Reporting and evaluating absolute-structure and absolute-configuration determinations

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Detailed practical and numerical information is provided for undertaking and evaluating absolute-structure and absolute-configuration determinations. The interpretation of numerical values of x, the Flack [*Acta Cryst.* (1983), A**39**, 876–881] parameter, and its standard uncertainty u are explained in terms of the inversion-distinguishing power. Moreover, the conditions to obtain reliable values of $x(u)$ are detailed. Further explanatory material is provided on the use of right-handed axes, valid intensity data, the application to macromolecular structures, the dangers of polar-dispersion errors, Euclidean normalizers of space groups, the detection and reporting of molecular symmetry, enantiopurity and optical activity in solution. New CIF data names are introduced.

1. Introduction

We have described the fundamental notions and conceptual basis of absolute structure and absolute configuration (Flack & Bernardinelli, 1999). However, certain practical aspects deriving from that analysis need to be treated in greater detail to be of practical use to the structure analyst. Our detailed study of the printed text of all articles in Vol. 52 of *Acta Crystallographica Section C* (1996) and computer searches on the 1996 CIF archive, together with information drawn from other sources, has enabled us to prepare the current practical guide to absolute-structure and absolute-configuration determination together with their evaluation and reporting.

Two examples of misunderstandings, each with a short explanation, will now be cited. The full texts of Flack & Bernardinelli (1999) and the current paper need to be read for a detailed understanding. Kilbourn et al. (1997) in a publication entitled *Absolute configuration of* (+)-α-dihydro-tetrabenazine, an active metabolite of tetrabenazine, reported their determination of the absolute configuration of an organic compound based on the following results: '...the absolute structure parameter refined to −0.4 ± 0.3 for the assignment shown in Fig. 2. When the opposite configuration was tested, the parameter was +1.3 ± 0.3.' The authors have clearly not understood how to interpret the Flack (1983) parameter and are unaware that their experiment has not been able to determine the absolute configuration of the compound studied. Retoux et al. (1996) in their study of (R_S)-4-p-toluenesulfinylcyclohexa-1,4-diene-carboxylic acid ethyl ester, $C_{16}H_{18}O_3S$, space group $Pna2_1$, are able to state: 'The absolute configuration was assigned to agree with the known chirality of the sulfoxide group as established by the synthesis of ... and the method described by Flack (1983) was used to confirm the absolute configuration $\chi = 0.33$ (11) [compared to $\chi = 0.67$ (11) for the inverted absolute structure].' In space group $Pna2_1$, their compound is necessarily present as a racemate within the crystal structure.

2. Estimation

2.1. Interpreting numerical values of $x(u)$

The numerical estimate of the Flack (1983) parameter x and its standard uncertainty u are obtained by some numerical procedure (refinement). It is clear from its definition that x has a physically meaningful range of $0 \leq x \leq 1$, as shown in Fig. 1(a). However, as the estimate of x is obtained from experimental data with random statistical fluctuations, it may well be that the estimate lies outside the physically meaningful range. To see what the possible extent of this statistical range of x may be, one uses the known properties of the Gaussian probability density function $N(\mu, \sigma)$. For a measured x following a Gaussian distribution, there is a 99.98% chance that the observed value of x will obey $(\mu - 3\sigma) \leq x \leq (\mu + 3\sigma)$. As in our case μ is limited to the physical range $0 \leq \mu \leq 1$, it is evident that an estimate of x will fall, with a very high probability, in the range $-3u \leq x \leq (1 + 3u)$. This is shown in Fig. 1(b). Values of $x(u)$ lying outside this statistical range were few and far between in Vol. 52 of *Acta Crystallographica Section C* (1996), and it is thought that the most probable reason for the outsiders is that of a blunder. It is also worth pointing out that for values of $x > 0.5$, the model of the crystal structure is inverted with respect to the major component of the crystal. This is indicated in Fig. 1(c). It is normal practice to invert the structure to obtain a value of $x \leq 0.5$. In the rest of this text, we assume that this has indeed been carried out.

