香港中文大學
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Rethinking the Nature and Extent of Inductive Effects in Organic Compounds

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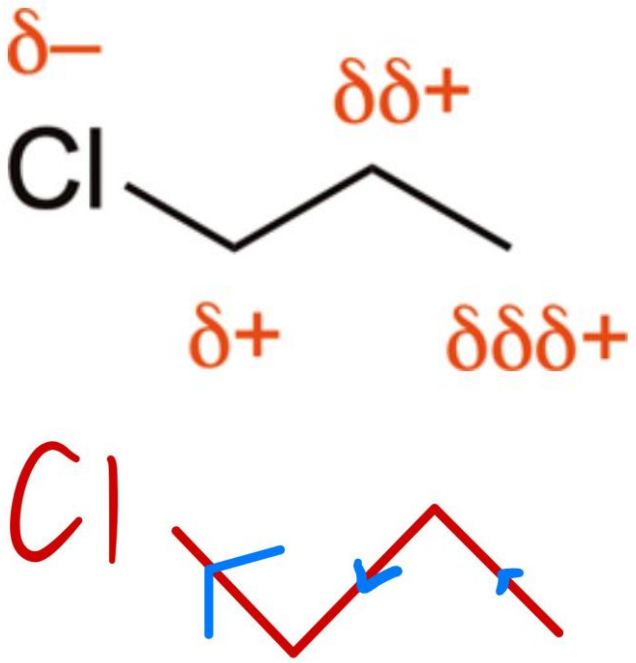
Reviewing Inductive Effect

Inductive effect review

- Introduced by Lewis in 1916
- Transmitted through a σ-bond frameworks and decreases with distance
- Polarizability was treated as “small correction” in early models
- Early models lacked quantum-chemical calculations of charges distribution
- IUPAC definition:
- Transmittion of charge through a chain of atoms by electrostatic interaction



Classic symbolic representation
Cl←CH2←CH2←CH3

Importance Of The Paper

- Taught in first year undergraduate courses:
- A cornerstone in chemistry
- Common presented in organic chemistry textbooks

