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

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Abstract

Exploration of the local chemical space of molecular scaffolds is a highly promising route to discover novel molecules with desired structure and function. Considerable success has been achieved in data-driven exploration of the chemical space of small organic molecules for photovoltaic and pharmaceutical applications. However, structure-property databases spanning the local chemical space of transition metal (TM) complexes, which are widely used in homogeneous catalysis, are not available. In this work a Python-based workflow, *ChemSpaX*, that is aimed at automating local chemical space exploration for any type of molecule, is introduced with special emphasis on TM catalysts. *ChemSpaX* uses 3D information to place functional groups on an input structure. The newly placed substituents are selectively optimized using a computationally cheap force-field optimization method to yield 3D molecular geometries. In representative applications of *ChemSpaX*, it is shown that the generated structures have a reasonable quality for usage in computational screening applications. We demonstrate *ChemSpaX* via three catalytic applications involving functionalization of 1) various intermediates in (potential) (de)hydrogenation catalysis via Mn- and Ru-based pincer complexes 2) cobalt porphyrin complexes 3) a bipyridyl functionalized cobalt-porphyrin trapped in a M_2L_4 type cage complex. The quality of geometries was assessed using energetic (error in net reaction energy) and spatial (root mean squared deviation) metrics by comparison against DFT and GFN2-xTB calculations. Results show that geometries generated by *ChemSpaX* often have performance close to GFN2-xTB optimized geometries although several challenging cases are also identified. 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. *ChemSpaX* is open-source and aims to bolster and democratize the efforts of the scientific community towards data-driven chemical discovery.

Keywords: catalysis; data-driven chemistry; chemical space; transition metal complexes; open source;

1 Introduction

Chemical research has been driven by the ability and the need to create molecular scaffolds with desired (bio)chemical functions. Experimental chemistry, largely guided by intuition, chemical knowledge, and serendipity has been reasonably successful in discovering functional molecular scaffolds which can be improved further. For example, catalysts are decorated with diverse functional groups to explore their activity and stability, and devise possible strategies for improvement.

Although *in vitro* functionalization can reveal chemical design principles that underlie high activity, selectivity and stability, it is time and resource intensive. Computational molecular design has emerged as particularly promising in this regard, thanks to recent advances in quantum chemical methods and high performance computing [1, 2, 3, 4, 5, 6, 7, 8]. High-throughput computational methods can guide towards development of highly effective functionalization strategies by systematically exploring geometries in the local chemical space of a given scaffold [9].

The chemical space is vast and a global exploration is difficult [10, 11]. Therefore, machine learning (ML) and other cost-effective computational methods are attractive solutions to navigate the chemical space in the search of novel molecules and materials [12]. A data-driven statistical approach, rooted in quantum and statistical mechanics (QM and SM) is needed to explore and understand the chemical space [13]. Such an approach is strongly dependent on the availability of trustworthy structure property databases (SPDBs). For (small) organic molecules, reliable data sets such as the GDB datasets (11, 13 and 17) exist which are being used for diverse data-driven chemical discovery applications [14, 15, 16, 17, 18, 19, 20, 21]. In contrast to small organic molecules, development of data-driven approaches have proven more challenging for transition metal complexes (TMCs). TMCs are often used as *bio-inspired* homogeneous catalysts which account for over 15% of all industrial catalytic processes and enable key catalytic transformations such as for pharmaceuticals, fine chemicals, and energy applications [22, 23, 24, 25, 26, 27, 28, 29]. Recent studies have revealed the promise of data-driven quantum chemical methods to understand structure-function relations in TMCs [30, 31, 32, 33, 34, 35]. Availability of structure-property data from QM calculations and/or experiments is central to the success of data-driven chemical approaches. SPDBs of homogeneous catalysts are currently not available [28]. SPDBs with a dense representation of the chemical space of catalytic scaffolds can help discover design principles leading to development of sustainable catalytic systems for various applications [36, 37, 28, 38, 39, 40, 41]. Representations of the molecular structure is of high importance in SPDBs. Several approaches have been developed in this regard recently. For organic molecules string based SMILES representation is a popular and effective approach to encode the molecular structure of organic molecules [42, 43]. Generally SMILES encoding does not work well for TMCs and generation of 3D geometries using SMILES is an active research area [44, 45].

