Absolute-structure determination using *CRYSTALS*

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Synopsis Report and recommendations from an investigation of absolute-structure analysis using tools available in the software CRYSTALS.

Abstract A study of post-refinement absolute-structure determination using previously published data was carried out in the software CRYSTALS. We show that absolute-structure determination may be carried out optimally using the analyses available in CRYSTALS, and that it is not necessary to have the separate procedures *absolute-structure determination* and *no interest in absolute structure* as proposed in Flack, H.D. (2014). Chimia, 68, 26-30.

Keywords: Absolute structure; Flack parameter; Least-squares refinement.

1. Introduction

Three elements have combined to make this study of absolute-structure determination feasible and significant.

The first element is the *CRYSTALS* software package (Betteridge *et al.*, 2003). This study relied on its flexible least-squares refinement procedures associated with its capacity for optimising and analysing weights. Also of great importance is the capacity of *CRYSTALS* to present data analysis in visual form. The normal probability plots, the plots of D_{obs} against D_{single}, the histograms of observed values of the (Flack, 1983) x parameter and the plots for evaluating data coverage and completeness were of particular value. *CRYSTALS* version 14 build 5792 was used for these analyses; a Windows version is available for download from http://www.xtl.ox.ac.uk/tag/crystals-release.html

The second element is a list and analysis of a very varied set of crystal-structure determinations of non-centrosymmetric crystal structures (Flack, 2013). All determinations of non-centrosymmetric crystal structures published in *Acta Crystallographica* C in the years 2011 and 2012 were analysed in a recent publication (Flack, 2013). This means that for those structures for which the deposited X-ray

diffraction intensity data were suitable, the intensity data had been separated into the following three classes: paired (*h k l* and $\bar{h}\ \bar{k}\ \bar{l}$) acentric reflections, unpaired acentric reflections and centric reflections. Moreover plots of A_{obs} against A_{model}, and D_{obs} against D_{model} had been prepared. $A(hkl)$ and $D(hkl)$ are respectively the average intensity of Friedel opposites *h k l* and $\bar{h}\ \bar{k}\ \bar{l}$, $A = ½[|F(h\ k\ l)|^2 + |F(\bar{h}\ \bar{k}\ \bar{l})|^2]$ and their difference $D = |F(h\ k\ l)|^2 - |F(\bar{h}\ \bar{k}\ \bar{l})|^2$. (Flack, 2013) also provided a comparative table of values drawn from these publications which are identified by their co-editor code in the following. This table of values is available at http://dx.doi.org/10.1107/S0108270113014789/ln3158sup1.pdf.

The third element is a complete set of recommendations for best procedures for absolute-structure determination (Flack, 2014). These recommendations are based on the following works: Bernardinelli & Flack (1985), Le Page *et al.* (1990), Flack & Bernardinelli (1999), Flack & Bernardinelli (2000), Flack & Bernardinelli (2008), Flack (2008), Hooft *et al.* (2008), Hooft *et al.* (2010), Flack *et al.* (2011), Thompson & Watkin. (2011), Parsons *et al.* (2012), Parsons *et al.* (2013), Flack (2013) and Flack (2014).

This study is thus an experimental test of the procedures of (Flack, 2014) using *CRYSTALS* (Betteridge *et al.*, 2003) on selected data sets from (Flack, 2013). In this way, it has been possible both to make the rather idealized recommendations of (Flack, 2014) of practical value for the structure analyst, and to ensure that the procedures implemented in *CRYSTALS* follow these recommendations. As will be explained in this paper, some minor modifications to the recommendations proved to be necessary and some minor bugs in *CRYSTALS* were corrected. Furthermore, it has been possible to find an excellent procedure for analysing the effect of selection and weighting of intensity data used in the post-refinement determination of the (Flack, 1983) parameter, using tools that have been available in *CRYSTALS* for several years.

