Quantification of “fuzzy” chemical concepts: a computational perspective

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Chemical concepts considered as “fuzzy” due to their lack of clear physical basis:

- Chemical Bond
- Aromaticity
- Strain
- (Hyper)conjugation
- Atomic charges, etc.

These so called “fuzzy” chemical concepts provide:

- guidelines for the design of novel molecules and materials
- help in the understanding of molecular structure and properties
- play an important role in the development of molecular modelling approaches
Goal of this review:

• To provide an overview of the existing schemes used to quantify each concept.

• To deliver guidelines and illustrate the pros and the cons that enable the appropriate scheme choice.

• To demonstrate their utility through representative applications in the recent literature.
Overview of the most common strategies developed to quantify chemical bonds with the purpose of predicting the properties and reactivity of molecules:

The numbers of electrons in a bond (bond order)

- Two main families of definitions for the description of the atom inside the molecule:

  → The Hilbert Space: partition in the space of the basis functions used to describe the wavefunction. **Drawback**: approach restricted to atom-centered basis sets, the results are strongly basis set dependent.

  → The Real Space: partition of the molecular electronic density. Reduced basis set sensitivity. Atoms have either sharp or fuzzy (interpenetrating) boundaries.
The Chemical Bond (2)

- Successful partitions of electronic density (real space) include:
  - **Hirshfeld (fuzzy)**, generates overlapping atoms that most closely resemble free atoms.
  - **Bader’s Quantum Theory of Atoms in Molecules (QTAIM, sharp)**, atoms are defined by the region of space where the electron density gradient connects to the same maximum (Fig. 1a); the overall space is separated by sharp, mutually exclusive surfaces (basins, Fig. 1b).
  - **Electron Localization Function (ELF) / Localized Orbital Locator (LOL)**, both founded on the consideration of the kinetic energy of the electrons. The ELF/LOL domains are associated with atomic cores, lone pairs, and bonds (Fig. 1c). The electronic population of the bonding basin defines the number of electrons shared in a bond.
The Chemical Bond (3)

Figure 1. All plots obtained from B3LYP/6-31G* electronic density.

(a) Gradient paths (blue) for CH$_3$NH$_2$, in the H-C-N plane. Bond paths (green), surfaces defining atoms in molecules (red), density contour lines (black).

(b) QTAIM basins for the C (blue) and N (red) atoms of CH$_3$NH$_2$.

(c) ELF basins for CH$_3$NH$_2$ (gold), isovalue 0.85.

(d) Electrostatic potential of CH$_3$NH$_2$ for an isodensity surface of 0.02 a.u.
Overview of the existing schemes used to quantify charge distribution.

Derivation of atomic charges:

- Atomic charges → not a quantum mechanical observable.
- Three different strategies used to define and derive charges:
  
  (1) They can be fit to reproduce a molecular property, such as charge distribution on the vdw surface.
  They can be generated based on the description of the atom in a molecule from either:
  (2) a partitioning in the space of the basis functions
  (3) a partitioning of the electron density
(1) Charges derived from electrostatic potential (ESP):

- Traditionally represented as electrostatic potential energy maps (Fig. 1d).

- The aim of ESP charges is to reproduce the electrostatic potential in order to model electrostatic interactions between non-bonded atoms.

- The major drawback: these charges mainly describe the surface of the molecule (charges of “buried” atoms are ill-defined); they are rarely used to rationalize chemical trends.
(2) Partitioning in terms of atomic orbitals:

- **Mulliken population analysis:**
  - Strong dependence on the number of basis functions.
  - Contribution of the overlap between basis functions of two different atoms is distributed equally between the two atoms.

- **Natural Population Analysis (NPA):**
  - Less basis set dependent.
  - Relates the molecular density to the sum of atomic orbital contributions.

- **Distributed Multipole Analysis (DMA):**
  - Uses a multicentre multipole expansion to describe the charge distribution.
  - Good alternative for modelling electrostatic interactions between non-bonded molecules.
(3) Partitioning the electron density:

- **QTAIM** → the overall space is split into mutually exclusive atomic domains (basins). Integrating the density within the basins (Fig. 1b) gives the atomic charge.

- **Hirshfeld (Stockholder) partitioning** → Uses the density of a “promolecule” (superposition of the densities of all the atoms positioned as in the real molecule). They resemble the isolated atom densities but reflect the influence of the molecular environment. **Drawback**: the atomic charges depend upon the (arbitrary) choice of atomic reference densities.

