

SHELXL refinement against neutron diffraction data

TOPAZ Workshop, Oak Ridge, June 16th 2015

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<http://shelx.uni-ac.gwdg.de/SHELXL/>

Introduction

SHELXL is an old program for refining crystal structures, of both small and macromolecules. Although primarily intended for refinement against X-ray data, it may also be used for refinement against neutron diffraction data.

The SHELX programs are available free of charge for academic use for the Windows, Linux and MacOSX operating systems. They have strictly zero dependencies: no other programs, libraries, DLLs, environment variables etc. are required to run them.

SHELX was developed starting in about 1969 but first officially released in 1976. A version (now deceased) for simultaneous refinement against X-ray and neutron data was described by Orpen *et al.* (1978).

Recent SHELXL improvements for refinement against neutron data

If a NEUT instruction is inserted before the (first) SFAC instruction, neutron scattering lengths are used instead of X-ray scattering factors. In addition, H and D atoms are treated as normal atoms when referenced in other instructions, but HFIX or AFIX may still be used to place and refine them. The default bond lengths to H and D are increased so that they correspond to the internuclear distances rather than the distances between the electron density maxima.

However geometric restraints may work better than AFIX type constraints, because of the significant scattering power of the H and D atoms for neutrons.

The enhanced CHIV instruction

For refinements against neutron data with the NEUT instruction, the CHIV (chiral volume) restraint can now be used as for X-ray data when an atom makes exactly three bonds to non-H/D atoms, in which case further bonds to H or D are ignored. Thus no special action is needed for this restraint when moving from X-ray to neutron refinement.

If an atom makes a total of exactly three bonds *including* bonds to H or D, a CHIV instruction with the default value of zero may be used to restrain planarity, e.g. for -NH-, -NH₂, -ND- and -ND₂ amides or aromatic -CH- and -CD- groups. Using NEUT together with AFIX has a similar effect, but operates as a constraint.

The new form of CHIV is particularly useful for aromatic rings where the H or D atoms may bend slightly out of the plane of the other atoms.

Mixed Deuterium/Hydrogen sites

D has the advantages of a numerically larger scattering length (6.67fm) than H (-3.74fm) and much less incoherent scattering. However when deuterium is incorporated, e.g. by repeated crystallization from D₂O, the D/H ratio may differ for different sites. To save parameters, a free variable (fv) can be used for chemically equivalent sites. Using fv(2) for the D occupancy and 1-fv(2) for H so that they sum to 1.0:

```

EXYZ H21 D21
EADP H21 D21
PART 1
D21 2 . . . 21 . . . . .
PART 2
H21 5 . . . -21 . . . . .
PART 0
    
```

A simpler approach would be to refine the occupancy q of D (possibly as a free variable) and to calculate the fraction p of deuteration by:

$$P = (0.64073 * q) + 0.35927$$

Then EXYZ, EADP, PART and H21 are not required. However the current SHELXL objects to negative occupancies even when disguised as a fv. In the next release this will be changed when NEUT is set.

HKLF 2 or HKLF 4?

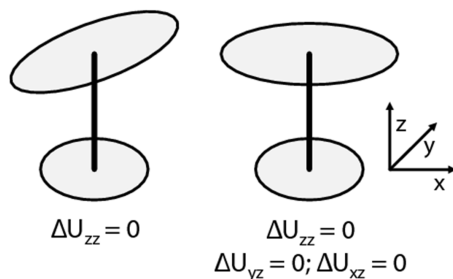
SHELX HKLF 2 format allows a different wavelength to be specified for each reflection. This was originally intended for use in combination with the LAUE instruction so that the wavelength-dependence of the anomalous scattering contributions f' and f'' could be taken into account for X-ray data.

This is not important for most isotopes for neutron data, but HKLF 2 format (without LAUE) is still useful because it enables the wavelength to be taken into account when refining isotropic extinction. The price to pay is that reflections with different wavelengths cannot be merged until this correction has been refined (but before calculating the electron density maps).

It is not clear how important an anisotropic extinction refinement would be, or whether it could be performed as part of the data processing. X-ray data are often scaled empirically (e.g. with SADABS) so that the intensities of equivalent reflections are made more equal; this could also be done for neutrons, but requires highly redundant data.

