ChemSpaX: Exploration of chemical space by automated functionalization of molecular scaffold

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Abstract

Local chemical space exploration of an experimentally synthesized material can be done by making slight structural variations of the synthesized material. This generation of many molecular structures with reasonable quality, that resemble an existing (chemical) purposeful material, is needed for high-throughput screening purposes in material design. Large databases of geometry and chemical properties of transition metal complexes are not readily available, although these complexes are widely used in homogeneous catalysis. A Python-based workflow, *ChemSpaX*, that is aimed at automating local chemical space exploration for any type of molecule, is introduced. The overall computational workflow of *ChemSpaX* is explained in more detail. *ChemSpaX* uses 3D information, to place functional groups on an input structure. For example, the input structure can be a catalyst for which one wants to use high-throughput screening to investigate if the catalytic activity can be improved. The newly placed substituents are optimized using a computationally cheap force-field optimization method. After placement of new substituents, higher level optimizations using xTB or DFT instead of force-field optimization are also possible in the current workflow. In representative applications of *ChemSpaX*, it is shown that the structures generated by *ChemSpaX* have a reasonable quality for usage in high-throughput screening applications. Representative applications of *ChemSpaX* are shown by investigating various adducts on functionalized Mn-based pincer complexes, hydrogenation of Ru-based pincer complexes, functionalization of cobalt porphyrin complexes and functionalization of a bipyridyl functionalized cobalt-porphyrin trapped in a M2L4 type cage complex. Descriptors such as the Gibbs free energy of reaction and HOMO-LUMO gap, that can be used in data-driven design and discovery of catalysts, were selected and studied in more detail for the selected use cases. The relatively fast GFN2-xTB method was used to calculate these descriptors and a comparison was done against DFT calculated descriptors. *ChemSpaX* is open-source and aims to bolster the efforts of the scientific community towards data-driven material discovery.

Keywords: catalysis; data-driven material design; density functional tight-binding theory; chemical space exploration; open source;

1 Introduction

The discovery of novel molecules is important for many industries. The usage of computational methods for the design or selection of highly selective catalysts has been described as a holy grail of chemistry [1]. Computer-aided drug discovery (CADD) led to the discovery of the HIV

protease inhibitors ritonavir, indinavir and saquinavir. This discovery proved to be the key in reversing rapid growth in deaths due to AIDS in the US [2, 3]. This is one of the many examples that show that CADD has been playing a key role in the discovery of drugs and will continue to do so [4, 5]. Efforts are being made in the energy and chemicals sector to successfully apply computer-aided methods for discovery of new materials. For example, in the design of materials for lithium-ion batteries, hydrogen production and storage materials, superconductors, photovoltaics and thermoelectric materials [6, 7, 8, 9]. A roadmap for materials by computational design is given by Alberi et al., where it is discussed that a common need in material design is the need for high-throughput computational and experimental techniques as a foundation for the materials-by-design paradigm [10].

The chemical space is vast and global exploration of chemical space is difficult [11]. It is experimentally impossible and time-consuming to find the optimal molecule or material from nearly infinite possible combinations. Therefore, machine learning (ML) and other cost-effective computational methods are an attractive solution to the combinatorial problem of material and catalyst design [12]. Von Lilienfeld and coworkers propose that exploration and understanding of chemical space can be done by combining physical theories, data sets of quantum mechanics (QM) and statistical mechanics (SM) properties, and ML methods that incorporate physical and chemical knowledge [13]. These combinations of QM, SM and ML approaches are called QML models. In QML models, modern statistical learning theory is applied to predict electronic and atomistic properties and processes in molecules and materials [13]. However, there are challenges that need to be addressed before a complete workflow for *in silico* design of chemicals and materials can be achieved.

The first challenge is that computational methods should support scientists in adjusting their hypothesis after synthesis of a material has happened. This is part of the molecular design cycle [14]. To enable this cycle, a systemic approach for the local exploration of the chemical space of the synthesized material is needed to learn more about the chemistry involved. This approach can then be expanded to generate new candidate molecules and adjust the initial hypothesis. By building upon experimental knowledge in a systemic way together with automated computational high-throughput screening (HTS), larger subsets of chemical space can be covered.

The second challenge is that even when accurate simulations are available, the process of molecular design is still limited by the search strategy used to explore chemical space and the representation of a molecule in chemical space [15]. A differentiable continuous space is required to enable the use of gradient-based optimization and make larger jumps in chemical space [15]. An example of molecular representations is shown in literature, where autoencoders are used to map molecule structures onto a continuous latent space. The latent space preserves chemical similarity principle and thus can be used for the generation of analogue structures [16]. Another often used representation is the sorted Coulomb Matrix (CM), this representation was applied successfully in the ML screening of thousands of catalysts [17]. These representations require that the molecular structure that is represented is of reasonable quality, while consumption of computational resources for the generation of the structure is kept to a minimum.

