Prediction of Acid Dissociation Constants of Organic Compounds Using Group Contribution Methods

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Abstract

In this paper, group contribution (GC) property models for the estimation of acid dissociation constants (K_a) of organic compounds are presented. Three GC models are developed to predict the negative logarithm of the acid dissociation constant pK_a: a) a linear GC model for amino acids using 180 data-points with average absolute error of 0.23; b) a non-linear GC model for organic compounds using 1622 data-points with average absolute error of 1.18; c) an artificial neural network (ANN) based GC model for the organic compounds with average absolute error of 0.17. For each of the developed model, uncertainty estimates for the predicted pK_a values are also provided. The model details, regressed parameters and application examples are highlighted.

Keywords: Acid Dissociation Constant, pK_a, Group Contribution Method, Artificial Neural Network, Amino Acids, Organic Compounds

1. Introduction

The acid dissociation constant (K_a) of a compound, which expresses the extent to which the compound in its aqueous solution is dissociated into its ionic form, is sought after by many chemists, biochemists and product formulators. Although experimental measurements would yield the most satisfactory results, it is not always convenient to setup and conduct experiments for K_a determination. This is because the organic compounds that weakly dissociate lack adequate spectral differences in the dissociated and undissociated forms. Besides, in the cases where a compound is unstable or is insufficiently soluble in water, experimental K_a determination is impossible (Tong and Wen, 2008).

The currently available pK_a (negative logarithm of K_a) compilations provide values for only a small fraction of known or possible acids and bases (Perrin, Dempsey and Serjeant, 1981). This motivates the development of advanced pK_a prediction models.

This paper is organized as follows. First, we give a definition on pK_a and highlight its significance in several research areas (Section 1.1). After a brief introduction of the main existing methods for pK_a prediction (Section 1.2), we focus on the powerful group contribution (GC) methods and present more details about these methods in Section 2. Three different GC models are then developed to predict pK_a for amino acids and other classes of organic compounds. The performances of these models are evaluated and compared in Section 3.1. Finally, in Section 3.2, several examples are shown to help the reader in understanding how to apply the developed models for predicting pK_a.

1.1 Definition and Significance of pK_a

In aqueous solution, acids (generically represented by HA) undergo a protolytic reaction with water. This equilibrium reaction is given as:

$$HA + H_2O \leftrightarrow H_3O^+ + A^- \quad (1)$$

The equilibrium constant (in this case, the acid dissociation constant K_a) for the reaction given in Eq. (1) is expressed as Eq. (2), which relates the activity of the dissociated form of the acid (a_{A^-}) to the activity of its undissociated form (a_{HA})

$$K_a = \frac{[a_{H_3O^+}][a_{A^-}]}{[a_{H_2O}][a_{HA}]} \tag{2}$$

As the K_a measurements are generally made in dilute aqueous solutions, the concentration of water remains nearly constant and therefore, its activity can be taken as unity. The general expression of K_a is then derived from Eq. (2), as

$$K_a = \frac{[a_{H3O^+}][a_{A^-}]}{[a_{HA}]} \tag{3}$$

By taking negative logarithm on both sides of Eq. (3) and rearranging the terms, the relation between the pH of the solution and the pK_a of HA can be obtained, given as Eq. (5).

$$-\log(K_a) = -\log([a_{H3O^+}]) - \log\left(\frac{[a_{A^-}]}{[a_{HA}]}\right) \tag{4}$$

$$=> pK_a = pH + \log\left(\frac{[a_{HA}]}{[a_{A^-}]}\right) \tag{5}$$

In the special case, when the activity of HA equals that of A^-, pK_a is identical to pH.

pK_a is very significant in many different areas. For example, during liquid-liquid extraction, when an organic compound is to be separated from an aqueous solution, the undissociated form of the compound usually is more soluble in the organic phase. Hence, the pH of the aqueous phase can be adjusted to its optimum value if the pK_a of the organic compound is known (Green and Perry, 2008). In preparative chemistry, considering the effects of pH on the properties of reactants as well as the possible intermediates and products, conditions for synthesis are selected by making use of pK_a (Perrin, Dempsey and Serjeant, 1981).

1.2 Existing Methods for pK_a Prediction

Nowadays a large number of experimental pK_a data are available, thus one can predict pK_a of new compounds by extrapolating or interpolating the pK_a of database compounds of the same type. Besides this, theoretical calculations and semi-empirical correlations based on thermodynamics and quantum chemical foundations have also been used for pK_a prediction in various works (e.g., Jensen, Swain and Olsen, 2017 use isodemic reactions, where the pK_a is estimated relative to a chemically related reference compound, to make COSMO-based and SMD-based predictions. The pK_a values of 53 amine groups in 48 druglike compounds are computed.)

1.2.1 Linear Free Energy Relationships (LFER)

The Hammett-Taft equation quantifies the electronic effect of organic functional groups (or substituents) on other groups to which they are attached. This equation is a linear free energy relationship (LFER). It is widely used for pK_a prediction (Metzler, 2012) and is as shown in Eq. (6).

$$pK_a = pK_a^0 - \rho \sum \sigma_i \quad (6)$$

where pK_a^0 indicates the pK_a value for unsubstituted reference compounds; σ_i is the substituent constant for the substituent *i;* and ρ is the proportionality constant for the particular equilibrium dissociation reaction i.e. it is the measure of the sensitivity of the reaction to the presence of electron-withdrawing or electron-donating substituents, for example the ρ for phenylacetic acids is 0.49, while that for phenols is 2.23. It should be noted that, currently only a limited number of substituent constants are available, which limits the applicability of the LFER method for pK_a prediction.

1.2.2 Theoretical calculations

There are several first-principle theory based methods for pK_a prediction. The Kirkwood-Westheimer equation (Kirkwood and Westheimer, 1938) quantifies ΔpK_a for a charged or a dipolar substituent as follows,

$$\Delta pK_a = \frac{e\mu cos\phi}{2.3\ kTR^2 D_{eff}} \tag{7}$$

In Eq. (7), ϕ is the angle between the line joining the centre of the ionizing group to the centre of the dipole and the axis of the dipole, e is the electronic charge, k is the Boltzmann constant, T is the temperature in K, μ is the dipole moment, R is the distance between two charges, D_{eff} is the effective dielectric constant. The largest limitation of the Kirkwood-Westheimer method is that it is applicable only to ellipsoidal molecules with point charges at their foci only.

pK_a can also be estimated based on thermodynamic cycles that relate the gas phase to the solution phase, where state-of-the-art quantum chemical techniques coupled with an appropriate solvation model are used (Shields and Seybold, 2013). Jang *et al.* (2001) predicted the pK_a values for a series of 5-substituted uracil derivatives using density functional theory (DFT) calculations in combination with the Poisson-Boltzmann continuum-solvation model (Im, Beglov and Roux, 1998).

Even though theoretical calculations can yield good results in predicting pK_a, these methods are not very attractive for some applications due to their high computational cost. For instance, in drug formulation design, the pK_a of active ingredients (AIs) is a very important property for selecting AIs because the pK_a value indicates the aqueous solubility of the AI and the ability of the AI to permeate through the gastro-intestinal membrane. In order to

perform a fast AI pre-screening, a quick and reliable pK_a prediction method is more preferable than an accurate but very computationally expensive one.

