Influence of the refinement strategies on the wave functions derived from experiment

Bruno Landeros-Rivera, Julia Contreras-García, Paulina M Dominiak

► To cite this version:

Bruno Landeros-Rivera, Julia Contreras-García, Paulina M Dominiak. Influence of the refinement strategies on the wave functions derived from experiment. *Acta Crystallographica Section B: Structural Science, Crystal Engineering and Materials* [2014-..], 2021, 77 (5), pp.715-727. 10.1107/S2052520621008258 . hal-03373992

HAL Id: hal-03373992

<https://hal.science/hal-03373992>

Submitted on 11 Oct 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Influence of the refinement strategies on the wave functions derived from experiment

BRUNO LANDEROS-RIVERA,^{a*} JULIA CONTRERAS-GARCÍA^a AND PAULINA

M. DOMINIAK^b

^a*CNRS, UMR 7616, Laboratoire de Chimie Théorique, Paris, France, and* ^b*Biological and Chemical Research Centre, Department of Chemistry, University of Warsaw, Poland. E-mail: brunolanderos@hotmail.com*

Abstract

The synergy between theory and experiment found in the X-ray wave function refinement, XWR, makes it one of the most compelling techniques available for chemical physics. The foremost benefit of XWR – obtaining wave functions constrained to experimental data – is at the same time its Achilles heel, because of the dependency of the results on the quality of both empirical and theoretical data. The purpose of this work is to answer the following; What is the effect of the refinement strategy and manipulation of input data in the physical properties obtained from XWR? With that in mind, cutoffs based in data resolution and $F/\sigma(F)$ ratios were applied for both steps of XWR, the Hirshfeld atom refinement (HAR) and the X-ray constrained wavefunction fitting (XCW), for four selected systems: sulphur dioxide, urea, carbamazepine and oxalic acid. Also, the effects of changing the weighting scheme or the method to transform $\sigma(F^2)$ to $\sigma(F)$ were analysed. The results show that while HAR always reaches the same result, XCW is extremely sensitive to the crystallographic

data manipulation. This is a result of the variability of the experimental uncertainties for different resolution shells, and of not having proper standard uncertainties. Therefore, the use of distinct constraints for each resolution interval in XCW is proposed to fix this instability.

1. Introduction

Quantum Crystallography (QCr) is becoming a complete domain of natural sciences that combines several diffraction techniques (e.g., X-ray, or neutron diffraction) with quantum mechanical methods, to analyse the electronic structure of matter (Genoni & Macchi, 2020). The information obtained from QCr is fundamental for the prediction of the physicochemical properties of systems that are of interest to material or biological sciences (Genoni et al., 2018).

One outstanding procedure formulated within QCr is the X-ray wavefunction refinement (XWR) developed by Jayatilaka and coworkers (Jayatilaka, 1998; Grabowsky et al., 2012; Wońska et al., 2017), which consists of two steps: first, the Hirshfeld atom refinement (HAR) is applied to X-ray diffraction data, in which the electron density is modeled by means of Hartree-Fock or DFT calculations, and the atomic positions and anisotropic displacement parameters are refined by the usual least-squares procedure (Capelli et al., 2014). In the second step, an X-ray constrained wavefunction (XCW) fitting is applied (Jayatilaka & Grimwood, 2001), where the method of Lagrange multipliers is used to “constrain” the *ab initio* calculation to reproduce the experimental structure factors to within a desired level of agreement. Alternatively, with the purpose of providing a physical interpretation for the later procedure which has no analogue in classical crystallography, it was proposed that the fitting actually corresponds to a “restraint” of the wave function to take into account a “perturbation” that is introduced via the experimental structure factors (Genoni

& Macchi, 2020; Ernst *et al.*, 2020). This perturbation is caused by all the physical phenomena present in the crystal that are not taken considered in HAR (assuming the same level of theory is used in both, HAR and XCW), such as bulk or correlation effects. The HAR-determined atomic and thermal parameters are used as input and kept fixed during XCW. Some of the advantages that XWR has shown over conventional crystallographic refinements (those based on the independent atom model, IAM) are the possibility of determining anisotropic parameters for hydrogen atoms (Woińska *et al.*, 2016), the consideration of relativistic effects (Bučinský *et al.*, 2019) and the description of multireference character systems (Genoni, 2017).

The significance of the synergy between theory and experiment that is manifested in HAR is undeniable. The nuclei positions in the quantum mechanical calculations are iteratively changed, via the least-squares procedure, so that the selected model can reproduce as closest as possible the experimental structure factors. This synergy is at the core of QCr, and makes it one of the most compelling techniques for chemical physics. This said, the other side of the coin is the inexorable dependency of the results on the quality of both empirical and theoretical data. The accumulation of experimental errors will affect the computation of the wavefunctions, and vice versa, the selection of the quantum model will have an effect on the “measured” geometric parameters (bond distances, angles, etc.), or the electronic properties derived from the constrained wavefunction. Thus, the foremost benefit of XWR – obtaining wave functions constrained to experimental data – is at the same time its Achilles heel.

A systematic analysis of the impact of the theoretical framework in the prediction of the structural factors has already been performed. The effect of the Hamiltonian, basis set, thermal smearing and partition models (Grimwood & Jayatilaka, 2001; Bytheway *et al.*, 2002b; Jayatilaka & Dittrich, 2008; Chodkiewicz *et al.*, 2020), the inclusion of an explicit (Bytheway *et al.*, 2002a) or an implicit (Dittrich *et al.*, 2012) crystalline

environment through the model of surrounding charges and dipoles, and the use of a multi-determinant approach (Genoni, 2017) on HAR are well documented. However, the influence of the experimental model set-up on the XWR results has not been scrutinised in depth. Recently, it has been shown that HAR provides rather similar results for data integrated at different resolutions for accurately measured reflections of the oxalic acid (Sanjuan-Szklarz *et al.*, 2020). Notwithstanding, the outcome is not necessarily true for diffraction data of poorer quality.

In view of the above, the purpose of this work is to answer the following; *What is the effect of the refinement strategy and manipulation of input data on the physical properties obtained from XWR?* Clearly, a good (or at least decent) data collection is indispensable for any type of refinement to make sense (Dauter, 1999; Müller, 2009; Thompson, 2019), but that discussion is out of the scope of this work. We rather focus on studying the effect of different resolution and $F/\sigma(F)$ cutoffs, the method of computation of $\sigma(F)$ from $\sigma(F^2)$, and the use of different weighting schemes. Despite the fact that the application of cutoffs is known to be troublesome, in particular in charge-density analysis (Henn & Meindl, 2014), its employment is common practice. Hence the importance of analysing the influence of the application of these procedures in XWR. In particular, we explore the variations in the input data of XCW, produced as a consequence of changing the HAR strategy. This point is crucial because it is not clear what physical meaning can be attributed to cases where the constraint is sizeable compared with the thermal electronic energy (Genoni *et al.*, 2017). Hence in this experiment-theory interplay, having an optimal starting point for XCW is crucial, as was observed for the case of ammonia (Capelli *et al.*, 2014), *i.e.*, a better model was obtained from applying HAR than by performing a XCW fitting using as input the refined parameters derived from a multipole refinement that was performed in the original work (Boese *et al.*, 1997).

2. Methodology

2.1. Theoretical framework

The key statistical variable in XWR is the χ^2 function, which is defined as:

$$\chi^2 = \frac{1}{N_R - N_P} \sum \frac{\Delta_i^2}{\sigma_i^2} \quad (1)$$

where N_R and N_P are the number of reflections and refined parameters, respectively. $\Delta_i = F_i^{obs} - F_i^{calc}$ provides the difference between the observed and calculated structure factor amplitudes (SF): F_i^{obs} and F_i^{calc} , respectively. Additionally, this function is weighted by σ_i^{-2} , where σ_i are the experimental standard deviations of each SF (statistical weighting scheme). In HAR the χ^2 is minimised by a variation of the refinement parameters in a least-squares procedure, with the aim of attaining the value $\chi^2 \approx 1$. Achieving this target rests on the assumption that the weighted residuals follow a normal distribution, and on average the model is within an acceptable error, *i.e.*, that $\Delta_i \sim \sigma_i$. The employment of the statistical weighting scheme assumes that the measurement errors are uncorrelated and, therefore, the variance-covariance matrix is diagonal. However, this requirement is not always met, in which case the use of the χ^2 function as an agreement factor may be unreliable (Henn, 2019). This situation will be explored later in this work.