The RIGU rigid-bond restraint

Classical rigid bond restraint:
Hirshfeld (1976)
Acta Cryst. **A32**,
239-244.

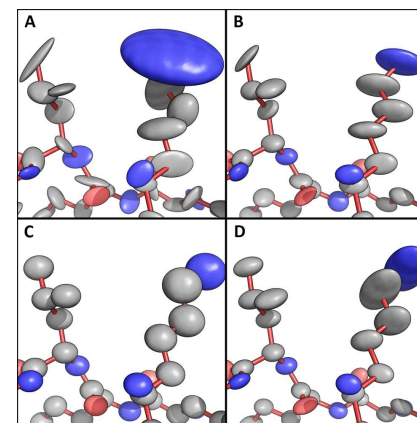


Enhanced rigid bond restraint
RIGU.

The enhanced rigid bond restraint **RIGU** involves three restraints rather than one. In addition to making the motion of the two atoms along the bond joining them similar, the relative motion of the two atoms is restrained to be at right angles to the bond.

RIGU for macromolecular refinement against X-ray data

A: unrestrained anisotropic refinement



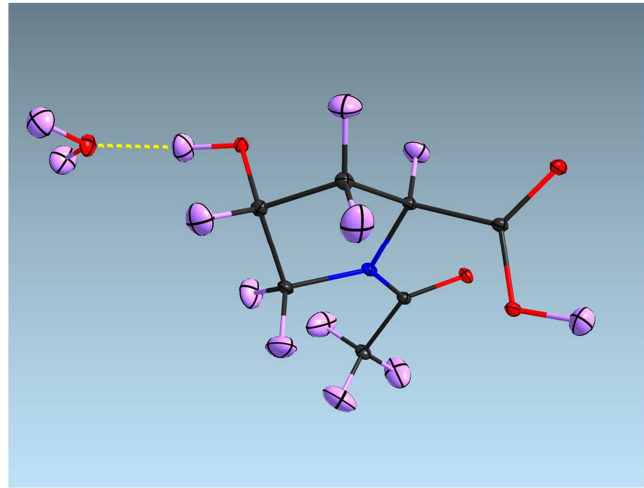
B: **DELU** (rigid bond) plus **SIMU** (similar ADPs) restraints

C: Individual isotropic plus TLS rigid groups

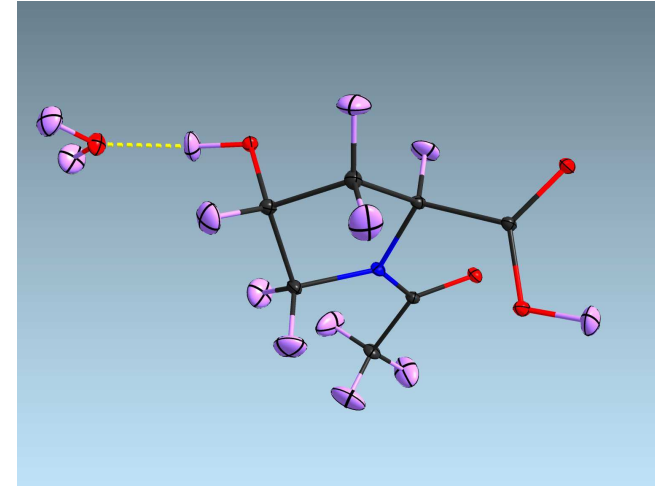
D: **RIGU** restraints

But can RIGU be used for anisotropic refinement of hydrogen atoms against neutron diffraction data?!

Refinement against 9K neutron data without RIGU



Refinement against 9K neutron data with RIGU



RIGU for anisotropic neutron refinement of H/D-atoms

Even without RIGU restraints, the two largest principal components of the hydrogen ADPs are approximately at right angles to the bonds. With RIGU this is even more so. So at first sight RIGU fits rather well.

However the motion of the hydrogen atoms along the bonds is appreciably larger than that of the atoms to which they are attached, because they have smaller masses.

