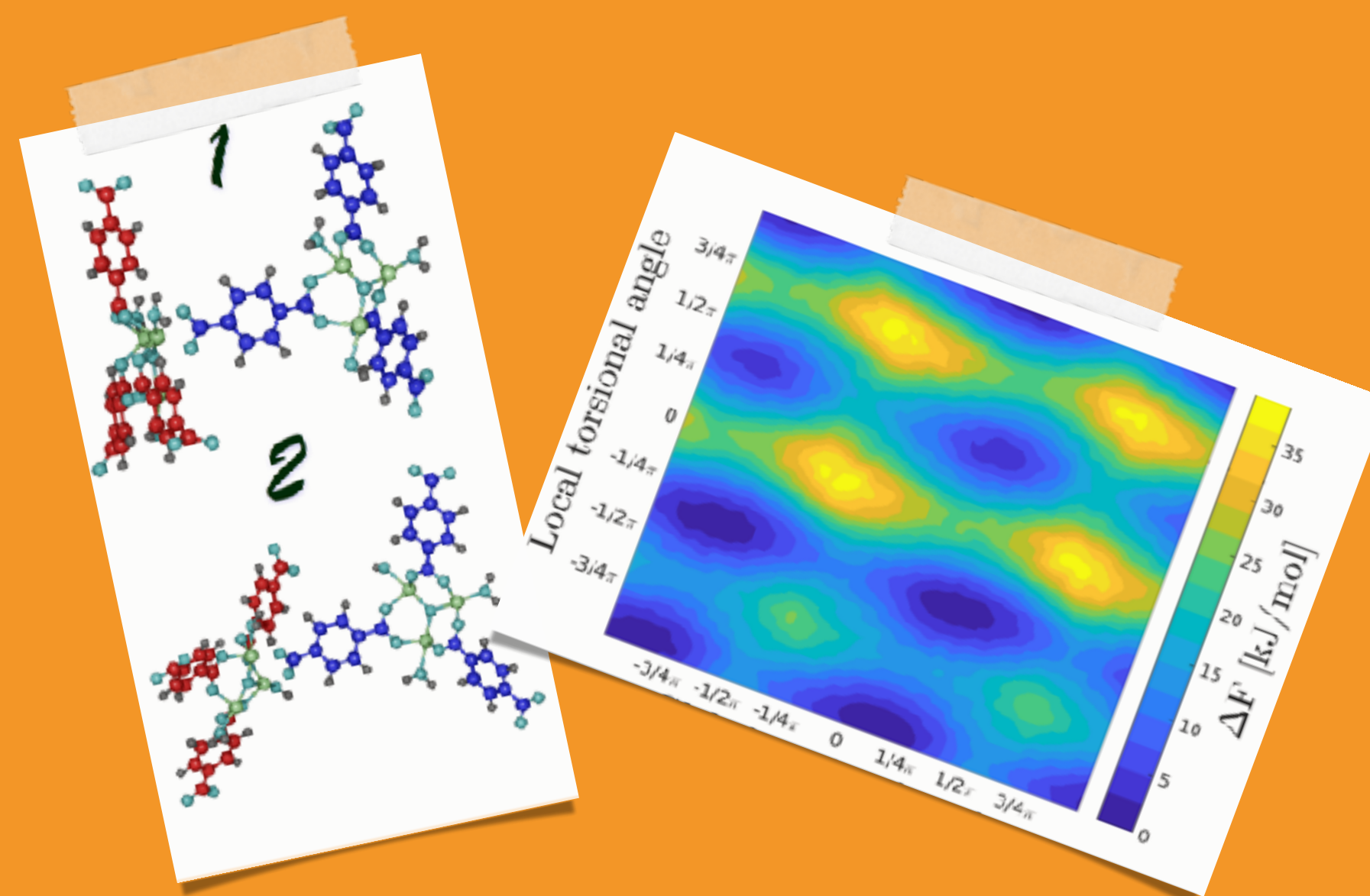


# Modelling dynamics and thermodynamics of conformational transitions during the assembly of molecular crystalline materials

WCPM-CSC Seminar Series - Warwick University - 2.12.2019

Matteo Salvaglio





**VISION:** develop rational approaches to the design of material synthesis processes



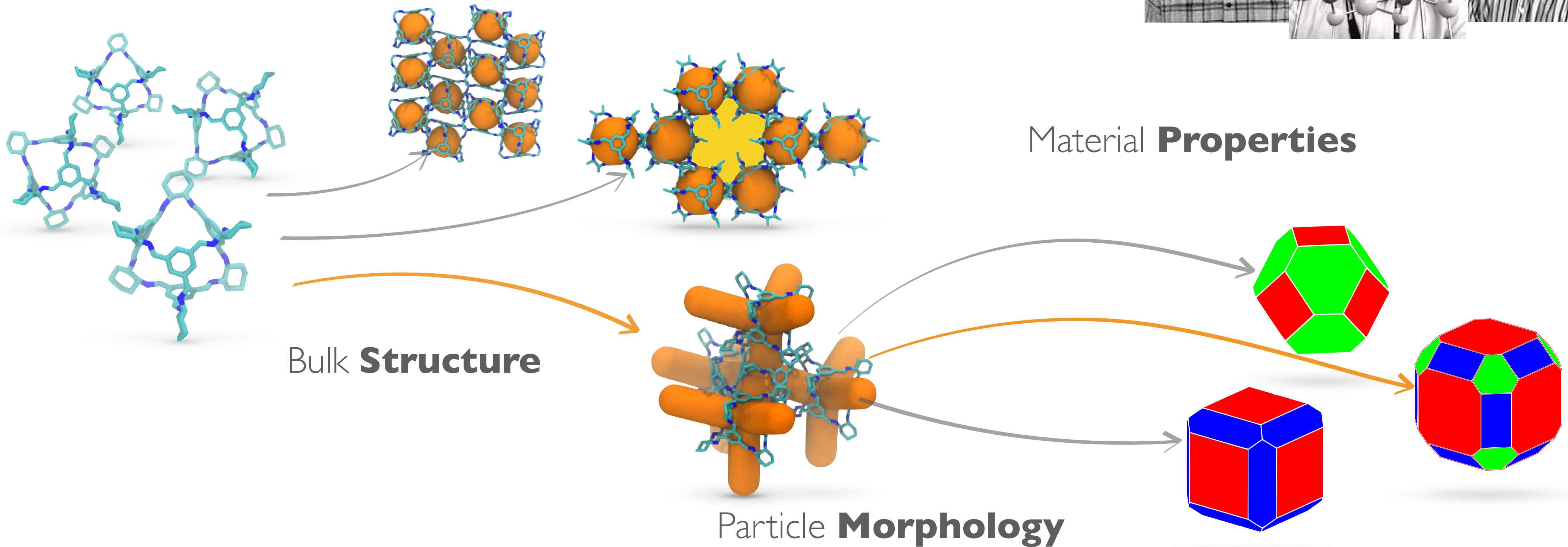
**OUR RESEARCH:** Develop a fundamental understanding of materials synthesis with state-of-the-art molecular simulation methods.



**THERMODYNAMICS**

**KINETICS**

**MECHANISMS**







**VISION:** develop rational approaches to the design of material synthesis processes



**OUR RESEARCH:** Develop a fundamental understanding of materials synthesis with state-of-the-art molecular simulation methods.

**THERMODYNAMICS**

**KINETICS**

**MECHANISMS**

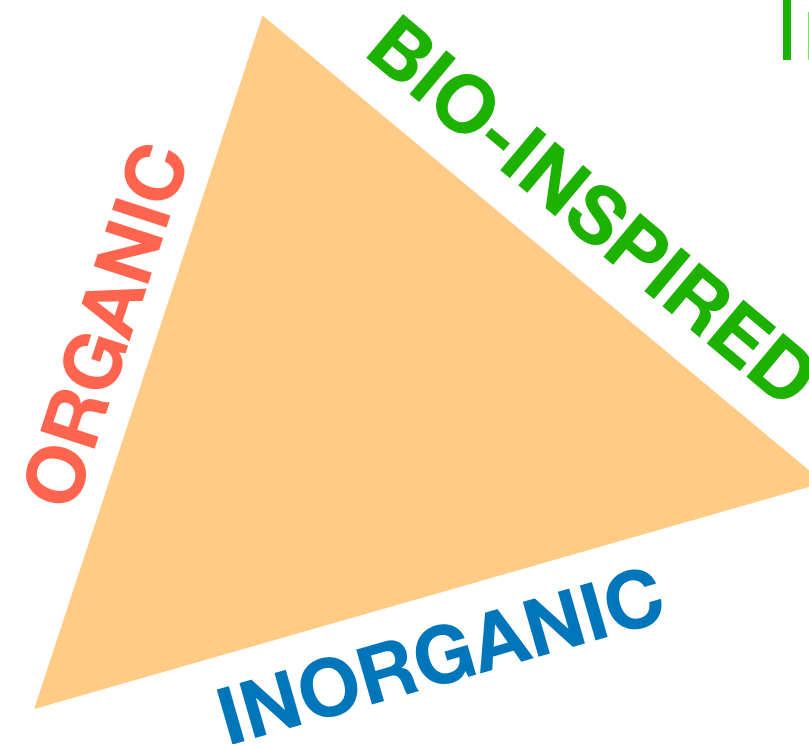


**APPLICATIONS / ONGOING PROJECTS**

Crystal growth of organic materials (API)

Polymorphism in molecular crystals

MOF synthesis

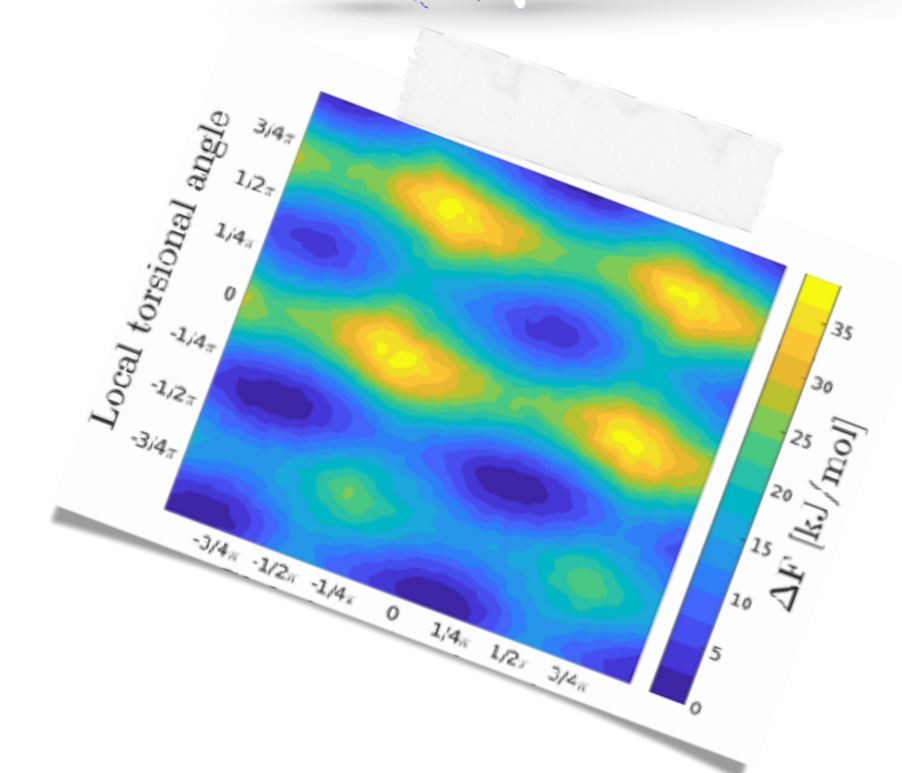
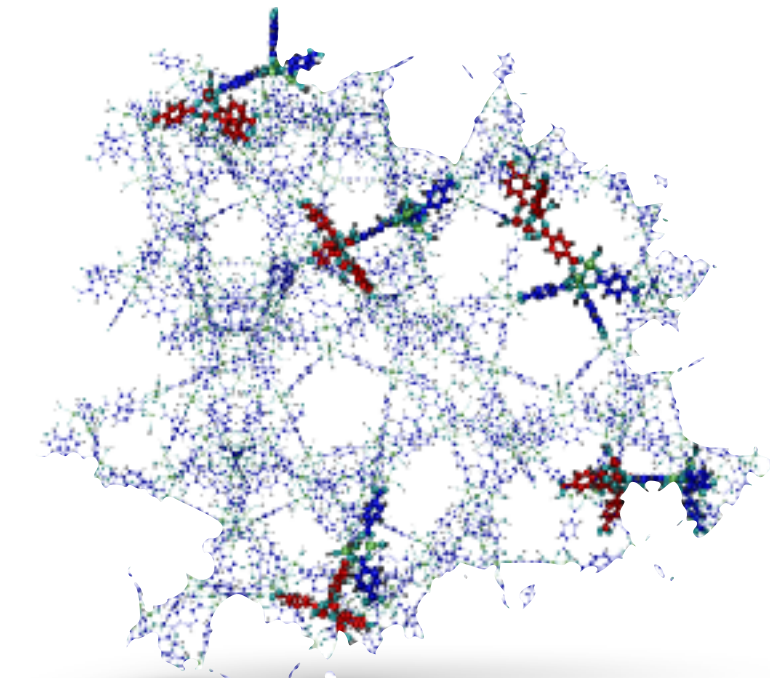
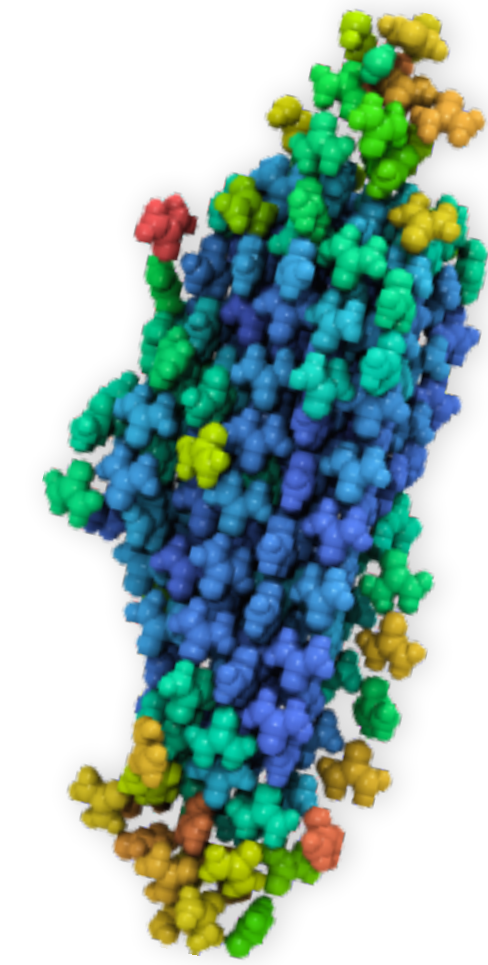


Nucleation of bio-inspired liquid-like peptide organelles

Crystal growth @ solution/electrode interfaces  
Nucleation from solution

# Outline

- Setting the stage: Modelling the effect of the environment on (organic) crystals nucleation and growth: the case of urea ←
- Interplay between conformational complexity and crystals assembly:
  - Early stages of MOF self-assembly ←
  - Ibuprofen crystal/solution interfaces ←





# Modelling nucleation & growth from solution: Challenges & Tools

Nucleation & crystal growth are dominated by **molecular level processes**



**Atomistic resolution** is key

Nucleation & crystal growth are **collective processes**, the environment (i.e. solution) cannot be neglected!



explicitly **simulate ensembles** of solute & solvent **molecules** in “**realistic conditions**”

Nucleation and growth are dominated by **rare events**



Characteristic **nucleation times** in “experimental conditions” **exceed timescales** accessible to brute-force simulations.

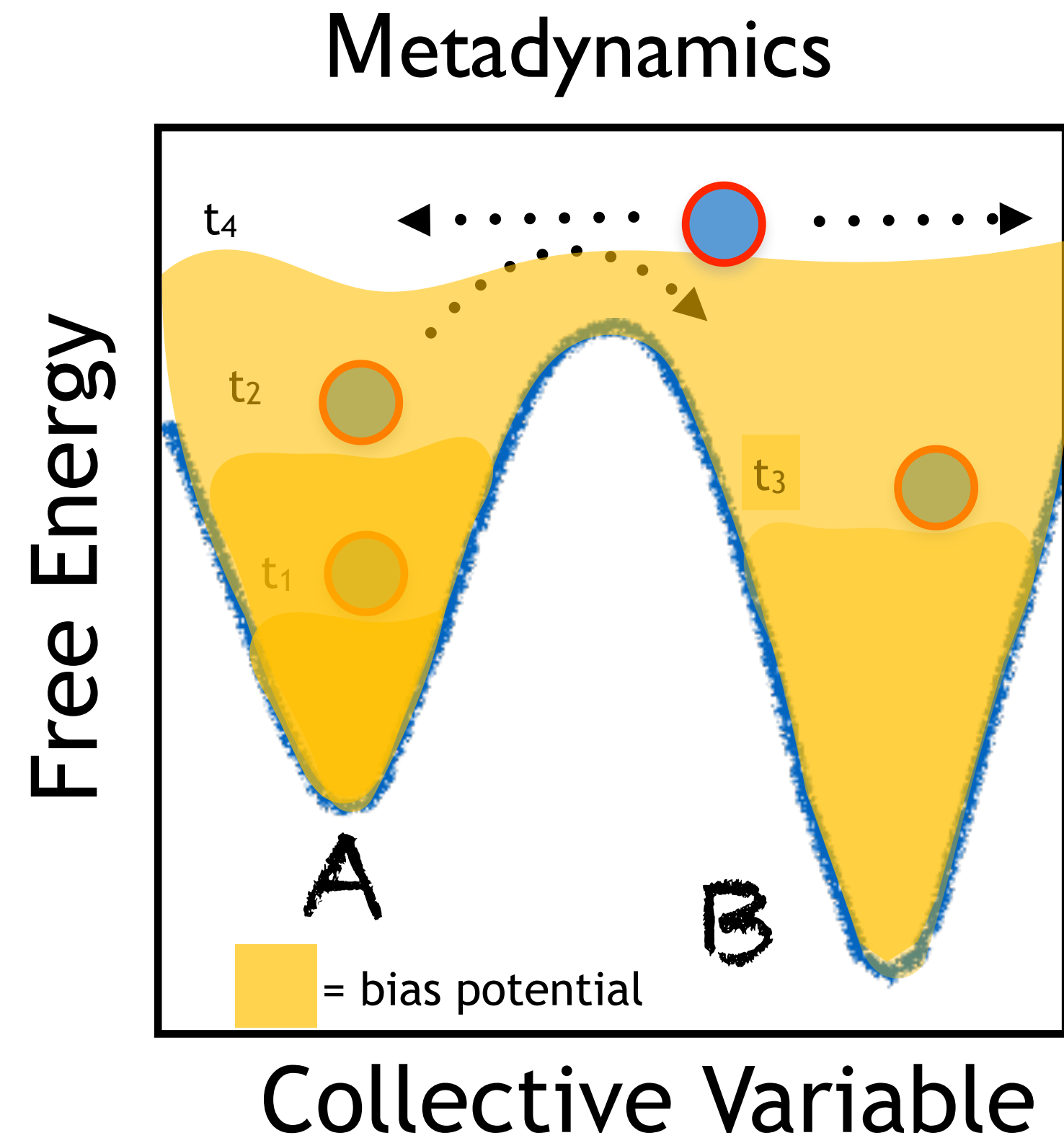
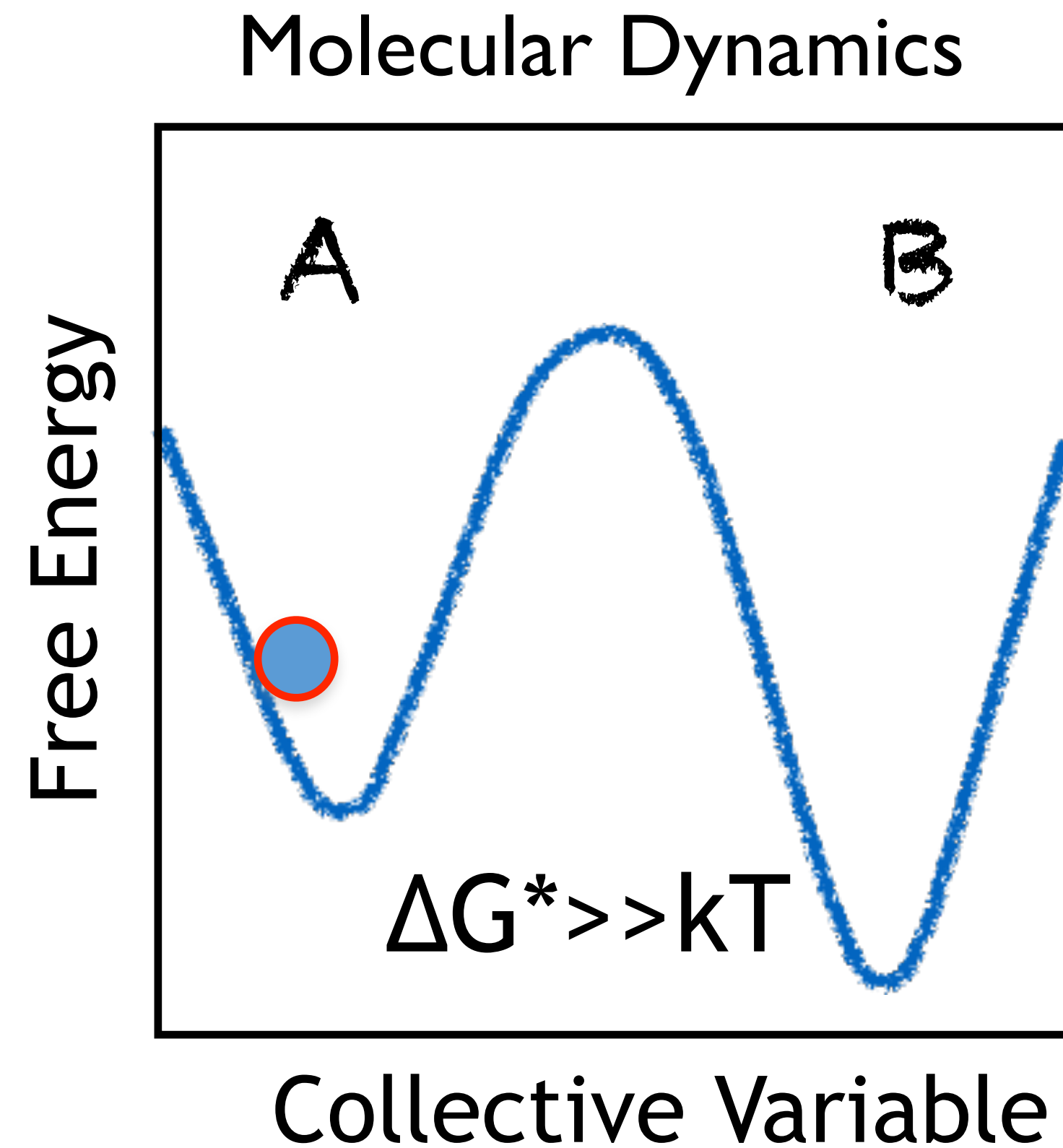
1

We use **classical potentials** to efficiently propagate dynamics

2

We need **enhanced sampling methods** to reach relevant timescales

# Tackling the sampling problem with metadynamics

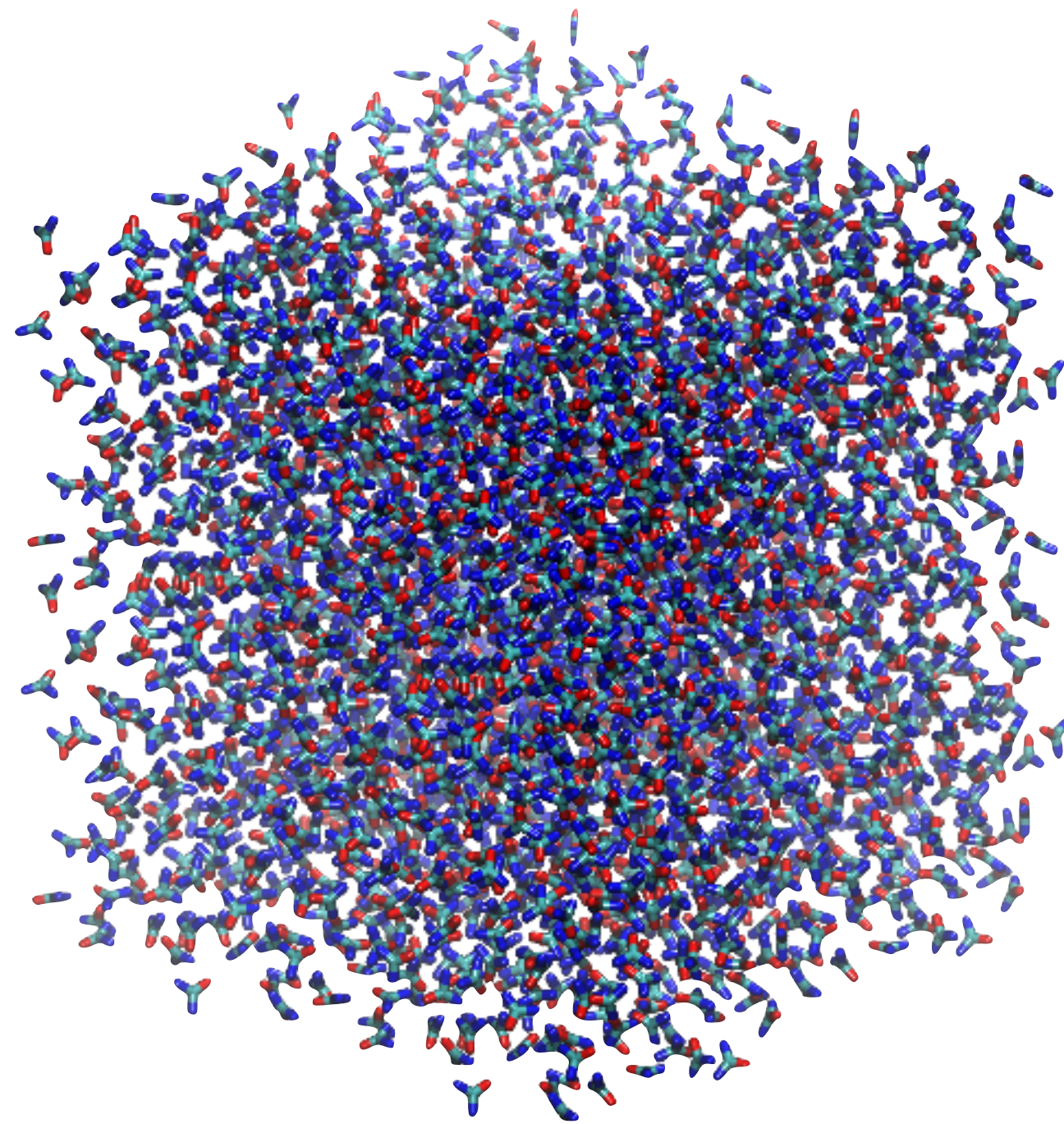


- Metadynamics: an adaptively built potential “fills” the free energy basins and pushes the system across high free energy barriers
- Important fluctuations are enhanced!
- The negative of this potential allows to recover a **free energy** surface (FES) in CV space



# Collective Variables: the case of Urea

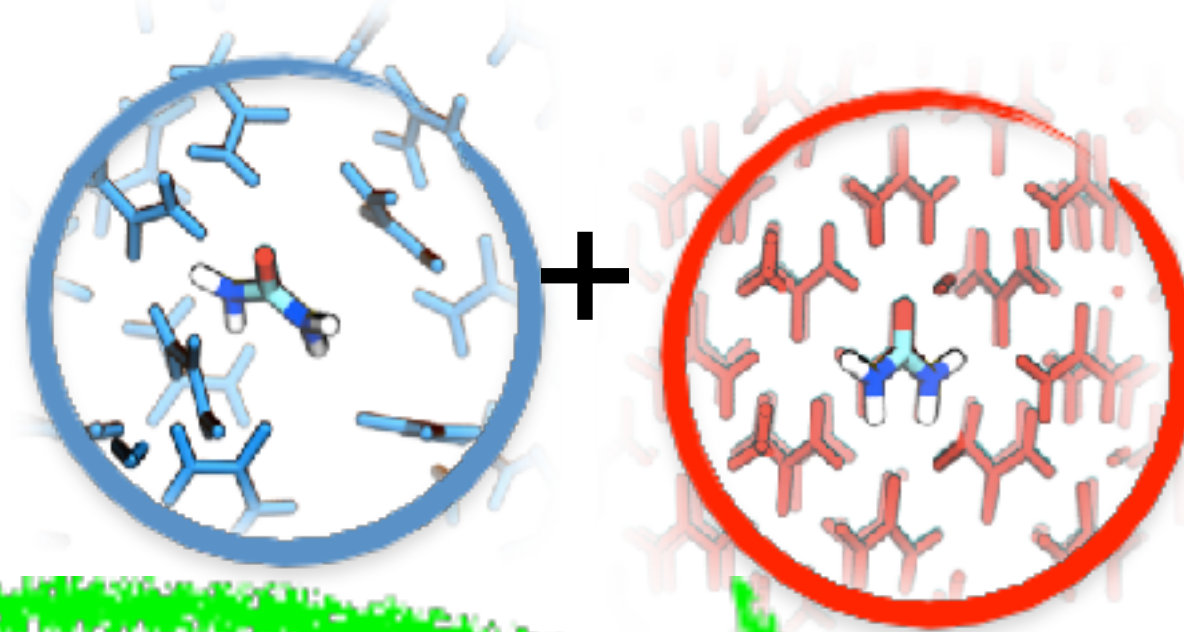
Cartesian coordinates



high dimensional space  
**not human-readable**

**Other examples of CVs:**  
Steinhardt order parameters, cell parameters, volume, potential energy, entropy ...

local density

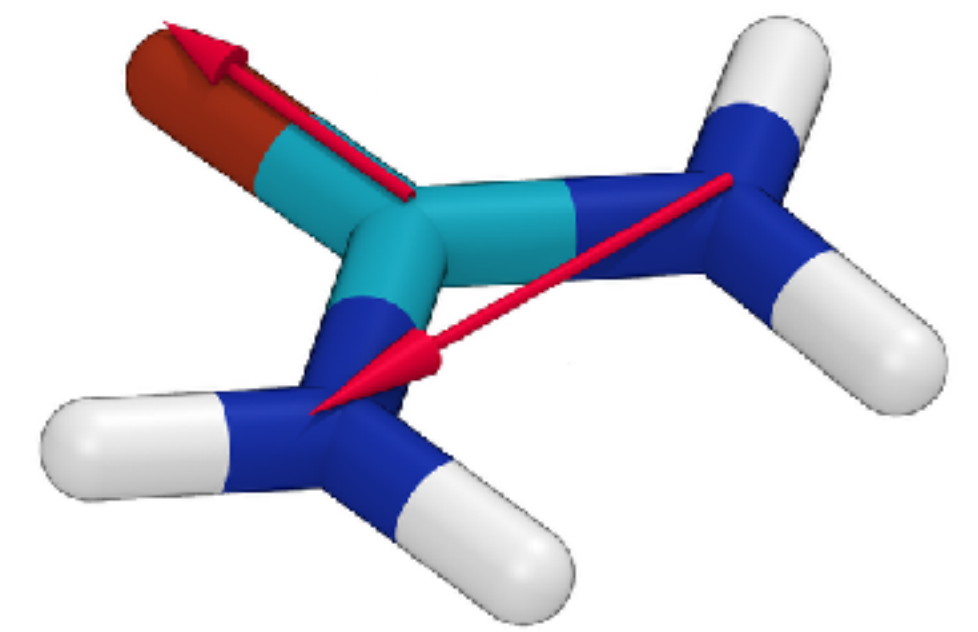
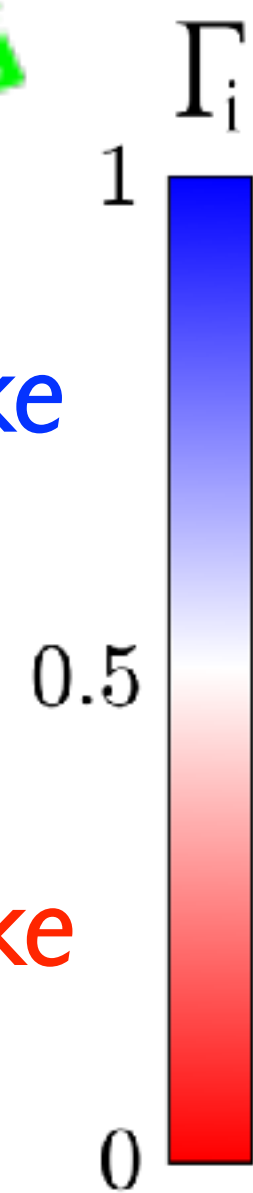