2. Experimental

2.1. Obtaining unbiased atomic parameters

The first step in the (Flack, 2014) recommendations seeks atomic parameters (positional coordinates and atomic displacement parameters) unbiased by the effect of resonant scattering. It was first considered that the safest way to achieve this result would be to undertake least-squares refinement on data containing both $|F_{obs}|^2$ of the centric reflections and A_{obs} of the paired acentric reflections. The data of unpaired acentric reflections are not used in such a procedure. Such data correspond to a crystal twinned by inversion with the two domains present as 50% of the crystal, modelled exactly by a (Flack, 1983) parameter of $x = 0.5$. So in forming the values of A_{obs}, an unweighted average of $|F_{obs}(h\ k\ l)|^2$ and $|F_{obs}(\bar{h}\ \bar{k}\ \bar{l})|^2$ is taken in order to have intensity data corresponding to a well-defined physical state. The standard options of *CRYSTALS* do not allow such a refinement. However, from

the spreadsheet of each structure made for (Flack, 2013), it was possible to generate a file containing the required data which was read into *CRYSTALS*. The structure determinations fg3257, qs3016, bm3104III and eg3071I were treated in this way. Least-squares refinements were carried out on each of these data sets, fixing the (Flack, 1983) parameter at a value of 0.5. Results very similar to those published by the original authors were obtained.

The treatment of the data of ov3013I revealed the limitations of this technique. Least-squares refinement on data as generated above was highly unstable. The cause of this instability was easy to detect. The published data set has 481 paired acentric, 1778 unpaired acentric and 3 centric reflections for 343 variable parameters. Consequently the ratio of number of data to number of parameters is approximately 1.4 [*i.e*. (481 + 3)/343]. This condition was circumvented by undertaking the least-squares refinement on all data (*i.e*. 2x481 + 1778 + 3 reflections) and allowing the (Flack, 1983) parameter to vary from a starting value of 0.5. The refinement became stable and yielded results very similar to those of the authors of ov3013I. The purpose of the variable (Flack, 1983) parameter is not to determine its value but to ensure that the atomic parameters are unbiased by the effect of resonant scattering. This technique is one of the standard options of *CRYSTALS* and was used subsequently in the remaining structures which we studied: wq3001, wq3017, fn3089I, fg3255III and ku3043. Reanalysis of fg3257, qs3016, bm3104III and eg3071I using this method resulted in no significant changes in the value of the Flack parameter or its standard uncertainty.

2.2. Determination of the Flack parameter

Following the recommendations of (Flack, 2014), one determines the value of the (Flack, 1983) parameter by making a straight-line fit passing through the origin, to D_{obs} against D_{single}. This is often called a post-refinement determination of the (Flack, 1983) parameter and could be carried out directly in *CRYSTALS* without the need for any modification of the software. The value of the (Flack, 1983) parameter calculated according to the techniques described here is labelled ‘Post refinement Flack’ in the output of *CRYSTALS*. The appropriate D_{obs} are obtained from the paired acentric reflections, implying that the unpaired acentric and the centric reflections are not used in this calculation. D_{single} is a model value for a single crystal (*i.e*. untwinned by inversion) using the atomic parameters determined as described in §2.1. The slope of the straight-line fit to D_{obs} against D_{single} is equal to $1 - 2x$, where x is the (Flack, 1983) parameter. So a slope of 1 corresponds to $x = 0$, a slope of -1 to $x = 1$, and a slope of zero to $x = ½$. An absolute value of the slope greater than one does not have a physical interpretation. Two aspects of the calculation required experimentation. The first concerns the selection and rejection of data points and the second is the choice of weights.

2.2.1. Selection of data

It is necessary to recall that D_{obs} values are always contaminated by random uncertainty and systematic error (Flack, 2014). For a good data set, the D_{obs} against D_{single} plot displays a scatter of points around a straight line passing through the origin. Data points whose D_{obs} values are dominated by random uncertainty and systematic error are distributed around the straight line $D_{single} = 0$, the value of $|D_{obs}|$ often being much larger than the value of $|D_{single}|$. The resonant scattering signal in such data points is obscured by the experimental errors. As a result of these considerations, data were included in the post-refinement determination of the (Flack, 1983) parameter by using the criterion $|D_{single}|/u(D_{obs}) > z$, where in *CRYSTALS* the value z can be set in the 'Absolute Structure Analysis' tool in the box labelled 'Filter(1)'. A value of $z = 0.0001$ includes almost all the data whereas $z = 0.5$ includes only the most significant. In the days of serial diffractometers, (Le Page *et al.*, 1990) used the value of $|D_{single}|/u(D_{obs})$ as a criterion for the choice of those reflections most sensitive to the effects of resonant scattering.

2.2.2. Weighting scheme

Two systems of weights were the subject of study.

