Determination of the absolute structure of a compound by single-crystal X-ray diffraction

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Introduction

Some molecules which contain identical atoms linked together in the same order, and with a similar geometrical structure, can be found in several different forms. If a molecule includes at least one asymmetric carbon atom, it is possible to have two different configurations which are mirror images of each other, but cannot be superimposed: these two configurations are called enantiomers. Despite their similar geometry, they can have very different chemical properties and biological effects. In the pharmaceutical world, most drugs contain only one of the two enantiomers. It is therefore important to be able to characterize the absolute configuration of these molecules to ensure effective medication and avoid unwanted side effects. Single-crystal X-ray diffraction can be used to determine the chirality of the compounds through the determination of the Flack parameter.[1]

Material and methods

Using a four-circle goniometer with Kappa geometry, a small single-crystal (0.21 x 0.08 x 0.05mm) was irradiated with Copper radiation (λ=1.5418 Å) emitted by an X-ray tube. The X-ray wavelengths are comparable with inter-atomic distances within a crystal and can therefore be used to determine the structure of the crystal at an atomic level[2] The sample crystal diffracts the incident beam with varying angles of diffraction according to the material analysed. The X-ray scattering pattern is detected by a CCD (Charge-Coupled Device) detector and is analysed to produce a diagram showing the intensity of the X-rays detected according to the diffraction angles. The positions of the diffraction peaks allow the determination of the unit-cell parameters and the symmetry elements (Space Group). The integrated intensities can then be used to reconstruct the electron density map and consequently identify the position of the atoms in the unit-cell. This structure can then be refined by the least-squares method[2] and the model can be assessed through reliability factors which represent the agreement of the observed structure factors with those calculated from the refined model.
For structures which crystallize in a non-centrosymmetric Space Group, it is possible to determine their absolute configuration using the Flack parameter, which takes into consideration the anomalous dispersion effect in the scattering pattern. The Flack parameter x is evaluated as follows:

$I_{hkl}=(1-x)|F_{hkl}|+x|F_{-h-k-l}|$

I_{hkl}: Intensity of the reflection hkl
F_{hkl}: Structure factor for the reflection hkl

If the refined Flack parameter is close to 0, then the structure is likely to be correct. If it is close to 1 then the atomic coordinates need to be inverted to generate the other enantiomer. Finally, a Flack parameter of 0.5 indicates the presence of a racemic mixture.

Results and conclusion

Single-crystal X-ray diffraction enabled us to determine and refine the structure of a pharmacologically active molecule (Figure 1) which crystallises in a chiral Space Group (Table1).

Molecular Formula	$C_{26}H_{22}F_3N_3O_3.(C_5H_5N)_3$
Crystal system	Monoclinic
Space Group	$P2_1$
Unit-cell parameters	a=5.6607(4) Å b=28.130(2) Å c=11.6278(9) Å β=100.210(7) °

Tableau 1 : Cristal data summary

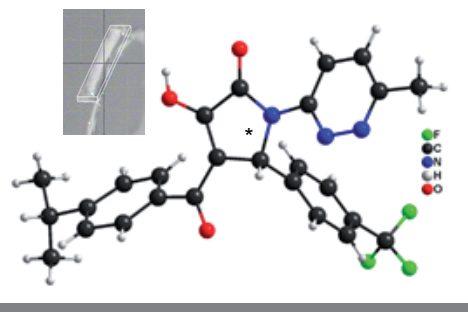

Figure 1 : View of the molecular structure (the asymmetric carbon is indicated by *) and a photograph of the measured crystal

The refined Flack parameter for this structure has a value of 0.1(2) which indicates that the assigned absolute structure is correct.

1. Flack H. D., Acta Cryst. (1983), **A39**, 876-881
2. Bragg W.L., Proc. Cambridge Philos. Soc.(1913), **17**, 43-57
3. Betteridge et al., J. App. Cryst. (1999), **36**, 1487

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