

University of Nebraska - Lincoln

DigitalCommons@University of Nebraska - Lincoln

Faculty Publications -- Chemistry Department

Published Research - Department of Chemistry

7-15-2021

Aromatic Substitution: Another View

Charles A. Kingsbury

Follow this and additional works at: <https://digitalcommons.unl.edu/chemfacpub>

 Part of the [Analytical Chemistry Commons](#), [Medicinal-Pharmaceutical Chemistry Commons](#), and the [Other Chemistry Commons](#)

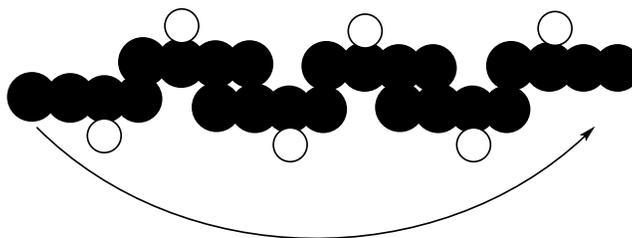
This Article is brought to you for free and open access by the Published Research - Department of Chemistry at DigitalCommons@University of Nebraska - Lincoln. It has been accepted for inclusion in Faculty Publications -- Chemistry Department by an authorized administrator of DigitalCommons@University of Nebraska - Lincoln.

Aromatic Substitution: Another View

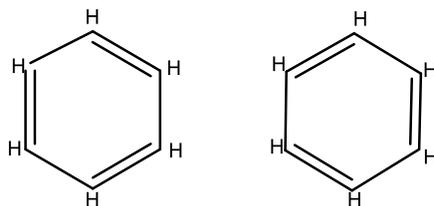
Charles A. Kingsbury
Department of Chemistry
University of Nebraska – Lincoln 68588-0304
Email: ckingsbu@gmail.com

Abstract: Electrophilic substitution on substituted benzenes is reviewed in terms of molecular orbitals. The HOMO falls into two classes. For all meta director C-X groups, a node passes through the ring and through the substituent C-X bond. With ortho/para director C-X groups, a node perpendicular to the one described above, passes through the ortho-meta bonds.

Early chemists struggled to find ways of representing organic molecules. Kekule originally used images resembling “sausages” to represent carbon, with bumps in contact between sausages to represent covalent bonds,¹⁻³ Even so, this was an advance. Mende’ev, did not show a single chemical structure in his seminal text of the same era.⁴ Archibald Couper and Alexander Crum Brown were among the first to use simple lines to represent chemical bonds, and that has been preserved in chemical thinking to this day.⁵⁻⁷ Kekule himself represented benzene as a hexagon with alternating single and double lines for bonds following his famous dream.³



Benzene in the early style of Kekule



Later Kekule benzene

In the 1910's and 1920's, G.N. Lewis experimented with cubes in edge contact to represent chemical bonds, but proceeded to electron dot methodology.⁸ Lewis structures are used to this day in chemical education.^{7,8} Resonance theory was developed about the same time or slightly later.¹⁰ “Valence bond” quantum theory was another major development.¹¹⁻²⁰ Valence bond theory retains its

influence today with authoritative contributors.²¹⁻²³ Undergraduate texts continue to use using Kekule's hexagon and the pronouncement that benzene is a "hybrid" of two (or more) of these structures.²⁴ According to valence bond theorists, these structures do not have objective reality (i.e. demonstrable independent existence).²¹⁻²³ In the minds of undergraduates, the "objective reality" or its absence is all too often replaced by "naïve realism."^{26,27}

For undergraduates, the analogy is often used that a mule is a hybrid of a horse and a donkey, not a horse some of the time and the donkey the rest of the time.²⁴ Undergraduates say that if people wish to represent a mule, they do just that; they do not show two irrelevant precursors. The answer is, of course, that there is no adequate valence bond representation of benzene that is usable in undergraduate courses. Later, a circle was added to the benzene structure to represent electron delocalization in the ring.²⁵ The phenomenon of nmr ring current in aromatic molecules shows that electrons do circulate if it had ever been doubted.²⁸

Substituents on the benzene ring further complicated the situation. Additional resonance structures are added to Kekule's benzene to show electron donation or withdrawal, i.e. more horses and donkeys for the undergraduate. English scientists advanced the curved arrow formalism that is heavily used today.^{29,30} "Curved arrows" are used as tokens to show electron enhancement or removal from certain positions of the benzene ring. These are useful but are not universally appreciated.³¹ Most instructors warn the class that "curved arrows" have little intrinsic significance in-and-of themselves.

