MESOPOROUS MATERIALS FOR DRUG DELIVERY

A Quantum-Mechanical Simulation

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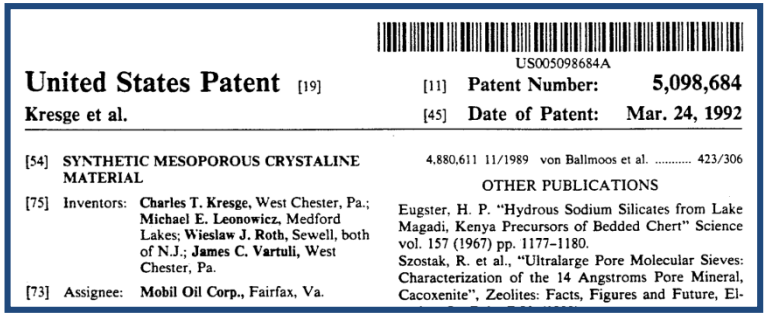
MESOPOROUS SILICA MATERIALS

FIRST SYNTHESIZED IN 1990s BY MOBIL OIL Corp.

- **Ordered** arrangement of homogeneous pores
- Pores: **mesoporous** size (2-10 nm)
- **High surface area**: up to 1000 m^2g^{-1}



US005098684A

United States Patent [19]

Kresge et al.

[11] **Patent Number: 5,098,684**

[45] **Date of Patent: Mar. 24, 1992**

[54] **SYNTHETIC MESOPOROUS CRYSTALINE MATERIAL**

[75] Inventors: **Charles T. Kresge**, West Chester, Pa.; **Michael E. Leonowicz**, Medford Lakes; **Wieslaw J. Roth**, Sewell, both of N.J.; **James C. Vartuli**, West Chester, Pa.

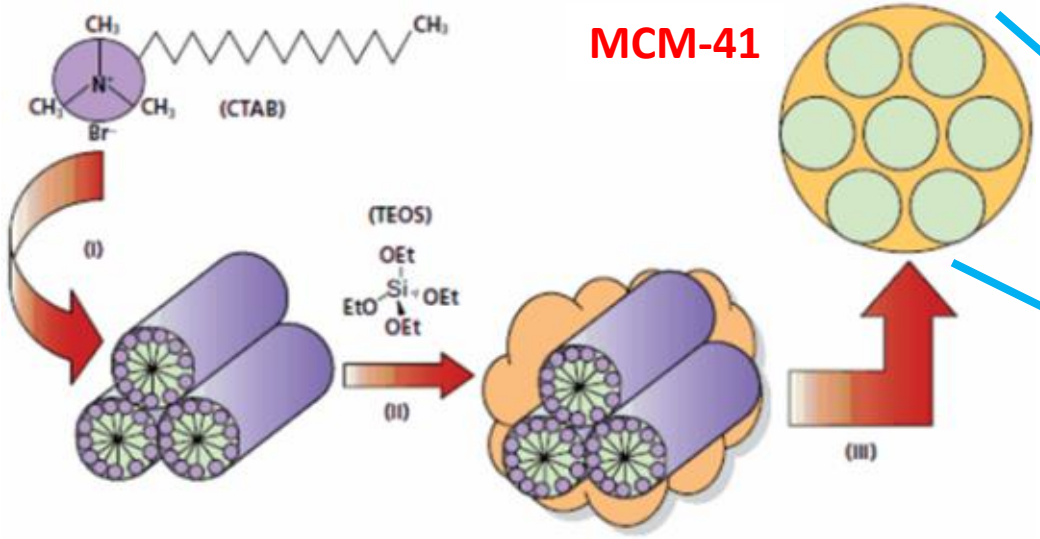
[73] Assignee: **Mobil Oil Corp.**, Fairfax, Va.

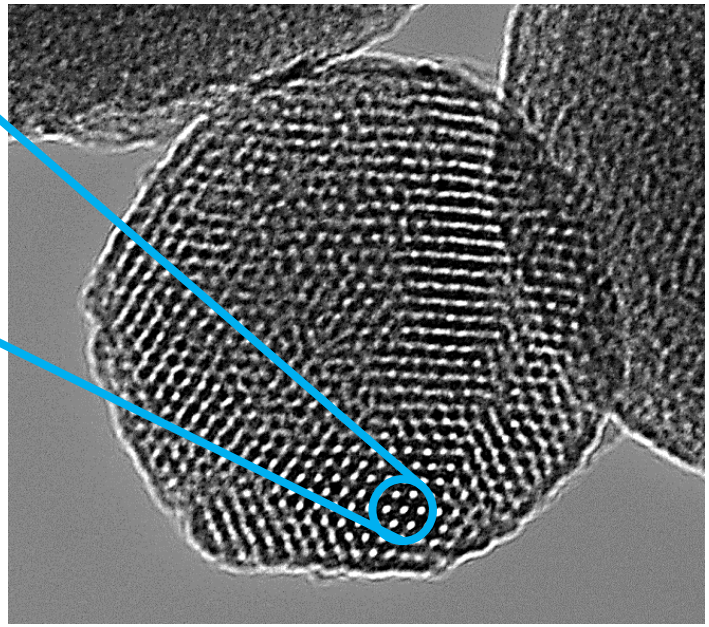
4,880,611 11/1989 von Ballmoos et al. 423/306

OTHER PUBLICATIONS

Eugster, H. P. "Hydrous Sodium Silicates from Lake Magadi, Kenya Precursors of Bedded Chert" Science vol. 157 (1967) pp. 1177–1180.

Szostak, R. et al., "Ultralarge Pore Molecular Sieves: Characterization of the 14 Angstroms Pore Mineral, Cacoxenite", Zeolites: Facts, Figures and Future, El-





Ordered at the *long* range
Amorphous at the *short* range

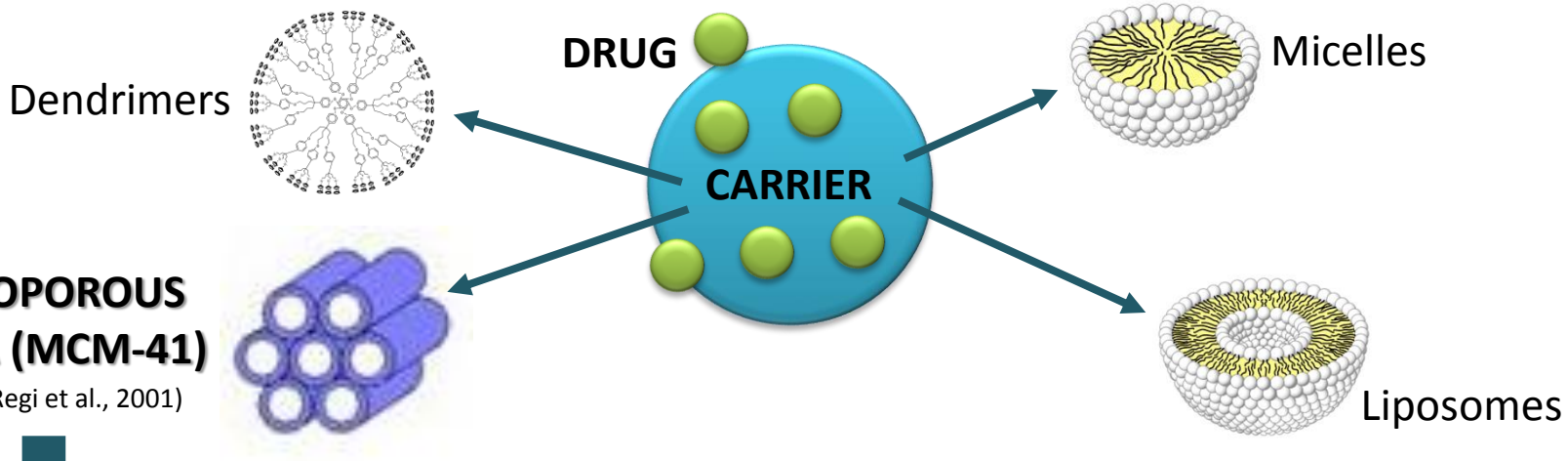
APPLICATIONS

Separation - Catalysis – Sensors – **Drug Delivery**

MESOPOROUS SILICA MATERIALS FOR DRUG DELIVERY

DRUG DELIVERY SYSTEM

Pharmaceutical formulation that can control the dissolution rate of the active principle in the body and/or target specific organs.