Has clear implications for teaching

Teaching should reflect latest research data

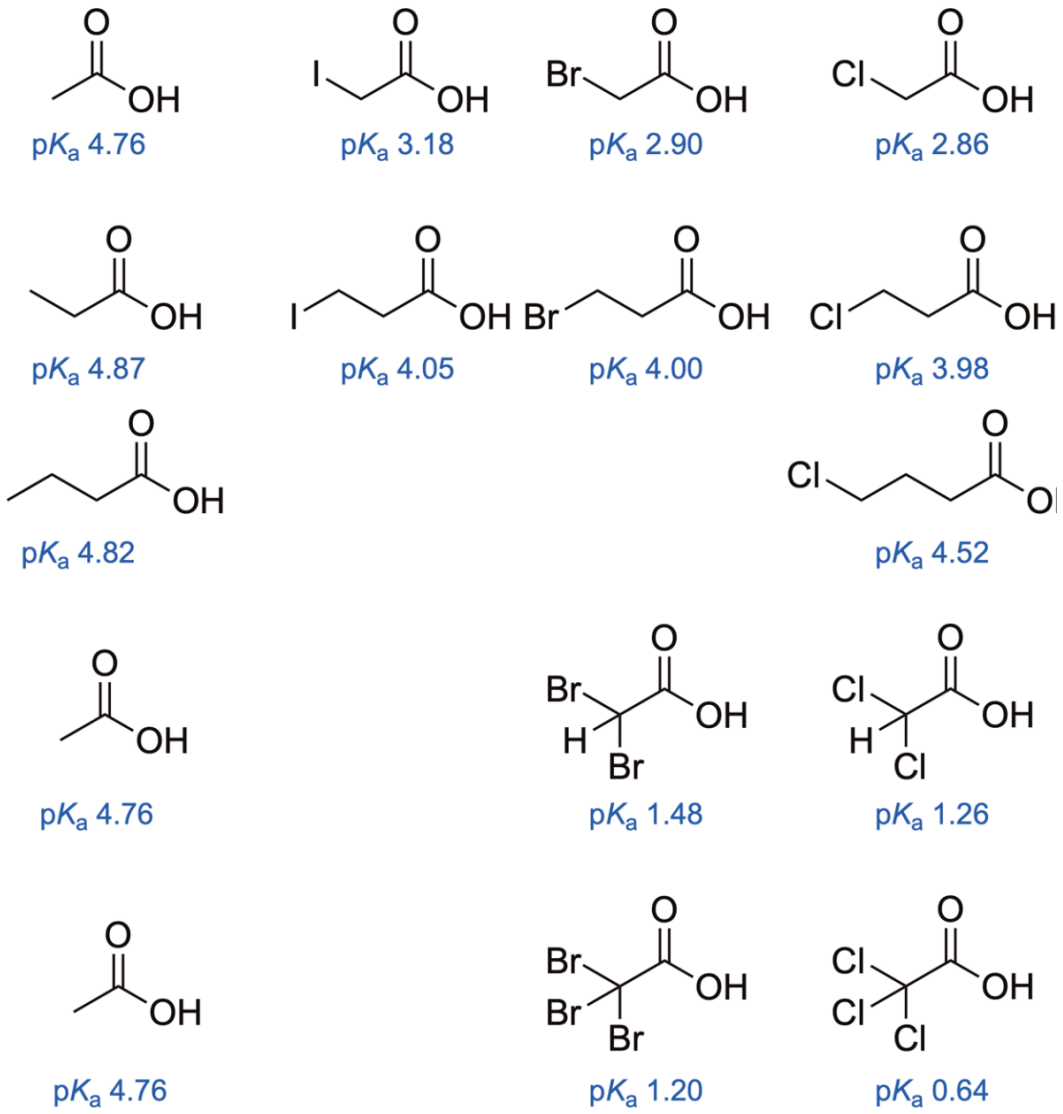
Common Textbook Claims

Inductive effects on pKa and acidity

- Halogenation makes carboxylic acid more acidic
- Greater number of halogens gives a larger effect

- Effect of inductive effect is larger for more electronegative elements (?)
- Closer halogen gives larger inductive effect (?)

Which is logically consistence to the experimental data(?)



es for representative (halo)carboxylic acids.

Contradiction of Inductive Effect

Morden research shows the gas phase acidities in trihaloacetic acids do not align with the inductive model

^{13}C NMR chemical shift of pentane, 1-chloropentane and 1,1,1-trichloropentane does not support simple long range bond-by-bond effect

Computed substituent parameters shows:
F, 0.364; Cl, 0.444; Br, 0.482,
which means Br > Cl > F in enhancement of acidity

Method Overview

Evaluating charge distribution in the molecule

Benchmark data based on the alignment of dipole moments from point charges with those from overall density

(2024)

Determinating charge distribution

- NPA charges (used mainly)
- Hirshfeld
- CM5 charges

Software and functional

DFT

PBEh1PBE functional

Orbital basis set:

aug-cc-pVTZ

Gaussian 09

Reason for selection

Balance between accuracy and computational cost

Neutral Aliphatic Molecules

- F shows the largest effect at C1
- C2 shows slight changes in the presence of F
- On or beyond C3, F shows no effect

