Theory of hopping conduction in proteins

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Quantum-chemical results of the investigation of the energy transport mechanism in proteins, obtained using the most advanced form of the theory of disordered systems, are briefly reviewed without giving any mathematical formulation. The calculated large values of the band gap for polypeptide chains including collagen models and two native proteins – pig insulin and hen egg white lysozyme rule out the possibility of intrinsic conduction in them. The Anderson localization studies of the frontier orbitals of the aperiodic polypeptide chains and the two native proteins indicate strong localization of these orbitals on one or two amino acid residues, thereby making charge transport through phonon-assisted variable-range hopping mechanism quite probable at physiological temperature. The calculated hopping frequencies and the frequency-dependent a.c. conductivity values obtained using the random walk theory fall in the same range as those for typical inorganic amorphous conductors. It, therefore, means that proteins can become hopping conductors on doping with electron acceptors or electron donors. Various biological implications of this result are discussed.

THE mechanism of energy transport in proteins is a fundamental problem of quantum biology. Various important biological processes such as vision, transmission of nervous impulses, respiration, muscle contraction, the early stages of photosynthesis, mitochondrial function and bioluminescence, involve energy changes from one form to the other and utilize the energy released in the hydrolysis of adenosine triphosphate (ATP) molecules. In all these processes, the site at the protein macromolecule where ATP hydrolysis takes place is often separated by a large distance from the site where the energy is released. So the question arises: 'How is the energy transferred from one point to the other?' or 'What is the physical mechanism of this energy transport along the large protein molecules?'. An answer to this was attempted by Szent Gyorgyi[1] when he postulated that during biochemical processes, the transformations occurring at any part of the protein macromolecule are transferred to its other parts through electron transport. Szent Gyorgyi[2] later on also gave a theory according to which there is a close relationship between conduction in proteins and cancer. According to him, an easy energy and charge transport in proteins and DNA is necessary for the normal functioning of the cell and that if this flow of charge and energy in these biopolymers is hindered, it can lead to cancerous state.

The conductivities of proteins have been investigated both experimentally and theoretically since Szent Gyorgyi's hypothesis in 1941. The early measurements performed on proteins showed a weak semiconductivity in proteins which is possibly but not necessarily due to electron transport[3–7]. Since in all these experiments, the materials used were native proteins with an unknown amount of inorganic and organic impurities, it was impossible to interpret these experimental results correctly. Later on some transport measurements were also carried out[8,9] on these biopolymers but the same is true for these experiments too.

On the theoretical side, the investigation of the electronic conduction in proteins has been a very challenging task due to the complexity of the protein macromolecules. Proteins are composed of one or more polypeptide chains (made up from 20 different amino acid residues) that for parts of their lengths can be folded in an apparently random way or form regular β-pleated sheet or α-helical structures. The sequence of amino acids in a great number of proteins is known, though the conformations of only a few smaller protein molecules have been determined with the aid of X-ray diffraction. Further, under biological conditions, there are ions and water molecules which make the determination of the electronic structure of these biopolymers more difficult. In view of all this, it has not been possible to determine the electronic structure of proteins and thus investigate electronic conduction in them in one step. Investigation of electronic conduction in these biopolymers has, therefore, been carried out stepwise by different workers during the last nearly 50 years using a

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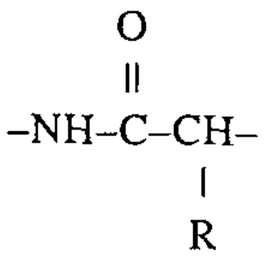
combination of various techniques with rather large-scale computations. It is only recently that it has been shown that proteins can become hopping conductors of electricity on doping. The various steps involved in these investigations are presented here without any mathematical formulation so as to be comprehensible to a general reader.

