Ion-Neutral Reactions in the Ion Source of a Mixture of CO₂/CH₃OH, CO₂/C₂H₅OH, and CO₂/2-C₃H₇OH by Packed Capillary Supercritical Fluid Chromatography-Mass Spectrometry (SFC-MS)

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Ion neutral reactions in the gas phase in mixtures of ROH/CO₂, R = CH₃, C₂H₅, and 2-C₃H₇ were studied by supercritical fluid chromatography-mass spectrometry (SFC-MS). Three main reaction series were found for this system; ionization followed by α -cleavage, formation of clusters, and formation of protonated dialkyl ethers from the corresponding alcohol. The ion chemistries were similar for the three alcohols, but that of 2-propanol was somewhat more complex. (J Am Soc Mass Spectrom 2007, 18, 2173–2179) © 2007 American Society for Mass Spectrometry

Supercritical fluid chromatography (SFC) performed with CO₂ as the mobile phase has several limitations. Moderate and very polar compounds are poorly eluted due to low solute-solvent interactions [1]. Different approaches have been taken to address this limitation [2–9], and alternative fluids have been tested [10–13]. Levy and Ritchey have described the effects of different modifiers on various functional classes of test solutes in 1986 [6]. When SFC is coupled to MS, the modifiers can form several reagent ions. The variety of reagents of different Brønsted acids gives the possibility to choose the correct reagent for a particular type of analysis [14, 15]. The chemistry of ion-molecule interactions in the gas phase may provide an elegant substitute for the chromatographic pre separation step in conventional MS analysis. Pure CO₂ has been reported to act as a reagent gas for charge exchange (CE) with solute molecules [16–18]. Using modified CO₂, mixed CE/CI mechanisms can be reflected in the mass spectra [19]. This work presents results of the ion-neutral reactions in the gas phase, which take place when mixtures of polar modifiers (methanol, ethanol, and 2-propanol) are introduced into the CO₂ mobile phase and expand through the direct fluid interface. The structure of the reagent ions were studied by collision induced dissociation (CID) and deuterium labeling. Previous reports of ion-neutral reactions in these alcohols [20–24] provided an excellent basis for our study.

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Experimental

Instrumentation

SFC-MS data were collected by using an Isco 100DX syringe pump (Isco Inc., Lincoln, NE) attached to a double focusing mass spectrometer with EB geometry (DX303; JEOL, Tokyo, Japan). The SFC column was installed in a Carlo Erba high-resolution gas chromatograph (HRGC/MS; Instrument Teknikk Scandinavia AS, Oslo, Norway). The total ion chromatograms (TIC), reconstructed ion chromatograms (RIC), and mass spectra were recorded using Shrader interface and software (Shrader Analytical and Consulting Laboratories, Inc. Detroit, MI). Chromatography was performed using a 60 cm long, 450 μ m o.d., 320 μ m i.d., fused silica column packed with 5 μ m Intersil C₁₈ particles (Keystone Scientific Inc., Bellefonte, PA). The column outlet and the union connected to the column entrance were both equipped with a stainless steel frit with 2 μ m pore size (2400 Keystone Scientific). Valco zero dead volume unions (1/16 in. to 1/16 in.) were used. The injector (Valco C14W; Valco Instruments Co. Inc., Houston, TX) with 0.5 μ L injection loop was connected to the column by 7 cm long deactivated 50 μ m fused silica capillary tubing. Constant pressure in the chromatographic system was maintained by a 12 cm long, 15 μ m i.d. linear restricter. The temperature on the restricter tip was kept at 200 °C, and the flow rate was 1.8 cm/s. The ion source temperature was 150 °C and the column oven was held at 100 °C. The electron energy used was 230 eV in CI mode. The pressure in the ion source was 66 to 133 Pa. Argon was used as collision gas in the CID

Table 1. Mixing ratios and length of applied restrictors

Vol % modifier in CO ₂	Methanol		Ethanol		2-Propanol	
	P. line ^[cm]	M. line ^[cm]	P. line ^[cm]	M. line ^[cm]	P. line ^[cm]	M. line ^[cm]
5	10	38	10	20	10	21
10	20	36	20	19	20	20
15	40	45	40	24	40	25
20	60	48	60	25	60	16
25	80	48	80	25	80	26
30	80	37	80	20	80	20

P: primary solvent line; M: modifier line.

experiments. The pressure of Ar was increased until the precursor ion intensity was reduced by 50%.

