RSC Advances

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2026, **16**, 21397

Digitized dataset of aqueous acid dissociation constants

Jonathan W. Zheng, Olivier Lafontant-Joseph and William H. Green *

The acid dissociation constant (pK_a) quantifies the acidity of a compound, which is crucial for applications including drug design, environmental fate studies, and chemical synthesis. However, high-quality open-source digital pK_a datasets are scarce, which limits the ability for researchers to search for properties of individual compounds, while also limiting the potential of data-driven predictive models. In this work, we release the IUPAC Digitized pK_a Dataset, a digital version of a critically-assessed collection of data compiled up to 1970. The dataset includes metadata such as temperature, measurement method, assessed reliability of data, and chemical identifiers such as SMILES and InChI strings. The dataset spans 24 222 entries across 10 564 unique molecules, making it the largest FAIR open-source dataset publicly available for aqueous pK_a data. Herein, we detail the data digitization and checking process, and assess the informational space spanned by the data. We compare the new digital dataset to other widely-used datasets. Several pK_a predictors have been trained using these other datasets, but often have not been reliably tested due to overlap between the training and test data. We use the data to train a macroscopic pK_a predictor and determine its accuracy using overlap-free test data. The full dataset is available at https://doi.org/10.5281/zenodo.7236452, and the models and data splits used in this study are available at https://doi.org/10.5281/zenodo.18165948.

Received 24th March 2026
Accepted 24th March 2026

DOI: 10.1039/d6ra02418a

rsc.li/rsc-advances

Introduction

The acid dissociation constant (also known as pK_a) is an important property involved in pharmacokinetics, environmental fate, chemical manufacturing, organic synthesis, analytical chemistry, thermodynamics, and numerous other applications.[1–11] pK_a is defined from the equilibrium constant of the acid dissociation reaction for species AH in a solvent as:

$$\mathrm{AH(solv.)} \rightleftharpoons \mathrm{H^+(solv.)} + \mathrm{A^-(solv.)} \quad (1)$$

where AH refers to an acid and A^- is the conjugate base. The equilibrium constant corresponding to this reaction is

$$K_a = \frac{a_{A^-} \times a_{H^+}}{a_{AH}} \quad (2)$$

wherein a_S refers to the activity of species S,[12] and the pK_a is defined as

$$pK_a = -\log_{10}(K_a) \quad (3)$$

Under this definition, pK_a strictly refers to proton loss. The International Union of Pure and Applied Chemistry (IUPAC) prefers to call the cation H^+ a "hydron" rather than a proton, as the term encompasses such isotopes as the deuteron.[13] In this work, we will use the term "proton" interchangeably with "hydron" due to its wider current acceptance.

A common way of representing proton gain is by reporting the pK_a of its conjugate acid, a term sometimes called the "basic pK_a". In this convention, the "basic pK_a" of compound B numerically represents the acidic dissociation constant for BH^+, the conjugate acid of B, or:

$$\mathrm{BH^+(solv.)} \rightleftharpoons \mathrm{B(solv.)} + \mathrm{H^+(solv.)} \quad (4)$$

This is sometimes confusingly referred to as the "pK_a of B", with the understanding that the value refers to the conjugate acid's acidity since B itself is basic. To avoid ambiguity in this work, we use the convention that the pK_a of a species strictly refers to its acidic dissociation, as in eqn (1). We use the term pK_{aH}(B) (as recently recommended by IUPAC)[14] to designate the pK_a corresponding to the conjugate acid, *i.e.* $pK_a(BH^+)$.

Often, AH contains several ionizable protic sites, and there might be several isomers of HA in equilibrium, such as zwitterions and uncharged protomers. The macroscopic pK_a corresponds to the equilibrium constant for an overall charge transition, so the species A^- in eqn (1) is an equilibrium mixture of several isomers with protons bonded to different atoms. In contrast, the microscopic pK_a refers to the acidity of a specific microstate (corresponding to a specific isomer of AH losing a proton at a specific ionization center to form a specific isomer of A^-). Whereas the former is most commonly measured, *e.g.* by measuring the pH at equilibrium after half of the initial AH has been deprotonated, the

Massachusetts Institute of Technology, Department of Chemical Engineering, USA. E-mail: whgreen@mit.edu

latter is more readily obtainable using simulations. A macroscopic pK_a can be computed from the microscopic pK_a values by Boltzmann-weighting the respective microstates.[15–17] For monoprotic acids without tautomers, the macroscopic and microscopic pK_a values are the same. For polyprotic acids with large separation between pK_a values and no tautomeric effects, they are also approximately the same. In all other cases, the macroscopic and microscopic pK_a can be different. Most data in this compilation are macroscopic pK_a values, and do not include any information about different acidity centers.

Owing to the importance of pK_a in numerous applications, considerable effort has been made to accurately predict pK_a values across a range of solvents, primarily in water. Early methods typically involved group-based methods, in which the pK_a of acids are assigned based on linear free energy corrections, and often depend on specific moieties. Popular examples include the Hammett equations (for benzoic acid derivatives) and Taft equations (which estimates pK_a effects of adding groups to a parent compound).[18]

Deep learning has recently emerged as a tool for quick and accurate prediction of chemical properties.[19–25] However, large collections of data are required to tune large numbers of parameters in these models. Recently, numerous pK_a prediction models leveraging deep learning have been developed and made publicly available.[11,26–33] These models are trained on open-source datasets, which include large quantities of pK_a data, and sometimes also calculations (or "synthetic data") to augment the experimental data.[31–34] Despite the apparent good performance of the models, low data quantity and quality remain major obstacles. Furthermore, though many recent efforts claim to predict microscopic pK_a values, they are actually trained on macroscopic pK_a data. A contributor to this issue is that many datasets do not list the measurement method or type of pK_a, and so this information is not immediately obvious to the modelers. Several additional data-related issues are listed below.

Limitations of existing datasets

Several datasets are currently utilized in machine learning applications or as reference sources, but have issues in data quality, quantity, provenance, reported conditions, and other issues.

ChEMBL

The ChEMBL database[35–37] is a widely-used[26,32,34,38] biochemical data repository. Among numerous other data such as bioactivity, it also includes approximately 3 million pK_{a1} and pK_{aH1} (strongest proton loss and proton gain values, respectively) for about 2 million molecules, computed using the ChemAxon Protonation tool (Marvin).[39] The values appear to correspond to ChemAxon calculations in the macroscopic static pK_a mode at 0.1 M ionic strength ("static" means that charged forms of input molecules are converted to neutral forms prior to calculation).[40,41]

Because the data are computed rather than experimental, and owing to the very large size of the data, they have been typically used for pretraining (though sometimes used exclusively for training). However, the data has been shown to include some incorrect values, and commonly are misused in modeling studies due to a misinterpretation of the meaning of "acidity" and "basicity" for amphiprotic compounds.[40]

Though widely-used and by far the largest set of values, it originates from computations, which limits the predictive power of models to the error of the calculations. Each datapoint is provided without an estimate of uncertainty, making it difficult to know which values are accurate. Also, only pK_{aH1} and pK_{a1} are reported, which limits the ability to model polyprotic compounds.

iBonD

The iBonD database was developed by Prof. Jin-Pei Cheng and collaborators at Tsinghua University. It is comprised of more than 40 000 pK_a entries across a variety of solvents, compiled from existing academic literature. It is widely used for manual search as a reference source as well as in machine learning.[42]

The recent work by An *et al.*,[43] Luo *et al.*,[32] and Nevolianis & Zheng *et al.*,[11] have separately transformed portions of the iBonD data into tabulated forms more convenient for data science applications. The data have been used in several machine learning models.

The data entries are reported to have undergone individual curation and evaluation, and a single acidity center for each dissociation is reported. However, metadata such as temperature and assessed reliability of data are not reported. Additionally, some errors in non-aqueous data (due, for instance, to different choices of energy scales) are present.[11]

DataWarrior

The DataWarrior software suite[44] includes a compilation of pK_a data with unknown provenance. Some recent models were trained on this data,[27] which includes close to 10 000 entries. Due to the lack of provenance and uncertainty estimates, the quality of the data are unclear.

Other datasets not analyzed in this work

A few other datasets have been used to train models. QSAR Toolbox[45] is a software that includes approximately 30 000 pK_a entries. The quality of the data is unclear, and distinctions are not always made between "acidic" and "basic" pK_a values, so additional processing may be required; nevertheless, the data have been used for modeling.[30]

Another potential data source is crowdsourced data, such as in Online Chemical Modeling Environment (OCHEM), which includes provenance but includes inconsistent, mixed-quality metadata, thereby requiring additional processing before usage.[46]

Other data are proprietary and hence not applicable for open-source research. The largest described collections of pK_a data are held by companies: for instance, the S + pKa model was trained on 70 669 datapoints that combined information from Bayer Pharma, Roche, Genentech, and Bayer CropScience.[47,48]

Overall challenges

Despite their issues, the datasets mentioned above are frequently used as training or reference data. Sometimes, several of these datasets are combined, with duplicate values

removed on the basis of prioritizing data from more reliable sources.[27,30] But the overall quality of available digitized pK_a data, including provenance and metadata, remains low.

Hence, there is a need for high-quality data to use for pK_a prediction, as well as further clarity on how these datasets relate to one another.

Aims of this work

Herein, we introduce a large, high-quality dataset of acid dissociation constants with provenance of all original sources. The dataset includes 24 222 entries spanning 10 564 unique compounds, with pK_a values spanning up to six proton gains and six proton losses. The dataset includes rich metadata not included in any other compilation, such as temperature, pressure, assessed reliability, and measurement method, as well as chemical identifiers SMILES and InChI strings.

We discuss the intended use cases for this data: as a reference source, and for machine learning. We compare this dataset to the iBonD and DataWarrior collections. We show that all commonly-used pK_a datasets (including this one) include data overlaps with common benchmarks, requiring data pruning for fair comparison. Finally, we analyze macroscopic pK_a models trained on variants of this data and the ChEMBL database using Chemprop.[49]

Dataset background

This article details the digitization and curation of data presented in three reference books published by the International Union of Pure and Applied Chemistry (IUPAC):

(1) Serjeant: ionisation constants of organic acids in aqueous solution; E. P. Serjeant and Boyd Dempsey; Oxford/Pergamon (1979) (Oxford IUPAC chemical data series).[50]

(2) Perrin: dissociation constants of organic bases in aqueous solution; D. D. Perrin; Butterworths (1965).[51]

(3) Perrin Supplement: dissociation constants of organic bases in aqueous solution, Supplement 1972; D. D. Perrin; Butterworths (1972).[52]

IUPAC provided written permission to scan and digitize the data, provided that the output data are reviewed by IUPAC, posted in an IUPAC-owned repository, and support the FAIR (Findable, Accessible, Interoperable, Reusable) data principles. With their permission, we scanned and digitized the reference books. A digitized copy of Perrin (1965) was obtained from the Internet Archive with IUPAC's permission.