Benzene with electron donating groups uniformly gives more ortho and para electrophilic substitution products. The meta product is usually minor. Curved arrows are used to show that the ortho and para positions are enriched in electron density by resonance. Alkyl benzenes do not fit the "curved arrow" methodology very well. Instructors must invoke hyperconjugation to achieve an explanation of experimental results, i.e. high levels of ortho and para substitution products.³²⁻³⁴ Students are bothered by the necessity of leaving hydrogen dangling out in space in hyperconjugative resonance structures.^{35,36}

Halogen substituents X are overall "deactivating" presumably because, it is said, of the inductive effect of the electronegative halogen. However, they are ortho/para directing because resonance returns electron density to the ortho and para positions. Overlap of the benzene ipso carbon p orbital with bromine or iodine 4p or 5p orbitals would not be likely. The oxygen of phenol or anisole should have a stronger inductive effect than all halogens except fluorine, yet the oxygen is o/p directing and activating. The dipole moment of phenol (1.53D) is scarcely less than propan-2-ol (1.69D), although the differences might be interpreted in terms of bond distances.³⁷ So the resonance effect of delocalized oxygen electrons has little effect upon dipole moment. Nitrobenzene is less reactive than benzene due, it is said, to a combination of inductive electron withdrawal from every position, and resonance electron withdrawal specifically from ortho and para positions. The dipole moment of nitrobenzene (4.22D) is substantially larger than that of 2-nitropropane (3.76D).³⁷

Other problems remain: trifluorotoluene is deactivated and CF₃ is meta directing. If the inductive effect of the CF₃ group were dominant, the meta position should be less reactive than para. However, trifluorotoluene is said to have "no-bond" resonance which places additional positive charge density on ortho and para positions, rendering these positions less reactive than meta. "No bond resonance" leaves a fluoride dangling in space. Valence bond theorists emphasize that these and other resonance structures are not an actual entities. The average undergraduate is left with the impression that "what is displayed is not real" is more like politics or religion than science. The problem has been

recognized before, and some reconciliation has been suggested, with reference to Pauling.³⁸

Ingold advanced the “electromeric effect” to explain the response of certain substituents to the approach of the electrophile. Ingold stated the existence of “temporary polarization effect simulated by the electrophilic reagent.”³⁹ Kovacic and Hiller have given evidence for coordination of the electrophile with substituents on the aromatic ring.³⁴ Kovacic and Hiller show mechanisms whereby the complexed group migrates from the complexed aromatic substituent X to the ipso position and then to the ortho position. Kovacic shows a pi complex of the migrating group, or a bridged (covalent) structure. Complexation with the electrophile would be unlikely in the case of toluene ($X=CH_3$) where mostly ortho product is found in nitration.^{33,34,39}

Olah and coworkers found evidence for an array of encounter or pi complexes of the NO_2^+ electrophile with the ring (essentially in the gas phase).⁴⁰⁻⁴² However, this array of complexes would be problematic in solution. However, the literature confusion due to nitrosation followed by oxidation was considered, in some detail.^{40,43} Olah and coworkers consider a three-stage mechanism: (1) formation of the complex of $^+NO_2$ with the aromatic ring, (2) a SET (single electron transfer) process from the ring to $^+NO_2$, and (3) collapse to the classical σ complex, i.e. the “Wheland intermediate”, followed by a rapid loss of H^+ .^{10,33} Solvent or dielectric constant effects were not considered. The energetics for these gas phase reaction steps seemed rather low. For example ΔE for (gas phase) reaction with benzene is -7.9 kcal, whereas with the deactivated fluorobenzene the energy was -8.9 kcal. The SET process itself may have an energy requirement as low as 3.3 kcal. The SET process is not considered likely for highly deactivated aromatic substrates such as nitrobenzene. Kochi also emphasized pre-association followed by SET.^{44,45} The SET general process was postulated early on by a number of workers.⁴⁶

