Weakly Bound Clusters of Biological Interest

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Received February 8, 2000

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1. Introduction

Gas-phase studies concerning interactions between neutral or charged species in molecular clusters allow for the investigation of the forces which govern structures and reaction mechanisms of complexes existing in condensed phases. For example, formation of solvated electrons[1] or local structural order of liquid mixtures[2] can be apprehended by means of an interplay between observations of bulk behavior[3,4] and the ensemble of results of cluster experiments,[5] ab initio[6−9] and empirical[10,11] potential-energy calculations, and molecular dynamics simulations.[12−14] The aim of this review is to show how this vast body of methods which have been acquired during the past decades about organic molecular complexes can be applied to problems of biological interest. The emphasis is set on weakly interacting systems since noncovalent bonds play crucial roles in biological structures.[15,16] The secondary structure of a protein, a long polypeptide chain of covalently bound amino acids, is a simple and well-known example.[17] The 20 natural amino acids are each characterized by a different side chain (residue) which is more or less acidic or basic, hydrophilic or hydrophobic, and is thus capable of different bond formation.[18] Due to the formation of hydrogen bonds between nearby C═O and N−H groups, protein polypeptide backbones can be twisted into α-helixes, even in the gas phase in the absence of any solvent.[19] A protein function is determined more directly by its 3D structure and dynamics than by its sequence of amino acids. Three-dimensional structures are strongly influenced by weak interactions between residues, but the central importance of van der Waals, hydrogen, and ionic bonds is not limited to structural effects. Life relies on biological specificity, which arises from the fact that several individual weak bonds are needed to attach biomolecules.[20,21] Molecular recognition relies on these weak bonds which can only be formed if designated partner atoms are precisely positioned.[22]

Let us consider two illustrative situations. DNA is a polynucleotide, each nucleotide being composed of a phosphate group, a sugar, and one of the four canonic nucleic acid bases adenine (A), thymine (T), cytosine (C), and guanine (G).[23] Genes are sequences of these bases and constitute the genetic information contained in DNA. In living organisms, the reading of this information is initiated by the binding of proteins to specific control regions. A gene is expressed or repressed because controlling proteins recognize and bind at specific sites of the DNA double helix. Reversible binding is achieved by ionic bridges which are formed between phosphate and positively charged amino acid residues as well as by stacking interactions between aromatic amino acid residues or hydrogen bonding between phosphate, sugar, nucleic acid bases of DNA, and hydrophilic residues. Typically, specific binding to a given site in the humane genome requires the formation of weak

10.1021/cr990061j CCC: $35.00
Published on Web 09/14/2000

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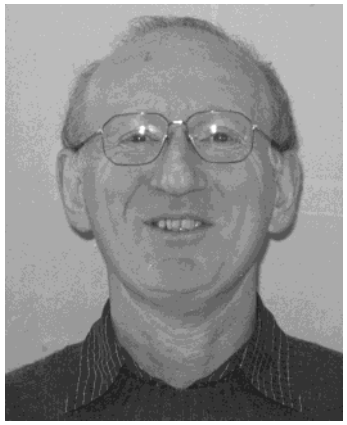
bonds between approximately 16 consecutive base pairs of the DNA double helix[24] and a recognition element which is often an α-helix in natural proteins.[25] The design of artificial ligands capable of reading the genetic information can take benefit from the investigation of these weak bonds[26,27](see section 4.3).

The immune system provides another example where the combination of a given antigen only with its relevant antibody is the consequence of many individual local interactions summing to give a very high-affinity interaction.[20] A small substituent, called hapten, on a foreign invader is specifically recognized because it is held in a small region called a pocket or cleft by weak interactions with a small number of given molecules of the antibody surface.[28] The progesterone-binding pocket is shown as an example in Figure 1. The specificity is such that tailormade antibodies can recognize the chiral center of α-amino acids.[29] Investigation of the biospecificity of interactions between large macromolecules such as DNA



Jean Pierre Schermann was born in Paris in 1940. He studied at the Ecole de Physique et Chimie and earned his Ph.D. degree from the Université of Orsay in 1969. After one year as an NSF Postdoctoral Fellow at GSFC (NASA), he joined the Université Paris Nord in 1973 as a Professor, where he has been Head of the Communication department and Chairman of the Physics department. His research interests have been atomic clocks, ion trapping, and laser isotope separation and are currently concerned with clusters of biological interests.

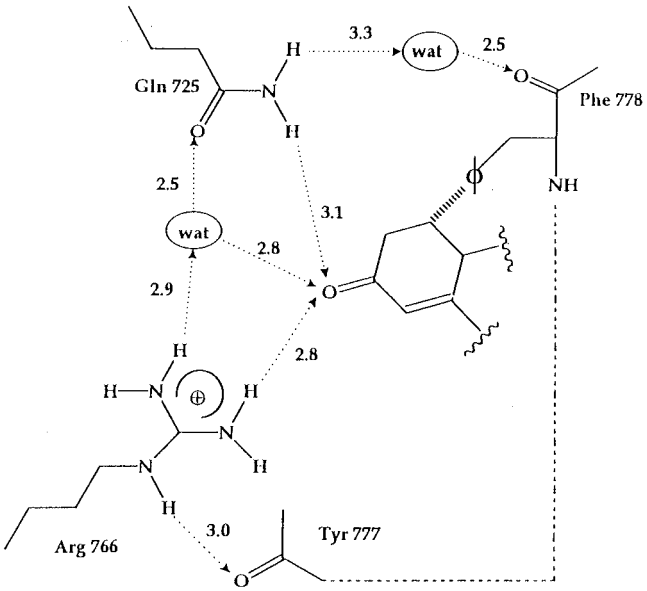


Figure 1. Crystal structure of the binding pocket of the progesterone hormone to its protein receptor is displayed as an example for molecular recognition determined by well-identified weak interactions. The hydrogen-bond network established between the hormone keto group, the side chain NH_2 group of glycine 725, and the guanadinium group of arginine 766 ensures the biological specificity. The situation is not unique since nearly all steroid hormones have 3-keto groups and their receptors have a glycine in position 725 which has been conserved during evolution. The water molecule provides additional specificity and rigidifies the weak bond network. Hydrogen-bond lengths are in angstroms. (Reprinted by permission from Williams, S. P.; Sigler, P. B. *Nature* **1998**, *293*, 394. Copyright 1999 Macmillan Magazines Ltd.)

and proteins thus requires a detailed analysis of interactions between elementary building blocks such as amino acid residues and nucleic acid bases or other small molecules.

The vast majority of the understanding of how biomolecules recognize and interact with one another originates from the comparison between X-ray crystallographic[30] or spectroscopic (NMR, UV, infrared,

circular dichroism.) experimental data obtained from measurements in the liquid or solid state and empirical force fields.[17] The simplicity of empirical potential-energy functions allows for simulation of the dynamical behavior of biomolecules containing up to tens of thousands of atoms for time scales as long as nanoseconds. However, to improve the accuracy of modeling, some force-field parameters can be derived from ab initio calculations.[31] These calculations, usually designated as *gas-phase* calculations, consider interactions between isolated molecules and are limited to small size model systems.[32,33] The confrontation between high-level calculations and experimental results which is common place in the field of molecular clusters[34] becomes highly desirable for complexes involving molecules of biological interest.

The structure of clusters of elementary components of biomolecules and its relationship to molecular recognition is not the only scope of this review. Important biochemical processes such as radiation-induced damages to DNA or enzymatic activity are strongly influenced by molecular parameters such as ionization potentials or electron affinities. The determination of the dependence of these quantities upon the ubiquitous presence of water as a solvent is an important goal of cluster studies. The local degree of hydration in biological systems strongly influences biomolecule structures and reactivity.[35−38] Solvation effects which are also studied by M. Orozco in this issue will be considered here with emphasis on experimental methods.

Historically, quantum chemistry calculations concerning biological systems appeared long before[39] the first experimental works such as those of Sukhodub,[40,41] Levy,[42] Schlag,[43] and Grotemeyer.[44] During recent years, several experimental techniques which had been originally applied to clusters of organic molecules have been extended to the study of molecular clusters of biological interest. The simultaneous possibility of high-level quantum chemistry calculation for molecules containing a sufficient number of atoms has prompted fruitful comparisons between experiment and theory. The aim of this review is first to present experimental techniques which are currently available for the study of organic molecular clusters and then to describe problems encountered when these techniques are extended to systems of biological interest. Taking examples from the work of several groups and with some emphasis on our own work, we illustrate this field of research by describing some case studies.

2. Experimental Techniques Available for the Study of Molecular Clusters

A recent review of experimental methods applied in the molecular cluster field has been given by Castleman and Bowen.[45] Most of these methods are described and updated in great details by other contributors of this issue, and we will thus only deal with the tools, cluster sources, ionization processes, and spectroscopies, which can most easily provide quantitative information on molecular properties relevant to the study of systems of biological interest. Among molecular parameters which can be compared to results of quantum chemistry calculations, the most important are intermolecular distances, angles and binding energies, spectral shifts of absorption and fluorescence of excited states, ionization potentials, and electron affinities.

Cluster sources produce neutral or ionized species. A large fraction of molecules of biological interest (nucleic acid bases, amino acids, etc.) have very low vapor pressures, even at temperatures above 200 °C, and easily decompose. Ion sources such as high-pressure electrical discharges[5,46] or laser vaporization[44,47,48] usually deliver intense ion beams but rely on ionization processes which are not easily controlled and can induce important fragmentation processes. Here, we will thus pay special attention to small molecular systems and to the widely used neutral clusters sources which are based on supersonic expansions.[49] The size distributions of the obtained beams being rather broad, cluster mass selection is necessary to study any variation of molecular parameters with cluster size. It would be desirable to directly consider the neutral systems without any ionization. Size-selective deflection of a neutral cluster beam by a helium beam is such an elegant approach[50] which is described in this issue. However, most techniques use a combination of ionization, mass spectrometric analysis by means of electric and/or magnetic fields, and spectroscopic diagnostics, these three steps occurring in different orders. Among those techniques, we will further describe the Rydberg electron transfer (RET) method, which can be applied to a sizable number of clusters of biological interest and allows for the study of neutral complexes thanks to a nonperturbative and reversible ionization process and leads, aided by theoretical calculations, to the determination of cluster geometries.