To evaluate a potential absolute-structure determination one proceeds by first analysing the value of u to see whether the data contain significant information for this purpose. Later, if the value of u is satisfactory, one may examine the
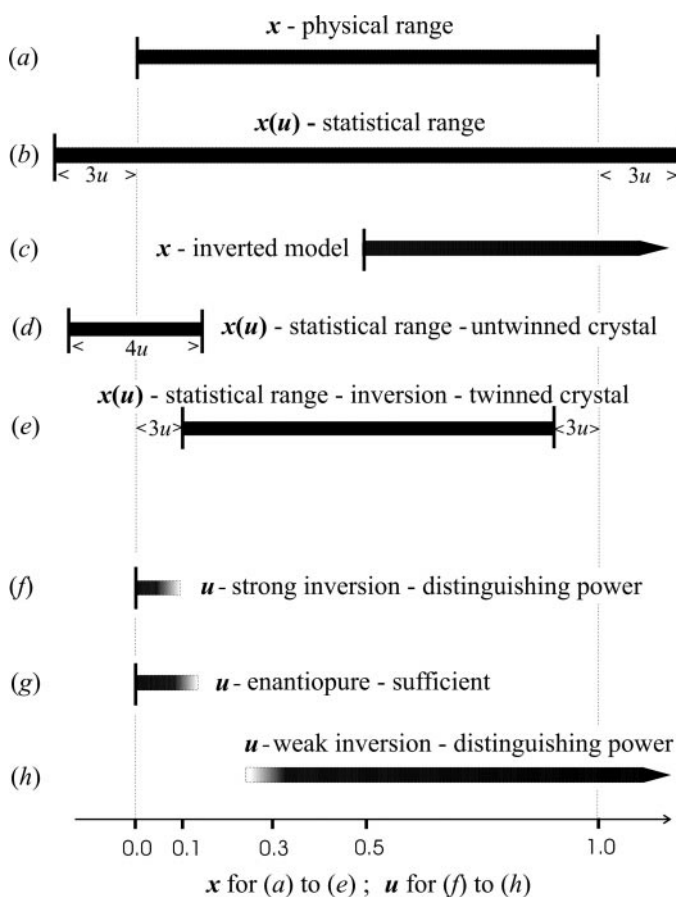
Figure 1
Domains of values of x, its u and the inversion-distinguishing power: (a) the physical domain of x; (b) the statistical domain of x; (c) the domain of x where the crystal and the model are inverted one with respect to the other; (d) the statistical domain of a crystal untwinned by inversion; (e) the statistical domain of a crystal twinned by inversion; (f) the domain of strong inversion-distinguishing power; (g) the domain of enantiopure-sufficient inversion-distinguishing power; (h) the domain of weak inversion-distinguishing power. For (f), (g) and (h), the horizontal lines are of varying intensity. In the part of the line which is black, the inversion-distinguishing power may be deduced from the value of u alone. In the part of the line which is grey, the inversion-distinguishing power may *not* be deduced from the value of u alone. In (b), (d) and (e), arbitrary values of u have been drawn and in practical applications the value of u yielded by the experiment must be used.

value of x itself. To this purpose, attention was drawn by Flack & Bernardinelli (1999) to the reciprocal relationship between the inversion-distinguishing power of the data and the value of u: the larger the value of u, the lower the inversion-distinguishing power; the smaller the value of u, the higher the inversion-distinguishing power. To quantify this relationship we consider again a Gaussian distribution $N(\mu, \sigma)$ of the estimate of x. An observed value of x will almost certainly lie in a domain of width 6σ centred on the mean μ. This width of 6σ, or in practical applications $6u$, must be compared to the physical domain $0 \le x \le 1$ of width 1 for the Flack (1983) parameter.

When the inversion-distinguishing power is weak, the Gaussian width $6u$ must not only cover the whole physical domain but also take into account the statistical fluctuations in the data. It seems reasonable to specify a lower limit on u

which allows $6u$ to encompass a domain $-0.5 \le x \le 1.5$ of width 2. Thus when $6u > 2$, $u > 0.3$ and the inversion-distinguishing power is weak. This is shown in Fig. 1(h).