local order

**Collective Variable**

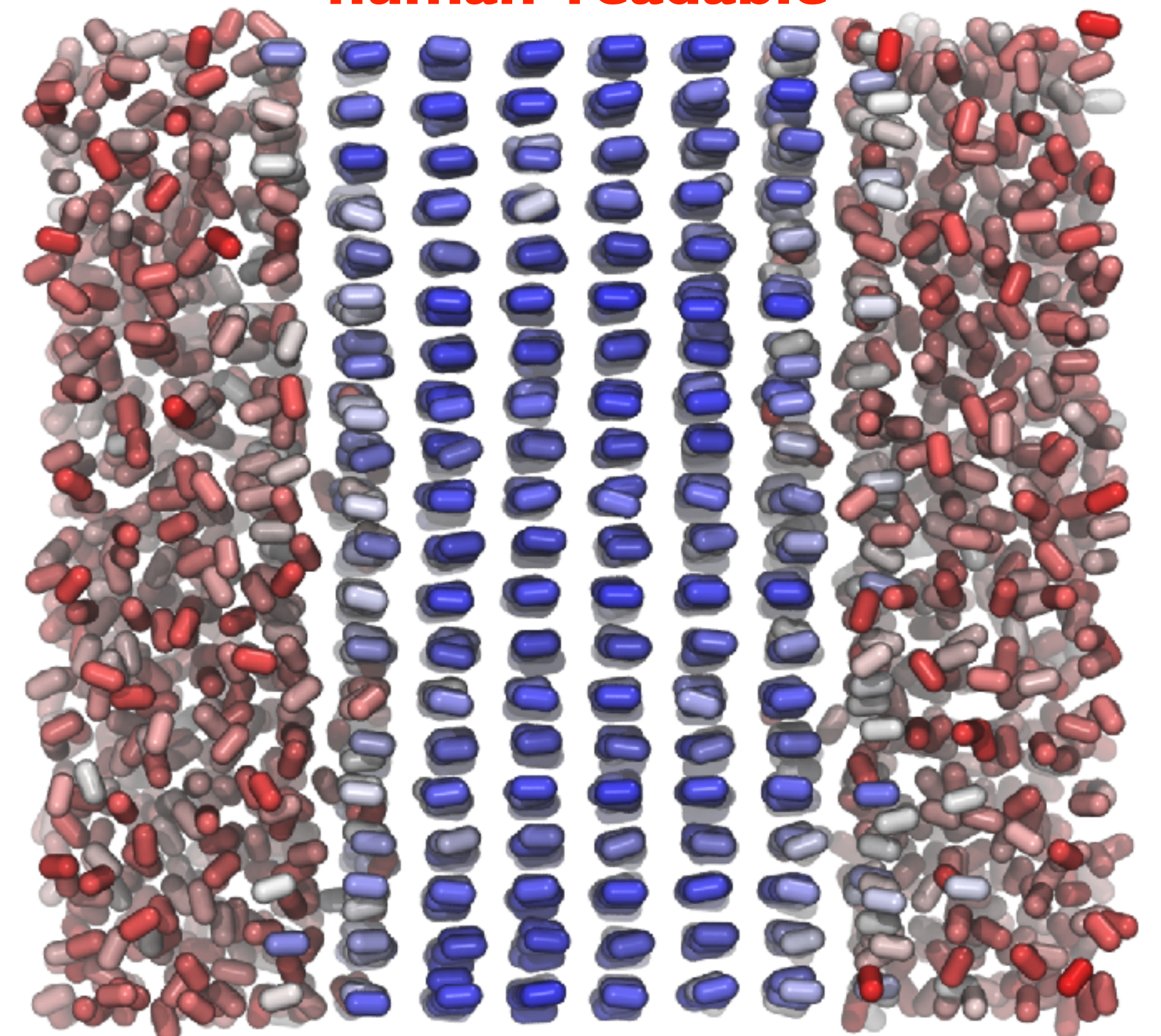
Crystal-like

Liquid-like



low dimensional space

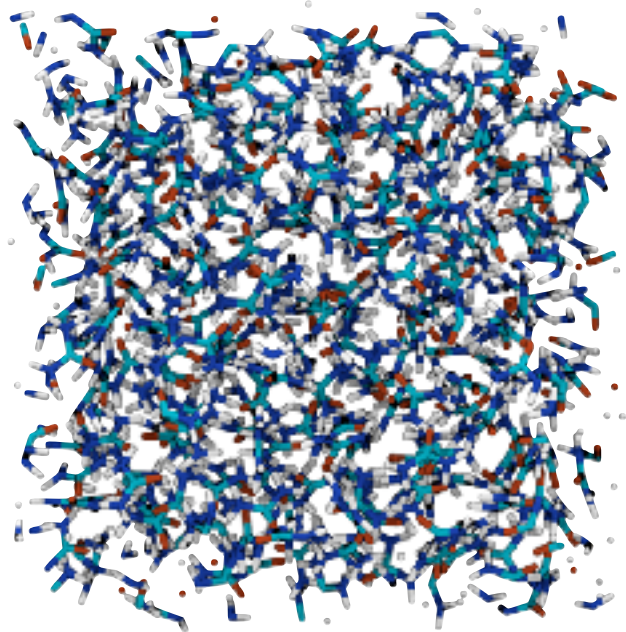
**human-readable**



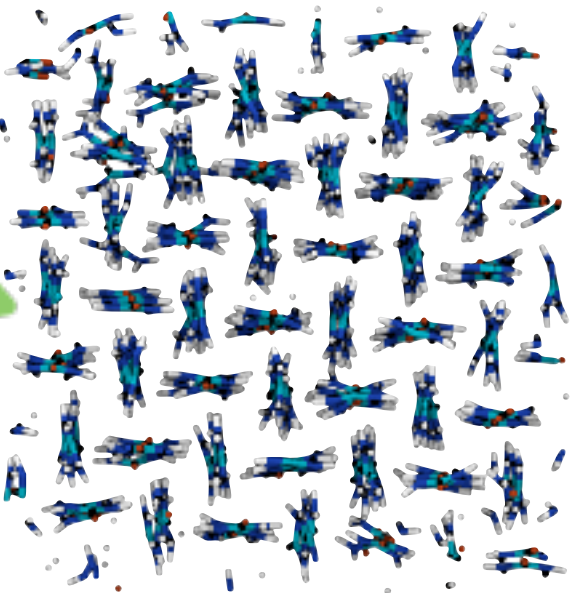
the C=O bond only is shown



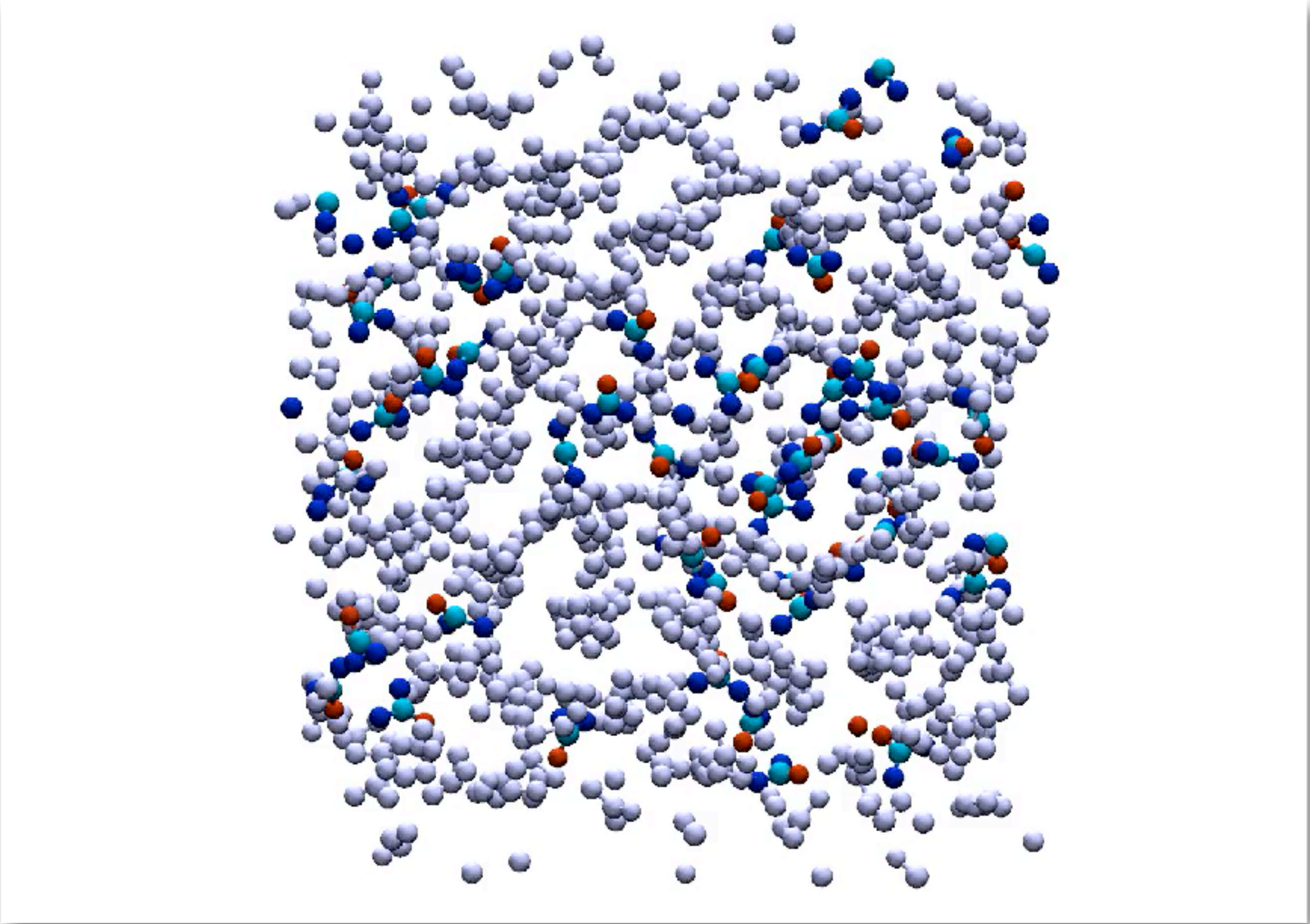
# Sampling (extremely) rare fluctuations: urea nucleation from its melt



**Liquid**

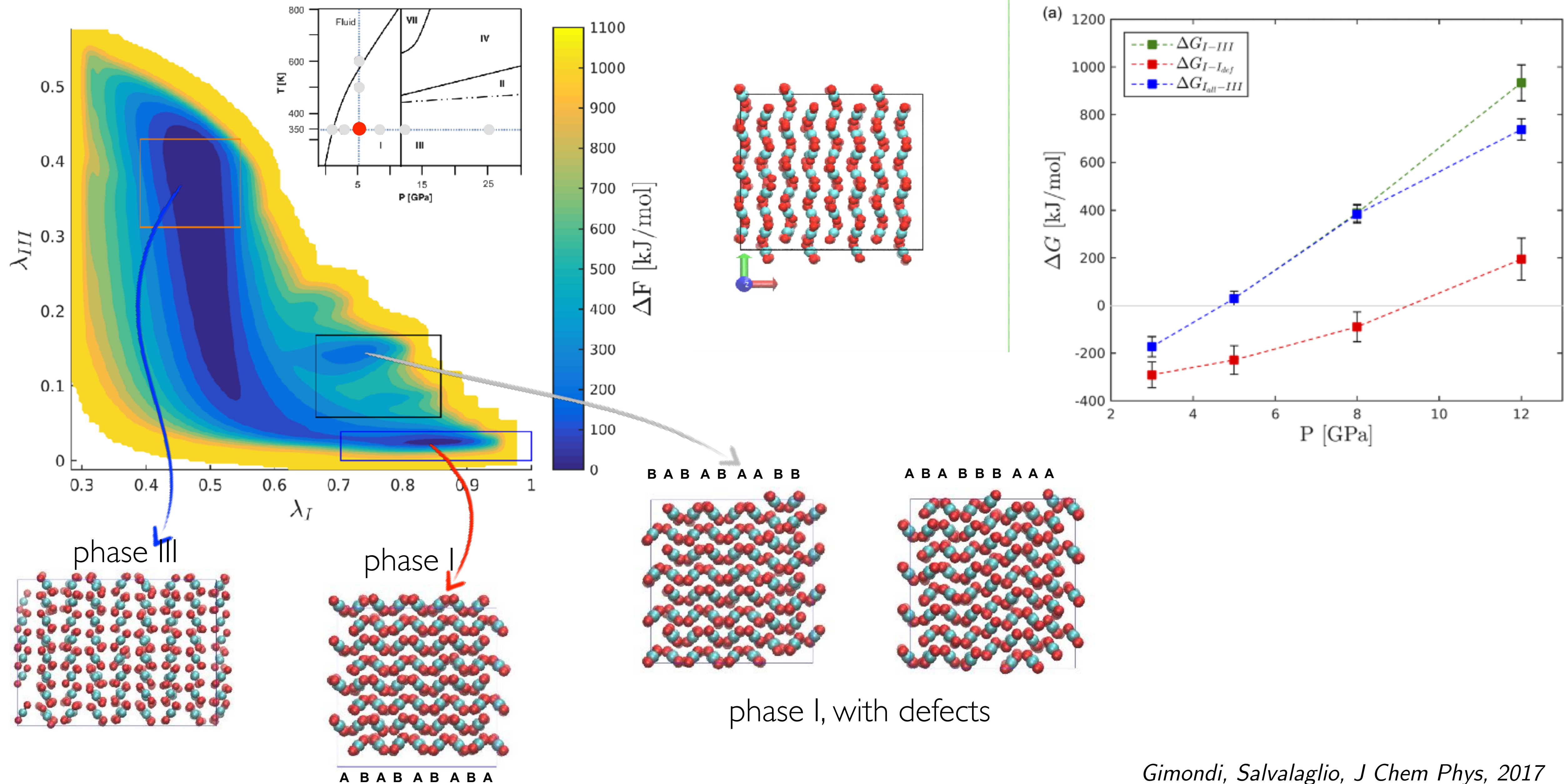


**Crystal**



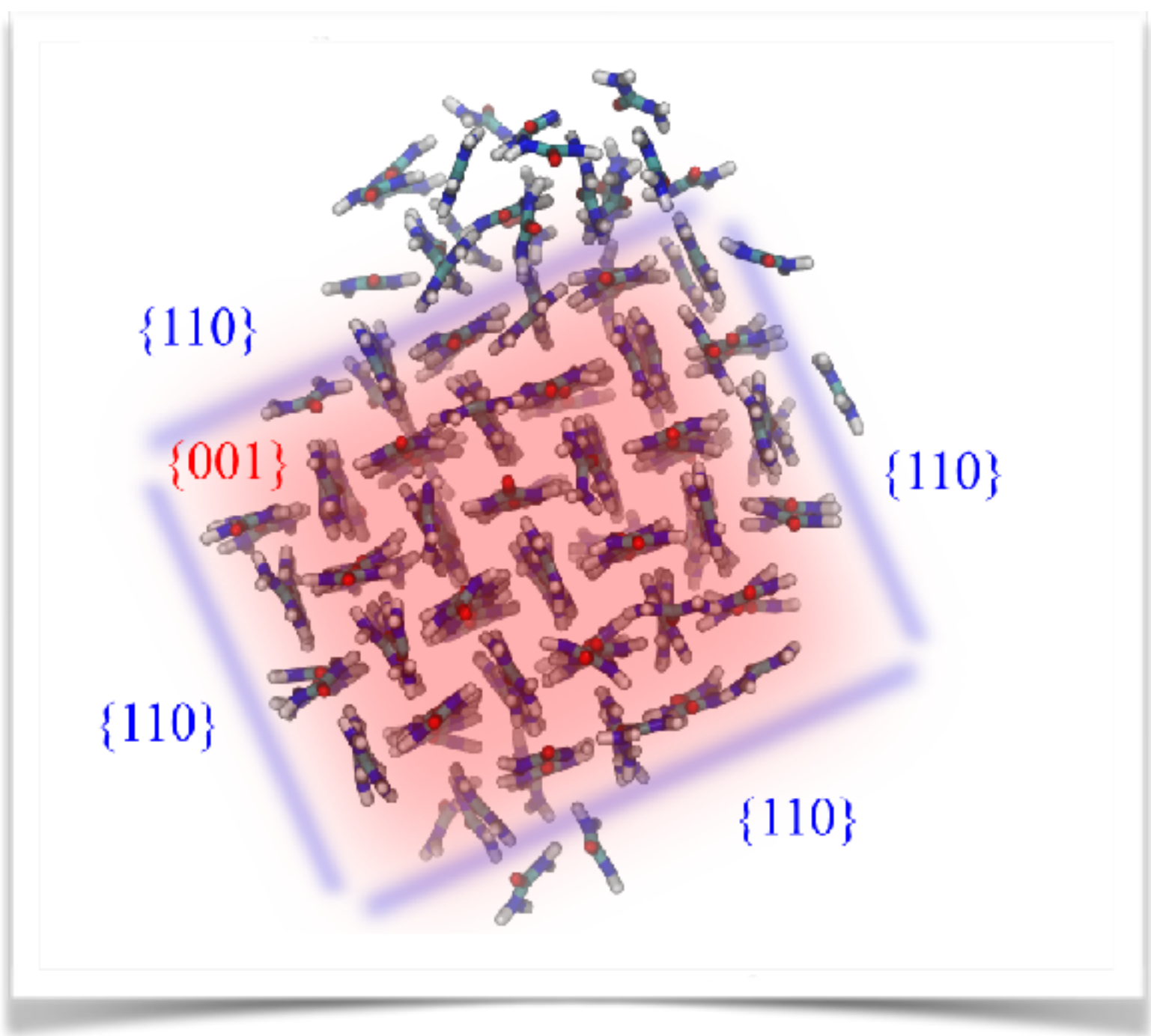
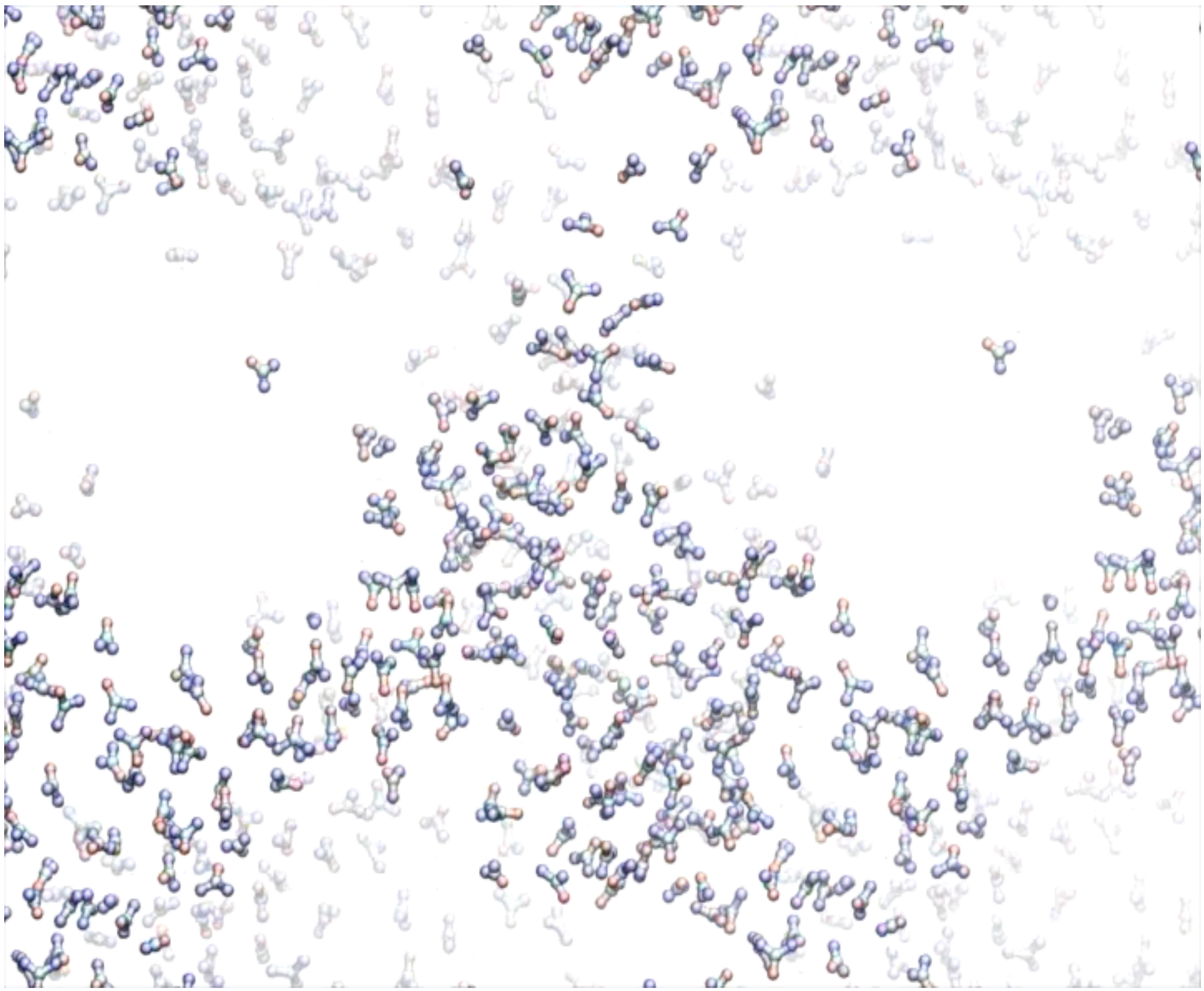
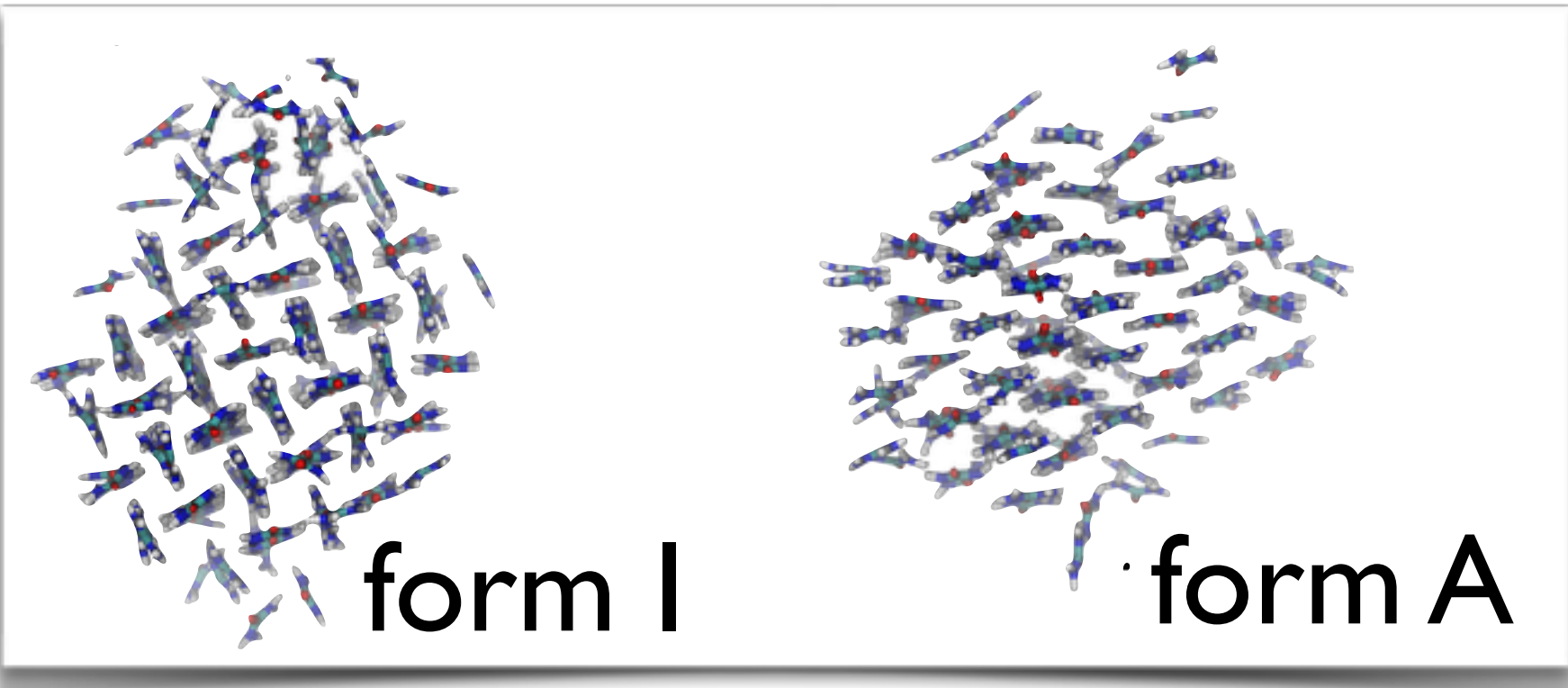


# Sampling of phase transitions in molecular solids, discovery of new states



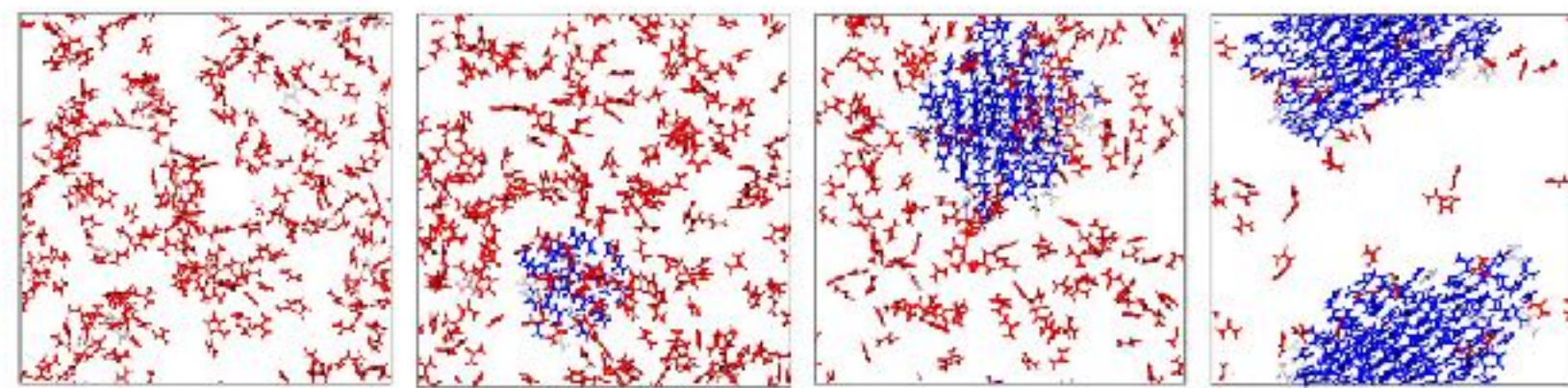
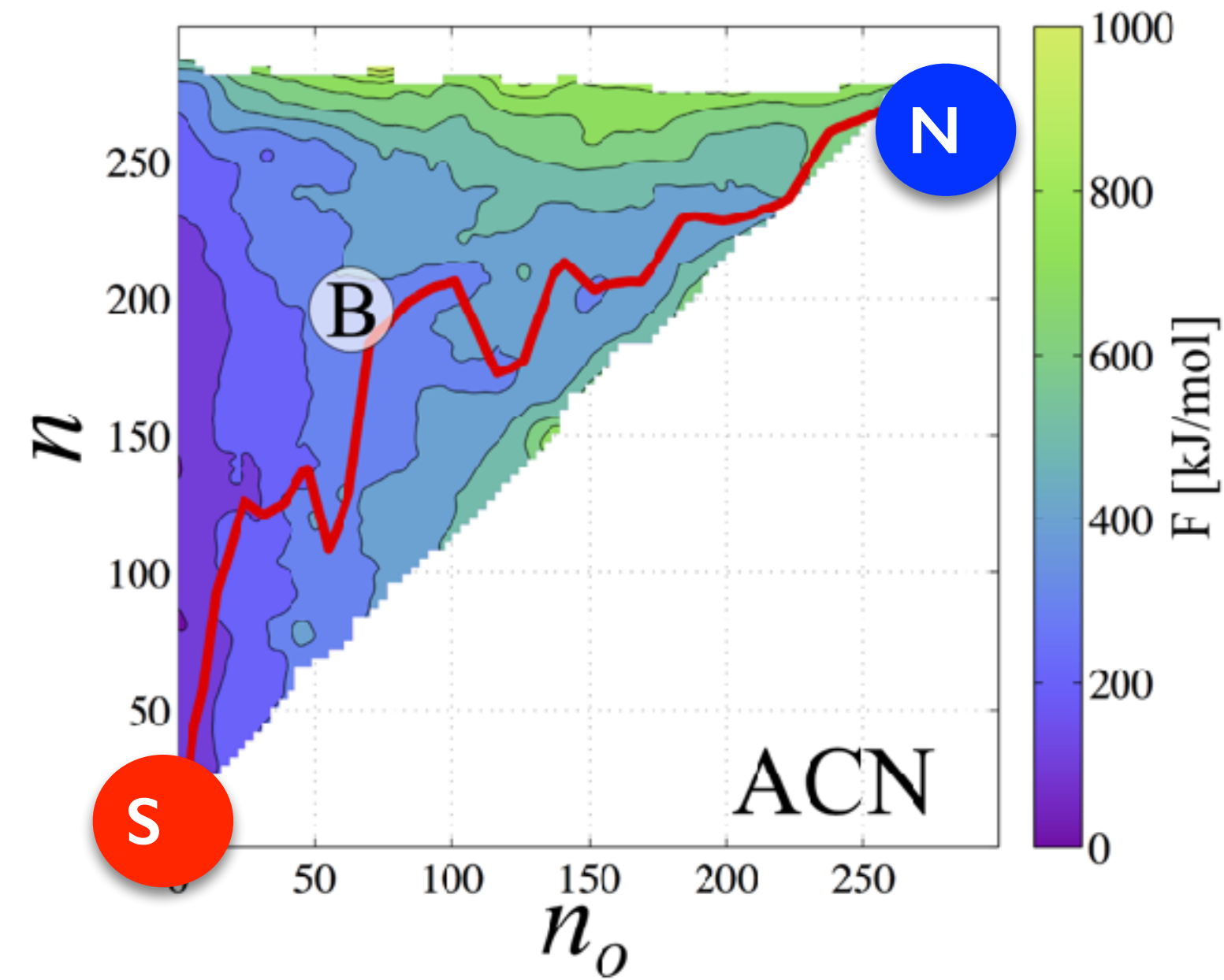
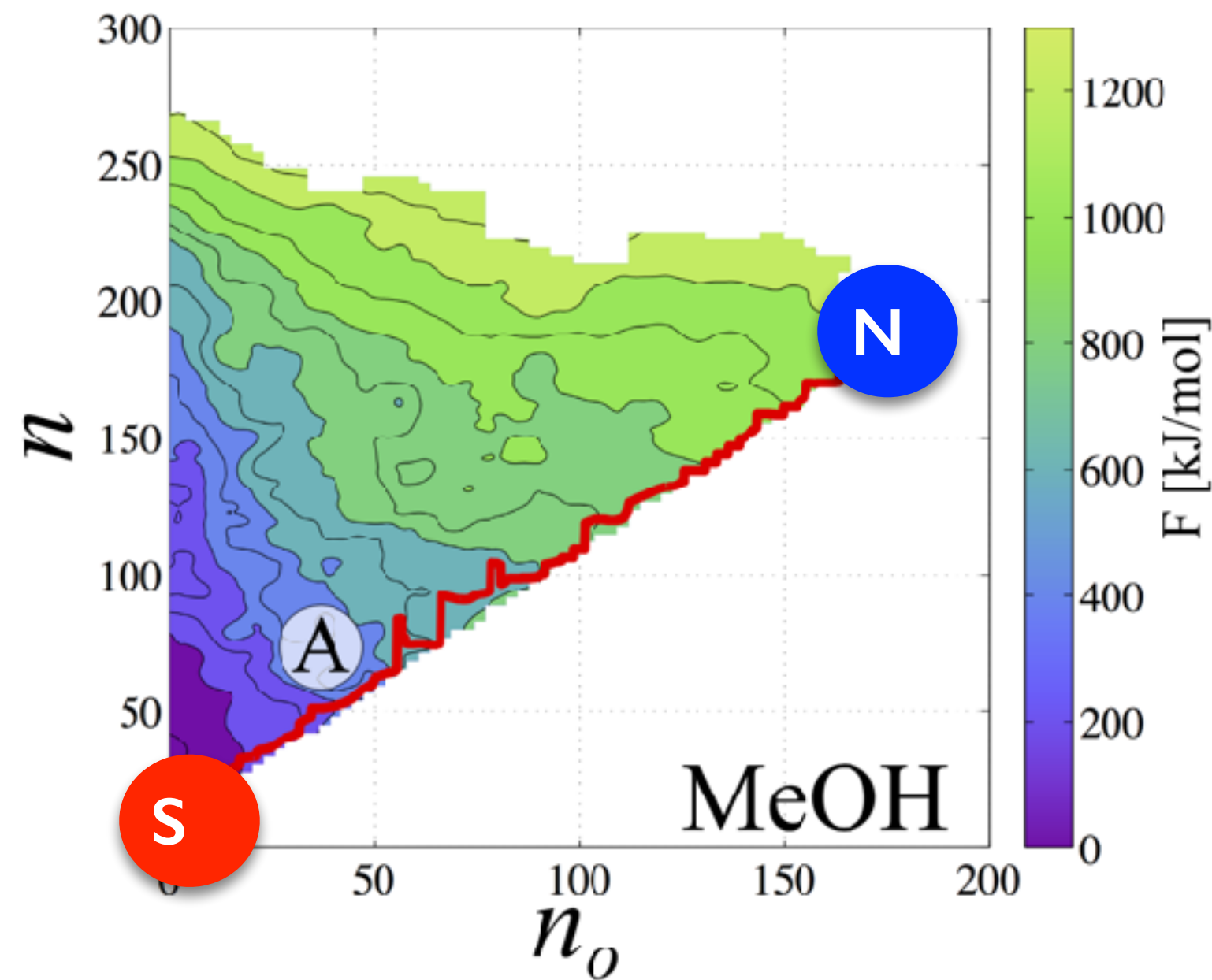


