ESRF	**Experiment title: Correlating crystal structure with physical properties of zopiclone**	**Experiment number**: CH-856
Beamline: BM16	**Date of experiment**: from: 15 Apr 2000 to: 16 Apr 2000	**Date of report**: 1st Sep 2000
Shifts: 3	**Local contact(s)**: Olivier Masson	*Received at ESRF:*

Names and affiliations of applicants (* indicates experimentalists):

Dr Norman Shankland, University of Strathclyde, UK G4 0NR (*)

Dr Kenneth Shankland, Rutherford Appleton Laboratory, UK OX11 0QX (*)

Prof. William I. F. David, Rutherford Appleton Laboratory, UK OX11 0QX (*)

Dr Alastair J. Florence, University of Strathclyde, UK G4 0NR

Prof. Christopher S. Frampton, Roche Discovery Welwyn, UK AL7 3AY

Report:

Aim

This proposal set out to solve the structure of the anhydrous monoclinic phase of zopiclone from powder diffraction (XRPD) data.

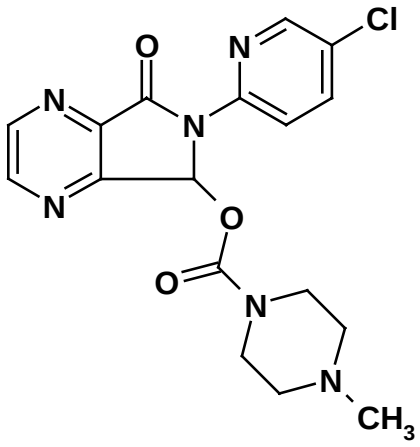

Figure 1 Zopiclone, a non-benzodiazepine hypnotic drug

Experimental

Preliminary diffraction scans revealed mixtures of phases amongst the powder samples (3 phases known to us). Therefore, we proceeded to produce the desired monoclinic anhydrous phase as follows:

1. **A sample of zopiclone recrystallised from toluene was loaded into a capillary, and quickly identified as zopiclone dihydrate. The unit cell was in good agreement with the previously known crystal structure:**
   ***a* = 16.48198, *b* = 7.14579, *c* = 17.40102 Å, β = 109.805°; *V* = 1928 Å^3 @ 298K**
2. **Next, the end of the capillary was broken, exposing the powder directly to the warm flow from the Cryostream.**
3. **Then, a scan loop was set up covering 2 - 4.5º 2θ to monitor, as a function of time and temperature:**
   - **(i) the disappearance of a peak at *ca.* 2.95°, characteristic of the dihydrate;**
   - **(ii) the appearance of a peak at ca. 3.2°, characteristic of the desired anhydrous phase.**

The conversion occurred slowly and, in the event, dehydration had to be encouraged by raising the temperature to 370 K. This, however, created another problem, in that the desirable anhydrous monoclinic showed signs of transforming into the undesirable anhydrous orthorhombic phase. Therefore, the sample temperature was reduced to 325 K as a compromise between two things:

(i) limiting further formation of the orthorhombic phase;

(ii) prohibiting re-hydration of the anhydrous monoclinic phase – which, to compound all other problems, is hygroscopic!

After indexing the anhydrous monoclinic phase to:
***a* = 15.19954, *b* = 7.15009, *c* = 17.65143 Å, β = 111.22°, *V* = 1788 @ 325K**
the space group was deduced as $P2_1/c$ *via* a probabilistic (Bayesian) approach, and the intensities extracted from the diffraction pattern *via* a Pawley fit. The crystal structure was then solved using a simulated annealing approach, as embodied in the *DASH* structure solution package.

Summary

Synchrotron data proved essential to maximise the chances of indexing the pattern and solving the structure. BM16 is a most appropriate beamline for these experiments, with the combination of high beam intensity at short wavelength, and multicrystal detector, and the ease with which variable-temperature work can be performed. Most importantly, by solving the crystal structure, we managed to prove the hypothesis which was set up in the experimental proposal, namely that differences in hygroscopicity (an important physical property in relation to formulation and manufacture of medicinal products) between the polymorphic forms of zopiclone can be accounted for by differences in their respective molecular packing arrangements.