Energy/structure database of all proteinogenic amino acids and dipeptides without and with divalent cations

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Abstract

We present a structural data set of the 20 proteinogenic amino acids and their amino-methylated and acetylated (capped) dipeptides. Different protonation states of the backbone (uncharged and zwitterionic) were considered for the amino acids as well as varied side chain protonation states. Furthermore, we studied amino acids and dipeptides in complex with divalent cations (Ca\textsuperscript{2+}, Ba\textsuperscript{2+}, Sr\textsuperscript{2+}, Cd\textsuperscript{2+}, Pb\textsuperscript{2+}, and Hg\textsuperscript{2+}). The database covers the conformational hierarchies of 280 systems in a wide relative energy range of up to 4\,eV (390\,kJ/mol), summing up to an overall of 45,892 stationary points on the respective potential-energy surfaces. All systems were calculated on equal first-principles footing, applying density-functional theory in the generalized gradient approximation corrected for long-range van der Waals interactions. We show good agreement to available experimental data for gas-phase ion affinities. Our curated data can be utilized, for example, for a wide comparison across chemical space of the building blocks of life, for the parametrization of protein force fields, and for the calculation of reference spectra for biophysical applications.
Proteins are the machinery of life. We here present a first principles study of the conformational preferences of their building blocks: In Figure 1 we summarize the subjects of this study, the 20 proteinogenic amino acids and dipeptides, different possible protonation states, and the 6 divalent cations Ca$^{2+}$, Ba$^{2+}$, Sr$^{2+}$, Cd$^{2+}$, Pb$^{2+}$, and Hg$^{2+}$. In past studies, a wide range of different approximate electronic structure methods has been applied to some of the 20 proteinogenic amino acids, see, for example, references [1–56]. These studies have deepened our understanding of the conformational basics of individual building blocks, but a systematic comparison of properties of the different building blocks is complicated when relying on data from different sources. On the one hand this is due to the molecular models that may differ in protonation states and backbone capping. On the other, the simulations can differ in several ways:

- Different sampling strategies or methods to generate conformers may have been used. Also search-dependent settings, like energy cut-offs, can have a significant impact on the results.
- The levels of theory that have been applied range from semi-empirical to Hartree-Fock (HF) to density-functional theory (DFT) up to coupled-cluster calculations, see references [1–56] for example.
- Numerical settings, e.g., basis sets or for the geometry optimization, can differ substantially and might lead to different results.

A further point that limits a quantitative comparison is the accessibility of the data from different studies. Energies, for example, often have to be extracted from table footnotes and/or the structural data is not always accessible in the Supporting Information of the respective articles, sometimes even only accessible as figures in the manuscript. The data set presented here renders such limitations obsolete by covering a comprehensive segment of chemical space exhaustively, using a large scale computational effort. This study treats all proteinogenic amino acids, their dipeptides and their interactions with the divalent cations Ca$^{2+}$, Ba$^{2+}$, Sr$^{2+}$, Cd$^{2+}$, Pb$^{2+}$, and Hg$^{2+}$ (see Figure 1 for an overview) on the same theoretical footing. The importance of peptide cation interactions may be highlighted by the fact that about 40% of all proteins bind cations [57–59]. Especially Ca$^{2+}$ is important in a multitude of functions, ranging, for example, from blood clotting [60] to cell signaling to bone growth [61]. Such calcium mediated functions can be disturbed by the presence of alternative divalent heavy metal cations like Pb$^{2+}$, Cd$^{2+}$, and Hg$^{2+}$ [59,62,63].

The conformations and total energies of each molecular system are calculated from first principles in the framework of density-functional theory (DFT) [64,65] using the PBE generalized-gradient exchange-correlation functional [66]. Energies are corrected for van der Waals interactions using the Tkatchenko-Scheffler formalism [67]. A $C_6[n]/r^6$ term is computed as a pairwise sum over all atoms, where $r$ is the interatomic distance and a cut-off for short interatomic distances
Figure 1: Top left and center: Schematic depiction of the backbone conformations of uncharged, zwitterionic, and dipeptide forms of the amino acids considered in this work. Side chains are indicated by the letter R. Top right: Divalent ions considered for complexation with the 20 proteinogenic amino acids. Lower five rows: Side chains, including different protonation states where applicable, of the 20 proteinogenic amino acids considered in this work.
is applied. $C_6[n]$ coefficients were obtained from the self-consistent electron density. The method is further referred as PBE+vdW. This level of theory is robust for potential-energy surface (PES) sampling of peptide systems [68–74]. The curated data is provided as basis for comparative studies across chemical space to reveal conformational trends and energetic preferences. It can, for example, further be used for force-field development, theoretical studies at higher levels of theory, and as a starting point for theoretical calculations of spectra for biophysical applications.

