Eur. Phys. J. D **20**, 309–316 (2002)
DOI: 10.1140/epjd/e2002-00185-0

THE EUROPEAN PHYSICAL JOURNAL D

Editorial

Molecular physics of building blocks of life under isolated or defined conditions

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Received 29 August 2002
Published online 13 September 2002

Abstract. In this paper we motivate the study of biomolecular building blocks under isolated or well defined conditions. We explain why we believe that especially gas phase investigations in combination with quantum chemical calculations can provide new insights into molecular properties, such as structure, molecular recognition, reactivity and photostability. Although the gas phase represents far from *in situ* conditions, these findings are important for a detailed understanding of biology. We give a short historic overview of gas phase studies of biomolecular building blocks under isolated conditions, present some examples and report the current status of this field. We explain the new quality of synergy between experiment and quantum theory and the unique opportunities therein to discover new pathways for reactivity and to understand biological processes on an atomic level. We sketch the content of this special issue and give a further perspective of the research field of "Spectroscopy of biomolecular building blocks under isolated or defined conditions" and explain the possible connectivity to biology.

Introduction

The success of life on earth is based on the high chemical and photochemical stability of the building blocks of life, the highly confident and fast reproduction mechanisms of organisms, the high efficiency and selectivity of biochemical processes and the endless time for optimization by the trial and error of evolution. Life in its different forms is very complex. The understanding of life on a molecular level is therefore one of the most interesting and challenging research subjects of humanity. Molecular biologists, biochemists, biophysicists, physicists, chemists and theoreticians work in this field. A good example of such interdisciplinary cooperation is the discovery of the DNA structure by Watson and Crick, a physicist and a chemist [1].

Nowadays the modular structure of biological relevant molecules, such as DNA, RNA and peptides is reasonably well understood and the transcription codes are well known. Most of the current research in biology and biochemistry is based on this knowledge and has achieved great progresses in the understanding and in the manipulation of these processes. However, still fundamental aspects concerning the building blocks of life and their inter- and intramolecular properties are not yet fully understood. Therefore the investigation of peptide, protein, DNA and RNA structures, dynamics and reactivity on an atomic level is still a highly relevant research field which is especially important for the understanding of biological function and the selectivity of biological processes by molecular recognition.

Since biology takes place in a condensed medium, the most widely used experimental approaches have been X-ray crystallography, NMR, IR and UV spectroscopy. Modelling by force-fields is needed to support the assignments of spectral data and for visualization of molecular processes. With the help of these methods it has been possible to unravel many macromolecular structures. The experimental methods work best for frozen, rigid molecular structures and their resolution typically suffers when thermal motion causes disorder resulting in a broad distribution of molecules with different conformations, different charge states (protonated molecules, deprotonated molecules, zwitter ions), different tautomeric forms or different environments, such as different solvents or just different solvent orientation. In such broad ensembles the spectroscopic information of the individual molecule is washed out or manipulated by the environment. As a result, important properties of the bare molecules are buried under the inhomogeneous broadening and it is difficult to distinguish which property are intrinsically intramolecular as opposed to being imposed by the environment is still poor.

As mentioned above, biologists can already play the piano of the genetic code and therefore have practical and very powerful tools for the investigation of biological processes. However, a lot of work remains to be done in the field of proteomics. For example fundamental aspects of peptide folding (dynamics and structure), molecular recognition, biocatalysis, the photostability and repair mechanisms of DNA are not yet fully understood. Most of the experiments in this field deal with native macromolecular structures in solution. This approach to directly listen to the rules of nature in its full complexity is clearly justified by its success. On the other hand, the reductional approach which limits itself to minimal systems or even to just the building blocks of life themselves may, however, provide a detailed understanding as to how nature has arrived at precisely these rules and why nature has chosen exactly these building blocks. The current understanding of DNA and peptides is the picture of independent beads in a chain. This is generally justified for neutral systems in the ground state, as for example for DNA replication. When, however, we consider charged systems, excited electronic states, photoabsorption, photoreactivity, charge delocalization and charge transfer [2] electronic energy transfer and multiple excitations [3] cooperative processes of several beads become important or essential.

As mentioned above, the fundamental question why nature has chosen this set of building blocks of life over all other options remains unanswered. In order to elucidate the systematic behind nature's preferences, the building blocks of life need to be explored in all their different forms, such as different charged forms, different tautomers, different conformers and various substitutions. Up to now surprisingly, even for the basic building blocks of life many chemical and physico-chemical properties are unavailable or only known imprecisely. Such properties are dipole moments, ionization energies, electron affinities, proton affinities, electronic structure, radiationless processes, photodynamics and reactivity, as well as energetics, flexibility of structures, non-covalent bond strengths to other building blocks of life or to solvent molecules.

A good example which shows that exact properties of molecules in the gas phase and an interdisciplinary approach can be helpful is the issue of "charge transfer in DNA". Charge transfer in DNA has for a long time in the subject of great controversy: one group found wire-like charge transfer [4], an other group normal tunneling-like behavior [5]. In their studies both groups, however, used different donor and acceptor complexes. Finally after several years it was clarified that under certain conditions the positive charge can be injected into DNA and charge hopping between guanine residues and final trapping in guanine dimers or trimers occurs [6–8]. Here the knowledge of the existence of a hopping model [9], as originally found in the gas phase, the knowledge of ionization energies of the nucleic acid bases [10–15] and the fact that charges in π stacked dimers are strongly stabilized (see gas phase results on benzene [16] and naphthalene [17] dimers) could have been the key for a confident interpretation of the observed processes in a much earlier stage of this research.

