

Noncovalent Interactions: A Challenge for Experiment and Theory

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I. Introduction

A common phenomenon resulting from the interaction of atoms is the formation of molecules, under certain conditions. This well-known type of interaction is termed covalent and yields a new chemical species with properties completely different from those of the original systems. As early as 1916, i.e., well before the quantum theory of the chemical bond was established, covalent interactions were first

described theoretically by G. N. Lewis.¹ After more than 80 years of intense study, the processes of formation and breaking of covalent bonds are now well understood, and their theoretical treatment is straightforward. Moreover, reliable characteristics of covalent interactions can be obtained at various theoretical levels (e.g., beyond *ab initio* Hartree–Fock and Density Functional Theory).

Modern chemistry is based on the understanding of the chemical bond. The chemical bond implies the distribution and delocalization of electrons over the entire molecule resulting in a strong, i.e., covalent interaction. The covalent description is fully adequate when the molecule is considered in free space, i.e., isolated from its surroundings. Modern theoretical *ab initio* quantum chemistry methods have been extremely successful in describing the electronic structure of isolated molecules to a degree of precision that in some cases comes very close to high-resolution spectroscopic results. From the experimental viewpoint, there is quite a variety of spectroscopic methods to look at a molecule in the gas phase, i.e., under conditions where it can be considered unperturbed from collisions or other external forces, for instance, in molecular beams from supersonic jet expansions. These high-resolution spectroscopy methods are based on molecular quantum mechanics, group theory, and phenomenological Hamiltonians with well-defined matrix elements, offering very powerful and well-understood algorithms of interpretation.^{2,3}

Atoms and molecules can interact together leading to the formation of either a new molecule (reactive channel) or a molecular cluster (nonreactive channel). The former is clearly again a covalent interaction; the latter one in which a covalent bond is neither formed nor broken is termed a noncovalent or van der Waals (vdW) interaction. This nomenclature is, however, not well-defined and the term vdW interactions is sometimes used only for certain noncovalent interactions (mostly dispersion, see later). Furthermore, in solid-state science, the term metallic bond is distinguished from covalent bond. Noncovalent interactions were first recognized by J. D. van der Waals in the last century⁴ and helped him to reformulate the equation of state for real gases. Noncovalent interactions lead to the formation of a molecular cluster while covalent interactions lead to the formation of a classical molecule.

The properties of the original subsystems in a molecular cluster are relatively unperturbed compared to the isolated molecules. Nevertheless, the

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Klaus Müller-Dethlefs was born in 1950 in Wilster, Germany. After studying chemistry and physics at the University of Göttingen, he received his Ph.D. in 1979 at Imperial College from the University of London for his work on soot formation with F. Weinberg, supported by a stipend from the Evangelisches Studienwerk Villigst. With a research fellowship of the Deutsche Forschungsgemeinschaft, he worked with J. P. Taran at ONERA (Chatillon, Frankreich) on coherent anti-Stokes Raman scattering (CARS) in flames. At the Institut für Physikalische und Theoretische Chemie der Technischen Universität München, he established the ZEKE method with its new applications in chemistry. Müller-Dethlefs was granted his habilitation in Chemistry in 1991, and in 1994 he received the Rudolf-Kaiser-Preis of the Stiftungsverband für die Deutsche Wissenschaft in recognition of his development of ZEKE Spektroskopie. In 1995, he was appointed to the Chair of Physical Chemistry in the Department of Chemistry, The University of York, England. He held guest professorships at the Université de Bourgogne, Dijon, 1985, at Laboratoire Aimé Cotton, Orsay, 1992, at the Institute of Atomic and Molecular Sciences, Taipei, Taiwan, 1998, and at the Institute for Molecular Sciences, Okazaki, Japan, 1999. He has been chairperson of several international conferences. Recently, he was awarded the Tilden Lectureship 2000/2001 by the Royal Society of Chemistry.



Pavel Hobza was born in 1946 in Přerov, Czechoslovakia, and graduated from Czech Technical University in 1969. In 1974, he received his Ph.D. (with Professor R. Zahradnik) and, in 1988, the D.Sc. degree; after 1989, he became Associated Professor of Charles University in Prague. Since 1989, he has been employed at the J. Heyrovský Institute of Physical Chemistry, Czech Academy of Sciences, Prague. After postdoctoral study with Professor C. Sandorfy at the Université de Montréal, Montréal, he spent several periods as a visiting professor and a visiting scientist at Université de Montréal, Montréal; Friedrich-Alexander-Universität Erlangen-Nürnberg; and Technische Universität München. Since 1998, he has been head of the Department of Chemical Physics at the J. Heyrovský Institute. He has been a fellow of the Learned Society of the Czech Republic since 1998. Dr. Hobza has authored or coauthored about 180 papers and two books. These studies dealt mainly with molecular interactions and their role in physical chemistry and biodisciplines.

formation of a noncovalent cluster does affect properties of the subsystems, and these changes are important for the detection of cluster formation. The

stronger the noncovalent interaction, the larger the changes in the properties of the subsystem. Most pronounced changes occur in H-bonded systems, and the change of stretch frequencies upon complex formation can be as large as hundreds of inverse centimeters (cm^{-1}). Noncovalent interactions are considerably weaker (by 1 or 2 orders of magnitude) than covalent interactions. The role of noncovalent interactions in nature was fully recognized only in the last two decades; they play an important role in chemistry and physics and, moreover, are of key importance in the bio-disciplines. The structures of liquids, solvation phenomena, molecular crystals, physisorption, the structures of bio-macromolecules such as DNA and proteins, and molecular recognition are only a few phenomena determined by noncovalent interactions.

Noncovalent interactions play a special role in supramolecular chemistry, which has been defined by Lehn⁵ as “chemistry beyond the molecule”. Noncovalently assisted synthetic procedures are used to assemble various types of supramolecular species. These syntheses rely on the stabilization provided by noncovalent interactions between recognition sites incorporated within precursors. As a recognition motif utilized to guide the synthesis, various types of noncovalent interactions can be used. These are, specifically, hydrogen bonds (H-bonds), stacking interactions, electrostatic interactions, hydrophobic interactions, charge-transfer interactions, and metal coordination.⁶ Unconventional polymers composed of covalent and noncovalent bonds differ dramatically from standard, conventional polymers with just covalent bonds. They possess novel physical, optical, electrochemical, photochemical, biological, and catalytic properties. Targeted synthesis of macro- and supramolecular structures of various sizes, shapes, and functionality has now become possible.⁷ Supramolecular chemistry offers incredible applications in various fields such as medicinal chemistry (drug delivery systems),^{8–11} host–guest chemistry,¹² catalysis,^{13–15} and molecular electronics.¹⁶

The existence of a condensed phase probably represents the most important example of noncovalent interactions. The vast majority of chemical processes occur in solution, and the condensed phase affects the structure, properties, and reactivity of a system dramatically and plays an even more important role in biology (life originated in the liquid water phase). There are two basic models for describing solvation phenomena. Both rely to a large extent on noncovalent interactions which are characteristic for the gas phase. The first model considers a discontinuous solvent, and a large majority of current molecular dynamics/empirical potential methods utilize pair additive force fields. It implies that any polarization of the solute by the solvent (and vice versa) is ignored and the total energy of a the system is calculated additively, i.e., as the sum of solute–solute, solute–solvent, and solvent–solvent terms. This model thus represents only an extension of the gas-phase model. In the second model, called the continuous model, polarization of a continuous solvent by a discrete solute is considered in addition to

the gas-phase noncovalent solute–solute interactions. Evidently, both liquid models utilize gas-phase noncovalent interactions and any progress in the description of the liquid phase depends on new developments in the description of noncovalent interactions.

Covalent and noncovalent interactions differ considerably and have completely different origins. A covalent bond is formed when partially occupied orbitals of interacting atoms overlap and consists of a pair of electrons shared by these atoms. Covalent interactions are of short range and covalent bonds are generally shorter than 2 Å. Noncovalent interactions are known to act at distances of several angstroms or even tens of angstroms and overlap is thus unnecessary (in fact overlap between occupied orbitals leads only to repulsion). The reason for the attraction between interacting subsystems must be sought elsewhere and it can lie only in the electrical properties of the subsystems. Noncovalent interactions originate from interaction between permanent multipoles, between a permanent multipole and an induced multipole, and finally, between an instantaneous time variable multipole and an induced multipole. The respective energy terms, called electrostatic, induction, and dispersion are basically attractive (only the electrostatic term, depending on the orientation of the subsystems, can be attractive or repulsive). The repulsive term, called exchange–repulsion, connected with the above-mentioned overlap of occupied orbitals, prevents the subsystems from approaching too closely.

The total stabilization energy of a molecular cluster lies usually between 1 and 20 kcal/mol, considerably smaller than the binding energy of a covalent bond of about 100 kcal/mol. To describe and study noncovalent interactions, it is essential to apply the most accurate methods of quantum chemistry, and experimental studies of these interactions belong to one of the most challenging tasks of contemporary science.

It is useful to consider how covalent and noncovalent interactions differ. First, there is the difference in stabilization energy and equilibrium distance: noncovalent clusters have a characteristic stabilization energy of a few kilocalories per mole with closest intersystem distances of about 2 Å, while covalently bound molecules have typical binding energies of about 100 kcal/mol with typical interatomic distances below 1.5 Å. Entropy always plays a dominant role in noncovalent interactions and its change accompanying cluster formation is always negative; the $T\Delta S^\circ$ entropy term is usually, at room temperature, comparable to the enthalpy term ΔH° . The change of the Gibbs' free energy accompanying the formation of a cluster is thus close to zero. For covalent interactions, the energy (enthalpy) is larger than the entropy term, and therefore, the respective change of free energy is determined mainly by the energy term. An important difference concerns the potential energy surface (PES), which is much richer for noncovalent clusters. The number of energy minima of larger clusters is enormous, and to find these on a PES requires some effective search method. Further, noncovalent clusters show different dynamics compared to rather

rigid covalent molecules, and the term nonrigid or floppy system is sometimes used for these systems. The dynamical character of noncovalent molecules requires a rather different theoretical and experimental description. For noncovalent clusters, the essentially statistical quantum-chemical description at 0 K should be combined with a statistical description at nonzero temperature, because dynamical characteristics of noncovalent complexes are more pronounced than those of covalent molecules. It is true that standard statistical methods based on partition functions can be applied, but computer experiments represent the method of choice, and their importance in the description of noncovalent interactions in the future will be even more pronounced. This state-of-the-art technique allows the determination of practically a complete set of properties of a molecular cluster at different temperatures. The *conditio sine qua non* for performing computer simulations is the knowledge of an empirical potential describing all intermolecular and intramolecular interactions. For that, a method of quantum and theoretical chemistry is required that yields energies and forces. Empirical potentials can be obtained purely from theoretical (*ab initio*) calculations or a combined approach can be used: some terms in a potential originate from theoretical calculations and others from experiments. Finally, there also exist potentials parametrized completely to experimental results. Before using any empirical potential, its quality should be carefully tested, and use of a good *ab initio* potential might be as good as an empirical approach.

This review aims at providing a perspective of how our understanding of noncovalent chemistry will develop in the next millennium through experimental and theoretical methods. This review is concerned with describing the information obtained from a variety of experimental methods and the guidance that can be obtained from theoretical computations. It is certainly impossible to cover the whole experimental and theoretical area,^{17–20} and we will mainly focus on topics related to our own work. We present some important examples that shed some light on basic features and principles that we should be able to resolve in due course. In particular we would like to convince the reader that progress in this field can only be made by close cooperation between experiment and theory: the described molecular clusters serve as examples of how to reveal the geometric structures and other properties. We are aware that some points discussed in the review are controversial (e.g., inclusion of counterpoise corrections and the applicability of the Density Functional Methods) and that not everyone would agree with these opinions. We stress that the review reflects the personal view of both authors.

The first part of the present review will be concerned with an overview of theoretical methods to study molecular clusters. The second part will then briefly touch on the experimental methods. Further on, a few selected illustrative examples on noncovalent interactions will be presented for which coopera-

tion between theory and experiment has been able to provide a conclusive result.

II. Theoretical Description of Noncovalent Interactions

The motivation for the application of theoretical *ab initio* methods to molecular clusters comes from the need to determine the structure of the cluster, its stabilization energy, its (intermolecular) vibrational frequencies and the potential energy and free energy surfaces.

The primary property of an isolated (rigid) system is its structure, and a main goal is to determine the equilibrium structure of such a system. In the case of nonrigid (floppy) systems, the situation is different since these systems are dominated by large amplitude motions that makes the concept of equilibrium structure meaningless (see the ammonia dimer below). The majority of molecular clusters are nonrigid systems, and hence, the potential energy surface represents their primary property. Structures of global and local minima of the surface are found by optimizing the stabilization energy and not the total energy. Stabilization energy thus plays a central role in noncovalent interactions. The geometry of a cluster is observable only by resolving rotational structure, which is not always possible. The key role in the world of noncovalent interactions is played by vibrational frequencies, which are more easily observable, and their detection is straightforward even for large clusters. Moreover, vibrational frequencies are very sensitive to the quality of the PES and can serve as a test of quality of the respective calculation procedure.

A. Stabilization Energy

Both classical methods of quantum chemistry, perturbation and variation theory, can be used for the determination of stabilization energy. In perturbation theory, the stabilization energy is determined directly as the sum of various energy terms such as electrostatic, induction, dispersion, and exchange-repulsion. In contrast, the variation method determines the stabilization energy indirectly as the difference between the energy of the molecular cluster (supersystem) and the energies of the isolated subsystems.

