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Solvation of Propanediol Ions by Water Molecules in the Gas Phase

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The thermochemical properties of protonated hydrates of 1,2- and 1,3-propanediols have been investigated using electrospray ionization-high pressure mass spectrometry. The binding enthalpies, entropies, and free energies of the stepwise hydration of protonated propanediols with one to three waters are reported. The observed negative entropy change [$\Delta\Delta S^o_{1,3}$ for the addition of the third water to 1,3-propanediol·$H^+(H_2O)_2$ suggests a stable structure due to an increased number of hydrogen bonds and the loss of the intramolecular hydrogen bond in the water cluster ion. The thermochemical properties of two isomers of butanediol were also investigated in order to further elucidate the structures of the protonated propanediols. (J Am Soc Mass Spectrom 2004, 15, 1123–1127) © 2004 American Society for Mass Spectrometry

Knowledge of the thermochemical properties of non-covalent bonds, particularly those involving water and biologically significant molecules, is fundamental in understanding the molecular interactions and changes in protein conformations. The role of ionic clusters and the thermodynamics of cluster formation is of interest to many wide ranging areas of chemistry such as stratospheric chemistry and polar stratospheric clouds [1], the chemistry in the ionosphere [2], and the elucidation of enzymatic reaction mechanisms [3].

A major advancement in methods to study solvated ions came with the development of electrospray mass spectrometry. This technique provided a solution to the difficulty of solvating doubly-charged ions [4] and provided information on the sites of protonation and proton affinities of gas-phase aromatic compounds [5]. Our laboratory has recently implemented this technique for the study of hydration of organic ions [6], thereby validating our experimental technique and method and providing new insights into the thermochemical properties of alkylammonium ions.

Leikin and co-workers have reported differential effects of 1,2- and 1,3-propanediol on collagen self-assembly [7]. 1,2-propanediol was found to weakly inhibit fiber assembly and did not affect the interaction between collagen helices in fibers while, at the same concentration, 1,3-propanediol strongly suppressed fibrillogenesis and eliminated the attraction between collagen helices. The ability of these two diols to inhibit fiber assembly differs by more than an order of magnitude. Leikin proposed that hydrogen-bonded water clusters bridging opposing collagen fiber helices were disrupted by competition due to the formation of crucial hydrogen bonds with 1,3-propanediol. It was suggested that the efficiency to destabilize fibers is dependent on the ability of a species to compete with water for crucial hydrogen bonds and disrupt water bridges.

In the present work, we sought to gain further insight into the interactions between water and the propanediols, and to contribute to a better understanding of fibrillogenesis inhibition. Reactions of protonated propanediols and water were studied using a variable temperature high pressure source mass spectrometer. Two protonated butanediols were also investigated to further characterize the effect of water on the propanediol structure.

Experimental

Apparatus

Experiments were carried out using a PE-Sciex API-1 (Sciex, Thornhill, Ontario, Canada) single quadrupole mass spectrometer having a variable-temperature, high pressure equilibrium ion source. We [6] as well as others [8, 9] have described details of this apparatus and experimental procedure and so only a brief outline of the apparatus and approach is presented here. Hydrated clusters of protonated propanediols were generated by spraying a 0.05% aqueous dilutions of propanediol at flow rates of 3 μL/min through an electrospray needle held at 6000 V at atmospheric
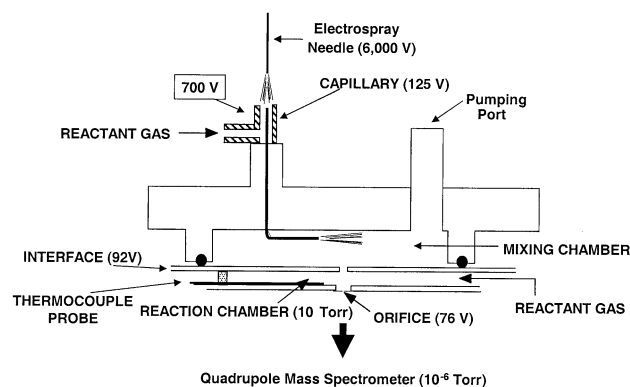
Figure 1. Schematic of the high-pressure electrospray ion source.

