A Conformation-Dependent Hydrophobicity Index

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Rational algorithms for predicting molecular partition coefficients have been the subject of much research over the past few years, given the demonstrated correlation of this molecular property with biological activity. Of these, the most successful have been based upon the selection of simple fragments within structures with which a hydrophobicity value can be associated. Analysis of a compound into a series of these fragments, followed by simple addition of their hydrophobicity parameters, can then be used to predict the partition coefficient between octanol and water. Although originally suggested by Rekker, the method has been pursued vigorously and extended by Hansch and coworkers. The efforts of the latter have resulted in the widely used ClogP program. While this software has proven useful for rigid small molecules, its extension to flexible oligopeptides and molecules in which tautomer or zwitterion formation can occur has proved difficult. Although there are a number of empirical approaches to improving its predictive accuracy, the physical basis for such corrections remains unclear.

As part of an integrated program aimed at understanding the detailed nature of peptide recognition by monoclonal antibodies, we have become interested in the calculation of such properties as peptide hydrophobicity and positions of high electrostatic potential. Given the inability of current methods to compute logP for flexible molecules, we have therefore begun to develop a modified approach for obtaining fragment parameters that allow for the conformational distribution of an oligopeptide in solution. In this paper we will present our algorithm for obtaining parameters relating the solvent-exposed area of fragments to the free-energy change describing molecular partition coefficients between octanol and water. Initially, using the AMBER force field, a full determination of the low-energy conformations of a given peptide is carried out and the solvent exposed area of fragments within these conformations determined. The free energy of solvation of the peptide is then computed based upon existing solvation parameters for the atoms in a given fragment, the contribution from each conformation being related to its Boltzmann population. Use of experimental logP values then yields a set of fragment parameters for the solvation energy of the peptide when it is moved from the gas phase into octanol. Use of these fragment values together with Monte Carlo solvation studies of a peptide in aqueous solution can then be used to predict its partition coefficient. Since this procedure derives parameters from a family of low-energy conformations, the values allow for molecular flexibility, removing the need for any non-physical empirical adjustments as in the ClogP program. This method may also allow the rational inclusion of tautomerism into the prediction of logP values, since it is rooted in thermodynamics, removing the need to exactly determine the extent of tautomerization of a given molecule in both the octanol and aqueous phases. An initial set of parameters for selected fragments used in oligopeptides will be given, and their accuracy in predicting experimental logP values for di- and tripeptides will be discussed. A comparison of our algorithm with existing computational methods will also be presented.

Molecular Mechanisms of Specificity in DNA-Ligand Interactions

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One of the central problems in the study of the mechanism of DNA-antitumor drug interactions is the existence and nature of sequence specificity with respect to the base pairs of DNA. This paper presents results of a theoretical exploration of this problem for a particularly important group of such drugs, namely the groove binding ligands. The great majority of the investigated antitumor agents of this category show a marked specificity for the minor groove of AT sequences of B-DNA. Contrary to current concepts and some proposals, hydrogen bond formation between the ligands and the receptor bases of DNA or contacts between specific hydrogen atoms on the ligand and on the bases do not appear to be the main determinants of this specificity. The essential factor responsible for this preference is the strong concentration of the electrostatic molecular potential in this groove of these sequences in B-DNA. This distribution of the potential renders difficult the conception of drugs specific for the minor groove of GC sequences and is responsible for the failure in this respect of lexitropsins and isolexins. Nevertheless, for the first time in theoretical computations, a particular isolexin was conceived that should bind preferentially to the minor groove of GC sequence; this is a neutral ligand composed of three furan or imidazole rings linked by NH groups. An increased GC specificity, moreover, is predicted for vinylexins (analogs of isolexins with C=C linkers), and an increased binding energy, with the specificity conserved, can be obtained for such monocationic ligands. In fact, monocationic vinylexins should form a family of universal groove binding ligands whose AT or GC specificity can be dictated by the arrangement of their hydrogen bond donor or acceptor heteroatomic ring systems.