Symmetry-constrained Monte Carlo to predict the experimental crystal structure of small organic molecules

Giovanni Macetti[a], Luca Sironi[a], Leonardo Lo Presti[a]

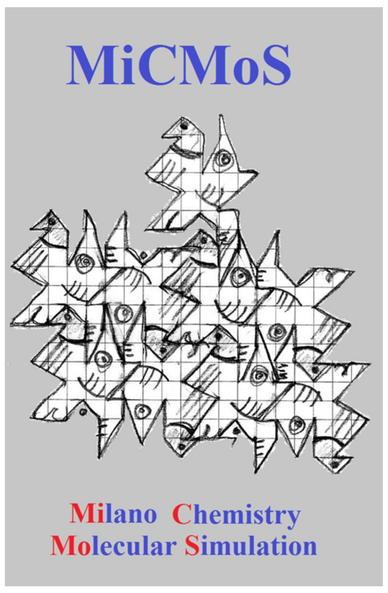
a. Dipartimento di Chimica, Università degli Studi di Milano, Milano, Italy

e-mail: giovanni.macetti@unimi.it

1. Introduction

- Crystal structure prediction (CSP) is a pivotal challenge in the field of material science,[1-3] with strong implications from pharmaceuticals to advanced materials engineering.
- Despite the significant progress achieved in the last years, the accurate prediction of the most thermodynamically stable polymorphs remains and intricate endeavour, especially for flexible organic molecules with numerous degrees-of-freedom.[4-5]
- To address this challenge, we presented a novel multi-step method, called symmetry-constrained Monte Carlo (SC-MC), that takes into consideration both the thermodynamics and the dynamical stability of crystals.[6].
- This method shares the same philosophy of the Milano Chemistry Molecular Simulation (MiCMoS) platform.[7]

2. Software



MiCMoS

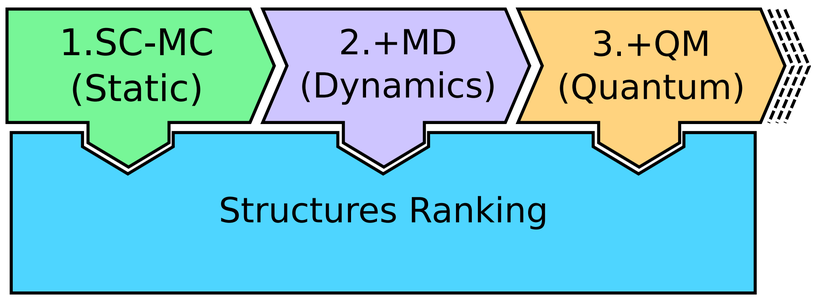
- Classical Monte Carlo (MC), Molecular Dynamics (MD) and PIXEL calculations
- Calibrated for small organic molecules
- Crystallographic oriented

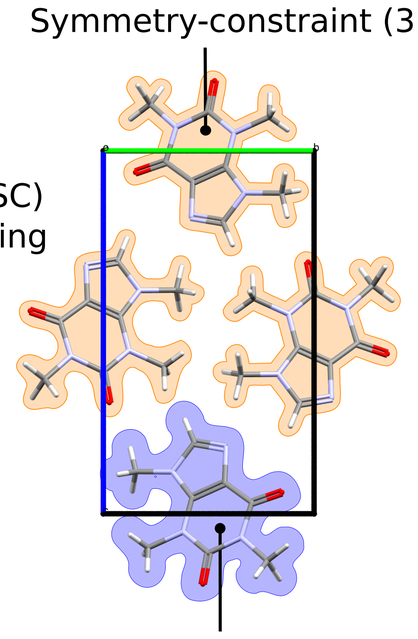
More information

Download and try it!

