

Electron Density and Chemical Bonding II

Theoretical Charge Density Studies

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Dietmar Stalke

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Reliable Measurements of Dipole Moments from Single-Crystal Diffraction Data and Assessment of an In-Crystal Enhancement

B. Dittrich and D. Jayatilaka

Abstract Using seven examples of high-quality data sets of amino acids it is shown that accurate molecular dipole moments can be obtained from experimental diffraction data. Recommendations for practical modeling choices are given when using the Hansen/Coppens multipole model. Multipole-model results, including those from invariom refinement, are found to be less accurate than results from a basis-set description. The question whether a molecular dipole-moment enhancement in the solid state is fact or artifact is studied by a number of techniques: A theoretical molecule embedded in a cluster of point-charges gives a substantial enhancement, in agreement with Hirshfeld atom refinement with point charges and dipoles. The experimental techniques, multipole refinement and wavefunction fitting, lead to smaller dipole-moment enhancements than the theoretical predictions.

Keywords Single-crystal X-ray diffraction • molecular dipole moment • dipole-moment enhancement • multipole model • wavefunction fitting • hirshfeld-atom refinement

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B. Dittrich (✉)
Institut für Anorganische Chemie der Universität Göttingen, Tammannstr. 4, 37077 Göttingen,
Germany
e-mail: bdittri@gwdg.de

D. Jayatilaka
Chemistry, M313, School of Biomedical, Biomolecular and Chemical Science, University
of Western Australia, WA 6009 Crawley, Australia

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1 Introduction

Intermolecular forces are of great interest in chemistry and physics. The classical electrostatic interaction energy between two species can be expanded in a multipole series. Its most important term (for neutral species) is the dipole moment [1]. The dipole of a system is of fundamental and continuing interest.

When non-spherical scattering models were introduced in the late-1960s [2–4] and optimized throughout the 1970s [5–7] it became possible to obtain dipole and higher multipole moments from accurate single-crystal X-ray diffraction data. The basic characteristic common to these different non-spherical scattering models is that they provide an analytical description of the electron density distribution $\rho(\mathbf{r})$ (EDD) in terms of products of atom-centred radial and spherical harmonic angular functions. Only the populations of the latter angular functions (and possibly a radial scaling parameter κ) are adjusted (via a least-squares procedure) to reproduce the intensities of the diffraction experiment. The Hansen/Coppens approach [7] has proven to be successful throughout the last decades in that it has enabled experimental characterization of solid state electronic structure and bonding.

Lately, the multipole model [5, 7] has undergone significant development and a change in philosophy. Instead of the multipole parameters being refined from the X-ray data, they can alternatively be predicted by fitting to theoretical data obtained from quantum mechanical calculations [8]. Not only the multipole parameters but also H-atom vibration parameters (the atomic displacement parameters or ADPs) can additionally be derived from theoretical calculations or other external sources of information like neutron diffraction [9–11]. Programs and schemes have been developed to transfer electron-density parameters from atoms in smaller molecules into larger molecules where the chemical environment is similar. Thus, the traditional role of the experimental measurements determining bonding density has been depreciated in favour of an emphasis on accurate geometric parameters, especially for larger molecules. The significance of these developments on dipole-moment determination from X-ray diffraction data requires substantial characterization.

Even more recently, sophisticated quantum mechanical methods have been developed to refine the geometric and electronic parameters of the crystal structure. For example, it is now possible to refine geometric parameters by using non-spherical scattering models based on quantum mechanical calculations [12, 13] (so-called Hirshfeld atom refinement). Remarkably, this leads to accurate X—H bond distances in excellent agreement to distances from Neutron diffraction. It is also possible to combine quantum mechanical methods directly with the least-squares refinement of the electronic structure parameters describing the electron density (X-ray constrained wavefunction methods) [8, 14–20]. Again, the impact of these methods on dipole-moment determination from X-ray diffraction data merits further study.

Earlier studies aimed at obtaining an experimental dipole moment from diffraction data by refinement of multipole parameters have been comprehensively reviewed in the past [21, 22]. A mathematical definition of the dipole moment and detailed background information can also be found in these review articles. The common consensus is that obtaining reliable dipole moments is a “challenging” undertaking but certainly worthwhile, because the diffraction experiments “are unrivalled in their potential to provide this information in such detail” [22]. This latter comment refers to the fact that, unlike in many other experiments, all the components of the dipole moment are determined from an X-ray diffraction study. Further, dipole moments of molecular fragments can be obtained.

Nevertheless, dipole-moment determinations from multipole refinement frequently remain unreliable, with enhancements in the dipole moment in excess of $\geq 100\%$ having been reported. Several reasons for this have been clearly enunciated [22] including the fact that the definition of a dipole moment in a crystal from a periodic charge density requires a well-defined partitioning of a molecule in a crystal [23].¹ Further limitations include data quality, especially for data pertaining to non-centrosymmetric crystals where phases are less well determined [25, 26], and – what is of interest in this paper – limitations in the modelling process.

In this article we seek to characterize the situations in which an accurate dipole moment can be determined from X-ray diffraction data using the multipole model, Hirshfeld-atom refinement and X-ray constrained wavefunctions. Several questions are addressed:

- *What are the expected accuracies for dipole moment magnitudes? Are there possible pitfalls?*

We investigate this question by fitting the multipole model to static structure factors for 22 small organic molecules.

