

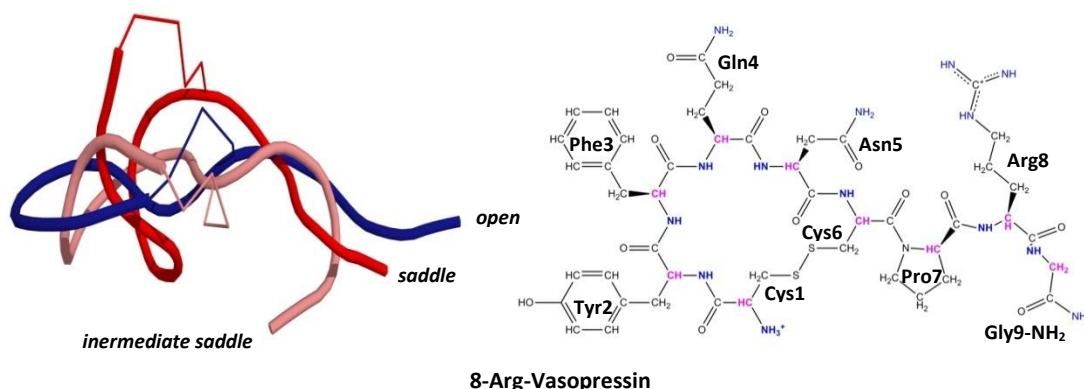
Molecular Dynamics and Umbrella Sampling Simulations of 8-Arg-Vasopressin

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A long-term (5 μ s) molecular-dynamics simulation of 8-Arg-Vasopressin was performed in aqueous solution at 300 K. Two main conformational ring states were identified *via* DASH [1] analysis: **DRS_{open}**, a stretched, *open* conformation with no intramolecular hydrogen bonds in the ring; and **DRS_{saddle}**, a folded, *saddle*-like conformation with strong hydrogen bonding interactions between the carbonyl oxygen of the ring residue Tyr² and the amide protons of the ring residues Asn⁵ and Cys⁶. Only one transition between both main states was observed during the 5 μ s simulation run. In addition to these two main states, a sparsely populated DASH state, **DRS_{intermediate}**, was found with mixed conformational characteristics of the two main states. Umbrella Sampling [2, 3], post-processed with WHAM [4-6], was used to estimate the free energy profile for the conformational change from *open* to *saddle* and led to a reaction path *via* **DRS_{intermediate}** (see video clip [7]), with barrier heights of 7.7 kcal mol⁻¹ and 14.2 kcal mol⁻¹ and a free energy difference between the *open* and *saddle* states of 4.0 kcal mol⁻¹.



8-Arg-Vasopressin (AVP) is a neurohypophyseal hormone with a wide range of endocrinological and neurological functions, e.g. water homeostasis, blood pressure regulation and mediation of social and sexual behavior. Main structural characteristics are a 6-residue ring closed *via* disulphide bridging, and a α -amidated 3-residue tail. Figure: Structure and backbone conformations (blue: *open*; red: *saddle*; rose: *intermediate*; cartoon: backbones; sticks: disulphide bridges; not shown: sidechains)

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