# Nucleation in solution

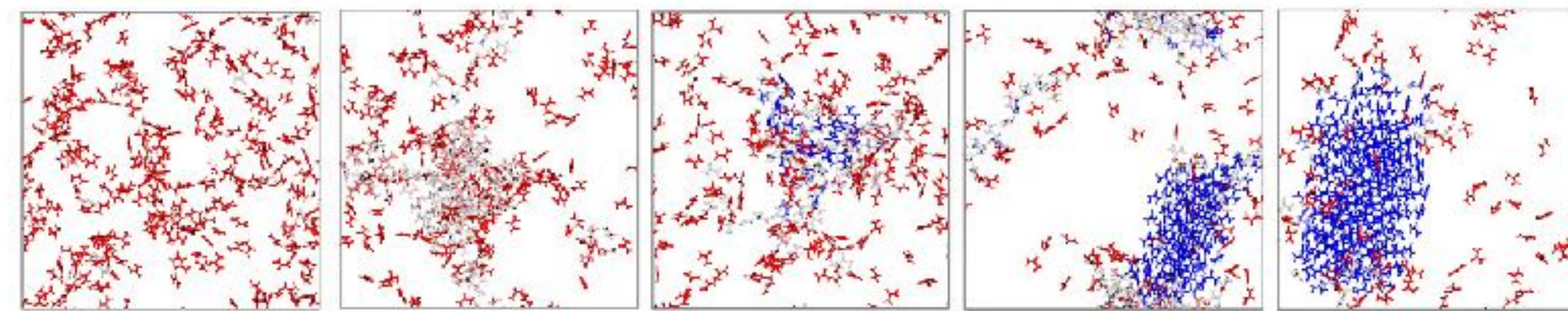




# Nucleation mechanism is solvent dependent



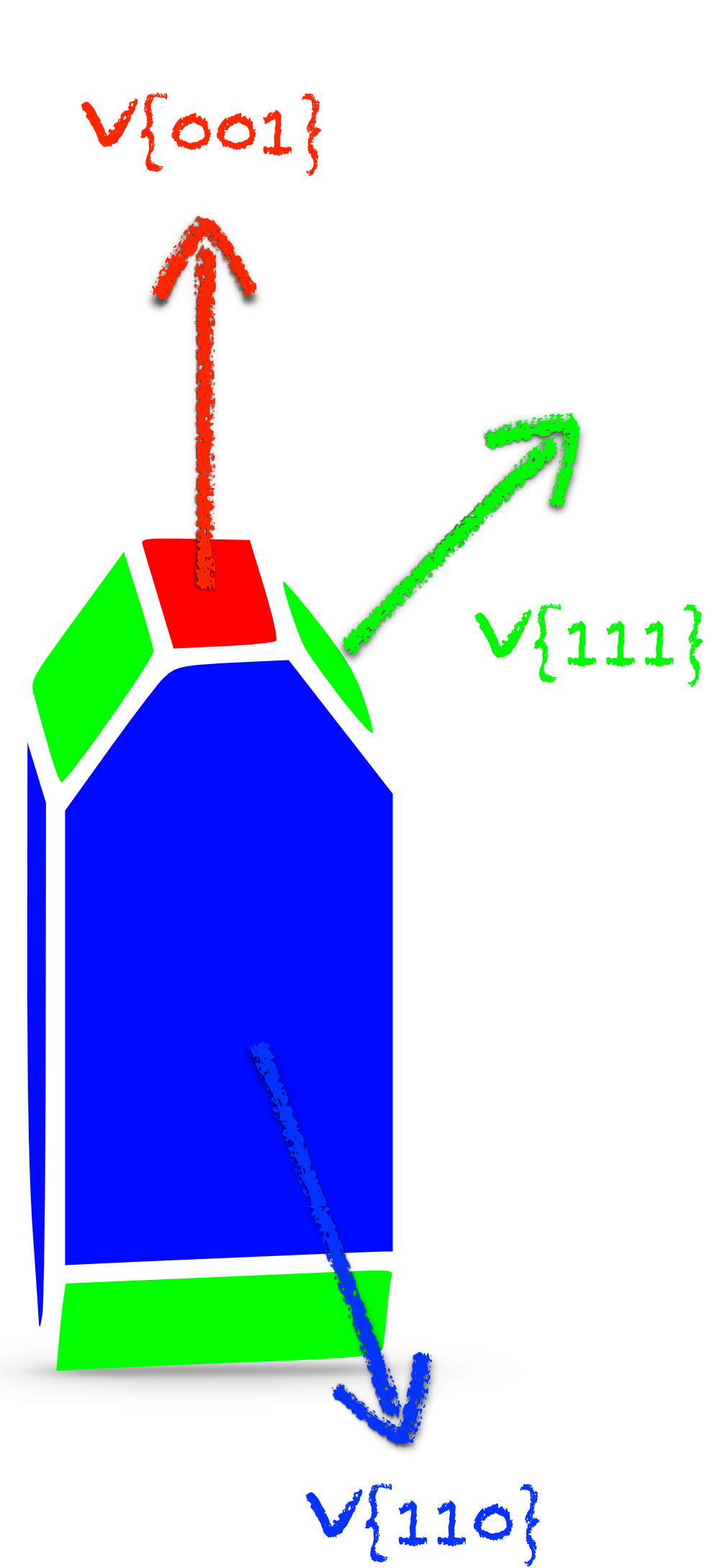
*single-step*  
*MeOH, EtOH*



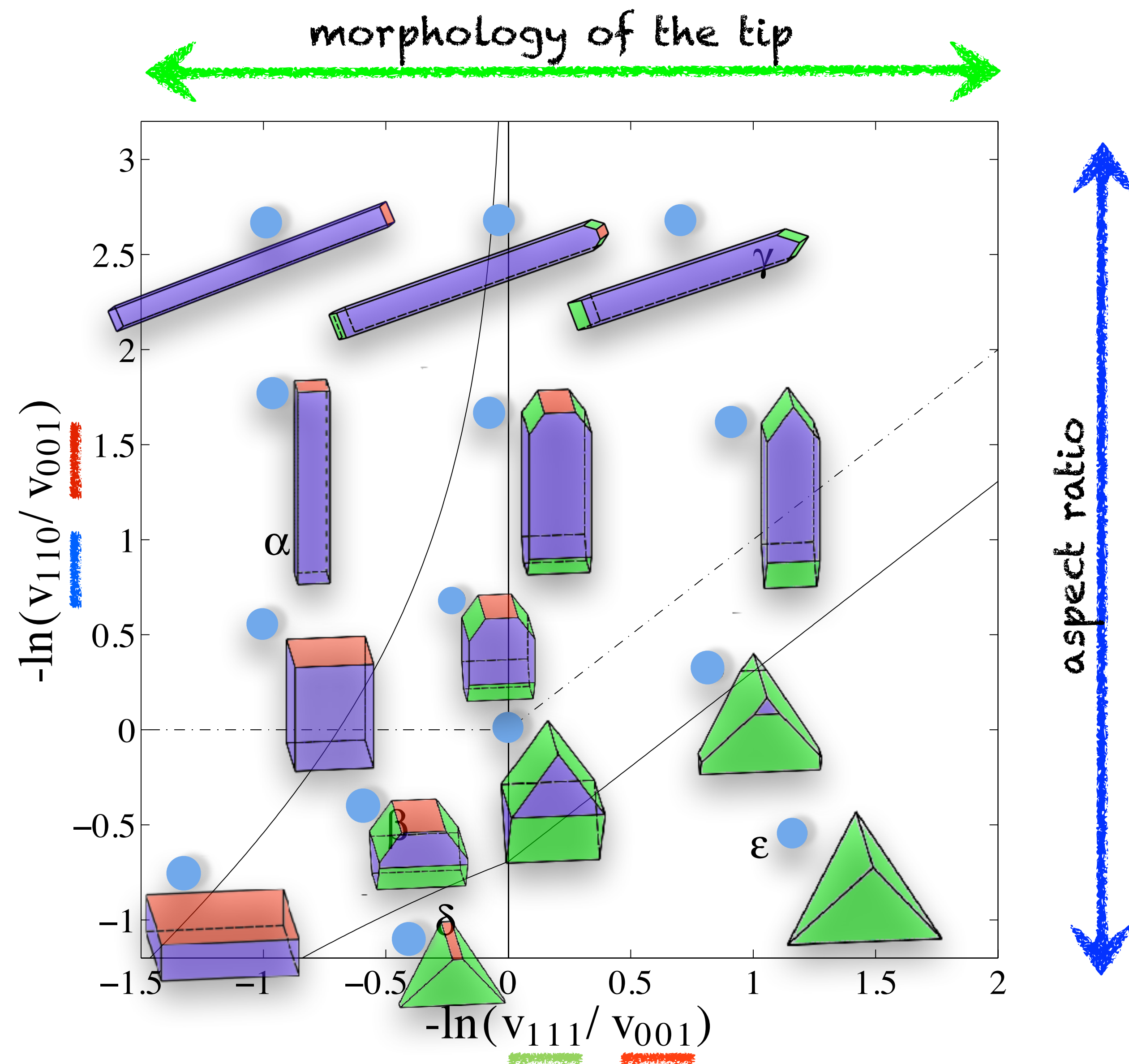
*two-step*  
*water, ACN*



# Steady state crystal shapes depend on relative growth rates



Wulff-Chernov construction



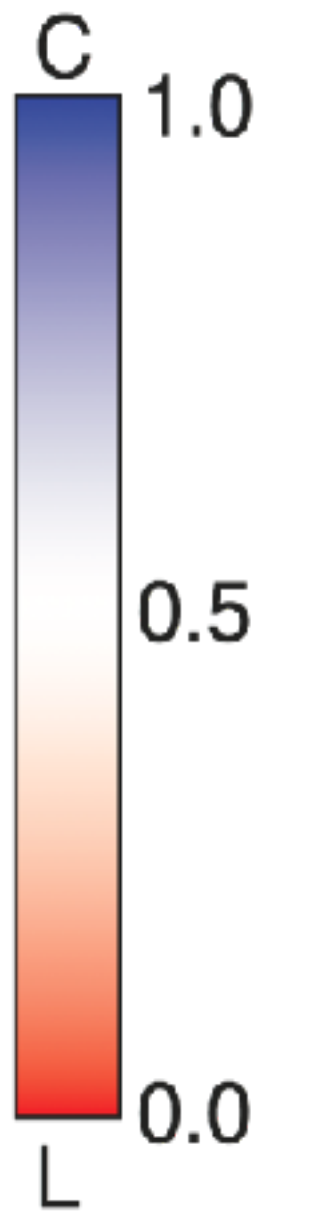
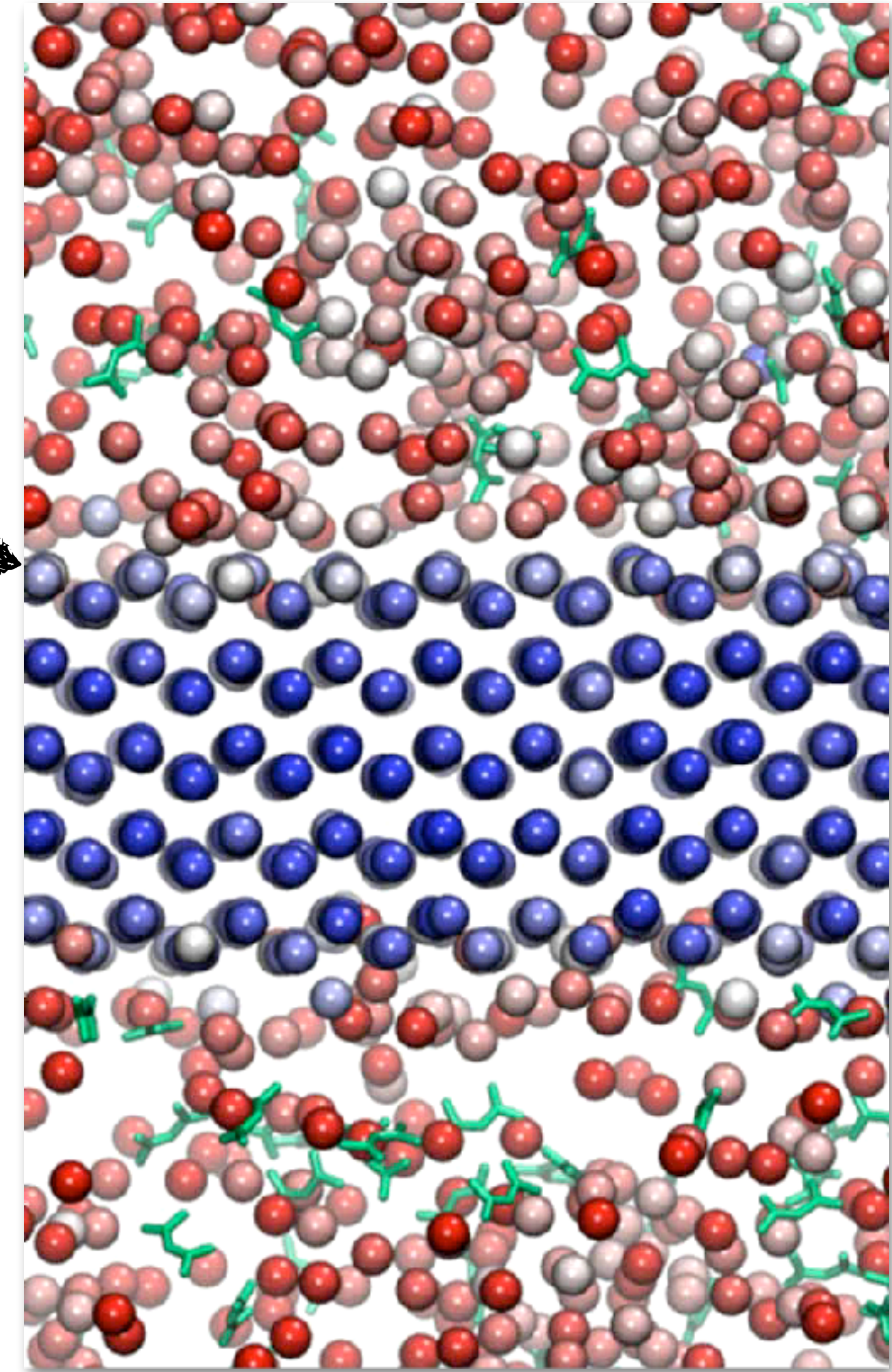
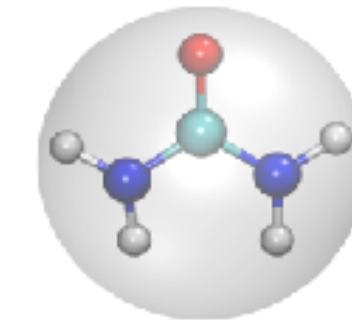
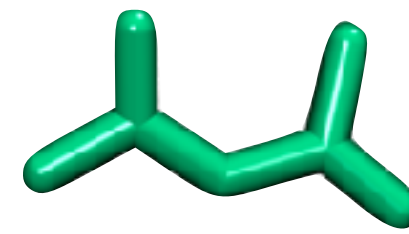
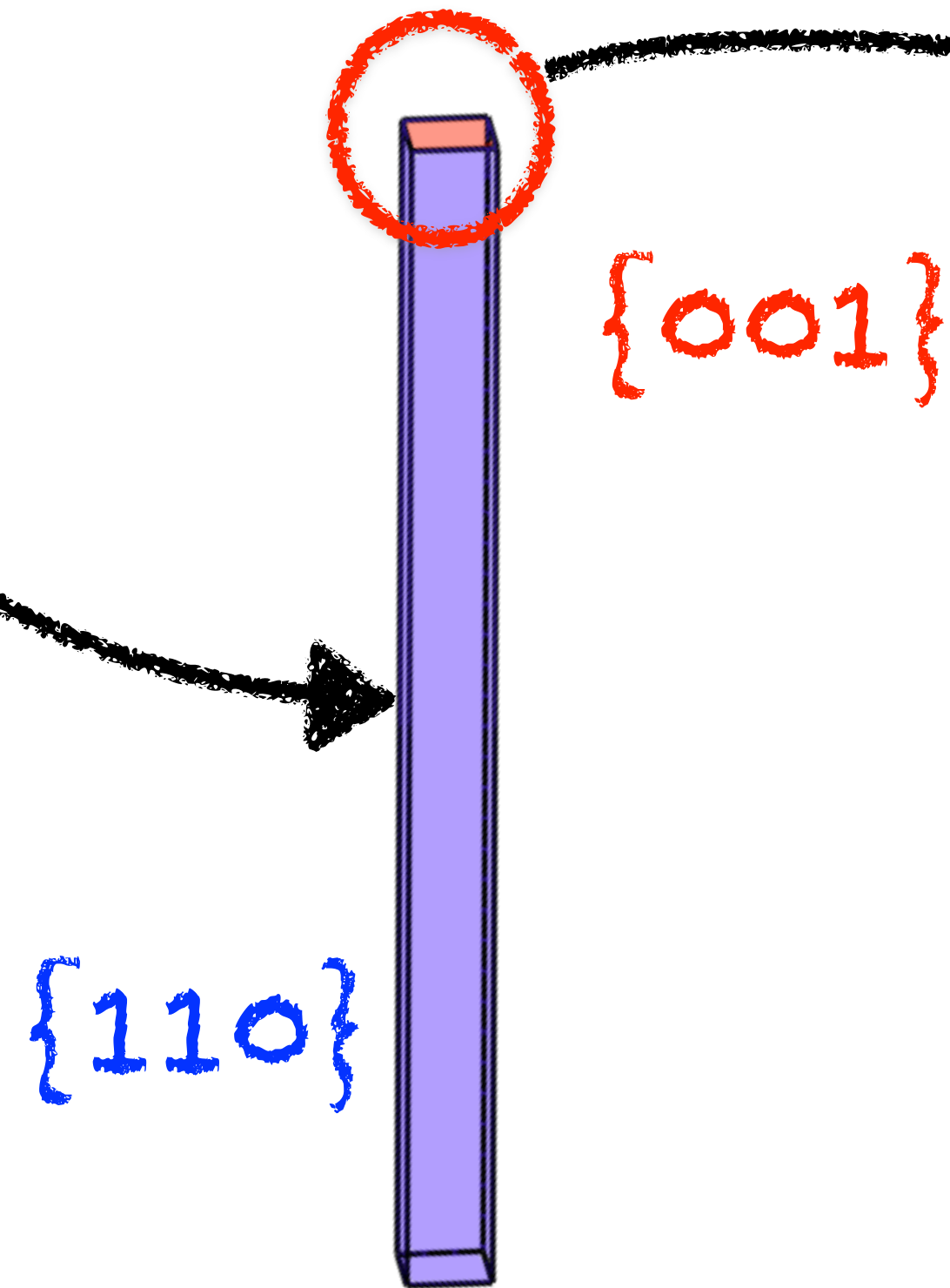


# a molecular model to investigate crystal growth



S. Piana et al. Nature 2005

Classical all-atom  
Molecular Dynamics

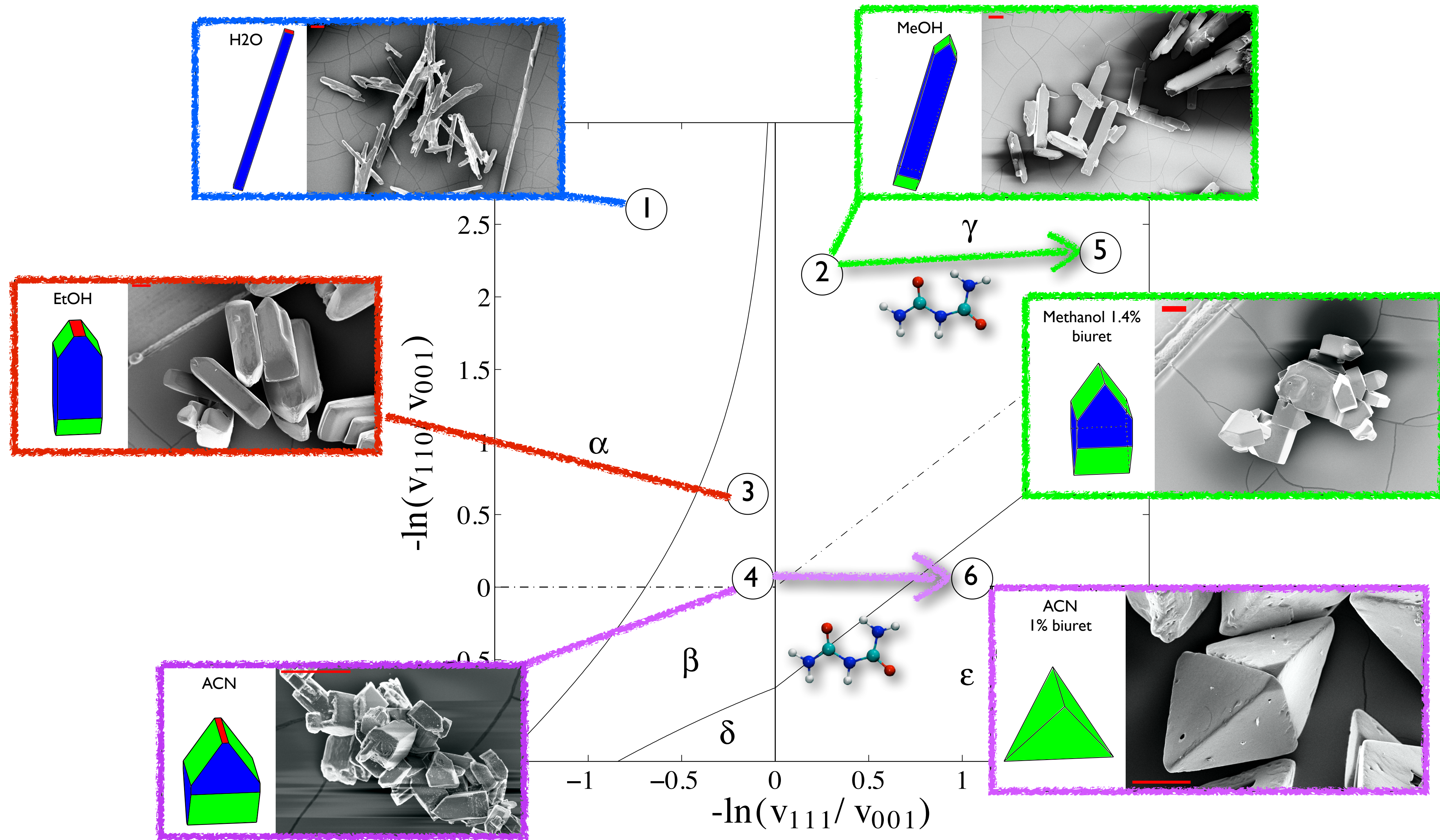


crystal scale  
 $\sim 10-100 \mu\text{m}$

molecular scale  
 $\sim 0.1-10 \text{ nm}$



# Habits Prediction

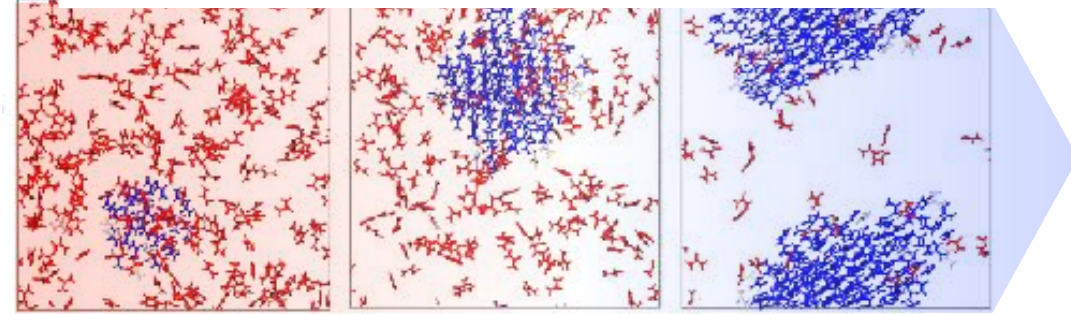




# Urea nucleation and growth

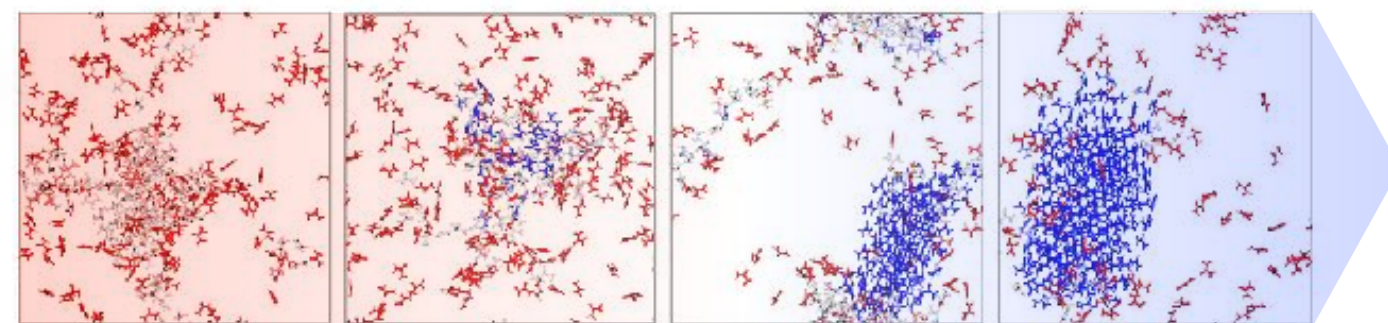
Solvent affects the **nucleation mechanism**

MeOH, EtOH

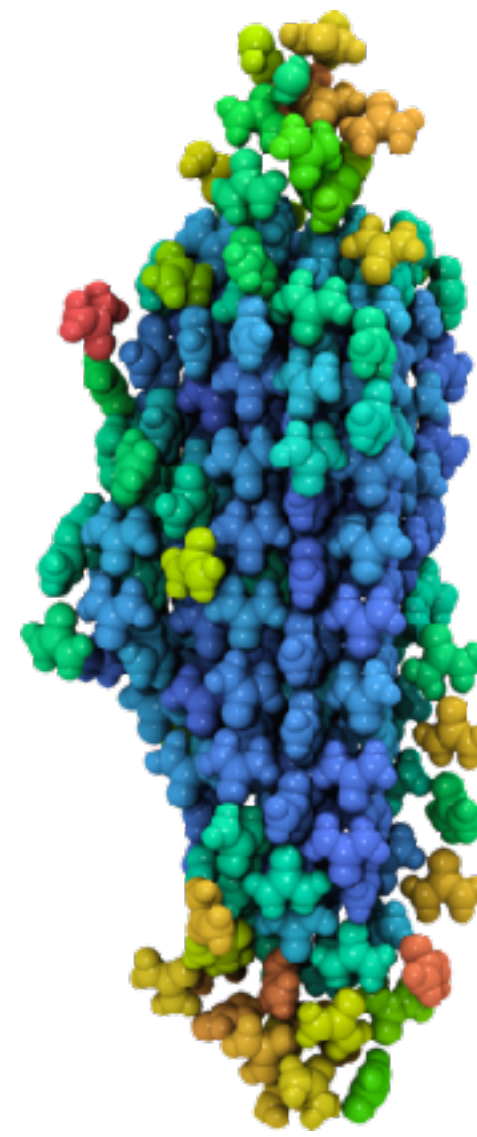
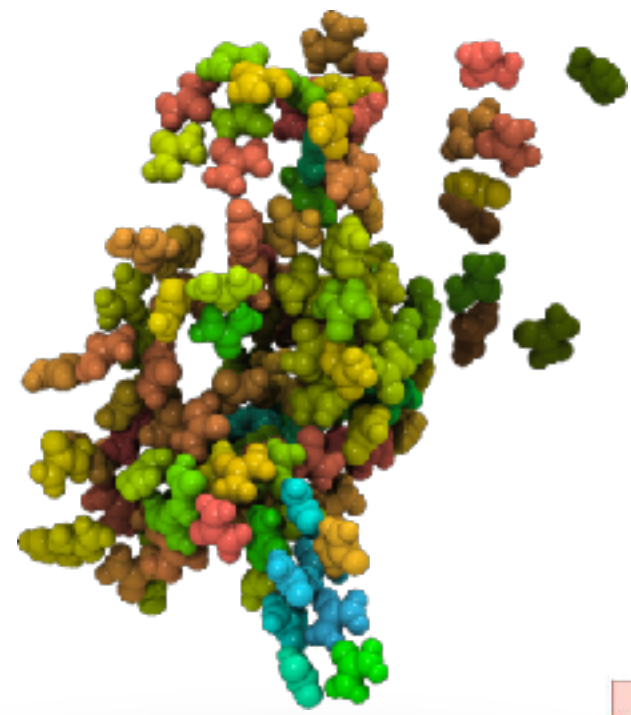


single-step

two-step

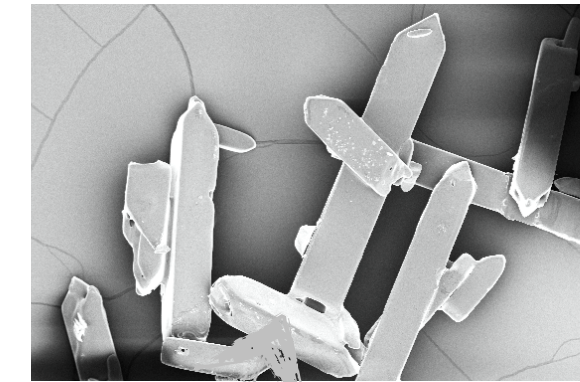


water, ACN

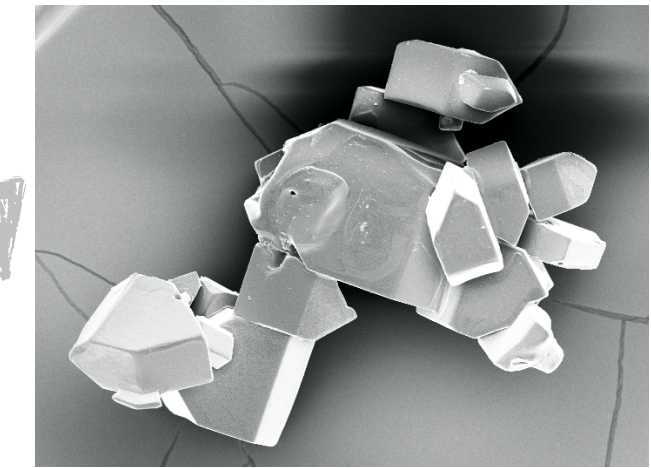


Solvents and additives **anisotropically modulate growth rates** on different crystal faces