Investigation of intrinsic conduction in proteins

On the theoretical side, two pathways for electronic transport in proteins were initially proposed. The hydrogen bonded network

–C=O...H–N–C=O...H–N

which runs perpendicular to both α-helical and β-pleated sheet structures and provides an extended π-electron conjugated pathway was suggested by Coulson. Brillouin[10] on the other hand, proposed that conduction in proteins may take place along the main polypeptide chain. He viewed that the



groups of the polypeptide chain form the elementary unit cell with the various R groups acting as impurity centres.

The calculations by Suhai[11] for the β-pleated polyglycine structure taking into account interactions both along the hydrogen-bonded networks and along the main polypeptide chains simultaneously showed that the most favourable pathway of electronic transport in proteins is the main polypeptide chain rather than the hydrogen-bonded π-electron network. This conclusion also got support from some independent experiments that include pulse radiolysis, flash photolysis, e.s.r and n.m.r. measurements on proteins all of which indicate charge carrier migration along polypeptide chains (see e.g. ref. 12 and references therein).

Homopolypeptides and periodic polypeptides

Various band structure calculations on periodic polypeptide chains have been performed[13] both on the semiempirical and *ab initio* Hartree–Fock levels. The band structures of all the 20 homopolypeptides and various polydipeptides have been calculated[14] along the main polypeptide chain on the basis of *ab initio* Hartree–Fock LCAO SCF CO method[15,16]. The effects of basis set[17], electron correlation[18–21] and environment (both water and ions)[22–25] on the band structures of some homopolypeptides and polydipeptides have also been investigated. Since the band structure calculations of the periodic multicomponent polypeptide chains by the direct SCF method are not very easy (in view of the large size of the unit cell), the electronic density of states (DOS) of multicomponent periodic polypeptide chains (containing up to seven amino acid residues) in the antiparallel β-pleated sheet conformation have been determined by Bakhshi and coworkers[26–28] on the basis of *ab initio* matrix block NFC method[29–31]. The seven components chosen for the study include serine (ser), glycine (gly), cysteine (cys), asparagine (asn), histidine (his), aspartic acid (asp) and tryptophane (try). In choosing these seven components, the aim has been to develop a model of a real 20-component protein chain. The calculated value of fundamental band gap in all these periodic chains (including homopolypeptides) is found to be very large and, therefore, there is no possibility of intrinsic conductivity in these chains at physiological temperature.

Aperiodic polypeptide chains

Aperiodic polypeptide chains are a more realistic model of proteins. There have been some studies on the aperiodicity effects in proteins[32,33] using a semiempirical method. The electronic DOS of up to 7-component aperiodic polypeptide chains in the antiparallel β-pleated sheet conformation have been determined[34,35] on the basis of the *ab initio* matrix block NFC method.

In Figures 1 and 2 are shown the DOS distributions for both the valence and conduction band regions of

