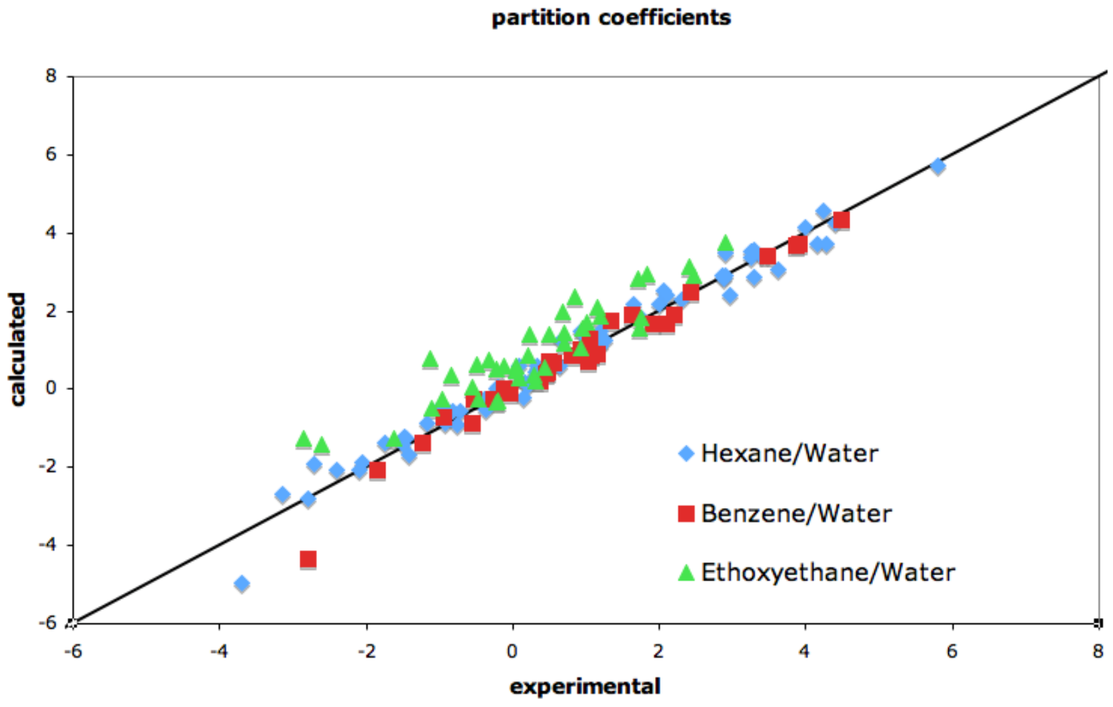
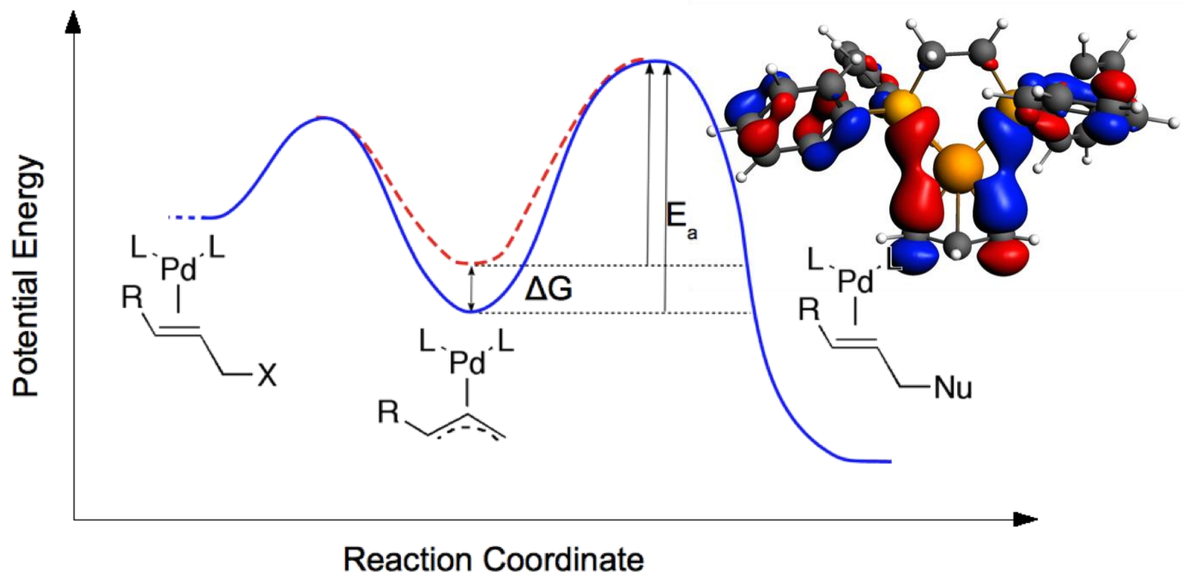
Modeling & Simulation for Pharma

Reducing costs & time through computer-aided design





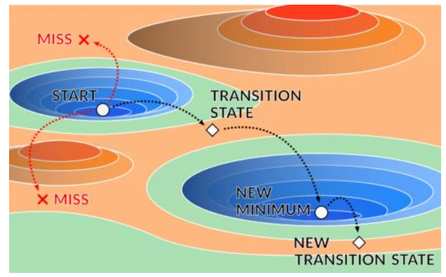
SCM
Software for Chemistry & Materials

Fedor Goumans, Chief Customer Officer

goumans@scm.com

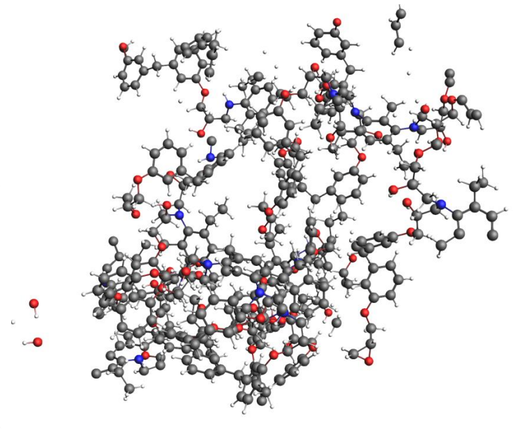
Why bother with Computational Chemistry?

- Accelerate research, reduce costs & environmental impact
  - Reduce experimental search space (virtual screening)
  - Quicker optimization through structure-property insights
  - New developments from machine learning



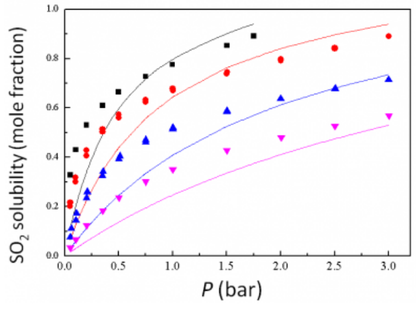
- Synergy experiment-calculations
  - Ask relevant questions
  - Understand limitations model
  - Experimental constraints

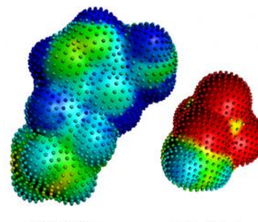
???



Formulation => best mixture for solubility?