Special conditions, such as low temperatures, gas phase or defined environments as well as the observation of selected or even single molecules, can prevent the inhomogeneous line broadening which tends to mask important details. Suppression of such broadening allows the observation of new conformers and tautomers, new electronic states and new relaxation mechanisms, which can be important for the explanation of the stability of the building blocks of life and consequently their complexes and the success of life on earth.

Independent of the direct applicability of these data for biological studies, investigating the building blocks of life is an interesting research for its own sake: it would be absurd, for example, if on the one hand we search with enormous effort and financial support for extra-terrestrial life and the beginning of the universe while on the other hand not being interested in the basic properties of the building blocks of life and their complexes.

An other motivation to study individual biological molecules in the gas phase and under defined conditions is the need to distinguish between intrinsic and externally imposed properties. Especially the measured differences between gas and condensed phase behaviour may be helpful for identifying environmental influences on the building blocks of living systems. The investigation of complexes of increasing sizes can mimic the transition from the isolated molecule to solution or bulk.

The greatest advantage of specific and detailed experimental results under well defined or gas phase conditions, however, is that they can be directly compared to theory. By definition, calculations are "gas-phase" calculations since they consider the isolated system *in vacuo*. Dependent on the properties investigated and the necessary accuracy, one has to distinguish different levels of theory: force field, DFT and *ab initio* calculations. Force-field parameters have been mostly determined by fitting them to condensed-phase data when available or by using *ab initio* calculations of small model molecules, such as for example N-methylacetamide as a model for peptide bonds. In contrast to high-level quantum chemistry calculations (*ab initio* and DFT methods) force field methods are not well suited for charged systems and in principle are not able to calculate electronic excited states, *i.e.* the states which are involved in photoabsorption and radiationless processes and hence photostability. Clearly they also can not account for electronic effects such as electron correlation and reactivity. Therefore force field calculations describe only a small part of molecular reality such as structure and molecular recognition. Only high level quantum calculations are able to access the full spectrum of processes.

The comparison of experimental and quantum chemical calculations allows for a direct test and calibration of theory and thus very much increases the confidence in theory. Testing and method development is important because theory alone has access to the shape of the potential surface, the atomic charge densities, the contribution

of individual forces to binding energies and solvation and, hence, provides very detailed insights into intra and intermolecular processes. Also theory can extrapolate to solution by adding more and more solvent molecules until the first solvent shells are filled. This together with increasing computer power makes theory an increasingly important research field and a link between spectroscopy under defined conditions and biology.

Current stage of research in gas phase spectroscopy

"Well-defined conditions" exist in crystals, matrices, self-organized mono-layers or other ordered systems. In the following we concentrate on the research field of "biological molecules in the gas phase and quantum theory", because we believe that in this field recently a lot of progress has been made and that this research field can now provide new important results for amino acids, small peptides, nucleic acid bases and nucleotides.

Ab initio calculations have been carried out before any experimental investigation of amino acids in the gas phase existed [18,19]. Due to lack of computer power at the time, initially only the simplest amino acid glycine was calculated. Subsequently, the first microwave spectra of glycine [20,21] disagreed with theory. Later this disagreement was resolved by the discovery of a second conformer [22–24]. This early example already shows one general problem of the gas phase spectroscopy of biologically relevant molecules: the structural complexity of molecules of biological relevance resulting from different conformers, different tautomers, different charge states, etc. In the gas phase each molecular structure shows its own sharp IR or UV spectrum with all vibrational and rotational details. The spectra of all co-existing structures superimpose, leading to very complex spectra. Therefore assignments become difficult and support by high-level theory is needed. However, at the same time, these detailed spectral structures provide a new chance for science because they contain important information about intramolecular properties.

An other problem arises from the fact that most of the biologically relevant molecules have extremely low vapor pressure and at high temperatures typically quickly degrade [18]. In sophisticated experiments by using thermal heating it has been shown that intact evaporation is possible for amino acids (UV spectra [25,26] microwave spectra: [20,21], He I photoelectron spectra: [27–30], fluorescence spectra: [31–33]) and nucleic acid bases (mass spectrometry of dimers [34–36], resonant enhanced multiphoton ionization: [37–40], ionization spectroscopy [41], He I photoelectron spectra [10–15], Rydberg electron transfer [42–44], photodetachment photoelectron spectroscopy [45,46], IR spectroscopy [47,48]), but not for natural peptides [25,51] and nucleotides. Only recently some di- and tripeptides have been brought into gas phase by thermal heating [52,53]. In these model peptides the polar C and N terminal were substituted by non-polar groups to reduce the intermolecular binding energy in bulk, thus facilitating vaporization by thermal heating.

