Microchemical Journal 126 (2016) 155–161

Contents lists available at ScienceDirect

Microchemical Journal

journal homepage: www.elsevier.com/locate/microc

Trifluoromethyl benzyl alcohol as a "shift reagent" in ion mobility spectrometry: The effect of intramolecular bridges, ion size and shift reagent-ion binding energy in ion mobility

Roberto Fernandez-Maestre [a,*], Dairo Meza-Morelos [a], Ching Wu [b]

[a] Universidad de Cartagena, Campus de San Pablo, Programa de Química, Cartagena, Colombia
[b] Excellims Corporation, 20 Main Street, Acton, MA, USA

ARTICLE INFO

Article history:
Received 8 October 2015
Received in revised form 14 November 2015
Accepted 8 December 2015
Available online 17 December 2015

Keywords:
Trifluoromethyl benzyl alcohol
Adduct
Ion mobility spectrometry
Mass spectrometry
Shift reagent
Buffer gas modifier

ABSTRACT

α-Trifluoromethyl benzyl alcohol (F) was introduced as a "shift reagent" in the buffer gas of an electrospray ionization ion mobility spectrometer coupled to a quadrupole mass spectrometer to explain the mobility shifts of selected compounds; ion mobilities depended on ion sizes and F-ion adducts binding energies calculated using Gaussian 09 at the X3LYP/6-311++G(d,p) level. The mobility shifts with the introduction of F in the buffer gas were: −13% (ethanolamine), −10.6% (serine), −8.6% (threonine), −7.3% (phenylalanine), −7.0% (tyrosine), −6.2 (tributylamine), −5.1% (valinol), −4.7% (methionine), −3.9% (tryptophan), −3.1% (tribenzylamine), −1.3% (2,6-di-tert-butyl pyridine, DTBP), −1.2% (2,4-lutidine, 2,4-dimethyl pyridine), and −0.1% (atenolol). These mobility shifts showed a decreasing trend with the increase in molecular weight from ethanolamine to tribenzylamine excluding some ions due to steric hindrance (2,4-lutidine, DTBP and tetraalkylammonium ions), formation of intramolecular bridges (atenolol and methionine) or low binding energy with F (valinol). Ethanolamine (61.1 g/mol) showed the largest mobility shift (−13%) due to its low molecular weight and tribenzylamine showed the smallest one due to its large size. We found a similar trend in mobility shifts when methyl chloro propionate, trifluoromethyl benzyl alcohol, ethyl lactate, nitrobenzene or 2-butanol were used as SRs. We also found that penicillamine adducts with F were not seen in the mass or mobility spectra probably because of the formation of an intramolecular bridge in this compound; F produced the average lowest mobility shifts of all SRs tried before, even of smaller size (methyl chloro propionate, phenylethanol, ethyl lactate, nitrobenzene, and 2-butanol) because of the inductive effects exerted by the three fluorine atoms that decreased F proton affinity and hindered its adduction to analyte ions. In summary, intramolecular bridges, size, inductive effects, steric hindrance and adduct binding energy were used to explain mobility shifts when trifluoromethyl benzyl alcohol was used as a "shift reagent" in ion mobility spectrometry.

1. Introduction

Ion mobility spectrometry (IMS) separates gas-phase ions according to their size to charge ratios and is widely used for the detection of illegal substances in airports and customs. Shift reagents (SRs) are used in mobility spectrometers to change ion mobilities and separate analytes that overlap in IMS by selective adduction with analyte ions.

Mobility shifts produced by injection of SRs in the buffer gas are explained by the formation of slow SR–ion adducts; the SRs decrease ion mobilities depending on their proton affinity and size, inductive effects, SR–ion binding energy, ion charge delocalization and steric hindrance [1]: large SRs affect the mobilities of analytes because their adducts have large collision cross-sections and, therefore, undergo more collisions than small adducts produced by small SRs; high SR–ion binding energies would increase adduct average lifetime, increasing the number of collisions against the buffer gas decreasing adduct mobilities; most of the binding energy comes from hydrogen bonds between the SR oxygenated groups and the ion's positive charge. Theoretical calculations have demonstrated that ethyl lactate SR affected more glucosamine ion mobility because the ethyl lactate–glucosamine adduct was more energetically stable than that of ethyl lactate–caffeine. Intramolecular hydrogen bonds sterically hinder SR adduction to ions and delocalize the positive charge weakening SR–ion interactions [2]; steric effects can deter the attachment of SR molecules, SR proton affinities increase the SR–ion binding strength, and inductive effects increase or decrease this interaction but these parameters are taken into account when calculating SR–ion binding energies [3].

