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On QM/MM and MO/MO cluster calculations of all-atom anisotropic displacement parameters for molecules in crystal structures

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The practical aspects of *ab initio* calculation of anisotropic displacement parameters (ADPs) for molecules in crystal structures are investigated. Computationally efficient approaches to calculate ADPs are QM/MM or MO/MO methods, where quantum chemical calculations are split into a high-level and a low-level part. Such calculations allow geometry optimizations and subsequent frequency calculations of a central molecule in a cluster of surrounding molecules as found in the crystal lattice. The frequencies and associated displacements are then converted into ADPs. A series of such calculations were performed with different quantum chemical methods and basis sets on the three zwitterionic amino-acid structures of L-alanine, L-cysteine and L-threonine, where high-quality low-temperature X-ray data are available. To scale and compare calculated ADPs, X-ray ADPs from invariom refinement were used. The future use of calculated ADPs will include the investigation of systematic errors in experimental X-ray diffraction data. Completion of an isotropic structural model is already possible. Calculated ADPs might also make it possible to perform charge-density studies on data sets of limited resolution/coverage as obtained from weak scatterers, high-pressure measurements or to deconvolute electron density obtained from the maximum-entropy method.

1. Introduction

Thermal motion and electron density are convoluted, and one cannot clearly distinguish between them from X-ray diffraction (XRD) data alone (Hirshfeld, 1976). However, if either the thermal-motion behaviour or electron-density distribution $\rho(\mathbf{r})$ (EDD) are known to a good approximation, either information can, in principle, be used to obtain the missing property from an experiment. Following this line of thought, the ability to calculate anisotropic displacement parameters (ADPs) for molecules in crystal structures would allow application of charge-density methodology to data sets of 'normal resolution' (defined by fulfilling or exceeding *Acta Cryst. C* data-resolution requirements), since a considerable number of least-squares parameters could be omitted. Recent efforts have shown that this could indeed be a feasible approach. A known EDD was imposed on a single-crystal X-ray diffraction data set of limited resolution to obtain ADPs deconvoluted from the EDD (Dittrich *et al.*, 2008). In our efforts towards this goal we have attempted to use these ADPs as fixed parameters in a charge-density study of normal-resolution data (Dittrich *et al.*, 2009). Since this largely amounts to block-matrix refinement,[1] an independent source of information on ADPs would be preferred and we investigate here how ADPs can be calculated efficiently *via* cluster calculations. Suitable and computationally efficient approaches appear to be QM/MM and MO/MO methods such as the ONIOM[2] implementation (Svensson *et al.*, 1996; Dapprich *et al.*, 1999) of the *Gaussian* (Frisch *et al.*, 2009) program, where a quantum chemical calculation is split into a high-level and a low-level part. QM/MM calculations can be considered a mature method and have found many uses, for example in structural biology (Senn & Thiel, 2007). They allow geometry optimizations of a central molecule in a cluster of surrounding molecules as found in the crystal lattice. A recent application in crystallography was the geometry optimization of an excited-state molecule in a cluster of surrounding ground-state molecules (Kaminski *et al.*, 2010).

A C program to generate input clusters for use with the *Gaussian* program was coded. Earlier versions have already seen use for generating clusters for the amino acid sarcosine (Dittrich & Spackman, 2007) and the explosive FOX-7

[1] In the present case, however, ADPs are kept fixed and blocks of parameters are not refined in turn.

[2] QM/MM stands for quantum mechanics/molecular mechanics and MO/MO stands for molecular orbital/molecular orbital, where different methods/basis sets can be combined. Svensson *et al.* (1996) introduced ONIOM as an abbreviation for 'our own *n*-layered integrated molecular orbital and molecular mechanics'. The connotation to the shell-like structure of an onion was most likely intended.

Table 1
Structures, their crystallographic details and citations of earlier structural work performed on them.

Structure	Space group	Z, Z'	Experimental temperature (K)	Resolution in $\sin\theta/\lambda$ (Å^{-1})	Radiation
L-Alanine†	$P2_12_12_1$	4, 1	23	1.08	Mo $K\alpha$
L-Cysteine‡	$P2_12_12_1$	4, 1	30	0.72	Mo $K\alpha$
L-Threonine§	$P2_12_12_1$	4, 1	19	1.35	Ag $K\alpha$

† References: Lehmann *et al.* (1972); Destro *et al.* (1988, 1989); Gatti *et al.* (1992); Wilson *et al.* (2005). ‡ References: Kerr & Ashmore (1973); Kerr *et al.* (1975); Moggach *et al.* (2005). § References: Shoemaker *et al.* (1950); Ramanadham *et al.* (1973); Janczak *et al.* (1997); Flaig *et al.* (1999).

(Meents *et al.*, 2008) for calculating the internal contribution of H-atom ADPs (Whitten & Spackman, 2006). Details on the program and its use can be found below in §4.

