Display and Analysis of Protein Binding-site Topologies Using Accessible Surfaces

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We have found that, with an appropriate selection of probe distance, the accessible surface, originally defined by Richards,[1] has a remarkable capacity for revealing the overall structure and fine details of binding site topology. A rapid algorithm has been developed for computing a contour representation of this surface: the surface of points that are at least a probe distance plus the van der Waals radius away from each atom of the binding site. When the probe distance is 1.4 to 1.6 Å, the surface develops extremely useful properties. It displays the accessible volume whose surface defines the optimum position for the centers of ligand atoms. Since the volume of accessible space is quite small, its surface gives a much sharper picture of the effective shape of the binding site than does the van der Waals surface. The surface can be colored to represent electrostatic potential or absolute field strength. The latter representation displays local polarity, an indication of hydrophylic and hydrophobic surface character. The utility of the surface in defining the space available to naturally aligned molecules and ligands has been examined using crystal data for 15 crystals of molecules of low molecular weight and seven protein ligand complexes. Different proteins were found to have striking and recurrent topological features; fine structured narrow shafts, tunnels, grooves and slit-like pockets that connect to and contrast with broad convex surfaces. By focusing attention on the spaces and surfaces accessible to ligand atoms, the surface is ideally suited to applications in computer-assisted molecular design and is fully compatible with a wide range of other graphical and computational tools.

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Large-scale Computational Methods and Visualization in Molecular and Materials Design

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During the last decade we have witnessed a rapid increase in the use of computationally intensive methods in the study of biological systems such as nucleic acid and protein structures. In part, this development was driven by the increased availability of computational hardware that, in turn, has stimulated the development and use of more accurate theoretical/computational approaches. This lecture focuses on the two key approaches in theoretical molecular science: quantum mechanics and statistical mechanics. Quantum mechanical simulations are now possible for significant parts of biologically active molecules. For example, Hartree-Fock theory allows the calculation of molecular properties, such as stable conformations, relative heats of formation, charge distributions and vibrational properties of molecules, with about 10–15 first-row atoms with high-quality basis sets. Calculations on larger molecules leads to a disk-storage problem that can be circumvented with direct SCF schemes, albeit at the price of more computing time that is limited by an N^4 scaling problem.

An alternative quantum mechanical many-body technique, known as (spin) density functional theory, provides a surprisingly accurate and computationally efficient molecular orbital method that scales only with a third power. This molecular density functional approach allows the calculation of molecular geometries, charge distributions, electrostatic potentials, and relative energies of similar quality as Hartree-Fock theory with some correlation. Density functional methods can be readily applied to metallic and organometallic systems, thus opening up new possibilities in biochemical research. Calculations on molecular systems with up to 70 atoms (including Zn atoms) using polarized double-zeta basis sets illustrate the capabilities as well as current limitations of this approach.

The speech of supercomputers, combined with the convenience of graphics workstations, enables quantum mechanical calculations on the semiempirical level to be carried out in an interactive fashion. A prototype of such an integrated, distributed processing system will be discussed in conjunction with the semiempirical MOPAC code. Advances in the development of molecular force-field and statistical mechanics techniques, such as the free-energy perturbational approach, have opened up new ways of approaching the drug design problem. Here, sufficient computational power is of the essence, but certainly no guarantee for reliability, because many theoretical and computational assumptions and approximations, which are inherent in a force-field approach, have to be carefully checked before quantitative predictions can be made with chemical accuracy. The lecture will conclude with an outlook on future developments in theoretical/computational methodologies as well as computing technologies.