- *What are the accuracies for dipole moments determined from multipole-model scattering-factor databases?*

Structure refinements with scattering-factor databases like the invariom database [27] offer rapid access to dipole moments, and it is important to quantify their performance with respect to dipole-moment evaluation. This is achieved by comparison with experimental results (from refined multipoles) in Table 5.

¹ It must be noted that definitions can be made for the unit-cell polarization, which are independent of the charge density and hence are well defined for periodic systems [24].

Table 1 Crystallographic details of the structures studied. The radiation (Rad.) used and the resolution (Res.) reached (in $\sin \theta/\lambda$, i.e. in \AA^{-1}) are given

Structure	Spacegr.	Z, Z'	Temp.	Rad.	Res.	Ref.
L-Alanine	$P2_12_12_1$	4,1	23 K	Mo $K\alpha$	1.08	[30]
L-Cysteine	$P2_12_12_1$	4,1	30 K	Mo $K\alpha$	0.72	[31]
L-Glutamine	$P2_12_12_1$	4,1	100 K	Mo $K\alpha$	1.08	[32]
D,L-Serine	$P2_1/a$	4,1	20 K	Mo $K\alpha$	1.19	[33]
L-Threonine	$P2_12_12_1$	8,1	19 K	Ag $K\alpha$	1.35	[34]
D,L-Aspartic Acid	$C2/c$	8,1	20 K	Ag $K\alpha$	1.37	[35]
D,L-Histidine	$P2_1/c$	4,1	100 K	Mo $K\alpha$	1.22	[28]

- *What are the accuracies for dipole moments determined from experimental data (refined multipoles/wavefunction fitting)? What in-crystal enhancements may be expected when compared to the theoretical prediction (invariom/single-point calculation)? Can theory provide a benchmark to discern enhancements of dipole moments being “fact or artefact”?*

We address these issues by investigating the dipole moments for seven amino acids for which X-ray diffraction data were obtained from the original authors or were available in the literature. These are compared to reference values obtained from invariom refinement, from ab initio quantum mechanical calculations for isolated molecules and for molecules in a crystal environment. These latter are obtained from self-consistent crystal-field embedded molecular ab initio quantum mechanical calculations. We have also used the X-ray constrained wavefunction method to produce benchmark dipole moments as an alternative to the multipole model. Finally, variations in the dipole moment due to geometric positions from different refinement models are investigated.

2 Experimental Datasets

The structures of the genetically encoded amino acids have been extensively studied. However, dipole moments from X-ray diffraction have not frequently been reported for these molecules, with the exceptions of D,L-histidine and L-alanine [28, 29]. We have therefore chosen to focus on accurate structure determinations of seven amino acids previously reported in the literature for our study (Table 1). In all cases only one single molecule crystallizes in the asymmetric unit. Molecules chosen are L-alanine [30], L-cysteine [31], L-glutamine [32], D,L-serine [33], L-threonine [34], D,L-aspartic acid [35] and D,L-histidine [28]. High-resolution data were provided by the respective authors or were available electronically. In the case of L-cysteine, high-resolution data were not determined.

2.1 Experimental Challenge: Hydrogen Scattering

Even when carefully modelling the information content of the Bragg data, complications in determining dipole moments are likely to arise due to the X-ray

scattering properties of hydrogen atoms. These properties, comparably weak scattering with limited resolution in reciprocal space, for decades have been known to cause concern regarding the reliability of properties based on least-squares refined parameters of H-atoms [36]. Since H-atoms are often situated at the molecular periphery and often far away from the centre of mass, their influence on the molecular dipole moment can be significant.² Accurate X–H bond distances are therefore imperative. Neutron diffraction experiments are the preferred source of accurate X–H bond distances; but results for particular molecules or bonding environments are usually not available due to the considerable additional experimental effort. Favourable developments with the advent of spallation Neutron sources might change this situation in the future.

Technical improvements help to reduce the problem caused by the scattering properties of hydrogen. A recent study used external information from periodic calculations to try to limit the flexibility of the screening parameters [37] for C, N and O. Scattering-factor databases [27, 38, 39] provide even more accurate “hybrid” scattering factors, also for hydrogen atoms. For the theoretical databases [27, 39] these hybrid scattering factors are obtained by combining fixed multipoles from the database – with the order of the expansion $l \geq 1$ – with refined monopole and dipole populations. In that sense hybrid scattering factors for H-atoms can be seen in analogy to constraints or restraints, since they reduce the flexibility of the least-squares refinement model by adding prior chemical information. Furthermore, X–H distances from geometry optimizations can now be used. They are included in the invariom database [27] and can be retrieved with the program INVARIOMTOOL [40]. In Sect. 5.1 we show how hybrid hydrogen scattering factors and fixed X–H bond distances can increase the reliability of the determination of dipole moments from multipole refinements.

2.2 *Experimental Challenge: Data Resolution*

Apart from a careful treatment of hydrogen scattering, another requirement for the determination of reliable dipole moments from multipole refinement of X-ray diffraction is good quality low-temperature intensity data, preferably extending high into reciprocal space. These are required in order to refine the large number of possible least-squares parameters per atom (three positional, six displacement and up to 25 multipole parameters up to $l_{\max} = 4$, not counting radial screening parameters). Low temperature is mandatory, since experimental conditions are more favourable, e.g. regarding the significant reduction of atomic displacements and thermal diffuse scattering [41]. For further (experimental) requirements concerning multipole refinements of X-ray diffraction we refer to [42].