A series of calculations on the three amino acids L-alanine, L-cysteine and L-threonine were performed to obtain approximate ADPs and assess their quality. High-quality XRD data were available from the literature or from the authors. Structures with only one molecule crystallizing in the asymmetric unit of the unit cell were chosen to facilitate ADP comparisons. In the calculation we treat a central molecule of interest with various high-level basis sets, and the surrounding layer of molecules with lower-level force-field (QM/MM) or quantum chemical approximations (MO/MO). Both neutron diffraction experiments, mostly at room temperature,[3] but also charge-density or high-quality structure determinations at low temperature have already been performed on these molecules (see Table 1 for references). Hence, re-refinement of the X-ray data using non-spherical invariom scattering factors (Dittrich *et al.*, 2004, 2005, 2006) was possible to generate high-quality starting structures free of bias from the independent-atom model. We focus on the most recent data sets at the lowest temperature. Table 1 contains selected experimental details of these structures that provided input geometries for all our calculations.

Concerning the input geometry, structural information from invariom refinement is suitably accurate for successful two-layer ONIOM geometry optimizations, and we find that accurate H-atom bond distances as included in the invariom database (Dittrich *et al.*, 2006) are crucial for convergence. Alternatively, geometries from Hirshfeld atom refinement (Jayatilaka & Dittrich, 2008) could have been used. Moreover, electrostatic embedding using point charges from a fit to the electrostatic potential (Besler *et al.*, 1990) is usually required. It has been shown that the 'internal' modes of H-atom vibrations can indeed be predicted from such calculations (Whitten & Spackman, 2006). The next step, obtaining all-atom vibrational frequencies that can be converted to ADPs, requires a realistic description of molecular translation and rotation in the cluster, including the interaction between central and surrounding molecules, which is the focus of this work. The level of theory required for such a realistic description is investigated, initially using data measured at a temperature of around 20 K. Predicted ADPs are then used in refinements on X-ray data in place of freely refined ADPs, after applying an isotropic overall scale factor to account for lattice modes. We use the crystallographic R factor as a simple way to judge the success of the various theoretical approximations involved on the basis of experimental data.

2. Experimental data and initial refinement procedure

X-ray data of L-alanine (Destro *et al.*, 1988), L-cysteine (Moggach *et al.*, 2005) and L-threonine (Flaig *et al.*, 1999) were obtained from the authors or the web site of the IUCr journal *Acta Crystallographica, Section C*. Data were chosen to have been measured at very low temperatures of around 20 K. Table 1 lists earlier work and selected crystallographic details of the three structures chosen. To obtain a suitable and consistent starting model for our quantum chemical calculations, X-ray data were remodelled with invarioms by invoking the program *INVARIOMTOOL* (Hübschle *et al.*, 2007), thereby taking into account the non-spherical electron density in the valence shell. Details of invariom refinement and model compounds used are given in the supplementary information.[4] Bond distances to hydrogen atoms were set to theoretical distances as provided in the database. Clusters of molecules were generated from the molecular structures after invariom refinement, with the program *BAERLAUCH*, as described in §4.

3. Theoretical background

The theory of molecular vibrations is well understood and explained in many textbooks (see *e.g.* Wilson *et al.,* 1955). Equally this holds for molecular vibrations in crystallography, for example as introduced by Willis & Pryor (1975). The novel aspect of this study is the use of a cluster to provide the environment of a central molecule including hydrogen bonding. Translational, rotational and screw (TLS) motion (Schomaker & Trueblood, 1968) are partly described this way while phonon modes are ignored. Earlier studies based on a theoretical calculation of a single molecule (Flaig *et al.*, 1998) relied on a TLS fit that is not required here. We refer the reader to these four references and next focus on practical questions on the calculation of ADPs by *ab initio* methods.

4. *BAERLAUCH* to generate clusters from X-ray structures

The computer program *BAERLAUCH* was coded. It allows the generation of variable-sized clusters as specified by user input from fractional coordinates, where a minimum distance from each atom of the central molecule is given, and

[3] ADPs refined from neutron diffraction are often reported in the literature, while intensities from neutron diffraction are usually not available.

[4] Supplementary data for this paper are available from the IUCr electronic archives (Reference: TN5019). Services for accessing these data are described at the back of the journal.

writes input for ONIOM calculations with the program *Gaussian* (Frisch *et al.*, 2009). *BAERLAUCH* is based on the C source code of the program *CRYSTAL96* by Larry Finger (Geophysical Laboratory, Carnegie Institution of Washington, USA) and Martin Kroeker (Organic Chemistry, Technical University of Darmstadt, Germany). The code was retrieved from the Crystallography Source Code Museum (http://www.ccp14.ac.uk/ccp/web-mirrors/source_code_museum/museum/) and modified/extended for our own purposes. Code for space-group symmetry evaluation has been left basically unchanged.

The main *BAERLAUCH* functionality is the generation of clusters. A 4 Å cluster is one in which all molecules surround a central molecule and contain an atom that is within 4 Å of any atom of the central molecule. Such a cluster necessarily contains atom pairs separated by more than 4 Å because complete molecules are generated. Besides the user-specified cluster size, method, basis set, number of central processing units and memory requirements as user-specified input, *BAERLAUCH* mainly requires unit-cell/space-group information and fractional coordinates. To verify the input and to visualize the clusters generated, a *SCHAKAL99* (Keller & Pierrard, 1999) file is generated. When the aim is for a force-field description of the surrounding cluster, force-field atom types also need to be specified. The input file format is given in the supplementary information. The main program output is given in a *Gaussian03/09* (Frisch *et al.*, 2009) file that can be used directly for QM/MM or MO/MO ONIOM calculations. *BAERLAUCH* can be obtained from the correspondence author free of charge as a binary for Windows and Linux operating systems.