Once HAR is converged, if χ^2 is far from unity, then an XCW fitting is performed. The refinement parameters obtained from HAR are kept fixed during the XCW fitting, where the Lagrangian

$$L = E - \lambda(\chi^2 - \chi_0^2) \quad (2)$$

is minimised so as to reproduce the X-ray structure factors within a desired level that is normally chosen to be unity ($\chi_0^2 = 1$). E is the usual Hartree-Fock or DFT energy, and λ is the Lagrangian multiplier, which is progressively increased until the

desired error threshold is achieved. For the initial value, $\lambda = 0$, L corresponds to the single point energy of the HAR determined geometry, and χ^2 is computed for the non-constrained wave function, which is equivalent to the final value obtained with HAR as long as the same level of theory has been used for both processes. The second term in right side of the equation is the one interpreted as a perturbation for the cases where $\lambda > 0$. (Ernst *et al.*, 2020). Hence the strong dependence of XCW of both, the refined parameters and the χ^2 values estimated from HAR. Therefore, it is important to look for refinement strategies that lead to χ^2 values closer to unity so that the variations in L with respect to the energy of the unconstrained calculation are minimal.

2.2. Computational details

Sulphur dioxide (SO₂) was taken as our model for the analysis of the effect of varying the HAR strategy, along with the reflection data manipulation, in the computation of χ^2 and the refined parameters that serve as input for XCW. The reason is that this system is simple and has been well characterised by theory and experiments (Powers & Olson, 1980; Cioslowski & Mixon, 1993; Xenides & Maroulis, 2000; Grabowsky *et al.*, 2012). For the first part of this work, HAR calculations were performed with the *Tonto* program (Jayatilaka & Grimwood, 2003), at the BLYP/cc-pVTZ level of theory. The combination of this density functional and basis set has shown very good performance in the literature (Jayatilaka & Dittrich, 2008; Woińska *et al.*, 2017). All coordinates and anisotropic parameters were refined freely, with the inclusion of a cluster of atomic charges and dipoles for all the surrounding molecules (cutoff distance of 8 Å) in order to simulate the crystal environment. In addition, urea, carbamazepine and oxalic acid were also studied for the sake of comparison with the trends observed in the residuals obtained from the SO₂ refinement. These systems were selected because medium to excellent quality data with resolution higher than 1.0 Å⁻¹ are available and

literature on their HAR is accessible. The corresponding data were taken from: a) Sulphur dioxide (Grabowsky, 2020), b) urea (Birkedal *et al.*, 2004), c) carbamazepine (Sovago *et al.*, 2016), and d) oxalic acid (Kamiński *et al.*, 2014). From the later, out of the 14 data sets the third one (oxa3) was chosen because it has the larger completeness (99%), high redundancy (8) and resolution ($1.15 \text{ \AA}^{-1}$). Following previous works, the six closest water molecules were included in the refinement (Sanjuan-Szklarz *et al.*, 2020).

For the sake of a proper comparison among the refinement procedures of the four systems, the reflections employed in all cases were merged (including Friedel pairs), in order to exclude possible effects of contrasting systems with different redundancy. The number of unique reflections (refined parameters) are 1080 (14), 1045 (27), 16011 (271) and 3051 (64) for SO_2 , urea, carbamazepine and oxalic acid, respectively. For urea, carbamazepine and oxalic acid, the original data available in the literature (already merged) was introduced directly as input in *Tonto* in F^2 . For SO_2 , the original data, which contained 1677 reflections (Friedel pairs not merged) was subjected to an IAM refinement with SHELXL (Sheldrick, 2015) to generate a file with unique reflections (Friedel pairs merged) that was employed as input for *Tonto*, also in F^2 . For this purpose, the *LIST 4* and *MERGE 3* commands were activated in the SHELXL input file. Unless otherwise stated, this data was used in all refinements in order to apply the same strategy than in the other systems. Since the SO_2 crystal is non-centrosymmetric and has a relatively heavy atom, a finer refinement should take into consideration effects of anomalous dispersion, which requires additional approximations in the scattering model (as well as Friedel pairs unmerged). This topic will be analysed in Section 3.4. No extinction correction was applied to any of the refinements. Also, anharmonicity was not considered in the scattering models because Kuhs rule (Kuhs, 1988) cannot be satisfied in some of the cases where resolution cutoffs are applied. The particular

procedures applied during HAR will be described in each of the Results subsections.

In the second part of this research, XCW fitting computations on SO₂ were performed with the same λ intervals and maximum values, but with different initial conditions. These were preceded by a converged HAR to complete a XWR, employing the same level of theory. The atomic charges, delocalization indexes and critical points of the Laplacian were calculated from the final wavefunctions with the AIMALL software (Keith & AIMall, 2019). A BLYP/6-31G(d,p) level of theory was chosen in order to compare with the topological analysis that had been previously carried out for this system (Bader *et al.*, 1984; Muchall, 2001), to avoid problems due to Laplacian's basis set sensitivity. The results obtained with this procedure are virtually the same than those derived with cc-pVTZ basis set. The comparison of the calculated electronic properties with the different XCW fittings allowed to understand the effects of modifying the treatment of experimental data in the physical results estimated from XWR.

3. Results

3.1. Sigma-cutoffs

The presence of outliers is inherent to the experiment. Within X-ray data treatment, these are normally removed by applying sigma cutoffs. This section is devoted to the analysis of the effect of such cutoffs. The χ^2 and $R_1(\%)$ values for different $F < n \cdot \sigma(F)$ (with $n = 0 - 4$) cutoffs applied to the full data sets of sulphur dioxide and urea are shown in Figure 1. As expected, there is a considerable improvement (lowering of almost a unity) in the $R_1(\%)$ of SO₂ already at $n = 2$. On the other hand, the opposite is observed for χ^2 ; it increases as n increases (*i.e.*, χ^2 goes from 5.65 for the full data to 7.20 with $n = 4$). In the case of urea, χ^2 goes from 3.40 for full data to 4.35 with $n = 1$, but stays invariant for larger n values. For carbamazepine and

oxalic acid (Figure S1), only slight increases (less than 0.40) are observed for $n = 4$. For all the studied systems, more than 75% of the total reflections are kept after the cutoffs with $n = 4$ (Table S2). This behaviour seems to be counter-intuitive because it would imply that the electron density model improves (or at most remains invariant) when outliers are introduced. Nevertheless, as can be seen in Table 1 for the case of SO₂, HAR converges to the same S–O distances and O–S–O angles independently of the applied cutoff. This is also true for the ADPs (see Table S1). Moreover, if R_1 and χ^2 are computed for the set of reflections that fulfil $F > 4 \cdot \sigma(F)$ (825 in this case), the same value is reached ($R_1=2.06\%$ and $\chi^2=7.20$) regardless of the cutoff applied. The possible explanation of this result is that when outliers are included in the refinement their contribution to the sum in eq. (1) is small ($\Delta_i/\sigma_i \approx 0$), while the $1/(N_R - N_P)$ factor increases, leading to a smaller χ^2 . This is most likely to happen with high-resolution data, which have smaller intensity/ $\sigma(I)$ ratios, I/σ , as can be seen in Figure 2b. Indeed, the number of reflections with resolution higher than 0.50 Å is reduced by 36.5%, 33.1%, 32.4% and 24% for SO₂, urea, carbamazepine and oxalic acid, respectively, when the cutoff with $n = 4$ is applied. In contrast, the number of reflections with resolution lower than 0.83 Å are only reduced by 0.0%, 1.0%, 5.3% and 2.2%, correspondingly for the same systems and $n = 4$. The difference in I/σ could be caused by an underestimation of the strong reflections uncertainties. It is anticipated that this outcome would have an impact on XCW. Depending on whether sigma cutoffs are applied or not, the refined parameters will be the same but the initial χ^2 will differ. Consequently, for the same λ_{max} values the XCW will arrive to different wave functions because the strength of the applied constraints is not the same in each situation.

Fig. 1. The χ^2 and $R_1(\%)$ values for different $F < n \cdot \sigma(F)$ (with $n = 0 - 4$) cutoffs applied to sulphur dioxide and urea during HAR.

