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THEORETICAL STUDIES OF THE CIRCULAR DICHROISM OF HEMOGLOBIN - INTERSUBUNIT INTERACTIONS, Robert W. Woody, Dept. of Biochemistry, Colorado State University, Fort Collins, CO 80523.

Previous calculations of the circular dichroism (CD) associated with the Soret band of hemoglobin (M.-C. Hsu and R.W. Woody, J. Amer. Chem. Soc. 93, 3515 (1971)) have shown that intersubunit interactions make significant contributions to the rotational strength of the Soret band. In view of the functional significance of intersubunit interactions in hemoglobin ("heme-heme" or allosteric interactions), these earlier studies have been extended, taking advantage of the availability of more exact coordinates and data for both liganded and unliganded forms of hemoglobin. Earlier calculations neglected the coupling of transitions on different heme groups of the tetramer. This effect has now been considered, using the classical polarizability theory of DeVoe (J. Chem. Phys. 41, 393 (1964)). This contribution gives for metHb a predicted ellipticity of +21000 at 425 nm, and -14750 at 407.5. For deoxyHb, values of +1550 at 440 nm and -650 at 420 nm were obtained. The changes in relative orientation and distances of the hemes associated with the binding of ligands therefore lead to a very large change in their contribution to the CD. Calculations on the interaction of aromatic side chains with the heme gave a more positive Soret rotational strength for deoxyHb than for metHb. Much of the difference results from intrasubunit interactions. By comparison, the difference between the calculated Soret rotational strengths of sperm whale metMb and deoxyMb is in the same direction, but much smaller. However, there are significant intersubunit interactions in hemoglobin which also change markedly on deoxygenation. (Supported in part by USPH GM 22994).

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ROLE OF WEAK POLAR AMINO ACIDS IN PROTEIN EVOLUTION
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Correlation between polarity of an amino acid and its mutability during protein evolution was studied as well correlation between exteriority of a residual site on tertiary structure of proteins and its mutability. 20 amino acids were grouped according to their polarity into three; i.e. polar (Arg, Lys, His, Gln, Asn, Asp and Glu), weak polar (Ala, Pro, Gly, Thr and Ser) and non-polar (Cys, Val, Met, Ile, Leu, Phe, Tyr and Trp) groups.

First, it was shown that about 80% of substitutions of amino acids in homologous proteins occurred within the groups of amino acids having similar polarities both in the interior and exterior of the proteins.

Second, the weak polar group was found to be replaced in the interior by the non-polar group more frequently than by the polar one but in the exterior by the polar group more frequently than by the non-polar one. Also, it was found that in the interior the non-polar group is replaced by the weak polar one more frequently than by the polar one and in the exterior the polar one is replaced by the weak polar one more frequently than by the non-polar one. Those facts reveal a bifacial character of weak polar group, i.e., this group behaves like the non-polar one in the interior and like the polar one in the exterior of proteins. Existence of such a weak polar group, besides the polar and non-polar ones, seems to have an essential role in the mechanism to preserve the tertiary structure of proteins, in spite of many amino acid substitutions, during protein evolution.

Third, the higher mutabilities of residual sites in the exterior were confirmed to be general in the seven homologous proteins investigated no matter what their biological functions are.

Fourth, higher mutability and frequency of the weak polar group in the exterior than in the interior were shown to contribute significantly to the higher mutability in the exterior of the proteins.

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Proton Relaxation Enhancement in Biochemistry: A Critical Appraisal.

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Proton Relaxation Enhancement (PRE) has been widely applied in biochemistry to obtain information on macromolecular dynamics and has even been used to propose mechanisms of enzyme action. It has been shown however that considerable problems can arise in the application of the technique (Burton et al, Eur. J. Biochem. (1977) 75, 445-453). In the light of these problems the use of the technique in a large number of biological systems is re-examined. These systems include pyruvate kinase, phosphofructokinase, liver alcohol dehydrogenase, carboxypeptidase, lysosyme, enolase and carbonic anhydrase.

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NON-INTERACTING SUBSTRUCTURE MODEL OF FOLDING AND UNFOLDING TRANSITION IN GLOBULAR PROTEINS.

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Conformations in the process of folding and unfolding transition are assumed to consist of non-interacting substructures linked linealy by polypeptide chains of random conformation. Each of the substructures consists of an uninterrupted segment of the polypeptide chain folded into exactly the same local conformation as in the native state. No interactions are assumed to exist between substructures. The above model (or assumption) coresponds fairly exactly to the currently popular model of folding, in which increasingly longer-range interactions come into play as the folding proceeds. When the above assumption is made, an exact partition function can be calculated for a non-repetitive finite system of protein with the long-range interactions. The entropy of the system, S, is calculated as a function of the enthalpy of the system, H, by making use of the above assumption. This function S(H) contains the same amount of information as in the partition function, and is suitable for the discussion of the statistical mechanical character of conformational transitions. The calculation is carried out in two cases. (a) The two-dimensional lattice protein. For this theoretical model the exact S(H) curve had been obtained by a Monte Carlo method. The comparison of the S(H) curve obtained here with the exact one reveals the validity of the non-interacting substructure model. (b) Some actual proteins. In these cases interaction free energies between amino acid residues are assumed, which are dependent on the area of contact and their polarities.

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ABSTRACTS

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