Differences are small

Largest effect is near H1

Hyperconjugation matters

Main message:
In neutral molecules, the effect is short-range

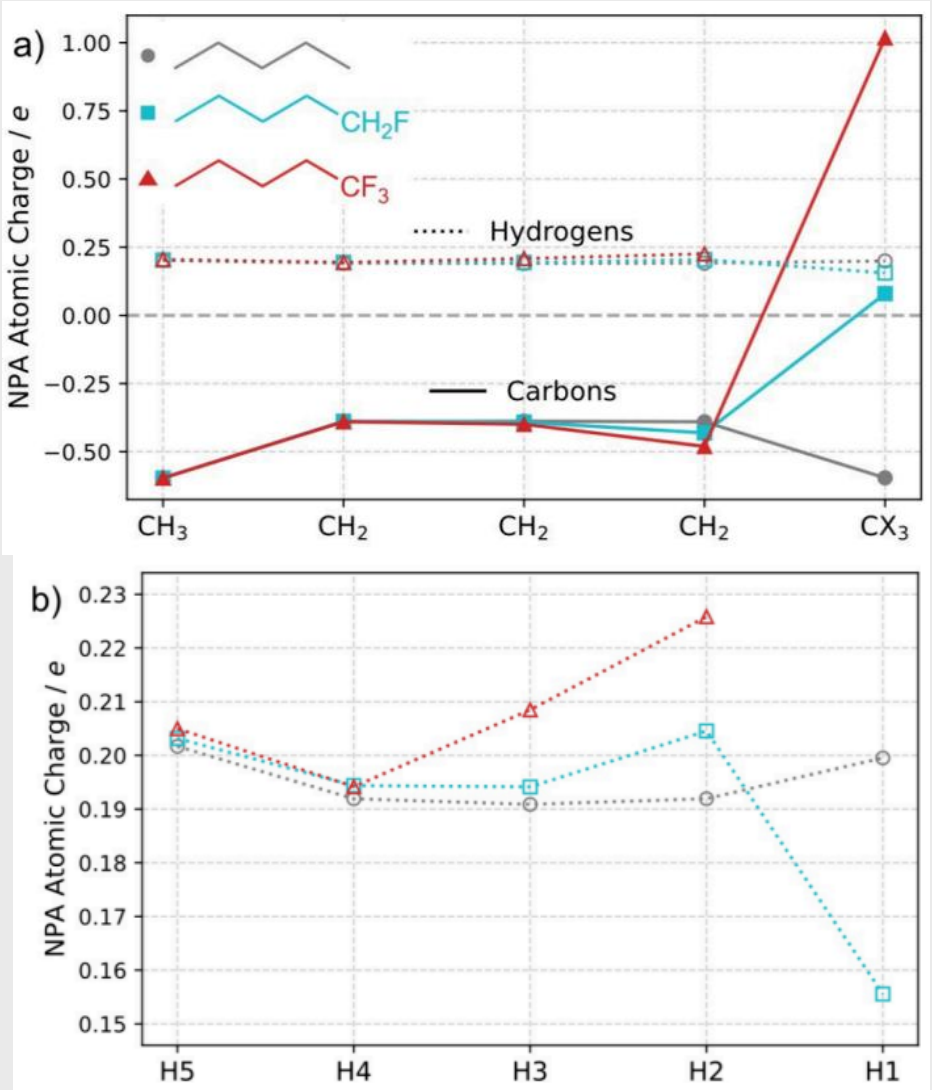


Figure 5. (a) NPA charges on hydrogen and carbon in pentane, 1-fluoropentane and in 1,1,1-trifluoropentane; (b) expansion of NPA charges on the hydrogen atoms along the pentane chains.

Why is C2 unusual?

Figure 6. Hyperconjugation resonance forms representing n to π^* anomeric-type interaction for 1-fluoropentane.

- C2 does not follow a simple inductive picture
- Hyperconjugation from an F lone pair makes C2 more electron-rich
- Obvious F > Cl > Br > H at C1 for inductive effect
- At C2, inductive withdrawal and hyperconjugation compete with each other
- Effect in C2: Br > H ≈ Cl > F
- Only Br appear shows inductive effect with smaller hyperconjugation effect

