Differential mobility spectrometry as a measure of ion solvation: The roles of solvents and ionic structures for separating quinoline-based drugs

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ABSTRACT

Using differential mobility spectrometry (DMS) and computational chemistry, we have examined the ability of several isomeric quinoline drug molecules to form ion/molecule clusters with water (aqueous microsolvation)

Ion structure is demonstrated to influence binding energies (BEs) of water molecules to these quinolinium ions with more hindered charge sites displaying less solvation in both DMS data and calculated BDEs

Continued expansion of this combined technique to other ions and solvent systems is on-going, and we are continuing to evaluate the relationships between gas-phase and condensed-phase solvation (i.e., solubility, cell permeability)

INTRODUCTION

The in vitro measurement of a drug's solubility and permeability – gauges of its bioavailability – can achieve unequivocal and useful results during drug design. However, these experiments can be time-consuming, labor-intensive, and expensive, and ultimately require LC-MS for drug quantitation. In this study, we employed MS coupled to differential mobility spectrometry (DMS) to investigate possible relationships between the observed degree of drug molecule solvation in the DMS with the cellular permeability of these drugs. Here, we examined the behavior of several substituted quinolines to probe these relationships. Additionally, we observed the degree of ion solvation for five pairs of isomeric substituted quinolines and uncovered a role of structure and steric hindrance on ion solvation that may relate to cell permeability.

In addition to the DMS data, we employed computational modeling of the quinolinium/water clusters – proposed to be central to the DMS' mode of action - to investigate properties of primary (sometimes secondary) solvation shells. These aqueous microsolvation studies of methylquinolinium derivatives provides insight into propensity for water clustering, perhaps relating to bulk water solubility of these species.

MATERIALS AND METHODS

Sample Preparation:
The various quinoline molecules (Figure 4) were prepared in-house (Pfizer) and purified by HPLC (95%)

DMS-MS/MS Conditions:
A DMS system (Figure 1) [1,2] was mounted in the atmospheric region between the mass spectrometer's sampling orifice and an ESI source (+5500 V). In each experiment, one of ten (10) individual quinoline solutions (100 ng/mL each in 50/50 H_2O/ACN + 0.1% formic acid) was infused into the ESI source (10 µL/min). The DMS temperature was kept at 150 ° C, and the nitrogen curtain gas was operated at 30 psi. When desired, volatile solvents (chemical modifiers) [3,4] were added to the curtain gas at 1.5% (v/v). As the DMS' Separation Voltage (SV) was stepped from 0 to 4000 V (in 250-V increments), the Compensation Voltage (CV) was scanned from -60 V to +15 V in 0.15-V increments. Dispersion plots (CV versus SV, Figure 3) [5] reveal the extent of quinolinium solvation in the DMS.

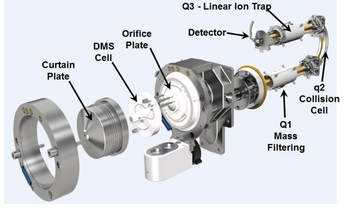


Figure 1. Exploded diagram of the differential mobility spectrometry-mass spectrometer (DMS-MS) employed in this study. Quinolinium signals were recorded as MRM (multiple reaction monitoring) signals for each ion.

MATERIALS AND METHODS

Basin Hopping / Density Functional Theory Calculations:
All calculations were performed using the Gaussian suite of programs (G09) [6]. A basin hopping (BH) search strategy [7,8] was employed to identify likely candidate cluster structures from thousands of possibilities. All unique isomers found with the BH algorithm were subsequently used as input structures for density functional theory (DFT) calculations at the B3LYP/6-311++G(d,p) level of theory.[9] To calculate cluster binding energies (BEs), the total energy of the cluster global minimum was subtracted from the sum of the individual product total energies:

$$BE = (E_{Quinolinium} + ZPE_{Quinolinium} + E_{Water} + ZPE_{Water}) - (E_{Cluster} + ZPE_{Cluster}) \quad (1)$$

Here, $E_{Quinolinium}$, E_{Water} and $E_{Cluster}$ are the electronic energies of the quinolinium, water molecule, and cluster, respectively. Zero point energies (ZPEs) were also included; thus, the reported BEs are equivalent to D_0 dissociation energies, which represent the maximum BEs for each cluster. It is expected that these calculations will capture the observed DMS behaviour because charge-multipole interactions between the ion and the first solvent molecule should dominate over the multipole-multipole interactions associated with further solvation.[3] Lastly, we included corrections for basis set superposition error (BSSE) and a GD3 empirical dispersion correction.

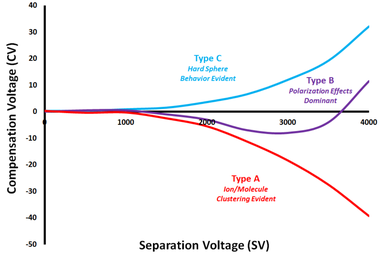
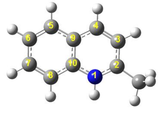


Figure 2. Generic dispersion plot (CV versus SV) with the three DMS behavior types displayed.

