

Role of quantum chemical calculations in molecular biophysics with a historical perspective

Alexander K. Kukushkin · Karl J. Jalkanen

Received: 14 August 2008 / Accepted: 2 August 2009 / Published online: 30 August 2009
© Springer-Verlag 2009

Abstract We discuss how the basic principles of quantum chemistry and quantum mechanics can be and have been applied to a variety of problems in molecular biophysics. First, the historical development of quantum concepts in biophysics is discussed. Next, we describe a series of interesting applications of quantum chemical methods for studying biologically active molecules, molecular structures, and some of the important processes which play a role in living organisms. We discuss the application of quantum chemistry to such processes as energy storage and transformation, and the transmission of genetic information. Quantum chemical approaches are essential to comprehend and understand the molecular nature of these processes. To conclude our work, we present a short discussion of the perspectives of quantum chemical methods in modern biophysics, the field of

experimental and theoretical chiral vibrational and electronic spectroscopy.

Keywords Molecular biophysics · Proteins · Nucleic acids · Quantum nanobiology · Quinones · Photosynthesis · Vibrational circular dichroism · Raman optical activity

1 Introduction: historical notes on quantum ideas and concepts in biophysics

This introduction is aimed at giving a short review of the development of quantum mechanical and chemical ideas and concepts in molecular biophysics. The formulation of the basic postulates of quantum theory was followed by publications discussing possible applications of this new theory to biology. Niels Henrik David Bohr and Erwin Rudolf Josef Alexander Schrödinger played a significant role in these discussions. In August of 1932 Bohr presented the public lecture at the International Congress of Light Therapists in Copenhagen in which he examined the significance of the *Principle of Complementarity* for understanding the fine organization of living organisms. This lecture was first published in “Nature” in 1933 [1]. Bohr wrote that, at a first glance, the essentially statistical nature of atomic phenomena contradicts the strikingly fine organization of living organisms. However, he found the properties of atomic processes that classical mechanics fails to describe, that find their place only within the complementary mode of description, to be as important for describing the behavior of living organisms as they are for describing the specific properties of inorganic matter. As an example of this, he cites carbon assimilation by plants, on which nutrition of animals so strongly depends. To

Dedicated to Professor Sandor Suhai on the occasion of his 65th birthday and published as part of the Suhai Festschrift Issue.

A. K. Kukushkin (✉)
Faculty of Physics, M.V. Lomonosov Moscow State University,
Vorobjevy Gory, 119992 Moscow, Russian Federation
e-mail: akouk@mail.ru

K. J. Jalkanen
Bremen Center for Computational Materials Science (BCCMS),
University of Bremen, Am Fallturm 1, 28359 Bremen, Germany

K. J. Jalkanen
Nanochemistry Research Institute (NRI), Curtin University
of Technology, GPO Box U1987, Perth, WA 6845, Australia

K. J. Jalkanen
Department of Molecular Biophysics, German Cancer Research
Center [Deutsches Krebsforschungszentrum] (DKFZ),
Im Neuenheimer Feld 580, 69120 Heidelberg, Germany

understand these phenomena one has to deal with and understand the individual steps of the photosynthetic processes. Analogously, the non mechanical stability of atomic structures is clearly exhibited in the properties of chlorophyll and hemoglobin, very complex chemical compounds playing fundamental roles in the mechanics of assimilation in plants and in animal respiration, respectively [1, 2]. Clearly, as early as 1932, Bohr imagined how the biophysics of photosynthesis would have to be described with the use of quantum theory.

Schrödinger devoted a book [3] to the relations between physics and biology. This book was based on the lectures he gave in February of 1943 in Dublin. In this work he discussed heredity problems in the context of quantum mechanics [3, 4]. Quantum mechanics was the first theoretical theory which accounted from first principles for the vast variety of possible aggregates/complexes of atoms and molecules actually encountered in Nature. Consequently, one may safely assert that there is no alternative for the molecular explanation of the heredity substance. In fact, these predictions helped stimulate future progress and advances in molecular biology by focusing on the quantum molecular nature of biology. This stimulated the investigation of biological processes both experimentally and theoretically at the molecular level, which of course required and still requires the development of better tools, methods, and instruments.

In 1935, while studying mutagenesis in *Drosophila* exposed to ionizing radiation, Timoféeff-Ressovsky et al. [5] determined the size of genes (as the size of the mutation regions) and hypothesized that genes are simple physicochemical units [5]. Frank and Teller [6] applied quantum mechanical ideas to study energy migration and photochemical action of solar energy absorbed in photosynthesis. Jordan [7] treated biological macromolecules as orderly organized solids and deduced their properties from the energy band structure. Using these considerations, he explained the action spectrum of photo inactivation of the enzyme urease and the mechanisms of gene interaction and mutation. Further progress in the adoption of the ideas and tools of atomic physics in biophysics was largely due to the works of Pauling and Corey [8], Watson and Crick [9], Franklin and Gosling [10, 11] in which X-ray crystallography helped decipher two of the most important biological structures, the α -helical structure of proteins and the double helical structure of DNA. Just a decade before, Szent-Gyorgui [12] suggested that proteins have the properties of semiconductors. This suggestion was followed by calculations of the protein energy spectrum made by Laki (cited from Ref. [13]) and Evans and Gergely [14]. This was the beginning of the second period (1955–1984) of spreading quantum concepts throughout the life sciences.

Experimental and theoretical methods of quantum physics were increasingly imported into biochemistry, biophysics, and molecular biology and became routine tools. The various optical methods (absorption spectroscopy, fluorescence spectroscopy, and Raman scattering) and radio spectroscopic techniques [electron spin resonance (ESR) and nuclear magnetic resonance (NMR)] were used in studies of the structure and properties of biologically important molecules. When the energy levels of biological molecules needed to be calculated, researchers used a simple quantum mechanical method of molecular orbitals proposed by Hückel (see Ref. [15]). The results achieved with this method were described in the monograph “Quantum Biochemistry” by Pullman and Pullman [15]. Later, molecular calculations were mostly done with the use of approximate methods based on the Roothaan and Roothaan–Hall equations. A comprehensive overview of quantum mechanical approaches in molecular biology can be found in the proceedings of a symposium [4] held at the Laboratory of Biophysics of Stanford University, March 1963, and in the collections of papers “Theoretical Physics and Biology” [16].

Significant advances in the theory of optical spectroscopy were made in 1956 when Moffitt [17] developed a theory of the exciton spectrum of absorption for α -helical polypeptides, which was based on Davydov’s exciton theory of light absorption in molecular crystals [18]. Calculations of the exciton spectra correctly described the splitting of the 190-nm band and the optical activity of α -helical structures [17]. In the early 1960s, Yomosa [4, 19] and Suard et al. [20] used the self-consistent field (SCF) approach to calculate (in a π -electron approximation) the electronic structure and the energy spectrum for the peptide group and for a polypeptide with H-bonds. The calculated results agreed well with the experimental spectroscopic data (cited from Ref. [4]), but were inconsistent with the theoretical estimates for the thermal energy of activation of electric conduction in proteins made by Cardew and Eley [21]. Their calculations abated the vigorous debate over the semiconductor properties of proteins, which were then thought to be essential for understanding the mechanism of enzyme catalysis in redox processes [16, 20, 21].

It was during this time that ESR spectroscopy, a method based on quantum physics, founds its way into biology. Biological applications of ESR received comprehensive coverage in the collection of papers entitled “Free Radicals in Biological Systems” [22], which included selected articles from the proceedings of a symposium held at Stanford University in March of 1960. To our knowledge, the ESR signal from a biologically important substance was obtained for the first time in 1954 by Commoner et al. [23] in experiments with various lyophilized specimens of biological origin. When they began their work, only a

low-sensitive spectrometer was at their disposal, and they could not then study specimens without subjecting them to lyophilization. A variety of tissues were studied: plant leaves and roots, muscle, brain, liver, lung tissue, myocardium, kidneys, and frog eggs. For all specimens, the concentration of free radicals was determined per gram of dry weight. Free radicals appeared to be most abundant in tissues with high metabolic rates, such as green leaves, liver, and renal tissue. Numerous research papers followed this pioneering study. Gordy et al. [24] recorded ESR signals from irradiated amino acids and proteins. Ehrenberg [25] and Beinert (cited from Ref. [22]) described ESR spectra of model semiquinones and flavin-dependent enzymes. Free radicals were detected in live, functional plant and animal cells [26–28]. Overall, those studies produced new insights into the mechanisms of redox processes in mitochondria and chloroplasts [29].

In the early 1960s, low-temperature radiospectroscopic studies of photosynthetic objects provided evidence of the electronic nature of the primary events in photosynthesis. In this context, of particular interest, is a study by Sogo et al. [28] reporting a result that came as a surprise. It turned out that the rise time of the ESR free radical signal recorded upon illumination of chloroplasts at room temperature was approximately equal to that at -140°C . This observation suggested the purely electronic nature of this signal, obviously unrelated to diffusion-controlled processes. Two years later, Sogo et al. [29] showed that the ESR signal at $g = 2.0025$ detected previously [28] in *Rhodospirillum rubrum* chromophores could be also observed at 77 K. This fact was thereafter confirmed with optical methods. Arnold and Clayton [30] described reversible changes in absorption at 420 nm during illumination of *Rhodobacter sphaeroides* chloroplasts at 1 K. Soon afterward, Chance and Nishimura [31] detected temperature-independent cytochrome oxidation in the purple photosynthetic bacterium *Chromatium* and then determined the cytochrome oxidation rate as a function of temperature down to 30 K [32].

In their study of 1966, De Vault and Chance [32] interpreted the accumulated data, suggesting a tunneling mechanism for electron transfer (ET) from cytochrome to bacteriochlorophyll (BChl) in *Chromatium*, and estimating the rate of this process using the known formula for the probability of a quantum particle tunneling through a barrier. This was the first evidence for the existence of a purely quantum mechanical effect in photosynthesis (in addition to the photon absorption by the pigments). After that study by De Vault and Chance [32], many theoretical descriptions of the experimentally obtained temperature dependence of the ET rate were developed that employed and made use of various assumptions, see for example, Chernavsky and colleagues [33, 34], Hopfield [35], Jortner

and colleagues [36–38], Dogonadze et al. [39], Petrov and colleagues [40], and Sarai [41]. For reviews of studies addressing the basis of ET in biological systems, see Jortner [42] and Petrov [13].

Yet another phenomenon that was discovered during this period was damped oscillations. Experiments showing damping oscillations in the oxygen flash yield with flash-illuminated plant preparations, the oscillation period being equal to four flashes, needed to be explained and understood [43, 44]. To explain this phenomenon, Kok et al. [45] put forth a hypothesis that the water-splitting oxygen-evolving system in plants can exist in different discrete states. By that time, picosecond techniques made it possible to study the temporal characteristics of the events involved in the primary charge separation in bacterial reaction centers [46, 47]. The data obtained provided evidence that quantum transitions between discrete states take place during photosynthesis.

More recently, the photosynthetic reaction center from the purple bacterium *Rhodospseudomonas viridis* was determined by new crystallographic techniques by Deisenhofer et al. [48]. The bacterial reaction center became the first of the protein complexes of photosynthetic membranes whose structure was known at a resolution of 3 Å. This was a major breakthrough in the field. Knowledge of the spatial structure of the photosynthetic reaction center resulted in new problems and questions coming to the forefront. Their solution brought interesting and unexpected results. First, in the course of very complicated femtosecond spectroscopy measurements, a fast process of ET from the excited primary electron donor to the primary acceptor was detected. Its time constant was estimated at 3 ps at room temperature. Moreover, on cooling down to 10 K, this process becomes 1.5–2.0 times faster [49–51]. Second, shortly thereafter, quantum oscillations of electron donor fluorescence in the spectral region from 695 to 930 nm were revealed by Vos et al. [52–54] in the bacterial reaction center, which have a period of 260 fs.

These findings caused a flow of theoretical studies in which quantum mechanical approaches were used to describe the characteristics of ET obtained in experiments. For example, the explanations given by Bixon [55] and Michel-Beyerle et al. [56] were based on the Marcus theory of the electron transport [57]. They quantitatively described the mechanism of charge separation in the bacterial reaction center. Specifically, they derived a formula for the rate of ET and provided a rationale for why this process is unidirectional. The term unidirectional is commonly used to describe a fast ET along the electron carrier chain within the protein subunit L of the reaction center. According to Michel-Beyerle et al. [56], this effect is accounted for by an interaction of electron donors and electron acceptors with polar groups of the proteins and by asymmetry (in the sense

of M and L chains) of polarizing Coulomb interactions. The electrostatic control of ET in the bacterial reaction center was also addressed by Parson et al. [58]. Molecular displacements during charge transfer (CT) were computed by standard molecular dynamics methods [59]. Using the density matrix operator, Mukamel and colleagues [60] made calculations of ET by superexchange between the electron donor and the primary acceptors in the bacterial reaction center. A vast literature on various aspects (including quantum ones) of ET in the reaction center was reviewed in Shuvalov's book [61].

2 Quantum chemical properties of biologically important substances

Biophysical studies applying quantum chemical methods can have various foci. There are works which focus on the electronic properties of biological substances for an explanation of the experimental data, those which focus on the correlation between the structure and biological activity, and finally those which focus on understanding biophysical processes occurring at the molecular and sub-molecular level.

2.1 Quantum mechanical calculations for proteins, peptides, and model systems

Calculations of the electronic properties of proteins relate to the semiconductor hypothesis concerning proteins [10] and to the experiments of Cardew and Eley [21]. First, Evans and Gergely studied the π -electron structure of a network consisting of peptide groups [14]. They used the linear combination of atomic orbital (LCAO) molecular orbitals Hückel molecular orbital (HMO) approximation, and assumed that the π -electron system was composed of $2p_z$ -orbitals of carbon, oxygen, and nitrogen atoms. The energy levels obtained were classified into three bands of width of approximately 0.1–0.3 eV. The lowest bands were occupied by electrons and the highest orbital was empty. The values of the energy gap between the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) (highest occupied and lowest unoccupied bands), the so-called HOMO–LUMO gap, were calculated to be 3.05 eV (410 nm) and 4.23 eV (290 nm) for the cases of trigonal (tr) and pyramidal (pyr) symmetry of the nitrogen atom, respectively. The width of the bands depended on the resonance integral value β_{NO} between the neighboring peptide groups, which is very sensitive to the length of the H-bonds. Because of the very small value of β_{NO} (–0.2 eV), it may be expected that the centers of the bands are approximately equal to the energies of three molecular orbitals of the isolated peptide group (in eV);

$\varepsilon_1 = -15.99$ (tr N), -16.8 (pyr N); $\varepsilon_2 = -12.77$, -14.03 ; and $\varepsilon_3 = -9.39$ and -9.60 , respectively. These results were supported by the experimental investigation of the temperature dependence of the electroconductivity by Cardew and Eley [21]. The values of the HOMO–LUMO gap calculated for glycine, polyglycine, and hemoglobin were 2.92, 3.12, and 2.75 eV, respectively. However, the predicted optical absorption in the region of 290 and 410 nm for diglycine, triglycine, or polyglycine was not seen in the experimental absorption spectra [21].

