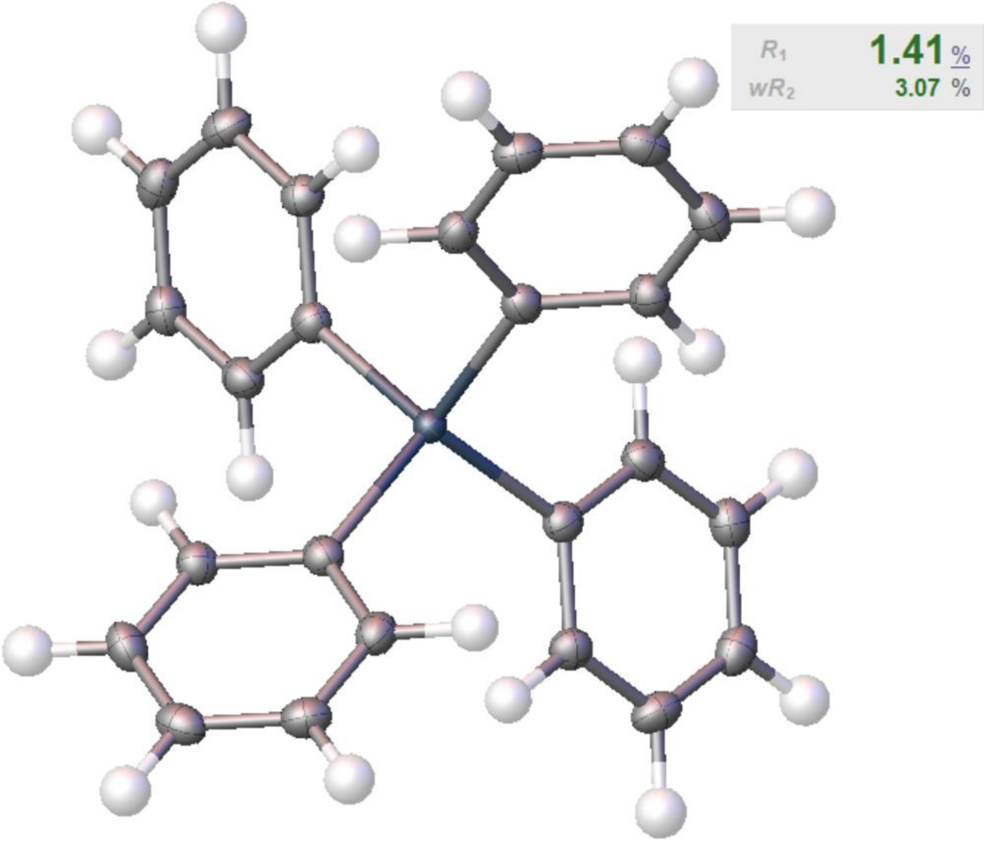
- Thermal paramaters refined on non-H atoms
- Hydrogen thermal parameters fixed
- C-H bonds lengthened to 1.09 Å
- No Q-peak corrections
- A test of charge calculations for large K-shells!