Feng, Zheng and Zerner reviewed earlier work on aromatic substitution in a highly informative manner (which see).⁴⁷ They carried out a computational study of aromatic nitration, including configuration interaction effects. Their thesis is that electron transfer (later termed SET) from toluene or xylene to the nitronium ions, followed by radical recombination to afford the classical σ complex. The situation is unclear for benzene itself. Deactivated aromatics evidently proceed by the classical mechanism. This is one of the few studies that considered solvent or dielectric constant effects. Higher dielectric media stabilize NO_2^+ thus reducing the likelihood of electron transfer from the aromatic system to NO_2^+ . Xylene is considered to undergo predominant ipso attack. Feng, et al considered the electron transfer mechanism in toluene and xylenes to account for the ortho/para ratios.⁴⁷

Classical resonance theory does an acceptable, if cumbersome job in accounting for substituent effects in aromatic substitution. Does a molecular orbital approach offer any simplification?

Mechanism of Substitution

Table I lists the HOMO eigenvalues for various aromatic substituents X. Either a two-electron (the classical mechanism) or a one-electron (SET) process would be initiated from these frontier orbitals.^{48,49} Note that these eigenvalues parallel reactivity in electrophilic substitution quite closely. Substituents to the left of fluorine are meta directors.

Table I
Aromatic Substituent X
Ground State Eigenvalues for HOMO, **H**

NO ₂	SO ₃ H	CF ₃	COOH	F	Cl	H	SCH ₃	CH ₃	OH	N(CH ₃) ₂
-0.370	-0.365	-0.357	-0.350	-0.34	-0.35	-0.335	-0.326	-0.322	-0.317	-0.294

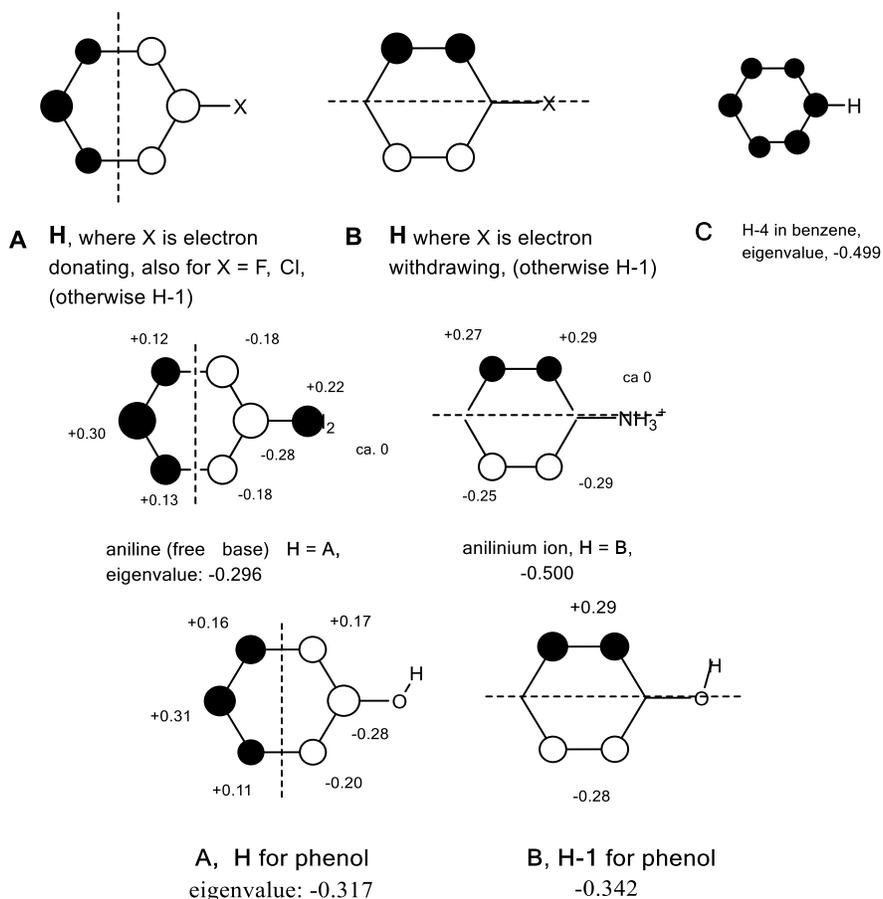
In trifluoromethoxybenzene, the eigenvalues (**H** -0.357, **H-1** -0.358) are almost the same. It would be interesting to see if all products, ortho, meta and para, occur in electrophilic substitution. (**H-1** is the orbital lying just below the HOMO **H**). An inexplicable point occurs for the sulfur analog of anisole. Sulfur is less electronegative than oxygen, yet thioanisole shows lower values for both **H** (-0.326), and **H-1** (-0.342) than anisole (**H**, -0.311, **H-1**, -0.339), or even toluene (**H**, -0.322) implying less reactivity. Obviously there is much yet to be learned.