The contradictions between the optical spectral simulations and the results of Cardew and Eley's experiments demanded new and better quantum chemistry calculations. Such calculations were carried out using more advanced methods in France by Suard and colleagues [20, 62, 63]. In these works the study on the electronic structure of proteins has been carried out for the determination of the width and positions of the energy bands produced by the interaction of the π -electron systems of the peptides through H-bonds. In doing so, the isolated peptide group has been considered as a six-electron system, including the four conjugated π electrons of CONH peptide moiety and the perpendicular lone-pair (n) of the carbonyl oxygen. Two peptide groups connected through an H-bond are thus represented as a 12-electron system and so on. The method applied in that work was the self-consistent treatment of Roothaan [64], in which the approximations of Pariser and Parr [65] have been used in an improved manner [20] with the help of a Löwdin's orthogonalized set of atomic orbitals [66]. The main conclusions from this work are the following. The energy band width obtained by an SCF treatment is considerably larger than that obtained by Evans and Gergely [14] (of the order of 1 versus 0.25 eV in the Hückel approximation). The lowest transition energy shows only very small variations as the number of peptide units increases. This result corresponds to the lack of an observable displacement of the longest wave length of absorption in proteins with respect to that of mono-peptides [67]. The energy gap for the singlet–singlet transition is of the order of 5 eV, a result which seems to forbid the possibility of an intrinsic semiconductivity in proteins.

A similar investigation of the electronic structure of peptides and proteins was carried out by Yomosa [19]. Using the zero-integral-overlap approximation within the Roothaan method the energies of the one electron molecular orbitals were (in eV): $\varepsilon_1 = -15.34$; $\varepsilon_2 = -11.25$; $\varepsilon_3 = -0.93$. The excited states of the peptide group had energies: ${}^1E_{2\rightarrow 3} = 6.672$; ${}^3E_{2\rightarrow 3} = 2.603$; ${}^1E_{1\rightarrow 3} = 10.058$; ${}^3E_{1\rightarrow 3} = 6.937$. By introducing an interaction between these configurations, the energies of the excitations (in eV) were: ${}^1E_- = 6.547$ (189.5 nm); ${}^1E_+ = 10.182$ (121.8 nm); ${}^3E_+ = 2.306$; ${}^3E_- = 7.234$.

The experimental absorption data gives values of 197 nm for dimethylformamide and 185 nm for glycine, respectively. Thus sufficient agreement exists between the calculated and experimental values of the oscillator strengths of the corresponding transitions. In the work of Yomosa the energy structure of the infinite crystal of peptide groups bonded by H-bonds were calculated. The width of the first triplet exciton zone with center near 2.58 eV turned out to be equal to 10^{-5} eV, the second singlet zone (the center near 6.65 eV) to be 0.47 eV; and the zone of conductivity (near 10.2 eV) to be 0.21 eV. These data clearly showed that the intrinsic conductivity of proteins is impossible. Subsequently, the authors of experiments [21] were shown not to have taken into account some complicated experimental circumstances such as ionic and surface conductivity of the samples. Later on, calculations taking into account the 2p and 3d-orbitals of the peptide group [13] were carried out. However, it is necessary to note that for these calculations the investigators did not take into account the polarization of the surrounding media by the excess charge. Taking these effects into account could change the position of conductivity zone. Lyons has pointed out the necessity to take into account the polarization effects for studies of organic molecular crystals [68]. The quantitative estimation of the energetic spectrum of the polar states for organic crystals of conjugated hydrocarbons was fulfilled by Blumenfeld and Benderskiy [69]. The spectrum of the polar states for a network of peptide groups was calculated in [70]. From these estimates it was determined that the energy level corresponding to conductivity zone has an energy ($\Delta E = 3.1$ eV) greater than the energy of the ground state of the system. This is smaller than the gap determined by Yomosa [19]. Recently, it has become apparent that the next problem to address is how to best determine and take into account the role of the protein surroundings on the electronic properties in the primary photosynthetic processes under low temperatures [71] and also later, at room temperature, where things get even more complicated.

2.2 The quantum chemistry studies of the nucleic acids

The quantum chemical studies of nucleic acids may be divided into three parts. In the first part the scientists have studied the electronic and optical properties of the components of native nucleic acids. One important example is Tinoco's paper "Hypochromism in Polynucleotides" [72]. In this paper the author proposed the first explanation of hypochromism where the native DNA has about 30% less absorption at 260 nm than the denatured sample.

Tinoco supposed that it takes place because of the energy migration between the adjacent pairs of bases. This phenomenon is explained by the anisotropy of tensor for

the dipole–dipole interaction. Using perturbation theory, he gave the following formula for hypochromic effect:

$$\frac{F_{oa}}{f_{oa}} = 1 - \frac{k\lambda_{oa}^2 f_{oa}}{N} \sum_{i=1}^N \sum_{j \neq i}^N G_{ij} \vec{e}_i \vec{e}_j - \frac{4k\lambda_{oa}^2}{N} \sum_{a' \neq a} \sum_{i=1}^N \sum_{j \neq i}^N \frac{G_{ij} \vec{e}_i \vec{e}_j f_{oa'} \lambda_{oa'}^2}{\lambda_{oa}^2 - \lambda_{oa'}^2} \quad (1)$$

In this formula the author used the notations.

F_{oa} the oscillator strengths for polymer per one chromophore in absorption band oa

f_{oa} the oscillator strengths for monomer chromophore in absorption band oa

$$f_{oa} = \frac{2303mc^2}{\pi e^2 N_0} \int \varepsilon_{oa} d\omega = 4.32 \cdot 10^{-9} \int \varepsilon d\omega,$$

k is a constant value, which equals $3e^2/8\pi^2 mc^2$.

λ_{oa} the wavelength (A°) of absorption maximum for monomer in bands oa

G_{ij} the tensor dipole–dipole interaction

$$G_{ij} = \left[\vec{e}_i \vec{e}_j - \frac{3(\vec{e}_i \vec{r}_{ij})(\vec{e}_j \vec{r}_{ij})}{r_{ij}^2} \right] \frac{1}{|\vec{r}_{ij}|^3}$$

\vec{e}_i, \vec{e}_j the unit vectors in the directions of the transition moments in the chromophores i and j

\vec{r}_{ij} the distance between centers of chromophores i and j

Tinoco applied this formula to calculate the hypochromic effect for native DNA. Based on the formula, Tinoco calculated the value of F_{oa}/f_{oa} as function of the angle φ between the axis of symmetry of the bases and the direction of H-bonds in the base pair under consideration. At the same time the angle φ changed from 0 to π . At $\varphi \approx 60^\circ$, the ratio of the oscillator strengths becomes equal to 0.7. This corresponds to a hypochrome effect of about 30%. This value coincides with the one determined for native DNA. The derived function permits one to determine the direction of the dipole transition moment lying in the plane, which is perpendicular to the DNA axis.

Subsequently a similar approach was applied by Rhodes [73]. Applying first-order perturbation theory, he derived an expression which relates the hypochromism to the geometry of the transition moments of the mononucleotide residues in the polymers. Additionally, the hypochromism of biopolymers was considered by DeVoe [74]. He presented a local-field treatment of hypochromism that is physically equivalent to Tinoco–Rhodes consideration, but which may be easier to introduce intuitively. In addition,

DeVoe studied the contribution of the solvent to hypochromism. It may be noted that Nesbet [75] and Bolton and Weiss [76] pointed out that Tinoco and Rhodes derived their equivalent hypochromism formulas by assuming strong coupling, which is not present in DNA. Going back to the original work of Kirkwood [77] Tinoco corrected both his formulas as applied to polymers [78] and polynucleotides [72]. See the erratum of references [72] and [78] for the complete set of original equations and the newly derived/corrected equations. We have presented the original equation in Eq. 1. The correction in Ref. [72] is as follows:

$$\frac{F_{oa}}{f_{oa}} = 1 - \frac{4k\lambda_{oa}^2}{N} \sum_{a' \neq a} \sum_{i=1}^N \sum_{j \neq i} \frac{G_{ij} \vec{e}_i \vec{e}_j f'_{oa'} \lambda_{oa'}^2}{\lambda_{oa}^2 - \lambda_{oa'}^2} \quad (1 \text{ correction})$$

The quantum chemistry properties of the nucleic acids and their constituents were studied and discussed by Pullman and Pullman [79]. They used conventional Hückel theory to calculate the electronic characteristics of biologically important molecules. Subsequently, Veillard and Pullman [80] produced π -electron calculations using the semi-empirical antisymmetrized molecular orbital (ASMO) SCF method [65, 81]. Later, Bradley et al. [82] used united Veillard–Pullman π charges with σ -charges determined by the method of Del Re [83] to get a set of net charges summarizing both σ and π contributions. To eliminate the shortcomings in these methods Rein et al. [84] proposed the iterative extended Hückel method which led to further improvement.

Using this method Rein et al. [84] calculated atomic charge distributions for nucleotide bases, dipole moments and the orbital energies of the LUMO and HOMO. Analyzing the energy of highest occupied π orbitals of nucleotide bases, the authors noted that the highest occupied orbital was not always of π symmetry.

Although some interesting and exciting electronic properties of nucleic acids have been obtained using the Hückel method, there still exists some non-uniqueness due to choice of the parameters used in this and other semi-empirical methods. This can be seen by comparing the results of the various works [85, 86] where different sets of parameters were used. Moreover, some properties of nucleic acids, such as the electronic absorption spectra (the energy of the transitions in triplet states), require the application of more accurate methods, for example, the SCF methods: unrestricted Hartree–Fock (UHF), time-dependent density functional theory (TDDFT); and finally Greens functions integral approaches.

Many such studies were undertaken by a strong group of Ukrainian scientists [87–92]. In these papers the following problems were attacked. Danilov et al. [87] studied the

π -electron structure the Watson–Crick base pair by the methods of the SCF in the Pariser–Parr–Pople (SCF-PPP) approximation [65, 81]. The ground and excited states were investigated. The authors determined the H-bond contribution to the energy of the base pair, and the energies of singlet and triplet transitions. Moreover, the CT states were discussed in connection with the proton tunneling in DNA and problems involved in mutations, aging, and tumors [93]. These results were discussed in the light of proton transfer along H-bonds.

In Ref. [88], the tautomerization of bases was investigated using the SCF-PPP approximation. The authors estimated the rate constant for tautomeric transformation. They came to the conclusion that transformation is possible only for the excited states of base pairs. Danilov et al. [89] considered the electronic aspects of photodimerization of the nucleic acid bases. As is well known, the ultra violet irradiation of bacteria and phages brings about mutations and lethal destruction. As a rule, the mutations are composed of transition from G–C to A–T and possibly deletions and insertions. On the molecular level these processes are explained by the intra- and intermolecular photodimerization. It is known [94] that the photodimerization of the bases takes place in the triplet states of bases. That's why the authors of this paper carried out the calculations studying the electronic characteristics of the pyrimidine bases in their lowest excited states. They used the SCF method for open shell systems because using this method one obtains different wave functions for the excited singlet and triplet states. Moreover, this method permits one to calculate the characteristics of the ground and excited states in the identical approximation. The authors calculated the π -bond orders for the lowest triplet states of thymine (T), uracil (U), and cytosine (C), and in addition, the bond orders and the electron density on the atoms C₅ and C₆ were determined (see Fig. 1 below for atom numbering, reproduced from Ref. [90], same number scheme as used in Figure 1 in Pulman [95] and in Figure 4.4 in Lewin [96]). It turned out that in the triplet state, the bond order of the C₅–C₆ bond strongly diminishes and favors the dimerization reaction [97]. This is consistent with UV damage to DNA via dimerization, which is repaired by the photolyase class of proteins in the presence of blue light. The energy of the first singlet transition for thymine was found to be 4.71 eV, which is in good agreement with the experimental result.

In Ref. [90] the π -electron structure of the base pairs was calculated using a semi-empirical SCF method; more precisely, the energetic characteristics of the ionized states of the base pairs were calculated. The values of the ionization potential (IP) and electron affinity (EA) were

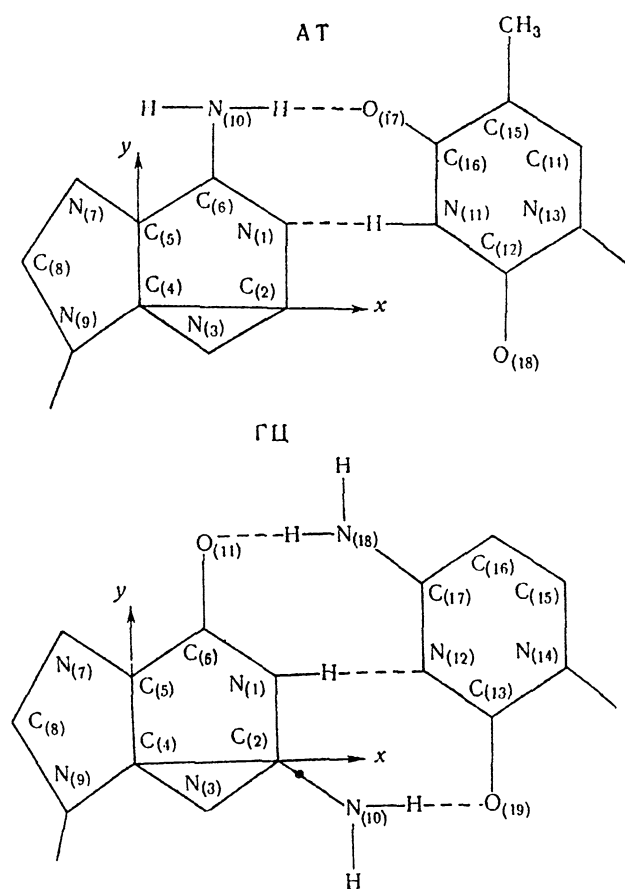


Fig. 1 Atom numbering for adenine–thymine (A–T) and guanine–uracil (G–C), reproduced from Ref. [90]

calculated by using the wave functions for the cation and anion constructed from the molecular orbitals for the ground and excited state orbitals obtained using open shell methods. The authors calculated the values of the IPs and the EAs for adenine (A), A–T and guanine (G), G–C base pairs and the π -electron density on all of the atoms.

These results demonstrated that the electron donating and electron accepting capabilities of the G–C pair are larger than those of the A–T pair. A comparison of the electron density in the cationic and ground states showed that in the transition to the cationic state the electron density changes mainly in the purine bases on atoms C₅ and C₈ of the A–T and the G–C pairs, respectively. This means that the electron donor of the A–T pair is an adenine, and the electron donor of G–C pair is a guanine. Considering the anionic and ground states, one can see that the acceptors of the electrons are the pyrimidine bases. In this case the largest change of the electron density takes place on the C₁₄ and C₁₆ atoms of the A–T pair, and on the C₁₅ and C₁₇ atoms of G–C pair, respectively. See atom numbering in Fig. 1 and Ref. [90]. During the transition of the base pairs from the unionized to the ionized state, the

essential changes in the electron density takes place on the proton-donor and proton-acceptor atoms of the same H-bonds. In doing so, these changes bring about an alteration/change in the form of proton potential curve and, consequently, a change in the proton transfer process along the corresponding H-bond, see for example the hypothesis due to Löwdin [93].