R_1	1.41 %
wR_2	3.07 %

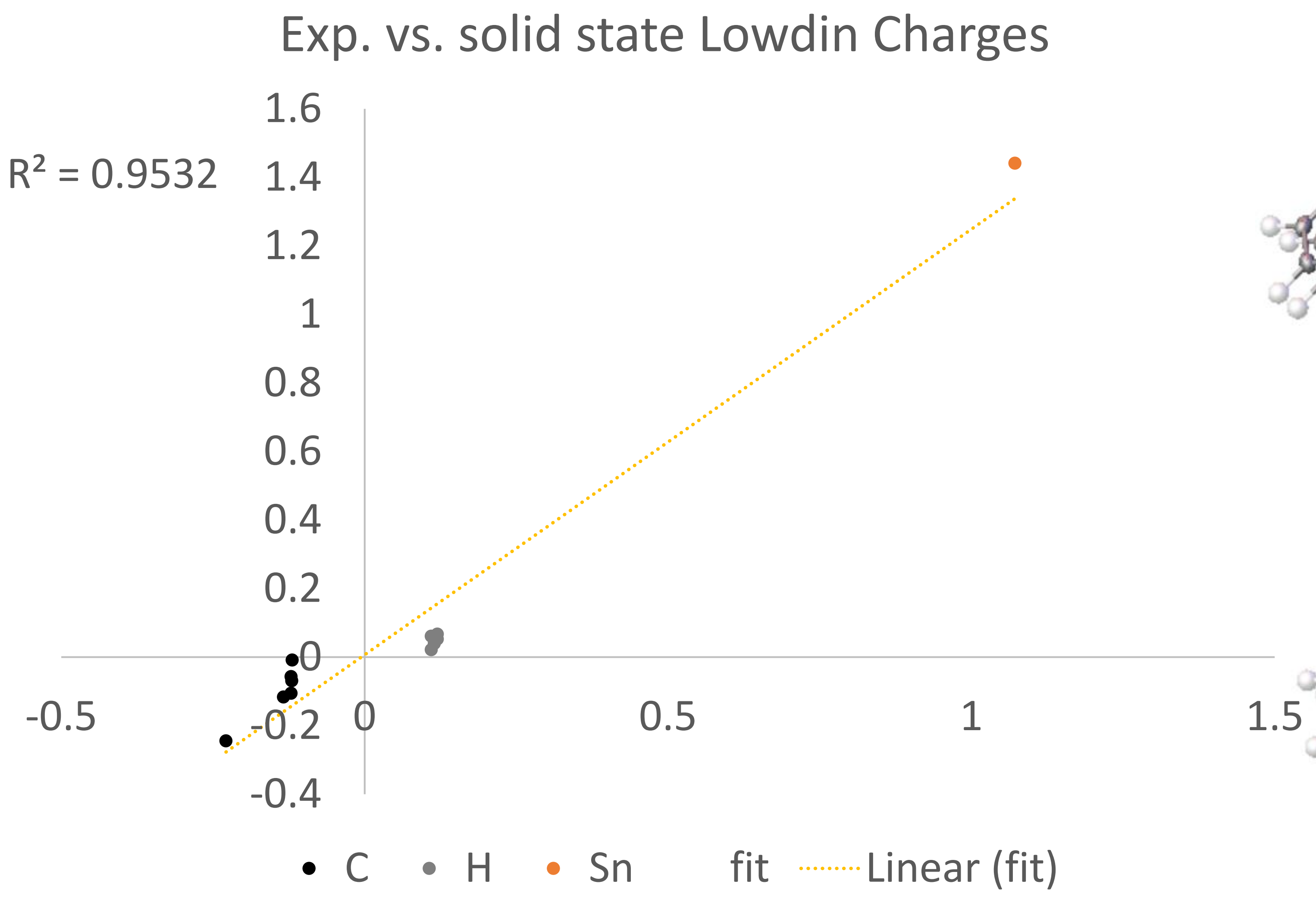


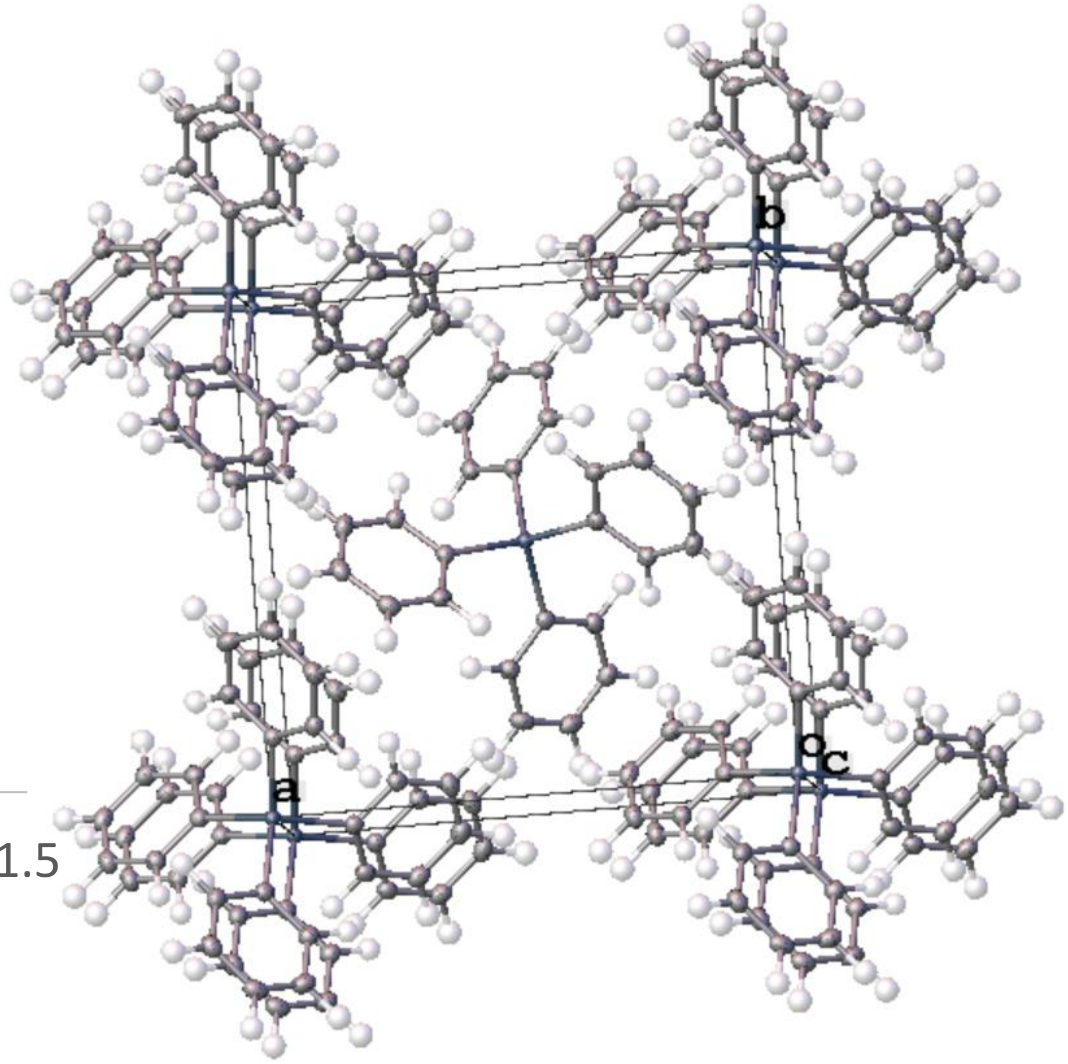
Good correlation



