Charge Density from X-ray Diffraction. Applications

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Outline

I. Why charge density?
II. Topology of the electron density
III. The electrostatic potential
IV. The transferability principle
I. Why charge density?

II. Topology of the electron density

III. The electrostatic potential

IV. The transferability principle
Every interaction between atoms leaves its fingerprint in $\Delta \rho$. 

- Covalent bond
- Ligand-metal interaction
- Hydrogen bond
Δp reveals the electronic structure of the atom.
Population of d-orbitals from $P_{lm}$ parameters

$\Delta \rho$ around metals in transition metal complexes reminds of d-orbitals. Ex.: Pyrite

$\Delta \rho$ can be projected into the basis of d-orbitals.

d-orbitals population $\rightarrow P_i = M^{-1}P_{lm}$

Projection matrix

Stevens Inorg Chem 19 (1980) 813
Example: Mn$_2$(CO)$_{10}$

Holes in the deformation density pointing toward the ligands

<table>
<thead>
<tr>
<th>d</th>
<th>Population</th>
<th>Relative Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>$d_{z^2}$</td>
<td>0.76(3)</td>
<td>14.2%</td>
</tr>
<tr>
<td>$d_{x^2-y^2}$</td>
<td>0.65(4)</td>
<td>12.1%</td>
</tr>
<tr>
<td>$d_{xy}$</td>
<td>1.27(4)</td>
<td>23.6%</td>
</tr>
<tr>
<td>$d_{xz}$, $d_{yz}$</td>
<td>2.69(3)</td>
<td>50.1%</td>
</tr>
</tbody>
</table>

Relative populations: Depopulated, Populated
Electron transfer between atoms through the **electrostatic moments**

\[
\rho_T(r) = \sum_{\alpha} Z_{\alpha} \delta(r - r_{\alpha}) - \rho(r)
\]

**Charge density**

**Monopolar moment**

\[
Q = \int \rho_T(r) dr
\]

**Dipole moment**

\[
\mu_i = \int \rho_T(r) r_i dr
\]

**Quadrupole moment**

\[
\Theta_{ij} = \int \rho_T(r) (3r_i r_j - r^2 \delta_{ij}) dr
\]
Electrostatic moments are related to molecular and crystal properties
Ex. Crystal packing

Head-to-tail alignment of dipole moments

T-packing of quadrupolar molecules
**Dipole enhancement**: Increase on the dipole moment induced by the crystal environment.

- Dipole moment is related to properties of the crystal (e.g., optical properties).
- Very large dipole enhancements have been reported. However, some of them could be overestimated.
- Reduction of the dipole moment has been observed.

Electrostatic energy from the electrostatic moments

\[ E_Q = -\int \int \frac{\rho_{T,A}(\mathbf{r}_A)\rho_{T,B}(\mathbf{r}_B)}{|\mathbf{r}_A - \mathbf{r}_B|} d\mathbf{r}_A d\mathbf{r}_B \]

6-dimension integral transformed into a sum

\[ E_Q = \frac{Q_A Q_B}{r} - \sum_i \frac{r_i}{r^3} (Q_A \mu_{i,B} - Q_B \mu_{i,A}) + \]

\[ + \sum_{i,j} \frac{3r_i r_j - r^2 \delta_{ij}}{r^5} \left( \frac{1}{3} Q_A \Theta_{ij,B} + \frac{1}{3} Q_B \Theta_{ij,A} - \mu_{i,A} \mu_{j,B} \right) + \ldots \]
Comparison with theoretical calculations

Experimental deformation density

Theoretical deformation density
PHF/6-31G**

Pseudoatom model from the theoretical electron density structure factors

Comparison with theoretical calculations

Ex. $\text{YBa}_2\text{Cu}_3\text{O}_{6.98}$

$z = 0.355$ (Cu)

$z = 0.378$ (O)

Qualitative agreement between theory and experiment

Experiment

Theory (LAPW)

I. Why charge density?
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Molecular structure (bonds, rings, etc…) can be retrieved from the total electron density.

Ex. $B_4H_4^{2-}$

Atoms (mountains)  Ring (valley)

Bond (saddles)

Bader in *The Application of Charge Density Research to Chemistry and Drug Design*, 1991
The topological analysis is based on the calculation of the gradient of $\rho(\mathbf{r})$.