Both approaches have advantages and drawbacks. Using the perturbation method, the stabilization energy is calculated directly and not as an energy difference, and it is therefore free of any inconsistency originating from different descriptions of supersystems and subsystems which are typical of variational treatments (see later). Furthermore, various energy terms have a clear physical meaning. On the other hand, perturbational calculations are more demanding than variational ones, and thus have not yet been used so much for a treatment of *large* molecular clusters. The method is well suited for determining interactions between rigid systems, but its use is limited for systems for which many intramolecular and intermolecular degrees of freedom have to be optimized *simultaneously*. The perturbational ap-

proach, in the form of symmetry-adapted perturbation theory (SAPT),^{21,22} has been used for highly accurate calculations of rigid systems, which provide a benchmark for supermolecular calculations. Extensive studies in the past years have provided accurate stabilization energies of various molecular complexes: (He)₂,^{23a} He⋯HF,^{23b} He⋯CO,^{23c} Ar⋯HF,^{24a} Ar⋯CH₄,^{24b} (H₂O)₂,²⁵ (Ar)₃,²⁶ (Ar)₂⋯HF,²⁷ H₂⋯CO, D₂⋯CO,²⁸ (CO₂)₂.²⁹

What is the relationship between the interaction energies evaluated by variational supermolecular and perturbational methods? The answer is unambiguous—using the same basis set and covering the same portion of correlation energy, identical interaction energies must be obtained. One very serious problem of variational calculations is basis set inconsistency (see later). Convincing evidence regarding the necessity of including full counterpoise corrections have been obtained from comparisons of interaction energies evaluated by perturbation (SAPT) and variation methods.³⁰ The variation method is nowadays used almost exclusively³¹ for the evaluation of stabilization energies of larger systems. The stabilization energy (ΔE) of a molecular cluster R⋯T formed from subsystems R and T is evaluated following eq 1:

$$\Delta E = E(\text{R}\cdots\text{T}) - E(\text{R}) - E(\text{T}) \quad (1)$$

where $E(\text{R}\cdots\text{T})$, $E(\text{R})$, and $E(\text{T})$ denote total energies of molecular cluster R⋯T, and subsystems R and T. The total energy is determined as the sum of Hartree–Fock (HF) and correlation energy (COR), i.e., the total stabilization energy consists of HF and COR components. The correlation part of the stabilization energy ΔE^{COR} is important for any type of molecular cluster and its neglect can lead to severe errors. Beyond-HF energies can be determined with various computational procedures covering different portions of the total correlation energy. The full configuration interaction (FCI) method and coupled cluster method covering single, double, and triple excitations iteratively (CCSDT) represent ideal methods of choice³² but are (and will be also in the near future) impractical for larger molecular clusters. A compromise between economy and accuracy represents the coupled cluster method covering single and double excitations iteratively and triple excitations in a noniterative way, the so-called CCSD(T).³³ This method represents the most robust tool for the evaluation of correlation energy of molecular clusters and should preferentially be used over other coupled cluster levels as well as over higher levels of Møller–Plesset perturbation theory (MP3, MP4SDQ, MP4SDTQ).³⁴

The most economical and widely used second-order MP theory (MP2) requires special comments. The method is applicable to extended complexes and gives surprisingly good estimates of the correlation energy. This is due to mutual compensation of the neglected higher-order contributions. Using standard versions of MP2 code, clusters consisting of as many as several dozen atoms can be treated. A very promising development for the evaluation of interaction energies of really large molecular clusters with hundreds of atoms comes from local models of electron correlation.³⁵ The scaling of the local MP2 method with the

number of atomic orbitals is similar to that of the HF method; further, the local MP2 method yields smaller values of the basis set superposition error (see below) than the canonical MP2 methodology.³⁶ The development of the local MP2 approach is still not finished, and care should be paid when applying existing codes to molecular clusters since the genuine MP2 correlation interaction energy might considerably be underestimated.³⁷

The use of the popular density functional density theory^{38,39}(DFT) in the realm of molecular clusters is very attractive because the method is much less computationally demanding than beyond Hartree–Fock methods. Because the DFT energy includes an exchange term and a contribution to the electron correlation energy, it was believed that it is well suited for descriptions of molecular clusters. Real progress in the application of DFT to molecular clusters began with the introduction of nonlocal (gradient) corrections.⁴⁰ The current DFT methods are known to work well for H-bonded systems in terms of structure, dipole moments, energetics, and vibrational properties.^{41–44} However, its use for weaker molecular complexes is very insecure because none of the existing functionals describe the London dispersion energy.^{41,45} The DFT method also fails for another important class of molecular clusters, namely charge-transfer complexes, where these methods predict unrealistically deep energy minima.⁴⁶ In view of the growing number of attempts to use DFT for DNA and other biomolecules, it must be stressed that the method completely fails for stacked complexes (e.g., stacked DNA base pairs)⁴⁷ and must be therefore used for these purposes with caution.

Before choosing the computational technique, care should be paid to the suitability of a single reference description. If more reference states contribute to the ground energy, then suitable multireference computational methods should be applied.

The choice of basis set represents a complicated problem, and a basis set as large as possible should be used.⁴⁸ The basis set applied should contain polarization and diffuse functions, and to obtain reliable stabilization energies, more sets of these functions are desirable. Among various basis sets, the correlation-consistent basis sets of Dunning,⁴⁹ starting from the aug-cc-pVDZ, can be recommended, because extrapolation to the basis set limit is consistently possible. There are several advantages of the variation approach (e.g., easy applicability, high accuracy, explicit inclusion of important phenomena such as many-body interactions and charge-transfer effects), but also an important drawback, which is the basis set inconsistency, which leads to the basis set superposition error (BSSE). The BSSE originates from the different descriptions of the supersystem and the subsystems; the basis set of the supersystem is larger than that of the subsystems. This error, which is a purely mathematical artifact, is eliminated by the counterpoise (CP) method suggested by Jansen and Ross⁵⁰ and Boys and Bernardi.⁵¹ If the aim of a calculation is to obtain the stabilization energy at a certain geometry, the situation is straightforward. Simple addition of the BSSE to the stabilization

energy yields the corrected stabilization energies which are much less basis set dependent. If extended basis sets are used, the BSSE converges to zero. The convergence is, however, very slow, and basis sets containing higher polarization functions (g and h) are required for keeping the BSSE of a rather small molecular cluster below 0.1 kcal/mol (see, e.g., calculations for the water dimer^{52–55}). For larger clusters containing dozens of atoms, there is no other choice than to use the CP procedure since corrected stabilization energies are closer to the theoretical stabilization energy limit. The use of CP corrections is, however, much more significant in the case of gradient optimization of the cluster geometry. Optimization of the cluster structure with a small or medium basis set without consideration of BSSE can lead to a completely different structure. The problem of CP-corrected gradient optimization was solved recently,⁵⁶ and the method developed there allows the CP-corrected gradient and Hessian of a complex to be evaluated at any *ab initio* level. As an example of the failure of the standard gradient optimization technique, the (HF)₂ dimer can be mentioned.⁵⁷ Standard gradient optimization at the MP2/6-31G** level yields the cyclic C₁ structure as the global minimum while the “quasi-linear” structure corresponds to a saddle point. Performing the CP-corrected optimization⁵⁷ at the same theoretical level, the global minimum corresponds to the expected “pseudo-linear” structure, and the cyclic structure is just a saddle point. It must be mentioned that by extending the basis set the correct structure of the global minimum can already be obtained by the standard gradient optimization. However, for large molecular clusters, extended basis sets that would reduce the BSSE are often too computationally demanding. For a smaller basis set, the resulting geometry optimization can be affected by neglecting the BSSE in the optimization procedure. The use of the CP-corrected optimization is particularly significant when the BSSE is large. Generally, correlated calculations which require the use of diffuse polarization functions are connected with a rather large BSSE even if basis sets of TZ + P quality are used. CP-corrected optimization thus represents the method of choice for noncovalent clusters with stabilization energy governed by correlation/dispersion energy. A very important problem concerns the difference between in-plane (mostly H-bonded) and out-of-plane, i.e., stacked (mostly dispersion controlled) structures. Both very different structures are usually very similar in stabilization energy, and CP-corrected optimization produces much more reliable results as seen in the phenol·water·argon system⁵⁸ and the fluorobenzene·HCF₃ cluster.⁵⁹

B. Vibrational Frequencies

Formation of a molecular cluster gives rise to *intermolecular* vibrations. Intermolecular frequencies are usually much smaller than intramolecular ones and are typically around 100 cm⁻¹, frequently even below 50 cm⁻¹. Harmonic frequencies are easily determined even for large noncovalent clusters using Wilson FG analysis and the procedure is available in various commercially distributed codes. Vibra-

tional frequencies are, however, not harmonic, and “anharmonic” effects should be considered. However, the term “anharmonic vibrations” is somewhat misleading since it implies the harmonic approximation as a starting point. Often, intermolecular vibrations in clusters involve hindered rotations, and it makes no sense at all to use the language of harmonic oscillators. Similarly, “anharmonic” corrections to the harmonic frequencies can often go in the wrong direction. Given these cautions, here we keep the term “anharmonic” in the sense of nonharmonic. The PES obtained by high-level correlated *ab initio* calculations can be used for evaluating highly accurate anharmonic vibrational frequencies. The agreement between calculated frequencies and their experimental counterparts is usually much more satisfactory when anharmonic effects are fully taken into account. This requirement is especially true for noncovalent clusters with a high degree of nonrigidity.

The standard approach to the vibrational problem for large noncovalent clusters is perturbation theory.^{60,61} If the zero order Hamiltonian (usually harmonic oscillator) is a good approximation to the true vibrational Hamiltonian, perturbation theory represents a very efficient and reliable tool for calculating vibrational frequencies. In the traditional approach, the matrix representation of the molecular Hamiltonian is diagonalized by means of successive contact transformation. This procedure will fail, however, in the case of an accidental resonance. This is often the case if we deal with large systems with many vibrational modes. In this case, the terms connecting the resonant levels have to be treated variationally.^{61,62} Recently, considerable progress has been achieved in developing new procedures based on perturbative treatment for the calculation of anharmonic frequencies.^{55,62–64} The potential energy function is constructed as a low-order polynomial (up to the fourth order) expressed in normal coordinates. The force constants are obtained by least-squares fitting of energies, gradients, and Hessians calculated at geometries close to the global minimum on the PES. If it is not possible to work with extended basis sets (due to the cluster size) then energies, gradients, and Hessians should be obtained from the CP-corrected PES. The main advantage of this approach stems from its computational efficiency. The number of Hessians required scales linearly with the number of vibrational modes. Thus, the method can be used even for large systems while respecting the full dimensionality of the problem. The applicability of the procedure is, however, less straightforward for noncovalent clusters, since they are nonrigid systems. The vibrational dynamics of floppy systems cannot be described in the framework of a single-reference Hamiltonian, and therefore, the perturbation series used are necessarily strongly divergent. In such a case, the only alternative is a more exact treatment of the large amplitude vibrational modes including all relevant parts of the coordinate space. This requires calculation of the global PES which becomes computationally prohibitive even for systems with relatively few degrees of freedom. However, the

number of large amplitude motions is usually a small fraction of the total number of vibrations. Consequently, the large amplitude vibrations can be removed from the perturbative treatment and the Schrödinger equation for the effective large amplitude Hamiltonian is solved variationally (for methods used for solving the Schrödinger equation for non-rigid molecules, see ref 3).

Literature on higher-dimensional anharmonic vibrational calculations of noncovalent clusters based on *ab initio* correlated calculations includes a variational six-dimensional intermolecular vibrational frequency calculation for the adenine...thymine Watson–Crick base pair⁶⁵ and a 12-dimensional vibrational frequency calculation for the water dimer by perturbation theory.⁵⁵ Also, a six-dimensional frequency calculation for the water dimer based on various empirical potentials was reported recently by LeForestier et al.⁶⁶ Other rigorous treatments of vibrations in clusters were reported.^{67–70}

C. Potential Energy Surface

Generally, the PES of a molecular cluster is very rich and contains a large number of energy minima. The global minimum can normally be detected experimentally relatively easily, while secondary minima (and saddle points) can be elucidated through the effects of tunneling splittings.^{71–74} These minima can be theoretically ascribed only if the whole PES is known. The number of energy minima increases very rapidly with the cluster size and the number of subsystems. While there is just one energy minimum on the water dimer PES,^{52–55} there are 11 minima on the uracil dimer PES,⁷⁵ 284 minima on the benzene...Ar₈ PES,⁷⁶ and more than 1000 minima on the adenine...thymine ... (H₂O)₂ PES.⁷⁷ The localization of every minimum is tedious, if not impossible, by standard methods based on experience and chemical intuition. It is necessary to use some effective search method for determining the geometry of the energy minima: these methods are based on computer experiments, mostly using molecular dynamic (MD) and Monte Carlo (MC) simulations.

Generally, MD and MC simulations can be performed at any theoretical level, including the semi-empirical or empirical level, yielding energy and forces. We have witnessed enormous progress over recent years in so-called *ab initio* MD, specifically in first-principles MD by the Car-Parrinello method.^{78,79} This approach represents very significant progress particularly because it is parameter-free, includes all many-body terms as well as charge-transfer and can be used even for formation and/or breaking of covalent bonds. The use of the Car-Parinello method for molecular clusters is, however, limited due to the fact that the plane-wave density functional method (as well as any other density functional method) does not cover the London dispersion energy (see later). The use of the method for charged or polar clusters where dispersion energy plays a minor role is justified.^{80,81} The vast majority of MD simulations is (and will be in the near future) based on an empirical potential. Such an approach is applicable for molecular clusters but cannot be applied for MD simulations of chemical

reactions. The quality of MD simulations depends critically on the performance of the simulation technique but also on the quality of the empirical potential used. This fact is very frequently ignored and it is believed that long MD simulations always yield reliable results. However, the combination of high-level MD simulations with a poor potential leads only to poor results. An empirical potential should correctly describe all intermolecular and intramolecular degrees of freedom for any type of molecular cluster. These requirements are extremely strict, and usually only a certain empirical potential is applicable to a specific class of molecular clusters. One must bear in mind that more elaborate techniques of quantum chemistry (e.g., semiempirical or *ab initio* Hartree–Fock) also fail to simultaneously describe all types of molecular clusters (e.g., H-bonded and London dispersion clusters). Present empirical potentials also fail for charge-transfer complexes and in situations where many-body terms are important. Probably the only way to control the quality of an empirical potential is to compare its performance (stabilization energy, structure, and geometry, vibrational frequencies) with that of nonempirical correlated *ab initio* calculations. Comparison should be made for selected representatives of the class of molecular clusters studied.