A commercial version of these data sources is separately available under OpenEye Scientific Software.[53] That collection was parsed independently of this collection and includes additional database features such as tautomer enumeration, as well as the aqueous data from Kortum[54] and the non-aqueous data from Izutsu.[55] The number of data in that collection is slightly different than in this work, as we were unable to resolve the structures of some compounds and thereby did not report them.

This work is a digitized adaptation developed from IUPAC source data with permission. We emphasize that this manuscript should not be considered an official IUPAC technical report (which would be published in the journal *Pure and Applied Chemistry*). We make no guarantees on the faithfulness of the digitization process to the print source, or for strict adherence to IUPAC conventions.

The data are publicly available at https://doi.org/10.5281/zenodo.19112621. At the time of publication, the version of the dataset is 2.3d, and the data are provided under a CC BY-NC 4.0 license.

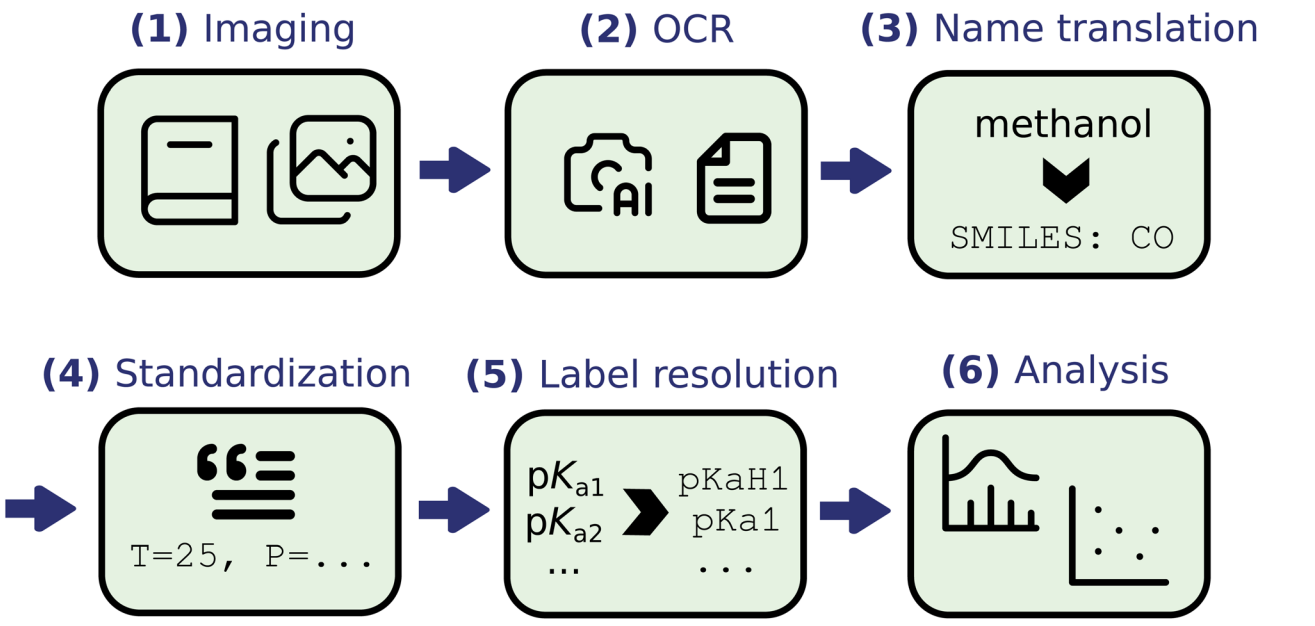


Fig. 1 Visualization of digitization workflow. Images were converted to text *via* OCR, and then processed with various cheminformatics workflows.

Methods

Dataset construction through digitization

A general discussion of the workflow is depicted in Fig. 1 and described below:

(1) Digital scans of the reference books were obtained. With IUPAC's permission, the reference books were scanned by the authors in the MIT Libraries, or a digital copy was obtain from the Internet Archive.

(2) Optical character recognition (OCR) was employed to convert the scanned images into text, ordering the data into tables using Amazon Textract.[56] Information from these tables were further parsed and processed into categories of data, *e.g.* pK_a type, chemical name, reference, method used, and so on.

(3) The IUPAC names of the compounds were translated into SMILES and InChI strings using OPSIN,[57] ChemAxon molconvert,[39] PubChem,[58–60] and the Chemical Identifier Resolver.[61] SMILES strings were accepted only if the same string was unanimously returned by 2+ methods. Of the entries with translations missing, inconsistent, or from only one translation source, we manually parsed the IUPAC names into SMILES strings following IUPAC conventions for naming. We note that tools have recently been developed to expedite and automate this process, such as MoleculeResolver, but were not used in this work.[62]

(4) The dataset was standardized to reduce the number of unique entries and make the data more amenable to data processing. For instance, "room temperature" was converted to 25 °C, and pressures were parsed into a separate column wherever applicable.

(5) To resolve the pK_a type, we followed patterns in the reference books to confidently assign labels for a majority of the entries (for example, in the data compiled by Perrin, pK_a data in descending order corresponded to pK_{aH} data, whereas in ascending order corresponded to amphiprotic molecules). For approximately 4000 entries, we could not automatically discern the pK_a type and therefore manually assigned them based on their numeric values and chemical structures.

(6) The data were analyzed and visualized, checking also for errors and outliers.

Validation of dataset values

All of the digitization efforts were manually double-checked by human reviewers. We double-checked that the dataset transcriptions were faithful to the original print sources.

The data were checked to identify suspicious entries that needed verification or correction, such as entries with abnormally high or low pK_a values, missing locants in chemical names, common typos in the metadata, species with high deviation among multiple measurements, and implausible chemical structures.

ChemAxon's Protonation software predictions were checked against pK_a values for all of the species. The majority of calculated values agreed with our experimental data within 1 pK_a unit, though a few datapoints showed large disagreement, usually due to inconsistencies in acidity type assignment. If

Table 1 Column headers in dataset

Column header	Description
unique_ID	Identifier corresponding to each unique compound in the corresponding source; note this is unique to the entry rather than to the molecular identifier, as separate sources may contain the same compound
SMILES	Isomeric SMILES string canonicalized in rdkit
InChI	InChI string corresponding to compound; unique molecular identifiers conducive to look-up
pka_type	Type of acid dissociation; *e.g.* pK_a = acid dissociation, pK_{aH} = dissociation of conjugate acid (sometimes called "basic" pK_a), pK_b = base association
pka_value	Numerical value of pK_a
T	Temperature of measurement (in °C), standardized to a numeric value if possible
remarks	Comments about this entry from the print source; *e.g.* ionic strength, experimental considerations
method	Experimental method for this entry
assessment	Critical assessment of source's reliability. The original authors (Perrin, Serjeant) assessed errors in pK_a as: ≤0.005 for "reliable" entries, ≤0.04 for "approximate", >0.04 for "uncertain", and high errors for "very uncertain"
ref	Code corresponding to citation for original source of the data
ref_remarks	Additional comments that apply to all entries with the "unique_ID" with the same reference
entry_remarks	Additional comments that apply to all entries with this "unique_ID"
original_IUPAC_names	IUPAC names from the original print sources
name_contributors	Method(s) of obtaining SMILES strings from IUPAC names
num_name_contributors	Number of methods used to obtain SMILES strings from IUPAC names
original_IUPAC_nicknames	If applicable, secondary/common names that were also supplied in print source
source	Source book (Serjeant, Perrin, or Perrin Supplement; see main text)
pressure	If available, pressure of the measurement (units typically of atm or bar)
acidity_label	"A" for acidic, "AH" for conjugate acid, "B" for basic, or "other"
original_*T*	Original unprocessed temperature from the print source
cosolvent	Cosolvent information parsed from the entry

deviations exceeding 4 pK_a units were observed, we manually reviewed the data in our collection and made corrections if necessary.

We reviewed entries with large deviations for the same acidity type at a given temperature. We also confirmed that pK_{aH} values were lower than pK_a values for amphiprotic compounds.

Results and discussion

Dataset layout

The dataset is presented as a .csv with column headers described in Table 1. The headers include chemical identifier information (IUPAC names, SMILES strings, and InChI strings); pK_a descriptors (a pK type, numerical value, and acidity label); experimental conditions (temperature, pressure, method, cosolvent); metadata (data provenance, name-to-structure translation methods); and critical assessment (reliability, extra comments).

We intend for this dataset to be useful for both experimental and machine learning applications. We intend that the InChI strings will allow users to look-up chemicals by a unique ID. From a computational perspective, we hope that the SMILES strings will aid the development of machine learning models and quantum chemical workflows, since many software packages requires SMILES strings as inputs.

