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REGULAR ARTICLE

The application of quantum chemistry and condensed matter theory in studying amino-acids, protein folding and anticancer drug technology

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Abstract The adaptation of methods from quantum chemistry and condensed matter theory for studying biological molecules has proved fruitful in developing our understanding of the electronic and conformational structure and thereby the functionality of amino-acids and proteins. Professor Suhai has been at the forefront of these developments and has made contributions in many areas of this vast field of research. In this article, we focus on three such areas, namely, (1) amino acids, (2) bacteriorhodopsin and (3) anti-cancer drugs involving especially Ru and Rh. We show how advances in density functional theory (DFT) have been used to calculate the electronic structure and density in amino-acids so that they can be compared with X-ray diffraction studies. We also demonstrate how ideas from the theory of phase transitions in condensed matter may be applied for studying phase transitions in bacteriorhodopsin, DNA and proteins. Finally, we highlight some of the recent work done in bringing DFT together with quantum chemistry modelling in studying metallopharmaceutical complexes and conformations of peptides.

Keywords Quantum chemistry · Amino acids · Bacteriorhodopsin · Protein folding

1 Background and outline

In recent years, there has been much progress in the application of techniques from quantum chemistry and physical modelling to study the biological systems. Thus electronic structure calculations based on Hartree–Fock (HF) theory and density functional theory (DFT) have been used to give information about the structure of amino-acids and proteins as well as helping in the understanding of protein and DNA folding. However, the complexity of these types of calculations has meant the simulations of proteins and large biological molecules, with a view to learn about their structure in the condensed or globular phase, being dependent on effective interatomic forces that have had to be constructed. In addition, physical theories based on statistical mechanics and phase transitions have a role to play in furthering our understanding of the energy and structural aspects of large biomolecules. Coupled with these theoretical/computational approaches there have been great advances in the application of Raman and optical spectroscopies for studying the structures and conformations of biomolecules. Increasingly, there is a view that a combined experimental and theoretical approach is required to answer questions in the field of molecular biophysics [1]. In this article, we give a brief overview of how these approaches have been applied to a number of specific systems.

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

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2 Electronic structure of glycine: recent advances in the exchange energy and potential of density functional theory

Glycine [2] has been recently studied using the Hartree–Fock approximation supplemented by second-order Möller–Plesset perturbation theory (MP2). Though the so-called Löwdin correlation energy [3], defined as the difference between the exact ground state energy (E) and the HF results (E_{HF}), is clearly neglected in the above study, the pioneering work of Möller and Plesset [4] showed that the HF ground-state density $n(\mathbf{r})$ is already very valuable. This is because the HF density is accurate to second-order in the difference between the Fock operator and the exact (non-relativistic) Hamiltonian.

Returning to glycine, after the brief background set out above, the HF approximation plus MP2 was first employed [2] to predict the equilibrium nuclear structure. Of course, because of the complexity of the potential energy surface, it was only possible to say with some certainty that the predicted structure will be one of the lowest lying conformers of glycine: the smallest amino acid. It is nevertheless worth noting that in reference [2], the zwitterionic structure sometimes noted in the present context is not low-lying according to the HF approximation employed.

2.1 Exchange energy density and exchange potential in glycine

The focus in reference [2] was the Dirac single-particle(s) idempotent matrix γ_s calculated from the HF wave functions $\psi_i(\mathbf{r})$. This is then defined by

$$\gamma_s(\mathbf{r},\mathbf{r}') = \sum_{\text{occupied } i} \psi_i^*(\mathbf{r})\psi_i(\mathbf{r}') \tag{1}$$

and it is the orthonormality of these wave functions which lead to the idempotency of the Dirac matrices, γ_s.