- Fuzzy (interpenetrating) atoms are consistent with the intuitive picture of a chemical bond as being the overlap between two atoms.
(3) Partitioning the electron density:

- Figure 2 shows the charges generated by the schemes previously discussed for a series of substituted methyl group.
- An overall trend in line with chemical intuition is present.
- The magnitude of the charges varies significantly.

**Figure 2.** Charges on the methyl group in the series Me-X with X=(Li, BeH, BH₃, CH₃, NH₂, OH and F) at the HF/6-31G**//HF/6-31G* level except for Hirshfeld-I (computed at the same level in a modified version of Q-Chem).

The difference in electronegativity between carbon and the connected atom is divided by 2 to fit in the same scale and denoted by ΔEN/2.)
Conjugation and Hyperconjugation (1)

- Quantification of π-conjugation and hyperconjugation using electron density criteria.

**Electron density based analysis:**

Methods and indices that measure the extent of electron delocalization based on functions of the electron density.

- Ellipticity, magnitude of the electron density curvature, \( \rho(r) \).
- Analysis of the contour line diagram of the Laplacian distribution, \( \nabla^2 \rho(r) \).
- The two-electron density (pair density)

All these methods require *a priori* division of the molecular space into regions (atomic domains or basins), which are typically performed using QTAIM, ELF or LOL.

They identify strong π-conjugative interactions (aromaticity) but do not detect a partial π-character in situations with weak conjugation.
Conjugation and Hyperconjugation (2)

- The extent of lone pair \( \rightarrow \sigma^* \) delocalization can be rationalized through the analysis of the ELF basin populations. ELF shows evidence for favorable lone pair interactions with neighboring \( \sigma^* \) orbitals (Fig. 3)

**Figure 3.** *Left:* the ELF lone pair/CO population of methoxy-methanol decreases/increases in the *gauche* conformation (as compared to the *trans* conformation) *Right:* the delocalization of the QTAIM oxygen basin is smaller in the *gauche* than in the *trans* conformation.
Many quantitative relationships have been established based on data characterizing molecular structure and thermochemistry derived from both experiment and computations.

1. **Torsional Strain:**
   - Resistance of a bond to twisting.
   - The energetic maxima of torsional strain increase with bulkier functional groups (Fig. 4) and can be energetically quantified by examination of the rotational profile around a bond of interest.

**Figure 4.** Rotational barriers of ethane, n-butane, 1,2-difluoroethane, 1,2-dichloroethane, and 1,2-dibromoethane show torsional strain of the central C-C bond. Energy profiles computed at the M06-2X/6-311+G(d,p) level.
2. Ring/Cage Strain:

Determined by establishing the difference between the energy of the compound of interest and a hypothetical “strainless” model. After determination of an ideal “strain-free” heat of formation the strain energy can be determined by subtracting the ideal value from the actual heat of formation of the strained compound obtained either by experiment or computation (Table 1).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Experimental $\Delta H_f$</th>
<th>Strainless $\Delta H_f^a$</th>
<th>Estimated strain energy</th>
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<tbody>
<tr>
<td>Cyclopropane</td>
<td>12.7</td>
<td>−15.0</td>
<td>27.7</td>
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<tr>
<td>Cyclobutane</td>
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<td>−20.0</td>
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<td>Cyclopentane</td>
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<td>Cyclohexane</td>
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<td>Tetrahedrane</td>
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<td>136.1</td>
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<td>Cubane</td>
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<td>Adamantane</td>
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<td>−38.1</td>
<td>6.0</td>
</tr>
</tbody>
</table>

*a* Derived from Benson group increments, see text. *b* Value computed at the G3MP2 level.

Table 1. Actual and hypothetical strainless heats of formation (kcal/mol) for bicyclic and cage systems. The difference between these values gives an estimate of the conventional strain energy.
In contrast to quantification of the chemical bond and atomic charges, where defined quantum chemical schemes exist, attempts to estimate molecular strain energies proceed in an indirect manner. These evaluations frequently rely on experimental observations.

The method or scheme chosen for the quantification of chemical concepts that lack a truly unique definition and are not directly associated with experimentally observable values (chemical bond, atomic charges, (hyper)conjugation, and molecular strain) should be carefully determined based on its specific application.
References


Thank you for your attention