1.2.3 Group contribution based methods

The compounds of the same class usually have small differences in their pK_a values. For example, the pK_a of 1-aminoheptane is 10.67 at 25 °C, which is just slightly lower than the pK_a value of 10.70 for ethylamine. In general, the pK_a of primary amines falls into the range of 10.6 ± 0.2. Also, if the alkyl-chain-substituted amines are compared with cyclic amines, the pK_a is raised by 0.2 units for one ring and 0.3 units for two rings (Perrin, Dempsey and Serjeant, 1981). By employing analogical methods, one can perform pK_a estimations. However, in order to accurately predict pK_a for a certain compound, one needs quite a lot of information about other compounds with similar molecular structures.

As indicated in the three types of prediction methods (see Sections 1.2.1 – 1.2.3), all have certain limitations, which motivates the development of new methods for fast and reliable pK_a predictions. It is also clear that the pK_a value or the degree to which a compound dissociates in its aqueous solution depends mostly on the molecular structure of the compound. This inspires us to develop group contribution (GC) based models that are applicable to all different classes of organic compounds.

1.3 pK_a of Amino acids

Amino acid molecules have at least one acidic group and one basic group. This allows intramolecular acid-base equilibrium reaction resulting in the formation of a dipolar tautomeric ion known as the zwitterion or internal salt (Cheung, 1995). The dissociation of amino acids in aqueous solutions is represented as follows.

$$H_3N^+.R.COOH\ (R^+) + H_2O \rightleftharpoons H_3N^+.R.COO^-(R^\pm) + H_3O^+$$

where $K_{a1} = \frac{[a_{R^{\pm}}][a_{H_3O^+}]}{[a_{R^+}]}$ (8)

and

$$H_3N^+.R.COO^-(R^{\pm}) + H_2O \rightleftharpoons H_2N.R.COO^-(R^-) + H_3O^+$$

where $K_{a2} = \frac{[a_{R^-}][a_{H_3O^+}]}{[a_{R^{\pm}}]}$ (9)

From above, we know that an amino acid typically has at least two dissociation constants with the first one corresponding to the case when the COOH group is deprotonated and the second one corresponding to the case when the H_3N^+ group gets deprotonated in aqueous solution. Considering this unique behaviour, amino acids have been considered separately from other organic compounds in this work in the same way as in our previous GC-based property estimation models for amino acids (Jhamb *et al*. 2018).

2. Methods and Tools used for pK_a Model Development

2.1 Experimental Dataset

In the present study, the first dataset (dataset – 1) comprises experimental pK_a values of 180 amino acids while the second dataset (dataset – 2) contains pK_a values of 1622 organic compounds that are not amino acids. The experimentally measured pK_a values in both datasets are collected from the KT-Consortium database and handbooks containing the dissociation constants of organic compounds (Kortüm, Vogel and Andrussow, 1961; Perrin, 1965). Table 1 provides an overview of the datasets used for developing GC-based pK_a prediction models. The 180 amino acids in dataset – 1 are grouped according to the amino acid type. For instance, totally 13 amino acids including L-Alanine, N-acetyl-L-Alanine, and N-ethyl-L-Alanine are classified into the 'L-Alanine' group. Similarly, the 1622 organic compounds are also classified into several groups.

Table 1: Overview of the datasets used for model development

Dataset – 1		Dataset – 2	
Derivatives of following amino acids	Number of data points (ND)	Classes of organic compounds	Number of data points (ND)
L-Alanine	13	Ethers	3
β-L-Alanine	1	Derivatives of alkanes	6
L-Arginine	1	Amines	253
L-Asparagine	3	Aromatics	161
L-Aspartic acid	2	Carboxylic acids	323
L-Cysteine	9	Sulfonic acids	7
L-Glutamine	1	Nitriles	9
L-Glutamic acid	12	Aldehydes	16
Glycine	23	Amides	61
L-Histidine	8	Sulfonamides	60
L-Isoleucine	2	Alcohols and thiols	105
L-Leucine	6	Ketones	76
L-Lysine	2	Hydrazines	13
L-Methionine	1	Heterocyclic [1 ring, 1 heteroatom]	80
L-Ornithine	2	Heterocyclic [1 ring, 2 heteroatoms]	109
L-Proline	2	Heterocyclic [1 ring, 3 heteroatoms]	2
L-Phenylalanine	10	Heterocyclic [1 ring, 4 heteroatoms]	1
L-Serine	7	Heterocyclic [2 rings, 1 heteroatom]	31
L-Threonine	3	Heterocyclic [2 rings, 2 heteroatoms]	9
L-Tyrosine	10	Heterocyclic [2 rings, 3 heteroatoms]	4
L-Tryptophan	2	Heterocyclic [2 rings, 4 heteroatoms]	5
L-Valine	5	Heterocyclic [3 rings, 1 heteroatom]	12
Aminobenzoic acids	16	Heterocyclic [3 rings, 2 heteroatoms]	3
Aminonaphthalene sulfonic acids	2	Others	273
Aminobenzenesulfonic acids	3		
Aminosulfonic acids	1		
Aminophosphonic acids	4		
Others	29		
Total	180	Total	1622

From Section 1.3, it is known that amino acids generally have at least two groups which can dissociate and hence possess at least two pK_a values correspondingly. Notably, for amino acids with a polar or an electrically charged side chain, there is even a third dissociation constant as well. For example, L-Cysteine has a thiol group (–SH) in its side chain which can also get deprotonated besides the –COOH and $–NH_3^+$ groups.

For the amino acids included in dataset – 1, only the first dissociation constant has been chosen, i.e., the pK_a value corresponding to the deprotonation of the –COOH, $–SO_3H$, or $–PO_3H_2$ group, depending on whether the amino acid is carboxylic, sulphonic, or phosphonic. For amino acid esters where these three groups do not exist, the pK_a associated with the deprotonation of the $–NH_3^+$ group has been chosen.

When developing property models, the experimental dataset is often divided into a training set and a validation set. This approach should not be employed for GC models since the validation set is usually formed by randomly selecting the experimental data points. When some data points (or compounds) are selected for validation, some of the functional groups and model parameters may be excluded for model training, which will thereby limit the application domain of the resulting model. On the other hand, when only a proportion of the experimental data are used for parameter regression, large uncertainties of predicted property values could be resulted (Hukkerikar *et al.*, 2012).

2.2 Group Contribution Methods

Several group contribution (GC) methods have been developed for pure-component property predictions, for instance, Joback and Reid (1987), Lyman *et al.* (1990), Marrero and Gani (2001), Hukkerikar *et al.* (2012) etc. In this work, the Marrero and Gani (MG) GC method, also used previously for amino acids (Jhamb *et al.* 2018) and other organic compounds (Hukkerikar *et al.* 2012), has been used.

In the MG GC method, a multilevel scheme is adopted where the property estimation is performed at three levels. The first level has a large number of simple groups that allow for the representation of a wide variety of organic molecules. The second level of estimation involves groups that can capture the proximity effects and can differentiate among isomers. The third level estimation includes groups that provide a further more detailed description of the molecular structures; hence, this level allows estimation of complex heterocyclic and poly-functional acyclic molecules. The MG GC-model has the form (Marrero and Gani, 2001),

$$f(X) = \sum_i N_i C_i + w \sum_j M_j D_j + z \sum_k O_k E_k \quad (10)$$

Here, the function $f(X)$ is a function of property X. This may contain additional adjustable model parameters (universal constants) depending on the property involved. In Eq. (10), C_i is the contribution of the first-order group of type-i that occurs N_i times. D_j is the contribution of the second-order group of type-j that occurs M_j times. E_k is the contribution of the third-order group of type-k that has O_k occurrences in a component. w and z are weighting factors set to 1 or 0 depending on whether the second and third order groups are used for property prediction or not. Therefore, Eq. (10) is a general model for all the properties and the definition of $f(X)$ is specific for each property X.