Methods

Molecular models

This study covers a total of 280 molecular systems (summarized in Figure 1). The number is the product of these chemical degrees of freedom that were considered in our study:

20 proteinogenic amino acids. In case of (de)protonatable side chains, all promomers (different protonations states) were considered as well.

2 different backbone types, either free termini (considered in uncharged or zwitterionic form) or capped (N-terminally acetylated or C-terminally amino-methylated).

7 summarizing that the respective amino acid or dipeptide was considered either in isolation or with one of six different cation additions: $\text{Ca}^{2+}$, $\text{Ba}^{2+}$, $\text{Sr}^{2+}$, $\text{Cd}^{2+}$, $\text{Pb}^{2+}$, or $\text{Hg}^{2+}$.

Conformational search and energy functions

For the initial scan of the PES, the empirical force field OPLS-AA [75] was employed, followed by DFT-PBE+vdW relaxations of the energy minima identified in the force field. The identified set of structures was then subjected to a further first-principles refinement step, \emph{ab initio} replica-exchange molecular dynamics (REMD). An overview of the procedure is given in Figure 2 and the steps are described in more detail below.

Force-field based (OPLS-AA) [75] \textbf{global conformational searches (Step 1)} were performed for all dipeptides and uncapped isolated amino acids and with $\text{Ca}^{2+}$. These searches employed a basin hopping search strategy [76, 77] as implemented in the tool “scan”, distributed with the TINKER molecular simulation package [78, 79]. We here used an in-house parallelized version of the TINKER scan utility that was first used in reference [70]. In this search strategy, input structures for relaxations are generated by projecting along normal modes starting from a local minimum. The number of search directions from a local minimum was set to 20. Conformers were accepted within a relative energy window of 100 kcal/mol and if they differ in energy from already found minima.
Figure 2: Schematic representation of the workflow employed to locate stationary points on the potential-energy surfaces of the respective molecular systems.
by at least $10^{-4}$ kcal/mol. The search terminates when the relaxations of input structures do not result in new minima.

After that, **PBE+vdW relaxations (Step 2)** were performed with the program FHI-aims [80–82]. FHI-aims employs numeric atom-centered orbital basis sets as described in reference [80] to discretize the Kohn-Sham orbitals. Different levels of computational defaults are available, distinguished by choice of the basis set, integration grids, and the order of the multipole expansion of the electrostatic (Hartree) potential of the electron density: For the chemical elements relevant to this work, “light” settings include the so-called tier-1 basis sets and were used for initial relaxations. “Tight” settings include the larger tier-2 basis sets and ensure converged conformational energy differences at a level of few meV [80]. All energies discussed here (if not mentioned otherwise) are results of PBE+vdW calculations with a tier-2 basis and tight convergence criteria (“tight” settings). Relativistic effects were taken into account by the so-called atomic zero-order regular approximation (atomic ZORA) [83,84] as described in reference [80]. Previous high-level quantum chemistry benchmark calculations at the coupled-cluster level, CCSD(T), for polyalanine systems [85] and alanine dipeptides with Li$^+$ [69] demonstrate the reliability of the PBE+vdW method for this class of systems.