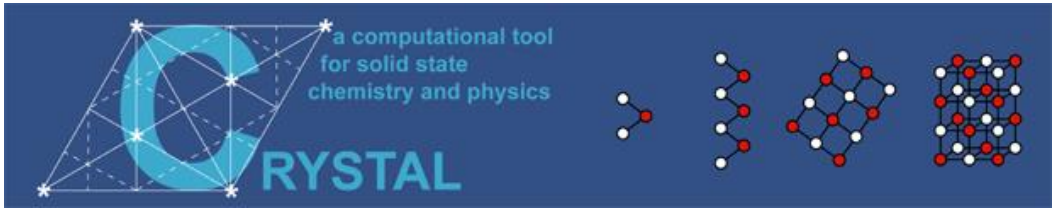
- ✓ Its morphological and chemical features can be easily tuned → it can host a great variety of compounds.
- ✓ Functionalization possible.
- ✓ Mesoporous Silica Nanoparticles → intracellular delivery.

→ Confinement in mesoporous materials can stabilize the amorphous phase of molecules (Mellaerts et al., 2007) (Quian et al., 2012)

→ Increased solubility of hydrophobic drugs

QUANTUM-MECHANICAL SIMULATIONS

STATIC CALCULATIONS



CRYSTAL09

Theoretical Chemistry Group (University of Turin)

www.crystalsolutions.eu

Periodic DFT calculations

Functional: **B3LYP**

Gaussian Basis Set: **VTZ(d)**

with (B3LYP-D*) and without the Grimme long-range **dispersion** correction

(Grimme, 2001 / Civalleri et al., 2008)

MPPCRYSTAL

(massively parallel version for High Performance Computing)

SuperMUC, LRZ (Munich, DE)

PRACE project 2012-2013

MOLECULAR DYNAMICS

www.cp2k.org

b-initio VASP ackage imulation ienna

www.vasp.at

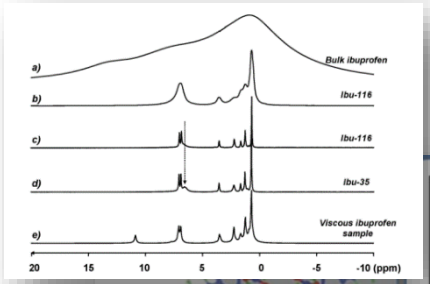
PBE functional

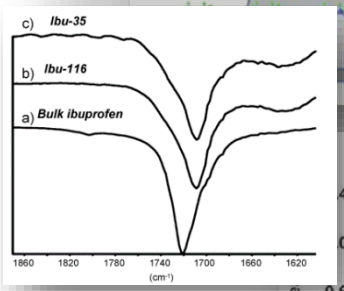
Grimme D2 correction for **dispersion**

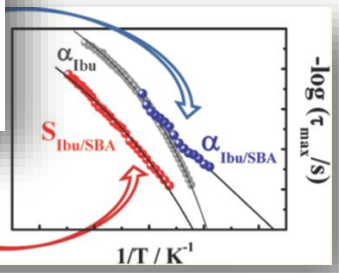
NVT – 300K

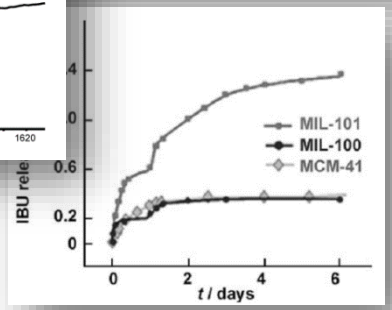
OBJECTIVES

Experimental results





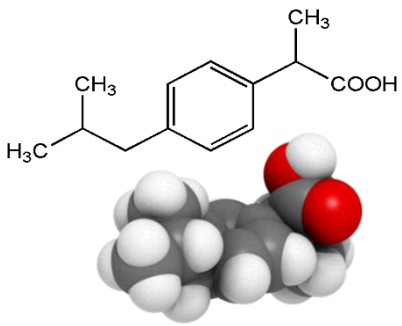




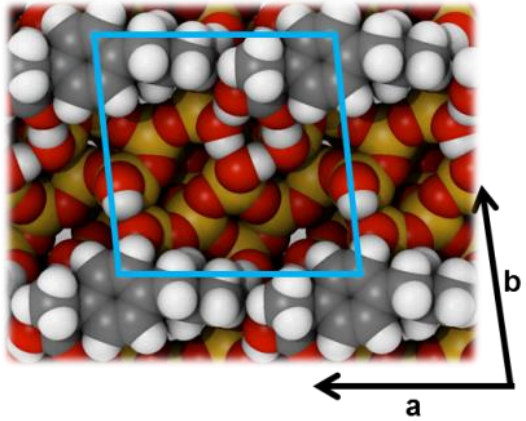
Averages
Difficult interpretation
Few details at molecular level

Molecular Modeling

- **Help interpretation of experiments**
- **Provide atomistic details of the interaction**
- **Give the energetics of the system**

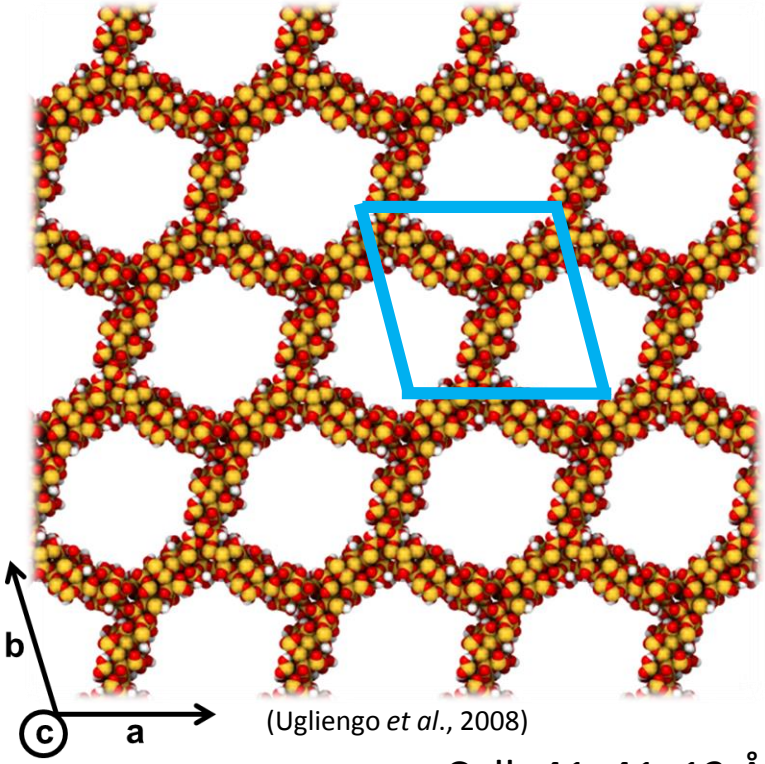


IBUPROFEN

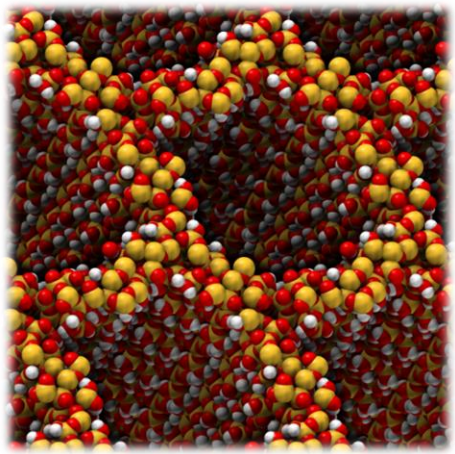


Delle Piane, M. et al. *J Chem Theory Comput* **2013,** *9* (5), 2404-2415

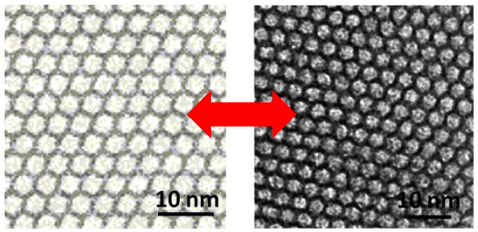
MCM-41: A REALISTIC MODEL



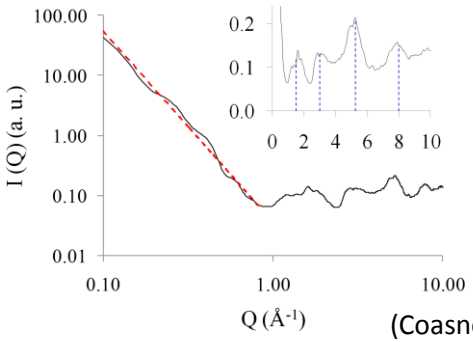
(Ugliengo *et al.*, 2008)