5. Practical details of the computational procedure

Two-layer ONIOM calculations were initially performed at the Hartree–Fock (HF) level of theory with the basis sets 3-21G or 6-31G(d,p) for the central molecule to be geometry optimized at the high level. Surrounding molecules in the cluster, the low level, were treated with the universal force field UFF (Rappé *et al.*, 1992). These combinations generally enabled us to perform *initial* optimizations at comparably low computational cost, while still being able to cover a large fraction of organic chemistry. Convergence with these method/basis-set combinations allowed us to predict successful convergence with other methods/basis sets in all three cases studied.

Unlike in calculations of isolated molecules, where convergence is easily achieved, cluster calculations fail if the cluster is not a suitable model for the crystal. The initial task prior to interpretation of the results is therefore to achieve convergence.

Convergence mainly depends on a cluster of suitable composition and size. The size was initially varied, and it was observed for the three reported cases, and a number of other cases not discussed here, that cluster sizes of 13–21 molecules are common for crystals of small molecules. Cluster sizes depend on the space group and packing (Kitaigorodskij, 1961). Two other factors are crucial to achieve convergence: the quality of the initial structure and electrostatic embedding. Both are usually mandatory for reaching it. To obtain high-quality input structures, the above-mentioned invariom refinements were performed. Such refinements allow one to correct asphericity shifts (Coppens *et al.*, 1969) and to set theoretical X—H bond distances from the invariom database also for such data sets where high resolution ($\sin\theta/\lambda \geq 1$ Å^{-1}) is not reached.[5] Electrostatic embedding involved the use of potential-derived atom-centred point charges (Besler *et al.*, 1990) for all but the central molecule in a cluster. A single-point energy calculation of only the central molecule was performed to obtain point charges prior to optimization from a fit to the electrostatic potential. These charges were then assigned to all molecules surrounding the central one with the program *BAERLAUCH*. To minimize the computational effort, cluster sizes were chosen to be as small as possible while still allowing convergence to be reached. In addition, clusters were chosen to provide a balanced environment with the same number of molecules in each direction of the central molecule of interest. The centre of mass of the cluster then remains close to that of the isolated molecule.

From all calculations for which results are reported below in §6, analytical vibrational frequencies were determined (Ochterski, 1999). In contrast to isolated molecules, where 'tight' or 'very tight' convergence criteria and accurate numerical integration grids are recommended and usually necessary to obtain a meaningful result, we found that the slow convergence due to the large number of atoms in the cluster usually grants the location of the correct minimum, which is then sufficient to avoid the occurrence of negative frequencies.[6] To make sure that only the vibrations of the central molecule were analysed, infinite masses were assigned to the surrounding cluster molecules (as suggested by M. A. Spackman, University of Western Australia, Perth, Australia). All $3N$ frequencies of the central molecule were next converted to atomic displacements by the program *XDVIB* (Koritsánszky *et al.*, 2003). This amounts to a molecular Einstein approach. *XDVIB* was locally modified in order to read in all $3N$ vibrational frequencies for the central molecule and not $3N-6$ ($3N-5$) ones for isolated (linear) molecules. After conversion of frequencies and their corresponding Cartesian displacements into ADPs in the crystal frame, calculated ADPs were used in place of refined ADPs.

Prior to refinement against experimental data, calculated ADPs need to be scaled. The necessity for scaling frequencies as obtained from quantum chemical calculations is well known (Scott & Radom, 1996), whereas the precision of such scale factors is not (Irikura *et al.*, 2005). We therefore chose to use the experimental ADPs for providing reference magnitudes, also since systematic experimental errors might require such scaling anyway. We decided that a single scale factor would

[5] Even when neutron data are used, setting X—H bond distances can improve convergence behaviour.

[6] The *Gaussian03/09* option opt = CalcFC improves the convergence behaviour and is highly recommended. Usage of tight or very tight convergence criteria is recommended, but does not change ADPs by much.

create the least bias. To obtain this scale factor, a least-squares procedure described earlier (Blessing, 1995) was followed, evoking the program *UIJXN* assuming unit weights. Only the diagonal elements of the invariom ADPs were used as reference data.[7] The single scale factor obtained from *UIJXN* was then used to scale the calculated ADPs to replace experimental ADPs from invariom refinement.[8] Auxiliary programs for reading/writing *XD* input files and for converting input for *UIJXN* were written for that purpose.