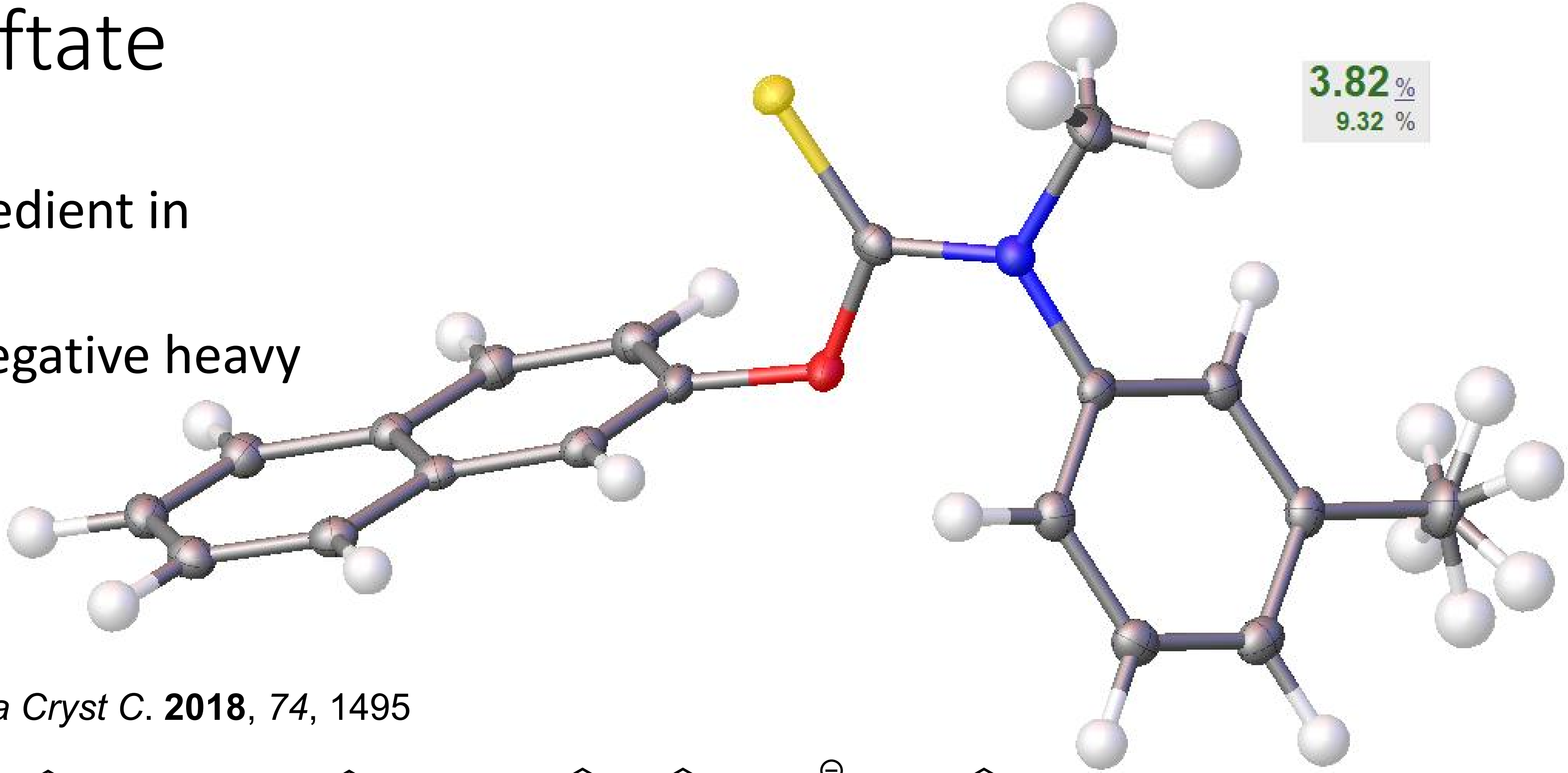


Good correlation also with solid-state charges



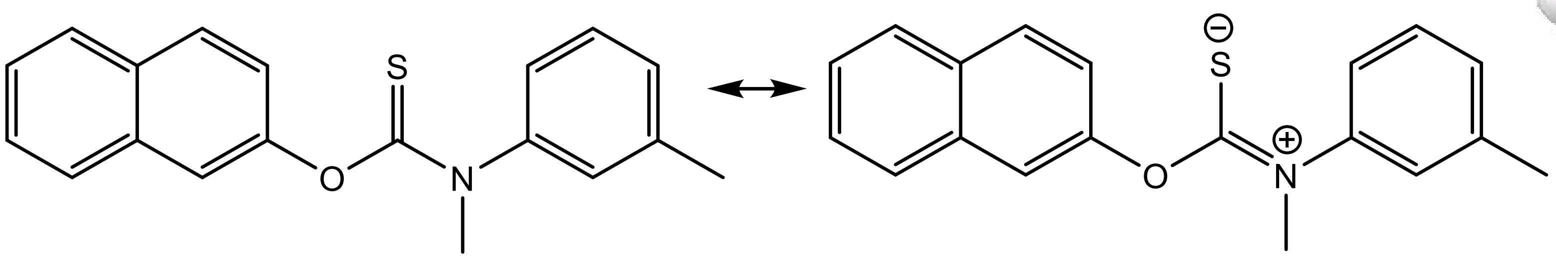


Tolnaftate