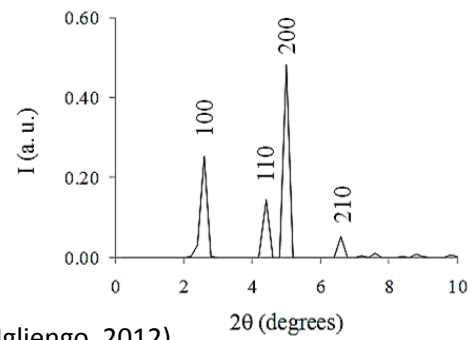
Cell: 41x41x12 Å
579 atoms
Pore Ø = 35 Å
7.2 SiOH/nm^2



Neutron scattering

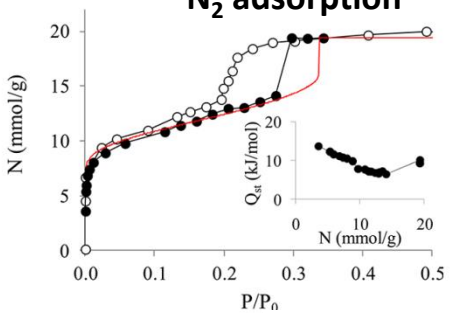


X-ray diffraction

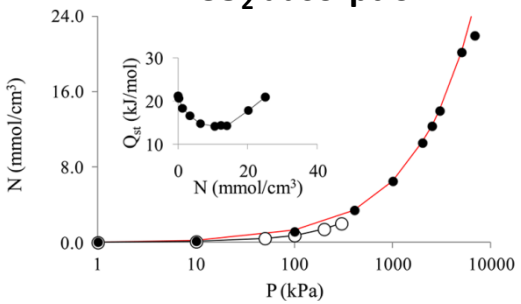


(Coasne & Ugliengo, 2012)