6. Results and discussion

6.1. The influence of cluster size on ADPs

Initially the influence of the cluster size on the calculated ADPs was studied in all three amino-acid structures. The method/basis HF/3-21G:UFF was chosen to address this question, since computational requirements are bearable with UFF, but quickly become prohibitive for a QM treatment of the whole system. Cluster sizes were increased systematically from 13, 15, 17, 19 to 21 molecules. For L-alanine this corresponds to distances of 3.5, 3.75, 4.25, 4.5 and 4.75 Å from any atom of the central molecule to any atom of a surrounding molecule. For a 13-molecule cluster of L-alanine convergence could only be achieved after a restart of a failed optimization. For smaller clusters than the ones chosen, convergence was not reached, while for even larger clusters, *i.e.* 23 molecules of L-alanine, similar convergence problems were encountered as for the 13-molecule cluster. For L-cysteine and L-threonine, which crystallize in the same space group as L-alanine, the same series were calculated. Here the distances chosen for cluster generation were 3.25 (13), 3.75 (15), 4.0 (17), 4.25 (19) and 5.5 Å (21) for cysteine and 3.0 (13), 3.75 (15), 4.5 (17), 4.6 (19) and 4.65 Å (21) for L-threonine, with the cluster size in parentheses in each case. Fig. 1 shows that a cluster of 17 molecules yields the best agreement with the experimental ADPs for L-alanine and hence would seem most suitable, whereas for L-cysteine the best agreement can be reached with a cluster of 13 as well as 15 molecules. For L-threonine clusters of 15 and 17 molecules give almost the same quality of fit.

A consistent finding in all three cases is that increasing the cluster size above 17 molecules does not lead to better results. The high-layer method/basis HF/3-21G ignores correlation effects and is considered inadequate for accurate calculations, but seems suitable to initially determine the optimal cluster size for organic molecules. This was confirmed by a series of calculations where the high-layer method/basis B3LYP/6-31G(d,p) was chosen. These calculations yield very similar results, as seen in Fig. 1.

For subsequent calculations we chose a 15-molecule cluster in all three cases, as depicted in Fig. 2. The smallest cluster for which convergence can be achieved with ease can probably already be seen as a suitable cluster; the small 15-molecule cluster also minimizes the computational effort.[9] A systematic investigation of the best cluster sizes depending on the packing patterns in other space groups than $P2_12_12_1$ would certainly be interesting, but is not within the scope of this work.

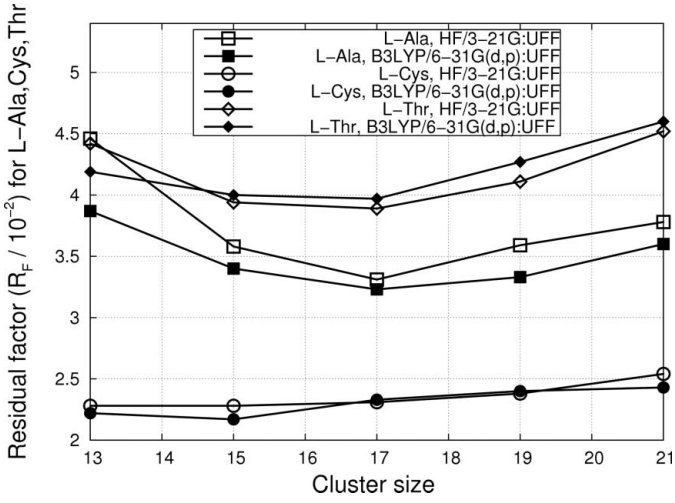

Figure 1
R factor plotted *versus* increasing number of molecules in chosen clusters for L-alanine, L-cysteine and L-threonine with the method/basis-set combinations HF/3-21G:UFF and B3LYP/6-31G(d,p):UFF.

6.2. The influence of the basis set and the method chosen

After having decided on a suitable cluster size, we next focus on comparing different methods and basis sets. For that purpose the quality of the basis-set description of the central molecule was systematically altered. Calculations with the Pople basis sets 3-21G, 6-31G(d,p), 6-311G(d,p), 6-311G(2d,2p) and 6-311++G(2d,2p), chosen for their computational efficiency, were performed. Potential-derived point charges of only the central molecule were calculated each time prior to optimization by single-point energy calculation. Different levels of theory were also considered. To study the influence of electron correlation on ADPs, Hartree–Fock results were compared to results from density functional theory (DFT) (with the hybrid B3LYP and the double-hybrid density functional B2PLYP), and to results from Møller–Plesset second-order correlation energy correction. The role of van der Waals interactions is considered explicitly in the B2PLYP method (Grimme, 2006). Overall four methods were compared: HF, MP2,[10] B2PLYP and the B3LYP functional. As in our initial calculations, these method/basis-set choices were

[7] Using all six elements of the U_{ij}'s gave nearly identical results.
[8] The scale factor could of course also be obtained without any experimental input, since an empirical procedure where scale factors are determined by systematic variation is also feasible. Nevertheless, since these ADPs are used in refinements on experimental data, they are not independent of experiment in a strict sense, even more so since phonon modes are not predicted in cluster calculations.
[9] The dipole moment of the whole cluster seems to correlate with the quality of ADPs. For both L-cysteine and L-threonine the dipole moment is minimal for the 15-molecule cluster, for L-alanine it is the second lowest. We assume that, not only for zwitterions, a low cluster dipole moment is characteristic and indicative of a balanced environment.
[10] For MP2 calculations the *Gaussian* keyword density = current needs to be used.