(i) The standard uncertainty u of D_{obs}, derived from the diffraction experiment and associated data reduction, was used to calculate weights as $w(h\,k\,l) = 1/u^2[D_{obs}(h\,k\,l)]$. If the errors in D_{obs} are random and adequately represented by $u(D_{obs})$, it is to be expected that this choice of weights would prove to be satisfactory.

(ii) The optimized weights of §2.1 for the refinement of atomic parameters were used for the determination of the (Flack, 1983) parameter. It was hardly expected that such weights would be satisfactory. The mean properties of $A(h\,k\,l)$ (or $|F(h\,k\,l)|^2$) and $D(h\,k\,l)$ are quite different one from another as a function of $\sin(\theta)/\lambda$ or other parameters. Moreover their dependence on atomic parameters and the (Flack, 1983) parameter are also strikingly different.

In *CRYSTALS*, there is a check-box option to choose either the counting statistical weights, $1/u^2_{obs}$,, or the weights as determined and applied in the main least squares.

2.2.3. Results and evaluation

Figure 1 contains plots from bm3104III, $x = -0.01(4)$. The data is of high quality and completeness, measured at low temperature with Cu $K\alpha$ radiation, the heaviest element in the material is oxygen and it has a Friedif_{stat} value of 22. Fig. 1(a) shows a plot of D_{obs} against D_{single} for all data. The D_{obs} are distributed about the vertical line $D_{single} = 0$, a clear indication that many D_{obs} are contaminated by random uncertainty and systematic errors. Fig. 1(b) is plotted from the same data by selecting those data points for which $|D_{single}|/u(D_{obs}) > 0.5$. Although there is a wide scatter of points, it is evident that they follow a straight line of approximately unit slope passing through the origin, in agreement with the value of the (Flack, 1983) parameter found by a least-squares fit. Fig. 1(c) shows a histogram of

individual observed (Flack, 1983) *x* parameters for all data. $x_{obs}(hkl)$ (see Watkin, 2016) is defined as: $x_{obs}(hkl) = ½ [1 - D_{obs}(hkl)/D_{single}(hkl)]$. The histograms peak close to the value of the (Flack, 1983) parameter obtained by least-squares fit of D_{obs} to D_{single}. A notable feature of the histogram is the high frequency of x_{obs} values with $|x_{obs}| > 5$. Upon applying the criterion $|D_{single}|/u(D_{obs}) > 0.5$, as shown in Fig. 1(d), the extreme values with $|x_{obs}| > 5$ are eliminated, demonstrating that they arise from data points with large $|D_{obs}|$ and small $|D_{single}|$.

Figure 2 contains plots from wq3001, $x = 0.02(2)$. The data is of high quality and completeness, measured at low temperature with Mo $K\alpha$ radiation, the heaviest element in the material is zinc and it has a $Friedif_{stat}$ value of 558. Figs. 2(a), 2(b), 2(c), 2(d) are similar to Figs. 1(a), 1(b), 1(c), 1(d) respectively. In the plot of Fig. 2(a) of D_{obs} against D_{single} for all data (2089 Friedel pairs), it is evident that there are two classes of data points: (i) those distributed about $D_{single} = 0$, and (ii) those distributed about a straight line passing through the origin of approximately unit slope. Applying the criterion $|D_{single}|/u(D_{obs}) > 2.0$ results in Fig. 2(b) (for 397 Friedel pairs) in which the noise along the D_{obs} axis is largely eliminated leaving the straight line of data points of unit slope. Fig. 2(c) shows the histogram of x_{obs} values. As for bm3104III, there are a large number of x_{obs} values with $|x| > 3$ which are eliminated on applying the criterion $|D_{single}|/u(D_{obs}) > 2.0$.

Figure 3 contains plots from fg3255III, $x = 0.58(2)$. The data is of high quality and completeness, measured at low temperature with Mo $K\alpha$ radiation, the heaviest element in the material is chlorine and it has a $Friedif_{stat}$ value of 113. Figs. 3(a), 3(b), 3(c), 3(d) are similar to Figs. 1(a), 1(b), 1(c), 1(d) respectively. In the plot of Fig. 3(a) of D_{obs} against D_{single} for all data, the data points cluster around the origin with no apparent straight-line dependence. Applying the criterion $|D_{single}|/u(D_{obs}) > 0.5$ results in Fig. 3(b) showing clearly the straight line of data points passing through the origin of slightly negative slope. The x_{obs} histogram in Fig. 3(c) displays the highest frequency of x_{obs} values occur near $x = 0.5$ and again there is a high frequency of x_{obs} values with $|x| > 7$. The latter are eliminated when the criterion $|D_{single}|/u(D_{obs}) > 0.5$ is applied.

