Peptide simulation – it's all in the folds

Swiss chemists have devised a computer program for simulating the way peptides and small proteins fold up into their three-dimensional active forms. The simulation technique could revolutionize the way drug designers assess peptides as potential pharmaceutical leads, because it enables them to more accurately model the shape and structure of peptides and consequently the way in which they might interact with target enzymes and receptors.

The development of peptides as therapeutic agents has developed rapidly in recent years, especially with the emergence of combinatorial chemistry, which allows countless variations on the peptide theme to be generated simultaneously by simply mixing and matching several amino acids. While making peptides has never been easier, the trial comes in testing them. Even with high-throughput screening techniques being continually developed, there is no substitute for a solid understanding of the relationship between structure and activity when it comes to fine-tuning the chemistry and pharmacology in preparation for safety testing and ultimately clinical trials.

Solving the problem

Now, Dieter Seebach, an organic chemist at the Swiss Federal Institute of Technology in Zurich and his colleagues in the physical chemistry department, believe they have a solution to at least part of the problem [Daura, X. *et al.* (1999) *Angew. Chem., Int. Ed. Engl.* 38, 236–240]. They can model the way a simple two-dimensional string of amino acids will fold up when added to a solvent. They use a program, GROMOS, developed by colleague Wilfred van Gunsteren. Obtaining information about peptides is critical. This is because an understanding of their interaction with proteins will form the basis of their potential pharmaceutical applications. Until now, however, this information has remained elusive or at best only a loose approximation to their true structures.

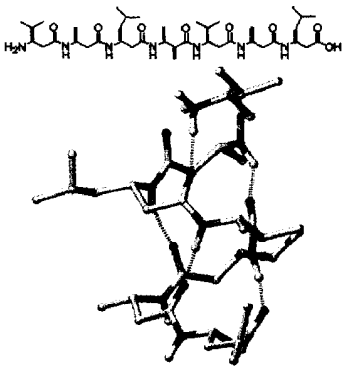

Figure 1. *The synthetic β-heptapeptide forms a right-handed helical structure upon addition to solvent.*

The system used by the team is based on molecular dynamics in which each atom in the system is treated as if it were a solid moving ball and Newton's equations of motion are applied. This approach avoids trying to solve extremely unwieldy quantum equations, which are fine for stationary molecules, but require massive amounts of computer power when a molecule is in motion. Seebach points out that even now it is not possible to directly observe the motions of individual atoms during the folding process experimentally, and that it is crucial to any simulation that it can be verified as being close to experimental reality nevertheless. He and his team have found that the flexing and bending of peptides with atomic detail are now within the reach of computer simulation.

Molecular dynamics

The researchers have used molecular dynamics to study the folding of two synthetic β-peptides, a hexapeptide and a heptapeptide composed of β-amino acids. They chose these molecules because they are not only attractive as peptide mimetics for medicinal purposes but also stable to peptidase. In solvent, the heptapeptide is known to fold up into a left-handed helix as hydrogen bonds form between charged groups along the peptide backbone (Fig. 1). The hexapeptide twists into a right-handed spiral.

By using NMR data, which reveal the connections between atoms in a molecule, the team found that the hexapeptide does not form a perfect helix but one with some distortion at three positions. They could use the molecular dynamics program to mimic this distortion within a few fractions of a nanometre and so model the peptide's structure as it exists in solution. The molecular dynamics program could also accurately predict the respective geometries of the two peptides.

Protein and peptide folding is a perennial problem in understanding structure–activity relationships at a fundamental level. Being able to model precisely the behaviour of a strand of amino acids in three dimensions will boost the medicinal chemist's ability to model interactions with proteins. Team member Karl Gademann explains how important this might be, 'The results obtained with our latest simulations are very attractive and with the wealth of data becoming available through the Human Genome Project on the primary structure of proteins, our approach may help to answer questions about the three-dimensional structure of those proteins and, hence, their biological function'.

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