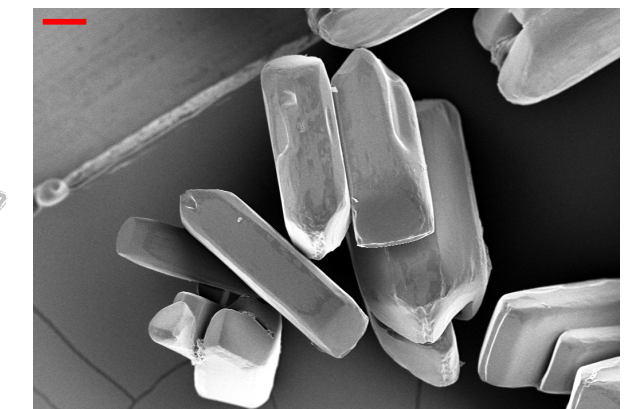
MeOH



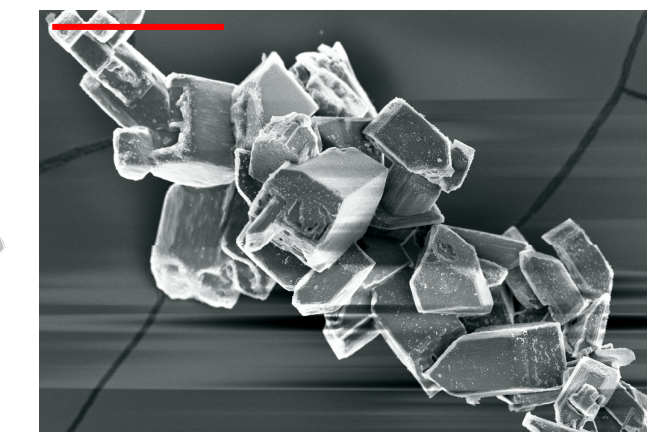
MeOH+biuret



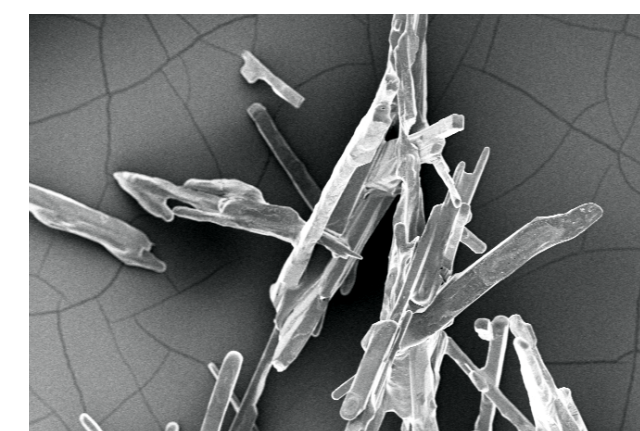
EtOH



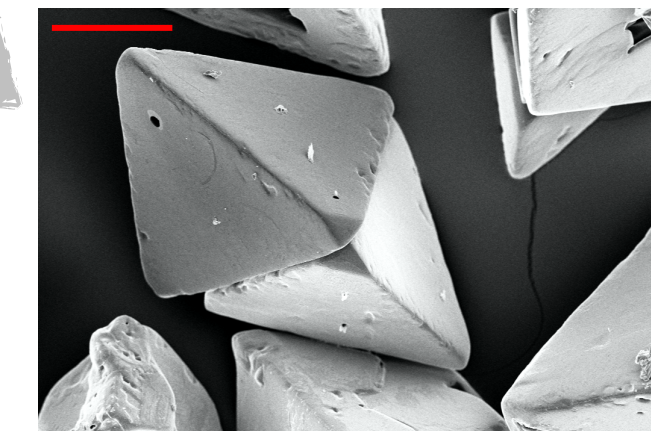
ACN



water



ACN + biuret





# Pros & Cons

- Rich insight into nucleation/phase transition mechanisms
- Identification of competing forms in the early stages of nucleation
- Solvent effects on growth dynamics are implicitly accounted for
  
- Need for ad-hoc identification/training of order parameters/collective variables
- Very few examples on flexible molecules

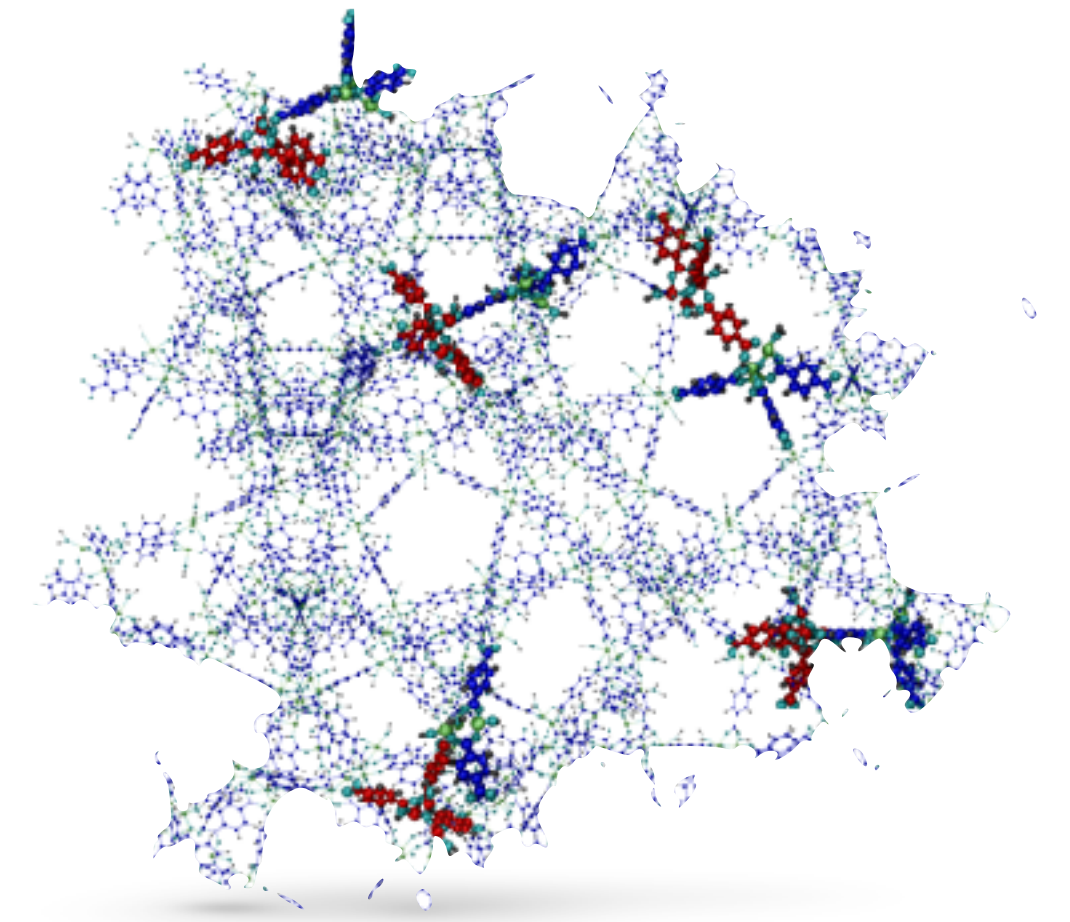
*[Gobbo, Bellucci, Tribello, Ciccotti, Trout, JCTC 2018]*



# Conformational diversity and self assembly

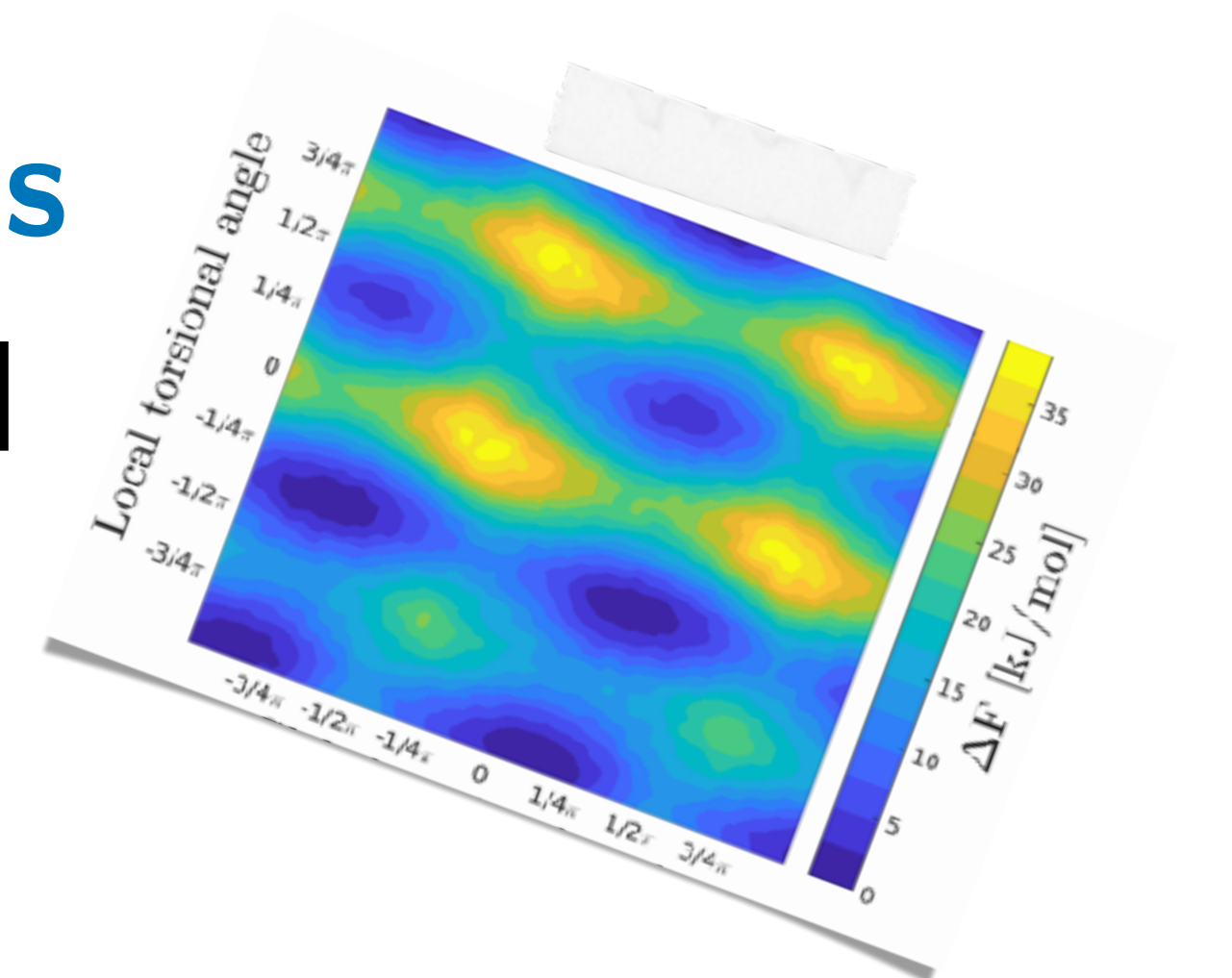
## MOF early stages of nucleation:

Order is determined by the interplay between conformational diversity and solvent composition



## Conformational complexity at Ibuprofen interfaces

Interplay between conformation, solvent structure and growth

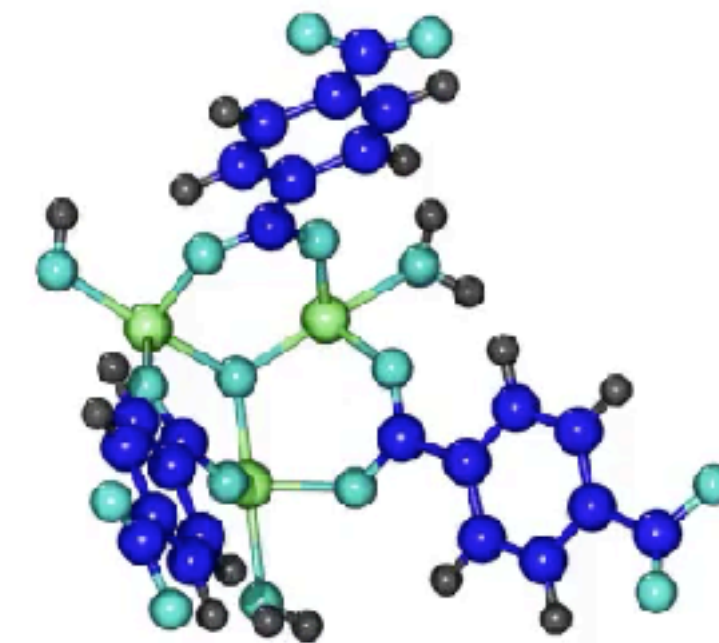




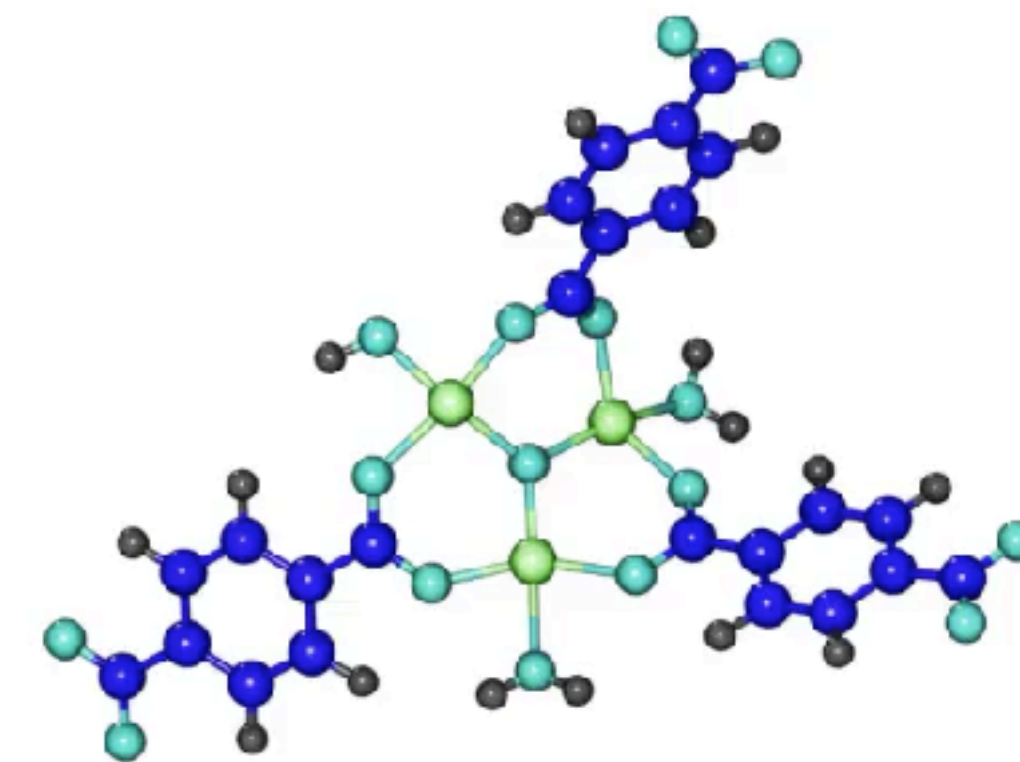
# MIL101-Cr Early stages of Self-Assembly

- Three isomers of the **half Secondary Building Unit** (SBU) of MIL-101 (Cr).
- Nucleation follows rapidly the formation of these intermediates.
- Question: What is the impact of the solution composition on the **formation of SBUs**?

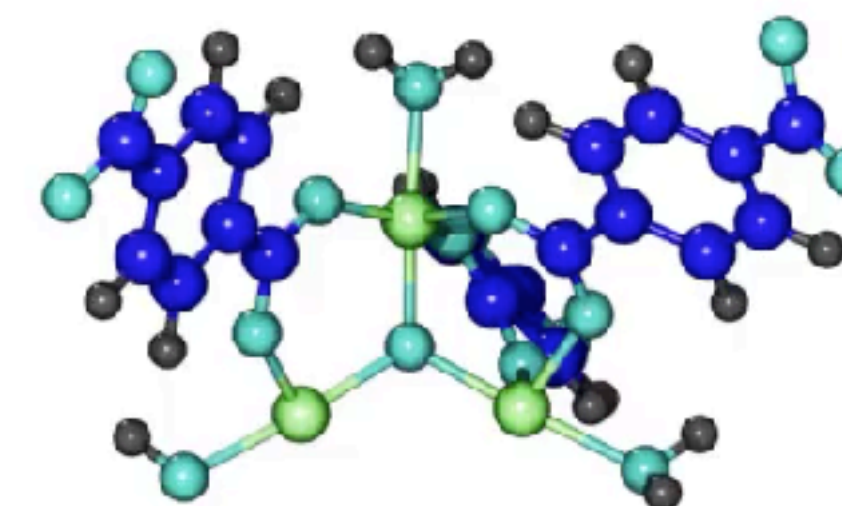
**MLA**



**MLB**



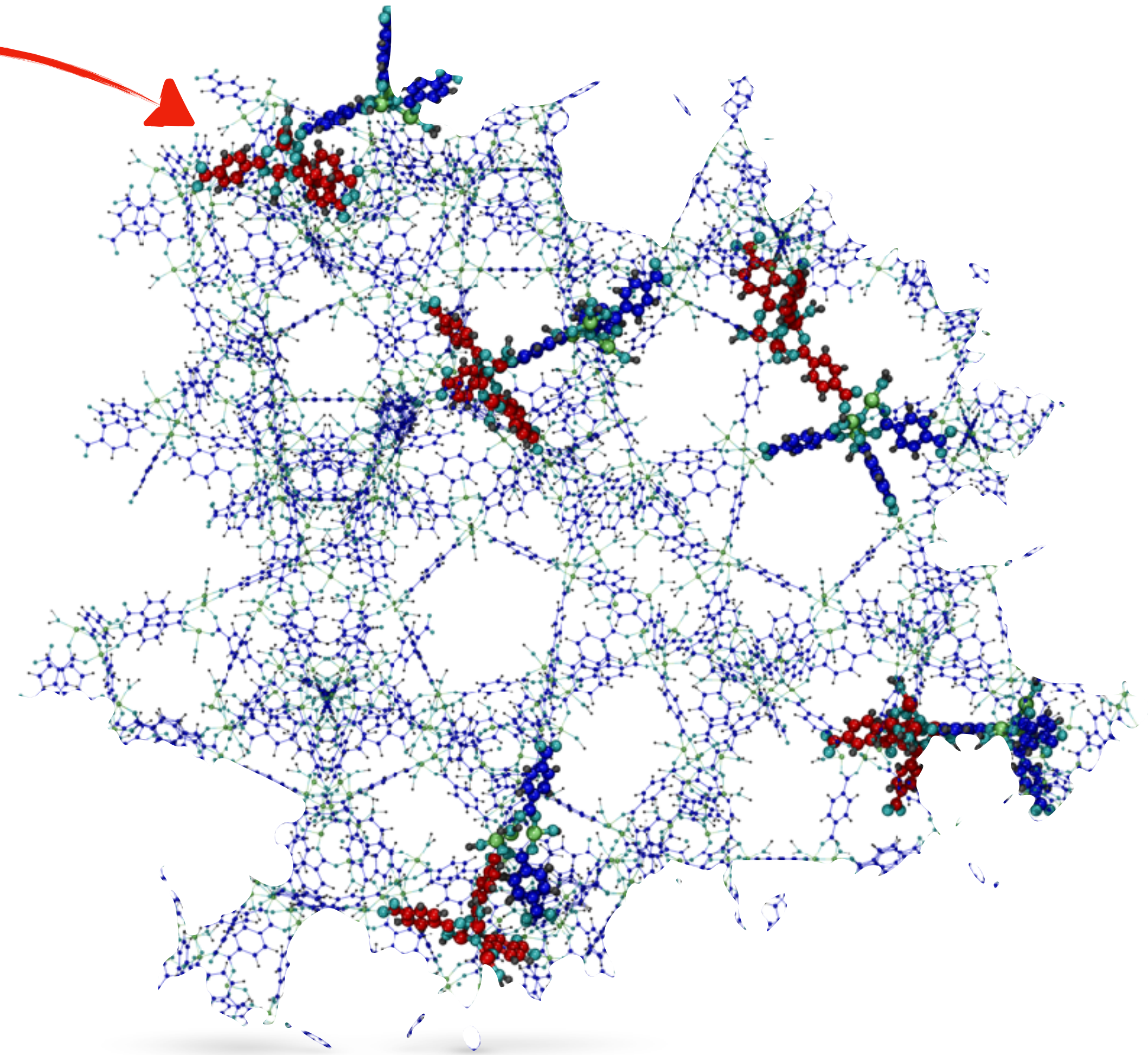
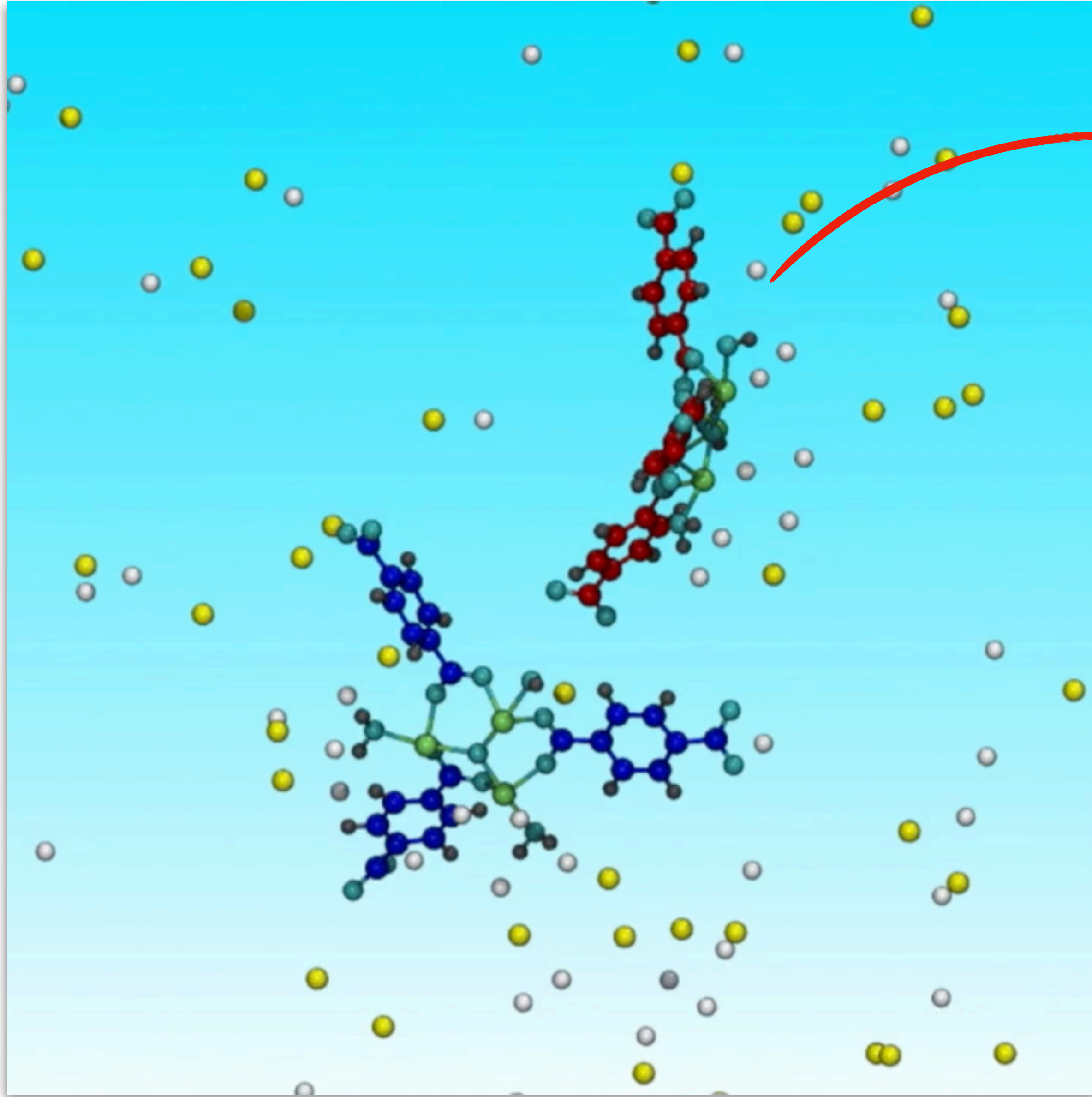
**MLC**



Color code: Cr – lime, C – blue, O – cyan, H – grey.



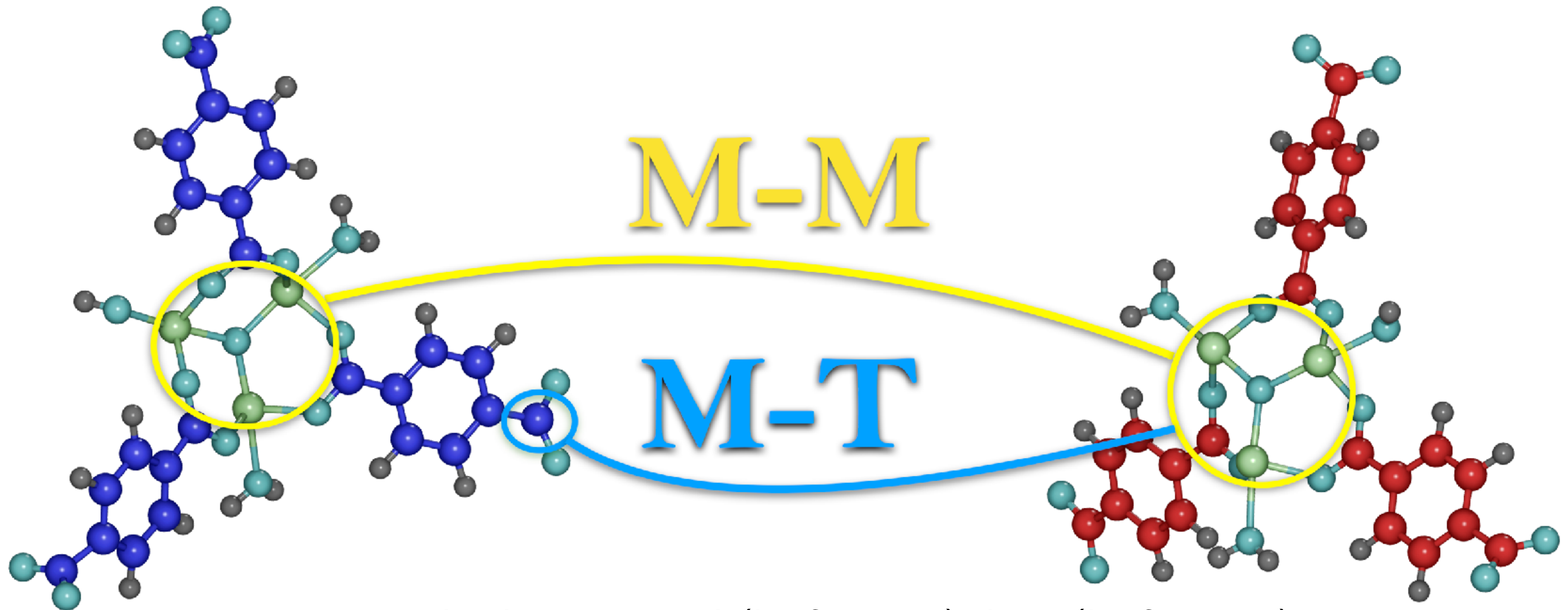
# SBUs assembly from half-SBUs





# Representing the configuration space of SBUs

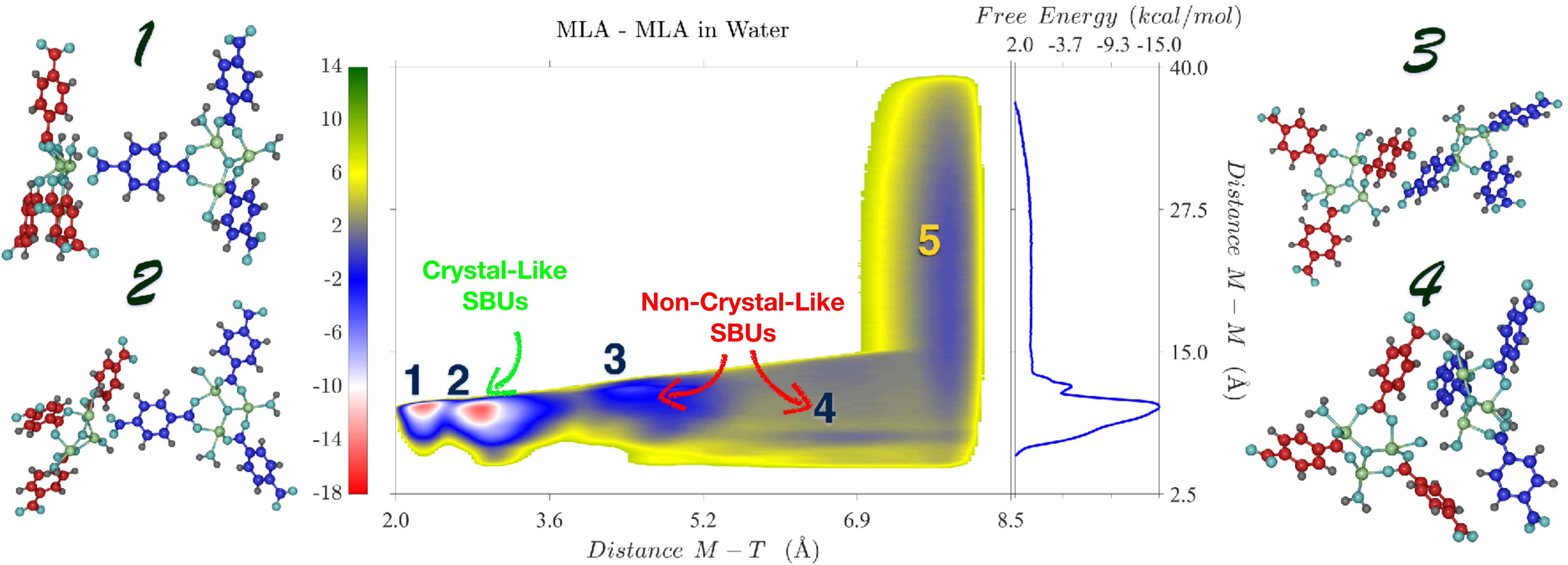
- **M-T**: smallest distance between Cr of the metal centre (M) and terminal C of any of the terephthalate linkers (T).
- **M-M**: smallest distance between Cr of the two metal centers (M).