²One way to resolve the issue is to choose a sample devoid of hydrogen altogether.

Since high-resolution data were not available in the case of L-cysteine, we use recently introduced methodology [43] to obtain an experimental dipole moment despite limitations in data resolution by including ADPs from a previous invariom refinement [33] in a block-matrix refinement of L-cysteine. This procedure and the low data-collection temperature of 30 K allowed to reach the same accuracy as achieved for the other examples.

Requirements for data resolution are more modest for invariom refinements and when using other databases. Nevertheless, despite the success of the suggested block-matrix refinement procedure for L-cysteine, high-resolution data are certainly preferred or even required for the multipole refinements used in our comparative studies.

3 On the Ability of the Multipole Model to Reproduce Theoretical Dipole Moments

The initial question raised is simple: How well does the multipole model allow to reproduce theoretical dipole moments from a DFT calculation with the B3LYP functional and the comparably extended basis-set D95++(3df,3pd)? In order to answer this question twenty-two molecules exhibiting a dipole moment were chosen (see Table 2 for details). They can be considered representative of organic chemistry with some relevance to biological systems. The test set is neither complete nor exhaustive; e.g. zwitterionic compounds are not part of it. For the amino acids, which are zwitterionic in the solid state, multipole projections of the isolated-molecular dipole moments are given in Sect. 5.1.

Geometries of the test-set molecules were optimized with tight convergence criteria in the program GAUSSIAN [44] followed by a frequency calculation to make sure the global minimum was reached. From the resulting wavefunction, real structure factors for a unit cell with dimensions of 30 Å in space group P_1 were calculated with the program TONTO [45], following a procedure introduced earlier [46]. This way a “projection” of the isolated-molecular density onto the multipole model was achieved. Multipole parameters were then refined using these static theoretical structure factors, “simulating” experimental data. Typical R-Factors from such a refinement are around 0.5% (better when heavier nuclei are present), with residual electron density features less than 0.05 e/Å³. Better figures of merit cannot be achieved with the standard Hansen/Coppens multipole model, since the core density remains unadjusted unlike in a recent study [47], and since the order l of the multipole expansion is limited to four for the valence region.

In all refinements a consistent refinement strategy was applied. Chemical constraints and local-atomic site symmetry were used where possible. However, it was assured that such choices did not affect the resulting dipole moments when compared to a full refinement of all possible multipoles: differences were found to be negligible. On the other hand, more substantial changes were caused by refining

Table 2 Ability of the multipole model to reproduce dipole moments from theory

Compound	Formula sum	μ_0	μ_1	μ_2	μ_3	μ_4	μ_5
Water	H ₂ O	1.9	1.5	1.5	2.0	1.6	1.5
Formaldehyde	CH ₂ O	2.4	2.1	2.0	2.2	2.1	2.0
Methanol	CH ₃ O	1.7	1.5	1.5	1.8	1.6	1.5
Methaneamine	CH ₅ N	1.3	1.2	1.2	1.4	1.2	1.2
Formamide	CH ₃ NO	4.0	3.5	3.3	3.7	3.6	3.4
Formic acid	CH ₂ O ₂	3.9	3.6	3.4	4.0	3.7	3.5
Ethanol	C ₂ H ₆ O	1.6	1.2	1.2	1.5	1.3	1.2
Methoxymethane	C ₂ H ₆ O	1.3	1.6	1.5	1.7	1.7	1.5
Ethaneamine	C ₂ H ₇ N	1.3	1.1	1.1	1.3	1.2	1.1
Acetone	C ₃ H ₆ O	3.1	2.8	2.4	3.0	2.9	2.6
Acetamide	C ₂ H ₅ NO	3.9	3.6	3.3	3.7	3.7	3.5
Propane-2-ol	C ₃ H ₈ O	1.6	1.4	1.3	1.8	1.5	1.3
Acetic acid	C ₂ H ₄ O ₂	4.4	4.2	3.7	4.5	4.3	4.0
2-Methylpropan-2-ol	C ₄ H ₁₀ O	1.6	1.6	1.4	1.9	1.6	1.5
Methanethiol	CH ₄ S	1.6	2.1	2.1	2.2	2.1	1.4
Phenol	C ₆ H ₆ O	1.3	1.5	1.5	1.8	1.6	1.5
Aniline	C ₆ H ₇ N	1.6	2.0	2.1	2.0	2.1	1.9
Ethanethiol	C ₂ H ₆ S	1.7	2.6	2.7	2.7	2.4	1.5
Chloromethane	CH ₃ Cl	2.0	2.2	2.2	2.3	2.3	1.2
Propane-1-thiol	C ₃ H ₈ S	1.8	3.0	3.1	3.0	2.7	1.3
Dichloromethane	CH ₂ Cl ₂	1.7	2.2	2.3	2.3	2.3	1.5
Chloroform	CHCl ₃	1.1	1.7	1.9	1.7	1.7	1.2

