

QSPR modelling of potentiometric $\text{HCO}_3^-/\text{Cl}^-$ selectivity for polymeric membrane sensors [†]

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Abstract: Since the development process of new sensors is long and tedious, it would be very helpful to develop a model that could predict sensor properties based on active compound structure without real synthesis and characterization of the corresponding sensors. In this work, the model for prediction of $\log K(\text{HCO}_3^-/\text{Cl}^-)$ was constructed based on 40 ligand structures suggested in literature for carbonate sensing. Substructural Molecular Fragments (SMF) were used to describe the structure of compounds, where fragments were considered as sequences of bonds and atoms. The Projection on Latent Structures (PLS) method was used to calculate the regression model. The obtained model was tested in prediction of selectivity of newly synthesized ligands.

Keywords: membrane sensor; carbonate ionophore; QSPR; PLS

1. Introduction

Polymeric membrane electrodes offer numerous advantages and their properties can be tuned in a wide range by modification of membrane composition. However, the process of selection of an appropriate ligand to construct the sensor for particular task is time consuming and requires ligand synthesis, sensor preparation and characterization. It would be very helpful for researchers to make a model that allows prediction of sensor properties of an electrode based on the structure of the employed ionophore.

Using the computational chemistry, different characteristics of chemical compounds can be predicted. Quantitative relations between physical or chemical properties of organic compounds and their chemical structures can be set with QSPR (Quantitative Structure Property Relationship). This methodology is widely applied nowadays, e.g. in pharmaceutical investigations, specifically, a search of new drugs [1]. There are QSPR models for various materials such as nanomaterials [2], catalysts [3], ionic liquids [4]. Recently an application of QSPR for predicting the sensor properties of membrane electrodes was suggested [5]. It was possible to relate the structure of the organic ligand with the selectivity constant of corresponding membrane sensor for Ca/Mg.

This study aims to expand this approach to anion-selective sensors where ligand selection is much more challenging than in case of metal cations, due to a wide variability of geometries of inorganic ligands and their hydrolysis in case of weak acids.

Amongst anions there are ones with important biological industrial roles. The example of such anions is carbonate anion. Therefore, it is important object for making a predicting selectivity to carbonate against chloride anions QSPR model.

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2. Materials and methods

2.1. Dataset

The dataset of 40 samples was composed with literature sources and experimental data. The summary table with compositions of all samples and literature sources can be found in the supplementary. Whereas the number of anions' (especially carbonate anion's) ionophores are small in consequence of the reasons that we have already discussed earlier, there are a few articles about carbonate ionophores. A great part of data was extracted from IUPAC review "POTENTIOMETRIC SELECTIVITY COEFFICIENTS OF ION-SELECTIVE ELECTRODES" with summary table of anions existing in 2002 [6]. Considering the significant shortage of carbonate ionophores, we had to add in table ionophores with Cl/HCO₃ selectivity that are converted to HCO₃/Cl selectivity according to Nikolsky-Eisenman equation:

$$E = E_I^0 + \frac{RT}{z_I F} \ln(a_I + \sum K_{IJ} a_J^{z_I/z_J}). \quad (1)$$

All of the structures of ionophores are available in Table S1 in Supplementary.

We also assured that all this data was obtained in the narrow range of pH (7.0-8.6) for understanding which ion prevailed in solution examined.

All the membranes described in literature are based on polyvinylchloride (PVC) as polymer. In contrast, there are three plasticizers: nitrophenyl octyl ether (NPOE), dioctyl adipate (DOA) and dioctyl sebacate (DOS), that is also known as bis(2-ethylhexyl) sebacate (BEHS). Ion-exchanger is tridodecylmethylammonium (TDMA) with Cl⁻ or NO₃⁻ as anions.

Due to a small number of carbonate ionophores examined we had to compile the resulting database with membranes that differ in not only ionophores but plasticizers. We took different plasticizers into account and added their dielectric constant (is also known as relative permittivity) as a descriptor for adjusting our model and making it more comprehensive.

The selectivity coefficients of these ionophores varied from -5.8 to 6.2 in the logarithmic scale. The average selectivity logK (HCO₃/Cl) was -1.425 and the median value was -2.6.