Color code change: C red (half-SBU 1), blue (half-SBU 2)



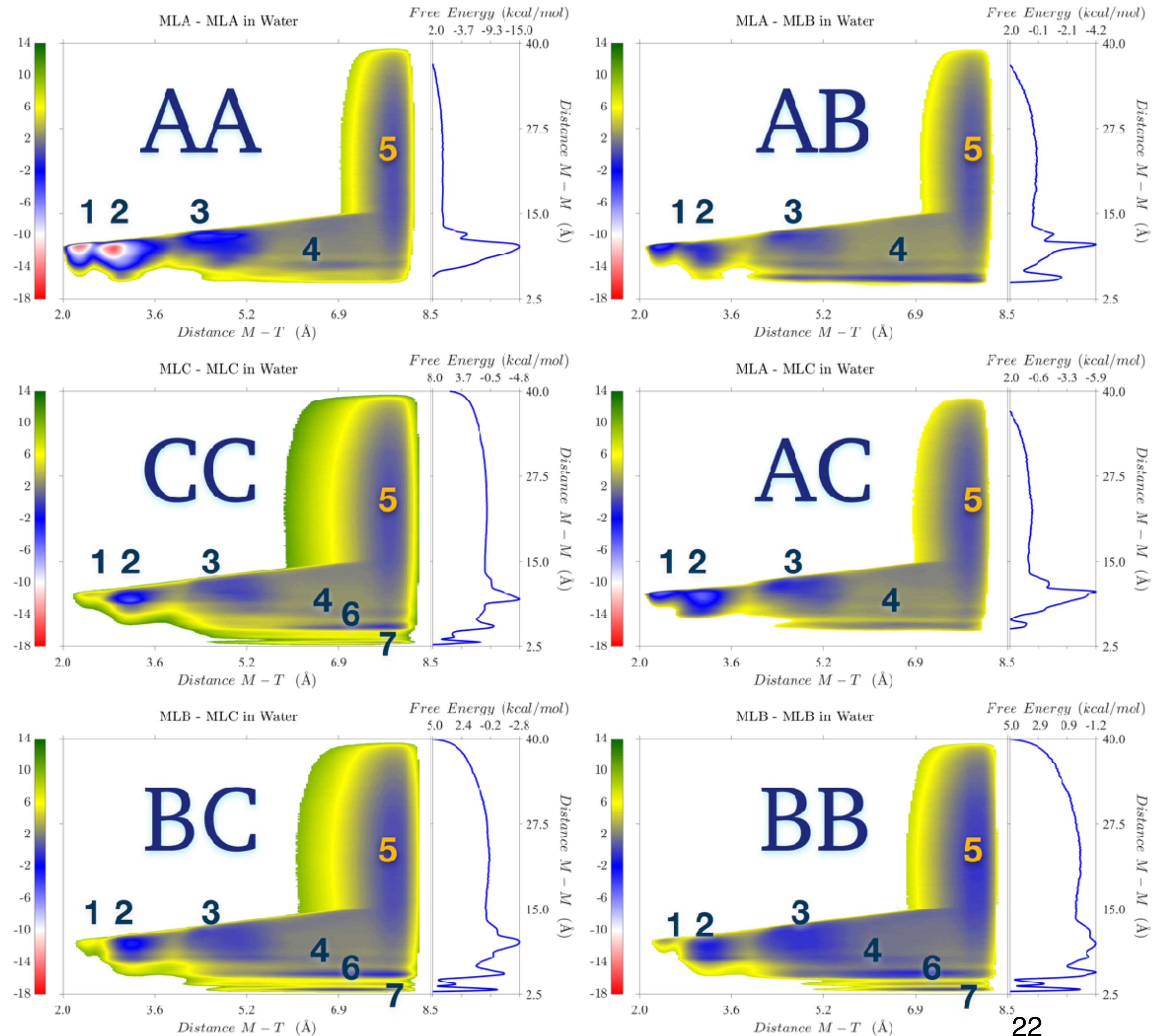
# A typical dimerization FES





# FES: SBUs in water

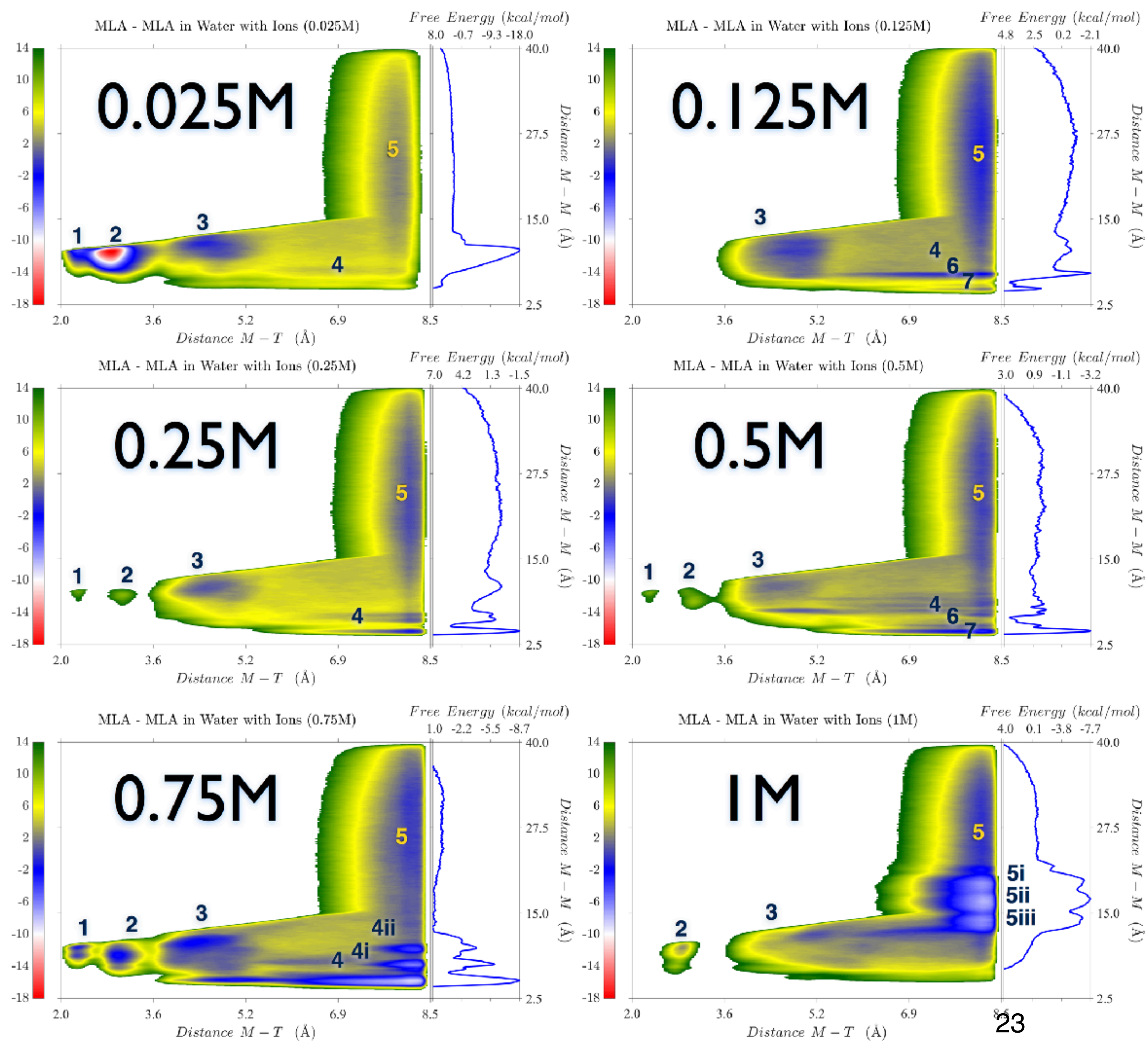
- All possible couples of half-SBUs are simulated
- AA forms the most stable SBU
- BB, BC, CC significantly less likely to form stable SBUs.





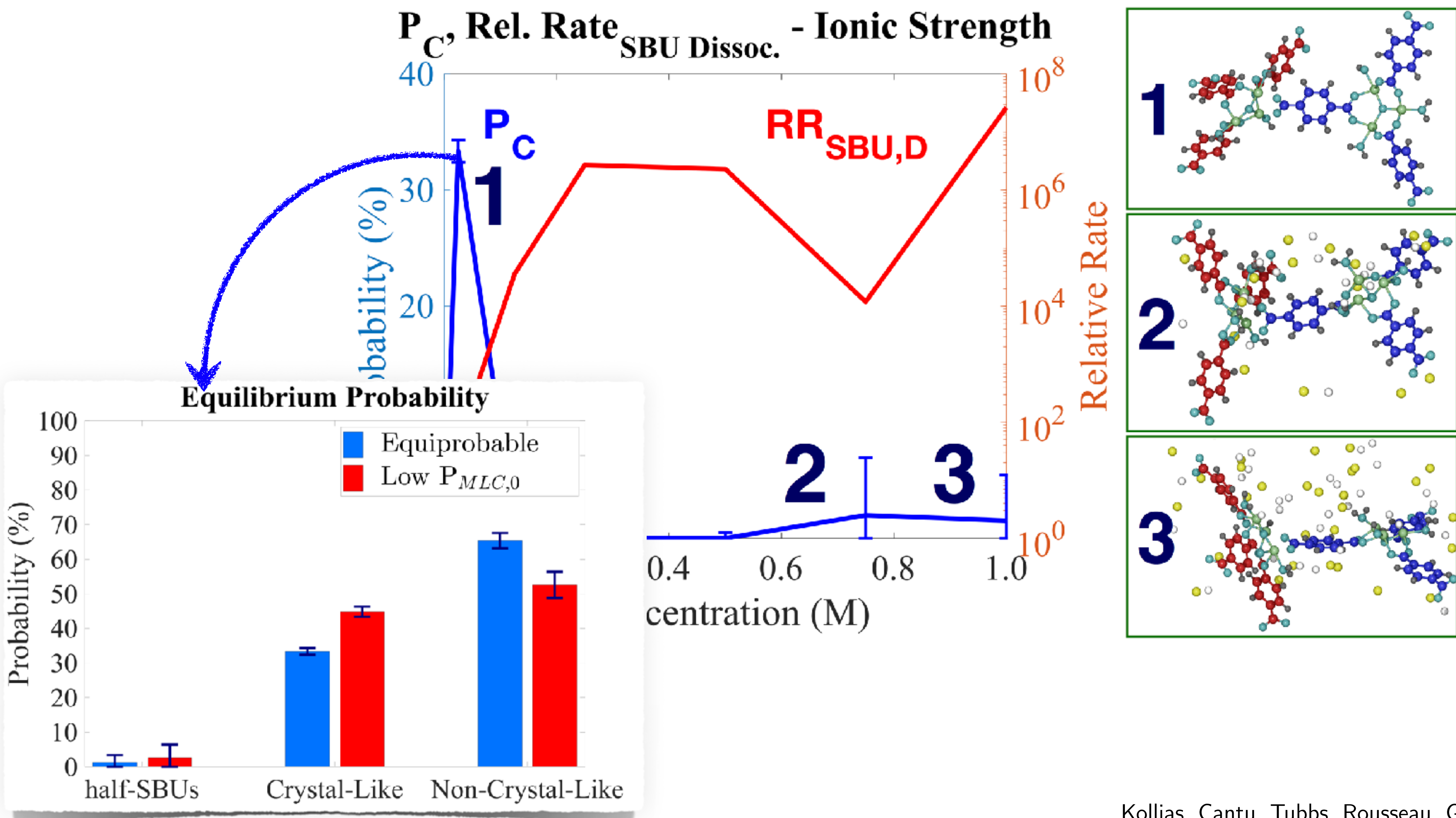
# Introducing ions (AA)

- Free energy surfaces at increasing ionic strength ( $\text{Na}^+$ ,  $\text{F}^-$  in water).
- Different states dominate as number of ions increases.
- Complexity increases as more M-M interactions emerge.



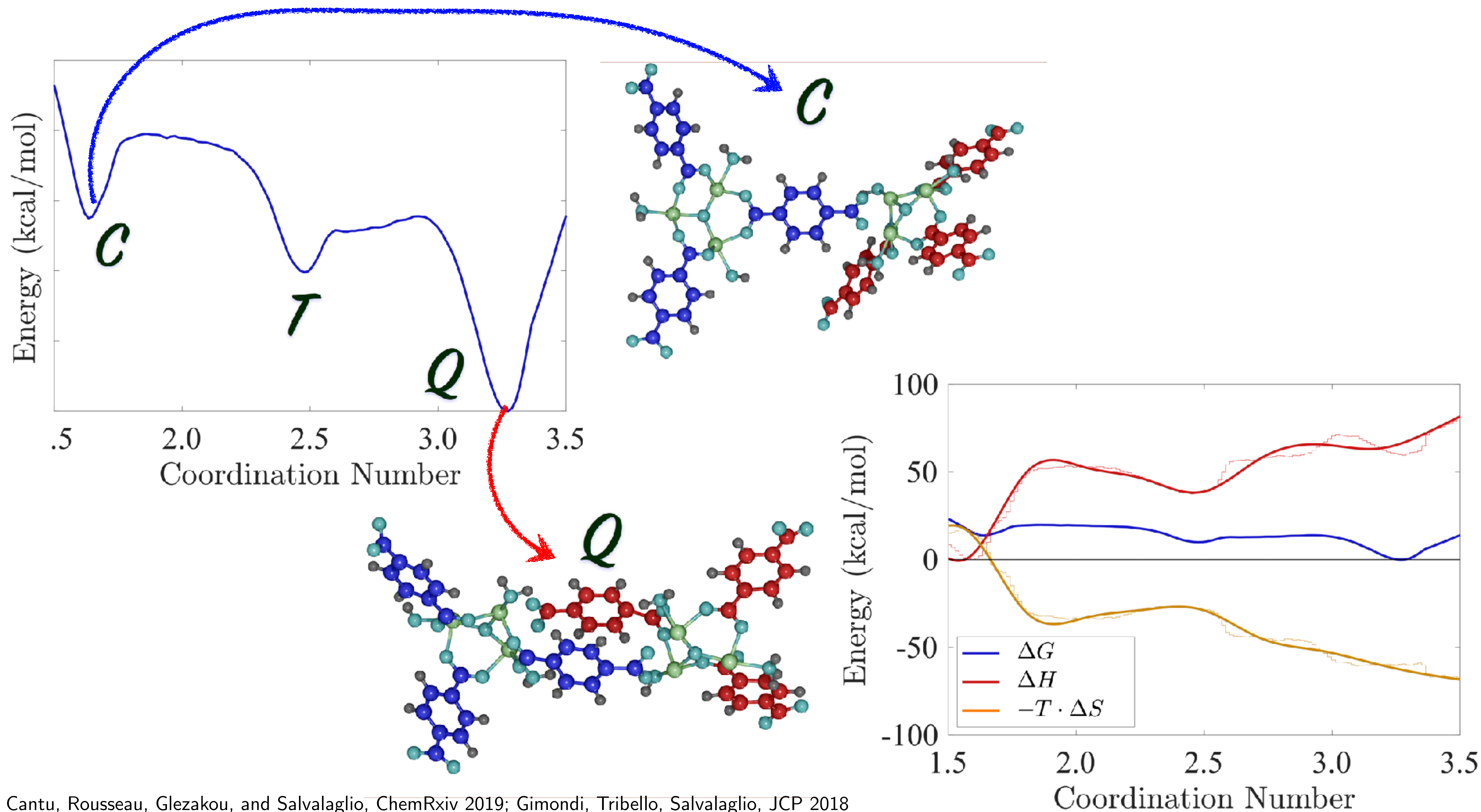


# TOM1: Solution Composition affects the abundance of crystal-like SBUs





# TOM2: Configurational entropy drives the conformational rearrangement of SBUs

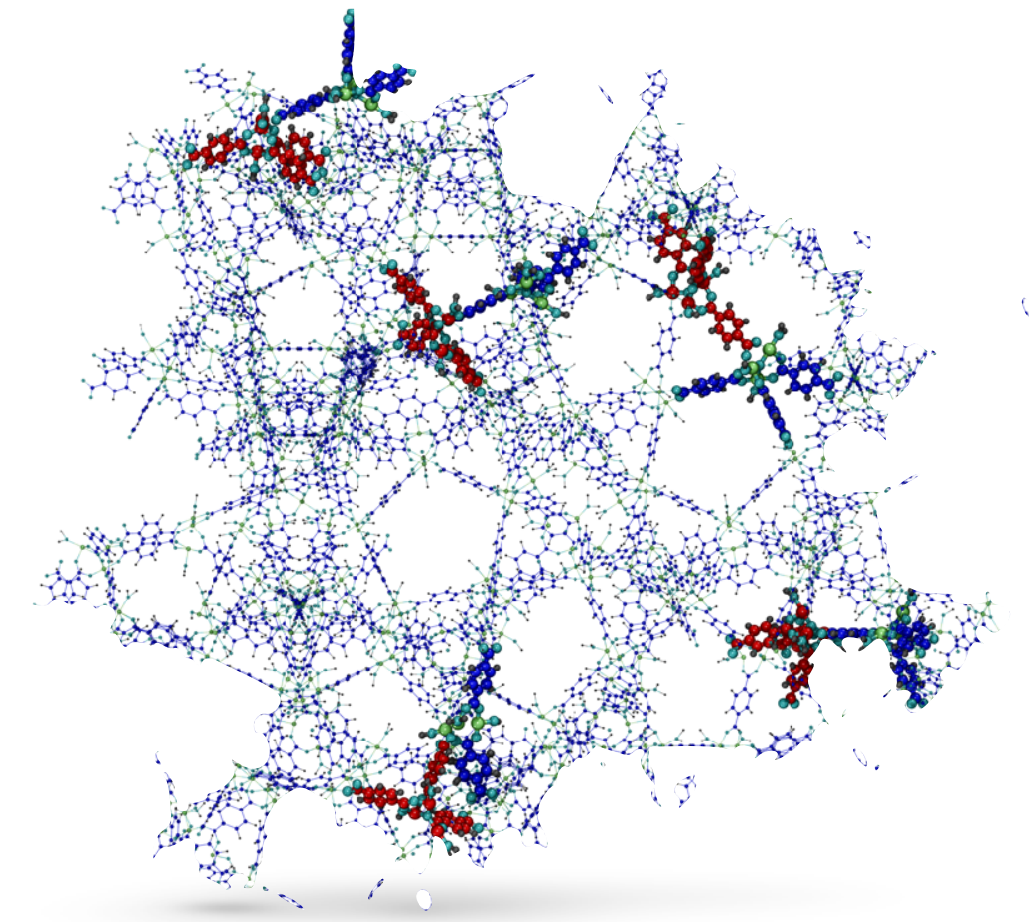




# Conformational diversity and self assembly

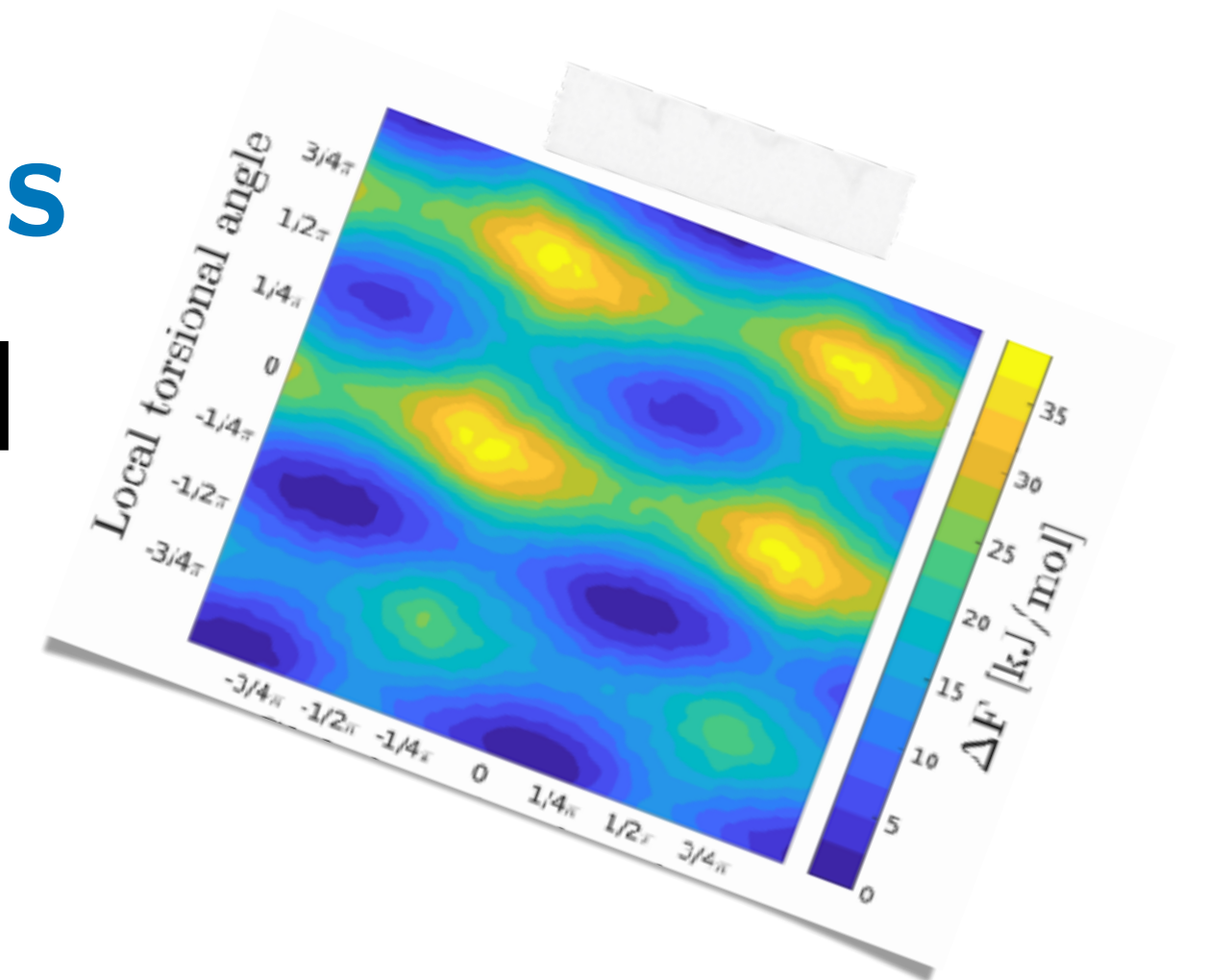
## MOF early stages of nucleation:

Order is determined by the interplay between conformational diversity and solvent composition



## Conformational complexity at Ibuprofen interfaces

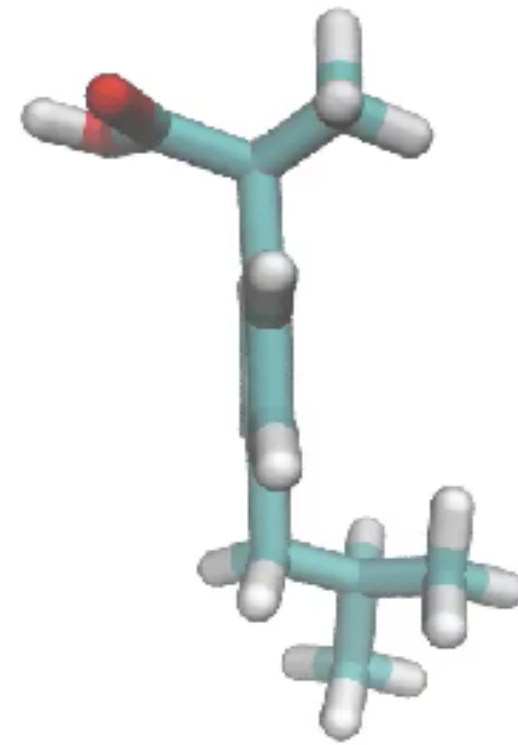
Interplay between conformation, solvent structure and growth



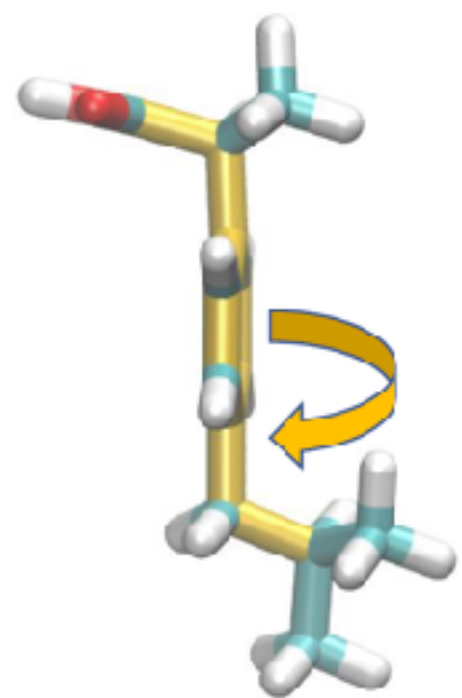


# Ibuprofen

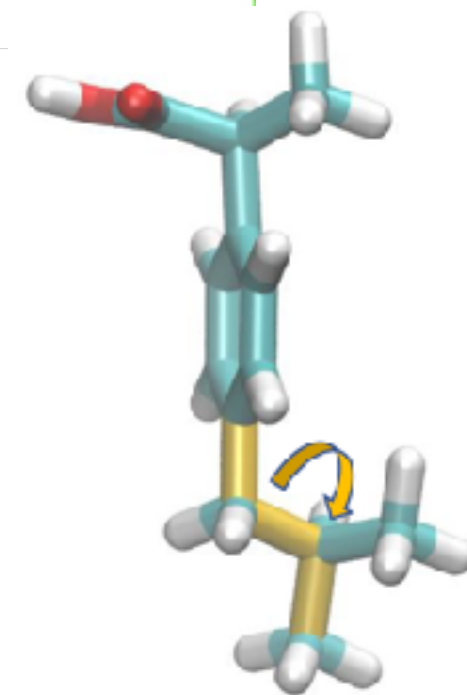
## Molecular configuration and conformational isomerism



Conformational descriptors

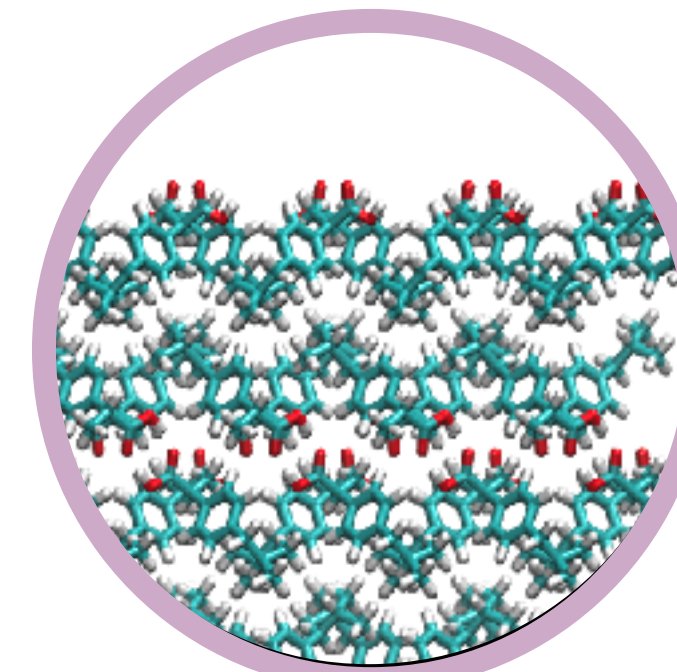


global torsional angle

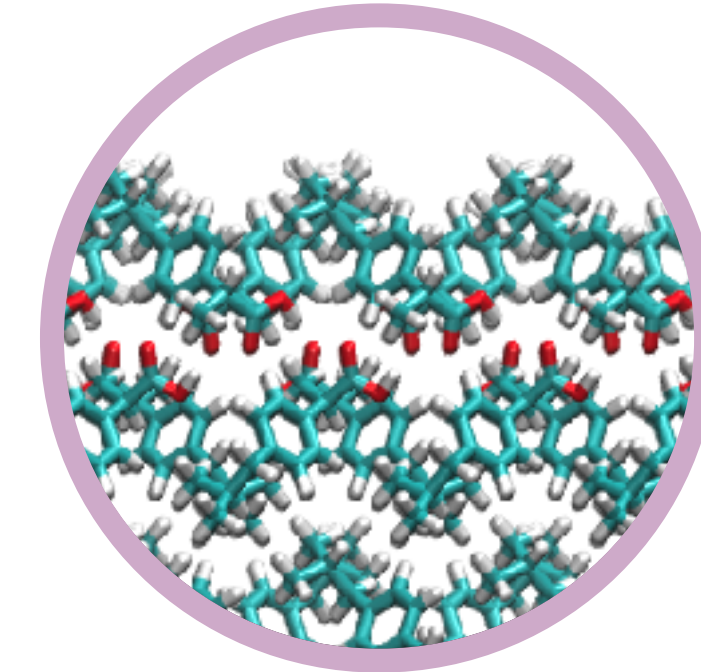


local torsional angle

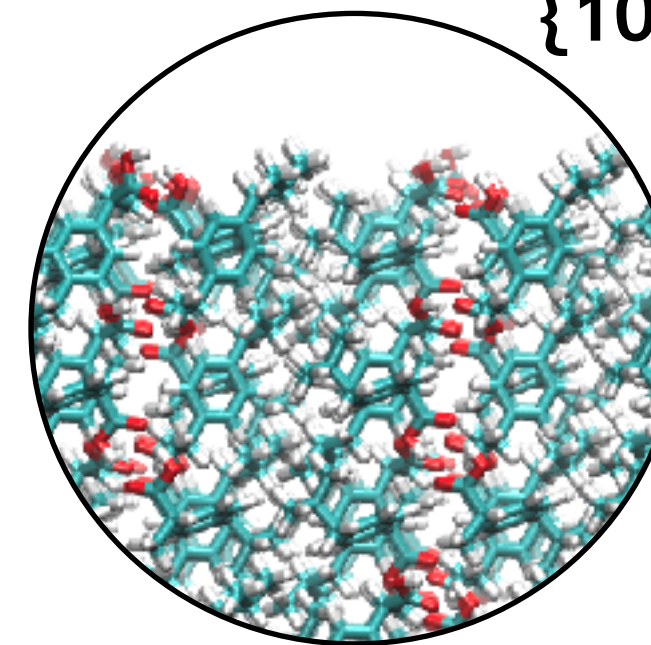
## Morphologically dominant faces BFDH and experimental studies



