Accurate and Rapid Prediction of pKₐ of Transition Metal Complexes: Semiempirical Quantum Chemistry with a Data-Augmented Approach

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Rapid and accurate prediction of reactivity descriptors of transition metal (TM) complexes is a major challenge for contemporary quantum chemistry. Recently developed GFN2-xTB method based on the density functional tight-binding theory (DFT-B) is suitable for high-throughput calculation of geometries and thermochemistry for TM complexes albeit with a moderate accuracy. Herein we present a data-augmented approach to improve substantially the accuracy of GFN2-xTB for the prediction of thermochemical properties using pKₐ values of TM hydrides as a representative model example. We constructed a comprehensive database for ca. 200 TM hydride complexes featuring the experimentally measured pKₐ's as well as the GFN2-xTB optimized geometries and various computed electronic and energetic descriptors. The GFN2-xTB results were further refined and validated by DFT calculations with the hybrid PBE0 functional. Our results show that although the GFN2-xTB performs well in most cases, it fails to adequately describe TM complexes featuring multicarbonyl and multihydride ligand environments. The dataset was analyzed with the partial least squares (OLS) fitting and was used to construct an automated machine learning (AutoML) approach for the rapid estimation of pKₐ of TM hydride complexes. The results obtained show a high predictive power of the very fast AutoML model (RMSE ~ 2.7) comparable to that of the much slower DFT calculations (RMSE ~ 3). The presented data-augmented quantum chemistry-based approach is promising for high-throughput computational screening workflows of homogeneous TM-based catalysts.

Introduction

Proton transfer reactions are ubiquitous in chemistry. The propensity of proton transfer from a chemical species is related to its acidity constant (pKₐ). In the context of the transition metal (TM) complexes, pKₐ has a direct relevance to their (bio)chemical activity and stability. In homogeneously catalysed (de)hydrogenation reactions such as hydrogenation of CO₂ to formates/formic acid⁴ and dehydrogenation of aqueous methanol⁵, the pKₐ of TM-based catalysts has been recognized as an important design parameter. For example, the pKₐ of a TM hydride determines the strength of an acid necessary for the H₂ evolution.⁶ Loss or gain of protons can open up undesirable conversion paths or even initiate the decomposion and/or deactivation of the catalyst.

Accurate estimation of the thermodynamic properties such as pKₐ of TM complexes is a major challenge for quantum theoretical methods. Computational methods for rapid and accurate screening of such thermodynamic properties are highly desirable. Density functional theory (DFT) has been extensively applied to estimate thermodynamic properties of TM complexes.⁵,⁶ However, the DFT based prediction workflows commonly face major challenges with respect to the accuracy of the calculations (basis set; XC functional; solvation model) and the computational costs. The method accuracy in DFT towards prediction of thermochemical properties can be addressed by validation against the experimental data. However, the computational cost for predicting molecular geometries and thermochemical properties remains an important challenge, in particular, when the applications in high-throughput computational screening are sought for. Despite the advances in software and hardware architectures, DFT based calculations for moderately sized TM complexes (> 50 atoms) can take several hours to complete in most cases on a modern supercomputer. Furthermore, the electronic structure of TM complexes, particularly for the 3d metals, is a major challenge for DFT.⁷ The cost and accuracy of DFT makes it challenging for its direct use in high throughput (HT) computational screening of TM complexes.

Data-driven or semiempirical quantum chemical approaches can be used to circumvent the low throughput of DFT for predicting geometries and thermochemical properties.⁷-¹¹ Recently a GFN2-xTB method (the latest one from the GFN(n) family), based on the density functional tight-binding approach has been introduced for the rapid prediction of geometry and thermochemical properties of TM complexes.¹² However, because of its semiempirical nature, the accuracy of the GFN2-xTB is fundamentally limited by the thermochemical span of the training set of molecules and the level of theory used in the parametrization. We propose that the accuracy of the GFN2-xTB method can be improved using machine learning a target chemical property such as the pKₐ values (Figure 1).
Density functional theory (DFT) calculations have been successfully applied to estimate pK_a of diverse classes of molecules.\textsuperscript{13–16} However, fewer studies have been carried out to compute the pK_a of TM complexes. Previously, DFT was successfully used to compute the pK_a of hexa-aqua TM complexes because of its relevance to biochemical activity of TM cations. Munoz and co-workers reported a theoretical approach to estimate the pK_a of biologically relevant pyridoxamine-Cu(II) complexes.\textsuperscript{21} Recently Cundari and co-workers\textsuperscript{22} applied DFT calculations to estimate the pK_a of methane adducts of 3d TM complexes.

Accurate treatment of solvent effects, especially in a protic and hydrogen bonding environment often pose a major challenge for the reliable computation of pK_a values. \textit{Ab initio molecular dynamics} (AIMD) simulations with fully explicit solvent have been used to address solvation effects in computation of pK_a of TM complexes in protic environments.\textsuperscript{13,14,23} The reader is referred to a review by Luber and co-workers\textsuperscript{24} for a comprehensive overview of AIMD-based protocols for computing pK_a.