It is very clear from a study of Figs. 1, 2 and 3 that the criterion $|D_{single}|/u(D_{obs}) > z$ is a very powerful and useful tool for the selection and analysis of data for the determination of absolute structure. The value of *z* has to be chosen from a study of plots of the types presented in the Figures. In *CRYSTALS*, the value of *z* may be set by the user. If the default value fails to yield sufficient reflections for the analysis, *CRYSTALS* suggests an alternative value.

Figure 4 contains normal probability plots of $w^{½}[D_{obs} - (1\text{-}2x)D_{single}]$ from fn3089I, $x = 0.38(2)$. The data is of high quality and completeness, measured at low temperature with Mo $K\alpha$ radiation, the heaviest element in the material is iron and it has a $Friedif_{stat}$ value of 389. Fig. 4(a) and 4(b) show the normal probability plots for two different weighting schemes. In Fig. 4(a) the weighting scheme is that based on the experimental standard uncertainties of the D_{obs}, *i.e.* $u(D_{obs})$. In Fig. 4(b) the

optimized weighting scheme is that used in the least-squares refinement of atomic parameters described in §2.1 . The normal probability plot shows how closely the weighted errors follow a Gaussian distribution and deviations from a straight line with unit gradient highlight deviations from the expected distribution of errors. Fig 4(b) shows that the weights used for least-squares refinement of all the parameters in the structure against all data are not appropriate for the post-refinement determination of the Flack parameter as they give rise to an error distribution which is too narrow, and hence a normal probability plot slope of approximately 0.5. Underestimation of weights arises from overestimation of the standard uncertainties associated with each observation. The normal crystallographic practice of augmenting standard uncertainties using a function of $|F|$ and $|F|^2$ in order to account for systematic error in the standard crystallographic model, or underestimated $u(|F|^2)$ from an instrument, is not necessary in this case.

Referring to Table 1, one sees that in all cases but one (ov3013I), the standard uncertainty of the (Flack, 1983) parameter derived by the methods of §2.2 is on average a factor of 3.5 smaller than the value quoted by the original authors (minimum and maximum values are 1.9 and 8.0 respectively). The value of the (Flack, 1983) parameter itself changes little between the two methods of determination. The only data set for which the standard uncertainty of the (Flack, 1983) parameter determined by the procedures described in §2.2 is larger than that found by the authors of the publication is ov3013I, *i.e*. values of x: authors' : 6(3), this work: 5(17). A study of the histogram of all x_{obs} values in Fig. 5 helps to show how such a situation can arise. The histogram has the usual high frequency of x_{obs} values for $|x| > 28$, however no frequency peak is visible in the centre part of the histogram for $|x| < 28$. There is no preferred value of x and a very large standard uncertainty on x is a reasonable result in this case.

3. Concluding remarks

The results of this study are clear. Absolute-structure determination may be carried out under the very best conditions in *CRYSTALS* using a variety of complementary tools for analysis and selection of data. The tools permit visualisation of the agreement between D_{obs} and D_{single}, and analysing the spread of x_{obs} values ensures the validity of the calculation. Moreover it is not necessary to have the separate procedures *absolute-structure determination* and *no interest in absolute structure* as proposed in (Flack, 2014). One proceeds as follows:

(i) Using the complete set of diffraction intensities, merged and averaged in the point group of the space group, least-squares refinement is undertaken varying all general and atomic parameters defining the crystal structure. Initially the Flack parameter can arbitrarily be set to zero. If, once the atomic model has stabilised, analysis of D_{obs} and D_{single} give a strong indication that the absolute structure of the major (or only) constituent of the sample is incorrect, the model should be inverted. If the analysis is ambiguous, the (Flack, 1983) parameter should be refined from a starting value of

0.5 simultaneously with the other parameters to ensure that the values of the atomic parameters (coordinates and atomic displacement parameters) are unbiased by the effect of resonant scattering. The least-squares weights may be adjusted to improve the fit, paying attention to obtain a uniform distribution of weighted residuals as functions of $\sin(\theta)/\lambda$ and $|F|^2$. Plots of $|F_{obs}|^2$ against $|F_{calc}|^2$ and normal probability plots of $w^{½}[|F_{obs}|^2 - |F_{calc}|^2]$ allow the outliers to be identified and the validity of the weights and standard uncertainties to be evaluated. The result of this part of the procedure is a set of unbiased atomic parameters with as small and realistic standard uncertainties as allowed by the data.