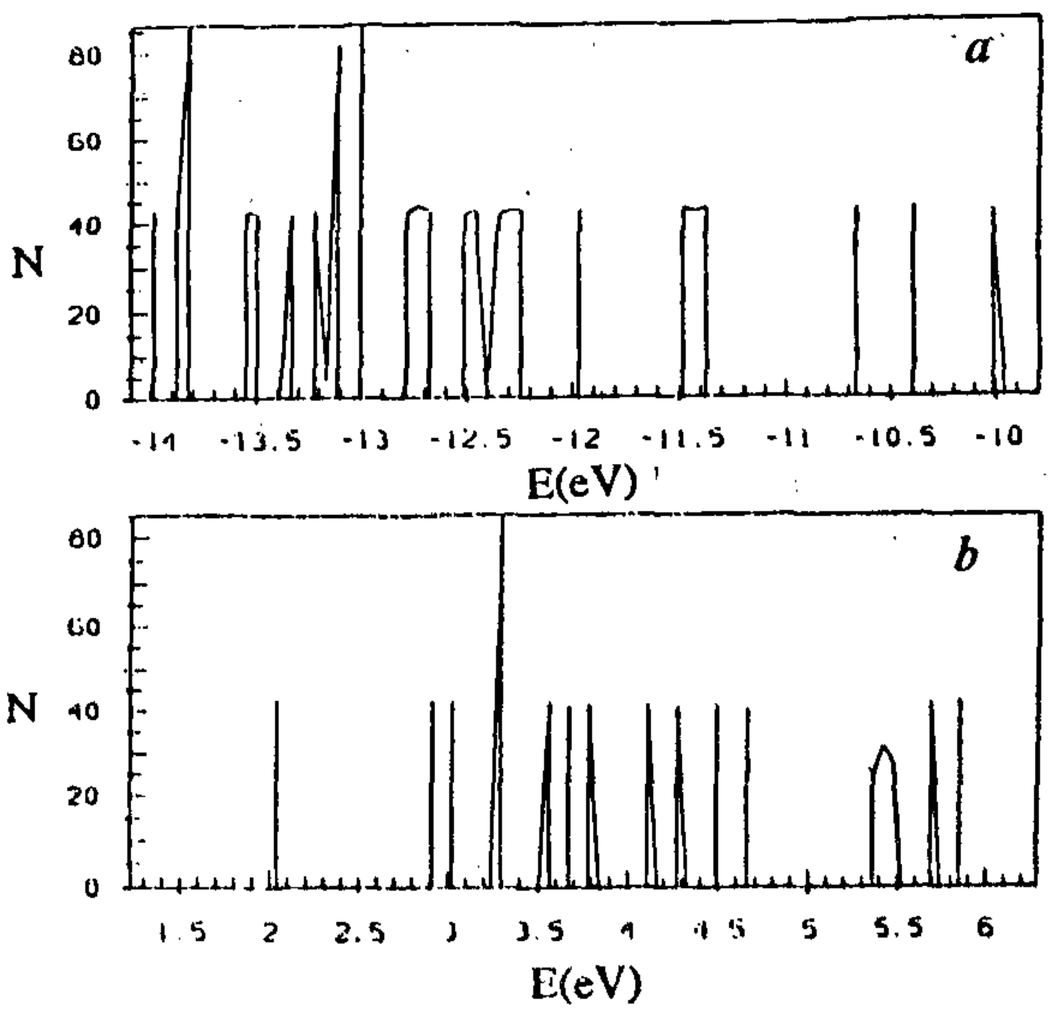


Figure 1. The density of states for periodic poly (ser–gly–cys–asn–his–asp–try) *a*, valence band region; *b*, conduction band region.

