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QSPR Modeling for Predicting Sensitivity of Membrane Sensors Based on Modified Diphenylphosphoryl Acetamide Ionophores †

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Abstract: Given the complexity and time-consuming nature of discovering effective ionophores for potentiometric sensors, a model that could predict sensor attributes based on ionophore structure without the exhaustive steps of synthesis and characterization would be greatly beneficial. In this research, the Quantitative Structure-Property Relationship (QSPR) approach was utilized to forecast the sensitivity of potentiometric sensors towards Cu^{2+}, Cd^{2+}, and Pb^{2+}. This study was centered on four new diphenylphosphoryl acetamides ionophores. Molecular descriptors, representing structural properties, were employed to detail the structure of these ionophores. The derived model showcased a reasonable correspondence between its predictions and the experimental sensitivity values.

Keywords: QSPR; ion-selective electrode; potentiometric sensor; ionophore

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1. Introduction

Potentiometric sensors, known as ion-selective electrodes, have gained significant attention due to their simplicity, cost-effectiveness, and precision in measuring ion concentrations in aqueous solutions. Their widespread application spans pharmaceutical [1] and environmental [2] among other fields. While there are various types of ion-selective electrodes, the focus has predominantly shifted to those with plasticized polymeric membranes. This is attributed to the adjustable analytical performance of such membranes by modifying the active substance, ion-exchanger, and solvent-plasticizer. However, the process of identifying an appropriate ionophore for these sensors is extensive and intricate, necessitating assumptions about ionophore structure, synthesis, purification, and subsequent sensor characterization.

It was shown that the Quantitative Structure-Property Relationship (QSPR) approach can be instrumental in predicting sensor attributes based on ionophore structure [3]. Within this methodology, molecular descriptors detail the structure of chemical compounds, indicating the presence of specific atoms, bonds, and their mutual positions. These descriptors are then related to the property of interest through mathematical modeling. While QSPR has been applied to diverse areas, including drug discovery and environmental concerns [4], its application to potentiometric sensors is relatively recent.

Recent research has indicated the potential of QSPR in modeling the sensing attributes of ionophore-based potentiometric sensors. For instance, the selectivity coefficients for newly synthesized carbonate ionophores have been predicted with commendable precision using QSPR [5]. This study endeavors to broaden the scope of QSPR in potentiometric sensors, aiming to predict the sensitivity of new ionophores towards heavy metal ions: Cu^{2+}, Cd^{2+}, and Pb^{2+}. While QSPR models detailing ionophore structures in relation to the electrochemical response of sensors exist, their application to novel, unexplored ionophores remains uncharted. This research seeks to bridge this gap. Building on the discovery that certain diphenylphosphoryl acetamides exhibit enhanced extraction ability towards metal ions, this work constructs a QSPR model for potentiometric sensitivity towards Cu^{2+}, Cd^{2+}, and Pb^{2+}.

2. Materials and methods

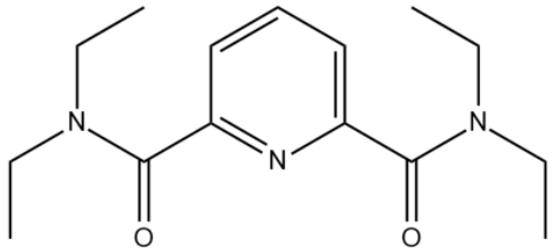
2.1. Dataset and descriptors

A comprehensive dataset was assembled from literature sources, detailing the response of sensors with PVC-plasticized membranes towards Cu^{2+}, Cd^{2+}, and Pb^{2+}. The emphasis on these metals was influenced by their recognized toxicity and the heightened attention they receive in environmental studies. A significant portion of this dataset, comprising 35 structures and their associated potentiometric responses, was derived from [6]. To enhance the dataset with a focus on phosphorus-containing ionophores, an additional six substances (##36–41, Table S1, Supplementary Materials) were incorporated.

To describe the structures of these ionophores, Substructural Molecular Fragments (SMF) were employed, a method reminiscent of our previous endeavors [5]. These SMF, obtained using the ISIDA software package, a recognized tool for QSPR modelling [7], serve as sequences of atoms interconnected by chemical bonds within a molecular structure. Much like the approach in our earlier work, a molecule is visualized as a graph, and its descriptors, in essence, are subgraphs. Each SMF descriptor represents the frequency of specific fragments or subgraphs within a molecule. Only the shortest paths between atoms, ranging in length from 2 to 9 atoms, were considered for this study.