Low dimensional encoding of molecular representations of TMCs, while certainly desirable for ML applications, co-exists with the need to know the 3D geometry due to high structural sensitivity in catalysis. Therefore, automated approaches to rapidly generate accurate 3D molecular representations are also needed. Some automated tools have recently been developed to generate molecular geometries of TMCs [46, 47, 48, 49, 50, 51, 52, 32]. While these tools represent a significant progress in automated and rapid generation of molecular geometries, we sought to develop an easy-to-use tool which can quickly create reasonably accurate molecular geometries in the local chemical space of a given molecular scaffold.

In this manuscript we present *ChemSpaX*, a Python-based workflow that can be used for automated exploration of the chemical space of molecules. 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. The user has full control of the placement of substituent groups and can guide the exploration of the local chemical space. 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*. The local chemical space of a pre-optimized input molecular scaffold can be explored by automatically placing ligands from a pre-defined ligand library. Color code used for elements: gray = C, white = H, red = O, pink = Ru, dark-blue = N and turquoise = F.

The computational methods employed in this manuscript are presented in the next section. A description of the code implementation to develop *ChemSpaX* follows. Subsequently, representative applications of *ChemSpaX* are presented. The first representative application involves Ru and Mn catalysts based on pincer ligands. Pincer ligands have emerged as versatile ligand platform enabling a plethora of catalytic reactions [53, 54, 55, 56]. First, the functionalization of a Ru complex derived from the commercially available Ru-MACHO [25] is described. TMCs based on the MACHO ligand framework have shown versatile activity in catalyzed (de)hydrogenation reactions [57, 58, 59, 60, 61, 62]. Analyzing the chemical space of the Ru-MACHO catalytic scaffold can be a valuable asset for multiple applications. Next, the functionalization of Mn-pincer complexes as potential (de)hydrogenation catalysts is studied [63]. With this application the chemical space of an earth-abundant alternative to RuPNP is explored. Manganese is known to be a cheap, abundant and biocompatible alternative to precious-metal catalysts [64, 59, 65, 66]. The quality of geometries generated by *ChemSpaX* is compared against higher-level DFT and GFN2-xTB methods.

Secondly, we apply *ChemSpaX* to generate a database of ~ 1100 functionalized Cobalt Porphyrin (referred to as 'Co porphyrin' in the rest of this manuscript) complexes. Co porphyrins exist as stable metalloradicals and are used to catalyze carbene and nitrene transfer reactions [67, 68, 69, 70]. 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.

Finally, the functionalization of a bipyridyl functionalized Cobalt-porphyrin trapped in a M_2L_4 type cage complex (referred to as ' M_2L_4 cage' in the rest of this manuscript) is presented. This cage complex confines the Co porphyrin catalyst, which can lead to changed catalyst properties

[71, 72, 70]. The quality of *ChemSpaX* generated M_2L_4 cage geometries is compared against semi-empirical and force-field based xTB optimization methods. This case shows how *ChemSpaX* can be used to functionalize diverse and challenging molecular scaffolds.

2 Computational methods

2.1 Open Babel

Conversions between MDL Molfile and XYZ format were done using Open Babel [73, 74]. Open Babel was also used to perform Generalized Amber Force Field (GAFF), and the Universal Force Field (UFF) optimizations [75, 76].

2.2 Semiempirical tight-binding

Grimme lab's xTB package (version 6.3.3) was used for semi-empirical tight-binding calculations [77]. The GFN2-xTB, and GFN-FF methods were used for geometry optimization [78, 79, 80, 81]. The M_2L_4 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 [82, 83]. Thermochemical parameters such as the Gibbs free energy were computed using the hessian matrix calculations. These GFNn (n= 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 [84]. The BP86 exchange-correlation functional was used for geometry optimizations together with the def2SVP basis set [85, 86]. This combination of functional and basis set have shown reliable geometry predictions accompanied with low computational costs [87, 88]. 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 corresponded to a local minimum on its respective potential energy surface (PES). Thermochemical parameters such as the Gibbs free energy were computed using the gas phase hessian calculations. Single point (SP) DFT calculations were performed on the gas-phase optimized geometries using the SMD solvation (THF) model [89]. 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 [86, 90]. All DFT calculations were performed with Grimme's D3 dispersion corrections [91]. These composite methods (geometry optimization followed by SP), BP86/def2-SVP//XC/def2-TZVP (THF), are denoted as XC(THF) or XC(GAS) depending on the exchange-correlation (XC) functional used. All geometries were pre-optimized with a combination of Openbabel's GAFF and UFF methods and/or GFN2-xTB before being subjected to full DFT based optimization. We did not conduct any conformational search.