The geometrical structure of a weakly bound complex can be determined by means of a large variety of experimental approaches. Generally, one measures one or several molecular parameters and relates them to the results of quantum chemistry calculations. Among these parameters, moments of inertia can be directly derived from rotational spectroscopy either by microwave,[51] combined UV and microwave,[52] or rotational coherence measurements.[53] However, up to now, only relatively small systems, such as benzonitrile−water, have been studied and application of these techniques to larger systems of biological interest may require an important effort for the interpretation of experimental results. We will thus emphazise spectroscopies which have already proved their applicability to reasonably large complexes already containing up to 40 or 50 atoms. The use of each of those spectroscopic tools requires some conditions, and none of them seems to be universal.

2.1. IR Spectroscopy

Infrared spectroscopy is a powerful means to investigate hydrogen bonding in condensed phase. During recent years, it has been applied to molecular clusters in different versions. Although direct detection of infrared photon absorption with a bolometer is possible but rather difficult, indirect detection

schemes are preferred. One of them combines resonant infrared (IR) absorption and two-color resonantly enhanced multiphoton spectroscopy (REMPI). If the neutral $M\cdots(S)_N$ cluster absorbs an infrared photon by excitation of one of the intermolecular vibrations M−S, the vibrational ground-state population is depleted. If one sets the first resonant UV laser on a specific transition leading to a product cation, one observes depletion signals when tuning the IR laser through the different active IR transitions. This technique has been applied with great success[54] to the study of intra- or intermolecular stretching vibrations of aromatic chromophores interacting with solvents such as water or methanol. The absorption spectra of the $M\cdots(S)_N$ clusters differ from the isolated chromophore M spectrum. The combinations of the IR and UV shifts coupled to mass analysis of the positive ion[34,55] products constitute unambiguous signatures.

2.2. UV Spectroscopy

Among the molecular parameters of complexes which can be experimentally determined, one of the most sensitive to the quality of results of quantum chemistry calculations are intermolecular binding energies. REMPI can provide the binding energy D_0 of the ground state of a mixed $M\cdots(S)_N$ cluster where a molecular species M is under study in the presence of solvents S. M acts as a chromophore and must possess a well-resolved ultraviolet (UV) absorption and/or fluorescence spectrum. The first UV photon resonantly excites M to its S_1 or S_2 electronic state;[56] then a second UV photon ionizes the cluster. Fragments $M^+\cdots S_{M\leq N}$ are detected after mass spectrometry analysis. If the adiabatic ionization potential $IP_{ad}(M-S_{N-1})$ of the fragment is already known, one obtains the binding energy $D_0(M-S_N)$ from the measurement of the appearance potential $AP(M^+-S_N \rightarrow M^+-S_{N-1})$ of the fragment.[57]

2.3. Cluster Cations

van der Waals and hydrogen interactions are also widely investigated in charged complexes. For cations, two complementary methods provide a wealth of information. Zero-kinetic-energy photoelectron spectroscopy (ZEKE) and mass-analyzed threshold ionization (MATI) take advantage of the existence of long-lived molecular Rydberg states ($n \approx 150$). Their ionization by a delayed pulsed electric field leads to the observation of threshold ions in well-defined energy states.[58−60] As in REMPI, the first UV photon excites the $M\cdots(S)_N$ complex in its S_1 state. A second tunable UV excitation, aided by weak (inhomogeneous) electric fields, brings the complex to a narrow band of long-lived high n and l state very close to the ionization limit. In ZEKE-PFI spectroscopy, weakly bound Rydberg electrons are detected by pulsed-field ionization (PFI) in conjunction with time-of-flight, while in MATI spectroscopy, the cation products from the field-ionization process are mass-analyzed. In both cases, very precise measurements of the shifts of the ionization limits induced by the presence of solvents and their analysis by means of ab initio calculation provide geometries and vibrational frequencies of complexes in both neutral S_0 and cation D_0 states.[61]

2.4. Cluster Anions

A large number of neutral molecular clusters, however, do not contain any chromophore suitable for high-resolution spectroscopy in the visible or UV region. A first possibility to overcome this problem is direct ionization of the studied neutral complexes by means of VUV and XUV synchrotron[62] or laser[63] radiation. One can then encounter difficulties in trying to distinguish between different evaporation products. Electron attachment to neutral clusters or cluster anion photodetachment then offers alternative methods which do not require the existence of well-resolved visible or UV spectroscopy but rather the possibility of producing stable, or at least sufficiently long-lived, anions. The existence of negative ions is the result of a subtle competition between attractive and repulsive forces which allow for the more or less temporary attachment of electrons to neutral atomic or molecular systems. Molecular cluster anions open a wide field of investigation because their excess electrons can occupy very different orbitals. Usually, these electrons are bound into valence orbitals and then belong to the electronic cloud of a single or a small number of molecules, but they can also be trapped by long-range forces into very diffuse orbitals or even be delocalized over a whole assembly of molecules. One must thus consider two very different types of anions, "conventional" or "valence", anions where excess electrons undergo the usual valence attractions from nuclei and repulsions from other electrons and multipole-bound anions into which an extra electron is trapped by the dipole and/or the quadrupole field from a highly polar and/or quadrupolar molecule or from a small assembly of such molecules. Generally, a molecular system of a given size can lead to the production of anions corresponding to only one of the preceding two possibilities. However, as we will further show, some molecules[64] or clusters[65] of biological interest can give birth to anions with excess electrons in either diffuse or valence orbitals.

Several reviews have already been devoted to different aspects of molecular cluster anion studies. In particular, ab initio calculations of the electronic structure of anions have been considered by Simons and Jordan.[66] Electron attachment to clusters has been the subject of several reviews.[5,67,68] Size effects upon electron and anion solvation have been described by Jortner.[1] State-of-the-art spectroscopy of negative ions has been discussed by Boesl and Knott.[69]

$S_1 \leftarrow S_0$ electronic transitions and ionization potentials of neutral molecular clusters are among the important parameters determined by UV spectroscopy. The electron affinity (EA) and vertical detachment energy (VDE) of a molecule M, which relate the energetic properties of an M^- anion to those of its neutral parent, plus electron at infinity, the $M + e_\infty$ system, are key properties of anions. If the nuclear configuration of the molecule M is kept unchanged after electron capture, the difference between the

electronic energies of $M + e_\infty$ and M^- is the vertical electron affinity EA_V, which is experimentally accessible by means of free electron transmission spectroscopy (ETS)[70] and can be estimated by application of Koopmans' theorem.[71] The electronic energy difference between the anion and the neutral molecule at the anion nuclear configuration is the vertical detachment energy (VDE), which can be accurately determined by photoelectron spectroscopy (PES). Following electron capture, intra- and intermolecular energy transfers take place in a molecular cluster anion and the adiabatic electron affinity EA_{ad} corresponds to the anion in its totally relaxed internal state. When the sign of EA_{ad} for an isolated molecule is negative, this quantity is difficult to obtain experimentally or usually not predictable theoretically. As we will further show, it is possible to determine it by solvating such a molecule and studying the properties of the corresponding cluster anions.

Photodetachment-photoelectron spectroscopy of anions (PES) is a powerful technique which provides very accurate measurements of vertical detachment energies (VDE) and allows for the determination of adiabatic electron affinities when these quantities are positive. It requires intense anion cluster sources.[72,73] Following mass selection, anions are crossed with a fixed-frequency laser and photodetached electrons are energy-analyzed. Energy distributions of the photodetached electrons are spectral signatures of the anion excess orbitals. Conventional anions have excess electrons which belong to the molecular electronic clouds. Removal of these excess electrons induces nuclear reorganization, and vibrational features of the obtained neutrals are observed in PES spectra. In a series of anion complexes $(M-(S)_N)^-$, it is fundamental to determine whether the excess electron is localized on a single M molecule acting as an electron chromophore or if it is delocalized over the whole assembly.[74] If the profile of the PES spectra of the complexes remains similar to the profile of the M monomer, it is clear that the complex must be considered as a solvated anion $M^- - (S)_N$.

A large number of solvents and molecules of biological interest have permanent dipole and/or quadrupole moments. In the gas phase, an electron interacting with a molecular species which possess a large dipole and/or a large quadrupole Q is attracted by a long- range potential, respectively, $(-\mu \cos\theta)/r^2$ and/or $(-Q/4r^3)(3\cos^2\theta - 1)$, and undergoes a short-range repulsion in the vicinity of the molecular cloud, even if no valence orbital is available. An excess electron can then be trapped in a very diffuse orbital if the created potential well is deep enough to support a bound state. The dipole or the quadrupole moment Q must be larger than critical values $\mu_{crit} \approx 2.5$ D and $Q_{crit} \approx 45$ D Å, respectively. The corresponding weakly bound anions can be created by means of different methods. High-intensity sources use injection of slow or fast electrons in the high-pressure region of a supersonic expansion. Three-body collisions between secondary electrons and polar systems followed by evaporation provide the necessary mechanism for stabilization of the nascent anions against autodetachment. The photoelectron spectra which can be obtained with those anion sources have sharp peaks which constitute PES signatures of the existence of these anions. They also demonstrate that dipole-bound anions possess very nearly the same nuclear configurations as their neutral parents.

PES can be combined with IR vibrational predissociation. A molecular cluster anion $(M_PS_N)^-$ is prepared and submitted to IR excitation in the region of resonance of an intermolecular M−M vibration, usually a hydrogen-bonding vibration. Vibrational predissociation corresponds to an energy exchange between this M−M vibration and one or several much weaker intermolecular M−S vibrations, leading to evaporation of at least one of the solvent S molecules. By monitoring the evolution of a $(M_PS_{R\leq N-1})$ anion signal as a function of the IR frequency, one can observe the influence of solvation and by measuring the IR shifts of the resonances identify the hydrogen bonds. For example, the nature of the water network of water cluster anions has been investigated by studying the OH stretch absorption of $(H_2O)_6^-\cdots Ar_{n\geq 6}$ clusters.[75] The need for a well-resolved UV spectrum is replaced by the need for a nonevaporative electron attachment process such as multipole binding of electrons, which probably constitutes one of the mildest ionization processes.

A large fraction of polar molecular clusters have resulting multipole (dipole and/or quadrupole) moments larger than the critical values required for electron binding.[76] For a given neutral polar cluster, it may happen that several configurations are possible, each corresponding to a different binding energy with respect to the dissociation limit and thus a different probability of existence in a supersonic expansion. The determination of the resulting dipole moment of a given cluster is a very strong hint concerning its geometry. Rydberg electron transfer (RET) spectroscopy, which is described in section 3.3, relies on the relationship between electron attachment properties of polar clusters and their resulting dipole moments. Several different situations are possible, the most simple one being the existence of a single populated isomer with a rigid configuration. Some cluster potential-energy surfaces vary smoothly as a function of an intermolecular coordinate, and the corresponding configurations are more or less floppy. Finally, two isomeric configurations with very different geometries can have nearly the same binding energies and can be nearly equally populated. RET spectroscopy is a fruitful method which allows for the distinction between these different situations (see section 3.3 and Figure 2a−c).