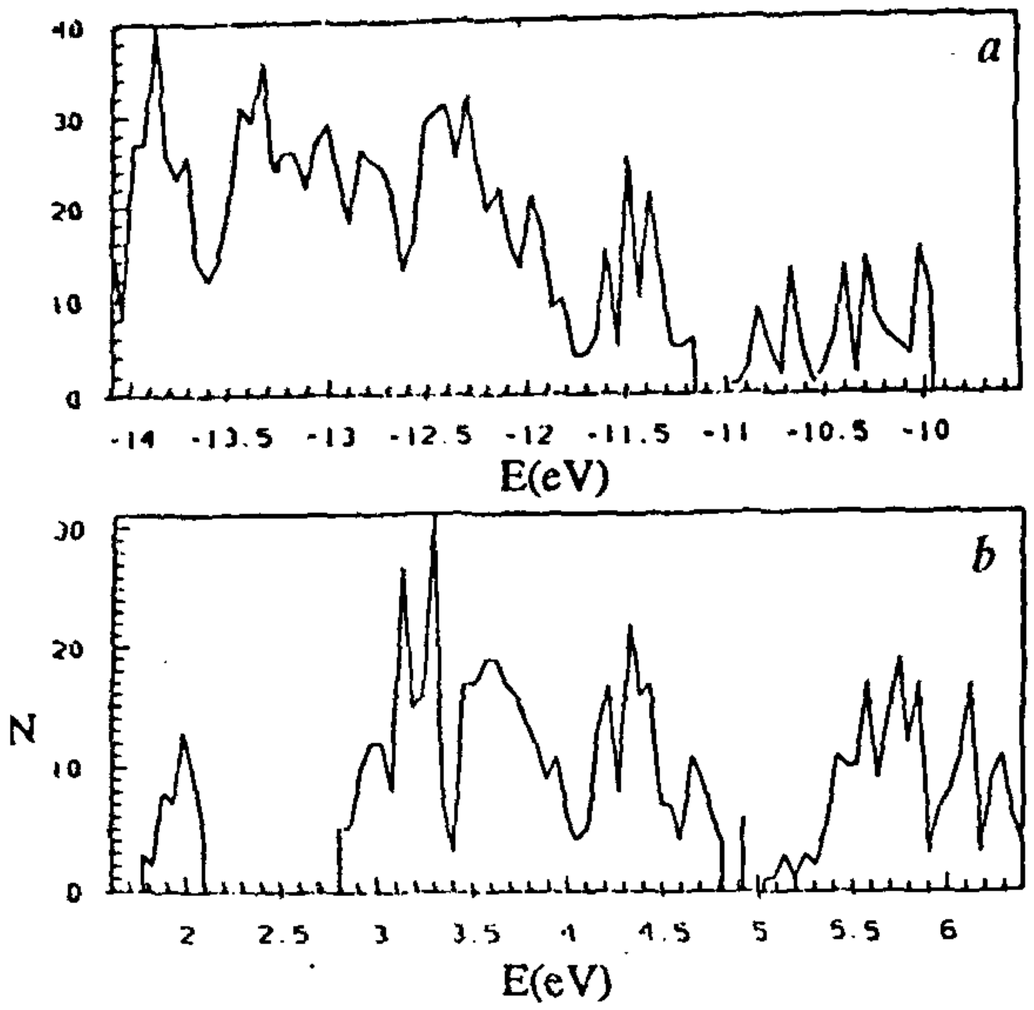


Figure 2. The density of states for aperiodic poly (ser, gly, cys, asn; his, asp, try) in the composition (1:1:1:1:1:1:1) *a*, valence band region; *b*, conduction band region.

periodic and aperiodic 7-component polypeptide chains in the composition (1:1:1:1:1:1:1) respectively. The DOS curves of aperiodic polypeptide chains look strikingly different from those of the periodic polypeptide chains. The sharp and well-separated peaks characterizing periodic chains are replaced by very broad regions of allowed energy states with a few small gaps in between. Similar results have also been observed for the periodic and random copolymers of conducting polymers[36]. As a result of this broadening, the fundamental energy gap in the case of aperiodic polypeptide chains is somewhat smaller than that of corresponding periodic polypeptide chains (because the valence bands move up and the conduction bands move down in energy), though its value is still too large for semiconduction to be possible at physiological temperature.

Investigation of extrinsic conduction in proteins

There is no possibility of intrinsic conductivity in periodic and aperiodic polypeptide chains due to their large fundamental energy gap. Since the DOS curves of aperiodic chains are very broad with a few small gaps, there is a possibility of extrinsic conduction (on doping with electron acceptors or with electron-donors) in these chains. To decide about the nature of this extrinsic conduction (whether coherent Bloch-type conduction or charge transport through hopping), the Anderson localization properties[37,38] of the wavefunctions of the frontier orbitals (i.e. the energy levels in the upper part of the valence band region or the lower part of the conduction band region) were investigated from aperiodic polypeptide chains using inverse iteration technique[26,39]. These are the regions of interest if a charge transfer is to take place *in vivo* due to the interaction of proteins with electron-acceptors or donors or with DNA. The results[27,35] showed that the wavefunctions are localized on one or two amino acid residues, thereby making charge transport through hopping rather probable. Assuming a charge transfer of 0.1e per unit of the aperiodic chain (which *in vivo* is rather probable), the hopping frequencies or the primary jump rates (i.e. the number of jumps from one localized state to another localized state per unit time of the phonon-assisted hopping at a given temperature *T*) were calculated using the generalized form of the theory of Mott and Davis[40] for the case of the arbitrary number of orbitals per unit site. The results show that the primary jump rates calculated for proteins fall in the same range of orders of magnitude as for amorphous semiconductors.

