

**SPECIAL FEATURE:
HISTORICAL****Equilibrium Studies of the Solvated Proton by High Pressure Mass Spectrometry. Thermodynamic Determinations and Implications for the Electrospray Ionization Process****Paul Kebarle***

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ORIGIN OF THE MEASUREMENTS AND SIGNIFICANCE TO GENERAL CHEMISTRY AND GAS-PHASE ION CHEMISTRY

The paper selected as a historical feature by the *Journal of Mass Spectrometry*, 'The Solvation of the Hydrogen Ion by Water Molecules in the Gas Phase. Heats and Entropies of Solvation of Individual Reactions: $\text{H}^+(\text{H}_2\text{O})_{n-1} + \text{H}_2\text{O} \rightarrow \text{H}^+(\text{H}_2\text{O})_n$ ' by Kebarle, Searles, Zolla, Scarborough and Arshadi, reprinted directly preceding this article, was indeed a milestone in the research of my group. It and the subsequent work that it spawned had a significant impact in several areas: gas-phase ion thermochemistry, solvent effects on ions in solution, theoretical quantum mechanical calculations of reactions involving ions, modeling of solvent effects on ions and modern analytical mass spectrometry involving ion desolvation methods such as matrix-assisted laser desorption/ionization (MALDI) and electrospray.

In this commentary, I will attempt to give a brief overview of the developments in the above areas. Before covering this material, I want to describe briefly how we came to do the work in the reprinted paper.¹ The paper¹ has two novel features: (a) the species involved are complexes between ions and solvent molecules and (b) conditions were found where ion–molecule reaction equilibria are established and the positions of the equilibria can be determined, and in doing this one obtains the thermochemistry for the reactions, i.e. the free energy ΔG° , the enthalpy ΔH° and the entropy change ΔS° . Thermochemical results from ion equilibria in solution, compiled in the form of acid–base dissociation constants, stability constants for ion–ligand complexes and electrochemical reduction potentials, represent the quantitative backbone of ion chemistry in solution. The

ion–solvent equilibria first measured in the reprinted paper and subsequently developed to include many other gas-phase ion equilibria and their thermochemistry, led thus to a bridging of the fields 'ions in solution' and 'ions in the gas phase.'

The work leading to the 1967 paper¹ and the subsequent developments did not originate as a deliberate attempt to determine ion–molecule equilibria in the gas phase. The occurrence of equilibria was observed accidentally when performing experiments under unusual conditions.

Radiation chemistry was an important research area in the years after World War II, i.e. in the 1950s and 1960s. The effects of ionizing radiation were very much brought to the fore by the development of nuclear weapons. The ionic part of the reactions induced by ionizing radiation in gases was amenable to mass spectrometric investigation. The first investigations of ion–molecule reactions, with more or less conventional low-pressure mass spectrometers, by Talrose and Lubimova,² Stevenson and Schissler³ and Field, Franklin and Lampe⁴ were in part inspired by the interest in radiation chemistry.

To achieve numerous ion–molecule collisions, the ion sources were gradually operated at higher and higher pressures. At pressures of 1 Torr (1 Torr = 133.3 Pa), abundant ion–molecule reactions are observed. However, conventional radiation chemistry of gases was studied at 1 atm and there were reasons to believe that at such high pressures the outcome of the ion–molecule reactions might be different.⁵ For this reason, my first postdoctoral fellow, Nata Godbole and I decided around 1962 to try to observe ion–molecule reactions mass spectrometrically at or near 1 atm.

Three modifications of conventional mass spectrometers were required to achieve that task: reduce the ion source gas outflow by making the ion exit slit very small; increase the pumping speed outside the ion source; and increase the penetrating power of the ionizing medium. The first two changes had been applied