When the inversion-distinguishing power is strong, one proceeds in a similar way by requiring that domains around the values of $x = 0.0$, $x = 0.5$ and $x = 1.0$ should be well defined and clearly distinguishable from one another. This requires five domains, each of width $6u$, centred at $x = 0.0, 0.25, 0.5, 0.75$ and 1.0, meaning that the physical domain of width 1.0 corresponds to $4 \times 6u = 24u = 1.0$. Thus when $u < 0.04$, the inversion-distinguishing power is strong, as is shown in Fig. 1(f).

It may be that some other prior information is available from which one can deduce that the formation of inversion twins is impossible. The most obvious case is that of a chemical compound known to be enantiopure. In this case one may be less stringent than in the previous paragraph and only require that domains around $x = 0.0$ and $x = 1.0$ be well defined and clearly distinguishable. This requires three domains of width $6u$ centred at $x = 0.0, 0.5$ and 1.0, meaning that the physical domain of width 1.0 corresponds to $2 \times 6u = 12u = 1.0$. We will call this an enantiopure-sufficient inversion-distinguishing power; it is presented in Fig. 1(g).

Once the strength of the inversion-distinguishing power has been established, the value of x itself may be examined in relation to u. For a weak inversion-distinguishing power, no interpretation of the value of x can be made. Consequently, in the rest of this paragraph we are dealing with the cases of strong or enantiopure-sufficient inversion-distinguishing power. For the interpretation of x based on an enantiopure-sufficient distinguishing power to be valid, one requires *a priori* biological, chemical or physical evidence that the compound is truly enantiopure. For a valid absolute-structure determination, one needs both a strong or an enantiopure-sufficient inversion-distinguishing power and a value of x close to zero within statistical fluctuations. For these cases, $|x| < 2u$, as shown in Fig. 1(d), assures a valid absolute-structure determination from a single crystal which is not twinned by inversion and for which the refined atomic model and the crystal correspond to each other. Crystals twinned by inversion (Flack & Bernardinelli, 1999, §3.3 therein) correspond to $x \ne 0$ and these may be identified from the experimental value of $x(u)$ if $x > 3u$, as indicated in Fig. 1(e). It is not possible to determine the absolute structure of a crystal twinned by inversion as the crystal is constituted by a mixture of inverted structures. For a truly enantiopure substance, $x > 3u$ should not occur as this implies that the crystal is not enantiopure. Should such a result occur, one should critically examine both the entire procedure used in the crystal growth and the crystal structure analysis, and the experimental basis for the proof of enantiopurity.

In this section we have shown that $u > 0.3$ implies a weak inversion-distinguishing power, that $u < 0.1$ implies an enantiopure-sufficient inversion-distinguishing power, and that $u < 0.04$ implies a strong inversion-distinguishing power. The converse of any of these propositions is not true and the presentation in Figs. 1(f), 1(g) and 1(h) of lines of fading

intensity is intended to make this clear. However, for an inversion-distinguishing power to be assigned to a level outside of the numerical ranges fixed above, a whole host of information needs to be presented and critically evaluated.

2.2. Obtaining reliable values of $x(u)$

One must ensure that x and its u have been calculated using a valid algorithm in order to undertake an absolute-structure determination correctly. As x is one of many parameters of the physical model of a crystal structure, the values of which are to be found by optimization based on some general criterion, it is essential in the final cycles of optimization that all parameters be varied jointly and simultaneously. If this prescription is not followed, two effects may occur separately or together: (*a*) the value of x may not correspond to the best value for the optimization criterion and (*b*) u may be incorrectly estimated, most frequently underestimated. From current usage and publications, several examples will now be described where the prescription is being violated with the danger of producing biased results.