Since cooling of the large number of internal degrees of freedom of large molecules is essential to reduce the population of vibrationally and rotationally excited states, the application of a supersonic rare gas co-expansion constituted great progress in simplifying and improving the spectra [54]. To solve the problem of low vapor pressure of molecules of biological interest, pulsed laser desorption techniques were developed which are able to transfer fragile molecules into gas phase without decomposition. For spectroscopy, laser desorption, which usually produces very hot molecules, was combined with a co-expansion with rare gases and a supersonic beam (indole [55]). By this technique already in 1988 multiphoton ionization and laser induced fluorescence spectra of laser desorbed small peptides were recorded with high quality [56]. Unfortunately this very interesting research field was then nearly abandoned, presumably due to the following reasons:

(i) the laser desorption technique showed still large sample intensity fluctuations and as a result recording spectra of laser-desorbed molecules was complicated and time-consuming;
(ii) the separation and assignment of conformers was difficult. Note that for example the coexistence of 5 conformers was found for tryptophan [31–33] and phenylalanine [57,58] and even 10 for tyrosine [57,58]). Double resonance techniques to attribute the peaks to the individual conformers and tautomers were not yet available;
(iii) high-level theoretical methods and sufficient computer power were not yet available to perform accurate calculations of structures and relative conformer energies of the aromatic amino acids tryptophan, tyrosine and phenylalanine.

Hence, the time was simply not ripe for spectroscopic experiments on biologically relevant molecules and their detailed interpretation. In parallel to the development of laser desorption techniques of neutrals also new powerful vaporization methods were developed for ions, such as electrospray ionization (ESI [59,60]), matrix assisted laser desorption/ionization (MALDI [61,62]) and laser desorption/laser ionization [63,64]. These new sources pushed the mass limit for mass spectrometric investigations beyond 100 000 Dalton and suddenly mass spectrometric analysis of large peptides and proteins became feasible. Because of their wide applicability in biology these techniques attracted strong attention, but by this reduced interest in optical spectroscopy of amino acids and small peptides in the gas phase.

We believe that new problems (i) to (iii) above can be overcome and a breakthrough can be achieved. Boosted by experiments on molecular clusters, in recent years new experimental, technical and theoretical developments have taken place:

(i) new *ab initio*, density functional and semiempirical calculation methods and algorithms were developed;

(ii) new desorption methods and their combination with storage techniques allow the production of high densities of large molecules;
(iii) new double resonance spectroscopy techniques allow selection of isomers;
(iv) spectroscopic methods, such as ion drift techniques and laser spectroscopy techniques were applied to electrosprayed molecules;
(v) new lasers and new IR generation techniques extend the conventional wavelength range and increase laser power and stability of laser intensity.

(i) With the enormous progress of computer power and the development of less CPU time-consuming methods (DFT, local MP2 etc.) it has now become possible to calculate structures and IR spectra of small peptides, nucleobases and nucleobase dimers at a high level of theory in the ground state (peptides [65,66], nucleotides and nucleotide dimers [67–70], for review see [71], see also articles 1, 2, 5–8, 12, 13, 18–24 and 32 of this issue) or even in excited electronic states (see articles 5 and 6 of this issue). For example diffuse dipole-bound anion states of nucleic acid bases energies [72], charge resonance states of the uracil dimer [73] and excited states for the chromophore of the green fluorescent protein in dependence on protonation [74] have been calculated. Due to considerable progresses in software and hardware, computational chemistry clearly is a field of increasing activity in fundamental research as well as in the pharmaceutical industry. In the strategy to compare quantum theory predictions to experimental data obtained in the gas phase we see a unique opportunity for connecting gas phase investigations to biology.

(ii) Years after the first application of the desorption technique to biological relevant molecules by Levy and co-workers (small peptides [56]), others [75–91] also developed sophisticated new laser desorption techniques to produce stable, high density beams of large non-volatile neutral molecules of biological interest, such as nucleic acid bases and their tautomers ([75–81], articles 1 and 4 of this issue), their dimers [82–84], nucleosides [85], amino acids [86–89] and small peptides [84]. Perhaps the most interesting application of laser desorption is that such high densities of sample molecules can be created in a molecular beam that efficient complex formation can take place. This allows a direct investigations of dimers ([82–84], see articles 1, 12 and 23 of this issue) or larger clusters, providing a first step to the understanding of molecular recognition.

MALDI [61,62], ESI [63,64] and the new technique of "laser induced liquid beam ionization" (LILBID) [92] allow for efficient transfer of large and ultra-large charged molecular systems into the gas phase. The most astonishing example up to now is the mass spectrometry analysis of a whole virus [93]. New ion trap techniques are very promising links to combine ESI and MALDI with laser-spectroscopic techniques. Storage of electrosprayed molecules in traps allows for the combination of pulsed laser excitation methods with the continuous electrospray source. So far only a few research groups perform spectroscopy on electro-sprayed molecules ([94–100], articles 30 and 31 of this issue), but this community is clearly increasing. These experiments, which use ESI as an inlet source, in principle allow spectroscopic access to ultra-large systems and therefore to a great variety of biologically relevant molecules in the gas phase.

(iii) New spectroscopy methods, such as UV/UV [101, 102], IR/UV ionization hole-burning ([98,103–105], see also articles 1, 4 and 8 of this issue), UV fluorescence detected IR [106], IR infrared photoinduced Rydberg ionization [107], zero kinetic energy electron photoelectron [108], IR multiphoton dissociation [109], high resolution infrared [47,48,110,111], messenger detected IR ([112–115], see also article 18 of this issue), visible photodissociation [97], stimulated Raman (article 10 of this issue), rotational coherence [116,117], nano- [118], pico- and femtosecond time resolved (see also articles 9 and 15), UV high-resolution [119,120], Rydberg electron transfer ([42, 43], see paper 16 of this issue), anion photoelectron spectroscopy [45,46] and IR and UV spectroscopy in liquid He droplets [121] have been or can be combined with laser desorption and applied to molecules of biological relevance or model systems. In the meanwhile even the ultra-accurate microwave spectroscopy has been combined to laser desorption [118,119].