pressure. A schematic diagram of the source is shown in Figure 1. Ions were drawn through a pressure reducing capillary (CAP) into the mixing chamber (MC) formed by a plate mounted on a standard API-1 interface plate but insulated from it. The backing plate and capillary were set at 125 V and the interface plate at 92 V. Pressure within the MC was maintained at 10 torr by throttling a mechanical pump through an adjustable valve. In the MC, ions encountered a known concentration of reactant gas, water vapor at 10–60 mTorr diluted in a nitrogen buffer. The reaction chamber (RC) was formed between the interface and orifice plates, the latter maintained at 76 V. Ions drifted into the reaction chamber and equilibrium was established there prior to the ions being sampled through a 100 μm sampling orifice centered in a 50 μm thick Ni foil. The sampled ions were scanned using a quadrupole mass spectrometer, and detected by a channel electron multiplier. The distance between the back of the MC and the interface plate was 0.88 cm and 0.58 cm between the interface and orifice plates.

The ideal equilibrium source would have no electric fields within it to induce ion motion, but this condition is unattainable in practice. In this work, the fields within the reaction and detection regions of our apparatus were set to maximize ion intensities while minimizing the possibility of perturbing thermalized water cluster ion distributions. The electric field strengths were calculated to be 3.9 V/cm·torr in the MC and 2.7 V/cm·torr in the RC. These value are comparable to those used by Klassen, et al. [8] in the apparatus upon which ours was modeled, and lower than the values used by Castleman and coworkers that have been shown to be acceptable for attaining equilibrium distributions of cluster ions [10, 11]. In addition, we have previously shown that perturbations in ion ratios as a function of electric field strength are absent in this configuration of the apparatus [6]. Mass dependent discrimination of signal intensities in ion transmission are a possibility in any quadrupole mass analyzer, but they are likely to be most severe for the lowest molecular weight species, the protonated diols and their first

hydration states. Hovey and Likholyot [12] showed that to compensate for this, measured ion intensities should be weighted by the square root of ionic mass. Applying this correction to an ion ratio would amount to a ΔG_{298} of 0.2 kcal/mol, well within our experimental uncertainty.

Under typical operating conditions of 10 torr in the MC-RC region and $\sim 6 \times 10^{-7}$ torr in the quadrupole region, gas flow rates through the sampling capillary were measured at 760 L·torr/min. The Poisuille equation was used to estimate a flow of 1.1 L·torr/min through the sampling orifice under these conditions. The reaction gas mixture of water and nitrogen was delivered at a total flow rate of 2.3 L·atm/min, but was divided between a countercurrent flow of 2 L·atm/min at the sampling capillary and 0.3 L·atm/min into the RC. Water concentrations were measured using a relative humidity probe inserted into the reaction gas flow stream. The possibility of a gradient in water concentration between the RC and MC is unlikely for two reasons. First, the distance between the two chambers is short and the connecting aperture is of a large cross section. Second, the reaction gas is supplied externally to the capillary and, while altered in composition by the electrospray vapor and atmosphere, this flow will have a propensity to modulate any tendency in the development of a gradient.

Reaction temperatures were measured using a thermocouple placed at the Ni foil of the orifice. Temperatures above ambient were attained using the built-in API-1 external source heater. Sub-ambient temperatures were achieved by cooling the source housing with a liquid nitrogen-cooled stream of "zero grade" air gas flowing through the coils of 1/8 in. o.d. copper tubing wrapped around the source housing in a blanket of glass wool.

Materials

Gases, both nitrogen and "zero grade" air, for these experiments were obtained from in-line purification systems. A Whatman (Haverhill, MA) Model 76-803 Zero Grade Air generator was used to remove hydrocarbons and water vapor from laboratory high pressure air lines. A Whatman Model 75-72 Nitrogen Generator was used to produce 0.995 fractional purity nitrogen, free of hydrocarbons, oxygen, and water using the same high pressure laboratory air lines. Doubly distilled deionized water was obtained using a laboratory scale water purifier (HydroServices, Research Triangle Park, NC) from house distilled water. Reagent grade diols were obtained from Sigma-Aldrich. (St. Louis, MO) and used as received.