Scheme 1 covers predictions from orbital coefficients derived from the pop = reg option of the Gaussian system, for formation of the classical σ complex. Scheme 2 covers coefficients from aromatic radical cations, i.e. the SET intermediate.⁵⁰

How does electrophilic substitution occur? Norman and Radda have postulated a ground state dominance for highly reactive electrophiles but a σ complex dominance (and presumably the transition state leading to the σ complex) for lesser reactive electrophiles.⁵¹

For the classical mechanism, the electrophile will directly form a sigma bond to the ring carbon to form the σ complex intermediate. To do this, formally it will require a pair of electrons. Where can the electrophile find these electrons? The aromatic ring has, say, 21 pairs of electrons (in benzene itself). Some are 1s type electrons in low lying orbitals, which can be ignored. Others are associated with C-H and C-C bonding in the benzene x/y plane. For benzene, about nine additional orbitals may be discounted. The leading candidates seem to be **H** and **H-1** (cf. Scheme 1), which fortuitously also have the correct geometry. These extend in the z direction from which the electrophile must approach. These should be the most reactive toward the electrophile on a basis of high energy, consistent with frontier orbital theory.^{48,49} Another potentially significant orbital is **H-4** in benzene (cf. **C**), although its low energy is less favorable. "Electron withdrawing substituents" like nitro or various carbonyl groups lower the HOMO energy, (cf Table I). "Electron donating" (by classical resonance) substituents, e.g. the OH of phenol, the NR₂ of anilines, or alkyl substituents seem to raise the orbitals energy level, although their behavior is quite complex. Scheme 1 illustrates the molecular orbital coefficients.^{52,53} The drawings are locally made and given for rough illustration purposes only.

Scheme 1
Substrates for Classical Electrophilic Substitution.



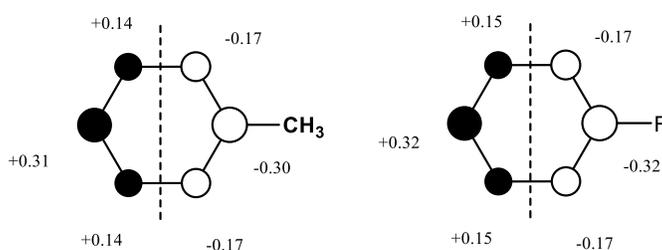
Aniline and anilinium ion afford useful examples. The anilinium nitrogen should withdraw electrons by virtue of its positive charge. The nitrogen of the aniline free base should be electron donating, by present conventional resonance theory. The positively charged nitrogen in anilinium ion renders the HOMO as **B**, and should be a meta director. Aniline itself gives **A**, and should be an o/p director. The nitrogen itself shows a remarkably low coefficient

For phenol, the HOMO orbital (eigenvalue -0.317) is of the **A** class and **H-1** much lower (-0.342). Why the highest occupied molecular orbital, **H**, lies above that of benzene (**H** -0.335), despite the electronegativity of oxygen and **H-1** lies lower, is not understood at present (anisole is similar). The most reactive positions of phenol should be para and ipso. However, the relative energetics for formation of the ipso σ complex is 28 kcal less stable than the para σ complex. [The electrophile is H^+ in these trials]. The σ complexes at the ortho and meta positions of phenol are 2.8 and 17 kcal less stable than para. If solvent effects were studied, these energy differences would be modified. Szabo, et al. investigated solvent effects.⁵⁴ In nitration in solution, phenol forms 60-70% para product, and 30-40% ortho, and ca. 3% meta.³⁴

For toluene the differences are: the ipso σ complex is 7.2 kcal less stable than the para σ

complex. The ortho σ complex is 0.86 kcal less stable than para, and meta, 4.1 kcal less stable. Solvent effects were briefly investigated. Using the Onsager model at ϵ 78, (H^+ was the presumed electrophile), the results were very similar to the above. Where Cl^+ is the assumed electrophile, the ipso σ complex is 3.8 kcal less stable than the ortho σ complex and 4.1 kcal less stable than para. Kovacic and Hiller give 35% para and 62% ortho in chlorination.³⁴ For Friedel Crafts alkylation (with $^+CH_3$ as the presumed electrophile), the ipso σ complex is 4.5 kcal less stable than the ortho σ complex, and 5.6 kcal less stable than the para.

