Crystal Structure Prediction of Molecular Crystals from First Principles: Are we there yet?

Cong Huy Pham,1,2 Emine Kucukbenli,3 and Stefano de Gironcoli1,4

1Scuola Internazionale Superiore di Studi Avanzati, Via Bonomea 265, 34136 Trieste, Italy
2International Center for Theoretical Physics, Strada Costiera 11, 34151 Trieste, Italy
3École Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland
4CNR-IOM Democritos National Simulation Center, Via Bonomea 265, I-34136 Trieste, Italy

(Dated: May 4, 2016)

Accurate molecular crystal structure prediction is a fundamental goal in academic and industrial condensed matter research and polymerism is arguably the biggest obstacle on the way. We tackle this challenge in the difficult case of the repeatedly studied, abundantly used aminoacid Glycine that hosts still little-known phase transitions and we illustrate the current state of the field through this example. We demonstrate that the combination of recent progress in structure search algorithms with the latest advances in the description of van der Waals interactions in Density Functional Theory, supported by data-mining analysis, enables a leap in predictive power: we resolve, without prior empirical input, all known phases of glycine, as well as the structure of the previously unresolved ζ phase after a decade of its experimental observation [Boldyreva et al. Z. Kristallogr. 2005, 220, 50-57]. The search for the well-established α phase instead reveals the remaining challenges in exploring a polymorphic landscape.

PACS numbers: 61.43.Bn 61.66.Hq 71.15.Mb

I. INTRODUCTION

Molecular polymorphism, the observation of different crystal structures made up of the same molecules, has been a central problem standing in the way of affordable and reliable crystal structure prediction (CSP) which would greatly accelerate the development of new materials for applications in solid state chemistry, material science and pharmaceutical science. The key challenges for ab initio CSP of molecular crystals can be summarized as i) the computational cost of thermodynamical exploration of a rich polymorphic phase space, ii) the accuracy needed to resolve similarly-low energies among polymorphs, and iii) the fact that kinetic factors may control the crystallization procedure rather than thermodynamic ones.

The past decade witnessed these challenges being tackled by the scientific community and the progress can be followed through the blind tests organized yearly by the Cambridge Crystallographic Data Centre. The exponential growth in the hardware performance and new, efficient algorithms tailored for molecular crystals have allowed a wider region of the phase space to be explored. The increased computational performance also enabled a transition from empirical interatomic potentials to more accurate but time consuming quantum mechanical techniques, mainly Density Functional Theory (DFT). This transition did not guarantee however an increase in predictive power in all cases: the standard DFT functionals do not describe properly van der Waals (vdW) interactions, which forces CSP studies to employ approximate semi-empirical corrections. These approximations to vdW interactions strongly affect the energy ordering of explored structures, which is a core information in predicting polymorphism. Hence, to render CSP predictions reliable, a fully ab initio method, able to obtain an accurate lattice energy including the vdW interactions, has been highly desirable.

Recently a breakthrough in the description of vdW interactions in DFT has been made: many new non-local functionals that accurately describe the dispersion interactions have been proposed and demonstrated unprecedented success in a wide range of systems from molecules, molecular crystals to layered materials, with a computational cost comparable to that of standard functionals. It has been recently shown that even in difficult cases such as glycine crystals, where polymorphs show energy differences as little as 1 kcal/mol, new non-local functionals can yield the correct stability ordering as well as accurate pressure evolution.

Encouraged by these results we combine this critical progress in DFT with recent developments in evolutionary CSP, specifically adapted for molecular structure search, and perform a fully ab initio CSP search on glycine crystals, without semi empirical corrections in the energy description, using neither information on cell geometry nor the symmetry of the experimentally observed polymorphs. We thus assess whether state-of-the-art ab initio CSP can pass the challenging blind test of exploring the phase space of polymorphic glycine.

