Light-Atom Structures: Absolute Configuration Determination and Beyond

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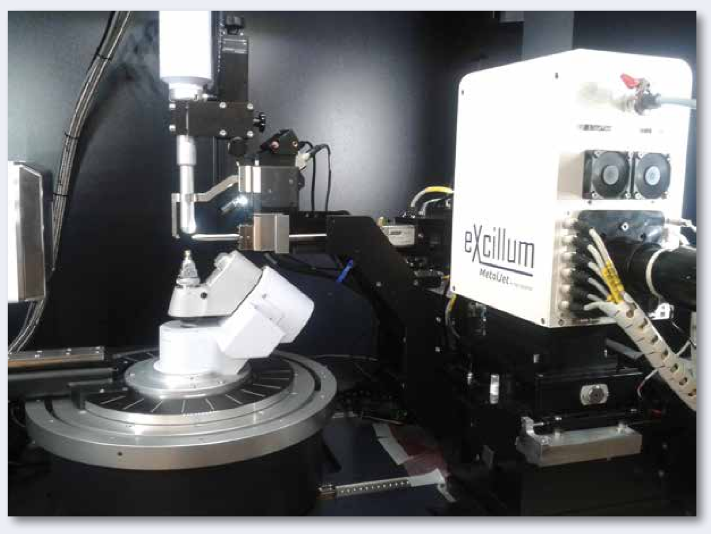
Introduction

The determination of the absolute configuration for light atom structures is central to research in pharmaceuticals and natural products synthesis [1,2,3]. In the absence of elements heavier than silicon, it is often problematic to make a significant assignment of the absolute configuration. Besides the introduction of new methods to evaluate the Bijvoet differences [4,5] and improvements in refinement software [6], the assignment of the absolute structure for light atom compounds has become easier with the advent of high-intensity microfocus sources, as the increased flux density improves the anomalous signal by improving the counting statistics. In order to maximize the anomalous signal, X-ray sources with Cu anodes are usually used for the absolute structure determination. However, these data are usually limited to a maximum resolution of about 0.80 Å. Microfocus X-ray sources with Mo radiation and the recently introduced METALJET X-ray source [7] allow for the collection of high quality data with a resolution beyond 0.80 Å. Selected data from these microfocus sources will be shown with an emphasis on the determination of the absolute structure.

High-Brilliance Microfocus X-ray Sources for Absolute Structure Determination

High-brilliance microfocus X-ray sources with Mo targets enable the collection of high quality data beyond 0.40 Å within a reasonable amount of time. This allows not only a more accurate modelling of the electron density by using aspherical scattering factors, but also enables a reliable determination of the absolute structure, despite the significantly lower anomalous signal obtained with Mo-Kα radiation [8].

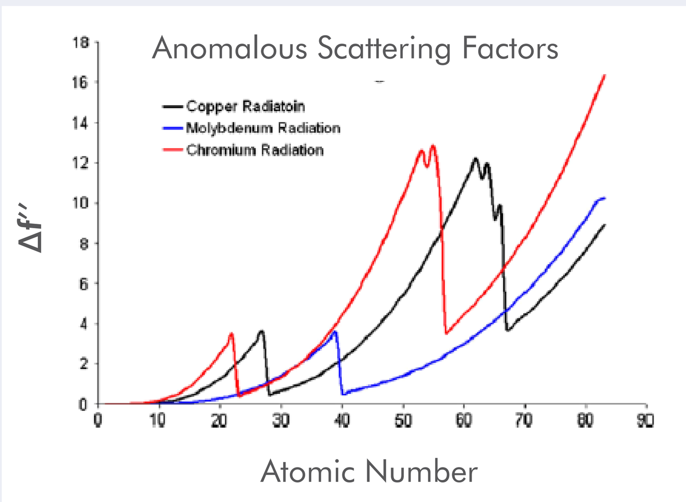
In the recently introduced METALJET X-ray source, the X-rays are generated by an electron beam that is focused on a high-speed jet of a molten Ga alloy. Such a high-speed liquid metal-jet target allows for power loads larger than 100 kW/mm² in a spot size of 20 μm or smaller [7]. Using the latest HELIOS multilayer optics, the METALJET source delivers an unprecedented intensity of > 4 x 10^{11} photons/(s mm²) for a focused beam (FWHM = 0.07 mm, 7.5 mrad divergence), thus delivering the brightest X-ray beam of all available home lab X-ray sources, at only 200 W.