In this work, the set of groups proposed for the prediction of physical properties of amino acids by Jhamb *et al.* (2018) to account for zwitterionic structures and the amphoteric nature of amino acids has been used. That is, the pK_a prediction for amino acids in this work makes use of the traditional MG-GC groups along with these newly introduced groups.

2.2.1 Linear GC model

As described by Constantinou and Gani (1994) and later by Marrero and Gani (2001), the selection of an appropriate function *f(X)* has to achieve additivity in the contributions C_i, D_j,

and E_k in order to demonstrate the best possible fit of the experimental data. In addition, the expressions should be able to provide sufficient extrapolating ability and therefore ensure a wide range of applicability.

In this work, a linear property model function was first selected for the prediction of pK_a of amino acids in dataset – 1 and all the other organic compounds in dataset – 2.

$$pK_a - pK_{a0} = \sum_i N_i C_i + w \sum_j M_j D_j + z \sum_k O_k E_k \quad (11)$$

In Eq. (11), pK_a is the negative logarithm of the acid dissociation constant and pK_{a0} is an adjustable model parameter. C_i, D_j, and E_k are group contributions to be regressed. Note that both *w* and *z* are set to 1, which means the second- and third-order groups are also considered in model development.

2.2.2 Nonlinear GC model

Besides the above linear GC model, a 4th-order polynomial GC model was also tested for pK_a prediction, as shown below.

$$a\,(pK_a)^4 + b\,(pK_a)^3 + c\,(pK_a)^2 + pK_a + pK_{a0} = \sum_i N_i C_i + w \sum_j M_j D_j + z \sum_k O_k E_k \quad (12)$$

pK_a is the negative logarithm of the acid dissociation constant; *a*, *b*, *c* and pK_{a0} are adjustable model parameters; C_i, D_j, and E_k are group contributions to be regressed. *w* and *z* are set to 1.

2.2.3 Artificial Neural Network GC model

Artificial Neural Network (ANN)-GC method has been widely used to predict physical, thermodynamic, and transport properties, such as vapor-liquid equilibrium data (Petersen, Fredenslund and Rasmussen, 1994), solubility data (Gharagheizi *et al.*, 2011a), flash point (Gharagheizi, Alamdari and Angaji, 2008) and surface tension (Gharagheizi *et al.*, 2011b). In this work, a very popular ANN architecture (Bishop 1995) comprising of a three-layer feed

forward neural network including an input layer, a hidden layer, and an output layer, is employed as shown in Figure 1. The input layer receives molecular structure information, in this work these are the 144 first-order groups present in the molecule, indicated by the input vector *p* with a size of 144×1. The hidden layer transfers the information received from the input layer and delivers it to the output layer where the pK_a value is predicted.

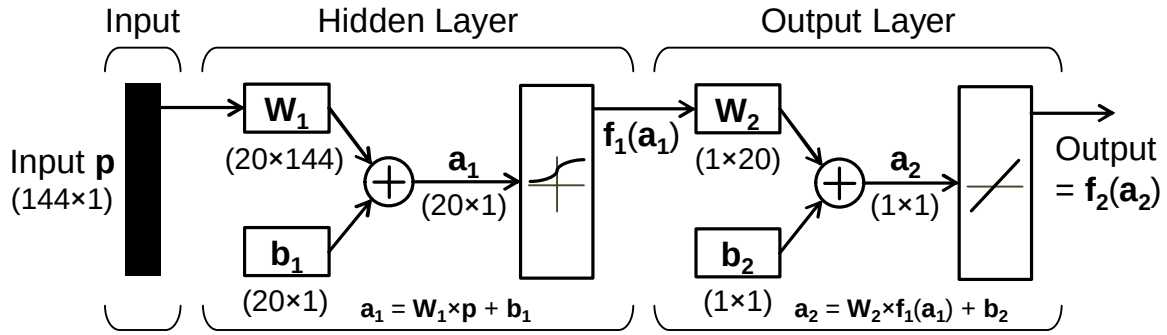


Figure 1: Schematic structure of the employed three-layer artificial neural network (the sizes of weight matrices W_1 and W_2 and bias vectors b_1 and b_2 are given in the brackets)

The number of neurons in the hidden layer, also the number of rows in the weight matrix W_1, is an important adjustable parameter for network training. The selection of this number depends fully on the specific problem being solved. Generally, with too few neurons the network may not be powerful enough for predicting properties. However, with a too large number of neurons, the network tends to perform "over-fitting". In this work, we started to train the ANN with 5 neurons in the hidden layer and gradually increased the number until no significant improvement in the performance of the network (or a desired accuracy) was achieved. By following this procedure, 20 neurons in the hidden layer were finally identified. Therefore, the final three-layer ANN has a 144-20-1 architecture. As illustrated in Figure 1, for a specific compound with a known group composition vector *p*, the output from the hidden layer $f_1(a_1)$ is calculated by Eq. (13) and the output from the output layer $f_2(a_2)$ (i.e., predicted pK_a) is determined by Eq. (14).

$$f_1(a_1) = f_1(W_1 \times p + b_1) \quad (13)$$

$$f_2(a_2) = f_2(W_2 \times f_1(a_1) + b_2) \quad (14)$$

A sigmoid transfer function and a linear transfer function were employed in the hidden layer and in the output layer, respectively. The combination of a sigmoid and a linear transfer function has been shown to be very powerful for building three-layer feed forward neural networks. The mathematical formulations of the employed transfer functions are given as follows.

$$f_1(x) = \frac{1}{1+e^{-x}} \quad (15)$$

$$f_2(x) = x \quad (16)$$

2.3 Parameter Regression and Uncertainty Analysis

The Levenberg–Marquardt optimization algorithm (Levenberg, 1944; Marquardt, 1963) implemented in MATLAB was employed to regress the parameters in the linear and nonlinear GC models. The minimization of the objective function $S(\boldsymbol{P})$, defined as the sum of squares of the difference between the experimental pK_a^{exp} and model predicted pK_a^{pred}, provides the values of unknown parameters $\boldsymbol{P}^*$.

$$S(\boldsymbol{P}) = \sum_{j=1}^{N} (pK_{a_j}^{exp} - pK_{a_j}^{pred})^2 \quad (17)$$

The subscript j indicates the compound and N is the total number of compounds in the dataset.

In the ANN-GC model, there are four fitting parameters, two weight matrices (W_1 and W_2) and two bias vectors (b_1 and b_2). They were obtained by minimizing an objective function, which in this work is the Mean Square Error (MSE) between the output (predicted pK_a) and

the experimental pK_a for all the compounds in the dataset. This optimization process was also performed by using the Levenberg-Marquardt algorithm, which is available in the neural network toolbox of MATLAB.

$$MSE = S(\boldsymbol{P})/N \tag{18}$$

After the estimation of model parameters, uncertainty analysis can be performed to quantify the uncertainties in the predicted property values. The methodology discussed in Hukkerikar *et al.* (2012) is employed to estimate confidence interval of the predicted pK_a at the α_t significance level.

$$pK_{a_{(1-\alpha_t)}}^{pred} = pK_a{}^{pred} \pm \sqrt{diag\left(J(\boldsymbol{P}^*)\, COV(\boldsymbol{P}^*)\, J(\boldsymbol{P}^*)^T\right)} \cdot t\left(v, \frac{\alpha_t}{2}\right) \tag{19}$$

where the Jacobian matrix $J(\boldsymbol{P}^*)$ calculated using $\partial f/\partial \boldsymbol{P}^*$ represents the local sensitivity of the property model f to variations in the estimated parameter values $\boldsymbol{P}^*$. $COV(\boldsymbol{P}^*)$ is the covariance matrix of the estimated model parameters. v is the degrees of freedom (the total number of data points minus the number of unknown parameters). $t\left(v, \frac{\alpha_t}{2}\right)$ is the t-distribution value corresponding to the v degrees of freedom and $\alpha_t/2$ percentile (α_t is 0.05 for 95% confidence interval). The property prediction method can be considered as reliable if the experimental value falls into the calculated confidence interval.