D. Free Energy Surface

Populations of various structures of a cluster, which are proportional to the change of the Gibbs' free energy, can be determined by computer simulations for either the N,V,T canonical and N,V,E microcanonical ensemble, combined with the quenching method⁸² (N, V, E, and T refer to the number of molecules in a system, its volume, energy, and temperature, respectively). In the N,V,T canonical ensemble, the cluster is in temperature equilibrium with the surroundings, and accordingly, the N,V,T ensemble gives information of the behavior of the cluster when it is interacting with the surrounding. In the N,V,E microcanonical ensemble, all the systems have the same energy and each system is individually isolated. Clearly, the N,V,E and N,V,T ensemble results must coincide in the limit of infinitely large systems.^{83,84} However, small molecular clusters are all but infinite size systems. This has important consequences for the probability $p(E) = \Omega(E)\exp(-E/kT)$ [where $\Omega(E)$ is the density of states with energy E] of finding the NVT ensemble at energy E . Whereas small systems approach the one degree of freedom limit, $p(E) = \exp(-E/kT)$, large systems with high densities of states possess canonical probabilities which approach a δ -function peaked at the energy of a corresponding microcanonical ensemble.⁸⁴

The calculation of populations from quenching is possible in a rather narrow energy interval. The energy should be sufficiently high to allow a high frequency of interconversions among different isomers. The basic advantage of this technique is the fact that it enables an evaluation of relative populations for all structures on the PES, i.e., to pass from the PES to the free energy surface (FES). Such

calculations require long simulation runs and are thus feasible only for relatively small clusters. Using the free energy perturbation/MD procedure, we obtain relative ΔG values for much larger clusters, but only for small sections of the PES. These calculations need significantly less simulation time.

The comparison of theoretical and experimental results requires some comments. First, the temperature T of the cluster formed in a particular experiment should be known. The stabilization enthalpy at 0 K and the PES characteristics can be used only if T is zero or very low. In many cases, however, the temperature is higher and an entropy term should be considered. This means that the FES characteristics and not the PES characteristics should be utilized for comparison with experimental results. Care should be taken with the type of simulations, N,V,E or N,V,T. Simulations in the N,V,E ensemble give properties of a cluster that does not interact with the surroundings, while simulations in the N,V,T ensemble correspond to a situation when the cluster is in thermal equilibrium with the surroundings.

E. Classification of Noncovalent Interactions

On the basis of perturbation theory, the total stabilization energy of noncovalent complexes can be partitioned into various energy contributions. The electrostatic, induction, charge-transfer, and dispersion terms form the dominant attractive contributions. The relative importance of these energy terms differ for specific types of noncovalent clusters. In some rather rare cases, one particular energy term is dominant. More typically, several attractive terms contribute to the overall stabilization of noncovalent clusters and H-bonded complexes provide a typical example. Nevertheless, the electrostatic interaction plays a dominant role, and in the case of polar subsystems, it is possible to identify the total stabilization energy with the electrostatic energy term.⁸⁵

Interactions with Participation of Hydrogen: H-Bonds, Improper (blue-shifting) H-Bonds and Dihydrogen Bonds. H-bonded complexes are by far the most important and numerous noncovalent complexes.³¹ Complexes with H-bonds are stabilized by electrostatic, induction (charge-transfer), and dispersion energy terms. The electrostatic term, with its mainly dipole–charge and dipole–dipole contributions, is most important and gives H-bonds their typical (and very important) directionality. The formation of a H-bond of the X–H \cdots Y type is accompanied by an elongation of the X–H bond which causes a decrease (red-shift) of the respective X–H stretching frequency. The red-shift is easily observable and provides unambiguous evidence about the formation of a noncovalent complex. Most H-bonds have electronegative atoms as X, with Y either an electronegative atom having one or two lone electron pairs or a group with a region of excess of electron density (e.g., π -electrons of aromatic systems). H-bonds with X,Y = F, O, N are best known.³¹ The concept of H-bonds has been extended to C–H \cdots Y bonding, and both C–H \cdots Y (Y = electronegative atom) as well as C–H $\cdots\pi$ types of H-bonds have been observed.^{86,87} If the hydrogen atom

of a CH group is acidic, it can form quite strong H-bonds. Otherwise, the CH \cdots Y H-bonds are much weaker than OH \cdots Y or NH \cdots Y H-bonds. Nevertheless, CH H-bonds could play an important role in biomolecular structures due to their large number. Frequently, however, the criteria for an H-bond (elongation of the C–H bond and a red-shift of the C–H stretching frequency) are not satisfied and CH is just in contact with atom Y and no H-bond is formed. This is called a CH \cdots Y contact. For example, geometrical and vibrational analysis⁸⁸ have shown that, contrary to the original expectation,⁸⁹ there is no reason to consider the C–H \cdots O contact in the adenine \cdots thymine Watson–Crick base pair as a third H-bond.

What is the driving force for geometrical and spectral manifestations of H-bonding? By natural bond orbital analysis it was shown⁹⁰ that it is charge-transfer (CT) from the lone pairs or π -molecular orbitals of the electron donor (proton acceptor) to the antibonding orbitals of the X–H bond of the electron acceptor (proton donor). An increase of electron density in these antibonding orbitals causes elongation of the X–H bonds, which causes the red-shift of the X–H stretching frequency. This is accompanied by a very small CT that usually does not exceed more than 0.01 e^- . The CT is, however, considerably more important for ionic clusters.

H-bonds determine the structure of bio-macromolecules such as DNA and proteins and play a key role in the important biophysical process of molecular recognition. H-bonding is also a motif frequently used in supramolecular syntheses.

The other two types of intermolecular bonds with participation of hydrogen, namely the improper (blue-shifting) H-bond and the dihydrogen bond, were described only recently, and they are less numerous than H-bonds. The C–H $\cdots\pi$ improper (blue-shifting) H-bond was theoretically predicted⁹¹ in carbon proton donor \cdots benzene complexes. The manifestation of this bond is completely opposite to that of a normal H-bond, i.e., instead of an elongation of the X–H bond and a red-shift of the X–H stretch vibrational frequency upon complex formation, there is a contraction of the bond length and a blue-shift of the stretch frequency. The existence of a C–H $\cdots\pi$ improper H-bond in the chloroform \cdots fluorobenzene complex was confirmed experimentally by double-resonance infrared ion-depletion spectroscopy.⁹² The family of improper H-bonds was extended to improper H-bonds of the C–H \cdots O and C–H \cdots X $^-$ (X = halogen) types occurring in fluoroform \cdots ethylene oxide⁹³ and X $^-$ \cdots H₃CY (X, Y = halogen) complexes.⁹⁴ Natural bond orbital analysis demonstrated⁹⁴ that the improper (blue-shifting) H-bond in the latter complexes originates in a geometrical restructuring of an electron acceptor after CT from an electron donor. Contrary to H-bonds for which CT from the electron donor is directed to the closest X–H bonds, for improper H-bonding, the CT is directed to the remote part of the electron acceptor.

The dihydrogen bond of the type M–H \cdots H–Y was originally found⁹⁵ in metal complexes (M = metal element) and later detected⁹⁶ in the H₃BNH₃ dimer.

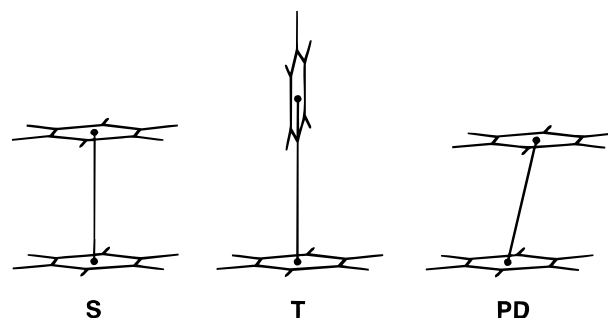


Figure 1. Structures of the benzene dimer.

The explanation of this unconventional H-bond is straightforward:⁹⁷ two hydrogens may interact weakly if one is bound to an electropositive element and the other to a very electronegative element. Consequently, one hydrogen has positive and the other has negative charge and there is a multipole attraction between these hydrogens.

Electrostatic Interactions. The majority of dipolar systems contains hydrogen, and hence, they form H-bonds. Electrostatic interactions are also dominant for the interaction of quadrupoles, like benzenes. The global minimum of the benzene dimer corresponds to the T-shape structure (Figure 1) with monomers located in perpendicular planes.⁹⁸ On the basis of the principle of maximum overlap (maximal dispersion energy), it was originally believed that the global minimum had a parallel-sandwich structure (structure S in Figure 1). However, on the basis of simple quadrupole–quadrupole interactions, the parallel-sandwich structure was excluded and the T-shaped structure supported.⁹⁸ The quadrupole–quadrupole energy term is repulsive for the former structure while it is attractive for the latter one. These qualitative estimates were later fully supported by highly accurate *ab initio* calculations.⁹⁹ The quadrupole–quadrupole interaction discussed in the benzene dimer not only plays an important role in noncovalent complexes but also is important for the structure of proteins. The structure of crystalline phenylalanine is to a large extent determined by the interaction of phenyl groups. In an investigation of the crystal structures of phenylalanine, a high occurrence of T-shaped and parallel-displaced (PD) structures of the phenyl groups was found.¹⁰⁰ The quadrupole–quadrupole interaction is attractive only for the T- and PD-structures; all other structures show repulsive quadrupole–quadrupole interaction.

Here, it is necessary to refer to the frequently used “ π - π theory” introduced by Hunter and Sanders¹⁰¹ for the description of interaction of aromatic π -systems. These empirical rules are misleading and redundant. The position of π -charges as well as the π - σ charge splitting introduced in this theory is almost arbitrary. With another choice of these “parameters”, a different optimum structure is obtained. Instead of artificially introducing the σ and π charges, it is enough to recognize the role of molecular quadrupoles (see above).

The electrostatic motif represents an important recognition feature and also plays a part in determining the structure of bio-macromolecules.

Charge-Transfer Interactions. The formation of intensely colored charge-transfer complexes in

nonpolar solvents was first theoretically inferred by Mulliken.¹⁰² The condition for the formation of a CT complex (from two components) requires that one system is a good electron donor (i.e., having a low ionization potential) and the other a good electron acceptor (i.e., having a high electron affinity). Charge-transfer (or electron donor–acceptor, as it is also called) complex formation implies electron flow from the donor to the acceptor. Donors and acceptors are classified according to the type of orbital donating or accepting the electrons as follows: donors, n , σ , π (n = nonbonding orbitals); acceptors, v , σ^* , π^* (v = vacant orbitals). The strongest charge-transfer complexes are of $n-v$ type and those of $\pi-\pi^*$ type are the weakest.

Dispersion Interactions. Dispersion interactions are less directionally specific than electrostatic interactions. They mostly contribute to the stability of a cluster while its structure is determined by electrostatic interactions. This is, for example, the case for stacked DNA base pairs. Stability of these pairs stems from dispersion energy while their structure is determined by dipole–dipole electrostatic interactions (see below). Dispersion energy plays an important role in stabilizing clusters of bio-macromolecules, where it may be the dominant attractive term. Dispersion energy is of vital importance in stacking interactions in bio-macromolecules and may be more important than stabilization by charge-transfer.

Ion-Mediated Interactions. The presence of a metallic cations provides a very significant interaction center connected with a large stabilization energy as well as with strong directionality. On increasing the size of the cation, both effects become weaker. This is even more true for aromatic cations where the positive charge is highly delocalized, thus losing the high directionality. Because molecular cations possess high electron affinity, the charge-transfer energy term can be an important attractive contribution.

Hydrophobic Interactions. Hydrophobic interactions occur in aqueous solutions of low-molecular organic substances, as well as of biological macromolecules. Hydrophobic interactions represent the tendency of nonpolar groups (especially hydrocarbon groups) to associate in aqueous solutions. This association is accompanied by little change of enthalpy (ΔH close to zero), and thus the process of association of nonpolar groups is governed by entropy effects. Because any association of systems is always connected with a negative entropy change, this decisive change in entropy is related to the ordering of molecules that surrounds the hydrocarbon residues in the original conformation. It should be emphasized that hydrophobic interactions are inseparably connected with the structure of liquid water. Hydrophobic interactions thus basically differ from the noncovalent interaction discussed previously, which are due to energy stabilization.

III. Experimental Methods for Studying Noncovalent Interactions

Molecular clusters provide ideal systems for experimentally studying noncovalent interactions, be-

cause they can easily be prepared under isolated, unperturbed conditions in supersonic jet expansions. Molecular clusters have been widely investigated over the last two or three decades.¹⁰³ Noncovalent interactions lead to the formation of noncovalently bound clusters when a compound, generally seeded in helium, neon, or argon, is expanded in a jet. The expansion conditions and concentration of the seed molecule determine the distribution of clusters in the jet. Selection of experimental conditions can also lead to a range of cluster temperatures. Major efforts have been carried out in the last 20 years to devise and employ experimental methods that allow the structure and dynamics of molecular clusters to be selectively studied. This can be done through spectroscopic analysis or mass selective detection, or both, depending on the system studied.

An important concern is the accessibility of different energy minima on the PES. If local minima of similar energy (within ~ 200 cm^{-1}) of the global minimum are present on the PES and if they are separated by sufficiently high barriers, different cluster structures can be formed and be frozen out in the jet expansion. These different isomers cannot interconvert, and in a microwave or REMPI experiment, it will be nontrivial to identify the isomer that corresponds to the global minimum. Rotational resolution for determination of moments of inertia, UV and IR hole burning, REMPI, and ZEKE spectroscopy provide tools to identify isomers and to study structural changes upon electronic excitation and ionization.