Chemicals

Carbon dioxide (SFC-grade) was purchased from Scott Specialty Gases (Breda, The Netherlands). Methanol, (HPLC-grade) was obtained from Rathburn Chemicals Ltd., Walkerburn, Scotland. Ethanol and 2-propanol were obtained from A/S Vinmonopolet, Norway. Methanol-d₄ and ethanol-d₆ were obtained from Cambridge Isotope Laboratories (Andover, MA). Dimethyl ether was purchased from Gerling Holtz and Co. (Hamburg, Germany). Diethyl ether was obtained from Den Norske Eterfabrikken AS (Oslo, Norway).

Mixing Systems

To prepare mixed mobile phases, a simple on-line system [25], flow of the primary solvent, CO₂, is split into two paths: the primary solvent line and the modifier line. The latter presses the modifier through. The

densities and viscosities of the pure fluids have been estimated theoretically using Lucas method [26]. The lengths of lines, and the resulting mixing ratio (M/CO₂) of CO₂ and modifiers (M) are presented in Table 1.

In experiments for formation of proton bound methanol clusters, CO₂ was introduced into the ion source as a mobile phase while methanol was injected into the ion source from a heated glass reservoir (off-line mixing system). The temperature in the reservoir and the transfer line was kept at 100 °C. Methanol was introduced into the ion source until the pressure of 40 Pa was reached, then CO₂ was leaked into the ion source until the pressure increased to about 133 Pa.

Results and Discussion

The CI mass spectrum of CO₂ mixed with 30% methanol is presented in Figure 1a. The reagent ions produced are dominated by protonated methanol, CH₃OH₂⁺ *m/z* 33, which is the precursor to all the higher-order ion-neutral reactions observed. The amount and size of cluster ions, (CH₃OH)_{*n*}H⁺, 1 ≤ *n* ≤ 4, increase with

Figure 1. The CI mass spectra of CO₂ and methanol introduced into the ion source (a) as a mixture, and (b) separately.

Figure 2. The relative concentration of alcohol and alcohol-ether clusters as a function of mixing ratio in (a) methanol, (b) ethanol, and (c) 2-propanol.

increasing mixing ratio and decreasing temperature, Figure 1b. The highest methanol cluster obtained in this work is protonated tetramer, $(\text{CH}_3\text{OH})_4\text{H}^+$, at m/z 129. Figure 2 shows the relative concentrations of several of the most abundant ions formed as a function of mixing ratio of methanol with CO_2 . A fragment ion formed from the protonated methanol is protonated formaldehyde, CH_2OH^+ at m/z 31, due to the elimination of H_2 . In addition, CH_3^+ at m/z 15 is also formed from protonated methanol after expulsion of water. The ions at m/z 29, HCO^+ , appear only at a higher ion source repeller voltage (2 V or higher). The HCO^+ ions are formed by successive loss of H^+ and H_2 from CH_3OH^+ , formed due to CE ionization. The ions at m/z 31, m/z 29, and m/z 15 react with methanol exclusively via proton transfer.

