Experimental report

20/10/2021

Proposal: 7-05-531 **Council:** 10/2020

Title: The Effect of Framework Structure and Composition on Molecular Mobility for Controlled Anticancer Drug Release by Zeolites

Research area: Chemistry

This proposal is a new proposal

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Experimental team: Markus APPEL

Local contacts: Markus APPEL

Samples: Zeolite empty / Si5, Al1, O12
Zeolite + 5FU / Si5, Al1, O12 (C4, H3, F, N2,O2)

Instrument	Requested days	Allocated days	From	To
IN16B Si 111 BATS	4	2	24/03/2021	26/03/2021

Abstract:

Zeolites are a promising group of materials for use in controlled delivery systems of anticancerdrugs such as 5-Fluorouracil (5-FU) as they are crystalline, relatively cheap and possess channels and cavities that are suitable for the accommodation of different drug molecules. We aim to use quasielastic neutron scattering experiments to determine the mobility rates and mechanisms of 5-FU in zeolite faujasite (FAU), whilst varying the counterion (H+ and Na+) and Si/Al ratio (Si/Al = 5 and 80). Measurements will also be carried out on zeolite Beta, where the Si/Al is kept constant, but the counterion is varied between H+ and NH4+. Experiments on IN16B would probe the relatively slow tranlational diffusion throughout the framework, complementing upcoming experiments on OSIRIS (ISIS) probing faster rotational motions. This will allow for both validation of molecular modelling work carried out so far on 5-FU mobility. The study will result in a detailed understanding of how framework characteristics such as topology, and the nature/concentration of counterions affects molecular mobility of 5-FU in zeolite materials for the development of cheaper, tunable controlled drug dosage forms.

Experimental Report

Experiment Title: The effect of framework structure and composition on molecular mobility for controlled anticancer drug released by zeolites.

Equipment: IN16B (BATS option)

Background: The aim of the experiment was to determine the mobility rates and mechanisms of anticancer drug 5-Fluorouracil (5-FU) in zeolite H-Beta (HBEA), whilst varying the Si/Al ratio (Si/Al = 19 and 180). This may allow for optimisation and development of molecular modelling work carried out so far on 5-FU mobility. The study has resulted in our better understanding of how framework characteristics such as the concentration of counter-ions affects molecular mobility of 5-FU in zeolites. We also have a better idea of the qualitative localised motions, which may take place upon encapsulation. This makes for the development of cheaper, tuneable controlled drug dosage forms. Experiments on IN16B allow for a much longer timescale to be probed therefore developing on our previous experiments on OSIRIS (ISIS) probing faster rotational motions.

Samples measured:

1. Zeolite H-BEA with Si/Al: 19 loaded with anti-cancer drug 5-Fluorouracil (5FU) (1.7242 g)
2. Zeolite H-BEA with Si/Al: 19 non-loaded (1.8461 g)
3. Zeolite H-BEA with Si/Al: 180 loaded with 5FU (1.612 g)
4. Zeolite H-BEA with Si/Al: 180 non-loaded with 5FU (1.8685 g)

Sample powder in aluminium foil envelope, wrapped into a cylinder and inserted into sealed hollow standard aluminium cell holders of 15 mm diameter.

Temperatures measured:

- 2 K (used for the resolution function),
- 300 K,
- 350 K,
- 400 K

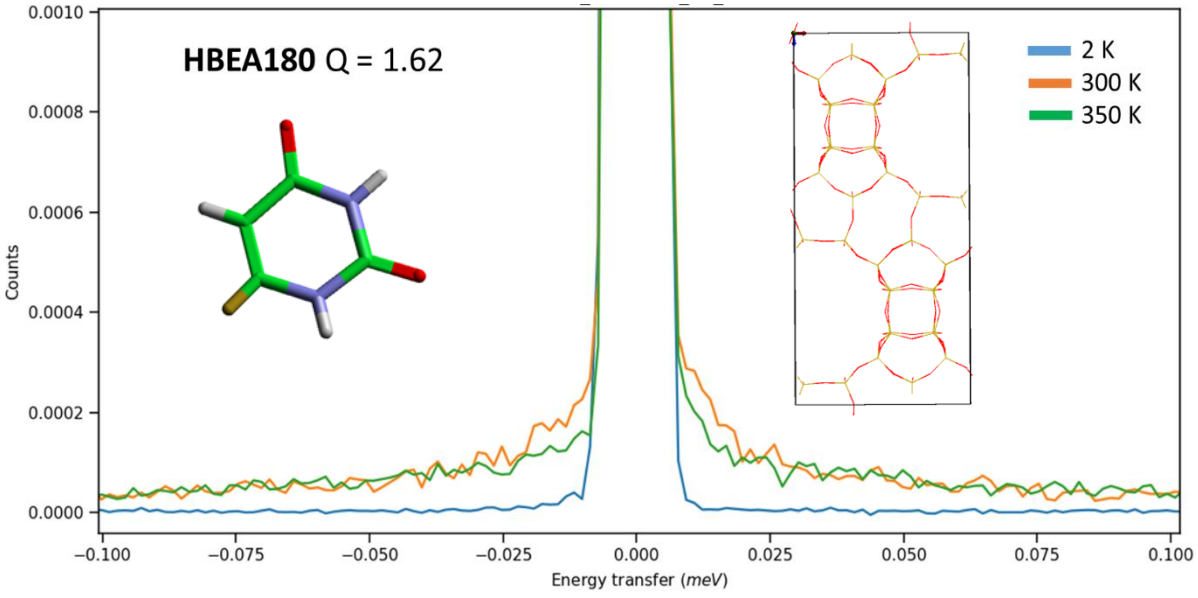

Fig.1 QENS spectra of zeolite HBEA with Si/Al 180 loaded with 5-Fluorouracil (5-FU) at Q=1.62. Inset a unit cell of HBEA 180 and a molecule of 5-FU

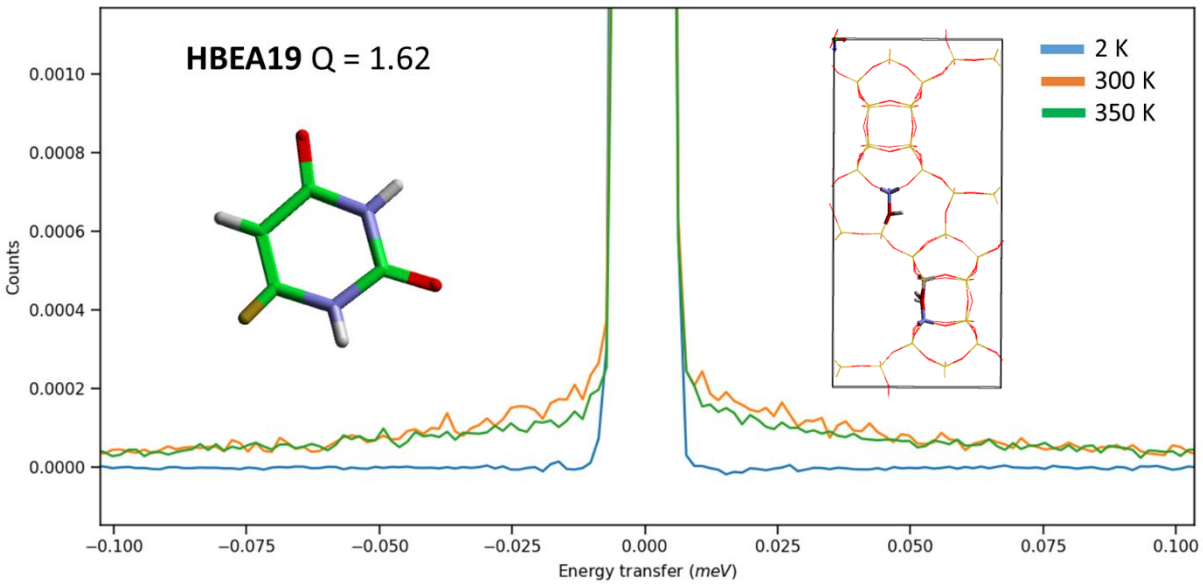

Fig.2 QENS spectra of zeolite HBEA with Si/Al 19 loaded with 5-FU at Q= 1.62. Inset a unit cell of HBEA 19 and a molecule of 5-FU