A Bruker D8 Kappa DUO with 2 IμS microfocus sealed tubes (left) and the METALJET X-ray source in a D8 VENTURE (right).

Absolute Structure and Anomalous Dispersion

Absolute structure determination for an enantiopure crystal is the determination of the spatial arrangement of a chiral molecule (absolute configuration). Due to the anomalous scattering, the diffraction from such a crystal shows a change in the phase and amplitude of inversion-related reflections **H**(*hkl*) and **H**(*-h-k-l*). This causes small but measurable differences in the intensities of those reflections, which leads to the break-down of Friedel's law: **I**(*hkl*) ≠ **I**(*-h-k-l*). In order to account for the anomalous dispersion, a correction has to be applied to the atomic scattering factor of an anomalous scattering atom: $\mathbf{f} = \mathbf{f}_0 + \Delta\mathbf{f}' + i\,\Delta\mathbf{f}''$. $\Delta\mathbf{f}'$ describes the change in the amplitude, while $\Delta\mathbf{f}''$ represents the change in the phase angle. The dispersion corrections for a given atom mainly depend on the wavelength. The dependence on the scattering angle is very small since the phenomenon results from the interaction of an incident X-ray with a core electron. Therefore, the terms $\Delta\mathbf{f}'$ and $\Delta\mathbf{f}''$ of an element are treated in practice as constants for a given wavelength.



	Δf"(Cu-Kα)	Δf"(Ga-Kα)	Δf"(Mo-Kα)
Cl	0.70	0.53	0.16
S	0.56	0.44	0.12
O	00.32	0.023	0.006

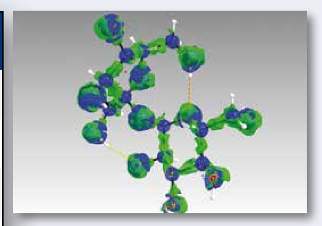
Dependence of the anomalous dispersion correction Δf'' on the atomic number for different wavelengths (taken from ref. [2]). Comparison of Δf'' for selected elements, showing that Δf'' for Ga-Kα is weaker than that for Cu-Kα, but significantly higher than that for Mo-Kα .

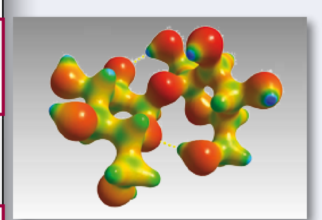
Case Studies for Absolute Structure Determination

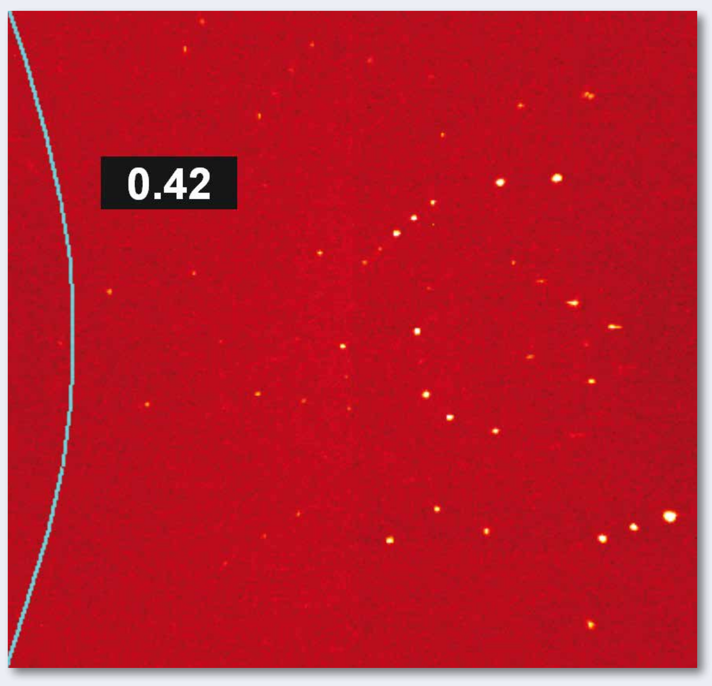
Case Study 1: Sucrose crystal $C_{12}H_{22}O_{11}$
a = 7.7189(2) Å, b = 8.6628(2) Å, c = 10.8085(3) Å,
ß = 102.999(1)°, Z = 2, $P2_1$,