A. Microwave Spectroscopy

Microwave (MW) spectroscopy is very much at the heart of molecular physics.¹⁰⁴ It is a method of very high resolution optical spectroscopy and has a sound foundation in molecular quantum mechanics. Once a microwave spectrum is obtained and assigned, it yields the three rotational constants A , B , and C (assuming we are dealing with an asymmetric top), and from these rotational constants, the moments of inertia and hence the most probable structure can be obtained. The deduction of the structure from the moments of inertia is not straightforward. Particularly for molecular clusters,^{105,106} the amount of independent data is rarely greater than the number of structural parameters (a requirement for unambiguous structure identification), and the moments of inertia thus serve only as constraints on a structure.¹⁰⁷ Moreover, Kraichman's equations cannot be used for clusters, so that isotopic substitution does not generally yield useful structural data. Finally, for nonrigid systems, the observed moments of inertia correspond to a vibrationally averaged structure (see ammonia dimer). It is therefore generally desirable to determine the potential energy surface.

B. Vibration Rotation Tunneling Spectroscopy

A useful extension of the available frequency range came from the introduction of far-infrared vibration rotation tunneling (FIR–VRT) spectroscopy.¹⁰⁸ This spectral range of 20–150 cm^{-1} allows the study of

transitions between vibration-rotation-tunneling states in molecular clusters, with a resolution comparable to microwave spectroscopy. The application of this technique has been pioneered by Saykally and co-workers and has been extensively applied to water clusters (see below). Basically a CO₂ laser provides an intense mid-infrared beam that is used to pump a molecular gas far-IR laser. The output frequency can be tuned over large ranges by mixing the far-IR laser output with a microwave source to achieve tuning of 65 GHz. Far-IR spectra are obtained by increasing the optical path length using a slit valve jet expansion.¹⁰⁹

Direct millimeter wave Orottron radiation sources, previously unavailable due to technical difficulties, have become available recently.¹¹⁰ Winnewisser and co-workers have applied such sources of widely tuneable radiation successfully for the study of molecular clusters.¹¹¹

C. Vibrational Spectroscopy

Vibrational spectroscopy is a well-established method in chemistry. For the study of molecular clusters, detection schemes of the highest sensitivity are required.¹¹² For ground-state vibrational absorption, for instance in the OH stretch vibrational region, infrared lasers incorporating frequency mixing schemes and optical paramagnetic oscillators (OPOs) have been employed.^{87,113–115} Spectra are obtained by measuring the depletion of a fluorescence^{116,117} or an ionization signal⁸⁷ when scanning the IR laser. Some of the most significant advances in this field include bolometric detection,^{18,118} IR absorption in slit jets,¹¹⁹ and cavity ring down spectroscopy.^{120,121}

Over recent years, near-IR measurements have contributed greatly to the development of full multidimensional potential energy surfaces for hydrogen-bonding systems. The HF dimer presents a particularly good example where a full 6D-potential has been developed out of a concerted effort between experiment and theory.¹¹⁹

An alternative method, the stimulated Raman pumping of vibrational states, is particularly attractive because very low-frequency intermolecular vibrations can be accessed.^{122–125} Again detection can be made through a fluorescence¹²⁴ or ionization loss detection scheme.¹²⁶ This scheme is particularly attractive for populating vibrational states in the S₀ state and then applying REMPI and ZEKE spectroscopy to these excited vibrational states.¹²⁵

D. REMPI and Hole Burning Spectroscopy

These techniques are sufficiently sensitive to allow identification of the low frequency, intermolecular vibrations which characterize the intermolecular potential energy surface. For electronic excitation spectroscopy, laser-induced fluorescence and resonance-enhanced multiphoton ionization (REMPI) have been employed extensively. Particularly, two-color, two-photon REMPI (R₂PI) provides the advantage of soft ionization, thus avoiding fragmentation of the cation cluster. When different isomers of

clusters are present in the jet, the application of hole-burning spectroscopy is of particular advantage. The population of one isomer can be burned out by employing an additional UV laser (or IR laser). The REMPI spectrum then shows the depletion of that isomer and the spectral transitions associated with the isomer can be identified. Recently, additional information has come from the study of rotational structure of the electronic transition. Simons and co-workers have shown^{127,128} that even at moderate laser resolution (0.2 cm⁻¹) the rotational structure can be deconvoluted and rotational constants obtained with quite good precision. Changes in the direction of the transition moment have been identified by this technique. With a better laser band width (0.03 cm⁻¹), the analysis of the rotational structure (using an asymmetric rotor simulation) has been extended in our laboratory to the simulation of partially rotationally resolved ZEKE spectra using an electron spectator model.¹²⁹ From the deconvolution of the rotational structure of the cation, the rotational constants for the cation are obtained and, thus, its moments of inertia and structure.

E. ZEKE Spectroscopy

Since its introduction in 1984,^{130,131} ZEKE photoelectron spectroscopy has advanced considerably to become a high-resolution technique¹³² that is widely applicable for studies of molecules and clusters.^{129,133–139} One of the most significant innovations of recent years has been the realization that fractional Stark state selection via electric field ionization (FSSFI) allows a significant improvement in ZEKE spectral resolution.¹⁴⁰ In this approach, an offset pulse selectively ionizes the more fragile “red” Stark states, while the more resilient “blue” Stark states survive and are shifted down in energy upon application of a second pulse of opposite direction. Dietrich et al.¹⁴⁰ demonstrated that the spectral resolution of peaks in the ZEKE spectrum of benzene could be improved by more than a factor of 8 using FSSFI. Recently, this FSSFI approach was also applied to mass-analyzed threshold ionization (MATI) spectroscopy,¹⁴¹ a variant of ZEKE spectroscopy. MATI is particularly useful for cluster studies, where it facilitates unambiguous identification of the ionized species, and can be used to follow cluster fragmentation.^{142–148} With this high-resolution MATI spectroscopy,¹⁴¹ rotational structure in the molecular cluster cation spectrum can be partially resolved and a fitting procedure can be used to determine the rotational constants.¹⁴⁹

IV. Illustrative Examples

A. Ammonia Dimer

Molecular clusters are not rigid at all in most cases and *show large amplitude motion*. The intermolecular vibrations are of low frequency, and hence, classical concepts of molecular spectroscopy like the harmonic oscillator and rigid rotor approximations break down. An important example is the ammonia dimer, first studied by Nelson et al. They concluded from analysis

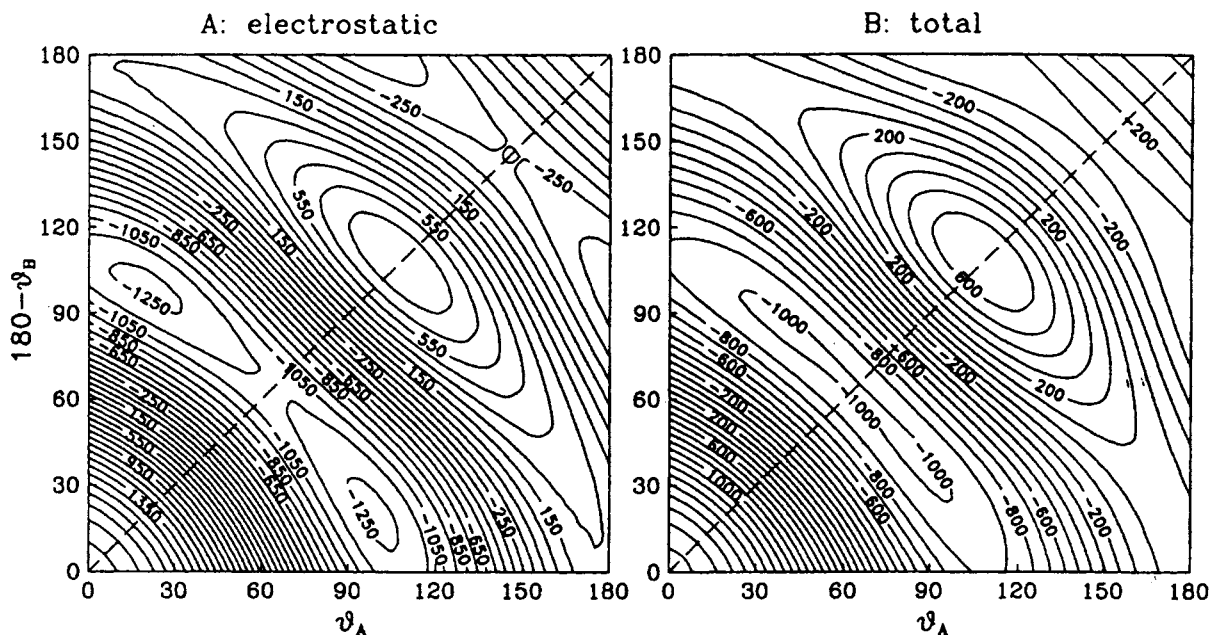


Figure 2. $(\text{NH}_3)_2$ potential (cm^{-1}) from Olthof et al.¹⁵⁶ (A) Electrostatic dipole–quadrupole–octopole interaction energy calculated at the experimentally determined equilibrium distance ($R = 3.23 \text{ \AA}$). (B) Total potential at $R = 3.373 \text{ \AA}$. The diagram illustrates that the same valley for interchange tunneling is present in both cases.

of the microwave spectrum of the dimer that it could not have a hydrogen-bonded geometry.^{150,151} This conclusion was in sharp disagreement with a number of high-level *ab initio* calculations (see citations in ref 150). Without going into the particulars of the analysis discussed at that time, it can be said that the arguments employed in deducing the non-hydrogen-bonded geometry are very convincing and conclusive. In particular, no donor–acceptor interchange tunneling could be found in the spectra. This was in stark contrast to the observations made previously in homogeneous dimers such as $(\text{HF})_2$ and $(\text{H}_2\text{O})_2$.¹¹² The key to the solution of this riddle lies in a proper understanding of the tunneling motion that dominates systems such as the ammonia or the water dimer. For the analysis, this requires use of the molecular symmetry group,³ the group of feasible elements of the permutation inversion group, instead of the point group. The molecular symmetry group fully characterizes floppy systems undergoing large amplitude motion, whereas the point group only describes rigid systems undergoing only small (infinitesimal) amplitude motion. A group theoretical analysis based on the G_{36} molecular symmetry group led Nelson and Klemperer¹⁵² to the conclusion that the interchange tunneling will be quenched if the internal rotation effects are large compared to the interchange tunneling matrix elements. The first part of this puzzle was revealed by a subsequent analysis by Loeser et al. and Havenith et al. of the FIR–VRT spectrum of the NH_3 dimer.^{153–155} Their use of a much broader spectral range revealed that the energy structure of the dimer is much more complex than was suggested by the first microwave study. This study also revealed that tunneling motion is the dominant feature in the spectra. Even the monomer inversion motion is not quenched in the dimer and the G_{144} molecular symmetry group has to be used in the analysis.^{153–155} The very complicated spectral

structure in the far-infrared spectrum of the ammonia dimer escaped full understanding until a most enlightening theoretical investigation by Olthof et al.,^{156,157} who carried out a fully quantum mechanical calculation of the rotation-tunneling states of the NH_3 dimer on an *ab initio* potential that later was slightly adjusted. These results helped to fully reproduce both the far-infrared spectra as well as the earlier microwave spectra. The calculations showed that the NH_3 dimer has an equilibrium configuration significantly distorted from the linear H-bonded minimum, with an extremely low barrier (7 cm^{-1}) for the tunneling interchange between the donor and the acceptor (Figure 2). The results from the model potential agree quantitatively with all spectroscopic information, microwave and far-infrared; they reproduce the electric dipole moments and nuclear quadrupole coupling constants reasonably well.¹⁵⁸ Figure 3 illustrates the vibrationally averaged and equilibrium structures of the dimer. The important conclusion from this theoretical work is that if a potential is so soft that barriers between a H-bonded structure and non-H-bonded structure become lower than the zero point energy, the definition of an equilibrium structure becomes completely meaningless. What is observed in the spectra in the form of rotational constants is a vibrationally averaged structure, and this is what was seen in the earliest microwave spectra.

In conclusion, the ammonia dimer is a system which exhibits extremely large amplitude motion. It is indeed hydrogen bonded, but the potential is so shallow with respect to the bending motion that the vibrationally averaged structure resembles a non-hydrogen-bonded system. Recently, measurements of the FIR–VRT spectrum of the deuterated ammonia dimer by Karyakin et al.¹⁵⁹ has confirmed the quantitative correctness of the potential of Olthof et al.^{156,157} by finding the predicted reduction in the

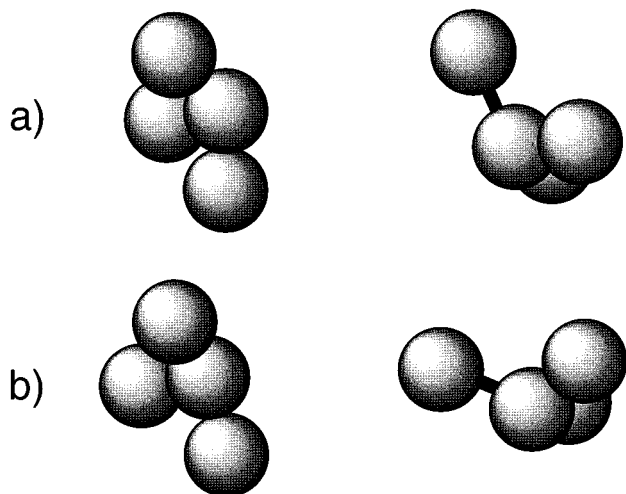


Figure 3. Schematic diagram showing (a) vibrationally averaged and (b) equilibrium structures for the ammonia dimer.

tunneling splitting, which are substantially smaller in the ND_3 dimer.