- Active ingredient in Tinactin
- Terminal negative heavy atom

Ho et al., *Acta Cryst C*. **2018**, *74*, 1495



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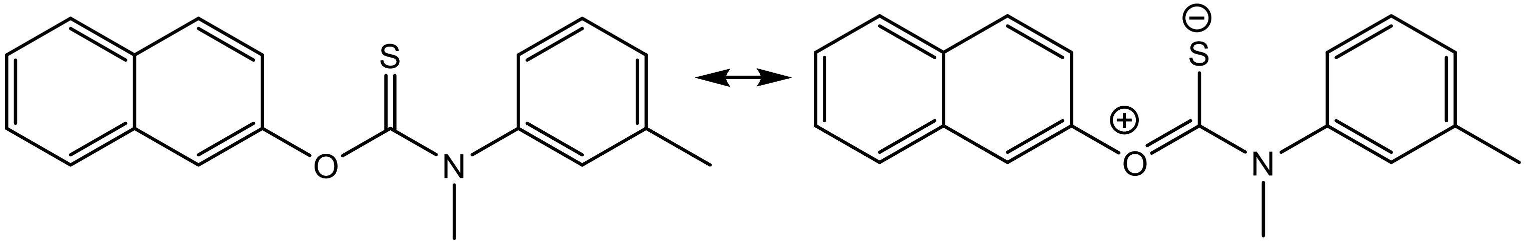
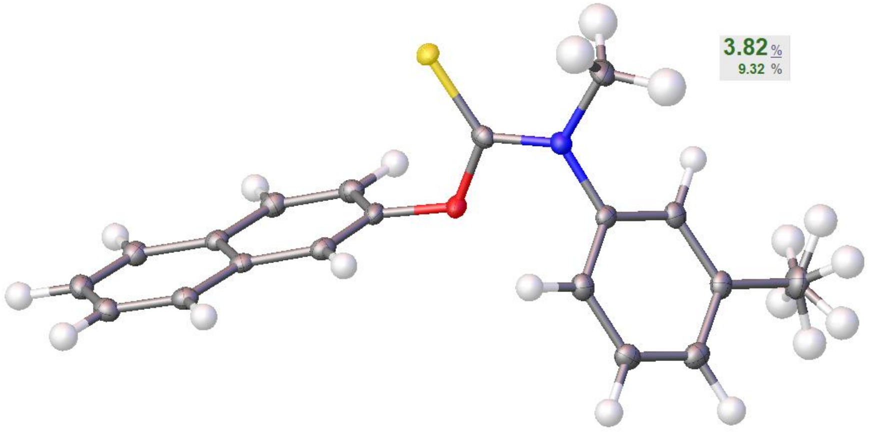
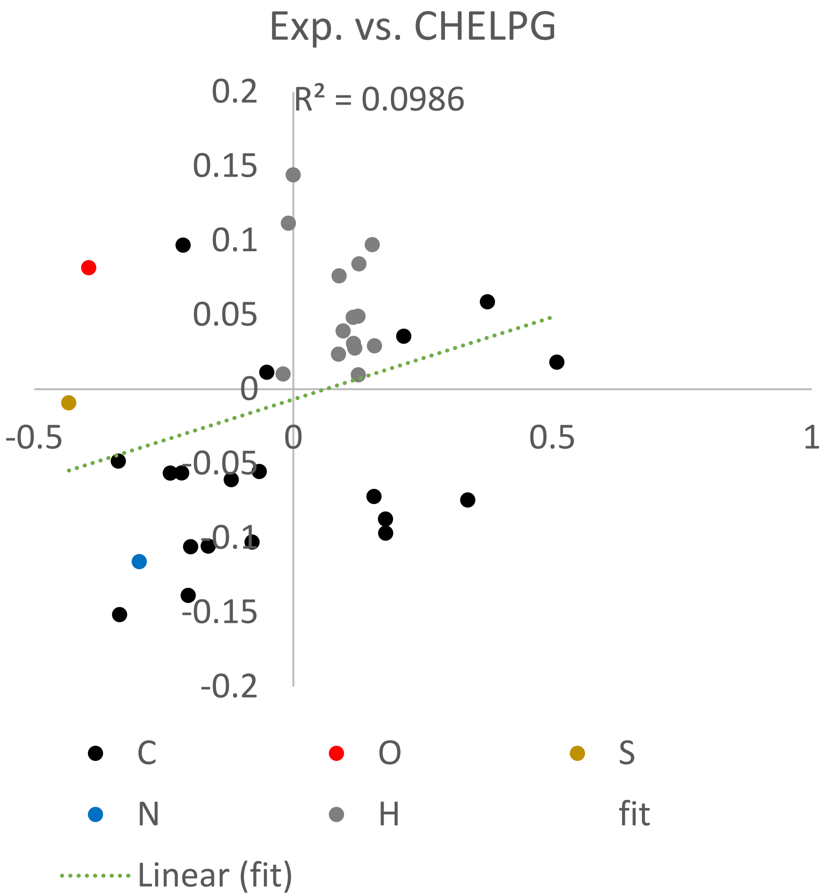