A terminological area of note is the naming of "acidic" and "basic" pK_a values for compounds that form zwitterions in solution. Historically, an ampholyte such as glycine often has its lower pK_a labeled as an acidic pK_a and its higher pK_a as a basic one; however, such ordering is inconsistent with the microstates of the relevant protomers undergoing dissociation. Such labels have led to serious confusion in model development in recent years. For this reason, although the 3 source books used the historical "acidic" and "basic" naming precedent, we have in this work elected to use pK_{aH} and pK_a terminology, which has recently been recommended by IUPAC.[14] For further discussion about potential confusion with pK_a terminology, we refer interested readers to our previous work on this topic[40] and to recent literature.[63]

Dataset contents

This dataset includes 24 222 entries spanning 10 564 unique chemical species. Most compounds include multiple pK_a values with the same dissociation type but at different experimental conditions. Considering each pK_a type as unique regardless of

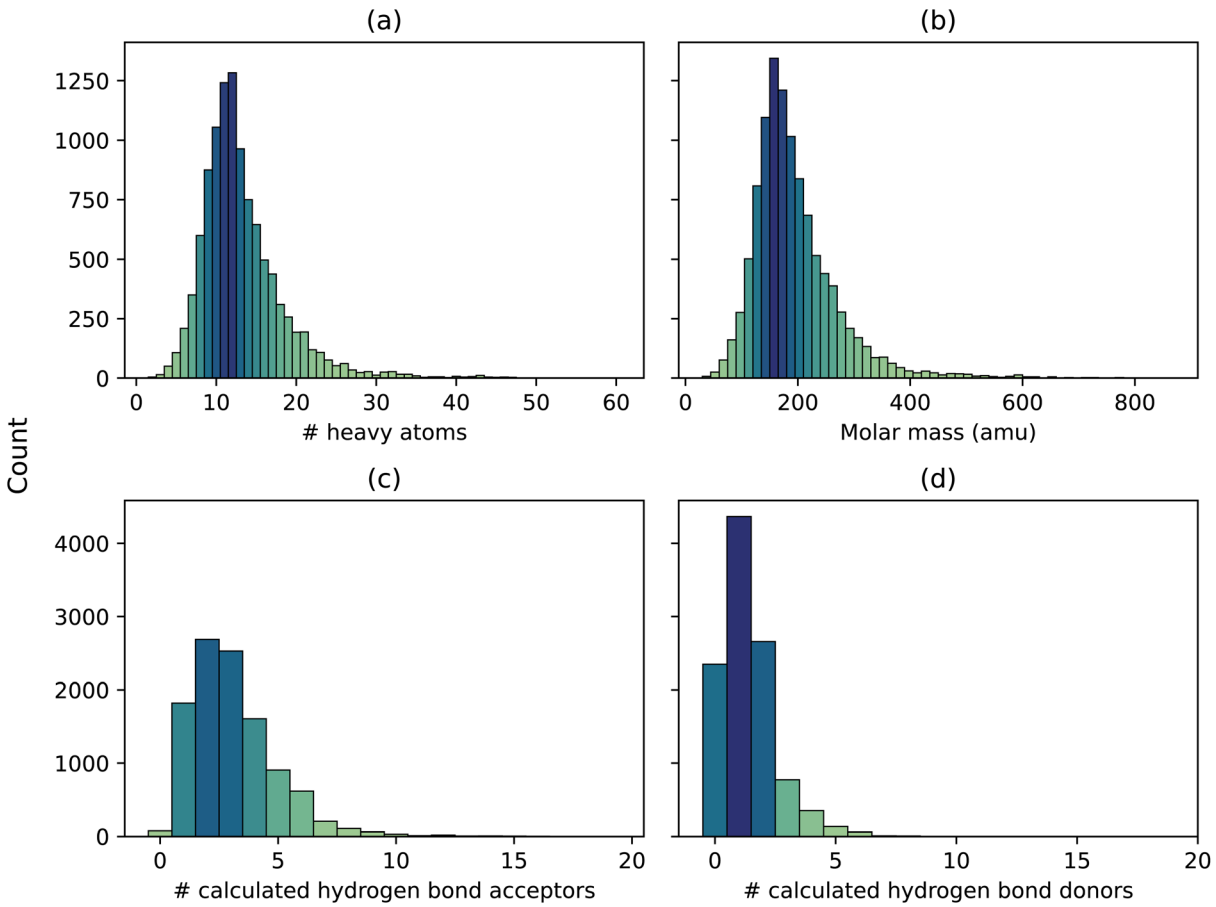


Fig. 2 Summary dataset distributions, including: (a) number of heavy atoms, (b) molar mass, (c) calculated hydrogen bond acceptors, and (d) calculated hydrogen bond donors. The latter two properties were computed using rdkit v2024.03.1. Darker color represents higher density of points.

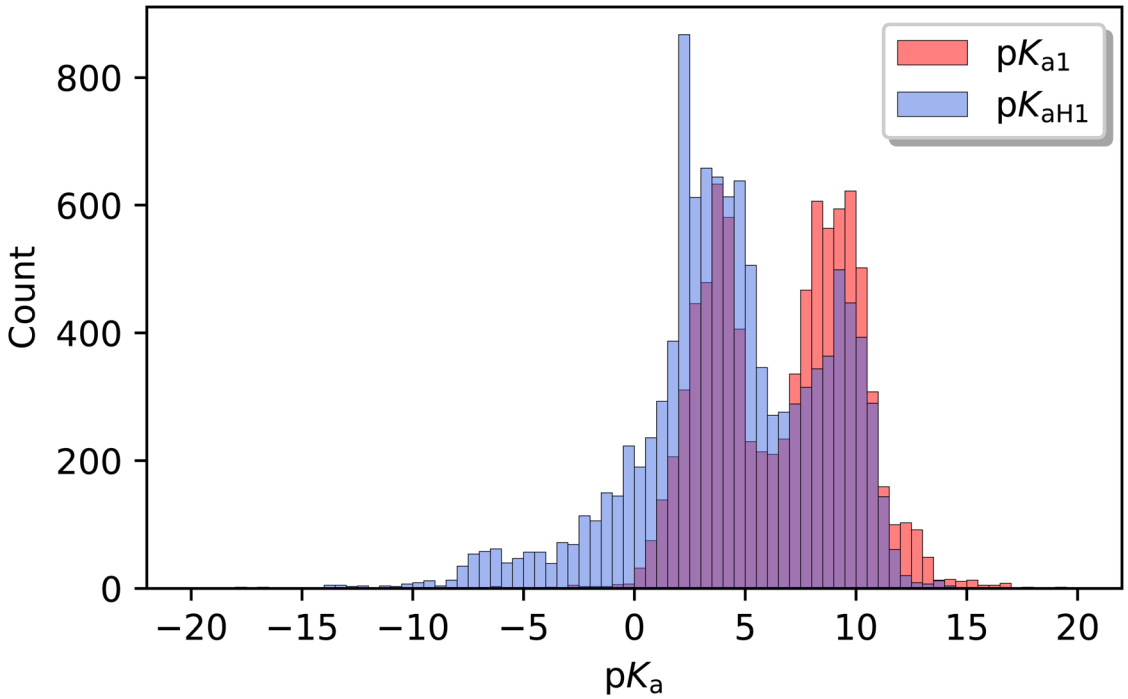


Fig. 3 First acidic and basic pK_a values in the dataset, across all species, at approximately 25 °C. For acids with multiple values near room temperature, one value between 20–30 °C was reported. Both distributions exhibit peaks at around 4 and 9 pH units, while the basic dissociation shows a long left-skewed tail. Overlapping bins are shown in purple.

experimental condition, there are 14 681 such entries, reflecting the polyprotic and amphoteric nature of some of the 10 564 species.

The compounds are mostly small organic molecules, centered around 10 heavy atoms, with a right tail indicating some larger molecules including a few drug compounds (Fig. 2). Most of the molecules have at least one site that can accept a proton (Fig. 2c), and many compounds include at least one hydrogen bond donor site (Fig. 2d).

The distributions of pK_{a1} and pK_{aH1} shown in Fig. 3 both have peaks around 4 and 9 pK_a units. The majority of pK_{a1} values fall in the range of 3 to 11, representing weak-to-medium acids and bases. But there are a significant number of data on very weak bases (pK_{aH1} < 3) and very weak acids (pK_{a1} > 11).

A large variety of pK_a types is present in this dataset. The data include both pK_{aH} and pK_a up to six charge states (Fig. 4). Most entries are related to first and second dissociations. Just one compound includes a sixth proton gain pK_{aH}, whereas around ten include a sixth proton loss pK_a.

pK_a data are recorded across a number of conditions, including temperature, pressure, experimental method, and evaluated reliability.

Most entries reported herein were measured near or at room temperature (Fig. 5). A small number of entries are measured or calculated at elevated temperatures, allowing the temperature dependence of pK_a to be visualized or estimated.

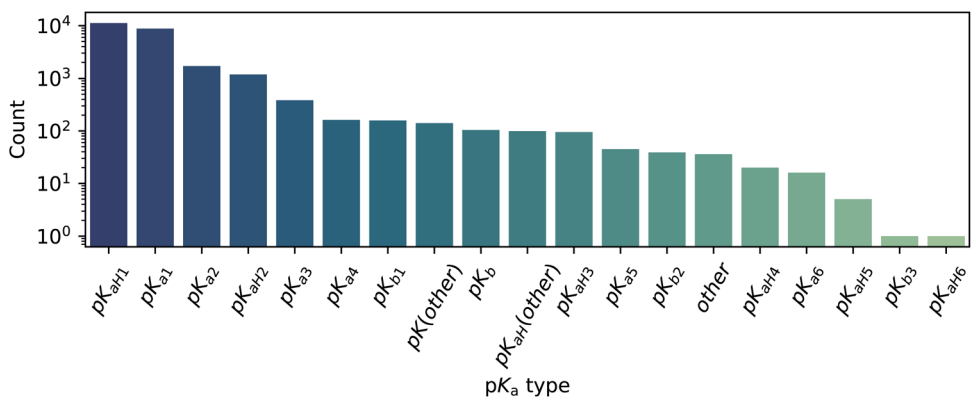


Fig. 4 Distribution of pK_a types across all compounds and temperatures in the dataset (log-y scale). Most entries are for first and second dissociations, with slightly more first basic than first acidic pK_a values. Darker color represents higher density of points.

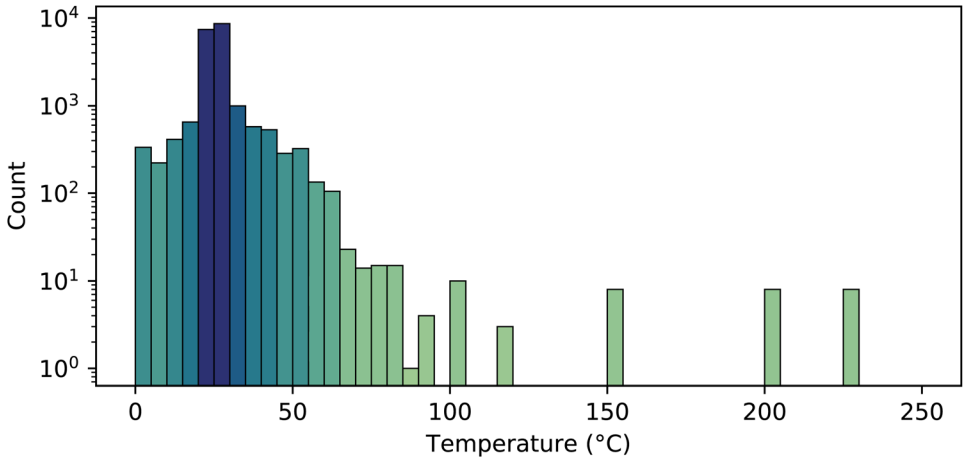


Fig. 5 Temperature distribution for all entries in the dataset (log y-scale). The vast majority of entries are at room temperature, although a few entries are recorded as high as 225 °C. Values above 100 °C were either obtained at elevated pressures, or computed from temperature-based extrapolations at 1 bar. Darker color represents higher density of points.