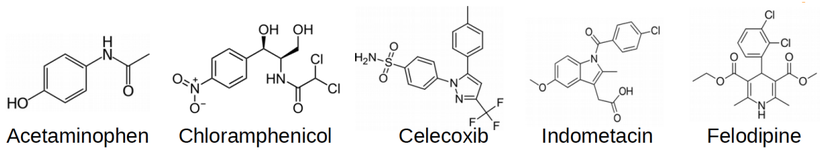
Production => optimize catalyst (ligands, solvent -> lowest E_a)

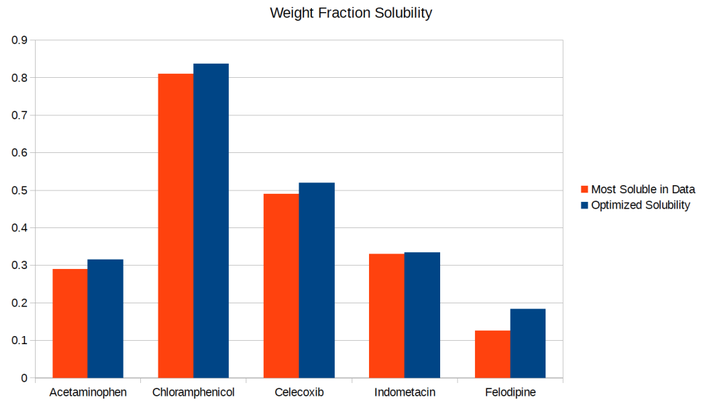




Modeling properties in pharma

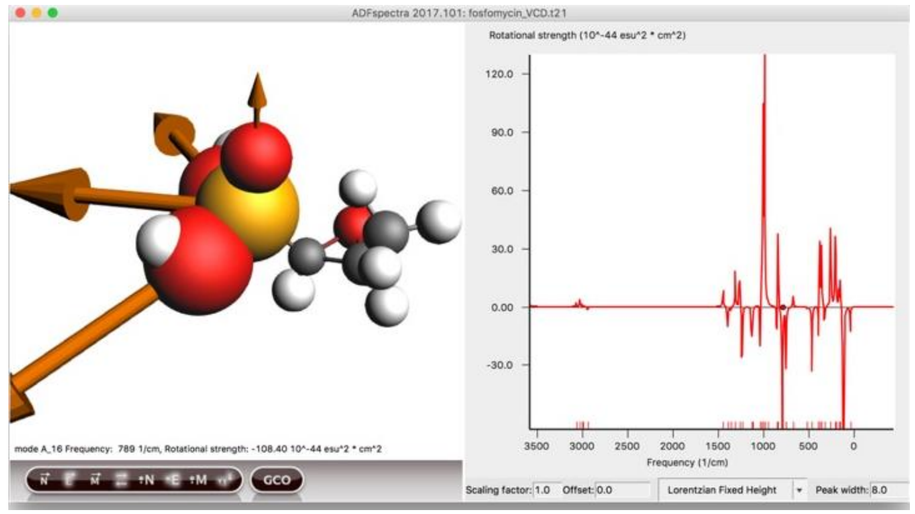
- **Solubility & co-crystal screening**
  - Screen solvent (mixtures) for solubility
  - Screen excipients for solubility
  - Screen co-crystals



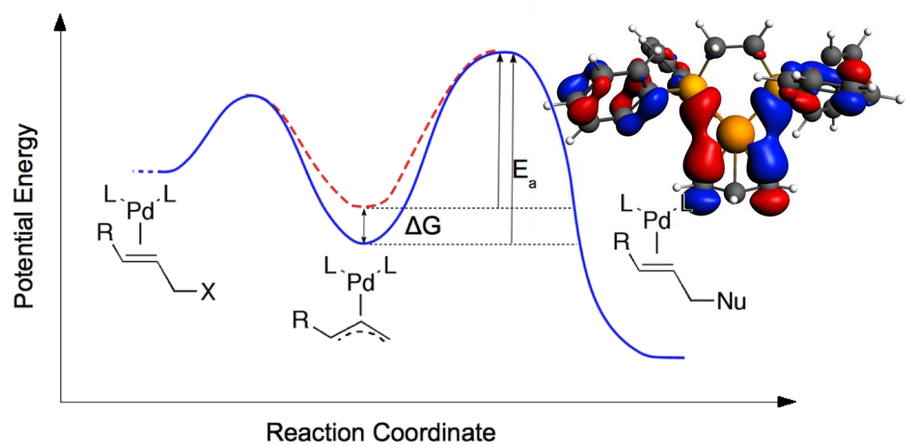


- **Liquid-Liquid extraction**
  - Screen biphasic solvent mixtures

- **Spectroscopy**
  - Help determine structure & AC
  - VCD, NMR, IR, UV/VIS, XANES

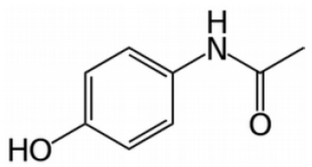


- **Reactivity & Catalysis**
  - Stability assessment (e.g. Fukui function)
  - Map reaction pathways
  - Optimize catalyst

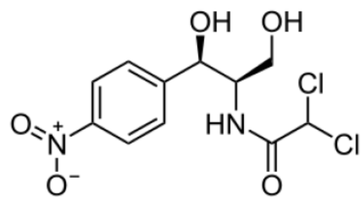


Drug solubility with COSMO-RS

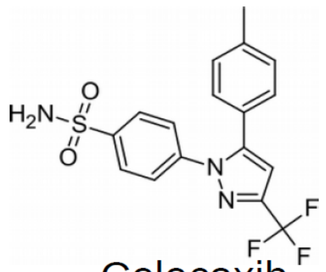
- Find best excipient for water-insoluble drugs
- Screen co-polymers with COSMO-RS => maximize solubility