Table 1. *geometric parameters of sulphur dioxide obtained for different $F < n \cdot \sigma(F)$ cutoffs.*

n	S–O bond (Å)	O-S-O Angle (°)
0	1.4282(3)	117.40(4)
1	1.4282(3)	117.40(4)
2	1.4282(3)	117.40(4)
3	1.4282(4)	117.40(4)
4	1.4282(4)	117.40(4)

3.2. Resolution cutoffs

Genoni *et al.* suggested that it is possible to recover correlation effects of the valence components of the electron density from XCW when the fitting is performed with low to medium-resolution data (Genoni *et al.*, 2017). They also observed that when high-resolution data is introduced the core density components predominate in the fitting, hindering proper description of valence density correlation in simultaneous fashion. The “observed” structure factors used in that work were computed from a CCSD calculation, so they didn’t have an associated uncertainty linked to experimental precision. The authors warned about the possible complications when using real X-ray diffraction data, such as the presence of noise, which causes that low-medium and high-resolution reflections have different weights. Hence, this is one of the reasons why it is important to add to this study the effect of resolution cutoffs as present in experimental data sets.

HAR calculations were performed for SO₂, urea, carbamazepine and oxalic acid, with resolution cutoffs of 0.83, 0.70, 0.50 Å, as well as for the full data (each case was refined separately). By virtue of clarity, reciprocal resolution (Å⁻¹) will be employed to avoid confusion when talking about low and high resolution. The corresponding values are 0.60, 0.71, 1.00 Å⁻¹, and full resolution. No sigma cutoffs were applied during these refinements in order to avoid the combination of different effects. The final χ^2 values are reported in Figure 2a. For SO₂ and urea it is clear that χ^2 increases significantly for low resolution cutoffs. For oxalic acid only a slight increase is noted, while for carbamazepine χ^2 shows a more stable value around 2. In contrast, the R₁ values for all systems show smaller variations (Figure S2), and increase for high angles. Likewise, if χ^2 is computed in each refinement for the set of reflections for which the resolution is lower than 0.60 Å⁻¹ (115 for sulphur dioxide), its value increases from 18.26 when the 0.60 Å⁻¹ resolution cutoff is applied, to 23.92 for the full data set. This trend was also observed for the other systems when applying the same procedure, where the χ^2 increases are from 15.40 to 20.19 for urea, from 1.19 to 3.16 in carbamazepine, and from 1.59 to 2.69 in oxalic acid. Therefore, comparing with the findings of the previous section, these results suggest that the introduction of the high-resolution data in the refinement (which fulfils that $F > 4 \cdot \sigma(F)$) worsens low-resolution data modelling, especially for the systems with larger I/ σ variations. Thus, the decrease of χ^2 with full resolution data is partially caused by an increase in the $1/(N_R - N_P)$ factor, but not by an improvement in low-resolution data modelling. One possible explanation for this phenomenon is that HAR is modelling better high-resolution data, which predominates when introduced in the refinement, at the expense of scarifying the description of low-resolution reflections. Another hypothesis (compatible with the previous one), is that the least-squares refinement is biased by the fact that the number of reflections for each resolution shell is very disproportionate, *i.e.*, there are more high-angle than low-

angle reflections. We believe this observation requires further exploration, particularly for different levels of theory.

In spite of the large differences of χ^2 for low and high resolution data sets, the S-O distances and O-S-O angles converged essentially to the same values (Table 2), which is consistent to what has been reported (Woińska *et al.*, 2016). The thermal parameters are also very similar for each refinement (Table S3). This result is outstanding considering that for sulphur dioxide (as well as for the other systems) less than 15% of the total reflections are kept after the $0.6 \text{ \AA}^{-1}$ cutoff (Table S4). Thus, this fact poses a serious problem for the choice of λ_{max} in XCW. Depending on the resolution cutoff used, the XCW will start from virtually the same geometric and thermal parameters, but with the initial χ^2 (for $\lambda = 0$) fluctuating between 5 and 18 (see eq. 2).

In agreement with the suggestion made in the previous section, this tendency can be related to the I/σ values found for each resolution. In Figure 2b, the mean I/σ for all data up to the corresponding cutoff resolution are depicted. There is a clear relation with the χ^2 values, *i.e.*, the more constant the mean I/σ is, the more stable χ^2 is and vice versa. On that account, it is preferable to employ data with small variations of I/σ within different resolution intervals if this type of cutoffs will be applied during the refinement. Later on, the relationship of this fact with a possible correlation between the residuals and $\sigma(F)$ will be discussed. Another hint for calculating χ^2 values that show smaller variations for different resolution shells can be obtained from the analysis of oxalic acid. If instead of performing cutoffs, the data is reintegrated for a desired resolution (Sanjuan-Szklarz *et al.*, 2020), then χ^2 changes less drastically with regard to the case where a cutoff was applied (Figure S3). It should be noted that a small (but acceptable) variation of the cell parameters is observed for the reintegrated data. This last result points to an important sensitivity of χ^2 with respect to the determination and manipulation of the reflections uncertainties. For this reason, the computation of

$\sigma(F)$ from $\sigma(F^2)$ was also explored.

Fig. 2. Values of a) χ^2 , and b) I/σ as a function of the resolution cutoffs for SO_2 , urea, carbamazepine and oxalic acid. The last values correspond to the full resolution of each data set, which is different for every system.

Table 2. *geometric parameters of sulphur dioxide obtained for different resolution cutoffs.*

Resolution ($\text{\AA}^{-1}$)	S–O bond ($\text{\AA}$)	O–S–O Angle ($^\circ$)
0.60	1.4280(8)	117.41(9)
0.71	1.4280(6)	117.41(7)
1.00	1.4282(3)	117.41(5)
Full	1.4282(3)	117.40(4)

3.3. Computation of $\sigma(F)$ from $\sigma(F^2)$

Tonto always works with F , so whenever the input data is in F^2 then both, the intensities and their corresponding $\sigma(F^2)$ are transformed by *Tonto* to F and $\sigma(F)$. Although F^2 can trivially be transformed into F by taking the square root, this is not the case of the reflections standard uncertainties. There is not a unique way to perform the transformation of $\sigma(F^2)$ to $\sigma(F)$, which could be especially problematic for very small F values (Watkin, 2008). Therefore, the $\sigma(F)$ will ultimately depend

on the procedures employed by the different crystallographic programs in which the input files for *Tonto* are generated. In order to study the effect of computing $\sigma(F)$ from $\sigma(F^2)$, we compared the results obtained from HAR for two methods: a) performing this transformation directly with *Tonto* ($\sigma(F)_{Tonto}$ method), and b) by carrying out the transformation with SHELXL (Sheldrick, 2015), and then introducing these F and $\sigma(F)$ into *Tonto* ($\sigma(F)_{SHELX}$ method). The same data described in the Computational details were used as input for both methods. For the $\sigma(F)_{SHELX}$ method an IAM refinement was done in SHELXL, from which a new set of reflections given in F and $\sigma(F)$ were generated by activating the *LIST 3* command in the input file. This command creates an FCF file with $h, k, l, F, \sigma(F)$ format, where all equivalents (including Friedel pairs) are merged, scaled, and dispersion and extinction corrections, if applied, are included (*i.e.*, contribution from dispersion is removed from the reflections). These reflections were used as input for a new HAR performed with *Tonto*. In the case of SO₂, dispersion was not considered in the scattering model of the IAM refinement (by using the DISP E 0 0 0 instruction) so that the generated reflections are not dispersion-free, and the results can be compared with those of the $\sigma(F)_{Tonto}$ method. No sigma or resolution cutoffs were applied during these refinements (except for carbamazepine, as described in Table 3). A description of the algorithms used by *Tonto* and SHELXL for the transformation of $\sigma(F^2)$ to $\sigma(F)$ can be found in the Supplementary Information.

The χ^2 and R_1 residuals for the application of the two methods on the HAR of SO₂, urea, carbamazepine and oxalic acid are depicted in Table 3. The χ^2 values are reduced to almost a half when $\sigma(F)_{SHELX}$ method is employed. However, R_1 converges to the same value for both cases, suggesting that HAR is not seriously affected by the method of choice. Indeed, the same bond lengths, angles and ADPs for SO₂ are obtained from the $\sigma(F)_{Tonto}$ and $\sigma(F)_{SHELX}$ methods. Hence, χ^2 has a noticeable dependence of

the method used for calculating $\sigma(F)$ from $\sigma(F^2)$, regardless of the quality of the experimental data. Thus, XCW will be susceptible to the arbitrariness for the method used to carry out this transformation.