Gradient lines are perpendicular to isodensity contours

$$\rho(\mathbf{r})$$

$$\nabla \rho(\mathbf{r}) = \begin{pmatrix} \frac{\partial \rho(\mathbf{r})}{\partial x} \\ \frac{\partial \rho(\mathbf{r})}{\partial y} \\ \frac{\partial \rho(\mathbf{r})}{\partial z} \end{pmatrix}$$
Gradient lines start at atomic positions.

The volume filled by the set of gradient lines starting at a nuclear position is the **atomic basin**.

Atomic basins are limited by **interatomic surfaces**. No gradient line crosses interatomic surfaces: **zero flux surfaces**.

\[ \nabla \rho(r) \cdot \mathbf{n} = 0 \]
Atomic basins define a partition of the space. This partition is...
• …complete: It fills all the space
• …disjoint: There is no basin superposition

Ex. KMgF$_3$


http://web.uniovi.es/qcg/papers/watoc/watoc52.html
**Critical points**: Points yielding the condition

\[ \nabla \rho(\mathbf{r}) = 0 \]

In the maps, they appear as points where gradient lines converge or diverge.

They correspond to:
- Local maxima \( \rightarrow \) atomic positions
- Saddle points
  - Max. in 2 directions, min in 1 \( \rightarrow \) bond critical point
  - Min. in 2 directions, max in 1 \( \rightarrow \) ring critical point
- Local minima \( \rightarrow \) cage critical points

<table>
<thead>
<tr>
<th>Notation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3, -3)</td>
<td>Atomic positions</td>
</tr>
<tr>
<td>(3, -1)</td>
<td>Bond critical point</td>
</tr>
<tr>
<td>(3, +1)</td>
<td>Ring critical point</td>
</tr>
<tr>
<td>(3, +3)</td>
<td>Cage critical points</td>
</tr>
</tbody>
</table>
**Bond critical point**
- Density minimum along the bond
- Density maximum in the directions perpendicular to the bond

Ex. CO

Gillespie, *Chemical Bonding and Molecular Geometry*, 2001
**Bond path**: Two gradient lines starting at the atomic nuclei and ending at the bond critical point.
QTAIM: Quantum Theory of Atoms in Molecules

- Electron density topology is interpreted in terms of quantum mechanics.

Atomic basin ↔ Atom

Atomic properties = Integrals on the atomic basin

Bond path ↔ Bond

Bond properties = Properties at the bond critical point
**Molecular graphics:** representation of nuclei, critical points and bond paths

Visualization of the interactions in the molecule or the crystal

![Diagram](image)

H···H interaction

Matta in *Hydrogen Bonding – New Insights*, 2006
In the experimental $\rho$ there is information about the bonds in the crystal
**Laplacian** of the electron density

\[ \nabla^2 \rho(r) = \frac{\partial^2 \rho(r)}{\partial x^2} + \frac{\partial^2 \rho(r)}{\partial y^2} + \frac{\partial^2 \rho(r)}{\partial z^2} \]

\( \nabla^2 \rho(r) > 0 \)  Excess of kinetic energy: electrons are delocalized

\( \nabla^2 \rho(r) < 0 \)  Excess of potential energy: electrons are localized

Laplacian shows the shell structure of the atom

Ex. Argon

*Image credit: Bader, Atoms in Molecules, 1990*
**Laplacian** shows electron pair position

Ex. $\text{H}_2\text{O}$

- **O-H bonds**
  - $\nabla^2 \rho(r)$

- **Lone pairs**
  - $\nabla^2 \rho(r)$

Bader *Atoms in Molecules*, 1990
Closed shell vs shared shell

Closed shell (ex. ionic bond, H-bond)

- Electron density contracts towards the atoms
- $\lambda_3$: large
- $\lambda_1, \lambda_2$: small
- $\nabla^2 \rho_b > 0$
- Kinetic energy dominates

Shared shell (ex. covalent bond)

- Electron density accumulate in the bonding region
- $\lambda_3$: small
- $\lambda_1, \lambda_2$: large
- $\nabla^2 \rho_b < 0$
- Potential energy dominates
**Shared interactions** (covalent bond)
- Combination of atomic valence shells
- Region of negative laplacian between the atoms
- Negative laplacian at the bond critical point