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by previous workers²⁻⁴ but not radically enough. For example, in earlier work increased pumping was sought using additional pumping lines with ~1 in diameters. As a graduate student I had encountered the classical text on vacuum technique by Saul Dushman and had picked up the equations required for evaluating what pumping speed was required for a given gas load. On that basis, I could calculate that for an ion source at near atmospheric pressure one would need pumping speeds of some 500–1000 L s⁻¹ and if that was to be achieved with 1 in pumping lines, hundreds of such lines would be required. Another coincidence also helped. While doing postdoctoral work with Fred Lossing at the Canadian National Research Council in Ottawa, we had been interested in detecting, with a mass spectrometer, free radicals produced by flash photolysis. Such apparatus had been constructed by Kistiakowsky and Kydd⁶ at the Chemistry Department of Harvard. As this was toward the end of my postdoctoral work, I was looking for jobs and had an interview at the Dow Chemical Laboratory near Framingham, MA, which is near Boston. On my way back after the interview (the Director of the laboratory was Fred McLafferty and I did not get the job), I had a few hours stayover in Boston and decided to try to visit the laboratory of Kisti and Kydd. It was a Saturday and the Harvard campus was very quiet. I found my way to a door that said 'Dr Kydd.' It was open, but when I entered, nobody was there. I spent a few minutes looking around the laboratory. On one large table were many broken, sometimes quite pulverized, UV light sources which were electrical discharge sources made of helical fused-silica tubes. I could see that the flash discharges had been too powerful. The central piece in the room was a giant, 20 in diffusion pump mounted inside a rack and the top lid of the pump was off. When I peeked into the pump I could make out on the wall, a small, black box that looked like an ion source and on the diametrically opposed wall was another small box that looked like an ion detector. Then it dawned on me that this was a time-of-flight mass spectrometer where the 'flight tube' was the open diameter of the pump. So here was a radical solution. If you want high pumping speed use a very large pump and do your mass spectrometry in the throat of the pump.

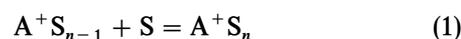
When I returned to Ottawa, I soon forgot about the flash photolysis idea, but a few years later the high pumping speeds needed for the near atmospheric pressure mass spectrometer reminded me of the radical solution, 'work in the throat of the pump,' and we used this idea, although with a relatively smaller 6 in diffusion pump, and we approached the 'in-the-throat' idea more gradually. As a penetrating ionization medium, we used α particles from a polonium α source. Mass analysis was obtained with a 90° magnetic sector on which we fitted an electron multiplier, a novelty at that time. Soon we saw the first ions and mass spectra, when working at ion source pressures between 10 and 300 Torr. The mass spectra were very hard to interpret. When a single gas was introduced, such as nitrogen, oxygen or argon, we did not see any ions which could be attributed to the gas used, i.e. no N-containing ions were observed with N₂, no O₂⁺ ions with O₂, and so on. One observation that became significant was the

presence of ion groups whose mass differed by 18 units. Of great help was the report by Knewstubb and Tickner⁷ of the mass spectrometric observation of H₃O⁺(H₂O)_n cluster ions in gas discharges at low pressures. Our ions seldom had H₃O⁺ as the core ion. Rather, core ions of all kinds of possible masses occurred when the above 'pure' gases were used.

It took us some time to realize that even though water vapor was the major impurity in the gases used, and therefore hydrates X⁺(H₂O)_n were observed, other impurities present at much lower levels determined the nature of the observed core ion. The picture became clearer after we worked⁸ with some neat gases with high gas phase basicities such as NH₃, which led to core ions which were predominantly NH₄⁺ and clusters of NH₄⁺(NH₃)_n.

Today, the detection of trace gases at levels as low as parts per billion represents the well established analytical technique known as atmospheric pressure ionization (API)⁹ or, at lower pressures, chemical ionization (CI).¹⁰ Today also, complete accounts can be given¹¹ on how the initial ions produced by the primary ionization of the major gas (air or N₂ in API) are converted by ion-molecule reactions to analyte ions involving the trace gas analyte. At the time when the first API experiments were performed,^{1,5,8} the sensitivity to trace gases represented an undesired hurdle. To avoid mass spectra dominated by unknown trace impurities, the major gases used had to be extremely pure and the gas handling systems had to be of ultra-high vacuum quality, i.e. of glass and metal only so as not to retain previously used compounds. When such changes were made, the ions observed became more predictable. Thus, H₃O⁺(H₂O)_n ions were observed with water vapor in the ion source and not X⁺(H₂O)_n due to some unknown trace impurity B with high proton affinity which took the proton away from H₃O⁺.