The third challenge is that advances in this field also highly depend on the availability of trustworthy QM data sets. For (small) organic molecules, reliable data sets like the GDB-13 or GDB-11 database exist which are being used to train generative models [18, 19, 20]. In these virtual screening workflows, 3D coordinates are generated from the simplified molecular-input line-entry system (SMILES) strings and these complexes are analyzed further. Large data sets are not readily available in the field of homogeneous catalysis and the alternative approach of using synthetic data generated *in silico* would become expensive due to the high computational cost of accurate QC methods like DFT [21, 22, 23]. This unavailability stems from the fact that

transition metal (TM) complexes are regularly used in homogeneous catalysis and it is known that TM-complexes pose an issue for the SMILES, since SMILES strings inherit the imperfections of the valence model [24]. Generating 3D XYZ coordinates from SMILES strings for TM-complexes is an area of active research [25]. In the *molSimplify* code, a divide-and-conquer technique is used to get the correct 3D geometry of any complex. Force fields for organic components are being used together with a databases of quantum-mechanically derived rules for the metal–organic bonds [26, 27, 28, 29, 30]. For the exploration of local chemical space for TM complexes, using a SMILES string as starting point is thus something that needs additional research. An alternative to SMILES based chemical space exploration is to directly make use XYZ coordinates of a pre-optimized molecular structure as input. This is the approach that has been taken in this research, which allowed chemical space exploration for any type of geometry.

In this manuscript *ChemSpaX*, a Python-based workflow that can be used for automated molecular design workflows, is presented. *ChemSpaX* aims to make the exploration of local chemical space of both organic and inorganic complexes as easy as possible. The exploration is done by automated placement of substituents on a given molecular scaffold while maintaining the quality of the initial scaffold. This process is supposed to simulate the workflow used by experimental chemists in which a molecular structure is tested and explored by placing various functional groups. Several molecular scaffolds are already present in literature and can be used for an automated exploration of local chemical space. If a particular complex is known for its high catalytic activity, the 3D coordinates of this complex can be used as a starting point for exploration in the neighbourhood of its chemical space. With *ChemSpaX* it is possible to automate this exploration of the local chemical space. The user has full control of the placement of substituents groups and can thus guide the exploration of the local chemical space based on chemical intuition. A general overview of the approach used in *ChemSpaX* is given in Figure 1.

Figure 1: A general overview of the approach used in *ChemSpaX*. Using a library of pre-defined ligands and a pre-optimized molecular scaffold, the local chemical space of this input geometry can be explored. Color code used for elements: gray = C, white = H, red = O, pink = Ru, dark-blue = N and turquoise = F.

The key features of *ChemSpaX* are presented in the next section. Subsequently, representative applications of *ChemSpaX* are presented. First, the functionalization of Ru-based complexes with a PNP ($\text{PNP} = (\text{P}(\text{H}_2)\text{CH}_2\text{CH}_2\text{N})_2$) backbone (RuPNP) involved in a (de)hydrogenation reaction is studied [31, 32, 33, 34, 35, 36]. This hydrogenated metal-dihydride complex is an important intermediate in catalyzed (de)hydrogenation reactions [37, 38, 39, 40, 41]. These reactions are widely applied in the pharmaceutical, fine chemicals, and energy storage/conversion industries [42, 43, 44, 45, 46, 47]. Analyzing the properties of these RuPNP intermediates by exploration of the chemical space can thus be a valuable asset for multiple applications. For RuPNP, a comparison of the quality of geometries generated by *ChemSpaX* and calculated electronic or thermochemical properties with higher-level DFT and GFN2-xTB methods is presented.

Secondly, the functionalization of Mn-pincer complexes as potential (de)hydrogenation catalysts is studied. This study is an extension of previous work by our research group [37]. With this application the chemical space of a more climate-friendly alternative to RuPNP is explored. Manganese is known to be a cheap, abundant and biocompatible alternative to precious-metal catalysts [48]. Again, the quality of geometries generated by *ChemSpaX* is assessed. Furthermore, we also present a thermochemical analysis of formation of various catalytically relevant intermediates and adducts.

Thirdly, the generation of a database of ~ 1100 functionalized Cobalt Porphyrin (referred to as 'Co porphyrin' in the rest of this manuscript) complexes is shown. Co porphyrins exist as stable metalloradicals and have been used to catalyze carbene and nitrene transfer reactions [49, 50, 51, 52]. Automated generation of this database shows the possibility of systemic exploration of local chemical space. The generated database is used to investigate quality of geometries generated by *ChemSpaX* and the propagation of errors upon creation of larger geometries. Additionally, a comparison of electronic properties calculated by GFN2-xTB and DFT is made.

Lastly, the functionalization of a bipyridyl functionalized Cobalt-porphyrin trapped in a M2L4 type cage complex (referred to as 'M2L4 cage' in the rest of this manuscript) is presented. This cage complex confines the Co porphyrin catalyst, which can lead to changed catalyst properties [53, 54, 52]. This case shows how *ChemSpaX* can be used to automatically functionalize structures that are more difficult to functionalize. The Root-mean-square deviation of atomic positions (RMSD) of various optimization methods is compared for the M2L4 cage.

2 Computational methods

2.1 Open Babel

Conversions between MDL Molfile and XYZ format were done using Open Babel [55, 56]. For structures generated by *ChemSpaX* the Generalized Amber Force Field (GAFF) followed by the Universal Force Field (UFF) optimization method as implemented in Openbabel was used [57, 58]. This order of optimization gave a reasonable geometry based on pre-defined molecular connections.