It is now possible to investigate neutral (see above), radical anionic [42–46] radical cationic ([9], see also paper 26 of this issue), charge-separated [122], deprotonated [94–97], protonated [73,100] (model systems [113–115]) and zwitterionic species [123]. Double resonance spectroscopy methods in particular allow for a clear separation of isomers, their vibrational and electronic spectra, providing a qualitative determination of the relative stabilities of their isomers and an analysis of their non-covalent interactions. Laser desorption, laser ionization and laser dissociation experiments were able to detect charge migration in tri- and tetrapeptides [9]. Short laser pulse time resolved experiments can detect excited state fluorescence lifetimes [118] and follow proton transfer [124,125] or ultrafast non-ergodic dissociation dynamics (model systems [126]) in real time. New methods make it possible to investigate and follow isomerization and folding processes of dipeptides as a first step towards the understanding of the dynamics of peptide folding [53].

(iv) Due to the large number of conformers in ultra-large systems it becomes increasingly difficult to obtain detailed structural information. By using sophisticated drift tube methods one can distinguish structural patterns, such as helical structures of model peptides compared to strongly folded structures ([127,128], see article 11 of this issue and references therein). Proton affinities of different sites in proteins can be weighted against each other [129], and intramolecular [130] and intermolecular [131] binding energies can be determined.

(v) New technical developments support the recent progresses in the investigation of biologically relevant molecules. For example diode-pumped lasers have highly stable laser output leading to a significant reduction of fluctuations in the intensity of laser-desorbed particles. New mixing crystals and techniques open new wavelength

ranges in the IR and the UV regions or simply increase intensity or resolution. Fast digital oscilloscopes allow recording of spectra of a large number of molecules and molecular complexes.

This special issue

The above mentioned progress catalyzed the growth of the new research field of "Isolated molecules of biological interest in the gas phase". This special issue collects some articles which deal with gas phase spectroscopy and/or quantum chemistry and present them together with work performed under other well defined conditions.

Our aim is to attract attention to this new field, give a glimpse of the existing research therein and show the existing overlap between gas phase results, highlighting theoretical calculations and results gained under defined conditions in bulk material. The hope is that the new confrontation between different experimental (NMR, X-ray *vs.* gas phase) or theoretical (force-field *vs.* quantum chemistry) approaches will lead to an intense exchange of knowledge, improvement of methods and assignments and new research strategies. This issue is a first attempt in this direction. The content is by far not complete and does not equally cover the whole spectrum of research in this field.

For this issue the emphasis is on the most fundamental biomolecular building blocks, such nucleic acid bases, nucleotides, amino acids and small as well as large peptides and complexes thereof. Investigations include quantum theory together with vibrationally and electronically resolved spectroscopy with different excitation and detection schemes. New double resonance techniques permit assignments of conformer, isomer and tautomer structures which often coexist in molecules and complexes of biological interest. For example, it is possible for the first time to experimentally explore the great variety of the tautomers of the nucleic acid bases guanine, adenine and cytosine and their model systems (see papers 1, 4, 7 and 8 of this issue). Their different properties concerning photostability as well as their intermolecular bonding might contain the information how building blocks work together (inter-base proton transfer charge transfer, thymine-dimer formation, repair mechanisms etc.) and why nature has chosen exactly this set of nucleic acid bases. It is now also possible to form complexes of dipeptides in the gas phase. Such complexes are model systems for β-sheets. The conversion of α-helices to larger β-sheet aggregates cause BSE and Creutzfeld-Jakob and other prion diseases [132,133] clusters of templates with model peptides can help to find new drugs which are able to block β-sheet formation and thus prevent or cure these diseases (paper 23 in this issue).

As outlined above, the great advantage of specific and detailed experimental results under well-defined conditions is the possibility of direct comparison with theoretical calculations. The comparison of these experimental results with theoretical results provides a direct test of computations and helps improve theory. This is important because theory can provide very detailed insights into intra and intermolecular processes in biologically relevant molecules at an atomic level. This successful concept is applied in most of the experimental contributions (see articles 14, 7, 8, 10, 12, 16, 18 and 23 of this issue). Besides providing an assignment of the spectra to different conformers, tautomers or charge states, this combination makes it possible to explore the shape of the potential energy surface, to calculate atomic charge densities and to analyze the contributions of individual forces to intermolecular binding energies and solvation.