In Ref. [92] the electronic structure of the DNA base pairs in the excited states was considered relative to Löwdin's hypothesis about the mechanism of mutations [93]. The history of this question is the following. Löwdin assumed [93, 98] that due to the absorption of ultra violet radiation by a DNA molecule it is possible that the rate constant for proton tunneling strongly increases. The changing proton position in the H-bond may be induced by alternation of the form of the proton potential energy curve because of redistribution of the electron density in the molecule. In Refs. [99–101] the authors studied the electronic structure of the molecular state corresponding to the electronic transition from the HOMO to LUMO. It was shown that this state is the state with the CT. The study of proton potential curve showed that in the excited state the rate constant of proton tunneling strongly increases. These results were used for the explanation of mutagenic effect of ultra violet light. However, in Ref. [87] it was shown that the lowest energetic state of system under consideration was not the state containing the transition $n \rightarrow n + 1$, but the state in which the excitation is localized on the one of the two bases. It turns out that the results in Refs. [99–101] are related to higher excited levels; the authors investigated the electronic structure of the excited triplet and singlet states by the semi-empirical ASMO SCF method taking into account the interaction of 24 singly excited configurations. For the T₁ state of two pairs the excitation completely localized on the pyrimidine base, namely on the C₁₄–C₁₅ bond. In so doing the electron densities on the donor and acceptor proton atoms practically do not change. The phenomenon also takes place for the S₁ state pair for A–T and G–C. That's why the excitation of these pairs does not bring about an increasing rate constant of proton tunneling. The excited singlet and triplet states of the adenine–thymine and guanine–cytosine base pairs were estimated using the configuration interaction method and the SCF open shell method in a semi-empirical approximation [91]. The determined values of the singlet–singlet transitions agreed with the experimental results, and it was shown that the forming of a pair from separate bases does not lead to an essential change in the strength of the first absorption band and therefore can not explain the hypochromic effect in DNA. The value of the transfer charge for the first singlet excited state is calculated to be 0.1 for A–T pair and 0.18 for G–C pair (in the electron charge units), respectively. The CT in the lower triplet state is negligibly

small. The participation of the first excited singlet and triplet states in proton tunneling appears to be a highly unlikely mechanism for photo-induced mutation.

The calculations of ground state potential energy curves for the nucleic bases relative to the problems of tunneling and tautomeric equilibrium were made by several groups of workers [102, 103]. However, the results obtained by the different approximations were not always in agreement. Using a semi-empirical SCF approximation Rein and Harris [102] have found a double well potential in both a model that did not include the possibility of tautomeric displacements in the two N–H...O–H-bonds, and in a model which involves simultaneous rearrangements involving more than one H-bond of the guanine–cytosine base pair. Analogous results were obtained by Blizzard and Santry [104]. By applying an ab initio method it was later found that a calculation which contains only one H-bond turns out to yield no double-well [103]. These contradictions were considered by Maranon and Sorarrain in Ref. [105]. The calculations were made using the CNDO/2 approximation. The calculations were performed with the proton placed at various points along the axis of their respective H-bonds. In order to consider the effects of cooperativity on the doubly H-bonded structure, the computations were first previously restricted to nuclear configurations which could arise from single displacement of the proton under consideration and then simultaneous displacements of both protons were analyzed. The results of this work are as follows. In the first case, for the single displacement of the two protons there is not a double well potential curve. The changes of the potential energy for the simultaneous displacement of proton of two H-bonds between adenine and thymine do have double well character. The height of the barrier was 3.75 eV. The analysis of the structure of the eigenvectors involved in the observed optical transitions has shown that the π lone-pair orbitals are perhaps the main contributors to the formation of the H-bonds. The estimation of the magnitude of the equilibrium constant between the normal and tautomeric forms ($K \approx 10^{-32}$) showed that the simultaneous double proton tunneling tautomerization is rare and negligible. That's why it is not a cause of error in the cellular reproduction.

The interesting results, received by the complete active space with second-order perturbation theory (CASPT2) method, based on the second-order Møller–Plesset perturbation theory (MP2) applied on a complete active space SCF reference wave function, mean that the conical intersection of the energy hypersurfaces for the ground state and the $^1(\pi\pi^*)$ state is responsible for ultrafast decay of singlet excited state of cytosine [106]. In Ref. [107], it was shown that the fluorescence lifetimes of DNA and RNA nucleosides fall on the subpicosecond time scale.

This is an efficient waste of energy in order to prevent photoreactions of unwanted lethal consequences.

Quantum chemistry calculations have played an important role in studying the structure of nucleic acid structure. In 1980s it was shown that the physical properties, conformations and the biological functions in many respects are determined by the non-bonded interactions [108]. The non-bonded interactions were calculated using atom–atom potential functions having the form:

$$U(r_{ij}) = (e_i e_j) / (\epsilon r_{ij}) - A_{ij} r_{ij}^{-6} + B_{ij} r_{ij}^{-12} \quad (2)$$

$$U(r_{ij}) = (e_i e_j) / (r_{ij}) - A_{ij}^{(10)} r_{ij}^{-10} + B_{ij}^{10} r_{ij}^{-12} \quad (3)$$

Equation 2 was used for calculating all the non-bonded atom–atom interactions except those non-bonded interactions between the atoms involved in H-bonds (the hydrogen atom and the hydrogen acceptor, either an oxygen or a nitrogen atom), for which Eq. 3 was used. In Ref. [109] the procedure of parameter choice (A_{ij} and B_{ij}) was proposed on the theoretical basis the experimental data about the types and energies of intramolecular interactions in the crystals and complexes of nucleic acids components. The atomic charges used in Eqs. 2 and 3 were obtained by quantum chemistry methods. The effective charges on atoms the authors [108, 109] have received by summation of the π -electron charges, determined by the Hückel method [109], and σ -electron charges, calculated with help of parameter suggested by Berthod and Pullman [110]. By using these new non-bonded atom–atom potentials for calculating the non-bonded interactions, important and new results were obtained. Possible mechanisms involving intermediate mis-pairings errors in biosynthesis of nucleic acids were studied. Here one used non-bonded interaction energy calculations to investigate possible mis-pairings, to investigate possible conformational changes of the double helix within A- and B-families of nucleic acids, and to analyze the conformations of the nucleic acid fragments containing nucleotide mis-pairings. Finally the parameter and potential choice for calculation of the energy of non-bonded interactions in nucleic fragments was investigated. These results led to the use of a separate potential for the non-bonded interactions involving H-bonded atoms.

Subsequent researchers have also developed separate non-bonded potentials for calculating the non-bonded interactions for H-bonding. What has been a real challenge is to be able to reproduce the cooperative effects involved in H-bonding and the CT. The dipole moment of molecular gas phase water molecules and bulk water molecules are very different. Hence Jorgensen and coworkers have developed the optimized potentials for liquid simulations force field. Other groups have tried to implement polarizable atoms in their force fields. A general theory which adequately treats these all of these effects for the both the

ground and all excited electronic states has not yet been found. There are many different solutions to this problem, none being highly general and transferable. There are many force fields developed for only water, and one must choose a potential to use not only for water, but also for all the bonded and non-bonded interactions for atoms within large biomolecules, between them for the non-bonded interactions, and finally also between the atoms in the molecules and the solvent. Experimental neutron diffraction data has shown that the water molecules near the protein and nucleic acid surface are different from bulk water molecules. Hence the possibility to have different kinds of water molecules in one's experiment and in one's simulation, and hence different potentials for different types of atoms. The whole concept of molecular mechanics force fields is based on being able to parameterize the intermolecular and intramolecular interactions. Quantum mechanics has been used for the intermolecular potentials, but has failed in determining the non-bonded potentials, due to an inability to accurately calculate the dispersion forces and interactions by Hartree–Fock and most density functional theory (DFT) level calculations. Here the experimentally determined non-bonded interaction potentials have been more accurate than those derived from theory. But one requires very good experimental data to derive the non-bonded potentials experimentally. This data is available for amides and proteins, but not for all types of molecules. With the recent development of *ab initio* DFT methods by the Bartlett group [111], so-called optimized effective potentials for electron correlation, this may change. But to date, no systematic derivation of the non-bonded potentials for all of the various atom types used in molecular mechanics force fields with all other atoms has been undertaken. Clearly such work is very important. In addition, for heavy metals, relativistic calculations are required. Relativistic pseudopotentials have been developed for many heavy atoms, but not for all. And these relativistic pseudopotentials involve some parameterization, so one is able to reproduce with relatively good accuracy the experimental data one has used in the parameterization. But as one has seen with molecular mechanics force fields and various exchange–correlation (XC) functionals which did not include vibrational frequencies during their development, one can produce/derive a set of potentials, parameters and XC functionals which reproduce one or more property, but do pretty bad for other properties. Hence the problem is one of generalizability and transferability.

The main results of the early sub-molecular studies [109, 112–115] are the following. All types of base pairs in the tautomeric forms could be incorporated into the double helix with no short interatom contact arising and without drastic changes of the sugar–phosphate backbone. All known experimental data on spontaneous errors in nucleic

acid biosynthesis could be explained by formation of such pairs.

New insight into the nature of the electronic spectra of nucleic acid bases came with the work of Hug and Tinoco Jr [116]. Earlier explanations for the electronic properties of nucleic acid bases were based on separate σ - and π -electronic structure calculations. However, it is known that π -electron estimations do not take into account the polarization of the σ core that is important in molecules containing several different hetero-atoms. In the early works one only used single Slater determinant descriptions for describing the excited states which included all valence electrons [117, 118]. However, a single Slater determinant description of the excited states of benzene and other aromatic molecules is qualitatively insufficient. Hence in Ref. [116] the authors calculated the spectra of nucleic acid bases, their tautomers, and ions with an all valence electron SCF-MO method (CNDO-CI) that included configuration interaction for the excited states. As a basis set the authors used 1s orbitals for hydrogen atoms and 2s, 2p Slater orbitals for atoms in the first row. The singly excited configurations are obtained by using the virtual orbitals of the ground state calculation. The 120 configurations which are lowest in energy were used. It was shown that the spectra of pyrimidine and purine bases can be divided into two groups, namely the cytosine and uracil type and adenine and hypoxanthine type. Due to an additional proton at one of the nitrogen atoms of the six-membered ring, uracil and hypoxanthine type spectra differ from cytosine and adenine type spectra. In pyrimidine bases, the presence of this proton leads to an increase in intensity of the transition lowest in energy and a decrease in intensity and shift toward higher energy of the second level to lowest one. In purine bases the excited states are more similar to those of purine itself but distinctly different from those of the underlying indole system. Adenine-type spectra are characterized by the fact that the lowest transition is localized mainly at N₇=C₈ in the five-membered ring, whereas the transition spreads out over the fragment C₂=N₃-C₄=C₅-N₇=C₈ and corresponds to the lowest transition in triene. In hypoxanthine-type spectra these two transitions are interchanged. Protonation at N₇ in the five-membered ring reverses this change and leads back to an adenine type spectra. The results of this article showed that not only $n \rightarrow \pi^*$ transitions, but also $\pi \rightarrow \pi^*$ transitions, are profoundly affected by protonation and tautomerization.

The mispairing ability of a nucleotide base analog, N⁴-aminocytosine, was considered in work [119] by an *ab initio* molecular orbital method. The structures of the isomers of N⁴-aminocytosine were optimized with the 3-21G basis set by use of gradient optimization techniques. This basis was used for the calculations of relative energies and dipole moments. N⁴-aminocytosine, a nucleotide

analog of cytidine, is a potent mutagen. It can be incorporated as a residue in DNA, causing transitions from AT to GC and from GC to AT. The calculations of the energies and dipole moments of isomers of N^4 -aminocytosine have shown that N^4 -aminocytosine might exist as any of the four isomers under influence of some other components in its vicinity. This possibility may be the origin of the mutagenic activity of N^4 -aminocytosine. In results of calculations it was shown that the G–C-like base pair becomes more stable than G–C base pair itself when N^4 -aminocytosine is incorporated instead of cytosine. However, an A–T-like base pair becomes less stable than A–T base pair itself when imino-E form of N^4 -aminocytosine is substituted for thymine. The authors remarked that this might be related to the effects of the incorporation of N^4 -aminocytosine in DNA replication.

Tarashima studied optical anisotropy of synthetic polynucleotides [120]. In Ref. [120] the π -electron polarizability of uracil and adenine was considered, and it was shown that the index of refraction in the visible and ultraviolet region plays an essential role in birefringence. Helical polynucleotides have been shown to have a negative birefringence. This means that the refractive index along the minor axis is larger than one along the major helical axis. The larger transverse polarizability of helical polynucleotides originates from the base pairs which are stacked with their molecular planes normal to the major helical axis. That's why the negative birefringence is a reflection of the base stacking. Moreover, polarizability plays a part in molecular interactions as a component of the van der Waals forces. In Refs. [121, 122] it was shown that the stability of double helices originates from the stacking energy of bases rather than the H-bonds. The stacking energy is determined by dipole–dipole, dipole–polarizability, and polarizability–polarizability interactions. In Ref. [120], the Hückel method and the SCF are used for the calculations of polarizability. The theoretical values obtained by the Hückel method are consistently larger than the experimental results. The results obtained with SCF theory are in good agreement with observed values. It shows that the SCF method is better than the Hückel method for the calculation of polarizability. The polarizability of the adenine–uracil pair estimated as the sum of the polarizabilities of adenine and uracil is compared with solving the eigenvalue problem for the A–U pair as an entity. The latter method gives considerably larger polarizability than the first method. Comparison of the calculated and experimental data for the two methods shows that the latter method is the superior when it comes to estimating the polarizability of the A–U pair. The transition moment of the A–U pair decreases in comparison with the sum of the transition moments of A and U. On this basis, the author has suggested that the delocalization of

π -electron through the H-bonds may be part of the cause for hypochromism.

In addition to the electronic properties of DNA presented in Refs. [123, 124], one-dimensional models have been applied to calculate the energy bands of the delocalized electrons in DNA [125]. The single site potentials used for the calculations are (1) the δ -function or (2) the harmonic oscillator potential. The parameters of these potentials are defined by fitting the experimental value of 2.42 eV for the band gap. The authors studied the periodic diatomic chain with such potentials, and a disordered chain in the quasi-periodic or virtual limit. The relevant gap for a pure A–T chain is 2.296 eV, for a pure G–C sequence the gap is 1.816 eV. Afterwards, the authors replaced the disordered chain by an ordered one with each site carrying a potential which is the average of the different types of potentials. Thus, for the δ -function chain this procedure gave an energy gap of 2.057 eV, and for the harmonic oscillator case the energy gap is 2.056 eV. However, when considering the possibility of charge transport in DNA there are many contradictions within standard ET theory [126–128].

Muon spin relaxation studies of DNA have revealed distinct differences in the behavior of double stranded DNA compared to single stranded DNA [129] and the free bases. For interpretation of the results *ab initio* DFT calculations have been performed. Recently, the CT and exciton states of stacked DNA base oligomers were studied by long-range corrected TDDFT functionals for an improved determination of CT states among low lying electronic excitations of stacked DNA base oligomers [130]. The results suggest that the CT states of DNA oligomers are higher in energy than the bright exciton states.