DFT-based methods typically require geometry optimization and calculation of hessian matrix to estimate the Gibbs free energy of protonated and deprotonated complexes. Even for relatively small complexes (~50 atoms) with a single TM center, DFT calculations can take several hours to converge. AIMD simulations typically require several days to be able to compute a single pK_a value of a TM complex. A model based additive ligand acidity constants (LAC) was proposed by Morris and co-workers, which avoids DFT calculations and can compute pK_a of TM hydrides.\textsuperscript{25} Additive LAC method uses the ligand acidity constants of ligands coordinated to the metal centre, the charge and the conjugate base form of the metal complex, the location of TM metal in the periodic table and a correction related to the stability and geometry of the metal centre. While simple, reasonably accurate and motivated by physical principles, the additive LAC model requires knowledge of acidity constants of coordinating ligands, which makes it difficult to use directly in high throughput screening workflows. Cundari and co-workers recently reported ML based methods for the estimation of pK_a of methane adducts of TM complexes and demonstrated the potential of ML for catalyst design via rapid property prediction.\textsuperscript{26} The potential of GFNn-xTB methods towards rapid and accurate prediction of pK_a was recently demonstrated in the SAMPL6 challenge by Grimme and co-workers.\textsuperscript{27} They demonstrated that the workflows based on GFN1-xTB and GFN2-xTB methods resulted in rapid and accurate prediction of experimental pK_a of 24 drug like molecules. The performance of GFN2-xTB has also been tested upon a large number of TM complexes taken from the Cambridge structural database.\textsuperscript{27,28} However, the performance of GFN2-xTB towards prediction of thermochemical properties of TM complexes has not been extensively validated against experimental and/or DFT computed data.

Therefore, research objectives in this study are two-fold: 1) systematically improve the accuracy of the GFN2-xTB method for prediction of experimental pK_a of TM hydrides via a data-augmented approach, and 2) assess the suitability of GFN2-xTB and GFN2-xTB/DFT (i.e. DFT energy refinement on GFN2-xTB optimized geometries) for predicting pK_a as compared with the conventional full DFT computational protocol. The presented data-augmented approach leads to a systematic improvement in the accuracy of GFN2-xTB method for predicting the experimental pK_a of TM hydrides at negligible additional computational cost. As a final test we use our data-augmented approach to predict the ligand pK_a of TM complexes and estimate the pK_a of TM hydrides for whom ambiguous values have been reported in the literature.

### Computational Methods

#### Semiempirical tight-binding calculations.

Semiempirical tight-binding calculations were carried out using the xTB code.\textsuperscript{12,29} We applied the GFN2-xTB method\textsuperscript{30} recently developed by the Grimme group. Molecular geometries were subject to geometry optimization using the verytight criteria. Hessian matrix calculations were performed for all optimized geometries to verify the absence of imaginary frequencies and that each geometry corresponds to a local minimum on their respective potential energy surface (PES). Solvent effects were implicitly accounted for using the GBSA solvation mode\textsuperscript{31,32} as implemented in xTB.\textsuperscript{7}

#### Density Functional Theory calculations.

DFT calculations were carried out using the Gaussian 16 C.01 program package.\textsuperscript{33} Geometry optimizations were carried out using the PBE0 (also denoted as PBE1PBE)\textsuperscript{34} exchange-correlation functional, def2-SVP\textsuperscript{35} basis set and the Grimme's dispersion corrections (D3 version)\textsuperscript{16}. The choice of the PBE0 functional is motivated by our previous experience for prediction of reliable results for TM complexes in good agreement with experimental data.

Furthermore, our initial test showed the superior performance of the PBE0 method for the prediction of experimentally determined ligand pK_a (N-H function) of several representative TM complexes. The DFT computed-energies were additionally refined by single point (SP) calculations using the PBE0-D3 method together with the SMD variation of the IEFPCM implicit solvent model of Truhlar and workers\textsuperscript{37} and the combination of the LANL08 basis set\textsuperscript{38} on the metal center and the cc-pvTZ basis set for all other atoms.\textsuperscript{39}

All complexes were computed at their lowest spin state and higher spin states were not considered in our calculations. All geometries were pre-optimized first at GFN2-xTB level and then subject to full DFT based optimization.

#### Machine Learning Methods.

We performed DFT-B based geometry optimizations for 177 complexes in the gas phase and in solution. The output files were analysed to extract 17 descriptors (see Table 2) based on the computed electronic structure, geometry and energetics, which were stored in the dataset along with the experimentally measured pK_a values obtained from the literature. For ML
modelling we took two approaches: 1) linear regression via the ordinary least squares (OLS) fitting using sklearn library in python\cite{40}. 2) Automated ML using auto-sklearn library in python\cite{41,42}. Auto-sklearn allows a rigorous search of a number of ML regression models and hyperparameters. The Pearson correlation coefficient ($r^2$ score) was used as a metric for the optimization of the ML model. The dataset was split into the training and test sets (80:20 split). The ML model was trained on the training set and its performance was tested on the test set which it has not seen before. Cross-validation (CV) set via k-fold (5 folds) sampling was used while optimizing the ML model.

The ML models were further tested for their accuracy on an additional dataset of ligand $pK_a$ of TM complexes. ML models have been solely trained on TM hydrides and their performance on ligand $pK_a$ demonstrate their general applicability. We further use the ML models to assign $pK_a$ values of complexes, for which multiple $pK_a$ values have been reported in the literature and compare the results with the DFT-based predictions. The accuracy of ML models is assessed via calculation of root mean squared error (RMSE) wherever labelled data is available and compared against the performance of the DFT based methods wherever possible.