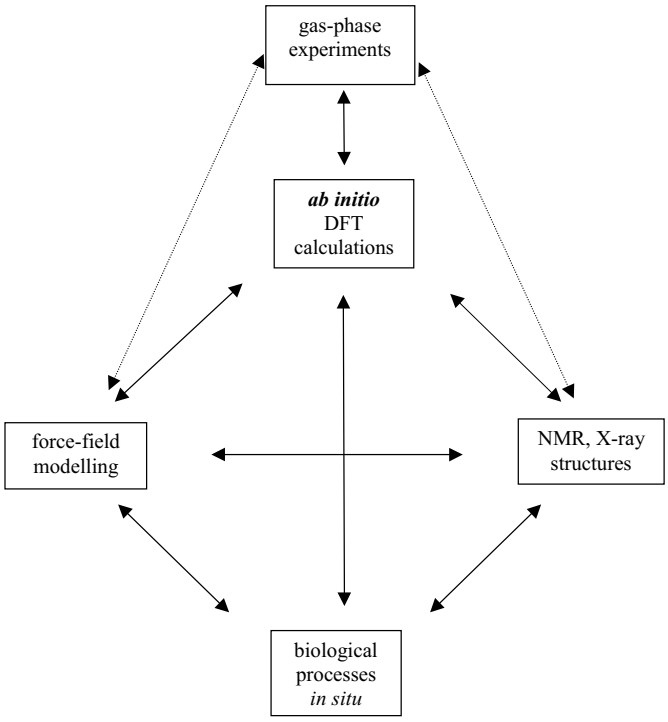

Fig. 1. Gas phase experiments are not directly correlated to biological processes *in situ*. They can explore in detail intra- and intermolecular properties which can be directly compared to quantum chemical calculations. This test of theory is important because then in a second step theory can extrapolate to solution and provide new detailed insights into biological processes. The increasing computer power and the development of new theoretical methods makes quantum theory to an increasingly important link between spectroscopy under defined conditions and biology.

Furthermore, theory can extrapolate to solution by adding more and more solvent molecules and a solvent continuum. This together with increasing computer power makes quantum theory into an increasingly important link between spectroscopy under defined conditions and biology. For example Domcke and co-workers (paper 6 of this issue) showed, that by quantum chemical calculations new concepts for the non-radiative decay of DNA bases can be proposed which might be the important missing link to explain the photostability of DNA.

Clearly gas phase experiments and quantum theory are not directly correlated to biological processes *in situ* (see Fig. 1). However, they can explore detailed intramolecular and intermolecular properties which are up to now

unknown or known with low accuracy. We believe that it is worth to enter the research field

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also because it is simply interesting for its own sake. Molecules of biological relevance and their aggregates are interesting not only because of their large numbers of atoms (large number of vibrations, large density of states etc.), but they also have extraordinary properties. For example, they contain hetero atoms, have different tautomers and structures, large dipole moments, many groups for H bond formation are flexible can transfer protons. The spirit of detailed experimental and theoretical investigations of building blocks of life was and is disseminated in alternating Gordon (2001, 2003) and European Science Foundation (2000, 2002, 2004) conferences. We hope that this special edition helps to draw attention to this field and will stimulate collaboration with neighbouring fields.

R.W. would like to thank the *Volkswagenstiftung* and the Fond der *Chemischen Industrie*.