2.2 Semiempirical tight-binding

Grimme lab's xTB package (version 6.3.3) was used for extended DFTB calculations [59]. The GFN2-xTB method and GFN-FF methods were used for geometry optimization [60, 61, 62, 63]. The RuPNP geometries were optimized using an extended density functional tight-binding approach, by applying the GFN2-xTB method with *verytight* criteria. Hessian calculations were also performed for these geometries to verify the absence of imaginary frequencies and that

each geometry corresponds to a local minimum on its respective potential energy surface (PES). The Mn-pincer complexes and Co porphyrins were optimized using GFN2-xTB without hessian calculations. The M2L4 cage geometries were optimized using GFN2-xTB and GFN-FF.

The GBSA solvation method as implemented in xTB was used with THF as solvent for most optimizations, to implicitly account for solvent effects [64, 65]. These GFNn (n= 0, 1, 2, FF) methods are denoted as GFNn-xTB(THF) or GFNn-xTB(GAS) depending on whether GBSA solvation was used.

2.3 Density Functional Theory

2.3.1 Pincer complexes

Gaussian 16 C.01 was used to perform DFT calculations [66]. The BP86 exchange-correlation functional was used for geometry optimizations together with the def2SVP basis set [67, 68]. This combination of functional and basis set have shown reliable geometry predictions accompanied with low computational costs [69, 70]. Geometry optimizations were performed in the gas phase. Hessian calculations were performed for these geometries to verify the absence of imaginary frequencies and that each geometry corresponds to a local minimum on its respective potential energy surface (PES). Thermochemical parameters such as the Gibbs free energy were calculated using the gas phase hessian. Single point (SP) DFT calculations were performed on the gas-phase optimized geometries using the SMD solvation (THF) model [71]. SP calculations were performed using BP86 or PBE1PBE (also known as PBE0) functional with the def2TZVP basis set to further refine the obtained (free) energies and other thermochemical/electronic properties [72]. All DFT calculations were performed with Grimme's D3 dispersion corrections [73]. These composite methods, BP86/def2-SVP//XC/def2-TZVP (THF), are denoted as XC(THF) or XC(GAS) depending on the exchange-correlation (XC) functional used and if a SP calculation with solvation was done.

All geometries were pre-optimized with a combination of Openbabel's GAFF and UFF methods or GFN2-xTB before being subjected to full DFT based optimization. In this research no conformational search was conducted. The catalysts are represented as M-L where M represents the metal center and L the ligand. This lead to the formation of M(X)-L(H) species. The thermodynamic stability of the formed M(X)-L(H) species was estimated by computing the Gibbs free energy and total energy change under standard conditions upon addition of the H-X moiety.

$$\Delta G_{\text{HX}}^{\circ} = G(\text{M(X)} - \text{L(H)}) - G(\text{M} - \text{L}) - G(\text{H-X}) \quad (2)$$

$$\Delta E_{\text{HX}}^{\circ} = E(\text{M(X)} - \text{L(H)}) - E(\text{M} - \text{L}) - E(\text{H-X}) \quad (3)$$

2.3.2 Co porphyrins

TeraChem v1.94V-2019.08-beta was used to perform GPU-accelerated DFT SP calculations [74, 75, 76] on selected Co-Porphyrin geometries optimized using the GFN2-xTB method. The PBE1PBE exchange-correlation functional was used with empirical dispersion corrections [72, 77] in combination with the LANL2DZ basis set which uses an effective core potential (ECP) [78].

2.4 Root-mean-square deviation of atomic positions (RMSD)

The RMSD is used to compare two molecular structures. In this approach, the minimal difference between the position of the same atom on both molecular structures is used. The RMSDs were calculated using a Python program which uses the Kabsch or Quaternion algorithm to align the two molecular structures [79, 80, 81]. If for example the two molecules **p** and **q** with n points (atoms) are compared, the RMSD is defined as:

$$RMSD(\mathbf{p}, \mathbf{q}) = \sqrt{\frac{1}{n} \sum_{i=1}^n \|p_i - q_i\|^2} \quad (4)$$

$$= \sqrt{\frac{1}{n} \sum_{i=1}^n ((p_{ix} - q_{ix})^2 + (p_{iy} - q_{iy})^2 + (p_{iz} - q_{iz})^2)} \quad (5)$$

3 Code implementation

ChemSpaX is a python tool that allows the automated functionalization of molecular structures, aimed at easing the creation of an automated workflow for quantum chemistry calculations. An overview of the overall workflow of *ChemSpaX* as described in this section is shown in [Figure 2](#). The user has to supply: a molecule that needs to be functionalized (*skeleton*), which sites on the skeleton should be functionalized (*functionalization_list*) and what substituent should be placed on the supplied site (*substituent*). Substituents can be chosen from a pre-made database included in *ChemSpaX* or users can supply new substituents in XYZ or MDL Molfile format. Based on the user input, the substituent is placed optimally on the skeleton. Information for the correct placement of a substituent is kept in a CSV file, here the central atom of the substituent group and its centroid vector are stored. After a geometrically correct placement, the GAFF and UFF optimization methods from Open Babel are used to selectively optimize the newly placed substituent via a constrained optimization protocol [55, 56]. In this constrained optimization protocol, the skeleton is frozen. This combination of GAFF and UFF was found by trial-and-error. The choice for this combination is explained in the SI.