Compounds are ordered according to their molecular size. Dipole moments are given directly for the theoretical computation with B3LYP/D95++(3df,3pd) (μ_0), or for different multipole models: μ_1 using κ only, with $l_{\max} = 4$ for H, which is the default in the 2006 version of the invariom database [27], μ_2 using an additional shared κ' for $l \geq 1$ of all non-H atoms, μ_3 same as μ_1 , but limiting $l_{\max} = 1$ for H, μ_4 , same as μ_1 , but limiting data resolution to $\sin \theta/\lambda_{\max} = 0.8 \text{ \AA}^{-1}$. Very similar values than for μ_1 can be obtained when omitting the shared κ' for carbon atoms and were obtained by keeping the scale factor at 1 (μ_5), which improved agreement for S-containing compounds

or not refining the scale factor – which should ideally be unity for theoretical data – and the κ/κ' parameters. Also, the order of the multipole expansion for H-atoms considerably influenced the result obtained (see Table 2). In *experimental* multipole refinements this order l is mostly chosen to be $l \leq 1$ for H, since multipoles with larger l can usually not be refined: As discussed above, correlations and lack of information due to H-atom scattering properties do not allow refinement.

Data resolution can also influence the results. In the currently developed version of the invariom database, simulated data are calculated up to a resolution of $\sin \theta/\lambda_{\max} = 1.44$ with limiting indices of h , k and l of 50, and cut to a more spherical shell of data to 1.2 \AA^{-1} resolution. This procedure was also used here. Results of the different refinements are given in Table 2.

Keeping the level of the multipole expansion at $l \leq 1$ for H-atoms yields a better average agreement for compounds consisting of only C, H, N and O. However, when heavier elements are present, the agreement gets worse and including higher multipoles for hydrogen atoms gives better bond distances in refinement with

experimental data. Furthermore, significant changes in the dipole moments are observed when the resolution is cut to 0.8 \AA^{-1} and superior results are often (but not always) obtained in that case.

Improvements with data cut to 0.8 \AA^{-1} are probably due to the over-proportional information content of valence electron density in low-order reflections, whereas for heavier elements correlations [43] of the multipole parameters or the frozen core approximation could cause the disagreements seen. It can be observed that dipoles differ most when heavier nuclei like S and Cl are present, and that κ' -parameters are helpful for obtaining a more reliable estimate in such cases. Another factor are Fourier truncations effects, which we are currently investigating. Since the results can deviate by more than 70% (e.g. for chloroform), it is recommended to use fixed κ values from theory in experimental multipole refinements to avoid parameter correlations. Either those fixed κ/κ' values proposed earlier [37, 48] or values obtained from, e.g., the invariom [27] or other databases [38, 39] should be used in our opinion. Fixing the scale factor to unity leads to better agreement with heavier elements present, pointing to the fact that the core density is not well represented by the multipole models' Slater functions in our data generated from Gaussian basis sets. However, fixing some of the "sensitive" model parameters does not generally aid in increasing model flexibility and the ability of the multipole model in reproducing the theoretical dipole moments. It also reduces the characteristic of providing an experimental result.

It is to be expected that the multipole-model dipole moments deviate from the theoretical result, since the density representation used is quite different and more sophisticated in ab initio calculations. In summary one needs to be aware that the classical Hansen/Coppens multipole model cannot fit fine details of the electron density distribution, thereby affecting the dipole moment. Even if an experimental (thermally smeared) electron density might be fitted better than the static structure factors used in this chapter, limitations of the experimental multipole-model approach in accurately reproducing molecular dipole moments become evident.

4 Dipole-Moment Enhancements from Theory

Efforts to theoretically predict changes in the molecular dipole moment when moving from the gas phase to the bulk have initially been challenging, since computations on periodic systems were unfeasible. Nevertheless, elegant predictions based on lattice sums [49, 50] provide good estimates of the effect of crystal packing and hydrogen bonding on molecular electron density [51], despite the approximation of an average uniform electric field, which might be inappropriate for larger molecules and strongly hydrogen-bonded systems. The increase or decrease of the dipole moment has been defined [22] as:

$$\Delta\mu = 100(\mu_{\text{mol. in solid}} - \mu_{\text{single mol.}})/\mu_{\text{single mol.}} \quad (1)$$

Another important step forward in obtaining theoretical solid-state dipole moments was the introduction of Bader's Quantum Theory of Atoms in Molecules (QTAIM) [52], which provides an atomic partitioning scheme for isolated-molecular as well as periodic EDD. One characteristic of Bader's partitioning scheme is that atomic fragments each have a dipole moment. Since the sum of QTAIM fragments and their properties are additive, they reproduce space completely, and a molecular dipole moment can be calculated from the sum of the individual atoms in the gas phase or the bulk. Hence, QTAIM provides an attractive route to accurate dipole moments and their possible enhancements from first principles [53–55]. QTAIM results are not discussed in this study, but are provided, e.g., in [53].

4.1 Dipole-Moment Enhancements from Simple Theoretical Cluster Calculations

The simplest way to obtain dipole-moment enhancements from theory are calculations on molecular clusters which we will now discuss. An obvious approximation made in such an approach is the choice of the distance threshold, for which surrounding whole molecules are included.