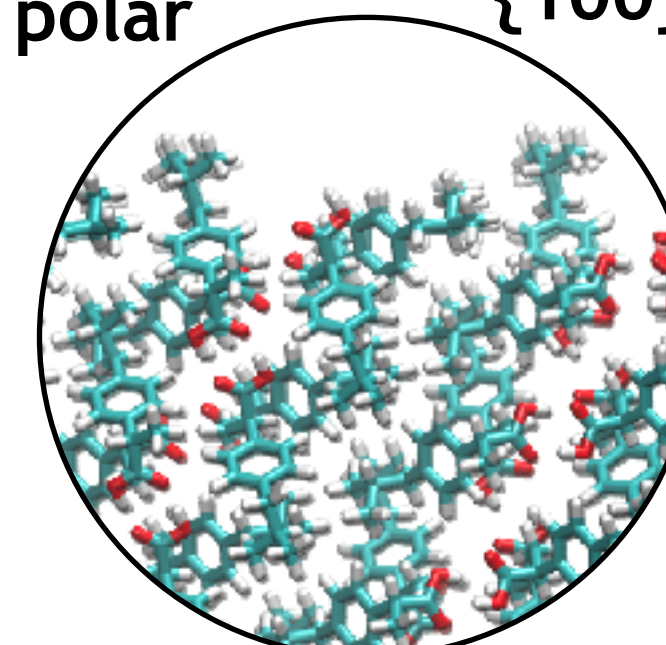
{100} polar



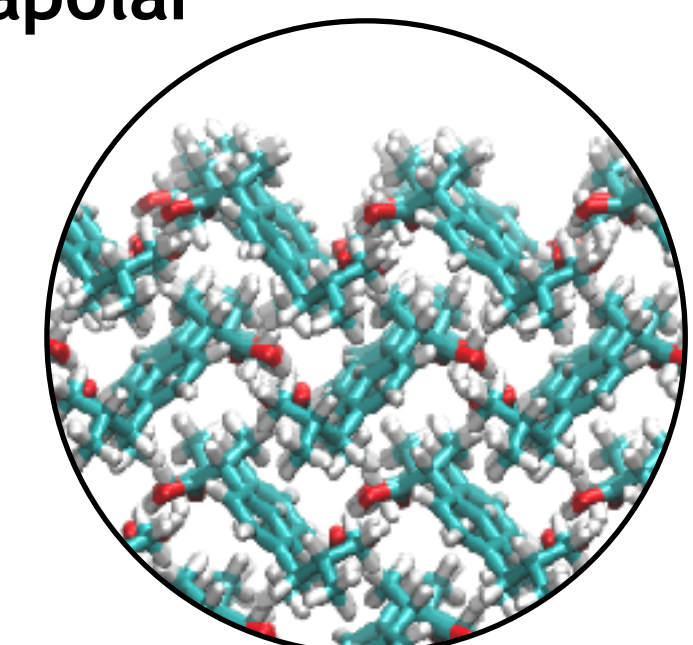
{100} apolar



{011}



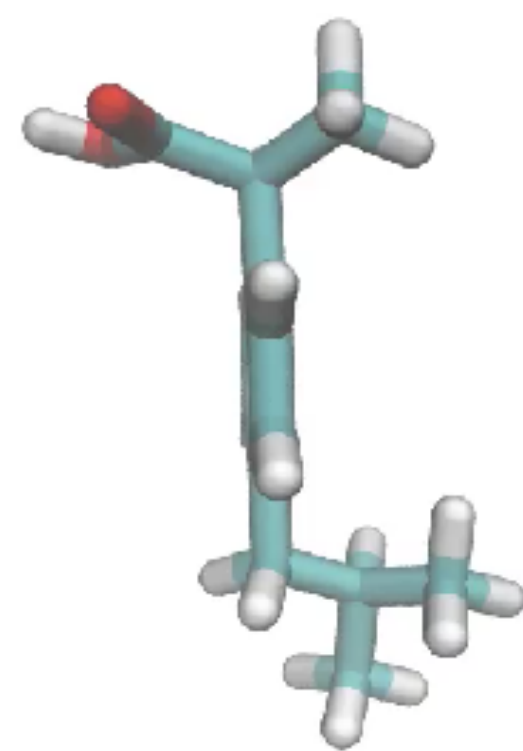
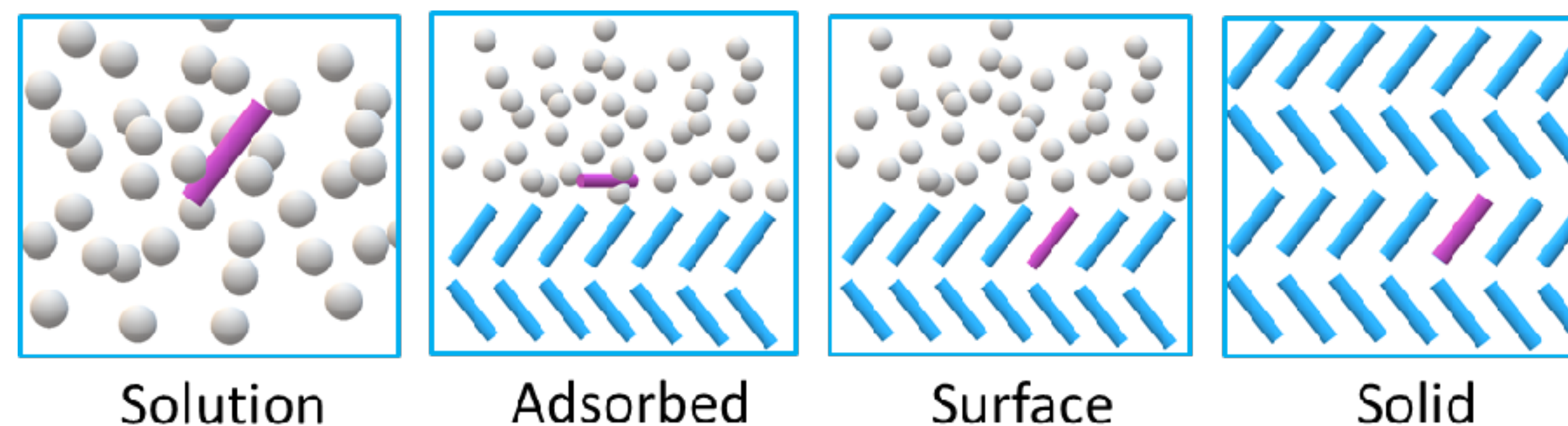
{110}



{002}



# Ibuprofen Conformational Isomerism



**Molecular Dynamics Simulations**

Transition rate and probability



**Markov State Model**

Equilibration time

Mechanism

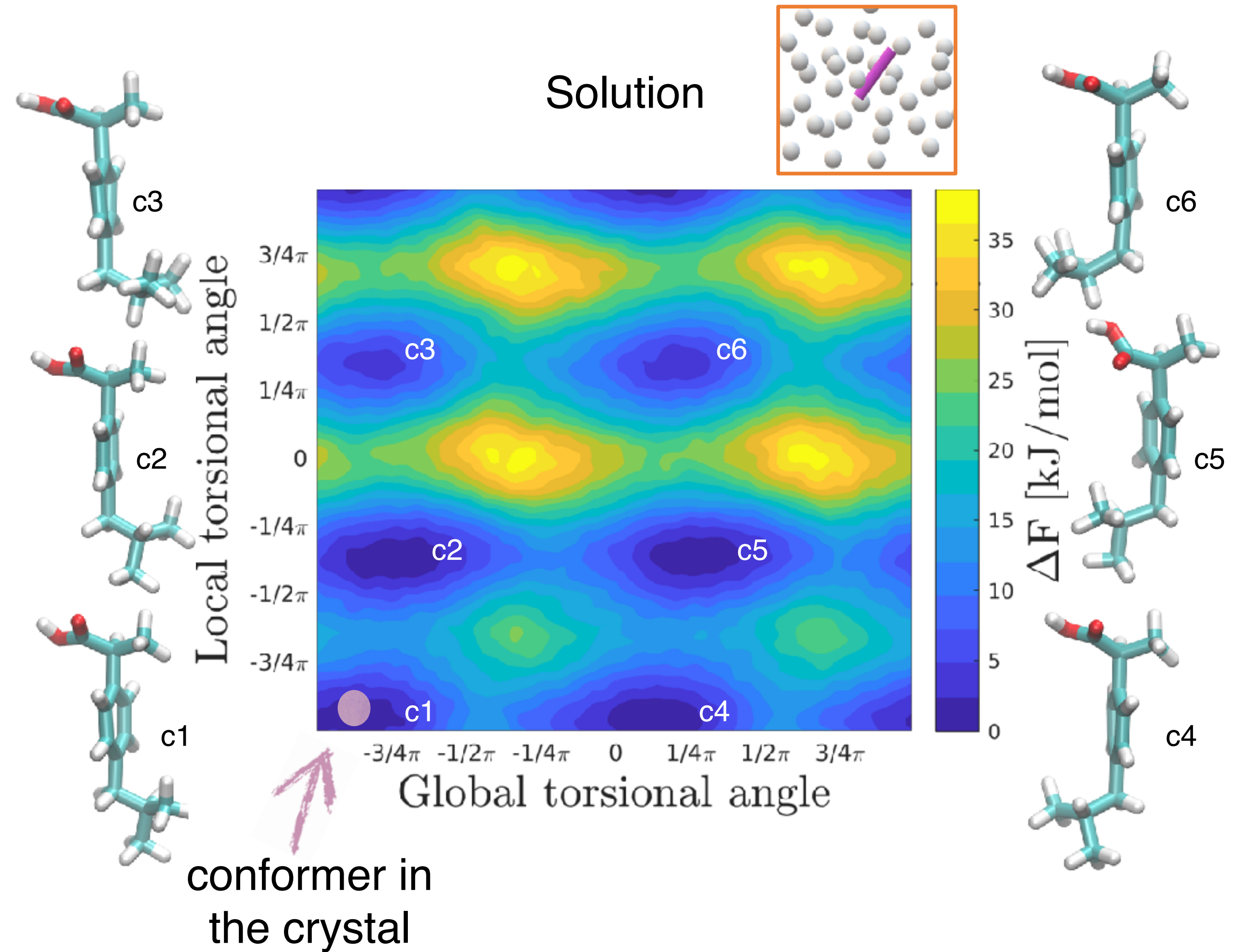
Equilibrium probability distribution

**Metadynamics**

Equilibrium probability distribution



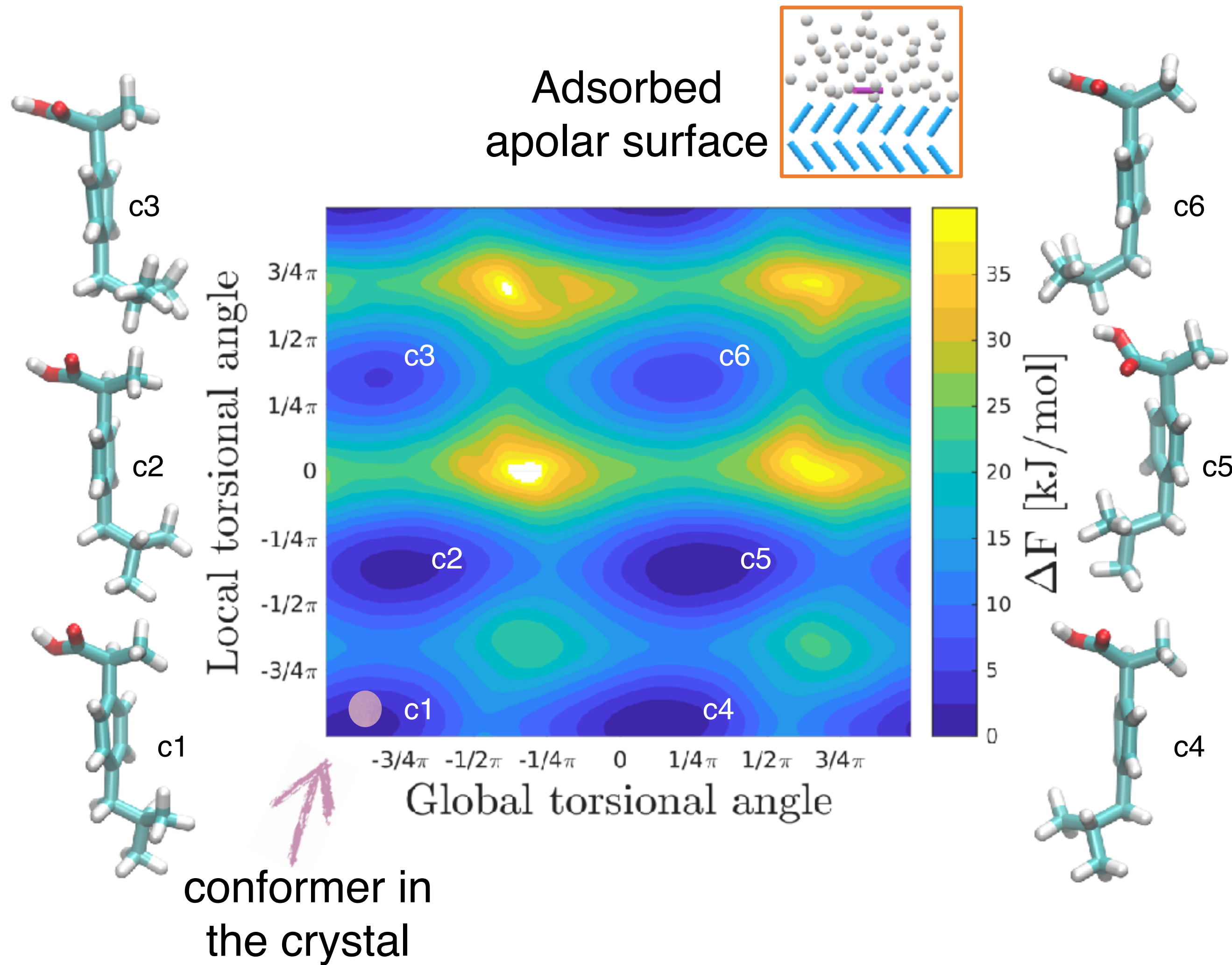
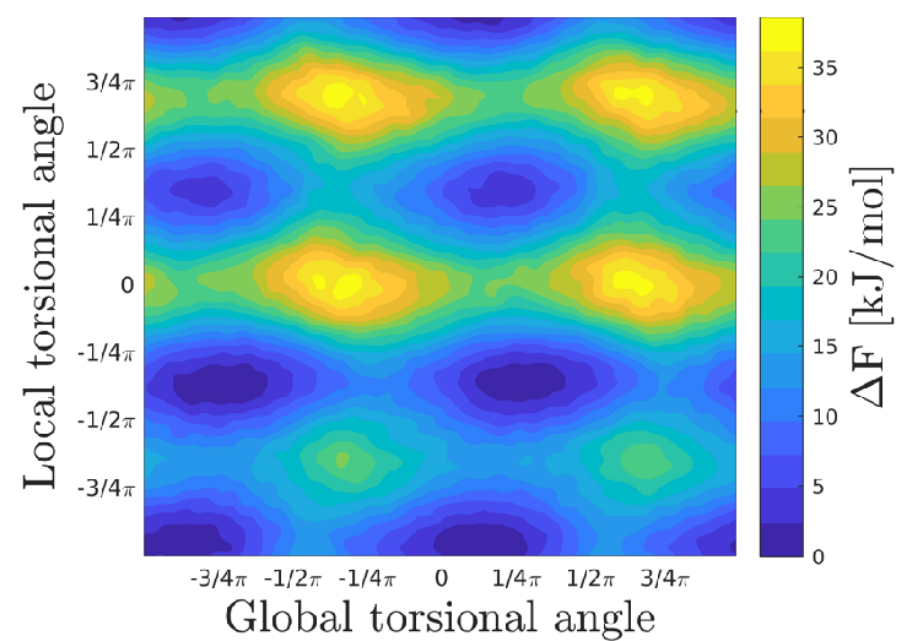
From metadynamics: **conformational free energy landscape**





# From metadynamics: **conformational free energy landscape**

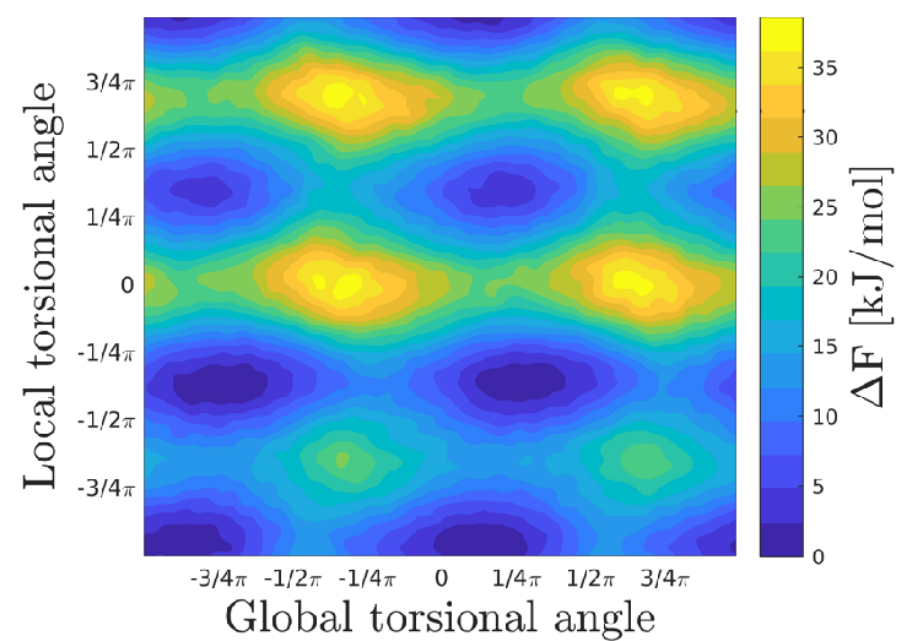
Solution



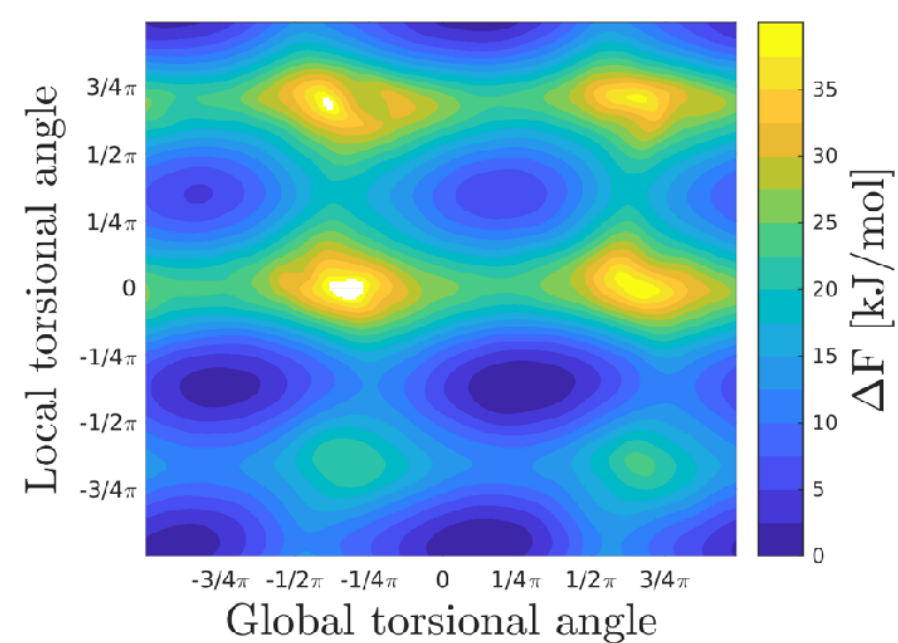


# From metadynamics: **conformational free energy landscape**

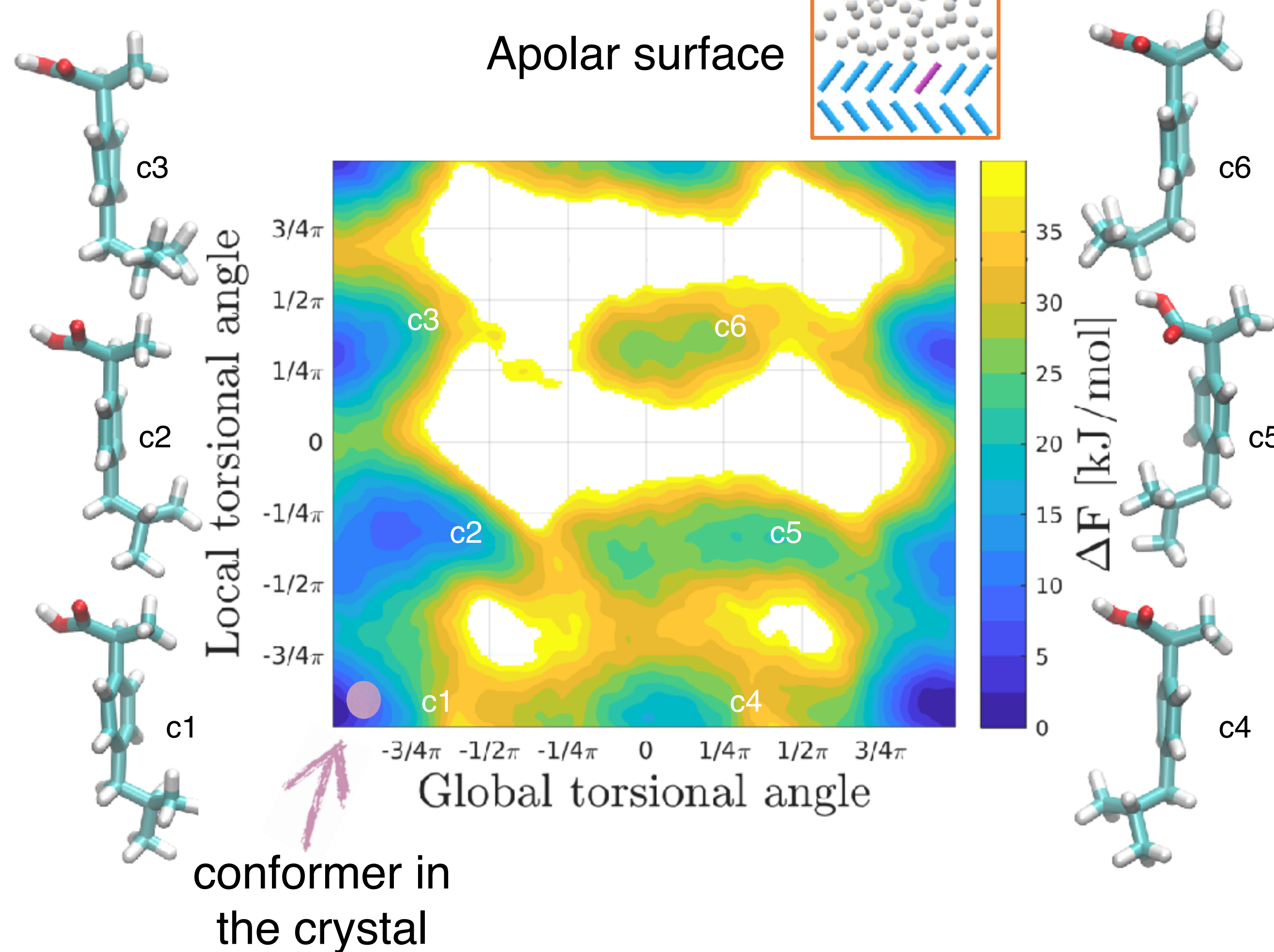
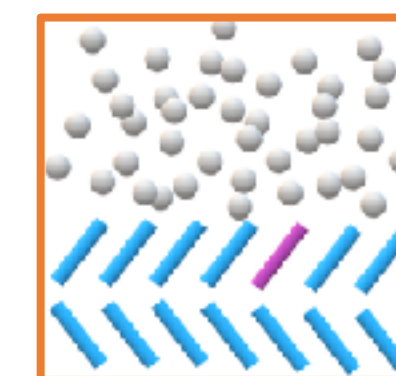
## Solution



## Adsorbed



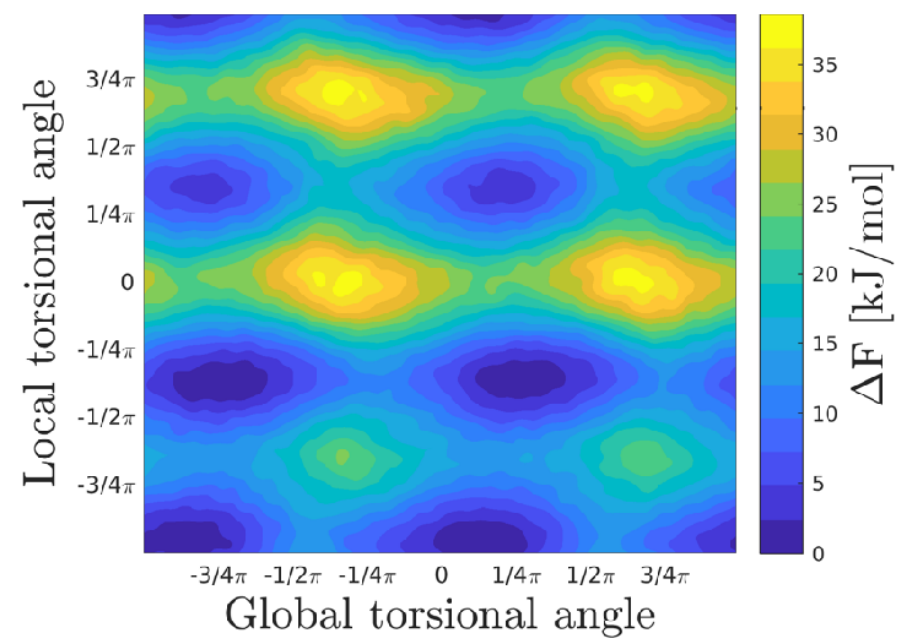
## Apolar surface



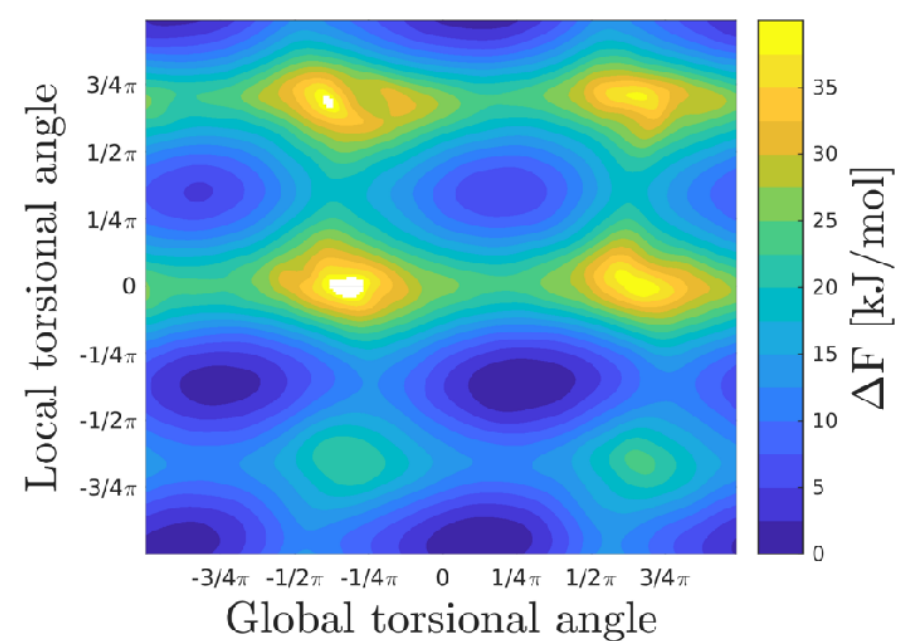


# From metadynamics: **conformational free energy landscape**

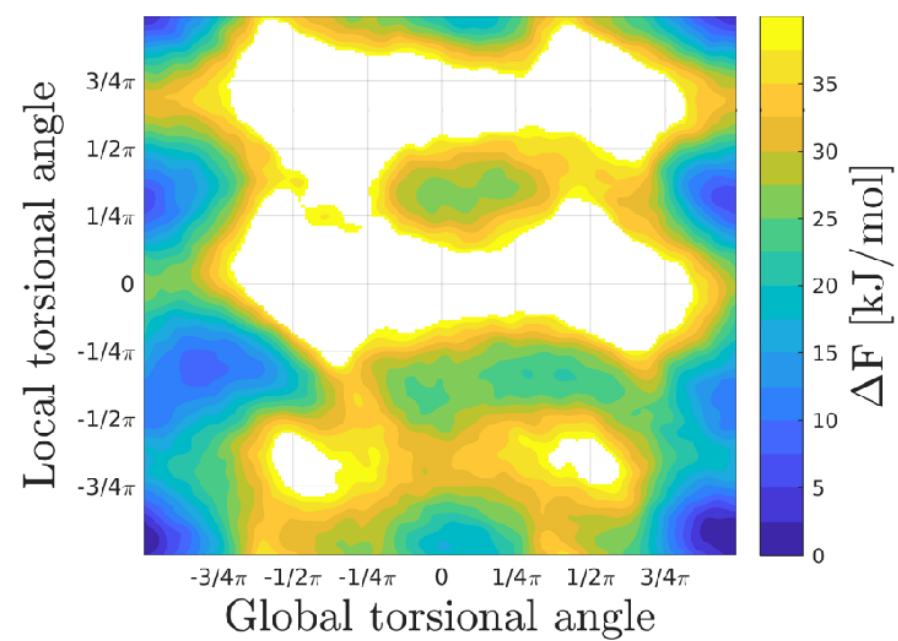
## Solution



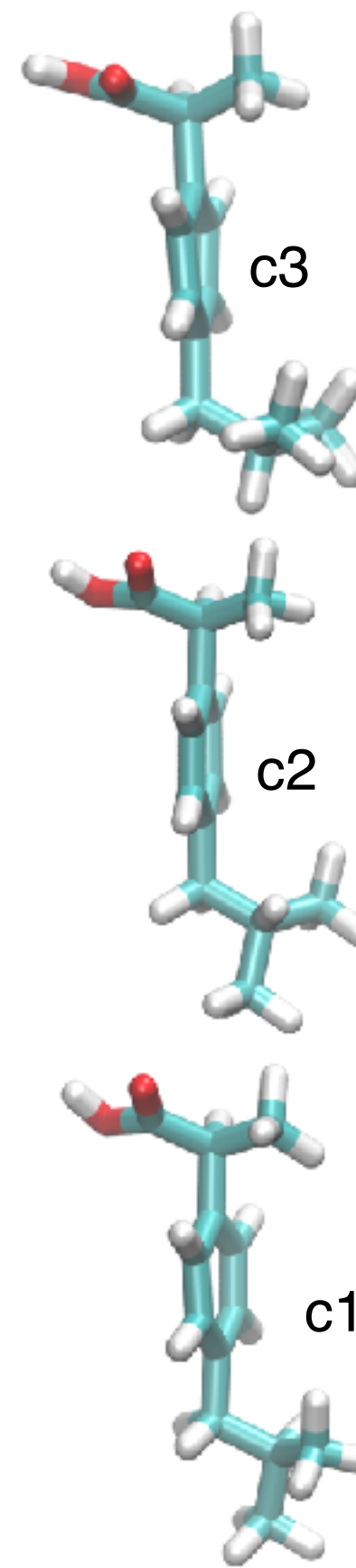
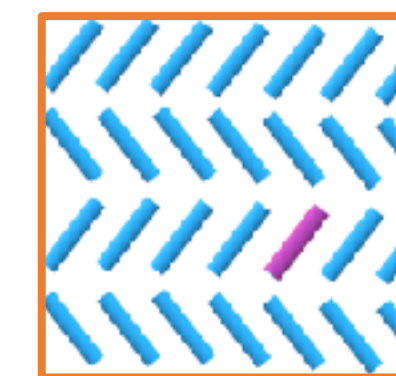
## Adsorbed



