Forces in molecular recognition: Comparison of experimental data and molecular mechanics calculations

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SUMMARY

NMR studies of the rotation barrier of the disaccharide of the glycopeptide antibiotic vancomycin have been used to test the performance of computer simulation techniques using molecular mechanics. In the absence of any solvated water, no correlation could be found between experiment and calculation. By introducing solvent water molecules into the binding region of the antibiotic, the NMR results could be simulated both qualitatively and quantitatively within experimental error without using massive computational resources.

INTRODUCTION

Computational methods are in widespread use to predict the low energy conformations of molecules, their intra- and inter-molecular interactions, and their mobility [1]. In most cases, the simulations are performed without consideration of the solvent, which, particularly in the case of water, may perturb the energy of the system to such an extent that the calculated gas-phase conformational preferences are overwhelmed. In order to assess the accuracy with which the COSMIC computational chemistry package [2] may be used to predict the conformational preferences of water soluble molecules, we have attempted to simulate molecular motion within the glycopeptide antibiotic vancomycin [3].

Vancomycin (see Fig. 1) consists of a heptapeptide aglycone glycosidically linked to a disaccharide, and contains both hydrophobic and hydrophilic domains. As depicted in Fig. 1, the front face is the one that binds the peptide target for antibiotic action and will subsequently be referred to as the ‘binding face’. Proton NMR studies, particularly using nuclear Overhauser effects (see below) have shown that within vancomycin there exist regions of relative inflexibility (owing to

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the extensive cross-linkage of the amino acid side chains), and regions of higher mobility [4,5]. For example, the rotational frequency of the side chain of the N-terminal residue, N-methyleucine, is faster than the overall rotational frequency of the molecule. The isopropyl terminus undergoes the fastest rotation with a reduction in frequency towards the peptide backbone. Similarly, the rotational frequency of the disaccharide with respect to the aglycone is higher than the overall molecular rotational frequency. Thus, vancomycin is a useful system with which to test experimental methodology for two main reasons:

(i) Unlike in completely flexible molecules, the motion of the flexible regions may be measured with respect to inflexible, conformationally restricted regions. In other words, it is possible to determine the position of flexible portions of the molecule relative to known positions within the inflexible regions. For example, the conformations populated by the disaccharide of vancomycin relative to the aglycone may be studied by observing the proximity of hydrogen nuclei within the disaccharide to hydrogen nuclei within the conformationally restricted triaryl system involving rings 2, 4 and 6 of the aglycone (see Fig. 1 and 2).

(ii) Vancomycin contains both hydrophobic and hydrophilic regions and so the populations of the various conformations available to freely rotatable regions are considerably influenced not only by other parts of the antibiotic, but also by the solvent.

The interconnection of the glycone and the aglycone portions of the molecule is the region of high mobility investigated in the following studies. These studies concentrate on the information that may be derived using moderately powerful computing systems (VAX 11/780).

A powerful means of determining the rate of molecular rotations faster than the overall rotational frequency of the molecule using NMR spectroscopy is through the rate of build-up of nuclear Overhauser effects (NOEs) [6]. The rate of build-up is related to the frequency of the rotation via the rate of change of a vector connecting two hydrogen nuclei perturbed by the rotation (the correlation time). It is also related to the time-averaged distance ($r$) between these nuclei (specifically to $r^{-6}$). Knowledge of the time-averaged distance between nuclei allows a qualitative estimate of