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The effect of adduction energy and intramolecular bonding in the mobility of dextromethorphan and diphenhydramine with 2-butanol in the buffer gas in ion mobility spectrometry

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ABSTRACT [1]

Ion mobility spectrometry (IMS) separates gas-phase ions moving under an electric field according to their size to charge ratio. We used electrospray ionization IMS-mass spectrometry and computational chemistry to study the mobility shifts of the drugs dextromethorphan (Dx) and diphenhydramine (Dy) with the introduction of 2-butanol (B) as a shift reagent (SR) caused by non-covalent adduction of Dx and Dy with B. The binding energies of 2-butanol-ion adducts were calculated using Gaussian 09 at two different levels of theory: M06-2X/6-311++(d,p), used to discuss the present results, and B3LYP-GD3/6-311++(d,p). We found the reduced mobility (K_0) of Dx to decrease by 1.4% and that of Dy by 0.4% when the concentration of 2-butanol changed from 0.14 to 1.4 mmol m^{-3} in the buffer gas. This was unexpected from the molecular weights of these compounds, Dx 272.4 g/mol and Dy 256.4 g/mol (small ions suffer large mobility shifts), nor from the apparent steric hindrance on the positive nitrogen in Dx for the adduction of 2-butanol molecules. This hindrance should have produced a smaller mobility shift for Dx than for Dy due to a reduction in clustering with 2-butanol. However, these shifts could be explained on the interaction energies of these ions with 2-butanol. The formation of $DxBH^+$ was favored over that of $DyBH^+$ due to the formation of more stable hydrogen bonds when the adduction occurred in the nitrogen (−19.9 vs. −9.4 kcal/mol) or the oxygen atoms (−32.1 vs. 11.3 kcal/mol), with the outcome that DxH^+ showed two favorable adduction sites vs. only one in DyH^+. Additionally, an intramolecular N—H—O bond (−13 kcal/mol) was formed in DyH^+, which hid and stabilized the positive charge by delocalization making it unavailable for adduction with 2-butanol. These results justify the larger mobility shift of DxH^+ over DyH^+ with the injection of 2-butanol. These experiments are important because they explain the mobility shifts of ions upon the introduction of SRs in the buffer gas in IMS. This may be fundamental for the separation of overlapping peaks and the reduction of false positives when searching for illegal substances and explosives in airports and customs using IMS, which is the preferred method for these procedures.

1. Introduction

Ion mobility spectrometry (IMS) is an instrumental technique that separates gas phase ions drifting in an electric field according to their size to charge ratio. IMS is the method of choice for the detection of illegal drugs, chemical agents and explosives in airports and customs. In 1897, Ernest Rutherford measured the mobility of ions formed through ionization with x-rays [1] and used ion mobilities to characterize the ions [2]. Ions of similar size have similar mobilities and are difficult to separate by IMS because the ion mobilities are a function of size-to-charge ratios. In the drift region, ions are accelerated by the electric field, but are also decelerated by collisions with the buffer gas. The combination of decelerations and accelerations thermalizes the ions and averages the ion mobility to a characteristic parameter, the mobility constant, K:

$$K = \frac{v}{E} = \frac{L^2}{V.t_d} \quad (1)$$

where v is the velocity of the ion in cm s^{-1}, E the electric field in the drift region in V cm^{-1}, L the length of the drift region in cm, V the total voltage drop across the drift region in volts, and t_d the time the ion spends traveling the distance L in s. Velocity, v, is proportional to E for electric fields of less than approximately 500 V cm^{-1} (at ambient pressure) [3]. The arrival times depend on several experimental parameters but can be normalized to reduced mobilities (K0), a distinctive constant of every ion, using Eq. (2):

$$t_{d\ (\text{unknown})} K_{o\ (\text{unknown})} = t_{d\ (\text{chemical standard})} K_{o\ (\text{chemical standard})} \quad (2)$$

where td is the drift time in ms.

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[1] Reduced mobility (K_0), ion mobility spectrometry (IMS), dextromethorphan (Dx), diphenhydramine (Dy), 2-butanol (B), shift reagent (SR).

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Dextromethorphan (Dx) and diphenhydramine (Dy) are compounds used in the pharmaceutical industry in the preparation of antihistaminics and cold medications. Because of the new requirements on cleaning verification, methods to rapidly identify peaks in the mobility spectra are required and IMS is an important choice [4]. One IMS method for these verifications is the introduction of SRs in the buffer gas. SRs cluster to ions in the buffer gas and selectively change their mobilities [5]. We have separated different analytes with overlapping peaks in the mobility spectrum using SRs such as ethyl lactate, nitrobenzene, 2-butanol, trifluoromethyl benzyl alcohol, methyl 2-chloropropionate, water, ammonia and methanol in the buffer gas [5–13]. These separations are produced because analytes have different structures and interact differently with the SRs. Analytes's parameters such as size, interaction energy with SRs, proton affinity, steric and inductive effects, number of adduction locations in the SR, and intramolecular hydrogen bond strength have been used to explain the effect of SRs on mobility reduction. Strong SR-ion interaction energies increase adduct average lifetimes; adducts are larger than the analytes and these larger lifetimes increase the collisions against the buffer gas yielding a larger mobility decrease. Large SRs produce adducts with large collision cross sections with the same results. The number of adduction locations in the SR increases the probabilities of collisions resulting in adduction [13]. The other parameters, proton affinities, steric and inductive effects and intramolecular hydrogen bonds, are taken into account when calculating SR-ion interaction energies [14]. Steric hindrance of bulky substituents shields the positive charge of the ion from the attachment of SR molecules, and may delocalize the positive charge [9]. Intramolecular hydrogen bonds in analytes cause limited change in the ion mobilities when SRs are added to the buffer gas because these bonds hinder the attachment of SR molecules to the positive charge of ions and delocalize the charge, which deter clustering [7].

