SYRACUSE UNIVERSITY

TECHNOLOGY TRANSFER AND INDUSTRIAL DEVELOPMENT

Deuterium Exchange as a Route to New Polymorphs

New process isolates polymorphs of crystalline APIs

Scaling up production of new drugs typically encounters problems involving unforeseen and often troublesome new polymorphs. How much simpler it would be if all likely polymorphs of the API were known in advance.

Polymorphic forms often have very similar energies. Cases are known of polymorphs that have very small energy difference where the less stable form appears to persist indefinitely.

It has recently been shown that for hydrogen bonded crystals differences in the zero point energy are an appreciable and may be a dominant contribution to the enthalpy difference of polymorphs.

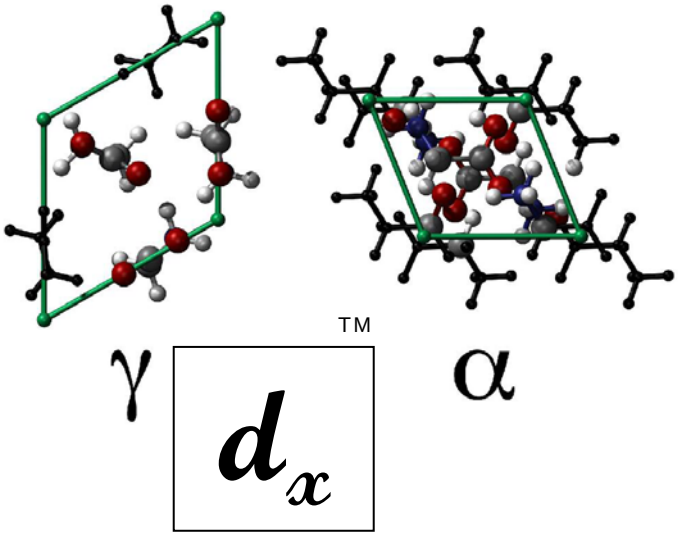
The new method uses deuterium exchange to reveal polymorphs that otherwise would not have been found under the conditions used. Some may be entirely new.

In some cases it may be appropriate to create seed crystals of the new polymorphs for use in making large amounts of the chosen form.

Computational methods can be used to assess whether the relative energies of known polymorphic forms will be changed by deuterium substitution.

It has been found experimentally that deuterium substitution has a large effect on the rates of interconversion of polymorphic forms.

The new method can be incorporated into any pharmaceutical screening program and can provide information of significant added value in the drug approval process.



2-220 Center for Science and Technology / Syracuse, New York 13244-4100
315-443-5196 / Fax: 315-443-8469 / techtran@syr.edu / http://techtransfer.syr.edu

SELECTED PUBLICATIONS

Rivera, Sharon A.; Allis, Damian G.; Hudson, Bruce S.. Importance of Vibrational Zero-Point Energy Contribution to the Relative Polymorph Energies of Hydrogen-Bonded Species. Crystal Growth & Design (2008), 8(11), 3905-3907.

O'Leary, Daniel J.; Allis, Damian G.; Hudson, Bruce S.; James, Shelly; Morgera, Katherine B.; Baldwin, John E. Vicinal Deuterium Perturbations on Hydrogen NMR Chemical Shifts in Cyclohexanes. Journal of the American Chemical Society (2008), 130(41), 13659-13663.

Williams, Robert W.; Schluecker, Sebastian; Hudson, Bruce S.. Inelastic neutron scattering, Raman, vibrational analysis with anharmonic corrections, and scaled quantum mechanical force field for polycrystalline L-alanine. Chemical Physics (2008), 343(1), 1-18.

DeCiantis, Christopher L.; Jensen, Danielle K.; Hudson, Bruce S.; Borer, Philip N. A Nucleic Acid Switch Triggered by the HIV-1 Nucleocapsid Protein. Biochemistry (2007), 46(32), 9164-9173.

Ouellette, Wayne; Hudson, Bruce S.; Zubieta, Jon. Hydrothermal and Structural Chemistry of the Zinc(II)- and Cadmium(II)-1,2,4-Triazolate Systems. Inorganic Chemistry (Washington, DC, United States) (2007), 46(12), 4887-4904.