In reference [2], γ_s has then been employed, following Dirac [5], to calculate the important exchange energy, E_x, related to γ_s by

$$E_x = -\frac{e^2}{4}\int \frac{\gamma_s^2(\mathbf{r},\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|}\mathrm{d}\mathbf{r}\mathrm{d}\mathbf{r}' \tag{2}$$

Though not unique, the natural definition of the exchange energy density $\varepsilon_x(\mathbf{r})$ from Eq. 2 is

$$\epsilon_x(\mathbf{r}) = -\frac{e^2}{4}\int \frac{\gamma_s^2(\mathbf{r},\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|}\mathrm{d}\mathbf{r}' \tag{3}$$

which, of course, from Eqs. 2 and 3, satisfies $E_x = \int \epsilon_x(\mathbf{r})\mathrm{d}\mathbf{r}$. Slater [6] (see also Kleinman [7] and Holas and March [8]) then defined an approximate non-local exchange potential, denoted below by $V_x^{Sl}(\mathbf{r})$, using the analogy with electrostatics through $E_x = (1/2)\int n(\mathbf{r})V_x^{Sl}(\mathbf{r})\mathrm{d}\mathbf{r}$, as

$$V_x^{Sl}(\mathbf{r}) = \frac{2\epsilon_x(\mathbf{r})}{n(\mathbf{r})} \tag{4}$$

The idempotency of γ_s was subsequently used by one of us [9] to evaluate Eq. 3 far from all nuclei in a molecule or cluster as

$$\epsilon_x(\mathbf{r}) = -\frac{1e^2}{2\,r}n(\mathbf{r}) \quad |\mathbf{r}| \to \infty \tag{5}$$

and hence from Eqs. 4 and 5 the Slater potential $V_x^{\mathrm{Sl}}(\mathbf{r}) \to -\frac{e^2}{r}$ as $|\mathbf{r}|$ tends to infinity. This latter result means that the physically important self-interaction correction is included in Slater's proposal for the exchange potential.

For glycine, contours of equi-density $n(\mathbf{r})$ have been calculated in reference [2] and for a particular plane are exhibited in Fig. 1. Using the HF density matrix γ_s, $\varepsilon_x(\mathbf{r})$ has also been calculated from equation (3) and again the equi-energy contours are displayed in Fig. 2. They are seen to be remarkably similar in shape to those of $n(\mathbf{r})$ in Fig. 1. Third, the Slater exchange potential is displayed in the same manner in Fig. 3, essentially by dividing $\varepsilon_x(\mathbf{r})$ in Fig. 2 by $n(\mathbf{r})$ in Fig. 1, according to Eq. 4.

The remarkable similarity in shape in Figs. 1, 2, 3 is reflecting the fact that a type of local density approximation (LDA) is a starting point for glycine, though not the 'free-electron'-like form $\epsilon_x(\mathbf{r}) = -C_x[n(\mathbf{r})]^{4/3}$ or the corresponding $V_x(\mathbf{r}) = -(4/3)C_x[n(\mathbf{r})]^{1/3}$ for the exchange potential.

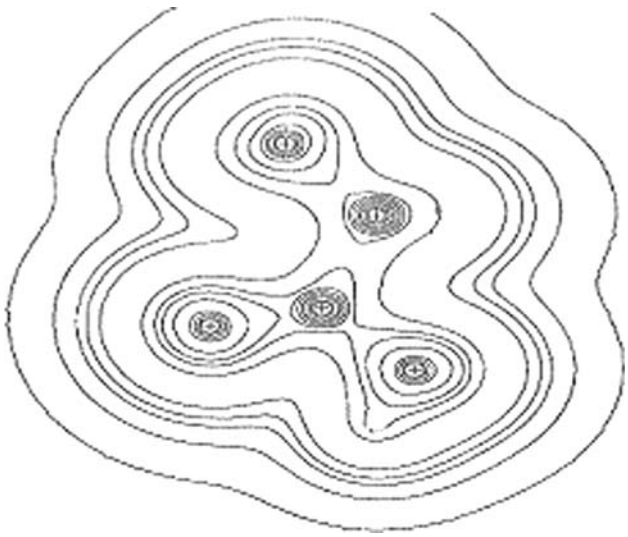

Fig. 1 Shape of equi-density contours for lowest conformer of glycine, in the plane through the five heavy nuclei. Contours are plotted at values of 100, 50, 20, 10, 5, 3, 2, 1, 0.1, 0.05, 0.03, 0.01 and 0.001 e/A^3 (redrawn from reference [2])