A.C. conductivity of proteins

In the above studies, since it was not possible to calculate the DOS curves for a polypeptide chain containing 20 amino acids, real proteins were modelled using 4-7 components and for calculations, the sequences of the amino acids in protein models were generated by a Monte Carlo program.

Recently the above calculations have been extended to periodic and aperiodic collagen models[41,42] and two native proteins, pig insulin and hen egg[43,44] white lysozyme. The DOS in the case of native proteins were determined using an extended NFC method so as to be able to take into account the cross-links. The electronic DOS of the collagen models and the two native proteins and the Anderson localization studies of the frontier orbitals (both HOMOs and LUMOs) of these proteins and their corresponding calculated values of the hopping frequencies for the first and the second neighbour hoppings confirm the conclusions obtained from aperiodic polypeptide chains. One very interesting result of these studies and the one which is under further investigation is that most of the frontier orbitals of the native proteins are found to be Anderson localized on the residues that play an important role in the activities of these proteins. It, therefore, means that the frontier orbitals of a native protein influence its biological activity.

Using the hopping frequencies calculated above and applying the generalized form (for an arbitrary number of orbitals per site) of the random walk theory of Lax and coworkers[45–47], the frequency dependent a.c. hopping conductivities of these proteins have been calculated. The calculated a.c. conductivity of hen egg white lysozyme as a function of frequency, for example, is