2.2.1. Sparse-matrix least squares. Least squares is the most common procedure used for estimating $x(u)$. In this method, simultaneous joint variation of parameters implies that full-matrix least squares must be used in the final cycles of refinement (see also, Schwarzenbach *et al.*, 1989). However, in the *SHELXL*93/97 program (Sheldrick, 1993/1997) a value for the Flack (1983) parameter is calculated by the *hole-in-one* algorithm which does not involve simultaneous joint refinement of x with the other parameters. x is held constant at zero during the least-squares refinement of the atomic parameters. After the final shifts in these have been applied, structure amplitudes are calculated to correspond to this final model. It is at this stage that the necessary totals are accumulated to evaluate x and its standard uncertainty in what amounts to a single-variable single-cycle linear regression. The atomic coordinates nevertheless correspond to a value of x of zero. The documentation and output of *SHELXL*93/97 clearly indicate that *hole-in-one* may lead to erroneous values of x itself. In a series of tests run for us by Dr A. L. Spek of the University of Utrecht we have also found that the uncertainty u of x may be underestimated by a factor of up to 3 by *hole-in-one* compared to full-matrix least squares. In *SHELXL*93/97, full-matrix least-squares refinement of the Flack (1983) parameter may be obtained by way of the TWIN/BASF instructions; we recommend that this procedure be used in all cases. Negative twin fractions are reset to 0.001 in *SHELXL*97 and clearly it is inappropriate to use the reset value of x in the tests described in §2.1. [The non-reset value of x may nevertheless be recovered by the artifice of inverting the structure model and refining again to convergence. The twin fraction obtained is greater than one and corresponds to $1 - x$ (Linden, 1999).]

2.2.2. Stabilized least squares. In the case of highly correlated parameters, the normal-equations matrix may become very ill-conditioned in a least-squares refinement. Two closely related techniques, namely shift-limiting restraints and the Levenberg–Marquardt method, are frequently used in crystallographic refinement programs to produce a better-conditioned normal-equations matrix. These techniques work by adding positive values to the terms on the principle diagonal of this matrix. Consequently, if this stabilized matrix is used for the calculation of the standard uncertainties, they will be systematically underestimated. The shift-limiting restraints or the Levenberg–Marquardt terms should be removed prior to the matrix inversion needed for the calculation of the uncertainties (see Schwarzenbach & Flack, 1999). There were no clear reports of instability in the refinement of the Flack (1983) parameter in Vol. 52 of *Acta Crystallographica Section C* (1996). It is not clear whether this is entirely due to the inherent stability of this linear parameter or to the covert use of some stabilization technique during the least-squares refinement.

3. Reporting and evaluating

3.1. Right-handed axes

As emphasized and discussed by Rogers (1975), right-handed sets of axes must be used at every stage of an analysis of absolute structure. Of particular danger for the structure analyst are basis transformations performed to bring the unit cell into a standard setting. To maintain right-handed axes, any basis transformation matrix must have a positive determinant. A transformation matrix with a negative determinant will transform a right-handed set of axes into a left-handed set of axes, and conversely. The sign of the determinant can not be spotted simply by counting the number of positive and negative elements in the transformation matrix.

3.2. Intensity data

General considerations on the choice of intensity data and their treatment have been presented by Flack & Bernardinelli (1999). It should be pointed out that if intensity data are averaged in the Laue symmetry, values of the Flack (1983) parameter in the neighbourhood of 0.5 will be obtained. Some of the papers in Vol. 52 of *Acta Crystallographica Section C* (1996) do indeed show values of x very close to 0.5. These may arise from true equivolume inversion twins or from averaging under the Laue symmetry. In general, there was insufficient information available to determine whether a mistake had been made. In version 1.8 of *TEXSAN* (Molecular Structure Corporation, 1997) for Unix (Linden, 1999), the signs of reflections are scrambled during the sorting/merging process of data reduction even if the averaging is being undertaken in the non-centrosymmetric crystal point group. This also leads to values of x very close to 0.5.

