Exploring the physicochemical properties of pesticides using differential mobility spectrometry and machine learning-based modelling

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INTRODUCTION

We have recently demonstrated how the monitoring of ions within the environment of a differential mobility spectrometer (DMS) contains a wealth of information about the physicochemical properties of those molecules.(Liu et al., 2015, 2017; Walker et al., 2018) The compensation voltage (CV) required to transmit an ion at a specific separation voltage (SV) in the presence of chemical modifier molecules (e.g., methanol) correlates strongly with several properties, including pka/pkb, solubilities, and cell permeabilities. By analyzing the DMS data of these ions using machine learning (ML) based models, physicochemical property prediction is realized.

In an effort to continue our expansion of these DMS applications, we present our recent research detailing our analysis of a large collection of pesticides. Here, we demonstrate that analyses using DMS provide both the fast separation of these pesticides, including the differentiation of many isomeric pesticides, but also the ML-based prediction of both collision cross sections (CCSs) and acetylcholinesterase binding affinities (a measure of many pesticides' efficacy in terms of biological action).

MATERIALS AND METHODS

Sample Preparation. A pesticide standard kit containing over 200 pesticides was used as the target sample for this study. After dilution in 50/50 acetonitrile/water + 0.1% formic acid, each compound was present at 100 ng/mL and subjected to ESI(+) prior to DMS analysis. The kit contained information on LC retention times and optimized MRM transitions and collision energies.

DMS-MS Conditions. A differential mobility spectrometer (Figure 1) was mounted in the atmospheric region between the sampling orifice and ESI source (5500V) of a hybrid triple quadrupole – linear ion trap mass spectrometer (Figure 1). The fundamentals of the DMS device have been described elsewhere. (Schneider et al., 2010) The temperature of the DMS cell was maintained at a selected temperature (150, 225, or 300 ºC) during the course of an experiment, and the nitrogen curtain gas was operated at 10 psi. In this study, the separation voltage (SV) was held at a constant value (3250, 3500, 3750, or 4000 V) while the compensation voltage (CV) was scanned from -40 V to +20 V in 0.10-V increments. During these CV ramps, the MS recorded optimized MRMs for each pesticide. During independent DMS experiments, the transport gas (curtain gas) was doped (1.5% mole ratio) with one of several volatile organic molecules (methanol, acetonitrile, isopropanol) and shifts in each pesticide's characteristic CV were recorded..

Data analysis, CCS, Acetylcholinesterase Binding Energy Calculations, and Machine Learning (ML) Modeling. All data were analyzed using a research version of PeakView® Software (SCIEX) and the DMS ionogram data (SV versus CV versus Intensity) were output to Orange Canvas (v. 3.4.2) – a Python-based machine learning interface. These data were treated with a Random Forest regression, wherein this supervised ML uses multiple decision trees and statistically analyzes outcomes to generate a predictive model. The data (DMS) and associated meta data, including m/z, MOBCAL-modeled CCS values,(Mesleh et al., 1996; Shvartsburg and Jarrold, 1996; Ieritano et al., 2019) calculated Log S values,(Tetko et al., 2005) and calculated acetylcholinesterase binding energies (AutoDock Vina; Trott and Olson, 2010) were randomly split differently for each tree, of which there were 10 trees. The data were randomly binned into 5 folds and the algorithm was run a total of 5 times (matching the number of folds), each time leaving 1 fold out of the training set for cross validation. This allows us to infer relationships in the labeled data sets.

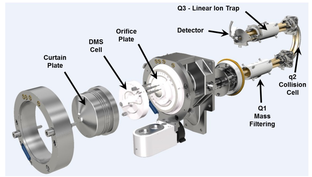
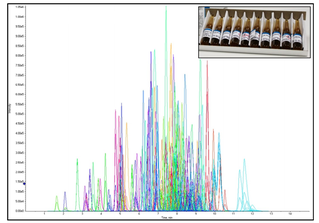


Figure 1. Exploded view of the DMS system employed in this study, including the hybrid quadrupole linear ion trap mass spectrometer.

RESULTS

Examining a pesticide standard kit using DMS instead of LC-MS

Figure 2. Typical LC-MRM trace for analysis of a pesticide standard kit containing over 200 species.



For this study, we chose to analyze the pesticide standards kit using DMS instead of LC as the separation mechanism before MS or MS/MS. Besides having some advantage in terms of time required to obtain separation of ions, the separation afforded by DMS can be easily modified by changing the "chemical environment" within the DMS cell itself. This modification is done by simply adding a small amount (1.5% mole ratio) of volatile organic molecules to the DMS cell's transport gas.

Figure 3. Overlaid DMS "ionograms" (analogous to LC-based "chromatograms") displaying how the addition of different organic modifiers to the DMS cell changes the peak capacity (CV range) that the pesticides encompass during analysis.
Note that acetonitrile and methanol provide much broader CV ranges for analysis and separation of pesticides than do water or no modifier (i.e., Nitrogen Only) conditions.