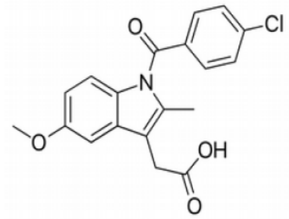
Acetaminophen



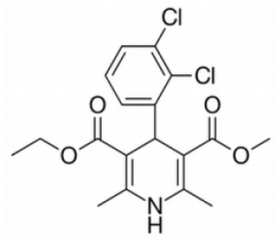
Chloramphenicol



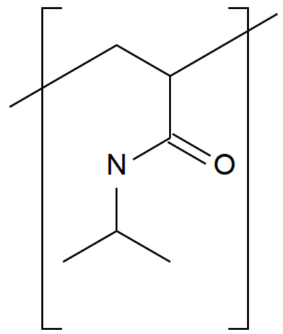
Celecoxib

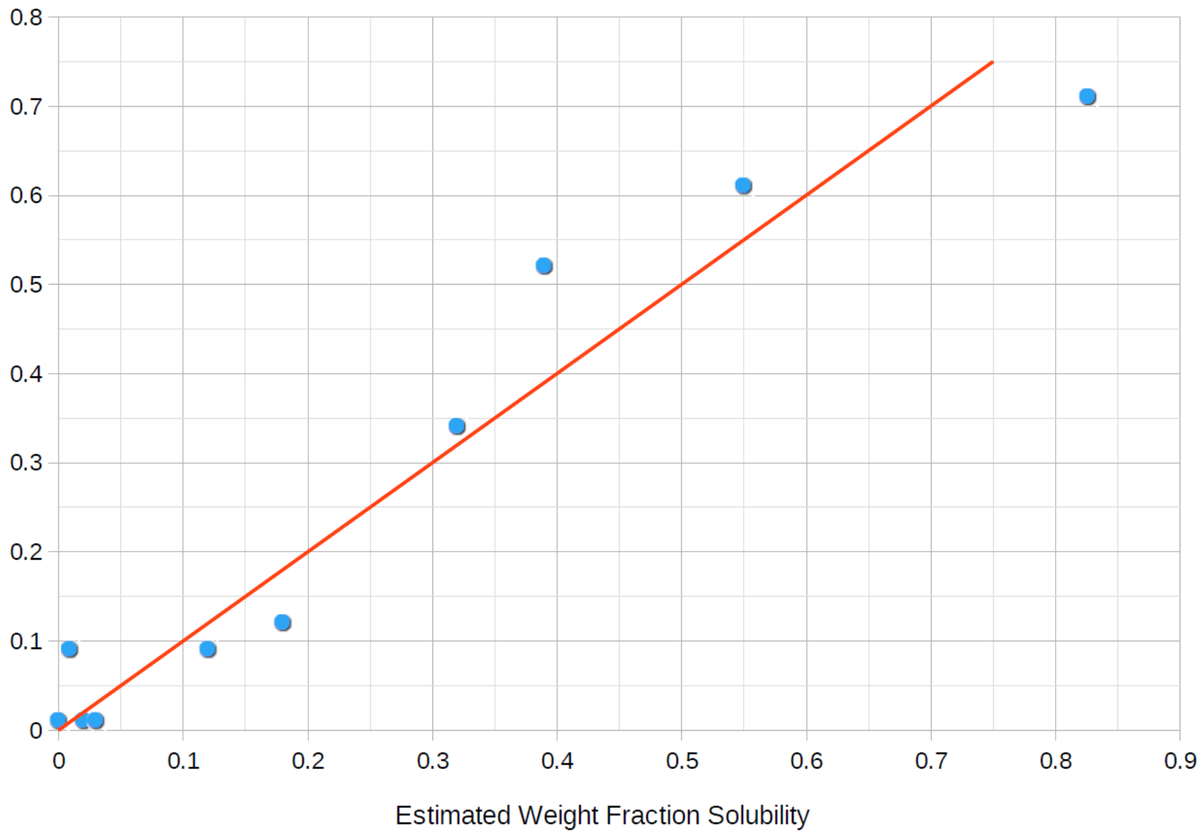


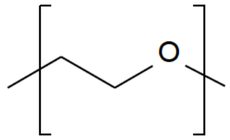
Indometacin

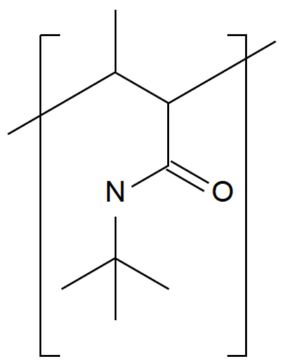


Felodipine





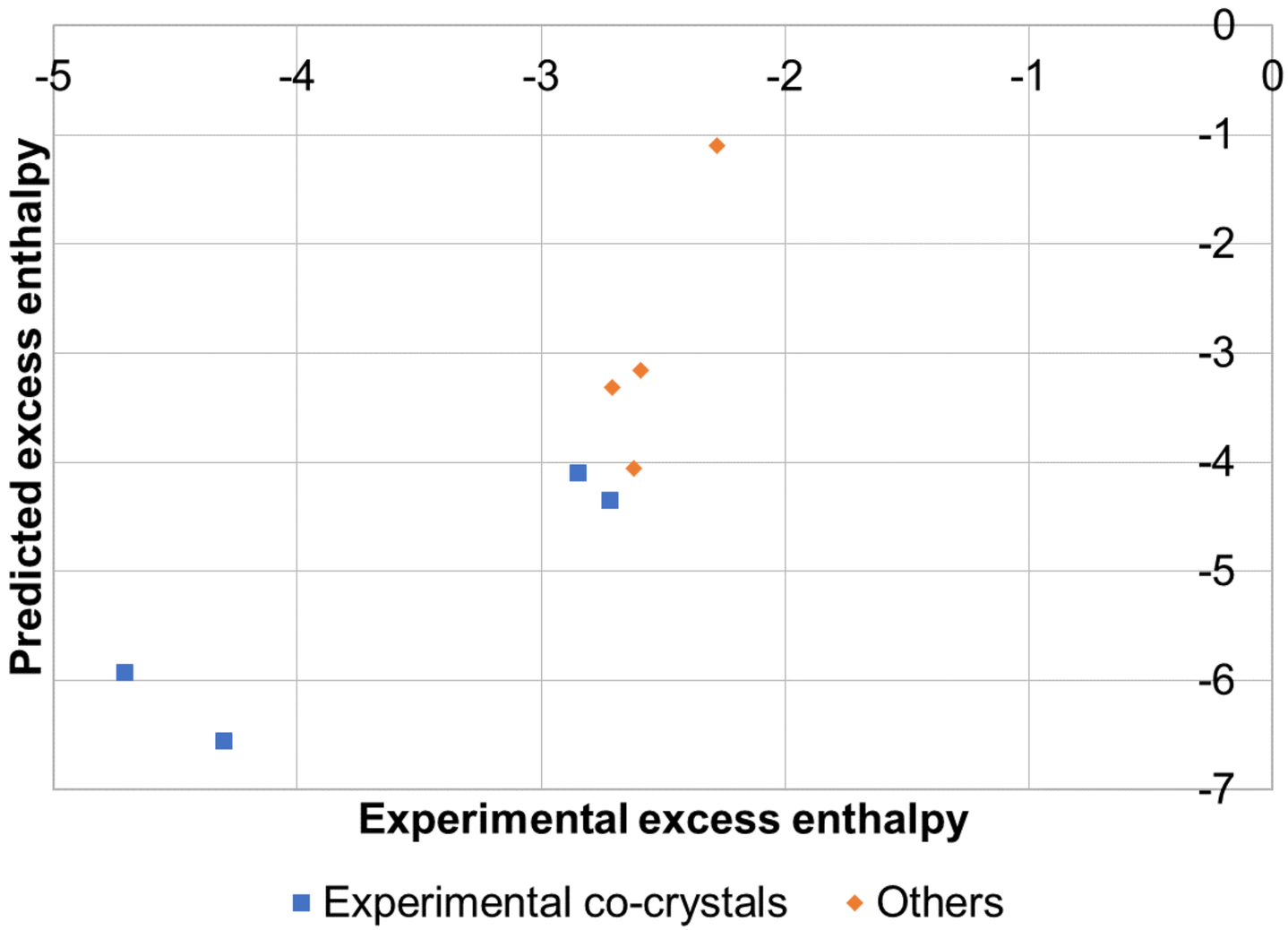


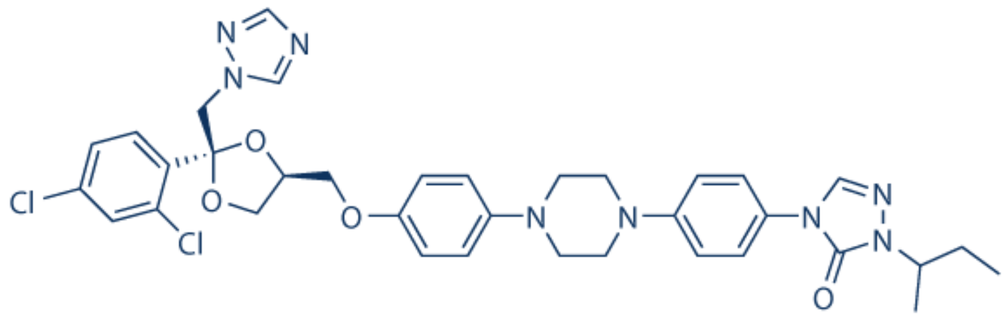


3 common features
(library ~200 monomers)

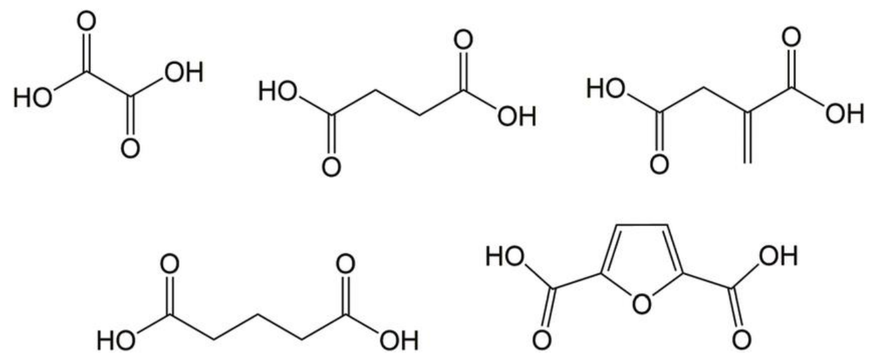
Co-crystal screening with COSMO-RS

- Improve solubility, stability, mechanical properties of API
- Screen candidates for co-crystallization