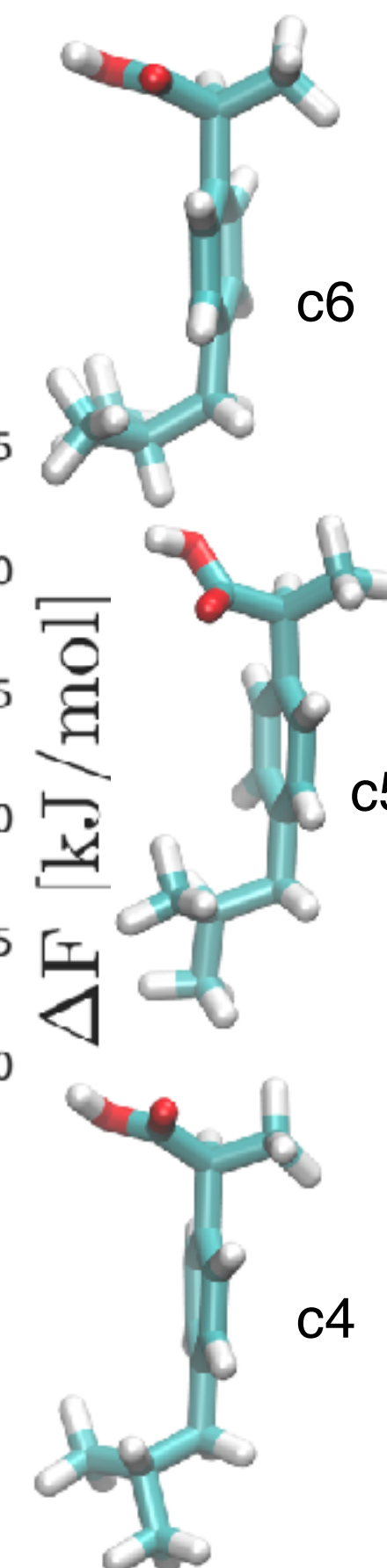
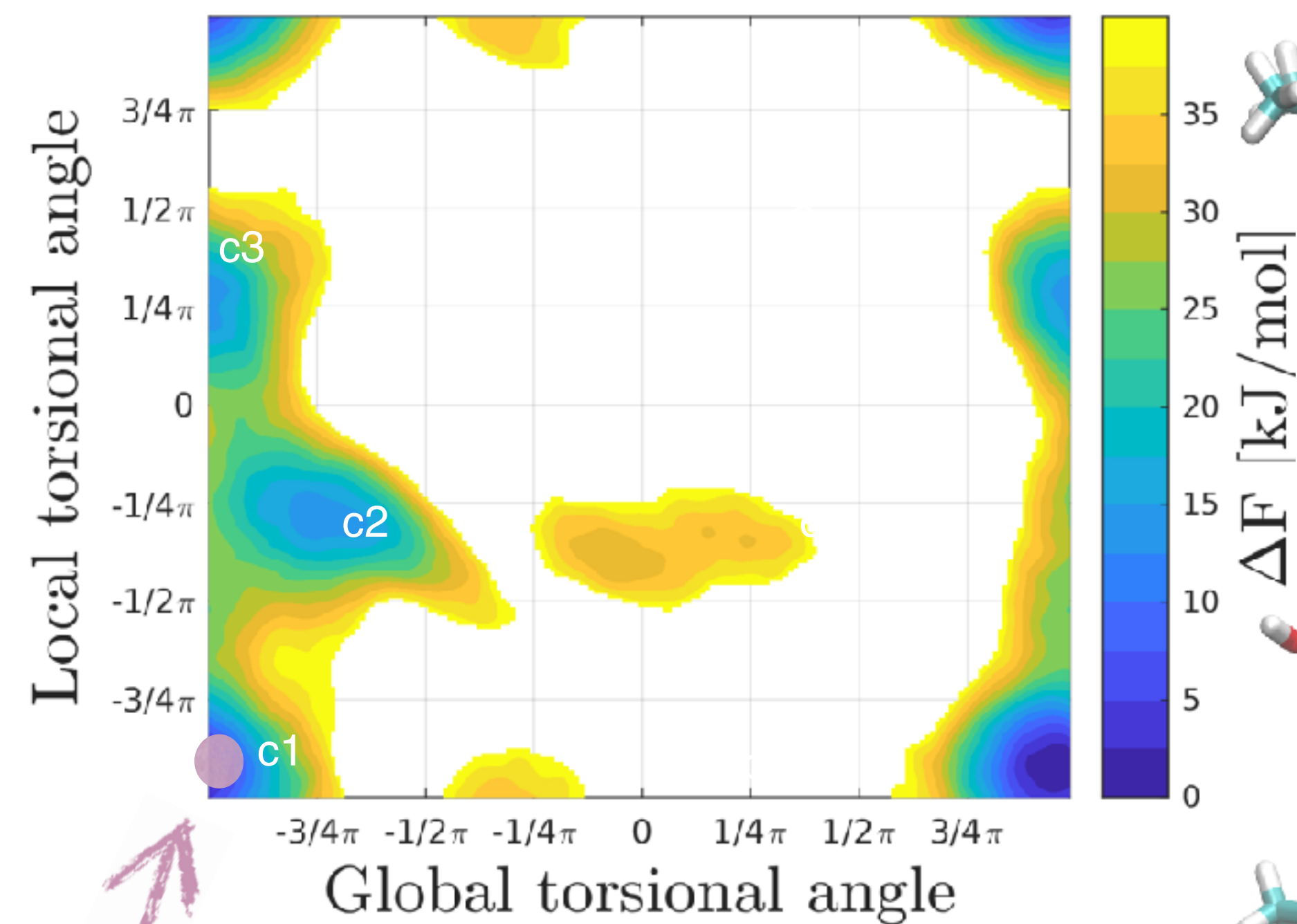
## Surface



## Solid

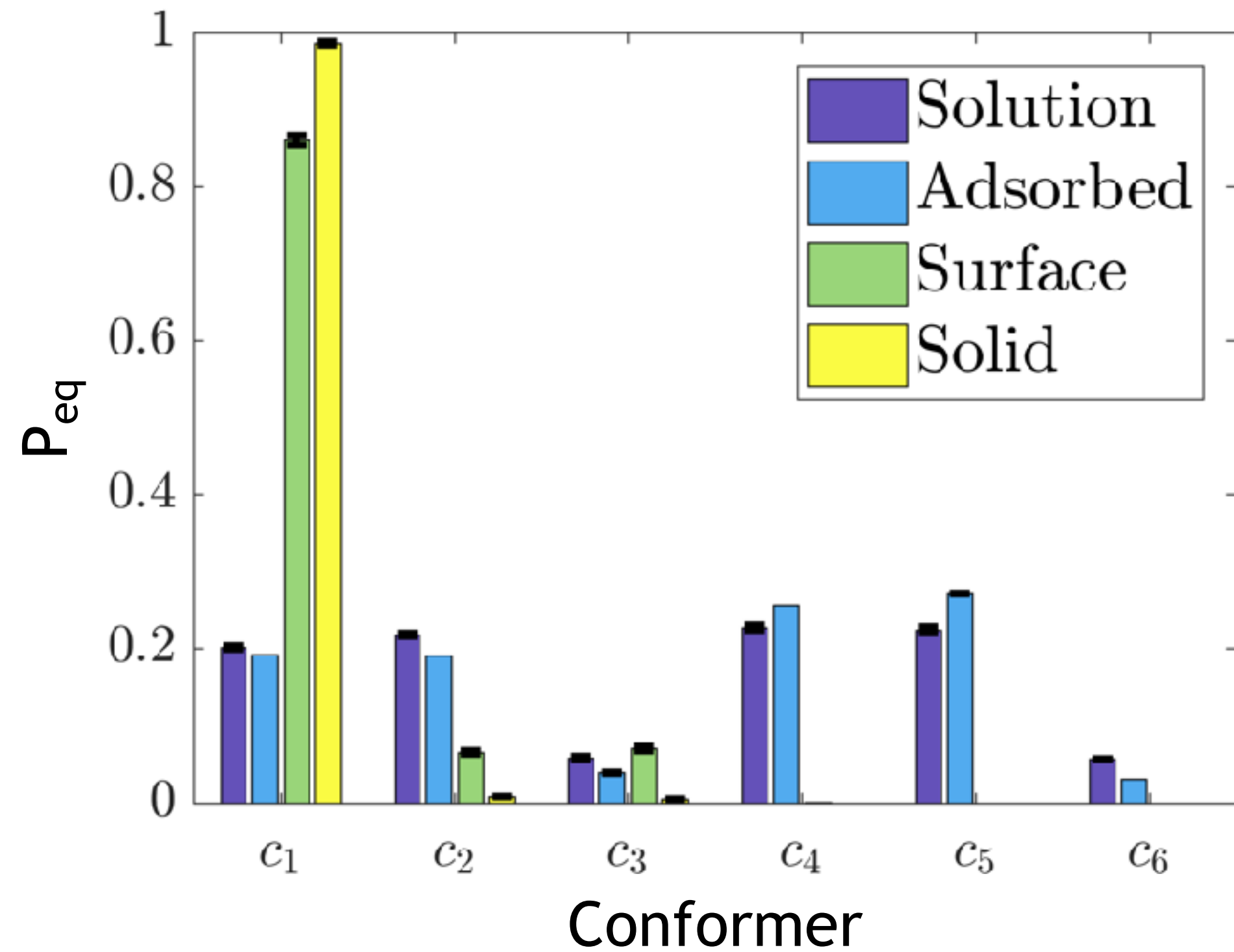


conformer in  
the crystal

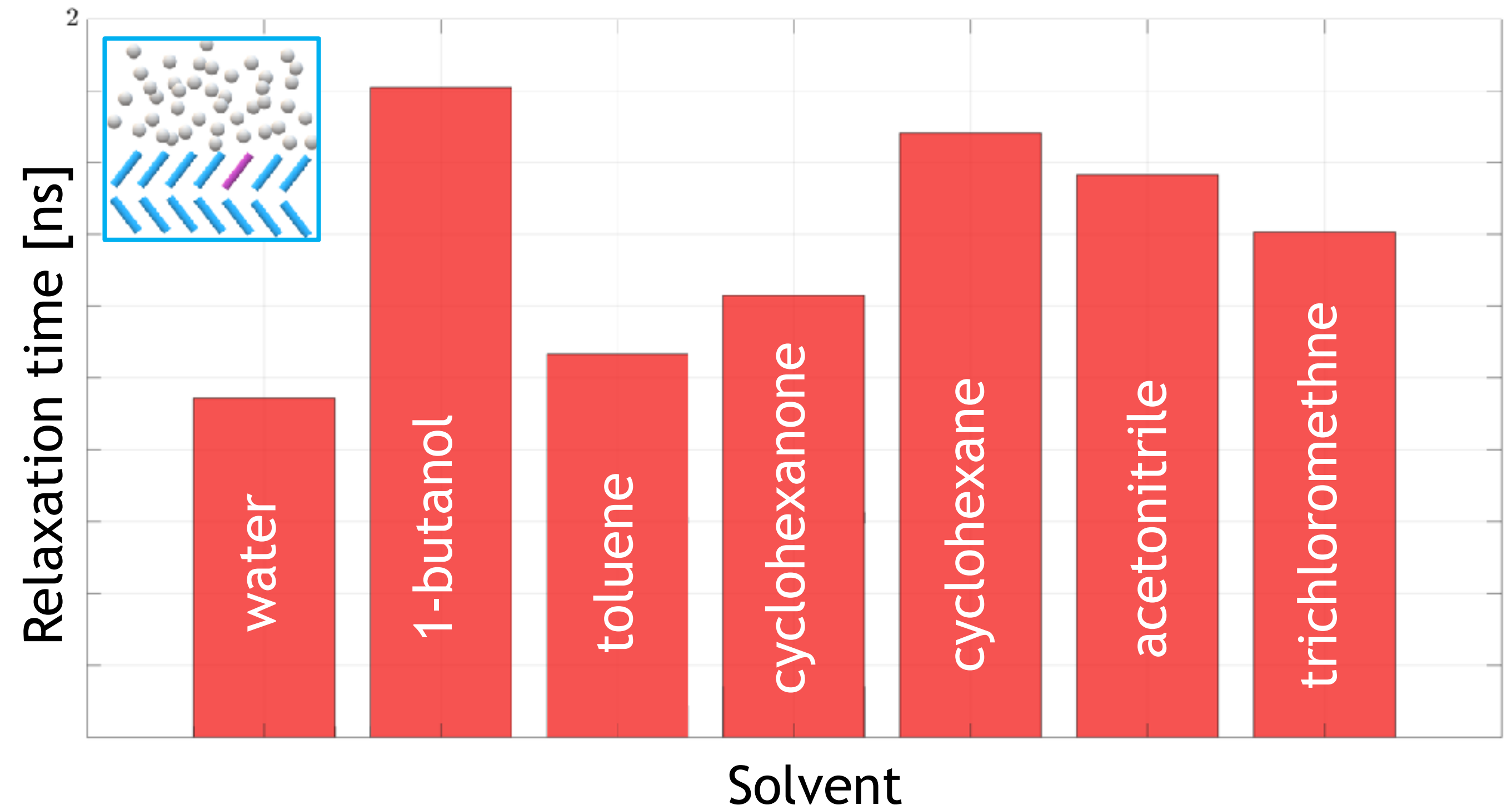




# Ibuprofen Conformational Isomerism



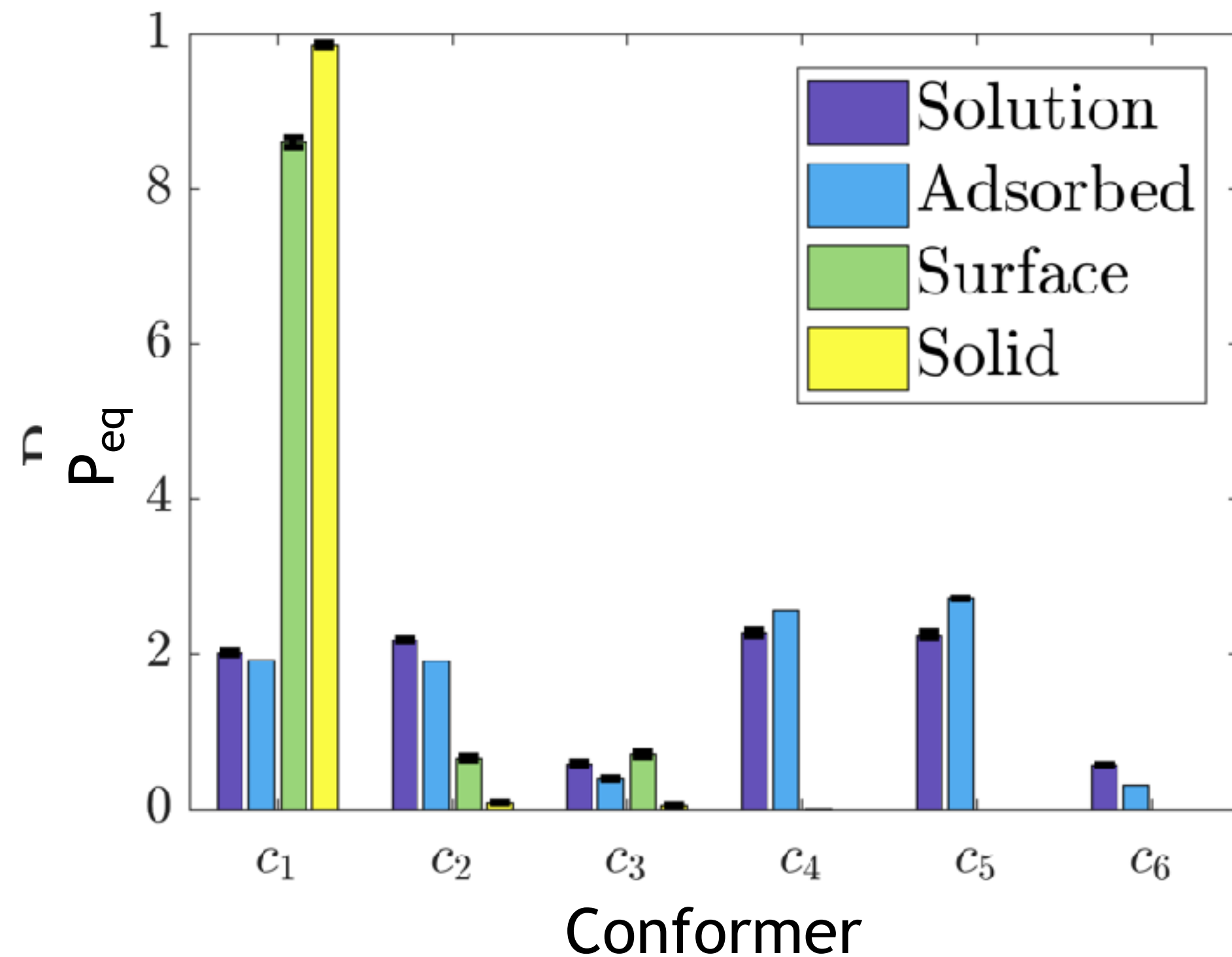
State-to-state transitions may be limited by conformational rearrangements



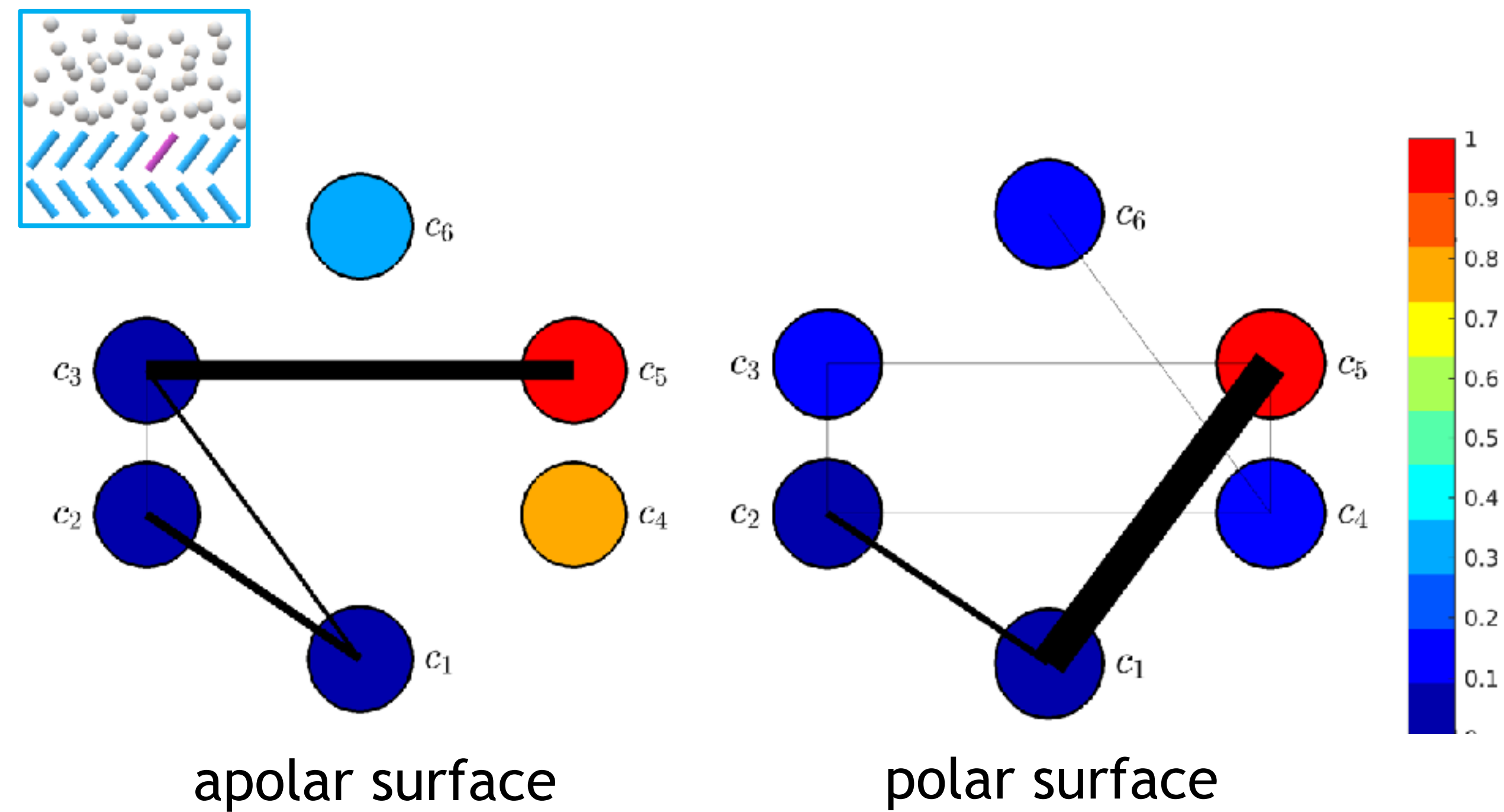
Freedom of conformational rearrangement may limit growth kinetics



# Ibuprofen Conformational Isomerism



State-to-state transitions may be limited by conformational rearrangements

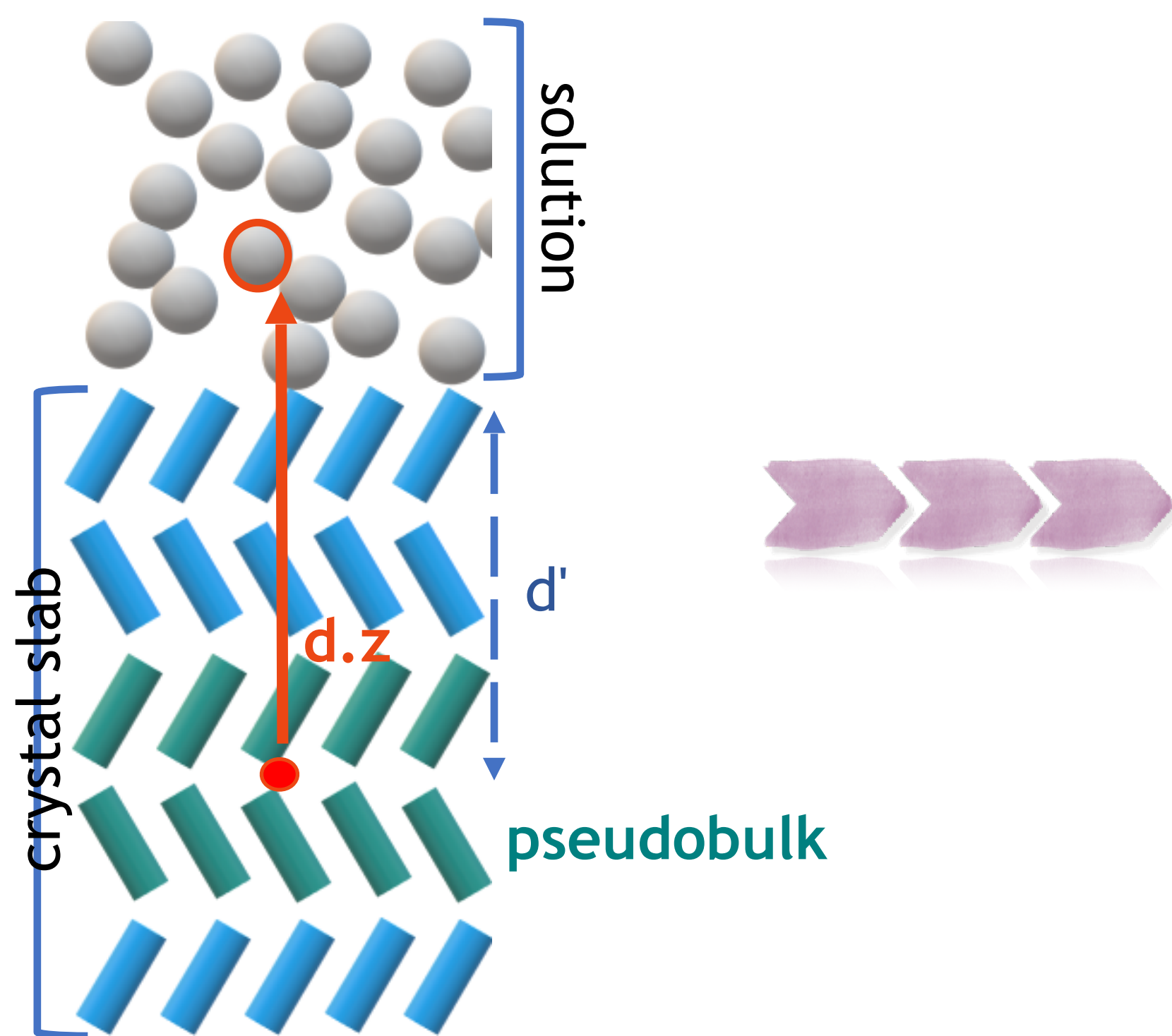


Rearrangement mechanism changes

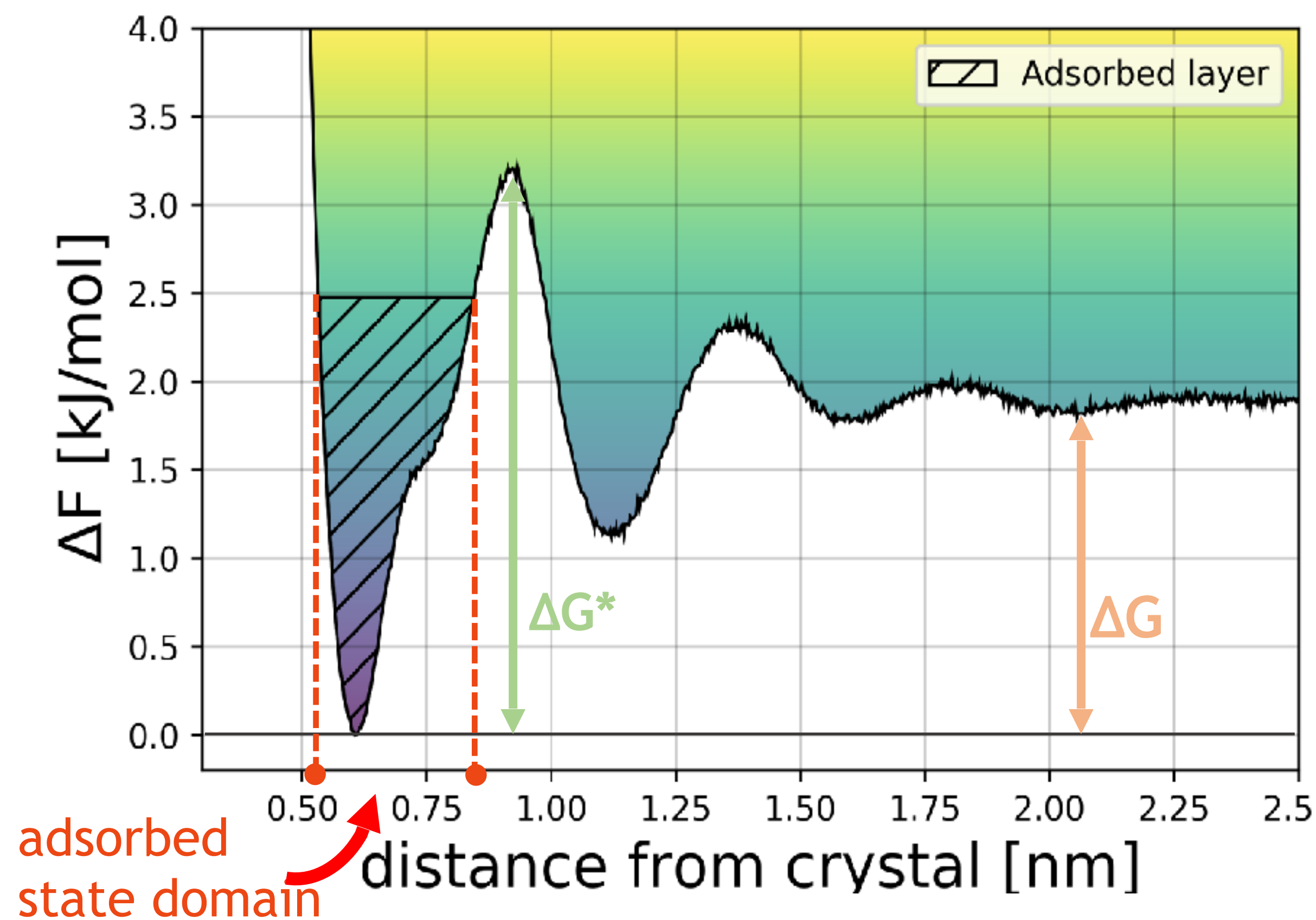


# Solvent Dynamics and Thermodynamics

Evaluating the distance of each solvent molecule from the bulk of the crystal

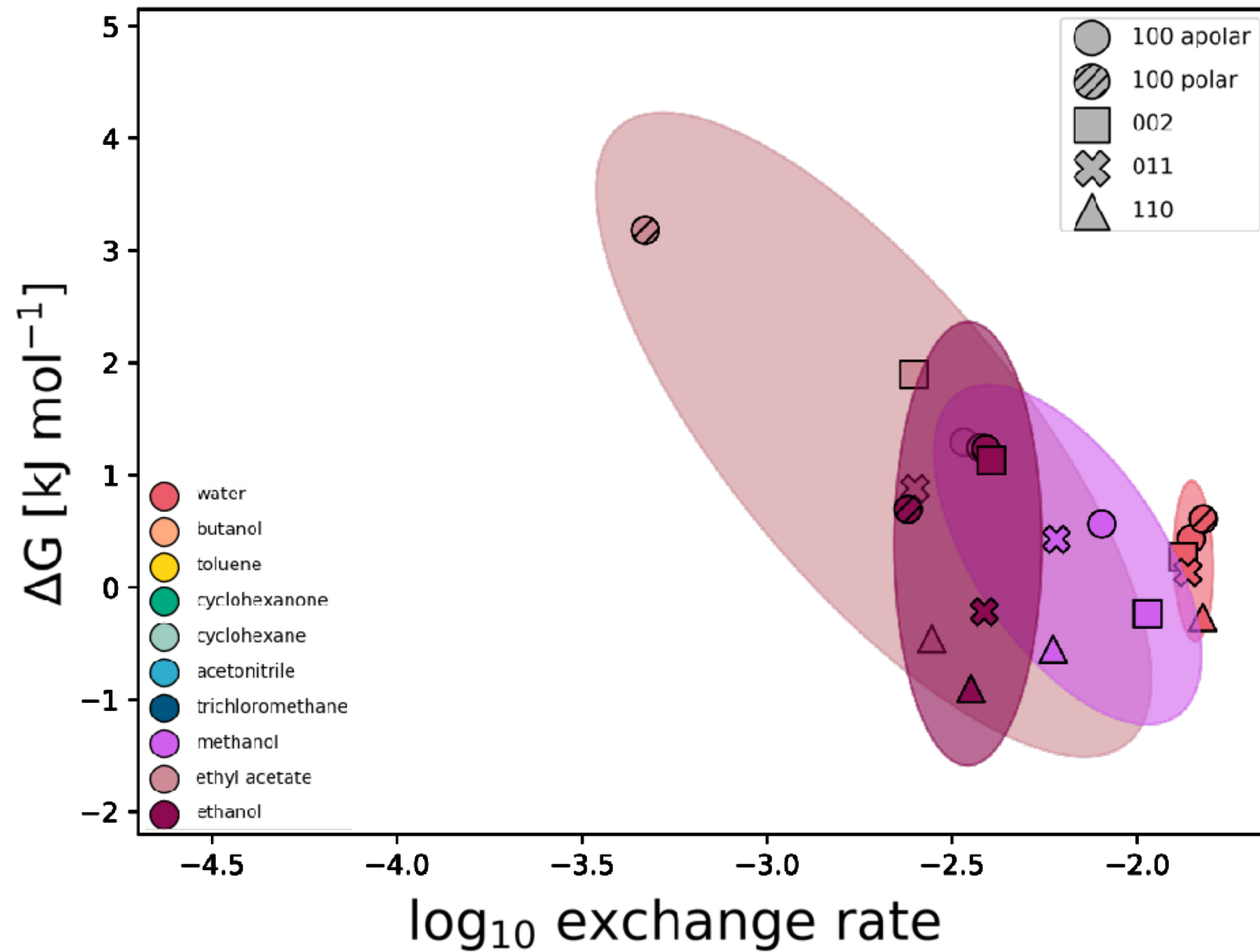


- Free energy of desorption of a solvent molecule ( $\Delta G$ )
- Exchange rate between adsorbed state and solution bulk from standard MD simulations