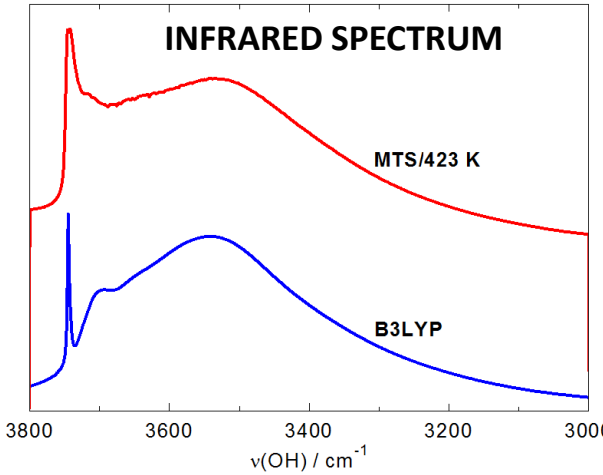
N_2 adsorption



CO_2 adsorption

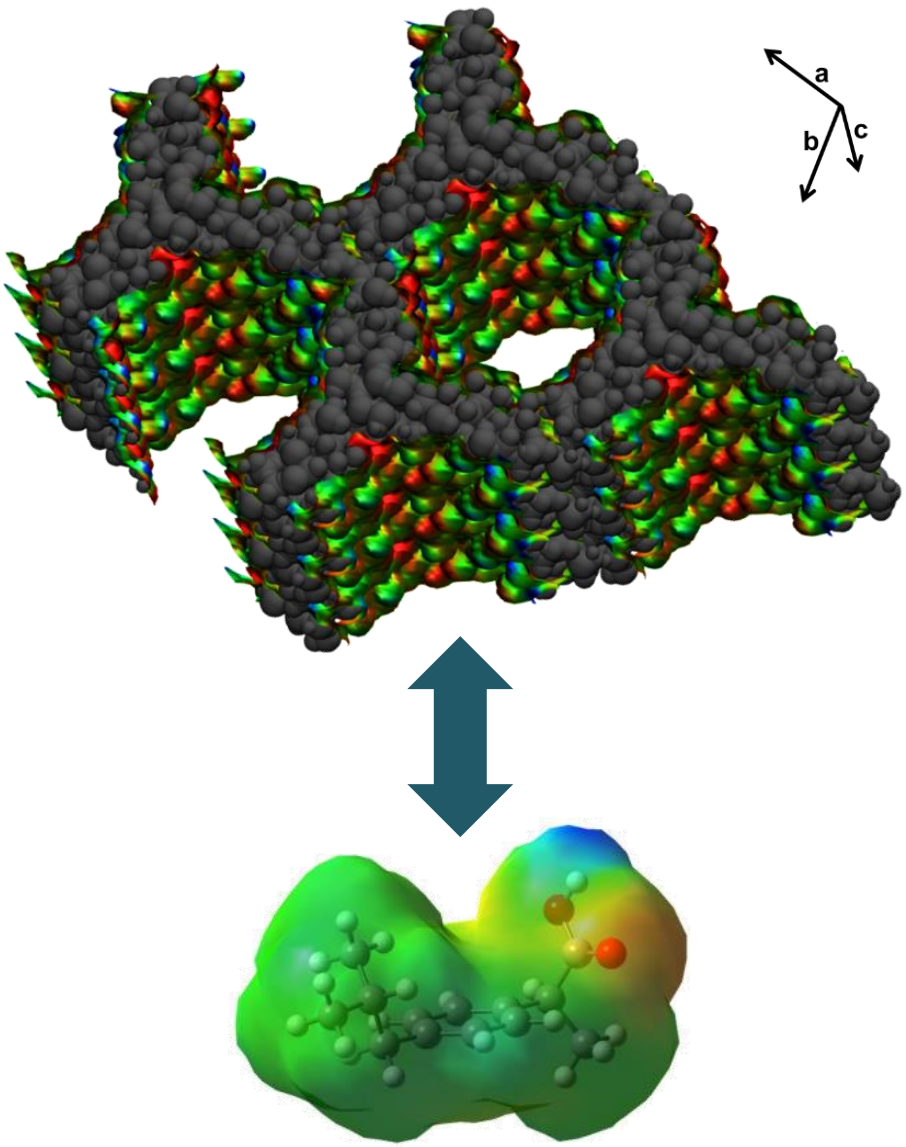


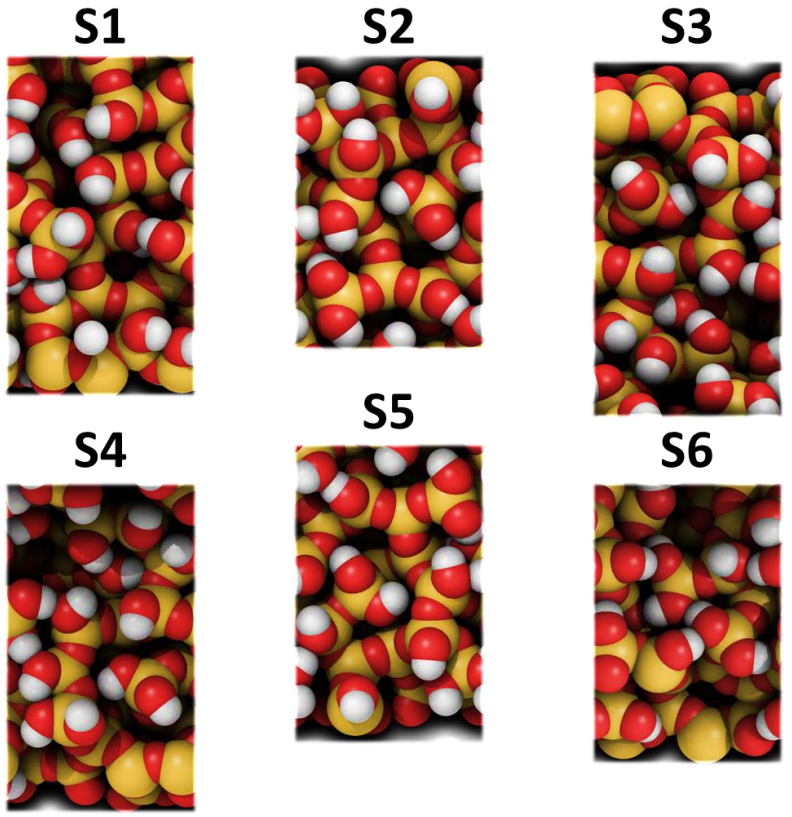
INFRARED SPECTRUM

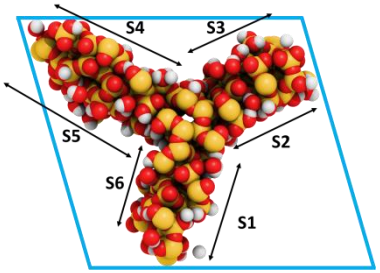


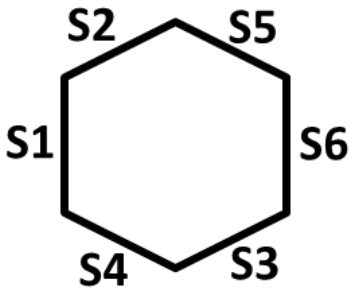
INSIDE THE PORES OF MCM-41

Potential mapped on the electron density



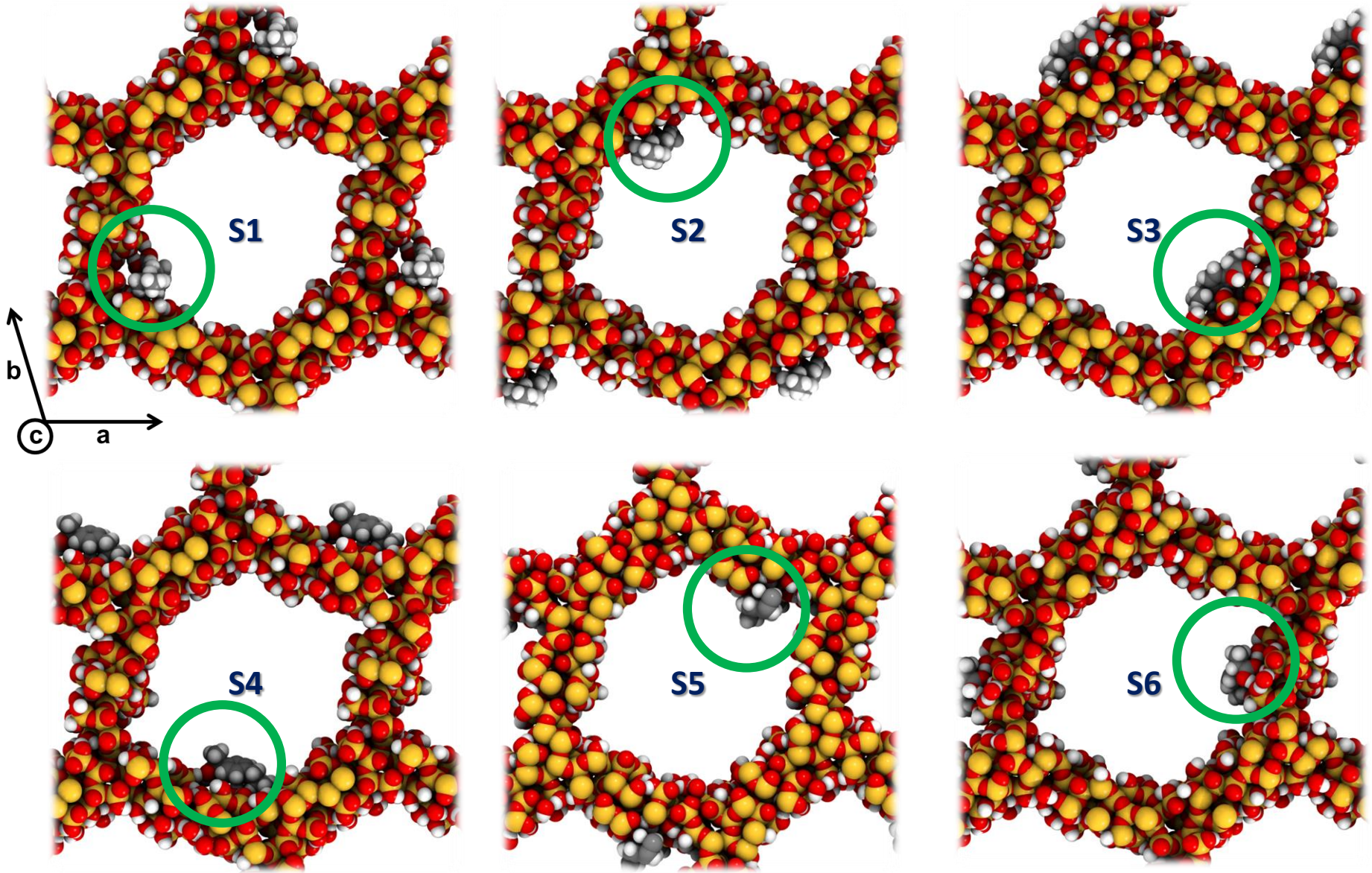






IBUPROFEN IN THE PORE – SINGLE LOADING

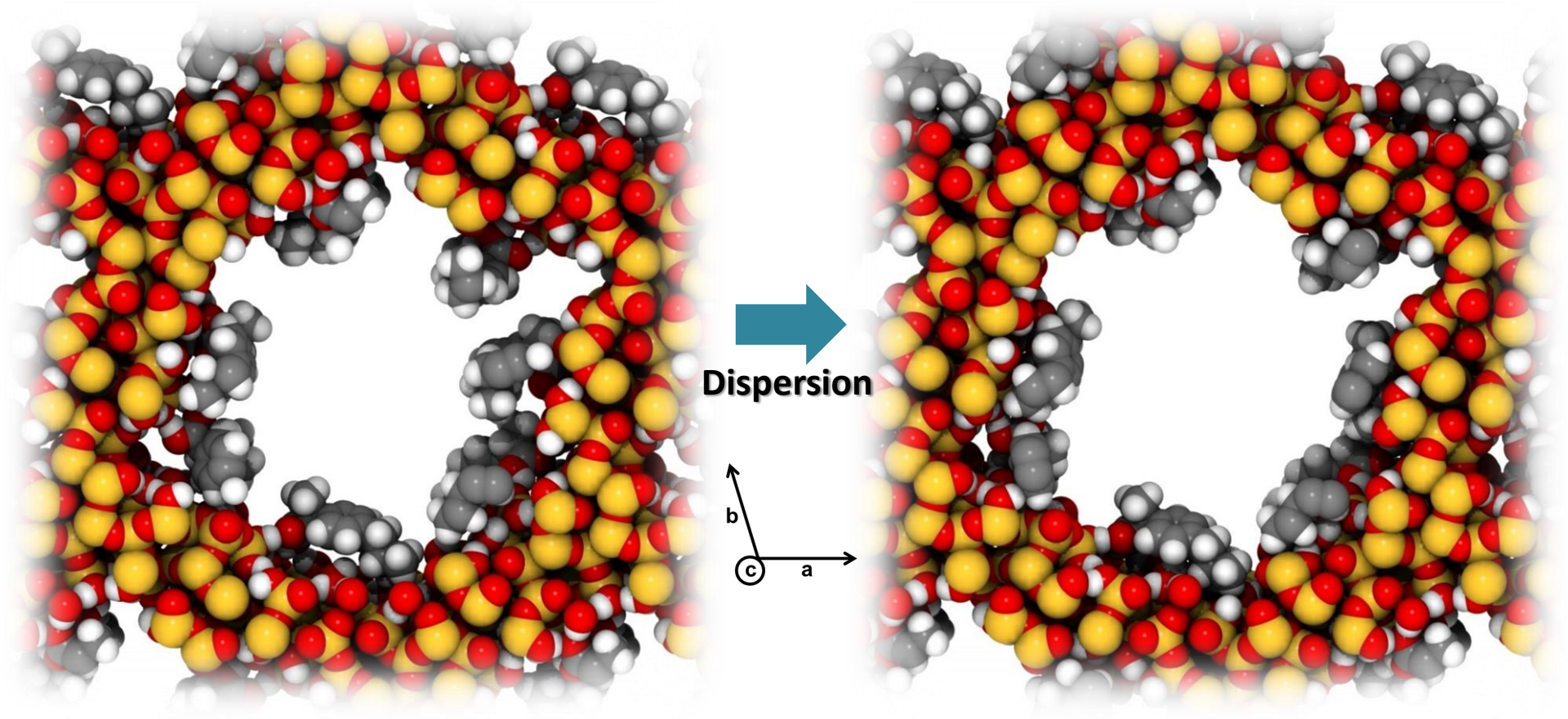
B3LYP-D*