**Determination of $pK_a$.**

Several methods have been proposed in the literature for estimating $pK_a$ by means of DFT calculations.\cite{15} For an acid-base titration between an acid AH and base B to produce the conjugate base A and conjugate acid BH, one can express the $pK_a$ of AH as

$$\begin{align*}
AH + B &\rightleftharpoons A + BH \\
pK_a(AH) &= pK_a(BH) + \frac{\Delta G}{2.303 RT} \tag{1}
\end{align*}$$

$$\Delta G = G(A) + G(BH) - G(AH) - G(B) = [G(BH) - G(B)] - [G(AH) - G(A)] \tag{2}$$

B is a reference base with a known $pK_a$ of its conjugate acid form, BH. The quantities $G(BH)$ and $G(B)$ are constant for a given solvent at a fixed temperature. Therefore, for a given solvent and temperature $pK_a(AH)$ is a linear function of $G(AH) - G(A)$. We define proton affinity (PA) as the difference between the Gibbs free energy of protonated ($G(AH)$) and deprotonated species ($G(A)$) i.e.

$$PA(AH) = G(A) - G(AH) \tag{3}$$

Equivalently one can also express the $pK_a(AH)$ using the PA and solvated Gibbs free energy of a proton.

$$\begin{align*}
AH &\rightleftharpoons A + H^+ \\
pK_a(AH) &= \frac{[G(A) - G(AH) + G(H^+)]}{\frac{2.303 RT}{PA(AH)} + \frac{2.303 RT}{2.303 RT}} \tag{4}
\end{align*}$$

It can be shown that eq(1) and eq(4) are equivalent and $pK_a$ can be expressed as a linear function of PA at fixed temperature and for a given solvent.

For both DFT and GFN2-xTB calculations, we discovered that the PA computed using Gibbs free energy (eq(3)) correlates perfectly with the PA computed using electronic energies only (i.e. $PA = E(A) - E(AH)$). We therefore use electronic energy to compute the $pK_a$ ($\approx E(A) - E(AH)$) in our ML models. For further details please refer to Figure-SI-3 and Figure-SI-4 in the SI.

**Results and Discussion**

**$pK_a$ dataset**

A data-augmented approach requires reliable data. Generation of data by experimentation and simulation is one of the key propelling factors towards the rise of data-driven chemical sciences. However, well curated experimental datasets on TM complexes with measured/computed thermodynamics properties are rare. The Cambridge structural database (CSD) partly serves this purpose by providing geometries and measured/calculated properties of TM complexes but lacks experimentally measured or computed $pK_a$ values of TM complexes. In fact, to the best of our knowledge no open datasets on experimentally measured $pK_a$ values of TM complexes along with geometric information are available. To address this we curated experimental $pK_a$ data for over 200 TM complexes from literature (Figure 2).

Most of these complexes are transition metal hydrides where the $pK_a$ of M-H bond has been measured. The dataset is provided with 3D coordinates of the TM complexes (acid and conjugate base form) computed using GFN2-xTB. The dataset, referred to as $pK_a$MH is provided as a .csv file and includes the DOI of original references and review papers that cite the measured $pK_a$. $pK_a$MH consists of 201 TM complexes in 6 different solvents and 14 metal centers (Figure 2).

In the process of curating the dataset we observed that a uniform experimental method was not always used in determination of $pK_a$ of TM hydride complexes. On many occasions the $pK_a$ was indirectly determined e.g. using linear
correlations with a reduction potential or via thermodynamic cycles. In some cases where the conjugate base complex was unstable, \( pK_a \) was determined by indirect methods.\(^3,4\) The \( pK_a \) data is therefore also expected to contain errors related to the measurement/estimation method.

**GFN2-xTB and DFT calculations.**

We computed the solvated PA for all complexes using GBSA implicit solvation method as implemented in xTB. Figure 3 compares the computed PA and the experimental \( pK_a \) values for 172 complexes in \( pK_a \)MH. Our results show that the solvated PAs based on the electronic energy (\( E(A) - E(AH) \)) (\( R^2=0.74, \text{RMSE} = 5.73 \)), is a good descriptor of the experimental \( pK_a \). There is a minimal loss of accuracy when using \( PA = E(A) - E(AH) \) as a descriptor as compared to \( PA = G(A) - G(AH) \) (see SI).

For individual solvents the estimation of the experimental \( pK_a \) using the GFN2-xTB computed PA results in RMSE’s of 4.6 (MeCN; \( N = 79 \)), 5.7 (THF; \( N = 14 \)), 3.4 (DCM; \( N= 40 \)) and 4.1 (DCE; \( N = 31 \)) (see SI). A worse correlation (\( R^2 = 0.46; \text{RMSE} = 8.2 \)) is observed for GFN2-xTB/DFT computed PA. Removal of 10 outlier complexes however improved the correlation (\( R^2 = 0.77; \text{RMSE} = 5.5 \)). The outlier complexes mainly consisted of complexes with multiple carbonyl (CO) groups (see Figure-SI-22) with the exception of complex 159 ([HFe(Py2Tstacn])\(^2\)). The \( pK_a \) of complex 159 was experimentally determined in a solvent mixture of acetonitrile and water but computed in pure acetonitrile. Our calculations suggest that GFN2-xTB may have limited accuracy in describing the M-CO bonds. This aspect is discussed later in the manuscript.

The correlation between the PA and the experimental \( pK_a \) is rather surprising taking into account that different solvents are involved and the solvation free energy of proton or that the PA and \( pK_a \) of a reference base were not considered (eq(1) and (4)). We speculate that this is related to a small variation in the solvation free energy of \( H^+ \) across the range of solvents considered. These results indicate that PA is a good descriptor of \( pK_a \) of TM complexes.