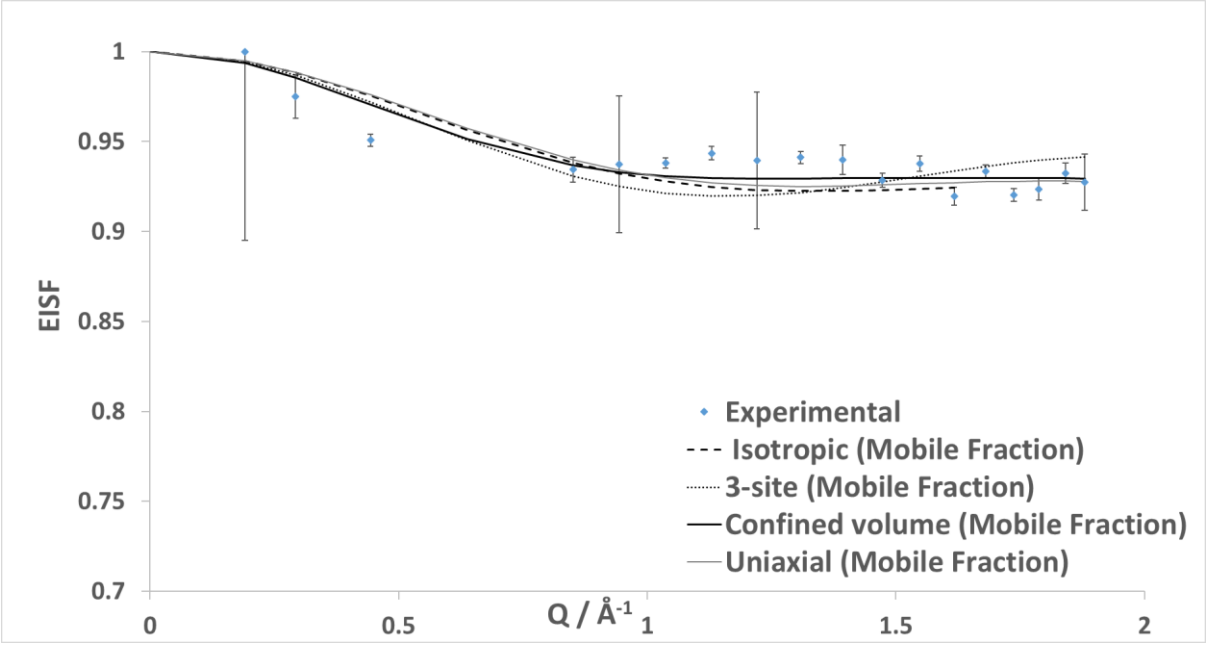

Fig 3. Elastic Incoherent Structure Factor (EISF) of HBEA 19 at 300 K. The experimental data (blue dots) are compared with different theoretical models. Data point for Q= 0.64 A^{-1} excluded.

Initial QENS spectra obtained of system HBEA 180 with 5-FU and HBEA 19 with 5-FU are shown in figures 1 and figure 2 at temperatures of 300 and 350 K compared with the resolution measurement taken at 2 K. The clear first observation is that of a very large elastic component suggesting the vast majority of protons in the system are stationary over the timescale probed by the instrument, even at the higher temperatures. We suggest this is due to constraints on motion imposed by the zeolite framework. Preliminary fitting suggests this quasi-elastic component is slightly larger for the HBEA 180 system, concurrent with the presence of fewer brønsted acid sites strongly interacting with the drug molecule.

The data obtained so far should allow for both qualitative and quantitative analysis of the motions present and any differences between zeolite hosts. Broadening of the elastic peaks can be observed

in figures 1 and 2 at high Q values, which demonstrates movement of the 5-FU drug molecules within the zeolite host. The EISF is plotted in figure 3 for HBEA 19 at 300 K. A number of models such as the isotropic, 3-site, confined volume and uniaxial models can potentially fit to the experimental data points. Incorporation of a significant immobile fraction is necessary. As such, a range of localised motions will be present, and classical molecular dynamics (MD) simulations currently in progress will be crucial for aiding the data interpretation before drawing final conclusions on the effect of Si/Al on the mobility of 5-FU in zeolite Beta.

Problems: Issues with instrument set up, for higher sample temperatures, a certain fraction of neutrons are re-scattered such that a side peak grows on the right side of the elastic line. The left side is acceptable. The positive energy interval of about +5 to +20 μeV needs to be excluded from the analysis.

Counting times and settings: BATS standard setting Ires 6 was used (low repetition rate, 14 degree slit on the pulse choppers) yielding a resolution of ~ 5 μeV FWHM of the elastic line. Typical counting time was 2 hours per temperature.

Conclusions: From the data obtained we are able to determine the mobility of 5-FU in zeolite BEA with varying Si/Al ratios and have observed localised motion of the drug molecules within the zeolite hosts. Further, in depth analysis of the data is required, including calculating the Full Width Half Maximum of the QENS spectra.