For fluorobenzene, the differences seem more pronounced. The ipso σ complex is 16.2 kcal less stable than para. The ortho σ complex is 2.3 less stable than para (with H^+ as electrophile). With the putative Cl^+ as electrophile, the ipso σ complex is 13 kcal less stable than para and 9 kcal less stable than ortho. In **all** cases studied, the ipso σ complex was substantially less stable.

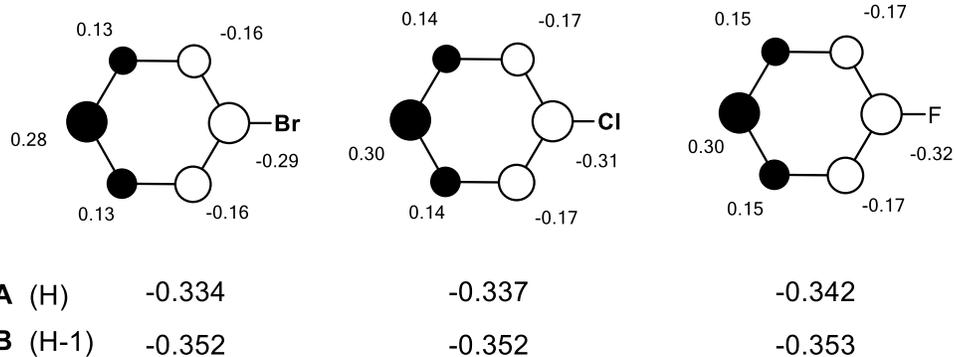


Yet, formation of the ipso σ complex must occur in certain cases. Ipso attack does occur in *t*-butylbenzene and trimethylsilylbenzene where replacement of *t*-butyl and trimethylsilyl groups, by the electrophile occurs.⁵⁵ Perrin and Skinner were among the first to emphasize ipso attack in electrophilic substitution, followed by Kovacic.^{36,57-61}

So why would an electrophile form the ipso σ complex when the energetically more favorable ortho σ complex (and transition state) would be less than 2 Å distant? In view of the relatively high ipso coefficient in **A**, the electrophile may initially interact favorably with the ipso position of the aromatic ring, but the reaction does not pass over the high transition state energy to form the unstable ipso σ complex. Much depends upon how specific the transition state is leading to the σ complex. At some point, the approaching electrophile may migrate from near ipso over to the ortho position where the barrier to the σ complex is less unfavorable. This would be similar to the mechanism described by Kovacic.³⁴ A fundamental question is whether bonding (or antibonding) in the approach to the transition state is specific or diffuse. Theoreticians speak of intersecting potential energy surfaces, and their consequences in some detail. The number of references is too numerous to list.⁶³⁻⁶⁷

Since **A** shows every ring position seems to have a favorable coefficient, yet little meta substitution product is formed. It is possible that the meta position is attacked by the electrophile, but the high transition state energy leads to a shift to the ortho or para position.

Electronegative substituents seem to lower many eigenvalues especially for **A**, but seem to have a relatively small effect on orbitals such as **B** where the node passes through the C-X bond. Some evidence of the effect of electronegativity occurs for the halogen substituents. The electronegativity order is, of course, $Br < Cl < F$. Note that the eigenvalue for **B** is roughly constant, but that of **A** diminishes quite significantly.



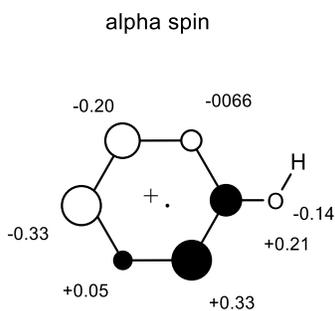
Electronegative substituents X may cause an inversion in which **A** drops to **H-1**. For example, benzoic acid/or benzaldehyde give **B** as HOMO at-0.352. **A** is lower in energy at-0.356. Since **B** is then the frontier orbital, meta electrophilic substitution occurs.

