Cellular Biophysics
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Energy And Entropy In Water Structure

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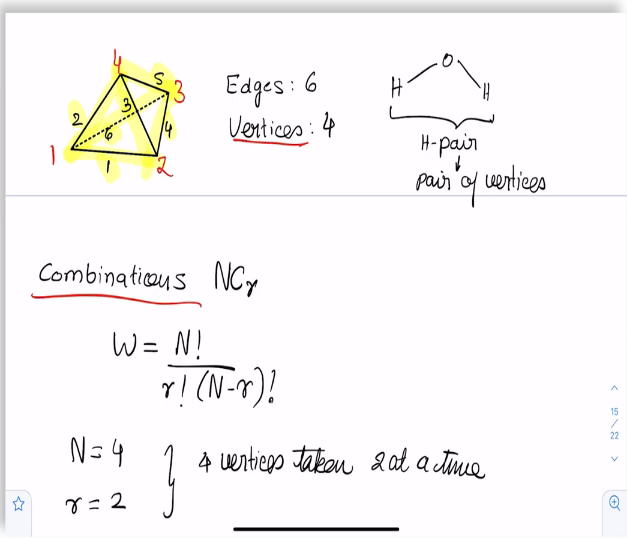


Edges : 6

Vertices : 4

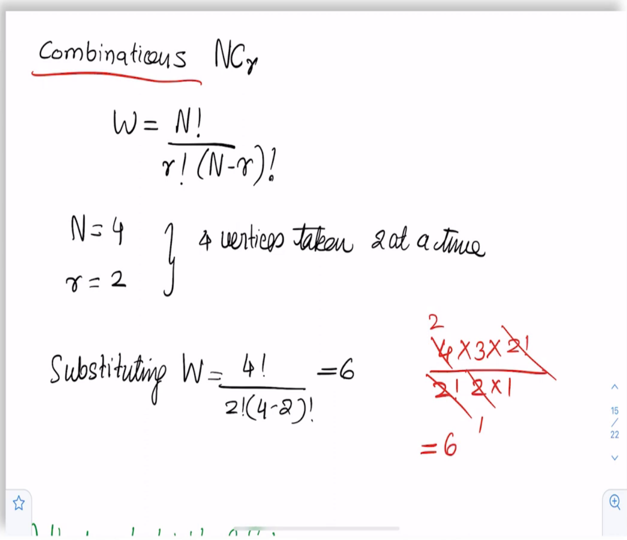
H-pair

pair of vertices

Combinations NC_r

$$W = \frac{N!}{r!\,(N-r)!}$$

$N=4$, $r=2$ } 4 vertices taken 2 at a time



Combinations NC_r

$$W = \frac{N!}{r!\,(N-r)!}$$

$N=4$, $r=2$ } 4 vertices taken 2 at a time

Substituting $W = \frac{4!}{2!(4-2)!} = 6$

$$\frac{\overset{2}{\cancel{4}} \times 3 \times \cancel{2!}}{\cancel{2!}\,\underset{1}{\cancel{2}} \times 1} = 6$$

So, like I will see the combinatorics of this pairwise selection of vertices can be mathematically understood using some simple arithmetic, we say that a tetrahedron that you see on the left side over here is consisting of 6 edges, 1, 2, inside 3, 4, 5, and 6. So, I can just say 3 is above, so this one 2 3 4, 1 2 3, 4 5 6, I miss this 6 the number of vertices on the other hand are 4, and you can count to confirm. So, 1 2 3 4, that is the number of vertices.

The hydrogen atoms, the way we placed them in this combinatorial concept of redundancy is a pair of hydrogen atoms at each pair of vertices and then we modified so we can write the number of combinations as $^{N}C_{r}$ where N is W is equal to, I am sorry where the combinations are given as

$$W = N!/(r!(N-r)!)$$

where the number of vertices are in total number of vertices 4, taken 2 at a time this is what we did.