IBUPROFEN IN THE PORE – HIGHEST LOADING

B3LYP

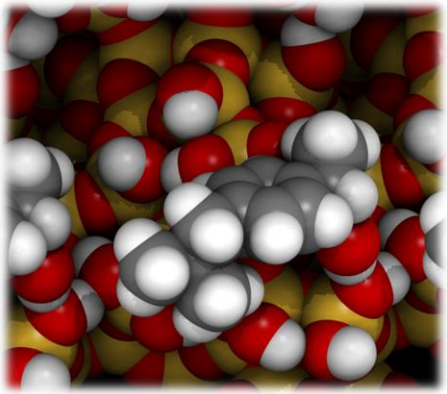
B3LYP-D*

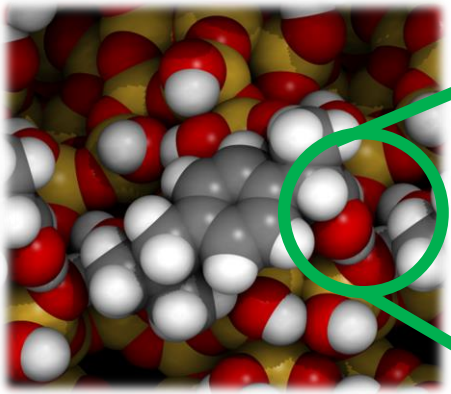


IBUPROFEN IN THE PORE: INTERACTION FEATURES

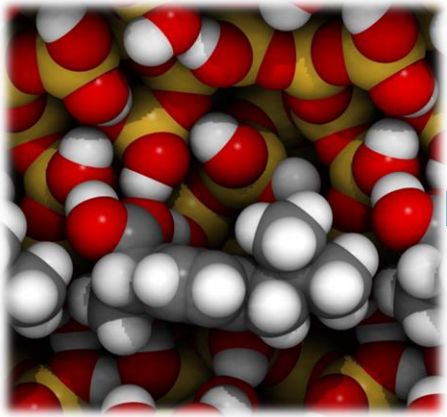
B3LYP B3LYP-D*

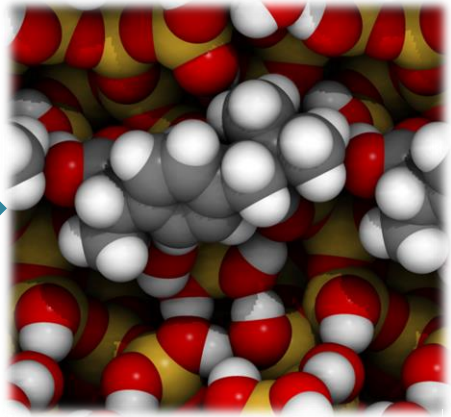
S6

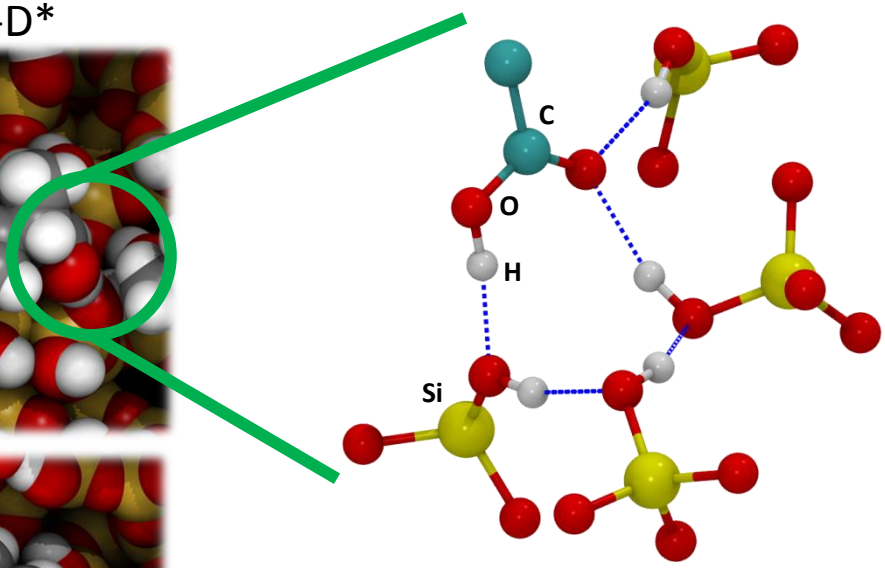




S2





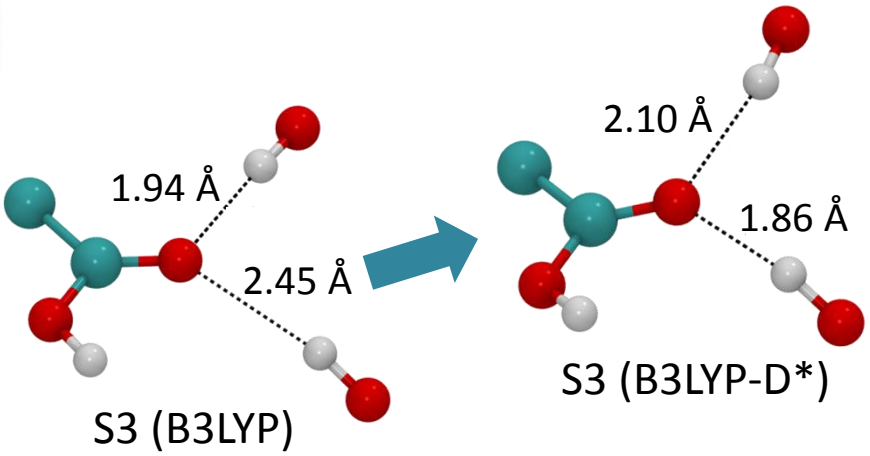


The wall is deeply restructured to maximize H-bond interactions with ibuprofen:

Surface deformation = up to 35 kJ/mol

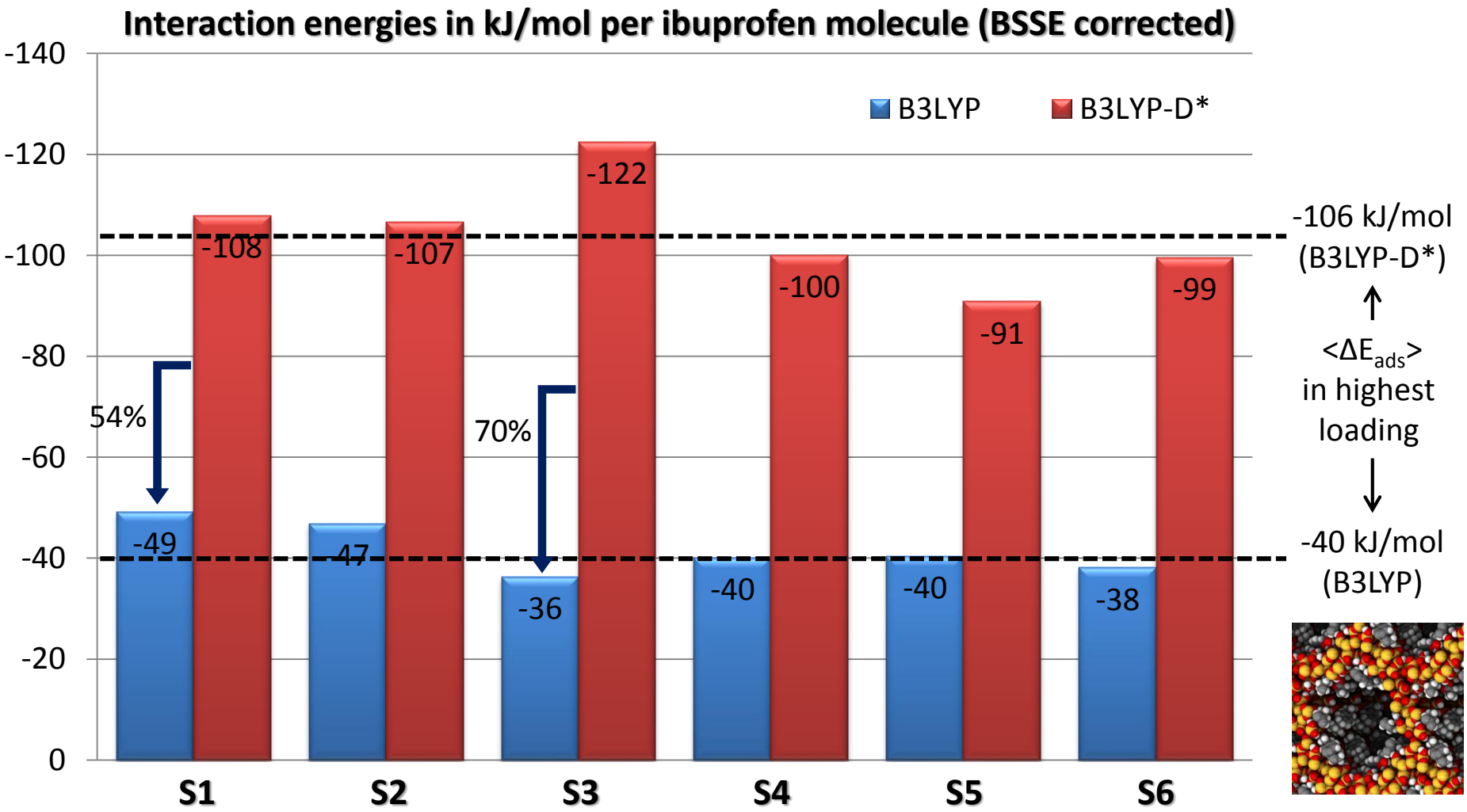
Dispersion interactions allow the molecule to take full contact with the pore walls

Accounting for vdW forces has a strong influence also on the local interaction between ibuprofen COOH and surface SiOHs



S3 (B3LYP) S3 (B3LYP-D*)

MCM-41/IBUPROFEN: INTERACTION ENERGIES



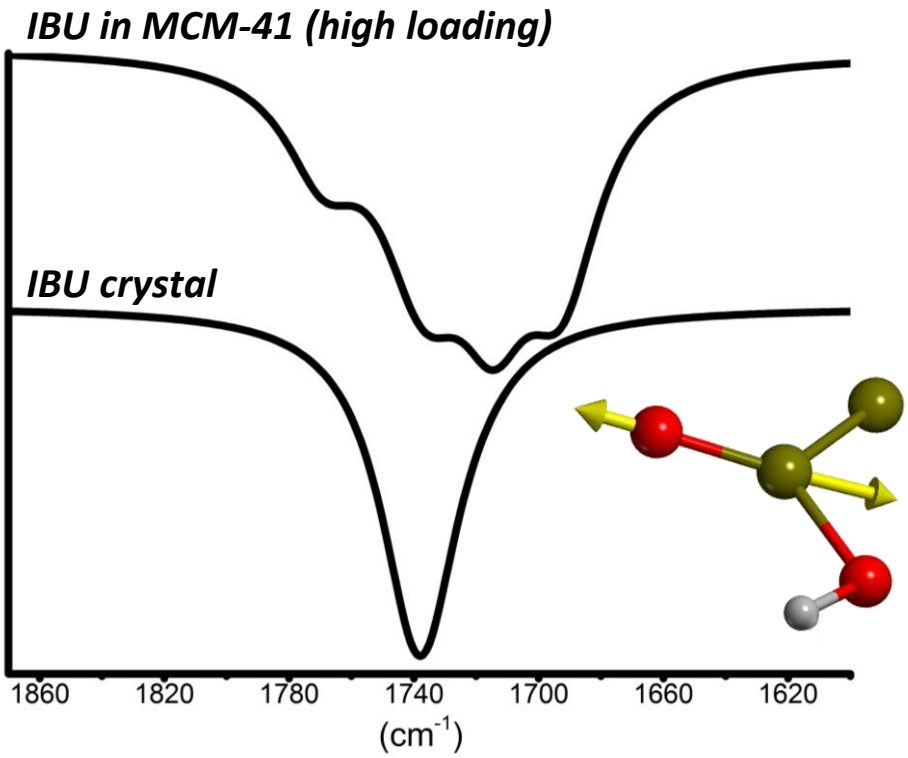
Weak dependence on the adsorption site

Dramatic role of dispersion interactions

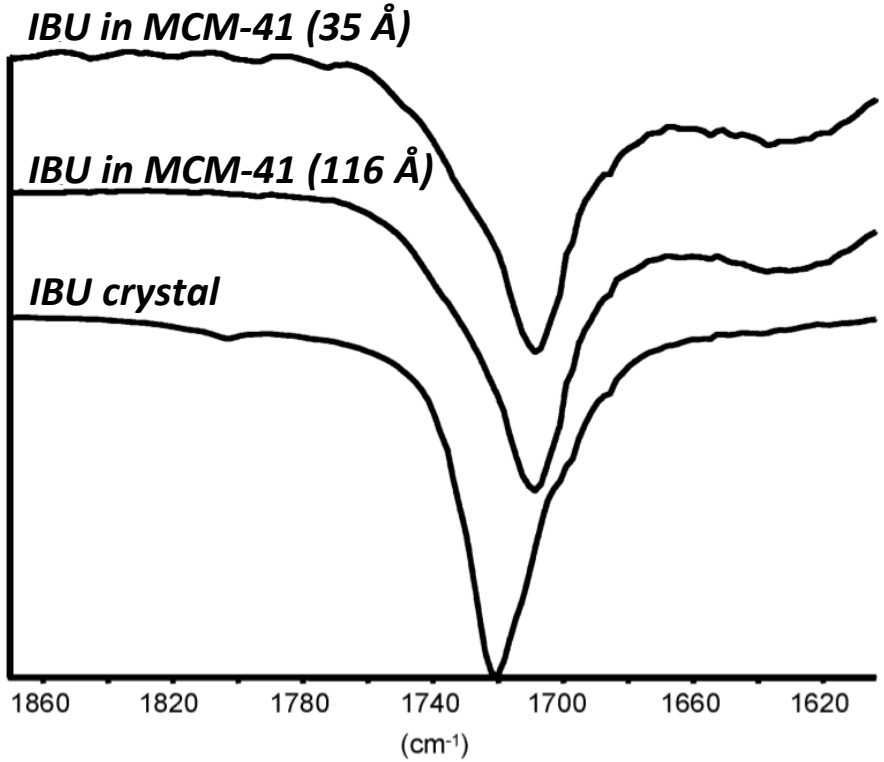
MCM-41/IBUPROFEN: SPECTROSCOPIC FEATURES