Itraconazole



example co-crystal candidates

Optimize solvent mixtures for extraction

- Remove impurities or extract (natural) products

Specify solvents

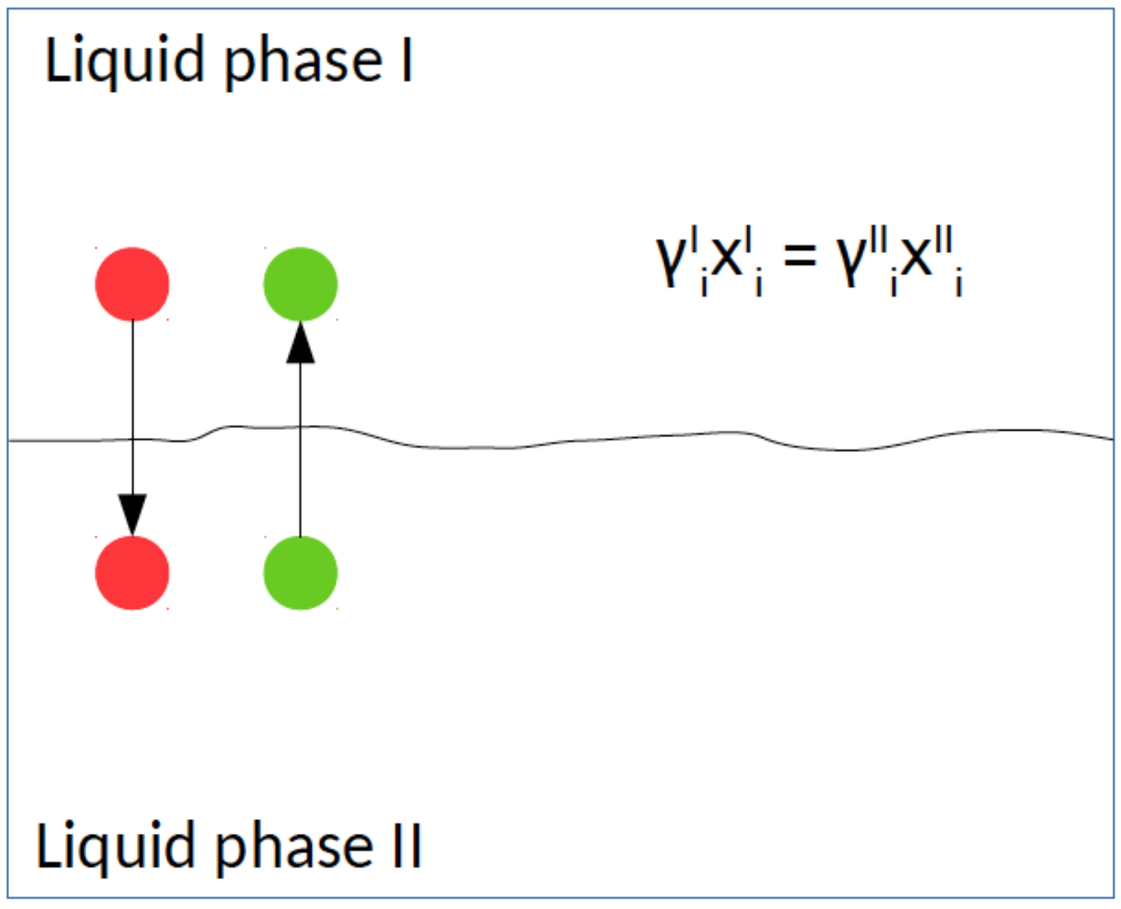
Water
Methanol
Ethanol
1-Hexanol
Diethyl ether
Benzene
Toluene
Acetic acid
2-Hexanone
DMF
THF
Dioxane
…

Specify solutes

Acetic acid 
Water 

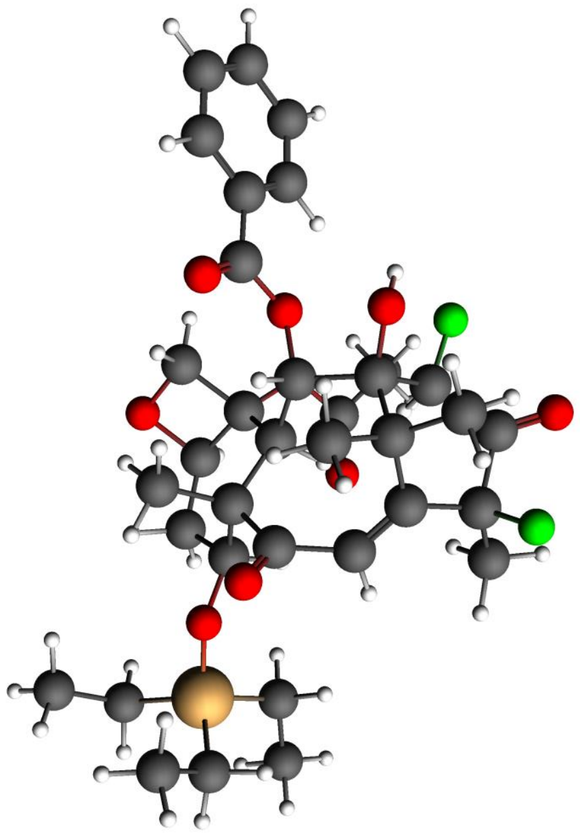
Specify problem conditions

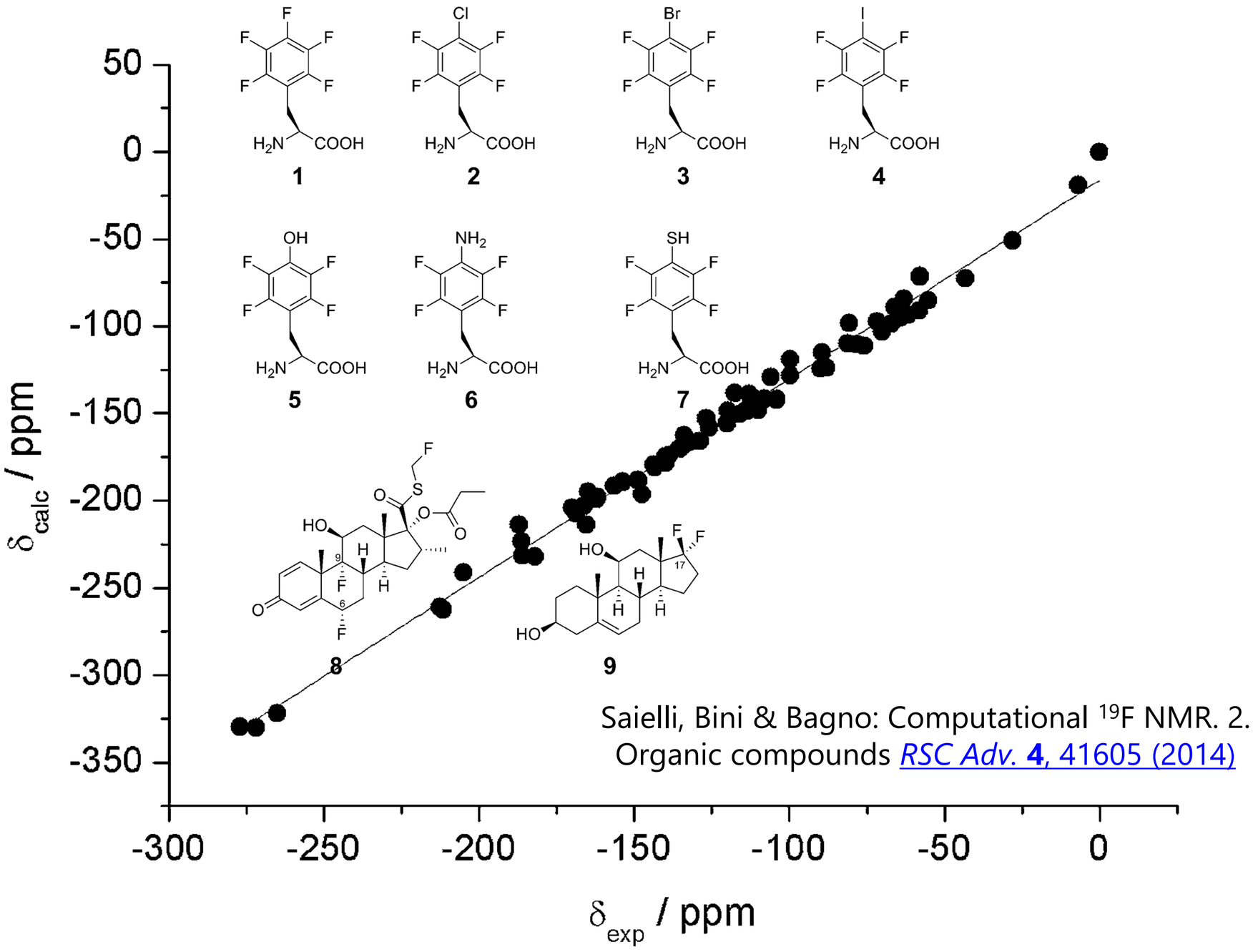
Optimization direction: maximize
Maximum number of solvents: 3
Temperature: 298.15K (or range)
…