Glycine, NH₂CH₂COOH, the smallest aminoacid, is an excellent test case for CSP studies as its already rich polymorphism under ambient conditions is amplified and becomes less understood at higher pressure (see Fig.1). A clear example to this is the ζ phase, which is reported to be stable at ambient conditions for at least three days. Interestingly, despite its stability, and at least three CSP studies devoted to Glycine so far, a decade after its observation, the ζ phase has not been structurally resolved yet.
The stability order of polymorphs at ambient pressure, \( \gamma > \alpha > \beta \), with indicated \( Z \) molecules in unit cell, is given. The form readily obtained by evaporation of aqueous solutions is \( \alpha \)-glycine, which for long was believed to be the most stable phase instead of the later discovered ground-state phase \( \gamma \). Pressure evolution of ambient pressure phases show that while \( \gamma \) and \( \beta \) phases quickly lose single crystal nature or undergo a phase transition within a few GPa, \( \alpha \) phase stays stable up to 23 GPa, the highest pressure reached in experiments. A reversible, hysteresis-free single-crystal to single-crystal transition occurs from \( \beta \) to \( \delta \) phase at 0.76 GPa. Single crystals of the \( \gamma \) phase instead undergo an extended polymorphic transformation in the wide range of 2.7-7.6 GPa, to a high-pressure polymorph, the \( \epsilon \) phase, accompanied with the fragmentation of single crystals into powder. Upon de-compression, the \( \epsilon \) phase is stable down to 0.62 GPa. Where a new, irreversible phase transition occurs to the \( \zeta \) phase, a new polymorph which is reported to be stable at ambient conditions for at least three days.

The complex polymorphism of glycine highlights the importance of performing an extensive search in phase space, while practical concerns limit any CSP study to explore primarily the lowest energy structures. In this study we use evolutionary algorithms (EA) as implemented in the USPEX package to address this interplay efficiently. We perform three test suits with \( Z=2, 3 \) or 4 glycine molecules in the unit cell. At the first generation, 30 structures are created randomly. After energy ordering, the 20% of the population that is energetically least favorable is discarded. Among the remaining, a fingerprint analysis is performed and potential parents whose fingerprint is within a threshold distance of 0.01 from any lower energy structure are discarded as well. The so-determined unique structures are eligible as parents and are allowed to procreate. The 30 new structures of the next generation are created from parents through the following operations: heredity (cross-over of two structures) (40%), softmutation (translation and rotation based on estimate of soft vibrational modes) (20%), rotation of the molecule (20%), and random structure generation (20%). In addition, the three best parents are directly cloned to the next generation. In all simulations, the maximum number of generations was 20.

### II. METHODS

#### A. Evolutionary Search

We use EA as implemented in the USPEX package to search for the low-energy structures of glycine with \( Z=2, 3 \) or 4 molecules in the unit cell. At the first generation, 30 structures are created randomly. After energy ordering, the 20% of the population that is energetically least favorable is discarded. Among the remaining, a fingerprint analysis is performed and potential parents whose fingerprint is within a threshold distance of 0.01 from any lower energy structure are discarded as well. The so-determined unique structures are eligible as parents and are allowed to procreate. The 30 new structures of the next generation are created from parents through the following operations: heredity (cross-over of two structures) (40%), softmutation (translation and rotation based on estimate of soft vibrational modes) (20%), rotation of the molecule (20%), and random structure generation (20%). In addition, the three best parents are directly cloned to the next generation. In all simulations, the maximum number of generations was 20.

#### B. ab initio Calculations

For every structure generated by USPEX, the geometry and cell relaxation is performed using vdw-DF functional which was implemented in the QUANTUM ESPRESSO package. A kinetic energy cutoff of 80 Ryd and a charge density cutoff of 560 Ryd are used. The Brillouin zone sampling resolution was gradually increased in three steps during relaxation: resolution of \( 2\pi \times 0.12 \text{ Å}^{-1} \), \( 2\pi \times 0.10 \text{ Å}^{-1} \) and \( 2\pi \times 0.08 \text{ Å}^{-1} \) respectively. Energies and geometries of the last step with the densest k-point are used throughout the study. PAW pseudopotentials are taken from the PSLibrary project. By using this setup all structures are fully relaxed within a convergence of less than 0.1 mRy for absolute total energy, 0.5 mRy/a.u. for the forces on atoms and less than 0.005 GPa for the stress tensor.

#### C. Cluster analysis

The cluster analysis is performed by using single linkage clustering, where two structures with fingerprint distance less than distance threshold \( d \) are considered to
belong to the same cluster. Since USPEX definition of fingerprint does not include any information on the enthalpy of the structure, a constraint is added such that two structures with enthalpy difference more than 0.5 kJ/mol are not allowed to form a cluster. This constraint is found necessary only when the clustering analysis is performed for all the encountered structures, while limiting the analysis to low enthalpy region, such constraint was not necessary as each cluster was successfully identified with distance only.