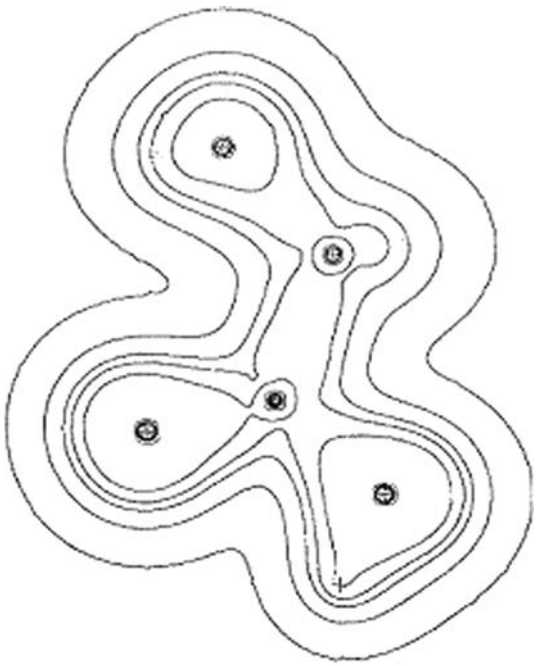

Fig. 2 As for Fig. 1, but contours are now for constant energy density. Complete shape similarity would imply the validity of a local density approximation, though not the Dirac–Slater $(n(\mathbf{r})^{4/3})$ form (redrawn from reference[2])

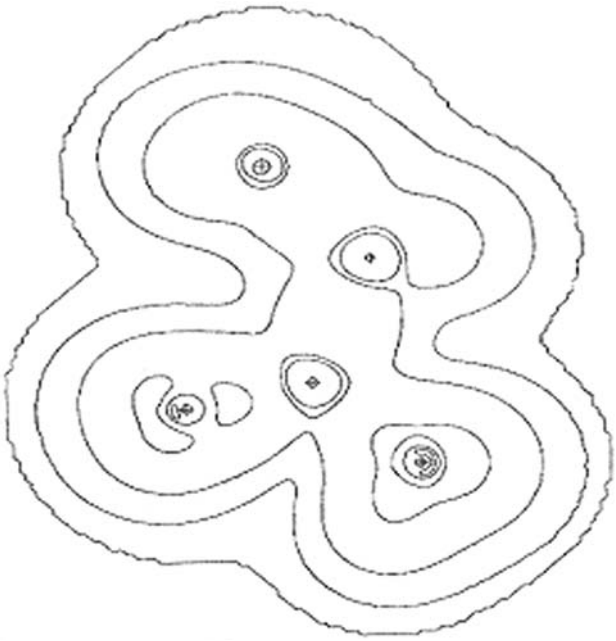

Fig. 3 Contours of Slater approximation to the exchange potential in glycine, calculated using Fig. 2 for the exchange energy density and Fig. 1 for the ground state electron density of glycine. Note that this Slater potential already embodies the self-interaction correction (redrawn from reference[2])

2.2 Transcending the Slater exchange potential

Quite recently, Della Sala and Görling [10] have transcended the approximation $V_x^{\mathrm{Sl}}(\mathbf{r})$ given in Eq. 4, but based on the somewhat drastic assumption that the single-Slater determinant formed from the occupied HF orbitals $\psi_i(\mathbf{r})$ entering Eq. 1 is equal to that of the analogous Slater determinant formed from Kohn–Sham orbitals obtained from a one-body potential $V(\mathbf{r})$, rather than the non-local Fock operator used, for example, in reference [2]. Howard and March [11, 12] subsequently gave an exact formal completion of the Della Sala–Görling proposal, and this completion has been used in obtaining practical approximations by March and Nagy [13].

2.3 Possible calculation of Dirac matrix from a ground state density $n(\mathbf{r})$ obtained either from X-ray diffraction experiments or from quantum Monte Carlo simulations

One really requires for accurate DFT calculations on glycine the exchange (x)—correlation (c) potential $V_{xc}(\mathbf{r})$, rather than just an approximation to the exchange-only potential discussed above. Then the one-body potential of $V(\mathbf{r})$ can be written in the form

$$V(\mathbf{r}) = V_{\mathrm{Hartree}}(\mathbf{r}) + V_{xc}(\mathbf{r})$$

where

$$V_{xc}(\mathbf{r}) = \frac{\delta E_{xc}[n]}{\delta n(\mathbf{r})}.$$

Since the functional $E_{xc}[n]$ is unknown currently, March and Suhai [14] have proposed to use $n(\mathbf{r})$ obtained by means of X-ray diffraction measurements. Presently, we know of no suitably accurate X-ray data for glycine but, for instance, formamide has been analysed by Howard et al. [15]. Subsequently Holas and March [16] have proposed a way to refine the idempotent matrix set up by Howard et al. [15], with the measured density $n(\mathbf{r})$ on its diagonal, such that this matrix is derivable from a local potential $V(\mathbf{r})$ as used in DFT [17].