2.3 The pigments, cofactors, and so on

A detailed review of calculations of the electronic properties of pigments and cofactors by HMO method was presented in Ref. [15], where the following themes were also considered: the principles of the MO method, the electronic structure of important biochemical substances, and the electronic aspects of enzyme reactions. In the Hückel method there exists some non-uniqueness (ambiguity) originating in the choice of the parameters of the method. However, the ideas presented by the authors of this book, especially the idea of the role delocalized π -electrons in the bioenergetical processes, remain important. The stereoelectronic properties of photosynthetic and related systems were investigated by many groups of scientists. They have used the different methods of quantum chemistry. Otten [131] and Nagae and Yomosa [132] have presented the PPP π -electron SCF-MO CI studies of BChl

a^+ . Knop and Stichtenoth [133] and Gouterman with colleagues [134] have presented PPP calculations on chlorine; and Maggiora and Weimann [135] presented CNDO/S all valence electron studies. In work [136] the authors applied CNDO/S3. The most promoted method was used by Shipman with colleagues [137, 138]. In the work [137] ab initio CI calculations on the ground and lower excited singlet and triplet states of magnesium chlorine and chlorine were made. This work deals with the electronic characteristics and spectra of two reduced porphyrins, chlorine and magnesium chlorine. These molecules are important as simple analogs of chlorophyll systems, because the intense red absorption band of the chlorine is also an essential feature of the spectra of chlorophylls. The detailed characterization of many low-lying singlet and triplet states of chlorine and magnesium chlorine was compared to experimental data. The calculations included the configurational composition of each state and the corresponding transition energies, oscillator strengths, and electron density.

Such calculations were made for ethyl chlorophyllide *a* (Et-Chl *a*) [139] and ethyl bacteriochlorophyllide *a* (Et-BChl *a*) [140]. In [138] similar calculations were carried out for Et-Chl *a* and Et-BChl *a* cation radicals (Et-Chl a^+ and Et-BChl a^+). These substances are very similar to chlorophyll *a* (Chl *a*) and bacteriochlorophyll *a* (Bchl *a*), which have essential biological significance. The biochemical significance of Chl a^+ and Bchl a^+ is determined by the photosynthetic energy conversion in green plants and purple bacteria. The photo-oxidation of in vivo photosynthetic systems is apparent as a bleaching of the long wavelength absorption band attributed to Chl *a*-containing or BChl *a*-containing reaction centers, and formation of oxidized systems which bring about EPR and optical spectra characteristic of π -cation radicals [141, 142]. The observations from EPR and ENDOR studies maintained the idea of a bridged dimeric cation as the species formed after ET in the photo-oxidation process [142].

The ab initio configuration interaction method used in these works has been described in detail in papers [143, 144]. Briefly, the configurations for given excited state are built from an orthonormal basis of molecular orbitals which are taken from SCF ground state wave functions. Details of the ground state ab initio SCF calculations, which use a basis of floating spherical Gaussian orbitals obtained using the molecular fragment technique [145, 146] have been presented in works [147, 148]. It is of interest to compare the results of Petke et al. [138] with those of Otten [131] and Nagae and Yomosa [132]. When comparing the computed optical spectra in [138] with the PPP results, a general qualitative agreement is seen in the description of absorption spectrum up to 20,000 cm^{-1} which is shown to consist of many low-intensity “background” transitions. At the same time PPP calculations

predict only a pair of transitions as contributing to the high-intensity region from 23,000 to 28,000 cm^{-1} ; whereas the results of Petke et al. [138] shows four intense transitions in this region. This means that last work shows a larger total number of states over the full spectrum than is predicted from PPP results. It may well be due to both the extensive CI formulation applied here, and the treatment of all side chains and substituents. In work [149] the calculations of the electronic structure of the anion-radical and excited states of Ni-porphyrins were made using by the PPP π -electron SCF-MO CI method. For all cases the atomic charges and bond orders were determined. The calculated values were applied for the explanation of the optical properties of molecules under consideration.

Plato et al. carried out a molecular orbital investigation of dimer formations of Bchl *a* [150]. The space structure of the primary electron donor in bacterial photosynthesis is very important because of its role in the charge separation in the reaction center. Norris et al. first proposed that the primary donor is a BChl dimer. Deisenhofer with colleagues have presented an X-ray analysis of RC of *Rhodospseudomonas viridis* [48] and demonstrated the existence of a BChl dimer. The theoretical study of one or several stable dimeric conformations of BChl might help to understand the function of the dimer on the primary photosynthetic events. The three stable dimer configurations of BChl *a* were obtained by a SCF molecular orbital calculations (all valence electrons, restricted Hartree–Fock, INDO-parameterization, perturbational treatment of spin polarization). The method included geometry optimization by energy minimization. The results from magnetic resonance experiments were also compared with calculated spin-density distributions of the cation radicals: the largest energy of binding was received from a strong overlap of the π -systems together with the formation of two symmetrical Mg–O bonds between the monomeric components. This structure was very similar to the X-ray determined structure of the BChl *b* dimer in *Rhodospseudomonas viridis* reaction center [48]. Possible perturbations of the dimer structure by the protein environment were discussed.

In Ref. [151] the calculated isotropic hyperfine coupling (hfc) constants [B3LYP/EPR-II//BLYP/DZVP(D)] of the Chl *a* radical cation and anion were reported which were in good agreement with the experimental results, especially for the methyl groups. No larger differences in the hfc constants between Chl $a^{+\bullet}$ and (Chl a') $^{+\bullet}$ were predicted. At the same time the enol forms of Chl $a^{+\bullet}$ gave rise to significantly altered hfc constants in comparison with the respective keto form. In addition to the chlorophyll systems, the epimer and O1 enol of Bchl *a* have also been calculated. From a comparison with experimental data it was concluded that the enol forms do not occur in

photosynthetic reaction centers. On the basis of calculations under consideration an enolic form of Chl *a* was therefore unlikely to contribute to P700.

In Ref. [152] DFT/B3LYP calculated structural parameters using the 6-31G(d) basis set showed agreement with the X-ray diffraction data for the structure of ethyl chlorophyllide (A). Normal vibration frequencies and absolute IR intensities of ethyl chlorophyllide (A) were also calculated. The role of saturated substituents in stabilization of radical ion states of chlorophyll was discussed. The effective force field of ethyl chlorophyllide (A) was obtained in independent and dependent internal coordinates. The IR vibrational spectrum was modeled and the experimental IR spectrum of chlorophyll (A) was interpreted on the basis of the calculation.

The study of the IR spectra and structures of all-*trans*- β -carotene and its 15,15-*cis* isomer was carried out by Berezin and Nechaev [153], also using DFT B3LYP/6-31G(d) calculations, to help understand the protective function of carotene in photosynthesis of higher plants. Effective harmonic force fields were determined and used to interpret the experimental infrared (IR) bands, and in particular, the β -ionone-ring vibrations were found to be important. Using the structural similarity between natural carotenoids and stable radical molecules, they have put forward the hypothesis that the methyl groups of the β -carotene molecule play a protective, shielding role, that is, these groups are stabilizing biradical excited triplet state that arises in the process of triplet–triplet energy transfer.

Now we turn to the quinones, which are known to play a major role in photosynthesis and respiration. Moreover, they have been detected in a large number of enzymes and proteins. The main function of quinones is to mediate the electron transport. Eriksson et al. have applied hybrid and gradient-corrected density functional methods to study theoretically the electronic and magnetic properties of neutral and charged quinone and plastoquinone radicals [154]. More precisely, the systems studied were the 1,4-benzoquinone ground-state singlet and first excited state triplet, the radical anion, the radical cation, and the singly and doubly protonated anion radical. H-bonded water molecules were taken into account in the studies of the radical anion, and influence of the hydrocarbon tail at the 3-position was studied for anion, cation, and protonated quinone. The H-bonded group is found to increase the EA of the quinones by ca. 0.6 eV. This is of crucial importance for the understanding of the photosynthetic processes. Further, the energetics of the electron–proton/H-atom transport in the quinone pool between photosystem II and I (PS II and PS I) in higher plants were considered.

O'Malley studied spin density and hyperfine coupling for H-bonded 1,4-naphthoquinone and phylloquinone anion radicals to clarify the influence of the H-bond

on the above-mentioned characteristics [155]. The influence of H-bonding on the spin density distribution was shown to lead to a redistribution of Z spin density from the semiquinone carbonyl oxygens to the carbonyl carbon atoms. The effect of in plane and out of plane H-bonding was studied. Out of plane H-bonding was shown to give rise to a significant delocalization of spin density on to the H-bond donor heavy atom. Good agreement was observed between calculated and experimental hyperfine couplings. Comparison of calculated hyperfine couplings with experimental determinations for the A1 phylloquinone anion radical presented in PS I of higher plant photosynthesis indicated that in vivo radical may have a H-bond to the O₄ atom only as opposed to H-bonds to each oxygen atom in alcohol solvents. The H-bonding situation appears to be the reverse of that observed for QA in the bacterial type II reaction centers where the strong H-bond to the quinone O₁ oxygen atom is present. Perhaps for different types of reaction centers the presence or absence of the non-heme Fe(II) atom may well determine which type of H-bonding situation exists at the primary quinone site which may determine the direction of subsequent ET.

Rinyu et al. [156] performed semi-empirical quantum chemical calculations (AM1 implemented in MOPAC93) to determine the role of the head group substituents in the redox functions of the quinones. In this work the authors presented the IP and the atomic charges by Mulliken population analysis of ubiquinone species substituted with different isoprene subunits (2,3-methoxy-5-methyl-6-isoprenyl-1,4-ubiquinone and 2,3,5,6-tetramethyl-1,4-ubiquinone). The authors assumed that the stabilization of light separated charges depends on the steric and/or electronic properties of quinones bound to the photosynthetic reaction center protein. The symmetric charge distribution of duroquinone is unfavorable for the point of view of the charge stabilization.

Effects of solvent on structural and electronic properties of spin label (4-amino-2,2,5,5-tetramethyl-3-imidazoline-N-oxyl) were studied by Ikryannikova et al. [157]. Imidazoline-based nitroxide radicals were applied as spin probes for medium pH and polarity. These spin labels are used in studies of bioenergetics processes. Practical application of spin probes is based on sensitivity of their EPR spectra to molecular mobility and properties of environment (polarity, pH, microviscosity). Strictly speaking, the properties of these spin labels depend on protonation of radical and aqueous shell. The calculations were performed with DFT using the Perdew, Burke, and Ernzerhof (PBE) XC and the Becke (B) exchange and Lee, Yang and Parr (LYP) correlation (BLYP) XC functionals. These generalized gradient approximation (GGA) XC functionals are functions of the electron density gradient in addition to the electron density. The PBE XC functional is

one of the best GGAs [158]. The BLYP GGA XC functional has been often used for calculations of spin density in nitroxide radicals. The results demonstrate that the spin probe protonation occurred at the nitrogen atom of the imidazoline ring rather than at the amino group. The authors demonstrated that the protonation of 4-amino-2,2,5,5-tetramethyl-3-imidazoline-N-oxyl results in a decrease in a spin density on the nitrogen atom of the nitroxide fragment. For study of spin-label hydration effects, the authors created a water shell around a spin-label molecule, gradually going from 2 to 41 water molecules surrounding the probe. The spin density on the nitrogen atom of the nitrogen atom of the nitroxide fragment increased with the extension of the water shell around spin probe. Protonation and hydration of spin-label molecule produced certain changes in bond lengths and valence angles. The main conclusion of this work is the following. The H-bonded cluster of more than 41 water molecules could be viewed as the model for simulation of spin probe hydration effects.

Quantum mechanical/molecular mechanical (QM/MM) calculations combining the DFT B3LYP/6-31G(d) and U-B3LYP/631G(d) XC functionals with the NAMD2 and AMBER4 force fields were used to study the electronic properties of one of the two domains of the plant blue-light receptors of the Phot family. These receptors mediate plant phototropism and contain two light, oxygen, and voltage (LOV)-sensitive domains as photoactive elements. The Phot-LOV1 domain from *Chlamydomonas reinhardtii* was studied [159]. The electronic properties and structural changes that follow blue-light absorption were studied by combined QM/MM simulations of the photocycle of the Phjt-LOV1 domain of *Chlamydomonas reinhardtii* [159]. This allowed one to resolve the structural changes and study the electronic processes accompanying flavin-cysteiny adduct formation. The calculations allowed authors to study the pathway for flavin-cysteiny adduct formation. This process proceeds via a neutral radical state provoked by hydrogen atom transfer from the reactive cysteine residue, Cys57, to the chromophore flavin mononucleotide. The adduct formation does not produce any larger scale conformational changes in the Phot-LOV1 domain.

Jalkanen and colleagues applied the modern quantum chemistry methods for the prediction of vibrational spectra and structures for biomolecules in the different surroundings [160–166]. They presented the structures, energies, vibrational frequencies, vibrational absorption (VA) intensities, vibrational circular dichroism (VCD) intensities and Raman scattering intensities for the conformers of small peptide Leu-enkephalin (LeuE). This peptide is biologically active and found endogenously in many animals and humans [160]. The author used the hybrid B3LYP XC potential and the 6-31G* basis set.

The VA and VCD spectra simulated by Abdali et al. have been compared to the measured VA and VCD spectra of LeuE in DMSO [167]. On this basis the structure of LeuE has been proposed. Only the non-ionic neutral species of LeuE was taken into account, as this is the species thought to be present in the nonpolar membrane environment where LeuE binds. The crystal structure of LeuE bound to its receptor has not yet been solved. The question of the species and conformation in solution versus bound to the receptor is still being investigated, as LeuE is thought to bind via an induced fit, versus the lock-and-key mechanism. In doing so, it has been shown that many receptor proteins are more rigid on binding, and it may actually be easier to get a crystal structure for the ligand bound receptor than it is to get either the crystal structure for either the free ligand or free receptor.

3 Quantum chemistry studies the bioenergetic processes

3.1 The generation and transfer of charged states in photosynthesis

After Deisenhofer et al. determined the structure of the bacterial photosynthetic reaction center [48], Kuhn considered the mechanism for the electron transport in the reaction center [168]. The rate constant of the electron transport between the different carriers was calculated by Fermi's golden rule; $K = (2\pi/\hbar)\epsilon^2 S$. In the formula the electron perturbation energy (ϵ) is the matrix element of perturbation energy on the electron wave functions of donor and acceptor before and after the ET. The value S is the Franck–Condon factor. In this work the ET rates were determined for all stages of the electron transport in the reaction center. In doing so, the protein part of reaction center was taken into account as a rigid dielectric continuum, so that the free energy loss by solvent reorganization can be neglected. The electron wave functions in the corresponding matrix elements were chosen as the functions given by the free electron model. The rate constant for different stages of the electron transport in reaction center were in good agreement with the experimental data.

In work [169], called “Theoretical investigation of the rates of electron transfer processes $Q_1^- + Q_2 \rightarrow Q_1 + Q_2^-$ and $Q_1^- + Q_2^- \rightarrow Q_1 + Q_2^{2-}$ in photosynthesis”, the characteristics of the quinones were estimated to study the influence of surroundings on the rate of the electron transport between Q_1 and Q_2 . The study was carried out by using the Marcus theory of long-range electron transport in solution [57]. The molecular reorganizational parameter λ , the free energy change ΔG^0 for the overall reaction, the electronic matrix element H_{AD} were calculated from the

INDO-optimized geometries of molecules Q_1 , Q_2 , and histidine. The study has given the standard reduction potential of the process $Q_1^- + Q_2 \rightarrow Q_1 + Q_2^-$ as 127 mV and the midpoint potential of $Q_1^- + Q_2(H^+) + H^+ \rightarrow Q_1 + Q_2H_2$ as 174 mV at 300 K at pH 7. The experimental value is 130 mV for the first process; for the second process, the midpoint potential is not precisely determined. Both the transfer processes took place in the absence of Fe^{2+} ion. The main role of Fe^{2+} ion appears to be the support of the rigidity of the matrix by holding the two histidine molecules firmly in place. The authors deemed that the Marcus theory of long-range ET can be successfully applied to the study of ETs in the semirigid condensed phase that is located inside the thylakoids.