Basis of the Experiment

Cluster formation can be represented by a series of stepwise association reactions of the form represented by the general reaction:

$$IL_n{}^+ + L \leftrightarrows IL_{n+1}{}^+ \tag{1}$$

where $IL_{n+1}{}^+$ designates a cluster ion composed of an ion, I, containing n ligands of constituent L. Collisions of energetically activated intermediates in the clustering sequence with a third-body are necessary for stabilization of the complexes. Taking the standard state to be 1 atm, and making the usual assumptions [10] concerning ideal gas behavior and the proportionality of the chemical activity of an ion cluster to its measured intensity, the equilibrium constant $K_{n,n+1}$ and the free energy $\Delta G^\circ_{n,n+1}$ for the nth clustering step is given by:

$$lnK_{n,n+l} = ln\frac{[IL_{n+l}]}{[IL_n][P_L]} = -\frac{\Delta G^0_{n,n+l}}{RT}$$

$$= -\frac{\Delta H^0_{n,n+l}}{RT} + \frac{\Delta S^0_{n,n+l}}{R} \tag{2}$$

$$\Delta G^0_{n,n,+l} = \Delta H^0_{n,n+l} - T\Delta S^0_{n,n+l} \tag{3}$$

Here, $[IL_{n+1}]$ and $[IL_n]$ represent the respective measured ion intensities, P_L the pressure (atm) of the clustering species (L), $\Delta G^\circ_{n,n+1}$, $\Delta H^\circ_{n,n+1}$, and $\Delta S^\circ_{n,n+1}$ the standard Gibbs free energy, enthalpy, and entropy changes, respectively, R the gas-law constant, and T absolute temperature. By measuring the equilibrium constant $K_{n,n+1}$ as a function of temperature, the enthalpy and entropy change for each sequential association reaction can be obtained from the slope and intercept of the van't Hoff plot ($lnK_{n,n+1}$ versus $1/T$).

Results and Discussion

We have previously demonstrated that, under the conditions used for these measurements, the ion currents for the species of interest are sampled from an equilibrium distribution with no observable perturbation [6]. In addition, this previous work yielded thermodynamic values that were equivalent to previous publications. Equilibrium constant measurements were performed by measuring the ion intensities I_n and I_{n+1} of the corresponding hydrates as a function of water concentration. Equilibrium constants were determined at different temperatures, and used in a van't Hoff plot to obtain the enthalpy and entropy changes. The data were fit by a linear regression and values reported along with their 95% confidence intervals. The van't Hoff plots for the hydration of the propanediols are shown in Figure 2. Table 1 summarizes these results.

Table 1 shows that we were able to determine energetics only for the addition of the second and third waters to $(1,2\text{-propanediol})H^+$. Our inability to measure the addition of the first water is a consequence of very low ion intensities for the unhydrated ion, $(1,2\text{-propanediol})H^+$ at the maximum temperature our apparatus can reach. The calculated values for this first hydration that appear in Table 1 were estimated in the
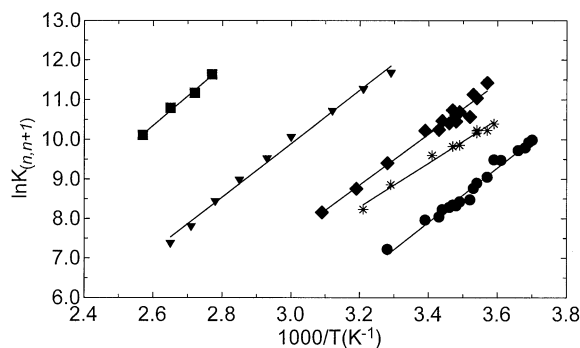
Figure 2. The van't Hoff plots (natural logarithm of the equilibrium constant versus the reciprocal absolute temperature) of the filled square *(0,1)*, filled diamond *(1,2)*, filled circle *(2,3)* hydrations of $H^+(1,3\text{-propanediol})$ and filled triangles *(1,2)*, asterisks *(2,3)* hydrations of $H^+(1,2\text{-propanediol})$.

following manner. Making use of the equilibrium constant observed at 377 K, we calculated the free energy at that temperature to be −9.4 kcal/mol. Based on earlier work from our laboratory using the same experimental technique and apparatus [6], the mean $\Delta S^\circ_{0,1}$ of nine n-alkylammonium hydration data sets was determined to be −23.5 cal/(deg. mol). Using the ΔG_{377K} and this value of ΔS° from the n-alkylammonium results, $\Delta H^\circ_{0,1}$ is estimated to be −16.4 kcal/mol. Since experimental techniques that employ van't Hoff plots lead to enthalpy changes derived from slopes, which are often represented as straight lines over moderate temperature ranges, the enthalpy change for the 1,2-propanediol is assumed to be constant. This is a reasonable assumption since the enthalpy change is a weak function of temperature due to the negligible difference in the heat capacity, ΔC_p, between products and reactants [11]. Our inability to observe reasonable signal intensity for the unhydrated $(1,2\text{-propanediol})H^+$ within the range of temperatures attainable in our apparatus suggests that strong binding exists between the first water ligand and the unhydrated ion; our current experimental technique is unable to break this bond. Most likely, this is a consequence of a very stable internal hydrogen bonded structure for the singly hydrated ion.