The two different structures of ions at m/z 45 are either CO_2H^+ or $\text{CH}_3\text{OCH}_2^+$. As mentioned earlier, the primary ions react with methanol almost exclusively via

proton transfer, although water and a trace of a condensation product between methanol and CH_2OH^+ to form $\text{CH}_3\text{OCH}_2^+$ at m/z 45 can also be formed, eq 1. If the condensation product is formed, an ion at m/z 50 in the mass spectrum of CD_3OD in CO_2 is expected. However, this is probably not the case, rather a mass shift of only one mass unit (to m/z 46, CO_2D^+) is obtained, which confirms the structure of m/z 45 as a protonated carbon dioxide ion. The resolution of the instrument was high enough to split these ions.

m/z 31

m/z 45

The possible structures of ions at m/z 47, $\text{C}_2\text{H}_7\text{O}^+$, are protonated dimethyl ether or protonated ethanol. Either ion could conceivably be formed by an appropriate rearrangement of the excited $(\text{CH}_3\text{OH})_2\text{H}^+$ cluster ion when H_2O is eliminated. The structure of ion m/z 47 in the methanol/ CO_2 mixture is found by comparing its CID mass spectrum with the CID mass spectra of protonated dimethyl ether and protonated ethanol and by experiments utilizing deuterated compounds.

For protonated dimethyl ether, the kinetically most favorable fragmentation path is the elimination of CH_4 (eq 2) that forms the main signal at m/z 31 [27]. The signal at m/z 29 corresponds to HCO^+ and is due to a further elimination of hydrogen from m/z 31, eq 3.

In the CID mass spectrum of protonated ethanol, the main fragment ion is found at m/z 29, C_2H_5^+ , which is formed by elimination of H_2O , eq 4. Signals at m/z 28, m/z 27, and m/z 26 correspond to C_2H_4^+ , C_2H_3^+ , and C_2H_2^+ , respectively.

m/z 47

m/z 31

m/z 31

m/z 29

m/z 47

m/z 29

Also ions at m/z 19, H_3O^+ , are present in the mass spectrum, corresponding to loss of ethene. The CID mass spectrum of the ion at m/z 47 in the mixture of methanol/ CO_2 matches the CID mass spectrum of protonated dimethyl ether although the relative intensities of some of the ions vary. The differences might be due to variance in internal energy, caused by different production paths of the precursor ions. The protonated dimethyl ether is synthesized in situ by proton transfer and therefore may contain more energy than the ions formed by a nucleophilic displacement reaction. Also, experiments with deuterium labeled methanol, CH_3OD , show CH_3D elimination as a dominating reaction pro-

cess, which support the structure of the m/z 47 as a protonated dimethyl ether ion. We therefore conclude that the structure of the ion at m/z 47 in the mass spectra of methanol is protonated dimethyl ether. This agrees with the results reported by Henis in 1968 [21].

The protonated dimethyl ether ion $(\text{CH}_3)_2\text{OH}^+$ at m/z 47 undergoes an association reaction with methanol producing a collision stabilized ether-methanol proton bound dimer $(\text{CH}_3)_2\text{OH}^+(\text{CH}_3\text{OH})$, at m/z 79, and an ether-methanol proton bound trimer $(\text{CH}_3)_2\text{OH}^+(\text{CH}_3\text{OH})_2$ at m/z 111, eq 5. A relatively high concentration of modifier is required to produce the ion at m/z 111. Ions at m/z 79 and m/z 111 can be produced by displacement reactions of $(\text{CH}_3\text{OH})_2\text{H}^+$ and $(\text{CH}_3\text{OH})_3\text{H}^+$ with CH_3OH , as illustrated in eq 6. Thus, ether-methanol proton bound clusters can be proposed as resulting from both the bimolecular reaction of CH_3OH and $(\text{CH}_3\text{OH})_2\text{H}^+$, CH_3OH and $(\text{CH}_3\text{OH})_3\text{H}^+$, and from clustering of protonated dimethyl ether with methanol.