Though a few minor improvements are still required for the model potential to give exact agreement with experiment, for instance, for the nuclear coupling constants,¹⁵⁸ at present, this is the most complete study of a hydrogen-bonded dimer with quantitative agreement between experiment and theory. The solution of the riddle of the ammonia dimer through close cooperation between experiment and theory is very remarkable considering the main features that dominate the structure and dynamics of such weakly bound systems: (i) potential energy surfaces can be extremely shallow; (ii) movement can be of very large amplitude; (iii) for this system, tunneling motion dominates the energy states and hence the structure of the vibration rotation tunneling spectra.

B. Water Clusters: Transition from Planar to Three-Dimensional Structures

Water clusters are of special interest since they provide insight into the properties of the most important liquid: water. What can be expected is that by studying the pairwise additive and nonpairwise additive properties, by going from the dimer to the oligomers, it will become feasible to establish the essential features of the structure and dynamics of the corresponding bulk material. Though this may sound like a straightforward strategy, in practice, it is a rather challenging task both experimentally and theoretically. A very good example is the water dimer.^{25,52–55,66,112,160–170}

It is useful to establish what is presently known about larger water clusters ranging from the water trimer to the water octamer. Structures of the water dimer and water oligomers are shown in Figure 4. Major success has come from the application of FIR–VRT spectroscopy of these species.^{108,109} Terahertz VRT relies on the formation of clusters in seeded supersonic jets. This leads to very low temperatures for these systems, which therefore tend to acquire their lowest energy equilibrium structure. However,

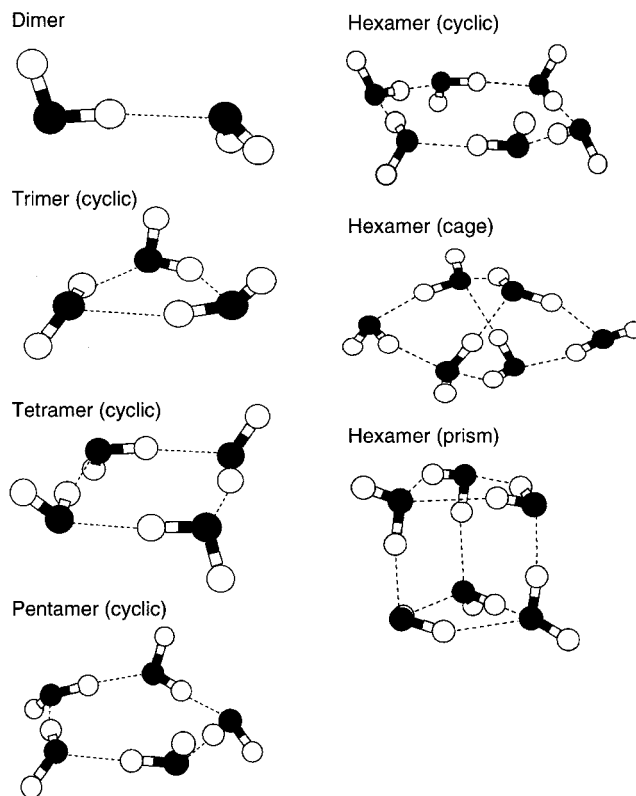


Figure 4. Structures of water dimer and water oligomers.

since these systems generally have many stationary points and many equivalent geometric structures separated by transition states, the structure and dynamics are strongly influenced by the tunneling motion.

The first detailed experimental study of the water trimer using FIR–VRT spectroscopy was reported by Pugliano and Saykally.¹⁷¹ Subsequently, this initial study has been augmented by considerable further experimental^{172–174} and theoretical work.^{175–179} The water trimer exhibits a cyclic triangular structure whose dynamics are dominated by a fast tunneling motion, the pseudorotation or torsion, that corresponds to the flipping of the external protons through the plane of the hydrogen-bonded triangular skeleton by rotation about the hydrogen bonds. An additional internal motion occurs by so-called donor tunneling which involves interchange of the hydrogen-bonded donor proton of a water monomer with its external proton. This process proceeds through a transition state in which one of the water monomers donates both of its protons in a bifurcated hydrogen bond to its neighboring monomer. In addition to the tunneling motion, the overall rotation of the trimer has to be taken into account to interpret the VRT spectra. Extensive theoretical work, using *ab initio* potentials^{177,180} and a model Hamiltonian for pseudorotation tunneling,^{175,176} and a diffusion Monte Carlo approach^{178,179} led to a comprehensive picture of the rotational tunneling motion in the water trimer, particularly for the 87.1 cm^{-1} band in $(\text{H}_2\text{O})_3$.¹⁷⁶ This work has recently been supplemented by analysis of two further bands at 42.9 and 65.6 cm^{-1} to provide a complete description of the VRT transitions of $(\text{H}_2\text{O})_3$ up to 150 cm^{-1} .¹⁸¹

The water tetramer- $(d_8)^{173}$ and pentamer- $(d_{10})^{182}$ were found to show tunneling structures which agreed with the theoretically predicted cyclic, quasi-planar equilibrium structures. The proposed structures are planar rings, again dominated by a pseudorotation hydrogen quantum tunneling motion. There seems to be a consensus now that the tetramer and pentamer can be described by cyclic quasi-planar equilibrium structures, analogous to that of the trimer. The story starts to be particularly interesting for the water hexamer which is now believed to be the first three-dimensional structure of water clusters displaying a cage form.^{183,184} The structural changes and bonding mechanisms in passing from the isolated molecule through dimer, trimer, tetramer, pentamer, hexamer, and so on show the increased characteristics of hydrogen bond cooperativity and their effects on the cluster structures and binding energies.^{161,185–188} Studying these cooperative forces in water,¹⁸⁹ Xanthopoulos predicted an exponential decrease in the average inter-oxygen separation (R_{OO}) with increasing cluster size for cyclic ($n = 3, 4, \text{ and } 5$) water clusters.¹⁹⁰ The R_{OO} in this study converged to the bulk value by $n = 5$ or 6 for rotationally cold clusters. This corresponds to the R_{OO} in ordered ice. At this point, the importance of many-body interaction terms should be stressed. It was shown that three-body terms are important, and for accurate description of the larger clusters even fourth-body terms should be included.¹⁷⁹

In deducing bulk properties from the properties of neutral molecular clusters, it is important to realize that under most experimental conditions temperatures are very low. Provided that the lowest part of the potential energy surface is accessible, the system will be in the lowest energy configuration, i.e., in the global minimum. The dynamics are then entirely dominated by the tunneling motion. However, at higher temperatures, there may be entropy effects and the system may spend most of its time in minima configurations of the free energy surface. At present, there is little doubt that the minimum energy structures of the water trimer, tetramer, and pentamer correspond to quasi-planar cyclic rings and that the heptamer, octamer, and larger clusters are expected to show three-dimensional geometries. For the water hexamer minimum energy structure, there seems to be a more subtle crossover in geometry between cyclic planar and three-dimensional structures. These findings are in striking contrast to those of earlier beam electric deflection experiments performed more than 20 years ago, which seemed to indicate that under the particular experimental conditions water clusters ranging from the trimer up to the hexamer exhibit nonpolar behavior.¹⁹¹ From the results of the beam deflection experiments, it was deduced that the stable structures were cyclic. The work of Liu et al. on the other hand provides conclusive evidence that the water hexamer has a cage configuration, a three-dimensional structure, under the experimental conditions of around 5 K.¹⁸⁴ Due to the low temperature involved, VRT experiments basically explore regions of the potential energy surface that correspond to minimum energy conformations. In deflection experiments, a completely different scenario may prevail,

and the temperatures involved could be sufficiently high to allow for a richer variety of aggregates including equilibrium between different conformers, and even the possibility of solid–liquid-like transitions. These ideas were recently explored by Rodriguez et al. in a theoretical study of isomerization and melting and polarity of model water clusters.¹⁹² They considered the water hexamer and octamer. These authors employed *ab initio* methods and empirical force-field models to explore the energetics, structural features, polarity, and melting transitions in water clusters containing up to eight molecules. For $(\text{H}_2\text{O})_6$, five conformers of similar energy with different geometries and dipole moments were found with the cyclic arrangement being the only nonpolar aggregate. For $(\text{H}_2\text{O})_8$, the most stable structures all correspond to nonpolar cubic-like D_{2d} and S_4 conformers. Using effective pseudo-potentials, classical molecular dynamics experiments were carried out from low temperature up to the melting transition. Melting transitions were monitored by following changes in dipole moments and the number of hydrogen bonds, and for $(\text{H}_2\text{O})_6$ and $(\text{H}_2\text{O})_8$, the melting transitions were found at 50 and 160 K, respectively.

In conclusion, studies of water clusters up to $n = 8$ provide conclusive evidence that (i) at low temperatures (~ 0 K) the cluster structures and dynamics are completely dominated by hydrogen bond rearrangement at the global minimum energy structure; (ii) fluctuation between different isomers in “melting” is the dominant process at higher temperatures (> 100 K); (iii) cooperative effects are important, i.e., it is necessary to go beyond two-body terms and consider many-body terms.

This has to be seen in the context that many of the unusual properties of water originate from its special ability to form networks of hydrogen bonds.^{185,186} This network comprises individual molecules acting simultaneously as both hydrogen bond donor and acceptor. In ice, the hydrogen bond coordination number is four, with each water molecule donating its two hydrogens to hydrogen bonds and accepting two others from its neighbors. This still holds approximately in liquid water, where the average coordination number is still nearly four.¹⁹³ For surfaces of liquid water, ice, and aerosols, in aqueous solutions containing nonpolar solutes and in other restricted or water deficient environments, unoccupied H-bonding sites will be prevalent. What is largely unexplored are the preferred structures, the degree of cooperative strengthening and the magnitude of the dynamic coupling in such hydrogen bond deficient networks. It is in precisely such environments that we are able to see the unusual properties water takes both as a solvent and as a reaction partner.¹⁹⁴

C. Microsolvation of Aromatic Systems by Water Clusters

In particular, it is of interest to look at the transition from quasi-planar water clusters to three-dimensional structures. Whereas the situation may still be somewhat ambiguous for the water hexamer,

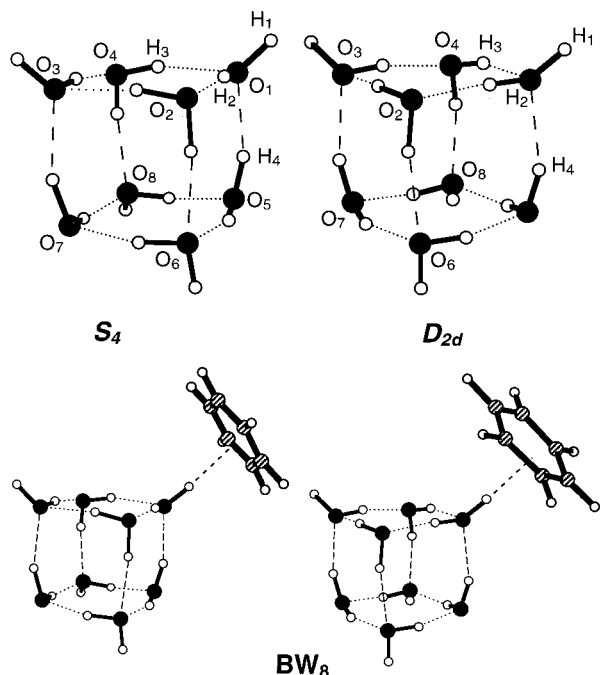


Figure 5. S_4 and D_{2d} structures of water octamer and benzene...water₈.

there seems to be little doubt that the water octamer structure presents a new three-dimensional hydrogen-bonding structural motif which seems to be strongly favored compared to all others. The structure very much favored from *ab initio* theory^{195–197} and model potential calculations^{198,199} is a H-bonded cube. Of the possible cubic isomers, the S_4 and D_{2d} octamer structures have attracted attention. Gruenloh et al. conducted a resonant ion dip infrared spectroscopic study of benzene...water₈, BW_8 .¹¹³ For the two benzene...water₈ isomers identified, the R2PI spectra are nearly identical to one another but shifted by about 5 cm⁻¹. This was sufficient to record interference-free resonant ion dip infrared spectra of both of these clusters. The OH stretching IR spectra of the two BW_8 isomers resemble each other except for the double donor OH stretch transitions near 3550 cm⁻¹. Minimum energy structures, vibrational frequencies, and infrared intensities calculated from density functional theory supported the assignment (to the topology of the BW_8 isomers) as cubic water octamers of S_4 and D_{2d} symmetry, for which dangling hydrogen bonds are attached to the benzene surface through a π -hydrogen bond. Additional features were assigned to two isomers of B_2W_8 . The OH stretch IR spectra of these isomers seem to be the corresponding S_4 and D_{2d} analogues of B_2W_8 in which each of the benzene molecules forms a π -hydrogen bond with a different dangling OH group on one of the W_8 subclusters. The two structures for the (water)₈ moiety and the BW_8 structure are depicted in Figure 5.

Further evidence from the cubic-like structure of the water octamer comes from recent work by Janzen et al. who studied the phenol...(H₂O)₈ cluster by REMPI spectroscopy and infrared-ultraviolet and ultraviolet-ultraviolet hole burning.²⁰⁰ This method allows different isomers to be distinguished through

hole burning. The results indicate a cubic-like structure for the (H₂O)₈ attached to the OH hydrogen of the phenol, supported by *ab initio* calculations. The most stable structure found was a regular cube made of eight water molecules with insertion of phenol into one edge. For the water moiety, this structure is equivalent to cyclic phenol (H₂O)₄ with another (H₂O)₄ ring on top of it, a structure similar to the one obtained by Buck et al.^{201,202}

In conclusion, the water clusters (H₂O)_n show cyclic quasi-planar structures for $n = 3–5$. The structure for the higher clusters is definitely three-dimensional for $n = 8$, with a cube-like structure favored for $n = 8$. For $n = 6$ and 7, the situation is still not unambiguous, but a three-dimensional structure for $n = 8$ is quite definitive and supported from both experiment and theory. New spectroscopic data on larger water clusters should become available in the future, and progress in the theoretical field should result in significantly improved model potentials, including many body interactions. This should considerably enhance our understanding and modeling of liquid water, still one of the biggest challenges to science.