Observations^{8a,b} of the mass spectral intensities of NH₄⁺(NH₃)_n with neat NH₃ and of H₃O⁺(H₂O)_n with neat H₂O vapor^{8c} at increasing pressure of the solvent vapor and at different ion source temperatures indicated that ion-molecule equilibria were present. Thus, at constant temperature when the solvent S pressure was increased a shift of the cluster ion intensities to higher *n* was observed. An increase in ion source temperature at constant pressure led to shifts towards lower *n* values. Realizing that if equilibria really did occur then their determinations would lead to far more important results than the radiation chemistry investigations, we concentrated fully on developing conditions for equilibria measurements. If equilibria were present the ion peak intensities *I_n* should obey the equilibrium equations, i.e. for the ion A⁺-solvent molecule S association reactions (1):



$$K_{n-1,n} = \frac{I_n}{I_{n-1}P_S} \quad (2)$$

at solvent pressure *P_S*, the equilibrium constant expression Eqn (2) should be obeyed, and experiments showed that this was most often the case.

Even though relationships such as Eqn (2) were found to be obeyed, we remained skeptical for some time. The

conditions in conventional mass spectrometer ion sources are far removed from thermal equilibrium conditions, so why is one able to observe thermal equilibria at high pressures? Understanding came only gradually. The high pressures used slowed very much the diffusion of the ions to the wall, which increased greatly the residence time of the ions in the ion source. The ions were thus partially trapped in the ion source. The long time allowed the reaction equilibria to be established. The high-pressure gas was also ideal for thermalizing the ions. The low intensity of ionizing radiation used led to low ion and electron concentrations so that ion–electron recombination was slower than diffusion to the wall, so that the ion loss kinetics were first order. This dependence led to simple kinetic conditions in the ion source.

Further reassurance that equilibria were present and were being determined came from the actual thermochemical values that were obtained. The values of $\Delta H_{n-1,n}^\circ$ and $\Delta S_{n-1,n}^\circ$ obtained were of the right order of magnitude. There were very few data available in the literature with which to compare the results. This becomes clear from the reprinted paper.¹ Thus, on p. 6397 we try to establish that the determined $\Delta H_{n-1,n}^\circ$ values are of the right order by comparing them with estimated values for the enthalpy of hydration of the proton, H^+ , which corresponds to the enthalpy change for the transfer of 1 mol of protons from the gas phase to aqueous solution. Values for these quantities based on thermodynamic cycles had been obtained (see Refs 11 and 12 in the 1967 paper¹). Another comparison with literature results is given by Eqns (2) and (3) in Ref. 1, which assume that the hydration exothermicity of H_3O^+ by four additional water molecules should be similar to that for Na^+ . Note that the literature values for Na^+ are based on electrostatic calculations, i.e. Ref. 18 in Ref. 1. Both comparisons illustrate that not only were there very few literature data available with which to make comparisons, but also that these data were unsuitable and unreliable. Classical electrostatic calculations seldom provide accurate data. What was missing were good *ab initio* theoretical calculations. These came later (see subsequent discussion). There were also no literature data for the entropy changes, $\Delta S_{n-1,n}^\circ$, with which the experimental results¹ could be compared. However, because the reactions were expected to be dominated by the large loss of translational entropy due to the association of the solvent molecule with the ion, it could be shown (see p. 6393 in Ref. 1) that the experimental $\Delta S_{n-1,n}^\circ$ values are of the right magnitude.

The measurement of ion–solvent and ion–ligand equilibria were extended to many other positive ions (NH_4^+ , Li^+ , Na^+ , K^+ , Rb^+ , Cs^+ , Pb^+ , Sr^+ , $C_2H_5^+$, CH_3CO^+ , etc.) and negative ions (OH^- , F^- , Cl^- , Br^- , I^- , CN^- , NO_2^- , NO_3^- , etc.) with a variety of ligands (H_2O , CH_3OH , CH_3CN , SO_2 , phenol, etc.). For a review of early work, see Kebarle,¹² and for later work from various laboratories, see Keese and Castleman.¹³

Improvements to the apparatus¹ used also followed. Since we had decided that it would be far more interesting to measure ion–molecule equilibria than to solve problems in radiation chemistry, we could move to lower ion source pressures in the 3–10 Torr region. The ionizing radiation could be much less penetrating at

these pressures and we settled on 2000 V electrons. The electron beam could be pulsed and this allowed kinetic measurements so that not only the equilibrium ion ratios but also the kinetics of the approach to equilibrium could be determined. The fully developed, pulsed high ion source pressure mass spectrometer and the methodology used have been described.¹⁴ Other research groups joined the field. High ion source pressure instruments for equilibria determinations were used by Meot-Ner and co-workers,¹⁵ Tang and Castleman,¹⁶ Meisels *et al.*,¹⁷ Jennings and co-workers,¹⁸ Stone *et al.*,¹⁹ Hiraoka *et al.*,²⁰ McMahon and co-workers²¹ and, more recently, Bowers and co-workers²² and Jarrold and co-workers.²³