Ionic strength is sometimes also recorded. For most applications of pK_a, it is assumed that the ionic strength is near zero. Most of the ionic strength measurements in this dataset are low. The ionic strength is presented in many different formats; for example, either directly as ionic strength I, as c in molar concentration, as m in concentration per kilogram of water, or as κ in specific conductance of water (in 10^{-6} ohm^{-1} cm^{-1}). In many cases the value provided is approximate, or only a range is given. At the time of publication, the ionic strength is included in the remarks column, rather than parsed in a separate column.

The vast majority of measured data in this compilation are from electrochemical or optical methods (Fig. 6), which are only capable of discerning macroscopic pK_a values. Only 30 measurements were made with NMR, which can provide information about the microstates. Hence, this dataset is intended to be used as a macroscopic pK_a database, though it is in principle possible to employ physical chemical information (such as through quantum chemical simulations) to decompose the macroscopic values into the corresponding microstates.

Table 2 shows the details of the original print sources. The works by Perrin were focused largely on basic (pK_{aH}) values, whereas that of Serjeant was focused on acidic values. Notably, acidic pK_a values prior to 1961 are missing – those were compiled by Kortum *et al.*[54] for 1056 compounds, and published only in German. The Kortum work contains values for aliphatic and alicyclic carboxylic acids, aromatic carboxylic acids, phenolic acids, and other acids including phosphoric acid

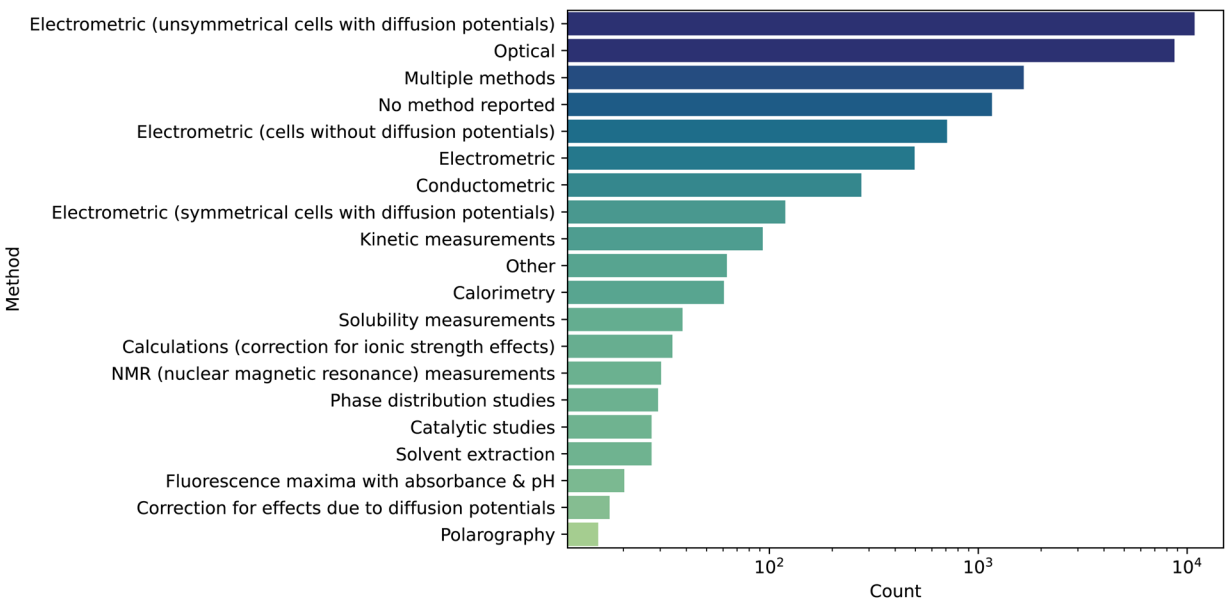


Fig. 6 Measurement methods employed for each datapoint. The majority of measurements were obtained using electrometric experiments. Darker color represents higher density of points.

Table 2 Summary of reference sources and their contents. Future versions of the dataset may have some slight differences

Reference source	# Entries	# Molecules	Description
perrin	7769	3433	Values mostly for organic bases, collected up to 1961[51]
perrin_supp	7147	3914	An add-on to the first Perrin compilation, collected from 1961 to 1970, mostly of values for organic bases. Includes some corrections to Perrin, which were incorporated in this digitization[52]
serjeant	9295	4108	Supplement to work by Kortum *et al.*[54] Data collected from 1961 to 1970, mostly of acidic dissociations[50]

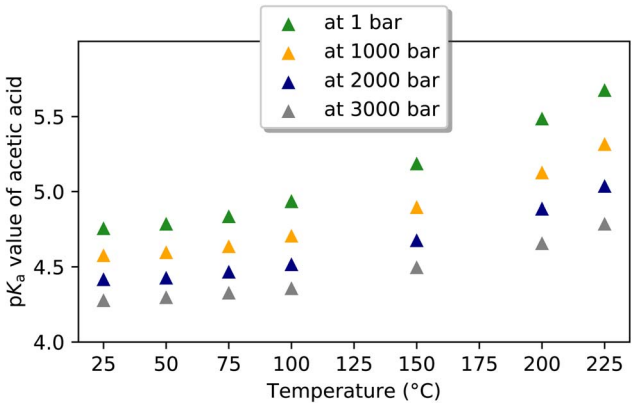


Fig. 7 Isobars for acetic acid pK_a varying across temperature.

ethers, and sulfonic, phosphonic, and phosphinic acids. We unfortunately were unable to translate the Kortum work with high confidence, and hence it is not included herein. We hope to incorporate this data in the future.

Representative data examples

Herein, we present representative examples that underscore the breadth of the available data and metadata.

Variation across temperature and pressure. Fig. 7 shows one of the few species whose pressure and temperature values were measured at widely varying conditions. The maximum difference in pK_a value among all the experimental conditions is about 1.3 pK_a units. Examples of isobars and isotherms are shown in the SI.

Most acidic and basic compounds. Table 3 shows the eight most acidic and basic compounds in the dataset. The most acidic compounds in this dataset donate protons from C–H or N–H bonds, not O–H as might be expected. All of the strong acids have exceptionally strong stabilization of the conjugate anion due to the inductive effects of nitrate or nitrile groups. All of the strong bases shown include at least one N–C=N moiety, which forms a resonance-stabilized cation upon protonation.

Usage as reference data

We intend that the data should be used as reliable reference data. We aim to follow FAIR (Findability, Accessibility, Interoperability, and Reuse) principles to allow users to readily, freely access the data.

- Findability – each compound has a unique identifier. Rich metadata are provided, with descriptions that explicitly describe the type of data.
- Accessibility – the data and metadata can be accessed freely (through free download) – currently through Zenodo – in a .csv file.
- Interoperability – the .csv format with chemical identifiers allows it to be readily used in cheminformatics workflows and beyond.
- Reusability – license information is provided in the README included in the download repository, and sources are given for each datapoint.

Because the data is released in a digital format, it is also readily updateable. Errors in the database can be pointed out by users and subsequently fixed in the datasheet.

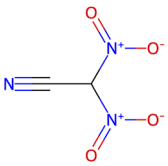
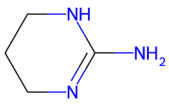
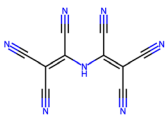
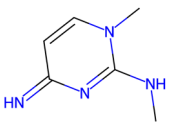
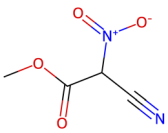
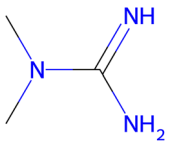
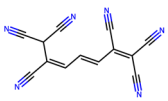
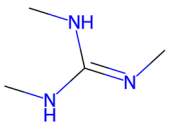
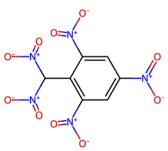
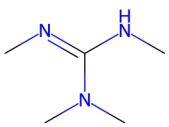
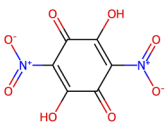
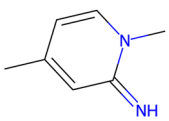
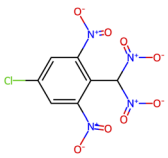
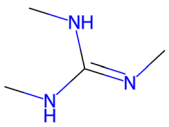
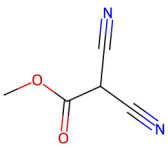
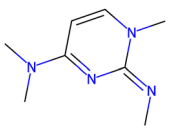
Comparison to other datasets

We compared the chemical diversity and pK_a values of the species in this dataset to those of data in other commonly-used pK_a datasets in machine learning.

Chemical space. Fig. 8 shows that approximately half of each dataset directly intersects with compounds in other datasets. The IUPAC dataset includes 5391 compounds not included in iBonD or DataWarrior.

Fig. 9 shows the chemical space spanned by the compounds, represented by a UMAP plot.[64] The domain is fairly consistently covered among the IUPAC, DataWarrior, and iBonD datasets, with overlapping points spanning practically all regions of this UMAP plot. That said, there are regions of chemical space where more examples are present for certain datasets *versus* the others. In particular, the bottom-right region contains mostly IUPAC data, which correspond mostly to simple nitrogen-containing heterocyclic compounds (such as pteridine and pyrimidine derivatives). In contrast, the top-center, top-left, and bottommost regions of the UMAP plot are somewhat more

Table 3 Strongest acids and bases in the dataset (at ambient conditions)

pK_{a1}	Acidic molecule	pK_{aH1}	Basic molecule
−6.4		14.1	
−5.8		14.0	
−5.2		14.0	
−3.9		14.0	
−3.5		13.9	
−3.0		13.9	
−2.8		13.9	
−2.8		13.9	

heavily populated by the aqueous iBonD data, which correspond to sulfonamides and large, druglike molecules.

Fig. 10 shows that the distributions of the molecular weights covered by the IUPAC, iBonD, and DataWarrior sets are very similar, focusing on small organic compounds, though iBonD includes more large molecules. The great majority of the molecules in all 3 datasets have molecular weights of less than 300 amu, which may limit the applicability of these datasets for modeling larger, more complex biochemical or pharmaceutical compounds.