For the seven zwitterionic organic molecules studied, a cluster based on a 3–5 Å threshold was used. This corresponds to including all surrounding molecules that are closer than this distance threshold to any atom of the central molecule. Typical cluster sizes, including the examples of the amino acids studied here, are 14–21 molecules. Input files were generated with the program BAERLAUCH [56], and require only atomic positions, a cut-off radius and the space group. To decide which cluster size was required, we geometry optimized the central molecule in the field of surrounding molecules using the ONIOM implementation [57] of quantum mechanics/molecular mechanics (QM/MM) in all seven cases (results not shown here). In case the optimization converged, the cluster size was considered to be sufficient also in single-point cluster calculations. Computational details of the ONIOM procedure for molecular crystals are given in [56].

Calculations with a field of point charges are not expensive to perform, since the environment of the cluster is represented by few additional Gaussian functions. In principle, the method and basis set chosen for the calculations can be as sophisticated and extended as the computer permits. Computational requirements are similar to single-point calculations. Cluster calculations with a field of point charges yield a wavefunction file of an "isolated" molecule. This is in contrast to ONIOM cluster calculations, where the geometry of the central molecule can be optimized, but no isolated-molecule wavefunction file is written in GAUSSIAN [44], since the phase relationship between the different level wavefunctions is undefined. A projection onto the multipole model is technically only possible

Table 3 Total dipole moment (in [D]), individual components and enhancement (in %) for seven amino acids from a simple point charge model with basis-set B3LYP/6-31 G(d,p)

Iteration	x	y	z	Dipole	Enhancement
0	0.3	0.4	-12.4	12.4	-
1	0.7	0.0	-14.4	14.4	16
2	0.7	0.0	-14.7	14.7	19
3	0.7	0.0	-14.8	14.8	19
0	2.5	0.9	11.0	11.3	-
1	3.5	0.5	14.2	14.6	29
2	3.6	0.3	15.0	15.4	36
3	3.7	0.2	15.2	15.7	39
0	10.5	5.0	-4.5	12.4	-
1	13.1	6.1	-4.6	15.2	23
2	13.7	6.2	-4.6	15.7	27
3	13.8	6.3	-4.6	15.9	28
0	-5.4	-11.8	4.8	13.8	-
1	-7.1	-14.9	5.7	17.4	26
2	-7.5	-15.5	5.9	18.2	32
3	-7.6	-15.7	5.9	18.4	33
0	7.7	-4.1	-6.5	10.9	-
1	9.8	-4.8	-8.5	13.8	27
2	10.2	-4.9	-9.2	14.6	34
3	10.3	-4.9	-9.2	14.7	35
0	-4.2	-3.8	-10.0	11.5	-
1	-4.8	-4.9	-12.1	13.9	21
2	-4.9	-5.2	-12.6	14.5	26
3	-4.9	-5.2	-12.7	14.6	27
0	14.3	-0.3	-6.6	15.8	-
1	19.9	1.0	-10.0	22.3	41
2	20.3	1.1	-10.4	22.8	44
3	20.4	1.1	-10.5	22.9	45

Iteration 0 refers to the single molecule only, whereas iteration 1,2 and 3 refer to a calculation, where the atomic point charges from the previous iteration surround the central molecule

when a wavefunction file exists. We therefore did not pursue the ONIOM procedure to obtain dipole-moment enhancements in this study.

The main interest for performing single-point calculations in a cluster of point charges was to get a simple estimate of dipole moments in a cluster, thereby presenting a simple model of a crystal. Therefore, we also limited the size of the basis set to 6-31 G(d,p) in the calculations reported in Table 3. The DFT functional used was B3LYP.

The result from these simple calculations is that substantial dipole-moment enhancements can be observed for all seven amino acids studied. Hence, one could expect them to occur frequently when a molecule becomes part of a crystal lattice. However, these results depend on the approximation of a finite inhomogenous field around the molecule and do not include any experimental information except for the molecular geometry. This result will therefore be verified by experiment and by more sophisticated methodology comparing experiment and theory in Sect. 5.1.

4.2 Theoretical Estimate of Dipole-Moment Enhancements with Cluster Charges and Dipoles

A better model for a crystal is accomplished when atomic point charges are complemented by molecular dipole moments in generating the field around a molecule. Like in Sect. 4.1 the purpose is to assess a possible dipole-moment enhancement from a cluster calculation. Apart from including dipole moments of surrounding molecules and from using the program TONTO [45, 46] rather than GAUSSIAN [44], the procedure is analogous. Coordinates after invarioms refinement were chosen as a suitable starting geometry. We note in passing that the HF dipole moment (Table 4) can directly be compared to the invarioms and the DFT single-point dipole moment reported in Table 5. Invarioms aim to reproduce the theoretical values from electron-density fragments. With the basis-set electron density model available in TONTO we can also confirm the well known fact that the Hartree–Fock theory overestimates the dipole moment when compared to calculations that include electron correlation [58]. However, results in Table 4 show that the Hartree–Fock result is a valid estimate and even underestimates the relative in-crystal enhancement seen for DFT. In perspective, molecules studied here exhibit similar enhancement $\Delta\mu$ in the bulk as seen for the point-charge model reported above. Surrounding molecules within a radius of 8 Å were taken into account.