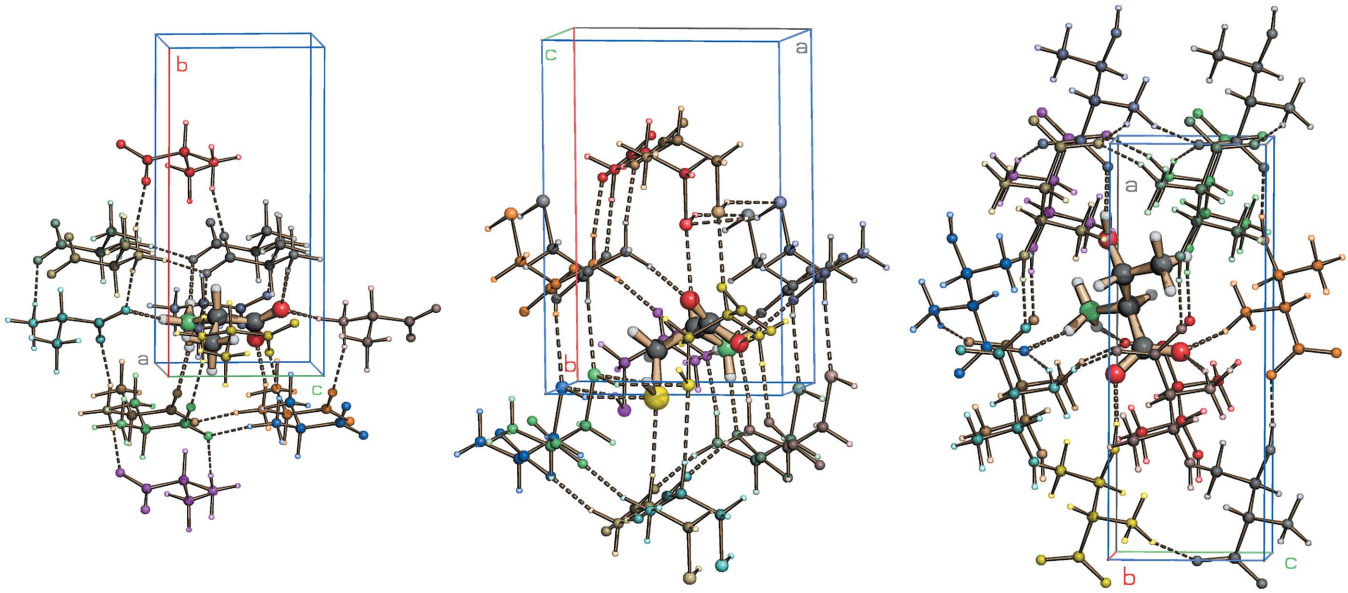

Figure 2
SCHAKAL representations (Keller & Pierrard, 1999) of the clusters of (*a*) L-alanine, (*b*) L-cysteine and (*c*) L-threonine (left to right) used in most of the optimizations consisting of 15 molecules each. The respective unit cells are included. The central molecule which is geometry optimized is highlighted.

combined with the UFF force field (Rappé *et al.*, 1992), leading to different sets of ADPs.

As for studying a suitable cluster size in §6.1, method and basis-set performance was assessed by using calculated ADPs directly in the experimental refinements, replacing the freely refined ADPs after applying a single least-squares ADP scale factor as described in §5. We can see in Fig. 3 that extended basis sets are not needed and that the 6-31G(d,p)[11] basis usually gives a good fit to the experimental X-ray ADPs at around 20 K. However, this basis set does not consistently yield superior results in all three cases. Nevertheless, taking into account the computational effort of using more extended basis sets leads us to the conclusion that there is currently no need for considerably increasing the basis-set size for ADP calculations of this kind. Nevertheless, improving the description of the central molecule will certainly remain an option while more experience is being gained with these calculations.

The B2PLYP functional by Grimme (2006) does not lead to an improvement when compared to the B3LYP functional. An MP2 treatment is superior to all other methods for L-alanine, but inferior to the B3LYP functional for the 6-31G(d,p) and 6-311G(d,p) bases both in terms of computational requirements as well as the performance with the experimental data in terms of *R* factor for L-threonine; since the B3LYP functional also performs rather well for L-cysteine, we conclude that acceptable results can be obtained with DFT and the B3LYP functional, which is a good compromise in terms of computational requirements. When computational efficiency is an important factor, the HF method is a good choice, especially since systematic improvements of the other methods are not seen in a consistent manner, possibly due to remaining systematic errors in the X-ray data or to favourable error cancellation of the various theoretical approximations involved.