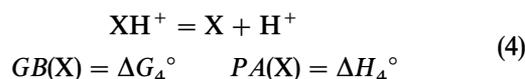
Even though then state-of-the-art quantum chemical computations would have been able to provide good predictions of binding energies for ion–molecule complexes such as $H_3O^+H_2O$, at the time when the paper¹ appeared, no such calculations had been made. However, publication of the results¹ led to a stream of theoretical computations for the $H_3O(H_2O)_n^+$ system of which we quote only a few here.^{24–26} Both the early calculations^{24,25} and more recent work²⁶ predicted values within a few kcal mol⁻¹ of the experimental results.¹ Similarly, recent experimental results based on the very different collision-induced dissociation (CID) energy threshold technique²⁷ have provided results in excellent agreement with the ion equilibria data.¹² Hence the 30-year-old data¹ which were essentially the first quantitative data obtained with the then new equilibrium technique have stood up very well, much better than we would have dared to hope at the time.

The availability of the experimental data for other core ions such as the alkali metal ions¹² and other metal ions¹³ further stimulated *ab initio* theoretical work²⁸ which also led to the development of ion–solvent molecule pair potential functions. These were used for modeling by Monte Carlo or molecular dynamics techniques, of ion–solvent molecule interactions where one ion interacted with a large number of solvent molecules.²⁹ Recent work by Karplus and co-workers³⁰ provides an illustration of such modeling to determine hydration thermodynamics of proteins. Gas-phase ion equilibrium solvation data for charged carboxy groups determined by Meot-Ner³¹ provide guidance for the simulation of the interactions.³⁰

A very important extension of gas phase ion thermochemistry based on ion–molecule equilibria occurred with the first measurements of proton transfer equilibria such as



Determination of the equilibrium constant K_3 , the equilibrium constant for reaction (3), leads to the free energy change ΔG_3° . The basicity of a compound X is defined by the free energy change ΔG° for the deprotonation reaction (4) while the proton affinity corresponds to the ΔH° change for the same reaction:



The free energy ΔG_3 obtained for the proton transfer equilibrium (3) thus provides the difference in the gas-phase basicity whereas ΔH_3 provides the difference in

the proton affinities:

$$\begin{aligned}\Delta G_3 &= GB(\text{NH}_3) - GB(\text{CH}_3\text{NH}_2) \\ \Delta H_3 &= PA(\text{NH}_3) - PA(\text{CH}_3\text{NH}_2)\end{aligned}\quad (5)$$

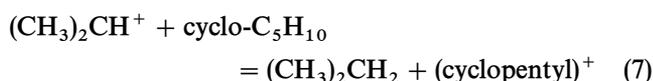
Determination of proton transfer equilibria involving a series of compounds with gradually increasing basicities can be used to obtain a scale of relative basicities. The scale can then be calibrated to one known absolute basicity ΔG_4° determined by some other method, yielding a scale of absolute basicities. An analogous procedure with enthalpy changes leads to scales of proton affinities.

Proton transfer equilibria measurements were initiated independently and at approximately the same time with the ion cyclotron resonance (ICR) mass spectrometer^{32,33} and the high-pressure mass spectrometer.³⁴ The proton transfer equilibria measurements with the low-pressure ICR ion source were made possible by the development of the trapped ion cell by McIver³⁵ which trapped the ions in the z direction by means of electric fields. This, combined with the magnetic trapping field in the x,y direction, increased the ion residence times to seconds and in later developments to hours. It is interesting to note that the trapped ion cell development³⁵ was an essential contribution to the subsequent development of the Fourier transform (FT) ICR, i.e. the FTMS method.³⁶

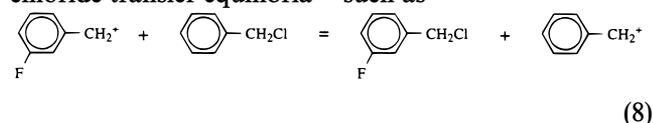
Proton transfer measurements involving acids, as for example



led to gas-phase acidity scales.^{37,38} Hydride ion transfer equilibria such as

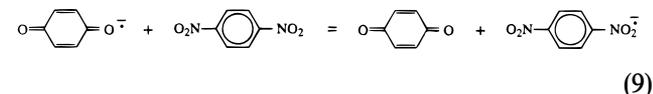


initially investigated by Meot-Ner and Field³⁹ and later also determined in the present laboratory, as well as chloride transfer equilibria⁴⁰ such as



led to scales of hydride and chloride ion affinities which provide a measure of the stabilities of carbocations.