It is recommended to use a DFT optimized geometry as input skeleton. When a new functional group is placed on the skeleton, the skeleton itself is fully constrained, hence the FF optimization only influences the newly placed functional group. This choice was made to keep the core of the geometry as close to its DFT optimized input structure as possible while preventing steric hindrance from newly placed substituents cheaply. The resulting geometries can be used for screening purposes or can be further optimized using semi-empirical methods or DFT.

Figure 2: Overall workflow of ChemSpaX. 1) The user supplies a skeleton XYZ, *functionalization_list* and substituent. 2) The XYZ files are converted to MDL Molfiles to conserve correct bonding info. 3) The central atom of the substituent group and the centroid vector are used to rotate and translate the substituent group towards the functionalization site. 4) *atom_to_be_functionalized* is replaced by the substituent group. 5) The skeleton and substituent group are merged in one MDL Molfile with correct bonding information from input MDL Molfiles. 6) GAFF optimization is done to prevent steric hindrance. 7) Additionally, UFF optimization is done to prevent GAFF related issues. 8) Optionally, xTB optimization can be used for further optimization of the functionalized skeleton. 9) If there are no functionalizations left to do, the program is done and the functionalized skeleton is saved in MDL Molfile format. Else the functionalized skeleton will be used as input and the process starts again at step 1.

4 Results and discussion

4.1 Pincer complexes

In this section the functionalization of the ligand scaffold of Ru and Mn based pincer complexes was investigated. For all pincer complexes the activated catalyst ($M-L$) has a Lewis acid site on the metal and the ligand can act as a Bronsted base. This means that the metal can coordinate with an electron donating species while the ligand can accept a proton [37, 38]. For the (de)hydrogenation reactions, the outer-sphere Noyori-type mechanisms, involving proton transfer to the amido ligand and hydride transfer to the metal center are typically proposed. For the Mn-pincers, potential deactivation/inhibition through the metal-ligand cooperative addition of alcohol/water/base are studied [37]. The properties of the pincer complexes' intermediate with an electron donating species on the metal and a proton on the ligand are thus an important factor to ensure that the desired product is synthesized. The Noyori-type mechanism involved in these reactions together with an example 3D structure of the Mn-pincer are shown in Figure 3.

Figure 3: A representative proposed Noyori type cooperative catalytic cycle for dehydrogenation of methanol in aqueous phase is shown (left) together with an example Mn-pincer complex (right). Color code used for elements: gray = C, white = H, red = O, pink = Mn, dark-blue = N.

In section 4.1.1 the functionalization strategy for both pincer complexes is shown. Subsequently, the quality of geometries generated by *ChemSpaX* is compared to higher level methods in section 4.1.2. An investigation of thermochemical is done in section 4.1.3. A comparison of the HOMO-LUMO gap calculated using xTB versus DFT is shown in the SI.

4.1.1 Functionalization strategy

The Ru-based complexes had a PNP backbone coordinated to a Ru(II) center stabilized by Co and H ligands shown in Figure 4. For these RuPNP complexes, 288 geometries were generated by functionalization of the M-L complex and the M(H)-L(H) variant. 27 geometries were selected for BP86(GAS) optimization. BP86(THF) and PBE1PBE(THF) single-point (SP) calculations were done on the optimized geometries. Generally, the phosphorus sites were functionalized first and the carbon moieties on the PNP ligand backbone were functionalized second. This strategy is shown in Figure 4.

For the Mn-based complexes five representative ligand scaffolds were considered, PNP-(bis(3-phosphaneylpropyl)amine)-¹, SNS-(azanediylbis(ethane-1-thiol))-, CNC-(bis(2-(1H-3λ⁴-

¹This is not the same PNP ligand as used for the Ru complexes. The PNP ligand used for Mn complexes contains a propyl bridge while the one used for Ru complexes contains an ethyl bridge

Figure 4: Functionalization strategy for the RuPNP pincer complexes.

imidazol-3-yl)ethyl)amine)-, PNN-(N¹-(2-phosphanylene)ethane-1,2-diamine)-, and PCP-(N¹,N³-bis(phosphanylene)benzene-1,3-diamine)- backbones coordinated to a Mn(I) center stabilized by two CO ligands. 1225 geometries were generated using *ChemSpax* and optimized using GFN2-xTB(THF). Functionalizations were done on the M-L and M(X)-L(H) complex. From these 1225 geometries, 545 geometries containing the PCP, PNN and CNC ligand backbones were selected for DFT optimization using BP86(GAS). BP86(THF) (SP) calculations were done on the optimized geometries. Functionalizations were performed symmetrically, all four R1 sites were kept the same and both R2 sites (only 1 in case of PCP backbone) were functionalized with the same group. However, R1 and R2 were not constrained to be the same. The various backbones and the functionalization strategy are shown in Figure 5.

Figure 5: Functionalization strategy for Mn-pincers with various donor (R1) and backbone (R2) groups.

