

A way to determine how partial charges of atoms in a molecule are distributed

Atomic partial charges are subtle variations in electron distribution in a molecule. They can now be measured by an innovative experimental method that exploits a phenomenon known as electron diffraction. The results provide insights into molecular interactions, potentially leading to applications in drug discovery and materials science.

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The problem

Understanding the properties of molecules and materials, as well as their chemical synthesis pathways, requires a thorough knowledge of chemical bonding. Deep insights into bonding enable greater control over material properties and reactivity. Electrostatic forces are fundamental to chemical bonds, ranging from simple ionic compounds such as sodium chloride, in which electrons are transferred between atoms, to complex macromolecules such as DNA, in which electrostatic forces contribute to structural stability. These forces are commonly described using the concept of atomic partial charges: the distribution of electrons between bonded atoms. Electron distribution in molecules influences molecular bond strength and reactivity, enabling the prediction and control of bond behaviour in various environments. Controlling these processes is therefore key to designing new materials and tailoring their structural characteristics¹.

Concepts such as electronegativity (the ability to attract electrons) and atomic charge are central to explaining various chemical properties and behaviours, including charge transfer and bond polarity, strength and reactivity². However, atomic partial charges lack a precise quantum-mechanical definition^{3,4}, and there is no general experimental method to quantify them for individual atoms in compounds. This fundamental gap hinders the precise prediction and control of chemical reactivity and material properties.

The discovery

We have developed a broadly applicable method for the experimental determination of partial charges, called ionic scattering factor (iSFAC) modelling. iSFAC modelling is based on the analysis of crystal structure using 3D electron diffraction, a technique that directs a fine beam of electrons at a nanocrystalline material and measures how the electrons are scattered. Electrons are charged particles, so they interact with the electrostatic potential in the crystal, making electron diffraction sensitive to the partial charges of every atom of the molecular compound at an absolute scale. Modelling the electrostatic potential map resulting from electron diffraction by iSFAC enables the partial charges of every atom in a chemical compound to be determined.

More specifically, iSFAC modelling combines determinations of how each atom – as either a non-charged or charged particle – would, in theory, scatter the

electron beam and thereby contribute to the electrostatic potential map. Refining this combined factor by comparing the models with experimental data generates an estimate of each atom's partial charge. Previously, such charges were estimated only through computational methods, such as electrostatic potential fitting or electron density partitioning, but these methods can give ambiguous results. iSFAC modelling can not only measure partial charges experimentally, but also provide benchmarks for theoretical models that could link experiments with computational chemistry. For example, it shows how the carboxylate molecular group ($-\text{COO}^-$) in amino acids has negatively charged carbon atoms, whereas the carboxyl group ($-\text{COOH}$) in the antibiotic ciprofloxacin has a positively charged carbon atom (Fig. 1).

The implications

We demonstrated the method's broad applicability by analysing various crystalline compounds, including ciprofloxacin, the amino acids tyrosine and histidine, the industrial catalyst ZSM-5 and tartaric acid from wine. These examples show that molecular environments have a substantial influence on atomic charge distributions – for example, a chloride ion in ciprofloxacin hydrochloride has only about 40% of the full negative charge of an isolated chloride ion. The ability to determine partial charges experimentally has broad implications for fields such as drug development, catalysis and materials science, in which precise knowledge of charge distribution is crucial for modelling molecular interactions and optimizing functional properties.

Our approach advances the use of electron crystallography in structure determination far beyond resolving only the positions of atoms, by providing an experimental way to investigate the electronic properties of materials (Fig. 1). One exciting potential application of iSFAC modelling is the tuning and design of materials and chemicals with unprecedented precision.

Future research will focus on integrating these experimental charge measurements with computational models to enhance their accuracy. Ultimately, this would improve the predictive power of the method for designing pharmaceuticals with greater specificity and materials with customized functionality.