Verdal, Nina; Rivera, Sharon A.; Hudson, Bruce S.. Inelastic neutron scattering and periodic DFT studies of crystalline aromatic materials: Azulene. A test of ab initio methods. Chemical Physics Letters (2007), 437(1-3), 38-44.

Verdal, Nina; Hudson, Bruce S.. Inelastic neutron scattering and periodic DFT studies of crystalline aromatic materials: Biphenylene - A Mills-Nixon molecule. Chemical Physics Letters (2007), 434(4-6), 241-244.

Parker, Stewart F.; Refson, Keith; Williams, Kenneth P. J.; Braden, Dale A.; Hudson, Bruce S.; Yvon, Klaus. Spectroscopic and Ab Initio Characterization of the [ReH9]2- Ion. Inorganic Chemistry (2006), 45(26), 10951-10957.

Hudson, Bruce S.; Verdal, Nina. Vibrational dynamics in short, strong symmetric hydrogen bonds: General considerations and two examples. Physica B: Condensed Matter (Amsterdam, Netherlands) (2006), 385-386(Pt. 1), 212-215.

Hudson, Bruce S.. Vibrational spectroscopy using inelastic neutron scattering: overview and outlook. Vibrational Spectroscopy (2006), 42(1), 25-32.

Ciezak, Jennifer A.; Leao, Juscelino B.; Hudson, Bruce S.. Vibrational analysis of the inelastic neutron ascattering spectra of electron donor-acceptor complexes. II. Tetracyanoethylene-perylene by electronic structure calculations. THEOCHEM (2006), 767(1-3), 23-28.

Allis, Damian G.; Hudson, Bruce S.. Inelastic Neutron Scattering Spectrum of Cs2[B12H12]: Reproduction of Its Solid-State Vibrational Spectrum by Periodic DFT. Journal of Physical Chemistry A (2006), 110(10), 3744-3749.

Verdal, Nina; Wilke, Jeremiah J.; Hudson, Bruce S.. Conformational Distinguishability of Medium Cycloalkanes in Crystals via Inelastic Neutron Scattering. Journal of Physical Chemistry A (2006), 110(8), 2639-2646.

Rivera S.; Hudson, B.S. Rapid exchange luminescence: Nitroxide quenching and implications for sensor applications. *J. Am. Chem. Soc.* 2006, *128(1),* 18-19.

Hudson, B.S.; Allis, D.G.; Parker, S.F.; Ramirez-Cuesta, A.J.; Herman, H.; Prinzbach, H. Infrared, Raman, and Inelastic Neutron Scattering Spectra of Dodecahedrane: an I_h Molecule in T_h Site Symmetry. *J. Phys. Chem. A.* 2005, *109,* 3418-3424.

Verdal, N.; Kozlowski, P.M.; Hudson, B.S. Inelastic Neutron Scattering Spectra of Free Base and Zinc Porphines: A Comparison with DFT-Based Vibrational Analysis. *J. Phys. Chem. A.* 2005, *109,* 5724-5733.

Hudson, B.S.; Braden, D.A.; Allis, D.G.; Jenkins, T.; Baronov, S.; Middleton, C.T.; Withnall, R.; Brown, C.M. The crystalline enol of 1,3-cyclohexanedione and its complex with benzene: vibrational spectra, simulation of structure and dynamics and evidence for cooperative hydrogen bonding. *J. Phys. Chem. A.* 2004, *108(36),* 7356-7363.

Allis, D.G.; Kosmowski, M.; Hudson, B.S. The Inelastic Neutron Scattering Spectrum of $H_3B{:}NH_3$ and the Reproduction of Its Solid-State Features by Periodic DFT. *J. Am. Chem. Soc.* 2004, *126(25),* 7756-7757.

Hudson, B.S. Inelastic neutron scattering: A tool in molecular vibrational spectroscopy and a test of ab initio methods. *J. Phys. Chem. A.* 2001, *105,* 3949-3960.