Having computed the PA using GFN2-xTB and GFN2-xTB/DFT methods, we turn to estimate the \( pK_a \) using a full DFT approach. The DFT computed PA correlates well with experimental \( pK_a \) (\( R^2 = 0.84, \text{RMSE} = 4.5 \)) (see SI). For individual solvents estimation of experimental \( pK_a \) using DFT computed PA results in RMSE’s of 3.3 (MeCN; \( N = 69 \)), 2.3 (THF; \( N = 13 \)), 3.1 (DCM; \( N = 38 \)) and 2.3 (DCE; \( N = 30 \)) (see SI).
To further assess the performance of GFN2-xTB, we compared the accuracy of DFT, GFN2-xTB/DFT and GFN2-xTB for predicting experimental \( pK_a \) of TM hydride complexes in our database in acetonitrile solvent. We have chosen acetonitrile solvent for comparison since it has the largest share in the database and it is parametrized both in Gaussian and xTB packages. We identified 69 TM complexes for which both DFT and GFN2-xTB calculations were found to converge without errors. The resulting plot is shown in Figure 4. Going from GFN2-xTB (R² = 0.76; RMSE = 4.3) to GFN2-xTB/DFT (R² = 0.51; RMSE = 6.1) leads to a drastic deterioration of the predictive capability for experimental \( pK_a \). Full DFT based predictions were found to have better correlation and higher accuracy (R² = 0.86; RMSE = 3.3). These results further confirm that the GFN2-xTB predicted geometries are not always close to the DFT predicted minimum energy geometries.

To analyse this further, we calculated the difference in \( pA \) between DFT and GFN2-xTB \( \Delta pA = pA_{\text{DFT}} - pA_{\text{GFN2-xTB/DFT}} \). Here, \( e(A) = E(A)_{\text{DFT}} - E(A)_{\text{GFN2-xTB/DFT}} \) and \( e(AH) = E(AH)_{\text{DFT}} - E(AH)_{\text{GFN2-xTB/DFT}} \) are the individual errors in conjugate base (A) and acid type complexes. The mean and median values of \( e(A) \) are -35.2 kcal mol\(^{-1}\) and -30.6 kcal mol\(^{-1}\), and for \( e(AH) \) are -38.2 kcal mol\(^{-1}\) and -32.0 kcal mol\(^{-1}\). Complex 45 has a high \( \Delta pA = -66 \) kcal mol\(^{-1}\), with \( e(A) = -25 \) kcal mol\(^{-1}\) and \( e(AH) = -91 \) kcal mol\(^{-1}\). So the conjugate base form of complex 45 has high error. On the other hand, complex 43 which has a low \( \Delta pA = -1.4 \) kcal mol\(^{-1}\) has \( e(A) = -45.6 \) kcal mol\(^{-1}\) and \( e(AH) = -47 \) kcal mol\(^{-1}\). So both the acid and conjugate base forms for complex 43 have high error.

### Table 1

| Index | Complex | \( e(A) \)/
|-------|---------|------|------|------|
|       |         | kcal mol\(^{-1}\) | kcal mol\(^{-1}\) | kcal mol\(^{-1}\) |
| 7     | [Ni((P(Ph))\(_2\)(N(Bn)))\(_2\)]\(_2\) | -67.4 | -69.8 | -5.1 |
| 15    | [Ni((P(Cy))\(_2\)(N(Ph))\(_2\))]\(_2\) | -54.1 | -60.2 | -6.2 |
| 16    | [Ni((P(Cy))\(_2\)(N(Ph))\(_2\))]\(_2\) | -59.3 | -66.5 | -7.2 |
| 25    | [Pd(PNP)]\(_2\) | -44.8 | -35.9 | 8.9  |
| 28    | [Pd(depx)]\(_2\) | -37.6 | -44.8 | -7.3 |
| 30    | [Pd(Etxantphos)]\(_2\) | -54.8 | -66.3 | -11.4 |
| 26    | [Pt(PNP)]\(_2\) | -63.8 | -71.1 | -7.7 |
| 32    | [Rh[p((P(Ph))\(_2\)(N(PhOme)))]\(_2\) | -66.2 | -82.1 | -15.9 |
| 33    | [Rh[p(P(Cy))\(_2\)(N(Ph))]] | -59.5 | -64.6 | -5.2 |
| 45    | [CpCr(CO)]\(_2\) | -25.4 | -91.3 | -66.0 |
| 46    | [CpMo(CO)]\(_2\) | -12.4 | -60.9 | -48.5 |
| 47    | [CpW(CO)]\(_2\) | -10.0 | -48.8 | -38.9 |
| 52    | [Co(CO)]\(_2\)(OPh)]\(_2\) | -19.2 | -28.0 | -8.8 |
| 56    | [HCP*Mo(CO)]\(_2\) | -17.6 | -77.6 | -60.0 |
| 62    | [CpW(CO)]\(_2\)(PMe)]\(_2\) | -12.2 | -26.6 | -14.4 |
| 64    | [Mo(CO)]\(_2\)(PPh)]\(_2\) | -21.8 | -28.0 | -6.2 |
| 75    | [CpFe(CO)]\(_2\) | -25.9 | -16.0 | 10.0 |
| 78    | [Co*Fe(CO)]\(_2\) | -30.6 | -20.3 | 10.3 |
| 100   | [Co*Cr(CO)]\(_2\) | -38.1 | -55.7 | -17.6 |
| 102   | [CpCr(CO)]\(_2\)(OMe)]\(_2\) | -41.9 | -52.4 | -10.5 |

Complex 43 therefore has a lower overall error in \( pA \) due to favourable error cancellation on conjugate acid and base forms. The mean and median of the absolute \( \Delta pA \) were found to be 6.2 and 3.3 kcal mol\(^{-1}\), respectively, with a rather large standard...
deviation of 10.7 kcal mol\(^{-1}\) indicating an overall good agreement between DFT and GFN2-xTB with some highly skewed cases of large disagreement. The sign of \(\Delta PA\) encodes whether the acid (AH) or the base (A) form of complex has larger error as compared to DFT. \(\Delta PA < 0\) indicates a larger error in the acid form (AH) of the complex while \(\Delta PA > 0\) denotes that the conjugate base form (A) contributes to the overall error. Complexes (in acetonitrile) that featured a \(|\Delta PA| > 5\) kcal mol\(^{-1}\) have been tabulated in Table 1. Majority of complexes have a negative \(\Delta PA\) indicating the higher instability of the AH form of geometries computed by GFN2-xTB as compared to DFT.