6.3. The influence of the treatment of the surrounding cluster

The UFF force field must be considered too limiting in accurately describing hydrogen bonding as present in the three amino acids. More recent force-field implementations other than UFF necessarily share some limitations inherent to those methods. Hence, rather than comparing other force fields, we have chosen to alter the theoretical level of treating the surrounding cluster. Since the computational effort now increases substantially, only the basis sets 3-21G and 6-31G(d,p) were chosen to model the surrounding molecules.[12] These basis sets were combined with the two computationally least demanding methods from our initial benchmark, DFT and HF, with the basis set 6-31G(d,p) for the central molecule.[13] Future hardware and software development will facilitate increasing the sophistication of these calculations. Fig. 4 shows that the treatment of the surrounding cluster is of major importance for the quality of ADPs. Surprisingly, the higher level of theory (DFT) is

[11] Ochterski (1999) recommends choosing a fine grid for DFT calculations, as is the default in *Gaussian09*. An ultra-fine grid was tested [option Int(Grid = UltraFineGrid)] for L-alanine and L-cysteine. Differences in ADPs and scale factor are detectable but small.

[12] PM3, AM2 and HF/STO-3G did not allow us to consistently reach convergence in *Gaussian03* and were therefore discarded. We recommend the use of *Gaussian09* for ADP calculation.

[13] For L-threonine, MP2 calculations already required temporary disk space of $\simeq$ 1 TB and RAM memory of 24 GB. Computation time took weeks on a current Xeon 8 cpu server. We therefore decided that the computational requirements for MP2 MO/MO calculations are currently too high for a method that is supposed to be computationally efficient.

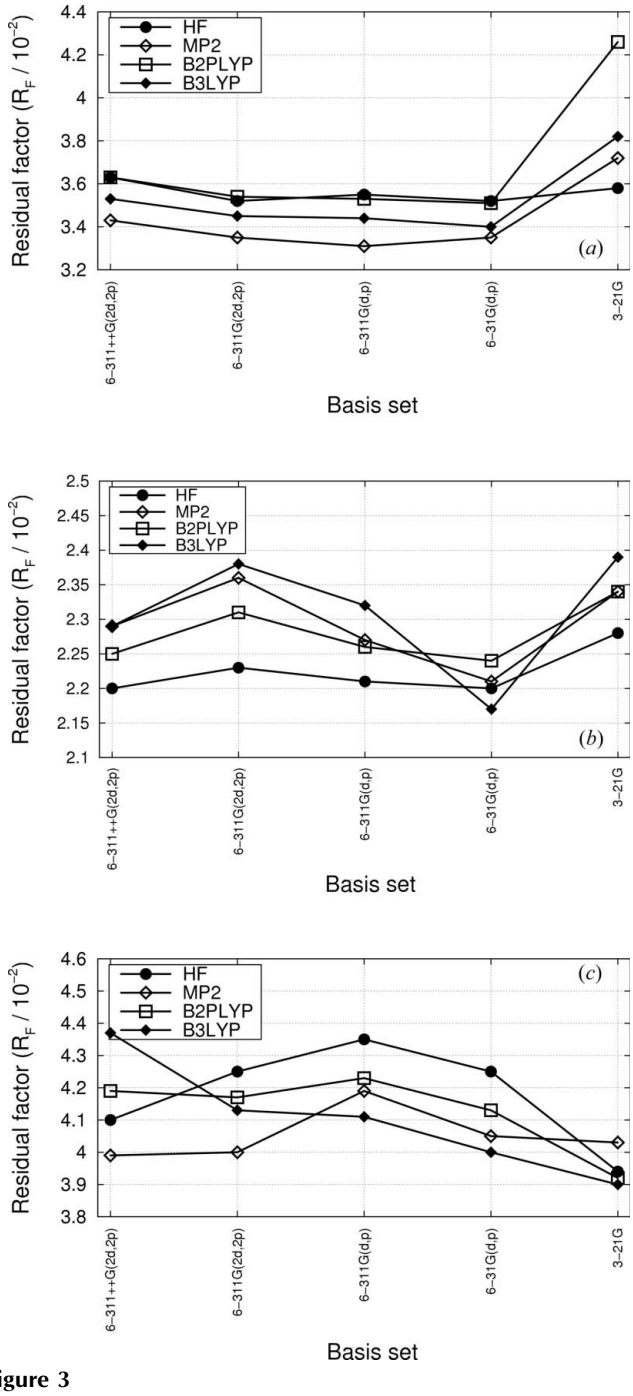

Figure 3
R factor plotted *versus* basis set for different methods for (*a*) L-alanine, (*b*) L-cysteine and (*c*) L-threonine.

inferior to the HF treatment in the MO/MO calculations, while it gives a superior result in the QM/MM calculations. The combination HF/6-31G(d,p):HF/3-21G seems sufficient to describe the surrounding cluster. Increasing the basis set to 6-31G(d,p) only leads to better results for L-alanine. This last point is unsatisfactory from a theoretical point of view and requires further study.