The catalysts are denoted as M-L where M represents the metal center and L the ligand. Reactive adsorption of a H-X species (X = H, Br, OH, *i*-PrO) over M-L leads to the formation of M(X)-L(H) species. The thermodynamic stability of the M(X)-L(H) was estimated by computing the Gibbs free energy and total energy change under standard conditions upon addition of the

H-X moiety.

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

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

2.3.2 Co porphyrins

TeraChem v1.94V-2019.08-beta was used to perform GPU-accelerated DFT SP calculations using the PBE1PBE XC and LANL2DZ basis sets with an effective core potential (ECP) on selected Co-Porphyrin geometries optimized using the GFN2-xTB method [92, 93, 94, 95].

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 positions 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 [96, 97, 98]. If for example the two molecules **p** and **q** with *n* points (atoms) are compared, the RMSD is defined as:

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

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

3 Code implementation

An overview of the workflow of ChemSpaX 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 shipped with ChemSpaX or users can create new substituents in XYZ or MDL Molfile format [99]. Information for the correct placement of a substituent is kept in a CSV file. The CSV file stores: 1) Coordinates of the *central atom* of the substituent group which coordinates directly to the sites defined in the *functionalization_list*. 2) Coordinates of the *centroid vector*. A centroid vector, for a tetrahedral substituent such as CH₃ is the vector connecting the central atom (C) to the centroid of the triangle formed by the three edges (hydrogens). for a planar substituent such as NH₂ the centroid vector connects the center of the line joining the two hydrogen atoms to N (central atoms).

The substituent group is first correctly oriented using rotation matrices and placed at a pre-defined distance from the substitution site. Next GAFF followed by UFF optimization methods from Open Babel are used to selectively optimize the newly placed substituent via a constrained optimization protocol while keeping the original molecular skeleton frozen [73, 74]. This combination of GAFF and UFF was found by trial-and-error (see SI). The correction in orientation of the substituent group prior to FF optimizations is needed to ensure a reasonable input geometry. The FF optimizations are based on MDL molfiles which contain the connectivity information between different atoms. When new substituents are placed the

connectivity information is carefully updated to ensure that no undesired overlaps/connections are present. FF optimization using the MDL molfiles as input rectifies the geometry and removes any physical overlap between different atoms/functional groups. It is recommended to use a DFT optimized geometry as input skeleton since the FF optimization only influences the newly placed functional group. This choice helps keep the core of the geometry as close to its DFT optimized input structure as possible upon serial functionalization, while preventing steric hindrance from newly placed substituents cheaply via force-field optimizations.

Figure 2: Overall workflow of ChemSpaX. 1) The user supplies the XYZ coordinates of a molecular skeleton, *functionalization_list*, and substituents. 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 exits and the functionalized skeleton is saved in MDL Molfile format. Else the functionalized skeleton will be used as input and the entire process repeats from 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 is described. In section 4.1.1 the functionalization strategy for both types of 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 properties is done in section 4.1.3.

4.1.1 Functionalization strategy

The functionalization strategy for the RuPNP complex is shown in Figure 3. This functionalization strategy resulted in 144 (M-L) complexes. For each M-L complex, its hydrogenated version M(H)-L(H) was also generated by functionalization of the M(H)-L(H) complex as skeleton, leading to a total of 288 geometries. Out of these, 27 pairs (M-L/M(H)-L(H)) were selected for BP86(GAS) optimization. BP86(THF) and PBE1PBE(THF) PS calculations were performed on the DFT optimized geometries.

Figure 3: Functionalization strategy for the RuPNP pincer complexes.