III. RESULTS AND DISCUSSION

The results of CSP can be visualized through the distribution of energy as a function of volume for the structures encountered during the search. As shown in the expanded view of a wide region in phase space (see left panel of Fig. 2), about 40% of all the structures lies within 4 kJ/mol of the experimentally known ground state structure, \( \gamma \). Focus- ing on this region of the energy landscape as shown in the right panels of Fig. 2 we see structures forming islands with varying size and shapes. This feature illustrates the added complication in the case of molecular CSP with respect to standard inorganic solids where a well-defined, isolated minimum would be observed for each phase. The shape and finite size of the islands can be understood considering that Glycine is very soft, therefore structures that are far off from the equilibrium lattice parameters are thermodynamically penalized only slightly as demonstrated in the inset of Fig. 2. This effect, combined with the numerical noise in geometry optimization, as well as an increased number of degrees of freedom in molecular crystals, is enough to give rise to crowding around each polymorphic minimum. Nevertheless islands are well separated and a clear assignment of polymorphs can be made for most of them. This is in stark contradiction with a very recent CSP study for glycine with empirical corrections for intermolecular interactions, which reported that the obtained energy-volume points were not separated well enough to clearly identify each polymorph, thus underlining the challenge of polymorphism for CSP\(^{12}\). In this study instead the separation between several islands are well represented down to very small energy differences (inset of Fig. 2). We believe this stems from the leap in accuracy and precision reached by the use of fully ab initio energetics together with last generation evolutionary algorithm tools.

![FIG. 2: (color) Results of ab initio crystal structure search for Glycine with cluster analysis. Left panel: Enthalpy vs volume distribution of all encountered structures for 2 molecules per cell shows that CSP with evolutionary algorithm allows a wide energy range to be explored while “survival of the fittest” algorithm keeps the focus on the thermodynamically low lying structures. Right panels: Expanded view of all explored structures compatible with 2, 3 and 4 molecules per cell in the lowest 4 kJ/mol range. All known phases of Glycine are identified with the right energy ordering along with a number of low-lying alternative polymorphs, including our prediction for the hitherto unresolved \( \zeta \) phase. As shown in the inset of the Z=4 panel, crowding around each polymorph, when compared with its equation of state, is compatible with numerical noise due to incomplete relaxation. The distance-based clustering techniques adopted here are however well suited to separate and identify the different low lying polymorphs even in presence of noise.](image)

In Fig. 3 we display a step by step clustering analysis where a bottom-up distance-based hierarchical clustering approach with single linkage is used to identify the unique polymorphs among all the structures obtained with CSP. In distance-based approaches, a similarity metric is defined so that a distance can be measured between data points, and clusters are constructed based on proximity. In this study we use as the metric the fingerprint-based cosine defined in the EA code USPEX\(^{12}\):

\[
D_{\text{cosine}}(1, 2) = \frac{1}{2} \left( 1 - \frac{F_{1} \cdot F_{2}}{|F_{1}| |F_{2}|} \right),
\]

\[
F_{AB}(R) = \sum_{A_{i,\text{cell}}} \sum_{B_{j}} \frac{\delta(R - R_{ij})}{4\pi R_{ij}^{2} N_{A} N_{B} \Delta} - 1,
\]

where individual structure fingerprints are defined as

where the double sum runs over all ith molecules of type A within the unit cell and all jth molecules of type B within a distance \( R_{\text{max}} \); \( \delta(R - R_{ij}) \) is a Gaussian-smeared delta function; \( R_{ij} \) is the distance measured from the centers of molecules \( i \) and \( j \); \( V \) is the unit cell volume; the function \( F_{AB}(R) \) is discretized over bins of width \( \Delta \); \( N_{A} \) and \( N_{B} \) are the number of molecules of type A and B, respectively.

