

Poster Presentation

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Mechanism of dehydration in a non-porous variable hydrate

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Paroxetine hydrochloride form II (PHCl-II) is a variable hydrate with a peculiar behaviour [1]. It changes its water content in response to changes in relative humidity with remarkable speed and in a completely reversible fashion. This is commonly observed for channel hydrates, but no continuous channels exist in the PHCl-II structure [2]. Powder diffraction results showed that loss of water produces an isostructural anhydrate, suggesting a simple, non-destructive mechanism of dehydration. The aim of the present contribution is to explain this unusual behaviour at a molecular level by using molecular dynamics simulations. Models of both the hydrated and anhydrous state could be created from the experimental hydrate structure by simple energy minimisation, which is in accordance with the experimentally observed smooth transition. A partially dehydrated supercell model was used to study the mechanism which allows water molecules to cross the steric barrier between adjacent solvent cavities. Since such transitions are rare on the simulation timescale (μs to ms), a steered molecular dynamics approach was applied. The results show that the passage of water molecules is facilitated by conformational changes, in which a ring system acts as a gate between cavities. When passing through the 'gate', water molecules are relayed between two chloride ions: as one $\text{Cl}\dots\text{HOH}$ hydrogen bond is broken, another $\text{HOH}\dots\text{Cl}$ one is formed. The progress of water molecules along the gated channel is not continuous, they spend a significant amount of time in each cavity between consecutive passages.

[1] M. F. Pina, J. F. Pinto, J. J. Sousa et al., *Mol. Pharmaceutics*, 2012, 9, 3515-3525, [2] J. A. K. Howard, P. Pattison, O. Chetina, *Private communication to the CCDC (EHOXEE)*, 2003

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