In cases of intermediate inversion-distinguishing power, it is of interest to supplement the standard intensity data by measurement of absolute-structure-sensitive Friedel opposites. Le Page *et al.* (1990) give invaluable advice concerning the choice and the precautions to be made in the measurement of these reflections. Grochowski (1997) and Grochowski & Serda (1997) give similar advice and also make use of

azimuthal scans measured on a six-circle diffractometer for establishing the absolute structure of a crystal of a compound containing only N, C and H. Although we do not consider it correct to use these extra measurements independently of the main data collection, it is not entirely clear how to incorporate them optimally. For example, in data measured using the precautions of Le Page *et al.* (1990), the systematic errors in intensity of Friedel opposites are nearly identical. This leads to a situation where the fit on the intensity differences between Friedel opposites is better than the overall fit of the data. In such cases the uncertainty in x will, by consequence, be overestimated. Some data we have examined indicate that this is happening, but more study is needed.

3.3. Hardware and software calibration

It is essential that structure analysts test their instrumentation hardware and software on delivery and after any modification by using reference substances. We have often used crystals of potassium hydrogen (+)-(2R,3R)-tartrate for this purpose, whereas Hynes & Le Page (1991) prefer sucrose.

3.4. Incorrect scattering factors

A referee has pointed out that a common cause of incorrect values of $x(u)$ is the inadvertent use of the wrong wavelength or element type.

3.5. Graphics

The visual perception, and hence the chirality, of objects represented by stereo pairs of diagrams is affected by whether they are prepared for and viewed by the 'wide-eyed' or the 'cross-eyed' technique (see *e.g.* Anderson & Farell, 1999). Authors should always check their diagrams to make sure that they correspond to the correct chirality.

3.6. Current limits to routine absolute-structure determination

It is of interest to know what practical conditions limit the determination of absolute structure from routine measurements in terms of anomalous-dispersion contribution, data completeness and other experimental factors. Our study of Vol. 52 of *Acta Crystallographica Section C* (1996) is very limited in its capacity to provide new evidence on this matter for the following reasons. Firstly, structure analysts have a natural and understandable tendency to prejudge the capacity of each crystal to furnish information on absolute structure; if this capacity is judged to be too small *a priori*, a treatment of absolute structure is not attempted and in the publication may not even be mentioned. Secondly, if an absolute-structure determination is judged to be too poor to merit the publication of the corresponding numerical values, a short note in the style 'Flack (1983) parameter indeterminate' is often recorded. Lastly, for substances where a part or the whole of the compound is of known absolute configuration, the structure is set accordingly and no confirmation by anomalous-dispersion effects is attempted. While the above procedures are certainly acceptable, it would nevertheless be preferable to produce a report such as: 'Flack parameter = -0.8 (10) (inconclusive)' or 'Flack parameter unstable'.

3.7. Macromolecular structures

Proteins represent an interesting class of compounds for which the absolute configuration is known *a priori* in very many cases. For some classes of protein, structure refinement is now being carried out to atomic resolution, resulting in interpretable anisotropic atomic displacement parameters (Merritt, 1999). With data of such quality it is clear that anomalous-dispersion effects need to be treated properly (Parkin, 1998). At present, it is common practice for Friedel opposites to be merged and for all f'' to be set to zero prior to the refinement stage. As yet no systematic study has been published to demonstrate the effects of this inconsistent procedure and only a few cases using unmerged Friedel opposites have appeared in the literature (Parkin *et al.*, 1996a,b).

3.8. Polar-dispersion error

Vol. 52 of *Acta Crystallographica Section C* (1996) contains a good proportion of papers that present non-centrosymmetric structures with significant dispersive scatterers and that make no mention either of absolute structure or of the Flack (1983) parameter and perhaps take no account of it. In some of these papers, the conditions are ripe for a significant polar-dispersion error leading to errors in bond lengths and angles. Cruickshank & McDonald (1967) give estimates of the size of the polar-dispersion error.