2.5. Real-Time Monitoring of Solute−Solvent Interactions

Hydration of biomolecules strongly influences their structure and reactivity, which can be monitored in real time by means of femtosecond laser techniques in liquid water.[77] In the gas phase, experimental studies have been conducted on inhomogeneous cluster anions into which an easily identified chromophore, usually a halide atom or molecule, more or less strongly interacts with its environment.

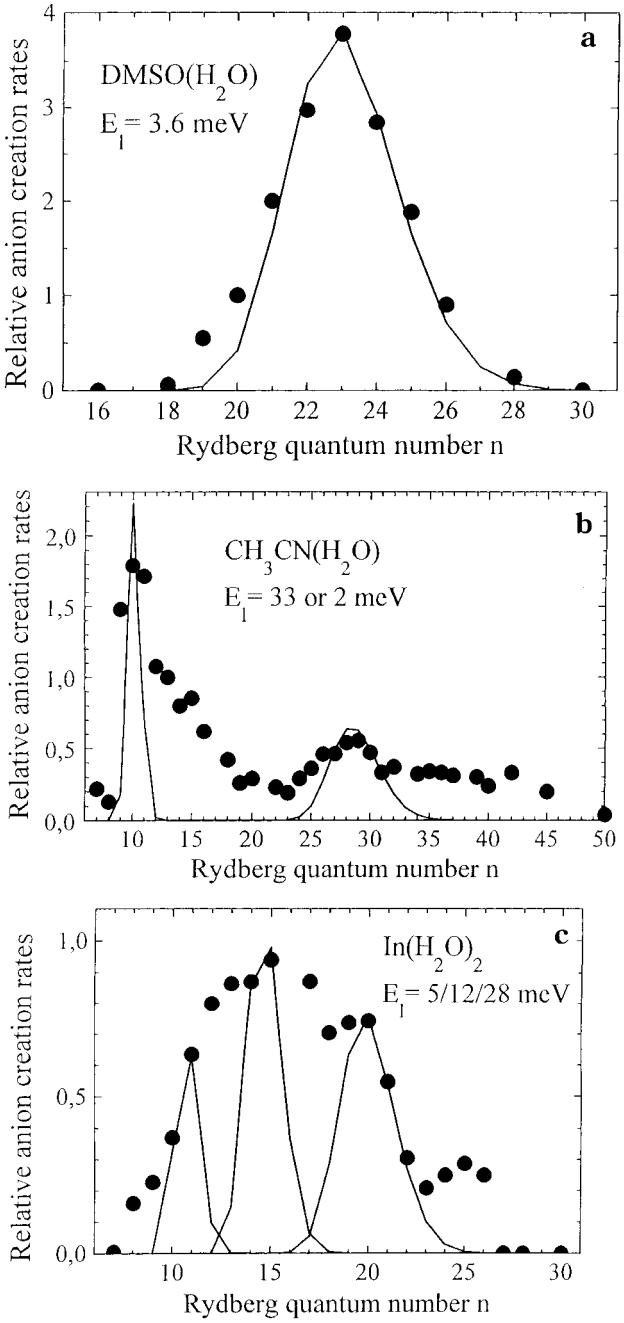


Figure 2. Dependence on the principal quantum number *n* of the relative rate constants for the formation of multipole-bound anions in collisions between laser-excited Rydberg atoms and hydrogen-bonded complexes. Solid circles correspond to experimental data, and solid curves are results of model calculations which provide the given respective electron binding energies. **(**a**)** *n*-dependence of the relative rate constant for the formation of $(DMSO\cdots H_2O)^-$ anions. The narrow curve is characteristic of electron attachment to a rigid neutral complex. **(**b**)** *n*-dependence of the relative rate constant for the formation of $(CH_3CN\cdots H_2O)^-$ anions. The peaks correspond to electron attachment to two rigid neutral isomers with respective dipole moments of 5.5 and 2.6 D. **(**c**)** *n*-dependence of the relative rate constant for the formation of $(Indole\text{-}(H_2O)_2)^-$ anions. The distribution of experimental values over a wide range of *n*-values is characteristic of the formation of a very floppy complex anion. The geometries of the neutral and the anion are very different (see Figure 5). The three solid curves and electron binding energies correspond to electron attachment to several vibrational states of the anion (see ref 8).

Experiments on iodine $I_2^-(S)_N$ anions, where solvent S stands for argon atoms and CO_2 or OCS molecules, have been among the most widely studied due to the favorable spectroscopic properties of the I_2 and I_2^- chromophores. Experimental measurement of the ratio of the uncaged and caged products as a function of the time delay between two photon pulses allows for the monitoring of solute−solvent interactions in real time. A femtosecond pump laser is in resonance with the $I_2^-[A^2\Pi_{g,1/2} \leftarrow X^2\Sigma_u^+]$ transition. A delayed femtosecond laser pulse is then used to either perform photoelectron spectroscopy[78] or to monitor the absorption of the $I_2^-(S)_N$ at the pump laser frequency.[79,80] Superimposed to anion−solvent interactions is electron delocalization into the molecular solvent species, a recurrent problem in molecular cluster anion studies. Since the dynamic of proteins in their water environment occurs on a picosecond time scale,[81] the preceding techniques are valuable for studying hydrated clusters of amino acid residues or nucleobases. Application of femtosecond techniques in the gas phase to other problems encountered in biological systems will also be considered in section 4.1.3.

3. Problems Specific to the Study of Molecules of Biological Interest in the Gas Phase

The extension of the experimental methods which have been described above for clusters of small molecules to clusters of larger molecules of biological interest can face several problems. A first step is the introduction of nonvolatile and thermally labile species in the gas phase.[82] This problem is not restricted to cluster studies but is also critical in mass-spectrometric studies of large biomolecules such as proteins[83] or DNA−drug complexes.[16] Another issue is that in order to minimize breaking of intra- or intermolecular bonds, ionization processes as least perturbative as possible are desirable. For example, the role of solvents is most often fundamental not only on structures,[38] but also with regard to chemical effects such as enzymatic activity.[84] A very efficient method for ionization of biomolecules such as electrospray tends to a nearly complete removal of water and can thus induce significant changes of the gaseous conformational structure of a protein.[37] In contrast, one of the most important features offered by cluster studies is the control of the number of solvent molecules surrounding a studied molecule and the possible determination of solvation-shell structures. Ionization processes which minimize evaporation of solvents are then welcome. Another problem must be considered in the investigation of the excited vibrational or electronic states of molecules involved in photobiological processes. In the liquid phase, due to the overlap of transitions from many thermally populated states, spectra of these large biomolecules are usually broad and structureless. Some of the optical spectroscopy methods which have been described above for the study of small molecules in the gas phase can be applied to larger systems thanks to well-established techniques such as supersonic molecular beams and more recent methods such as

liquid droplets,[2,85] liquid beams,[86,87] and helium droplets.[88−90]

3.1. Production and Ionization of Molecules of Biological Interest in the Gas Phase

Supersonic molecular beams are among the most widely used means of production of weakly bound clusters. The very low temperatures associated with the internal degrees of freedom are typically of the order of a few Kelvin for rotation and 100 K for vibration. This cooling simplifies spectra since few vibrational and rotational levels are involved in the ground state. Moreover, few configurations are populated. These advantages of supersonic expansions, however, rely on the possibility of producing sufficient partial vapor pressure of the molecules of interest, typically a few millibars. Most biologically related molecules (e.g., DNA bases, amino acids) have extremely low vapor pressures at room temperature and rapidly decompose when they are heated. According to the sensitivity of the used experimental technique, more or less high vapor pressures of the studied molecular systems are required. Instead of seeding molecules in rare gases before expansion, the use of a pick-up source can overcome the low-volatility problem. Argon,[91] xenon,[92] and helium clusters[90] or droplets[89] containing several thousands of atoms and even more have very large kinetic cross-sections and thus present a large probability for capture and accommodation[93] of molecules which are only present with vapor pressures as low as 10^{-6} mbars. The situation is then comparable to that of rare-gas matrix experiments[94] and allows for spectroscopy of very dilute solutes. The helium−helium binding energy being extremely small,[93] vibrational excitation of the solute molecules can thus be observed by monitoring the resonantly laser-induced evaporation of several hundred helium atoms.[88,89]

For molecules which cannot be seeded in rare gas expansions, laser desorption offers a powerful alternative to the production of neutral species in the gas phase. Once vaporized, those neutrals have been studied, for example, by means of dispersed fluorescence[42] in the case of different conformers of tryptophan or resonant two-photon spectroscopy (REMPI) in the case of dipeptides or polypeptides[44,95−97] as well as DNA bases.[98] Another possibility is the use of supercritical fluids, among which CO_2 is the most important and is, for example, used for extraction of caffeine. However, a large number of nonvolatile hydrophilic substances such as proteins are insoluble unless one uses aqueous microemulsion droplets with a surfactant.[99]

The two steps of vaporization and ionization are not necessarily separated. Mass spectrometry of large biomolecular ions (with masses between 1 and 10^3 kD) is routinely performed for accurate measurements of molecular weights and sequencing.[100] Two techniques which are among the most widely used for production of those large ions[101] are matrix-assisted laser desorption/ionization (MALDI)[47] and electrospray ionization (EI).[102]

3.2. Determination of Biomolecule Structures in the Gas Phase

Once produced, an important problem for large biomolecular ions is the determination of their structure in the gas phase and how it is related to the solution structure.[103] Different methods are currently used to determine gas-phase structures. Ion-mobility mass spectrometry relies upon the difference between collision cross sections of conformers drifting in a helium bath under the influence of a uniform electric field.[104−107] Highly folded conformations drift faster than unfolded ones and can thus be distinguished as in usual chromatography. Isotope labeling techniques take advantage of the difference between accessibility of labile hydrogen sites according to their positions in peptides and proteins. In highly folded conformations, hydrogen sites buried in hydrophobic cores are not exposed to a deuterated solvent and thus do not easily undergo H/D exchange. This method which allows for distinction between isomers and determination of reaction mechanisms requires long interaction times between ions and a surrounding low-pressure solvent gas which can be achieved in ion-cyclotron resonance (ICR) experiments.[108] Since biomolecular ion structures are strongly influenced by the presence or absence of a solvent, it is interesting to vary the degree of hydration. For example, under mild electrospray conditions, hydration of doubly protonated gas-phase ions of gramicidin S, a cyclic decapeptide with a mass of ≈1 kD, has been studied[109] and a transition has been observed between totally naked unsolvated ions and ions surrounded by up to 50 water molecules whose conformations are expected to be very close to those in solution. As in charged-water cluster mass spectra,[110] magic numbers corresponding to the most stable protein−water structures are observed. Completely desolvated ions produced by electrospray sources can be first separated from their source gas and further mixed to a bath gas in order to precisely control their solvation content. Controlled hydration of leucine−enkephalin, a small pentapeptide which is an endogenous neurotransmitter, has been obtained.[111] However, it is still not possible today to apprehend all the details of the influence of solvation upon chemistry,[112] structure,[113] spectroscopy,[114,115] or dynamics[79,116] as precisely as in the case of small- and intermediate-size cluster studies.