Crystal Structure Prediction

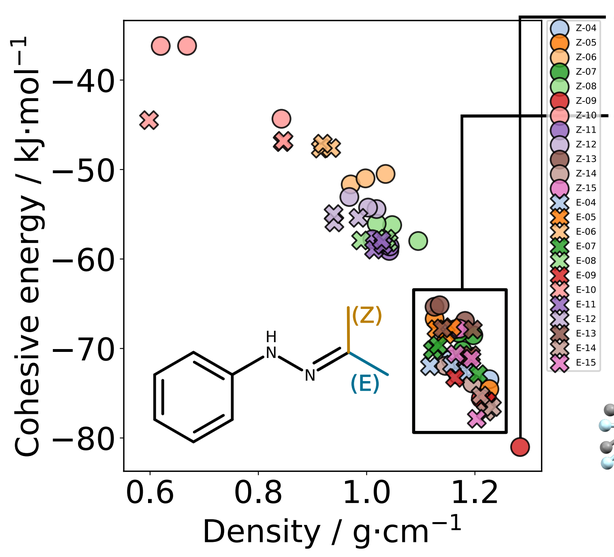
The algorithm:
1. Define topology and space groups
2. Define the symmetry-independent region
3. Run the Simmetry-Constrained Monte Carlo (MC-SC)
4. [optional] Run MD and QM calculations on promising structures
5. Rank the obtained structures





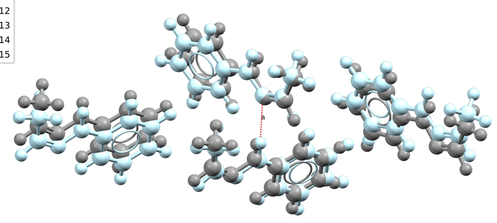
3. Results

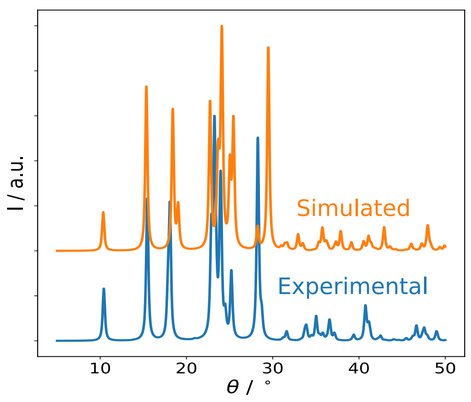
Acetaldheyde phenylhydrazone (APH): has 2 isomers, but only the (Z) one crystallizes
Space Group No.: 9 (Cc)
Exp. Lattice (Å,deg): **a**=5.465; **b**=16.963; **c**=8.176; **β**=108.25
Sim. Lattice (Å,deg): **a**=5.202; **b**=17.076; **c**=8.104; **β**=105.27



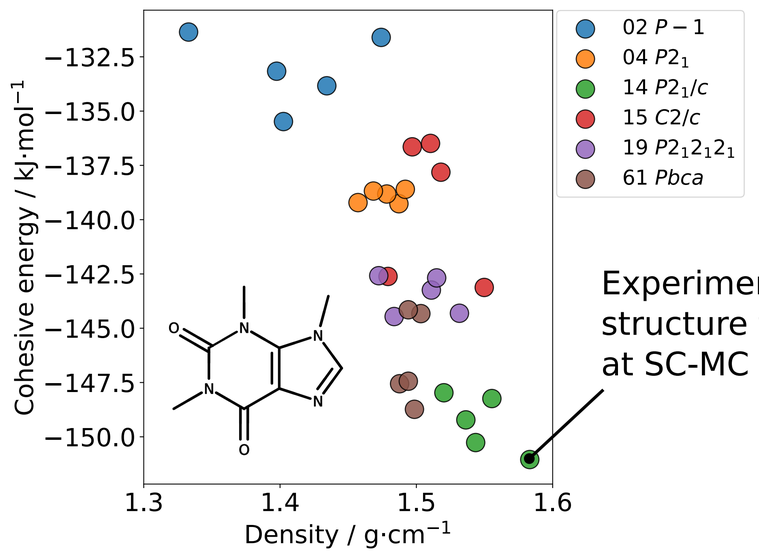
- The SC-MC algorithm correctly ranks the experimental Z-isomer as the most stable one.
- A group of plausible, but not observed, structures is found. They are both (Z) and (E)-isomers.