The **refinement (Step 3)** by ab initio REMD [86,87] is intended to alleviate the potential effects of conformational energy landscape differences between the force field and the DFT method. In REMD, multiple molecular dynamics trajectories of the same system are independently initialized and run in a range of different temperatures. Based on a Metropolis criterion, configurations are swapped between trajectories of neighboring temperatures. Thus, the simulations can overcome barriers and provide an enhanced conformational sampling in comparison to classical molecular dynamics (MD) [87,88]. The simulations were carried out employing a script-based REMD scheme that is provided with FHI-aims and that was first used in reference [89]. Computations were performed at the PBE+vdW level with “light” computational settings. The run time for each REMD simulation was 20 ps with an integration time step of 1 fs. The frequent exchange attempts (every 0.04 or 0.1 ps) ensure efficient sampling of the potential-energy surface as shown by Sindhikara et al. [90]. The NVT thermostat by Bussi et al. [91] was used. Starting geometries for the replicas were taken from the lowest energy conformers resulting from the PBE+vdW relaxations in Step 2. REMD parameters for the individual systems, i.e. the number of replicas, acceptance rates for exchanges between replicas, the frequency for exchange attempts, and the temperature range, are summarized in table S1 of the Supporting Material. Conformations were extracted from the REMD trajectories every 10th step, i.e. every 10 fs of simulation time. In order to generate a set of representative conformers, these structures were clustered using a $k$-means clustering algorithm [92] with a cluster radius of 0.3 Å as provided by the MMSTB package [93]. The resulting arithmetic-mean structures from each cluster were then relaxed using PBE+vdW with “light” computational settings. The obtained conformers were again clustered and cluster representatives were relaxed with PBE+vdW (“tight” computational settings) to obtain
Figure 3: Numbers of stationary points of the PBE+vdW potential-energy surface (PES) at the “tight”/tier-2 level of accuracy that were found for the different amino acids (A) or dipeptides (B) in isolation or with a Ca$^{2+}$ cation. Blue segments of the bars and blue shaded numbers give the amounts of stationary points located after Step 2 of the search procedure detailed in Figure 2. Red bar segments and red shading highlight the numbers of structures that were additionally located by applying Step 3 of the search protocol.

The final conformation hierarchies. This refinement step by REMD is essential as it is evident from the plots in Figure 3 that show the numbers of distinct new conformers identified after Step 2 and Step 3, respectively. Overall numbers of conformers identified in the searches are also given in Table S2 of the Supporting Material. After step 2, a total of 17,381 stationary points was found for the amino acids and dipeptides in isolation and in complex with Ca$^{2+}$. The refinement procedure in Step 3 increases this number to a total of 21,259 structures.

Initial structures for the Ba$^{2+}$, Cd$^{2+}$, Hg$^{2+}$, Pb$^{2+}$ and Sr$^{2+}$ amino acid and dipeptide systems were obtained by analogy (i.e. by replacing the Ca$^{2+}$ cation) from the amino acid and dipeptide structures binding a Ca$^{2+}$ cation. These structures were then relaxed with PBE+vdW employing “tight” computational settings and a tier-2 basis set. This adds 24,633 further cation-bound conformers. Detailed accounts of how many structures were found for which amino
acid/dipeptide in isolation or with the different cations can be found in Tables S3 and S4 of the Supporting Information. In total we collect 45,892 stationary points.

**Data Records**

The curated data, consisting of the Cartesian coordinates of 45,892 stationary point geometries of the PBE+vdW PES and their potential energies computed at the “tight”/tier-2 level of accuracy in the FHI-aims code, is provided as plain text files sorted in directories (see Figure 4). The folder structure is hierarchical and straightforward. The naming scheme is explained in the following:

Description of the file types:

- **conformer.(...).xyz** coordinates in standard xyz format in Å, readable by a wide range of molecule viewers, e.g. VMD, Jmol, etc.
- **conformer.(...) fhiaims** coordinate file in FHI-aims geometry input format:
  - for each atom of the particular system, the Cartesian coordinates are given in Å (atom [x] [y] [z] [element]). The electronic total energy (in eV) at the PBE+vdW level is given there as a comment.
- **control.in** FHI-aims input file with technical parameters for the calculations.
  - Please note that these files also include the exact specifications of the “tight” numerical settings for all included elements.
- **hierarchy_PBE+vdW_tier-2.dat** in each final subfolder, contains three columns: number of the conformer, total energy (in eV, PBE+vdW, tier-2 basis set, “tight” numerical settings, computed with FHI-aims version 031011), and relative energy (in eV, relative to the respective global minimum).

The curated data is publicly available from the NOMAD repository\(^1\) via the short DOI 10/z98\(^2\) [Data citation 1]. Furthermore, a website dedicated to this data set has been set up and allows users to browse and download the data and to visualize molecular structures online.\(^3\)

**Technical Validation**

The generated data for uncapped alanine is compared to a recent study by Maul et al.\(^12\) in order to ensure the quality of the generated data. In that reference, 10 low energy conformers of alanine were reported, spanning an energy range of approximately 0.26 eV between the reported lowest and highest energy conformers. The level of theory used by Maul et al. was DFT in the generalized gradient approximation.