Measurements of electron transfer equilibria^{41,42} such as



have provided the electron affinities of over 200 compounds.

The output from proton transfer, hydride transfer and electron transfer equilibria has provided some 3000 gas-phase basicities and proton affinities, gas-phase acidities, electron affinities and carbocation heats of formation.⁴³

As had been the case for the ion-solvent molecule data, the experimental proton transfer, hydride ion transfer and electron transfer data stimulated extensive *ab initio* computational work which provided comple-

mentary information on the energetics and also the structures of the ionic reactants. Since the reactions involved had direct counterparts in solution and involved mostly organic compounds, the combined experimental and theoretical work had a major impact on physical organic chemistry. Various long-standing questions and controversies were clarified and resolved. The following are just a few examples from a very large body of work: the anomalous order of basicities of alkyl amines in solution, i.e. the 'amine anomaly',⁴⁴ the Baker-Nathan effect,⁴⁵ which invoked hyperconjugation to explain the underlying electronic changes produced by substituent effects,⁴⁶ and the long-standing classical and non-classical norbornyl controversy.^{39,41,47}

Physical organic chemistry based on condensed-phase experimental work was a prominent and active branch of organic chemistry from 1950 to 1980. Today this discipline engages a considerably smaller number of organic chemists. While other factors may also be involved, the intervention of accurate and definitive data based on gas-phase ion equilibria and the information due to modern theoretical calculations played a very important role. In particular, these data provided a clear distinction between intrinsic effects at the molecular level and solvent effects. The unraveling of these effects allowed many talented condensed-phase organic chemists, engaged previously in physical organic chemistry, to cross into more fertile fields such as bioorganic chemistry.

GAS-PHASE ION CHEMISTRY AND FUNDAMENTALS OF ANALYTICAL MASS SPECTROMETRY

The beginnings of systematic development of gas-phase ion chemistry, which relates to the fundamentals of analytical mass spectrometry, can be seen in qualitative work such as that of McLafferty⁴⁸ aiming to explain the observed ions and abundances in electron ionization mass spectra, and in quantitative efforts such as the quasi-equilibrium theory of mass spectra.⁴⁹ Measurements of the activation energies for the observed fragmentations based on electron ionization and photoionization appearance potentials⁵⁰ represent the energetics complement to the theory of mass spectra and the first development of gas-phase ion thermochemistry.

The study of gas-phase ion-molecule reactions²⁻⁴ developed as a separate discipline which initially appeared to have no application to analytical mass spectrometry. As indicated in the preceding section, one of the applications was to radiation chemistry. However, ion-molecule reactions were of interest also for many other reasons; thus, the reactions, when exergic, proceeded without activation energies and the collision rates were very high. This was a truly new class of processes in reaction kinetics that had to be examined. Also, there were many applications other than radiation chemistry such as ionospheric reactions,⁵¹ gaseous electronics⁵² and, most importantly, the relationships between ionic reactions in the gas phase

and in solution which were described briefly in the preceding section. Ion-molecule reactions had grown to become the distinct field of gas-phase ion chemistry.⁵³

Ion-molecule reactions turned out to have an important analytical application. Chemical ionization (CI), introduced by Munson and Field,¹⁰ is viewed as the first 'soft' ionization technique and this technique still represents an important branch of analytical mass spectrometry. Gas-phase ion chemistry and its energetics component based on ion-molecule equilibria clearly represent⁵⁴ the fundamental basis for CI. Thus, the analyte ionization is based on proton transfer from the reagent ion to the analyte. Knowledge of the gas-phase basicities of these two reactants is essential for applications of the technique.

The newer and most important soft ionization techniques which are known as ion desorption methods, such as fast atom bombardment (FAB),⁵⁵ matrix-assisted laser desorption ionization (MALDI)⁵⁶ and electrospray ionization (ESI),⁵⁷ developed independently of ion-molecule reactions and gas-phase ion chemistry. Yet it is becoming clear that gas-phase ion chemistry, including the energetics of ion-molecule reactions provided by ion equilibria, supply much of the fundamentals for these new methods. I will limit my remarks to electrospray, with which I am most familiar, but many of them will be valid also for MALDI. First we consider briefly the mechanism of electrospray.