Activation energies and entropies for dissociation of ionic complexes or large biomolecules can be measured by absorption of blackbody photons[117] and thermal dissociation.[118] In the BIRD method (black body radiative dissociation), ions produced by electrospray are confined in a Fourier transform mass spectrometer ion cell and submitted to the dissociating radiation field created by the heated vacuum chamber at different temperatures. Another possibility consists of ion trapping in a heated bath of helium.[118] Arrhenius plots for the dissociation of protonated ions provide threshold dissociation energies which are typically in the 0.8−1.2 eV range. Results obtained on bradikinin dissociation rates performed with both methods are in good agreement. Other examples will be given further in section 4.2.4.

3.3. Microwave, Optical, and RET Spectroscopies of Molecular Clusters of Biological Interest in the Gas Phase

The presence of possible tautomers[119,120] and limited symmetry as well as the need for efficient cooling makes it difficult to obtain well-resolved spectra in gas-phase spectroscopic studies in the case of nonvolatile molecular species such as DNA base or amino acid complexes. Moreover, most of these species do not possess electronic transitions in the easily accessible UV region, and we will show in a following paragraph how RET spectroscopy offers an alternative route for the study of several systems.

Absorption millimeter wave and microwave Fourier transform spectroscopies provide accurate values of moments of inertia which, coupled to ab initio calculations, allow for the derivation of hydrogen-bond stretching force constants and dissociation energies in the case of van der Waals clusters. For example, the millimeter wave spectra of the purine molecule[121] and pyrimidine−water complexes[122] have been studied in free jet absorption experiments. The far-infrared vibration−rotation spectrum of uracil has been recorded by means of a pulsed slit valve specially designed for la ong-path-length and high temperatures up to 230 °C.[49] Assignment of this spectrum to the carbonyl stretching vibration of the diketo tautomer has clarified a previous ambiguous assignment obtained at much lower resolution.[123] This problem of tautomerism (see also section 4.1.3) has also been studied in matrix-isolated Fourier transform infrared experiments[124] as well as the determination of the most stable conformers of the simplest amino acid, glycine.[125] The advantage of studies performed in vapors or jets over matrix experiments is the elimination of intermolecular interaction with the surrounding trapping medium. Infrared spectra of uracil, thymine, and adenine have been recorded from 100 to 3700 cm^{-1} in absorption or emission at high temperatures (200−325 °C) without any observation of tautomerism.[126] The relative ease of these measurements is in contrast with problems encountered in jet experiments on UV spectroscopy of DNA bases. The first electronic spectrum of uracil was reported with a well-resolved fluorescence exhibiting sharp features assigned to diketo and enol−keto tautomers.[127] However, it was later shown that heating uracil may produce impurities and can possibly lead to wrong assignments.[128] A similar situation is present in Rydberg electron attachment to DNA bases experiments (except for guanine which decomposes before being observed in a seeded jet) where spurious signals can easily appear if the temperature of the supersonic jet oven is only raised 10 or 15 °C too high.[129,130] For guanine, the first vibronic REMPI spectrum has been recently reported by using laser vaporization.[98] This nucleobase was deposited as a thin layer on graphite, desorbed by means of 1.06 μm YAG laser and entrained in an pulsed argon expansion providing efficient cooling.

As already stated above, an important fraction of molecules and clusters of biological interest have sufficiently large dipole and/or quadrupole moments to bind electrons in diffuse orbitals.[76] DNA bases,[65,129,131] some amino acid residues,[56,132−136] and formamide[137] and its methylated derivatives[33] are examples of such systems giving birth to multipole-bound anions. Rydberg electron transfer (RET) spectroscopy consists of transferring electrons from highly excited atoms into diffuse orbitals of polar systems and provides a useful method for the discrimination between different geometrical configurations. For a given cluster size, the resulting dipole moment of the different configurations is, in a first approximation, the vector sum of the individual dipoles. Experimentally, cluster beams are crossed with a beam of laser-excited atoms in states with high principal quantum numbers n. Anions which are produced are mass-analyzed, and their nature (valence or multipole-bound) is determined by either performing field-detachment measurements or fitting the n-dependencies of the anion creation rates.[138] Those Rydberg n-dependencies are sharply peaked when rigid complex anions are produced, as shown in Figure 2a in the case of the mixed DMSO−water complex[139] (DMSO−water mixtures have known protein-dissolving properties).[140] When two nearly isoenergetic isomers of the neutral complexes are simultaneously present, two peaks appear as shown in Figure 2b in the case of the mixed acetonitrile−water complex.[129] Each peak corresponds to the production of different anions arising from electron attachment to either large or small resulting dipole configurations. If a neutral complex configuration is floppy, there is no well-defined resulting dipole but rather a broad distribution and the Rydberg n-dependencies for anion production are then sums of different contributions. An example is displayed in Figure 2c for indole−$(water)_2$ complexes[141] (see also Figure 5).

To determine which neutral configurations can give birth to multipole-bound anions and which ones cannot, the neutral cluster configurations and their respective dipole and/or quadrupole moments must be calculated with the help of either model potentials or ab initio methods. A semiempirical model of the intermolecular potential energies which follows the lines of the work of the group of Scheraga[10] has been described in detail in ref 11. Its crucial ingredients are partial atomic charges and hydrogen-bond parameters. Partial atomic charges are adjusted in order to reproduce the experimental values of the known isolated dipole and/or quadrupole moments when they are available. Hydrogen-bond parameters are determined by fitting the available neutral solvation energies of model clusters. Examples of cluster structures determined by RET spectroscopy and interpreted with this semiempirical model are given in the next section.

4. Case Studies

In this section, the different methods which have been reviewed in the previous section are illustrated with systems of biological interest.

4.1. DNA Base Complexes

Ab initio calculations of nucleic acid base pairs have been recently reviewed.[142] In a DNA double

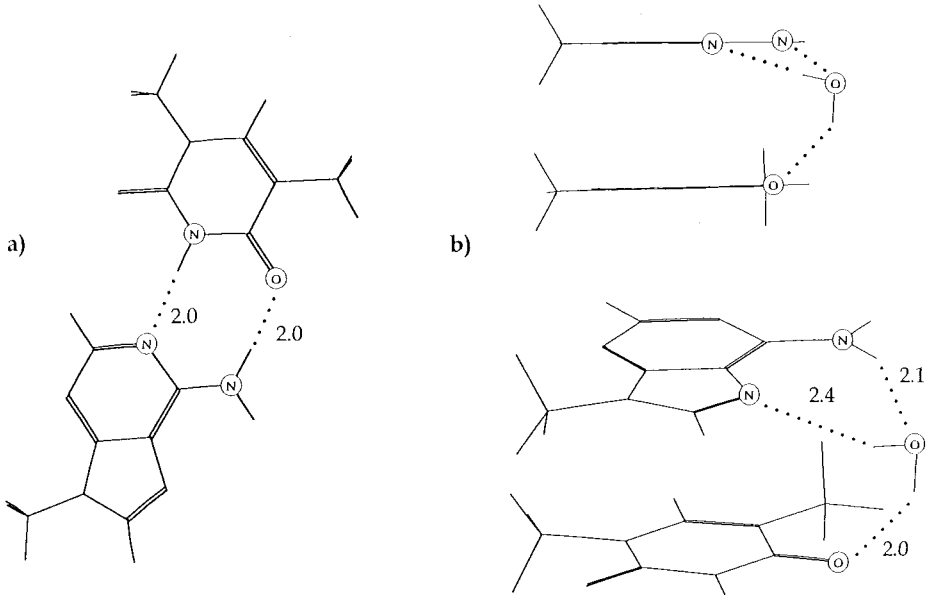


Figure 3. Influence of water upon the lowest energy structures of methylated adenine−thymine (MA−MT) pairs (respectively, methylated in N9 and N1) calculated by means of a semiempirical model (see ref 11). **(a)** H-Bonded lowest energy configuration of the isolated MA−MT pair, with a binding energy of 517 meV and a dipole moment of 2.1 D. In the presence of a single water molecule, the lowest energy configuration of the MA−MT pair becomes stacked (b**)**, with a binding energy of 979 meV and a dipole moment of 2.6 D. Hydrogen-bond lengths are in angstroms.

helix, each nucleobase is covalently linked to the sugar−phosphate backbone of one of the two strands through a nitrogen atom labeled N1 for pyrimidines (T and C) or N9 for purines (A and G). It also form forms a hydrogen-bonded pair with a complementary nucleobase of the other strand.[143] H-bonding competes with stacking interactions within each strand, but usually H-bonding is stronger than base stacking[144] and is more specific.[145] As shown by X-ray, NMR, and neutron studies in crystals or solutions,[17] two types of structures appear as fundamental: Crick−Watson and Hoogsteen complementary hydrogen-bonded pairs (A···T and C···G), which ensure the fidelity of DNA transcription by mutual recognition of adenine by thymine and cytosine by guanine. As compared to simpler molecules such as those considered in the preceding sections, the four A, T, C, and G bases offer a much wider field of investigation of H-bonding. Even if one forbids H-bonding through N9−H of purines and N1−H of pyrimidines, there are still 29 possibilities to form pairs with at least two cyclic N−H···O or N−H···N hydrogen-bonds.[146] It is not at all obvious that the Crick−Watson and Hoogsteen configurations are necessarily the most favorable when nucleobases are isolated in a vacuum where the double-helix constraints are removed.[147] A large number of ab initio calculations have been devoted to nucleobase pairs.[148−155] One of the aims of cluster studies is to validate or question those calculations by progressively adding constraints and solvent effects. An example is shown in Figure 3, where base pairing between methylated adenine (MA) and methylated thymine (MT) switches from a planar Crick−Watson hydrogen-bonded complex to a stacked complex by simple addition of a single water molecule.