In this study we use as the metric the fingerprint-based cosine defined in the EA code USPEX\(^{12}\):

\[
D_{\text{cosine}}(1, 2) = \frac{1}{2} \left( 1 - \frac{F_{1} \cdot F_{2}}{|F_{1}| |F_{2}|} \right),
\]

\[
F_{AB}(R) = \sum_{A_{i,\text{cell}}} \sum_{B_{j}} \frac{\delta(R - R_{ij})}{4\pi R_{ij}^{2} N_{A} N_{B} \Delta} - 1,
\]

where the double sum runs over all ith molecules of type A within the unit cell and all jth molecules of type B within a distance \( R_{\text{max}} \); \( \delta(R - R_{ij}) \) is a Gaussian-smeared delta function; \( R_{ij} \) is the distance measured from the centers of molecules \( i \) and \( j \); \( V \) is the unit cell volume; the function \( F_{AB}(R) \) is discretized over bins of width \( \Delta \); \( N_{A} \) and \( N_{B} \) are the number of molecules of type A and B, respectively.
The distance threshold used to define whether two data points belong to the same cluster is then monotonically increased. As a result the cluster population evolves from the situation where every data point forms a distinct cluster to the situation in which all data points belong to the same global cluster, revealing the bottom-up and hierarchical nature of the approach. Translated to the CSP problem, this data mining approach transforms the challenge of identification of unique polymorphs from the visual comparison of all structures into an easier decision on the value of the distance-threshold. The optimal distance threshold is such that each data cluster matches a unique physical polymorph. In the case of glycine a distance threshold around 0.05-0.1 is found to be appropriate to identify the low energy polymorphs successfully (see Supplementary Material Table.S1 and related .cif files). The so-determined optimal threshold can serve in advanced supervised learning techniques and be fed back in the CSP procedure to increase considerably the efficiency by reducing the generation of replicas of already explored structures.

The cluster analysis outlined above identifies all experimentally observed phases of glycine compatible with 2, 3 or 4 molecules per cell, as well as suggesting others, hereon named according to their enthalpy-per-molecule ordering. Phases 1 to 11 lie within approximately 2 kJ/mol of the experimentally most stable phase, γ. Among them one of the lowest energy polymorphs (phase 2) can be identified with ζ-glycine based on the excellent agreement with XRD results (Fig.4a) as well as its pressure evolution (Fig.4b). The structural identification of the ζ phase, previously experimentally observed but not resolved up to now, marks an important achievement for CSP and is a key result of our study. The search for α-glycine proved very demanding despite it being the experimentally most readily formed polymorph at ambient conditions. In this study the α phase could not be found even after 20 generations with the standard settings in USPEX. This difficulty revealed one of the remaining challenges of CSP: the effective exploration of the topology of an erratic and vast configuration space. Indeed, the fully ab-initio scheme advocated for in this work pays for the higher accuracy with a heavy computational cost that makes this effectiveness even more crucial. To improve on this aspect we weighted the random selection of the space group of the candidate structures according to the frequency distribution appearing in known organic crystal structure database (P2₁/c (36.59 %), P2₁2₁2₁ (16.92 %), P2₁ (11.00 %), C2/c (6.95 %), Pnca (6.35 %), Pbcn (4.24 %), and uniform otherwise). This procedure successfully produced the α phase at the 14th generation, demonstrating that incorporation of even mild and system unspecific experimental knowledge in the search strategy may have a significant impact to overcome the effectiveness challenge in the most demanding cases.

Indeed if more system specific information is available it can be used to further constrain and guide the phase-space search: limiting the search to the experimentally known, P2₁/c, space group of α-glycine, or fixing the cell
shape to its experimental value, resulted in its identification at the 15th and 8th generations, respectively. Combining the two constraints resulted in an even quicker discovery at the third generation.

Once the low energy structures are found and examined, the configuration space search can be further instructed to look for certain patterns. In the case of glycine, it is noteworthy that the crystal building block can be seen as a glycine dimer, with head to tail orientation. This feature is not seen in other ambient pressure polymorphs of glycine, and can be speculated to be one of the reasons for the α phase not being readily connected with other phases in the energy landscape. This correlates with the difficulty of generating the structure during the EA procedure, as well as with its exceptional stability under pressure. Instead, if the dimer unit is taken as building block in a CSP search, the α phase is found at the third iteration and new phases such as phase 8, phase 14, phase 24 and phase 38 are also discovered.

Hence the difficulty of exploring the α phase as well as the finding of new phases only after a dimer unit is employed, underlines the remaining challenges of CSP and calls for even more efficient methods for exploring new structures and innovative data analysis applications to guide the search on the go for a full optimization of resources. (see Supplementary Material Fig.S2-10 for details of all search attempts).