Krieger and co-workers [63] used an "under development" version of *ChemSpaX* to generate a database of 1225 Mn complexes based on five representative ligand scaffolds namely PNP-(bis(3-phosphanylpropyl)amine)-¹, SNS(azanediylbis(ethane-1-thiol)), CNC(bis(2-(1H-3 λ^4 -imidazol-3-yl)ethyl)amine), PNN(N¹-(2-phosphanylethyl)ethane-1,2-diamine), and PCP(N¹,N³-bis(phosphanyl)benzene-1,3-diamine) [100, 101, 102, 103, 104, 105, 106]. Out of these 1225 geometries, 545 geometries containing the PCP, PNN and CNC ligand backbones were selected for DFT optimization using BP86(GAS). This dataset of 545 complexes will be discussed further.

The functionalization strategy for PCP, PNN and CNC ligand based complexes is shown in Figure 4. Functionalizations were performed symmetrically keeping all four R₁ sites the same. Similarly both R₂ sites (only 1 in case of PCP backbone) were functionalized with the same groups. However, R₁ and R₂ were not constrained to be the same.

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 Mn-pincers with various donor (R_1) and backbone (R_2) groups.

4.1.2 Quality assessment of generated geometries

ChemSpaX uses FF optimizations on newly placed substituent groups in each iteration. Therefore we name geometries generated directly by *ChemSpaX* as "FF-geometries". To assess the quality of FF-geometries they were compared against GFN2-xTB and DFT. The quality of geometries was assessed along two dimensions: energy and spatial. When comparing geometries along the *energy* dimension, we computed the net energy change of a particular chemical reaction using SP calculations on FF-geometries at higher levels of theory (e.g. DFT or GFN2-xTB). For a given reaction the *ChemSpaX* generated FF geometries of reactants and product were taken. Each FF geometry underwent two calculations: 1) a SP calculations where the energy of the FF geometry was evaluated at DFT level of theory and the electronic energy change of the reaction $\Delta E_{FF//DFT-SP}$ was calculated 2) a full DFT based optimization was carried using the FF geometry as input resulting in a new geometry and energy at the DFT level of theory. The corresponding electronic energy change of the reaction ΔE_{DFT} was calculated. The difference between the reaction energies is computed using $\Delta E_{FF//DFT-SP}$ and ΔE_{DFT} to get $\Delta\Delta E_{FF}$ which is a metric for the quality of FF geometry for the reaction being investigated (Equation 6). A similar approach was used by Sinha and co-workers to assess the quality of GFN2-xTB optimized geometries against DFT (Equation 7) [107].

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

$$\Delta\Delta E_{GFN2-xTB} = \Delta E_{DFT} - \Delta E_{GFN2-xTB//DFT-SP} \quad (7)$$

Such a comparison allows us to estimate the range of error caused by the direct use of FF-geometries by skipping computationally expensive DFT optimizations, for example in high-throughput screening (HTS) workflows. Geometries were also assessed along the *spatial* dimension where we computed the RMSD between FF-geometries against GFN2-xTB, and DFT optimized geometries.

For RuPNP complexes we chose the hydrogenation reaction ($M-L + H_2 \longrightarrow M(H)-L(H)$) to investigate $\Delta\Delta E_{FF}$ and $\Delta\Delta E_{GFN2-xTB}$. The corresponding mean (μ) and standard deviation (σ^2) were also computed². We found $\mu(\Delta\Delta E_{FF}) = 7.20 \text{ kcal mol}^{-1}$ with $\sigma^2(\Delta\Delta E_{FF}) = 4.57 \text{ kcal mol}^{-1}$; and $\mu(\Delta\Delta E_{GFN2-xTB}) = 4.77 \text{ kcal mol}^{-1}$ and $\sigma^2(\Delta\Delta E_{GFN2-xTB}) =$

² $\Delta\Delta E_{GFN2-xTB}$: 20 pairs; ($\Delta\Delta E_{FF}$) 25 pairs M-L/M(H)-L(H) geometries

2.57 kcal mol⁻¹. This indicates an overall good agreement between the GFN2-xTB optimized structures and the structures generated by *ChemSpaX*.