4.1.1. Isolated Base Pairs

The pioneering investigation of DNA base complexes in the gas phase comes from the group of L. Sukhodub.[40] The instrumental technique was field ionization mass spectrometry,[41] and canonical (unmethylated) as well as methylated bases pair enthalpies of formation were measured. These early studies have since been experimentally pursued by several groups.[129,156,157] We performed a semiempirical calculation performed along the lines of ref 11 which shows that the lowest energy configuration of the gas-phase A···T pair (Figure 4) has a binding energy of 576 meV and a dipole moment of 3.0 D as compared to the Watson−Crick (WC) pair in a vacuum which has a binding energy of 511 meV and a dipole moment of 1.8 D. More elaborate calculations[146,158] also predict that WC A−T pairs do not seem to be the most energetically favored configurations, but up to now, experiments have still not been able to investigate the configurations of A−T pairs in the gas phase. The experimentally observed $(A\cdots T)^-$ ions are unfortunately valence anions,[129] and the RET method is not applicable here. To unambiguously distinguish between all possible configurations, precise vibronic spectra would thus be highly desirable. A first REMPI study of the G−C pair has recently been performed,[157] and intermolecular vibrations which reasonably match with calculated G−C WC pair vibrations have been observed. The G−C WC pair involves the formation of three hydrogen bonds and is the most energetically favorable configuration. Nucleobase pairing has also been studied in isolated oligonucleotides. Anions such as $(TGCA)_2^{3-}$ composed of two complementary strands have been prepared by electrospray, confined in a Fourier transform mass spectrometer and dissociated by infrared blackbody radiation (BIRD) at different temperatures.[21] Mea-

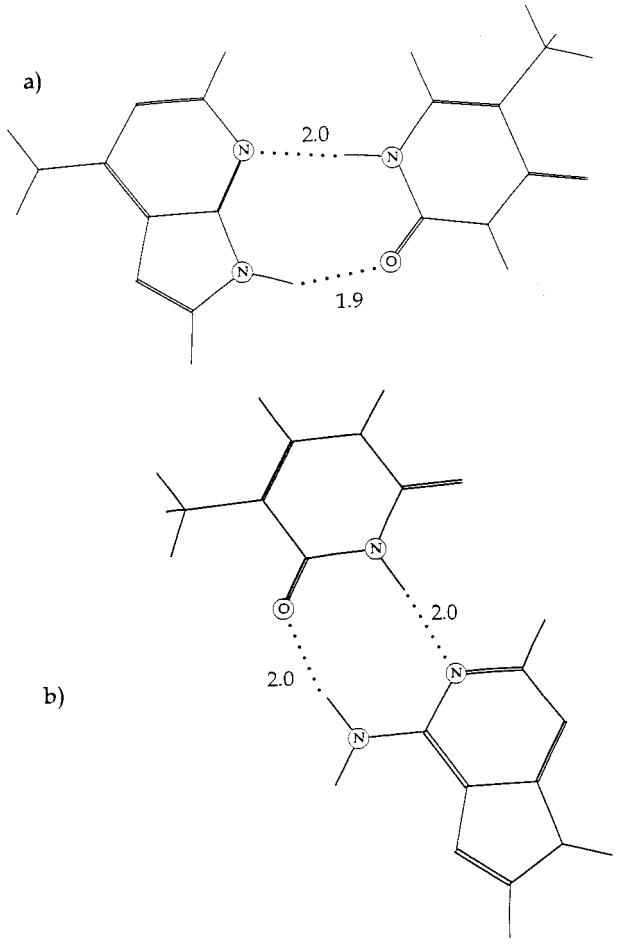


Figure 4. Structures of the isolated adenine-thymine (A−T) pair calculated by means of a semiempirical model. **(**a**)** Lowest energy configuration of the isolated A−T pair, with a binding energy of 576 meV and a dipole moment of 3.0 D. **(**b**)** Watson−Crick configuration of the A−T pair with a binding energy of 511 meV and a dipole moment of 1.8 D. Hydrogen-bond lengths are in angstroms.

sured gas-phase dimerization enthalpies have demonstrated that WC pairs can exist in a vacuum, in the absence of any solvent.

Molecular cluster studies have up to now been mostly restricted to hydrogen bonding in standard base pairs or model dimers.[159] Gas-phase studies and ab initio calculations of some other pairs, called wobble pairs, might also be very interesting. A messenger RNA (mRNA) contains base triplets (codons) which are recognized by complementary triplets (anticodons) of transfer RNA (tRNA). Each anticodon is specific of an amino acid, which becomes incorporated in the protein polypeptide chain growing in the ribosome. Three base pairs are formed during the recognition of a mRNA codon and a tRNA anticodon. The two first pairs are usual WC pairs such as G···C or A···U, but the third pair can be, for example, U···G or A···I where I stands for inosine (a base close to guanine but lacking an amino group). Study of the relative stabilities of these pairs may provide clues for the understanding of this violation of the Watson−Crick rules.[160]

4.1.2. Influence of Solvation upon Ionization Potentials and Electron Affinities of Nucleobases

The presence of water in cells plays an important role in the three-dimensional structures adopted by DNA oligomers and transfer RNA molecules.[35] Hydration also strongly influences ionization potentials and electron affinities of nucleobases. Knowledge of these last quantities is crucial for understanding the effects of ionizing radiations on DNA[71] since formation of radical cations and electron localization on bases leads to mutations and eventually to death of the cell. The evolution of ionization potentials (IP) of nucleobases as a function of the degree of hydration has been experimentally studied in thymine−water and adenine−water clusters by Herschbach and coworkers[161] and theoretically.[71,162] The predicted trend in ionization potentials is IP(T) > IP(C) > IP(A) > IP(G). It has been experimentally observed that IP-$(T\cdots(H_2O)_N)$ > IP$(A\cdots(H_2O)_N)$ for $0 \leq N \leq 3$. Cytosine could not easily be studied since it loses two hydrogen atoms and undergoes tautomerization. Guanine could not be studied in the supersonic expansion used, and one must thus rely on the predicted trend in ionization potentials (see above). This result implies that the hole should preferentially localize on G in single-stranded DNA. This issue is related to a currently debated problem of electron and hole transport in DNA[163−165] which may influence damages and repair of nucleobase sequences. The relative values of local ionization potentials are also leading factors in charge migration along other molecular backbones such as peptides.[166] Hydrated clusters of adenine have been recently studied[167] by means of resonant two-photon ionization. Monomer hydrates A $(H_2O)_n$ undergo extensive fragmentation because hydrogen bonding is strongly weakened in the $n\pi^*$ excited state.

Electron affinities of nucleobases have been experimentally measured by different groups.[64,65,70,73,168] To compare results, one must distinguish between different electron affinities since nucleobases are strongly polar and can bind electrons in different orbitals. Isolated adenine can only bind an electron in a multipole-bound state since its adiabatic valence electron affinity is negative. When two and more water molecules are added, electron binding into a valence orbital becomes energetically favored with respect to multipole binding as demonstrated by RET experiments.[130]

A rather similar situation is observed in cytosine,[169] which has a negative electron affinity when it is isolated. Solvation by a single water molecule[73,130] is sufficient to provide a positive electron affinity. In contrast, uracil and thymine exhibit different and interesting behaviors. Electron attachment to isolated U and T takes place in a multipole-bound state as predicted by theory[170] and experimentally demonstrated.[171,172] However, when a single argon atom is attached to uracil, a valence anion is observed, even if the argon atom evaporates. Uracil possesses a positive valence electron affinity equal to ≈63 meV which is smaller than the multipole-bound electron affinity equal to 86 ± 8 meV,[73] but the situation is reversed if only a single argon atom is attached. This

is due to a simple solvation effect since the excess electron−argon interaction is larger when the electron is localized in a valence orbital close to the solvent than in a diffuse orbital. In this particular case, it is thus possible to control the deposition of low-energy electrons either in a valence or a diffuse orbital.[64,65] From a biological point of view, this observation is anecdotal but it shows that molecules of biological interest can open new problems in the physics of clusters. Uracil−water complexes[173] have positive valence electron affinities as demonstrated by RET[171] and PES[65] experiments. The anions have been studied by means of ab initio calculations.[174,175]

4.1.3. Proton Transfer and Tautomerization of Nucleobases and Related Molecular Systems

Some rare tautomers of DNA bases can exist, and their occurrence can be a source of mismatches in base pairing which lead to mutations.[39,176,119,177] For example, a proton transfer can take place in the $N_A-H\cdots O_T$ and $N_T-H\cdots N_A$ bonds of the canonical A−T pair which, respectively, become $N_A\cdots H-O_T$ and $N_T\cdots H-N_A$ bonds to produce an imino−enol A*−T* pair. The energetics of this double proton transfer as well as the influence of hydration have been theoretically investigated[178] for isolated pairs as well as the influence of hydration.[152] Intrinsic acidities and basicities of the five nucleobases have also been theoretically investigated.[162] Although the problem of proton transfer in base pairs is very important,[179] experiments are still difficult due to lack of spectroscopic information concerning these pairs in the gas phase. Therefore, simpler model systems have been investigated. A fast G → C proton transfer has been recently observed in a REMPI experiment on the G−C DNA base pair but only on a nanosecond time scale.[157] The dynamics of tautomerization has been studied in 7-azaindole dimers with femtosecond resolution.[180−182] Two mechanisms can be invoked: the double proton transfer can occur as a cooperative process or a stepwise process. Interpretation of the experiments[180] demonstrates that the base-pair structure B−PS first gives birth to an intermediate state IS through an initial tautomerization sequentially followed by a second proton transfer leading to the full tautomer structure TS. The rates of tautomerization are deduced from the biexponential time behavior of the ionization signals of the pairs. The first step B−PS → IS occurs on a femtosecond time scale, while the second step IS → TS is much slower and takes picoseconds. These rates can be modeled by treating the proton motion as a tunneling in a double-well potential as suggested for DNA pairs in the early work of Löwdin.[39] The problem of proton-transfer reactions between noncovalently bound systems in the gas phase is of practical importance when hydrogen−deuterium exchange is used in mass-spectrometric experiments[183] and peptide fragmentation by low-energy collision-induced dissociation.[184] Its detailed study with simple systems such as formamidine−formic acid,[185] benzamidazole−water,[124] or 7-hydroxyquinoline−ammonia[186] complexes can be helpful for elucidation of IR spectra of DNA base−water complexes and provides insights on the formation of enzyme−substrate complexes.[187]

4.2. Peptide Bonds and Amino Acid Side Chains

Empirical force fields are widely used for the study of the structure and dynamics of proteins. Optimization of their parameters is built from information coming from different sources among which gas-phase geometries and vibrational spectra are either obtained from experiments or ab initio calculations of model compounds. The bonding parameters of the peptide backbone of proteins can be optimized from data concerning, for example, formamide or *N*-methylacetamide.[31] Rather simple molecules such as indole for tryptophan, imidazole for histidine, acrylamide for asparagine, and glutamine or methanol for serine and threonine, yield parameters for amino acid residues.[188] Cluster studies of some of these molecules are here reviewed.