2.2. Descriptors

We used Substructural Molecular Fragments (SMF) for encoding molecular structures in a matrix. A molecular structure can be described with this method by dividing the molecule into all possible fragments and writing the number of these fragments into matrix. These SMF were obtained by using "ISIDA QSPR" software [7]. There are two approaches for obtaining a molecule's SMF in ISIDA: sequences of atoms and/or bonds (topological path) and selected ("augmented") atom (atom-centered fragments) with its environment that can be atoms, bonds or both of them (Fig.1). In this work, atom and bond sequences were applied. A molecule was represented as a graph and its descriptors were, consequently, subgraphs.

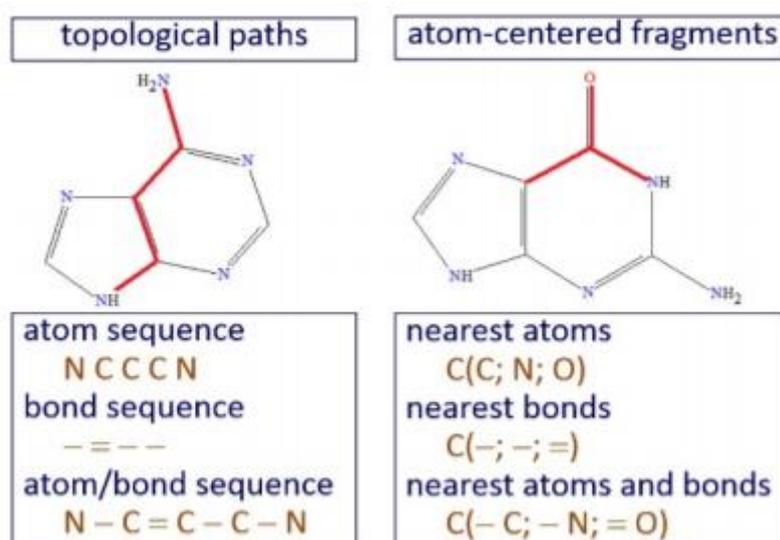


Figure 1. Two approaches of obtaining ISIDA SMF: topological path (left) and atom-centered fragments (right) [7].

Hence ISIDA SMF descriptors are numbers of fragments (or subgraphs) in a molecule with each element of the descriptor associated with one of the detected possible fragments. Only the shortest paths from one atom to the other were used. It should be noted that the length of sequences is limited. The minimal and the maximal lengths are, respectively, 2 and 15.

2.3. Projection on Latent Structures (PLS) modelling.

In order to relate molecular descriptors of ligands with selectivity coefficients of corresponding sensors we employed PLS regression algorithm. PLS regression searches for a set of components known as latent vectors that performs a synchronous decomposition of X and Y with the clause that these components explain as much as possible of the covariance between X and Y. Data matrix size was 40×1855 , where 40 is a number of samples and 1855 is a number of individual models.

3. Results and Discussion

The molecular descriptors obtained for the chosen ligands were calculated with ISIDA QSPR software [7]. The 40 ionophore structures and their properties, specifically, substructural molecular fragments (SMF) and permittivity of membranes were used as descriptors. The PLS model relating the descriptors with selectivity was evaluated according to the following parameters: root mean square error (RMSE) and squared determination coefficient (R^2). The result of QSPR modelling are shown in Figure 2. Each point in the graph corresponds to an item in the database, whereas straight lines represent the resulting models. Blue and red colours correspond to training and test samples, respectively.

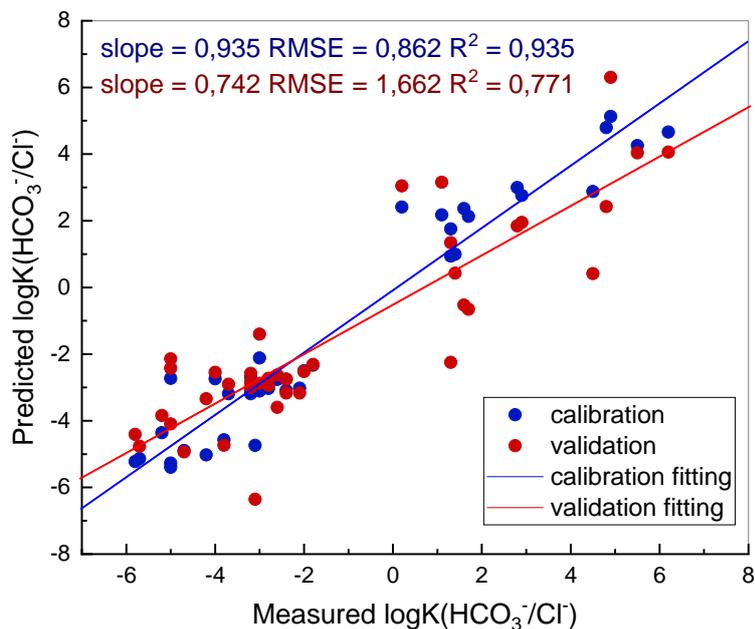


Figure 2. “Measured vs predicted” plot for QSPR model for predicting selectivity of membrane sensors.