Maximize the partition coefficient

Help assign spectra with DFT: NMR





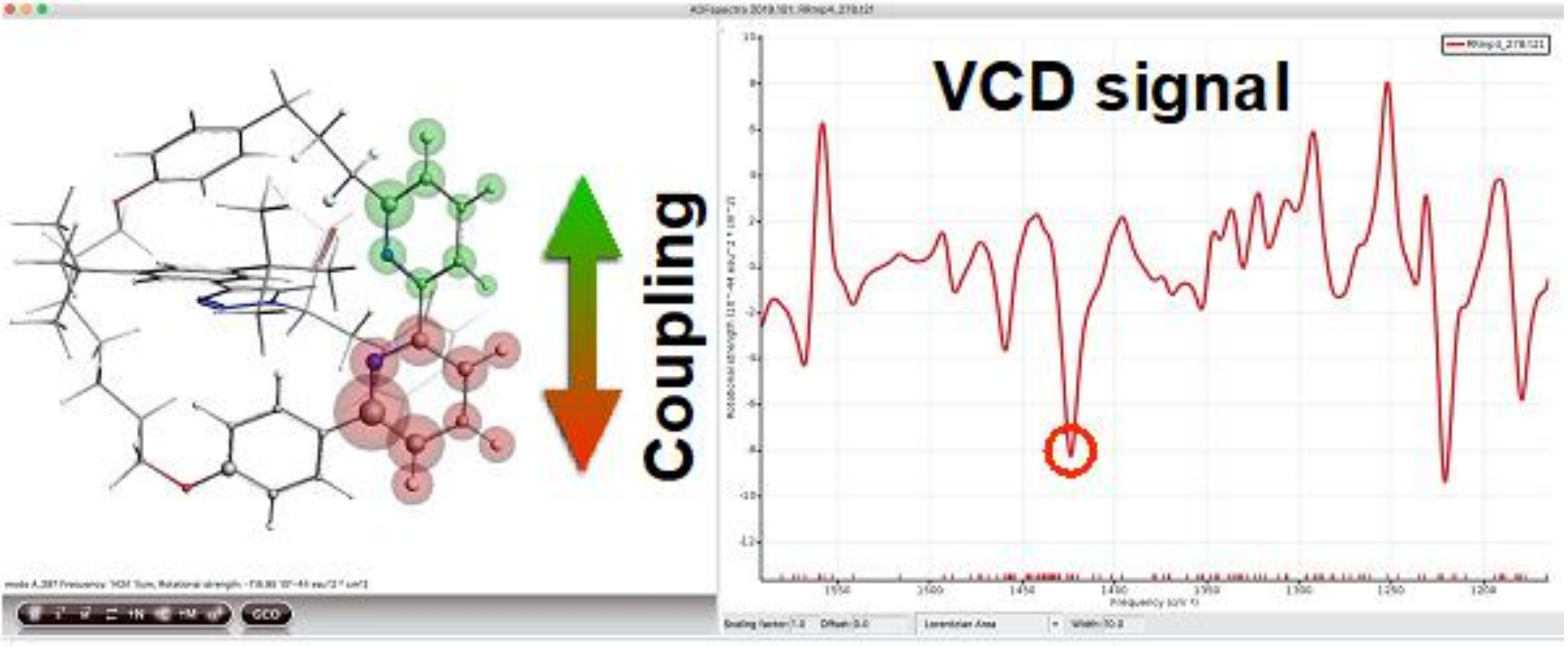
Saielli, Bini & Bagno: Computational ^{19}F NMR. 2. Organic compounds *RSC Adv.* **4**, 41605 (2014)

Good agreement between calculated (ADF, spin-orbit) and experimental ^{19}F NMR shifts for organic compounds, including taxol and fluoro-analine.

Determine absolute configuration (VCD)

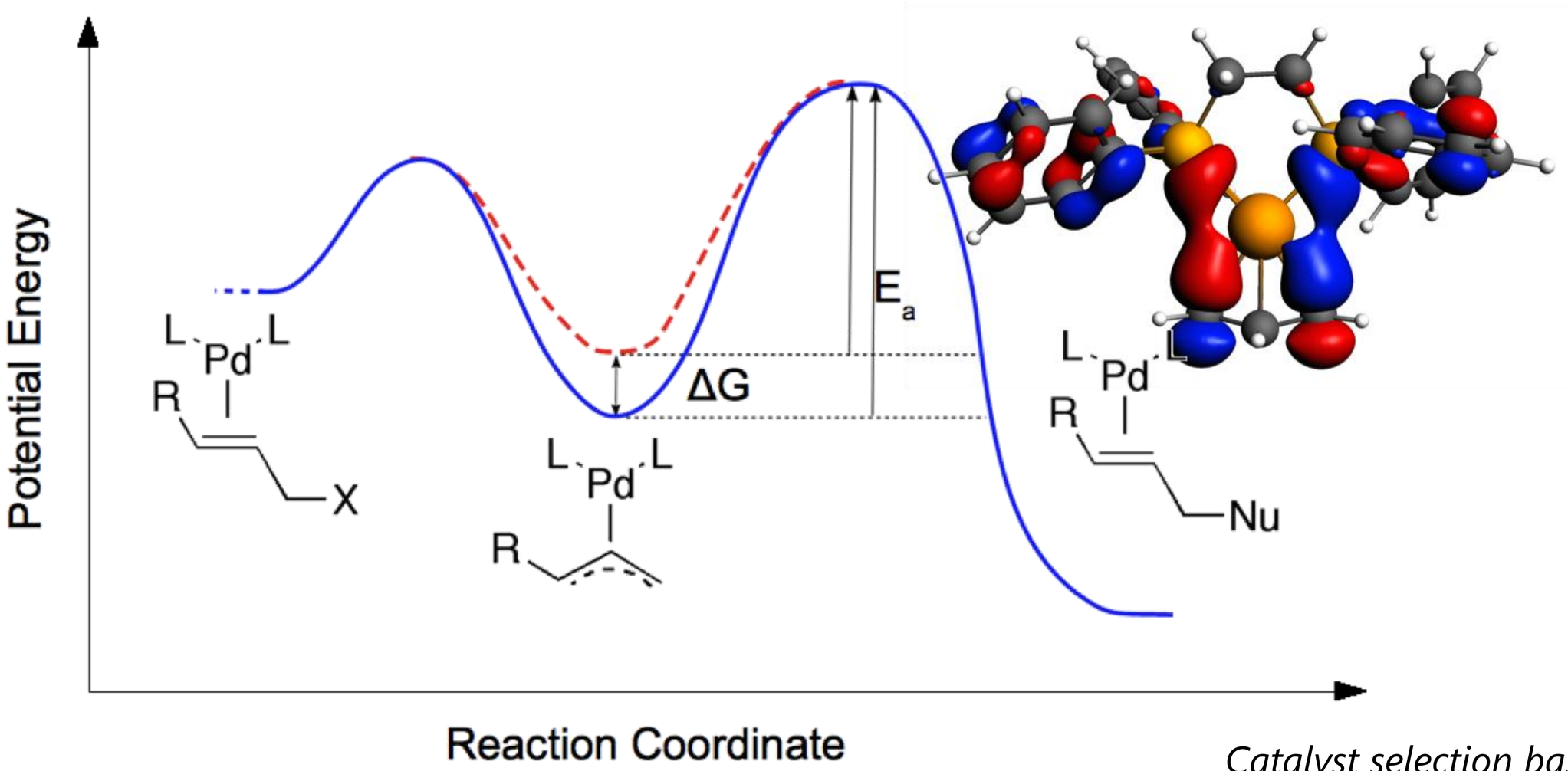
More confident AC assignment with Vibrational Circular Dichroism calculations

- Include conformers
- Include solvent effects
- Analyze coupling to establish robustness of peaks



Understand and improve catalysts: Pd allylation

Experimental + DFT study => Best catalyst: least stable intermediate
Bonding energy analysis: increased bite angle ->larger steric strain
Rational design: modify ligands and solvents to decrease E_a



Catalyst selection based on intermediate stability measured by mass spectrometry.
Nature Chem. 2, 417 (2010)