(ii) In the post-refinement step, the most reliable values of the Flack (1983) parameter and its standard uncertainty are calculated. For this purpose, only paired ($h\ k\ l$ and $\bar{h}\ \bar{k}\ \bar{l}$) acentric reflections are used and values of D_{obs} and D_{single} are calculated. D_{obs} comes directly from the observed intensities whereas D_{single} is a calculated value for a single crystal (*i.e.* untwinned by inversion) of the model obtained in stage (i). The value of the (Flack, 1983) parameter is obtained from a least-squares fit of a straight line passing through the origin, of D_{obs} against D_{single}. The slope of this line is equal to $(1 - 2x)$ where x is the (Flack, 1983) parameter. The D_{obs},D_{single} data points to be retained in this procedure are those with $|D_{single}|/u(D_{obs}) > z$. The default value of 0.5 may usefully be decreased in the presence of strong resonant scatterers (a value of $z = 0.0001$ includes almost all the data). The choice of an appropriate value of z is assisted by the graphical analyses presented. Smaller values of z allow more Friedel pairs into the calculation and small changes result in slightly lower values of $u(x)$, but very little change in x. The D_{obs} against D_{single} plots enable one to monitor the consequence of the inclusion of progressively less influential data as z is decreased. Further analysis of the effect of data selection is undertaken in Watkin (2016). Weights of $1/u^2(D_{obs})$ produced the most satisfactory results and are chosen in *CRYSTALS* by selecting the 'counting statistical weights' check-box. The fit of the data may be judged by the normal probability plot of $[D_{obs} - (1\text{-}2x)D_{single}]/u(D_{obs})$, by the histogram of (Flack, 1983) x parameters from individual D_{obs} values and by the D_{obs} against D_{single} scattergram. In the output of *CRYSTALS*, the value of the (Flack, 1983) parameter and its uncertainty determined by the methods described in this paper are identified by the label *Post-Refinement Flack*.