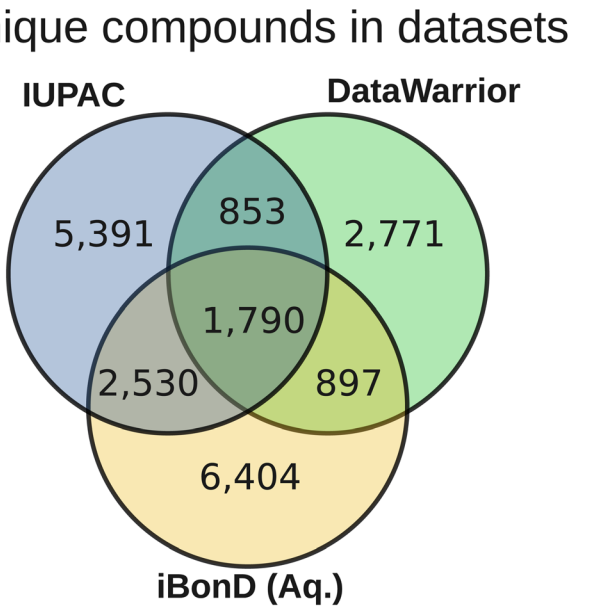


Fig. 8 Comparison of unique compounds in three large datasets: this dataset (top-left), DataWarrior (top-right), and iBonD aqueous values (bottom). Unique compounds were determined by identifying intersections of sanitized InChI strings among the datasets.

pK_a values. We compared overlaps of the IUPAC data with both the iBonD and DataWarrior datasets for pK_{aH1} and pK_{a1}. For both sets, approximately 95% of the data agreed within 0.5 pK_a units of the IUPAC data. The remaining 5% were almost all zwitterionic compounds with definitions of "acidic" and "basic" that are different from pK_{a1} and pK_{aH1}. These checks provided a way to verify the quality of the digitizations and identify possible errors in one or more of the datasets.

The distributions of data are shown in Fig. 11. Compared to iBonD, the IUPAC dataset includes more pK_{aH} values and a stronger left tail (very weak bases). Like the others, it includes peaks at approximately 4 and 9 pK_a units, and a weak right tail. These provide further evidence that the experimental datasets span a generally similar set of compounds.

Usage in machine learning

Another use case we foresee is usage of the data in machine learning models. Large quantities of high-quality data are important for developing accurate predictive models.

Before further discussion of this dataset, we must first comment on some highly-pervasive misusage of pK_a data, which has thus far evaded discussion in the literature. After addressing these issues, we then discuss the modeling results.

Evaluation datasets

pK_a models are generally evaluated on two common test sets, described below.

SAMPL. The SAMPL6-8 pK_a challenges span 100 molecules across 3 challenges, meant to simulate biomolecules or fragments, and each challenge includes approximately molecules of

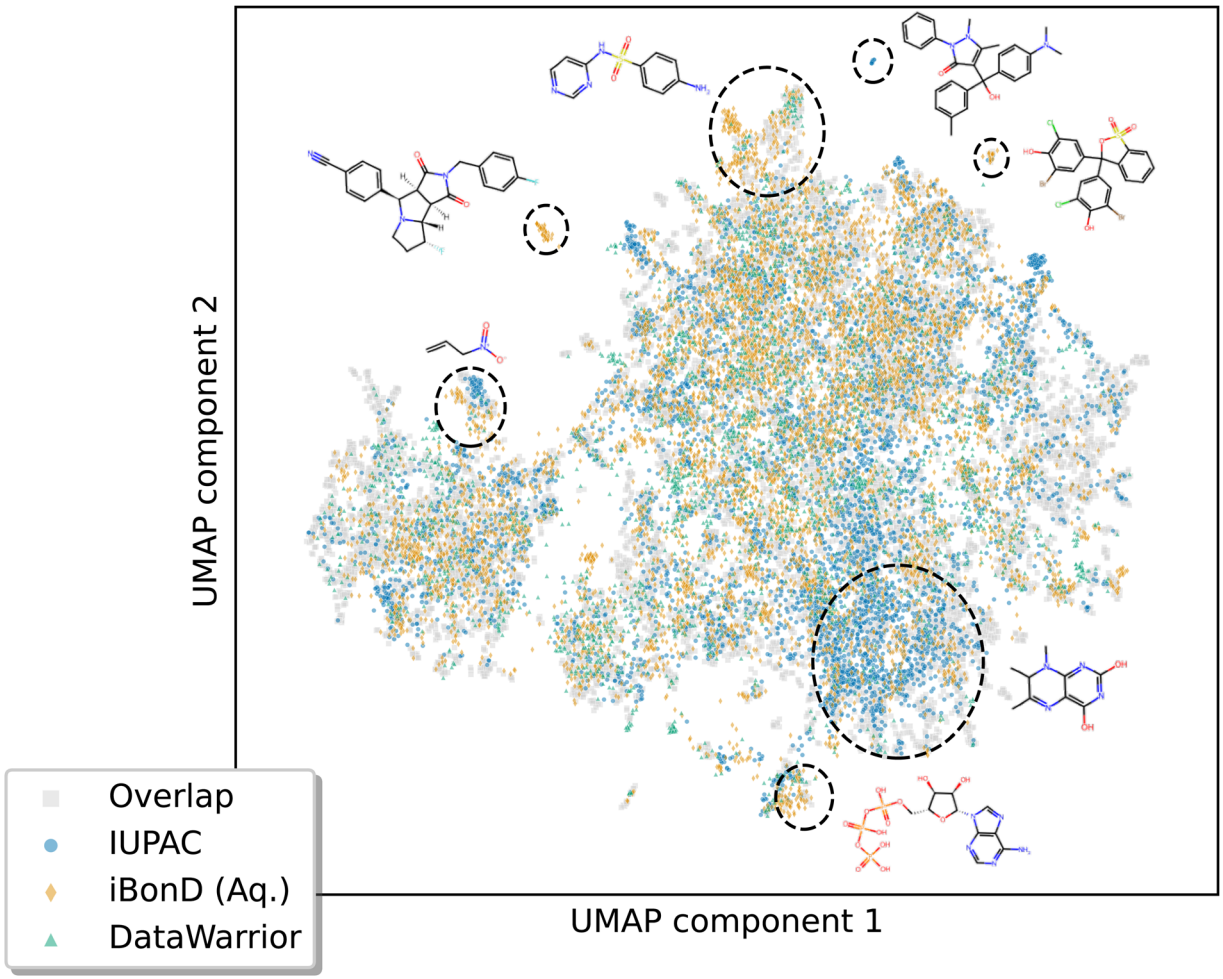


Fig. 9 UMAP visualization of the chemical space spanned by DataWarrior, iBonD aqueous, and the IUPAC dataset presented herein. UMAP was performed on the 2048-bit radius-3 count-based Morgan fingerprints computed for each chemical species. The dashed circles indicate regions of chemical space where most of the data are from this IUPAC dataset (bottom-right large cluster, topmost small cluster) or have few IUPAC data (the others).

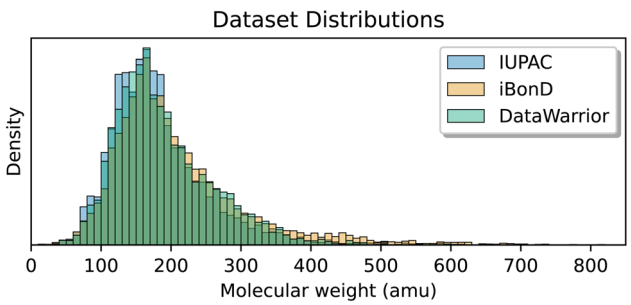


Fig. 10 Comparison of molar weights of datasets in this study. The histograms nearly completely overlap, indicating that the IUPAC, iBonD, and DataWarrior data have a very similar molecular weight coverage – centered on small molecules. The iBonD data includes slightly more large molecules than the other two datasets.

a specific type.[16] Each challenge includes both microscopic and macroscopic pK_a prediction tasks, but typically only the macroscopic targets are evaluated.

Novartis. The Novartis data is an external test set of several hundred small and druglike molecules.[27] Little else is known about the provenance of the set, as it was provided to Baltruschat *et al.* as an inhouse dataset.

Data leakage in existing datasets

To test the predictive power of a model, the test data should not overlap with training data. Data leakage, wherein the same molecule appears in both the test and training data, makes models appear more accurate than they really are. The ChEMBL, iBonD, and DataWarrior datasets, along with this dataset, all include some degree of overlap with the SAMPL and Novartis test sets, which could cause data leakage.

The ChEMBL, iBonD, and DataWarrior datasets. Many of the data in these datasets overlap with the SAMPL and Novartis datasets; in the case of ChEMBL, roughly half of the SAMPL data and nearly all of the Novartis compounds overlap with ChEMBL. The iBonD and DataWarrior datasets both have some overlaps with either or both of the SAMPL and Novartis datasets. Many

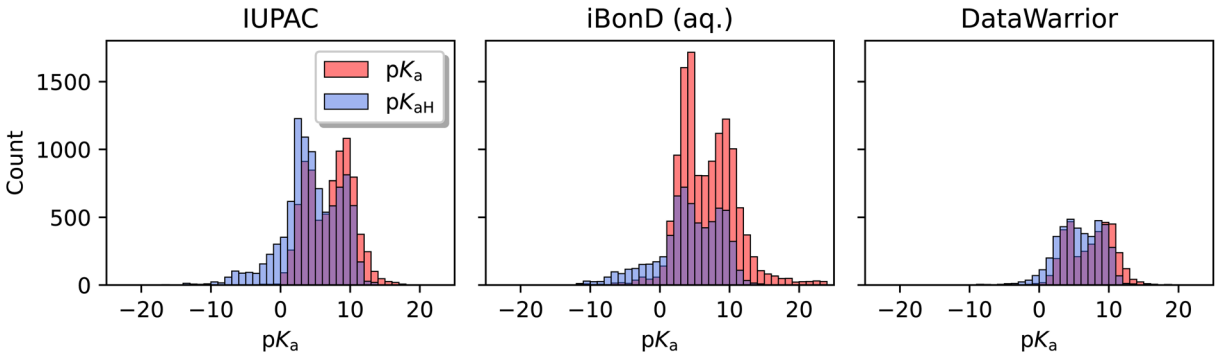


Fig. 11 Comparison of the pK_a value distributions between the IUPAC, iBonD, and DataWarrior datasets. Overlapping bins are shown in purple.

recent modeling papers that use these datasets do not mention these overlaps, and likely include data leakage in their benchmarks. A detailed discussion of data overlaps is provided in the SI.