Abbreviations: F, α-trifluoromethyl benzyl alcohol; DTBP or D, 2,6-di-tert-butyl pyridine; V, valinol; L, 2,4-lutidine; Ate, atenolol; SR, shift reagent; IMS, ion mobility spectrometry; MS, mass spectrometry; ESI, electrospray ionization.

* Corresponding author. Tel./fax: +57 5 6753718.
E-mail addresses: rfernandezm@unicartagena.edu.co (R. Fernandez-Maestre), dmezam@unicartagena.edu.co (D. Meza-Morelos), ching.wu@excellims.com (C. Wu).

http://dx.doi.org/10.1016/j.microc.2015.12.011
0026-265X/

SRs were introduced in the drift tube of mobility spectrometers to change ion mobilities two decades ago. In 1993, Eiceman et al. used ketones in the carrier gas to cluster hydrazine and monomethylhydrazine in air, avoiding the interference of ammonia [4] and, in 2007, Bollan et al. complexed hydrazines by introducing ketones into the buffer gas also to avoid ammonia interference [5]. SRs were introduced for the first time in the buffer gas (instead of the carrier gas) to separate overlapping compounds by Herbert Hill in 2006 [6]. These experiments in IMS in negative and positive modes were reviewed by Puton et al. [7]. Using this methodology, we separated serine and valinol [8], lysine and isoleucine, and phenylalanine and arginine [9], tetraethylammonium ions and valinol [2], and asparagine, valine, and tetraethylammonium ions [10] overlapping in an ion mobility spectrometer using different SRs in the buffer gas. Ghaemi and Alizadeh in 2014 used (S)-2-butanol to separate overlapping picoline enantiomers [11]. Similar experiments have been carried out although they are different from those described above [2,6,8–11] in that they do not introduce the SR from the end of the drift tube in the buffer gas but mixed with the analyte in the carrier or curtain gas; for example, Howdle et al. used polyethylene glycols as shift reagents to cluster lamivudine and identified noncovalent complexes with different drift times moving the peaks away from interferences [12].

Only since 2007, the origin and extent of these mobility shifts upon introduction of SRs in the buffer gas in IMS have been tried to explain; Levin et al. examined the effect of the introduction of polar SRs in the buffer gas and postulated effects due to hydrogen-bonding, electrostatic attraction, steric repulsion, and energetically feasible conformations [13]; Roscioli et al. demonstrated the importance of a similar proton affinity between the SR and the target analyte to produce changes in mobilities [14]; Campbell et al. found that increasing molecular weights (and m/z) is not the primary factor in mobility shifts but the binding energy and the steric hindrance on the charge site [15] and Rawat et al. developed models predicting changes in mobility provided by modifiers, and compared them with calculated models [16].

Although it has been used to selectively remove interferences and separate overlapping ions, the origin of selective ion mobility shifts with SR introduction in IMS has not been fully explained and the separation of ions with similar values of reduced mobilities (K_0) in IMS cannot yet be predicted [17]. The use of SRs to increase separations by selectively changing ion mobilities would improve one important IMS problem such as false positives in airports, customs and chemical warfare agent monitoring that are cumbersome and time consuming events [18]; the interference is overcome because there is a pure analyte signal in N_2 and others when introducing the SR because it is unlikely that the SR–analyte and SR–interference adducts have the same collision cross-sections and, therefore, the same drift times. In this paper, we studied the effect of ion sizes, SR–ion binding energies, steric hindrance and intramolecular hydrogen bonds on the ion mobility shifts; although binding energies have been used to explain mobility shifts in differential mobility spectrometry, they have been used very little, if any, in IMS; we also explained the incidence of inductive effects and proton affinity on the adduction capability of F to contribute to the quest of predicting the separation of overlapping ions by introducing SRs in the buffer gas in IMS.