A cursory analysis of entries in Table 1 reveals that the complexes with \(|\Delta PA| > 5\) kcal mol\(^{-1}\) either contain phosphine based ligands or multiple CO ligands or both. To compare the DFT and GFN2-xTB predicted geometries we made structure overlay plots of the acid and conjugate base forms of selected complexes which are presented in 5. The Pd based PNP complex \((25)\) shows a moderate \(\Delta PA\) of 8.9 kcal mol\(^{-1}\). Structure overlay figure (Figure 5) reveals that the GFN2-xTB optimization results in a hemi-labile PNP coordination in \([\text{Pd(PNP)}_2]\) complex, which probably contributes to a higher error for the conjugate base form. Contrastingly such hemi-labile coordination was not observed for the acid form of the complex \([\text{HPd(PNP)}_2]\). For complex \(30\), the planarity of phenanthroline ring is misrepresented in the acid form of the complex leading to a negative \(\Delta PA\) of -11.4 kcal mol\(^{-1}\).

Similarly the mismatch in orientation of benzene rings between GFN2-xTB and DFT in the acid form of complex \(32\) leads to a \(\Delta PA\) of -15.9 kcal mol\(^{-1}\). Interestingly for the dicarbonyl W complex \(62\) with a PMe\(_3\) ligand, the energy difference between acid and base forms are both relatively low. However, the acid form is more destabilized due to an underestimated C\(_{\text{CO}}\)-W-C\(_{\text{CO}}\) angle leading to a \(\Delta PA\) of -14.4 kcal mol\(^{-1}\). In comparison complex \(7\) has a \(\Delta PA\) of -5.1 kcal mol\(^{-1}\) but energy differences in excess of 60 kcal mol\(^{-1}\) for the acid and base forms (Table 1). The higher magnitude of \(\Delta PA\) in complex \(62\) despite better individual agreements of both the acid and base form with DFT stresses the importance of error cancellation in computing thermochemical properties at GFN2-xTB/DFT level of theory.

Analysis of molecular geometries of the di-carbonyl complexes \([\text{CpW(CO)}_2(\text{PMe})_3]\) \((62)\), \([\text{CpFe(CO)}_3]\) \((75)\), \([\text{Cp}^*\text{Fe(CO)}_2]\) \((78)\) and \([\text{CpCr(CO)}_2(\text{Ime})]\) \((102)\) revealed that the C\(_{\text{CO}}\)-M-C\(_{\text{CO}}\) angle is in general underestimated (by 12.2°, 13.3°, 16.5° and 36.2° respectively) in the conjugate base form of these complexes by GFN2-xTB. The increasing underestimated angles are reflected in larger energy difference for these complexes as well (Table 1). Interestingly the C\(_{\text{CO}}\)-M-C\(_{\text{CO}}\) does not have a large deviation in the acid forms of complexes \(75\) and \(78\) (also see Figure-SI-21). On the contrary the acid form of complex \(62\) has an underestimated C\(_{\text{CO}}\)-M-C\(_{\text{CO}}\) angle (~23°), and Complex \(102\) features largely (> 30°) underestimated C\(_{\text{CO}}\)-M-C\(_{\text{CO}}\) angle in both acid and conjugate base forms. Therefore, the erroneous representation of C\(_{\text{CO}}\)-M-C\(_{\text{CO}}\) angle or M-CO bonding in general is not systematically present in all complexes. The tricarbonyl complexes \(45\) - \(47\) and \(56\) all feature a very large and negative \(\Delta PA\) stemming from highly destabilized acid forms of these complexes (Figure 6). The structure plots of complexes \(45\) - \(47\) and \(56\) in their acid form reveal the inaccurate description of M-CO bonding in GFN2-xTB.

![Figure 6.](image)

The C\(_{\text{CO}}\)-M-C\(_{\text{CO}}\) angles between adjacent CO moieties are largely underestimated, for example by ~35° in complex \(45\) (acid form). It can therefore be inferred that GFN2-xTB optimized geometries are less reliable for metal carbonyl complexes. The unsystematic nature of the error makes prediction of p\(_K_a\) unreliable using GFN2-xTB optimized geometries. The prediction of PA involves taking an energy difference of the A and AH type conjugate base-acid complexes. This results in scenarios where favourable cancellation of error is possible. For example, complexes \(45\) - \(47\) and \(56\) have absolute errors (difference between predicted p\(_K_a\) and experimental p\(_K_a\)) of 30 – 38 pK\(_a\) units respectively at GFN2-xTB/DFT level of theory. However, the absolute errors on p\(_K_a\) predicted by standalone GFN2-xTB calculations on the same complexes are between 1.0 – 3.8 pK\(_a\) units indicating a favourable error cancellation at GFN2-xTB level of theory. Therefore, despite inaccurate representation of M-CO bonding the GFN2-xTB method gives consistent results when used standalone demonstrating its robust thermochemical predictive power. Moreover, examining the geometric overlays in Figure 5 the overlap of GFN2-xTB predicted and DFT predicted geometries have a good agreement in general despite significant mismatch for CO ligands. For example, the Cp/Cp\(^*\) ligands seem to overlap very well between the geometries predicted by two methods.