Size [mm³]	0.25 x 0.22 x 0.18
Source	Mo-IμS High Brilliance
Total time [d]	3
Exposure time [s/°]	6 - 100
Resolution [Å]	0.41 (0.51 - 0.41)
Multiplicity	7.7 (5.1)
<I/σ>	47.2 (18.3)
R1, wR2 [%] (IAM) R1, wR2 [%] (Multipole)	2.47, 6.63 1.48, 2.28
Flack x (u) Flack x (u) (Multipole) Parsons z (w)	0.00(15) 0.02(5) 0.03(4)

Sucrose (<|ΔF^2_{ano}|>/<F²> = 0.06% (Mo-Ka), 0.30% (Cu))







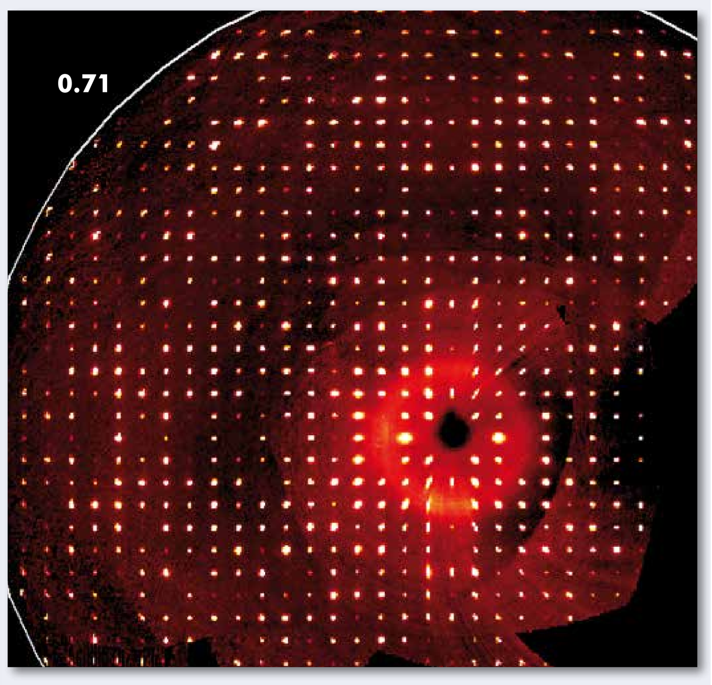
Typical diffraction pattern of the sucrose crystal, recorded with Mo-IμS HB (right), electron density and residual electron density (after IAM refinement,left, above) and electrostatic potential (left, below) of sucrose.

