A Brief Review of Spectroscopic Studies of Biomolecular Structures from Gas-Phase to Living Cells

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Structure and function of biomolecules are intimately related. In living cells, biomolecules interact and act in a highly concentrated, crowded and inhomogeneous medium. For simplicity, their structures are usually studied under homogeneous and diluted conditions. It is usually accepted that the 3-D structure of a biomolecule contains the information and thus a tremendous effort is devoted for example to the experimental determination of native structures of proteins through NMR or X-ray crystallography. Gas-phase studies that provide intrinsic structures in absence of any environment also emphasize the determination of well-defined and rigid conformations of a variety of biomolecular systems at very low temperature. However, a huge fraction of proteins are not structured and nevertheless play crucial roles due to their molecular recognition abilities, for example in cellular signalling.

Spectroscopic experiments conducted at room temperature in gas-phase strongly lack the conformer selectivity achievable in low-temperature studies but can sometimes be closer to the biological reality as long as not only structure but also dynamical flexibility is taken into account. Today, some experimental studies aim to combine the structural selectivity of ion mobility, the information brought by infrared spectroscopy and the possibility of varying temperature from near 0 K up to room temperature.

Water plays an essential role and hydration is thus widely investigated. Two extreme situations have mostly been considered. In low-temperature cluster studies, step-wise addition of water molecules emphasize preferential hydration sites corresponding to the most strongly bound species but the first hydration layer is then only very crudely approximated. On the contrary, spectroscopic investigations (IR, NMR, CD …) conducted in bulk water at room temperature provide an average but more realistic picture. Unfortunately, they most often do not distinguish between the very different situations encountered by water molecules, for example on biomolecular surfaces accessible to solvent or embedded in hydrophobic pockets. The role of temperature and hydration described in the preceding remarks can be illustrated in the case of the gas-phase and aqueous phase structures of the acetylcholine neurotransmitter. A drug-design point of view is then adopted through introduction of a pharmacophore model that is also used for nicotine and other drugs mimicking the biological role of acetylcholine. In particular, information brought by hydrated clusters and bulk studies may be compared in order to investigate the influence of hydration of nicotine in its receptor pocket.

Biomolecules can today be investigated under real biological conditions in living cells through NMR and spectroscopy. The obtained structures can then be compared to those deduced from aqueous phase studies. It is also possible to monitor in real time the fate of living cells until their death.