4.2.1. Models of Peptide Bonds

Formamide (F) is the simplest amide containing the peptide linkage. Hydrogen bonding between the carbonyl C═O and the amine NH_2 functional groups is responsible for its main physical and chemical properties and has been studied in solids,[189] liquids,[190] and clusters.[137,191] The replacement of hydrogen atoms by one or two methyl groups allows one to easily modify the possibilities of hydrogen bonding. The corresponding molecules, *N*-methylformamide (NMA), dimethylformamide (DMF), and *N*-methylacetamide (NMA), are strongly polar and have been studied as antitumor drugs.[192] By taking advantage of these large polarities, it is possible to directly determine the geometrical structures of the different homogeneous and mixed clusters by means of RET spectroscopy[137] since each configuration can be identified by its total dipole or quadrupole moment. For example, the existence of the head-to-tail configuration of the F···F dimer is demonstrated by the observation of a quadrupole-bound dimer anion. The study of hydrated complexes of formamide and its methylated derivatives is of interest for modeling interactions between proteins in water.[193] Guo and Karplus have considered F···NMA and $(H_2O)_{N=1,2,3}$ hydrogen-bonded clusters and shown that water molecules can cooperatively bind to the peptide group and modify the rotational barriers of the methyl groups.

Once such very small complexes have been studied, application of these force fields to larger scale biological problems must be tested. For example, molecular dynamics simulations of ribonuclease A surrounded by a finite hydration shell, considered as a very large cluster, have shown that some care is required in order to interpret the very fast diffusion of proteins in water.[81] Water molecules move too freely on the protein surface in such a model cluster, and artificial constraints must be added in the molecular dynamics calculation to confine water and to slow its motion as in a crystal.

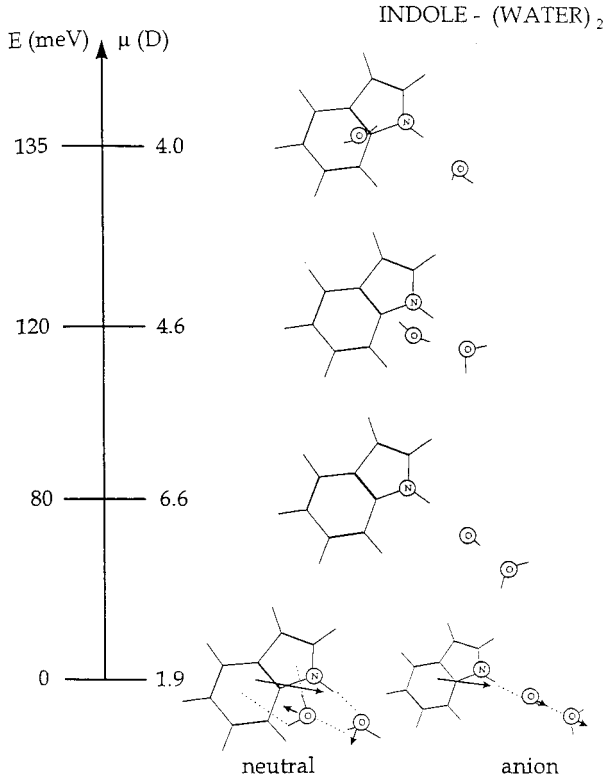


Figure 5. Optimized structures of the neutral−$(H_2O)_2$ complex calculated by means of a semiempirical model.[130] The binding energy of the lowest energy configuration is taken as the reference of binding energies (left vertical scale). For each configuration, the resulting dipole is given on the right side of the energy scale. Arrows represent dipole moments of the individual components of the complex. The large difference between the geometries of the neutral parent and its anion for this lowest energy configuration is due to dipole alignment which energetically favors electron attachment (the smaller size of the anion is not meaningful). Those calculations are compared to RET experimental results and ab initio calculations in ref 141.

4.2.2. Models of Amino Acid Residues

The influence of hydration upon properties of amino acid residues has been investigated with model molecules. For example, imidazole−water complexes have been considered in quantum chemistry calculations,[194−196] matrix,[197] and cluster experiments.[198,199] Spectroscopic properties of proteins[200] are related to UV (190−220 nm) spectra of the phenylalanine, tyrosine, tryptophan, and histidine residues, and thus, among those fluorophores, indole (In) is the most widely studied.[60,132,134,136] The structures of the lowest energy configurations of In···$(H_2O)_N$ complexes have been determined for $N = 1$ and 2. It is generally assumed that these configurations are energetically well separated from higher excited configurations. As shown in Figure 5, this is not necessarily true in usual supersonic expansions and disentangling experimental data can become more and more difficult when the number N of water molecules increases. IR depletion measurements coupled to high-level ab initio calculations are probably the most reliable method for distinction between isomeric conformations. The RET method offers a rather direct alternative since the isomers have different total dipole moments as shown in Figure 5.

The hydrogen-bond network between chemical groups is determinant for biospecificity. In the example of Figure 1, the selective affinity of progesterone, a steroid which is required for the maintenance of pregnancy, for its receptor requires the establishment of weak bonds between side chains of an arginine and a glycine of the receptor and a phenylalanine of progesterone, together with a water molecule. The 20 × 20 interaction possibilities between amino acid residues have been studied in crystallized proteins.[201] These data may not perfectly correspond to in vivo biological conditions, and cluster studies can model these interactions under different conditions. For example, hydrogen bonding between imidazole and indole has been studied by means of RET (see Figure 6) in the presence or absence of water,[199] and the binding energy of the imidazole dimer has been determined by blackbody infrared radiative dissociation.[202]

4.2.3. Disulfur Bonds

The tertiary structure of proteins is stabilized by establishment of disulfur bonds between cysteines. Two nearby $-CH_2-SH$ residues in a protein can lead to the formation of a simple valence $-CH_2-S-S-CH_2-$ disulfide bond. An important issue concerns the relationship between the gas-phase and the condensed-phase structures, and it has been addressed in the case of disulfide-containing proteins.[103] Dimethyl disulfide (DMDS) constitutes a model of the disulfur bond. Gas-phase reactions of DMDS have been studied,[203] and its electron affinity is positive.[204] Breaking of S−S bonds by electron reduction[205] causes protein to fold-up as shown by ion-mobility mass spectrometry of lysozime ions.[106] The lysozime protein has four disulfide bonds, but it has been demonstrated by pulse radiolysis that a single bond established between cysteine 6 and cysteine 127 localizes a negative charge due to the presence of a positive charge on an arginine residue. Reduction is thus highly specific since it only induces rupture of this 6−127 bond. This has been interpreted by modeling this bond and its environment. The disulfur bond and the arginine are modeled by complexes of DMDS and guanidinium cations ($(C(NH_2)_3^+)$),[206] respectively. This study is another example which shows how mechanisms concerning large biomolecules, once pinpointed by means of biochemistry methods, can be scrutinized by ab initio and/or gas-phase studies of model systems.

4.2.4. Zwitterions

In aqueous solutions, over a wide range of pH, amino acids have both a positive charge ($-NH_3^+$) and a negative charge ($-COO^-$) and are stable as zwitterions. These charged groups can strongly interact mutually or with water molecules, and this has been taken into account in empirical potential models.[207] In the gas phase, amino acids can exhibit different behavior. Glycine ($NH_2HCHCOOH$) is the simplest amino acid, and its microwave spectrum has shown that the neutral configuration is the most favorable for isolated glycine.[208] A similar result has been obtained by studying the vibrational spectrum of

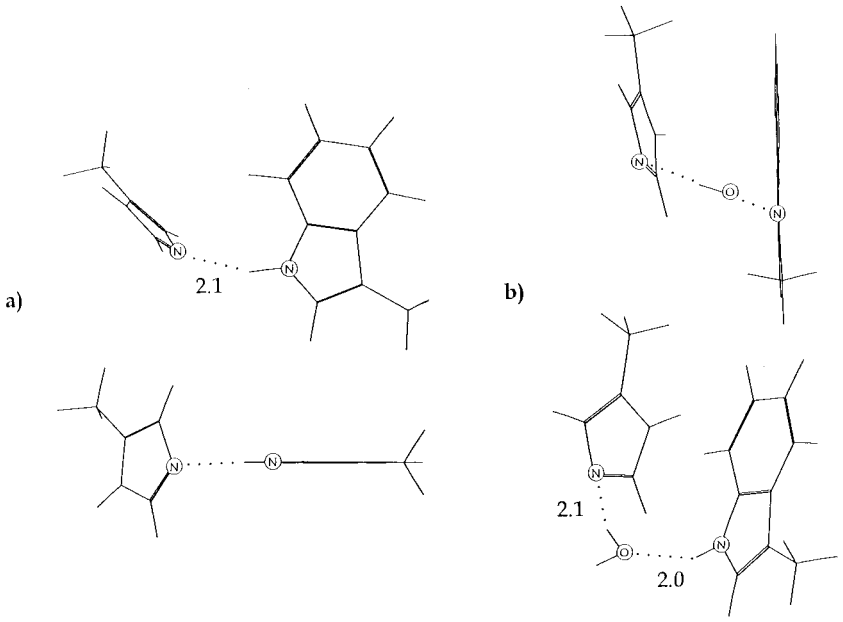


Figure 6. Optimized structures of neutral methyl−indole−methyl−imidazole complexes calculated by means of a semiempirical model. The binding energies (dipole moments) of the lowest energy configuration **(**a**)** and the hydrated configuration **(**b**)** are equal to 350 (6.4 D) and 884 meV (1.4 D), respectively. (Hydrogen-bond lengths are in angstroms).

glycine in rare gas matrixes and helium clusters.[90] The analysis of the O−H stretch region was carried out and demonstrated the existence of the three most stable conformers, one of them possessing an internal hydrogen bond. An internal proton transfer can, in principle, take place from the carboxyl to the amino group. Calculations predict that the zwitterion becomes the most stable form when at least two water molecules are present. The proton-transfer mechanism can be either intramolecular or water-assisted. To our knowledge, this prediction has still not been experimentally tested. Infrared-depletion, PES, or dipole moment measurements of glycine−water clusters should provide signatures of the transition between neutral and zwitterion structures. The situation is somewhat different for arginine since its guanadinine side chain ($-(CH_2)_3-NH-C((NH_2)_2)$[209] can accept a proton from the carboxyl and the corresponding zwitterion is predicted to be more stable than the neutral form.[117] The structure of cationized arginine ($Arg\cdots M^+$) changes as the size of the alkali-metal ion M^+ increases.[210] For the smaller metal ions (Li, Na), the neutral arginine solvates the metal ion, while for heavier metals (K, Rb, Cs), salt-bridge structures into which arginine is a zwitterion become more stable. An infrared study of isolated arginine has attempted to demonstrate the existence of both neutral configurations (with a COOH absorption band) and zwitterions (with a COO^- absorption band) in a supersonic beam of isolated arginine. The absence of any observed signal arising from the COO^- group of the zwitterionic form suggested the existence of a barrier for proton transfer in absence of solvent.