Fig. 4 also compares two experimental refinements without theoretical input (ignoring the scattering factor as 'theoretical' input) and puts the theoretical efforts into perspective: an

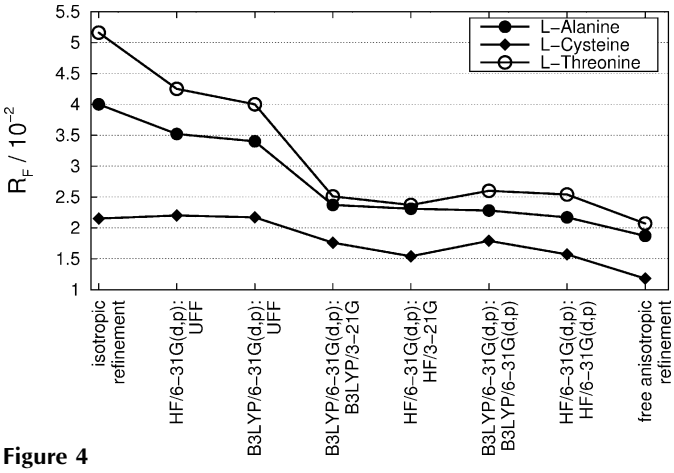

Figure 4
R factor for free isotropic and anisotropic refinements compared to HF/6-31G(d,p):UFF, B3LYP/6-31G(d,p):UFF QM/MM as well as B3LYP/6-31G(d,p):B3LYP/3-21G and HF/6-31G(d,p):HF/3-21G MO/MO predictions of thermal motion for all three amino acids studied.

isotropic refinement of thermal motion and the free refinement of ADPs are compared to using scaled theoretical ADPs. It becomes obvious that, while the results of a free refinement cannot be achieved by ADPs from our calculations, the results are definitely superior to the isotropic description. However, only the harmonic approximation was taken into account in our quantum chemical calculations. Hence, *anharmonic* vibrational motion, which can become significant at higher temperatures, has not been predicted at the current stage. We next want to test the range of applicability of the computational scheme against data measured at higher temperatures. It also remains to be studied whether calculated ADPs can help to identify systematic errors included in experimental ADPs, *e.g.* absorption effects. Calculated ADPs open up a number of other interesting applications, which remain to be studied in detail.

7. Conclusion

Information on anisotropic displacements in the crystal, molecular electron density, the interaction between molecules in the crystal lattice and on conformational flexibility is all included in experimental Bragg intensities. Full periodic calculations allow one to predict most of this information, but require a substantial computational effort. Computationally less demanding than periodic calculations are QM/MM or MO/MO approaches like the ONIOM implementation. We have shown that approximate all-atom ADPs can be calculated by ONIOM cluster calculations. The future aim is to make such calculations more routinely feasible and to establish this methodology as an alternative to neutron diffraction experiments.

Calculated atomic displacements were used in place of freely refined X-ray ADPs for the crystal structures of L-alanine, L-cysteine and L-threonine. The performance of several methods and basis sets was compared. The more sophisticated MO/MO calculations allow one to match the freely refined experimental ADPs quite well only after

refinement of a single scale factor. Despite the early stage of this research we can already reach a qualitative agreement between experiment and theory that is similar to the agreement between different X-ray and neutron diffraction experiments (Coppens *et al.*, 1984). The potential applications of calculated ADPs include refinement of data sets with limited coverage, as common for example in high-pressure crystallography. Studies of systematic errors included in experimental Bragg data by imposing ADPs *and* electron density are in progress. Charge-density studies of data sets that do not extend to high resolution and deconvolution of dynamic electron-density distributions as obtained from the maximum entropy method are conceivable. Future work will show whether calculated ADPs are sufficiently accurate for such purposes. Calculated ADPs are already an improvement in cases when experimental data only allow one to refine isotropic displacement parameters.