Although the term ion desorption may be justified as a basis of classification for historical reasons, the process involved in electrospray and also in MALDI is ion desolvation. The ions near the surface are not adsorbed or absorbed but are solvated. To get them to the gas phase one has to free them from the solvent. Hence there is a considerable resemblance with the process described in the selected paper¹ but in the reverse direction. In the paper,¹ the H_3O^+ ions are solvated by more molecules, which is a spontaneous (exergonic) process at a given temperature and solvent vapor pressure (see Fig. 6, Ref. 1), whereas in electrospray the ions are being desolvated. Essentially the same energetics apply. In the solvation direction the process occurs by itself and for sufficiently high solvent pressures continued solvation leads to the final, ion-in-liquid, state. This is not so in the desolvation direction. Supply of heat the electrolyte ions in the liquid solvent state leads only to solvent evaporation and continued evaporation leads to the solid electrolyte. A special 'trick' has to be used to desolvate individual ions. In electrospray, as described in greater detail elsewhere,⁵⁸ one obtains very small droplets of an electrolyte solution which are charged because they contain an excess of unipolar ions. These are positive ions when working in the positive ion mode. Supply of heat from the ambient air still leads only to solvent evaporation but the electrostatic repulsion of the excess positive charges keeps the charges apart and leads to coulombic disintegration of the shrinking droplets. Ultimately the combination of solvent evaporation and repeated coulombic disintegration leads to the formation of positively charged gas-phase ions. Essential in quantitative treatments, such as that by Iribarne and Thomson,⁵⁹ are the ion solvation energetics corresponding to $\Delta G_{n-1, n}^\circ$ values as obtained in the featured paper.¹

More interesting and important are the applications of the gas-phase ion thermochemistry, based on ion equilibria, to the mass spectra that are observed with ESI. Even though the ions originally come from solution their final state is the gas phase. The ions observed in the mass spectra will have to meet the requirements of the new gas-phase environment, i.e. their stability and structure are a subject of gas-phase ion chemistry and can be predicted on the basis of available gas-phase thermochemical data. Three examples will be given.

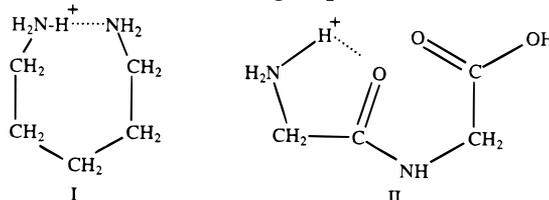
Intramolecular stabilization by intramolecular dicoordination of the proton by cyclization

Consider a peptide in slightly acidic aqueous solution. The terminal amino group and other basic residues will be protonated while the terminal carboxy group may be neutral. In solution the charged basic groups will be stabilized by strong hydrogen bonding to several water molecules. On transfer to the gas phase and removal of the solvent molecules from the basic groups, the peptide will 'respond' to the new medium by forming one or more strong intramolecular hydrogen bonds involving the protonated groups as the hydrogen donors and basic groups of the peptide such as the peptide carbonyl groups as the hydrogen acceptors. A more stable dicoordination of the protons is thus achieved by cyclization. The formation of such proton-bound cyclic structures is expected on the basis of early gas phase proton transfer equilibria determinations involving α, ω -alkyldiamines.^{60a} Proton transfer to the diamines was found to be much more exothermic than was the case for the alkylmonoamines and there was also a large loss of entropy. The magnitudes of both the enthalpy, ΔH° , and the entropy, ΔS° , were found to be consistent with interactions with a second basic group and loss of entropy due to cyclization.^{60b} The cyclized protonated 1,5-diaminopentane is shown in structure I.

Dicoordination of the proton by cyclization in protonated glycylglycine is shown in structure II, which was proposed by Cassady and co-workers,^{60c} while experimental evidence for the presence of such a stabilization was provided in work from this laboratory.⁶⁰ The internal cyclizations in gas-phase protonated proteins obviously will have a large effect on the gas-phase structures of these species particularly when polyprotonated species are present. For an account of such effects, see Williams and co-workers.⁶¹