3 Bacteriorhodopsin: models of electronic structure, melting and precursor phase transitions

From the amino acid glycine, we turn next to the retinal protein bacteriorhodopsin (bR). A body of work now exists on its electronic structure, to which Professor Suhai himself has contributed. Therefore, we refer briefly in this section to this work [18], which was motivated by experiments on the (polyene) chromophore in the above retinal protein. The observed red shift was one of the interesting findings of such experimental work.

The theoretical study of Howard et al. [18] was concerned more generally with the change in electronic structure of polyenes in interaction with other large organic molecules in particular, with the polyacenes. In this study, particular attention was given to (a) the variation of bond lengths brought about by the above interaction and (b) the HOMO–LUMO energy gap. Since the experiments on the (polyene) chromophore in bacteriorhodopsin referenced above will plainly require the incorporation of mechanisms in proximity, perturbations additional to those considered specifically by Howard et al. [18], the interested reader should refer to the recent study of such perturbations by Sakurai et al. [19].

With these quite brief comments on the electronic structure of bacteriorhodopsin, and the useful role of quantum-chemical studies, we turn to consider below topics more closely related to background in condensed matter chemical physics. After some general background on protein folding, we shall summarise next the results of work of March et al. [20] on the melting temperatures of bacteriorhodopsin, and especially its variation with pH on which experiments are available.

3.1 Melting temperature and a precursor phase change in retinal protein bacteriorhodopsin as a function of pH

With Professor Suhai, we (MSM) [20] have recently studied the melting temperature of bacteriorhodopsin as a function of pH. It is relevant to note in this context the recent review by one of us [21] which was concerned with melting and precursor phase transitions in chemically bonded assemblies.

The motivation for the work in MSM was the experimental investigation of Heyes and El-Sayed (HES) [22] on the melting and pre-melting temperatures of bR. Previous calometric and spectroscopic investigations had revealed two main phase transitions as the temperature of bR is increased [23–25].

There is a modest reversible pre-melting transition in the range 70°–80° C and a quite prominent transition at 96° C, which Jackson and Sturtevant [26] conclude is irreversible. The experimental work of HES was concerned with the measurement of the temperature dependence of the Fourier transform infrared spectrum of bR as a function of the pH and of the divalent cation regeneration with Ca^{2+} and Mg^{2+}.

Figure 4 shows the transition temperature as measured by HES for pre-melting and for melting as a function of pH for native bR. These workers stress the contrast between this behaviour and that found for the pre-melting transition temperature. The latter varies but weakly for these pH samples that exhibit a pre-melting transition.

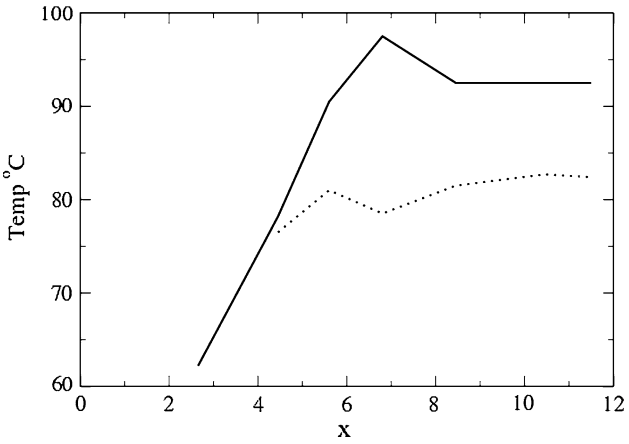

Fig. 4 Transition temperature for pre-melting (*dotted line*) and melting (*straight line*) as a function of pH(x) based on the data from HES [22]