4.1.2 Quality assessment of generated geometries

For data-driven chemical applications it is desirable to generate a large number accurate 3D geometries at a rapid pace. Therefore, a computationally efficient method which can produce molecular geometries close to full DFT optimized geometries is desirable [17, 82, 83]. Methods like FF, xTB and genetic algorithms (GA) are attractive solutions for *in situ* structure generation. For this work all input skeletons were optimized at the DFT level of theory. *ChemSpaX* uses FF optimizations on newly placed substituent groups in each iteration, hence these geometries are referred to as 'FF geometries' in this manuscript. In this work the quality of the *ChemSpaX* generated FF geometries and GFN2-xTB optimized geometries was assessed by comparison with DFT optimized structures. These DFT optimized geometries were used as a 'standard' for comparison.

We applied two methods to compare the quality of geometries. First, the electronic energy of reaction was used for comparison. In this comparison, for a given reaction the *ChemSpaX* generated FF geometries of reactants and product are taken. Each FF geometry undergoes two calculations: 1) a SP calculations where the energy of the FF geometry is evaluated at DFT level of theory and the electronic energy change of the reaction $\Delta E_{FF//DFT-SP}$ is calculated 2) a full DFT based optimization is carried resulting in a new geometry and energy at the DFT level of theory. The corresponding electronic energy change of the reaction ΔE_{DFT} is calculated. The difference between the reaction energies is computed using both $\Delta E_{FF//DFT-SP}$ and ΔE_{DFT} to get $\Delta\Delta E_{FF}$ which is a metric for the quality of FF geometry for the reaction being investigated. A similar approach was used in a previous work from our group to assess GFN2-xTB optimized geometries [84].

$$\Delta\Delta E_{GFN2-xTB} = \Delta E_{DFT} - \Delta E_{GFN2-xTB//DFT-SP} \quad (6)$$

$$\Delta\Delta E_{FF} = \Delta E_{DFT} - \Delta E_{FF//DFT-SP} \quad (7)$$

For RuPNP, $\Delta\Delta E_{FF}$ and $\Delta\Delta E_{GFN2-xTB}$ were compared. The mean (μ) of the $\Delta\Delta E_{FF}$ was found to be 7.20 kcal mol⁻¹ with a standard deviation (σ^2) of 4.57 kcal mol⁻¹. For $\Delta\Delta E_{GFN2-xTB}$ $\mu = 4.77$ kcal mol⁻¹ with $\sigma^2 = 2.57$ kcal mol⁻¹ was found. This indicates an overall good agreement between the GFN2-xTB optimized structures and the structures generated by *ChemSpaX*. For the Mn-pincer complexes only the $\Delta\Delta E_{FF}$ was calculated, which resulted in $\mu = 27.2$ kcal mol⁻¹ and a very high σ^2 of 26.1 kcal mol⁻¹. The FF geometries were compared against BP86(GAS) optimized geometries. The large difference in between FF and DFT based reaction energies for Mn pincers indicate that unlike for the Ru-PNP complexes the geometries of Mn-pincers generated by *ChemSpaX* are relatively less accurate.

The second methods used to assess the quality of geometries was RMSD between geometries produced by two different methods. For the RuPNP complexes, the Cartesian heavy-atom (all elements except H) root-mean-square deviation (hRMSD) was calculated [59]. With this method the average distance between two geometries (in Å) is calculated. Again, DFT optimized structures were used as the standard for comparison. Both FF ($\mu = 0.67$ Å; $\sigma^2 = 0.30$ Å) and GFN2-xTB ($\mu = 0.41$ Å; $\sigma^2 = 0.34$ Å) structures had a similar average hRMSD when compared to DFT structures. As observed with the electronic energy, the structures generated by *ChemSpaX* are in good agreement with GFN2-xTB optimized structures for RuPNP complexes. Generally, it was observed that the hRMSD's were mostly close to 1 Å and never exceeded 2.5 Å, both for FF and GFN2-xTB. Distributions of the hRMSD values are shown in the SI.

A selection of the geometries are visualized using structure overlay plots in Figure 6. The comparisons in these structure overlay plots are done in a similar way as calculating the RMSD, a) the FF optimized structure (silver), generated by *ChemSpaX*, is compared to a DFT opti-

mized structure (green) and b) a GFN2-xTB optimized structure (silver) is compared to a DFT optimized structure (green). FF optimization on newly placed substituents only as employed by *ChemSpaX* can thus generate promising geometries for HTS applications since the geometries are in reasonable agreement with higher-level methods like GFN2-xTB while being relatively less resource consuming.

Figure 6: Structure overlay plots of some selected TM complexes. a) shows FF optimized (silver) vs DFT optimized (green) structures and b) shows GFN2-xTB optimized (silver) vs DFT optimized (green) structures. The '-H' indicates that the complex is hydrogenated. Color code used for elements: red = O, purple = Ru, dark-blue = N and turquoise = F.