Table 3. Comparison of χ^2 and R_1 obtained from HAR in Tonto, using the $\sigma(F)_{Tonto}$ and $\sigma(F)_{SHELX}$ methods to compute $\sigma(F)$ from $\sigma(F^2)$. Full data sets for SO_2 , urea and oxalic acid were used.

Method	SO_2	Urea	Carbamazepine [†]	Oxalic acid
χ^2				
$\sigma(F)_{Tonto}$	5.64	3.39	2.29	2.06
$\sigma(F)_{SHELX}$	2.92	1.73	1.21	1.07
R_1				
$\sigma(F)_{Tonto}$	0.030	0.025	0.027	0.019
$\sigma(F)_{SHELX}$	0.030	0.025	0.027	0.019

[†] For carbamazepine, a sigma cutoff ($n = 2.18$) was applied during HAR with the $\sigma(F)_{Tonto}$ method for means of a proper comparison, since the $\sigma(F)_{SHELX}$ method suppresses all systematic absences and large negative intensities. Thus, in this way the same number or reflections was considered in the refinements performed with both methods.

3.4. Dispersion correction

Anomalous dispersion is negligible for small organic molecules, and becomes relevant as atoms are getting heavier in non-centrosymmetric crystalline structures. The spacegroup to which SO_2 belongs, $Aba2$, is non-centrosymmetric, and the sulphur atom is in the limit in which anomalous dispersion effects can become relevant. Thus, as mentioned in the computational details, using Friedel pairs merged could introduce small errors because this effect is ignored. In this section we analyse the effect of using data with Friedel pairs unmerged, and of including dispersion in the scattering model of HAR for this system. For this purpose, two types of reflection sets were used; set A , which includes dispersion, and set B for which the contribution of dispersion was removed with SHELXL. For generating the later set, the original data were used as input for an IAM refinement in SHELXL, activating the *LIST 6* command. The generated reflections using this procedure have the same characteristics as those generated with the *LIST 3* command (Section 3.3), but they are in F^2 and $\sigma(F^2)$ instead.

Four HAR were performed with *Tonto*: in **I**, set *A* was used with Friedel pairs merged, and dispersion ignored in the HAR scattering model. This is the same refinement used in the previous sections. In **II**, set *A* was used and dispersion was ignored in the scattering model too, but Friedel pairs were unmerged. This was achieved by introducing the original data directly in *Tonto*. Refinement **III** is similar to **II**, but dispersion was taken into account in the scattering model of HAR. Finally, in **IV**, set *B* was used and dispersion was not considered in the scattering model since it was already removed from the reflections. For this last refinement, the error caused the employment of using Friedel pairs merged is avoided, and thus can be thought of as an indirect way of considering dispersion effects. In all refinements the input data for *Tonto* were in F^2 .

The results of refinements **I-IV** are shown in Table 4. The first thing to notice is that refinements **I** and **II**, where dispersion was ignored in the scattering model of HAR, provide essentially same distances, angles and ADPs (Table S5). Nevertheless, there is a difference in the computed χ^2 of 2.03, although similar R_1 are obtained. Therefore, this strong discrepancy in the χ^2 is caused by the merging process, *i.e.*, employing the set with Friedel pairs unmerged increases χ^2 . When dispersion is included in the scattering model, as in refinement **III**, the geometric parameters and ADPs are slightly changed. Notwithstanding, the discrepancy in the distance and angles is less than 0.2%. In the case of ADPs, the largest difference among all the ADP values is 2.4%. Thus, the inclusion of dispersion in the HAR scattering model of SO_2 is not causing a relevant change in the refined parameters. Consistently, the R_1 is very similar to those of refinements **I** and **II**. Although the χ^2 shows a small decrease from 7.67 to 7.23 with respect to refinement **II**, it is still considerably bigger than that of refinement **I**. Thus, merging Friedel pairs has a greater impact on χ^2 than including dispersion in the HAR scattering model. Refinement **IV**, where dispersion

was taken into account indirectly, shows the same results as refinement **III**, indicating that HAR is consistent for both methods for considering dispersion (directly as in refinement **III**, or indirectly as in refinement **IV**). However, even though Friedel pairs were also merged in refinement **IV**, the χ^2 computed for this refinement is the largest one (10.00). The difference between the χ^2 computed with refinements **I** and **IV** is mainly caused by the merging process of SHELXL, which changed notably the $\sigma(F^2)$ values when the *LIST 4* or *LIST 6* commands are employed, although the F^2 were only marginally altered (Figure S4). Therefore, this is another example of how sensitive are the χ^2 values computed with HAR (with the statistical weighting scheme) to the origin of the reflection data, in particular to the manipulation of the experimental uncertainties.

Table 4. *geometric parameters and residual factors of HAR for the full data of SO₂, for refinements I-IV.*

Refinement	Friedel pairs	S–O bond (Å)	O-S-O Angle (°)	R ₁	χ^2
I disp. not included in model	Merged	1.4282(3)	117.40(4)	0.030	5.64
II disp. not included in model	Unmerged	1.4277(3)	117.43(4)	0.033	7.67
III disp. included in model	Unmerged	1.4266(3)	117.56(4)	0.033	7.23
IV disp. indirectly included in model	Merged	1.4265(3)	117.58(4)	0.030	10.00

3.5. Summary and discussion

The above results illustrate the potential of HAR to find accurate experimental structures, with the plus of obtaining a molecular wavefunction perturbed by the crystalline environment. Nevertheless, as with any model, it is important to know the effect of the choice of the parameters. We have shown that although the HAR-derived structures are stable, χ^2 is rather sensitive to the sigma or resolution cutoffs, and to the method for computing $\sigma(F)$ from $\sigma(F^2)$. Essentially, the same geometric and thermal parameters were reached in all cases. However, the χ^2 strongly varies depending on the mentioned manipulations of the crystallographic input data. This is relevant for

the application of XCW since, as can be seen from eq. (2), it depends on both the HAR refined parameters and χ^2 . It seems that even in cases where HAR shows a significant change, this is even more notorious in χ^2 . For instance, if the refinement of SO₂ is repeated with the condition that all $\sigma(F) = 1$ (which is equivalent to applying a unitary weighting scheme), the O-S-O angle decreases from 117.40(4)° to 116.33(13)°. Although this change is not big (about 1°), it is non-negligible. Simultaneously, χ^2 decreases by two order of magnitudes: from 5.64 to 0.09, whilst R₁ slightly increases by from 3.04% to 3.40%. Applying a unitary weighting scheme to crystallographic data as that of SO₂, which shows large of $I/\sigma(I)$ variations, is troublesome (Watkin, 1994) and could be recommended only at initial stages of refinement. Nevertheless, it was employed here merely to stress the importance of using an appropriate weighting scheme in XWR. Since (to our knowledge) the statistical weighting scheme has been the only one used for experimental data in XWR studies (as well as in XCW studies performed without previous HAR), we believe this point needs more attention and further exploration given the importance of extracting realistic information (other than geometries) from XWR.

As mentioned before, the suitability of using χ^2 (or more commonly, GooF) as an agreement factor depends on the quality of the standard uncertainties σ – these should be, as far as possible, free from systematic errors (Henn, 2019). Specifically, the utilisation of the statistical weighting scheme requires that the residuals (Δ_i^2) and the σ have no significant correlation, which is fulfilled when

$$\left\langle \frac{\Delta_i^2}{\sigma_i^2} \right\rangle \approx \frac{\langle \Delta_i^2 \rangle}{\langle \sigma_i^2 \rangle} \quad (3)$$

where the brackets stand for the arithmetic average. The left-side and right-side values computed for the HAR of SO₂ (full merged data, without any cutoff applied) are 5.57 and 2.27, respectively. This result strongly suggests that the application of

the statistical weighting scheme is not adequate in this case since the criterion of eq. (3) is not met. Furthermore, the presence of systematic errors for this system can be corroborated by the analysis of the function

$$n_1 = \frac{\chi^2 - 1}{\delta(\chi^2)} \quad (4)$$

where $\delta(\chi^2)$ is the standard deviation of χ^2 , which is computed as $(\frac{2}{N_R})^{1/2}$. It was proposed that $|n_1| > 3$ can be used as criterion for a significant difference of χ^2 from 1 (Henn, 2016). When applied to the same HAR of SO₂ a value of $n_1 = 107.8$ is obtained, confirming that the $\sigma(F)$ are not optimal. It is important to point out that eqs. (3) and (4) were formulated for $\sigma(I)$, while the implementation of HAR in *Tonto* works with $\sigma(F)$. Notwithstanding, the correlation between the residuals and $\sigma(F)$ could hardly be an aftereffect of the transformation of the later from $\sigma(I)$. Therefore, the inference that the statistical weighting scheme is not appropriate for SO₂ because of the in-adequateness of the $\sigma(F)$ remains valid.

