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Approaches to drug design using global energy minimization pattern recognition and molecular graphics modelling

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The synthesis of a large number of analogues of the hypothalamic neuropeptide thyrotrophin releasing hormone (TRH) has allowed the proposal of structure–activity relationships (SAR) and prompted attempts to explain the differential action of TRH centrally and peripherally. In the present study, the conformational parameter has been incorporated into traditional SAR calculations. The relatively small number of variable dihedral angles in this tripeptide has permitted an extensive search to be made of the potential surface of a series of centrally-active TRH analogues, using a SIMPLEX technique[1] combined with a model representing solvent effects[2]. Subsequent analysis of stable and metastable conformers by multidimensional scaling has facilitated comparison of conformations in 2D. In the absence of structural information on TRH receptors, preferred analogue conformers have been correlated with experimental potencies and have been found to agree for a unique conformer type, with a single exception which appears to act by a different mechanism to TRH[3]. For this study and a previous one of peripherally-active analogues[4], the solvent effect was found to be important. Of note is the finding that the calculated active conformer differs in each study, supporting a modulating role for TRH in the CNS. On the basis of these results, a novel TRH analogue has been 'designed' and using the above criteria it is predicted to be highly active. Theoretical analysis of drug–receptor interaction has historically used the enzyme–substrate system as a model[5]. A recent study in this laboratory has involved the prediction of the tertiary structure of the enzyme chloramphenicol acetyl transferase (CAT) from its amino-acid sequence. A combination of secondary structure prediction techniques, sequence homology with proteins of known structure, and molecular modelling on a spectrographics terminal, has led to the proposal of a tertiary structure for the enzyme–substrate complex compatible with a trimeric quaternary arrangement. A combination of these techniques may enable investigation of the conformational changes that induce biological effects following ligand binding and provide a more rational approach to the design of neuropeptide agonists and antagonists.

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Puck: real time modification of ribose pucker on a PS300

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3D graphic model building is now currently in use in studies of biological macromolecules, proteins and nucleic acids. This is now the rule for the crystallographers who have to build a model matching as accurately as possible their electron density map. In the case of nucleic acids, the ribose moiety is very important for determining the whole conformation of the ribose–phosphate chain. This pentose can undergo small or important conformational changes through a continuum of conformations, i.e. the so called 'pseudorotation pathway'. Only two parameters allow a full representation of all the possible sugar conformations: the phase of pseudorotation and the amplitude of deformation[1]. Up to now, the authors have only had access in Frodo[2] to two ideal and fixed conformations: C3'-*endo* and C2'-*endo*. Thus it was not possible to explore graphically the whole set of conformations. We have implemented this possibility in the PS300 version of Frodo using Puck, an additional option in the menu. By activating this function the user can:

- change interactively the pseudorotation parameters and the phase and the amplitude can be altered using dials.
- reverberate, on the base and on those parts of the nucleic chain which are fixed on the sugar, the effects of the resulting change of conformation.

The obtained effects are visualized in real time on the screen and the user can choose to modify or not the corresponding stored coordinates of the molecule as is the case in FBRT or TOR. The real time visualization of the change of pucker is made by calculating once a representative set of sugar conformations (φ is sampled in 2° steps and σ_m in 5° steps). By rotating the dial dedicated to each of the parameters one generates the index determining which instantaneous conformation should be displayed. One thus obtains a very satisfying impression of continuity.

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