SET Mechanism

Feng, Zheng and Zerner carried out a sophisticated computational study of aromatic nitration, including configuration interaction effects.⁴⁷ Their thesis is that electron transfer (SET) is the dominant process for toluene and xylene, followed by radical recombination to afford the classical σ complex. The situation is unclear for benzene itself. Deactivated aromatics evidently proceed by the classical mechanism since electron transfer from the aromatic to NO_2^+ is unlikely.. This is one of the few studies that considered solvent or dielectric constant effects. Higher polar media stabilize NO_2^+ thus reducing the likelihood of electron transfer from the aromatic system to NO_2^+ . Xylene is considered to undergo predominant ipso attack. Feng, et al considered the electron transfer mechanism in toluene and xylenes to account for the ortho/para ratios.

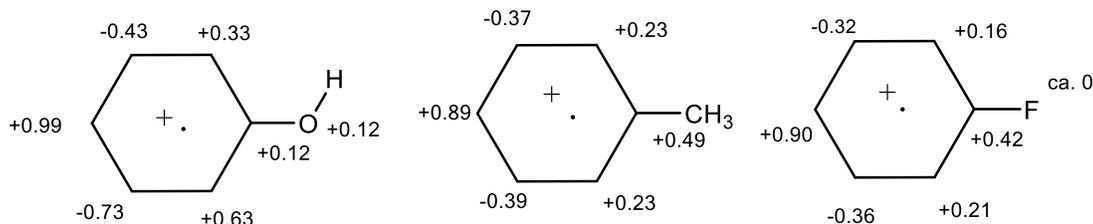
Olah and coworkers found evidence for many initial pi complex(s) in aromatic nitration, as did Politzer, et al.^{40-42,61} Olah and coworkers consider a SET process also to be dominant in nitration. The SET process may have an energy requirement as low as 3.3 kcal and decomposition of the SET complex to the conventional σ complex is of the order of 7 kcal. Szabo, et al., also predict a low energy requirement, but a sensitivity to solvation.⁵⁴ The SET process is not considered likely for highly deactivated aromatic substrates such as nitrobenzene, although halobenzenes are thought to afford this intermediate.

Scheme 2
Coefficients of the HOMO for Aromatic Radical/cation:



For phenol, orbital coefficients predict ortho/para substitution admirably. For toluene or fluorobenzene radical cations, the images resemble **B** in Scheme 1, and predict **no** para product. Orbital coefficients thus seem of no value for the SET path.

Previous workers used Mulliken total spin density rather than HOMO orbital coefficients.⁴⁷ This presents quite a different picture. In particular the high spin density in the para position for X= CH₃ and X=F suggest high reactivity at that position. For toluene, the total spin density vs. experimental results data are less in accord, unless ipso attack followed by rearrangement, as favored by Kovacic, is invoked.³⁴ Fluorobenzene, which yields 87% para, seems to fit the SET radical pair prediction fairly well.



Final Notes:

The SET mechanism of nitration indeed appears to be quite viable, but additional studies of the effects of higher dielectric constant would be useful. Returning to the two electron mechanism briefly, the use of molecular orbital coefficients shows several interesting features. However for activated substrates that react through **A** of Scheme 1, the question remains why the incidence of meta product does not equal ortho product. As indicated above, it may be a crossing potential energy effect leading to the transition state. Meta attack may occur, but the reaction may not pass over the higher transition state barrier to proceed to product. Similarly, for deactivated substrates that react via **B** (Scheme 1) equal amounts of meta and ortho products might be expected, but ortho is disfavored for similar reasons. So, as explained before, additional studies of crossover from one path to a lower energy path would be advisable.

In general, the treatment of this paper awaits a more sophisticated analysis than provided herein. The classical resonance theory treatment of electrophilic substitution will probably remain dominant for undergraduate education despite its cumbersome character, and unfortunate language.

Computational Details

All calculations were performed using Gaussian 03 at the mp2/6-31+G(d,p) level.^{68,69} The images of the HOMO levels provided by Gaussview were somewhat misleading, and are not emphasized in this paper. The data from the pop=reg calculation option were used instead. Frequencies were not always determined. Various "solvent" calculations were tested, e.g. dipole, PCM and SCIPCM, but these suffered convergence problems. The data reported are single point calculations using previously optimized structures at the mp2 level.