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References

Besler, B. H., Merz, K. M. & Kollman, P. A. (1990). *J. Comput. Chem.* **11**, 431–439.
Blessing, R. H. (1995). *Acta Cryst.* B**51**, 816–823.
Coppens, P., Dam, J., Harkema, S., Feil, D., Feld, R., Lehmann, M. S., Goddard, R., Krüger, C., Hellner, E., Johansen, H., Larsen, F. K., Koetzle, T. F., McMullan, R. K., Maslen, E. N. & Stevens, E. D. (1984). *Acta Cryst.* A**40**, 184–195.
Coppens, P., Sabine, T. M., Delaplane, G. & Ibers, J. A. (1969). *Acta Cryst.* B**25**, 2451–2458.
Dapprich, S., Komáromi, I., Byun, K. S., Morokuma, K. & Frisch, M. J. (1999). *J. Mol. Struct. (Theochem.)*, **461**, 1–21.
Destro, R., Bianchi, R. & Morosi, G. (1989). *J. Phys. Chem.* **93**, 4447–4457.
Destro, R., Marsh, R. E. & Bianchi, R. (1988). *J. Phys. Chem.* **92**, 966–973.
Dittrich, B., Hübschle, C. B., Holstein, J. J. & Fabbiani, F. P. A. (2009). *J. Appl. Cryst.* **42**, 1110–1121.
Dittrich, B., Hübschle, C. B., Luger, P. & Spackman, M. A. (2006). *Acta Cryst.* D**62**, 1325–1335.
Dittrich, B., Hübschle, C. B., Messerschmidt, M., Kalinowski, R., Girnt, D. & Luger, P. (2005). *Acta Cryst.* A**61**, 314–320.
Dittrich, B., Koritsánszky, T. & Luger, P. (2004). *Angew. Chem. Int. Ed.* **43**, 2718–2721.
Dittrich, B., McKinnon, J. J. & Warren, J. E. (2008). *Acta Cryst.* B**64**, 750–759.
Dittrich, B. & Spackman, M. A. (2007). *Acta Cryst.* A**63**, 426–436.
Flaig, R., Koritsánszky, T., Janczak, J., Krane, H.-G., Morgenroth, W. & Luger, P. (1999). *Angew. Chem. Int. Ed.* **38**, 1397–1400.
Flaig, R., Koritsánszky, T., Zobel, D. & Luger, P. (1998). *J. Am. Chem. Soc.* **120**, 2227–2238.
Frisch, M. J. *et al.* (2009). *Gaussian09*. Revision A.02. Tech. Rep. Gaussian, Inc., Wallingford, CT, USA.
Gatti, C., Bianchi, R., Destro, R. & Merati, F. (1992). *J. Mol. Struct. (Theochem.)*, **255**, 409–433.
Grimme, S. (2006). *J. Chem. Phys.* **124**, 034108.
Hirshfeld, F. L. (1976). *Acta Cryst.* A**32**, 239–244.
Hübschle, C. B., Luger, P. & Dittrich, B. (2007). *J. Appl. Cryst.* **40**, 623–627.
Irikura, K. K., Johnson, R. D. & Kacker, R. N. (2005). *J. Phys. Chem. A*, **109**, 8430–8437.
Janczak, J., Zobel, D. & Luger, P. (1997). *Acta Cryst.* C**53**, 1901–1904.
Jayatilaka, D. & Dittrich, B. (2008). *Acta Cryst.* A**64**, 383–393.
Kaminski, R., Schmokel, M. S. & Coppens, P. (2010). *J. Phys. Chem. Lett.* **1**, 2349–2353.
Keller, E. & Pierrard, J.-S. (1999). *SCHAKAL99.* Tech. Rep. University of Freiburg, Germany.
Kerr, K. A. & Ashmore, J. P. (1973). *Acta Cryst.* B**29**, 2124–2127.
Kerr, K. A., Ashmore, J. P. & Koetzle, T. F. (1975). *Acta Cryst.* B**31**, 2022–2026.
Kitaigorodskij, A. I. (1961). *Organic Chemical Crystallography*. New York: Consultants Bureau.
Koritsánszky, T., Richter, T., Macchi, P., Volkov, A., Gatti, C., Howard, S., Mallinson, P. R., Farrugia, L., Su, Z. W. & Hansen, N. K. (2003). *XD – a computer program package for multipole refinement and topological analysis of electron densities from diffraction data.* Tech. Rep. Freie Universität Berlin, Germany.
Lehmann, M. S., Koetzle, T. F. & Hamilton, W. C. (1972). *J. Am. Chem. Soc.* **94**, 2657–2660.
Meents, A., Dittrich, B., Johnas, S. K. J., Thome, V. & Weckert, E. F. (2008). *Acta Cryst.* B**64**, 42–49.
Moggach, S. A., Clark, S. J. & Parsons, S. (2005). *Acta Cryst.* E**61**, o2739–o2742.
Ochterski, J. W. (1999). *Vibrational Analysis in Gaussian.* Tech. Rep. Gaussian, Inc., 340 Quinnipiac St., Bldg. 40, Wallingford, CT 06492, USA.
Ramanadham, M., Sikka, S. K. & Chidambaram, R. (1973). *Pramana*, **1**, 247–259.
Rappé, A. K., Casewit, C. J., Colwell, K. S., Goddard, W. A., Skid, W. M. & Bernstein, E. R. (1992). *J. Am. Chem. Soc.* **114**, 10024–10039.
Schomaker, V. & Trueblood, K. N. (1968). *Acta Cryst.* B**24**, 63–76.
Scott, A. P. & Radom, L. (1996). *J. Phys. Chem.* **100**, 16502–16513.
Senn, H. M. & Thiel, W. (2007). *Atomistic Approaches in Modern Biology. From Quantum Chemistry to Molecular Simulations*, *QM/MM Methods for Biological Systems*, pp. 173–290. Berlin, Heidelberg, New York: Springer.
Shoemaker, D. P., Donohue, J., Shomaker, V. & Corey, R. B. (1950). *J. Am. Chem. Soc.* **72**, 2328–2349.
Svensson, M., Humbel, S., Froese, R. D. J., Matsubara, T., Sieber, S. & Morokuma, K. (1996). *J. Phys. Chem.* **100**, 19357–19363.
Whitten, A. E. & Spackman, M. A. (2006). *Acta Cryst.* B**62**, 875–888.
Willis, B. T. M. & Pryor, A. W. (1975). *Thermal Vibrations in Crystallography.* Cambridge University Press.
Wilson, C. C., Myles, D., Ghosh, M., Johnson, L. N. & Wang, W. (2005). *New J. Chem.* **29**, 1318–1322.
Wilson, E. B., Decius, J. C. & Cross, P. C. (1955). *Molecular Vibrations.* New York: Dover Publications.