Apart from the poor description of M-CO type complexes a notable challenge for GFN2-xTB method was identified to be its convergence failure for complexes with multiple hydrides. We found 16 TM complexes for which at least one or both of the base and acid forms did not converge. With the exception of dinitrogen complex \([\text{HCr(N)}_2(\text{P(Ph)})_3(N(Bn))_3(\text{dmpe})]^+\) (index \(97)\) for which the reason for convergence failure is not understood, all of these complexes have multiple M-H bonds indicating that GFN2-xTB method faces problems with such systems.

**Machine learning experimental pK\(_a\) using GFN2-xTB**

Given the standalone performance of GFN2-xTB methods in predicting experimental p\(_K_a\), it can be considered robust and a good starting point for thermochemical property calculations. We seek to improve the predictive capability of GFN2-xTB using a data-augmented approach. Our hypothesis is that GFN2-xTB already provides good geometric and energetic predictions. These predictions when used as features in a ML model, can be
used to learn the experimental pK\textsubscript{a}. We therefore use GFN2-xTB computed molecular geometry and energetic features to learn the experimental pK\textsubscript{a} of TM complex. The choice of features is driven by intuition and physical reasoning in the present work. A more rigorous and automated approach towards construction and identification of relevant features from DFT-B calculations is an ongoing effort in our group.

We selected a set of 17 features, which include HOMO and LUMO energy of AH and A, DFT-B computed partial charges on metal (AH and A) and hydrogen (which is to be deprotonated), atomic number, coordination number and coordination environment of metal centre in AH and A, dielectric constant of the solvent, solvated and gas phase PA, M-H bond length and total charge on AH complex (Table 2). Note that the total size of the dataset used for ML (168) is smaller than the dataset, for which experimental pK\textsubscript{a}'s have been curated. For 16 TM complexes DFT-B calculations did not converge (vide supra). We excluded complexes with multiple metal centres from our analysis (7 entries). Moreover some complexes had ambiguous pK\textsubscript{a}'s or pK\textsubscript{a} values that were later revised in the literature (5 + 3 entries), and 3 entries are actually that of ligand pK\textsubscript{a}. We applied an ordinary least squares fitting on 80% of the dataset to learn the experimental pK\textsubscript{a} and use the 20% of the dataset for testing the prediction of model learnt. The results are presented in Figure 7.

Table 2: Features used in the Machine Learning models and their coefficients learned by the OLS model.

| ML Features          | Weight | ML Features          | Weight |
|---------------------|--------|---------------------|--------|
| Solvated PA         | -40.20 | Gas PA              | -3.95  |
| HOMO (A)            | 11.08  | HOMO (AH)           | 2.86   |
| LUMO (A)            | -2.42  | LUMO (AH)           | -70.11 |
| Charge (AH)         | -5.22  | Epsilon             | -0.015 |
| Charge Metal (A)    | -11.45 | Charge Metal (AH)   | 14.15  |
| M-H max (AH)        | -8.23  | Charge Hydride (AH) | 23.03  |
| Coordination Number (A) | 30.65  | Coordination Number (AH) | -6.03  |
| cc (A)              | -10.73 | cc (AH)             | -7.33  |
| Metal Centre        | 4.17   |                     |        |

M = metal centre; cc = sum of atomic number of all elements that are coordinated to M; Epsilon = dielectric constant of solvent, charge (AH) = total charge on AH complex; charge Metal (A/AH) = charge computed on M via population analysis of DFT-B computed electron density.

The OLS model leads to a significant improvement in the predicting power of the DFT-B method for pK\textsubscript{a} of TM complexes in the database resulting in an R\textsuperscript{2} ~ 0.87 and an RMSE ~ 4.1 pK\textsubscript{a} units (Figure 7). Next, we explored the AutoML method provided by the auto-sklearn library in python. The details of the model are described in the computational methods section. The AutoML model found the K nearest neighbour (k-NN) algorithm to perform the best on our dataset. The complete ensemble of the learned ML algorithms is presented in the SI. The AutoML model resulted in an R\textsuperscript{2} = 0.94 and an RMSE = 2.7 for the test set (Figure 8). The AutoML model therefore outperforms OLS and has similar accuracy as pure DFT.
A particularly notable case is the WH(CO)₃(C₅H₄COO⁻) complex (index 99 in pKₐMH), for which an experimental pKₐ of 5.8 has been reported in water.⁴⁷ The OLS model predicted a pKₐ of 21.1 for this complex. Consistently a pKₐ of 18.0 is predicted by the LAC method.²⁵ The AutoML model predicted a pKₐ of 17.0 for this complex. This is the only anionic acid in the database, which could be reason for erroneous predictions by various models. This complex is therefore considered an outlier and it is excluded from training/test sets and not plotted in Figures 7-8.