This IUPAC dataset. This dataset includes one overlap with SAMPL. In the SAMPL6 data, molecule SM11 was reported to have a pK_{aH1} of 3.89 at room temperature. This compound is also present in this dataset, measured to be 3.85 at 20 °C.

Four compounds in the Novartis acid and base datasets[27] are also present in this dataset. Among those four, three have exact matches for pK_a type; one compound is in the dataset for a different acidity type (perrin3511) and may not be considered a leak.

All of these potential data leaks, from all datasets, are presented in the Zenodo repository associated with this manuscript. As both this dataset and others may be used in machine learning efforts, future works should be careful to remove these data from the training sets if evaluating on SAMPL or Novartis data to avoid data leakage.

Considerations for training a model. To ensure fair comparison, these points must be removed from the training data to fairly demonstrate a model's effectiveness. We encourage readers to use a thorough sanitization workflow to identify and filter identical compounds whose identifiers may differ due to tautomerization, stereochemistry, salt form, or charge.

The SAMPL7 challenge data also include two macroscopic pK_a measurements that correspond to an inexact quantity; *e.g.* "pK_a >12." It is not clear whether these values were pruned, or assumed to be equal to 12 when performing tests using SAMPL7. We urge researchers who use those datasets to clearly state how those values were processed.

Finally, we note that these data are for macroscopic pK_a values. In order to convert these into microscopic pK_a, the modeler must compute the energetics of each relevant microstate.[32,33] However, this process can be computationally expensive. If the modeler is using macroscopic data to predict values pertaining to a specific acidity center, then the modeler is actually reporting a microscopic pK_a, and assuming their numerical values are identical (which is true for monoprotic acids and bases, but there can be substantial differences for polyprotic species). If this is done, the modeler should clearly state this assumption.

Models for macroscopic pK_a prediction. To demonstrate usage of this data in machine learning, we trained a model using Chemprop v2.2.[49,65] Chemprop is a framework for training directed message-passing neural networks to predict properties. Chemprop models simultaneously learn a graph-based embedding for each compound as well as the weights of a feedforward neural network (which map from the encoding to the target property). The user provides chemical graph structures, encoded as SMILES strings, as well as the corresponding

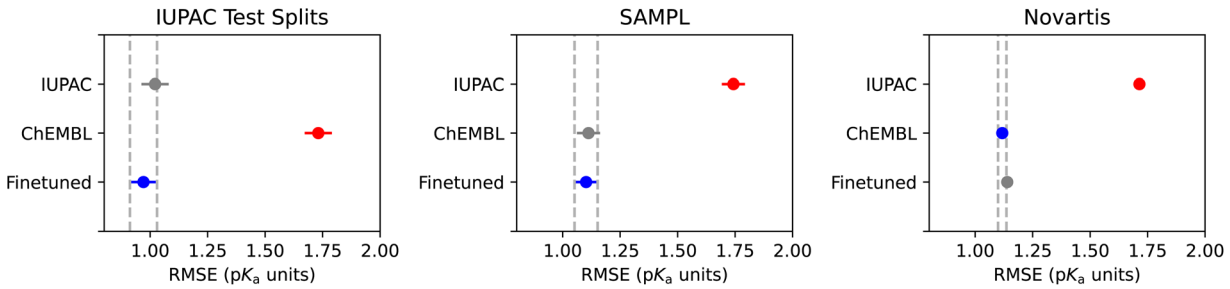


Fig. 12 Tukey's Honestly Significant Difference test applied to all test predictions, shown for the IUPAC, ChEMBL, and finetuned models, all trained using Chemprop v2.2. Each label includes 10 constituent models trained on separate training splits; these form the bounded ranges shown in the plots. Each dot corresponds to an average of all 10 model predictions. Test splits come from the IUPAC aqueous digitized data; and from the SAMPL and Novartis datasets, which largely include druglike molecules. Blue represents the "best"; gray shows statistically equivalent; and red shows statistically worse performance.

property (in this case, pK_a) during training. For further details, we refer readers to the corresponding references.

Extracting only pK_{a1} and pK_{aH1} values with high confidence near room temperature, we trained 10 separate Chemprop models, striping the training, validation, and test data in an 80%/10%/10% split such that all data in the whole data corpus was in a test split (the IUPAC model in Fig. 12). We also trained a set of 10 models on the ChEMBL dataset (labeled ChEMBL). Finally, we created a set of ten models (labeled Finetuned), wherein each model was initialized from a ChEMBL model and then finetuned on a split of the IUPAC data. That is, for each split i from 1 to 10, a model was trained on split i of ChEMBL and finetuned on split i of IUPAC. We pruned the training and pre-training data to avoid any overlaps with the test data in both the ChEMBL and IUPAC sets, and the ChEMBL data were further pruned to remove overlapping IUPAC compounds.

We examined three test cases: (1) the held-out test data from the IUPAC dataset, mostly representing a large variety of small molecules; (2) the SAMPL dataset, representing a few classes of druglike fragments; (3) the Novartis dataset, representing a broader diversity of druglike molecules.

In total, this yields 3 sets of models (IUPAC, ChEMBL, Finetuned), differing only in the data used to train them as well as their hyperparameters; and 3 test sets (IUPAC splits, SAMPL, Novartis). We conducted Tukey's Honestly Significant Difference (HSD) test[66] as implemented in SciPy,[67,68] to better assess whether statistically significant differences exist between the models.

Fig. 12 shows the performances of the models along with the corresponding Tukey's HSD tests. Each model consists of ten substituent models trained on separate splits of the data. For each composite model under examination (IUPAC, ChEMBL, or Finetuned), the ten substituent models produce the distribution of RMSEs illustrated in Fig. 12.

In all cases, the model pretrained on ChEMBL data and then finetuned on IUPAC data performed the best or statistically identically to the best models. For the small molecules data, the IUPAC-based models perform the best, but on the other hand, the ChEMBL model did much better than the baseline IUPAC model on the SAMPL and Novartis test sets. Only the finetuned model appears to have the most versatile test performance, with good performance across both small molecules and druglike molecules.

The errors shown here are slightly higher than those of other recently-released models. However, we emphasize that care was taken to remove molecules that appear in the test splits from the training splits.

All the models mentioned above, including our recommended best model created from the 10 finetuned models, are available for download; see the Data Availability section. We recommend leveraging the whole ensemble of the Finetuned model to make predictions; this is readily done in the Chemprop software, which can use all 10 finetuned models to obtain an average prediction and estimate ensemble uncertainty (or leverage the other suite of uncertainty tools available).

Potential limitations of dataset

We anticipate that several outstanding challenges may require additional effort for some computational workflows. We encourage readers to report such errors when they are discovered so that they may be fixed in future versions of the dataset.

SMILES translation. In this work, we translated IUPAC chemical names into SMILES strings by using programmatic methods such as OPSIN, or by manual effort. OPSIN is claimed to have about a 99.8% precision rate.[57] However, the names provided in the original reference works were often unconventional, as the names are grouped by scaffolds that do not necessarily relate to any acidic groups. For example, entry perrin3 is provided as "methane, C-amino-C-carbamoyl-", which would be more commonly referred to as "2-aminoacetamide" or just "glycinamide". These could reduce the quality of the automated naming algorithms.

We sometimes observed that different translation algorithms returned different SMILES strings, often due to inconsistencies in how locants are parsed. In these cases, as well as when zero or one algorithm(s) returned a valid result, we manually constructed SMILES strings based on the provided names, following IUPAC naming rules. Errors in SMILES strings may appear due to either failures in machine translation, inaccuracies in manual curation, or errors in the source material, though we expect such errors to be infrequent.

Another challenge is providing representative microstructures at the corresponding experimental conditions. Many of the compounds, including amino acids, are predominantly zwitterionic at room temperature and neutral pH conditions, which has implications for the pK_a values as well. However, we herein identify those species by their neutral tautomers only, as these are easier to obtain and common to search. Also, since these are generally macroscopic pK_a data, the structural distinctions are not crucial to using the data productively. We hence made no effort to represent any additional potentially relevant tautomers for each compound; each compound is labeled with just one SMILES string (and thereby one isomeric form). The SMILES strings provided in the dataset correspond to the tautomers provided by the SMILES translation software, or in the case of manual translation, by whichever form most literally was provided by the IUPAC name. Therefore, amino acids and all other potentially zwitterionic compounds are represented in their uncharged form.

Acidity center information. In some cases, it may be desirable to assign an ionization center to a pK_a, though this is not always possible; the values reported herein are macroscopic pK_a values corresponding to the thermodynamics of ensembles of microstates. Still, in many cases, especially if microscopic dissociation coefficients are sufficiently distinct from one another, one acidity center can be assumed to be responsible for the majority of the observed association/dissociation, especially in applications of physical chemistry. We made no effort to identify acidity centers in this work, though we note that they may be present in other IUPAC compilations.[69]

Chemical space. The dataset, as shown in Fig. 9, spans chemical space that is already well-spanned by other pK_a

databases, with the exception of a few molecular motifs. Additionally, this dataset focuses only on measurements in water, whereas other datasets such as iBonD include other solvents. Ongoing efforts and recent developments, such as the IUPAC dataset of pK_a values in dipolar non-hydrogen-bond-donor solvents released in 2025, can be used in combination with this work.[69] Further efforts should focus on increasing the chemical diversity of both the acids and solvents.

Other potential limitations. Errors may have also occurred in the OCR stage. After benchmarking various OCR tools, we used Amazon Textract software to extract text information from image scans of book pages. OCR technology at this time was not sufficiently capable of processing chemical nomenclature, with typos frequently appearing related to super- and subscripts, chemical names, and brackets and parentheses. Considerable effort was undertaken to manually review the digitization of all IUPAC names. Every chemical name was reviewed by a human and compared to the reference work to ensure validity. Still, infrequent errors in the transcription stage may exist, particularly in the "remarks" column which has more text than other fields.

Additionally, the "pK_a types" of some amphoteric molecules were manually assigned. Several pK values were sometimes provided in the reference works without any indication of dissociation type (*e.g.* pK_a *versus* pK_{aH}). Although we only included pK_a types we could assign with high confidence, it is still possible that some errors were made during this transcription phase.

The original tabulation of the source pK_a data was not always done in a consistent fashion, including the designation of acidity types and orderings. For instance, an entry may have been provided with pK_1 and pK_2 values, but the values may correspond to pK_{aH1} and pK_{a1}, or to two acidic dissociations, or to two pK_{aH} values. The authors of this work used their best judgment and cross-referenced experimental data to other literature and predictions by ChemAxon's Protonation software, but it is still possible that this step has introduced additional errors, especially in the Serjeant compilation. Indeed, the Serjeant compilation recommends citing the Perrin sources as the "major source of pK values" for amphiprotic compounds, which may include duplicated entries in the acidic and basic compilations. During data validation, we checked for compounds with large discrepancies, and manually corrected those. However, there is the possibility that we missed subtler errors or mislabelings.