Studies on Polyfunctional DNA Intercalators

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Polyfunctional intercalation has the potential of providing a mechanism for high-affinity binding to DNA. Such compounds could have interesting antitumor and antiviral properties. A topologically novel bifunctional DNA intercalator, 2, has been synthesized and its DNA binding studied in comparison with the binding of 9-aminoacridine, 1, and spermine diacridine, 3. Compound 2 shows a high affinity for calf thymus DNA as indicated by large increases in the helix-coil transition temperature. Viscometric analysis of helix extension using sonicated calf thymus DNA gave results characteristic of a double intercalator. Metachromic shifts in the absorption spectra of 2 were observed upon addition of DNA. Macrocycle, 2 reverses the supercoils in a closed circular supercoiled plasmid (pOP1Δ6). These data, and other experiments, support the conclusion that 2 binds to DNA as a bifunctional intercalator. DNA binding and molecular modeling studies of these polyfunctional DNA intercalators will be discussed.
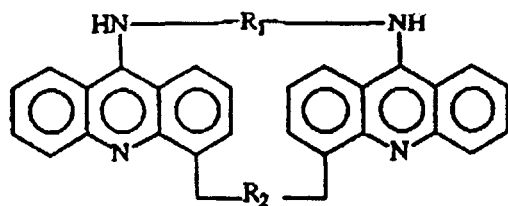

1 R_1 = H, R_2 = H
2 R_1 = $(CH_2)_3NH(CH_2)_4NH(CH_2)_3$, R_2 =
   $CH_2S(CH_2)_2NHCO(CH_2)_2CONH(CH_2)_2SCH_2$
3 R_1 = $(CH_2)_3NH(CH_2)_4NH(CH_2)_3$, R_2 = H

Structure and Molecular Modeling of the Anti-infective Drug Pentamidine

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Pentamidine (1a) is valuable for the treatment of *Pneumocystis carinii* infections in AIDS patients as well as trypanosomiasis. The molecule is terminated by the same aromatic amidine moieties as the DNA-binding drug berenil (1b), but the central chain is longer.
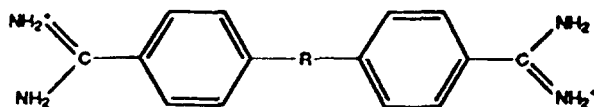
a: R = $-O-(CH_2)_5-O-$
b: R = $-NH-N=N-$

The crystal structure of berenil has been determined,[1] and its interaction with A–T rich regions of DNA has been investigated by graphic modeling and molecular mechanics.[1] The present study comprises a determination of the crystal structure of (1a) as the hydrated isethionate salt and an investigation of the conformational preferences and electronic properties of three important structural features of the pentamidine molecule, namely the junction between amidinium groups and benzene rings, the ether linkages and the central chain.

The crystals have unit cell dimensions a = 25.959, b = 14.105, c = 8.781 Å, β = 102.44° and exhibit symmetry consistent with space group C2/c. The structure has been refined to R = 0.06, with typical standard deviations of 0.006Å and 0.5° for nonhydrogen bond distances and angles. As in (1b), molecules of (1a) adopt a flat extended conformation and have twofold symmetry imposed by a crystallographic axis through the central methylene C atom. The planes of the amidinium groups and benzene rings intersect at 27° in (1a) but only 8° in (1b). However, the latter angle increased upon refinement using molecular mechanics of (1b) with DNA.[1] Our *ab initio* STO-3G calculations for the phenylamidium cation show that the energy is relatively insensitive to twists up to ca. 35°, with a minimum at 27°.

The C–O–C angle is 117.9° with no significant twist about either bond. This corresponds with one of the two energy minima found by STO-3G calculations for anisole.[2]

Superposition of the middle three atoms of (1a) onto the central chain of (1b) places the aromatic rings in similar regions of space with their inner edges in (1a) aligned with their outer edges in (1b). Thus, the vector from end to end of the central chain is 5.20 Å longer in (1a) than in (1b). For a polymer to have an isohelical fit with the minor groove of a DNA helix at a distance of 5.0 Å from the helix axis, a chain length of 4.61 Å between contacts with successive bases is required.[3] The bending and twisting needed to enable (1a) to conform to a helical template should reduce the length of the chain vector to around this value, thus enabling it to span one more base-pair than (1b).

This work was supported by the Science and Engineering Research Council under the Molecular Recognition Initiative.

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Accurate Redox Potentials from Theoretical Calculations

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