Software for Chemistry & Materials

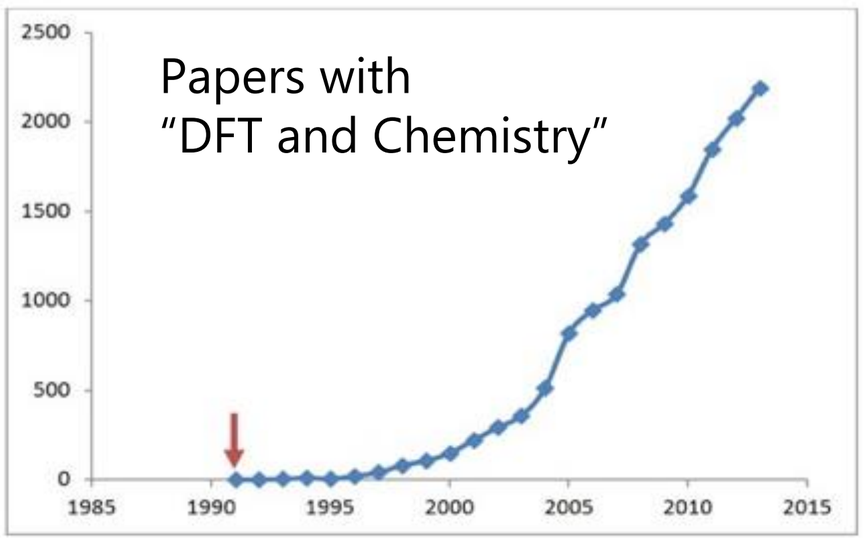
- SCM: Spin-off company from VU (1995)
  - Develop & market Amsterdam Density Functional (ADF)
  - Continued development: Amsterdam Modeling Suite

- ADF = first DFT code for chemistry (1970s)
  Baerends@VU (>'73), Ziegler@Calgary(+) (>'75)
  - 80s: support industry for catalysis Mitsui, Shell, Akzo, Unilever

- 22 people (15 senior PhD's) + 3 EU fellows
  - New development, support, document, optimize

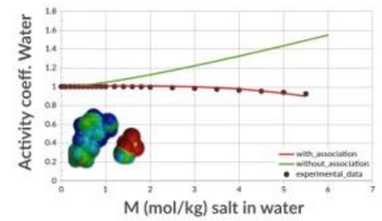
- Many collaborations non-profit & commercial
  - 160+ authors
  - New functionality, real-life pilot cases

- 1000s of users academia, government & industry



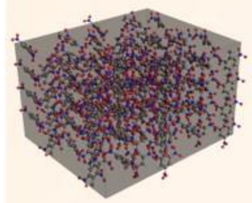
Amsterdam Modeling Suite

- ADF: powerful molecular DFT
  - Reactivity, spectroscopy
- BAND: periodic DFT, QE & VASP interface
  - (2D) Materials, spectroscopy, analysis
- DFTB & MOPAC: fast electronic structure
- ReaxFF: Reactive MD complex systems
- MLPotential
  - Backends SchNetPack, sGDML, PiNN, TorchANI
- COSMO-RS: fluid thermodynamics
  - VLE, LLE, logP, solubility
- AMSdriver: PES exploration, MD, MC
  - Hybrid: multi-layer, QM/MM, QM/QM'
- Integrated GUI, PLAMS: python scripting
- Interface with multi-scale and ML methods

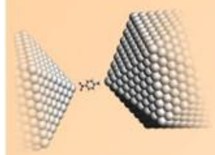


Continuum

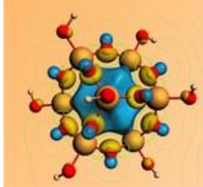
AMS driver GUI PLAMS



Materials



Nano



Atomistic

COSMO-RS
Fluid Thermodynamics & Property Estimation

ReaxFF
Reactive Force Field

MLPotential
Machine Learning Potentials

DFTB & MOPAC
Fast approximate DFT Semiempirical

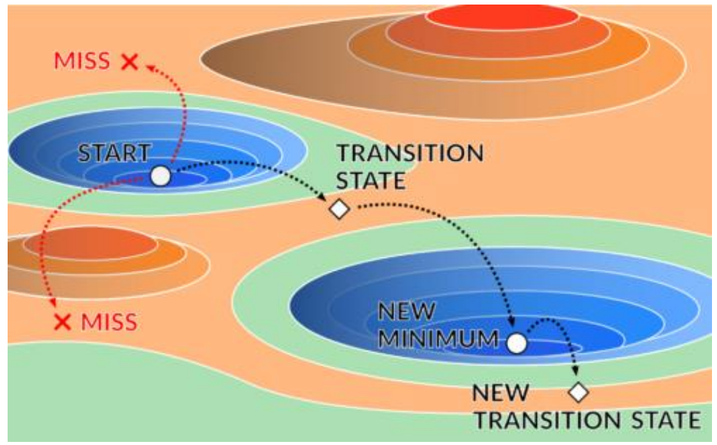
BAND
Periodic DFT

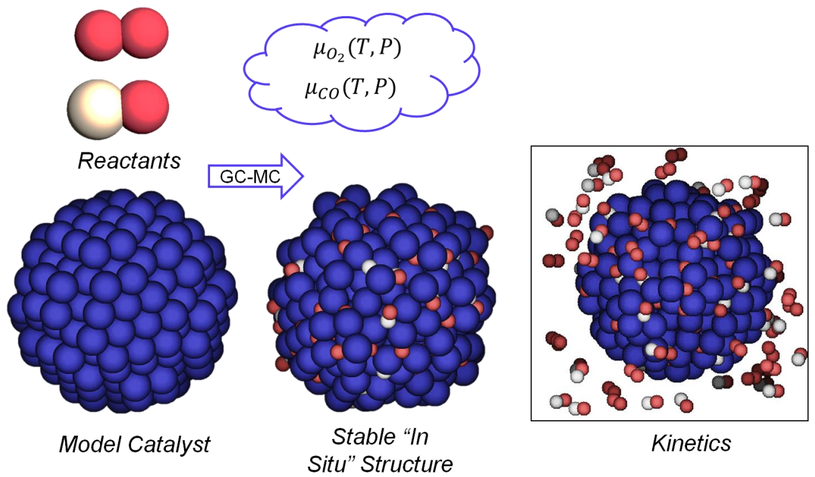
ADF
Molecular DFT

AMS driver: Potential Energy Surface

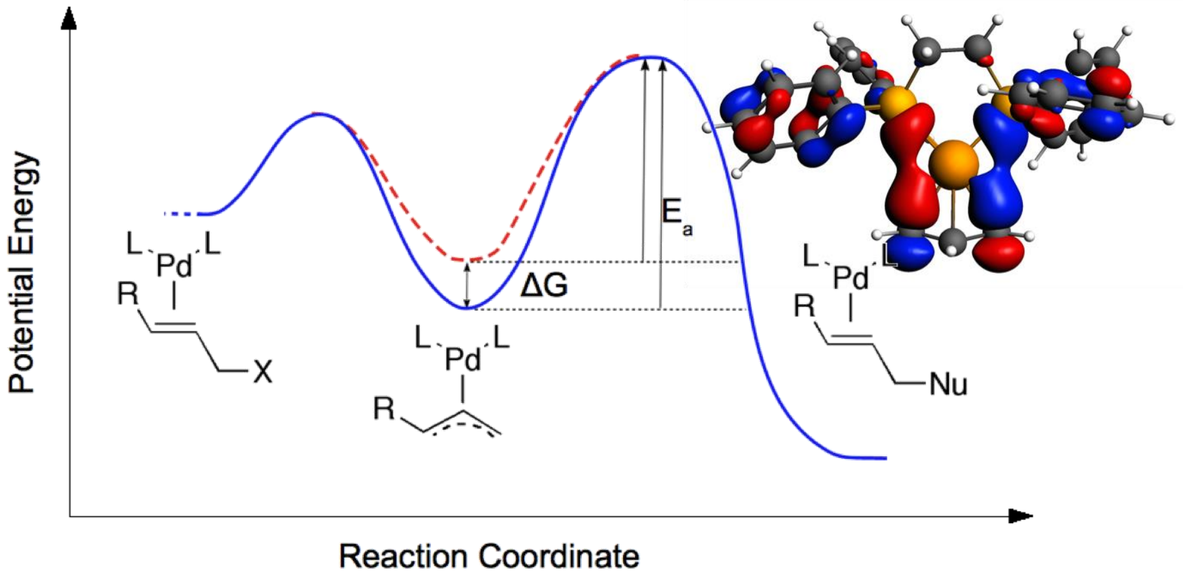
- Complex PES scans, automatic TS search
- Conformers
- Frequencies, phonons, stress & elastic tensors
- Molecular Dynamics, Monte Carlo

