Experimental report

01/03/2016

Proposal: 7-04-138 **Council:** 10/2014

Title: QENS study of methyl groups dynamics in felodipine

Research area: Physics

This proposal is a continuation of 7-03-101

Main proposer: Aleksandra PAJZDERSKA

Experimental team:

Local contacts: Miguel Angel GONZALEZ

Samples: C18H19Cl2NO4

Instrument	Requested days	Allocated days	From	To
IN16B	2	2	12/12/2014	14/12/2014

Abstract:

The aim of this project is to complete our previous experiment on felodipine. This compound possesses four methyl groups. Our QENS and 1H NMR experiments have revealed that two of those groups have a low activation energy (~5 kJ/mol), and NMR indicate that the other two CH3 have a much higher (~14 kJ/mol), but equivalent, activation energy. On the other hand, our calculations (DFT and molecular dynamics simulations), show that half of the methyl groups reorient easily (in agreement with the experiment), but that the other two groups exhibit a different behaviour. One of them has a very large activation energy (~25 kJ/mol from DFT) and appears immobile in the MD simulation, while the other has a lower barrier (~ 15 kJ/mol) and moves in the ns time scale. As the QENS experiment was done only on a TOF spectrometer, the neutron data do not allow us to resolve this apparent contradiction between NMR and simulation. Therefore in order to clarify the disagreement between experimental and theoretical predictions and conclude our study on felodipine we ask for 2 days of beamtime in the backscattering spectrometer IN16B.

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Title: QENS study of methyl groups dynamics in felodipine

Experiment held on IN16 12.12.2014 – 14.12.2014

Experimental group: A. Pajzderska, M. A. Gonzalez

Local Contact: M. A. Gonzalez

The compound under study was felodipine – a calcium channel blocker and one of the derivatives of 1,4-dihydropyridines. The molecule contains four independent methyl groups (denoted as A, B, C and D in figure 1). We focused on methyl groups dynamics, which is completed by means of other techniques such as ^{1}H NMR, ^{13}C high resolution NMR molecular dynamics simulations (MD) and periodic DFT calculations.

The sample for measurements was prepared by placing about 0.40 g of felodipine in an aluminium flat container (dimension of 30.0 mm x 40.0 mm) with a thickness of 0.25 mm (in order to get a transmission of about 0.9). The empty cell and a vanadium sample with a thickness of 1.0 mm were also measured to obtain the instrument background and resolution, respectively. The angle between the sample surface and the beam of incident neutrons was 135°. The incident wavelength was 6.27 Å allowing to explore the Q-range between 0.2 and 1.96 Å^{-1} and the energy range ±30 μeV with an energy resolution of 0.9 μeV (FWHM). The elastic scan (cooling at a rate of 1 K/min) and the quasielastic spectra were measured in the temperature range 2.5 K – 294 K. The temperature was stabilized by a helium-nitrogen cryostat with an accuracy of 0.01 degrees.

Raw data from IN16 were treated using LAMP standard macros (subtraction of background from empty cell, correction with the detector efficiency, normalization to the vanadium spectrum, correction for the sample absorption).

The quasielastic broadening is visible in temperature ranges: 50 K- 66 K and 200 K – 250 K. The spectra recorded at lowest temperature (2 K) suggested tunneling of methyl groups. The extracted experimental EISF from QENS spectra were compared with theoretical models assuming that 1, 2, 3 or 4 methyl groups are mobile in the experimental time scale window. At lower temperature reorientation of two methyl groups is observed, while at higher temperature only one methyl reorientation gives a measurable QENS broadening in the IN16 window.