References

1. A. Kekule', *Ann. der Chemie und Pharm.*, 1858, 106, 129-159.
2. A. Kekule', *Ann. der Chemie und Pharm.*, 1857, 104, 129-150.
3. A. Kekule', *Chemisches Ber.*, 1890, 23, 1302-1310.
4. D. Mendele'efe, "*The Principles of Chemistry*," English edition, "*A library of Universal Literature*," Part I, vol. 25. P.F. Coller and Son. Other volumes may have shown chemical structures, but these were not available to this writer.
5. A. S. Couper, *Comptes rendu*, 1858, 46, 1157-1160.
6. A.S. Couper, *Annales de chimie et de physique*, 1858, 53, 469-481.
7. A. Crum Brown, *Transactions of the Royal Society of Edinburgh*, 1864, 23, 707-720.
8. G.N. Lewis, *J. Amer. Chem. Soc.*, 1916, 38, 762-785.
9. G.N. Lewis, "*Valence and the Structure of Atoms and Molecules*," Chemical Catalog Co., New York, 1923.
10. G.W. Wheland, "*The Theory of Resonance and its Applications to Organic Chemistry*," Wiley, New York, 1944, and references cited.
11. C.A. Coulson, "*Valence*," Clarendon, Oxford, 1961
12. L. Pauling, *J. Am. Chem. Soc.*, 1932, 54, 3578 -3582.
13. L. Pauling, *J. Am. Chem. Soc.*, 1932, 54, 968-1003
14. L. Pauling, "*The Nature of the Chemical Bond and the Structure of Molecules and Crystals*," Cornell University Press, 1939.
15. L. Pauling, *Nature*, 1987, 325, 396.
16. D.L. Cooper, J. Gerratt, M. Raimondi, *Nature*, 1986, 323, 492-493..
17. R.P. Messmer, P.A. Schultz, *Nature*, 1987, 329, 492-492.
18. J. U. Gerratt, M. Raimondi, D.L. Cooper, *Nature*, 1987, 329, 492-493.
19. R.D. Harcourt, *Nature*, 1987, 329, 491-492.
20. R. McWeeny, *Nature*, 1986, 323, 666-667.
21. N.D. Epiotis, "*Unified Valence Bond Theory of Electronic Structure Applications*," Springer, Berlin 1983.
22. S. Shaik, P.C. Hiberty, "*The Chemists Guide to Valence Bond Theory*", Wiley-Interscience, Hoboken, NJ, 1983.
23. G. Gallup, *Valence Bond Methods, Theory and Applications*, Cambridge University Press, Cambridge, NY, 2002.
24. A. Streitwieser, C.H. Heathcock, E.M. Kosower, "*Introduction to Organic Chemistry*", 4th ed., Macmillan Publishing Co., New York, pp 10-17, 604-617.
25. J. March, "*Advanced Organic Chemistry: Reactions, Mechanisms and Structure*", 3rd ed., John Wiley & Sons, New York, 1985, pp. 46-56.
26. J.R. Searle, "*Seeing Things as They Are: A Theory of Perception*," Oxford University Press, 2015, pp. 15, 111-114.
27. M. Proietti, A. Pickston, F. Graffitti, P. Barrow, D. Kundys, C. Branciard, M. Ringbauer, A. Fedrizzi, *Science Advances*, 2019, 9, eaaw9832.