atomistic methods

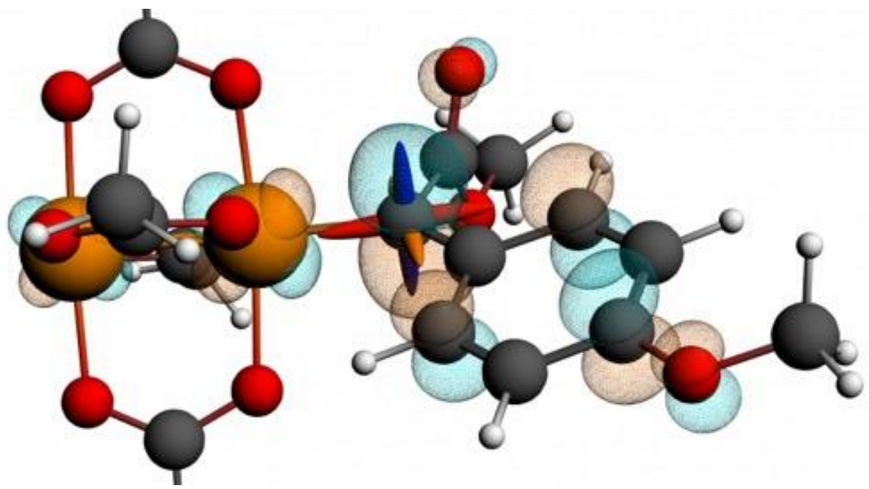




ADF: Molecular DFT



Bonding analysis: Understanding Catalyst-Substrate Interactions Nature Chem. 2, 417 (2010)



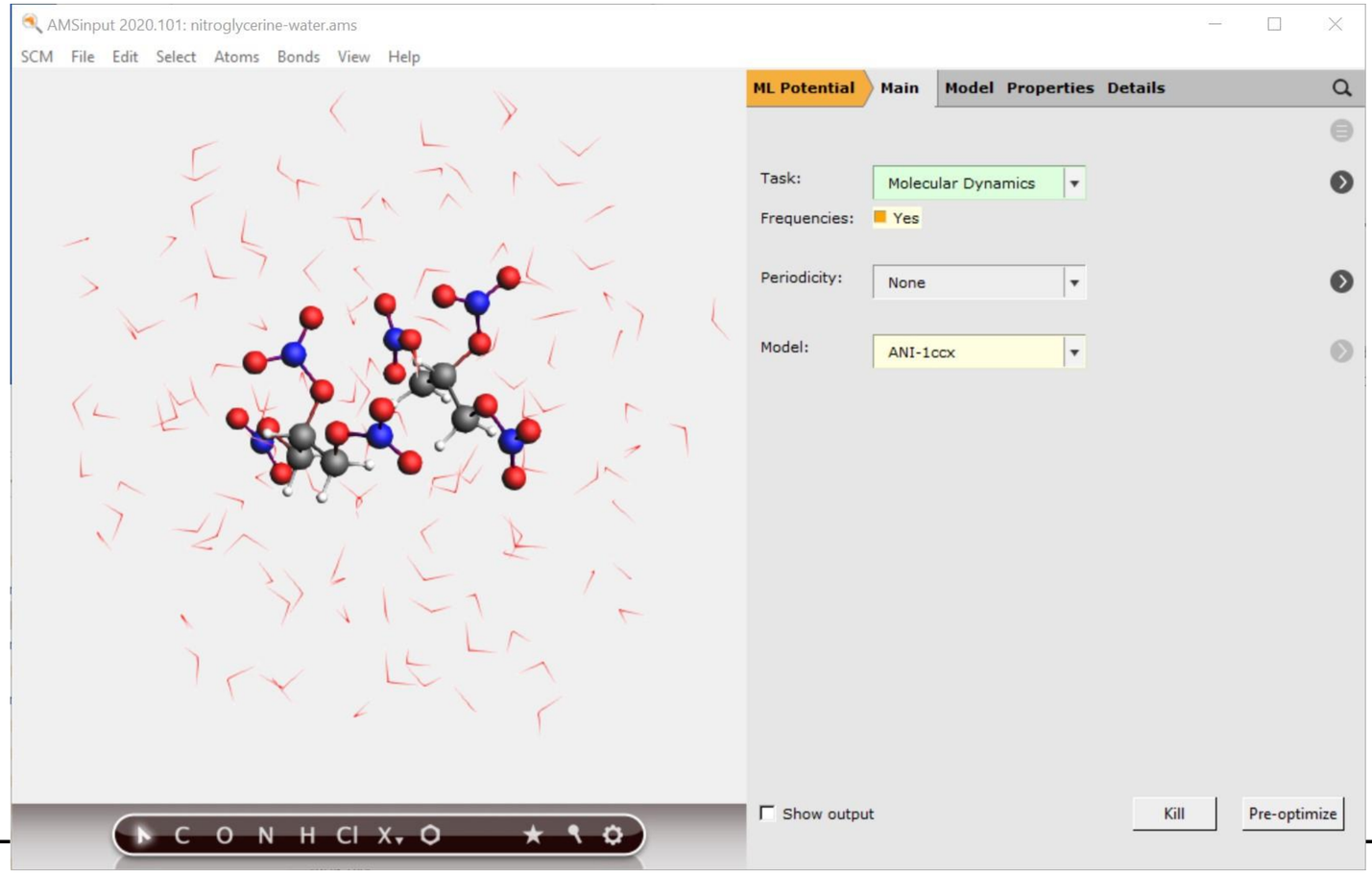
NMR calculations locate ^{13}C di-Rh carbene catalyst intermediate, Science, **342**, 351 (2013)

Strong & unique points

- All-electron Slaters, H-Og
- Relativity: ZORA (SR, **SOC**)
- Spectroscopy
  - EPR, NMR, IR (VCD), UVVIS, XAS
- Bonding analysis:
  - Fragment-based approach
  - ETS-NOCV, QTAIM, MO diagrams, NCI, Fukui function
  - Transfer integrals
- Environments
  - Subsystem DFT (FDE), QM/MM, QM/QM', polarizable force fields

Fast & Accurate - Machine Learning Potentials

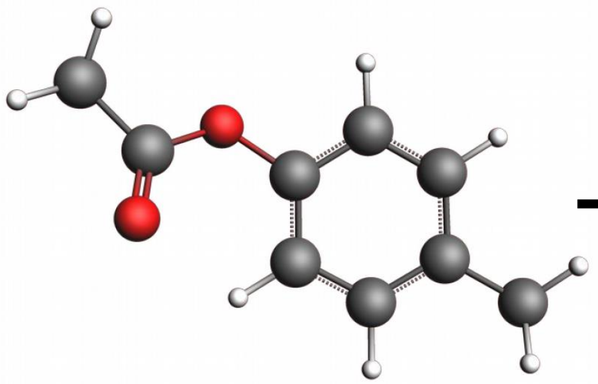
- Use machine learning potentials with AMS driver
  - PES scans, conformers, MD, reaction energies, …
  - Can also be used with multi-layer methods
  - Very fast & accurate when trained properly
- Automatically install popular ML Backends
  - Comes with ANI-1ccx, ANI-2x (H, C, N, O, F, Cl, S) potentials



