So they only have 1 kcal/mol due to the equilibrium between the folded and unfolded States

Do electrostatic interactions each contribute 5kcal/mol to the free energy of folding?

- No-because the charges are fully solvated (neutralised) by water in the unfolded • state
- The entropic contribution of 1kcal/mol remains

## Entropy of folding

- Entropy can be related to the number of states or degrees of freedom of the system
- S = k ln W --> Boltzmann's equation
- k = Boltzmann's constant

 W = number of states = for a molecule W is the number of different conformations For one molecule:

- $S=N_A k \ln W$  ( $N_A = Avogadro's number$ )
- Therefore S = R In W (R = gas constant = 2 cal  $K^{-1}$  mol<sup>-1</sup>; R = N<sub>A</sub>k)

For a mole of protein:

- $S = S_{native} - S_{unfolded}$ 
  - = R ln W<sub>n</sub> R ln W<sub>u</sub>
  - $= R \ln (W_n / W_u)$
- W<sub>u</sub> = 10<sup>100</sup> if there are 100 residues and if for every residue per Cire 10 conformations
  Therefore S<sub>folding</sub> = R ln (1/10<sup>100</sup>) = -0 40 logor<sup>1</sup> · 11
- Therefore at 300K
- G = free energy of folding
- The enthalpy of each H bid and the other non-covalent forces favour folding BUT entropy of the polypeptide chain greatly favours unfolding over the folded (ordered) state

ery unfavourable

- Therefore the free energy of folding a protein is typically only around 10 kcal/mol
- Therefore proteins are very easily destabilised by mutation or by a change in the • environment

## The hydrophobic effect also drives protein-protein interactions

- Hydrophobic effect for a buried surface area of 100<sup>-2</sup> (1nm<sup>2</sup>)
- i.e. 0.024 kcal/mol/<sup>2</sup> of buried surface area
- The principle driving force for protein folding (or protein-protein interactions) in • aqueous solution is the increased entropy of the water molecules that results from burying hydrophobic amino-acid side-chains