Alkali metal ion cationization of analytes

Analyte molecules which have gas-phase basicities that are lower than that of ammonia are seldom seen in ES mass spectra as protonated species. Thus, compounds that have basic functional groups which are due to the



weaker oxygen bases or to amide nitrogens are generally seen as adducts to sodium. The sodium may have been deliberately added to the solution as a salt. However, even without such addition, Na^+ salts at concentrations of $10^{-5} \text{ mol l}^{-1}$ are generally always present in 'pure' polar solvents such as water and methanol.⁵⁸ A given bond strength of the sodium ion-analyte ligand complex, Na^+L , is required for such sodiated ligands to be observed in the mass spectra. A considerable number of $\text{M}^+\text{—L}$ bond energy data for the alkali metal ions are available,^{13,62–65} where $\text{M}^+ = \text{Li}^+, \text{Na}^+$ and K^+ . Taft *et al.*⁶² have provided $\text{Li}^+\text{—L}$ bond energy data for some 60 different ligands, based on equilibria determinations. Data for a more limited ligand range for Na^+ and K^+ are also available.^{13,63–65} For the same ligand, the bond energy decreases in the order $\text{Li}^+, \text{Na}^+, \text{K}^+$ and qualitative values for the bond energies can be estimated from the more extensive data for Li^+ when data for Na^+ or K^+ are not available. An illustration of available bond energies for Na^+ and K^+ is given in Table 1. In general, if the ions obtained with ES have not been subjected to declustering by CID in the ES–MS interface, one expects to see Na^+ or K^+ adducts for ligands with bond enthalpies higher than $\sim 13 \text{ kcal mol}^{-1}$. This means that all ML^+ shown in Table 1 should be observable. All the ligands shown in Table 1 have polar groups, with the notable exception of benzene, which leads to bonding that is somewhat stronger than that with H_2O . The principal factor leading to bonding with benzene is the presence of two π clouds which, together with the six nuclear charges on the ring, lead to an electric quadrupole moment. The alkali metal ion settles on the C_6 symmetry axis near one of the π clouds.⁶⁴ The consequence to the analytical mass spectrometrists is that compounds with phenyl substituents and no other polar groups, such as oligomers containing an alkane chain and aromatic rings, can be observed as sodium adducts with MALDI⁶⁷ and presumably also ES due to the M^+ bond to the aromatic group.

The assumed structures and corresponding bond energies (from Table 1, given below) illustrate the

increase of bonding due to substituent effects and multiple coordination. Although not shown, there may be partial coordination of the Na in IV with the π -system of the N—C—O group.

The increases in bonding from III to VIII can be readily explained⁶⁵ as follows. The increase from III to IV is due to lone electron pair donation from the NH_2 group to the carbonyl group which increases the negative charge on the carbonyl oxygen. In structures V and VI there is dicoordination, and electron donation assistance by the OH and stronger donation by NH_2 . In VII the stronger dicoordination due to two carbonyl groups leads to stronger bonding while in VIII assistance by electron pair donation from the amide-amino group provides additional bond strengthening.

The observation of polysodiated ions from oligomers of polyethylene glycols by Fenn and co-workers⁵⁷ is readily understood on the basis of the bonding information provided in Table 1. Understanding the bonding in alkali metal cationized bioanalytes such as carbo-