Thus, in order to improve the metrics of HAR the following points are suggested: a) Refine against F^2 instead of F to avoid the need for applying cutoffs for the omission of imaginary SF , or having to transform $\sigma(F^2)$ to $\sigma(F)$. b) If possible, reintegrate data to a desired resolution instead of applying cutoffs. In this way better the chances of having systematic errors can be reduced (Henn, 2019). c) Use a weighting scheme other than the statistical if the $\sigma(F^2)$ are not optimal.

So far, there is controversy as to which weighting scheme should be used for the treatment of crystallographic data (Schwarzenbach et al., 1989; Watkin, 2008), and several strategies have been suggested (Spagna & Camalli, 1999). In order to examine the effect of changing the weighing scheme in HAR, as well as the use of F^2 instead of F , the refinement was repeated with the latest implementation of HAR in Olex2 (Dolomanov et al., 2009), where the least-squares refinement is performed

with `olex2.refine` and the non-spherical SF are computed with NoSpherA2 (Kleemiss et al., 2021) from electron densities obtained from quantum chemical calculations. The wavefunction was obtained from *Tonto*, using the same level of theory (BLYP/cc-pVTZ) and the same cluster of charges to simulate the crystal environment. The same input data described in the Computational details was used to compare with the results obtained from *Tonto*. Dispersion was turned off from the HAR scattering model for a proper comparison with the results of *Tonto*. The implementation of HAR in Olex2 refines against F^2 and, additionally, employs the SHELX weighting scheme (Sheldrick & Schneider, 1997; Wilson, 1976)

$$w = q \cdot \left[\sigma(F_{obs})^2 + (aP)^2 + bP + d + e \cdot \sin(\theta) \right]^{-1} \quad (5)$$

where the last term in the brackets is resolution dependent (Dunitz & Seiler, 1973), and a , b , c , d and e are adjustable parameters. The value of q is equal to unity when c is equal to 0, to $\exp[c \cdot (\sin(\theta)/\lambda)]^2$ when c is positive, and to $1 - \exp[c \cdot (\sin(\theta)/\lambda)]^2$ when c is negative. P is defined as

$$P = \left[(1 - f) \cdot F_{calc}^2 + f \cdot \text{Max}(F_{obs}^2, 0) \right] \quad (6)$$

where f is another adjustable parameter. This weighting scheme was developed with the aim of reducing statistical bias (Wilson, 1976). Normally, the parameters c , d and e are set to zero, and f is fixed to 1/3, which is what Olex2 does by default.

The comparison of the residual factors and geometric parameters of SO_2 , obtained from the full data refinements performed with *Tonto* and Olex2, are depicted in Table 5. Also, the corresponding ADPs are shown in Table S6. Notice that virtually the same results are obtained from performing HAR with either code using the statistical weighting scheme, which indicates that the effect of refining with F^2 instead of F is not significant. The χ^2 in the case of Olex2 is computed as GooF^2 , but defined in F^2

instead of F (eq. (1)). When HAR is repeated with the SHELX weighting scheme, a small variation in the distances and angles is observed, but the χ^2 drops significantly from 5.70 to 1.76. Furthermore, if the HAR in Olex2 is performed with dispersion-free reflections, generated from a previous IAM refinement using the *LIST 6* command in SHELXL (as explained in section 3.5), the χ^2 shows only a modest decrease to 1.45, and small changes in the geometric parameters consistent with those observed in Table 4. Thus, the selection of the weighting scheme has a pronounced effect on the final χ^2 values, but produces marginal changes in the refinement parameters.

Though the χ^2 computed from Olex2 using the SHELX weighting scheme and the dispersion-free reflection file is lower, it is still significantly different from unity according to eq. (4) – *i.e.*, $n_1 = 10.46$. It will be interesting to explore if the employment of the other resolution dependent parameters in the SHELX weighting scheme (eq. (3)) could improve the statistical description and provide values of n_1 lower than 3. Also, anharmonic effects could play an essential role, but unfortunately this type of refinement is not yet implemented in the version of Olex2 used in this work (version 1.3). Although anharmonic refinement has now been implemented in the alpha 1.5 version of Olex2, it is still an experimental feature and, thus, was not employed here. Nevertheless, it's important to stress that the SHELX weighting scheme was designed for IAM refinements, and probably more adequate weighting schemes developed for non-spherical refinements could be employed in HAR (Zhurov *et al.*, 2008; Zarychta *et al.*, 2011).

Table 5. *Comparison of the residual factors and geometric parameters of the HAR of the full data of SO₂, using Tonto and Olex2 with two different weighting schemes (w. s.).*

Method	S–O bond (Å)	O–S–O Angle (°)	R ₁	χ^2
<i>Tonto</i> (statistical w.s.)	1.4282(3)	117.40(4)	0.030	5.64
Olex2 (statistical w. s.)	1.4281(4)	117.40(4)	0.031	5.70
Olex2 (SHELX w. s.)	1.4288(5)	117.44(6)	0.030	1.76
Olex2 (SHELX w.s., dispersion-free, SHELX w.s.)	1.4269(6)	117.58(7)	0.030	1.45

From the above analysis, it is clear that the refinement strategy and manipulation of the crystallographic data (particularly of the experimental uncertainties) has a strong impact on the χ^2 agreement factor, whose adequateness in HAR has been questioned. This said, it is important to study the influence of the changes in χ^2 on the physical states that are reached by the subsequent application of XCW after HAR. The next section is devoted to this task.

3.6. XCW calculations for SO_2

Different XCW fitting procedures were applied to SO_2 , based on the findings of the previous sections. For the reference, $\mathbf{R}_{full}$, the full data set was used. For $\mathbf{S}_2$ and $\mathbf{S}_4$, cutoffs of 2σ and 4σ were employed, respectively. Finally, resolution cutoffs of 0.60, 0.71 and $1.00 \text{ \AA}^{-1}$ were used in $\mathbf{R}_{60}$, $\mathbf{R}_{71}$ and $\mathbf{R}_{100}$, respectively. For these, the same data described in the Computational details were employed as input for the previous HAR. Additionally, another fitting process, $\mathbf{R}_{LIST3}$, was carried out employing a reflection data generated with the $\sigma(F)_{SHELX}$ method for computing $\sigma(F)$ from $\sigma(F^2)$ (with the same procedure described in Section 3.3). Furthermore, another fitting, $\mathbf{R}_{LIST6}$, was performed using dispersion-free reflections (generated as delineated in Section 3.4).

In Figure 3 the χ^2 values as function of λ are shown for the different XCW fittings. In agreement with the previous sections, χ^2 has different values at $\lambda = 0$ for each case, being those of $\mathbf{R}_{LIST3}$ and $\mathbf{R}_{60}$ the smallest and largest ones, respectively. The first thing to notice is that it is not affordable to select a common λ_{max} given the variability found in χ^2 for each fitting. For $\mathbf{R}_{60}$ it was not possible to converge the SCF for $\lambda > 0.045$, whereas for $\mathbf{R}_{full}$ convergence up to $\lambda = 0.360$ was possible. It is interesting to note that $\chi^2(\lambda)$ curves are not merely displaced with different y-intercept, but their shape also changes. Indeed, the rate of change of χ^2 with respect

to λ for the first steps is proportional to its value at the y-intercept. This function varies smoothly or abruptly for low or large $\chi^2(\lambda = 0)$ values, respectively. Also, it may be inferred that none of the curves will coincide even when $\lambda \rightarrow \infty$. In order to explore the consequences of these facts on the physical states obtained from each fitting, some properties are compared at $\lambda = 0.000$ and $\lambda = 0.045$.

Fig. 3. The χ^2 as a function of λ for the various XCW fitting procedures. Steps of 0.005 were used in all cases.