3.9. Euclidean normalizers of space groups

There are two properties of non-centrosymmetric space groups which are needed in the treatment of absolute structure. The first concerns the identification of those directions for which the origin can not be placed by reference to the symmetry elements alone. The second concerns the coordinates of the inversion point to change a structure into its inverse. Separate solutions to these problems have appeared in the literature over the years (Bernardinelli & Flack, 1985; Flack & Schwarzenbach, 1988; Donnay & Le Page, 1978; Sheldrick, 1993, 1997). However, the necessary information also appears in the table of Euclidean normalizers of the space groups (Koch & Fischer, 1996) available in the *International Tables for Crystallography*, Vol. A (1996). In Table 15.3 therein, those space groups where the origin can not be fixed with respect to the symmetry elements may be recognized by an initial letter Z in the symbol for the Euclidean normalizer in column 3, and the free directions may be recognized by an ε in column 4. The point for inversion of the structure is indicated in column 6. Of course, the tables of Euclidean and affine normalizers of plane and space groups have far more general applications and practical uses than those mentioned here.

3.10. Molecular symmetry

In §6 of Flack & Bernardinelli (1999), three conditions for the successful deduction of absolute configuration from absolute structure were enumerated. The *space-group restriction* is easy to apply; in Vol. 52 of *Acta Crystallographica Section C* (1996) we detected no cases where the authors claimed to have determined an absolute structure or an absolute configuration from a centrosymmetric structure. On the other hand, there were claims in one form or another for absolute-configuration determination from non-centrosymmetric but achiral structures (see §1). We also noticed several articles in which the results justified a valid absolute-structure determination for a chiral structure, but in which the authors made no interpretation of its application to fixing the absolute configuration.

The *chiral molecular entity restriction* and the *solid-state enantiopurity restriction* require the identification of the crystallographic and the non-crystallographic symmetry of all of the molecules in the asymmetric unit. The chirality sense of the symmetry-independent molecules also needs to be identified with due account being taken for conformational changes which do not affect the chirality. For example, *PLATON* (Spek, 1999) determines the point symmetry of any molecular species in the structure and gives the stereochemical description (R or S) of chiral centres. We are unaware of software capable of indicating the chirality sense of an enantiomer not due to chiral centres. It is essential for the evaluation of absolute-configuration determinations that the crystallographic and non-crystallographic symmetry of all the molecules and the chirality relationships between independent molecules be reported. For this purpose, the most promising nomenclature suggested so far is that of Chernikova et al. (1991), but this would need to be extended for the current purposes. Crystal chemical studies of structures with more than one independent molecule in the asymmetric unit have already been published (see *e.g.* Brock & Dunitz, 1994 for a very informative review); these as well would benefit from the reporting of molecular symmetry in primary crystal structure publications and in database compilations. Structure analysts must always bear in mind that chiral crystal structures may be composed from achiral molecules or from racemates (see *e.g.* Jacques et al., 1994) and that racemization may take place on the same time scale as the crystallization process.

3.11. Enantiopurity

It seems frequently to be the case that there is an implicit assumption that chiral molecules have been crystallized from an enantiomerically pure mother liquor. Furthermore, precious little evidence is presented for its justification. For absolute-configuration determination, one requires a quantified statement of the enantiopurity of the bulk compound. Ideally this should take the form of a measure of the enantiomeric excess together with its standard uncertainty. Frequently, the establishment of enantiopurity is carried out by enantioselective chromatography; it is helpful here to recall very briefly some of the precautions necessary to obtain meaningful results. As the interaction between the enantioselective agent of the chromatography column and the test compound is specific, a column always needs calibrating with an enantiomeric mixture of the compound under the same conditions as those used for analysing the bulk compound (Francotte, 1996, 1997, 1999). It is not necessary that this calibration enantiomeric mixture be the racemate. In the pharmaceutical industry, measurements of the 'limit of detection' and 'limit of quantitation' are undertaken for patent requirements (Francotte et al., 1996). These limits must be closely associated with those meaningful for absolute-configuration determination.