With regard to the 1,3-propanediol data shown in Table 1, one might expect decreasing enthalpy and entropy changes for increasing extents of hydration as is observed for the 1,2-propanediol and in other systems such as the hydration of alkylammonium ions [6] and indeed for essentially any ionic system [5, 8–11, 13]. The decrease in ΔH anticipated for the addition of successive water molecules to the ion is reversed in going from the second to the third water. This is accompanied by the observation of a large decrease in entropy. The dramatic difference in the enthalpy and entropy changes of the second and third water addition to $(1,3\text{-propanediol})H^+$ suggests that $(1,3\text{-propanediol})H^+(H_2O)_3$ has a more stable structure than does the di-hydrated species.

It is not unreasonable to assume that the protonated

Table 1. Hydration energies of protonated propane- and butanediols

Ions	(n,n + l)	$-\Delta G°_{298K}$ kcal/mol	$-\Delta H°$ kcal/mol	$-\Delta H°$ cal/(deg. mol)
(1,2-propanediol)H^+	(0,1)	9.4[a]	16.4	23.5[b]
	(1,2)	7.3 ± 0.8	13.4 ± 0.4	20.6 ± 1.3
	(2,3)	5.4 ± 0.9	10.9 ± 0.4	18.5 ± 1.5
(1,3-propanediol)H^+	(0,1)	9.4 ± 1.9	14.6 ± 1.1	17.3 ± 2.9
	(1,2)	5.8 ± 1.3	12.6 ± 0.6	22.8 ± 2.1
	(2,3)	4.5 ± 1.2	13.6 ± 0.5	30.7 ± 1.9
(1,3-butanediol)H^+	(1,2)	5.5 ± 0.7	11.6 ± 0.3	20.5 ± 1.1
	(2,3)	4.4 ± 1.7	8.9 ± 0.8	15.1 ± 2.8
(1,4-butanediol)H^+	(1,2)	5.5 ± 0.9	12.3 ± 0.5	22.7 ± 1.5
	(2,3)	4.0 ± 0.7	11.3 ± 0.3	24.7 ± 1.1

[a]Free energy was calculated at 377 K.

[b]Entropy change was estimated from the average $\Delta S^o_{0,1}$ of previous alkyl ammonium hydration results [6].
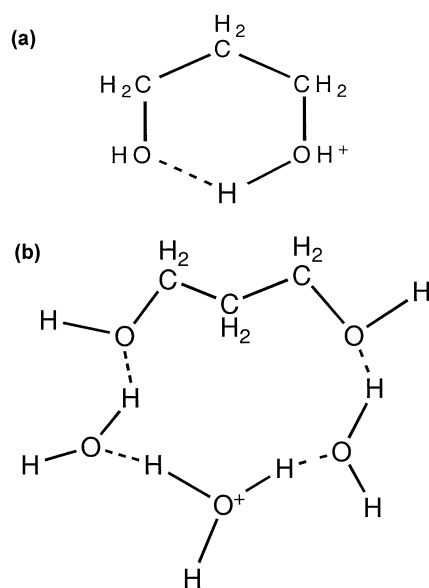
form of 1,3-propanediol contains an intramolecular hydrogen bond that induces a cyclic structure, this assumption is based on previous investigations of 1,3-propanediol and other bidentate ligands [14–17]. A schematic structure for the protonated ion, based on structures proposed previously [19, 20] is shown in Figure 3a. Upon the addition of water ligands to the protonated 1,3-propanediol, the ion can no longer be cyclic and the hydroxyl groups are free to move unrestrainedly. With the addition of the third water molecule to the ion, the structure of the system changes significantly, as suggested by the values of Table 1 and again assumes a different cyclic structure, one arising from intermolecular hydrogen bonds, in contrast to the intramolecular bonds of the protonated diol. A possible structure for this species is shown schematically in Figure 3b. Future efforts will be directed toward con-

