Absolute Configuration Determination: Is There More Information in the Data?

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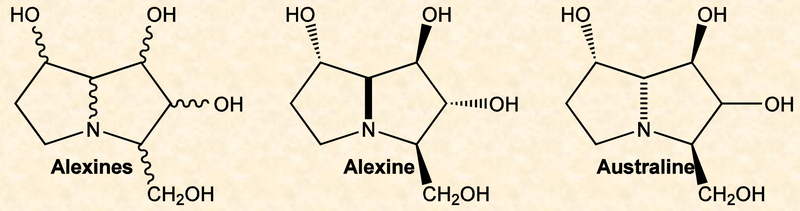
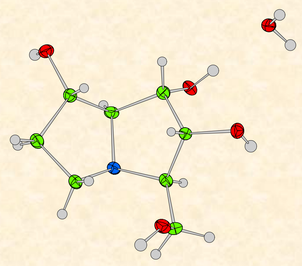
A new version of ***CRYSTALS*** *will be released late Autumn 2009*†

Case Study – 1-Epiaxlexine[1]

- Alexine, isolated from *Alexa leiopetala,*[2] was the first example of a class of 3-hydroxymethyltrihydroxy-pyrrolizidines, known as alexines.
- Alexines can be regarded as iminosugar analogues which have considerable potential as therapeutic agents[3].
- Alexines possess five chiral centers that give rise to 32 stereoisomers, including Australine which has been shown to inhibit various glucosidases.



- A new polyhydroxylated pyrrolizidine alkaloid, 1-epialexine was isolated from stems of *Castanospermum australe*.
- X-ray crystallographic analysis is essential to determine the absolute and relative configuration.
- Out of curiosity, the Flack x parameter[4] was refined and the Hooft y parameter[5] determined for 1-epialexine with data collected from the same crystal on our Nonius KCCD diffractometers (molybdenum source) and on an Oxford Diffraction Gemini.



	KCCD 1	Gemini–Mo	Gemini–Cu	KCCD 2
Flack x	-1.1 (9)	-1.5 (9)	-0.01(17)	-0.1(8)
Hooft y	-0.7(4)	-1.7(3)	-0.03(2)	-0.1(4)
G	2.3(8)	4.4(5)	1.06(4)	1.2(8)
P2(correct)	0.999	n/a	1.000	0.974
P3(correct)	0.933	0.992	1.000	0.726
P3(rac)	0.066	0.008	10^{-7}	0.726
P3(inverse)	0.001	$0.2x10^{-4}$	10^{-7}	0.019
Reflections	1943	1724	1476	1974
Friedel Pairs	875	777	650	902

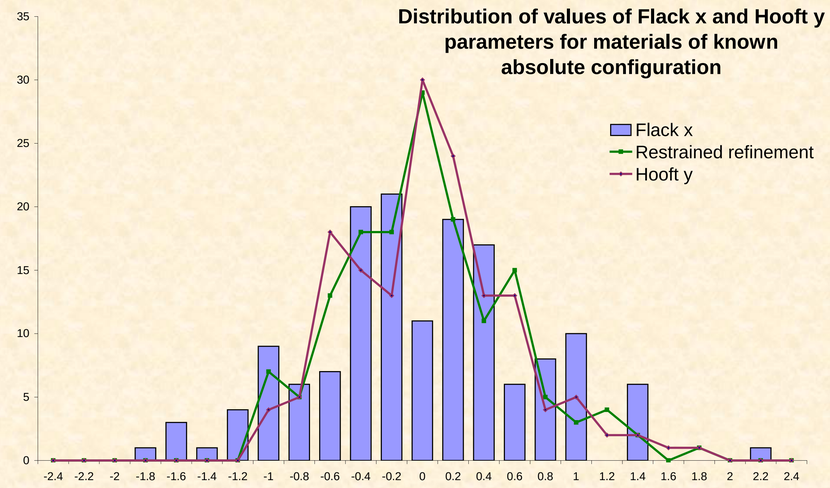
What does this mean? Is there more information in the data?

Flack x and Hooft y Parameters

- For two of the three 1-epialexine datasets with molybdenum radiation, the Flack x parameter was considerably outside the meaningful range for the parameter, and for all three, the s.u. value was exceptionally large, indicating that the absolute configuration could not be determined.
- In contrast, although the Hooft y parameter is similarly poorly defined, examination of the Bijvoet pairs using the Hooft method suggests that the absolute configuration could be determined with a high confidence.
- At ECM22, Parsons and Flack demonstrated that it is possible to improve the inversion distinguishing power of a refinement of L-alanine by using inversion-sensitive reflections as restraints:[7]