3.2 Proposals as to the nature of the reversible precursor transition in relation to melting

We summarise briefly below the proposals put forward by March et al. [20] concerning the nature of the precursor transition in relation to melting. These workers referred to the order–disorder theory of the melting transition going back to Lennard-Jones and Devonshire [27]. This model had one parameter, U, which in turn relates to a point defect energy. Evidently, the thermal energy $k_B T_m$ has its scale fixed by the parameter U in this model. Considering briefly the simpler case of a diatomic molecular solid such as built from N_2 molecules, experiment demonstrates that at sufficiently low temperatures the molecules attached to the lattice sites of a perfect translational crystal lattice are ordered orientationally. But on raising the temperature, a plastic phase is reached, preceding the melting transition, in which orientational disorder occurs. Pople and Karasz [28, 29] therefore proposed a phenomenological extension of the Lennard-Jones and Devonshire model, which is well summarised in the book on melting by Ubbelohde [30]. In the Pople-Karasz model the new feature was a barrier height, B, which had to be overcome to expose the additional degrees of freedom which contribute when disorder in the originally orientationally ordered molecules sets in. In the work of MSM, it is emphasised that the generalised statistical–mechanical model involving the coupling of the melting and the precursor 'orientational disorder' transition is reminiscent of Fig. 2 taken from HES [20]. What is to be stressed, though, is that there is now no certainty presently that the second parameter B, which must be introduced because of pre-melting, is directly associated with additional degrees of freedom embracing orientational disorder in bR. What seems evident however, from the initial linear increase of the melting temperature with increasing pH is

that once additional degrees of freedom enter the statistical–mechanical model, the melting curve is correlated with the transition temperature of the precursor phase change, leading to melting and pre-melting temperatures becoming essentially independent of pH. As seen from Fig. 4, there is a characteristic thermal energy (corresponding to $\sim 12°$ C) emerging for pH > 8. This ought to aid further attempts to generalise the Lennard-Jones and Devonshire model to embrace additional degrees of freedom revealed above the pre-melting transition, going beyond those considered in the phenomenological model of Pople and Karasz. The interested reader is referred to MSM for a full discussion. With this background, we want to turn to a discussion of the melting of DNA, the additional variable in this case being the salt concentration.

4 Melting of DNA

The idea of the melting of DNA refers to the dissocation of the two strands of a DNA molecule by heat. This process involves the breaking of the hydrogen bonds between complementary bases which in turn disrupts the base stacking. This melting, or denaturing, can also be caused by a number of other factors like salt concentration and the pH of the solvent. The melting temperature, T_m^{DNA}, used to characterise the denaturing, is the temperature at which half the base pair bonds have been broken. This melting is by its nature different from the melting refered to in the case of molecular solids, like bacteriorhodopsin. However, in both cases there is an energy barrier to overcome before melting takes place. In molecular solids, a disordering followed by a denaturing was postulated. By contrast, in melting DNA, only the breaking of bonds needs to be considered.

The thermal energy required to break all of the base pair bonds depends very strongly on ion-concentration in the solvent. This is because the ions (cation and OH^- groups) renormalise the base pair bond and an effective base pair bond needs to be considered. Any calculation of the melting temperature of DNA fragments thus needs to take into account this effective interaction by modelling the solvent ion–DNA interactions. Simulations on biopolymers in different solvent conditions have gone some way to addressing this. In the absence of sufficient theoretical work, we look to experiment to provide the necessary information. There has been much work done on the melting of DNA and the effect of salt concentration on the melting temperature. All the results appear to support a linear relationship between T_m^{DNA} and the salt concentration (Na^+). This may be seen in Fig. 5.

Replacing the NaCl salt solution with CsCl (i.e., Cs^+ ions) does not appear to affect the melting temperature.