For the Mn-pincer complexes we investigated reactive adsorption of H-X species ($M-L + H-X \rightarrow M(X)-L(H)$; X = H, Br, *i*-PrO, and OH) with the reaction energetics characterized by ΔE , and the respective FF geometries by $\Delta\Delta E_{FF}$ respectively. When the entire dataset was considered i.e. all three ligand systems, and all four H-X species, we found $\mu = 25.57$ kcal mol⁻¹ and σ^2 of 26.08 kcal mol⁻¹. We also investigated the mean and standard deviation values associates with each ligand and H-X species (Table 1). FF geometries associated with the PCP ligand were found to have the lowest μ and σ^2 values in general, followed by the CNC ligand complexes. The PNN ligand complexes had the highest μ and σ^2 . In terms of the H-X species considered, $\Delta\Delta E_{FF}$ computed for both HBr and H₂ showed lower μ while those for *i*-PrOH and H₂O showed highest μ . The reason for worse performance of *i*-PrOH and H₂O can be attributed to the observed recombination of O-H bond in many geometries during DFT based optimization leading to M(H-X)-L type complexes, or non-adsorbed H-X adducts.

Table 1: $\mu \pm \sigma^2$ for $\Delta\Delta E_{FF}$ for various H-X and ligands in kcal mol⁻¹.

Ligand	Br	H	OH	<i>i</i> -PrO
PCP	17.10 $\pm$ 4.76	10.80 $\pm$ 7.25	20.96 $\pm$ 9.36	25.60 $\pm$ 23.45
PNN	36.37 $\pm$ 16.83	28.05 $\pm$ 18.42	63.28 $\pm$ 36.79	56.06 $\pm$ 32.05
CNC	8.94 $\pm$ 8.08	12.16 $\pm$ 9.64	8.31 $\pm$ 10.97	16.92 $\pm$ 22.83

The distribution of $\Delta\Delta E_{FF}$ for the reactive adsorption of HBr for all the ligands and functionalization sites (R_1 and R_2) is shown in Figure 5. For the CNC ligand complexes variation of the functional group at the R_2 position with fixed R_1 (Figure 5 a)) led to similar $\mu(\Delta\Delta E_{FF}) < 10$ kcal mol⁻¹ for all groups except for $R_1 = CF_3$. Since functionalization site R_2 is primarily a ligand and backbone site, it seems that the effective relaxation of the ligand during DFT optimization is similar for the CNC complexes. Variation of the functionalization group at R_1 results in a wider spread in the $\Delta\Delta E_{FF}$ values for CF_3 , H and cy groups, while *i*-Pr substituents show most narrow distribution with $\mu(\Delta\Delta E_{FF}) = 9.01$ kcal mol⁻¹. The difference in distribution spread probably arises from the worse performance of force-field methods for geometric fragments close to the metal center leading to higher structure-energy sensitivity. All PNN ligand complexes showed high and widespread $\mu(\Delta\Delta E_{FF})$ values. Most notable is $R_1 = H$ which shows a rather large spread indicating large geometric relaxations when different ligands are introduced on the backbone sites. PCP ligand complexes are interesting for their almost linearly increasing $\mu(\Delta\Delta E_{FF})$ as the size of the functional group on the R_1 site is increased while the spread in energies is minimal (Figure 5 e)). Furthermore, the variation at site R_2 shows an almost constant $\mu(\Delta\Delta E_{FF})$ with similar spread (Figure 5 f)). This observation indicates the source of spread is related to a larger geometric relaxation near the metal site during DFT based geometry optimization. Site R_2 being farther away from the metal center seems to have minimal impact on the geometries and is rather well optimized by the force-field. This observation is consistent with the finding that variation of R_2 had minimal impact on thermochemical properties in Mn-PCP complexes [63]. We also compared the individual difference in energy between FF and DFT optimized geometries for M(X)-L(H) and M-L complexes. In general, we found that the energy of FF optimized M(Br)-L(H) complexes were closer to their DFT counterparts when compared to corresponding M-L complexes. This observation reveals that the M-L complexes have a larger contribution to the $\Delta\Delta E_{FF}$. We also observed that almost all cases where the M(X)-L(H) complexes had a larger contribution to the $\Delta\Delta E_{FF}$ were based on the CNC ligand (24 entries) with $\mu = 9.4$ kcal

Figure 5: Box plots showing the distribution of $\Delta\Delta E_{FF}$ for reactive adsorption of H-X (X = Br) for (a,b) CNC (c,d) PNN and (d,e) PCP ligand based Mn complexes. For each ligand functionalization effect of the donor (R_1) and backbone (R_2) groups on the spread of $\Delta\Delta E_{FF}$ is visualized.

mol^{-1} .