Bader *Atoms in Molecules*, 1990
**Closed shell interactions** (ionic bond, metallic bond, hydrogen bond…)
- Atomic valence shells keep separated
- Region of positive laplacian between the atoms
- Positive laplacian at the bond critical point

Bader *Atoms in Molecules*, 1990
Ligand-metal interactions
• Laplacian is positive at the bond critical point: closed shell
• Positive laplacian peaks in the metal for the depopulation of the d orbitals
**Ligand-metal interactions:** isolaplacian surfaces around the metal

Example: $\text{Co}_3\left(\text{C}_8\text{H}_4\text{O}_4\right)_4\left(\text{C}_4\text{H}_{12}\text{N}\right)_2\left(\text{C}_5\text{H}_{11}\text{NO}\right)_3$

- Electrons are localized in the negative laplacian region.
- There is no electron localization in most of the Co-O bonds.
- There is electron localization in some Co-O bonds, associated to magnetic interaction between metals.

\[ \nabla^2 \rho(r) = -900 \text{ eÅ}^{-5} \]

Clausen *JACS*, 130 (2008) 7988
**Agothic interactions:** Interaction of a metal with a C-H bond  
Ex.: EtTiCl₃(dmpe)

Delocalization induced by the interaction with the ligand

Bond critical point associated to the agostic interaction

**Intermolecular interactions**

Topology of $\rho(r)$ is extensively used for the detection and characterization of any kind of intermolecular interactions.

**Strong hydrogen bonds**

Gatti in *The Quantum Theory of Atoms in Molecules*, 2007

**Weak hydrogen bonds**


**π···π interactions**


**Halogen interactions**

Bui *Angew Chem*, 48 (2009) 3838

**Anion···π interactions**

Quiñonero *Angew Chem*, 41 (2002) 3389

**H···H interactions**

**X-H bond:** Properties of bond critical point reveal the change in the nature of the interaction and the bonding distance is reduced.

I → Pure closed shell, weak or medium H-bond

II → Closed shell with partial shared character, strong H-bond

III → Shared interaction, covalent bond

From 79 complexes X-H···F-Y in gas phase

From 11 experimental electron densities


I. Why charge density?
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**Electrostatic potential:** Electrostatic energy of a unit charge at the point \( \mathbf{r} \).

\[
V(\mathbf{r}) = \int \frac{\rho_T(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^2} (\mathbf{r} - \mathbf{r}') d\mathbf{r}'
\]

**Poisson’s equation**

\[
\nabla^2 V(\mathbf{r}) = -\rho_T(\mathbf{r})
\]

Outside nuclear positions

\[
\nabla^2 V(\mathbf{r}) = \rho(\mathbf{r})
\]

Isopotential lines

\[
V > 0 \quad V = 0 \quad V < 0
\]
Electrostatic potential around molecules

$V(r)$ is dominated by the positive contribution from the nuclei $V_{nuc}(r)$.

- Screening from the electrons makes $V(r)$ decay faster than $V_{nuc}(r)$.
- Large accumulations of electron make $V(r)$ negative.
Most intermolecular interactions involve two molecular regions
- One positively charged: donor, acid, electrophile...
- One negatively charged: acceptor, base, nucleophile...

Easily detected in the $V(r)$

Pullman in *Chemical Applications of Atomic and Molecular Electrostatic Potentials*, 1981

Ex.: Lone pairs that can be acceptors in H-bonds appear as local minima in $V(r)$
Electrostatic potential shows the active site – ligand complementarity

Ex: human aldose reductase

Ligand: NADP+  Active site  Active site + ligand

V(r) mapped in **molecular surfaces** (van der Waals, isodensity, Connolly…)

- Encloses almost all the electron density of the molecule

- Minima: Nucleophilic regions, H-bond acceptors

- Maxima: Electrophilic regions, H-bond donors

Ex: H$_3$PO$_4$
\( V(\mathbf{r}) \) is a scalar field like the electron density. Topological analysis can be performed in \( V(\mathbf{r}) \).

\[ \nabla \rho(\mathbf{r}) \]

\[ \mathbf{E}(\mathbf{r}) = -\nabla V(\mathbf{r}) \]

Similar topology

Different topology
Electric field \[ E(r) = -\nabla V(r) \]

Field lines reveal influence zones of the functional groups in the molecule.

