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FIRST REACTIONS

From Microsolvation to Cell Permeation: Novel Separation Science for Drug Discovery

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A new mass spectrometry method can quickly reveal a battery of compound properties.

The development of new drugs requires extensive analysis of their physiochemical properties. Chemical analysis will include an accurate definition of the mass and structure of the target compound. It also necessitates considerable effort to determine the solubility of a given drug candidate, along with a robust assessment of how it will behave in a variety of biological environments. Of critical importance is the ease with which it will cross permeable membranes, for example, the barrier between blood and the brain. This battery of required analyses comes at significant cost, and is both time- and compound-consuming. A challenge for analytical scientists is to develop a "one stop shop analysis" providing physiochemical properties on a single platform which would in turn drive down the costs of development. Liu et al. have done just this with a technique called differential mobility spectrometry coupled to mass spectrometry (DMS–MS) (Figure 1).[1] This method, originated by Gruvemont and Purves,[2,3] has more recently been commercialized by several companies, including Sciex, who have coauthored ref 1 along with researchers from Pfizer and the University of Waterloo Canada.

Differential mobility spectrometry records the movement of ions in the presence of modulated applied electric field against a counter flow of nitrogen gas. The ions pass between a pair of electrodes, which may be parallel or in an annular geometry; one electrode is maintained at ground potential while the other has an asymmetric waveform applied to it, composed of a high-voltage component which lasts for a short period of time and a longer low voltage component, of opposite polarity.[4] Separation of ions in DMS occurs under atmospheric pressure and room temperature conditions; as a consequence, the ions commonly cluster with neutral solvent molecules, and the mobility is therefore dependent on the action of the applied electric field on a desolvated, or partially solvated, ion. The output of a DMS measurement provides the voltage necessary to separate an ion (SV) coupled with the optimum voltage applied to compensate for this (CV) allowing good transmission of a given species. The compensation voltage can be thought of as a separation parameter superposed on the asymmetric waveform to equilibrate a given species, enabling it to pass through the electrodes.[5] The voltages applied to the electrodes can be tuned to allow a single moiety to pass through to a detector (usually a mass spectrometer) or can be scanned providing a spectrum of all of the species present in a mixture. One of the distinct advantages of all forms of ion mobility mass spectrometry over mass spectrometry alone is its ability to distinguish isobaric and isometric species or even species that are very close in mass, thus simplifying the resultant mass spectrum, akin to gas or solution chromatography. The orthogonal separation of DMS compared with MS means that, when combined, the revolving power is significantly enhanced, and hence DMS–MS has been successfully applied to the measurement of many different analytes, including peptides,[5,6] proteins,[7] metabolites,[8] and as in this work drug-like molecules.[9] What sets this study aside from much of what has gone before is that the authors have related the gas phase measurement to solution phase properties.

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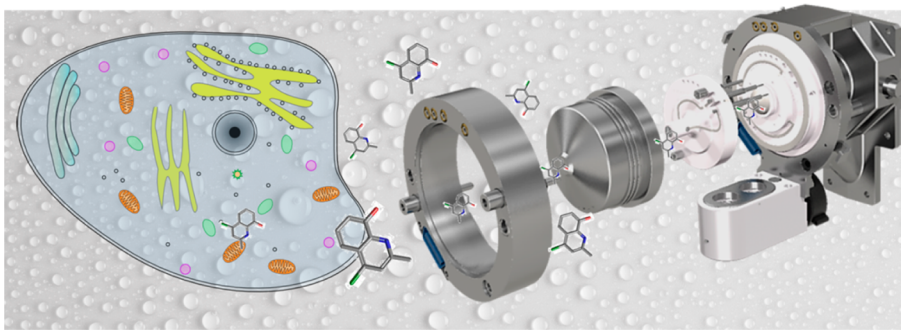

Figure 1. Physicochemical properties of drug-like molecules determined by microsolvation mobility and mass spectrometry.

the fact that the ions are partially solvated in the DMS process, and as they move through the DMS cell they experience many clustering and declustering events as a direct consequence of the applied electric fields. This means that the readout of the measurement is based on the ease with which the ion will solvate or desolvate; in other words, the transmission is a readout of solubility at a very fundamental level. Using 22 differently substituted forms of 2-methylquinolin-8-ol as an exemplar drug-like molecule in a careful set of complementary experiments, Liu et al. report that the DMS data of three sets of isomers from methoxy-, chloro-, and cyano-2-methylquinolin-8-ol derivatives track the cell permeability of each compound. Since the primarily pure nitrogen atmosphere of the DMS cell must have a dielectric constant closer to that of a cell membrane than that of a polar solvent, the clustering and declustering are representative of the passage of ions from extra- or intracellular cavities across a membrane. The more a given ion wants to be solvated, the less readily it will decluster and the lower the passive transfer rate of such a molecule is likely to be across a membrane. The correlation of both the cell permeability and the pK_a and pK_b values must be attributable to steric and electronic effects. The steric effects are explored by substituent-specific DMS behaviors of electron-donating (ED) and electron-withdrawing (EW) groups, where the DMS transmission maps well to Hammett parameters for some (although not all) of the isomers. The correlation weakens for 7-subsituted species, but holds extremely well when ED or EW groups are in the 5- and 6-positions.

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To better understand this, the authors have used DFT calculations and sophisticated sampling methods to model the gas phase and partially solvated forms. This provides insights to hydrogen bonding as well as charge density, which in turn can be related to putative resonance structures. The calculations find that the binding energy of the first solvent molecule to the ion provides the best comparison to the DMS measurement, supported by previous studies which have indicated the high binding energy for single water molecule to gas phase ions.[10]

These exquisite measurements use picograms of material and take approximately 2 min per drug. The data are highly reproducible, and despite the fact that the measurements are exclusively made on ions, they provide insights to the bulk phase properties of a given drug-like molecule, including acid−base equilibria, the rate at which it might cross a membrane, and of course its mass, all based on its affinity for a few solvent molecules. Liu et al. have shown the high potential for this analytical method to transform early stages of drug discovery as well its prospects for rational drug design.

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