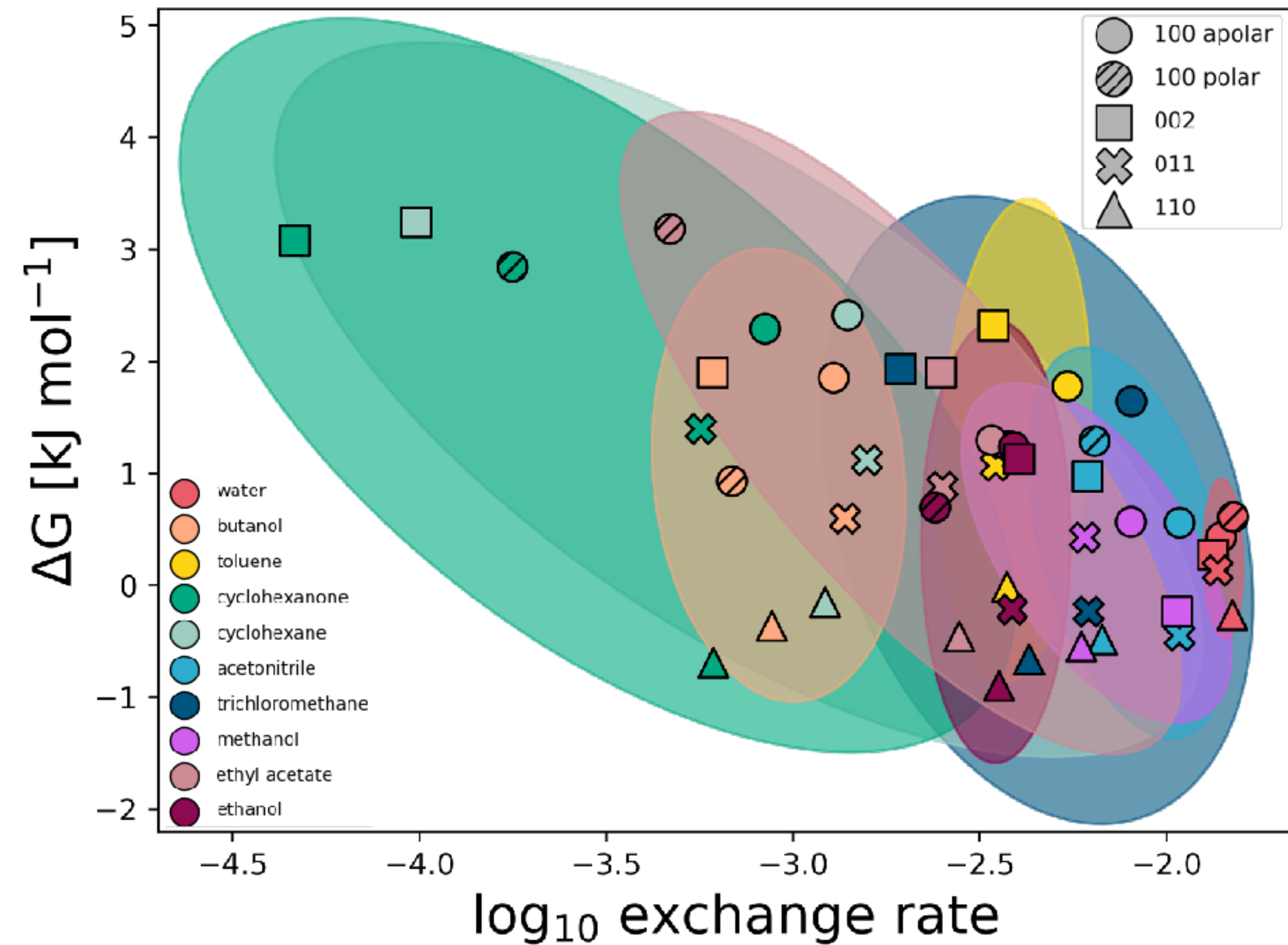


# Solvent Dynamics and Thermodynamics





# Solvent Dynamics and Thermodynamics

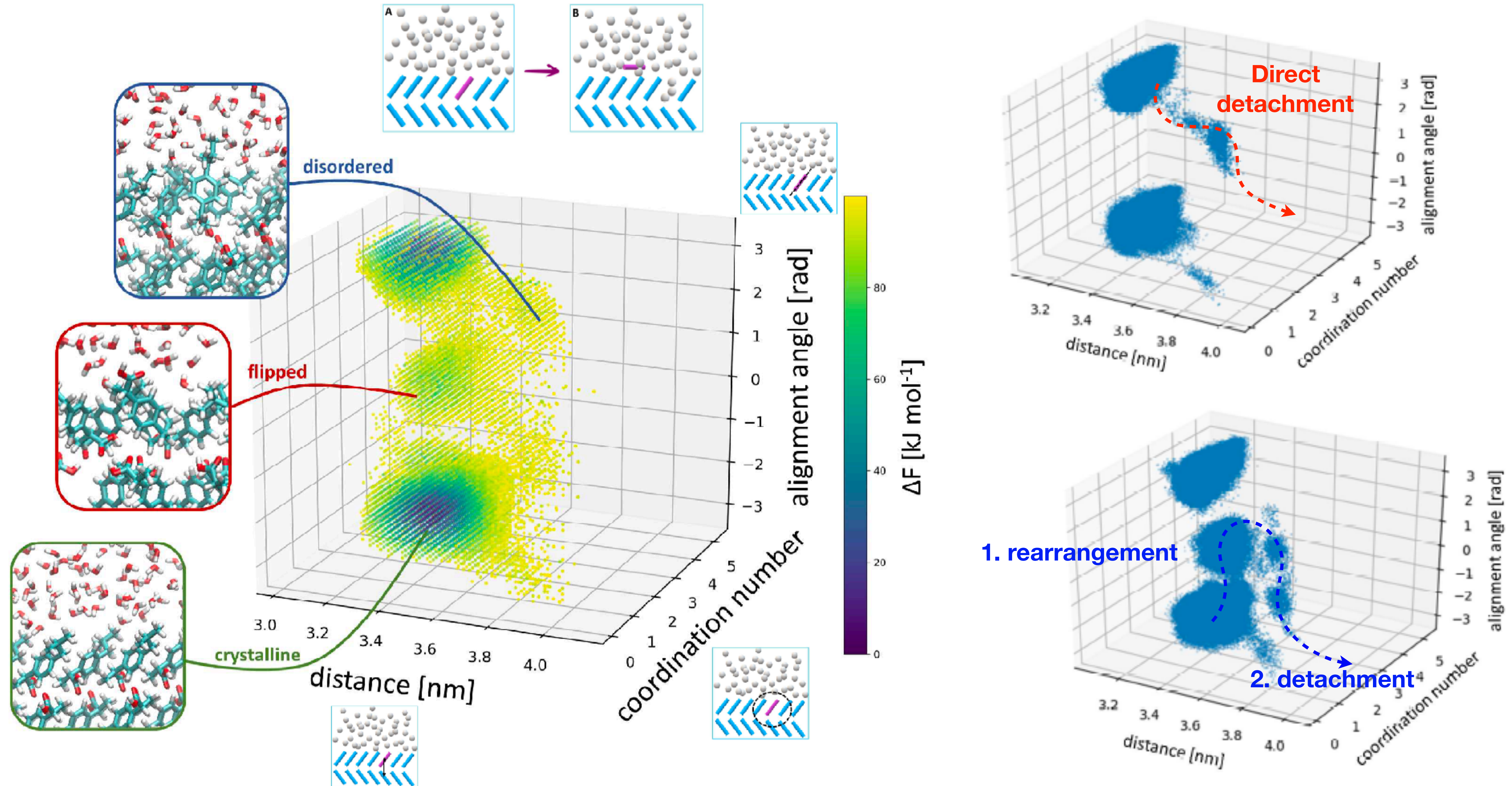


Solvent	Area
water	1
ethanol	10.6
acetonitrile	11.4
toluene	11.5
methanol	11.8
1-butanol	18.4
ethyl acetate	37.6
trichloromethane	41.6
cyclohexanone	78.1
cyclohexane	78.2

Screening for anisotropic surface-solvent interactions

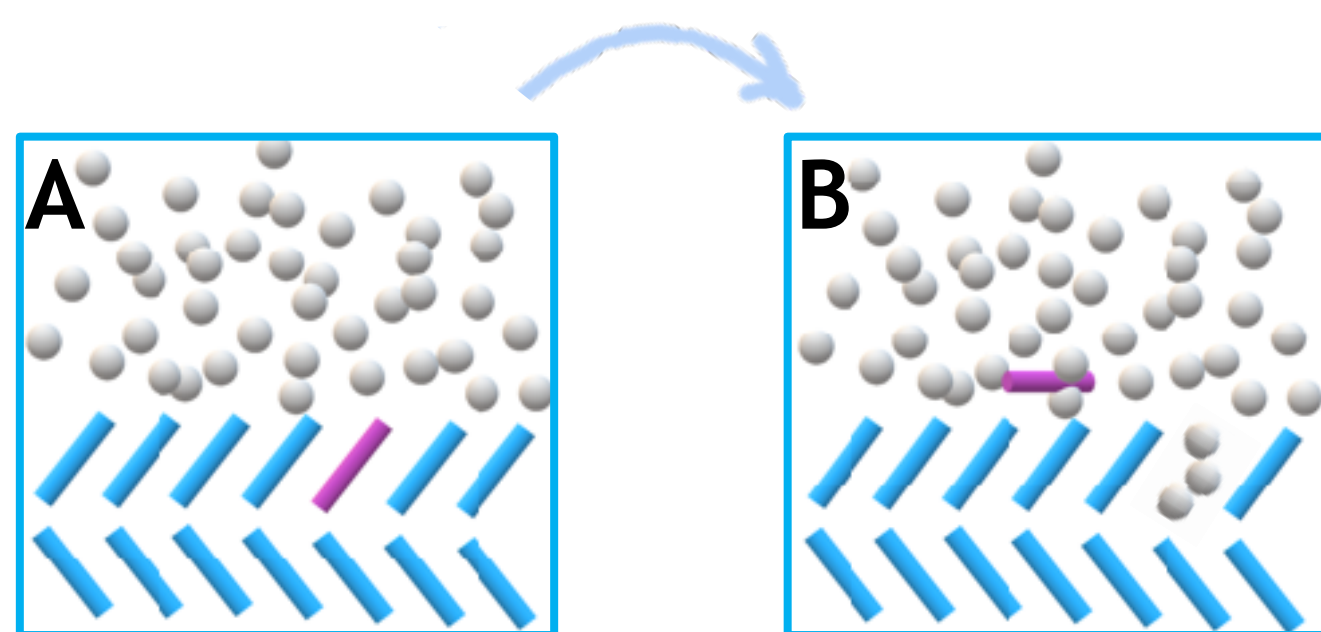


# Solvent and Conformational diversity impact the Formation of Surface Vacancies





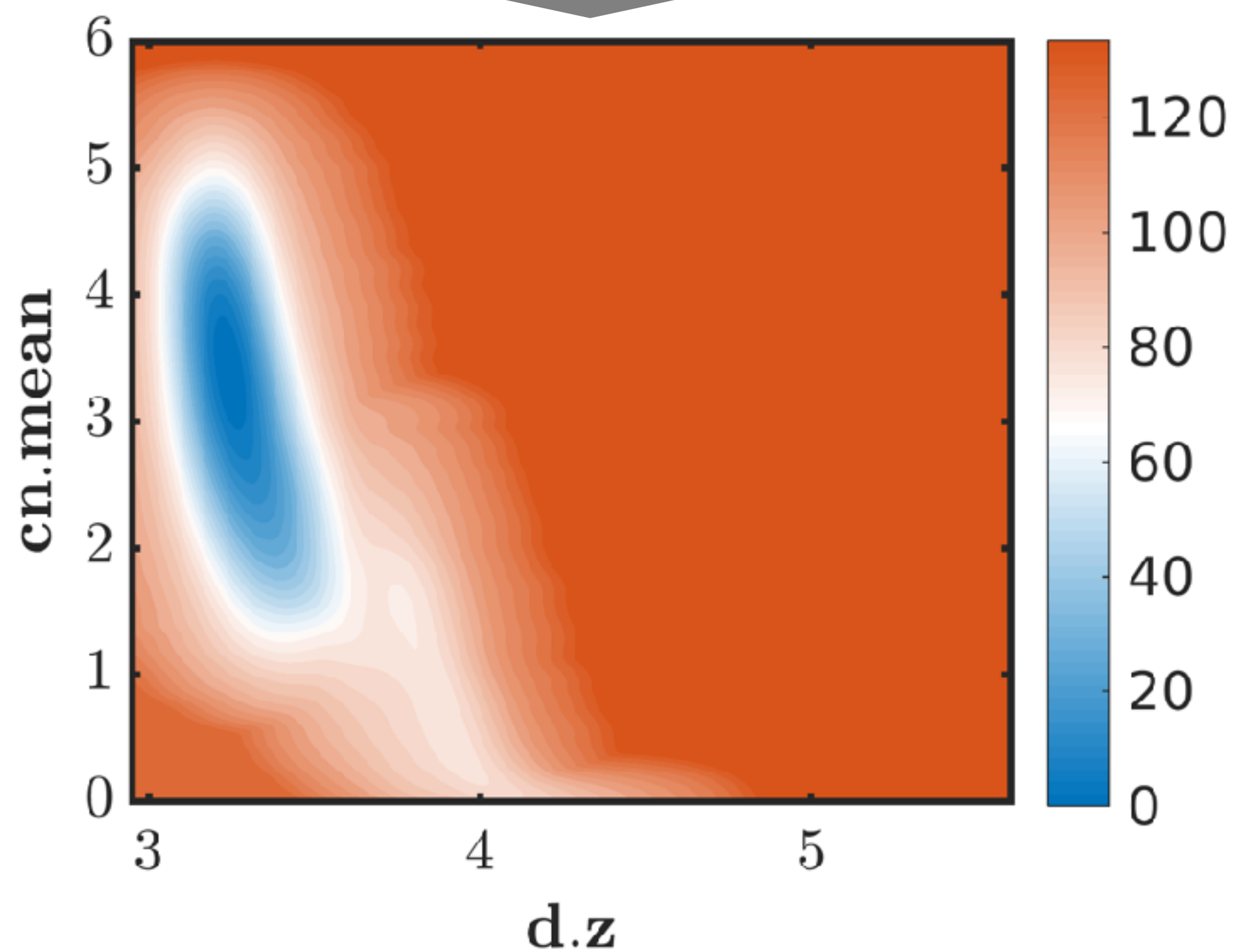
# Solvent Effect on the Formation of a Surface Vacancy



$F(\mathbf{s})$

From 30 independent simulations

MFI



For every  $i^{th}$  simulation

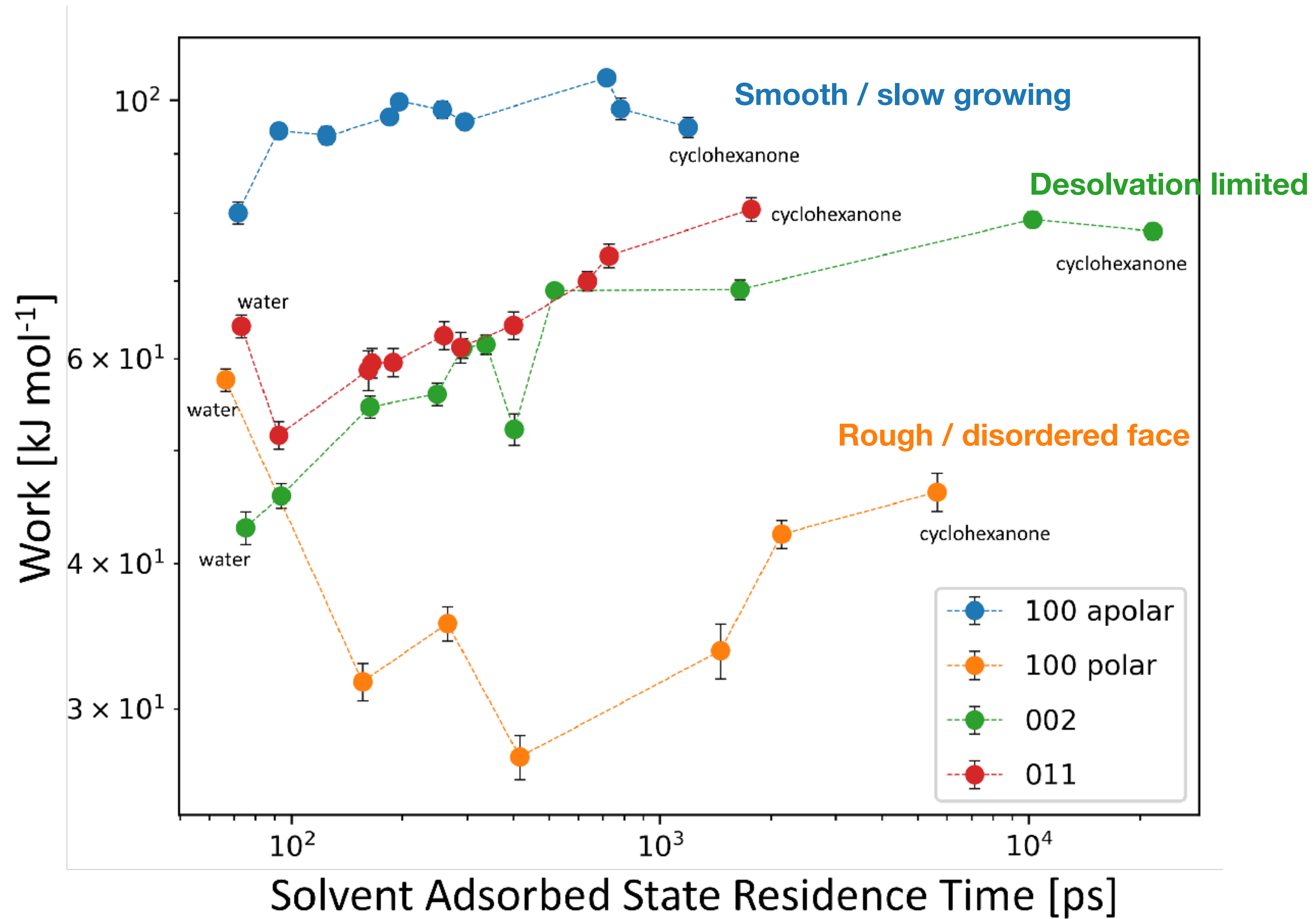
$$\langle V_i(\mathbf{s}) \rangle_u = \beta^{-1} \ln \frac{\int_{\Omega} e^{-\beta F(\mathbf{s}) + \beta V_i(\mathbf{s})} d\mathbf{s}}{\int_{\Omega} e^{-\beta F(\mathbf{s})} d\mathbf{s}}$$

mean

Average work necessary to obtain a surface vacancy defect



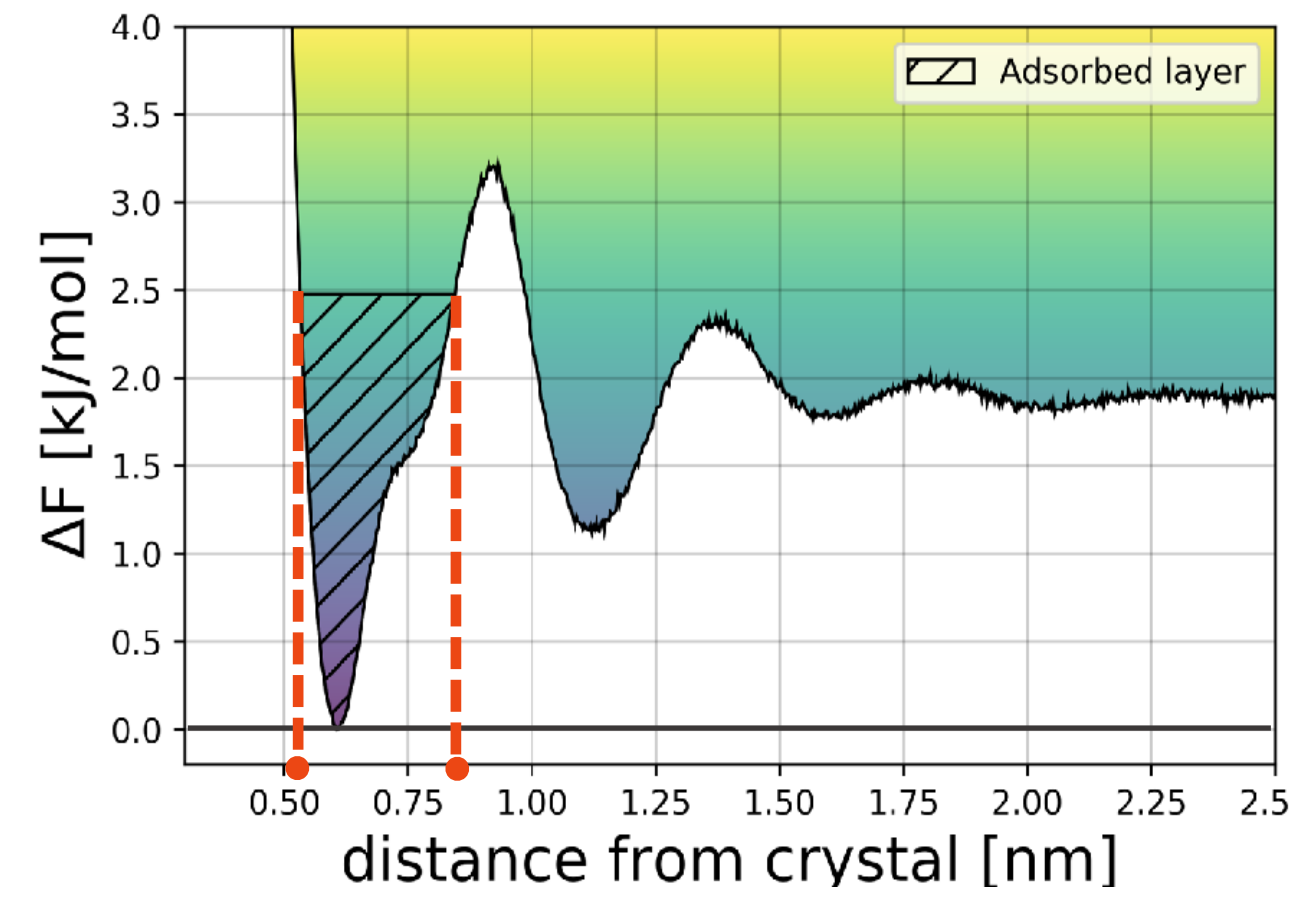
# Solvent Effect on the Formation of a Surface Vacancy



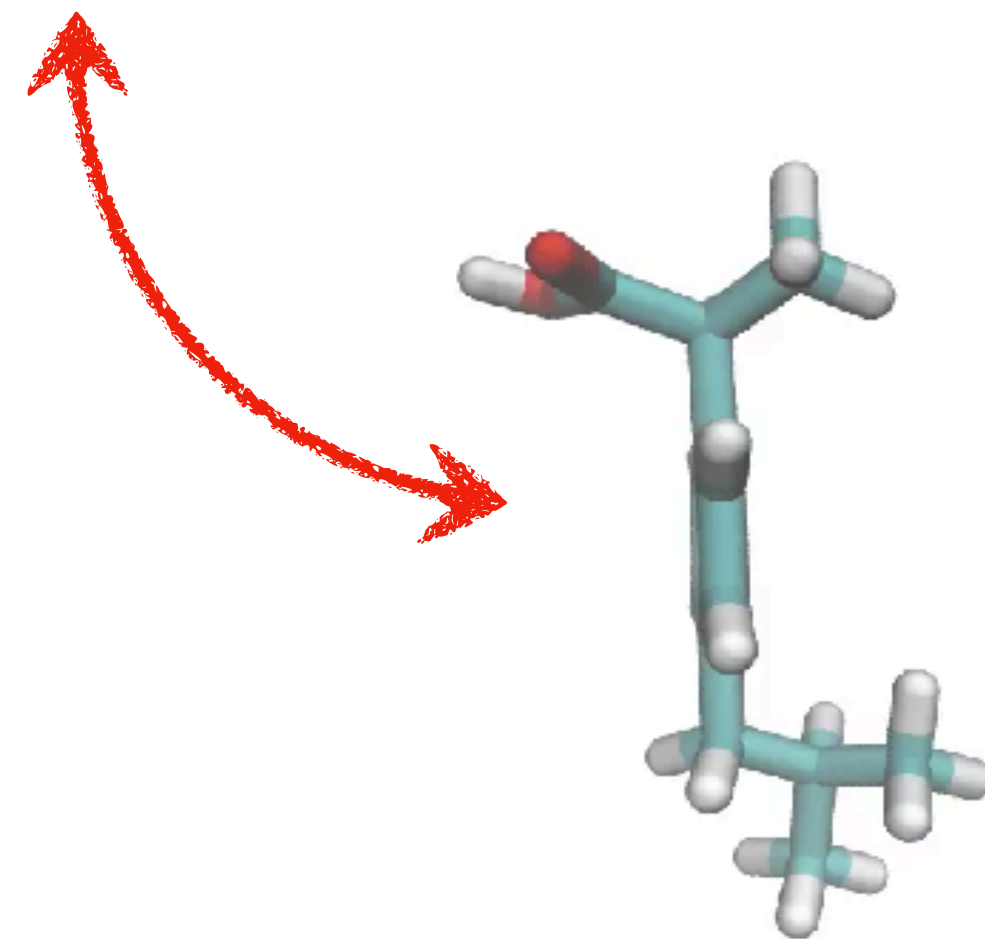
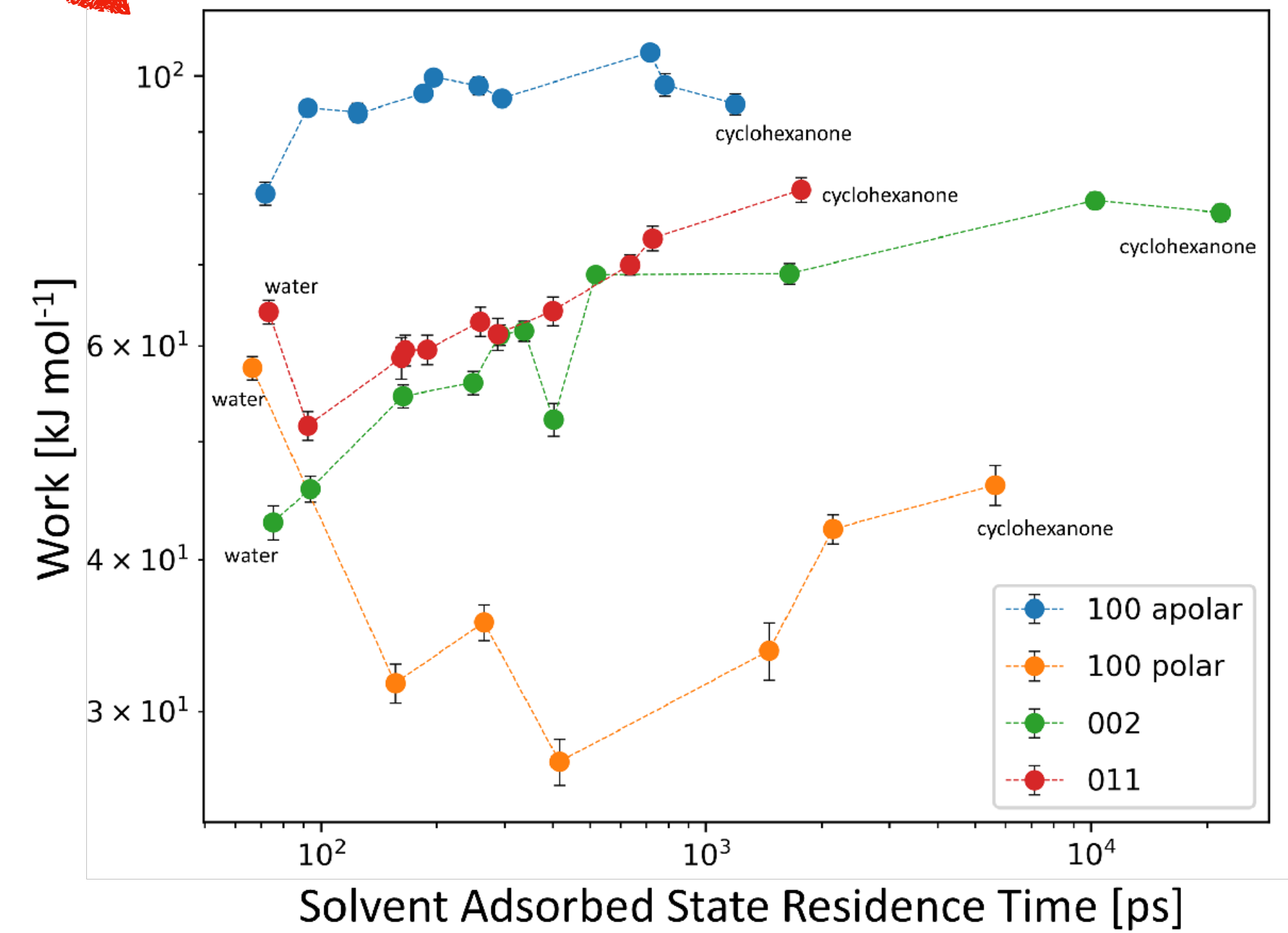


# TOM - ibuprofen

solvent-surface



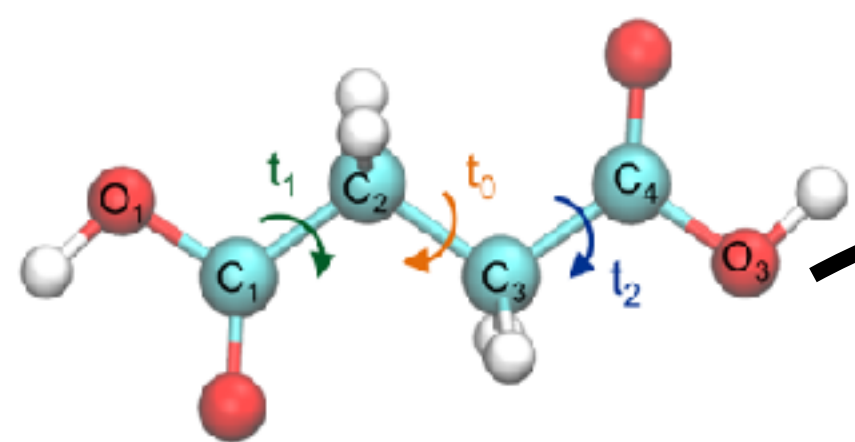
Interface defects



conformational diversity



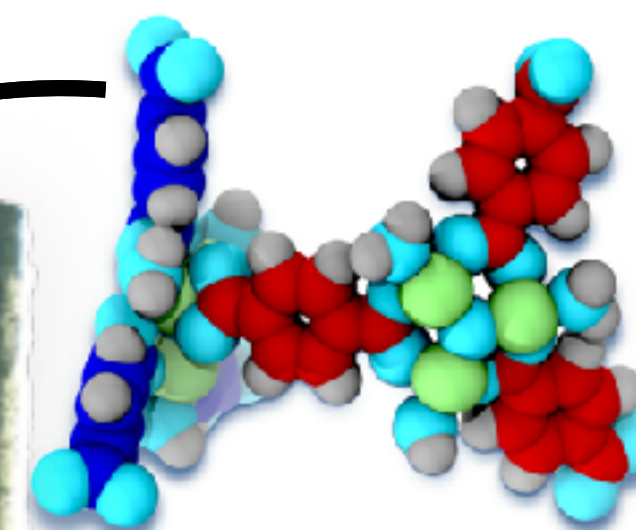
# Acknowledgements



Ilaria Gimondi

**EPSRC**

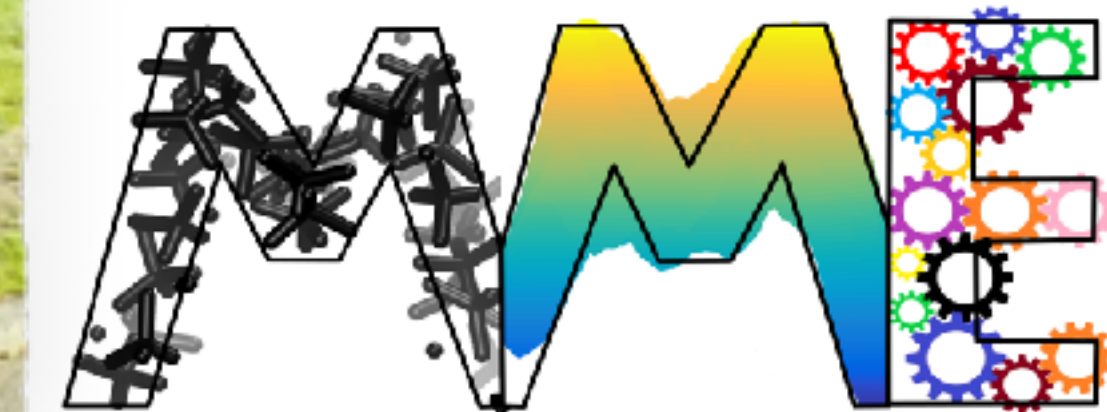
Engineering and Physical Sciences  
Research Council



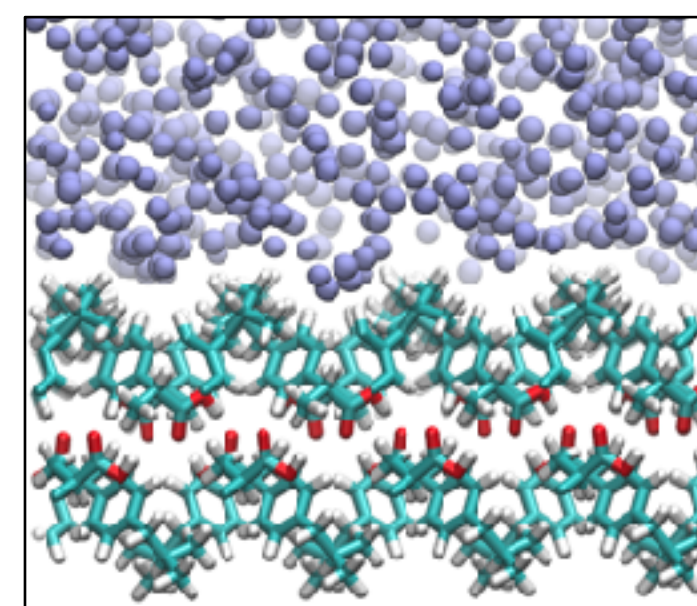
Loukas  
Kollias



**Pacific Northwest**  
NATIONAL LABORATORY



Molecular Modelling and Engineering UCL



Veselina  
Marinova

**PLUMED**