Semi-empirical and ab initio quantum mechanical methods turned out to be very useful for understanding of absorption spectra of the photosynthetic pigments and the electronic properties of primary donors and acceptors. The extensive review of results reported up to 1982 is presented and critically analyzed in book [170].

Now we consider the works in which peculiarities of ET in primary processes of photosynthesis were studied. The results determined from X-ray analysis of crystals of the reaction centers of the purple bacteria showed [48] that the pigment and cofactors (BChl of the special pairs, monomeric BChls, monomers of bacteriopheophytin and two quinones) are located symmetrically along L and M subunits of protein complex RC. However, in the kinetic experiments it was shown that the ET along L subunit occurred about five times quicker than along M subunit [171]. Why the electron chooses one of two similar paths is not clear? The study of the structure of the RC protein complex in detail showed the essential asymmetry in the location of the polar amino acid residues in L and M chains of the complex. That's why the assumption appeared that such asymmetry can influence the electronic properties and energetic characteristics of the nearest pigments in L and M chains of RC. The authors [172] explained the advantage of L chain by the protonation of glutamate near BChl of special pair of L chain; in that place in M chain the nonpolar amino acid valine being located. The calculations were carried out in model of electrostatic interactions of pigment molecules with the RC polar surroundings; the influence of this asymmetry on the electronic and energetic characteristics of special pair on which the CT begins was not studied. This problem was investigated in work [173] by quantum chemistry methods. The authors treated the influence of the environment nearest to the special pair of polar amino acids. The calculations were performed to evaluate/determine the nature of the electrostatic interaction between the π -electron system of dimer of special pair and the electrical charges on the amino acids of RC proteins. At first the authors have determined the one-electron

wave function (molecular orbitals) and corresponding one-electron energy for π -system of BChl molecule. The Roothaan method in NDO approximation was applied. The integrals of electrostatic interactions were estimated by the Mataga method [174]. The determinant of Roothaan equations was factorized by group orbital basis, which is the basis of irreducible representations of group D_{2h} . The molecular orbitals obtained are satisfactory, see data reported in Ref. [175]. After that the authors took into account the electrostatic influence of the nearest polar amino acids of RC on the electronic characteristics of the special pair. They considered the following amino acids: histidine (L168), histidine (L173), threonine (L248), histidine (M200), and tyrosine (M195). The specific arrangements of these amino acids are reported in work [48, 176]. The influence of the electrostatic interaction of polar amino acids and π -system of dimer is considered as the small perturbation in Hartree–Fock equations.

To solve this problem, the authors [173] used first order perturbation theory because the expectation value of the perturbation operator is less than the eigenvalue difference $|\varepsilon_i - \varepsilon_k|$. The resulting eigenvalue differences were: $\Delta\varepsilon_{9L} = -0.2$ eV; $\Delta\varepsilon_{9M} = 0.14$ eV; $\Delta\varepsilon_{10L} = -0.16$ eV; $\Delta\varepsilon_{10M} = 0.12$ eV. The energies ε_9 and ε_{10} for the special pair were determined using the one-configuration approximation, the ninth molecular orbital ψ_9 being the highest occupied orbital and the tenth one being lowest unoccupied orbital. The IP of BCH_{MP} for the first singlet excited state is 0.28 eV smaller than the IP of BCH_{LP} . The estimation the rate of ET by the Jortner formula [42] shows that the ratio of the rate constants for BCH_{MP} and BCH_{LP} is about ten. These results seem to be strange, because for BCH_{MP} the electron is transferred via the L-chain. However on the closer inspection of structure of RC it can see that the difference of distance between BCH_{MP} and BCH_{LP} on one hand and the primary acceptor BPH_L is not so large (near 0.1 nm) as compared with the average distance between the electron carriers. Perhaps the influence of charge of the nearest polar amino acids is more essential than the distance difference.

The electronic structure of the RC chlorophyll dimer was studied using the ab initio molecular orbital scheme and pseudocharges and dipoles method which takes into account the electrostatic effect of the surrounding proteins, pigments, and aqueous solvent [177]. Let us briefly review the structure of RC from the photosynthetic bacteria *Rhodospseudomonas viridis*. It consists of four protein subunits: L (light), M (medium), H (heavy), and cytochrome. The RC protein part surrounds the pigments: four BChls, two bacteriopheophytins, one menaquinone, one non-heme Fe, and one ubiquinone. The pigments make up two subunits, L and M that are almost symmetrical. The two BChls, named BC_{lp} and BC_{mp} , belonging to L and M-subunits

correspondingly, is usually called the “special pair P”. It is well-known that the ET processes proceeds only along the L-subunit. The cause of this is not clear. The total energies of BC_lp, BC_mp, and P; the differences from the energies when taking the electrostatic effect into account; and the dimerization energy were determined. The IPs of the above-mentioned components in gas phase and solvated system were determined. The main conclusions of the article are the following. First, the electron is removed slightly more easily in vacuum from BC_mp than from BC_lp. This is possible since the molecular plane of BC_mp is clearly distorted, but not so distinctly in BC_lp. Therefore, the ionization from BC_mp occurs more easily than from BC_lp. Perhaps, this smaller IP is determined partially by the chlorophyll molecular structures themselves, as this happens even when the electrostatic potentials of the surroundings is ignored. The tendency is for the IP of BC_mp to be enhanced by the addition of the electrostatic potentials creating the polarizable environment. The difference in the IPs of BC_mp and BC_lp is as large as 0.6 eV. The authors assumed/hypothesized that for the correct treatment to this problem the induced dipole moments should be included in the effective Hamiltonian for the ab initio MO method.

The ET between the primary and the secondary quinone of the bacterial RC has been investigated theoretically [178]. It was supposed that in this system that a mobile electron which is injected on one end of the chain can be transported to the opposite end by step-by-step switching the positions of the H-bonded hydrogens. In doing so, not only protons but also hydrogen atoms are involved. In such manner the formation of an H-bonded chain linking the two redox centers can play the essential role in the mechanism of ET. This type of the electron transport was called proton assisted electron transport (PAET). So PAET mechanism was considered in the next system: $Q_A^- \cdots H - His - Fe - His - H \cdots Q_B$.

The authors have replaced Fe^{2+} by Zn^{2+} to simplify computations. The energetic calculations have been performed with the ab initio self-consistent level of theory using GAMESS package and the standard 6-31G basis set, expanded with polarization functions on all atoms participating in H-bonds. The calculations of energy predicted that the various stages of the PAET mechanism were all slightly exergonic ($6.1 \text{ kcal mol}^{-1}$). The potential energy profile was proposed to describe the proton vibrations around two sites $Q^- \cdots H - His$ and $Q - H \cdots His$. The authors have calculated the vibrational frequencies associated with proton oscillation, solving the Schrödinger equation variationally. The calculated frequency for the proton oscillation is $2,656 \text{ cm}^{-1}$, shifting to $2,016 \text{ cm}^{-1}$ on deuteration. This result permits to verify calculations.

More recently quantum mechanical methods have been applied to nanotechnology. In work [179] the authors studied the atomic-scale coupling of photon to single-molecule junctions containing the biologically important component magnesium porphine (MgP). Chlorophyll, the main component of the photosynthetic systems, is a derivative of the MgP. The authors of this work showed the coupling of photons to a single molecule of MgP in a double-barrier junction of the scanning tunneling microscope through a two-step process of photo-induced resonant tunneling. In this process an electron is photo excited to a higher level in the tip and then tunnels resonantly to a molecular state of the MgP. For the interpretation of the experimental data, DFT calculations on the planar MgP molecule were performed with HyperChem 7.0. The energy separation between the LUMO and the LUMO+1 was reported to be $\sim 1.6 \text{ eV}$. This difference corresponds to 800-nm light observed in the tunneling electron-induced fluorescence spectra.

The time changes of pigment–pigment and pigment–protein interactions in antenna light-harvesting complexes of bacteria were investigated with a method that combines molecular dynamics simulations with quantum chemistry calculations and polaron model analysis [180]. These simulations were done on an 87055 atom system, contained a LH-II complex of *Rhodospirillum molischianum* build-in in a lipid bilayer and surrounded with appropriate water layers. The authors performed 400 ab initio quantum chemistry calculations for each of the 16 B650 BChls. The geometry of this system was determined/obtained from the preliminary molecular dynamical simulations. As a result of the approach, the fluctuations of pigment excitation energies as a function of time were determined. On the basis of these results the authors introduced a time-dependent Hamiltonian for the B850 exciton system determining the absorption spectrum from linear response theory. Furthermore, a polaron model was applied to study both the excitonic and coupled photon degrees of freedom by quantum mechanics. The constant of the exciton–phonon coupling and the phonon spectral function for polaron model were obtained from the molecular dynamics and quantum mechanical calculations. The proposed approach permits one to determine that excitons in the B850 BChl ring under consideration are spread over five pigments at room temperature. Moreover the model allows one to calculate the absorption and circular dichroism spectra of the B850 excitons.

3.2 The proton transport in photosynthesis

An intensively investigated area of application of quantum chemical approaches is the coupled electron and proton transport in bacterial and plant photosynthesis, namely:

early coupling events in the vicinity of the secondary quinone. One of the most important problems is what molecular properties of the system account for its ability to synchronize ET during Q_B reduction with proton uptake from the outer side of the membrane in chromophores of bacteria or thylakoids of higher plants [181]. Earlier, Tomchuk et al. studied theoretically the process of proton movement through the F_0 subunit of ATP synthase [182], using the polaron theory. The kinetic characteristics of the process, such as current density, polaron lifetime, and proton mobility, were estimated. In our study [183], we have surmised that ET from histidine L190 to the secondary quinone Q_B is followed by proton transfer. The hypothesis was tested in that study by calculating the energy of the quinone-histidine system. The semi-empirical modified neglect of diatomic overlap method [184] was used as the optimal one in terms of accuracy required for solving our problem versus the computing speed. The calculations were done for various positions of the proton between quinone and histidine for various redox states of Q_B (neutral, singly reduced, and fully reduced). Inspection of the shapes of the curves obtained allowed some qualitative conclusions to be drawn. Namely, when the quinone is in the singly reduced state, an H-bond is likely to form; the bond between the proton and the doubly reduced quinone is covalent and its formation changes the distance between Q_B and histidine. In the work [183], we assessed quantitatively the position of the proton between the histidine and Q_B . Specifically, the probability density function of proton positions and the respective energy levels of the proton were determined by numerically solving the Schrödinger equation for the hydrogen of histidine in the histidine- Q_B system. The main results are the following. In computations, we varied the redox state of plastoquinone Q_B (oxidized, singly reduced, and doubly reduced) and the distance between the nitrogen of histidine and the oxygen of Q_B . The calculated square moduli of the wave functions (which determine the probability density for the proton position along the line connecting the oxygen of quinone and the nitrogen of histidine) and the energy levels for the lowest three states of the proton are shown in Refs. [181, 183].

The single maximum of the ground-state wave function of oxidized plastoquinone is 1 Å away from the nitrogen of histidine. The maxima of the wave functions corresponding to the excited states are not shifted farther than 0.5 Å from this position. The lowest wave function of singly reduced plastoquinone Q_B^- has a broad maximum midway between the nitrogen of histidine and the oxygen of plastoquinone. The maxima of the wave functions corresponding to the excited states are far separated, suggesting H-bonding to the oxygen of Q_B . The single maximum of the ground-state wave function of doubly reduced plastoquinone Q_B^{2-} is

0.9 Å away from the oxygen of Q_B . Sequential reduction of Q_B shifts the maximum of proton position probability density in the direction from the nitrogen of histidine to the oxygen of Q_B . The resembling result was received in work [185] by the DFT/B3LYP/6-31(d) method.

So, the authors of the work [181] deemed that the same scheme of coupling of electron and proton transport may well take place in the cyt b_6f complex and oxygen-evolving systems in chloroplasts. Some results in support of this suggestion were obtained in paper [186], in which the results of quantum chemical calculations of the proton position in the tyrosine Y_z -His D1-190 in the water-oxidizing complex of higher plants were presented. The main result was the following. When the system under consideration was in the neutral state, the proton is located 1 Å away from oxygen atom of the Y_z . After the Y_z is oxidized, the proton is shifted 1.7 Å farther, to a distance of about 1 Å from the nitrogen atom of His D1-190.

In work [187] the authors calculated the energies of complexes $P^+Q_A^-$ and PQ_A in reaction center *Rhodobacter sphaeroides* taking into account their specific surrounding. The calculations were reported for the different stable positions of protons. The optimization of structure and calculations of energy were made by semi-empirical PM3 method and DFT method (basic 6-31G*, functional B3LYP). The authors demonstrated the essential influence of proton positions on energy of transition $P^+Q_A^- \rightarrow PQ_A$.

3.3 The ion channels and the other structures

The ab initio calculations [RHF + MP2 (FULL), basis 6-31 G**] were used to study proton migration in a tyrosine stack under the action of Mg^{2+} ions and the electrical field. This system was a model of the proton channel in tubulin [188]. In this system there is only the energetic barrier of 0.72 kcal mol⁻¹, easily surmounting by thermal movement.

Quantum chemical methods were intensively used to investigate the gating problem in the functioning of ion channels [189]. The results of Gaussian 98 calculations (DFT method, B3LYP functional, 6-311G⁺⁺ basis set) supported the hypothesis about the gating of bacterial ion channel. The authors studied the role of the proton(s) in gating of potassium channel [190]. The system under consideration included: one pair of guanidinium groups, the side chains of arginines responsible for carrying the proton current, a mobile proton and one, two, or three water molecules. Several guanidinium spacings have been tried, all in the range of carbon-carbon distances from 4 to 6 Å. The potential energy surface was received for each distance, and minimum path was found for the proton at B3LYP/6-311G** level. It was found that under some

conditions the proton could follow a path between guanidiniums that had no barriers greater than a few kT.

In work [191] the authors studied the quantum dynamics of the femtosecond photoisomerization of retinal in bacteriorhodopsin. On/after absorption of (a photon of) light, the all-*trans*-retinal is hypothesized to undergo a subpicosecond all-*trans* → 13-*cis* phototransformation involving torsion around a double bond. The reaction product initiates events in bacteriorhodopsin that cause pumping of a proton through the protein. Quantum-chemical studies suggest that three coupled electronic states (the ground state and two closely lying excited states) participate in the motion along the torsional reaction coordinate. The evolution of the protein-retinal system under consideration on these three electronic surfaces has been calculated applying the full multiple spawning method for non-adiabatic dynamics. With this method the time evolution of the population on the one of the product states, the 13-*cis* state, was investigated. The authors found that most of the population transfer occurs on a timescale of 300 fs, some population transfer continues during a longer timescale, extending beyond 1 ps. This paper gives us a framework for future studies of the photodynamics of retinal in bacteriorhodopsin and of other biological photo processes.