2.4 Statistical Performance Indicators

The evaluation of performance of the developed models is based on the determination of statistical indicators listed in Table 2.

Table 2: Statistical performance indicators used in this work

Indicator	Abbreviation	Formula
Average Absolute Error	AAE	$AAE = \frac{1}{N}\sum_j \left\lvert pK_{a_j}{}^{exp} - pK_{a_j}{}^{pred} \right\rvert$

Coefficient of determination	R^2	$R^2 = 1 - \left[\frac{\sum_j (pK_{a_j}^{exp} - pK_{a_j}^{pred})^2}{\sum_j (pK_{a_j}^{exp} - \mu)^2}\right]$

μ is the average of the experimental pK_a in the dataset

3. Results and Discussions

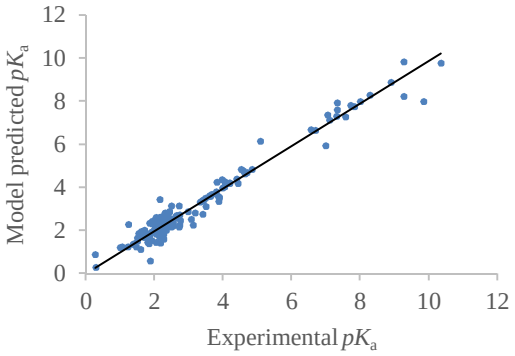
Three GC (linear, nonlinear, and ANN-based) models are developed to predict pK_a for amino acids and other classes of organic compounds. The performances of these models in predicting pK_a are evaluated in Section 3.1. Several examples are shown in Section 3.2 to help the reader in understanding how to apply the developed models for pK_a prediction.

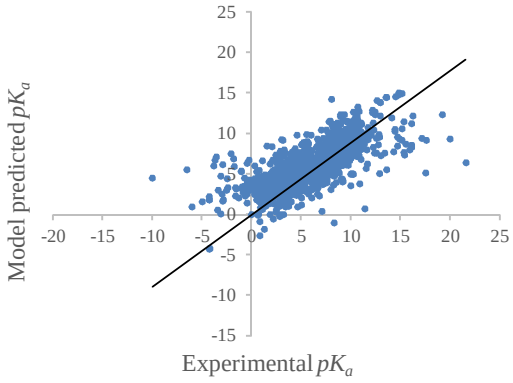
3.1 Model Performances

3.1.1 Linear GC model

The regressed model parameters pK_{a0}, C_i , D_j, and E_k are provided in the Supporting Information. The performance statistics of the developed linear GC model for predicting the pK_a of amino acids in dataset – 1 and the organic compounds in dataset – 2 are given in Table 3.

Table 3: Performance statistics of the developed linear GC model for the two datasets

Method	ND	R^2	Parity Plot	AAE
Linear GC	180 (Dataset – 1)	0.96		0.23

Linear GC	1622 (Dataset – 2)	0.57		1.62

For a clearer illustration, the statistical indicators of the model for different classes of compounds in both datasets have also been provided in Table 4.

Table 4: Statistical indicators of the linear GC model for different classes of amino acids (dataset – 1) and other organic compounds (dataset – 2)

Derivatives of following amino acids	AAE	R^2	Classes of organic compounds	AAE	R^2
L-Alanine	0.20	0.96	Ethers	7.02	-757.92
β-L-Alanine	0.03	--	Derivatives of alkanes	1.18	-3.23
L-Arginine	0.00	--	Amines	1.65	0.61
L-Asparagine	0.15	0.99	Aromatics	1.80	0.91
L-Aspartic acid	0.22	0.98	Carboxylic acids	1.03	0.31
L-Cysteine	0.17	0.99	Sulfonic acids	3.16	-0.16
L-Glutamine	0.74	--	Nitriles	3.45	-0.06
L-Glutamic acid	0.24	0.96	Aldehydes	1.26	0.50
Glycine	0.23	0.95	Amides	2.04	0.37
L-Histidine	0.20	0.99	Sulfonamides	1.46	-0.33
L-Isoleucine	0.12	0.56	Alcohols and thiols	2.29	0.22
L-Leucine	0.31	0.97	Ketones	2.19	0.40
L-Lysine	0.64	0.67	Hydrazines	1.38	0.60
L-Methionine	0.06	--	Heterocyclic [1 ring, 1 heteroatom]	1.74	0.43
L-Ornithine	0.40	0.89	Heterocyclic [1 ring, 2 heteroatoms]	1.50	0.57
L-Proline	0.00	1.00	Heterocyclic [1 ring, 3 heteroatoms]	2.14	0.45
L-Phenylalanine	0.37	0.88	Heterocyclic [1 ring, 4 heteroatoms]	0.09	--
L-Serine	0.11	0.99	Heterocyclic [2 rings, 1 heteroatom]	1.66	-0.05
L-Threonine	0.12	0.48	Heterocyclic [2 rings, 2 heteroatoms]	2.67	-0.32
L-Tyrosine	0.29	0.98	Heterocyclic [2 rings, 3 heteroatoms]	1.31	-1.38
L-Tryptophan	0.00	1.00	Heterocyclic [2 rings, 4 heteroatoms]	1.50	0.46
L-Valine	0.28	0.13	Heterocyclic [3 rings, 1 heteroatom]	1.54	0.42
Aminobenzoic acids	0.21	0.80	Heterocyclic [3 rings, 2 heteroatoms]	2.43	0.97
Aminonaphthalene sulfonic acids	0.32	0.88	Others	1.54	0.57
Aminobenzenesulfonic acids	0.37	0.98			
Aminosulfonic acids	0.00	--			
Aminophosphonic acids	0.09	1.00			
Others	0.26	0.91			

Figure 2 shows the absolute error between the linear-GC-model predicted pK_a and experimental pK_a for the 180 amino acids in dataset – 1. The compounds in dataset – 1 are first sorted according to the ascending order of the absolute error and the error is then plotted as the Y-axis value against the X-axis of 1 to 180. As illustrated, the absolute error in prediction for 158 amino acids is less than 0.5, while for 15 amino acids is between 0.5 and 1.0. Typically, N-substituted amino acids have absolute errors greater than 1.0. The maximum observed absolute error is 1.86 for 3-(dimethylamino) propanoic acid.