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EXPERT OPINION

Used as probes, electrons are very sensitive to charge in a sample and measure the electrostatic potential, so deducing partial charges from electron-diffraction experiments is a promising strategy. The authors' approach to measuring partial charges is elegant and should be widely applicable through integration into existing crystal structure-refinement

workflows. Tests on different molecules show that the method determines qualitatively reasonable partial charges for high-resolution structures and improves map quality.” (CC BY 4.0)

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FIGURE

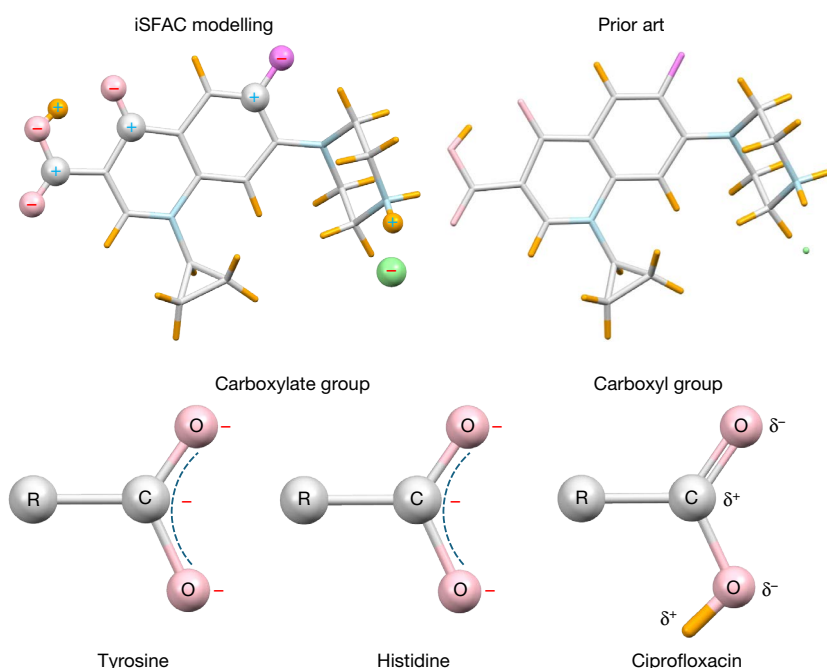


Figure 1 | A method for more-precise measures of the distribution of electrons in a molecule. The newly developed iSFAC modelling approach (top left) provides experimentally derived partial atomic charges, which reflect the distribution of electrons, for the antibiotic ciprofloxacin with greater resolution than prior art (top right). Grey, carbon; pale blue, nitrogen; orange, hydrogen; pale pink, oxygen; green, chloride; dark pink, fluorine. The larger the circle around the charge symbol, the greater the difference from the prior art model. This enhanced-precision charge mapping shows how local chemical environments influence atomic charge. For example, the carbon in the carboxylate groups (-COO^-) in the amino acids tyrosine and histidine (bottom left) carries a negative partial charge (δ^-), whereas the carbon in the carboxyl group (-COOH) of ciprofloxacin (bottom right) carries a positive partial charge (δ^+). R, undefined chemical group. Mahmoudi, S. *et al.* / *Nature* (CC BY 4.0)

BEHIND THE PAPER

When I started my PhD amid the chaos of COVID-19, my supervisor, T.G., handed me a paper⁵ that inspired the exciting but daunting idea of determining partial charges using electron diffraction. Our initial plan to analyse the charge of isolated metal atoms quickly failed. We realized we had to consider entire molecules, which made things more complex but more rewarding. Next, we discovered that hydrogen atoms could not be modelled in the same way as heavier atoms. I obsessed over and dreamt about possible solutions.

Eventually, braced for rejection, I e-mailed an idea to T.G. His simple reply — “Dear Soheil, yes, it makes sense” — gave the project new life. Guided by co-author Christian Schröder, I learnt how to use quantum-mechanical calculations to validate our assumptions. The most thrilling moment was seeing the first promising correlation between our quantum-mechanical results and the experimental data. The hard work had paid off, and the project had come together.

S.M.

REFERENCES

1. Brutiu, B. R., Iannelli, G., Riomet, M., Kaiser, D. & Maulide, N. *Nature* **626**, 92–97 (2024).
2. Racioppi, S. & Rahm, M. *Chemistry* **27**, 18156–18167 (2021).
3. Marenich, A. V., Jerome, S. V., Cramer, C. J. & Truhlar, D. G. *J. Chem. Theory Comput.* **8**, 527–541 (2012).
4. Cho, M. *et al.* *ChemPhysChem* **21**, 688–696 (2020).
5. Yonekura, K. *et al.* *IUCrJ* **5**, 348–353 (2018).

FROM THE EDITOR

This work stands out because of its ease of use. The authors report an elegant method that can be applied during electron-diffraction experiments to extract the partial charge states of atoms, a type of information that has been challenging to obtain when characterizing a crystal structure. This technique will enable a wide variety of scientists, from computational chemists to experimentalists, to acquire these insights routinely.

Editorial team, Nature