In paper [192] the authors studied the role of an H-bonded network in energy storage the light-driven proton pump in bacteriorhodopsin.

This problem is stated as follows: how bacteriorhodopsin accumulates the light energy absorbed by the chromophore. In this work the authors performed an *ab initio* QM/MM vibrational normal-mode analysis of the binding site for the proposed K intermediate state, which is generated 3 ps after photoabsorption and can be trapped at low temperature. A QM/MM routine [193] using the AMBER field were applied.

The QM/MM simulations were used to analyze and interpret the observed spectral changes and led to the conclusion that the H-bonds between water molecule 402, Asp85 and the Schiff base weaken. This observation/interpretation is essential to understanding the energy storage in bacteriorhodopsin.

The group of scientists [194, 195] have attempted to apply the modern methods of quantum chemistry for modeling the catalytic mechanisms of guanosine triphosphate (GTP) hydrolysis in the different GTP-binding proteins (so called G-proteins). The authors used *ab initio* QM/MM simulations. The program package of this QM/MM method was based on two programs: PC GAMESS [196] and program TINKER (URL <http://dasher.wustl.edu/tincer>).

It was shown that the GTP hydrolysis reaction for the different G-proteins proceeds in uniform fashion. The following sequence of reactions occurs. At the first stage the γ -phosphate group is removed from GTP. After that the reaction water molecule carries out a nucleophilic attack on

the phosphorus atom of the split phosphate group. At last the proton transfer and phosphate production take place. In doing so, a number of the stages in the hydrolytic reactions depend on the affinity of the catalytic amino acid for proton.

Using multiconfigurational quasidegenerate perturbation theory of the second order (the original technique aug-MCQDPT2) the authors of works [197–199] have calculated the maximum absorption wavelenths/energies of retinal conformers, chromophores of green fluorescence protein, and flared fluorescence protein (asFP5950) in different protonated states. The aug-MCQDPT2 method together with QM/MM technique provides the means of calculating the energies of the vertical electron transitions for the chromophores in condensed matter. The approach gives one a possibility to study the influence of medium on the optical properties of the chromophore group in proteins.

Of fundamental importance for understanding the mechanism of proton transport is the role of long-range coupled motion in an enzyme catalyzed reactions [200]. In the work the authors presented a description of an enzyme-catalyzed reaction dominated by proton tunneling. They studied the reaction pathway for tryptamine oxidation by aromatic amine dehydrogenase (AADH). AADH is a tryptophan tryptophyl quinone-dependent quinoprotein. It catalyses H transfer by quantum mechanical tunneling. Combining experiment determining the crystal structures of key intermediates and computer simulation with use of a combined QM/MM potential the authors obtained the following. It happened to be that data of the analysis of tunneling in AADH by computational methods is in agreement with the experimental kinetic data received by using stopped-flow methods. Moreover the proton transfer occurs by tunneling over ~ 0.6 Å. In this system tunneling is assisted by a short-range motion and no long-range coupled motion is needed. That's why the role of long-range coupled motions in promoted proton tunneling remains unsolved.

In Ref. [201] the structure and dynamics of the Fe–CO bond in the oxymyoglobin active site and its cobalt-substituted analog were studied. The author used the DFT, CMPD (Car–Parrinello molecular dynamics) [202, 203] and hybrid QM/MM approaches. The results of calculations testify that both in the gas phase and in the protein the Fe–CO bond is linear and that's why the hypothesis that the CO in MbCO is hindered is not true. The protein discrimination for Fe–CO bond is due to the H-bonding between the O₂ ligand and the His64 residue. It should be noted that the CMPD method was broadly applied in the investigations of the biological systems [201].

3.4 The oxygen evolving center in plants

The developed model for the water splitting system of thylakoid membranes using the molecular orbital study

system was presented in Ref. [204]. The authors of this work have made the molecular orbital calculations of the process of water oxidation. The *ab initio* LCAO MO UHF were used. It was shown that some valence states of manganese work as catalytic metal cations, which decompose H_2O into H^+ and OH^- (or OH radical). The potential energy curve for the H-bond between two water molecules was obtained for the different states of Mn ion located near water dimer. The authors proposed that the system under study must have a proton-accepting center which forms an H-bond with a water molecule to be oxidized by the manganese. Subsequently, this supposition was confirmed in the structural findings [205–207].

The quantitative model of water splitting system using quantum mechanical considerations was presented in Ref. [208]. It described the geometry of the O_2 evolving complex and the energetics of the process of water splitting. Two molecules of water are bound to four amino acid residues (histidines) by H-bonding in the active site, and this aids in the H_2O splitting by pulling proton through the H-bond. Four Mn atoms are divided into two groups: one group is in the active site and helps in the water splitting and other group is in the interface between the Mn-containing intrinsic protein and extrinsic proteins (14–18, 23–25, 32–34 kD), acting as an electron carrier between the O_2 evolving complex and P680. However, the modern structural data [204–206] were not taken into account in this work.

The new structural data were used in Ref. [209]. In the author's opinion, the problem of oxygen formation in photosynthesis is the following. It is not clear how it is possible to remove four protons and four electrons from two water molecules upon absorption of four quanta and while avoiding the formation of reactive oxygen species (Q_2^- , H_2O_2 , OH), and to produce a stable molecule of oxygen. The water-oxidizing complex is so efficient that it does not need help from additional defense systems such as antioxidants, superoxide dismutases, and catalases. In this work the new model of the oxygen evolving complex (OEC) based on the cubane-like Mn_3CaO_4 model [204] was proposed. In doing so, the authors used the ligand field theory and the rules of 18 and 10 electrons for stable shells of Mn and Ca ions respectively. By the same procedure they added to the model [204] chlorine and water molecules. The authors proposed the mechanism of water oxidation in which calcium ion and remote manganese Mn4 play the main role. The scheme of the redox state transitions between discrete S-states of OEC at excitation by short pulse of light was hypothesized/assumed. This model states that using manganese as necessary elements of OEC is determined by their transitional character. The presence of calcium in OEC is explained by its stability in states with completely filled shells and little affinity for an

electron in this state. The cubane-like cluster does not allow Mn4s to fill their molecular shells by electrons from nearby oxygens which requires Mn4 to oxidize the molecule of water. In this work the estimation of the system energy in S-states was carried out. The authors used the software package HyperChem and the semi-empirical method ZINDO. To simplify the calculations, they used HCOO^- groups instead of aspartic and glutamic acids, and the NH_4^+ group instead of histidine. To optimize the system the authors changed the length of the bonds with those molecules that were not obtained from the structure [204], i.e., four water molecules and the chlorine ion. This resulted in the bond energy in each of the S-states being negative. Hence this configuration of the system was stable.

Kusunoki presented the interesting new mono-manganese mechanism of the PS II oxygen evolving reaction catalyzed by a unique Mn_4Ca cluster [210]. This model is assumed to be composed of Y_z (Y161), Gln165, Asp170, Glu189, His190, His332, Glu333, His337, Asp342, and Ala344 from D1 protein, Glu354, and Arg357 from CP43 protein, a negative Cl^- ion suggested to be bridging between positive Arg357⁺ and Ca^{2+} ion, and a monomer-trimer type Mn_4Ca to be proposed. DFT/B3LYP computations have shown that the proposed structure is consistent with the observed EPR, extended X-ray absorption fine structure (EXAFS) and isotope ^{18}O exchange kinetics data in a Kok's S_1 -state cycle.

The structural models of the oxygen-evolving complex of PS II in the dark-stable S_1 state, as well as in the reduced S_0 and oxidized S_2 states, were considered in work [211]. In doing so, acid residues, water, hydroxide, and chloride ion have been taken into account. The authors applied the modern QM/MM hybrid methods for the description of the structural and electronic properties of the system under consideration. The proposed models were based on the X-ray diffraction structure of cyanobacterial PSII, which was made at 3.5 Å resolution (PDB access code 1S5L). The authors remarked that the proposed X-ray diffraction models remain rather controversial because of their small accuracy in the definition of the distances between atoms. The questions asked in this work are the following. What are the distances between the different Mn atoms? Where is the chloride ion located? What are the positions of the water molecules? The main results of this work are the following. For S_1 , S_0 , and S_2 states of system under study the structural and electronic characteristics were determined including the distances between atoms and bond angles. For these models the simulation of the EXAFS spectra were carried out. The authors considered that the proposed QM/MM models agreed with X-ray diffraction models and EXAFS spectrum data. The proposed location of calcium-bound chlorine ligand is consistent with pulsed

electron paramagnetic resonance data, received from acetate-substituted PSII. In that way this model is of essential interest for scientists working in this field.

In another work it was shown that the generally accepted QM/MM models have coincidence with the X-ray model [207], the differences being in the protonation states, in the number of ligated water molecules, or in the coordination of labile ligands which exist. Only two spin states of Mn were found for the S_1 base state. This is so called model A with Mn(1) = IV, Mn(2) = IV, Mn(3) = III, Mn(4) = III, in which the dangling manganese is pentacoordinated. In model B with Mn(1) = IV, Mn(2) = III, Mn(3) = III, Mn(4) = IV, the dangling manganese is hexacoordinated and has an additional ligated water. The essential result obtained by the authors was that the cubane-like model of the inorganic core of the OEC of PCII, ligated with water, OH^- , and Cl^- and protein ligands, was a stable molecular structure even in the absence of the surrounding protein environment. In that way this model is of essential interest for scientists working in this field.

4 Discussion, conclusions, and perspectives

Some words about application of the modern methods of quantum chemistry in biophysics. One of the most used spectroscopic techniques is NMR. Recently the prediction of NMR shielding via ab initio and DFT methods has undergone a revival. Originally HF method were used to predict NMR shielding and gauge invariant atomic orbitals were developed. It has been recently stated that the B3LYP method should not be used for the calculation of the ESR hyperfine structure (hfc) constants, nuclear resonance spin–spin coupling constants, magnetic shieldings and other properties [212]. Many groups continue to use the B3LYP method as it became the so-called Gold Standard for many DFT calculations, geometry optimizations (where dispersion forces and van der Waals interactions are not important), frequency calculations and VA or IR intensities [213]. But for magnetic properties, both ground and excited states, the B3LYP is NO LONGER the Gold Standard. The B3PW91 hybrid XC functional has been shown to be much better [212].

The calculation of the potential energy hypersurfaces is a much more difficult task for excited states as compared with the ground states. It is agreed that now the best method of calculation is the TDDFT [214] approach, applying for excited-state calculations. However this method gives the wrong results for some states low-lying $\pi\pi^*$ states [107, 215].

It is interesting to compare method of multiconfigurational SCF (MCSCF) and best DFT based methods. Now it is deemed that the first more adequately describes the experimental data. However it is not surprising because

DFT method contains more parameters in the basis functions and in the functional. At the same time the MCSCF method contains the free parameters only in the basis functions. The advantages and shortcomings of the different methods were discussed in work [216–218]. As a rule, the biological objects are the systems containing a lot of electrons and nuclei. That's why the choice of the quantum chemistry method of study is determined by the taste of author namely the aim of investigation, the computer capabilities, and so on.

In conclusion, let us remark the main stages of penetration of quantum chemistry methods in biology. At first, they were applied for explanation of the optical and electronic properties of relatively simple and afterwards complex component of living organisms. After that the scientists began to study the structure and the electronic characteristics of biopolymers, proteins and nucleic acids, and the large protein–lipid complexes for which were received X-ray diffraction structural models. Among these were the reaction centers of the photosynthetic bacteria and higher plants, the ion channels, the mitochondrial respiratory complexes. Approximately at the same time the quantum chemistry methods were used in studying the main biological processes such as the electron and proton transports in photosynthesis and respiration, the gating in ion channels, and visual reception.

Some other aspects of quantum chemistry applications in biophysics are discussed in articles [219, 220]. In addition to electronic circular dichroism, VCD has been developed to the point where it can now be routine used in not only organic chemistry [221], but also in the field of molecular biophysics [222]. Indeed in the group of Professor Sandor Suhai, to whom this special focus issue of TCA is dedicated, many of the pioneering works on determining the causes responsible for the large changes VA and VCD spectra of amino acid and peptide in aqueous solution versus those of amino acids and peptides in the gas phase or isolated in non polar solvents like carbon tetrachloride, carbon disulfide and chloroform and chloroform- D_3 have been undertaken on the alanine dipeptide, *N*-acetyl L-alanine *N'*-methylamide [223–228], L-alanine [162, 222, 225, 228–231], L-alanyl L-alanine [222, 225, 232, 233], L-histidine [234], tri-L-serine [165] and the work in this issue on capped L-histidine, *N*-acetyl L-histidine *N'*-methylamide [235]. Of course there is much more work to do, extending to large systems, in even more complex environments, for example, embedded in membranes. In addition, multi-dimensional IR and Raman techniques have recently been developed and multidimensional VCD has been proposed. In addition, surfaced enhanced Raman spectroscopy has been extended to biological systems and even preliminary reports of surface enhanced Raman optical activity. But the theory for these techniques still remained to be fully

developed, tested and benchmarked, before these techniques become routinely used in molecular biophysics, like the other techniques covered in the recent Cambridge University Press book, *Methods in Molecular Biophysics* by Serdyuk, Zaccai and Zaccai [236]. In addition the recently developed TDDFTB methods have been used to analyze the EA, ECD spectra of biomolecules [237, 238], in addition to utilizing wave function based methods [239, 240]. With the experimental synchrotron radiation circular dichroism technique now available for making measurements even farther in the UV range, clearly the tools of TDDFT and wave function based quantum mechanics have a lot to offer in the understanding and interpretation of the exciting new experimental results [241]. In addition, some non linear optical methods have been proposed [242] and a general perspective paper on molecules in both electric and magnetic fields has appeared [243]. The effects of the solvent on vibrational frequencies have also recently been investigated and a new partitioning of the contributions causing the solvent effects has been proposed [244]. So many effects which were thought to be well understood, both experimentally and theoretically, are being restudied and reinvestigated. This has been due to higher resolution and more accurate experimental data, which has pointed out some of the inadequacies of the previous theoretical descriptions. The articles in this special issue of TCA cover the areas of molecular biophysics, biophysical chemistry, chemical physics, mathematical biology, chemistry and physics, and bioinformatics, many citing the cutting edge contributions to these fields by Professor Suhai, his group and large number of collaborators. We want to take this opportunity to thank once again Professor Sandor Suhai for his many contributions to these fields, for his educating and mentoring many B.Sc., M.Sc., Ph.D., and postdoctoral students. He has been one of the leaders in these fields and with this special focus issue, all of the contributors have contributed what many feel are their best works in the past years. What better place to publish them than in this special focus issue of TCA.

With the passage of time the number of “quantized” processes which have been investigated has increased and is continuing to increase. The rejection neuromediator at the generation of postsynaptic potentials, the formation of the action potential, and the investigation of the repair mechanism by the photolyase class of proteins in the presence of blue light are just three examples of problems which require further investigations. The later biological repair process of DNA is initiated by the absorption of a photon of light. Hence the process starts on the excited state energy in a very complex environment and evolves in time [245, 246]. Clearly all of the tools and methods discussed in this review and covered in this special focus issue are needed to attack such problems. With this review we

have tried to bring you to the point where you can now read the many research articles which follow which have been submitted from top research laboratories and groups on all five continents working the multidisciplinary fields of molecular biophysics, biophysical chemistry, chemical physics, mathematical biology, chemistry and physics, and bioinformatics.