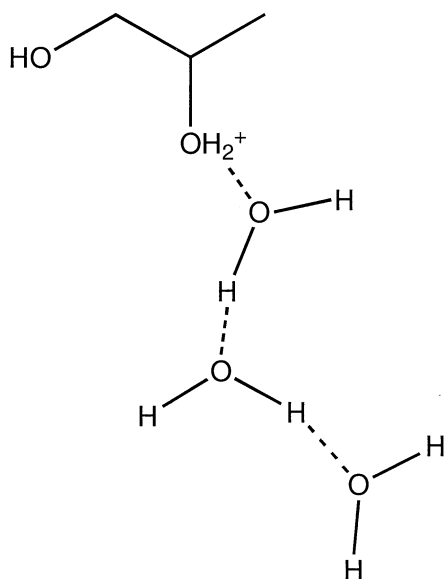firming the nature of this structure through appropriate calculations.

The proton most probably resides on propanediol of 1,3-propanediol·H^+(H_2O)$_n$ for n = 0, 1, 2, and not on water, since the diol's measured proton affinity is 210.3 kcal/mol and water's proton affinity is 165 kcal/mol [14, 18]. At n = 3, the proton possibly shifts to a water molecule. This conclusion is similar to the results of mixed monofunctional alcohols and water of the type (M)$_n$(H_2O)$_m$$H^+$, where M has a proton affinity greater than water, and n and m are the number of M and H_2O ligands, respectively, in the cluster ion [19, 20]. Hydrogen bonding is an important factor in the stability of the cyclic structure induced by the intramolecular hydrogen bond, but for larger cluster ions such as 1,3-propanediol·H^+(H_2O)$_3$, the critical factor is the number of hydrogen bonds that are formed. Hence, the number of hydrogen bonds formed influences the stability of the 1,3-propanediol·H^+(H_2O)$_3$, not the proton affinity of the diol.

The thermochemical properties of protonated 1,3- and 1,4-butanediols was determined in our study for the (1,2) and (2,3) hydration steps since a large negative entropy change was reported due to the formation of a cyclic structure upon protonation of 1,4-butanediol [14]. It was not possible to determine the equilibrium ratios for the (0,1) hydration step due to the presence of a water cluster ion [H^+(H_2O)$_5$], which is isobaric with the protonated butanediols [$C_4H_8(OH)_2$]H^+. Similarly, at temperatures less than 20 °C, H^+(H_2O)$_6$ is a minor ion that is isobaric with the protonanted butane diol monohydrate, thus the (1,2) hydration step of butanediol was not measured below 20 °C. (See Table 1.)

From the butanediol study, the hydration of 1,3-butanediol·H^+ results in a decreasing trend in the enthalpy, entropy, and free energy. This suggests to us the formation of a chain-like structure for the 1,3-butanediol·H^+(H_2O)$_3$, as shown in Figure 4, incorporating a water ligand hydrogen bound to the hydroxyl group of the diol and then to other water ligands in a chain. This is in contrast to the closed structure associated with the protonated hydroxyl group postulated for

Figure 3. Schematics emphasizing cyclic structures for (a) (1,3-propanediol)H^+ and (b) (1,3-propanediol)·(H_2O)$_3$$H^+$. Hydrogeen bonds are shown as dashed lines.

Figure 4. Schematic of 1,3-butanediol·$(H_2O)_3H^+$ emphasizing chain structure. Hydrogen bonds are shown as dashed lines.

the 1,3-propanediol. While one might expect similar behavior between the two 1,3-diols, the data in hand do not support such an expectation. The measurements of 1,4-butanediol·H^+, yielded enthalpy and entropy changes for the second and third uptakes that are equal within experimental error. This equivalence suggests an ordering of water ligands around the charge site and a network of hydrogen bonds which shows no preferential orientation of the water molecules. The lack of change in enthalpy and entropy values is perhaps expected, however, since 1,4-butanediol is predicted to have an intramolecular cyclic structure upon protonation [14].

Conclusions

Results suggest that the protonated form of 1,3-propanediol is capable of forming favorable stable structures with increasing degree of hydration compared to protonated 1,2-propanediol. The formation of stable gas phase structures of hydrated 1,3-propanediol at increasing degrees of hydration is due to its ability to form a network of hydrogen bonds. There is no reason to suspect that both propanediols should have similar thermodynamic properties and the same structures after protonation, and this is evident in our study. These results do, however, tend to confirm the hypothesis that 1,3-propanediol could inhibit collagen fibril self-assembly through the blocking of collagen intramolecular hydrogen bonds.

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