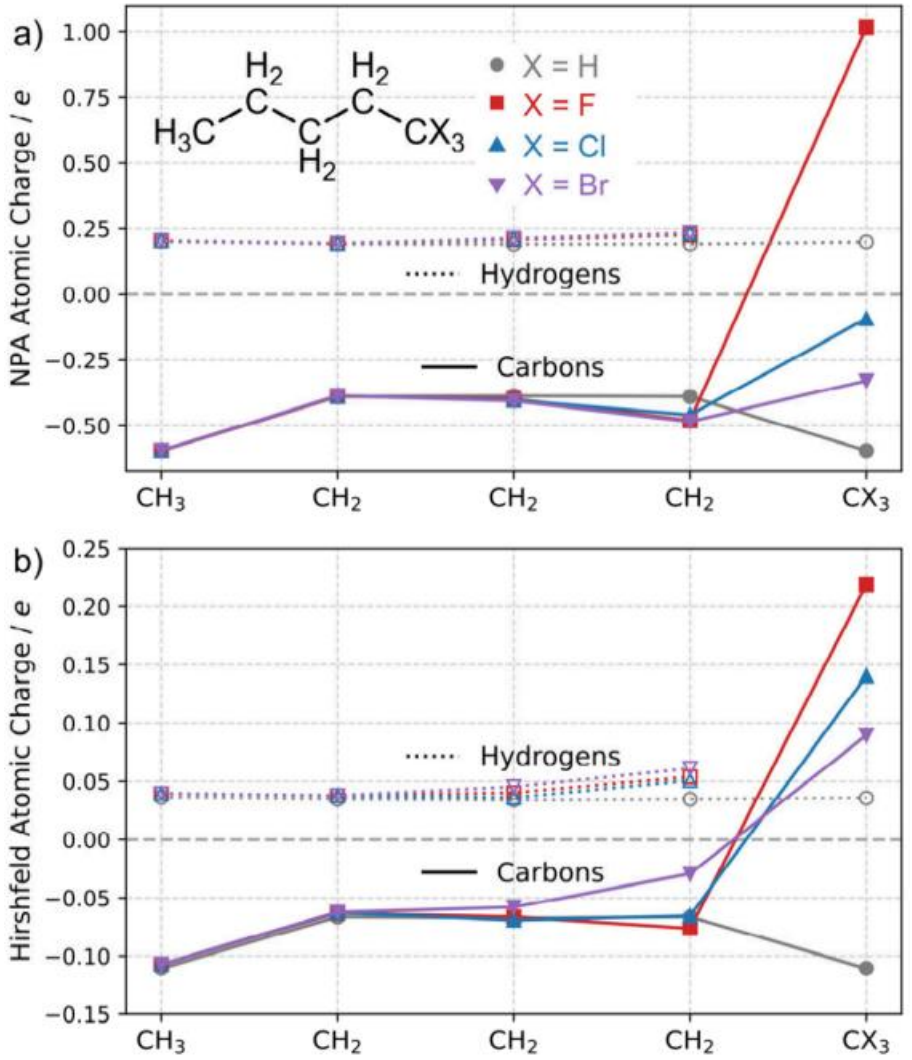


Figure 7. (a) NPA and (b) Hirshfeld atomic charges of trihalopentanes. Carbon (solid lines) and hydrogen (dotted lines).

Broader Neutral Examples

- 1-substituted pentanes with F, OH and NH_2
- The effects on C3-C5 are negligible
- Inductive withdrawal and hyperconjugation compete in C2
- Inductive strength: H > N > O > F