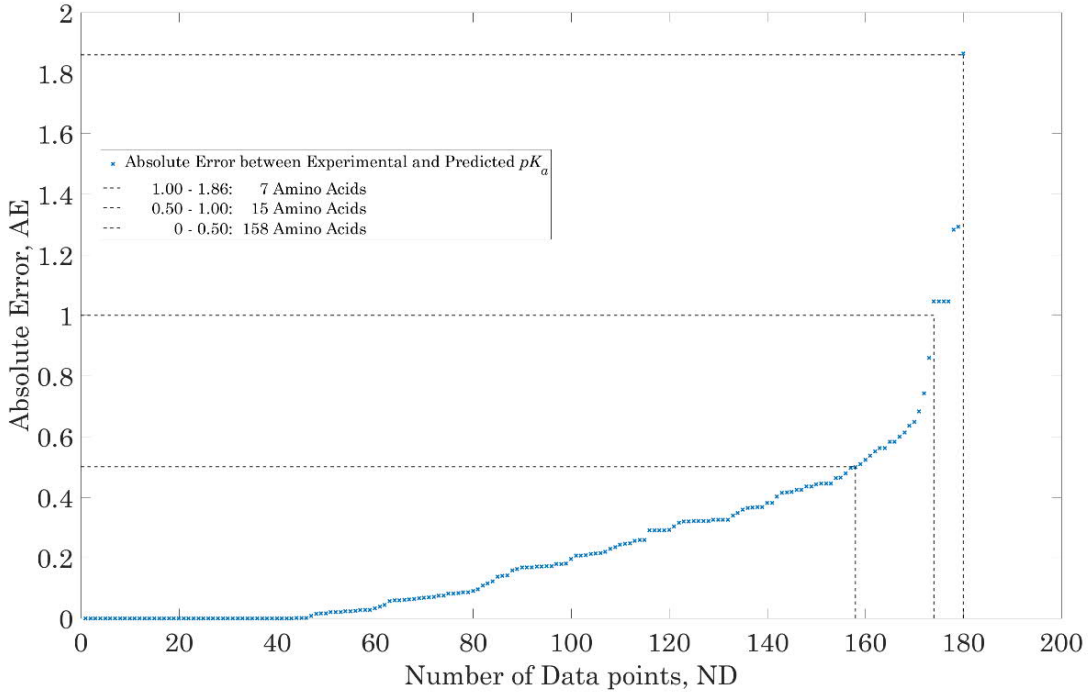


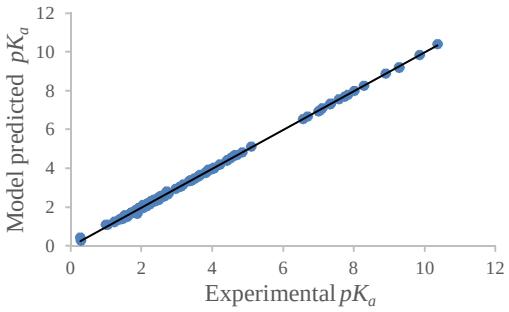
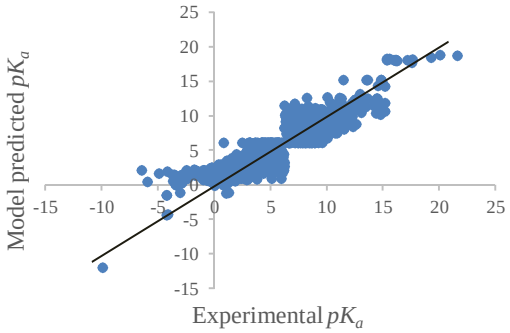
Figure 2: Absolute error between the linear-GC-model predicted pK_a and experimental pK_a for the 180 amino acids in dataset – 1

It can be concluded that the linear GC model shows a high performance in predicting the pK_a for amino acids. However, for the other organic compounds in dataset – 2, a satisfactory prediction cannot be achieved by employing linear GC correlations. In the next section, nonlinear GC models are developed for both datasets.

3.1.2 Nonlinear GC model

The regressed model parameters a, b, c, pK_{a0}, C_i, D_j, and E_k (see Eq. 12) are provided in the Supporting Information. The performance statistics of the developed nonlinear GC model for both datasets are given in Table 5. As can be seen, compared to the linear GC model, a significant improvement in the accuracy of pK_a prediction has been obtained for both datasets.

Table 5: Performance statistics of the developed nonlinear GC model for the two datasets

Method	ND	R^2	Parity Plot	AAE
Nonlinear GC	180 (Dataset – 1)	0.99		0.02
Nonlinear GC	1622 (Dataset – 2)	0.81		1.18

The statistical indicators of the nonlinear GC model for different classes of amino acids (dataset – 1) and organic compounds (dataset – 2) are presented in Table 6. It is seen that the model can accurately predict the pK_a for all kinds of amino acids. However, it is not able to successfully represent the pK_a for some other compounds, for example, the ethers, derivatives of alkanes, and hydrazines. Besides, for heterocyclic compounds with 3 heteroatoms, the model does not perform well either.

Table 6: Statistical indicators of the nonlinear GC model for different classes of amino acids (dataset – 1) and other organic compounds (dataset – 2)

Derivatives of following amino acids	AAE	R^2	Classes of organic compounds	AAE	R^2
L-Alanine	0.01	1.00	Ethers	3.16	-153.92
β-L-Alanine	0.03	--	Derivatives of alkanes	0.69	0.19
L-Arginine	0.00	--	Amines	1.12	0.79
L-Asparagine	3.97×10^{-3}	0.99	Aromatics	1.59	0.66
L-Aspartic acid	0.02	0.99	Carboxylic acids	0.88	0.57
L-Cysteine	0.03	1.00	Sulfonic acids	1.94	0.65
L-Glutamine	0.04	--	Nitriles	2.31	0.70
L-Glutamic acid	0.02	1.00	Aldehydes	0.88	0.90
Glycine	0.04	1.00	Amides	1.06	0.85
L-Histidine	0.02	1.00	Sulfonamides	1.00	0.42
L-Isoleucine	0.02	0.89	Alcohols and thiols	1.15	0.83
L-Leucine	0.02	1.00	Ketones	1.13	0.87
L-Lysine	0.03	1.00	Hydrazines	1.72	0.38
L-Methionine	3.00×10^{-3}	--	Heterocyclic [1 ring, 1 heteroatom]	1.61	0.69
L-Ornithine	0.03	0.99	Heterocyclic [1 ring, 2 heteroatoms]	1.41	0.68
L-Proline	0.06	1.00	Heterocyclic [1 ring, 3 heteroatoms]	2.13	0.56
L-Phenylalanine	0.08	1.00	Heterocyclic [1 ring, 4 heteroatoms]	1.59	--
L-Serine	0.04	1.00	Heterocyclic [2 rings, 1 heteroatom]	1.40	0.54
L-Threonine	0.02	0.99	Heterocyclic [2 rings, 2 heteroatoms]	1.67	0.46
L-Tyrosine	0.01	1.00	Heterocyclic [2 rings, 3 heteroatoms]	1.74	-2.60
L-Tryptophan	0.00	0.99	Heterocyclic [2 rings, 4 heteroatoms]	0.51	0.94
L-Valine	0.02	0.99	Heterocyclic [3 rings, 1 heteroatom]	0.99	0.79
Aminobenzoic acids	0.01	1.00	Heterocyclic [3 rings, 2 heteroatoms]	1.05	0.83
Aminonaphthalene sulfonic acids	0.04	0.99	Others	1.09	0.78
Aminobenzenesulfonic acids	0.00	1.00			
Aminosulfonic acids	0.02	--			
Aminophosphonic acids	0.04	1.00			
Others	1.30×10^{-3}	1.00			

Figure 3 shows the absolute error between the nonlinear-GC-model predicted pK_a and experimental pK_a for the 1622 organic compounds in dataset – 2. As indicated, the absolute error of 507 compounds is less than 0.5 and that of 351 compounds falls into the range of 0.5

to 1.0. 300 compounds have the error larger than 2.0 and the maximum observed absolute error is 8.69.