D. Aromatic System Dimers and Oligomers

The benzene–benzene interaction is of key importance as a prototype of interaction prevailing in aromatic π -systems.²⁰³ Its understanding is crucially important for the interpretation of diverse phenomena such as base pair stacking in DNA, intercalation of drugs into DNA, crystal packing of aromatic molecules, formation of tertiary structure of proteins, and porphyrin aggregation. Despite extensive experimental^{204–214} and theoretical efforts,^{215–223} our knowledge of the structural and dynamical properties of the benzene dimer is still limited. This concerns even the structure of the global minimum and the number of other stationary points on the potential energy surface.

The first step toward understanding the dimer structure was achieved by Arunan and Gutowsky,²¹³ who reported well-resolved rotational spectra of the dimer. With the pulsed nozzle Fourier transform microwave spectrometer, the authors obtained rotational constants from which the center of mass separation was estimated. The evaluated distance was consistent with the T-shaped dimer structure. It should further be mentioned that the distance between centers of mass (4.96 Å) is almost identical to that of nearest neighbors in the crystal.

A major step forward has recently come from the investigation of the structure and vibrational dynamics of the benzene dimer using the nonempirical model (NEMO) empirical potential parametrized using CCSD(T) calculations.²²⁴ In this study, gradient and Hessian calculations using the NEMO potential revealed the existence of just one energy minimum corresponding to the T-shaped structure (for various structures of the dimer see Figure 1). The parallel-displaced (PD) structure, which has been believed to be an energy minimum (and sometimes even the global minimum), was clearly identified as a transi-

tion-state structure separating two equivalent T-shaped dimer structures.

Due to a relatively high transition barrier ($\sim 170\text{ cm}^{-1}$), interconversion tunneling is unimportant in the energy region spanned by the available rotational spectra²¹³ and is thus neglected. The dimer undergoes a nearly free internal rotation along the axis connecting the benzene centers of mass in the T-shaped equilibrium geometry and a hindered internal rotation (the barrier being $\sim 46\text{ cm}^{-1}$) along the axis that is perpendicular to the “nearly free” internal rotation axis.

The tunneling splitting observed in the rotational spectrum²¹³ is probably due to this hindered rotation. An analysis assuming the latter rotation as an independent motion and using purely vibrational tunneling splittings indicates that the genuine value of the hindered rotation barrier is nearly twice higher than its *ab initio* value. Similarly, the difference $\Delta R = 0.25\text{ \AA}$ between the equilibrium ground-state value for the distance of the mass centers of the benzene monomers from *ab initio* calculation and experiment is strong evidence that the theoretical potential is much shallower than the correct one. In a complementary stimulated Raman study, some bands were observed in the $3\text{--}10\text{ cm}^{-1}$ region.²¹² These bands can now be assigned to the nearly free rotation and the “energy minimum path” bending motion.

Benzene trimers and tetramers were studied²²⁵ using the same empirical potential used for the benzene dimer. The important advantage of the NEMO potential is that it includes induction energy, allowing recovery of the many-body energy terms. The induction three-body term is, however, only one of several three-body terms. The others, involving exchange and dispersion, might be larger but their evaluation (especially dispersion) is rather difficult. For the benzene trimer, three energy minima were found. The most stable cyclic trimer structure explains the experimentally observed spectral shifts and binding energies.²²⁶ The calculated harmonic frequencies conform to the experimentally found intermolecular vibrations.²²⁷ For the tetramer, five structures were obtained. The experimentally found conformer^{228,229} does not represent the cyclic lowest-energy structure but rather a cyclic trimer with a monomer attached to one side. This can be understood from entropy considerations. These calculations show that a carefully calibrated empirical potential is well suited to describe larger benzene clusters that are out of reach for accurate *ab initio* quantum chemical calculations.

Many-body terms were shown to be important in the case of water clusters. When the polarity of the subsystems is decreasing, many-body terms are expected to be less important. We have, however, shown²²⁵ that for the cyclic benzene trimer the three-body term contributes about 5% to the overall stabilization. Moreover, the three-body contribution can be attractive as well as repulsive. Three-body terms in benzene oligomers are thus not negligible. Theoretical analysis has further shown²²⁵ that the four-body terms can be omitted. The importance of three body interactions was confirmed in a study of the

naphthalene trimer using *ab initio* calculations and an MM3 force field.²³⁰ The lowest energy structure was found to be the C_{3h} cyclic structure, which is consistent with experimental results.²³¹

E. Nucleic Acid Base Pairs

As is well-known, genetic information is stored and duplicated in DNA, which can thus be considered one of the most important molecules in our life. The functionality of DNA is predetermined by its unique three-dimensional, right-handed, double-helical structure. The structure of DNA is influenced by various contributions, among them the H-bonding and stacking interactions of nucleic acid (NA) bases.

The experimental characterization of base pairs is extremely difficult and very few reliable studies are available. There is still only one published gas-phase experiment on the energetics of H-bonded NA base pairs,²³² and gas phase experimental data on base stacking is absent; the same is true for the structure of NA base pairs. Presently, high-level quantum chemical calculations and computer simulations represent the only tools to obtain some reference data on structure, energetics, vibrational frequencies, and other properties of NA base pairs. These data are essential for understanding the function and properties of NA base pairs, and are also very important for the verification and/or parametrization of empirical potentials for molecular modeling of bio-macromolecules and their interactions.

The competition between base stacking and H-bonding of NA bases was first investigated by *ab initio* methods about 10 years ago. More recently, *ab initio* calculations on these clusters including correlation energy have become feasible and have produced more reliable results.^{233,234} These calculations provide a conclusive picture of the interaction of NA bases in the gas phase and can be summarized as follows.

(i) H-bonded pairs stabilized by electrostatic interactions are more stable than the stacked structures which are stabilized by dispersion interactions. Structures of selected hydrogen-bonded and stacked pairs are depicted in Figure 6.

(ii) For a consistent description of H-bonding and stacking interactions, the theoretical procedure must include the London dispersion energy, ruling out the use of Hartree–Fock *ab initio* and density functional methods. Also, semiempirical methods of quantum chemistry cannot be used.

(iii) Intermolecular vibrational frequencies of H-bonded base pairs are almost constant and do not depend on stabilization energy. For all NA base pairs, the buckle and propeller twist vibrations are the lowest and they are all in the region of $4\text{--}30\text{ cm}^{-1}$ in the harmonic approximation.

(iv) In-plane intermolecular harmonic vibrations of the adenine...thymine NA base pair are systematically overestimated with respect to anharmonic vibrations by about 50%, while the absolute differences among anharmonic and harmonic intermolecular out-of-plane vibrations are lower than 15%. The 50% error in vibrational frequencies is large, and care should be taken concerning the use of harmonic

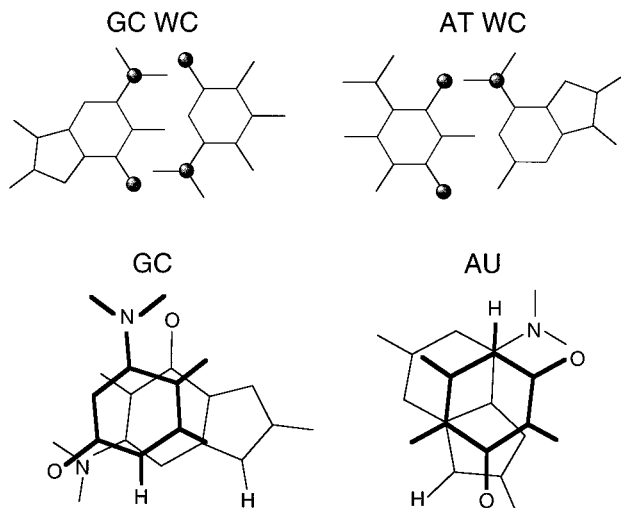


Figure 6. Hydrogen-bonded (Watson–Crick, WC) and stacked structures of guanine⋯cytosine (GC), adenine⋯thymine (AT), and adenine–uracil (AU).

intermolecular vibrational frequencies of NA base pairs. All anharmonic intermolecular frequencies are, however, systematically overestimated in comparison with harmonic ones. This provides an opportunity to use the standard harmonic approach to obtain at least an approximate description of the lowest vibrational frequencies of NA base pairs. It must be remembered that anharmonic treatment of such large clusters is extremely tedious.

(v) The stability order of *hydrogen-bonded* NA base pairs is not changed when passing from the ΔE to the ΔG description. Though the different NA base pairs vary greatly in stabilization energy, the entropy term is always nearly constant.

(vi) The entropy contribution differs considerably for *hydrogen-bonded and stacked structures*. This implies that energetically less favorable stacked structures can be favored compared to the H-bonded ones when passing from the ΔE to the ΔG description. To obtain the free energy and, hence, a reliable thermodynamic characterization for H-bonded and stacked base pairs, computer simulations are required, mainly molecular dynamics simulations.

(vii) The order of stability of various dimer structures of NA base pairs is different for the PES and FES. This indicates that experimental data should be compared with the FES and not with the PES. However, this would only be correct for experiments carried out at temperatures much higher than 0 K. The necessity to use the FES in contrast to the PES will be particularly important for those NA base pairs for which the difference in stabilization energy between H-bonded and stacked structures is small, and hence, the entropy contribution becomes most significant. In these cases, even the structure of the global minimum may be different for both surfaces.

(viii) Among various empirical potentials tested, the *Amber* potential with the Cornell et al. force field²³⁵ was found to best reproduce the *ab initio* H-bonding and stacking stabilization energies and is at present recommended for computer simulations of DNA and RNA. On the basis of the analysis of *ab initio* and empirical potential data, it is evident that

future force field generations should include an anisotropy and a polarization term. The polarization term would allow the inclusion of many-body effects.

It is surprising that such a good agreement between theoretical and experimental values concerning structure and function of DNA oligomers is found for standard MD simulations since only pair potentials are applied. This agreement is even more surprising when the highly ionic and polar character of DNA and surrounding water is considered. It is thus quite possible that the agreement obtained is fortuitous and (as is frequently the case in the field of noncovalent interactions) due to compensation of errors.

F. Negatively Charged Water Clusters

A striking feature of water networks is their ability to bind an “excess” electron under certain conditions in $(\text{H}_2\text{O})_n^-$ clusters.^{236–240} No consensus has yet been reached about either the network morphologies or the extent to which the weakly bound diffuse electron perturbs the intramolecular force fields of the water molecules.²⁴¹ Infrared spectroscopy of negatively charged water clusters can provide some insight into the structure of the corresponding network. Johnson and co-workers reported autodetachment spectra of the mass selected, anionic water clusters, $(\text{H}_2\text{O})_n^-$, $n = 2, 3, 5–9$, and 11 in the OH stretching region ($3000–4000\text{ cm}^{-1}$).^{242,243} The experimental finding was observation of an intense doublet in the spectra (Figure 7), split by about 100 cm^{-1} , for $n > 5$. With increasing cluster size, this intense doublet shifts gradually toward lower energy. This led to the conclusion that the common structural motif for the clusters from $n = 5–11$ is associated with single donor vibrations of water molecules embedded in a chainlike extended network (Figure 8). Theoretical calculations indicated that this chainlike $(\text{H}_2\text{O})_n^-$ species is consistent with the spectra. These results are in contrast to an interesting suggestion of Kim et al., who proposed that the cage isomer of $(\text{H}_2\text{O})_6$ rearranges upon electron attachment to form molecular tweezers, with the excess electron being trapped in a pocket formed by a pair of water molecules perched on a planar bed provided by the water tetramer.^{244,245} This would give rise to the observation of a doublet arising from the concerted motion of the OH stretches largely localized in the dimer trap.

Ionic charges involved in solvation in water and in water cluster present a further challenge to noncovalent chemistry. The discrepancy between the results of Ayotte et al.²⁴² and the tweezer model of Kim et al.^{244,245} clearly show that for anion systems our understanding of these water clusters is far less developed. This is partly due to the lack of very high-resolution spectroscopic information for these anions, due to the immense experimental difficulties. It also shows that the presence of a charge, though often ignored, is a major perturbation. At present, the issue of charge delocalization as a function of cluster size is under active debate and is not yet fully understood.

Surface versus Interior Ion States. Ion solvation occurs intrinsically at the microscopic level. It is believed that the nature of the solvation depends

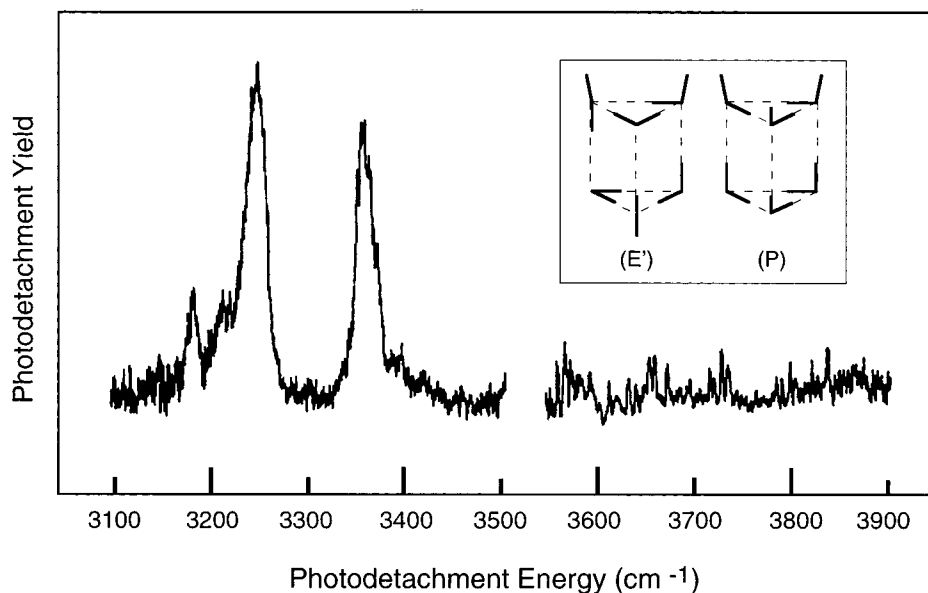


Figure 7. Photodetachment spectra of $(\text{H}_2\text{O})_6^-$.²⁴³ Structures in the insert are the calculated ground state of the anion (P) and the most stable form of the neutral (E').