As can be seen from Table 6, the geometric parameters obtained from HAR, which are the input for the corresponding XCW fitting procedures, are very similar in each case, being those of $\mathbf{R}_{LIST6}$ slightly more different. Any differences found for $\lambda = 0.000$ are attributed only to variations in the nuclei positions obtained from each refinement. Accordingly, the electronic energies are very close to each other at $\lambda = 0.000$, with differences of less than 0.0003 hartrees. Also, the delocalization index between S and O, as well as the charge on the sulphur atom (calculated within the QTAIM framework (Bader, 1985)), are identical up to the third decimal place. Nonetheless, different behaviours are seen for $\lambda = 0.045$. In contrast to the variability of χ^2 with respect to its initial values ($\Delta\chi^2$) observed in Figure 3, R_1 barely changes between the two different λ sets. The change in the electronic energy of the system for $\lambda = 0.045$

(ΔE) increases proportionally with the initial χ^2 value. For instance, the ΔE for $\mathbf{R}_{60}$ is 12 times larger than that of $\mathbf{R}_{LIST3}$. Although the differences in the ΔE for each fitting could be considered as an effect of including different level of perturbations, this interpretation does not explain why ΔE is largest for $\mathbf{R}_{60}$ if it is the fitting with the lowest number of reflections. Furthermore, the differences between $\mathbf{R}_{full}$, $\mathbf{R}_{LIST3}$ and $\mathbf{R}_{LIST6}$ can't be explained neither. In these cases, the number of reflections used for the XCW fitting is exactly the same, and the initial electronic energies are also virtually identical. Thus, the differences in ΔE are attributed to variations in the transformation of the experimental uncertainties, and their variability for different resolution shells. These results highlight the strong dependency of XCW on the manipulation of the crystallographic data, which complicates even more its interpretation.

In the case of the electron density-derived properties, some differences are observed in the second decimal place of the delocalization index and the S atomic charges, which are not substantial. For all fitting processes a trend is observed in which the S atom increases its charge, and the bond order decreases, in agreement with the ionic character of the S-O bond discussed in the original work (Grabowsky *et al.*, 2012). The fact that these QTAIM descriptors don't change significantly for each fitting in comparison with the energies, is probably a consequence that positions of the nuclei are fixed. It is necessary to look at more subtle electronic effects to pinpoint the differences.

Table 6. Comparison of physical properties calculated with the different XCW fittings at $\lambda = 0.000$ and $\lambda = 0.045$.

Property	$\mathbf{R}_{full}$	$\mathbf{R}_{LIST3}$	$\mathbf{R}_{LIST6}$	$\mathbf{S}_2$	$\mathbf{S}_4$	$\mathbf{R}_{100}$	$\mathbf{R}_{71}$	$\mathbf{R}_{60}$
$\lambda = 0.000$								
S-O (Å)	1.4273(3)	1.4273(3)	1.4257(3)	1.4273(4)	1.4273(4)	1.4272(4)	1.4267(7)	1.4265(9)
O-S-O(°)	117.42(4)	117.42(4)	117.58(4)	117.42(4)	117.42(4)	117.42(5)	117.44(8)	117.48(10)
χ^2	5.74	2.98	10.10	7.15	7.35	10.30	16.35	21.22
R_1	0.030	0.030	0.030	0.022	0.020	0.020	0.018	0.020
E (a.u.)	-548.6444	-548.6444	-548.6441	-548.6444	-548.6444	-548.6444	-548.6442	-548.6442
Del. index	1.463	1.463	1.462	1.463	1.463	1.463	1.463	1.463
Charge S	2.365	2.365	2.370	2.365	2.365	2.365	2.367	2.368
$\lambda = 0.045$								
$\Delta\chi^2$	0.87	0.37	1.54	1.17	1.22	2.12	4.80	7.34
R_1	0.029	0.030	0.030	0.021	0.020	0.018	0.016	0.017
ΔE (a.u.)	0.0104	0.0061	0.0220	0.0126	0.0129	0.0192	0.0471	0.0779
Del. index	1.433	1.441	1.413	1.430	1.430	1.428	1.438	1.448
Charge S	2.436	2.420	2.472	2.441	2.442	2.443	2.405	2.382

The topological analysis of the Laplacian of the electron density ($\nabla^2\rho(\mathbf{r})$) allows to examine more subtle changes. Figure 4a shows the (3, +3) and (3, -3) critical points of $\nabla^2\rho(\mathbf{r})$ for $\mathbf{R}_{full}$ at $\lambda = 0$, which are associated with local charge concentrations and depletions, respectively. In accordance with the analysis of Bader (Bader *et al.*, 1984), there is only one bonded (3, +3) critical point in each of the S-O bonds. In addition, there are one and two non-bonded (3, +3) critical points around the S and O atoms, correspondingly, as expected from the number and position of the lone pairs predicted by the Lewis structure. As can be seen from Figure 4b, the distribution of both type of critical points is symmetric with regards to the C_2 twofold axis of the SO_2 space group. The zero surface envelope of $\nabla^2\rho(\mathbf{r})$ also looks symmetric. The result is very similar for $\mathbf{R}_{60}$ at $\lambda = 0.000$, except for an extra (3, -3) found in $\mathbf{R}_{full}$ close to the oxygen atom. However, there is a notorious distortion of the distribution of the critical points for $\mathbf{R}_{full}$ and $\mathbf{R}_{60}$ at $\lambda = 0.045$, specially for the critical points around the oxygen atoms. For $\mathbf{R}_{60}$, the non-bonded (3, +3) critical points are displaced out of the plane containing the three atoms. This effect is even more prominent for $\mathbf{R}_{full}$ at $\lambda = 0.360$, although it is less important for $\mathbf{R}_{LIST3}$ at the same λ value (see Figure S5). A possible

explanation for these distortions is the manifestation of intermolecular interactions or the introduction of dynamical effects by the XCW fitting at large values of λ . For instance, the deformation of the zero surface of the Laplacian around the sulphur atom, as well as the displacement of the (3, +3) critical points, matches the direction of the vibration of the oxygen and sulphur atoms out of the molecular plane, as can be seen from the thermal ellipsoid (Figure S5). Even if anharmonic refinement up to 4th order is performed for the S atom, the distortion of the zero-surface envelope and the (3, +3) critical points of the laplacian around this atom is still observed at $\lambda = 0.360$, although it is significantly reduced (Figure S5). We believe this phenomenon requires further exploration with a large set of systems. Thus, the topology of $\nabla^2\rho(\mathbf{r})$ appears to be more sensitive to the initial χ^2 values for each XCW fitting. This observation should be crucial for the study of molecular crystals where “Lewis complementary” (Bader *et al.*, 1992) is important as, for example, in the formation of the HAL₃ synthon (Bui *et al.*, 2009).

Fig. 4. In a), the (3, +3) and (3, -3) critical points of the Laplacian of the electron density (depicted as green and red points, respectively) of SO_2 for $\mathbf{R}_{full}$ and $\mathbf{R}_{60}$ at $\lambda = 0.000$ and $\lambda = 0.045$. In b), the zero surfaces of the Laplacian are shown as blue transparent isosurfaces in the direction of the C_2 twofold axis.

As mentioned before, even though the above differences among the XCW fittings could be explained by the amount of information that is removed in the case of the sigma and resolution cutoffs, it is not obvious what the effect of changing the method for computing $\sigma(F)$ from $\sigma(F^2)$ is, (since the number of reflections is the same as in the reference). Therefore, we decided to decompose χ^2 into contributions from different resolution intervals in order to better understand the variations observed within each fitting. With this in mind, it is interesting to express χ^2 as:

$$\chi^2 = \frac{1}{N_R - N_P} \left[\sum_{i \in \alpha} \frac{\Delta_i^2}{\sigma_i^2} + \sum_{i \in \beta} \frac{\Delta_i^2}{\sigma_i^2} + \dots \right] = \frac{1}{N_R - N_P} [A + B + \dots] \quad (7)$$

where A and B stand for the sum of all Δ_i^2/σ_i^2 terms belonging to the resolution intervals α and β , respectively. In the ideal case where $\chi^2 \approx 1$, A and B should approximate the number of reflections associated with the corresponding resolution interval (in the absence of correlation between the residuals and the $\sigma(F)$).