We used DFT, GFN2-xTB, OLS and autoML models to estimate the pKₐ of complexes with multiple/revised pKₐ in the literature and ligand pKₐ. We further added 7 additional complexes, for which ligand pKₐ were reported in the literature. Note that the ML models are purely trained on pKₐ of metal hydrides and have never encountered ligand pKₐ. The assignment of ligand pKₐ tests the generality and transferability of our ML models. Furthermore, these test cases allow us to compare the accuracy of DFT, GFN2-xTB, OLS and AutoML models on an equal footing (Table 3).
Table 3. Experimental and predicted pK\textsubscript{a} for ligand pK\textsubscript{a} of TM complexes, and TM complexes with multiple/revised pK\textsubscript{a} reported in the literature. Estimate of pK\textsubscript{a} values based on DFT calculations are also given. The DFT based pK\textsubscript{a} was estimated using the equation for linear correlation of PA estimated using DFT vs. exp. pK\textsubscript{a} (\(0.6388x+171.41\)) (MeCN); \(0.4974x+136.09\) (CH2Cl2); \(0.4903x+132.69\); \(x\) is PA in kcal mol\(^{-1}\)). Values in parenthesis denote estimated pK\textsubscript{a} values via a reference base using eq(1). GFN2-xTB based pK\textsubscript{a} were estimated using the linear correlation of PA with exp. pK\textsubscript{a} (\(0.3385x-132.69\); \(0.3867x-30.71\) (MeCN); \(0.9972x+116.05\) (THF)).

| Species | index | Exp. pK\textsubscript{a} | OLS | AutoML | DFT | GFN2-xTB |
|---------|-------|--------------------------|-----|--------|-----|-----------|
| \([\eta^6-C6H6]Mn(CO)3]\) | 66    | 22.2                     | 27.6| 17.6   | 30.0 (26.8\(^{\circ}\)) | 22.3 |
| \([\text{PnP}]\text{Ru}^+\) | 73    | 20.7                     | 24.3| 12.3   | 18.6 (21.3\(^{\circ}\)) | 30.2 |
| \([\text{PnP}]\text{Ru}^+\text{CO}\) | 74    | 24.6                     | 32.7| 21.5   | 6.0 (4.8\(^{\circ}\)) | 31.9 |

RMSE

| \([\text{Rh}(\text{trop-NH})\text{trop-NH}]^+\) | - | 20.1\(^{\circ}\) | 24.9 | 21.5 | - |
| \([\text{Rh}(\text{trop-NH})\text{bipy}]^+\) | - | 18.7\(^{\circ}\) | 27.4 | 22.8 | - |
| \([\text{Rh}(\text{trop-dach})]^+\) | - | 15.7\(^{\circ}\) | 22.2 | 19.8 | - |
| \([\text{Ir}(\text{trop-NH})\text{phen}(H,H)]^+\) | - | 18.2\(^{\circ}\) | 21.7 | 23.4 | - |
| \([\text{Rh}(\text{trop-NH})\text{phen}(H,H)]^+\) | - | 18.6\(^{\circ}\) | 27.5 | 22.9 | - |
| \([\text{Rh}(\text{trop-NH})\text{phen}(Me,H)]^+\) | - | 19.0\(^{\circ}\) | 28.4 | 23.2 | - |
| \([\text{Rh}(\text{trop-NH})\text{phen}(Ph,H)]^+\) | - | 18.7\(^{\circ}\) | 27.6 | 22.8 | - |

Ambiguous pK\textsubscript{a} reported in literature

| \([\text{H}_2\text{Fe}(\text{CO})_6(\text{dppe})_2]^{2-}\) | 124 | <-5\(^{\circ}\) | -13.4 | -1.9 | -4.6 (-9.5\(^{\circ}\)) | -3.8 |
| \([\text{HFe}(\text{CO})_3(\text{P}ot)3]2^+\) | 136 | 0.1\(^{\circ}\) | 3.9 | 2.3 | 7.0 (10.6\(^{\circ}\)) | 8.1 |
| \([\text{HFe}(\text{CO})_3(\text{P}h)3]2^+\) | 137 | -1.1\(^{\circ}\) | 2.6 | 0.5 | 6.0 (9.1\(^{\circ}\)) | 7.3 |
| \([\text{HFe}(\text{CO})_3(\text{P}h)3]2^+\) | 139 | 1.3\(^{\circ}\) | 3.8 | 1.7 | 7.0 (9.1\(^{\circ}\)) | 8.3 |
| \([\text{HFe}(\text{CO})_3(\text{PCy})3]2^+\) | 155 | 4.4\(^{\circ}\) | 5.6 | 4.2 | 7.9 (8.1\(^{\circ}\)) | 9.3 |

Relative pK\textsubscript{a} values revised in literature

| \([\text{HCPFe}(\text{CO})_2]\) | 75 | 27.1 | 23.7 | 27.4 | 25.2 (27.4\(^{\circ}\)) | 26.7 |
| \([\text{HCP}^+\text{Ru}(\text{CO})_2]\) | 76 | 28.3 | 27.2 | 29.7 | 24.5 (29.8\(^{\circ}\)) | 28.9 |
| \([\text{HCP}^+\text{Fe}(\text{CO})_2]\) | 78 | 29.7 | 26.4 | 28.2 | 29.0 (30.2\(^{\circ}\)) | 31.2 |

RMSE

| \([\text{H}(\text{H})\text{Fe}(\text{CO})_3(\text{depe})_2]\) | 124 | 4.2 | 2.8 | 1.2 | 2.5 (0.9\(^{\circ}\)) | 1.0 |

\(^a\) Using \([\text{H}(\eta^6-C6H6)\text{Mn}(\text{CO})_3]^{1}\) (index 67 in pK\textsubscript{a}MH) as reference.
\(^b\) Using \([\text{HCP}^+\text{Fe}(\text{CO})_3]^{1}\) (index 200 in pK\textsubscript{a}MH) as reference.
\(^c\) Based on reaction with HOTT which has a pK\textsubscript{a} of -5 in water.
\(^d\) Using \([\text{H}(\eta^6-C6H6)\text{Fe}(\text{depe})_2]\) (index 147 in pK\textsubscript{a}MH) as reference.
\(^e\) These are not pK\textsubscript{a} values but relative acidities on a pK\textsubscript{a} scale in CD2Cl2. See reference 51.
\(^f\) Computed using \([\text{HFe}(\text{CO})_3]^{1}\) (index 53 in pK\textsubscript{a}MH) as reference.
\(^g\) Computed using \([\text{H}(\eta^6-C6H6)\text{Fe}(\text{CO})_3]^{1}\) (index 57 in pK\textsubscript{a}MH) as reference.