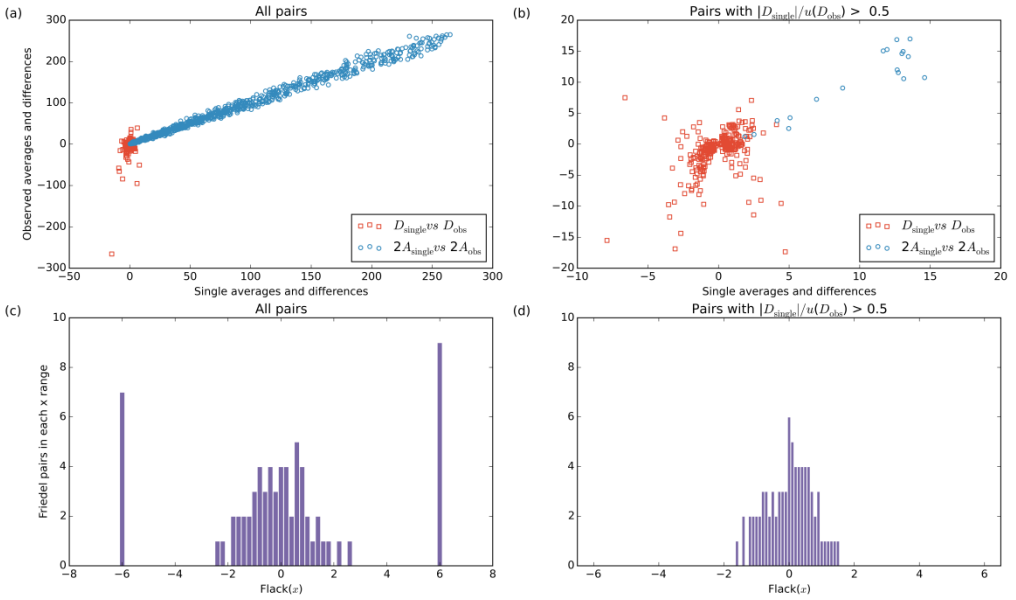

Figure 1 Plots from bm3104III, x = -0.01(4). Fig. 1(a); $D_{\rm obs}$ against $D_{\rm single}$ for all data (open red squares), $2A_{\rm obs}$ against $2A_{\rm single}$ (open blue circles) is included to show the quality of the fit of the data from the least-squares analysis described in section 2.1 Fig. 1(b); $D_{\rm obs}$ against $D_{\rm single}$ (open red squares) and $2A_{obs}$ against $2A_{single}$ (open blue circles) for data with $|D_{\rm single}|/u(D_{\rm obs}) > 0.5$. Fig. 1(c); histogram of individual observed (Flack, 1983) x parameters for all data. The extreme histogram bins at -6 and +6 contain all data points for x < -6.0 or x > 6.0 respectively. Fig. 1(d); like Fig. 1(c) but for data with $|D_{\rm single}|/u(D_{\rm obs}) > 0.5$.

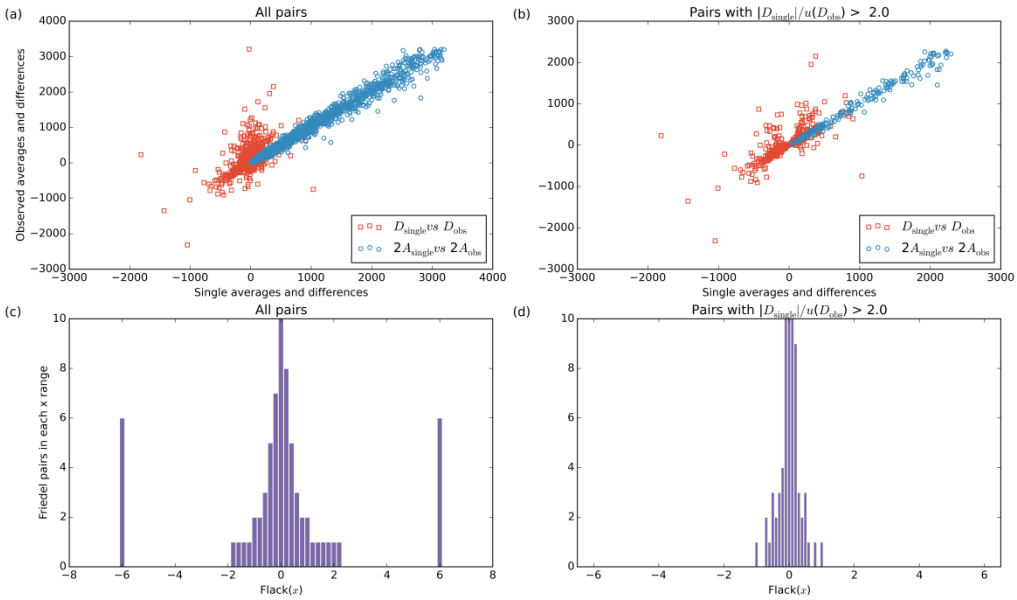

Figure 2 Plots from wq3001, x = 0.02(2). Fig. 2(a); D_{obs} against D_{single} for all data. Fig. 2(b); D_{obs} against D_{single} for data with $|D_{single}|/u(D_{obs}) > 2.0$. Fig. 2(c); histogram of individual observed (Flack, 1983) x parameters for all data. Fig. 2(d); like Fig. 2(c) but for data with $|D_{single}|/u(D_{obs}) > 2.0$.