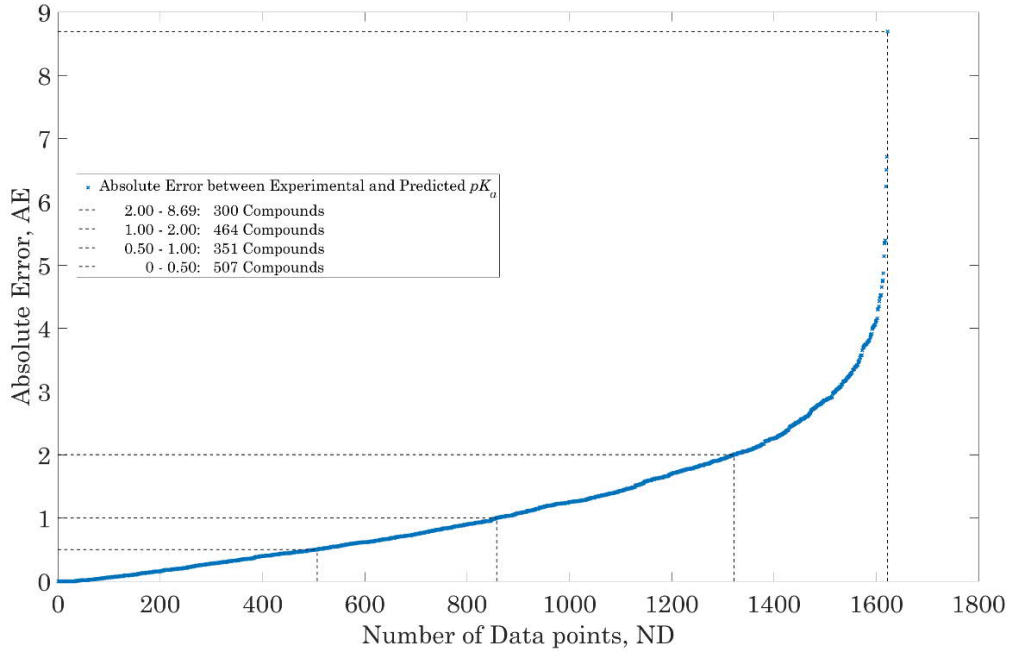


Figure 3: Absolute error between the nonlinear-GC-model predicted pK_a and experimental pK_a for the 1622 organic compounds in dataset – 2

It can be concluded that the nonlinear GC model performs very well in predicting pK_a for amino acids. However, the accuracy of the model for estimating pK_a of the other 1622 organic compounds still needs to be improved.

3.1.3 ANN-GC model

The ANN-GC model has been developed for predicting pK_a of the 1622 organic compounds in dataset – 2. The regressed parameters W_1, W_2, b_1, and b_2 are provided in Table S4 of the Supporting Information. The overall model performance and the performance indicators for different classes of compounds are shown in Table 7 and Table 8, respectively.

Table 7: Performance statistics of the developed ANN-GC model for dataset – 2

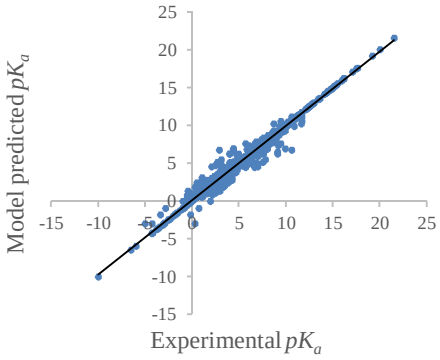
Method	ND	R^2	Parity Plot	AAE
ANN-GC	1622 (Dataset – 2)	0.98		0.17

Table 8: Statistical indicators of the ANN-GC model for different classes of organic compounds in dataset – 2

Classes of organic compounds	AAE	R^2
Ethers	1.12×10^{-6}	1.00
Derivatives of alkanes	2.57×10^{-6}	1.00
Amines	0.24	0.98
Aromatics	0.28	0.98
Carboxylic acids	0.13	0.96
Sulfonic acids	1.62×10^{-6}	1.00
Nitriles	0.28	0.99
Aldehydes	0.27	0.98
Amides	0.13	0.99
Sulfonamides	0.14	0.79
Alcohols and thiols	0.07	0.99
Ketones	0.12	0.99
Hydrazines	5.68×10^{-6}	1.00
Heterocyclic [1 ring, 1 heteroatom]	0.31	0.97
Heterocyclic [1 ring, 2 heteroatoms]	0.27	0.96
Heterocyclic [1 ring, 3 heteroatoms]	1.57×10^{-6}	1.00
Heterocyclic [1 ring, 4 heteroatoms]	1.15×10^{-8}	--
Heterocyclic [2 rings, 1 heteroatom]	0.44	0.90
Heterocyclic [2 rings, 2 heteroatoms]	0.46	0.93
Heterocyclic [2 rings, 3 heteroatoms]	1.83×10^{-6}	1.00
Heterocyclic [2 rings, 4 heteroatoms]	1.57×10^{-6}	1.00
Heterocyclic [3 rings, 1 heteroatom]	0.99	0.76
Heterocyclic [3 rings, 2 heteroatoms]	0.51	0.92
Others	0.01	0.99

Figure 4 shows the absolute error between the ANN-GC-model predicted pK_a and experimental pK_a for the 1622 organic compounds in dataset – 2. As seen, 89% of the 1622 compounds have absolute errors less than 0.5 and about 95% have absolute errors less than 1.0. The absolute error plot together with the estimated performance statistics indicates that the developed ANN-GC model can well represent the pK_a of the organic compounds.

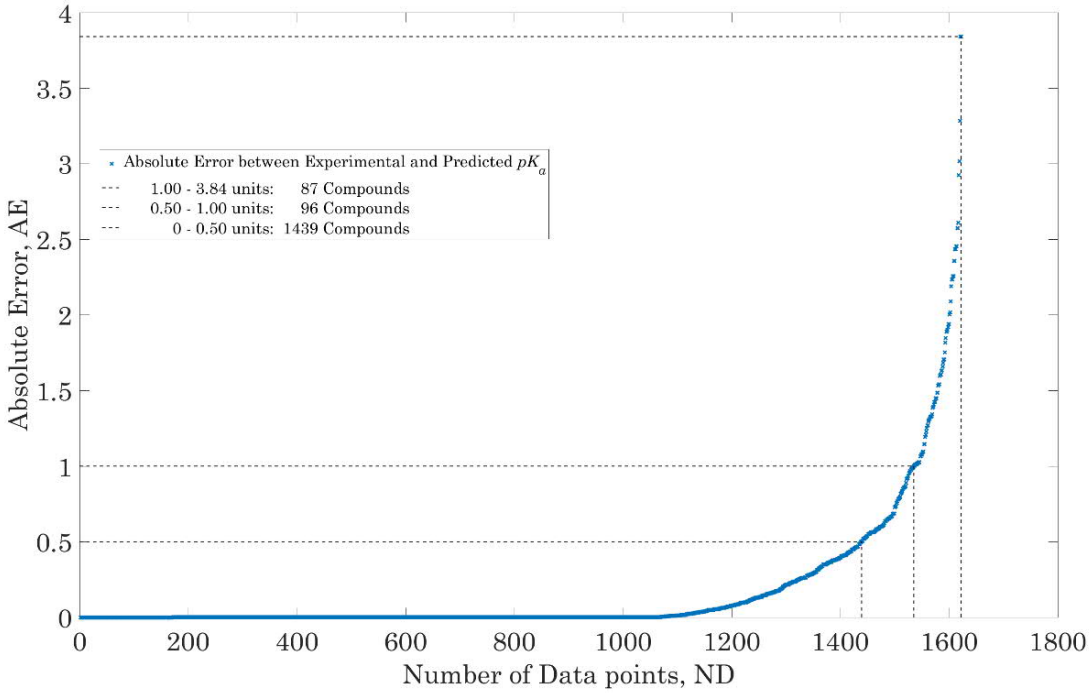


Figure 4: Absolute error between the ANN-GC-model predicted pK_a and experimental pK_a for the 1622 organic compounds in dataset – 2

3.2. Application Examples

In this section, three examples are provided where the linear GC model, nonlinear GC model, and ANN-GC model are employed to predict pK_a. The non-linear model for amino acids and the ANN-GC model for organic compounds will be available in ProPred (a property prediction tool within ICAS (Gani *et al.*, 1997). The examples given below are from a prototype of ProPred.