References

1. J.D. Watson, F.H.C. Crick, Nature **171**, 737 (1953)
2. *Electron Transfer I and I: From Isolated Molecules to Biomolecules*, edited by J. Jortner, M. Bixon (John Wiley & Sons Inc., New York, 1999)
3. D.L. Andrews, P. Allcock, Chem. Soc. Rev. **24**, 259 (1995)
4. C.J. Murphy, M.R. Arkin, Y. Jenkins, N.D. Ghatlina, S.H. Bossmann, N.J. Turro, J.K. Barton, Science **262**, 1025 (1993)
5. F.D. Lewis, T. Wu, Y. Zhang, R.L. Letzinger, S.R. Greenfield, M.R. Wasielewski, Science **227**, 673 (1997)
6. S.M. Gasper, G.B. Schuster, J. Am. Chem. Soc. **119**, 12762 (1997)
7. J. Jortner, M. Bixon, T. Langenbacher, M.E. Michel-Beyerle, J. Am. Chem. Soc. **120**, 12950 (1998)
8. B. Giese, S. Wessely, M. Spormann, U. Lindemann, E. Meggers, M.E. Michel-Beyerle, Angew. Chem. **38**, 996 (1999)
9. R. Weinkauf, P. Schanen, A. Metsala, E.W. Schlag, M. Bürgle, H. Kessler, J. Phys. Chem. **100**, 18567 (1996)
10. N.S. Hush, A.S. Cheung, Chem. Phys. Lett. **34**, 11 (1975)
11. G. Lauer, W. Schäfer, A. Schweig, Tetrahedron Lett. **45**, 3939 (1975)
12. D. Dougherty, K. Wittel, J. Meek, S.P. McGlynn, J. Am. Chem. Soc. **98**, 3815 (1976)
13. D. Dougherty, S.P. McGlynn, J. Chem. Phys. **67**, 1289 (1977)
14. S. Peng, A. Padva, P.R. LeBreton, Proc. Nat. Acad. Sci. USA **73**, 2966 (1976)
15. S. Urano, X. Yang, P. LeBreton, J. Mol. Struct. **214**, 315 (1989)
16. K. Ohashi, Y. Nakai, T. Shibata, N. Nishi, Laser Chem. **14**, 3 (1994)
17. Y. Inokuchi, K. Ohashi, M. Matsumoto, N. Nishi, J. Phys. Chem. **99**, 3416 (1995)
18. W.R. Oegerle, J.R. Sabin, J. Mol. Struct. **15**, 131 (1973)
19. S. Vishveshwana, J.A. Pople, Am. Chem. Soc. **99**, 2422 (1977)
20. R.D. Suenram, F.J. Lovas, J. Mol. Spectrosc. **72**, 372 (1978)
21. R.D. Brown, P.D. Godfrey, J.W. Storey, M.P., Bassez, J. Chem. Soc. Chem. Commun. 547 (1978)
22. R.D. Suenram, F.J. Lovas, J. Am. Chem. Soc. **102**, 7180 (1980)
23. H.L. Seilers, L. Schäfger, J. Am. Soc. **100**, 7728 (1978)
24. L. Schäfer, H.L. Seilers, F.J. Lovas, R.D. Suenam, J. Am. Chem. Soc. **102**, 6566 (1980)
25. D. Gross, G. Grodsky, J. Am. Chem. Soc. **77**, 1678 (1955)
26. C.R. McMillin, W.B. Rippon, A.G. Walton, Biopolymers **12**, 589 (1973)
27. L. Klasnic, J. Electr. Spectr. Rel. Phenom. **8**, 161 (1976)
28. P.H. Cannington, N.S. Ham, J. Electr. Spectrosc. **15**, 79 (1979)
29. K. Seiki, H. Inokuchi, Chem. Phys. Lett. **65**, 158 (1979)
30. P.H. Cannington, N.S. Ham, J. Electr. Spectr. Rel. Phenom. **32**, 139 (1983)
31. T.R. Rizzo, Y.D. Park, D.H. Levy, J. Am. Chem. Soc. **107**, 277 (1985)
32. T.R. Rizzo, Y.D. Park, L.A. Peteanu, D.H. Levy, J. Chem. Phys. **84**, 2534 (1986)
33. T.R. Rizzo, Y.D. Park, D.H. Levy, J. Chem. Phys. **85**, 6945 (1986)
34. L.F. Sukhodub, I.K. Yanson, Stud. Biophys. **59**, 209 (1976)
35. L.F. Sukhodub, I.K. Yanson, Nature **264**, 245 (1976)
36. L.F. Sukhodub, Chem. Rev. **87**, 589 (1987)
37. B.B. Brady, L.A. Peteanu, D.H. Levy, Chem. Phys. Lett. **147**, 538 (1988)
38. N.J. Kim, G. Jeong, Y.S. Kim, J. Sung, S.K. Kim, Y.D. Parks, J. Chem. Phys. **113**, 10051 (2000)
39. N.J. Kim, H. Kang, G. Jeong, Y.S. Kim, K.T. Lee, S.K. Kim, Proc. Natl. Acad. Sci. USA **98**, 4841 (2001)
40. N.J. Kim, H. Kan, G. Jeong, Y.S. Kim, K.T. Lee, S.K. Kim, J. Chem. Phys. **115**, 7002 (2001)
41. S.K. Kim, W. Lee, D.R. Herschbach, J. Phys. Chem. **100**, 7933 (1996)
42. C. Desfrançois, H. Abdoul-Carime, J.P. Schermann, J. Chem. Phys. **104**, 7792 (1996)
43. V. Periquet, A. Moreau, S. Carles, J.P. Schermann, C. Desfrançois, J. Electr. Spectr. Rel. Phenom. **106**, 141 (2000)
44. C. Desfrançois, V. Periquet, Y. Bouteiller, J.P. Schermann, J. Phys. Chem. **102**, 1274 (1998)
45. J.H. Hendriks, S.A. Lyapustina, H.L. Clercq, J.T. Snodgrass, K.H. Bowen, J. Chem. Phys. **104**, 7788 (1996)
46. J. Schiedt, R. Weinkauf, D.M. Neumark, E.W. Schlag, Chem. Phys. **239**, 511 (1998)
47. M.R. Viant, R.S. Fellers, R.P. McLaughlin, R.J. Saykally, J. Chem. Phys. **103**, 9502 (1995)
48. P. Colarusso, K.Q. Zahng, B. Guo, P.F. Bernath, Chem. Phys. Lett. **269**, 39 (1997)
49. M.T. Rodgers, P.B. Armentrout, J. Am. Chem. Soc. **122**, 8548 (2000)
50. R.M. Moision, P.B. Armentrout, J. Am. Chem. Soc. (submitted)
51. D.S. Nagara, J.-Y. Zhang, L. Li, Anal. Chem. **63**, 2188 (1991)