3D structures comparison and powder diffractograms

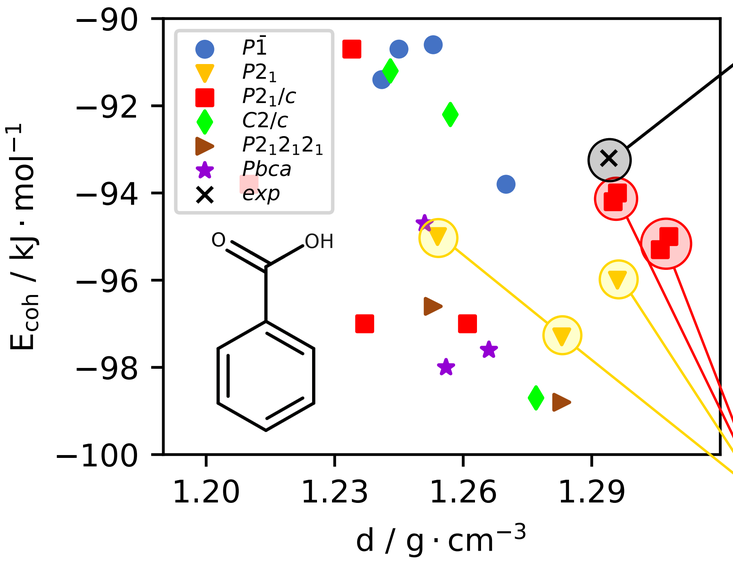




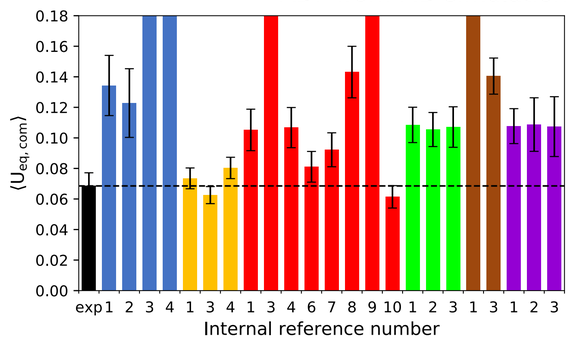
Isocaffeine (C) - Space Group: 14 ($P2_1/n$)
Exp. lattice (Å,deg): **a**=7.717; **b**=7.915; **c**=13.646; **β**=108.253
Sim. Lattice (Å,deg): **a**=7.278; **b**=8.103; **c**=13.526; **β**=105.257



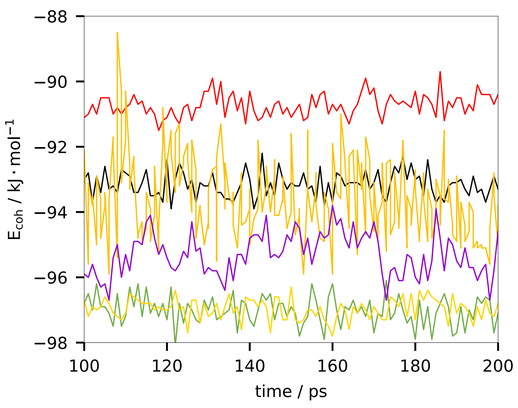
Benzoic Acid (BA): the molecule has few degrees of freedom and it is monomorphic, but ranking fails - Space Group No.: 14 ($P2_1/c$)
Exp. Lattice (Å,deg): **a**=5.4996; **b**=5.1283; **c**=21.950; **β**=97.37
Sim. Lattice (Å,deg): **a**=5.4146; **b**=5.4243; **c**=21.571; **β**=96.41



- The experimental structure is **not** among the best ones
- A pure static approach is not sufficient
- Molecular dynamics gives information on the mechanical stability of the structures



Cohesive energy oscillations for the $P2_1/c$ structures



- Only few structures are stable
- Two possible configurations: dimers (red squares) and catemers (most stable, yellow triangles)

4. Conclusions

- The new proposed CSP algorithm is cheap and works sufficiently well at the first SC-MC level.
- Dynamic and, eventually, Quantum parameters are sometimes necessary to list the correct ranking.
- More test cases are needed to further validate the method.
- Is the catemeric form of benzoic acid experimentally available?

5. References

[1] Gavezzotti, A. (1991) J. Am. Chem. Soc. 113, 4622.
[2] Price, S. L. (2014) Chem. Soc. Rev. 43, 2098.
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[4] Bowskill, et al. (2021) Annu. Rev. Chem. Biomol. Eng. 12, 593.
[5] Reilly, A. M. et al. (2016) Acta Cryst. B. 72, 439.
[6] Macetti, G., Sironi, L., Lo Presti, L. (2024) in preparation.
[7] Gavezzotti, A., Lo Presti, L., Rizzato, S. (2022) CrystEngComm 24, 922.