A comparison using the hRMSD was done in a similar manner for the Mn-pincer complexes. It was again observed that both FF ($\mu = 0.70 \text{ \AA}$; $\sigma^2 = 0.45 \text{ \AA}$) and GFN2-xTB ($\mu = 0.78 \text{ \AA}$; $\sigma^2 = 0.67 \text{ \AA}$) structures had a similar average hRMSD when compared to DFT structures, albeit with moderately high standard deviations. This is consistent with the previous observation from the RuPNP structures, that the structures generated by *ChemSpaX* are in good agreement with GFN2-xTB optimized structures. It should be noted here that the GFN2-xTB optimizations were performed in the solvated phase (GBSA(THF)).

The hRMSD of ligands bonded to the metal center was also compared for various backbones. This comparison is shown in Figure 7. As observed in the previous work, most PNN based complexes resulted in hemilabile ligands, this hemilability could arise as an artifact of xTB based geometry optimization or it can be genuinely present in the system [37]. Due to this hemilability, the spread of the PNN backbone hRMSD data was larger compared to the other backbones. For the PNN and CNC backbones it was observed that functionalization with electron donating substituents on the R1 site resulted in a higher hRMSD. For the PCP backbone it was observed that functionalization with *t*Bu on the R1 site specifically gave a larger hRMSD. This observation is expected to have the following underlying causes: 1) electron donating groups like *t*Bu are bulkier, have more number of atoms and a complex structure which increases the chance of accumulating an error (*vide infra*) 2) electron donating groups affect the electronic density in the entire complex, this will impact the structure of the skeleton which is currently frozen in FF calculations. When optimized with DFT, the skeleton would relax and this would lead to a higher hRMSD.

Figure 7: Comparison of hRMSD for the PCP, PNN and CNC ligand backbone of a) *ChemSpaX* generated FF structures compared to DFT optimized structures, b) GFN2-xTB optimized structures compared to DFT optimized structures. The various adducts bonded to the metal center are color coded, where 'no' means that no adduct is bonded to the metal center.

4.1.3 Comparison of ΔG and ΔE

Calculating the hessian is necessary to find the Gibbs free energy of reaction ΔG . Hessian calculation is also quintessential to ensure accurate and reliable geometry optimizations. However, it would be desirable to omit these computationally expensive calculations when filtering through a large number of molecular structures in high-throughput screening (HTS). In a previous study done by our group, it was observed that ΔG correlates well with ΔE for the proton transfer reaction [84]. In the present work we found a similar correlation to hold for the Ru-PNP and Mn-pincers (Figure 8). This correlation shows that ΔE scales well with ΔG and due to the observed minimal loss of accuracy, ΔE can be used instead of ΔG [84]. Thus, heavy resource-consuming hessian calculations can be skipped without losing a significant amount of accuracy in HTS applications (RMSE (Ru-PNP) = 1.7 kcal mol⁻¹; RMSE (Mn-pincers) = 1.9 kcal mol⁻¹). We would like to emphasize here that for accurate calculations hessian calculations must be performed to ensure that the optimized geometry is a minima on the potential energy surface.

Figure 8: Comparison between the Gibbs free energy of reaction (ΔG) and the electronic energy of reaction (ΔE) in a) DFT calculations for Mn-pincers, b) GFN2-xTB calculations for Mn-pincers and c) GFN2-xTB calculations for RuPNP [84].

4.2 Co porphyrin

Porphyrins are widely researched, for example, for their applications in biocatalysis, organic photovoltaics, molecular wires and many more [85, 86, 87, 88]. This wide variety of applications has been enabled by diverse design and synthesis of structurally diverse porphyrins [85]. Postfunctionalization is a common method to tune the electronic and chemical properties of porphyrins, where functional groups and substituents are introduced after the construction of the porphyrin macrocycles. However, experimental exploration of the chemical space of porphyrins is limited by synthetic and economic feasibility. This is where computer-aided molecular design tools can be helpful.

Apart from the chemical point of view, investigating the functionalization of porphyrins is also of use for further refinement of our workflow. When functionalizing a structure as implemented in *ChemSpaX* (freezing the skeleton and performing FF optimization only on the newly placed substituents), errors can be introduced. Stretching or compression of the skeleton structure is not taken into account since the skeleton is frozen. Relaxation of the skeleton upon placement of a new substituent group is thus barely taken into account. By investigating a structure that is close to 2D instead of 3D, like porphyrins, the assessment of the introduced errors and their propagation through the workflow of *ChemSpaX* is simplified.

We performed functionalization of Co porphyrins following a serial functionalization strategy² to create a database of ~1100 complexes. Section 4.2.1 discusses the functionalization strategy. Subsequently, the propagation of errors introduced in geometries generated by *ChemSpaX* is investigated in section 4.2.2. An investigation of the HOMO-LUMO gap is done in section 4.2.3.

4.2.1 Functionalization strategy

Figure 9 shows the functionalization strategy for Co porphyrin, the Co porphyrin skeletons were functionalized with various phenyl groups on the R1 sites to generate 10 skeletons. These skeletons were then used to generate 1120 functionalized Co porphyrin complexes. The functionalization was done serially as described in Code implementation. The sites X1-X5 on the phenyl rings (R1) were functionalized first. Finally, functionalizations were done on R2 and R3 respectively. The resulting complexes are shown for 3 different skeletons in Figure 10, where the

Figure 9: Functionalization strategy for Co porphyrin, phenyl groups were placed on the R1 sites and these newly placed phenyl groups were the first targets for functionalization. With this strategy a database of 1120 Co porphyrin structures was generated.

skeleton, 5th functionalization and 15th functionalization are shown in a column demonstrating the geometric complexity introduced upon functionalization.