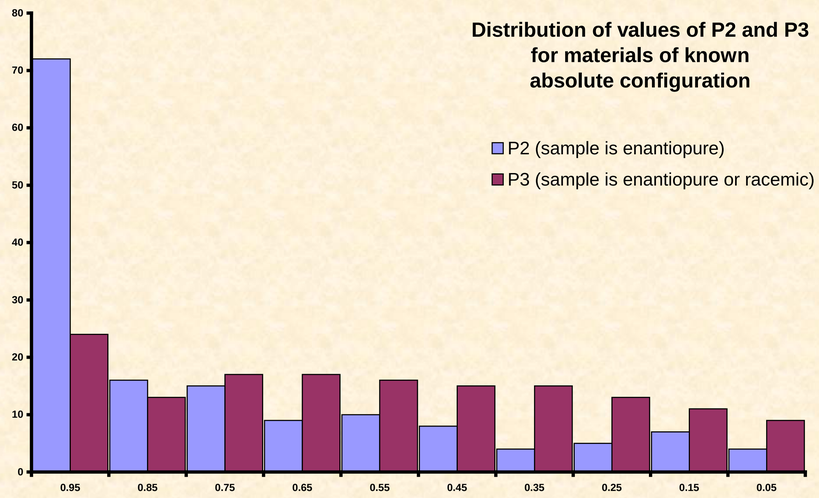
$$D_{obs}(\mathbf{h}) = \frac{I(\mathbf{h}) - I(-\mathbf{h})}{I(\mathbf{h}) + I(-\mathbf{h})} \cong (1 - 2x)\frac{\left|F(\mathbf{h})^2\right| - \left|F(-\mathbf{h})^2\right|}{\left|F(\mathbf{h})^2\right| + \left|F(-\mathbf{h})^2\right|}$$

- We examined 150 datasets‡,[8] for structures containing nothing heavier than argon (mean FRIEDIF = 6.1),[9] with known absolute configuration, and refined the Flack x parameter, carried out the Hooft analysis, and repeated the refinements with Friedel Difference restraints using CRYSTALS[6].



Probabilities

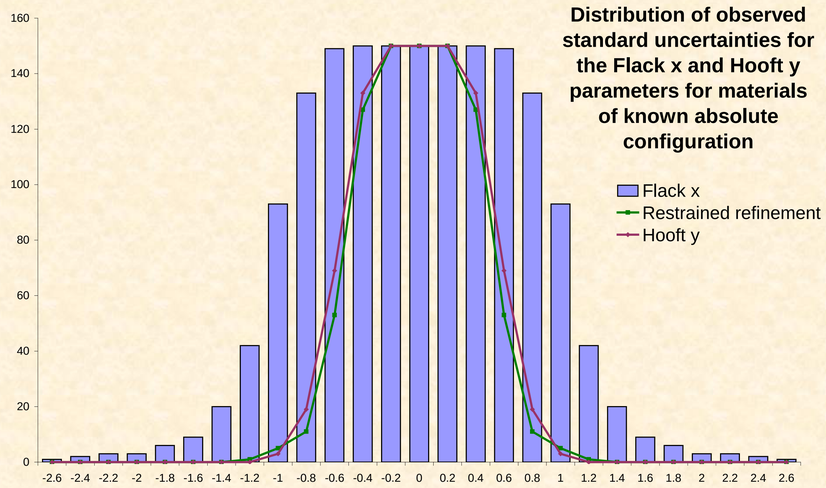
- The probability of the observed Bijvoet pairs being obtained can be estimated from the distribution of ΔFo and ΔFc subject to various hypotheses.
- This gives rise to the possibility of estimating the probability, P(2), that for an enantiopure material (only two choices) that the assigned hand is correct. Similarly, the probabilities of three outcomes, P(3), (correct assignment, 50:50 twin, incorrect assignment) can also be determined for a material of unknown enantiopurity.



- The observed distribution of P(2) (which should be 100% in the first bin for these samples) is reassuring whereas the distribution of P(3) correct probabilities is far from reassuring.
- It seems that the quality of modern data is such that the absolute structure determinations of enantiopure light atom structures using Mo radiation could be indicative based on the 80:20 rule.

Standard Deviations

- The standard uncertainty in the Flack parameter is the key to its interpretation.



- These results broadly support the suspicion that even without taking special care to measure all Friedel pairs, the Flack parameter tends to a value of less than 0.5. The observed mean and sample standard deviation, <x> = 0.003 ± 0.706, suggest that based on routine measurements of the X-ray data, the Flack parameter can be indicative. The corresponding plot for the Hooft parameter with a mean and sample standard deviation <y> = 0.034 ± 0.557 is substantially the same as the Flack distribution.
- The major difference between the Flack x and the Hooft y parameters appears to be the reduced standard uncertainty in y, seemingly giving it greater enantiomer distinguishing power. However, The Hooft y is computed statically from a finalised refinement, in a completely different way from the Flack x, so that while the behaviour of these two estimators can be expected to be largely similar, they can differ in detail, and in their response to unidentified errors in the data or short comings in the model.
- The distribution of P(2) for the enatiopure materials surveyed in this work suggests that the Flack criteria are conservative, and that with care, for some purposes a more liberal interpretation could be made.

† The absolute configuration analysis and Friedel restraint utility will be included in the next release of CRYSTALS.[6]

‡ Routine, unfiltered datasets, collected by members of the Oxford Chemistry DIY Crystallography Group in particular the SGD and GWJF groups.

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