28. J.H. Nelson, *"Nuclear Magnetic Resonance,"* Pearson Education, Inc., Upper Saddle River, N.J., 2003, p. 51.
29. W.O. Kermack, R. Robinson, *J. Chem. Soc. Trans.*, 1922, 121, 427-440.
30. A.R. Straumanis, S.M. Ruder, *J. Chem. Educ.*, 2009, 86, 1389.
31. G. Bhattacharya, G.M. Bodner, *J. Chem. Educ.*, 2005, 82, 1402-1407.
32. Ref. 25, pp. 64-66.
33. C.K. Ingold, *"Structure and Mechanism in Organic Chemistry,"* Cornell University Press, Ithaca, NY, 1953, p. 65.
34. P. Kovacic, J.J. Hiller, Jr., *J. Org. Chem.*, 1965, 30, 1581-1588.
35. More recent texts avoid this image, F.A. Carey, *"Organic Chemistry,"* 6th ed., McGraw-Hill, 2006, p. 169, also ref. 24, pp 196, 679
36. W.J. Hehre, L. Radom, P. v.R. Schleyer, J.A. Pople, *"Ab Initio Molecular Orbital Theory,"* John Wiley and Sons, New York, 1986, p. 350.
37. J.A. Dean, *"Handbook of Organic Chemistry,"* McGraw-Hill Book, Co., New York, 1987, 4-73.
38. C.R. Noller, *J. Chem. Educ.*, 1950, 27, 504-510.
39. Ref. 33, pp 64, 238-244.
40. P.M. Estevo, J. Walkimar, de M. Carneiro, S.P. Cardoso, A.G.H. Barbarosa, K.M. Laali, G. Rasul, G.K. Surya Prakash, G. Olah, *J. Am. Chem. Soc.*, 2003, 125, 4836-4849.
41. G.A. Olah, S. Kuhn, S.H. Flood, *J. Am. Chem. Soc.*, 1961, 83, 4571.
42. G.A. Olah, *Acc. Chem. Res.*, 1971, 4, 240.
43. C.A. Bunton, E.D. Hughes, C.K. Ingold, D.I.H. Jacobs, M.H. Jones, E.J. Minkoff, R.I. Reed, *J. Chem. Soc.*, 1950, 262 and references cited.
44. J. Kochi, *Acc. Chem. Res.*, 1992, 25, 39
45. S.V. Reynolds, J.K. Kochi, *J. Org. Chem.*, 2002, 67, 1728-1737.
46. J. Weiss, *Trans. Farad. Soc.*, 1946, 42, 116.
47. J. Feng, X. Zheng, M.C. Zerner, *J. Org. Chem.*, 1986, 51, 4531.
48. K. Fului, T. Yonezawa, H. Shingu, *J. Chem. Phys.*, 1952, 24, 402.
49. I. Fleming, *"Frontier Orbitals and Organic Chemical Reactions,"* 1978, Wiley, London, pp. 24-103.
50. See computational section.
51. R.O.C. Norman, G.K. Radda, *J. Chem. Soc.*, 1961, 2610
52. R.S. Mulliken, *Phys. Rev.*, 1932, 41, 49.
53. A.R. Albumia, P. Barelli, A. Delusa, *Theor. Chim. Acc.*, 2000, 104, 218-222.
54. K.J. Szabo, A.B. Hornfeldt, S. Gronowitz, *J. Am. Chem. Soc.*, 1992, 114, 6827-6834.
55. L.M. Stock, H.C. Brown, *J. Am. Chem. Soc.*, 1959, 81, 5615.
56. C.L. Perrin. *J. Am. Chem. Soc.*, 1977, 99, 5516-5518.
57. L. Ebersson, M. Hartshorn, M. Radner, *Acta Chem. Scand.*, 1994, 48, 437.
58. B.D. Bastts, V. Gold, *J. Chem. Soc.*, 1964, 4284.
59. V. Gold, R.W. Lambert, D.P.N. Satchell, *J. Chem. Soc.*, 1960, 2461.
60. P.B.D. de la Mare, E.A. Johnson, *J. Chem. Soc* 1963, 4076.
61. P. Politzer, K. Jarasuriya, P. Sjoberg, P. R. Laurence, *J. Am. Chem. Soc.* 1985, 107, 1174-1177
62. M.A. Paul, *J. Am. Chem. Soc.*, 1958, 90, 5239-5332; 5332-5333.
63. K. Hendricks, B. Braid, P. Bultinck, P. C. Hiberty, *Comp. Theor. Chem.*, 2015, 1053, 180-186.

64. A. Witkowski, Bulletin de l'Academie Polonaise des Sciences, Serie des Sciences Mathematiques, Astronomiques et Physiques, 1961, 9, 897.
65. K.R. Glaesemann, R.J. Goniad, S. Krishnamoorthi, V. Kowalski, J. Phys. Chem. A, 2000, 114, 8764-8771.
66. C.M. Nunes, L.P. Viegas, S.A. Wood, V.P. Rague, R. McMahon, R. Fausto, Angew. Chemie Intern. Ed., 2020, 59, 17622-17627.
67. X. Li, D.A. Brae, G.A. Parker, J. Chem. Phys., 2008, 129, 124305/1.
68. Gaussian 03, Revision C.02, Wallingford, CT, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople,
69. <http://dasher/wustl.edu/lectures/lecture21> covers much of the approximations unfortunate but necessary in computational determinations.