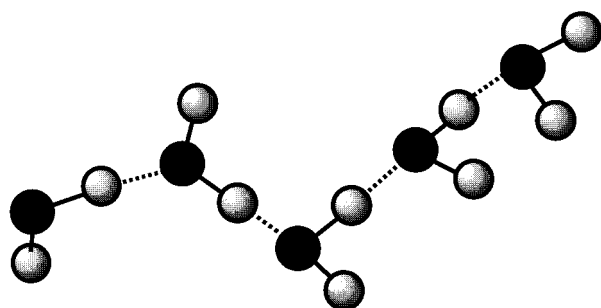


Figure 8. Structure of the $(\text{H}_2\text{O})_5^-$ chainlike isomer.

on the interplay between ion–molecule and molecule–molecule interactions.^{246–248} Ultimately, the magnitude and directionality as well as the competition between these interactions determine the solvent structure around the ion. This then determines the solubility or insolubility of salts in different solvents and how an ion establishes its specific solvent shell. The microscopic details of the solvation process can be explored by studying small clusters of molecules containing a single ion in the gas phase, thus yielding significant insight into the nature of the competing forces. These small ion clusters can then serve as models for larger bulk systems in both experimental and theoretical studies. Particularly attractive from the experimental perspective is the control over the cluster ion size that can easily be obtained using mass spectrometric methods. Halide hydration is an area of great interest due to the ongoing discussion concerning the structure of water or other solvents around an anion. Several classical simulation studies have suggested that the halide ion sits atop a neutral water cluster and the ion solvent interaction is apparently inadequate in strength to overcome the hydrogen-bonded network of the water cluster.²⁴⁹ Eventually, the ion becomes fully solvated with the addition of a sufficient number of water molecules. Figure 9 illustrates surface and interior solvation in the $\text{Cl}^-(\text{H}_2\text{O})_6$ cluster. The main questions are whether these surface states actually exist, and if so,

how many solvent molecules are needed for the different halide ions to cause the transition from a surface to an interior solvated state. Both the role of the solvent in the surface solvation phenomenon, its polarizability, and hydrogen-bonding character should be important in this context, and also the role of the solute, i.e., the nature of the anion itself, should be of high importance.

Using vibrational predissociation spectroscopy to explore the infrared spectrum of the cluster ions in the 2.6–3.6 μm O–H stretch region, Choi et al. and Johnson et al. have collected the vibrational spectra of $\text{Cl}^-(\text{H}_2\text{O})_{1-5}$ and $\text{I}^-(\text{H}_2\text{O})$.^{250,251} While Johnson et al. have obtained the infrared spectra of both $\text{Br}^-(\text{H}_2\text{O})_{1-6}$ and $\text{I}^-(\text{H}_2\text{O})_{1-6}$.^{252–255} For all three halide ion systems $\text{X}^-(\text{H}_2\text{O})_n$ ($\text{X} = \text{Cl}, \text{Br}, \text{and I}$), surface states have been tentatively suggested to exist for $n < 5$. Electronic action spectroscopy of $\text{I}^-(\text{H}_2\text{O})_{1-4}$ and $\text{I}^-(\text{CH}_3\text{CN})_{1-2}$ has also indicated that the systems adopt asymmetric, surface-solvated structures.^{256,257} Recently, Cabarcos et al. have extended this study to methanol as solvent in order to avoid the formation of two proton-donating hydrogen bonds, as is possible with water.²⁵⁸ The monoprotic nature of methanol limits the possible structural conformations of the cluster ions. Methanol will either hydrogen bond to the ion or to another methanol but not to both simultaneously as is possible with diprotic water. In this work, the vibrational spectra in the OH stretch regions, for $\text{Cl}^-(\text{CH}_3\text{OH})_{1-8, 10, 12}$, indicate consistently that the chloride anion undergoes asymmetric, that is surface solvation. This seems to be a feature of the polarizability of the anion, suggesting that the asymmetric hydration of such ions is not necessarily determined by the nature of the solvent but by the nature of the anion itself.

Weiser et al.²⁵⁹ have recently studied the infrared spectra of $\text{Cl}^-(\text{C}_2\text{H}_2)_n$ ($1 < n < 9$) anion clusters. Acetylene binds end-on to the halide ion, which results in a substantial reduction of the ν_3 antisymmetric frequency compared to the corresponding

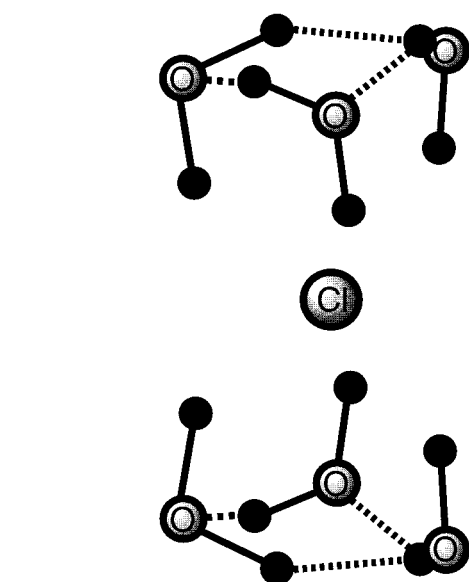
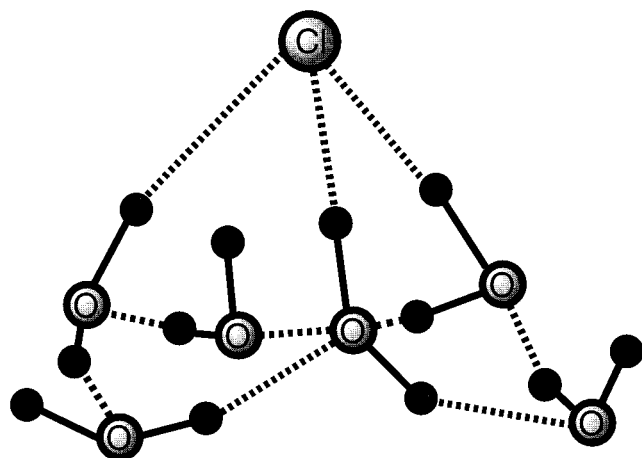


Figure 9. Surface and interior structures for $\text{Cl}^- \cdots (\text{H}_2\text{O})_6$.

absorption of the free acetylene molecule. The end-on approach of the acetylene molecule toward the halide is primarily due to charge–quadrupole forces. Additional ligands that are also bound end-on to the anion should repel each other because of repulsive quadrupole–quadrupole forces. For clusters containing up to six acetylene ligands, the spectra each feature a single dominant band, shifted to lower frequency from the ν_3 CH stretch band of free acetylene. These are consistent with interior solvation structures, with equivalent acetylene molecules bound end-on to a central chloride anion. For $n = 7, 8,$ and 9 complexes, the spectra show multiple peaks, providing evidence for acetylene molecules being situated in a second solvation shell.

G. Cation Solvation and Interactions of Cations

Intermolecular interactions in ionic complexes bridge the gap between weak van der Waals forces acting in neutral clusters and the strong chemical bonds of molecular species. Generally, ion neutral interactions are spectroscopically not well characterized, mainly due to the difficulties in the production

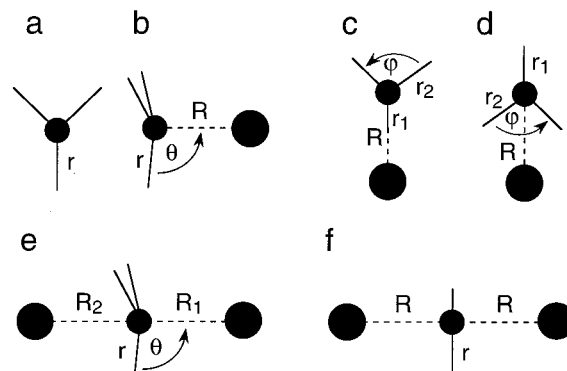


Figure 10. Structures of $\text{CH}_3^+ \cdots \text{Ar}_n$ complexes ($n = 0-2$). (a) $n = 0$ (D_{3h}); (b) $n = 1$, π -bound global minimum (C_{3v}); (c) $n = 1$, vertex-bound local minimum (C_{2v}); (d) $n = 1$, side-bound transition state (C_{2v}); (e) $n = 2$, global minimum (C_{3v}), $R_1 < R_2$; (f) $n = 2$, transition state (D_{3h}), $R_1 = R_2$.

of high number densities of charge complexes.^{135,260} (In this section, we focus on spectroscopic investigations of solvated cations. Thermochemical techniques for probing cationic cluster structures are reviewed in ref 261.) Infrared photodissociation spectroscopy^{114,262} in a tandem mass spectrometer has recently been shown to be successful for studying intermolecular forces in small ionic complexes.²⁶³ Dopfer and co-workers studied the $\text{CH}_3^+ \cdots \text{Ar}$ and $\text{CH}_3^+ \cdots (\text{Ar})_2$ complexes (Figure 10).^{264,265} It had been found previously by the study of proton bound dimers of the type $\text{A}-\text{H}^+ \cdots \text{Rg}$ (where $\text{Rg} =$ rare gas), where the two species A and Rg are held together by a linear proton bond, that the interaction strength in such dimers is correlated with the difference in the proton affinities (PA) of the two species.²⁶⁶ This conclusion had been confirmed by spectroscopic and *ab initio* studies. When the PA of A is much higher than that of the Rg atom, the $\text{A}-\text{H}^+ \cdots \text{Rg}$ complex can be viewed as an $\text{A}-\text{H}^+$ molecular ion that is only weakly perturbed by the Rg ligand. Increasing the PA of A destabilizes the linear proton bonds, and other bonding sites around the $\text{A}-\text{H}^+$ ion may become energetically more favorable for the Rg atom. In a recent combined spectroscopic and theoretical study of $\text{CH}_3^+ \cdots \text{Ar}_n$ complexes ($n = 1-8$),^{264,265} due to the high PA of CH_3^+ , the proton-bound planar structure of the $\text{CH}_3^+ \cdots \text{argon}$ dimer was found to be significantly less stable than the π -bound configuration with the Ar atom attached to the $2p_z$ orbital of the carbon atom and, therefore, closer to the center of the positive charge distribution. The *ab initio* calculations indicated that the high-binding energy of this unusual charge-transfer bound structure (~ 0.5 eV) is due to a partial charge transfer from argon into the vacant electrophilic $2p_z$ orbital of carbon. The formation of this rather strong charge-transfer bond is accompanied by a massive deformation of the CH_3^+ geometry: the geometry changes from a planar D_{3h} structure in the free ion toward a pyramidal C_{3v} configuration in the complex. This result was also confirmed by the analysis of the $\text{CH}_3^+ \cdots \text{Ar}_2$ complex. Once a single argon atom is attached to the CH_3^+ the electrophilic desire of the $2p_z$ orbital is already fulfilled, and the second argon atom will therefore provide very little additional change. The $\text{CH}_3^+ \cdots \text{Ar}_2$

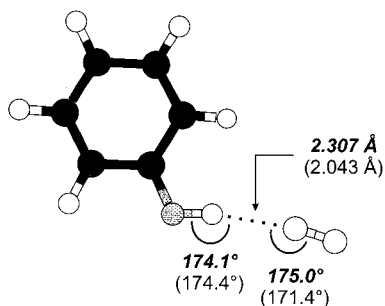


Figure 11. Structure of the global minimum hydrogen-bonded phenol...CO complex. The bond length and angles are given for the ground states of the neutral (S_0 , bold) and cation (D_0 , plain text in brackets).

hence consists of one rather tightly bound argon atom, with a second argon more weakly bound on axis, and C_{3v} symmetry overall ($R_1 < R_2$) as seen in Figure 10.

The interplay between dispersion and induction forces defines the structure of the first microscopic solvation shell of the molecular cation. As shown for the argon solvated CH_3^+ , the proton affinity of the solvating species is also very significant in determining the structure.

H. ZEKE Spectroscopy of Molecular Clusters

ZEKE spectroscopy has developed into one of the most powerful, high-resolution techniques for studying cationic molecular complexes.^{129,135–139} In this section, we review some recent work from the laboratory of the author who developed this spectroscopic method. The general approach for elucidating the structure of a complex using ZEKE spectroscopy relies on the comparison of intermolecular vibrational frequencies obtained from the ZEKE spectrum with vibrational frequencies from *ab initio* calculations. This procedure has been demonstrated to be reliable in a number of cases where additional experimental results have corroborated geometric structures obtained from this approach. Recent examples are provided by the ZEKE spectra of phenol... N_2 ²⁶⁷ and phenol...CO, where *ab initio* calculations pointed to a hydrogen-bonded in-plane structure,²⁶⁸ which was subsequently supported by direct evidence from an infrared spectrum of the phenol... N_2 cation.²⁶⁹ For the phenol...CO complex,²⁷⁰ two isomers are identified as stable minima in the *ab initio* calculations,²⁶⁸ but phenol...CO, with the C atom pointing toward the H of the OH group, is the only isomer observed experimentally.²⁷⁰ The hydrogen-bonded global minimum structure of the phenol...CO cluster is shown in Figure 11.

