

Considerations for Modeling Gas-Phase Nucleic Acid Adduction with Nitrogen Based Ligands

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Polyamines are small, highly charged cations found ubiquitously in nature. At physiological pH, polyamines are cationic. Consequently they have a tendency to form ionogenic bonds with negatively charged cellular constituents, like nucleic acids in DNA, proteins and phospholipids. Although, polyamines have been studied for a very long period of time and their essential role in a vast array of biochemical functions is recognized, the physiological functions of the polyamines are as yet unclear. Molecular dynamics simulations have been performed to complement recent ms/ms studies of DNA-polyamine complexes to obtain structural information. The question of most probable proton location became critical to interpreting the data. Here high level *ab initio* calculations of proton-transfer reaction coordinates between model systems are presented.

All *ab initio* calculations were performed with the Gaussian 98 package on an SGI ORIGIN server and Macintosh G4 workstation. Geometry optimizations were performed on a series of amine bases in the neutral and positively charged forms, H₂PO₄⁻, and H₃PO₄ at the B3LYP/6-311+G** level of theory. Polarization functions are necessary to effectively model noncovalent interactions, and diffuse functions are necessary for modeling charged molecules, such as the phosphate group. Electronic energies were obtained from calculations performed at both the B3LYP/6-311+G** and the RHF/6-31(d') levels of theory. Vibrational frequencies determined at RHF/6-31(d') are scaled by a factor of 0.9184 and then used to determine the zero point and enthalpy contributions to the interactions.

Proton transfer reaction coordinates were calculated for complexes of phosphoric acid (proton affinity (PA) = 1383 kJ/mol) with the nitrogen bases: ammonia (PA = 819.0 kJ/mol), methyl amine (PA = 899.0 kJ/mol), dimethyl amine (PA = 929.5 kJ/mol), trimethyl amine (PA = 948.9 kJ/mol) and ethyl methyl amine (PA = 942.2 kJ/mol). It has been shown that under physiological conditions these complexes exist as ion pairs with the phosphate group deprotonated and the nitrogen base protonated. Considering the large difference between the gas-phase acidity of the phosphoric acid and the gas-phase basicity of these test systems, it was expected that these complexes should not exist as ion pairs in the gas phase. The results presented here show that in all cases, with the exception of ammonia, the proton-transfer coordinate is characterized by a double well energy contour with barriers up to 16 kJ/mol and with minima separated by less than 5 kJ/mol. The ammonia-phosphoric acid system displays a single energy minimum with the proton residing on the phosphate with a binding enthalpy of 51.5 kJ/mol with respect to the separated neutrals. The methyl amine, ethyl amine, dimethyl amine and azetidine - phosphoric acid complexes are stabilized by 54.4, 62.4, 59.5, and 58.5 kJ/mol with respect to the separated neutrals, respectively. To the extent that a double-well energy surface actually exists, the experimental data is consistent with ion-pairs being transferred from the solution to the gas phase during the electrospray process.