The quality of FF geometries along the spatial dimension was analyzed via RMSD between geometries produced by DFT or GFN2-xTB based optimizations. Specifically we computed the cartesian heavy-atom (all elements except H) root-mean-square deviation (hRMSD) [77]. Both FF ($\mu = 0.67 \text{ \AA}$; $\sigma^2 = 0.30 \text{ \AA}$) and GFN2-xTB ($\mu = 0.41 \text{ \AA}$; $\sigma^2 = 0.34 \text{ \AA}$) structures had a similar average hRMSD when compared to DFT structures. 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 is done as follows: a) the FF optimized structure (silver), generated by *ChemSpaX*, is compared to a DFT optimized structure (green) and b) a GFN2-xTB optimized structure (silver) is compared to a DFT optimized structure (green).

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)) while the DFT optimizations are in the gas phase.

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.

The hRMSD analysis was performed for various ligands backbones. This comparison is shown in Figure 7. As observed by Krieger and co-workers, DFT and xTB based optimization of most PNN based complexes resulted in hemilabile ligands [63]. 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 R_1 site resulted in a higher hRMSD. For the PCP backbone it was observed that functionalization with *t*-Bu on the R_1 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 and may cause and may elicit shearing of the skeleton which is kept frozen in FF calculations. When optimized with DFT, the skeleton would relax and this would lead to a higher hRMSD. We that $\Delta\Delta E_{\text{FF}}(\text{HBr})$ and $\Delta\Delta E_{\text{FF}}(\text{H}_2)$ correlated well (Pearson correlation coefficient (R) = +0.87) opening up possibilities to reduce computational effort in screening through these intermediates. Krieger and co-workers had reported a similar albeit stronger correlation (R = 0.95) between ΔG_{HBr} and ΔG_{H_2} [63].

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. All energy values are in kcal mol⁻¹.

4.1.3 Comparison of ΔG and ΔE

Calculation of the hessian matrices of the geometry of reactant and product species is often needed to estimate the Gibbs free energy ΔG change in a chemical reaction. Hessian calculation is also quintessential to ensure accurate and reliable geometry optimization. However, it would be desirable to omit these computationally expensive calculations when filtering through a large number of molecular structures for example in a HTS workflow. Sinha and co-workers had reported a strong correlation between ΔG with ΔE for the proton transfer reaction [107]. In the present work we found a similar correlation to hold for the reactive adsorption of H-X species over Ru-PNP (X = H) and Mn-pincers (X = H, Br, *i*-PrO, OH) (Figure 8). This correlation shows that ΔE scales linearly with ΔG . The linear fit in Figure 8 shows that the difference in ΔE and ΔG is approximately constant and equals 15 kcal mol⁻¹. Therefore, ΔE can be used instead of ΔG with a minimal loss of accuracy, avoiding computationally expensive hessian calculations 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 when accurate results are really needed hessian calculations must be performed to ensure that the optimized geometry is a minimum on the potential energy surface.

Figure 8: Comparison between the net Gibbs free energy (ΔG), and the net electronic energy (ΔE) for the reaction $M-L + H-X \rightarrow M(X)-L(H)$ computed via a) DFT calculations for Mn-pincers, b) GFN2-xTB calculations for Mn-pincers and c) GFN2-xTB calculations for RuPNP [107]. Note that for plot b) data for $H-X = t\text{-BuOH}$, EtOH , and MeOH computed in the reference [63] was also included.

4.2 Co-porphyrin

Porphyrins are widely investigated, for example, for their applications in biocatalysis, organic photovoltaics, molecular wires and many more applications [108, 109, 110, 111]. This wide variety of applications has been enabled by the design and synthesis of structurally diverse porphyrins [108]. 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 macrocycle. 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 application perspective, 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. 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 strategy³ 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 R_1 sites to generate 10 new 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 (R_1) were functionalized first. Finally, functionalizations were done on R_2 and R_3 respectively.

Figure 9: Functionalization strategy for Co porphyrin. Phenyl groups were first placed on the R_1 sites and subject to further functionalizations. With this strategy a database of 1120 Co porphyrin structures was generated.

The resulting complexes are shown for 3 different skeletons in Figure 10, where the skeleton, and Co-porphyrin complexes at the end of 5th, and 15th functionalization are shown in a column demonstrating the geometric complexity introduced upon functionalization.