Mass analyzed threshold ionization (MATI) spectroscopy¹⁴² is a variant of ZEKE spectroscopy that allows the study of fragmentation processes of cationic complexes.^{143–148} For a generic cluster, $\text{A}\cdots\text{B}^+$, the precise dissociation energy can be identified by monitoring the disappearance of MATI signal in the “precursor” $\text{A}\cdots\text{B}^+$ mass channel and the concurrent appearance of signal in the product ion, B^+ , mass channel across the dissociation threshold as a function of internal energy of the cation produced from pulsed field ionization. Both phenol... N_2 and

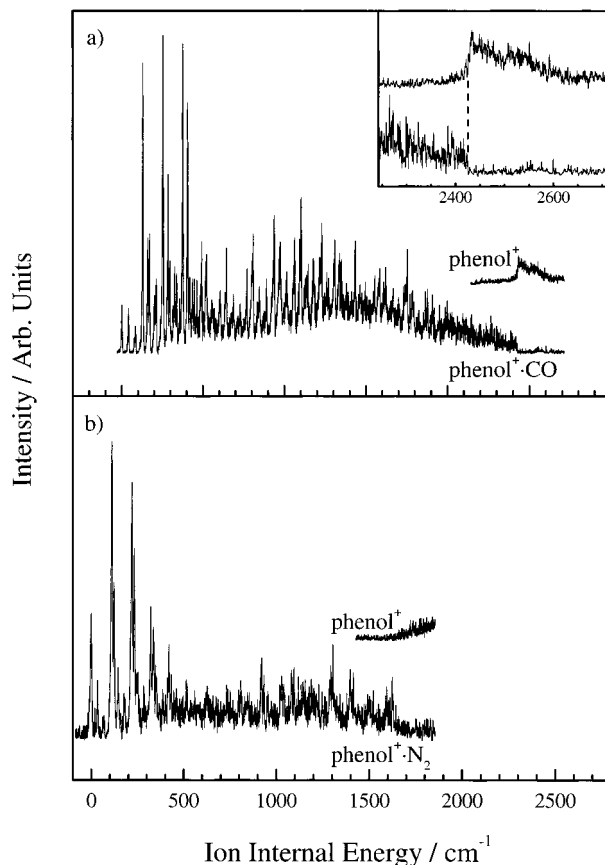
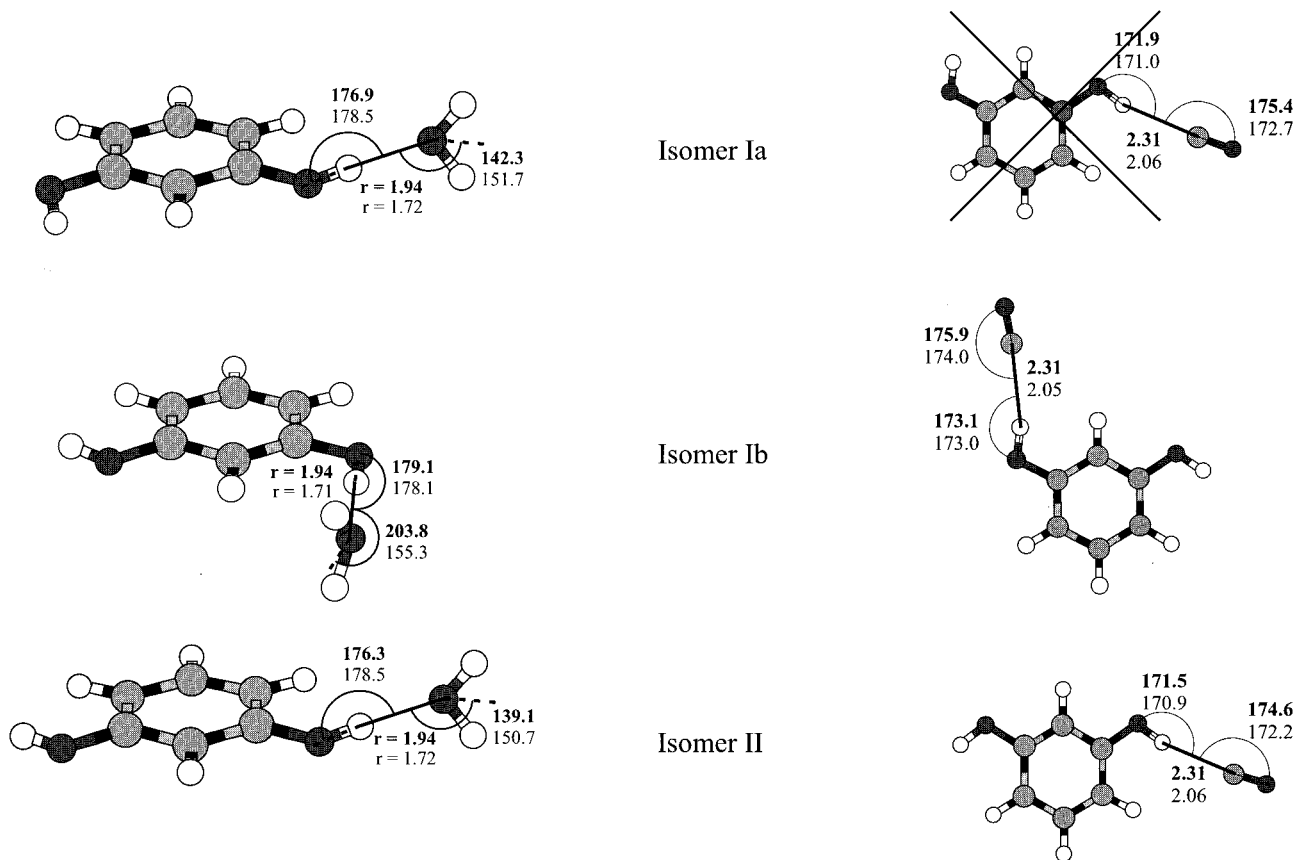


Figure 12. Mass resolved threshold ionization spectra of phenol... N_2 (top) and phenol...CO (bottom) with parent mass (122 amu) and fragment mass (94 amu) recorded simultaneously.

phenol...CO were studied^{268,270} by MATI spectroscopy to the dissociation limit of the cation. A comparison of both MATI spectra is given in Figure 12. Dissociation energies for the S_0 , S_1 , and D_0 states were determined as 659 ± 20 , 849 ± 20 , and 2425 ± 10 cm^{-1} , respectively, for phenol...CO and as 435 ± 20 , 535 ± 20 , and 1640 ± 10 cm^{-1} , respectively, for phenol... N_2 . The dissociation energies of the cationic and neutral phenol...CO complexes are considerably stronger than those of phenol... N_2 , demonstrating the extent to which the larger quadrupole of CO affects the strength of binding.

The preference of a solvent molecule for certain binding sites on a solute molecule is a problem of general chemical interest. In the low-temperature environment of a supersonic jet expansion, isomeric molecular complexes can be generated with a single solvent molecule “frozen” at different binding sites on the solute when the barrier for interconversion between isomers is sufficiently high. Dihydroxybenzenes such as resorcinol (1,3-dihydroxybenzene) can exist in different isomeric forms that are related through rotations of the OH groups.^{271–273} We have recently used REMPI, ZEKE, and hole-burning spectroscopy²⁷¹ for a study of the resorcinol...water²⁷⁴ and resorcinol...CO²⁷⁵ complexes to explore different solvent-binding sites which are available in these isomers and to identify spectral contributions from different isomers. In the related phenol... H_2O complex,^{276,277} the water molecule bonds to the phenol OH group through its oxygen atom. For resorcinol... H_2O ,



Resorcinol·H₂O

Figure 13. Energy minima of resorcinol...water and resorcinol...CO complexes. The missing resorcinol...CO isomer is crossed out. Bond lengths and angles are given for the ground states of the neutral (S₀, bold) and cation (D₀, plain text in brackets).

three rotational isomers have been identified.²⁷⁴ However, for resorcinol...CO, only two isomers were identified in the REMPI and ZEKE spectra and this observation was confirmed by hole burning.²⁷⁵ In contrast, *ab initio* calculations at MP2/6-31G* level of theory predict three isomers similar to resorcinol water, as depicted in Figure 13, with the three lowest energy minima corresponding to structures where the CO molecule binds through its carbon atom to one OH group of resorcinol. Since the CO ligand interacts more weakly with resorcinol than water, it is probable that the barriers for interconversion of rotational isomers are lower in resorcinol...CO than in resorcinol...H₂O. *Ab initio* calculations of the potential energy surfaces of the rotational isomers may serve to explain these observations.

I. Study of Noncovalent Interactions in Condensed Media

The dynamics of hydrogen bonding, which is responsible for the unique features of water and the structure of important molecular systems such as proteins or DNA, has been of particular interest for the last few decades. Initial investigations of hydrogen-bonded molecules in the condensed phase by infrared spectroscopy were followed by Raman spectroscopic

studies, measurements of the dielectric response function, NMR relaxation, and neutron and X-ray scattering. With the development of short-pulse lasers, generating intense radiation in the infrared, the vibrational dynamics in liquids can be monitored in real time.^{278–281}

Vibrational Relaxation in Liquids. In a recent study by Laenen et al., transient spectral hole burning was used²⁸² by pumping the OH stretching vibration of ethanol in ethanol-*d*₄.²⁸³ Transient spectral holes were identified in terms of specific structures within the hydrogen-bonded chains of ethanol molecules. Two spectral hole widths were identified as 35 and 55 cm⁻¹ dependent on the pumping excitation wavelength. For increasing excitation frequency, the spectral hole width was found to increase, which can be rationalized considering that with decreasing H-bond strength the distribution of possible H-bond angles and distances increases, thereby resulting in a corresponding increased spectral width of the respective structures.

Recently, measurement of anti-Stokes Raman scattering, probing the strong vibrational excitation with a picosecond laser pump pulse, has been rediscovered for the study of population relaxation dynamics.²⁸⁴ The relaxation dynamics in liquids or solids is

principally determined by noncovalent interactions between the probed molecule and its surrounding environment.²⁸⁵ For some vibrations, the coupling to the bath can be weak, and hence relaxation can be considerably slower than picoseconds. The earliest experiments were carried out more than 20 years ago;²⁸⁶ however, it is only now with high-quality solid-state picosecond and femtosecond laser systems that it has become possible to use anti-Stokes Raman scattering to study vibrational relaxation.

Transient infrared absorption has also been used instead of Raman spectroscopy to probe the vibrational redistribution following an intense short laser pulse resonant with a vibration of the bulk solvent. Recently, Nienhuys et al. performed a femtosecond infrared pump probe experiment to follow vibrational relaxation in water.²⁸⁷ A vibrational relaxation time of approximately 0.37 ps was found in ice, which was virtually independent of temperature. In contrast, an increase of relaxation time from 0.74 ps at 270 K to 0.9 ps at 363 K was observed in liquid water. It has been speculated that the structure of water is determined from a dynamic interchange of molecular clusters thus forming a dynamic hydrogen-bonded network. If infrared pump probing or anti-Stokes Raman probing could be made sensitive enough to probe intracluster energy transfer and intercluster energy transfer in real time, such a model of clusters interacting in a hydrogen-bonded network could be tested. Unfortunately, for the anti-Stokes Raman experiments, the Raman cross-section of water is very small and this is a very difficult experiment indeed.²⁸⁸

Nonoptical Measurements. Dynamic force spectroscopy is a new technique to study the force-induced association of a single specific bond. Forces are applied to these bonds with carefully controlled rates. Very recently, dynamic force spectroscopy was applied to single specific bonds between immunoglobulins of type G and protein A, a staphylococcal receptor for IgG.²⁸⁹ The resulting spectra of yield forces indicated the crossover from force-induced dissociation to spontaneous bond dissociation. The failure of mechanically unloaded bonds was also observed directly. Single bonds between biomolecules are of particular interest, because in many physiologically important situations, specific bonds between biomolecules are mechanically loaded. Specific biomolecular bonds exhibit very special physical properties as they result from an interplay of several weak interactions, e.g., electrostatic, van der Waals, hydrophobic and hydrogen bonds. These weak noncovalent interactions can combine to form an overall "strong bond" if matching adhesion molecules interact via their binding sites. Until recently, the understanding of such biomolecular bonds has mostly been based on concepts from equilibrium thermodynamics. Clearly, mechanical failure of bonds is a prime example of a nonequilibrium process, and hence mechanical bond strength cannot really be derived from equilibrium binding constants. As pointed out by Bell, bond failure is a statistical process and the lifetime of a bond depends on the mechanical load.²⁹⁰ Given sufficient time, even the strongest bonds will fail under the influence of tiny forces.

V. Conclusions

Why are noncovalent interactions so important in nature? The energy of noncovalent interactions under ambient conditions is comparable to the average thermal energy of the kinetic motion of molecules. This has an important consequence—even a rather strong *single* noncovalent bond can be broken. The much larger binding energy of a covalent bond implies that this bond can only seldom break under these conditions; consequently very low diffusion rates result which are incompatible with the existence of living cells.

Sometimes, however, a stable aggregate is required. The combination of *several* noncovalent bonds ensures a flexible but stable system. This is not speculation—DNA never unwinds (denatures) spontaneously under physiological conditions. J. D. Watson wrote²⁹¹ about noncovalent interactions in his classical book, *Molecular Biology of the Gene*: "...interactions in biological media must be sufficiently strong to ensure preferential bonding of a given functional group of the molecule with a functional group of a second molecule. Simultaneously, however, these interactions should not be too strong in order to avoid the formation of crystalline species within the cell".

A broad variety of noncovalent interactions is of vital importance for the proper function of bio-macromolecules. Strong and specific H-bonding is required for specificity of base pairing in DNA. Surprisingly, however, these strong H-bonds contribute little (if at all) to the overall stability of the DNA double helix. The stability of the double helix (and also of protein structures) is due to hydrophobic interactions and also (in the case of DNA) due to stacking interactions (due to London dispersion forces and CT). Similarly, nonspecific binding of proteins to DNA is governed by electrostatic, dispersion, and hydrophobic interactions while specific binding at much shorter distances is due to the formation of H-bonds between proteins and DNA.

To understand the function of bio-macromolecules such as DNA, RNA, or proteins or to be able to assemble various types of supramolecular species, one requires a deep knowledge of noncovalent interactions. Gas-phase experiments and quantum chemical and dynamical studies of noncovalent clusters with increasing number of solvent molecules provide key steps in this direction.

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VII. References

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