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Foreword

With the advent of ionization methods capable of transferring biomolecules directly from solution or off of surfaces into the gas phase, new applications and new frontiers in chemistry, biology, biophysics and medicine have blossomed. Specific noncovalent complexes between macromolecules or between macromolecules and a substrate that exist in solution can be readily observed in the gas phase. From a simple mass measurement, information about the stoichiometry of the complex, or the identity of a ligand can be obtained. Such measurements are becoming widely used, with applications ranging from screening combinatorial drug libraries against targets to investigating the heterogeneity of large macromolecular assemblies with masses in the hundreds of thousands and even millions of Da.

With the increasing acceptance of such applications by the broader biochemical and biological community, key questions about the nature of these macromolecules and their complexes in the gas phase remain. There is compelling evidence that large molecular ions in the gas can retain a "memory" of their solution-phase structure. This is not to say that the gas-phase structures are the same as those in solution, but rather significant elements of structural motifs that exist in solution may be retained in the gas phase. In the case of electrospray ionization, the transition from a fully hydrated ion in bulk solution to a purely solvent free ion with no water molecules attached can be made very "gentle", i.e., under some experimental conditions, very little excess energy is imparted into the gas-phase ion. Isomerization barriers between solvent free conformers can be higher than those accessible at thermal energies or even higher than dissociation energies in some cases. Consequently, the most stable gas-phase structures are not always formed following the desolvation process. Thus, some significant elements of solution structure may be "trapped" in the gas phase and can be probed using a host of powerful gas-phase methods. Many reports of the existence of the specific interactions that exist in solution for DNA duplexes, namely the Watson-Crick base pairing as well as other interactions, can be retained in the gas phase under certain experimental conditions. Other reports have documented ions unfolding and even folding in the gas phase.

Many new and novel methods for analyzing ion conformation and noncovalent complexes have been developed and applied to such problems, including ion mobility, proton-transfer reactivity, H/D exchange, spectroscopy, electron capture dissociation, ion-surface imprinting, etc. But important questions about the detailed nature of the conformations of macromolecular ions in the gas phase remain. For example, where are charges located on the molecule? What are the detailed structures of folded, partially folded, and even extended conformers in the gas phase? What are folding and unfolding energies in the absence of solvent? What is the nature of the water-biomolecule interface? How does water or other solvents directly influence structure? What elements of solution-phase structure can be retained in the gas phase? What elements are lost? Experiments have been designed to answer such questions and the results of these experiments yield information about how water or other solvents influence molecular conformation and often make it possible to infer information about specific interactions.

In addition to specific interactions, nonspecific complexes can be formed. These can be strongly bound complexes, such as those between salts and molecules, or they can be very weak interactions, such as those between an ion and one or more solvent molecules. Detailed information about water binding energies, and how water molecules interact with ions can be obtained from guided ion beam experiments, high pressure mass spectrometry, blackbody infrared radiative dissociation, infrared spectroscopy and theory. By investigating how ion structure changes as a function of the number of solvent molecules attached, detailed information about how solvent influences structure can be obtained. For example, amino acids are zwitterionic in water, but the nonzwitterionic form is most stable in the gas phase. How many water molecules are required to stabilize the zwitterionic form? How does water influence the interaction of metal ions with biomolecules? How many water molecules are required to stabilize trivalent metal ions? Answers to questions such as these can provide unique insight into how solvent influences fundamental interactions in biomolecules, such as electrostatic interactions, hydrogen bonding, and van der Waals interactions.

The articles in this special focus issue are a sampling of some of the work that is currently being done in this field. No such

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issue can be comprehensive and there was no attempt to make this special issue comprehensive. Rather, the 16 articles in this issue represent a snapshot of some of the exciting work that is being done in this area. We thank each of the authors for their contributions to this special issue and for their timely submissions and revisions. We also thank the numerous anonymous reviewers who have played a vital role in making such publications of high quality possible. We hope that you will enjoy this special issue.

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