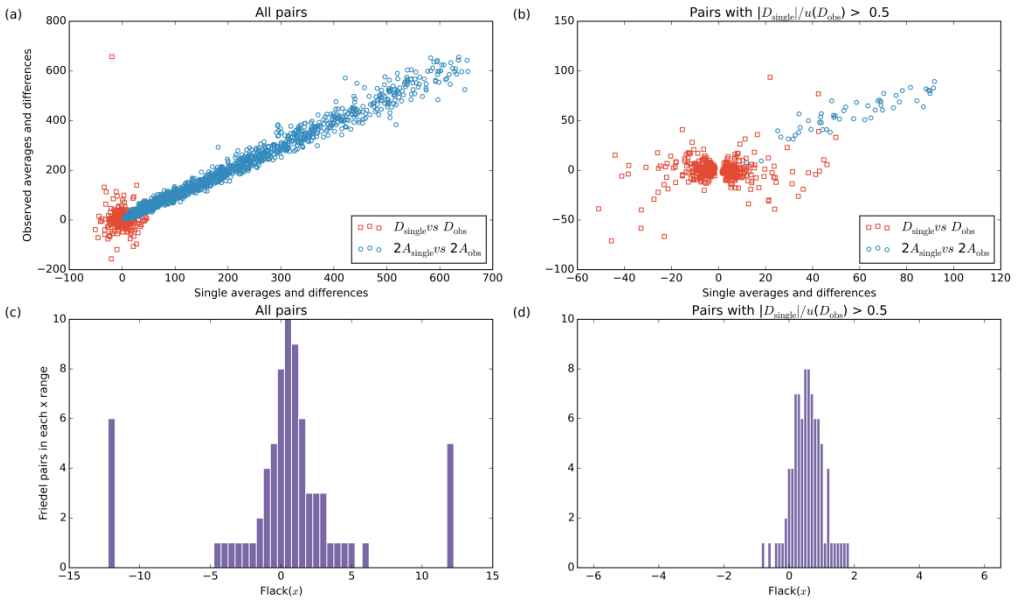

Figure 3 Plots from fg3255III, x = 0.58(2). Fig. 3(a); D_{obs} against D_{single} for all data. Fig. 3(b); D_{obs} against D_{single} for data with $|D_{single}|/u(D_{obs}) > 0.5$. Fig. 3(c); histogram of individual observed (Flack, 1983) x parameters for all data. Fig. 3(d); like Fig. 3(c) but for data with $|D_{single}|/u(D_{obs}) > 0.5$.

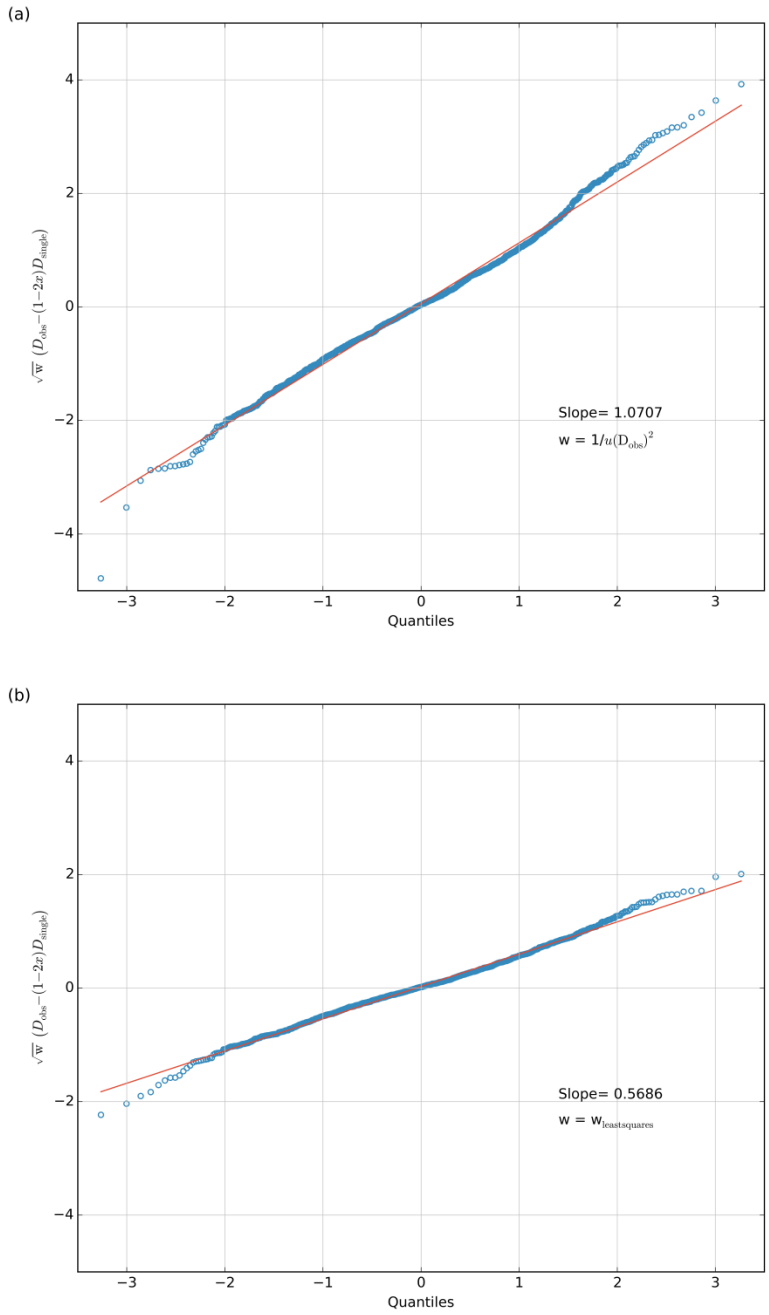

Figure 4 Normal probability plots of $w^{½}[D_{obs} - (1-2x)D_{single}]$ from fn3089I, x = 0.38(2). In Fig. 4(a) the weighting scheme is that based on the experimental standard uncertainties of the D_{obs}, *i.e.* $u(D_{obs})$. In Fig. 4(b) the weighting scheme is the optimized one used in the least-squares refinement of the atomic parameters described in §2.1.