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1. http://nomad-repository.eu
2. http://doi.org/z98
Figure 4: Schematic representation of folder organization of the data. Each folder, as exemplified for the Ca\(^{2+}\)-coordinated cysteine dipeptide, contains coordinate files in two formats (standard XYZ and FHI-aims input), the computational settings file for FHI-aims (control.in), and the energy hierarchies (PBE+vdW, “tight”/tier-2 level) per system.
Figure 5: (A) The conformational energy hierarchies for alanine after the global search and the local refinement together with the reference hierarchy at the DFT-PW91 level that was published by Maul et al. [12]. Conformers indicated by black lines were found in the global search, the conformers in red were located only after the local refinement step. The blue line in the reference conformational hierarchy represents a minimum not found in our search and not present at the PBE+vdW level. (B) Conformations of the alanine molecule. Conformers marked with an asterisk (*) were found in the local refinement step of our search strategy. The conformer labeled with X was found by Maul et al. in PW91 calculations [12] but is unstable at the PBE+vdW level.

approximation by means of the Perdew-Wang 1991 functional [94]. In our case, the force field based search step with subsequent PBE+vdW relaxations yields 5 conformers. The following \textit{ab initio} REMD simulations increase the number of conformers to 15 within an energy range of 0.43 eV. The respective conformational energy hierarchies after global search and after REMD-refinement are shown in Figure 5A. The results of our search (with the refinement step) are in good agreement with the data from reference [12] that is also shown in Figure 5A. Structures are shown in Figure 5B. Nine of the ten conformers identified by Maul et al. can be confirmed. The single conformer that is missing (highlighted by an X in Figure 5A) is not a stationary point of the PBE+vdW potential energy surface. Conformers 14 and 15 are classified as saddle points by analysis of the vibrational modes.

As a second test we compare the effect of a higher level density functional, the PBE0 hybrid functional with exact exchange [95] with the Tkatchenko-Scheffler van der Waals correction [67], on the predicted energy hierarchies and the geometries. The advantage of hybrid functionals has been show, for example, by Burke et al. [96], or for longer peptides in references [72,74]. In the present work, their impact was tested for three different amino acids: alanine, phenylalanine,
Figure 6: The deviations between conformers of Ala, Phe, and Trp at the PBE+vdW and the PBE0+vdW level of theory by means of (A) average RMSD, (B) maximal RMSD, and (C) mean-absolute error (MAE) and (D) maximal error of relative energies. Exact numbers are summarized in table 1.

and tryptophan. In particular, the aromatic ring systems of the latter two supposedly represent a challenge for semi-local DFT [72]. The building blocks were investigated in dipeptide and free-amino-acid configuration and with and without Ca$^{2+}$ ion. Figure 6 and table 1 summarize the results, namely average and maximal root mean square deviation (RMSD) of the Cartesian coordinates of all atoms between respective minima at the PBE+vdW and PBE0+vdW level as well as the mean absolute error (MAE) between the relative energies $\Delta E_i$ of the $n$ conformers of the two energy hierarchies at the PBE+vdW and PBE0+vdW level:

$$MAE = \frac{1}{n} \sum_{i=1}^{n} |\Delta E_i^{PBE+vdW} - \Delta E_i^{PBE0+vdW}|$$

Energy hierarchies can vary quite substantially when changing from PBE to PBE0 treatment, as indicated by the MAE values. In particular, this is the case for the amino acid-Ca$^{2+}$ or dipeptide-Ca$^{2+}$ systems. However, the geometries are rather consistent with low average RMSD values of all Cartesian coordinates of maximally up to about 0.1 Å. Even the maximal outlier observed has a tolerable RMSD of less than 1.5 Å.

The ultimate challenge for any simulation approach is the reproduction of experimental data. To that end, we compare to an experimental study by Ho et al. [97] that investigated the relative binding strength between the different
Table 1: The average and maximum RMSD (in Å) and the mean absolute error (MAE) and maximal error (in meV) of relative energies between PBE and PBE0 geometries for Ala, Phe and Trp and their dipeptides with and without Ca\(^{2+}\) ion.