52. M. Gerhards, C. Unterberg, Phys. Chem. Chem. Phys. **4**, 1760 (2002)
53. B.C. Dian, A. Longarte, T.S. Zwier, Science **298**, 2369 (2002)
54. D.H. Levy, Science **214**, 263 (1981)
55. H. von Weysenhoff, H.-J. Selzle, E.W. Schlag, Z. Naturforsch. **40a**, 51 (1985)
56. J.R. Cable, M.J. Tubergen, D.H. Levy, J. Am. Chem. Soc. **110**, 7349 (1988)
57. S.J. Martinez III, J.C. Alfano, D.H. Levy, J. Mol. Spectrosc. **156**, 412 (1992)
58. S.J. Martinez III, J.C. Alfano, D.H. Levy, J. Mol. Spectrosc. **158**, 82 (1993)
59. J.B. Fenn, M. Mann, C.K. Meng, S.F. Wong, C.M. Whitehouse, Mass Spectrom. Rev. **9**, 37 (1990)
60. M.L. Alexandrov, L.N. Gall, N.V. Krasnov, V.I. Nikolayev, B.I. Pavlenko, V.A. Shkurov, Rep. Acad. Sci. **277**, 379 (1984)
61. M. Karras, F. Hillenkamp, Anal. Chem. **60**, 2299 (1988)
62. M. Karras, D. Bachmann, U. Bahr, F. Hillenkamp, Anal. Chem. **57**, 2299 (1988)
63. U. Boesl, J. Grotemeyer, K. Walter, E.W. Schlag, Anal. Instrum. **16**, 51 (1987)
64. J. Grotemeyer, E. Schlag, Acc. Chem. Res. **22**, 410 (1989)
65. A.G. Császár, J. Am. Chem. Soc. **114**, 9568 (1992) and references therein
66. R. Kaschner, D. Hohl, J. Phys. Chem. **102**, 5111 (1998)
67. J. Sponer, P. Hobza, J. Am. Chem. Soc. **116**, 709 (1994)
68. J. Sponer, P. Hobza, J. Phys. Chem. **98**, 3161 (1994)
69. J. Sponer, J. Florian, P. Hobza, J. Leszczynski, J. Biomol. Struct. Dyn. **13**, 827 (1996)
70. J. Sponer, J. Leszczyïnski, P. Hobza, J. Phys. Chem. **100**, 5590 (1996)
71. For a review of the early work of J. Sponer and P. Hobza on nucleic acid bases see: J. Sponer, J. Leszczynski, P. Hobza, J. Biomol. Struct. Dyn. **14**, 117 (1996)
72. D.M. Smith, J. Smets, L. Adamowicz, J. Phys. Chem. A **103**, 5784 (1999)
73. J. Rak, A.A. Voityuk, N. Rösch, J. Phys. Chem. A **102**, 7168 (1998)
74. A.A. Voityuk, M.-E. Michel-Beyerle, N. Rösch, Chem. Phys. Lett. **272**, 162 (1997)
75. E. Nir, L. Grace, M.S. Brauer, M.S. de Vries, J. Am. Chem. Soc. **121**, 4896 (1999)
76. E. Nir, P. Imhof, K. Kleinermanns, M.S. de Vries, J. Am. Chem. Soc. **122**, 8091 (2000)
77. E. Nir, K. Kleinermanns, L. Grace, M.S. de Vries, J. Phys. Chem. A **105**, 5106 (2001)
78. E. Nir, P. Imhof, K. Kleinermanns, M.S. de Vries, J. Chem. Phys. **155**, 4604 (2001)
79. Chr. Plützer, E. Nir, M.S. de Vries, K. Kleinermanns, Phys. Chem. Chem. Phys. **3**, 5466 (2001)
80. F. Piuzzi, M. Mons, I. Dimicoli, B. Tardivel, Q. Zhao, Chem. Phys. **270**, 205 (2001)
81. M. Mons, I. Dimicoli, F. Piuzzi, B. Tardivel, M. Elhanine, J. Phys. Chem. A **106**, 5088 (2002)
82. E. Nir, Ch. Janzen, P. Imhof, K. Kleinermanns, M.S. de Vries, Phys. Chem. Chem. Phys. **4**, 740 (2002)
83. E. Nir, Ch. Janzen, P. Imhof, K. Kleinermanns, M.S. de Vries, Phys. Chem. Chem. Phys. **4**, 737 (2002)
84. E. Nir, K. Kleinermanns, M.S. de Vries, Nature **408**, 949 (2000)
85. E. Nir, P. Imhof, K. Kleinermanns, M.S. de Vries, J. Am. Chem. Soc. **122**, 8091 (2000)
86. T.R. Rizzo, D.H. Levy, in *Laser Mass spectrometry*, edited by D.M. Lubman (Oxford University Press, New York, 1990), p. 403
87. R.T.T. Karaiste, I.M. Atkinson, J.A. Shorter, A.E.W. Knight, F.R. Knee, Anal. Chem. **65**, 2776 (1993)
88. F. Piuzzi, I. Dimicoli, M. Mons, B. Tardivel, Q. Zhao, Chem. Phys. Lett. **320**, 282 (2000)
89. L.C. Snoek, E.G. Robertson, R.T. Kroemer, J.P. Simons, Chem. Phys. Lett. **321**, 49 (2000)
90. G. Meijer, M.S. de Vries, H.E. Hunziger, H.R. Wendt, Appl. Phys. B **51**, 395 (1990)
91. R. Cohen, B. Brauer, E. Nir, L. Grace, M.S. de Vries, J. Phys. Chem. **104**, 6351 (2000)
92. F. Sobott, A. Wattenberg, W. Kleinekofort, A. Pfenninger, B. Brutschy, J. Fresenius, Anal. Chem. **360**, 745 (1998) and references therein
93. M.A. Tito, K. Tras, K. Valegard, J. Hajdu, C.V. Robinson, J. Am. Chem. Soc. **122**, 3550 (2000)
94. L.-S. Wang, C.-F. Ding, X.-B. Wang, S.E. Barlow, Rev. Scient. Instrum. **70**, 1957 (1999) and references therein
95. X.-B. Wang, L.-S. Wang, Nature **400**, 245 (1999) and references therein
96. S.E. Rodriguez-Cruz, J.T. Khoury, J.H. Parks, J. Am. Soc. Mass Spectrom. **12**, 716 (2001)
97. S.B. Nielsen, A. Lapierre, J. U. Andersen, U.V. Pedersen, S. Tomita, L.H. Andersen, Phys. Rev. Lett. **87**, 228102 (2001)
98. Ch.J. Thompson. J. Husband, F. Aguirre, R.B. Metz, J. Phys. Chem. A **104**, 8155 (2000)
99. T.G. Spence, T.D. Burns, G.B. Guckenberger, V. Posey, L.A. Posey, J. Phys. Chem. **101**, 1081 (1997)
100. D. Nolting, S. Zhang, S. Wiedemann, R. Weinkauf, Int. J. Mass. Spectrom. (in preparation)
101. R.J. Lippert, S.D. Colson, Chem. Phys. Lett. **161**, 303 (1989)
102. J.A. Dickinson, M.R. Hockridge, E.G. Robertson, J.P. Simons, J. Phys. Chem. A **103**, 6938 (1999)
103. Ch. Riehn, Ch. Lahmann, B. Wassermann, B. Brutschy, Chem. Phys. Lett. **197**, 443 (1992)
104. Ch. Janzen, D. Spangenberg, W. Roth, K. Kleinermanns, J. Chem. Phys. **110**, 9898 (1999)
105. A. Fujii, T. Sawamura, S. Tanabe, T. Ebata, N. Mikami, Chem. Phys. Lett. **225**, 104 (1994)
106. M. Mitsui, Y. Ohshima, A.-i. Ishiuchi, M. Sakai, M. Fujii, J. Phys. Chem. **104**, 8649 (2000)
107. M. Gerhards, M. Schiwek, C. Unterberg, K. Kleinermanns, Chem. Phys. Lett. **297**, 515 (1998)
108. C.E.H. Dessent, K. Müller-Dethlefs, Chem. Rev. **100**, 3999 (2000) and references therein
109. M. Okumura, L.I. Yeh, J.D. Myers, Y.T. Lee, J. Phys. Chem. **94**, 3416 (1990)
110. M.W. Crofton, J.M. Price, Y.T. Lee, IR Spectroscopy of Hyrogen Bonded Charged Clusters, in *Clusters of Atoms and Molecules II*, edited by H. Haberland (Springer, Berlin, 1994), p. 44
111. F.N. Keutsch, R.J. Saykally, Proc. Nat. Acad. Sci. USA **98**, 10533 (2001)
112. M. Okumura, L.I. Yeh, J.D. Meyers, Y.T. Lee, J. Phys. Chem. **94**, 3416 (1990)
113. N. Scolà, O. Dopfer, Chem. Phys. Lett. **342**, 191 (2001)
114. N. Scolà, O. Dopfer, J. Phys. Chem. A (2002, in press)