Some data may be duplicated between the Perrin and Serjeant compilations, as both compilations were conducted independently. We include all available sets of compounds here without combining entries that appear in both compilations.

It is possible that inconsistencies or errors exist in the original tabulation, or differences exist among the three text compilations that may contradict one another. We urge the reader to check the associated references for desired datapoints when relying on individual datapoints.

Finally, as mentioned earlier, the chemical coverage of the experimental data may not be conducive toward certain applications, *e.g.* for modeling large pharmaceutical compounds. We anticipate that incorporating computed thermodynamic information with the data, or explicitly partitioning pK_a into group-based contributions, will help improve the generalizability of the predictive models.

We intend for this dataset to be a "living" resource, in the sense that any errors discovered throughout its usage can be corrected.

Conclusion

We have provided a digitized dataset that can be used for reference by researchers or as a data source for data-driven models. The dataset includes metadata such as temperature, references, method of measurement, assessed reliability, pressure, and general comments. We have also commented on and demonstrated use of the data for modeling applications, pointing out numerous cases where data leakage is present in commonly-used datasets for pK_a prediction. We emphasize once more that these data are macroscopic pK_a values, and therefore models trained on this data will only predict macroscopic pK_a.

We hope that this work joins other collections of pK_a data as a reference for applications in organic chemistry and computational modeling. We emphasize again that this digitization may include some errors, which can be corrected in future versions of the dataset. Because references are supplied, users can cross-reference a tabulated value with its source publication.

Finally, we hope that this work, in conjunction with high-throughput experimentation and advancements in data mining that sample diverse regimes of chemical space, will lead to the development of even more capable open-source tools and libraries for pK_a prediction used broadly in chemistry-related applications.

Author contributions

All authors contributed to the development and writing of the manuscript. J. W. Z. conducted the database generation, analysis, and model development. O. L.-J. conducted additional data cleaning and analysis. W. H. G. managed and planned the work.

Conflicts of interest

There are no conflicts to declare.

Data availability

The latest version of the IUPAC dataset is publicly available at: https://doi.org/10.5281/zenodo.7236452. At present, the data is provided under a CC BY-NC 4.0 license.

The models and data splits used in this study are available at: https://doi.org/10.5281/zenodo.18165948. The Chemprop package can be used to run the models, and is freely available on GitHub at https://github.com/chemprop/chemprop/.

Supplementary information (SI): pdf including additional examples of data analysis, information about reference works,

model training details, and data pruning. See DOI: https://doi.org/10.1039/d6ra02418a.

Acknowledgements

J. W. Z. and W. H. G. acknowledge the Machine Learning for Pharmaceutical Discovery and Synthesis Consortium (MLPDS) for funding. J. W. Z. further acknowledges funding from a Takeda Fellowship. We gratefully acknowledge Ye Li, Leah McEwen, and Stuart Chalk for many helpful discussions and invaluable contributions toward facilitating this work. We also acknowledge IUPAC members David Shaw, Glenn Hefter, and executive director Dr Lynn Soby. We acknowledge Prof. Ivo Leito, Sofja Tshepelevitsh, and Ivari Kaljurand for thoughtful discussions. We further acknowledge members of the Green group who assisted with data checking, including: Yunsie Chung, Xiaorui Dong, Michael Forsuelo, Kevin Greenman, Esther Heid, and Hao-Wei Pang. We thank PubChem scientists including Evan Bolton and Jeff Zhang for their support in resolving SMILES strings from IUPAC names, and for integration within PubChem. We thank the Internet Archive for providing the digitized copy of Perrin (1965) with IUPAC's permission. We further acknowledge usage of Amazon Textract and ChemAxon Molconverter (https://chemaxon.com). We thank Prof. Markus Kraft for many thoughtful discussions regarding this work.

References

1 D. T. Manallack, R. J. Prankerd, E. Yuriev, T. I. Oprea and D. K. Chalmers, The significance of acid/base properties in drug discovery, *Chem. Soc. Rev.*, 2013, **42**, 485–496.
2 A. Sabljic and Y. Nakagawa, *Non-First Order Degradation and Time-dependent Sorption of Organic Chemicals in Soil*, ACS Publications, 2014, pp 85–118.
3 L. Mamy, D. Patureau, E. Barriuso, C. Bedos, F. Bessac, X. Louchart, F. Martin-Laurent, C. Miege and P. Benoit, Prediction of the fate of organic compounds in the environment from their molecular properties: A review, *Crit. Rev. Environ. Sci. Technol.*, 2015, **45**, 1277–1377.
4 R. P. Bell, *The Proton in Chemistry*, Springer Science & Business Media, 2013.
5 R. Lu, J. Sun, Y. Wang and Z. He, Quantitative structure-retention relationship studies with biopartitioning micellar chromatography systems by amended linear solvation energy relationships in consideration of electronic factor, *Chromatographia*, 2009, **70**, 21–29.
6 I.-H. Um, H.-J. Han, J.-A. Ahn, S. Kang and E. Buncel, Reinterpretation of curved hammett plots in reaction of nucleophiles with aryl benzoates: change in rate-determining step or mechanism *versus* ground-state stabilization, *J. Org. Chem.*, 2002, **67**, 8475–8480.
7 I.-H. Um, J.-Y. Lee, H.-T. Kim and S.-K. Bae, Curved Hammett plot in alkaline hydrolysis of O-aryl thionobenzoates: change in rate-determining step *versus* ground-state stabilization, *J. Org. Chem.*, 2004, **69**, 2436–2441.
8 E. A. Castro, R. Aguayo, J. Bessolo and J. G. Santos, Kinetics and mechanism of the reactions of S-2, 4-dinitrophenyl 4-substituted thiobenzoates with secondary alicyclic amines, *J. Org. Chem.*, 2005, **70**, 7788–7791.
9 J. W. Zheng and W. H. Green, Experimental Compilation and Computation of Hydration Free Energies for Ionic Solutes, *J. Phys. Chem.*, 2023, **127**, 10268–10281.
10 L. C. Kröger, S. Müller, I. Smirnova and K. Leonhard, Prediction of solvation free energies of ionic solutes in neutral solvents, *J. Phys. Chem.*, 2020, **124**, 4171–4181.
11 T. Nevolianis, J. Zheng, S. Müller, M. Baumann, S. Tshepelevitsh, I. Kaljurand, I. Leito, I. Smirnova, W. Green and K. Leonhard, Solvation free energies of anions: from curated reference data to predictive models, *J. Am. Chem. Soc.*, 2025, **147**, 30626–30646.
12 M. Nic, L. Hovorka, J. Jirat, B. Kosata and J. Znamenacek, *IUPAC Compendium of Chemical Terminology*, International Union of Pure and Applied Chemistry, 2005.
13 *IUPAC Gold Book: Hydron*, 2025, DOI: 10.1351/goldbook.H02904.
14 C. L. Perrin, I. Agranat, A. Bagno, S. E. Braslavsky, P. A. Fernandes, J.-F. Gal, G. C. Lloyd-Jones, H. Mayr, J. R. Murdoch, N. S. Nudelman, *et al.*, Glossary of terms used in physical organic chemistry (IUPAC Recommendations 2021), *Pure Appl. Chem.*, 2022, **94**, 353–534.
15 P. Pracht, R. Wilcken, A. Udvarhelyi, S. Rodde and S. Grimme, High accuracy quantum-chemistry-based calculation and blind prediction of macroscopic pK_a values in the context of the SAMPL6 challenge, *J. Comput.-Aided Mol. Des.*, 2018, **32**, 1139–1149.
16 M. Işık, A. S. Rustenburg, A. Rizzi, M. R. Gunner, D. L. Mobley and J. D. Chodera, Overview of the SAMPL6 p K a challenge: evaluating small molecule microscopic and macroscopic p K a predictions, *J. Comput. Aided Mol. Des.*, 2021, **35**, 131–166.
17 S. Prasad, J. Huang, Q. Zeng and B. R. Brooks, An explicit-solvent hybrid QM and MM approach for predicting pK_a of small molecules in SAMPL6 challenge, *J. Comput. Aided Mol. Des.*, 2018, **32**, 1191–1201.
18 D. D. Perrin, B. Dempsey and E. P. Serjeant, *pK_a Prediction for Organic Acids and Bases*, Chapman & Hall, 1981.
19 F. H. Vermeire and W. H. Green, Transfer learning for solvation free energies: From quantum chemistry to experiments, *Chem. Eng. J.*, 2021, **418**, 129307.
20 Y. Chung, F. H. Vermeire, H. Wu, P. J. Walker, M. H. Abraham and W. H. Green, Group Contribution and Machine Learning Approaches to Predict Abraham Solute Parameters, Solvation Free Energy, and Solvation Enthalpy, *J. Chem. Inf. Model.*, 2022, **62**, 433–446.
21 F. H. Vermeire, Y. Chung and W. H. Green, Predicting Solubility Limits of Organic Solutes for a Wide Range of Solvents and Temperatures, *J. Am. Chem. Soc.*, 2022, **144**, 10785–10797.
22 Y. Chung and W. H. Green, Machine learning from quantum chemistry to predict experimental solvent effects on reaction rates, *Chem. Sci.*, 2024, 2410–2424.