Case Study 2: Larger Cytidine crystal
a = 5.0742(2) Å, b = 13.9292(6) Å, c = 4.7144(6) Å,
T = 100 K, Z = 4, $P2_12_12_1$

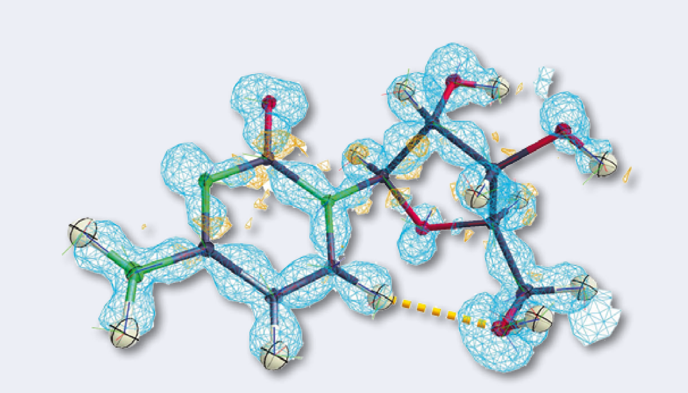
Size [mm³]	0.24 x 0.20 x 0.18	
Source	METALJET	μ-RAG
Exposure time	1 s/°, 1 h	1 s/°, 1 h
Resolution [Å]	0.71 (0.81 - 0.71)	0.81 (0.90 - 0.81)
Unique data	2981 (925)	2000 (499)
Multiplicity	6.97 (4.67)	7.86 (3.44)
<I/σ>	62.88 (49.12)	78.23 (43.02)
R1, wR2 [%]	2.73, 7.15	2.21, 5.86
Flack x Parsons q Hooft y	0.00(13) -0.01(3) 0.01(3)	0.00(13) -0.02(3) -0.01(3)

Cytidine (<|ΔF^2_{ano}|>/<F²> = 0.20% (Ga), 0.27% (Cu)): Assignment of the absolute configuration possible.

	INVARIOM Refinement
Resolution [Å]	10.11 - 0.71 (0.81 - 0.71)
Unique data	2981 (925)
Parameter (INV)	206
R1 (INV) [%]	1.77
Flack x (INV)	0.006 (25)



Simulated precession pattern of the 0kl layer.

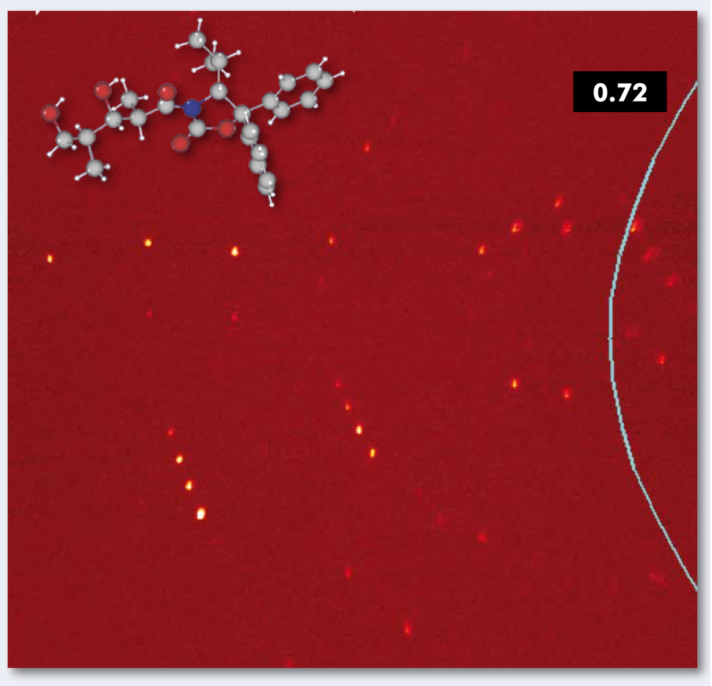


Deformation density for Cytidine.