$$m/z\ 79 \qquad m/z\ (79 + n32, \text{ for } n = 1 \text{ and } 2)$$

The amount of proton bound methanol clusters increases with increasing mixing ratio. The protonated tetramer is produced when the amount of methanol mixed with CO_2 is higher than 15%. Since adiabatic cooling occurs at the orifice of the restrictor tip, it might be assumed that the methanol clusters are formed before ionization takes place. If so, the relative intensity of the cluster ions should decrease with decreasing cluster size. However, the mass spectrum of CO_2 /methanol mixture shows cluster ions that decrease in intensity with increasing cluster size. Thus, the adiabatic cooling seems to play a minor role in the formation of the cluster ions. This hypothesis is also supported by the results obtained when methanol and CO_2 are introduced separately into the ion source. Mass spectra obtained in these experiments show nearly the same cluster pattern as in experiments where the methanol is subjected to the adiabatic cooling, Figure 1a and b. Thus, the methanol cluster ions are formed in the ion source by association reactions: CH_3OH_2^+ reacts with CH_3OH to form an intermediate, excited complex, $[(\text{CH}_3\text{OH})_2\text{H}]^+$, which can dissociate in two ways, either back to the original reactants or to give the products $\text{C}_2\text{H}_7\text{O}^+$ at m/z 47, and H_2O . The consequence of the high-pressure in the ion source is third-body collisions, which leads to stabilization of $[(\text{CH}_3\text{OH})_2\text{H}]^+$ and formation of a protonated methanol dimer, $(\text{CH}_3\text{OH})_2\text{H}^+$ (m/z 65), at ground level. The protonated dimer of methanol undergoes further

clustering to form protonated trimer and tetramer at m/z 97 and m/z 129, respectively.

The ion at m/z 65 may have two different structures; proton bound dimer of methanol or a proton bound complex between water and protonated dimethyl ether, $(\text{CH}_3)_2\text{OH}^+(\text{H}_2\text{O})$. The CID mass spectrum of m/z 65 shows the main signal at m/z 33, which corresponds to loss of CH_3OH and a minor amount of ions at m/z 47, which corresponds to loss of H_2O . The same pattern was observed in the CID spectrum of $(\text{CD}_3\text{OD})_2\text{D}^+$ m/z 74, where the main signal was found at m/z 38 and only trace amounts at m/z 54. Thus, since the main fragmentation path is due to loss of methanol, we propose that the main structure corresponds to proton bound dimers of methanol. These results are also supported by the work of Graul and Squires work [28]. However, the fragment ion at m/z 47 in the CID mass spectrum of m/z 65 may imply that the dimethyl ether-water complex was also present.

By analogy with methanol, one would expect two different structures for ions at m/z 97, $(\text{CH}_3\text{OH})_3\text{H}^+$ and $(\text{CH}_3)_2\text{OH}^+(\text{CH}_3\text{OH})(\text{H}_2\text{O})$, and for ions at m/z 129, $(\text{CH}_3\text{OH})_4\text{H}^+$ and $(\text{CH}_3)_2\text{OH}^+(\text{CH}_3\text{OH})_2(\text{H}_2\text{O})$. However, the CID mass spectra of m/z 97 and m/z 129 do not produce detectable quantities of product ions at m/z 79 and m/z 111, respectively, which otherwise might be formed by loss of H_2O . The results obtained in our work imply that the structure of ions at m/z 97 and m/z 129 corresponds to protonated trimer and protonated tetramer, respectively.

The lack of m/z 79 and m/z 111 in the CID mass spectra of the protonated trimer and tetramer of methanol can be explained in terms of the level of internal energy of the clusters that decrease with increasing cluster size. As mentioned earlier, the internal energy of the clusters are important for further reactions, e.g., rearrangement or dissociation reactions. The reaction between protonated methanol or methanol clusters and methanol is exothermic. By measuring the equilibrium constant at different temperatures, the enthalpy changes can be calculated for addition of each methanol molecule. Such experiments were performed by Grimrud and Kebarle in 1973 [29] and Ekeberg [30] in 1988. When the heat production of an exothermic reaction is low, the probability for rearrangement is decreased. In addition, since the pressure in the ion source is high, the ions formed are efficiently thermalized, which further reduces the probability for rearrangement reactions. To produce larger clusters, several collisions between ions and neutral molecules must take place in the ion source. Therefore, the protonated dimer might have enough internal energy to rearrange while the higher clusters exist on a lower energy level. Thus, we suggest that no rearrangements take place. The higher clusters have higher degrees of freedom, which make them even more stable.