In Figure 5, the sums corresponding to the resolution interval which comprises all reflections between 0.00 to 0.60 Å⁻¹ (labelled as A_{low}), are shown for some of the XCW fittings at $\lambda = 0.045$. Notice that changing the method for computing $\sigma(F)$ from $\sigma(F^2)$ leads to relevant differences since, in agreement with previous observations, the lowest A_{low} value is obtained from the $\sigma(F)_{SHELX}$ method. Moreover, the application of resolution cutoffs is also lowering A_{low} . The later result indicates that, for a fixed λ value, removing high-resolution reflections improves the modelling of low-angle data (since lower Δ_i^2/σ_i^2 are obtained in this way). This result is consistent with what was observed in Section 3.2, where possible explanations were proposed. Nonetheless, in neither case A_{low} is close to 115, which is the number of reflections in this resolution interval. Again, this is an aftermath of the large I/σ ratio for low-resolution reflections (Figure 2).

Fig. 5. Values of the sum of Δ_i^2/σ_i^2 comprising all reflections between 0.00 to 0.60 Å⁻¹ (A_{low}) for different XCW fittings for $\lambda = 0.045$. Note that the lower value in the graph is 600.

To understand the effect of increasing λ on the low and high angles data, the χ^2 of $\mathbf{R}_{full}$ was decomposed according to equation (3) in three resolution intervals:

0.00-0.60, 0.60-1.00 and 1.00-1.30 Å⁻¹, which were named $A_{low}(\mathbf{R}_{full})$, $B_{med}(\mathbf{R}_{full})$ and $C_{high}(\mathbf{R}_{full})$, respectively. The number of reflections of each interval are 115, 381 and 584, respectively, and thus $A_{low}(\mathbf{R}_{full})$, $B_{med}(\mathbf{R}_{full})$ and $C_{high}(\mathbf{R}_{full})$ are not expected to converge to the same value. The corresponding sums are shown in Figure 6, where the $A_{low}(\mathbf{R}_{60})$ was also added for means of comparison. The later converges faster and to lower values, in agreement with the tendency described in Figure 5. The λ needed for $A_{low}(\mathbf{R}_{full})$ to reach a similar value than $A_{low}(\mathbf{R}_{60})$ is about 8 times higher ($\lambda = 0.360$ v.s. $\lambda = 0.045$). This result demonstrates that, when high-angle reflections are introduced in the XCW fitting, larger λ values are needed for the convergence of low-resolution data, at the expense of reaching higher energy states. It should also be noticed that $B_{med}(\mathbf{R}_{full})$ converges faster, while $C_{high}(\mathbf{R}_{full})$ remains almost unchanged with increasing λ . From all these, it can be concluded that the changes in χ^2 induced by increasing λ in XCW are almost exclusively caused by fitting on low resolution reflections. For $\Delta\chi^2 = \chi^2_{\lambda=0.36} - \chi^2_{\lambda=0.00}$, 78.5 % of the change comes from the low-resolution interval, while this quantity is only 0.6 % for the high-resolution one. Nevertheless, this does not inevitably mean that changes in high-resolution reflections are unimportant. As can be seen in Figure S6, the mean relative errors (computed as $|(F_{exp} - F_{calc})|/(F_{exp})$ for the three resolution intervals follow a similar trend as in Figure 6. Notwithstanding, the mean relative errors for high-resolution reflections are one order of magnitude larger. Even though the rate of change is bigger for the low-resolution reflections for the initial λ steps, all rates (from low to high) converge to similar values at high λ values (Figure S7). Thus, the dominance of low-resolution reflections in the $\chi^2(\lambda)$ curves for SO₂ is a consequence of the difference in the measured I/ σ ratios for the different resolution intervals. Hence, caution is advised for the XCW fitting of crystallographic data with the variations of I/ σ observed for SO₂.

Fig. 6. The χ^2 decomposition in A_{low} , B_{med} and C_{high} for $\mathbf{R}_{full}$ and $\mathbf{R}_{60}$.

3.7. Summary of XCW and conclusions

In contrast to HAR, XCW is significantly sensitive to the manipulation of the crystallographic data. The application of sigma or resolution cutoffs lead to qualitatively different $\chi^2(\lambda)$ curves. Some important conclusions are obtained from the above analysis: a) Low-resolution data converges faster with respect to λ increments if high-angle reflections are removed. b) The low-angle reflections predominate in the $\chi^2(\lambda)$ curves behaviour. c) The mean relative error of high-resolution reflections could require large λ values before reaching a minimum, even if the χ^2 appears to be converged. This can become a problem when the numerical instabilities of the XCW fitting doesn't allow the SCF convergence for larger λ values. Even in the case that the final χ^2 would be close to unity, this does not imply that the reflections belonging to different resolution intervals fulfil $\Delta_i \approx \sigma_i$. Further information can be obtained from the application of the unitary weighting scheme to the XCW of SO_2 . As can be seen in Figure S8, χ^2 decreases linearly with λ in contrast to the case where the statistical weighting scheme is used. This result suggests that the abrupt changes in χ^2 observed for the first λ values in the standard XCW could be a consequence of the use of the statistical weighting scheme, which is inappropriate for systems with troublesome $\sigma(F)$.

Nevertheless, when the decomposition of eq. (7) is applied to XCW with the unitary weights, it is still the case that the rate of change of the residuals in the low-resolution interval is larger than that of the medium- and high-resolution data (Figure S9).

In view of the results obtained from this research, our overall recommendations for the improvement of XWR are the employment of F^2 in the refinement, the reintegration of data to a desired resolution, and the use of a weighting scheme different from the statistical. Although these advices are in general beneficial for all type of crystallographic refinements, they are of particular relevance to XWR because not only statistics will be improved. The quality of the fitted wavefunction obtained from eq. (2), as well as the physical properties derived from it, are inherently dependent of χ^2 , which was shown to be not only sensitive to the number of reflections used in the refinement but also to the reliability of the experimental uncertainties, and to the manipulation of these quantities such as the transformation of $\sigma(F^2)$ to $\sigma(F)$, or merging data with or without removing dispersion contributions with other software such as SHELX. Considering the last two points, it will also be recommendable to employ the reflections as directly obtained after data reduction without the manipulation with external refinement software. In addition another strategy for compensating the variation in the convergence of data of different resolution ranges (with respect to the increase of λ) is also proposed. It should be noted that by merging equations (1) and (7), the constraint optimisation would read:

$$L = E - \lambda \left[\sum_i \frac{1}{N_R - N_P} \left(\frac{\Delta_i^2}{\sigma_i^2} - \chi_{i,0}^2 \right) \right] \quad (8)$$

This equation highlights the fact that the parameter λ is a compromise for the fit to all experimental reflections. Indeed, a rigorous constraint optimisation, should have as many λ_i values as reflections:

$$L = E - \sum_i \frac{\lambda_i}{N_R - N_P} \left(\frac{\Delta_i^2}{\sigma_i^2} - \chi_{i,0}^2 \right) \quad (9)$$

This approach would be too expensive. Nevertheless, from Figure 6, an intermediate approach can be proposed:

$$\begin{aligned}
 L &= E - \sum_{i \in \alpha} \frac{\lambda_A}{\Delta N^A} \left(\frac{\Delta_i^2}{\sigma_i^2} - \chi_A^2 \right) - \sum_{i \in \beta} \frac{\lambda_B}{\Delta N^B} \left(\frac{\Delta_i^2}{\sigma_i^2} - \chi_B^2 \right) - \sum_{i \in \gamma} \frac{\lambda_C}{\Delta N^C} \left(\frac{\Delta_i^2}{\sigma_i^2} - \chi_C^2 \right) \\
 &= E - \frac{\lambda_A(A - \chi_A^2)}{\Delta N^A} - \frac{\lambda_B(B - \chi_B^2)}{\Delta N^B} - \frac{\lambda_C(C - \chi_C^2)}{\Delta N^C}
 \end{aligned}$$

where $\Delta N^A = N_R^A - N_P^A$, χ_A^2 is the level of agreement for resolution shell A , and so on.

The advantage of this approach is that it will allow to analyse the effects of different resolution shells separately (for instance, the correlation effects of valence and core densities). More detail about the proposed methodology is given in the Supplementary Information. This constraint optimisation will be the aim of future investigations.

Acknowledgements

B L-R. thanks CONACyT (CVU 366057) for the posdoctoral scholarship. Professor Simon Grabowsky is kindly acknowledged for providing us with the reflection data of the sulphur dioxide system.