„Real life" Sample 1: Diphenyloxazolidin-2-one derivate
a = 8.4167(17) Å, b = 13.761(3) Å, c = 19.304(4) Å,
T = 100 K, Z = 4, $P2_12_12_1$

Size [mm³]	0.12 x 0.10 x 0.09	
Source	METALJET	μ-RAG
Exposure time	2 - 4 s/°, 5 h	2 - 4 s/°, 9 h
Resolution [Å]	0.78 (0.88 - 0.78)	0.78 (0.88 - 0.78)
Unique data	4843 (1378)	4763 (1299)
Multiplicity	9.10 (4.28)	14.73 (3.88)
<I/σ>	35.94 (17.91)	45.95 (10.73)
R1, wR2 [%]	4.05, 10.54	4.89, 12.53
Flack x Parsons q Hooft y	0.00(18) 0.02(5) 0.02(4)	0.00(20) 0.05(3) 0.05(3)

Sample 1: (<|ΔF^2_{ano}|>/<F²> = 0.19% (Ga), 0.26% (Cu)): Assignment of the absolute configuration possible.

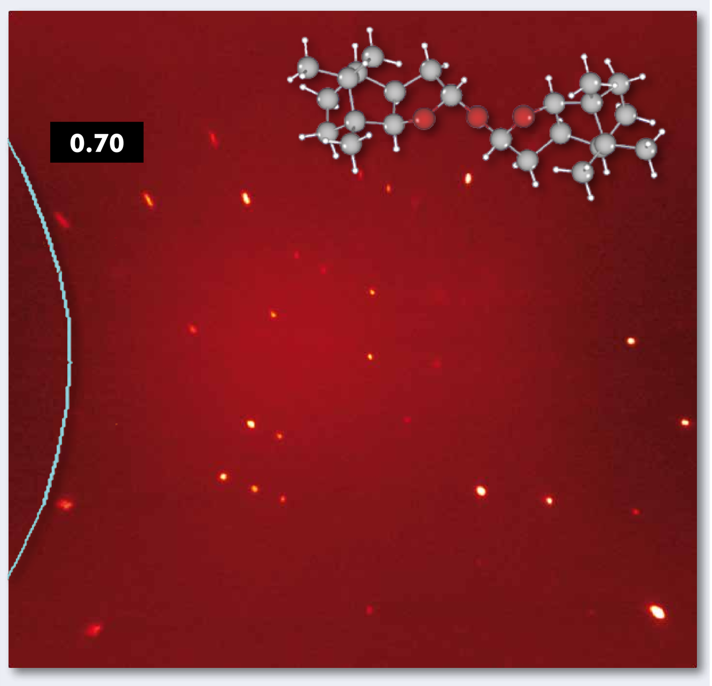


Typical diffraction pattern of the Diphenyloxazolidin-2-one derivate, recorded with the METALJET.

„Real life" Sample 2: Benzofuran derivate
a = 7.7975(2) Å, b = 12.8027(3) Å, c = 10.9201(3) Å,
ß = 101.965(1)°, T = 100 K, Z = 2, $P2_1$

Size [mm³]	0.15 x 0.05 x 0.04
Source	METALJET
Exposure time	3 s/°, 5h
Resolution [Å]	0.75 (0.85 - 0.75)
Unique data	5086 (1466)
Multiplicity	4.28 (1.87)
<I/σ>	36.46 (23.58)
R1, wR2 [%]	3.19, 8.42
Flack x Parsons q Hooft y	0.07(14) 0.05(4) 0.02(5)

Sample 2: (<|ΔF^2_{ano}|>/<F²> = 0.17% (Ga), 0.24% (Cu)): Assignment of the absolute configuration possible.



Typical diffraction pattern of the Benzofuran derivate, recorded with the METALJET.

Conclusion

X-ray sources with Cu anodes are usually used for the absolute structure determination due to the high anomalous signal for Cu radiation. However, the data resolution from Cu sources is limited to about 0.80 Å. Microfocus X-ray sources using energies higher than 8 keV, such as the Mo-IμS HB and the METALJET X-ray source, deliver data of high quality. Due to the shorter wavelength, a higher resultion can be achieved and, hence, more unique data are accessible. This allows for a more detailed description of the structural model using aspherical scattering factors, which also improves the precision of Flack parameter.

Literatur

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