Minima of potential associated to an nucleophilic group (carboxyl)

Field lines converge at the minimum. Influence zone of the carboxyl group

Border of the carboxyl influence zone

Region outside the carboxyl influence zone

Minimum of potential in the border of the influence zone. Minimum potential barrier for entering in the influence zone.
**Electrostatic interaction energy** between two molecules

\[
E_Q = \int V_A(r)\rho_{T,B}(r)\,dr = \int V_B(r)\rho_{T,A}(r)\,dr = -\int\int \frac{\rho_{T,A}(r_A)\rho_{T,B}(r_B)}{|r_A - r_B|} \,dr_A \,dr_B
\]

Electrostatic energy is one component of the total interaction energy.

In general, the main component of the total interaction energy is electrostatic.

Ex. Vancomycin complexes

Relative contributions to the interaction energy.
Electrostatic interaction of one molecule in the crystal

Example: Binding energy of one water molecule in AlPO_4-15

Electrostatic potential in the empty cavity

Electrostatic part of the binding energy

\[ E_Q = \int V_{\text{cavity}}(\mathbf{r}) \rho_{T,\text{water}}(\mathbf{r}) \, d\mathbf{r} \]

**ECDA: Experimental charge density approach** to the calculation of interaction energies.

\[ E_{AB} = E_Q + E_{vdw} \]

- \( r(r) \) from the pseudoatom model
- Atomic electrostatic moments

**6-exp potentials**

\[ Ae^{-Br} - \frac{C}{r^6} \]

**Ex.: Peptides**

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Transferability

- Two atoms in a similar environment present a similar electron density.
- Pseudoatom electron density or generalized form factors can be transferred between atoms.

Databases

There are databases of atomic parameters for building electron densities or form factors from experimental or theoretical electron densities.

Common databases

- ELMAM: Peptides

- UBDB: Atoms in biological molecules

- Invarion: Theoretical data

http://harker.chem.buffalo.edu/group/databank.htm
• Databases can be used for building a pseudoatom model of the electron density in macromolecules.
• From this electron density, properties such as the electrostatic potential can be derived.
Pseudoatom form factors from databases provide better residual maps than IA form factors

Ex. Peptide bond

Invarion deformation density  Residual density with independent atoms  Residual density with invarions

Dittrich, Angew Chem, 43 (2004) 2718
From the experimental electron density we have:
- Charge density in the crystal. Electron redistribution related to chemical bonding. Polarization induced by the crystal environment.
- Structural parameters corrected from bonding effects. Better structure model

Application of the transferability principle for enhancing the quality of the crystal structure by using electron density databases.

Ex. Agreement factor in triglicine using:
- IA form factors
- generalized scattering factors from a database
Transfer of generalized scattering factors is used for deriving thermal parameters without bonding effects at high temperatures.

Ex. Determination of specific heat from thermal parameters at different temperatures

From calorimetry

From thermal parameters

If high resolution X-ray diffraction data is available, databases are useful for building the starting model for charge density studies in macromolecules.
A more complex case: Human aldose reductase

316 residues
33% atoms disordered
P2₁ (Monoclinic)
3042 non-H atoms

V  156350 Å³
T  100 K
I  0.54 Å
Refl. measured  1175910
Refl. independent  511265
Refl. observed  405150
(sin(θ)/λ)ₘₐₓ  0.76 Å⁻¹
Rₘₑᵍₑ(F²)  0.029

319 atomic parameters of 1156 non-H atoms refined

Guillot Acta Cryst D64 (2008) 567
Final remarks

- In the experimental electron density there is valuable information about all kind of interatomic interactions, from chemical bonds to weak van der Waals interactions.

- Experimental electron density studies focus on topics such as chemical bond properties, characterization of non-covalent interactions or crystal environment effect on molecular properties.

- Topological analysis of the electron density in the framework of the Quantum Theory of Atoms in Molecules is extensively used for the interpretation of the experimental electron density.

- Electrostatic potential from the experimental electron density is extensively used for the analysis of intermolecular interactions.

- Transferability principle can be applied to increase the quality of structural information or to the estimation of electron densities in cases inaccessible to experiment.