5 Dipole-Moment Enhancements by Combining Theory and Experiment

Experimental determinations of dipole moments usually only provide the value in the solid state. Dipole-moment *enhancements* from experiment can only be obtained by comparing the dipole moment in the solid state with a single-molecule

Table 4 Dipole moments D in Debye from a Hartree–Fock and a DFT calculation on isolated molecules as well as their counterparts in the bulk modelled by a 8 Å cluster of point charges and dipoles

Structure	Basis	HF	HF _{bulk}	$\Delta\mu$ [%]	DFT	DFT _{bulk}	$\Delta\mu$ [%]
L-Alanine	DZP	12.6	17.1	+36	11.1	16.3	+47
	cc-pVTZ	12.2	17.3	+42	10.6	16.6	+57
L-Cysteine	DZP	11.7	16.4	+40	10.1	15.4	+52
	cc-pVTZ	11.3	16.7	+48	9.8	15.7	+60
L-Glutamine	DZP	12.7	17.7	+39	11.2	16.7	+49
	cc-pVTZ	12.4	17.8	+44	10.8	17.0	+57
D,L-Serine	DZP	14.0	19.2	+37	12.2	18.0	+48
	cc-pVTZ	13.5	19.2	+42	11.7	18.3	+56
L-Threonine	DZP	11.2	14.4	+29	10.0	13.6	+36
	cc-pVTZ	10.9	14.5	+33	9.6	13.6	+42
D,L-Aspartic Acid	DZP	11.6	14.9	+28	10.4	14.3	+38
	cc-pVTZ	11.2	14.9	+33	10.0	14.4	+44
D,L-Histidine	DZP	16.1	22.2	+38	14.1	20.8	+48
	cc-pVTZ	15.6	22.2	+42	13.7	21.3	+55

Table 5 Dipole moments D in Debye from invariom refinement (D_{inv}) and from a refinement of multipole parameters (D_{exp}) using the same multipole model and geometry

Structure	D_{inv}	D_{exp}	$\Delta\mu$ [%]	Theory	Multipole projection	$\Delta\mu$ [%]
L-Alanine	12.1	12.5	+3	11.4	(9.9)	+9
L-Cysteine	11.2	11.2	0.0	10.5	(9.4)	+6
L-Glutamine	13.1	13.4	+2	11.5	(10.8)	+14
D,L-Serine	13.5	12.9	-4	12.5	(11.1)	+3
L-Threonine	11.9	12.0	+1	10.0	(9.2)	+17
D,L-Aspartic Acid	13.1	11.4	-13	10.6	(8.8)	+7
D,L-Histidine	15.7	17.9	+14	14.5	(12.3)	+19

Results of a DFT single-point calculation (“Theory”) with the method/basis-set B3LYP/D95 ++(3df,3pd) are given in the right column for comparison. Results from a multipole projection of the DFT density are found to be systematically lower than the single-point results. Hence both single-point (and even more so multipole projection) gives a more pronounced enhancement than the invariom-database [27] fragments

(gas-phase) reference value from theory. A convenient choice for obtaining reference dipole moments for results from experimental multipole refinements is invariom modelling, since it allows a dipole-moment estimate even for large molecules at negligible computational cost. By calculating the difference between experimental dipole moment and the invariom result (1) an enhancement is obtained. To allow a fair comparison between dipole moments from experimental multipole refinement and invariom model we use the same multipole model [7] (i.e. the same local atomic site symmetry and chemical constraints) in both cases. This will be detailed below in the following section.

Invariom modelling is an attempt to apply the benefits of a scattering model that is superior to the independent atom model (IAM) to general small-molecule [33, 59] and ultra-high-resolution macromolecular crystallography [27, 60, 61]. Similar scattering-factor databases are available [38, 39]. In contrast to the experimental multipole refinement, in invariom refinement theoretically predicted multipole populations are kept fixed, so that the number of refinable parameters does not increase with respect to the IAM. Like in the IAM, only positional and displacement parameters are adjusted to the experimental Bragg data.

To put the following results into perspective we need to be aware that both invariom modelling and experimental multipole refinement only permit to obtain the molecular dipole moment within the accuracy the multipole model is capable to provide, as discussed in Sect. 3.

5.1 *Molecular Dipole Moments and Their Enhancement in the Solid State from Experimental Multipole Refinement and Invariom Refinement*

An invariom refinement was performed for the seven datasets considered (Table 1). The input files for invariom refinement were generated by the program INVARIOMTOOL

[40], which also generated input for our experimental multipole refinements. Therefore, the same multipole parameters were adjusted to the experimental data that were used as fixed scattering factors in invariom refinement. Chemical constraints, which are used in the program XDLSM [62] to reduce the number of least-squares parameters in case an identical chemical environment is assumed, were assigned in those cases, where the same invariom scattering factor name was found. Local-atomic site symmetry was chosen in analogy to the model compounds used to generate the database parameters. This way we assured that invariom and experimental multipole refinement were based on the same multipole model. In the multipole refinement, hydrogen atoms were treated as a hybrid scattering factor, where the radial screening parameters κ and the higher multipoles with $l_{\max} \geq 1$ were kept at the database values to increase the reliability of the dipole moments obtained (see comments in Sect. 2.1). The invariom geometry was kept. X–H bond distances were set to values obtained in geometry optimizations of model compounds as used in the invariom database [27]. In Table 5 we list the magnitudes of the dipole moments from both invariom and free multipole refinements.