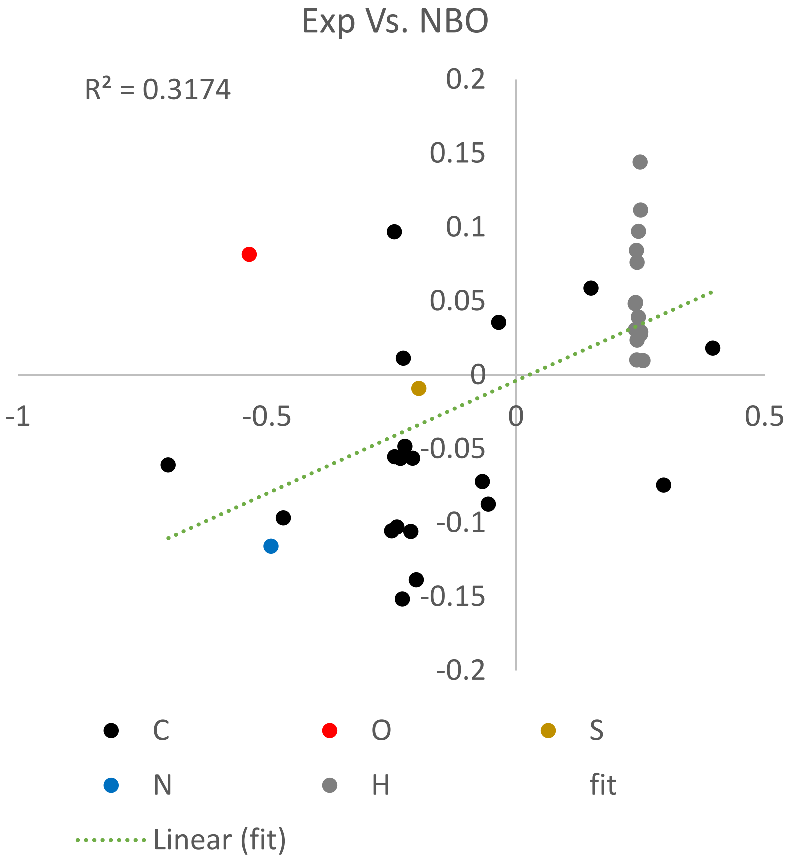
S
O
N
S
O
N



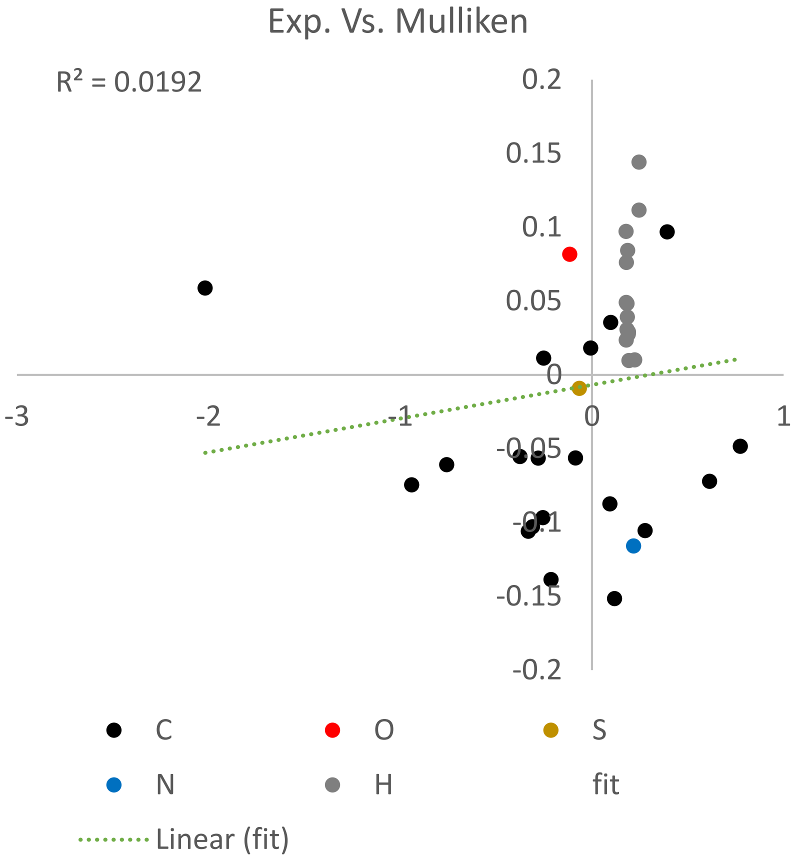
3.82 %
9.32 %



Exp. vs. CHELPG
R² = 0.0986
C
O
S
N
H
fit
Linear (fit)



Exp Vs. NBO
R² = 0.3174
C
O
S
N
H
fit
Linear (fit)



Exp. Vs. Mulliken
R² = 0.0192
C
O
S
N
H
fit
Linear (fit)

Conclusions from Studies of *p*-dimethylaminiopyridine

- Calculated atomic charges consistent from crystal to crystal and from test to test
- Higher resolution is best: idealy in the 0.7 Å range
- We can refine the occupancy and the thermal parameters of non-H atoms without correlation problems
- Probably best to tie the H *U*'s to neighbors
- Lengthening the C-H bonds to a more realistic distance has a minor effect on the charges; it increases their magnitude, and suppresses heteroatom charge, but gives better correlations.
- Terminal heteroatoms charge are underestimated without inclusion of Fourier difference "lone pair" electron density
- Qualitatively, charges are similar to theory (at least as similar as theories are to each other).

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1800105

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