Ibuprofen C=O stretching band: a sensitive probe

Simulated (B3LYP-D*)



Experimental (Azais et al., 2006)



Calculated bathochromic shift: 15 cm^{-1}

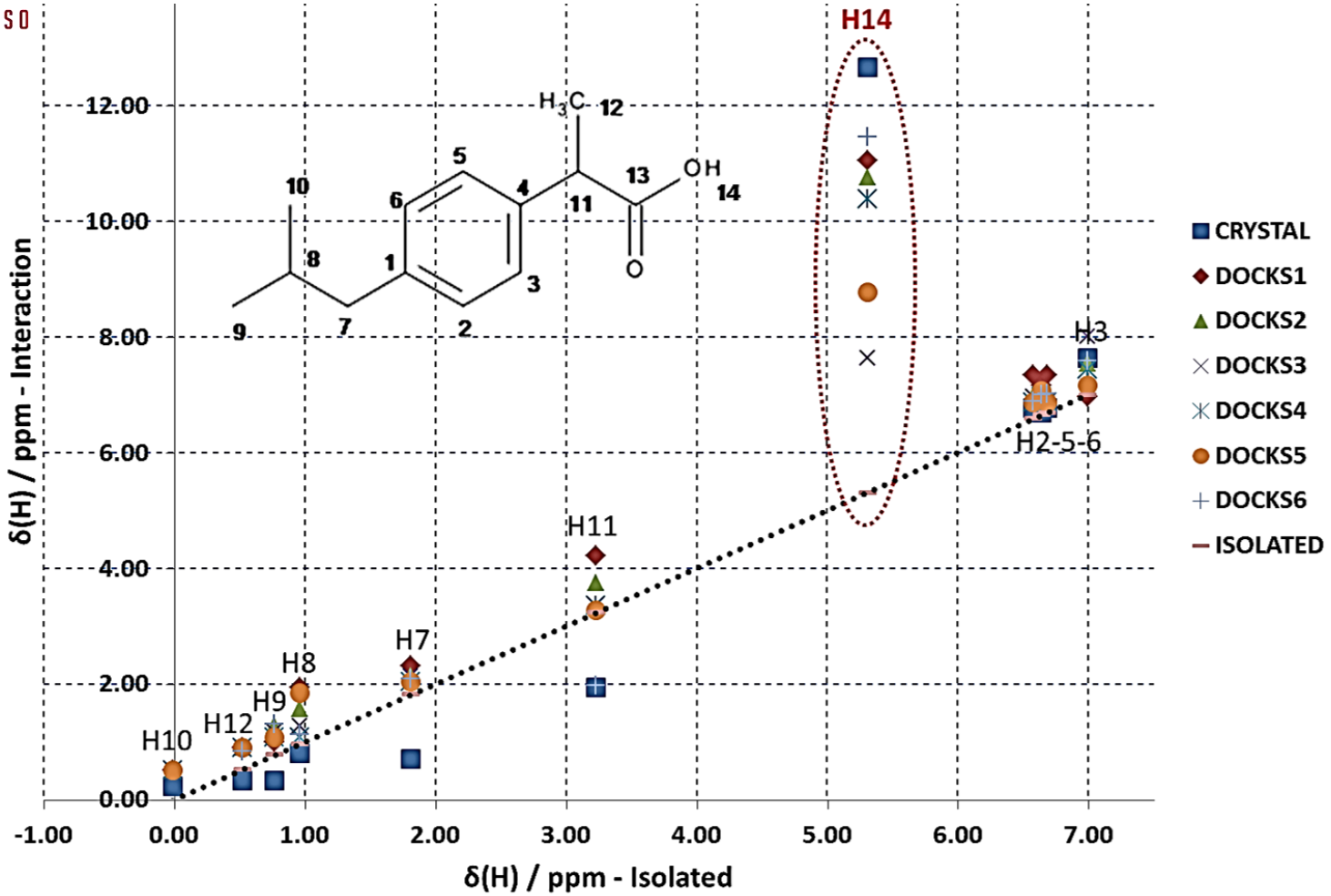
Observed bathochromic shift: 11 cm^{-1}

Clear indication that the observed broadness of the experimental ibuprofen C=O band may be due to slightly different adsorption situations.

MCM-41/IBUPROFEN: SPECTROSCOPIC FEATURES

PBE//B3LYP
PWscf - GIPAW

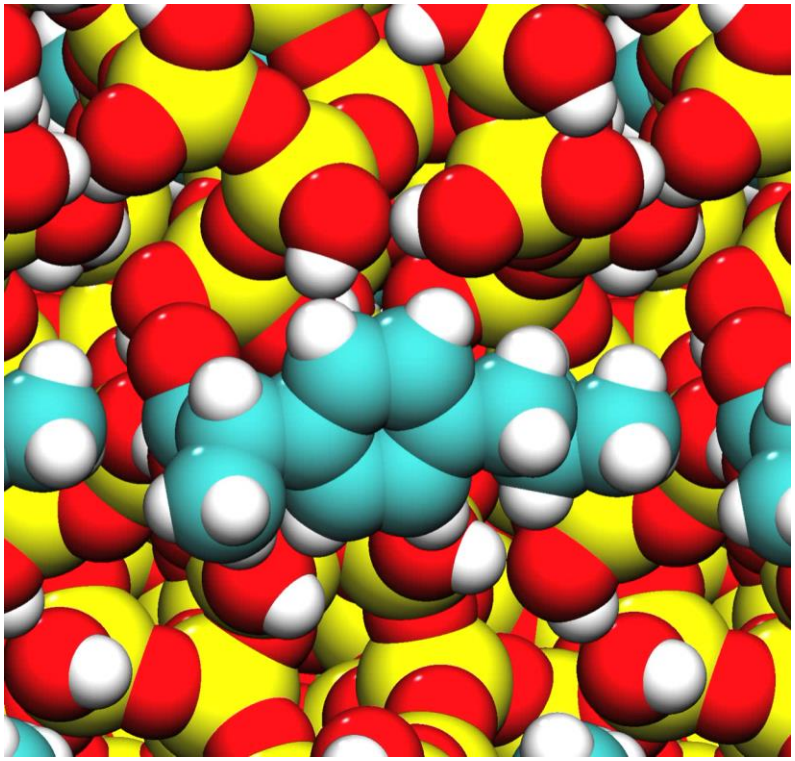
Courtesy of A. Pedone (UNIMORE)



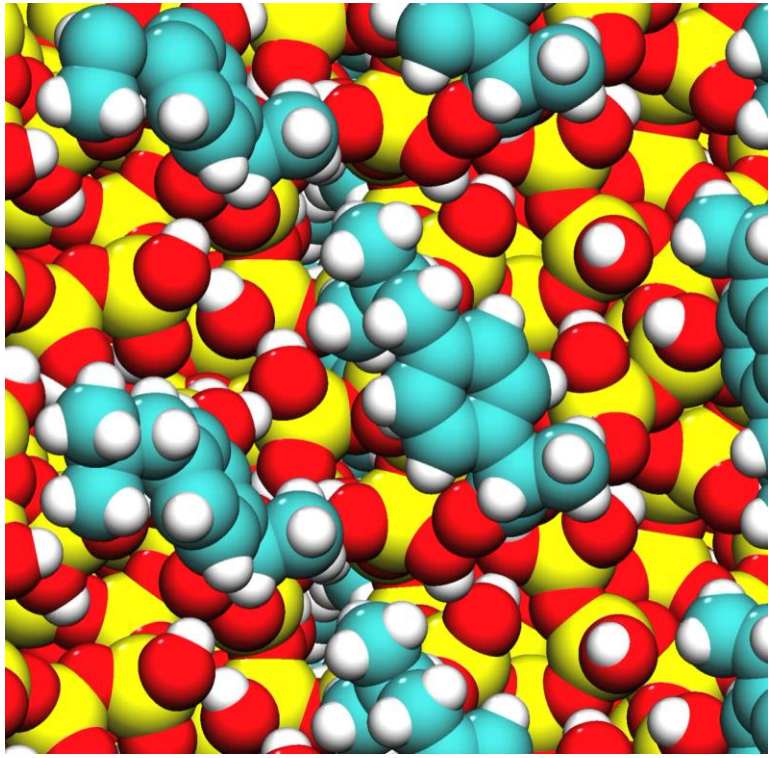
Only ibuprofen protons directly interacting with MCM, *i.e.* the carboxyl proton, are strongly affected by the environment.