The dispersed fluorescence of tryptophan, following UV excitation of the indole side chain, is broad and exhibits a large red shift.[211] This has been interpreted as an indication of the formation of a zwitterion in the excited state. This zwitterion would be stabilized in the excited state due to a sizable interaction between the large dipole of the tryptophan backbone, induced by the proton transfer between the amino and the carboxyl groups, and the indole ring.

A BIRD experiment[117] has shown that the binding energy is larger in an arginine dimer than in a glycine or an alanine dimer. The interpretation, which is supported by a semiempirical calculation, is that one of the arginines in the dimer is a zwitterion with a protonated guaninidine group and a deprotonated carboxyl. Betaine ($(CH_3)_3N^+CH_2COO^-$) is a natural methylated derivative of glycine which exists as a zwitterion in its ground state, and its protonated complexes with molecules of different basicities have been studied by means of BIRD.[212] This problem of zwitterion formation is not only important for the structure and function of proteins, but it is also encountered in the structure of turns and bends in RNA.[17]

4.3. Nucleobase−Amino Acid Residue Interactions

Binding of proteins to DNA plays a great role in the regulation and control of gene expression. Protein recognition of DNA sequences, such as binding sites of the RNA polymerase enzyme which deciphers the genetic code by producing messenger RNA, comes from a combination of a high affinity of the protein for DNA and a certain local conformation of the double helix. Regulatory proteins are capable of specific recognition of sequences of 14−20 base pairs. Some proteins called restriction enzymes which cleave DNA at extremely precise sites recognize even shorter sequences (4−8 base pairs). Hydrogen bonds between peptide bonds or hydrophilic amino acid side chains and DNA bases, such as those displayed in Figure 7, are among the most important interactions responsible for this impressive specificity of protein binding.[213] Although no general amino acid−base pair code has been found, there is a strong impetus to design artificial ligands which would achieve selec-

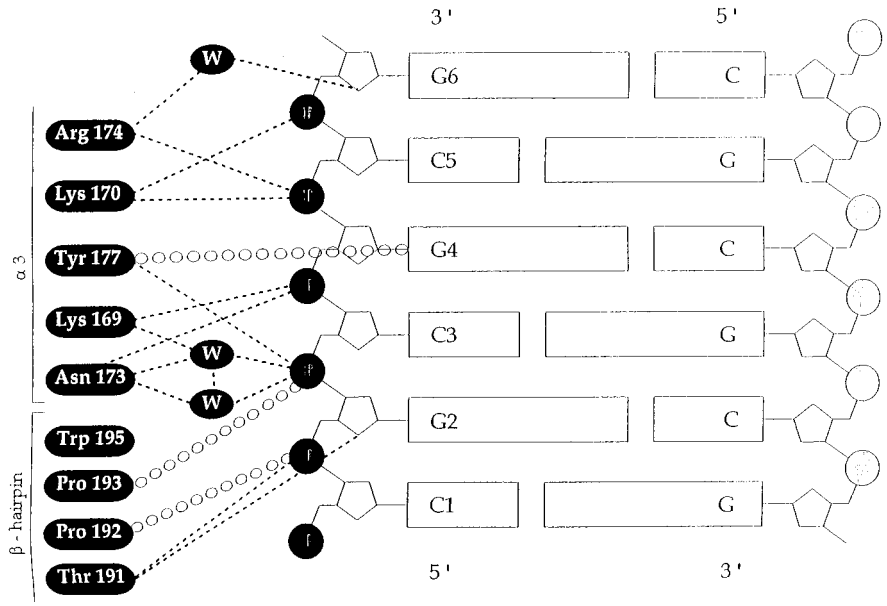


Figure 7. Specific interaction between a protein and DNA. The figure is a schematic representation of the contact region between a domain (called Zα) of an enzyme and a special form of DNA (called Z-DNA). Residues of one of the Zα domain helixes (α3) and of one of its β sheets interact and establish hydrogen bonds (- - -) with the phosphate backbone of DNA as well as van der Waals bonds (○) with phosphates and a nucleobase (G4). Three water molecules (W) are in key positions. This network of weak bonds is responsible for the very high affinity of Zα for Z-DNA. (Reprinted with permission from Schwartz et al. *Science* **1999**, *184*, 1843. Copyright 1999 American Association for the Advancement of Science.)

tive recognition of known sequences belonging to identified genes[214] in human cells.[25,27,215] Among them, hairpin polyamides containing imidazole (model of histidine), pyrrole, and hydroxypyrrole have demonstrated high capabilities for selective binding to DNA sequences.[26]

Interactions between amino acid side chains and nucleobases have been investigated by means of quantum chemistry calculations,[22] and some mixed dimers have been studied. Binding energies between methylated derivatives of cytosine and acrylamide which model residues of asparagine and glutamine have been measured[216] by means of the field ionization mass spectrometry technique.[41] DFT calculations show that the dimer structures are planar with double hydrogen bonds and antiparallel orientations of the monomer dipoles. Taking advantage of the strong polarity of several side chains, the RET method has been applied to structure determination of lowest energy configurations of nucleobase−model molecule complexes. Multipole-bound cluster anions containing adenine weakly bound to imidazole, pyrrole, and methanol (model for serine and threonine) and cytosine with imidazole have been observed. The structure of their neutral parents have been determined by comparison between RET experimental results and semiempirical calculations. For example, the adenine−imidazole dimer (Figure 8) has three low-lying hydrogen-bonded structures with respective binding energies equal to 305 (Figure 8a), 290 (Figure 8b), and 280 (Figure 8c) meV and corresponding dipole moments equal to 2.8, 5.9, and 3.7 D. Comparison between the calculated and measured electron binding energies, respectively, equal to 65 and 61 meV, lead to the conclusion that the observed anions are created from neutrals in the lowest energy configuration (Figure 8a).

4.4. Influence of Methylation

A crucial mechanism used by nature for activation or repression of genes is methylation of DNA bases. To shut off a gene for the entire life of an organism, some bases are methylated in a few critical regions within or close to silenced genes. Soon after replication of a methylated DNA region, some more methyl groups are even added to the new strands and impair the specific DNA interaction with proteins such as RNA polymerase. Acetylation is also an important process which modifies the wrapping of DNA around chromosomal proteins called histones and influences the transcription of genes.[217] Replacement of a hydrogen atom by a methyl group is not only used by nature, but it is also a well-known means to eliminate a possibility for hydrogen bonding, and several examples of cluster structure modifications have been observed.[117,137] Methylation can also affect intrinsic properties of molecules such as, for example, electron affinities and anion geometries of nucleobases which are slightly modified. Ab initio calculations of these subtle effects require high levels of theory. The experimentally measured electron binding energies of formamide and its methylated derivatives NMF and DMF are equal to 16.7, 15.7, and 13.6 meV, respectively. At the MP2 level, calculated values are only equal to 9.9, 9, and 8 meV, respectively. Calculations at the CCSD(T) level and inclusion of vibrational zero-point energies are necessary to reproduce experimental data.[33] For larger molecules such as 1,3 dimethyluracil and 1-methylthymine, RET measurements show a reduction of electron affinities with respect to canonical uracil and thymine. This trend is qualitatively confirmed by calculations at the MP2 level. Methylated anions are less distorted than unmethylated anions, with respect to the geometries of their neutral parents.[131]

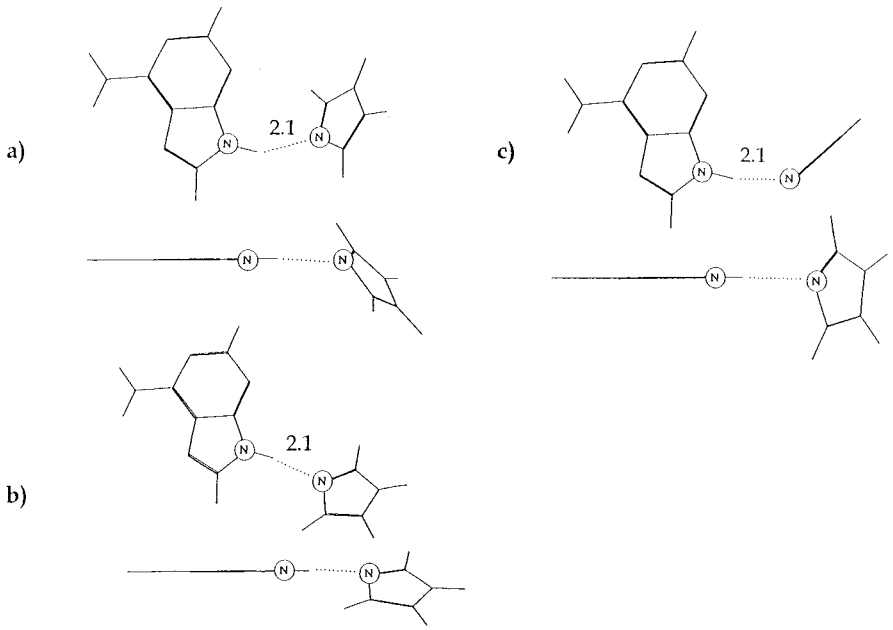


Figure 8. DNA base-amino acid residue interaction. The figure represents front and side views of optimized structures of the neutral adenine−imidazole complex calculated by means of a semiempirical model. The respective binding energies (dipole moment) of the lowest energy configuration **(**a**)** and the two upper configurations **(**b and c**)** are, respectively, equal to 305 (2.8 D), 290 (5.9 D), and 280 meV (3.7 D). Anions created from complexes in the configuration shown in part a have been experimentally observed by RET spectroscopy. (Hydrogen-bond lengths are in angstroms).