The first series of the protonated ethanol, $\text{C}_2\text{H}_5\text{OH}_2^+$, gives fragments such as $\text{C}_2\text{H}_4\text{OH}^+$ at m/z 45, CH_2OH^+ at m/z 31, C_2H_5^+ at m/z 29, and H_3O^+ at m/z 19. These

ions are formed by elimination reactions and α -cleavage. The second category corresponds to proton bound ethanol clusters of the general formula: $(\text{C}_2\text{H}_5\text{OH})_n\text{H}^+$, for $n = 1, 2, 3$, and 4 at m/z 47, m/z 93, m/z 139, and m/z 185, respectively. CID verified the structures of the clusters. Successive losses of ethanol molecules were observed. The third series starts with protonated diethyl ether at m/z 75, $\text{C}_4\text{H}_{11}\text{O}^+$, which may have two possible structures; (1) the protonated diethyl ether structure or (2) protonated 2-butanol structure. The CID experiments confirmed the protonated diethyl ether structure. The ion at m/z 75 undergoes association with ethanol producing diethyl ether-ethanol proton bound clusters, $[(\text{C}_2\text{H}_5)_2\text{OH}^+(\text{C}_2\text{H}_5\text{OH})_n]$, for $n = 1$ and 2, at m/z 121 and m/z 167, respectively.

As in methanol and ethanol, the mass spectrum of 2-propanol contains both proton bound 2-propanol clusters, $[(\text{CH}_3)_2\text{CHOH}]_n\text{H}^+$ ($n = 1, 2$, and 3, at m/z 61, m/z 121 and m/z 181, respectively), and a proton bound di-isopropylether-propanol cluster at m/z 163. The structure of di-isopropylether is confirmed by comparing the CID mass spectrum of ions at m/z 103 in the 2-propanol/ CO_2 mixture with CID mass spectra of protonated di-isopropylether and protonated 2,3-dimethyl-2-hydroxy-butanol.

However, the ion chemistry of 2-propanol proved to be more complex than the ion chemistry in methanol and ethanol. The main difference using 2-propanol is the formation of the cluster between the protonated acetaldehyde (m/z 45) with the neutral alcohol. In the case of methanol and ethanol the α -cleavage fragments react to generate the protonated molecular ion and some decomposition products of the protonated alcohol. Protonated acetaldehyde, however, gives several different reactions with the neutral alcohol, (1) Proton transfer reactions, (2) proton transfer followed by displacement reactions, and (3) ionic dehydration. The proton transfer followed by displacement of H_2O is not equal to the condensation reaction of the protonated molecular ion, which generates protonated diisopropyl ether. Due to steric interactions, the product is assumed to be formed by an $\text{S}_{\text{N}}2$ reaction. The reaction between protonated acetaldehyde and 2-propanol is suggested to take place by a condensation reaction followed by proton transfer and then a rearrangement reaction, which takes place before H_2O is repelled.

The proton affinities of acetaldehyde and 2-propanol are 768.5 kJ/mol and 793.0 kJ/mol, respectively, implying that proton transfer from protonated acetaldehyde to 2-propanol is exothermic by 25 kJ/mol [31]. However, if the product $[\text{CH}_3\text{CH} = \text{O}-\text{CH}(\text{CH}_3)_2]^{+*}$ is formed with sufficient internal energy, it can possibly undergo rearrangement reactions and further fragmentation with formation of an ion at m/z 69. This presumption is supported by the observation that the decomposition can be obtained by collisional activation (CA) of the precursor ion at m/z 87.

Protonated acetaldehyde undergoes ion-neutral reactions with 2-propanol and produces an ion-neutral

complex at m/z 105. A displacement reaction is observed between protonated 2-propanol and propanol where the ion at m/z 79 is formed. The difference in reactivity may be related to the lifetimes and relative stability of the reaction intermediates. Longer lifetimes are expected to allow the more complex condensation process to compete favorably with some bond cleavage. The discussions and type of experiments performed are equal to the study of utilizing methanol as modifier; therefore we refer to the chapters above for further details.