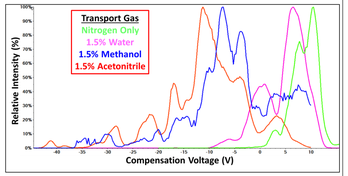
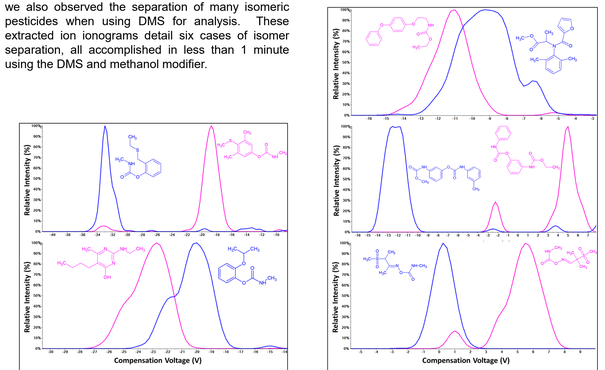


Figure 4. Besides providing a measure of CV separation for the pesticides within the standard kit, we also observed the separation of many isomeric pesticides when using DMS for analysis. These extracted ion ionograms detail six cases of isomer separation, all accomplished in less than 1 minute using the DMS and methanol modifier.



RESULTS

Detecting and separating pesticides is one thing – Evaluating their physicochemical properties is another

In earlier studies, we demonstrated that an ion's characteristic SV/CV patterns during DMS analyses actually can "encode" physicochemical properties for that species.(Liu et al., 2017; Walker et al., 2018) This allows the use of a molecule's DMS data to predict many different physicochemical properties for the species, including pKa/pKb, cell permeability, and collision cross sections (CCSs). The same features are made available here for the analyses of this pesticide standard kit, with CCS values, log S, and log P predicted here.

Figure 5. Effective prediction of CCS values using DMS data as the input for a ML-based model. (Top) By including only the DMS properties of the pesticide ions in the prediction, a good correlation is observed between the predicted and the MobCal-MPI calculated CCS values.
(Bottom) With the addition of additional molecular features in the ML-based model, here collectively referred to a "3D Structure), further improve the workflow's ability to predict the CCS value for the pesticide ions analyzed by using DMS.

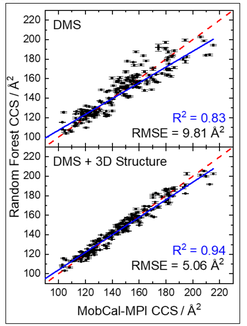


Figure 6. Comparing how well experimentally determined Log S values compare to (top) "AlogPS"-calculated and (bottom) DMS-ML predicted Log S values.

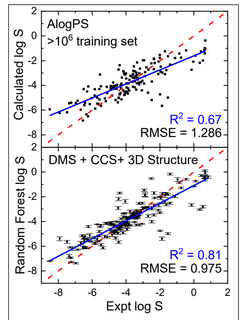
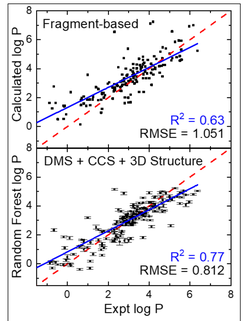


Figure 7. Comparing how well experimentally determined Log P values compare to (top) fragment-based-calculated and (bottom) DMS-ML predicted Log P values.



RESULTS

How do DMS-ML predictions and calculated acetylcholinesterase binding constants compare?

Figure 8. Besides log S and P, the DMS data and other meta features of the pesticides were applied to the ML-based prediction of acetylcholinesterase binding constants. Since the primary mode of action for most pesticides is the inhibition of this critical enzyme, there is value in having the ability to predict this binding constant reliably, quickly, and with high sensitivity.

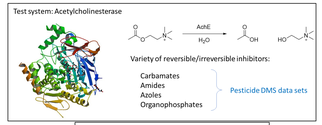
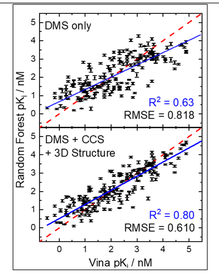


Figure 9. By using the DMS-MS data in the ML-based model, a reasonably good correlation between predicted and Vina-predicted acetylcholinesterase inhibition constant (pKi) was achieved (top); inclusion of additional meta data further improved the correlation, making the prediction more accurate.



CONCLUSIONS

By using DMS analyses and ML modeling, we are able to obtain good predictions for the physicochemical properties of a large number of pesticides. This includes both CCS values, as well as acetylcholinesterase binding affinities – a valuable measure of a pesticide's ability to bind to this critical enzyme.

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