IV. CONCLUSION

We presented a fully blind, fully ab initio crystal structure prediction test on Glycine, a system that has been examined several times in the past yet never fully grasped. A remarkable precision and a broad sampling is obtained in an affordable computational time thanks to last generation van der Waals density functionals and evolutionary algorithms at the leading edge. The comparison of our results with existing experimental studies enabled us to resolve the so-far unidentified ζ phase a decade after its first experimental observation. Further analysis of the results of the blind test allowed us to propose several new thermodynamically plausible structures with varying volume, compressibility and polarization. To address the experimentally well established but CSP-wise challenging α phase, we introduced an intuitive sampling strategy based on crystal structure relative frequency found in nature. This strategy successfully found this challenging phase and allowed us further insight in the energy landscape. Overall, the results of our blind test shows us that a reliable crystal structure prediction procedure is possible with incorporation of several complementary recipes to reach success, emphasizing that one-size-fits-all solutions are yet to be discovered. Fortunately, the leap in precision and sampling capability we have demonstrated with these new generation tools opens new paths for crystal structure prediction with data processing procedures such as clustering algorithms. Hence we strongly believe ab initio CSP as presented here has come a long way and that a new standard for structure prediction for molecular crystals is set, and an interdisciplinary horizon for computational science within this field is now open.

Acknowledgments

Work supported by the Italian MIUR through the PRIN 2010 initiative (PRIN 20105ZZTSE). Computational resources have been provided by SISSA and CINECA, Italy, and on Curie@TGCC-CEA through PRACE Project 2011050736.

* Current address: SISSA, Via Bonomea 265, 34136 Trieste, Italy
† Electronic address: degironc@sissa.it

1 S.M. Woodley, R. Catlow, Nature Mat. 7, 937-946, (2008).
2 G.R. Desiraju, Nature Mat. 1, 77-79 (2002).
3 J. Yang, W. Hu D. Usvyat, D. Matthews M. Schuetz, G.K.-L. Chan, Science 345, 610-643, (2014).
4 S.L. Price, Advanced Drug Delivery Reviews, 56, 301-319 (2004).
5 https://www.ccdc.cam.ac.uk/Community/Initiatives/Pages/CSPBlindTests.aspx
6 J.P. Lommerse, et al., Acta Crystallogr. B 66, 697-714 (2000).
7 D.A. Bardwell, et al., Acta Crystallogr. B 67, 535-551 (2011).
8 Q. Zhu, A.R. Oganov, C.W. Glass, H.T. Stokes, Acta Cryst. B, 68, 215-226 (2012).
9 M. Dion, H. Rydberg, E. Schroeder, D.C. Langreth, B.I. Lundqvist, Phys. Rev. Lett. 92, 236401 (2004).
10 O.A. Vydrov, T. Van Voorhis, J. Chem. Phys. 133, 244103 (2010).
11 R. Sabatini, E. Küçükbenli, B. Kolb, T. Thonhauser, S. de Gironcoli, J. Phys.: Condens. Matter 24, 424209 (2012).
12 A.R. Oganov C.W. Glass, J. Chem. Phys. 124, 244704 (2006).
13 E.V. Boldyreva, S.N. Ivashevskaya, H. Sowa, H. Ahsbahs, H.-P. Weber, Z. Kristallogr. 220, 50-57 (2005).
14 A.M. Lund, G.I. Pagola, A.M. Orendt, M.B. Ferraro, J.C. Facelli, Chem. Phys. Lett. 626, 20 (2015).
15 B.D. Cichos, J.C. Facelli, R. Sabatini, E. Küçükbenli, B. Kolb, T. Thonhauser, S. de Gironcoli, J. Phys.:Condens. Matter 21, 395502 (2009).
16 P. Giannozzi, et al., J. Phys.:Condens. Matter 21, 395502 (2009).
17 http://www.qe-forge.org/gf/project/pslibrary
18 S.L. Price, Chem. Soc. Rev. 43, 2008-2111 (2014).
19 A.R. Oganov, M. Valle, J. Chem. Phys. 130, 104504 (2009).
20 W.H. Baur, D. Kassner, Acta Cryst. B 48, 356 (1992).