23 S. Biswas, Y. Chung, J. Ramirez, H. Wu and W. H. Green, Predicting critical properties and acentric factors of fluids using multitask machine learning, *J. Chem. Inf. Model.*, 2023, **63**, 4574–4588.
24 K. A. Spiekermann, L. Pattanaik and W. H. Green, Fast predictions of reaction barrier heights: toward coupled-cluster accuracy, *J. Phys. Chem.*, 2022, **126**, 3976–3986.
25 K. P. Greenman, W. H. Green and R. Gómez-Bombarelli, Multi-fidelity prediction of molecular optical peaks with deep learning, *Chem. Sci.*, 2022, **13**, 1152–1162.
26 X. Pan, H. Wang, C. Li, J. Z. Zhang and C. Ji, MolGpka: A Web Server for Small Molecule pK_a Prediction Using a Graph-Convolutional Neural Network, *J. Chem. Inf. Model.*, 2021, **61**, 3159–3165.
27 M. Baltruschat and P. Czodrowski, Machine learning meets pK_a, *Chem. Inf. Sci.*, 2020, **9**, 1–12.
28 J. Wu, Y. Wan, Z. Wu, S. Zhang, D. Cao, C.-Y. Hsieh and T. M. F. Hou, SuP.-pK_a: Multi-fidelity modeling with subgraph pooling mechanism for pK_a prediction, *Acta Pharm. Sin. B*, 2022, 2572–2584.
29 Q. Yang, Y. Li, J. D. Yang, Y. Liu, L. Zhang, S. Luo and J. P. Cheng, Holistic Prediction of the pK_a in Diverse Solvents Based on a Machine-Learning Approach, *Angew. Chem., Int. Ed.*, 2020, **59**, 19282–19291.
30 J. Xiong, Z. Li, G. Wang, Z. Fu, F. Zhong, T. Xu, X. Liu, Z. Huang, X. Liu, K. Chen, *et al.*, Multi-instance learning of graph neural networks for aqueous pK_a prediction, *Bioinformatics*, 2022, **38**, 792–798.
31 F. Mayr, M. Wieder, O. Wieder and T. Langer, Improving small molecule pK_a prediction using transfer learning with graph neural networks, *Front. Chem.*, 2022, **10**, 866585.
32 W. Luo, G. Zhou, Z. Zhu, Y. Yuan, G. Ke, Z. Wei, Z. Gao and H. Zheng, *Bridging Machine Learning and Thermodynamics for Accurate pK_a Prediction*, JACS Au, 2024,.
33 C. Wagen, Physics-Informed Machine Learning Enables Rapid Macroscopic pK_a Prediction, *ChemRxiv*, 2025, preprint, ChemRxiv:2025-t8s9z-v2, DOI: 10.26434/chemrxiv-2025-t8s9z-v2.
34 O. Abarbanel and G. Q. K. Hutchison, QupKake: Integrating Machine Learning and Quantum Chemistry for Micro-pK_a Predictions, *J. Chem. Theor. Comp.*, 2025, **20**, 6946–6956.
35 A. Gaulton, L. J. Bellis, A. P. Bento, J. Chambers, M. Davies, A. Hersey, Y. Light, S. McGlinchey, D. Michalovich, B. Al-Lazikani, *et al.*, ChEMBL: a large-scale bioactivity database for drug discovery, *Nucleic Acids Res.*, 2012, **40**, D1100–D1107.
36 M. Davies, M. Nowotka, G. Papadatos, N. Dedman, A. Gaulton, F. Atkinson, L. Bellis and J. P. Overington, ChEMBL web services: streamlining access to drug discovery data and utilities, *Nucleic Acids Res.*, 2015, **43**, W612–W620.
37 B. Zdrazil, E. Felix, F. Hunter, E. J. Manners, J. Blackshaw, S. Corbett, M. de Veij, H. Ioannidis, D. M. Lopez, J. F. Mosquera, *et al.*, The ChEMBL Database in 2023: a drug discovery platform spanning multiple bioactivity data types and time periods, *Nucleic Acids Res.*, 2024, **52**, D1180–D1192.
38 C. Yang, C. Gong, Z. Zhang, J. Fang, W. Li, G. Liu and Y. Tang, In Silico Prediction of pK_a Values Using Explainable Deep Learning Methods, *J. Pharm. Anal.*, 2024, 101174.
39 ChemAxon Marvin, https://chemaxon.com/marvin.
40 J. W. Zheng, I. Leito and W. H. Green, Widespread Misinterpretation of pK_a Terminology for Zwitterionic Compounds and Its Consequences, *J. Chem. Inf. Model.*, 2024, **64**, 8838–8847.
41 ChemAxon Docs: Red and blue representation of pK_a values, https://docs.chemaxon.com/display/docs/calculators_red-and-blue-representation-of-pka-values.md, Accessed: 7-31-2024.
42 J.-P. Cheng, J.-D. Yang, X.-S. Xue, P. Ji, X. Li and Z. Wang, *iBonD Website*. https://ibond.nankai.edu.cn/, Accessed: 01 September 2024.
43 H. An, X. Liu, W. Cai and X. Shao, AttenGpKa: a universal predictor of solvation acidity using graph neural network and molecular topology, *J. Chem. Inf. Model.*, 2024, **64**, 5480–5491.
44 T. Sander, J. Freyss, M. Von Korff and C. Rufener, DataWarrior: An open-source program for chemistry aware data visualization and analysis, *J. Chem. Inf. Model.*, 2015, **55**, 460–473.
45 S. Dimitrov, R. Diderich, T. Sobanski, T. Pavlov, G. Chankov, A. Chapkanov, Y. Karakolev, S. Temelkov, R. Vasilev, K. Gerova, *et al.*, QSAR Toolbox–workflow and major functionalities, *SAR QSAR Environ. Res.*, 2016, **27**, 203–219.
46 I. Sushko, S. Novotarskyi, R. Körner, A. K. Pandey, M. Rupp, W. Teetz, S. Brandmaier, A. Abdelaziz, V. V. Prokopenko, V. Y. Tanchuk, *et al.*, Online chemical modeling environment (OCHEM): web platform for data storage, model development and publishing of chemical information, *J. Comput. Aided Mol. Des.*, 2011, **25**, 533–554.
47 R. Fraczkiewicz, M. Lobell, A. H. Goller, U. Krenz, R. Schoenneis, R. D. Clark and A. Hillisch, Best of both worlds: Combining pharma data and state of the art modeling technology to improve *in silico* pK_a prediction, *J. Chem. Inf. Model.*, 2015, **55**, 389–397.
48 R. Fraczkiewicz, H. Quoc Nguyen, N. Wu, N. Kausch-Busies, S. Grimbs, K. Sommer, A. Ter Laak, J. Günther, B. Wagner and M. Reutlinger, Best of both worlds: An expansion of the state of the art pK_a model with data from three industrial partners, *Mol. Inf.*, 2024, **43**, e202400088.
49 E. Heid, K. P. Greenman, Y. Chung, S.-C. Li, D. E. Graff, F. H. Vermeire, H. Wu, W. H. Green and C. J. McGill, Chemprop: a machine learning package for chemical property prediction, *J. Chem. Inf. Model.*, 2023, **64**, 9–17.
50 E. P. Serjeant and B. Dempsey, Ionisation constants of organic acids in aqueous solution, *IUPAC Chem. Data Ser.*, 1979, **23**, 160–190.
51 D. D. Perrin, *Dissociation Constants of Organic Bases in Aqueous Solutions*, Franklin Book Company, 1965, vol. 1.
52 D. D. Perrin, *Dissociation Constants of Organic Bases in Aqueous Solutions: Supplement*, Franklin Book Company, 1972, vol. 1.

53 A. M. Slater, The IUPAC aqueous and non-aqueous experimental pK_a data repositories of organic acids and bases, *J. Comput. Aided Mol. Des.*, 2014, **28**, 1031–1034.
54 G. Kortüm, W. Vogel and K. Andrussow, Disssociation constants of organic acids in aqueous solution, *Pure Appl. Chem.*, 1960, **1**, 187–536.
55 K. Izutsu, *Acid-base Dissociation Constants in Dipolar Aprotic Solvents*, Blackwell Scientific Publications Oxford, 1990, vol. 35.
56 Amazon Textract, https://aws.amazon.com/textract/.
57 D. M. Lowe, P. T. Corbett, P. Murray-Rust and R. C. Glen, Chemical name to structure: OPSIN, an open source solution, *J. Chem. Inf. Model.*, 2011.
58 Y. Wang, J. Xiao, T. O. Suzek, J. Zhang, J. Wang and S. H. Bryant, PubChem: a public information system for analyzing bioactivities of small molecules, *Nucleic Acids Res.*, 2009, **37**, W623–W633.
59 S. Kim, P. A. Thiessen, E. E. Bolton, J. Chen, G. Fu, A. Gindulyte, L. Han, J. He, S. He, B. A. Shoemaker, *et al.*, PubChem substance and compound databases, *Nucleic Acids Res.*, 2016, **44**, D1202–D1213.
60 S. Kim, J. Chen, T. Cheng, A. Gindulyte, J. He, S. He, Q. Li, B. A. Shoemaker, P. A. Thiessen, B. Yu, *et al.*, PubChem 2019 update: improved access to chemical data, *Nucleic Acids Res.*, 2019, **47**, D1102–D1109.
61 Chemical Identifier Resolver, https://cactus.nci.nih.gov/chemical/structure, Accessed: 12-1-2025.
62 S. Müller, How to crack a SMILES: automatic crosschecked chemical structure resolution across multiple services using MoleculeResolver, *J. Cheminf.*, 2025, **17**, 117.
63 R. Fraczkiewicz, What, This "Base" Is Not a Base? Common Misconceptions about Aqueous Ionization That May Hinder Drug Discovery and Development, *J. Med. Chem.*, 2025.
64 L. McInnes, J. Healy and J. Melville, UMAP: Uniform manifold approximation and projection for dimension reduction, *arXiv*, 2018, preprint, arXiv:1802.03426, DOI: 10.48550/arXiv.1802.03426.
65 D. E. Graff, N. K. Morgan, J. W. Burns, A. C. Doner, B. Li, S.-C. Li, J. Manu, A. Menon, H.-W. Pang, H. Wu, A. S. Zalte, J. W. Zheng, C. W. Coley, W. H. Green and K. P. Greenman, Chemprop V2: an Efficient, Modular Machine Learning Package for Chemical Property Prediction, *J. Chem. Inf. Model.*, 2025, **66**, 28–33.
66 J. W. Tukey, Comparing individual means in the analysis of variance, *Biometrics*, 1949, 99–114.
67 D. Chmiel, S. Wallan and M. Haberland, tukey_hsd: An accurate implementation of the Tukey honestly significant difference test in Python, *J. Open Source Softw.*, 2022, **7**, 4383.
68 P. Virtanen, R. Gommers, T. E. Oliphant, M. Haberland, T. Reddy, D. Cournapeau, E. Burovski, P. Peterson, W. Weckesser, J. Bright, *et al.*, SciPy 1.0: fundamental algorithms for scientific computing in Python, *Nat. Methods*, 2020, **17**, 261–272.
69 I. Leito, I. Kaljurand, M. Piirsalu, S. Tshepelevitsh, J. W. Zheng, M. Rosés and J.-F. Gal, Acid dissociation constants in selected dipolar non-hydrogen-bond-donor solvents (IUPAC Technical Report), *Pure Appl. Chem.*, 2025.