If the data to parameter ratio is poor, in addition to using RIGU it may be necessary to impose a minimum value for the principal U-components to prevent atoms from going NPD (e.g. XNPD 0.01).

Possible future improvements:

- (a) Take the atomic masses into account, **or**
- (b) RIGU could restrain only the motion at right angles to the bonds, and separate DFIX restraints could be used for the motion along the bonds for the non-hydrogen atoms.

Joint X-ray and neutron refinement

Advantages:

1. A much better data to parameter ratio, so refinements should be more stable.

Disadvantages:

1. The crystals may be too different.
2. The temperatures may differ.
3. Bond lengths to hydrogen are different for X-rays and neutrons.
4. The ADPs from X-ray data are contaminated by the bonding electrons.
5. Radiation damage differs (strongest for synchrotron X-ray data).
6. Systematic errors such as extinction and absorption differ, and so can only partially be mopped up by anisotropic temperature factors.

Joint X-ray and neutron refinement

Refining simultaneously against the X-ray and neutron data is an attractive idea. Despite several successful applications and specially modified versions of standard programs, it never really caught on.

1978 Orpen, Pippard & Sheldrick, *Acta Cryst.* **B34**, 2466-2372 (SHELX76).

1982 Wlodawer & Hendrickson, *Acta Cryst.*, **A38**, 239-247 (PROLSQ).

2009 Adams *et al.*, *Acta Cryst.* **D65**, 567-573 (PHENIX_refine).

An alternative approach is to use the non-hydrogen geometry from an X-ray refinement as restraints for a refinement against the neutron data. The anisotropic displacement parameters (ADPs) cannot be transferred so easily, but the Shade web server can be used to predict hydrogen ADPs (Munshi, Madsen, Spackman, Larsen & Destro (2008). *Acta Cryst.* **A64**, 465-475). Lübben, Dittrich *et al.* have recently achieved comparable theoretical predictions. These predictions are possible because the largest contributions are from the internal vibrations of the molecules, especially at very low temperatures.

Future plans - structure solution

It might be possible to create a special version of the new structure solution program SHELXT for the direct solution of structures from neutron data, but there are problems:

1. Negative peaks for H and a few other isotopes. This would require major changes to the program code.
2. The number of atoms to be found would be approximately doubled, reducing the chances of success, especially when the data are limited.
3. Different scattering factors would be needed for the isotropic refinement stage. This would be an easier problem to solve.

In practice in most cases, solving the X-ray structure first would be easier.

Future plans - structure refinement

For Laue data not measured with time-of-flight techniques, harmonics may contribute to the same total count and such reflections are often discarded. E.g. the reflection 1,1,1 with wavelength 2λ overlaps 2,2,2 with wavelength λ . It would be better to take the harmonics into account and refine against the total intensity as for twinned crystals. Possibly this is already implemented in other programs, but not yet in SHELXL.

This could be achieved with a new HKLF format similar to HKLF 5 for twins, in which each contributor to a combined intensity is scaled as if it were the only contributor. Alternatively the current data formats could be retained, without rejecting the reflections overlapped by harmonics, and a wavelength-dependent scaling function read in. SHELXL could then decide which harmonics need to be taken into account.

There are also improvements in the pipeline for validation, related to the free-*R* factor but without having to sacrifice 5-10% of the data for the free-*R* set (Grüne & Lübben, *PNAS*, *in press*). However these involve intensive computations.

Acknowledgements and references

I am very grateful to many SHELX users for suggesting improvements, reporting bugs and providing interesting test data. Documentation and tutorials may be found on the SHELX homepage (Google knows where).

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SHELXL (current version): Sheldrick, G.M. (2015). *Acta Cryst.* **C71**, 3-8.

SHELXT (structure solution): Sheldrick, G.M. (2015). *Acta Cryst.* **A71**, 3-8.

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shelXle (GUI for SHELXL): Hübschle, C., Sheldrick, G. M. & Dittrich, B. (2011). *J. Appl. Cryst.* **44**, 1281-1284.

SADABS (scaling of X-ray data): Krause, L., Herbst-Irmer, R. Sheldrick, G.M. & Stalke, D. (2015). *J. Appl. Cryst.* **48**, 3-10.