3.2.1 Prediction of pK_a using the linear and non-linear GC models (amino acids)

Since the linear and non-linear GC model performs well for amino acids only, an example for the prediction of pK_a of N-Acetyl L-Alanine is shown in Table 9.

Table 9: Prediction of pK_a for N-Acetyl L-Alanine (CAS: 97-69-8) using the linear and non-linear GC models

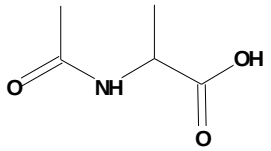
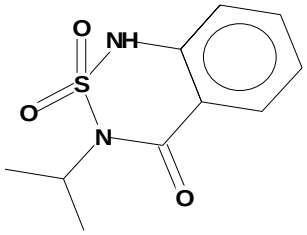
Compound: N-Acetyl L-Alanine Molecular formula: $C_5H_9NO_3$		**Molecular structure** 	
First-order groups	**Occurrences (N_i)**	**Group contribution (C_i)**	
		Linear Model	*Non-linear Model*
CH_3	2	0.3417	0.0194
CH	1	-0.3425	-0.0336
COOH	1	1.4441	-0.0912
NHCO	1	0.4817	0.0277
Second-order groups	**Occurrences (M_j)**	**Group contribution (D_j)**	
		Linear Model	*Non-linear Model*
$CH_m(NH_n)$-COOH (m, n in 0..2)	1	-2.8272	0.1457
Third-order groups	**Occurrences (O_k)**	**Group contribution (E_k)**	
		Linear Model	*Non-linear Model*
O=C-NH-CH_n-COOH (n in 0…2)	1	0.1240	-0.0482

Table 9 lists the number of occurrences and the contribution of first-order, second-order, and third-order groups present in the N-Acetyl L-Alanine molecule. According to Eq. (11) where pK_{a0} = 3.0683, the predicted pK_a of N-Acetyl L-Alanine is 2.63. According to Eq. (19), the calculated 95% confidence interval of the estimated pK_a is 1.79. It can be observed that the experimental pK_a (2.34) falls in the range of [0.84, 4.42], which indicates the reliability of the model. On the other hand, according to Eq. (12) where pK_{a0} = -1.0206, a = -0.0016, b = 0.0393 and c = -0.3250, the predicted pK_a for N-Acetyl L-Alanine is 2.38 which implies that in the case of amino acids both the linear and non-linear GC model have a good performance.

3.2.2 Prediction of pK_a using the nonlinear GC model for Bentazon (CAS: 25057-89-0)

In order to illustrate the pK_a prediction using the nonlinear GC model, an example with 1H-2,1,3-Benzothiadiazin-4(3H)-one, 3-(1-methylethyl)-2,2-dioxide, which is used as a herbicide, is shown in Table 10.

Table 10: Prediction of pK_a for 1H-2,1,3-Benzothiadiazin-4(3H)-one, 3-(1-methylethyl)-2,2-dioxide (CAS: 25057-89-0) using the nonlinear GC model

Compound:	**Molecular structure**
1H-2,1,3-Benzothiadiazin-4(3H)-one, 3-(1-methylethyl)-2,2-dioxide Molecular formula: $C_{10}H_{12}N_2O_3S$	

First-order groups	**Occurrences (N_i)**	**Group contribution (C_i)**
CH_3	2	0.1322
CH	1	-0.0182
aCH	4	0.0869
aC fused with non-aromatic ring	2	-0.6176
NH (cyc)	1	0.4334
N (cyc)	1	0.1982
CO (cyc)	1	0.2178
SO_2 (cyc)	1	0.4380
Second-order groups	**Occurrences (M_j)**	**Group contribution (D_j)**
$(CH_3)_2CH$	1	-0.0544
Third-order groups	**Occurrences (O_k)**	**Group contribution (E_k)**
aC-CO_{cyc} (fused rings)	1	0.1754
aC-NH_{ncyc} (fused rings) (n in 0..1)	1	0.2404
AROM.FUSED[2]	1	-0.2189

According to Eq. (12), the predicted pK_a is 2.47
(where, a = 3.759×10^{-4}, b = −0.0072, c = −0.0431, pK_{a0} = −1.3231)
The experimental pK_a is 2.92. Hence, the absolute deviation is 0.45.

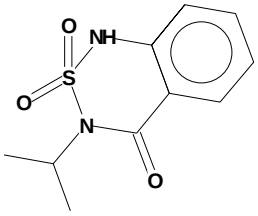
3.2.3 Prediction of pK_a using the ANN-GC model for Bentazon (CAS: 25057-89-0)

To compare the ANN-GC model with the nonlinear GC model, the pK_a prediction for the same compound, 1H-2,1,3-Benzothiadiazin-4(3H)-one, 3-(1-methylethyl)-2,2-dioxide is shown in Table 11.

Table 11: Prediction of pK_a for 1H-2,1,3-Benzothiadiazin-4(3H)-one, 3-(1-methylethyl)-2,2-dioxide (CAS: 25057-89-0) using the ANN-GC model

Compound:
1H-2,1,3-Benzothiadiazin-4(3H)-one, 3-(1-methylethyl)-2,2-dioxide
Molecular formula: $C_{10}H_{12}N_2O_3S$

Molecular structure



First-order groups	CH_3	CH	aCH	aC	NH(cyc)	N(cyc)	CO(cyc)	SO_2 (cyc)
Occurrences	2	1	4	2	1	1	1	1
	W_1							
	[-1.6829	6.4756	1.7533	0.7377	0.443	0.9212	2.6333	-0.1755
	1.0509	-0.2184	-2.1471	-1.2136	1.4681	0.8396	-1.0455	7.3758
	3.619	-2.4328	1.6553	2.1358	-0.222	-1.2836	-6.3658	1.3176
	4.7908	-4.4383	0.8453	1.6746	-0.3299	-2.5009	3.159	-0.1221
	0.8226	1.2565	0.5366	-0.1923	0.1443	-6.606	-0.5895	0.6971
	2.7329	6.3506	2.4439	5.4217	-4.8977	1.3109	-5.2433	0.7122
	-8.9644	-19.3123	11.4152	2.9152	-17.5028	5.2274	10.238	-8.6289
	0.8619	0.5316	-3.2969	3.7527	11.7938	-1.2256	-5.6679	-5.3864
	1.1437	-2.4476	0.1281	1.5644	1.1092	10.2064	0.2857	0.1515
	-0.6423	0.226	-1.544	0.1394	5.3677	-0.5433	-2.6248	4.8043
	1.1433	-2.3074	1.388	2.2463	2.8746	1.9733	-0.0806	3.7311
	4.6161	2.011	-3.8926	4.5683	-6.1653	-13.1146	-1.5625	7.5796
	2.7842	-1.8139	-1.0137	-0.2305	-5.2968	-1.779	2.0042	0.471
	2.9091	-3.0596	0.6423	-1.0794	-0.5082	1.0108	1.4972	6.0197
	-5.2623	6.3213	-4.5124	-0.5687	-2.2154	11.0957	0.5727	9.6914
	-0.0379	2.157	1.4917	-0.9739	2.458	5.8252	0.2285	5.0562
	6.3547	6.897	0.7735	-2.2172	-3.7028	1.37	10.668	1.3711
	-3.5484	20.4593	2.7547	9.418	6.3029	3.7152	8.6495	3.7617
	3.0958	-13.0759	3.5244	-5.4662	13.0565	-12.2072	2.812	3.5092
	5.4879	-5.8329	-0.0789	2.5132	-8.8739	5.0805	-4.625	-0.7204]

b_1	**Transformation of W_2**	b_2
-15.6497	11.2478	-2.3479
1.5128	-15.9438	
-15.1206	-6.0101	
-3.8606	-14.6460	
-8.8757	-12.7365	
-24.9630	8.3284	
9.1079	-9.0066	
13.3214	9.7666	
6.9750	-15.2921	
-1.2177	-12.5122	
-3.5163	17.6801	
11.6018	5.2121	
-1.5351	18.8958	
1.6159	13.7597	
9.8148	5.9600	
-4.6202	-18.6921	
4.1303	17.3304	
0.1458	6.0333	
-18.9379	6.0589	
27.8468	-5.7745	