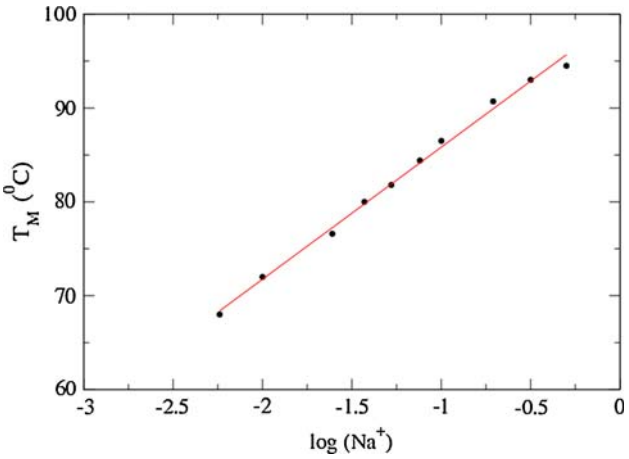

Fig. 5 Dependence of T_M on the log of salt (Na^+) concentration for a DNA fragment of the i-gene sequence of *E. coli* (redrawn after reference [31])

Further, the slopes, $dT_M/d(\log Na^+)$, remain roughly constant independent of the sequence and length of the DNA segment [31]. This reinforces the idea of the dominance of electrostatic ion–base pair interaction in determing the effective base pair forces.

In addition to the factors mentioned above, the melting temperature also depends on the length of the DNA segment and its sequence. Since a segment consists of G–C and A–T pairs, the barrier energy to overcome before melting is that of the breaking of these bonds. The GC pair consists of three hydrogen bonds while the AT pairs have only two bonds. So, it follows that to a good approximation, and for fairly long sequences, T_m^{DNA} depends strongly on the percentage of GC pairs (X_{GC}) in the sequence. A useful empirical formula for the temperature [31], in centigrade, expressing this relationship is

$$T_m^{\mathrm{DNA}} = T_0 + T_1 X_{\mathrm{GC}} + T_2(\log[\mathrm{Na}^+]) \tag{6}$$

where T_0 takes values between 65 and 75° C, $T_1 \sim 50$ and $T_2 \sim 16$.

5 Conformational studies of amino-acids and proteins

The problem of the equilibrium configurations of biological polymers is an important one, as a knowledge of the factors that influence it can provide the basis for an understanding of the structure and functions of cells and muscles. Thus, for example, the functioning of a protein is thought to depend on its structure. The designing of novel folds and the prediction of the most stable fold is therefore of great significance in the production of new enzymes with specific catalytic activities [32]. There have, consequently, been numerous attempts, using a wide variety of techniques, to investigate this general problem. For

instance, there have been efforts directed at solving the problem using a statistical–mechanical approach [33, 34], as well as by modelling the protein structures as a copolymer chain [35, 36]. Mean field theories of compact phases and first-order freezing transitions have also been constructed [37]. There have also been an increasing number of computer simulation studies of the equilibrium configurations of polymer structures [38–43]. Computer simulations affords a relatively simple approach with the added benefit that useful information about the mechanical response of polymers may be obtained by investigating the effect of stretching forces on a typical polymer chain. This allows a means of checking the validity of the inter-monomer forces employed in the description of the polymer. However, the complexity of the problem is such that polymer models tend to be minimal in the sense that they represent only the gross features of the polymer chain.

The dynamics of protein folding and unfolding is determined by the inter (and intra) monomer forces. Information about these forces can be gained experimentally from the force extension curves using the AFM and other techniques. Much of the early work on the computer simulations of polymer chains was done on ideal or near to ideal systems represented by self-avoiding walks. Biological macromolecules like proteins, DNA and actin have relatively large persistence lengths [44] and exhibit markedly different properties depending on their environment. Hence, in recent years the focus has shifted to less than ideal polymers. These systems have, in the main, been studied using the so called bead-spring and semi-flexible chain models. In a previous study we demonstrated that the bead-spring model, with a simple Morse potential describing the monomer interactions, can be used to give a good description of polymer chains in varying solvent conditons [45]. We also showed that it is possible to unambiguously identify poor, θ and good solvent regimes in these simulations by an examination of the structure factor of the configuration.

In addition to these approaches, there have been a number of investigations aimed at determining the conformational structure of amino-acids and peptides using a combination of spectroscopic data coupled with simulations based on DFT. Thus, for example, Suhai and coworkers [46–48] have applied self-consistent DFT within the tight-binding formalism to perform ab initio calculations and simulations of vibrational absorption (VA), vibrational dichroism (VD) and Raman optical activity (ROA) spectra. These spectra can be used to distinguish enantiomers and so prove to be particularly useful probes in configurational and conformational studies. In this vein, DFT with Monte Carlo simulations have also been used to investigate the chirality of the Ala-dipeptide chain in solution [49].