Drawing parallels with the previous methodology, where molecules were divided into possible fragments and tabulated into a matrix, the current approach also encapsulates the molecule in a matrix format. Each row of this matrix corresponds to a specific ionophore, while each column signifies the frequency of a particular fragment within that ionophore. As an illustrative example, Figure 1a showcases a chemical structure from the Supplementary Materials, and the accompanying table in Figure 1b offers a snapshot of the matrix, highlighting specific fragments and their occurrences within the structure. The resultant descriptor matrix, with dimensions 41 x 1095, encapsulates the 41 ionophores from the training set and their 1095 corresponding SMF molecular descriptors.

a)



b)

Fragment	N-C=O	N=C-C=C-C=C	C-O-C=O
Number of fragments	2	1	0

Figure 1. (**a**) The chemical structure of N2,N2,N6,N6-tetraethylpyridine-2,6-dicarboxamide. (**b**) Table with several fragments and their counts in the compound.

2.2. Regression Modelling

To correlate ionophore molecular descriptors with their potentiometric sensitivity towards copper, cadmium, and lead, we utilized the partial least squares regression method (PLS), a technique familiar from our prior studies. Represented as Y=XB, where Y is the sensitivity, X is the descriptor matrix, and B is the regression coefficients, PLS discerns the significance of specific descriptors. Separate models were crafted for each metal. Given our dataset's size (41 entries), a leave-one-out cross-validation was adopted. Model efficacy was gauged using Root Mean Square Error (RMSE) and the coefficient of determination R^2.

3. Results and Discussion

PLS models were constructed, correlating molecular descriptors of the ionophores in the training set with their potentiometric sensitivities to copper, cadmium, and lead. Figure 2a, a measured vs predicted plot for cadmium sensitivity, showcases a commendable correlation with a cross-validation error around 4 mV/dec. This suggests that the formalized ionophore description using SMF can predict the sensitivities of corresponding plasticized polymeric sensor membranes.

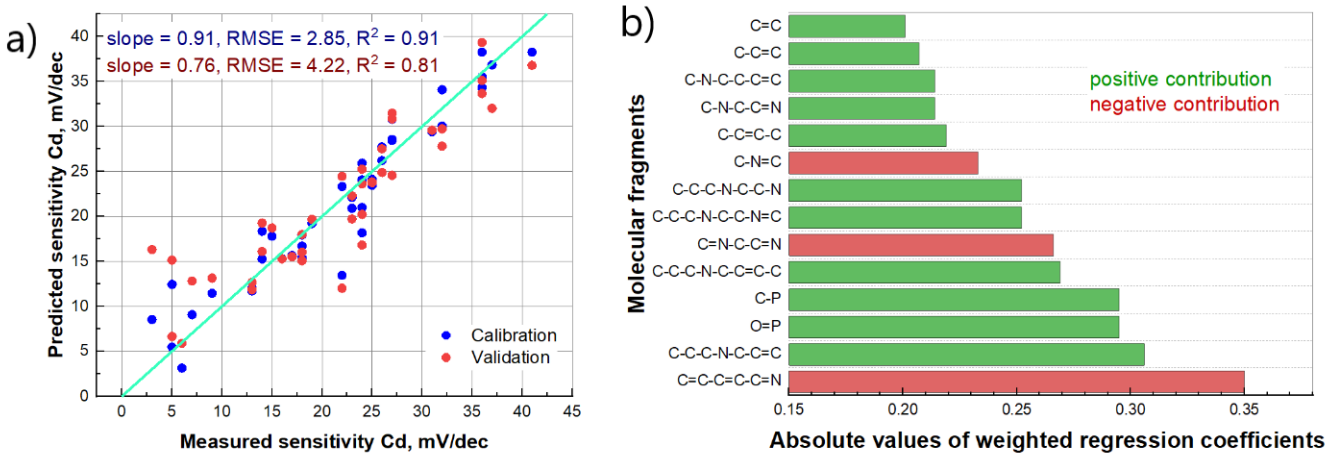
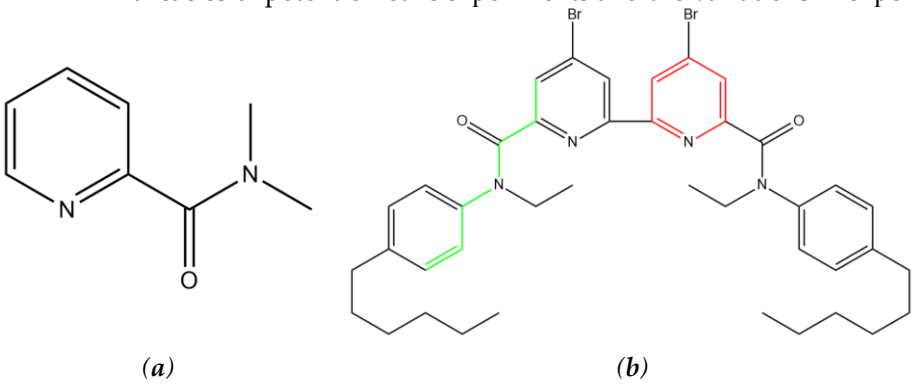


Figure 2. (a) Measured vs predicted scatterplot of cadmium sensitivity model, with four latent variables (LVs). The diagonal line shows the ideal correlation. **(b)** Fragments with the highest absolute contributions to cadmium sensitivity.