Input variable $\boldsymbol{p}$ = [2 1 4 2 1 1 1 1]' (the zero elements are removed). By following Eqs. (13-16), pK_a^{pred} = 2.9211. The experimental value of pK_a is 2.92. Hence, the absolute deviation is 0.0011.

Two more examples for pK_a prediction using the nonlinear GC model and the ANN-GC model can be found in the supporting information (Tables S6 – S7).

4. Conclusion

The prediction of acid dissociation constant (K_a) is very significant in many areas. In this work, three GC property models have been developed and tested for the estimation of the pK_a of organic compounds including amino acids. The linear GC model has a good performance (R^2 = 0.96, AAE = 0.23) only for amino acids. For the other classes of compounds, a nonlinear GC model and an ANN-GC model have been developed. The nonlinear GC model has a moderate prediction quality (R^2 = 0.81, AAE = 1.18) whereas the ANN-GC model gives a much better estimation (R^2 = 0.98, AAE = 0.17).

The developed models enable fast and preliminary pK_a estimations in the cases where the experimental measurements are difficult or not feasible. Currently, these models are being incorporated into a computer-aided molecular design framework to identify and analyse promising molecules with desirable properties.

References

1. Bettelheim, F., Brown, W., Campbell, M., Farrell, S., 2007. *Introduction to Organic and Biochemistry*. Belmont CA: Thomson Brooks/Cole.
2. Bishop, C.M., 1995. Neural Networks for Pattern Recognition. Oxford University Press.
3. Cheung, E., 1995. *Substituent Effects on the Tautomerization of Amino Acids*. Master of Science. Texas Tech University.
4. Gani R., Hytoft G., Jaksland C., Jensen A.K., 1997. An integrated computer aided system for integrated design of chemical processes. *Computers Chemical Engineering* 21(10), 1135–1146
5. Gharagheizi, F., Eslamimanesh, A., Mohammadi, A.H., Richon, D., 2011a. Representation/prediction of solubilities of pure compounds in water using artificial neural network− group contribution method. *Journal of Chemical & Engineering Data* 56(4), 720-726.
6. Gharagheizi, F., Alamdari, R.F., Angaji, M.T., 2008. A new neural network − group contribution method for estimation of flash point temperature of pure components. *Energy & Fuels* 22(3), 1628-1635.
7. Gharagheizi, F., Eslamimanesh, A., Mohammadi, A.H., Richon, D., 2011b. Use of artificial neural network-group contribution method to determine surface tension of pure compounds. *Journal of Chemical & Engineering Data* 56(5), 2587-2601.
8. Green, D., Perry, R., 2008. *Perrys's Chemical Engineers' Handbook*. 8th ed. New York: McGraw-Hill.
9. Hukkerikar, A.S., Sarup, B., Kante, T.A., Abildkov, J., Sin, G., Gani, R., 2012. Group-contribution+ (GC+) based estimation of properties of pure components: Improved property estimation and uncertainty analysis, *Fluid Phase Equilibria* 321, 25–43

10. Hukkerikar, A.S., Kalakul, S., Sarup, B., Young, D.Y., Sin, G., Gani, R., 2012. Estimation of environment-related properties of chemicals for design of sustainable processes: development of group-contribution+ (GC+) property models and uncertainty analysis. *Journal of Chemical Information and Modeling* 52(11), 2823-2839
11. Hukkerikar, A.S., Meier, R.J., Gani, R., 2013. A method to estimate the enthalpy of formation of organic compounds with chemical accuracy. *Fluid Phase Equilibria* 348, 23-32.
12. Im, W., Beglov, D. and Roux, B., 1998. Continuum solvation model: Computation of electrostatic forces from numerical solutions to the Poisson-Boltzmann equation. *Computer Physics Communications*, 111, 59-75.
13. Jang, Y., Sowers, L., Çağin, T., Goddard, W., 2001. First Principles Calculation of pKa Values for 5-Substituted Uracils. *The Journal of Physical Chemistry A* 105(1), 274-280.
14. Jensen, J., Swain, C., Olsen, L., 2017. Prediction of pKa Values for Druglike Molecules Using Semiempirical Quantum Chemical Methods. *The Journal of Physical Chemistry A* 121(3), 699-707.
15. Jhamb, S., Liang, X., Gani, R., Hukkerikar, A., 2018. Estimation of physical properties of amino acids by group-contribution method. *Chemical Engineering Science* 175, 148-161.
16. Kirkwood, J. and Westheimer, F., 1938. The electrostatic influence of substituents on the dissociation constants of organic acids. I. *The Journal of Chemical Physics* 6(9), 506-512.
17. Kortüm, G., Vogel, W., Andrussow, K., 1961. *Dissociation Constants of Organic Acids in Aqueous Solution*. London: Butterworths.
18. Levenberg, K., 1944. A method for the solution of certain non-linear problems in least squares. *Quarterly of Applied Mathematics* 2(2), 164-168.

19. Marquardt, D., 1963. An algorithm for least-squares estimation of nonlinear parameters. *Journal of the Society for Industrial and Applied Mathematics* 11(2), 431-441.
20. Marrero, J., Gani, R., 2001. Group-contribution based estimation of pure component properties. *Fluid Phase Equilibria* 183-184, 183-208.
21. Marrero, J., Gani, R., 2002. Group-contribution-based estimation of octanol/water partition coefficient and aqueous solubility. *Industrial & Engineering Chemistry Research* 41(25), 6623-6633.
22. Metzler, D., 2012. Chapter 3: Energetics of Biochemical Reactions. In: *Biochemistry: The Chemical Reactions of Living Cells, Volume 1*. New York, USA: Academic Press Inc., 176 - 178.
23. Peck, T., Hill, S., 2014. *Pharmacology for Anaesthesia and Intensive Care*. Cambridge University Press.
24. Perrin, D., 1965. *Dissociation Constants of Organic Bases in Aqueous Solution*. London: Butterworth.
25. Perrin, D., Dempsey, B., Serjeant, E., 1981. *pK_a Prediction for Organic Acids and Bases.* London: Chapman & Hall.
26. Petersen, R., Fredenslund, A., Rasmussen, P., 1994. Artificial neural networks as a predictive tool for vapor-liquid equilibrium. *Computers & Chemical Engineering* 18, S63-S67.
27. Shields, G.C., Seybold, P.G., 2013. *Computational Approaches for the Prediction of pKa Values*. Boca, Raton, Florida: CRC Press.
28. Tong, W., Wen, H., 2008. Preformulation Aspects of Insoluble Compounds. In: R. Liu, ed., *Water-Insoluble Drug Formulation*, 2nd ed. Boca, Raton, Florida: CRC Press, 62-87.