

HARRISON MEMORIAL MEDAL LECTURE

What you can learn from gazing at water

The winner of this year's Harrison Memorial Medal is Professor Roger Waigh, professor of medicinal chemistry, University of Strathclyde. Professor Waigh gave a lecture entitled "Hot dogs and cold water"

Over the past four or five years Professor ROGER WAIGH, University of Strathclyde, has been looking at water, and building up a picture that can be simulated on a computer. "To do this," he said, "we need to understand what water molecules like to do if they have no constraints, if there is nothing dissolved in them". There has been a big debate among physical chemists for the past 50 or 60 years — some say that water is just a homogeneous mixture and that water molecules will bond with each other at any angle that they happen to meet, others think that this cannot be right and that water prefers to bond like it does in ice.

Professor Waigh explained that if a solute is introduced into water, structures called clathrates form, which consist of five- or six-membered rings joined together. He compared this structure in shape to that of a football, made up of five-sided pieces of leather, blown up to form a circle. The structure has a cavity in the centre, and other cavities on the outside that will accommodate a guest molecule. This kind of cage structure is also found in water in the gas state, he added.

"Certain things that you can dissolve in water will either disrupt or reinforce this structuring effect," explained Professor Waigh. For example, sulphate and phosphate are structure makers, and urea and guanidine are structure breakers.

In genetic engineering it is quite common to express a protein that might be useful to human beings in a bacterium in large quantities. "Very often when the protein is isolated it has the wrong shape, it is not folded up as it should be and it is not active. What people do to get around that is to add urea or guanidine to a solution, which disrupts the structure that exists. Having freed the protein by breaking the structure of water, they will then add sulphate or phosphate to restructure the water and hope that the protein will fold up in the shape that they want," he said. This does work sometimes, he added.

Professor Waigh hypothesised that because biological reactions take place in water, the structure of water is important in ligand-receptor interactions. Receptors are most often proteins, he said, and if we want to know what these structures may be like then perhaps we should look at the clathrates.

COMPUTER SIMULATIONS

"Water molecules are extremely geometric, they like to be a certain distance away from other water molecules or solutes — we used this as a constraint in the computer



Professor Waigh receives his medal from Marshall Davies, President of the Royal Pharmaceutical Society

modelling that we did. Another constraint is the angle of the hydrogen-bonds."

Professor Waigh then talked his audience through the computer modelling program. It involves starting with a water molecule, selecting a hydrogen-bonding site, then sequentially adding water molecules to the model. After adding one water molecule, the structure is rotated through 180 degrees and another water molecule is added, it is then rotated again and the process continues. Once it reaches five water molecules it can satisfy the geometric requirements to form a ring. Once past the initial ring formation, it all happens very quickly and huge arrays of three-dimensional water structures are built. "This appears to be similar to what we believe is happening in a glass of water," he explained.

Professor Waigh said that if a simulation using the structure breakers, which are flat and triangular, is run in the modelling program, then rings cannot form. If it is run with the structure makers, which are tetrahedral in shape, like water, then the aggregate of rings forms.

He went on to share two ideas about water. "Adrenaline, a catecholamine, is a structure breaker, and may be recognised by its receptor at least partly by the water it carries with it," he said. This water will not be random, but will be hydrogen-bonded in a particular way, with particular cages. "With something like adrenaline, the binding of the adrenaline has to be followed by a change in the receptor, otherwise there

would be no consequence — we are talking about messenger molecules."

Professor Waigh offered the following idea to his audience for consideration. "The catechol part of the adrenaline structure is there to change the structure of the receptor. It is a very selective structure breaker. It is brought into contact with the protein by the recognition site, it then disrupts the water around the receptor, the receptor changes shape and something happens as a consequence — the signal is passed on."

He said the second idea was that because there are phosphates, which are structure makers, on the DNA, water may form an orderly bridge between the phosphates and in so doing hold the DNA in a particular shape. "There are plenty of other factors that influence this shape, but maybe water is one of them," said Professor Waigh. "Certainly it is consistent in that if you take water away, DNA changes shape."

DNA BINDING

Professor Waigh moved on to the "hot dog" part of his lecture, which was about DNA binding. He said that to read one coding sequence uniquely, you need to read about 12 base pairs. A natural product, eg, netropsin, can only read about four base pairs. To overcome this, Professor Waigh extended the molecule but this resulted in it going out of phase with the DNA. In theory this means that the hydrogen-bonding should not work, he explained. However, when he carried out binding studies he found that, in fact, it bound well, but non-selectively. The "hot dog" analogy refers to this hydrophobic molecule — a greasy lump. The driving force for the molecule to stick to the minor groove of DNA is not hydrogen-bonding, it is to liberate water. It is possible to modify the molecule by adding phase-restoring linkers to produce a molecule that will bind to a very restricted range of DNA structures, explained Professor Waigh.

He concluded his lecture by saying that the inside of the minor groove wall of DNA is not flat, and that his team has been designing molecules that will explore the "knobby bits". They have designed molecules that fit closely and read the DNA to the point where the molecule will only bind to one, four base-pair sequence and with very high affinity. "We hopefully have the starting point for being able to design molecules that potentially will be able to switch off a gene," said Professor Waigh. The kind of genes that he has in mind are those associated with cancer or parasitic diseases, however, he added that there may be no limits to what could be done in principle.

HARRISON MEMORIAL MEDAL

The Harrison Memorial Medal is awarded every two years for achievement by a pharmacist in the science and practice of pharmacy.