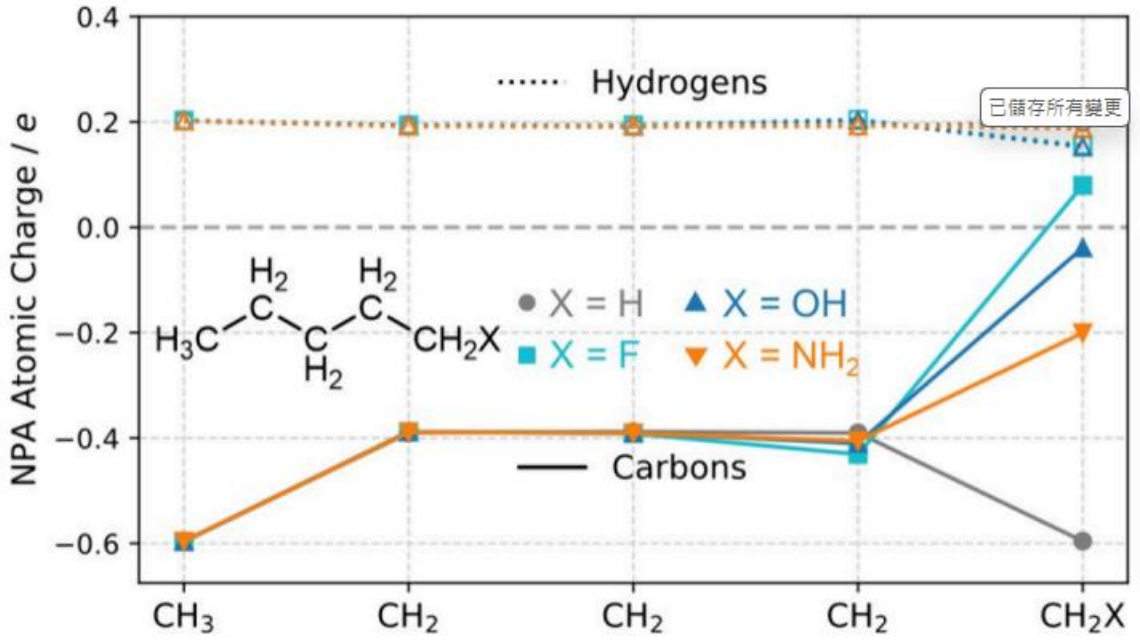


Figure 8. NPA atomic charges of 1-substituted pentanes. Carbon (solid lines) and hydrogen (dotted lines).

Electronegative elements in neutral compounds
No meaningful electronic effect beyond 2 bonds
Effects beyond one bond are small and complicated by hyperconjugation

Aromatic Case

The carbon charge in CF_3 shows same result as connecting

with sp^3 or sp^2 C

CF_3 exerts a net electron-donating effect at ipso-carbon, compared with CH_3, both in aliphatic and aromatic compounds

not what the textbook model would predict

A $+R$ contribution from fluorine appears to dominate rather than a simple $-I$ inductive effect.

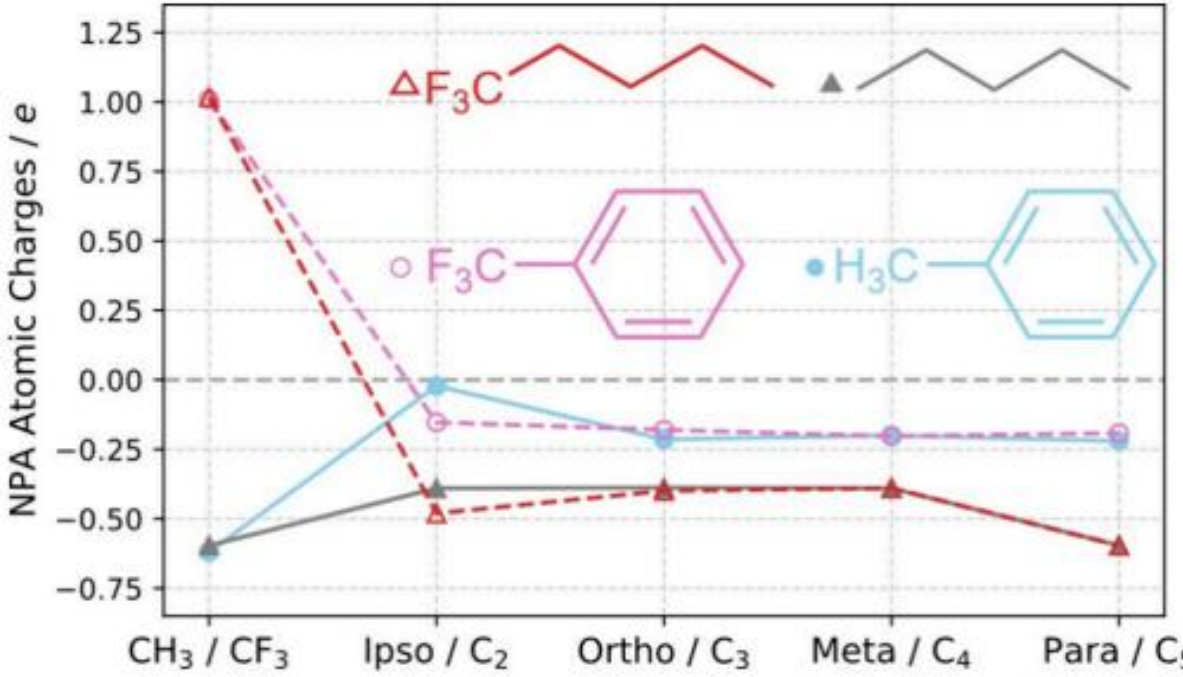


Figure 9. NPA atomic charges of trifluoro- and nonsubstituted pentanes and toluenes.