2. Experimental

2.1. Instrument

The methodology has already been described and only a summary is given here [18]. An electrospray-ionization (ESI) atmospheric-pressure ion mobility spectrometer interfaced to a quadrupole mass spectrometer was used in these experiments. Typical operating parameters for this instrument were: sample flow, 3 μl min^{-1}; ESI voltage, 15.6 kV; voltage at first ring, 12.1 kV; voltage at 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, 1000; pressure, 685–710 Torr; nitrogen flow, 0.94 l min^{-1}; and buffer gas temperature, 150 ± 2 °C. The instrument was operated in single ion monitoring ion mobility spectrometry (SIM-IMS), radiofrequency-only ion mobility spectrometry (IMS), and mass spectrometry (MS); in SIM-IMS mode the ion mobility spectrum of ions of a given mass to charge ratio or a range of masses is detected, in IMS mode the total ion mobility spectrum is obtained, and in MS mode mass spectra are obtained. Concentrations up to 2.3 mmol m^{-3} of F were introduced into the buffer gas.

2.2. Reagents

Phenylalanine, methionine, serine, tryptophan, tyrosine, threonine, ethanolamine, tribenzylamine, tributylamine, the drugs valinol, atenolol, and penicillamine, 2,4-lutidine, DTBP, tetramethylammonium (TMA), tetraethylammonium (TEA), tetrapropylammonium (TPA), and tetrabutylammonium (TBA) chlorides, trifluoromethyl benzyl alcohol, water, and acetic acid (ACS reagent grade, ≥97 or 98% purity) were purchased from Sigma Aldrich Chemical Co. (Milwaukee, WI, USA, Fig. 1). These analytes were tested because of their different molecular weights and structures required to test the effects of size and steric hindrance on the mobilities of these molecules with the introduction of F into the buffer gas. DTBP and 2,4-lutidine were selected for these experiments because they are the most used chemical standards. Solutions of the analytes and standards were prepared in ESI solution (47.5% methanol:47.5% water:5% acetic acid) and F was introduced as a pure liquid.

2.3. Computational–theoretical studies

The Gaussian 09 program was used to perform theoretical calculations at the X3LYP/6-311++G(d,p) level of theory at 150 °C [19]. Geometry optimization calculations were performed for the analytes and their protonated species, trifluoromethyl benzyl alcohol SR, and the SR–analyte protonated adducts. Then, molecule structures were used as starting points to determine the geometries and energies. The SR–ion binding energies (E_B) were estimated using $E_B = E_{adduct} - (E_{SR} + E_{protonated\ analyte})$ and the SR proton affinities subtracting the protonated SR energies from the SR energies [20].

3. Results and discussions

3.1. Introduction of the SR in the buffer gas produced SR–ion adducts

Fig. 2 shows the spectra of the electrosprayed solvent without introducing F in the buffer gas. In Fig. 2, the main reactant ion peaks were $(H_2O)_2H^+$, $(H_2O)_3H^+$, $(H_2O)_4H^+$, and $(H_2O)_5H^+$ at m/z 37, 55, 73, 91, and 109, respectively; the reactant ion mobility peak, $(H_2O)_nH^+$, at 16.66 ms corresponds to a reduced mobility of 2.10 $cm^2\ V^{-1}\ s^{-1}$ (Fig. 2b). The instrument is considered free of contamination because no significant peaks appear above 109 amu; contamination control is important to avoid adduction of contaminants with analyte ions because this changes ion mobilities [21]. All the species seen in the mass spectrum coalesced into a single mobility peak due to the equilibria $(H_2O)_nH^+ \leftrightarrow (H_2O)_{n-m}H^+ + mH_2O$. Because of the fast equilibrium in the drift tube between water adducts, the IMS peak had a weighted average of the mobilities of all water ions. Water adducts disappeared from the IMS and mass spectrum by clustering with F or by charge stripping to this alcohol when F was introduced in the buffer gas at 2.3 mmol m^{-3}; the protonated ion of F, FH^+, and its cluster with water, FH_3O^+, appeared at m/z 177.1 and 194.1 in the mass spectra, and at 20.58 and 22.23 ms, respectively, in the IMS spectra.

Fig. 3a shows the MS spectra of a 100-μM mixture of penicillamine, serine, threonine, phenylalanine, tyrosine, and tryptophan showing their protonated ions at m/z 106.1, 120.1, 150.2, 166.2, 181.2, and 205.2 in pure nitrogen buffer gas, respectively, and, their adducts with