The regression coefficients in PLS modeling, reminiscent of our prior studies, highlight the importance of molecular fragments for specific target properties. By eliminating variables with small regression coefficient values, the model's accuracy improved. A closer look at Figure 2b identifies fragments crucial for cadmium sensitivity. These fragments, selected based on their occurrence in at least five structures, align with chemical intuition. Further inspection reveals that fragments with the phosphorus atom or N,N-dimethylpicolinamide fragment (Figure 3a) are found to significantly influence cadmium sensitivity. The greatest sensitivity (41 mV/dec) to Cd^{2+} in the training dataset had compound with the chemical structure shown in Figure 3b. It not only encompasses the picolinamide fragment but also integrates other fragments that positively influence selectivity (such a fragment is highlighted in green) and those that detract from it (a fragment highlighted in red).

Overall, ionophores incorporating the picolinamide fragment, as illustrated in Figure 3a, demonstrated marked sensitivity towards cadmium when employed in plasticized polymeric membranes of potentiometric sensors. Furthermore, the presence of a pyridine structural unit was observed in ionophores, irrespective of their substantial or average Cd2+ sensitivity. However, some discrepancies, like the presence of a pyridine structural unit, were noted, possibly due to the limited dataset size. Such challenges underscore the intricacies of potentiometric experiments and the variations in experimental protocols.



(a) *(b)*

Figure 3. (**a**) N,N-dimethylpicolinamide fragment; (**b**) 4,4'-dibromo-N6,N6'-diethyl- -N6,N6'-bis(4-hexylphenyl)-[2,2'-bipyridine]-6,6'-dicarboxamide with highlighted C-C-C-N-C-C=C (green) and C=C-C=C-C=N (red) fragments.

The derived PLS models were utilized to forecast the potentiometric sensitivities of four novel ionophores, as detailed in Table S2. The chemical compositions of these compounds underwent analysis using an earlier refined set of molecular fragments. Subsequently, these descriptor rows were introduced into the three PLS models, aiming to predict sensitivity towards each metal cation. The outcomes are presented in Table 1.

Table 1. The experimental and predicted sensitivity. The standard deviation values for experimental data obtained over three identical sensors in three replicated measurements did not exceed ±1.5 mV/dec.

	Cu^{2+}		Cd^{2+}		Pb^{2+}	
	Experimental	**Predicted**	**Experimental**	**Predicted**	**Experimental**	**Predicted**
1	20.3	20.9	24.6	24.7	32.9	29.7
2	18.3	16.4	22.1	22.5	31.7	29.2
3	21.1	15.3	24.7	22.5	34.6	29.1
4	23.4	19.4	23.0	23.1	34.9	27.2

Table 3 presents a side-by-side comparison of QSPR predictions and potentiometric experimental results. In many instances, a notable correspondence between the model's projections and the empirical potentiometric data was observed. This congruence was especially evident for cadmium. However, for lead, the predicted values consistently registered below the experimental findings, though the model accurately mirrored the relative increase in sensitivity from copper to lead.

4. Conclusions

Drawing from the literature data on potentiometric sensitivity of plasticized polymeric membranes with various ionophores, we've showcased the potential of the QSPR model in predicting the potentiometric behavior of emerging ionophores, bypassing the need for actual synthesis and membrane characterization. Validating the QSPR model's predictions for sensitivities towards copper, cadmium, and lead using four newly synthesized diphenylphosphoryl acetamide ionophores in real potentiometric experiments, we observed a notable alignment between predicted and actual sensitivity values. This underscores the QSPR's promising role in crafting new plasticized membrane sensors with desired attributes. Much like our earlier findings on selectivity, this study reaffirms the feasibility of semi-quantitative predictions based on ionophore structure.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Table S1: Structures, sensitivity and literature sources of the ionophores that are collected for the database, Table S2: Chemical structures and IUPAC names of the diphenylphosphoryl acetamides.

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Conflicts of Interest: The authors declare no conflict of interest.

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