Ligand pK\textsubscript{a} for complexes 66, 73 and 74 proved difficult to predict for all the methods. GFN2-xTB performed worse (RMSE=6.9), followed by OLS (RMSE=6.0), AutoML (RMSE=5.8) and DFT (RMSE=4.8). For the trop\_2 family of complexes which are not a part of pK\textsubscript{a}MH, the AutoML model performs well with an RMSE of 4.0, while OLS showed a high RMSE of 7.5 indicating poor transferability of the OLS model. An estimated pK\textsubscript{a} <-5 was established for complex 124 based on its reactivity with HOTT (aqueous pK\textsubscript{a} = -5).\(^{52}\) Using the correlation of DFT computed PA with exp. pK\textsubscript{a}, we estimated a pK\textsubscript{a} of -0.5 for HOTT. Therefore, the pK\textsubscript{a} of complex 124 is expected to be <-0.5 in contrast to -5 as reported earlier.\(^{52}\) OLS predicts a highly negative pK\textsubscript{a} of -13.4. AutoML, DFT (using linear scaling relation) and GFN2-xTB predict similar pK\textsubscript{a} values of -1.9, -4.6 and -3.8. DFT calculations using a reference base predicts a more negative value of -9.5. While all values are <-0.5, the variation in predictions make it difficult to assign a particular value to the pK\textsubscript{a} of complex 124.

For complexes 136, 137, 139 and 155 a pK\textsubscript{a} value has not been measured in the literature, but rather an acidity scale was set up in CD2Cl2.\(^{51}\) Both DFT and GFN2-xTB methods consistently predict higher pK\textsubscript{a} values for these complexes in contrast to OLS and AutoML which predict smaller values. If we consider the relative acidities as per the acidity scale, pK\textsubscript{a} should follow 137 < 136 < 139 < 155. Only AutoML and GFN2-xTB predicted pK\textsubscript{a}s to follow this trend. For complexes 75, 76 and 78 literature values were earlier erroneously reported and were corrected in subsequent studies.\(^{53}\) All four approaches work well with low RMSE values in predicting the pK\textsubscript{a} of complexes 75, 76 and 78.

Summary and conclusions

In this manuscript we identify and address some of the key challenges for accurate and rapid prediction of thermochemical properties of TM complexes using quantum chemical methods.
approaches. We applied and compared two quantum chemical methods: semiempirical GFN2-xTB and hybrid DFT. Using pKᵈ as a model thermochemical problem we first curated a novel dataset pKᵈMH composed of pKᵈ of ~200 TM hydride complexes. Our calculations revealed that PA is a good descriptor of experimental pKᵈ. We further discovered that computationally expensive hessian calculations can be avoided when using PA to estimate experimental pKᵈs. Comparison of DFT and GFN2-xTB/DFT calculations revealed that while GFN2-xTB predicted geometries are close to DFT predicted geometries significant errors can occur in case of metal carbonyl complexes due to inaccurate representation of chemical bonding of M-CO functions. We further found out that despite such inaccurate geometric representations GFN2-xTB method is robust for thermochemical property predictions when used standalone. However, direct use of GFN2-xTB optimized geometries for DFT based single-point calculations is not recommended due to unsystematic nature of errors posed by GFN2-xTB optimized geometries. GFN2-xTB method faced convergence issues for multi-hydride TM complexes.

Using a data-augmented approach we computed features from GFN2-xTB and trained two different ML models to learn experimental pKᵈ. OLS method resulted in a reasonable accuracy (R² = 0.87, RMSE = 4.1) which is comparable albeit inferior to DFT based predictions. The autoML approach using auto-sklearn library improved the performance of GFN2-xTB approach to near DFT accuracy with a R² of 0.94 and RMSE of 2.7 on the test set. We further tested the ML models to predict the pKᵈ of TM complexes which underwent deprotonation at the ligand. Even though the ML models were trained on TM-hydrides the AutoML model performed reasonably well for predicting ligand pKᵈs showing its transferability.

Our calculations identify challenging cases for predicting geometry and thermochemical properties of TM complexes using GFN2-xTB methods. We further demonstrate the promise of GFN2-xTB method as a robust, fast and accurate semiempirical method for calculating thermochemical properties of TM complexes. Our data-augmented approach using AutoML approach can rapidly predict accurate experimental pKᵈ of TM complexes using GFN2-xTB calculations at near DFT accuracy. The data-augment GFN2-xTB approach developed in this work is promising for development of high throughput computational screening workflows for discovering TM catalysts. We expect pKᵈMH to accelerate development and application of data-driven chemistry approaches for TM complexes. Further extension of this dataset with ligand pKᵈs of TM complexes and automated construction of features for use in ML models are ongoing efforts in our group.

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Authors Contributions

J.J.L. carried out DFT and GFN2-xTB calculations under the supervision of V.S. V.S. conceived the project and performed machine learning calculations. E.A.P. played an advisory role and directed the project. All authors discussed the results and wrote the manuscript.

Conflicts of interest

There are no conflicts of interest to declare.

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