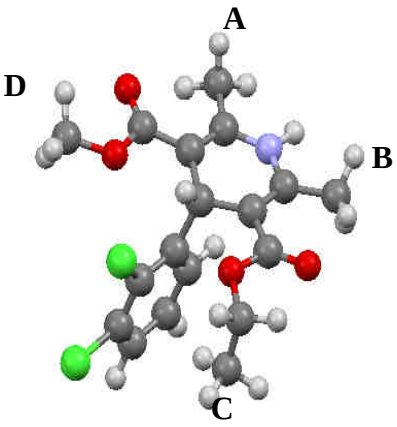

Fig. 1. Molecular geometry of felodipine with the applied notation for the methyl groups: A, B, C, D

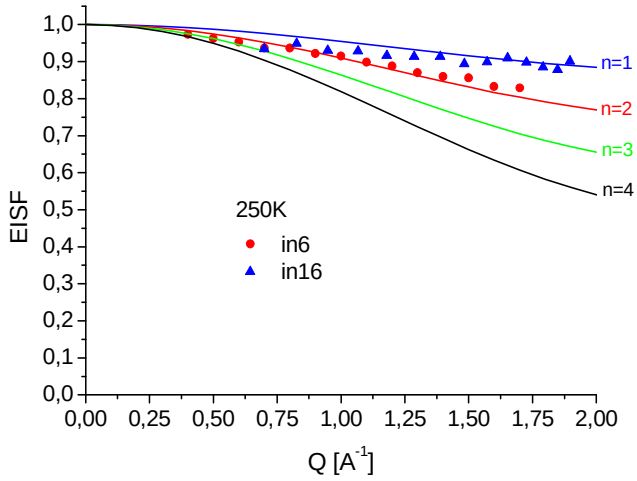

Fig. 2. Experimental (250 K) elastic incoherent structure factor extracted from measurements performed on IN6 (previous data) and IN16 (current data). Solid lines show the theoretical expectations assuming reorientations of n = 1, 2, 3 and 4 (lines) methyl groups

The results are in good agreement with previous QENS (IN6) and NMR data, as well as with the results of molecular dynamics simulations and DFT calculations. For two of the methyl groups the calculations show qualitatively the same behaviour: both groups (labeled A and B) have a low activation barrier (~5 kJ/mol) and their correlation times and activation energies agree with experiments (figure 3). However the other two methyl groups are not equivalent. One of them (D in Fig. 1) has an activation energy of approx. 15 kJ/mol and the correlation times from MD agree reasonably well with NMR and QENS (IN16). However the theoretical activation energy for the group C is much higher (~25 kJ/mol) and it appears almost completely immobile in the classical simulations (extending up to 10 ns).
This prediction is now confirmed by the present experiment, which allowed us to check how many methyl groups reorient in the studied temperature range and to understand better felodipine dynamics.

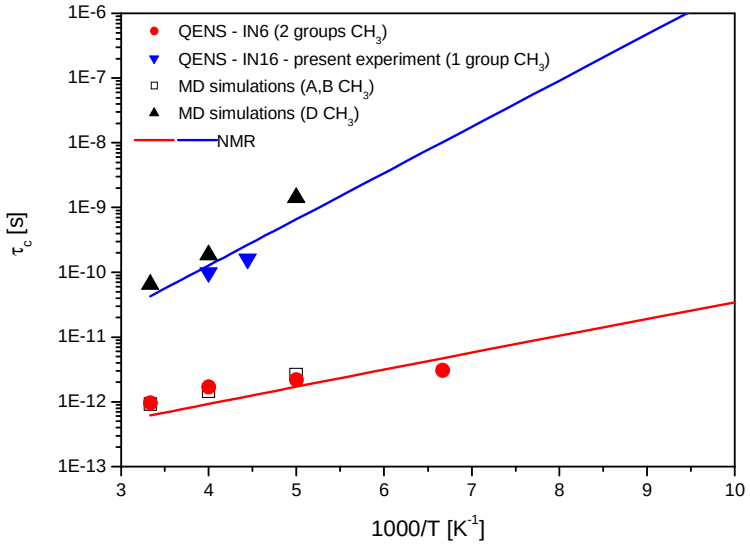

Fig. 3. Correlation times obtained from QENS (IN6, IN16), NMR measurements (solid lines) and MD simulations