²A serial functionalization strategy means the functional group were placed one after another leading to more complex functionalized structures.

Figure 10: Functionalization strategy for Co porphyrin shown for 3 different skeletons. For each skeleton the 5th functionalization and 15th functionalization are shown in 1 column. The phenyl rings are functionalized symmetrically. In the 5th functionalization the most left phenyl ring of the skeleton is functionalized, in the 10th functionalization the same substituents are placed on the upper phenyl ring and in the 15th functionalization on the most right phenyl ring. Color code used for elements: gray = C (metal center = Co), white = H, red = O, dark-blue = N and turquoise = F.

4.2.2 Error propagation of serial functionalization

The 1120 geometries were optimized using GFN2-xTB(THF). hRMSD between FF and GFN2-xTB optimized geometries was computed to compare the quality of the FF geometries generated by *ChemSpaX*, giving $\mu = 1.28$, and $\sigma^2 = 0.54$. Upon detailed analysis of the hRMSD it was observed that the hRMSD increases nearly linear for each subsequent functionalization on a skeleton. The error introduced by placing a new substituent group is thus propagated upon the next placement of a substituent. An example is shown in [Figure 11](#) where the hRMSD for each skeleton is plotted. The first 10 blocks of plots show the increasing hRMSD for each functionalization on a given skeleton. The last block shows the hRMSDs for all 10 skeletons, showing how the error increases almost linearly upon each functionalization regardless of the skeleton used for functionalization..

This finding could help users in devising an optimal strategy to get more accurate geometries at a balanced computational cost when using *ChemSpaX*. One can determine when an extra geometry optimization with a higher-level method, such as GFN2-xTB, is needed in between functionalizations by setting an hRMSD threshold. When this threshold is reached, the higher-level optimization method can be used to reduce the hRMSD and the functionalization can be continued with the optimized intermediate as a new skeleton.

Figure 11: Increasing hRMSD for each functionalization on a given skeleton. Where N is the number of functionalizations, starting from 0. 10 skeletons were created and 28 functionalizations were done for each skeleton. The first 10 blocks each represent a skeleton, while the last block on the bottom shows the increasing hRMSD for each skeleton grouped in 1 figure. After every 28th functionalization ($0 \leq N \leq 279$), a new skeleton is functionalized.

Analyzing hRMSD with the number of atoms in a structure we were able to identify 3 groups of data, namely:

1. hRMSD < 1.5 Å (low)
2. 1.5 Å < hRMSD < 2.0 Å (middle)
3. hRMSD > 2.0 Å (high)

A plot of hRMSD versus the number of atoms is shown in [Figure 12](#). For smaller complexes (< 150 atoms) the hRMSD grows linearly with the number of atoms. For larger complexes (> 150 atoms) hRMSDs can range from low to high with the highest hRMSDs being found in the heaviest functionalized structures with a higher number of atoms. The error introduced by *ChemSpaX* upon functionalization is thus propagated, but the hRMSD remains below 3.34 Å, even after 28 functionalizations on the same skeleton.

Structure overlay plots of the FF geometries (silver) and the GFN2-xTB optimized geometries

Figure 12: Plot of hRMSD against the number of atoms in a complex. The three hRMSD data groups are color coded accordingly.

(green) are shown in Figure 13. The upper half of the figure shows structure overlay plots of complexes with < 200 atoms while the lower half shows complexes with > 200 atoms, and diverse hRMSDs.

Figure 13: Structure overlay plots of selected Co porphyrin complexes. ChemSpaX generated (FF) structures (silver) are plotted against GFN2-xTB optimized (silver) structures. The upper half of the figure consists of structures with < 200 atoms and the lower half of the figure shows structures > 200 atoms. Color code used for elements: red = O, dark-blue = N and turquoise = F.

4.2.3 HOMO-LUMO gap prediction

Functional inorganic materials that are used for photocatalysis or photovoltaics require knowledge of the HOMO-LUMO gap, since this gap determines which wavelength of light is absorbed [89, 90, 91]. Additionally, the HOMO-LUMO gap can be used to predict the stability of TM complexes [92]. HOMO-LUMO gap prediction based on only the molecular structure as input using statistical methods, which avoids computationally expensive quantum chemistry calculations, can thus be a great resource to screen and develop functional inorganic materials [93].

We performed DFT based SP calculations on GFN2-xTB optimized geometries of 280 por-

phyrin complexes out of the 1120 complexes generated using *ChemSpaX*. It was found that the hRMSD (error between *ChemSpaX* generated FF structures and GFN2-xTB optimized structures) for 280 selected structures has a moderate correlation with the DFT computed HOMO-LUMO gap ($R = -0.46$) on the GFN2-xTB optimized geometry. This indicates that this hRMSD could potentially be a feature in advanced machine learning applications for electronic property prediction. Additional analysis for prediction of the HOMO-LUMO gap can be found in the SI.