References

- Bader, R., MacDougall, P. & Lau, C. (1984). *J. Am. Chem. Soc.* **106**(6), 1594–1605.
- Bader, R., Popelier, P. & Chang, C. (1992). *J. Mol. Struct.: THEOCHEM*, **255**, 145–171.
- Bader, R. F. (1985). *Acc. Chem. Res.* **18**(1), 9–15.
- Birkedal, H., Madsen, D., Mathiesen, R. H., Knudsen, K., Weber, H.-P., Pattison, P. & Schwarzenbach, D. (2004). *Acta Crystallogr., Sect. A: Found. Crystallogr.* **60**(5), 371–381.
- Boese, R., Niederprüm, N., Bläser, D., Maulitz, A., Antipin, M. Y. & Mallinson, P. R. (1997). *J. Phys. Chem. B*, **101**(30), 5794–5799.
- Bučinský, L., Jayatilaka, D. & Grabowsky, S. (2019). *Acta Crystallogr., Sect. A: Found. Adv.* **75**(5), 705–717.
- Bui, T. T. T., Dahaoui, S., Lecomte, C., Desiraju, G. R. & Espinosa, E. (2009). *Angew. Chem.* **121**(21), 3896–3899.
- Bytheway, I., Grimwood, D. J., Figgis, B. N., Chandler, G. S. & Jayatilaka, D. (2002a). *Acta Crystallogr., Sect. A: Found. Crystallogr.* **58**(3), 244–251.
- Bytheway, I., Grimwood, D. J. & Jayatilaka, D. (2002b). *Acta Crystallogr., Sect. A: Found. Crystallogr.* **58**(3), 232–243.
- Capelli, S. C., Bürgi, H.-B., Dittrich, B., Grabowsky, S. & Jayatilaka, D. (2014). *IUCrJ*, **1**(5), 361–379.
- Chodkiewicz, M. L., Woińska, M. & Woźniak, K. (2020). *IUCrJ*, **7**(6).
- Cioslowski, J. & Mixon, S. T. (1993). *Inorg. Chem.* **32**(15), 3209–3216.

- Dauter, Z. (1999). Acta Crystallogr., Sect. D: Biol. Crystallogr. **55**(10), 1703–1717.
- Dittrich, B., Sze, E., Holstein, J., Hübschle, C. & Jayatilaka, D. (2012). Acta Crystallogr., Sect. A: Found. Crystallogr. **68**(4), 435–442.
- Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. & Puschmann, H. (2009). J. Appl. Crystallogr. **42**(2), 339–341.
- Dunitz, J. t. & Seiler, P. (1973). Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem. **29**(3), 589–595.
- Ernst, M., Genoni, A. & Macchi, P. (2020). J. Mol. Struct. **1209**, 127975.
- Genoni, A. (2017). Acta Crystallogr., Sect. A: Found. Crystallogr. **73**(4), 312–316.
- Genoni, A., Bučinský, L., Claiser, N., Contreras-García, J., Dittrich, B., Dominiak, P. M., Espinosa, E., Gatti, C., Giannozzi, P., Gillet, J.-M., Jayatilaka, D., Macchi, P., Madsen, A. O., Massa, L., Matta, C. F., Merz Jr., K. M., Nakashima, P. N. H., Ott, H., Ryde, U., Schwarz, K., Sierka, M. & Grabowsky, S. (2018). Chem. - Eur. J. **24**(43), 10881–10905.
- Genoni, A., Dos Santos, L. H. R., Meyer, B. & Macchi, P. (2017). IUCrJ, **4**(2), 136–146.
- Genoni, A. & Macchi, P. (2020). Crystals, **10**(6).
- Grabowsky, S., (2020). Private communication.
- Grabowsky, S., Luger, P., Buschmann, J., Schneider, T., Schirmeister, T., Sobolev, A. N. & Jayatilaka, D. (2012). Angew. Chem., Int. Ed. **51**(27), 6776–6779.
- Grimwood, D. J. & Jayatilaka, D. (2001). Acta Crystallogr., Sect. A: Found. Crystallogr. **57**(1), 87–100.
- Henn, J. (2016). Acta Crystallogr., Sect. A: Found. Adv. **72**(6), 696–703.
- Henn, J. (2019). Crystallogr. Rev. **25**(2), 83–156.
- Henn, J. & Meindl, K. (2014). Acta Crystallogr., Sect. A: Found. Adv. **70**(3), 248–256.
- Jayatilaka, D. (1998). Phys. Rev. Lett. **80**(4), 798.
- Jayatilaka, D. & Dittrich, B. (2008). Acta Crystallogr., Sect. A: Found. Crystallogr. **64**(3), 383–393.
- Jayatilaka, D. & Grimwood, D. J. (2001). Acta Crystallogr., Sect. A: Found. Crystallogr. **57**(1), 76–86.
- Jayatilaka, D. & Grimwood, D. J. (2003). In International Conference on Computational Science, pp. 142–151. Springer.
- Kamiński, R., Domagała, S., Jarzemska, K. N., Hoser, A. A., Sanjuan-Szklarz, W. F., Gutmann, M. J., Makal, A., Malińska, M., Bák, J. M. & Wozniak, K. (2014). Acta Crystallogr., Sect. A: Found. Adv. **70**(1), 72–91.
- Keith, T. & AIMall, V. (2019). Overland Park KS, USA.
- Kleemiss, F., Dolomanov, O. V., Bodensteiner, M., Peyerimhoff, N., Midgley, L., Bourhis, L. J., Genoni, A., Malaspina, L. A., Jayatilaka, D., Spencer, J. L. et al. (2021). Chem. Sci. .
- Kuhs, W. (1988). Aust. J. Phys. **41**(3), 369–382.
- Muchall, H. M. (2001). ARKIVOC, **12**, 82–86.
- Müller, P. (2009). Crystallogr. Rev. **15**(1), 57–83.
- Powers, D. & Olson, H. (1980). J. Chem. Phys. **73**(5), 2271–2279.
- Sanjuan-Szklarz, W. F., Wońska, M., Domagała, S., Dominiak, P. M., Grabowsky, S., Jayatilaka, D., Gutmann, M. & Wozniak, K. (2020). IUCrJ, **7**(5).
- Schwarzenbach, D., Abrahams, S., Flack, H., Gonschorek, W., Hahn, T., Huml, K., Marsh, R., Prince, E., Robertson, B., Rollett, J. et al. (1989). Acta Crystallogr., Sect. A: Found. Crystallogr. **45**(1), 63–75.
- Sheldrick, G. M. (2015). Acta Crystallogr., Sect. C: Struct. Chem. **71**(1), 3–8.
- Sheldrick, G. M. & Schneider, T. R. (1997). Methods Enzymol. **277**, 319–343.

- Sovago, I., Gutmann, M. J., Senn, H. M., Thomas, L. H., Wilson, C. C. & Farrugia, L. J. (2016). Acta Crystallogr., Sect. B: Struct. Sci., Cryst. Eng. Mater. **72**(1), 39–50.
- Spagna, R. & Camalli, M. (1999). J. Appl. Crystallogr. **32**(5), 934–942.
- Thompson, A. L. (2019). Crystallogr. Rev. **25**(1), 3–53.
- Watkin, D. (1994). Acta Crystallogr., Sect. A: Found. Crystallogr. **50**(4), 411–437.
- Watkin, D. (2008). J. Appl. Crystallogr. **41**(3), 491–522.
- Wilson, A. (1976). Acta Crystallogr., Sect. A: Cryst. Phys., Diffr., Theor. Gen. Crystallogr. **32**(6), 994–996.
- Woińska, M., Grabowsky, S., Dominiak, P. M., Woźniak, K. & Jayatilaka, D. (2016). Sci. Adv. **2**(5).
- Woińska, M., Jayatilaka, D., Dittrich, B., Flaig, R., Luger, P., Woźniak, K., Dominiak, P. M. & Grabowsky, S. (2017). ChemPhysChem, **18**(23), 3334–3351.
- Xenides, D. & Maroulis, G. (2000). Chem. Phys. Lett. **319**(5-6), 618–624.
- Zarychta, B., Zaleski, J., Kyzioł, J., Daszkiewicz, Z. & Jelsch, C. (2011). Acta Crystallogr., Sect. B: Struct. Sci. **67**(3), 250–262.
- Zhurov, V. V., Zhurova, E. A. & Pinkerton, A. A. (2008). J. Appl. Crystallogr. **41**(2), 340–349.

iucr