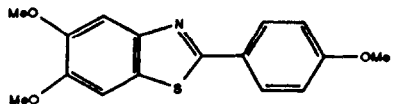
Abstracts from the Eighth Annual Meeting of the Molecular Graphics Society

The eighth annual meeting of the Molecular Graphics Society was held at the University of St. Andrews, St. Andrews, Scotland, from 29 to 31 March 1989. The abstracts from the meeting are collected below.

Crystal and Molecular Structure of a Potential Anti-oestrogenic Agent and Quantum Mechanical Modeling of Some Related Compounds

Paul C. Yates, Carol J. McCall and Malcolm F.G. Stevens
Pharmaceutical Sciences Institute, Department of Pharmaceutical Sciences, Aston University, Aston Triangle, Birmingham, B4 7ET, UK

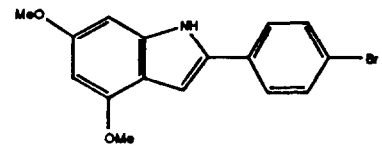
A series of compounds that may show structural and chemical similarities to the flavanoids have been synthesized, with a view to exploring their activity as antioestrogenic agents. These are related to the following benzothiazole compound, (I).



The three-dimensional structure of compound (I) has been determined by X-ray diffraction. Crystals of (I) are monoclinic, space group $P2_1/c$, a = 17.142(1)A, b = 11.165(1)A, c = 7.683(2)A, β = 101.34(1)°. 2 307 reflections have been refined to R = 0.039. The most interesting feature of the structure is a relatively large deviation from planarity. The angle of twist between the two ring systems is 21.3°.

We have performed semiempirical quantum mechanical calculations on this and related compounds. On optimizing all torsion angles, we found that the deviation from planarity increases for (I), giving a new twist angle of 43.9°. However, all the other structures remain planar when optimized.

Similar calculations were performed on the related indole compound shown below.



As with (I), the crystal structure shows a deviation from planarity. The twist angle of −28.6° increases to a value of −111.3° when the torsion angle optimization calculation is performed.

These results are rationalized in terms of steric interactions and crystal packing. The structure of a related benzothiazole and a related indole are predicted.

Graphical Description on the Solute Surface of the Solvation Energy and Solvent Transfer Energy

Giuliano Alagona, Rosanna Bonaccorsi and Caterina Ghio
CNR—Instituto di Chimica Quantistica ed Energetica Molecolare—Pisa, Pisa, Italy

Jacopo Tomasi
Dipartimento di Chimica e Chimica Industriale—Università di Pisa, Pisa, Italy

The graphical representation of quantum mechanical descriptions of solute properties on the solute molecular surface is attempted with the aid of color-coded surface point models.

The surface is defined in terms of suitably scaled van der Waals spheres, centered on each atom of the solute. For each sphere a set of regular polyhedra is defined. The computed properties, depending on the area of the almost equilateral triangle making up the polyhedron, are displayed as a color-coded point placed in the middle of the related surface.

We have considered a few properties of two solutes: dimethyl ether and propanol. The properties considered are the solvation free energy (its electrostatic and cavi-

tation components) and the solvent transfer energy, allowing a direct characterization of lipophilicity and hydrophilicity. As a byproduct, we obtain the electrostatic potential of the solute in vacuo and perturbed by the solvent field and the apparent charge distribution on the cavity surface, producing the solvent reaction field.

Other terms, such as the dispersion + repulsion contributions, might be added to the color-coded description of the molecular surface.

Hydrophobic Cluster Analysis: A Tool for Protein Modeling

L. Lemesle-Varloot, V. Bissery, A. Morgat, C. Gaboriaud and J.P. Mornon
Laboratoire de Minéralogie-Cristallographie CNRS URA09, Universités P6 et P7, Tour 16, 4 place Jussieu, F-75252 Paris, France

A new method for comparing and aligning protein sequences has been developed by our group. The method proves to be very practical for use in protein modeling by homology.

THE METHOD

This method, Hydrophobic Cluster Analysis (more commonly HCA), relies upon a two-dimensional (2D) representation of the amino acid sequence of a protein, on the surface of a virtual α = helix. On that surface, sets of adjacent hydrophobic residues are circled and termed Hydrophobic Clusters.[1]

The distribution, shapes and sizes of those clusters are the criteria that are compared from one protein to another.[2,3]

RESULTS

Proteins that are similar from a three-dimensional (3D) point of view and whose sequences had been declared not to be homologous with classical methods are found to be similar with the HCA method, whatever types of elements (α, β or αβ) the secondary structures of these proteins contain. (Examples are presented.[1])

ADVANTAGES

Our choice to focus upon the distribution of hydrophobic residues comes from the general observation that the hydrophobic core of a protein is better conserved, at a 3D level, than the surface loops. Moreover—and this is the main interest of the method for modeling by homology—hydrophobic clusters generally correspond well to secondary structures; thus, in a precise alignment of proteins, this prevents us from introducing insertions or deletions within the core that forms the backbone of the protein, which would be a disaster for modeling.

Another advantage of the method is the possibility to align numerous sequences at the same time (up to 20 or 30) in a family, which provides more reliable information and often allows us to point out particularly well-conserved residues as potential active sites.[4,5]

Finally, we found that we can predict secondary structures with great certainty when they correspond to precise shaped clusters previously recognized and checked.

FUTURE DEVELOPMENTS

Because the method still depends on human means, we have undertaken to make it as automatic as possible. Several HCA research topics are now under way and will be gathered within a 2D graphic interactive software (MANSEK).

The present HCA plot software can be obtained from J.P. Mornon upon request for the Macintosh or Fortran77+GKS.

REFERENCES

1 *FEBS Lett.* 1987, **224**, 149–155
2 *Biochem.* 1988, **27**, 592–596
3 *Biochem. J.* 1988, **225**, 901–905
4 *Gene* (in press)
5 *Molecular Endocrinology* (submitted)

Determination and Display of Map Local Maxima and Minima and Their Use in Molecular Modeling

D.J. Flanders and S.K. Yeap-Morpeth
Chemical Design Ltd., 7 West Way, Oxford OX2 0JB, UK

The determination and display of local maxima and minima is a major step toward being able to visualize the variation in the interaction between ligand and receptors. This is a necessary requirement to perform fitting and docking studies.

The paper will describe the methods used to determine the local maxima and minima within the map grid; in particular, we will discuss the variety of searching algorithms and the methods used to sort the resulting extremes. The detection of local extremes has been implemented for the following Chem-X map types:

(1) van der Waals surface
(2) Electrostatic potential
(3) Charge interaction
(4) Repulsive VDW energy
(5) Attractive VDW energy
(6) Summation of the charge, repulsive and attractive energy terms

Extremes are positioned at the grid points where the mapped function is a local maximum or minimum.

The paper will present a number of applications that demonstrate the use of this facility.