³A serial functionalization strategy means that the functional groups 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 geometries resulting from the 5th, and the 15th functionalization are shown in a column. The phenyl rings are functionalized symmetrically. In the 5th functionalization the left most phenyl ring of the skeleton is functionalized, in the 10th functionalization step the same substituents are placed on the upper phenyl ring, and on the right most phenyl ring in the 15th step. 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). The hRMSD between FF and GFN2-xTB optimized geometries was computed to compare the quality of the FF geometries generated by *ChemSpaX*, giving $\mu = 1.28\text{\AA}$, and $\sigma^2 = 0.54\text{\AA}$. 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. These results 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. The linear regression fits shown in Figure 11 can be used to estimate the hRMSD. One can generate these relations on a small sub-set of geometries in the functionalization scope by performing additional geometry optimizations at a higher level of theory. The predicted hRMSD can be used to set a threshold value. When this threshold is reached, a 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.

Structure overlay plots of the FF geometries (silver) and the GFN2-xTB optimized geometries (green) are shown in Figure 12. 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. Large hRMSDs result from divergent orientation of long alkyl chain substituents, and fluorine containing groups

Figure 12: 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 [112, 113, 114]. Additionally, the HOMO-LUMO gap can be used to predict the stability of TM complexes [115]. HOMO-LUMO gap prediction based on only the molecular structure as input using statistical methods, which avoid computationally expensive quantum chemistry calculations, can thus be a great resource to screen and develop functional inorganic materials [116].

We performed GPU accelerated DFT based SP calculations on GFN2-xTB optimized geometries of 280 porphyrin complexes out of the 1120 complexes generated using *ChemSpaX*. It was found that the hRMSD between FF geometries and GFN2-xTB optimized structures had a moderate correlation with the DFT (SP) computed HOMO-LUMO gap ($R = -0.46$) on the GFN2-xTB optimized geometry. This indicates that 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 M_2L_4 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 M_2L_4 cage was functionalized at 16 sites with various substituent groups. The results are shown in figure Figure 13. This serial functionalization yielded 16 structures and these were further optimized using GFN-FF and GFN2-xTB(GAS). The hRMSDs between FF geometries and those generated using the GFN-FF and GFN2-xTB optimization methods were calculated. The statistics shown for each optimization method in Table 2 revealed that the *ChemSpaX* generated FF geometries are

closer to the GFN2-xTB optimized geometries compared to GFN-FF optimized geometries.

Figure 13: A visualization of the functionalized M_2L_4 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 2: 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 work, an automated Python-based workflow for the exploration of local chemical space is presented. *ChemSpaX* can place substituents on specific sites of diverse molecular scaffolds 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 HTS applications 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 along the energy ($\Delta\Delta E$) and spatial (hRMSDs) dimensions. Generally FF geometries were found to be similar in quality compared to GFN2-xTB optimized geometries based on the hRMSDs, and $\Delta\Delta E$. Intramolecular movements pose a challenge for FF geometries which show high hRMSDs for complexes involving labile ligands. A use case of *ChemSpaX* enabled QM calculations was

the discovery of a strong linear scaling of ΔE and ΔG ($R^2 = 0.99$ for both RuPNP and the Mn-pincers). This correlation was found for both DFT and GFN2-xTB calculations allowing lower computational costs by skipping the calculation of hessian matrices to estimate ΔG . Analysis of functionalized Co porphyrins generated by *ChemSpaX* showed that the hRMSD increased linearly with the number of atoms in serial functionalization runs on a given skeleton. This observation paves the way for devising a strategy to optimally employ higher-level geometry optimizations in intermediate steps. hRMSD was found to be a potential feature in advanced machine learning applications to predict the HOMO-LUMO gap. It has been demonstrated 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. We are working to further improve *ChemSpaX* along diverse research lines. Improved force-field methods can definitely help improve the accuracy of *ChemSpaX*. A data-informed approach to estimate the hRMSD based on the identity of the skeleton molecule and functional groups placed can improve the predictive capabilities for screening applications. Parallelization of the code for placing functional groups 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, and also get recommendations about optimal strategies balancing speed and accuracy.

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 and democratize the efforts of the catalysis and molecular modelling communities towards data-driven material discovery. *ChemSpaX* is free, open-source and is available with an introductory Google colaboratory notebook which can be immediately used by researchers.

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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