Nitrogen only curtain gas → Type C
1.5% Water → Type B
1.5% IPA → Type A

All quinolinium cations yielded the most dramatic differences in DMS behaviors (i.e., CV, SV values under identical conditions) ***when water was used as the chemical modifier (Figure 3).***



Scheme 1. Generic 2-methylquinolinium structure (positions numbered).

RESULTS & DISCUSSION

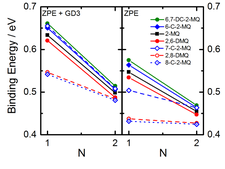
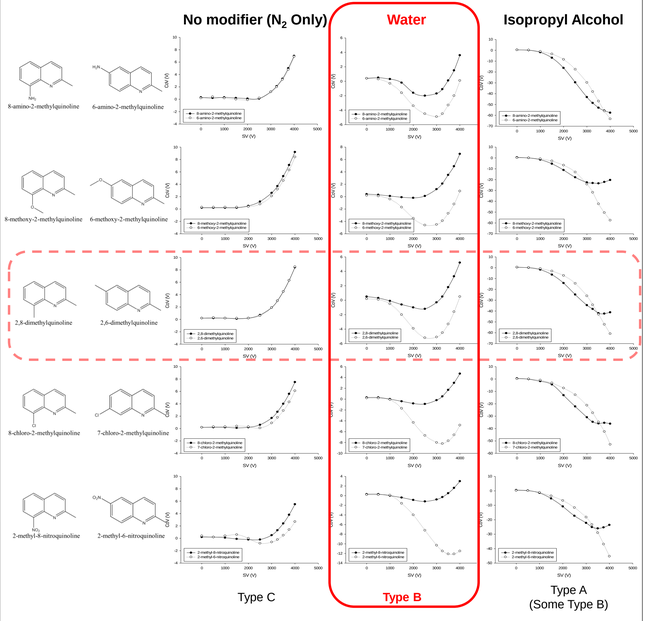


Figure 3. BH/DFT calculated binding energies (BEs) for several quinolinium ions with one and two molecules of water. Note the dramatic (50%) decrease in BE when a quinolinium ion bears a substituent in the 8-position.

6,7-DCMQ = 6,7-dichloro-2-methylquinolium
6-CMQ = 6-chloro-2-methylquinolium
7-CMQ = 7-chloro-2-methylquinolium
MQ = 2-methylquinolium
2,6-DMQ = 2,6-dimethylquinolium
2,8-DMQ = 2,8-dimethylquinolium
8-CMQ = 8-chloro-2-methylquinolium

RESULTS & DISCUSSION

Figure 4. Dispersion plots obtained during the DMS-MS analyses of the five pairs of substituted quinolinium ions. When no modifier (i.e., N_2 only) is added to the curtain gas/DMS cell's environment, little to no differentiation between each isomer pair is achieved as both ions exhibit Type C DMS behavior (i.e., hard sphere interactors). There is some differentiation at only the higher SVs when 1.5% isopropyl alcohol is added to the DMS cell; ions in each pair act like Type A ions (i.e., clustering with IPA is apparent) with Type B behavior evident at SV>3000V. However, in the presence of 1.5% water in the DMS cell, each ion behaves as a Type B ion, but to dramatically different degrees, as the isomers bearing a substituent in the 8-position transmit through the DMS at more positive CVs. Note that the ion/water clusters of both 2,6- and 2,8-dimethylquinolinium isomers (dashed red box) were the subjects of BH/DFT calculations here.



RESULTS & DISCUSSION

Figure 5. (a) BH/DFT optimized structures for 2,8-dimethylquinolinium clustered with 1 to 8 water molecules (as labeled). (b) BEs of two isomeric dimethylquinoliniums (2,6- and 2,8-) as a function of the number of clustered water molecules. Note that the sum of BEs for the 2,6- isomer is larger than the sum of BEs for the 2,8- isomer for N = 1-8. (c) Gibbs free energies of two isomeric dimethylquinoliniums (2,6- and 2,8-) as a function of the number of clustered water molecules.

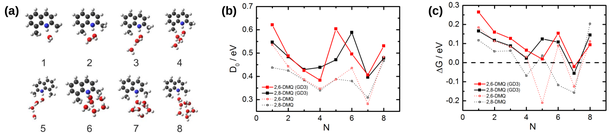
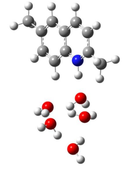
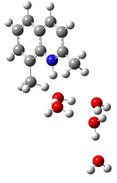


Figure 6. BH/DFT optimized structures for both (a) 2,6-dimethylquinolinium and (b) 2,8-dimethylquinolinium clustered with 5 water molecules. Note that the ion/water cluster has a more compact form for the 2,6-isomer relative to the 2,8-isomer due to the steric hindrance of the optimal H-bonding network for the latter.

(a) 2,6-dimethylquinolinium + 5 water



(b) 2,8-dimethylquinolinium + 5 water



CONCLUSIONS

The combination of DMS data and basin hopping/DFT calculations are beginning to shed light on the nature of microsolvated ions

Expansion of these experiments could lead to a greater understanding of the solvation of ionic species in bulk solution and the possible benefits that could bring (i.e., physicochemical property prediction)

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TRADEMARKS/LICENSING