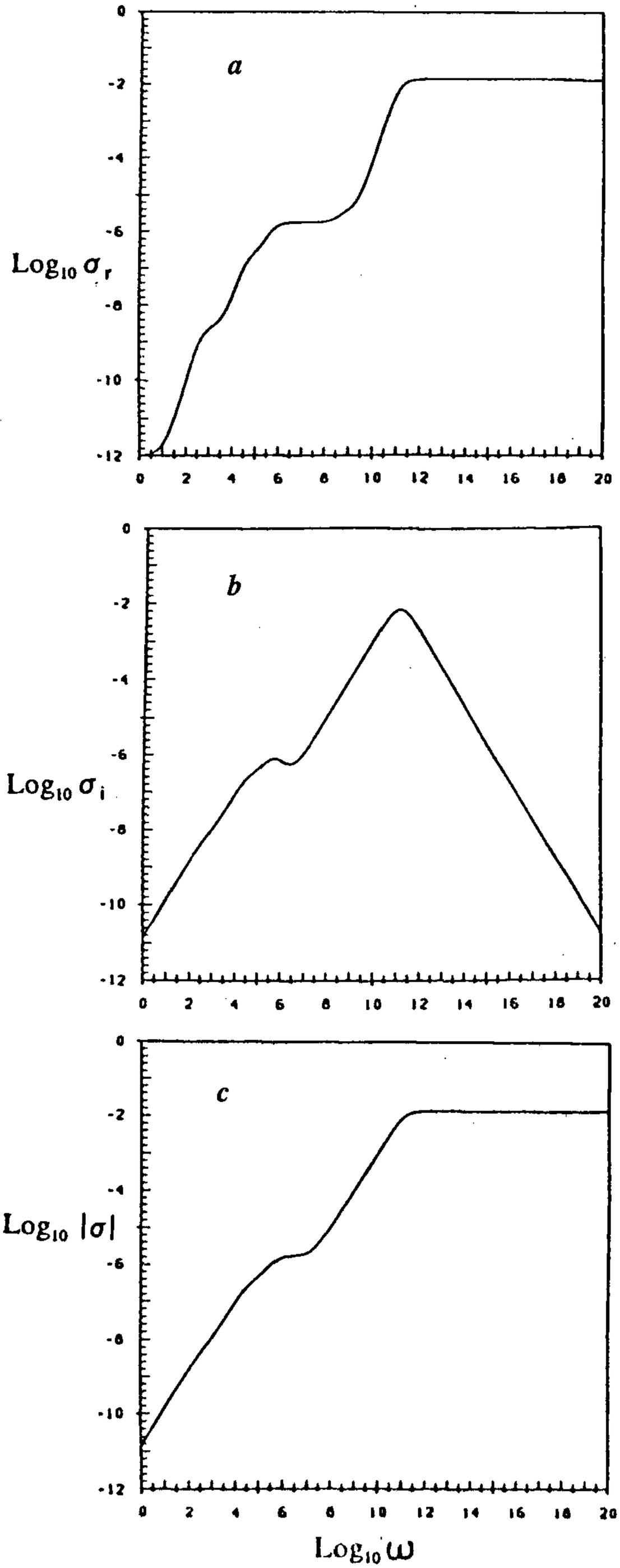


Figure 3. The a.c. conductivity of hen egg white lysozyme. *a*, the real part of the conductivity $\sigma_r(\omega)$; *b*, its imaginary part $\sigma_i(\omega)$; *c*, its absolute value $|\sigma(\omega)|$.

shown in Figure 3. For both the proteins, it is found that the calculated values of the absolute $\sigma(\omega)$ in the frequency range 10^4–$10^8\ \mathrm{sec}^{-1}$ fall between $10^{-8}\Lambda^{-1}\,\mathrm{cm}^{-1}$ and $10^{-5}\Lambda^{-1}\,\mathrm{cm}^{-1}$. These values lie between the curves of the chalcogenide glasses Te_2AsSi and As_2Se_3 and have in the most part of the curve the same order of magnitude as that of $Te_{48}As_{30}Si_{12}Ge_{10}$. Since all these substances are typical inorganic amorphous conductors, one may conclude that proteins are good amorphous conductors on doping.

It needs to be noted here that the phonon-assisted hopping transition of particles between spatially distinct locations is a phenomenon encountered in a diverse variety of solid state systems. For instance, in weakly doped and compensated semiconductors, the phenomenon of impurity conduction arises from hopping of electrons between impurity sites. Furthermore, in crystals with a narrow conduction band and strong electron–phonon interaction, a new quasi-particle, the small polaron is formed which at sufficiently high temperatures moves through the crystal by hopping from site to site. Another example of hopping motion in solids is the hopping diffusion of Frenkel excitons in molecular crystals. In the recent past, phonon-assisted hopping of electrons between soliton bound states has also been proposed as a possible dominant conduction mechanism in highly doped quasi-one-dimensional Peierls systems such as polyacetylene.

Conclusions

The recent results of *ab initio* quantum-chamisol calculations using the theory of disordered systems show that proteins, though insulating in their intrinsic state, can transport charge via phonon-assisted hopping mechanism on doping with electron-acceptors or electron-donors *in vivo*. The calculated values of the a.c. conductivity of proteins are found to be comparable to those of the inorganic amorphous conductors. These are the most accurate calculations performed on the electronic structure of proteins till now and the results obtained add to our understanding of the processes such as oxygen metabolism in animals, photosynthesis in plants, signal transmission via energy and charge transport and perhaps also carcinogenesis as originally postulated by Szent Gyorgyi. One should point out here that there are a large number of papers in the literature dealing with the electron transfer (ET) in large systems and a number of mechanisms of charge transport via proton/ion transport, electron tunnelling or with the help of through bond interaction (especially through the hydrogen bond) have been proposed (see e.g. references 48–51 and the various articles in *Chem. Rev.*, 1992, **92**). It is quite possible that these different mechanisms supplement each other in an aperiodic protein folded in a complicated way.

As a next step, it would be interesting to see how further refinements in the theory of disordered systems affect these conductivity results. Noteworthy in this regard are the treatment of electron correlation effects in the calculation of the electronic DOS of native proteins using better basis sets, the calculation of hopping frequencies via electron–phonon interaction matrix elements and last but not the least the treatment of the two-dimensional nature of the protein problem. It would also be worthwhile to work out the connections between the calculated microphysical quantities in the theory of hopping conduction and the quantities occurring in the other proposed theories. Perhaps these are the directions along which the future investigations shall take place.

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