4.3 M2L4 cage

The versatility of *ChemSpaX* is shown by the automated placement of substituents without introducing steric hindrance on a geometry that is more complex. An M2L4 cage was functionalized at 16 sites with various substituent groups. The results are shown in figure [Figure 14](#). This serial functionalization yielded 16 structures and these were further optimized using GFN-FF and GFN2-xTB(GAS). The hRMSDs between geometries generated by workflow of *ChemSpaX* (FF) were calculated against the GFN-FF and GFN2-xTB optimization methods. The statistics shown for each optimization method in [Table 1](#) reveal that the *ChemSpaX* generated FF geometries are closer to the GFN2-xTB optimized geometries compared to GFN-FF optimized geometries.

Figure 14: A visualization of the functionalized M2L4 cage which shows a) the input skeleton and b) the GFN2-xTB optimized geometry after placement of 16 substituents. The newly placed substituents are shown in a distinguished representation.

Table 1: Statistics for the hRMSD between various methods. The two optimization methods that are compared to each other are shown in the first row.

	GFN-FF v GFN2-xTB	FF v GFN2-xTB	FF v GFN-FF
μ	2.54 Å	2.14 Å	0.83 Å
σ^2	0.34 Å	0.25 Å	0.26 Å
Max. hRMSD	3.18 Å	2.46 Å	1.37 Å

5 Summary and conclusions

In this research, an automated Python-based workflow for the exploration of local chemical space is presented. *ChemSpaX* can place substituents on specific sites of many structures based on initial user input and uses FF optimization to optimize newly placed substituents. Use cases were shown by using a data augmented approach which utilized fast GFN2-xTB optimizations to compare structures generated by *ChemSpaX*. For selected use cases a comparison was also done against DFT optimized structures. Descriptors such as the (free) energy of reaction that can be used for high-throughput screening were studied in more detail for some of the presented use cases.

For the pincer complexes the quality of geometries generated by *ChemSpaX* was assessed using $\Delta\Delta E$ of reaction and hRMSDs. The $\Delta\Delta E$ and hRMSDs indicated a good agreement between *ChemSpaX* generated FF structures and GFN2-xTB optimized structures for RuPNP. For the Mn-pincers it was observed that hRMSDs were in agreement with GFN2-xTB, although the $\Delta\Delta E$ of reactions throw caution on direct use of *ChemSpaX* generated geometries in studying reaction energetics. A strong linear scaling of ΔE and ΔG ($R^2 = 0.99$ for both RuPNP and the Mn-pincers) was found. This correlation was found for both DFT and GFN2-xTB calculations. Due to this correlation, ΔG can be replaced by ΔE in high-throughput screening, which would lower the consumption of computational resources significantly.

Functionalized Co porphyrins generated by *ChemSpaX* were compared against GFN2-xTB optimized structures. The errors introduced upon placement of substituents (hRMSD) were investigated for these Co porphyrins. This investigation showed a nearly linear increase in hRMSD for serial functionalizations done on the same skeleton. Using this analysis, a user can devise the optimal strategy to employ a higher-level optimization method based on a hRMSD threshold, to balance speed and accuracy. hRMSD was found to be a potential feature in advanced machine learning applications to predict HOMO-LUMO gap. Additionally, it has been presented that structures generated by *ChemSpaX* in this research are reasonably close to GFN2-xTB optimized structures and that diverse molecular scaffolds can be functionalized using *ChemSpaX*.

To conclude, *ChemSpaX* can be used to generate satisfactory 3D geometric representations in the local chemical space of a given molecular scaffold, particularly including TM complexes. The generated structures, in conjunction with quantum chemical and statistical methods, can be used to generate structure-property databases enabling data-driven chemical design and discovery. There is room for improvement in *ChemSpaX*, which is in the early stages of development. Currently, when the user wants to functionalize multiple skeletons, *ChemSpaX* waits for the previous skeleton to be fully functionalized before moving on to the next. This poses an opportunity for parallelization of the code which is work in progress. Additionally, we are working on implementing a more flexible approach where the user can choose the frequency of intermediate optimizations with a high-level method based on a predicted hRMSD threshold.

With the development of *ChemSpaX*, an important challenge in HTS related to the generation of reasonably accurate 3D molecular geometries is addressed. This workflow is aimed at accelerating chemical space exploration and we hope that *ChemSpaX* will bolster the efforts of the catalysis and molecular modelling communities towards data-driven material discovery.

Data and software availability

The *ChemSpaX* workflow will be made public on our Github organization page: [EPiCs-group](https://github.com/EPiCs-group) (<https://github.com/EPiCs-group>). In addition to this manuscript, supporting information and all used datasets can be found:

- **full_datasets.zip** contains datasets per investigated complex in Excel workbook format.
- **geometry_files.zip** contains geometry files for all structures in MDL Molfiles or XYZ format.

Author contributions

The code for ChemSpaX was written by A. V. K. and V. S. DFT & xTB calculations were performed by A. V. K and V. S. Generation of functionalized structures, the compilation of datasets and analysis of DFT & xTB calculations was performed by A. V. K. under supervision of V. S. V. S. and E. A. P. conceived the project. E. A. P. played an advisory role and directed the project. All the authors discussed the results and wrote the manuscript.

Conflicts of interest

There are no conflicts of interest to declare.

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