Acknowledgments A.K. Kukushkin would like to thank all those who directly or indirectly contributed to this material. It is difficult to list all the names and I confine myself to expressing gratitude to my colleagues: S.A. Khuznetsova, S.V. Poltev, R.V. Belousov, and A.S. Rychkova. A.K. Kukushkin is indebted to Dr K.J. Jalkanen for the invitation to coauthor this manuscript with him on the occasion of Prof. Sandor Suhai’s 65th birthday and his, Professor Suhai’s, many contributions to molecular biophysics. K.J. Jalkanen would like to thank the German Cancer Research Center (DKFZ) in Heidelberg, Germany and Professor Sandor Suhai, Head of the Department of Molecular Biophysics, for his initial invitation to come to the DKFZ in the fall of 1994 from the National Center for Supercomputing Applications (NCSA) on the campus of the University of Illinois at Urbana/Champaign (UIUC), for introducing him to the field of molecular biophysics, and finally for the 3-month stay at the DKFZ in Heidelberg in 2009 (April to June 2009). KJJ would also like to thank Professor Thomas Frauenheim and Dr. Thomas Niehaus for the visiting research scientist position at the Bremen Center for Computational Materials Science (BCCMS) at the University of Bremen for the period of Oct. 2008 to March 2009 and my good Ukrainian friend and colleague Dr. Grygoriy Dolgonos for critical reading of our manuscript and valuable discussions on DFT and WFQM methods as applied to calculations for biomolecules. K.J. Jalkanen would also like to thank Curtin University of Technology for providing infrastructure support for the period of October 2008 to July 2009, during which time K.J. Jalkanen was an Adjunct Research Fellow at the Nanochemistry Research Institute (NRI). The DFG and the DAAD are also acknowledged for financial support for K.J. Jalkanen’s stay in Bremen and in Heidelberg during which time this review was coauthored with A.K. Kukushkin. Finally I would like to thank Professor Victor I. Danilov for sending me reprints of his very good papers, some of which are only available in the Russian literature.

References

1. Bohr N (1933) *Nature* 131:421
2. Bohr N (1958) *Atomic physics and human knowledge*. Wiley, New York
3. Schrödinger E (1945) *What is life? The physical aspects of the living cells*. McMillan, New York
4. Weissbluth M (ed) (1964) *Quantum Aspects of polypeptides and polynucleotides*. Biopolymers symposia no. 1. Wiley, New York
5. Timoféeff-Ressovsky NW, Zimmer KG, Delbrück M (1935) *Nachr Ges Wiss Gott* 1:189
6. Frank J, Teller E (1938) *J Chem Phys* 6:861
7. Jordan P (1938) *Naturwissenschaften* 26:693
8. Pauling L, Corey RB (1951) *Nature* 168:550
9. Watson JD, Crick FHC (1953) *Nature* 171:737
10. Franklin RE, Gosling RG (1953) *Nature* 171:740
11. Franklin RE, Gosling RG (1953) *Nature* 172:156
12. Szent-Gyorgui A (1941) *Nature* 148:157
13. Petrov EG (1984) *Fizika perenosa zaryadov v biosystemakh*. Naukova Dumka, Kiev (in Russian)
14. Evans MG, Gergely J (1949) *Biochim Biophys Acta* 3:188

15. Pullman B, Pullman A (1963) Quantum biochemistry. Wiley, New York
16. Marois M (ed) (1969) Theoretical physics and biology. In: Proceedings of the first international conference on theoretical physics and biology, Versailles, 26–30 June 1967. North-Holland Publishing Company, Amsterdam
17. Moffitt W (1956) *J Chem Phys* 25:467
18. Davydov AS (1951) Teoriya pogloshcheniya sveta v molekulyarnykh kristallakh. Akad. Nauk USSR, Kiev (in Russian)
19. Yomosa S (1964) π -Electronic structure of peptide group and hydrogen-bonded polypeptides. In: Weissbluth M (ed) Quantum aspects of polypeptides and polynucleotides. Biopolymers symposia no. 1. Wiley, New York, pp 1–33
20. Suard MG, Berthier G, Pullman B (1961) *Biochim Biophys Acta* 52:254
21. Cardew MH, Eley DD (1959) *Discuss Faraday Soc* 27:115
22. Chance B (1961) Free radicals and enzyme–substrate compounds. In: Blois MS, Brown HW, Lemmon RM, Lindblom RO, Weissbluth M (eds) Proceedings of the symposium on free radicals in biological systems, Stanford University, 1960. Academic, New York, pp 1–16
23. Commoner B, Townsend J, Pake GE (1954) *Nature* 174:689
24. Gordy W, Ard WB, Shields H (1954) *Proc Natl Acad Sci USA* 41:983
25. Ehrenberg A (1957) *Acta Chem Scand* 11:205
26. Beinert H, Sands RH (1959) *Biochem Biophys Res Commun* 1:171
27. Calvin M, Sogo PB (1957) *Science* 125:499
28. Sogo PB, Pon NG, Calvin M (1957) *Proc Natl Acad Sci USA* 43:387
29. Sogo PB, Jost M, Calvin M (1959) *Radiat Res Suppl* 1:511
30. Arnold W, Clayton RR (1960) *Proc Natl Acad Sci USA* 46:769
31. Chance B, Nishimura M (1960) *Proc Natl Acad Sci USA* 46:19
32. De Vault D, Chance B (1966) *Biophys J* 6:825
33. Grigorov LN, Chernavsky DS (1972) *Biofizika* 17:95 (in Russian)
34. Chernavskaya NM, Chernavsky DS (1973) *Stud Biophys* 35:149
35. Hopfield JJ (1974) *Proc Natl Acad Sci USA* 71:3640
36. Jortner J (1976) *J Chem Phys* 64:4860
37. Ulstrup J, Jortner J (1975) *J Chem Phys* 63:4358
38. Bixon M, Jortner J (1968) *J Chem Phys* 48:715
39. Dogonadze RR, Kuznetsov AM, Ulstrup J (1977) *J Theor Biol* 69:239
40. Kharkyanen VN, Petrov EG, Ukrainskii II (1978) *J Theor Biol* 73:29
41. Sarai A (1980) *Biochim Biophys Acta* 589:71
42. Jortner J (1980) *Biochim Biophys Acta* 594:193
43. Joliot P, Barbieri G, Chabaud R (1969) *Photochem Photobiol* 10:309
44. Joliot P, Joliot A, Bouges B, Barbieri G (1971) *Photochem Photobiol* 14:287
45. Kok B, Forbush B, McGloin M (1970) *Photochem Photobiol* 11:457
46. Shuvalov VA, Klimov VV (1976) *Biochim Biophys Acta* 440:587
47. Shuvalov VA, Sharkov AV, Matvets YA, Krukov PG (1978) *FEBS Lett* 91:135
48. Deisenhofer J, Epp O, Miki K, Huber R, Michel H (1984) *J Mol Biol* 180:385
49. Woodbury NW, Becker M, Middendorf D, Parson WW (1985) *Biochemistry* 24:7516
50. Martin J-L, Breton J, Hoff AJ, Migus A, Antonetti A (1986) *Proc Natl Acad Sci USA* 83:937
51. Breton J, Martin J-L, Fleming RG, Lumby JC (1988) *Biochemistry* 27:8276
52. Vos M, Rappaport F, Lumby J-C, Breton J, Martin J-L (1993) *Nature* 363:320
53. Vos M, Jones MR, Hunter CN, Breton J, Martin J-L (1994) *Proc Natl Acad Sci USA* 91:12701
54. Vos MH, Jones MR, Breton J, Lumby JC, Martin J-L (1996) *Biochemistry* 35:2687
55. Bixon J, Jortner J, Michel-Beyerle ME, Ogrodnik A (1989) *Biochim Biophys Acta* 977:273
56. Michel-Beyerle ME, Plato M, Deisenhofer J, Michel H, Bixon J, Jortner J (1988) *Biochim Biophys Acta* 932:52
57. Marcus RA, Sutin N (1985) *Biochim Biophys Acta* 811:265 (reviews on Bioenergetics)
58. Parson WW, Chu Z-T, Warshel A (1990) *Biochim Biophys Acta* 1017:251
59. Creighton S, Hwang J-K, Warshel A, Parson WW, Norris J (1988) *Biochemistry* 27:774
60. Zhang WM, Meier T, Cherniak V, Mukamel S (1988) *J Chem Phys* 108:7763
61. Shuvalov VA (2000) Preobrazovanie solnechnoi energii v pervichnom akte razdeleniya zaryadov v reaktsionnykh tseentrakh fotosinteza (Conversion of solar energy in a primary act of charge separation in photosynthetic reaction centers). Nauka, Moscow (in Russian)
62. Suard M (1962) *Biochim Biophys Acta* 59:227
63. Suard M (1962) *Biochim Biophys Acta* 64:400
64. Roothaan CCJ (1951) *Rev Mod Phys* 23:69
65. Pariser R, Parr RG (1953) *J Chem Phys* 21:466
66. Löwdin PO (1950) *J Chem Phys* 18:365
67. Ham SS, Platt JR (1952) *J Chem Phys* 20:335
68. Lyons LE (1957) *J Chem Soc* 5001
69. Blumenfeld LA, Benderskiy VA (1963) *J Struct Chem* 4:415 (in Russian)
70. Kukushkin AK (1970) *Vestn Mosk Univ Ser 3 Fiz Astron* 2:205 (in Russian)
71. Kukushkin AK, Tikhonov AN (1988) Lectures on biophysics of plant photosynthesis. Moscow State University Publication, Moscow
72. Tinoco I Jr (1960) *J Am Chem Soc* 82:4785; Erratum: (1960) *J Am Chem Soc* 83:5047
73. Rhodes W (1961) *J Am Chem Soc* 83:3609
74. DeVoe H (1964) In: Weissbluth M (ed) Quantum aspects of polypeptides and polynucleotides. Biopolymers symposia no. 1. Wiley, New York, p 251
75. Nesbet RK (1962) *Mol Phys* 5:63
76. Bolton HC, Weiss JJ (1962) *Nature* 195:666
77. Kirkwood JG (1937) *J Chem Phys* 5:479
78. Tinoco I Jr (1960) *J Chem Phys* 33:1332; Erratum: (1961) *J Chem Phys* 34:1067
79. Pullman B, Pullman A (1958) *Bull Soc Chim Fr* 766 (in French)
80. Veillard A, Pullman B (1963) *J Theor Biol* 4:37
81. Pople JA (1953) *Trans Faraday Soc* 49:1375
82. Bradley DF, Lifson S, Honig B (1964) In: Pullman B (ed) Electronic aspects of biochemistry. Academic, New York, p 77
83. Del Re G (1958) *J Chem Soc* 4031
84. Rein R, Fukyda N, Clarke GA, Harris FE (1968) *J Theor Biol* 21:88
85. Pullman B, Pullman A (1959) *Biochim Biophys Acta* 36:343
86. Hoffmann TA, Ladik J (1964) *Adv Chem Phys* 7:84
87. Danilov VI, Kuprievich VA, Shramko OV (1967) *Biofizika* 12:186 (in Russian)
88. Danilov VI (1967) *Biofizika* 12:540 (in Russian)
89. Danilov VI, Shramko OV, Dyadusha GG (1967) *Biofizika* 12:544 (in Russian)
90. Danilov VI, Kuprievich VA, Shramko OV (1967) *Biofizika* 12:606 (in Russian)