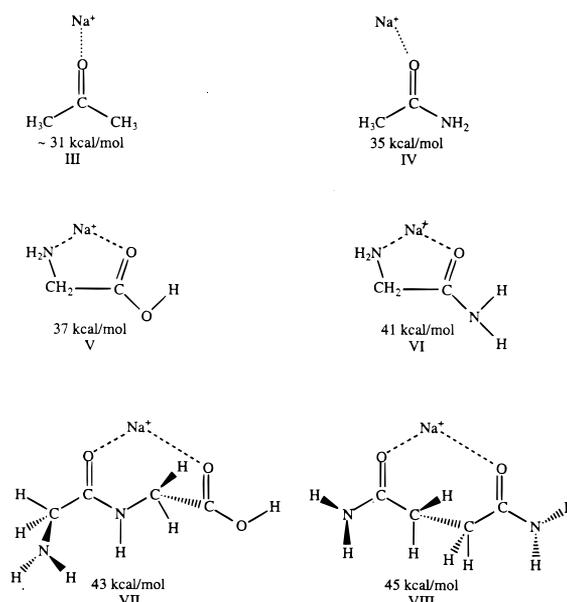


Table 1. $\text{M}^+\text{—L}$ bond enthalpies

Na^+		K^+ ^d	
L	ΔH° (kcal mol ⁻¹)	L	ΔH° (kcal mol ⁻¹)
H_2O	24 ^a	H_2O	17
Me_2CO	~ 31 ^b	NH_3	18
MeCONH_2	35 ^c	C_6H_6	19
MeCONHMe	36 ^c	MeNH_2	19
MeCONMe_2	38 ^c	$\text{Me}_2\text{NH}, \text{Me}_3\text{N}$	20
$\text{H}_2\text{NCH}_2\text{CO}_2\text{H}$	37 ^c	Me_2O	21
$\text{H}_2\text{NCH}_2\text{CONH}_2$	41 ^c	Pyridine	21
$(\text{H}_2\text{NCOCH}_2)_2$	45 ^c	Et_2O	22
$\text{H}_2\text{NCH}_2\text{CONHCH}_2\text{CO}_2\text{H}$	43 ^c	MeCN	24
		Me_2CO	26
		$(\text{MeOCH}_2)_2$	31
		HCONMe_2	31
		Me_2SO	35

^a From Ref. 66.

^b Estimated from Ref. 65.

^c From Ref. 65.

^d From Ref. 64.

hydrates and oligosaccharides and of peptides is of interest not only from the standpoint of the mass spectral detection via cationization but also in connection with analyte identification and sequencing by CID techniques. Thus, Beauchamp *et al.*⁶⁸ have demonstrated recently that sodiated peptides obtained with MALDI cleave on CID preferentially as specific amino acids, such as aspartic acid. Beauchamp *et al.* liken these selective cleavages to enzymatic digests in solution. This and other recent work on CID of cationized carbohydrates and glyco-biological compounds⁶⁹ signal the increasing importance of ion adducts and their gas-phase chemistry to MALDI and ES analytical mass spectrometry.

Subjecting bioanalytes to ion–molecule reactions such as solvation

An ion–molecule reaction chamber in which ions produced by electrospray can be subjected to ion–molecule reactions and equilibria was developed recently in our laboratory.^{60b} Determinations with this apparatus have involved only relatively small ions. Fenn and co-workers⁷⁰ have recently shown that such a reaction chamber can provide very illuminating results concerning polyprotonated proteins obtained with ES. The addition of more solvent molecules such as water to a polyprotonated protein allows the degree of protonation to be determined since in the presence of n protons, the peak should shift by $18/n$ units upwards per added water molecule. Such mass changes can be resolved even with a quadrupole mass spectrometer and solvation experiments of this type showed that the dominant species observed with ES-produced proteins are not the polyprotonated protein monomers but the dimers.⁷⁰ Fenn and co-workers also observed that on using different solvent adducts with increasing gas-phase basicities such as HOH, MeOH, EtOH, PrOH and BuOH, the highest basicity solvent molecules (BuOH) can lead to separation of the dimer into two monomers.

Probably the dimer was held together by dicoordination of protons where the proton bridges are due not to unimolecular cyclization (see structures I and II) but to

interactions of the protonated sites with basic groups of the other monomer. Solvation with sufficiently strong bases such as BuOH provides alternate modes for dicoordination of the proton and leads to dissociation of the dimer.

The observations of Fenn and co-workers⁷⁰ with the solvent series shown above fit rules established some time ago which deal with the strength of the hydrogen bond in proton bound dimers $BH^+ \cdots A$ based on determinations of ion–molecule equilibria⁷¹ and the kinetics of their dissociation.⁷¹ It was found that the strength of the $BH^+ \cdots A$ bond increases as the gas-phase basicity (proton affinity) of A increases. An additional rule that the reader might find useful is that the strength of the $BH^+ \cdots A$ bond decreases as the gas phase basicity of B increases.⁷²

The experiments by Fenn and co-workers⁷⁰ indicate that ion–molecule association reactions applied to biomolecules can provide very useful analytical information. Extensions of this method to other species such as non-covalently-bonded complexes will be of great interest.

CONCLUSIONS

The first quantitative measurements of the ion–molecule equilibria, presented in the selected paper,¹ led to the generation of abundant thermochemical data on ion–solvent molecule and ion–ligand reactions, gas-phase basicities and acidities, stabilities of carbocation and electron affinities. Initially these data found applications mostly in fields outside analytical mass spectrometry. However, with the discovery and development of the modern analytical ion–desolvation methods, such as FAB, MALDI and ES, ion–molecule interactions and ion solvation have moved to center stage. The thermochemical data relating to these phenomena have therefore become an essential part of the fundamental information that is required and familiarity with these data can be of great utility to the practising modern mass spectrometrists.

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