For comparison, molecular dipole moments from a single-point calculation of the experimental geometry are also given. The DFT basis was D95++(3df,3pd) and the functional B3LYP. In analogy to Sect. 3 we include values for the multipole projection of the single-point calculations, which are found to be systematically lower than the values from the single-point calculation. Again, limitations of the Hansen/Coppens multipole model in accurately reproducing dipole moments become apparent.

On the positive side we can see immediately that the extreme spread of values that was observed in a large number of studies [22] is absent. Experimental values are quite close to the theoretical results and reliable estimates from measured intensities are possible following our recommendations on H-atom treatment. However, the accuracy of the multipole model does not allow to clarify whether the enhancement itself is “fact or artefact.” This statement is supported by choosing the theoretical single-point dipole moments as reference for assessing a possible enhancement. Since these are systematically smaller than the invariom result, which appears to always yield higher dipole moments than the single-point result, the estimate of the enhancement is also systematically higher (Table 5, right column). These results would be even more pronounced were multipole-projection values (given in brackets in Table 5) of the single-point result taken, which are again systematically lower than the invariom result. Causes for the invariom result giving a higher dipole moment probably lie in the underlying approximation of summing a molecular density from fragments. In conclusion, a more flexible model is needed to answer the question of a possible enhancement. Relying on the answer from theoretical computations (see Sect 4.2) is insufficient, since theoretical calculations predict a pronounced dipole-moment enhancement in all cases in disagreement with experimental findings. We therefore look at results from X-ray constrained wavefunctions in the next section.

Table 6 Dipole moments D in Debye from Hirshfeld-atom refinement (D_{HAR}) and from X-ray constrained wavefunctions (D_{XCW}) from both Hartree–Fock and Density Functional Theory using the in-cluster HAR geometry and the DZP basis set

Structure	HF			DFT		
	D_{HAR}^3	D_{XCW}	$\Delta\mu/[\%]$	D_{HAR}^3	D_{XCW}	$\Delta\mu/[\%]$
L-Alanine	12.6	13.4	+6	11.0	11.9	+8
L-Cysteine	11.7	12.3	+5	10.1	10.7	+6
L-Glutamine	12.7	14.2	+12	11.2	12.8	+14
D,L-Serine	14.0	15.1	+8	12.2	13.1	+7
L-Threonine	11.2	12.9	+15	10.0	12.1	+21
D,L-Aspartic Acid	11.6	12.8	+10	10.4	11.4	+9
D,L-Histidine	16.1	17.1	+6	14.1	15.1	+7

5.2 Molecular Dipole Moments and Their Enhancement from Hirshfeld-Atom Refinement and Wavefunction Fitting

Wavefunction fitting [8, 15–18] can be expected to yield better accuracy for properties derived from experimental Bragg data than those derived from the multipole model, since a basis-set description of chosen sophistication can be used to model the electron density. We have chosen the DZP basis [63] already used in Sect. 4.1 (see Table 4). Wavefunction fitting requires a weighting of the experimental data with a multiplier [8] to extract the information content of the individual experimental observations and their standard uncertainties. Hence, the fitting procedure is more demanding than a single-point cluster calculation and needs several repetitions, gradually increasing the multiplier. Geometries obtained from Hirshfeld-atom refinement with cluster charges and dipoles were used and kept fixed. Geometries were assured to be consistent with the basis set this way, which would not have been achieved had invarioms geometries been used. Also, effects on the geometry due to small changes in the dipole moment are avoided.³ In Table 6 dipole moments obtained are given together with the isolated-molecule result already reported in Table 4. Since the same geometry is used, an enhancement or decrease is reported. A direct comparison to dipole-moment enhancements derived using the Hansen/Coppens multipole model (Table 5) is possible. Analogous to the multipole-model result a strong increase of the in-crystal dipole moment is not observed as it was predicted from theory. Trends from wavefunction fitting hence confirm the results obtained from the multipole model.

³ A change in dipole moment due to small adjustments of the geometry between Hirshfeld-atom and invariom refinement can be studied by comparing the dipole to the value given in Table 4, where the invariom geometry was used as input. It is found to be insignificant, with the largest difference being 0.1 Debye for Alanine.

6 Discussion: Agreement Between Experimental and Theoretical Results

We would like to obtain an experimental estimate of the dipole moment using as little prior information as possible, since the approximations used in theoretical approaches benefit from independent validation. Unfortunately, experimental data are necessarily limited in resolution. Therefore, a least-squares approach relying on experimental data does not allow an infinite number of parameters to be refined. This restriction leads to an inflexible model and consequently comparably inaccurate dipole moments: when attempting to reproduce the theoretical results limitations of the experimental multipole model approach become apparent.

Such restrictions do not apply to wavefunction fitting, since it combines theory and experiment, using the experimental data as additional information weighted by a multiplier. The quantum-chemical density model is required to fit the experimental data, while simultaneously minimizing the energy of the – now experimental – wavefunction. This allows obtaining a more accurate result at the expense of not providing an entirely experimental result in a strict sense. However, the multipole model also uses a frozen core and fixed radial functions from atomic calculations as input, so that the concept of a purely experimental result from X-ray diffraction seems questionable in general, although this point of view might be considered exaggerated. In spite of such technical details the following results emerge:

1. Accurate in-crystal dipole moments can indeed be obtained from X-ray diffraction.
2. The accuracy of the multipole model is limited, but it can nevertheless provide an estimate of the in-crystal result from experiment after careful modelling.
3. Despite its shortcomings, the multipole-model estimate for the seven experimental data sets studied here is satisfactory. It required taking into account invariom database κ -parameters and optimized X–H distances from model compounds.
4. An estimate of the molecular dipole moment for the crystal geometry can also be obtained entirely from scattering-factor databases without the need for expensive calculations. The invariom result anticipates some of the in-crystal enhancement when compared to single-point calculations for zwitterions.
5. For heavier nuclei (here: S, Cl) the multipole model fails to reproduce dipole moments accurately. Inclusion of κ' -parameter, which can often not be refined in a reliable manner from experimental X-ray diffraction data, is helpful but no remedy for the inaccuracy. Databases can provide κ/κ' values for different chemical environments. Fixing the scale factor in the multipole projection to unity can considerably alter the result, e.g. for sulphur containing compounds.
6. Concerning the enhancement of the dipole moment from experiment in the bulk, and for accurate determinations of dipole moments in general, studies should be preferably based upon a basis-set density representation like it is

used in wavefunction fitting. As a consequence, not only the accuracy but also the computational effort for providing an answer in each particular case is increasing.

7. Dipole moments from cluster calculations consistently predict a substantial in-crystal enhancement. Experimental results, both using the multipole model and wavefunction fitting, suggest a less pronounced enhancement for the amino acids.

7 Conclusion

Seven measurements of high-resolution Bragg data on amino acids published earlier were re-evaluated for a determination of their dipole moments with the Hansen/Coppens multipole model and by a basis-set representation as used in Hirshfeld-atom refinement/wavefunction fitting.

Initially, the general ability of the multiple model to reproduce dipole moments of isolated-molecular calculations was studied by a projection of twenty-two small-molecule electron densities with simulated structure factors. Theoretical dipole moments are usually reproduced within $\approx 20\%$ of the theoretical result, but can deviate by more than 70% when heavier elements are involved. For the zwitterionic amino acids a systematic underestimation of the dipole moment is seen in the multipole projection. Choices in the treatment of the radial screening parameters κ/κ' as well as the hydrogen-atom scattering are relevant for obtaining a reasonable estimate. Invariom modelling applied on the theoretical geometries – which is also based on the multipole model – equally allows reproducing the dipole moment within a similar range. Here, amino-acid dipole moments are overestimated with respect to the gas phase. On the positive side, the computational effort to obtain dipole moments from database density parameters is minimal. Molecular dipole moments could and should therefore be a routine result of accurate structure determinations. Design choices in the invariom database have been chosen to enable reliable estimates as far as possible.

Refinement of multipole parameters with experimental data allows obtaining the dipole moment of a molecule as part of the crystal. Based on refinements of the seven data sets mentioned, we made suggestions how to make experimental determinations more reliable. Hybrid scattering factors for H-atoms from database approaches and inclusion of accurate optimized X–H bond distances increase the reliability of the determination.

Comparing the experimental dipole and the theoretically predicted invariom moment (or the single-point values) allows assessing dipole-moment enhancements in the bulk, although model inaccuracies limit the reliability of the results. A similar comparison of isolated-molecular calculations and wavefunction fitting using a basis-set representation yields more accurate and consistent results. A density functional theory treatment (BLYP functional) with the DZP basis was performed for that purpose.

To get an estimate on possible dipole-moment enhancements from theory, molecular calculations embedding a central molecule in a field generated by a surrounding cluster of point charges were carried out. These calculations took into account crystal symmetry and used atomic coordinates from invariom refinement. Whereas a considerable enhancement in the bulk is predicted by these theoretical approaches, experimental multipole-model results seem to agree better with isolated-molecular values and do not predict such a considerable enhancement.

To obtain the best possible theoretical estimate for dipole-moment enhancements in the solid state while still taking into account the experimental diffraction data, Hirshfeld-atom refinement within a cluster of point charges and dipoles using density-functional theory and with Dunning's correlation consistent cc-pVTZ basis [64] was performed. Hirshfeld-atom refinement is currently the most sophisticated density model available to refine structural parameters from experimental diffraction data. Theoretical DFT dipole moments allowed putting the experimental results into perspective. The method predicts a significant in-crystal dipole-moment enhancement. However, the extent of the enhancement is a lot lower in wavefunction fitting (5–15% rather than 28–48% for DFT electron densities). It is conceivable that inclusion of molecular van der Waals interactions as provided in dispersion corrected density functionals [65] might bring theoretical estimates and experiment measurements of dipole moments in the solid state closer together.

Our conclusion is that density models more sophisticated than the Hansen/Coppens multipole model increase the reliability of dipole-moment determinations. The accuracy of invariom-database predictions could probably benefit from more accurate density descriptions as well. Wavefunction fitting can currently provide the most accurate experimental in-crystal dipole moment in the presence of high-quality data, albeit at a comparably high computational cost.

Note added in proof A recent experiment shone light on the discrepancy between Hirshfeld-atom refinement within a cluster of point charges and wavefunction fitting of the molecules.

Current program updates in TONTO now allow to perform wavefunction fitting in the presence of surrounding point charges. These lead to an additional enhancement with respect to fitting the molecule only — in better agreement with the experimental data.

We ascribe this to an additional electron density polarization in the vicinity of the core region, which cannot be retrieved with the frozen core in the standard Hansen/Coppens multipole model.

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