115. N. Scolà, O. Dopfer, Angew. Chem. (2002, in press)
116. P.M. Felker, J. Phys. Chem. **96**, 7844 (1992) and references therein
117. Ch. Riehn, A. Weickert, U. Lommatesch, M. Zimmermann, B. Brutschy, J. Chem. Phys. **112**, 3650 (2000)
118. L.A. Philips, S.P. Webb, S.J. Martinez III, G.R. Fleming, D.H. Levy, J. Am. Chem. Soc. **110**, 1352 (1988); F.J. Lovas, Y. Kawashima, J.-U. Grabow, R.D. Suenam, G.T. Fraser, E. Hirota, Astrophys. J. **455**, 201 (1995)
119. T. Korter, D. Pratt, J. Küpper, J. Phys. Chem. A **102**, 7211 (1998); S. Antolinez, A. Lesarri, S. Mata, S. Blanco, J.C. Lopez, J.L. Alonso, J. Mol. Struct. **612**, 125 (2002)
120. M. Schmitt, J. Küpper, D. Spangenberg, A. Westphal, Chem. Phys. **254**, 349 (2000)
121. F. Huisken, O. Werhahn, A.Y. Ivanov, S.A. Krasnokutski, J. Chem. Phys. **111**, 2978 (1999)
122. R. Weinkauf, J. Schiedt, Photochem. Photobiol. **66**, 569 (1997)
123. S. Xu, J. Michael Nilles, K.H. Bowen Jr, J. Chem. Phys. (submitted)
124. D.E. Folmer, E.S. Wisniewski, A.W. Castleman Jr, Chem. Phys. Lett. **318**, 637 (2000)
125. D.E. Folmer, L. Poth, E.S. Wisniewski, A.W. Castleman, Chem. Phys. Lett. **287**, 1 (1998)
126. E.W.-G.J.L. Herek, Z.H. Kim, A.H. Zewail, Science **279**, 847 (1998)
127. M.F. Jarrold, V.A. Constant, Phys. Rev. Lett. **67**, 2994 (1992)
128. D.E. Clemmer, J.M. Hunter, K.B. Shelimov, M.F. Jarrold, Nature **372**, 248 (1994)
129. P.D. Schnier, W.D. Price, E.R. Williams, J. Am. Soc. Mass Spectrom. **7**, 972 (1996)
130. W.D. Price, P.D. Schnier, E.R. Williams, Anal. Chem. **68**, 859 (1996)
131. W.D. Price, P.D. Schnier, E.R. Williams, J. Phys. B **101**, 664 (1997) and references therein
132. R. Mestel, Science **273**, 184 (1996)
133. S.B. Prusiner, Curr. Top. Microbiol. Immunol. **207**, 1 (1996)