5.1 Role of non-linear excitations in the denaturation of DNA

As stressed, for example by Peyrard and Bishop [50] the dynamics of DNA transcription is important in biophysics as it lies at the basis of life. However, the above authors also stress that difficulties in solving the problem reside in the complex roles played by RNA polymerases. It was already established some two decades ago [51] that a local denaturation of DNA is intimately involved. So, Peynard and Bishop have set up a statistical–mechanical model to study the thermal denaturation of the DNA double helix. Their model comprises two chains connected by Morse potentials designed to simulate the H-bonds. They then determine the temperature dependence of the interstrand separation. One conclusion they reach is that a mechanism involving an energy localization (analogous, they propose, to self-focussing) may well initiate the denaturation.

The idea that non-linear excitations could play a role in the dynamics of DNA goes back, at the very least, to the work of Englander et al. [52, 53]. These authors specifically proposed a theory of soliton excitations as an interpretation of the open states of DNA. This was followed the work of Yomosa [54, 55] who proposed a soliton theory for the open states in DNA and synthetic polynucleotide double helices. In this theory, kink and antikink solutions for the soliton equation were made to correspond to the open states with positive and negative helicities. The energy of the open form and the length of the open configuration which are theoretically estimated are of the same order as the values inferred from kinetic experimental data.

5.2 DNA Wigner crystals

In the biological context (cells, phages and globules), DNA is tightly packed in a liquid-like crystal. The structural aspects of this configuration are determined by the free energy of binding in this state. Thus a proper understanding of the electrostatic interactions in DNA is of the utmost importance. In recent years, two types of polyelectrolyte theories have been applied to the helix–helix interaction. While the Poisson–Boltzmann theory predicts repulsive forces between polyelectrolytes, the counterion condensation theory allows for an induced effective attractive interaction. It is this attractive inter-helix interaction which is necessary for the condensed state. For example, Shklovskii [56] has argued that the location of the charges on the DNA spiral results in a model one-dimensional Wigner crystal. He has also suggested that the idea of Wigner crystallization could also be applied to the self-assembly of other biological complexes. The conformation and packing of the DNA in the cellular compartments has important implications on the properties of the cells. The effective

interactions are mediated by the background of ions surrounding the DNA in the cells and it is not surprising, therefore, that they are strongly dependent on the salt dependencies. This is therefore another factor that needs to be taken into account in the description of condensed biomolecular complexes.

5.3 DFT studies of polypeptides

The alanine dipeptide is an example of a molecule that has been the subject of much study using both experimental spectroscopic methods and computer simulations to give information about its conformational structure. As this peptide is able to adopt either left-handed or right-handed helical conformations in aqueous solution, it has provided a test case where by effectiveness of experimental techniques and theoretical methods may be investigated. The sensitivity to chiroptical properties makes ROA a useful techinique in differentiating the chiral conformations. However, in order to utilise this technique to its full capacity, it is necessary to be able to simulate the Raman and ROA intensities. In the last decade, the Suhai group have developed a rigorous theoretical basis by which these spectra may be calculated giving results for the simulated ROA spectra that are in qualitative agreement with experimental data. Much of the details of this work may be found in a recent review of the applications of self-consistent DFT in the TB approximation together with experiment to study the structure of proteins, DNA and biomolecules [57]. Based on this success, Mukhopadhyay et al. [49] have demonstrated that time-dependent DFT with MC sampling of geometries is a suitable way to analyse polypeptides in solution.

6 Modelling of metal complexes: especially one containing ruthenium, and its potential relevance to anti-cancer drugs

A recent study [58] using quantum chemistry of a neutral complex model for the geometric and electronic stucture of the metal-based anti-cancer drug involving Ru has been made using Hartree–Fock theory. It was conjectured that this drug might bind to a receptor rather than to DNA. We have recently become aware of a detailed quantum chemical study on di-rhodium tetracarboxylate complexes which are an emerging class of anti-tumour agents. This study predicts, on theoretical grounds, that the dirhodium drug complex binds to guanine. It is a matter of some urgency, we believe, to gain decisive experimental evidence whether binding occurs to a receptor, or to DNA itself, for the Ru-based anti-cancer drug as well as for the di-Rh complex.

