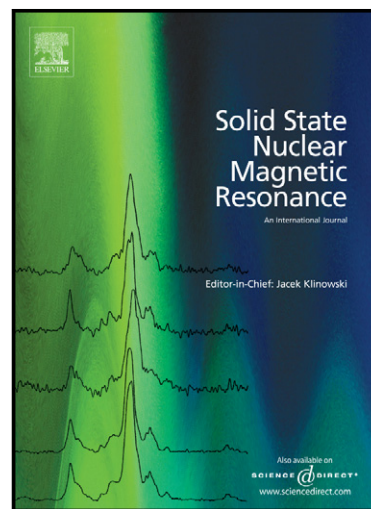


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Solid-state NMR and computational investigation of solvent molecule arrangement and dynamics in isostructural solvates of droperidol

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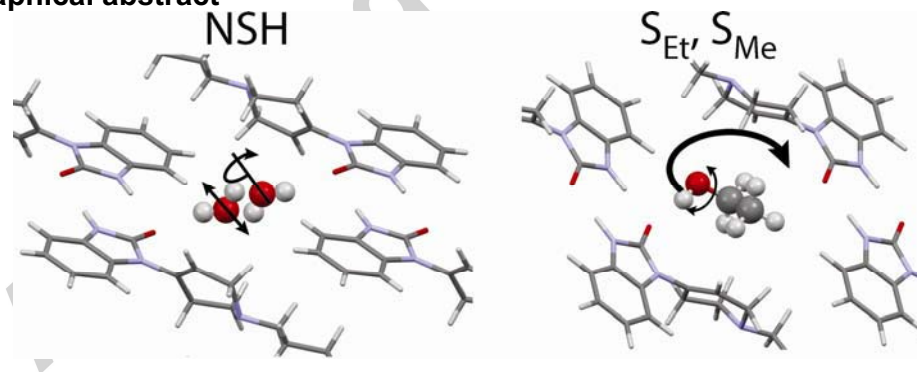
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Abstract

¹³C, ¹⁵N and ²H solid-state NMR spectroscopy have been used to rationalize arrangement and dynamics of solvent molecules in a set of isostructural solvates of droperidol. The solvent molecules are determined to be dynamically disordered in the methanol and ethanol solvates, while they are ordered in the acetonitrile and nitromethane solvates. ²H NMR spectra of deuterium-labelled samples allowed the characterization of the solvent molecule dynamics in the alcohol solvates and the non-stoichiometric hydrate. The likely motion of the alcohol molecules is rapid libration within a site, plus occasional exchange into an equivalent site related by the inversion symmetry, while the water molecules are more strongly disordered. DFT calculations strongly suggest that the differences in dynamics between the solvates are related to differences in the energetic penalty for reversing the orientation of a solvent molecule.

Keywords: droperidol; solid-state NMR; hydrates/solvates; isostructural solvates; solvent dynamics; spin-lattice relaxation; motional broadening; ab initio calculations

Graphical abstract



Highlights

- ¹⁵N CP/MAS NMR clearly distinguishes ordered and dynamically disordered systems.
- Spectral quality is strongly correlated to ABMS broadenings.
- ²H MAS NMR provides direct insight into the nature of the solvent motion.
- DFT calculations help to rationalise the differences in experimental observations.

Introduction

Solid-form screening of pharmaceutical molecules has demonstrated their propensity to adopt different forms, including polymorphs and solvates[1; 2]. It is not unusual for a pharmaceutical molecule to form more than five polymorphs[3; 4; 5] and, as reported, even in

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