91. Kuprievich VA, Danilov VI, Shramko OV (1967) *Mol Biol* 1:343 (in Russian)
92. Danilov VI, Kuprievich VA, Shramko OV (1967) *Dokl Akad Nauk* 177:1465 (in Russian)
93. Löwdin PO (1964) In: Weissbluth M (ed) *Quantum aspects of polypeptides and polynucleotides*. Biopolymers symposia no. 1. Wiley, New York, p 61
94. Beukers R, Berends W (1960) *Biochim Biophys Acta* 38:573
95. Pulman A (1969) *Ann NY Acad Sci* 158:65–85
96. Lewin B (1991) *Gene, Lehrbuch der molekularen Genetik, Zweite Auflage*. VCH, Weinheim, p 65
97. Kruglyak YA, Danilov VI, Kuprievich VA, Ogloblin VV (1972) *Theor Exp Chem* 6:28–33 (in English) [(1970) *Teoreticheskaya I Eksperimental'naya Khimiya* 6:33–39 in Russian]
98. Löwdin PO (1963) *Rev Mod Phys* 35:724
99. Ladik J (1964) *J Theor Biol* 6:201
100. Rein R, Ladik J (1964) *J Chem Phys* 40:2466
101. Rein R, Harris FE (1964) *J Chem Phys* 41:3393
102. Rein R, Harris FE (1965) *J Chem Phys* 43:4415
103. Clementi E, Mehl J, von Niessen W (1971) *J Chem Phys* 54:508
104. Blizzard AC, Santry DP (1969) *J Theor Biol* 25:461
105. Maranon J, Sorarrain OM, Grinberg H, Lamdan S, Gaozza CH (1978) *J Theor Biol* 74:11
106. Merchan M, Serrano-Andres L (2003) *J Am Chem Soc* 125:8108
107. Serrano-Andres L, Merchan M (2005) *J Mol Struct (Theochem)* 729:109
108. Poltev VI, Shulyupina NV (1984) *Mol Biol* 18:154 (in Russian)
109. Poltev VI (1983) In: Gaziev AI (ed) *Structural and functional aspects of DNA replication and reparation*. Institute of Biophysics, Pushchino, p 101 (in Russian)
110. Berthod H, Pullman AJ (1965) *J Chim Phys* 62:942 (in French)
111. Hirata S, Ivanov S, Grabowski I, Bartlett RJ, Burke K, Talman JD (2001) *J Chem Phys* 115:1635
112. Poltev VI, Shulyupina NV, Bruskov VI (1980) *Stud Biophys* 79:45
113. Chuprina VP, Khutorsky VE, Poltev VI (1981) *Stud Biophys* 85:81
114. Poltev VI, Chuprina VP, Shulyupina NV, Bruskov VI (1982) *Stud Biophys* 87:247
115. Chuprina VP, Poltev VI (1983) *Nucleic Acids Res* 11:5205
116. Hug V, Tinoco I Jr (1973) *J Am Chem Soc* 95:2803
117. Pullman A (1968) *Int J Quantum Chem Symp* 2:187
118. Snyder LC, Shulman RG, Neumann DB (1970) *J Chem Phys* 53:256
119. Aida M, Negishi K, Hayatsu H, Maeda M (1988) *Biochem Biophys Res Commun* 153:552
120. Tarashima S (1969) *Biopolymers* 8:199
121. DeVoe H, Tinoco I Jr (1962) *J Mol Biol* 4:500
122. Rein R, Pollak M (1967) *J Chem Phys* 47:2039
123. Eley DD, Spivey DI (1962) *Trans Faraday Soc* 58:411
124. O'Konski CT, Moser P, Shirai M (1964) *Biopolym Symp* 1:479
125. Solti NK, Pant MM (1975) *Indian J Biochem Biophys* 12:216
126. Warman JM, De Haas MP, Rupprecht A (1996) *Chem Phys Lett* 249:319
127. Olson EJC, Hu D, Hörmann A, Barbara PF (1997) *J Phys Chem B* 101:299
128. Dandliker PL, Holmlin RE, Barton JK (1997) *Science* 275:1464
129. Oganessian VS, Hubbard PL, Butt JN, Jayasooriya UA (2003) *Phys B Condens Matter* 326:25
130. Lange AW, Herbart JM (2008) Abstracts of OSU international symposium on molecular spectroscopy. <http://hdl.handle.net/1811/33397>
131. Otten HA (1971) *Photochem Photobiol* 14:289
132. Nagae H, Yomosa S (1977) *J Phys Soc Jpn* 42:998
133. Knop JV, Stichtenoth H (1972) *Z Naturforsch* 27A:1972
134. McHugh AJ, Gouterman M, Weiss C Jr (1972) *Theor Chem Acc* 24:346
135. Maggiora GM, Weimann LJ (1974) *Int J Quantum Chem Quantum Biol Symp* 1:179
136. Yip KL, Duke CB, Salaneck WR, Plummer EW, Loubriel G (1977) *Chem Phys Lett* 49:530
137. Petke JD, Maggiora GM, Shipman LL, Christoffersen RE (1978) *J Mol Spectrosc* 73:311
138. Petke JD, Maggiora GM, Shipman LL, Christoffersen RE (1980) *Photochem Photobiol* 31:243
139. Petke JD, Maggiora GM, Shipman LL, Christoffersen RE (1979) *Photochem Photobiol* 30:203
140. Petke JD, Maggiora GM, Shipman LL, Christoffersen RE (1980) *Photochem Photobiol* 32:399
141. Loach PA, Bambara RA, Ryan RJ (1971) *Photochem Photobiol* 13:247
142. Norris JR, Uphaus RA, Katz JJ (1971) *Proc Natl Acad Sci USA* 68:625
143. Petke JD, Maggiora GM, Shipman LL, Christoffersen RE (1978) *J Mol Spectrosc* 71:64
144. Whitten JL, Hackmeyer M (1969) *J Chem Phys* 51:5584
145. Christoffersen RE (1972) *Adv Quantum Chem* 6:333
146. Christoffersen RE, Spangler D, Hall GG, Maggiora GM (1973) *J Am Chem Soc* 95:8526
147. Spangler D, Maggiora GM, Shipman LL, Christoffersen RE (1977) *J Am Chem Soc* 99:7470
148. Spangler D, Maggiora GM, Shipman LL, Christoffersen RE (1977) *J Am Chem Soc* 99:7478
149. Maslov VG (1981) *Theor Exp Chem* 17:372 (in Russian)
150. Plato M, Trankle E, Lubitz W, Lenzian F, Mobius K (1986) *Chem Phys* 107:185
151. Sinnecker S, Koch W, Lubitz W (2002) *J Phys Chem B* 106:5281
152. Berezin KV, Nechaev VV, Ziganshina OD (2004) *J Struct Chem* 45:217
153. Berezin KV, Nechaev VV (2005) *J Appl Spectrosc* 72:164
154. Eriksson LA, Himo F, Siegbahn PEM, Babcock GT (1997) *J Phys Chem A* 101:9496
155. O'Malley PJ (1999) *Biochim Biophys Acta* 1411:101
156. Rinyu L, Nagy L, Kortvelyesi T (2001) *J Mol Struct (Theochem)* 571:163
157. Ikryannikova LN, Ustynyuk LY, Tikhonov AN (2004) *J Phys Chem A* 108:4759
158. Perdew JP, Burke K, Ernzerhof M (1996) *Phys Rev Lett* 77:3865; Errata: (1997) *Phys Rev Lett* 78:1396
159. Dittrich M, Freddolino PL, Schulten K (2005) *J Phys Chem B* 109:3006
160. Jalkanen KJ (2003) *J Phys Condens Matter* 15:S1823
161. Jalkanen KJ, Elstner M, Suhai S (2004) *J Mol Struct (Theochem)* 675:61
162. Jalkanen KJ, Nieminen RM, Frimand K, Bohr J, Bohr H, Wade RC, Tajkhorshid E, Suhai S (2001) *Chem Phys* 265:125
163. Han W-G, Elstner M, Jalkanen KJ, Frauenheim T, Suhai S (2000) *Int J Quantum Chem* 78:459
164. Bohr H, Jalkanen KJ (2005) In: Clark JW, Panoff RM, Li H (eds) *Condensed matter theories*, vol 20. Nova Science Publishers, Hauppauge, p 375
165. Jürgensen VW, Jalkanen KJ (2006) *Phys Biol* 3:S63
166. Jalkanen KJ, Nieminen RM, Bohr J (2000) Proceedings of the international conference BIOCATALYSIS-2000: FUNDAMENTALS & APPLICATIONS, June 10–15, 2000, Moscow, Russia. *Vestn Mosk Univ Ser 2 Khim* 41:4. Journal link: <http://www.chem.msu.ru/eng/journals/vmgu/00add/welcome.html>; PDF link: <http://www.chem.msu.ru/eng/journals/vmgu/00add/4.pdf>
167. Abdali S, Jalkanen KJ, Cao X, Nafie LA, Bohr H (2004) *Phys Chem Chem Phys* 6:2434

168. Kuhn H (1986) *Phys Rev A* 34:3409
169. Datta SN, Mallik B (1997) *Int J Quantum Chem* 61:865
170. Shipman LL (1982) Energy conversion by plants and bacteria. In: Govingjee (ed) *Photosynthesis*, vol 1. Academic, New York, p 403
171. Bylina EJ, Kirmaier C, Mc Dowell L, Holten D, Youvan DC (1988) *Nature* 336:182
172. Sadygov RG, Kukushkin AK (1991) *Biofizika* 36:990 (in Russian)
173. Parush OV, Sadygov RG, Kukushkin AK (1994) *Biofizika* 39:848 (in Russian)
174. Mataga N (1958) *Bull Chem Soc Jpn* 31:453
175. Xei XL, Simon JD (1991) *Biochim Biophys Acta* 1057:131
176. Deisenhofer J, Epp O, Miki R (1985) *Nature* 318:618
177. Sakuma T, Kashiwagi H, Takada T, Nakamura H (1997) *Int J Quantum Chem* 61:137
178. Peluso A, Di Donato M, Saracino GA (2000) *J Chem Phys* 113:3112
179. Wu SW, Ogawa N, Ho W (2006) *Science* 312:1362
180. Damjanovic A, Kosztin I, Kleinekathofer U, Schulten K (2002) *Phys Rev E* 65:031919
181. Kukushkin AK, Poltev S, Khuznetsova S (2002) *Bioelectrochemistry* 56:9
182. Tomchuk P, Procenko N, Krasnogolovets V (1985) *Biochim Biophys Acta* 807:272
183. Belousov RV, Poltev SV, Kukushkin AK (2003) *Biophysics* 40:606
184. Dewar MJS, Thiel W (1977) *J Am Chem Soc* 99:4899
185. Ziganshina OD (2005) The quantum mechanical calculations of the vibrational spectra and structure of cofactors of photosynthetic reaction center. Ph.D. thesis. N.G. Chernyshevsky Saratov State University Press, Saratov (in Russian)
186. Belousov RV, Belov AA, Kukushkin AK (2004) *Biofizika* 49:463 (in Russian)
187. Krasilnikov PM, Mamonov PA (2006) *Biofizika* 51:267 (in Russian)
188. Tulub AA, Stefanov VE, Skaletskii EK (2001) *Biofizika* 46:581 (in Russian)
189. Green ME (2001) *J Phys Chem A* 105:5298
190. Saprova A, Bystrov V, Green ME (2003) *J Mol Struct (Theochem)* 630:297
191. Ben-Nun M, Molnar F, Lu H, Phillips JC, Martinez TJ, Schulten K (1998) *Faraday Discuss* 110:447
192. Hayashi S, Tajkhorshid E, Kandori H, Schulten K (2004) *J Am Chem Soc* 126:10516
193. Hayashi S, Ohmine I (2000) *J Phys Chem B* 104:10678
194. Grigorenko BL, Nemukhin AV, Shadrina M, Topol I, Burts S (2007) *Proteins* 66:456
195. Nemukhin AV, Grigorenko BL, Shadrina M (2007) *Ros Khim Zh* 51:27 (in Russian)
196. Nemukhin AV, Grigorenko BL, Granovski AA (2004) *Vestn Mosk Univ Ser 2 Khim* 45:75 (in Russian) [<http://www.chem.msu.ru/rus/vmgu/042/abs001.html>]
197. Nemukhin AV, Bochenkova AV, Bravaya KV, Granovsky AA (2006) *Proc SPIE* 6449:6449N(1)
198. Bravaya KV, Bochenkova AV, Granovsky AA, Nemukhin AV (2007) *J Am Chem Soc* 129:13035
199. Bravaya KV, Bochenkova AV, Granovsky AA, Savitsky AP, Nemukhin AV (2008) *J Phys Chem A* 112:8804
200. Masgrau L, Roujeinikova A, Johannissen LO, Hothi P, Basran J, Ranaghan KE, Mulholland AJ, Sutcliffe MJ, Scrutton NS, Leys D (2006) *Science* 312:237
201. Rovira C (2003) *J Phys Condens Matter* 15:S1809
202. Car R, Parinello M (1985) *Phys Rev Lett* 55:2471
203. Marx D, Tuckerman M, Martuna GJ (1999) *Comput Phys Commun* 118:166
204. Kusunoki M, Kitaura K, Morokuma K, Nagata C (1980) *FEBS Lett* 117:179
205. Zouni A, Witt HT, Kern J, Fromme P, Krauss N, Saenger W (2001) *Nature* 409:739
206. Kamiya N, Shen JR (2003) *Proc Natl Acad Sci USA* 100:98
207. Ferreira KN, Iverson TM, Maghlaoui K, Barber J, Iwata S (2004) *Science* 303:1831
208. Raval MK, Biswal UC (1985) *J Theor Biol* 115:137
209. Denisenko AS, Kukushkin AK (2005) *Biofizika* 50:833 (in Russian)
210. Kusunoki M (2006) In: Proskuryakov II (ed) *Programme and abstracts of international meeting "photosynthesis in the post-genomic era: structure and function of photosystems."* NIA-Priroda, Moscow, p 104
211. Sproviero EM, Gascon JA, McEvoy JP, Brudvig GW, Batista VB (2006) *J Chem Theory Comput* 2:1119
212. Filatov M, Cremer D (2005) *J Chem Phys* 123:124101
213. Stephens PJ, Devlin F, Chabalowski CF, Frisch M (1994) *J Phys Chem* 98:11623
214. Runge E, Gross EKV (1984) *Phys Rev Lett* 52:997
215. Wanko M, Garavelli M, Bernardi F, Niehaus TA, Frauenheim T, Elstner M (2004) *J Chem Phys* 120:1674
216. Young DC (2001) *Computational chemistry: a practical guide for applying techniques to real-world problems*. Wiley, New York
217. Koch W, Holthausen MC (2000) *A chemist's guide to density functional theory*. Wiley-VCH, Weinheim
218. Parr RG, Yang W (1989) *Density-functional theory of atoms and molecules*. Oxford University Press, Oxford
219. Frauenfelder H, Wolynes PG, Austin RH (1999) *Rev Mod Phys* 71:419
220. Segall MD (2002) *J Phys Condens Matter* 14:2957
221. Stephens PJ, Devlin FJ (2007) *Vibrational circular dichroism*. In: Mennucci B, Cammi R (eds) *Continuum solvation models in chemical physics: from theory to applications*. Wiley, New York, pp 180–205
222. Jalkanen KJ, Bohr HG, Suhai S (2009) *Quantum molecular biological methods using density functional theory*. In: Bohr HG (ed) *Handbook of molecular biophysics*. Wiley-VCH, Weinheim, pp 7–66
223. Jalkanen KJ, Suhai S (1996) *Chem Phys* 208:81
224. Deng Z, Polavarapu PL, Ford SJ, Hecht L, Barron LD, Ewig CS, Jalkanen KJ (1996) *J Phys Chem* 100:2025
225. Jalkanen KJ, Bohr H, Suhai S (1997) *Density functional and neural network analysis: hydration effects and spectroscopic and structural correlations in small peptides and amino acids*. In: Suhai S (ed) *Theoretical and computational methods in genome research*. Plenum Press, New York, pp 255–277
226. Han W, Jalkanen KJ, Elstner M, Suhai S (1998) *J Phys Chem B* 102:2587
227. Bohr H, Jalkanen KJ, Frimand K, Elstner M, Suhai S (1999) *Chem Phys* 246:13
228. Jalkanen KJ, Degtyarenko IM, Nieminen RM, Cao X, Nafie LA, Zhu F, Barron LD (2008) *Theor Chem Acc* 119:191
229. Tajkhorshid E, Jalkanen KJ, Suhai S (1998) *J Phys Chem B* 102:5899
230. Frimand K, Jalkanen KJ, Bohr HG, Suhai S (2000) *Chem Phys* 225:165
231. Abdali S, Jalkanen KJ, Bohr H, Suhai S, Nieminen RM (2002) *Chem Phys* 282:219
232. Knapp-Mohammady M, Jalkanen KJ, Nardi F, Wade RC, Suhai S (1999) *Chem Phys* 240:63
233. Jalkanen KJ, Nieminen RM, Knapp-Mohammady M, Suhai S (2004) *Int J Quantum Chem* 92:239
234. Deplazes E, van Bronswijk W, Zhu F, Barron LD, Ma S, Nafie LA, Jalkanen KJ (2008) *Theor Chem Acc* 119:155

235. Jalkanen KJ, Ma D, Nafie LA, Zhu F, Barron LA, Aoki Y, Rohl AL, Gale JD (2009) *Theor Chem Acc* (this issue)
236. Serdyuk IN, Zaccai NR, Zaccai J (2007) *Methods in molecular biophysics*. Cambridge University Press, Cambridge
237. Tanaka T, Kodama TS, Morita HE, Ohno T (2006) *Chirality* 18:652
238. Sebek J, Gyurcsik B, Sebestik J, Kejik Z, Bednarova L, Bour P (2007) *J Phys Chem A* 111:2750
239. Rogers DM, Hirst JD (2004) *Biochemistry* 43:11092
240. Oakley MT, Hirst JD (2006) *J Am Chem Soc* 128:12414
241. Miron S, Refregiers M, Gilles A-M, Maurizot J-C (2005) *Biochim Biophys Acta* 1724:425
242. Tabisz GC, Cameron R, Qu W (2008) *Annu Rep Prog Chem C* 104:13
243. Buckingham AD (1998) *Annu Rev Phys Chem* 49:xiii
244. Varfolomeev MA, Abaidullina DI, Klimovitskii AE, Solomonov BN (2007) *Russ J Gen Chem* 77:1742 [also in Russian, (2007) *Zh Obshch Khim* 77:1677]
245. Bohr H, Jalkanen KJ, Malik FB (2005) *Mod Phys Lett B* 19:473
246. Jalkanen KJ, Jürgensen VW, Claussen A, Rahim A, Jensen GM, Wade RC, Nardi F, Jung C, Degtyarenko IM, Nieminen RM, Herrmann F, Knapp-Mohammady M, Niehaus TA, Frimand K, Suhai S (2006) *Int J Quantum Chem* 106:1160