It is of interest to consider what limits to the concentration of enantioimpurities are required for satisfactory absolute-configuration determinations. For a compound containing only atoms of low atomic mass, the mass of the crystal used for diffraction measurements is *ca* 1 µg and one may reasonably suppose that this has been crystallized from 1 mg of bulk compound. The crystal thus represents one part in 10^3 of the bulk. Moreover, one should require that not more than 1% (one part in 10^2) of the crystal should contain the enantioimpurity. Overall, one sees that the bulk compound should contain no more than one part in 10^5 of the enantioimpurity for the diffraction experiment on one single crystal to provide an absolute-configuration determination truly applicable to the bulk compound. This is, of course, a worst-case calculation in which all of the enantioimpurity finds its way into the particular crystal studied.

3.12. Optical activity

Very few papers on enantiomers in Vol. 52 of *Acta Crystallographica Section C* (1996) report measurement of the optical rotation in solution and precede the chemical name of the compound with the corresponding $(+)$, $(-)$ or $(\pm)$. The optical activity is a very useful way of characterizing or 'fingerprinting' the bulk compound, and presents a simple way of checking for some gross mistakes. Unfortunately, polarimeters require a higher concentration than that obtained by dissolving the single crystal used for diffraction measurements, for it would be most helpful to characterize the optical activity in solution of only this one single crystal. Harada (1996) has suggested that circular dichroism values might satisfactorily be used instead of measurements of optical activity.

3.13. Author declaration

The papers in Vol. 52 of *Acta Crystallographica Section C* (1996) were frequently mysterious as to whether the authors thought that they had or had not determined the absolute structure and deduced an absolute configuration from this. A clear statement by authors on this matter would be of use.

3.14. CIF data items

From our study of Vol. 52 of *Acta Crystallographica Section C* (1996), it became apparent that for some data items which need to be reported in absolute-structure and absolute-configuration determinations, there were no corresponding

data names and definitions in the existing CIF Core Dictionary. As a consequence of our proposals, some new or improved definitions of CIF data items have been accepted by the Core Dictionary Maintenance Group of the IUCr COMCIFS (International Union of Crystallography Committee for the Maintenance of the CIF Standard). The definitions are incorporated in version 2.1 of March 1999 of the CIF Core Dictionary (http://www.iucr.org/iucr-top/cif/cif_core/index.html). The three new data items are:

`chemical_absolute_configuration`, which provides standard codes for expressing the way in which the absolute configuration has been determined;

`chemical_optical_rotation`, which provides a stylized format for the optical rotation in solution of the bulk compound; and

`reflns_Friedel_coverage`, which provides a clearly defined manner of expressing the proportion of Friedel-related reflections present in the number of independent reflections.

3.15. What is still missing?

The full commented table of structures from Vol. 52 of *Acta Crystallographica Section C* (1996) and from the 1996 CIF archive is available as supplementary material for this paper.[1] Some types of error were expected at the outset while others were only recognized at a later stage and no attempt has been made to go back to make the list complete.

Taken together, the two papers in the present series (Flack & Bernardinelli, 1999; current paper) should suffice to clarify very many aspects of the determination and reporting of absolute structure and absolute configuration. However, the work has uncovered some points for which no satisfactory solution is available at present. We briefly gather together these topics in the current section.

One needs, especially for absolute-configuration determination, a rapid and simple method of establishing that the one single crystal used for diffraction measurements is characteristic of the bulk compound. It would be helpful, for example, to be able to measure the optical rotation on a solution made from the single crystal used for the diffraction experiments.

Reliable software is required both for detecting molecular symmetry and for comparing the chirality of two crystallographically independent molecules. Moreover, nomenclature for reporting this information is necessary.

All absolute-configuration determinations need to be accompanied by a numerical estimate of the enantiopurity *together with* its standard uncertainty.

The manner of optimally exploiting intensity measurements of selected absolute-structure-sensitive reflections needs further investigation.

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[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: KS0021). Services for accessing these data are described at the back of the journal.