<table>
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<th>System</th>
<th>RMSD\textsubscript{aver.}</th>
<th>RMSD\textsubscript{max.}</th>
<th>MAE</th>
<th>Max. Err.</th>
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<td>0.05</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>Ala+Ca(^{2+})</td>
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<td>0.04</td>
<td>25</td>
<td>38</td>
</tr>
<tr>
<td>Phe</td>
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<td>0.07</td>
<td>14</td>
<td>29</td>
</tr>
<tr>
<td>Phe+Ca(^{2+})</td>
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<td>1.44</td>
<td>109</td>
<td>202</td>
</tr>
<tr>
<td>Trp</td>
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<td>0.10</td>
<td>14</td>
<td>30</td>
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<tr>
<td>Trp+Ca(^{2+})</td>
<td>0.07</td>
<td>0.73</td>
<td>84</td>
<td>1049</td>
</tr>
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</table>

Amino acids and the Ca\(^{2+}\) cation. Ho \textit{et al.} investigate the Ca\(^{2+}\) affinity of 18 proteinogenic amino acids (excluding Glu and Asp) based on a combinatoric library of tripeptides. The tripeptide-Ca\(^{2+}\) complexes were fragmented by mass spectrometry experiments and the intensity of the respective peaks was recorded. From the probability of the Ca\(^{2+}\) staying attached to one amino acid over the other after fragmentation of the peptide chain, a ranking of binding affinities was deduced. In Figure 7 the x-axis represents the resulting experimental order of binding affinity. From our conformational study of bare amino acids and dipeptides and interacting with Ca\(^{2+}\) cations, we can calculate a binding energy

\[
E_{\text{binding}} = E_{\text{amino acid}} + E_{\text{cation}} - E_{\text{complex}}
\]

This binding strength is plotted in Figure 7 against the affinity order derived from the above described mass-spectrometry experiment by Ho \textit{et al.} The agreement is striking, especially when taking into account the differences between the combinatorics based experiment and our computational approach.

**Usage Notes**

The present data contains stationary-point geometries (mainly minima, but also saddle points since no routine normal-mode analysis was performed) on the potential energy surface of the 20 proteinogenic amino acids and dipeptides, either isolated or in complex with a divalent cation (Ca\(^{2+}\), Ba\(^{2+}\), Sr\(^{2+}\), Cu\(^{2+}\), Pb\(^{2+}\), Hg\(^{2+}\)). The users of this dataset may find openbabel [98](www.openbabel.org) to be a useful tool to convert FHI-aims and xyz files to other common file formats in chemistry.
Figure 7: Comparison of the theoretical binding energies of the Ca\(^{2+}\) cation to the experimental binding order (the order of amino acids on the x axis) by Ho et al. [97]. Perfect agreement of theoretical and experimental binding order would mean a monotonic descent of the values from left to right.

Further tables are provided in a Microsoft Excel file and as tab-delimited text files as Supporting Information to this article:  


Table S1 Parameters specific to the REMD simulations of the different systems: the number of Replicas, the probability of Acceptance as well as the Time between exchange attempts, and the Temperature range of the replicas.

Table S2 Number of conformers found in the different stages (after global search and after refinement) of the search scheme for amino acids, dipeptides, and complexes thereof with Ca\(^{2+}\) cations. For the amino acids, the basin hopping search was performed starting from the non-zwitterionic as well as from the zwitterionic state. These numbers are separated by a “+” in the respective column.

Table S3 Numbers of conformers found for the amino acids (AA) and their complexes with the investigated divalent cations.

Table S4 Numbers of conformers found for the dipeptides (Dip.) and their complexes with the investigated divalent cations.
Acknowledgements

MR performed the simulations. MR and CB curated the data. MR, CB, VB designed the study and wrote the data descriptor. The authors are grateful to Matthias Scheffler (Fritz Haber Institute Berlin) for support of this work and stimulating discussions and to Evgeny Blokhin and Claudia Draxl (Humboldt-Universität zu Berlin) for support with transferring the data to the NoMaD repository. Markus Schneider and Luca Ghiringhelli are gratefully acknowledged for their work on the script-based parallel-tempering scheme that is provided with FHI-aims and that was used in the present work.

References


\textbf{Data Citations}

Bibliographic information for the data records described in the manuscript.

1. Ropo, M., Baldauf, C., Blum, V. \textit{Ab initio amino acid data set} DOI: 10/z98 (2015).