In the search for new metallopharmaceuticals [59], which has been stimulated by the usefulness of the anti-cancer drug cisplatin, metal–metal bonded dirhodium tetracarboxylate complexes have been developed [60] but the mechanism of their anti-tumour activity is not fully understood. Since the quantum-chemical study on the above mentioned Ru anti-cancer drug, it has come to our notice that a related approach, but now extended to embrace the calculation of chemical intermediates and transition states, has been reported very recently [61].

Deubel and Chifotides (DC) [61] had as its primary aim to attempt to elucidate the mechanism of guanine binding to dirhodium tetracarboxylate compounds using a combination of DFT and a continuum dielectric model approach, whereas the approach to the neutral Ru complex mentioned earlier was based on the Hartree–Fock approximation, which, of course, by definition, does not include electronic correlation as the exchange-correlation energy functional needed to complete this theory is still unknown. Returning to the Ru complex, as emphasised by March et al. [58], it will be important in the future to relax the constraint of neutrality and to deal with possible anionic and/or cationic forms.

However, given the above uncertainties in each of the two quantum-chemical studies, both approaches recognised the importance for deeper understanding of the mechanism(s) underlying the metal-based anti-cancer agents and of finding the source of cell binding of the metal-based drugs. While, as already noted, March et al. [58] conjectured that binding may not be to DNA, but to a receptor, for the dirhodium complex the theoretical predictions of DC came down firmly on the side of bonding to guanine. Given their starting assumptions listed above, their arguments are convincing, but the amalgam of electronic structure DFT and the continuum dielectric model must mean that their interesting conclusions cannot be completely decisive. Therefore, DC conclude that their theoretical investigations' paves the way for future studies exploring how the differences and similarities in the Gua (guanine) reactions between the metal–metal bonded complexes and cisplatin affect the activity fo these anti-tumour agents with respect to their binding to DNA and other biomolecules'.

We propose that an NMR experiment be attempted with a view to seeing whether a C–H bond is accessible experimentally, formed between the dirhodium complex and guanine. Of course, since the nature of the (possible) receptor for bonding to the Ru complex is presently not known, the dirhodium complex study forms a natural starting point to attempt an answer to the question posed in this penultimate section.

So we conclude that, for the two metal-based anti-cancer drugs considered in this paper, decisive experimental evidence is now a matter of urgency as to whether (1) for

the the Ru-based drug NAMI-A, as conjectured by March et al. [58], the binding is to a receptor than to DNA, and (2) for the dirhodium complex, as quoted above from DC, whether the key bonding is to guanine.

7 Summary and future directions

The use of quantum-chemical studies has been helpful in giving some insight, via Hartree–Fock theory plus MP2, into the nuclear and electronic structure of (a) the smallest amino acid, glycine and (b) anti-cancer drugs involving metal-complexes, and especially the Ru complex involved in NAMI-A whch is presently undergoing clinical trials. It is proposed that NAMI-A interacts only indirectly with DNA, perhaps via receptor which may be a steroid hormone (e.g. estrogen). For the di-rhodium metal complex, it may be likely that guanine is a receptor. As to the relevance of conventional liquid and solid-state theories to problems in biophysics, illustrations have been given on the melting and pre-melting of the retinal protein bacteriorhodopsin as a function of pH and on DNA itself as a function of salt concentration.

As to future directions, we want to mention some areas which look worthy of fuller development in the interfaces between biology, physics and chemistry. In particular, we point to (a) the future role of nanotechnology [62], (b) the possible importance of developing further concepts and theories on self-assembly and (c) the area of biological flow problems.

While quantum chemistry has been used to study molecular interactions in free space (as reported in Sects. 4 and 9), it is a fact that most living systems, be it single cell, an organ, or a human being, are surrounded by and /or filled with fluids; for example aqueous solution and blood. Biologists are well aware that living systems interact with and respond to stimuli which are imposed by ambient flow of such fluids. Evidence is accumulating, for example, that complex blood flow patterns in the cardiovascular system are able to trigger biochemical responses at the level of cells which could lead to the onset of diseases (e.g. aortic heart valve disease: aneurysm, rupture etc.)

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