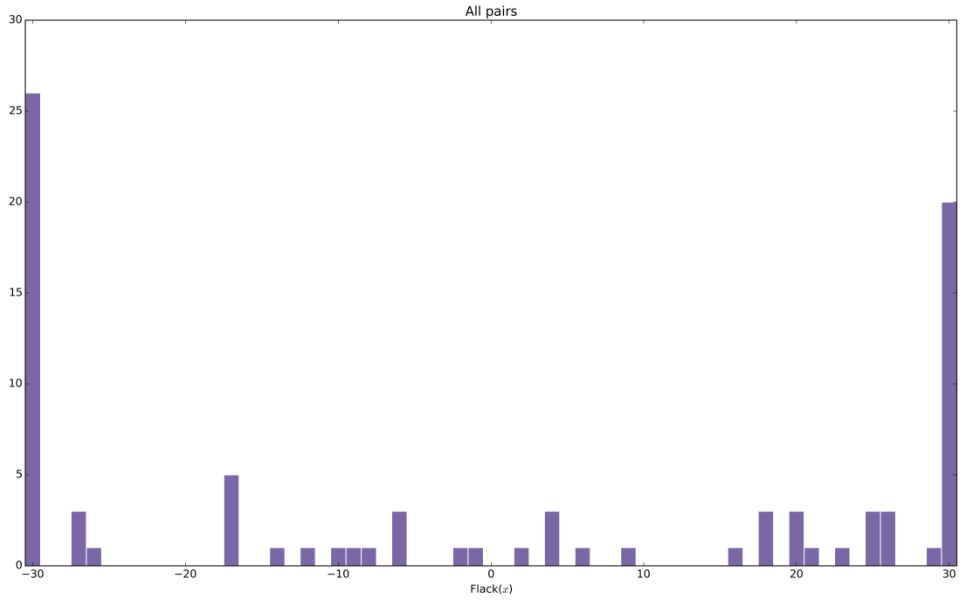

Figure 5 Histogram of all x_{obs} for ov3013I, x = 5(17). The extreme histogram bins at -30 and +30 contain all data points for $x \leq$ -30.0 or $x \geq$ 30.0 respectively

Table 1 Values of the (Flack, 1983) parameter. Each structure is identified by its co-editor code. The values of the (Flack, 1983) parameter are: *Published* taken from the published paper and *CRYSTALS* obtained by the method described in §2.2. *Filter* gives the chosen value of z in $|D_{single}|/u(D_{obs}) > z$.

Structure	Friedif$_{stat}$	Flack (1983) parameter, x			Friedel pairs		Citation
		Published	*CRYSTALS*	Filter, z	Total	Used	
bm3104III	22	-0.07(18)	-0.01(4)	0.5	1221	284	Frampton *et al.* (2011)
eg3071I	101	0.04(3)	0.048(16)	0.5	3637	513	Woelper *et al.* (2011)
fg3255III	113	0.59(6)	0.58(2)	0.5	2559	399	Ojala *et al.* (2012)
fg3257	279	0.028(11)	0.028(3)	0.5	3265	2764	Bojarska *et al.* (2012)
fn3089I	389	0.36(5)	0.38(2)	0.5	1367	425	Hendsbee *et al.* (2011)
ku3043	1386	0.50(6)	0.500(18)	0.5	156	95	Cora *et al.* (2011)
ov3013I	3	6(3)	5(17)	0.0001	482	399	Li *et al.* (2012)
qs3016	55	0.20(6)	0.20(3)	0.5	2107	310	Ślepokura (2012)

wq3001	558	0.00(2)	0.02(2)	2.0	2089	1226	Kefi *et al.* (2011)
wq3017	467	0.402(14)	0.411(6)	0.5	2530	1342	Zhong *et al.* (2012)

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