MCM-41/Ibuprofen - AIMD

Ab initio molecular dynamics simulation of the “high loading” structure
NVT @ room temperature (300 K)
PBE-D2
Production: 6 ps (…and more)



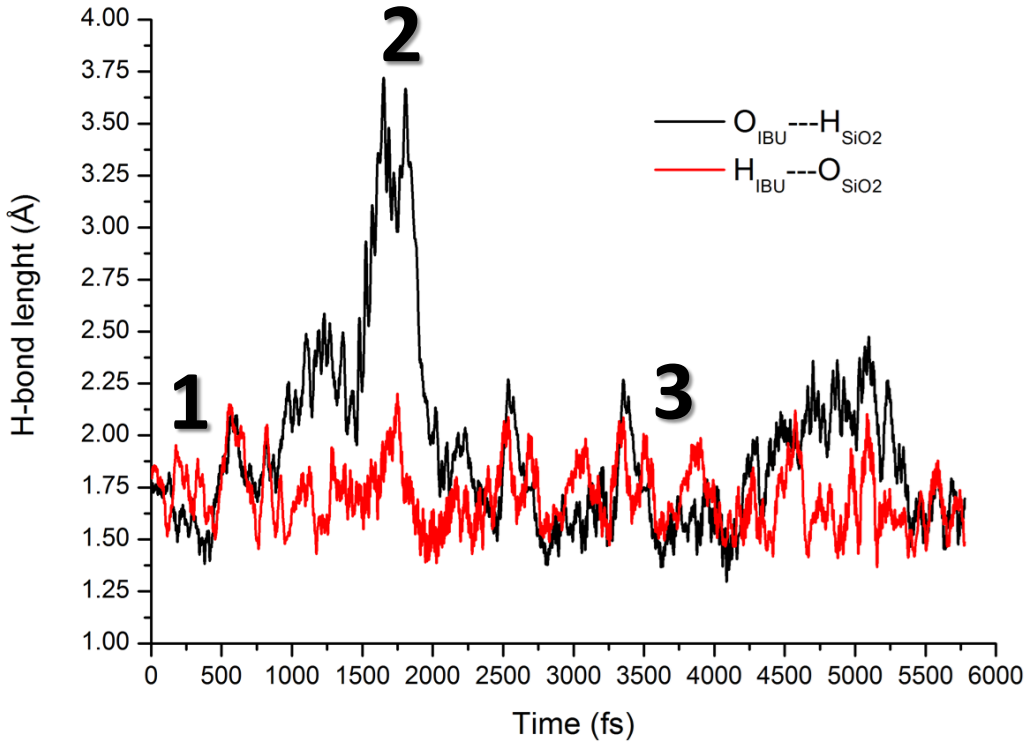
High mobility of IBU apolar part
Dynamics of the H-bonds



Impending aggregation of drug molecules through non specific vdW interactions

MCM-41/Ibuprofen - AIMD

DYNAMICS OF THE H-BONDS BETWEEN IBUPROFEN AND MCM-41



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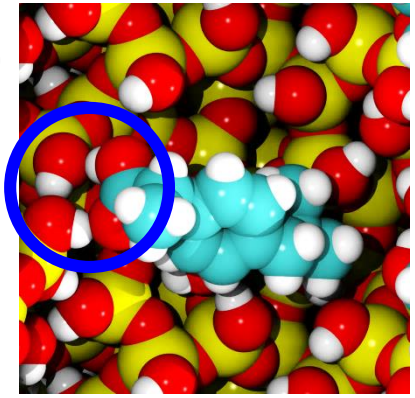

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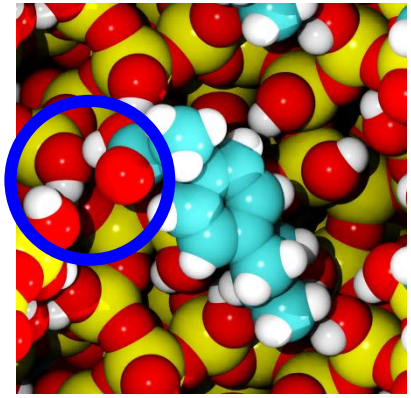

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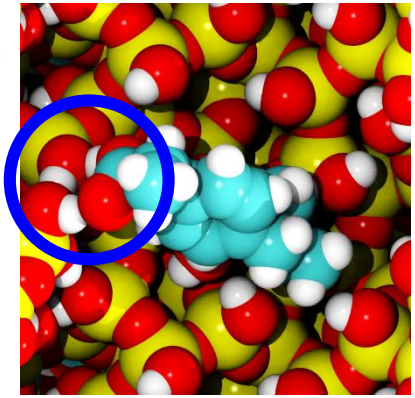
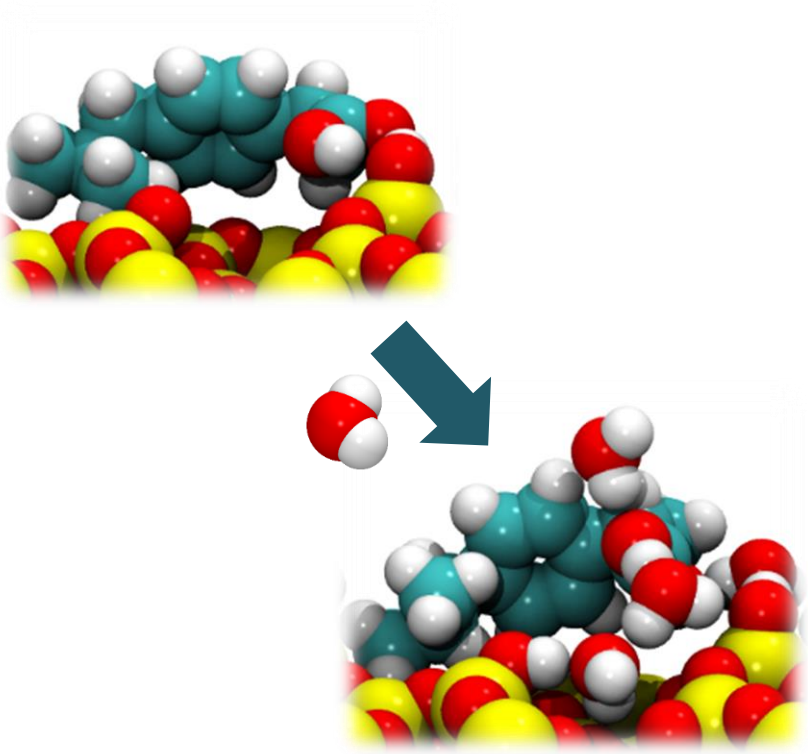


WHAT NEXT?

IBUPROFEN DIMERS ADSORPTION



EFFECT OF WATER ON THE DRUG-SILICA INTERACTION

(already studied for ibuprofen adsorbed on an hydrophobic silica surface)

ACKNOWLEDGEMENTS

P. Ugliengo

M. Corno

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R. Dovesi

B. Civalleri

R. Orlando

Theoretical Chemistry Group (UNITO)

A. Pedone

UNIMORE

PRACE

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ISCRA