Charged System Behaves Differently

- Deprotonation forms carboxylate anion
- Charge stabilization matters
- Longer alkyl chains make the acid stronger
- Conjugate base is better stabilized by polarizability

Polarizability is a major explanation of acidity,

not just a neutral-molecule inductive effect

Table 1. Calculated Ionization Enthalpies (kJ mol^{-1}) for Selected Carboxylic Acids $X(CH_2)_nCO_2H$

	n =	X = H	X = Cl	X = F
Acetic	1	1451.4	1395.8	1408.2
Propanoic	2	1449.6	1406.8	1416.6
Butanoic	3	1447.6	1419.4	1425.4
Pentanoic	4	1444.2	1426.4	1430.4
Decanoic	9	1442.8	1433.7	1438.0

Key Surprise: Cl beats F in intrinsic acidity

Computed Ionization Enthalpies show chloroacids are more acidic than corresponding fluoroacids

⬇

Does not match explanation of “the most electronegative F must win”

⬇

Polarizability is more important than electronegativity

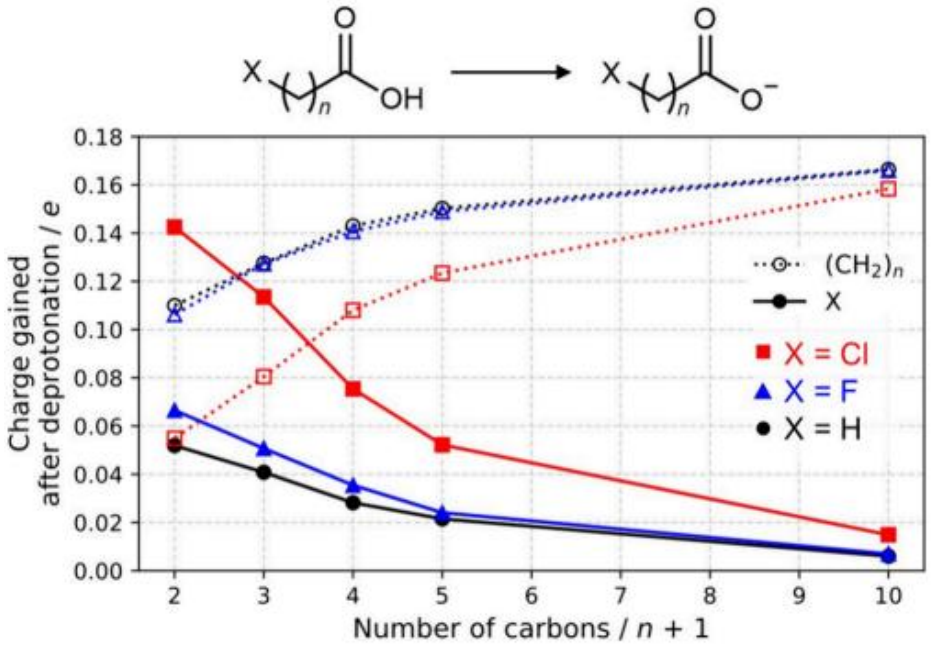


Figure 10. Change in NPA atomic charges of fluoro-, chloro- and nonsubstituted carboxylic acids. Dashed symbols show changes in charge of the alkyl chain $(CH_2)_n$ with solid lines showing the change in the charge of the substituent (X = H, F, Cl).

- Lower aqueous pKa of fluoroacids is mainly due to better solvation of the smaller carboxylate anion, not a stronger intrinsic inductive effect

Field Effect Considered

Old view: acidity change was explained by a through-space field effect from the C-X bond dipole

Problem: gas-phase results do not match the simple picture (Cl more acidic than F)

Carboxylate group and C-Cl bonds can effect each other through orbital polarization