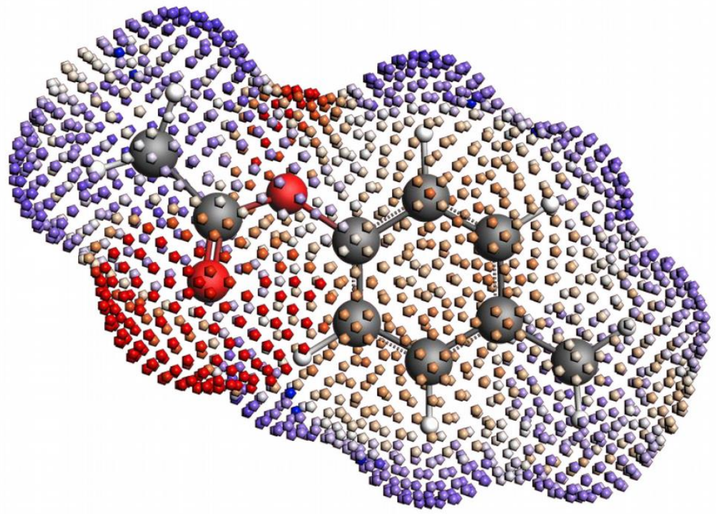
Demo video

Background: fluid thermodynamics from quantum chemistry

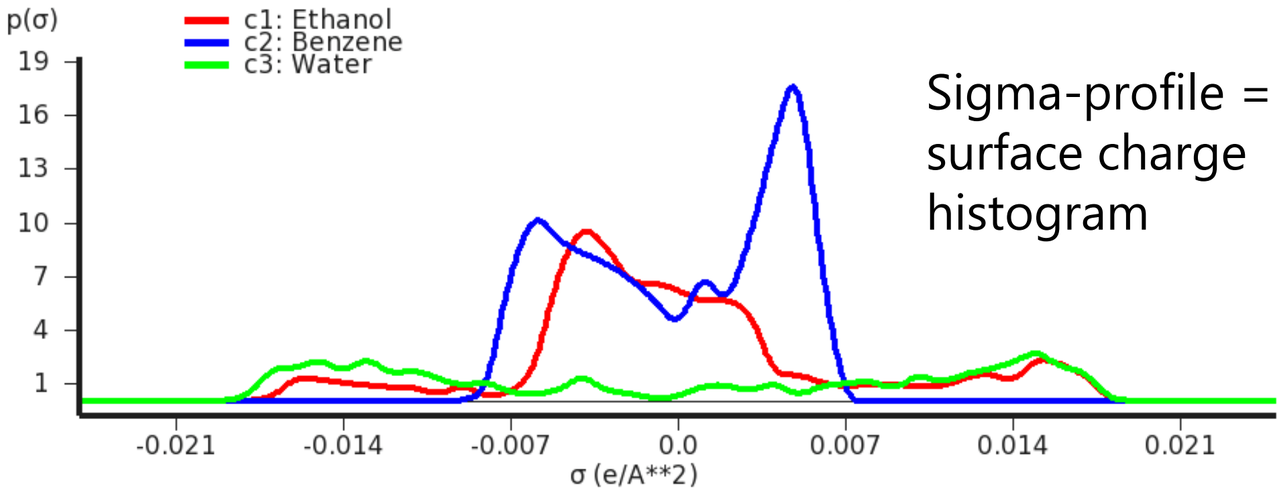
COSMO-RS: COntinuum Solvation MOdel + RS (Klamt), SAC (Sandler)
DFT-> chemical potential => activity coefficients => properties



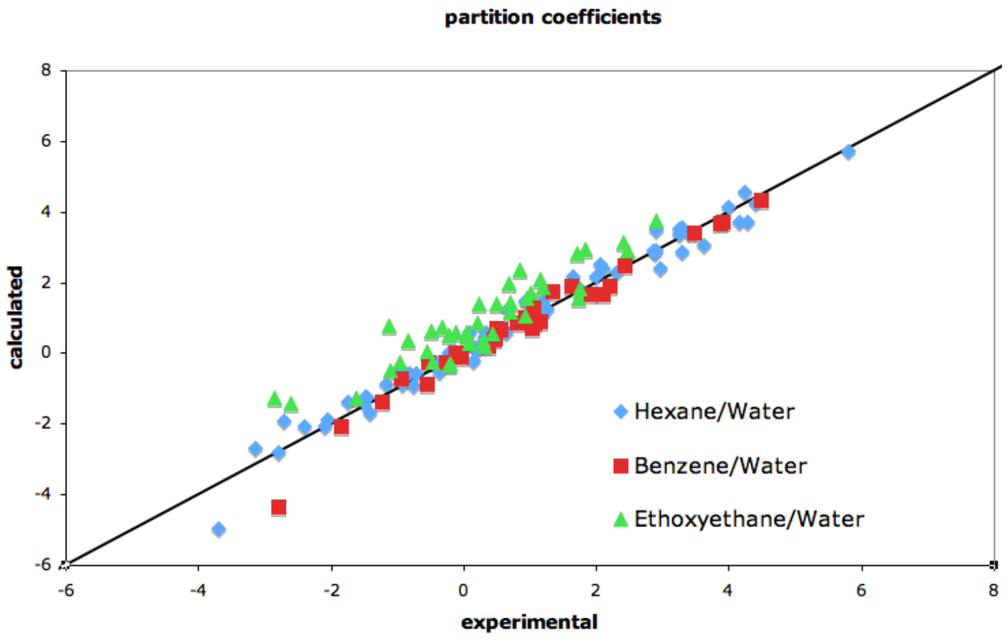
p-Tolyl acetic acid



Embedded in ideal conductor, surface charges calculated

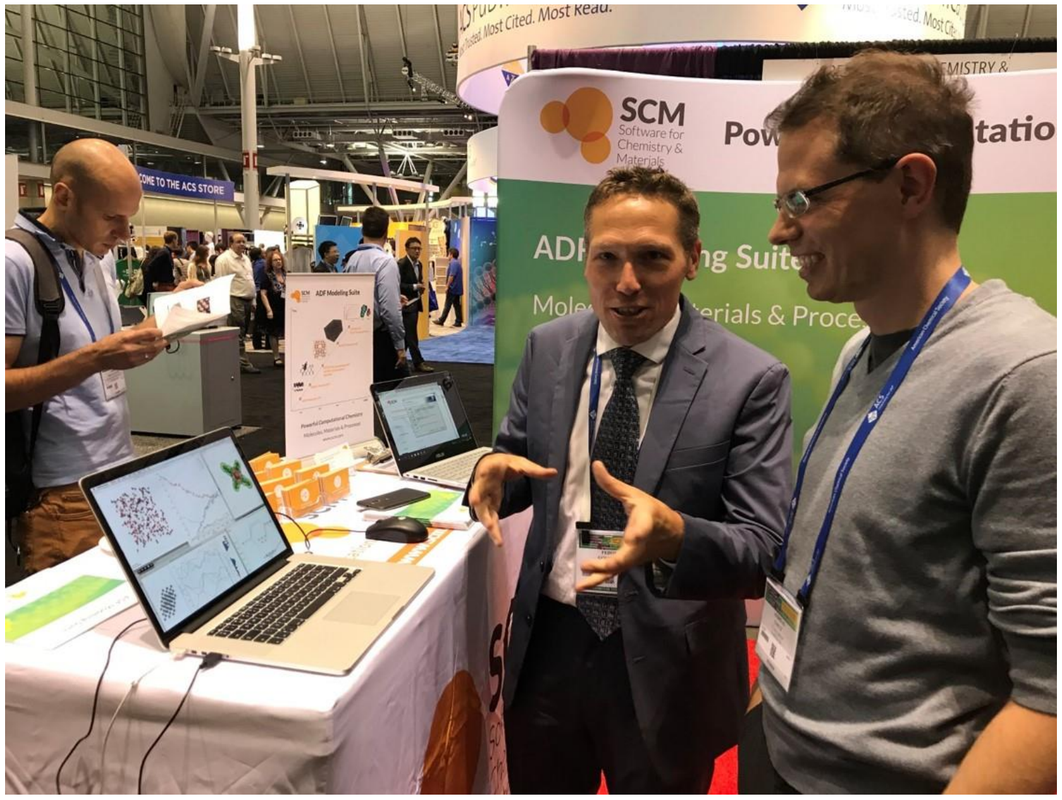


Sigma-profile = surface charge histogram



Discuss your research challenge!

Which research challenges are most urgent?



We love to hear from you!

goumans@scm.com

www.scm.com