A trend observed in these experiments is that the amount of alkyl ions increases with increasing molecular mass of RH, $\text{R} = \text{CH}_3$, C_2H_5 , and $2\text{-C}_3\text{H}_7$. When methanol, ethanol and i-propanol are used, the ratio between protonated alcohol and R^+ are 4:1, 3:1, and 1:1, respectively. Formation of these ions might influence the detection limit. If the sample molecules are able to be protonated, ionized by CE, and also have a significant alkyl cation affinity, the LOD will be higher. This is one example illustrating the importance of using a proper modifier.

The C_3H_7^+ ion is a possible proton donor and can be an important reagent ion for the detection of the analyte. The proton affinity (PA) of propene, $\text{CH}_3\text{CH} = \text{CH}_2$, is 750.3 kJ/mol [31], which in turn can improve the signal of the protonated analyte. This property is also present using ethanol. The difference between the PA of ethene and ethanol is about two times that of propene and 2-propanol. In addition, using ethanol as a modifier can improve the detection limit relative to using methanol. This is explained by a lower PA-value of ethene than that of methanol. This discussion is based upon an analyte that has a relatively low PA-value and fragments very easily. If the situation is such that the PA-value of the analyte is higher than the modifier, the reasons for choosing a modifier are opposite to what is taken into account here. In addition, the amount of ions formed increases with an increasing number of atoms in the modifier. The amounts of ions formed in the ion source increase in the following order: methanol, ethanol and 2-propanol.

Formation of protonated ethers from the corresponding alcohols is discussed above. The main reaction path when using i-propanol is assumed to correspond to a nucleophilic first-order substitution reaction. This assumption is supported by the high amount of C_3H_7^+ ions at m/z 43 relative to methanol and ethanol.

In contrast to utilizing ethanol, 2-propanol gives other adduct ions found at m/z 75. Using CID experiments and deuterium labeled compounds, this ion is identified to be $\text{C}_3\text{H}_7\text{OHCH}_3^+$. The most probable reaction path for formation of this adduct ion is a simple association reaction between CH_3^+ and $2\text{-C}_3\text{H}_7\text{OH}$.

The effect of the ion source repeller voltage on the ion-neutral reactions has also been studied. The general trend for all three alcohols is an increase of proton bound clusters with decreased ion source repeller voltage. When the ion source repeller voltage was in-

Figure 3. Intensities of the most abundant ions as a function of the ion source repeller voltage in the mass spectrum of 30% methanol in carbon dioxide.

creased, the mass spectra were dominated by protonated alcohol, ROH_2^+ , and the molecular ions of carbon dioxide. Only minor amounts of CO_2H^+ at m/z 45 were observed. This was the results of the low proton affinity (PA) of CO_2 compared with that of ROH . By choosing the appropriate ion source repeller voltage, different ionization conditions in the ion source were obtained. At high ion source repeller voltage, the mixture of CE and CI were observed as expected. The CO_2^+ has recombination energy ($\text{RE} = 13.8$ eV) that allows ionization and fragmentation of any organic compound. However, the fragmentation pattern depends on the amount of internal energy deposited in the ions, which in turn depends on the pressure in the ion source. At low ion source repeller voltage, CI conditions are obtained and the fragmentation patterns depend on the PA of the reagent ions and analyte. The intensities of the most abundant ions in the mass spectrum of the mixture of 30% methanol in carbon dioxide are plotted as a function of the ion source repeller voltage in Figure 3.

Conclusion

The use of 2-propanol as a modifier gives additional ions, which correspond to the different interaction products of acetaldehyde with the precursor alcohol. The formation of proton bound ether-alcohol clusters is due to association reactions, and is not caused by rearrangement or displacement reactions of higher order clusters followed by loss of water. The general trend for all three alcohols is the increase of proton bound clusters with decreased ion source repeller voltage. When using a high ion source repeller voltage, the mass spectrum is dominated by protonated alcohol and CO_2^+ .

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