Geometry also matters

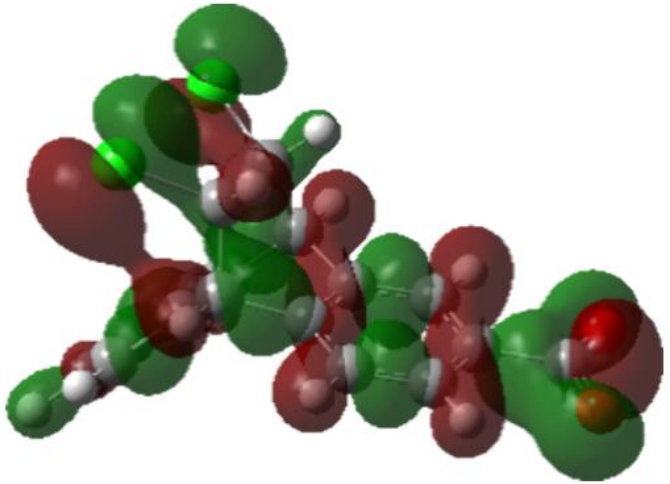


Figure 12. One of the molecular orbitals of anion **2a** showing that the orbital spans the molecule so that the charge on the carboxylate group will inevitably perturb the C−Cl bonds and *vice versa*.

MO of carboxylate anion

Acidity comparison

- Acidity depends on conjugate-base stabilization
- After deprotonation, Cl gains more negative charge than F and is more polarizable

1a is more acidic than 3a as the anion is better stabilized

Charges on the halogens, and amalgamated charges for the carboxylic acid/carboxylate groups are shown in the structures (**Figure S7**).

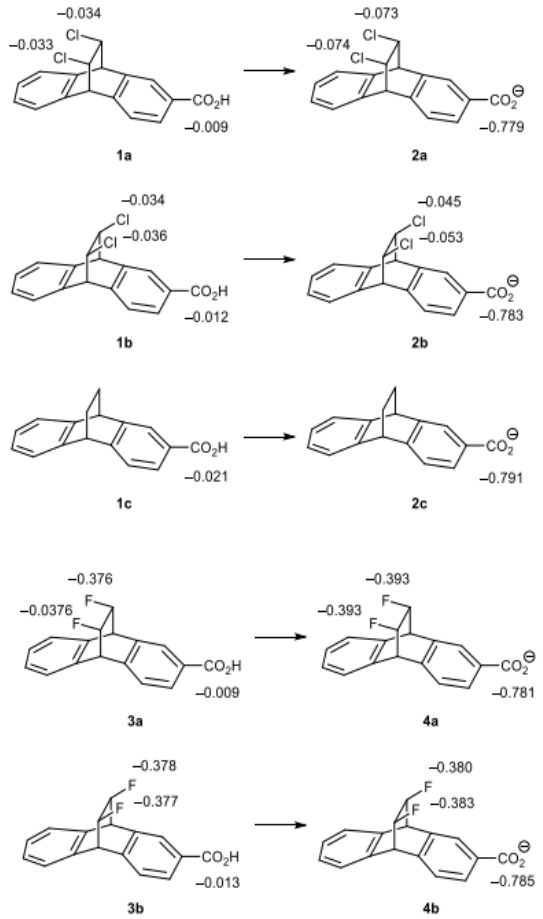


Figure S7. Calculated NPA charges for structures **1 – 4**.

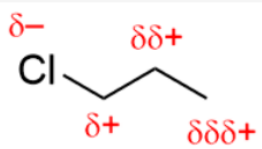
Upon deprotonation, Cl gains more negative charge than does F, although naturally F has a larger partial negative charge than Cl in both the carboxylic acid and the carboxylate.

What Should We Teach Instead?

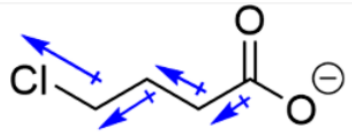
- In neutral molecules, inductive effects are mostly short-range
- The long bond-by-bond arrow diagram is too simple
- For acidity, it is better to focus on conjugate-base stabilization and polarizability when needed

Conclusion

- In neutral molecules, the inductive effect is mainly short-range
- Long-range acidity trends are not well explained by simple bond-by-bond inductive model
- In charged systems, polarizability is often more important than electronegativity alone
- Some textbook explanations of halogen effects need to be updated



no meaningful polarization beyond one bond



no evidence for bond dipoles attenuated by each bond

Bond polarization effects in neutral molecules are short range.

Charge stabilization longer range and best viewed as orbital effect.

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Q & A session

Thank You