Campbell et al. found that the primary factor in mobility shifts upon introduction of SRs in the buffer gas was the ion—SR interaction energy and the steric hindrance at the charge site instead of the molecular weights of SRs [15]. Levin et al. reviewed the effect of the introduction of polar SRs into the buffer gas due to hydrogen bonding, electrostatic attraction, steric repulsion, and energetically viable conformations [16]. The understanding of the phenomena that explain the mobility shifts with the introduction of SRs in IMS is important in order to predict the extent and selectivity of these shifts and to select the best SR for a given separation.

In this study, we used IMS to study the unexpected ion mobility shifts of the drugs Dx and Dy with the introduction of 2-butanol as a SR and explained these shifts based on the interaction energies of these ions with 2-butanol.

2. Materials and methods

2.1. Instrumental parameters

The methodology has been described in detail elsewhere, for which only a brief summary is given [11]. Operating conditions routinely used for the drift tube ion mobility spectrometer were: sample flow, 3 μl min^{-1}; electrospray voltage, 15.6 kV; voltage in the first ring, 12.1 kV; voltage in the gate, 10.80 ± 0.01 kV; gate closure potential, ±40 V; gate pulse width, 0.1 ms; scan time, 35 ms; number of averages per spectrum, 250; pressure, 685–710 Torr; nitrogen flow, 0.94 l min^{-1}; buffer gas temperature, 116 °C.

2.2. IMS instrument

The IMS instrument comprised an electrospray ionization source and a drift tube. The drift tube (5-cm I.D) had a desolvation (7.5 cm) and a drift region (25 cm) working in positive mode, separated by a Bradbury-Nielsen-type ion gate. The ion gate was a set of parallel wires that neutralized the ions and had approximately eighty parallel wires of 75-μm Alloy 46 (California Fine Wire Co., Grove Beach, CA, USA) separated 0.6 mm. Positive and negative wires alternated in the gate. With the gate open, wires had a voltage equal to the average of the voltage of the adjacent drift rings. The open-gate voltage was 10,800 V. To neutralize the ions, a closure potential was applied that was 40 V higher for a set of wires and 40 V lower for the other set, than the open-gate voltage. For these experiments, the gate voltages were 10,840 V and 10,760 V when closed. Ions were pulsed with a 0.1 ms pulse into the drift region. The drift tube was built of a series of stainless-steel guard rings between insulating ceramic rings (99.5% Al_2O_3, Advalue Tech., Tucson, AZ, USA), stacked on top of one another to form a completely enclosed tube. A counterbore on the external face of each drift ring supplied a pocket for the neighboring ceramic insulator. The tube had an electric field of 432 V cm^{-1} and was held inside a 2.5″-OD, 2.3″-ID alumina tube with an aperture all along its length to bring out the electric contacts of the rings; this ceramic tube was heated inside an aluminum oven. Steel rings were connected in series by 1 MΩ (drift region) or 0.5 MΩ (desolvation region) high-temperature resistors (Caddock Electronics Inc., ±1%). Adjustment of the length of the ion separation region was possible by addition or removal of stainless steel rings. A countercurrent of dry neutral gas was used as a clean and inert matrix through which ions drift and to keep the drift tube clean by keeping neutral compounds, introduced with the sample or coming from the atmosphere, from passing into the drift region. The nitrogen drift gas entered the bottom of the spectrometer, passed through the drift tube and exited through the ionization region [17]. The buffer gas was heated by passing it through a 2-m long stainless-steel tube coiled inside an aluminum heating block. The water content in the buffer gas, ~10 ppm, was measured with a GE Moisture Image Series 1 instrument (Billerica, MA). Custom LabView software (National Instruments, Austin, TX) collected the IMS data and controlled the ion gate. The electronics for IMS data acquisition and gate control were built at WSU.

2.3. MS instrument

The mobility spectrometer was coupled to a quadrupole mass spectrometer through a 40-μm pinhole. The mass spectrometer was an ABB Extrel (Pittsburgh, PA, USA) 150-QC quadrupole (0–4000 amu). A Keithley model 427 amplifier (Keithley Instruments, Cleveland, OH) was used to amplify the output signal from the electron multiplier detector of the mass spectrometer and to send it to the data acquisition systems. The mass spectrometer was controlled with Merlin software (version 3.0 ABB Extrel, Pittsburgh, PA), which collected the mass spectral data. The mass spectrometer operated in single ion monitoring IMS mode (only ions of a given mass to charge ratio or a range of masses were detected), radiofrequency-only IMS (IMS mode, the total ion mobility spectra were obtained), and mass spectrometry mode (mass spectra were obtained).

2.4. Reagents, sample preparation and injection

Dx and Dy were obtained from dissolution of over-the-counter drugs purchased from local stores [18]. Methanol, 2,6-di-tert-butyl pyridine, 2-butanol and acetic acid (reagent grade, ≥98% purity) were purchased from Sigma (Milwaukee, WI, USA). Solutions of the chemical standard and analytes were prepared at 10 μM and 100 μM concentrations, respectively, in electrospray solution (47.5% methanol: 47.5% water: 5% acetic acid) and were continuously injected and ionized by electrospray using a 15.6 kV voltage, a difference of 3.5 kV with respect to the target screen. A KD Scientific pump (model 210, Holliston, MA, USA) pumped the solutions using 250 μl gas tight syringes (Hamilton, Reno, NV, USA) at a flow rate of 180 μl hr^{-1} into 30-cm long, 100-μM ID capillary (Polymicro Technologies, Phoenix, AZ) connected to a 50-μm ID silica capillary by means of a stainless steel union (Valco, Houston, TX, USA). The end tip of this capillary was centered at a stainless steel