It can be seen, that the derived model allows semi-quantitative estimation of the selectivity coefficients based on the ligand structure. As far as each compound is an individual molecule, which is consisted of variety of molecular fragments, regressions coefficients allow evaluating the contribution of each fragment (represented as an independent variable in the matrix) in selectivity of the sensors. The largest coefficients signify variables (in this case, SMF that are encode fragments of molecules) with the most important impact. The fragments with the largest contribution in absolute value of the selectivity $\log K(\text{HCO}_3/\text{Cl})$ of potentiometric membrane sensors are shown in Figure 3.

As follows from the graph, the fragment $\text{C}=\text{C}-\text{C}=\text{C}-\text{C}-\text{F}$ makes the largest negative contribution and it is part of a longer fragment $\text{C}-\text{C}=\text{C}-\text{C}=\text{C}-\text{C}-\text{C}-\text{F}$ with a smaller contribution. The shortest fragment with negative contribution $\text{C}-\text{C}=\text{C}-\text{C}=\text{C}$ is included in the remaining fragments with the largest negative contribution. The fragment with positive contribution $\text{C}=\text{C}-\text{C}=\text{C}-\text{Hg}$ contains mercury in its composition. These observations give a valuable information for further design of the ligands with required selectivity.

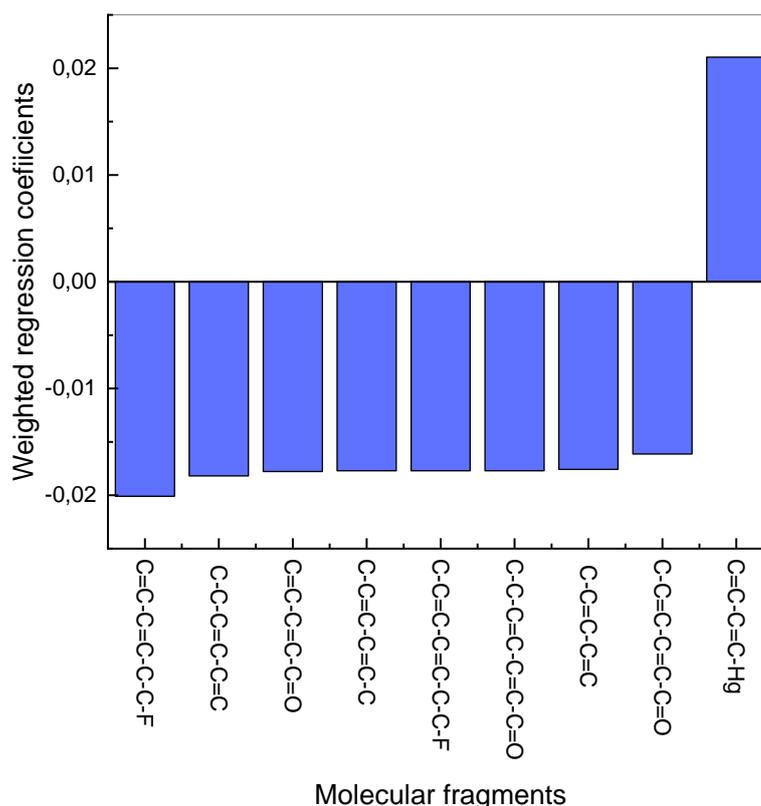


Figure 3. Fragments with the largest contribution in $\log K$ ($\text{HCO}_3^-/\text{Cl}^-$) values, where ‘-’ is a single bond and ‘=’ is a double bond.

4. Conclusions

Despite some problems with anions’ ionophores that are more fully described earlier in introduction we were able to collect the database with satisfying RMSE and R^2 for relatively small amount of data. We found the fragments with the highest impact in selectivity $\log K$ ($\text{HCO}_3^-/\text{Cl}^-$) of potentiometric membrane sensors and we believe that this will help in the future search for the new ionophores. It appears that semi-quantitative prediction of sensor selectivity is possible based on the ligand structure.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Table S1: QSPR modelling of potentiometric $\text{HCO}_3^-/\text{Cl}^-$ selectivity for polymeric membrane sensors supporting information.

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