References

Anderson, B. L. & Farell, B. (1999). *Nature (London)*, **401**, 342–343.
Bernardinelli, G. & Flack, H. D. (1985). *Acta Cryst.* A**41**, 500–511.
Brock, C. P. & Dunitz, J. D. (1994). *Chem. Mater.* **6**, 1118–1127.
Chernikova, N. Yu., Bel'skii, V. K. & Zorkii, P. M. (1991). *J. Struct. Chem.* **31**, 661–666.
Cruickshank, D. W. J. & McDonald, W. S. (1967). *Acta Cryst.* **23**, 9–11.
Donnay, J. D. H. & Le Page, Y. (1978). *Acta Cryst.* A**34**, 584–594.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Flack, H. D. & Bernardinelli, G. (1999). *Acta Cryst.* A**55**, 908–915.
Flack, H. D. & Schwarzenbach, D. (1988). *Acta Cryst.* A**44**, 499–506.
Francotte, E. (1996). *Chim. Nouv.* **14**, 1541–1552.
Francotte, E. (1997). *Chimia*, **51**, 717–725.
Francotte, E. (1999). Private communication.
Francotte, E., Davatz, A. & Richert, P. (1996). *J. Chromatogr. B*, **686**, 77–83.
Grochowski, J. (1997). *Acta Phys. Polonica A*, **91**, 745–756.
Grochowski, J. & Serda, P. (1997). *Acta Phys. Polonica A*, **91**, 961–968.
Harada, N. (1996). *Enantiomer*, **1**, 81–82.
Hynes, R. C. & Le Page, Y. (1991). *J. Appl. Cryst.* **24**, 352–354.
International Tables for Crystallography (1996). Vol. A, *Space-Group Symmetry*, 4th revised ed., edited by Th. Hahn. Dordrecht: Kluwer Academic Publishers.
Jacques, J., Collet, A. & Wilen, S. H. (1994). *Enantiomers, Racemates and Resolutions*. Reissue with corrections. Malabar, FL: Krieger.
Kilbourn, M. R., Lee, L. C., Heeg, M. J. & Jewett, D. M. (1997). *Chirality*, **9**, 59–62.
Koch, E. & Fischer, W. (1996). *International Tables for Crystallography* (1996). Vol. A, *Space-Group Symmetry*, 4th revised ed., edited by Th. Hahn, ch. 15. Dordrecht: Kluwer Academic Publishers.
Le Page, Y., Gabe, E. J. & Gainsford, G. J. (1990). *J. Appl. Cryst.* **23**, 406–411.
Linden, A. (1999). Private communication.
Merritt, E. A. (1999). *Acta Cryst.* D**55**, 1109–1117.
Molecular Structure Corporation (1997). *TEXSAN. Single Crystal Structure Analysis Software*. Version 1.8. MSC, 9009 New Trails Drive, The Woodlands, TX 77381, USA.
Parkin, S. (1998). Private communication.
Parkin, S., Rupp, B. & Hope, H. (1996*a*). *Acta Cryst.* D**52**, 18–29.
Parkin, S., Rupp, B. & Hope, H. (1996*b*). *Acta Cryst.* D**52**, 1161–1168.
Retoux, R., Molenkamp, J., Bonfand, E., Gosselin, P. & Maignan, C. (1996). *Acta Cryst.* C**52**, 2290–2292.
Rogers, D. (1975). *Anomalous Scattering*, edited by S. Ramaseshan & S. C. Abrahams, pp. 231–250. Copenhagen: Munksgaard.
Schwarzenbach, D., Abrahams, S. C., Flack, H. D., Gonschorek, W., Hahn, Th., Huml, K., Marsh, R. E., Prince, E., Robertson, B. E., Rollett, J. S. & Wilson, A. J. C. (1989). *Acta Cryst.* A**45**, 63–75.
Schwarzenbach, D. & Flack, H. D. (1999). *Encyclopedia of Spectroscopy and Spectrometry*, edited by J. Lindon, G. Tranter & J. Holmes, pp. 2271–2278. London: Academic Press.
Sheldrick, G. M. (1993/1997). *SHELXL93/SHELXL97. Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.
Spek, A. L. (1999). *PLATON. A Multipurpose Crystallographic Tool*. Utrecht University, Utrecht, The Netherlands. http://www.Cryst.Chem.uu.nl/PLATON.