4.5. Modeling of Hydrophobic Interactions

Hydrophobicity is a widely used concept by biologists. Hydrophilic side chains are preponderant on the surface of water-soluble proteins, and hydrophobic side chains are mostly confined in the core.[38] When a protein approaches another protein or DNA, some water molecules move from the surface of the interaction sites toward the bulk with a gain of entropy and some remain at the interface.[218] A statistical analysis of crystal structures of protein−protein complexes which are deposited in the Protein Data Bank has shown[219] that most interfaces have surfaces of the order of 500 Å^2 with a direct hydrogen bond per 150 Å^2. There is typically one water molecule per 100 Å^2 at interfaces. The presence of water molecules in the interfacial regions is thus responsible for the majority of hydrogen bonds which, however, are nonspecific, and the details of the hydrophobic effect are still debated.[220] Simplified models use highly idealized models of proteins where all amino acid details are ignored and residue−residue or water−residue interactions are nonspecific.[221] The individual properties of amino acids disappear, and only two classes are considered: hydrophobic and hydrophilic residues. These models can then be used to tackle the problem of protein folding and can include the effects of an aqueous solvent.

Cluster studies involving molecules such as benzene as a prototype of aromatic molecules, water, or methane have been performed in order to provide interaction potentials for modeling hydrophobic interactions.[222,223] REMPI, UV hole-burning, and resonant ion-dip infrared spectroscopy experiments, coupled to DFT calculations of benzene−(water)$_{N=8}$ clusters[34] have shown that a water "ice-cube" sits on the top of benzene with a single water molecule interacting with the π-cloud of benzene.[57] Competition between H$\cdots\pi$, $\pi\cdots\pi$, and H$\cdots$X interactions can be studied in great detail by means of molecular cluster experiments coupled to ab initio calculations.[224] In the future, it is possible that data derived from cluster experiments and corresponding ab initio calculations (for example, residue−residue or residue−water potential parameters) will be incorporated into the simplified models describing biomolecules in water.

4.6. Chiral Clusters

Amino acids (except glycine) and a large number of molecules of biological interest can have several stereoisomeric forms but, with rare exceptions, only exist as natural compounds in a single form.[225] In natural proteins, only the L form is found. The reason for this choice of nature is still mysterious. Among the possible explanations, the existence of a slight difference between energies of the enantiomers of a chiral molecule and thus between their thermal distributions, due to symmetry breaking by weak interactions, has been suggested[226] and recently tested on the model molecule CHFClBr.[227] It has been observed that the relative difference between vibration−rotation frequencies of the two enantiomers is smaller than 4×10^{-13}. From a more practical point of view, when a drug interacts with its receptor which is chiral, one of the enantiomers can have the desired biological activity while the other is useless or even poisonous. Thus, pharmaceutical production of single-isomer drugs is now highly recommended.[228]

A slow spontaneous racemization of amino acids has been observed in aging bodies. Enantiomeric excesses in amino acids of the Murchison meteorit have been measured in order to look for a possible extraterrestrial origin of life.[229] It may thus prove

helpful to design very sensitive mass-spectrometric detection schemes for discrimination between extremely small quantities of chiral compounds. Several molecular parameters can be used for chiral discrimination between van der Waals complexes. In a supersonic jet containing enantiomer species *R* and *S*, homochiral *R*−*R* or *S*−*S* and heterochiral *R*−*S* or *S*−*R* diastereoisomers are formed. While isolated enantiomers of a given species cannot be distinguished since their physical properties are identical, one can complex a studied species A with unknown chirality with a solvent B of known chirality, for example S_B. The diastereoisomers S_A-S_B and R_A-S_B can now be distinguished, for example, through their respective binding energies and thus their beam populations, their fluorescence[230] and hole-burning spectra,[231] REMPI spectra,[232] or their total dipole moments. The case of 2-naphthylethanol (NetOH) complexed by chiral alcohols is one of the most striking examples.[231] NapOH is a substituted naphthalene with an asymmetric carbon in a side chain, and it is a chromophore with a well-resolved S_0-S_1 transition. Shifts of the fluorescence excitation spectra are observed in the presence of chiral solvents (e.g., 2-methyl-1-butanol, secondary alcohols) with respect to the bare molecule spectrum. Homochiral and heterochiral pairs exhibit specific shifts which have been analyzed.[233] The observed chiral discriminations are due to subtle balances between different effects such as steric factors and additive dispersive interactions which are more important in the excited state.

A general method for chiral discrimination which is widely used in chromatography is based upon the difference between interactions of a studied chiral molecule and the environment introduced by a chiral stationary phase, allowing for separation between homochiral (*RR* or *SS*) and heterochiral (*RS* or *SR*) diastereoisomers.[234] Enantiomer separation between chiral inhalation anesthetics such as enflurane or desflurane can be performed in a conventional gas chromatograph.[235] Let us now examine how chiral discrimination can be directly performed in beams or very diluted media. Differences between electron-transfer or energy-transfer rates in the excited state can be sensitive to chirality of complexes, even when no spectral discrimination is observed in the fluorescence spectrum.[236] When chiral molecules do not possess well-resolved spectra but have large enough dipole moments, chiral discrimination may be achieved by comparing resulting dipole moments of the diastereoisomers. Multipole-bound anions of chiral molecules such as prolinol, a derivative of the proline amino acid, or pyroglutaminol and their dimers have been observed. The *S*−*S* and *S*−*R* enantiomers of pyroglutaminol have very different dipole moments (respectively, 2.83 and 0.02 D) and thus should, in principle, be very easily discriminated by RET. However, electron attachment is also sensitive to quadrupole moments (respectively, −9 and −50.8 a.u.) which must be taken into account, and only a very small difference is observed in the RET *n*-dependencies, but larger differences can be expected in more favorable cases.

It might also be possible to use polarized electrons in order to selectively ionize polar enantiomers, but the difference between electron attachment cross-sections of *R* and *S* species is very small. A single collision may thus not be sufficient for chiral discrimination but a large number of collisions with polarized electrons may be efficient. Individual scattering of low-energy polarized electrons by chiral molecules (e.g., camphor-like molecules containing ytterbium atoms)[237] has an asymmetry of the order of 10^{-4}, but observation of scattering of polarized electrons in thin organized films of chiral molecules[238] has indeed demonstrated that cooperative addition of a large number of elementary electron−molecule interactions can lead to a very large enhancement (10^3-10^4) of the asymmetry. Adding some chiral molecular perturbers in the drifting region of a gas-phase chromatography mass spectrometer[107] may provide a general method for complete gas-phase chiral discrimination.

5. Conclusion

A wide variety of techniques such as MALDI, electrospray, or liquid beams as well as helium clusters, which are currently used for studying either small molecules or large biomolecules, allow for the introduction of nonvolatile molecules in the gas phase, and some of the least perturbative methods can be applied to production of weakly bound clusters of molecules of biological interest. As compared to simple molecules such as benzene and its derivatives, DNA bases or amino acid residues offer much larger numbers of possibilities for hydrogen bonding or stacking interactions and are thus very demanding for precise spectroscopic tools. A vast arsenal is now available with, for example, IR depletion, VUV or RET ionization, BIRD, or very high-resolution PES.

Examples in this review mostly dealt with nucleobases, amino acid residues, and their more or less hydrated complexes, and some attention has also been paid to chiral systems. A vast number of cluster studies which are aimed to scrutinize noncovalent interactions between molecules of biological interest should have also been considered. For example, some neuromediators are derivative from amino acids (e.g., dopamine from tyrosine or GABA from glutamate), and it may be interesting to model interactions with their receptors in simple clusters. Many neurotransmitters, such as dopamine or 2-phenylethylalamine, possess an aromatic chromophore and a flexible chain with a terminal group such as an amino, amide, or carboxylic acid group. To provide a sensitive mass-spectrometric detection scheme, the REMPI spectroscopy of catecholamine neurotransmitters has been studied.[95] MP2 and DFT calculations have determined the conformation of protonated dopamine in the gas phase and in water.[239] Bare 2-phenylethylalamine and its hydrated clusters have been studied in supersonic beams by means of REMPI[240] and those of 2-phenylethanol by means of IR−UV depletion spectroscopy,[241] indicating the existence of a variety of conformers among which the most stable are folded due to formation of π-hydrogen bonding between the side chain and the chromophore. Interestingly, folded

conformations[242] play a selective role in receptors of GABA (γ-aminobutyric acid).[243] These studies could be used for improvement of force-field models used in the design of molecules which mimic small peptides with increased biological activity.[244]

The immune system uses antibodies which have binding domains recognizing antigens and effector domains which signal the beginning of processes which get rid of the antigen. Design of artificial receptors which mimic natural antibodies is an active research field[245,29] and understanding details of antigen−antibody interactions may prove useful. The determination of the crystal structure of a complex formed by an antibody and an hapten (here, nitrophenylphosphonate) has shown that the extraordinary specificity requires a number of precisely tuned weak interactions between amino acid residues and the hapten.[28] Moreover, this specificity is progressively optimized by replacements of residues. Starting from a germline antibody, those "somatic" mutations produce different mature antibodies and those with the highest affinity for the hapten are selected and cloned. Formation of new hydrogen bonds and π-stacking interactions increase this affinity. For example, replacement of a precise serine by a glycine increases the binding of the aromatic ring of the hapten to side chains of two nearby tyrosines and a leucine. Haptens which are commonly used in experimental immunology are proteins containing dinitrophenyl radicals. Antigen recognition can be studied in cluster-containing model molecules such as paradinitrobenzene[246] interacting with amino acid side chains.

Interactions between membrane proteins and carbohydrates are crucial in the earliest phases of human diseases, and their inhibition can be used for treatments.[247] Structures of carbohydrates are very complex, and their sequencing is difficult.[248] Interestingly, their crystal structures exhibit C−H···O hydrogen bonds[249] which have been analyzed by ab initio calculations.[250] It may be possible to investigate if those bonds[251] persist in the gas phase since monosaccharides, which are the simplest carbohydrates, have been laser-desorbed and their fragments mass-analyzed.[252]

The number of clusters of molecules of biological interest which should have been considered is very large, and this review has been voluntarily limited to a few cases where weak interactions have been studied. We have nearly discarded reactivity,[253] although hydrogen bonds can contribute to enzymatic activity.[187] We have also, for example, omitted interesting theoretical[188] and experimental gas-phase studies where metallic ions are involved, for example, in the binding of alkali ions to nucleobases[254] or copper ions to amino acids.[255]

The weakly bound clusters we have considered here represent an intermediate situation. The number of possible weak bonds which can be established and number of configurations which are thermally populated in beams are between those of simple organic molecules and real biomolecules. This allows for results obtained with different techniques under well-defined experimental conditions which can now be interpreted with a higher and higher degree of confidence by ab initio calculations. The validation of these calculations may be transferred to the developments of semiempirical models incorporating more refined parameters, which in turn could be applied to much larger biomolecular systems.

6. References

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