Substituting we get, 4! upon 2! times (4 – 2)! is equal to 6

$$W = 4!/(2!(4-2)!)= 6$$

Just check this. So, it is 4 x 3 x 2! in the numerator and in the denominator 2! times so we do not need to write that into(x) , so 4 - 2 is again 2, so 2 x 1

$$W = (4 \times 3 \times 2!)/(2! \times 2 \times 1)$$

So, we get rid of factorial 2 here, 2, 4 by 2 is 2, and so, we end up with 6.

$$W = (4 \times 3 \times \cancel{2!})/(\cancel{2!} \times 2 \times 1) = 6$$

So, our arithmetic was fine. What do we do with this?

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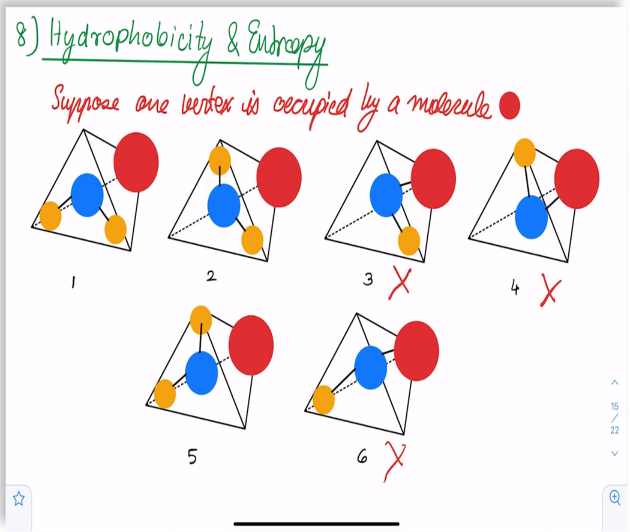
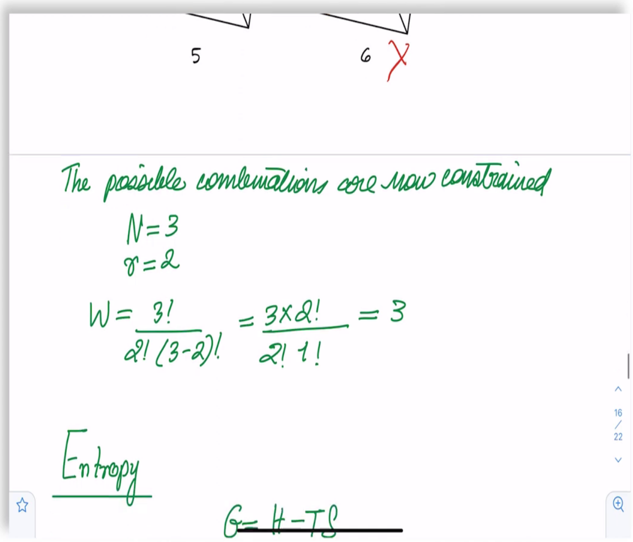


8) Hydrophobicity & Entropy

Suppose one vertex is occupied by a molecule ●



The possible combinations are now constrained

$N=3$

$r=2$

$$W=\frac{3!}{2!\,(3-2)!}=\frac{3\times 2!}{2!\,1!}=3$$

Entropy

$G = H - TS$

Now, we can use this little statistical redundancy question to conceptually understand another aspect of Pauling's idea of entropy and put it in the framework of hydrophobicity. And the idea is the following. If we now have a molecule that is a polar does not have even a weak charge and therefore a interact with H_2O, then in the if the number of molecules are sufficient enough, let us say in 1 tetrahedron.

Such a molecule occupies one of the positions of the tetrahedron which means that out of the 6 possible positions that the H_2O molecule could take this one, this one and this one are eliminated, we cannot have them which means that the possible combinations are now constrained which means we have now 1 2 3 vertices again taken two at a time and we end up with W is equal to 3, make sense.

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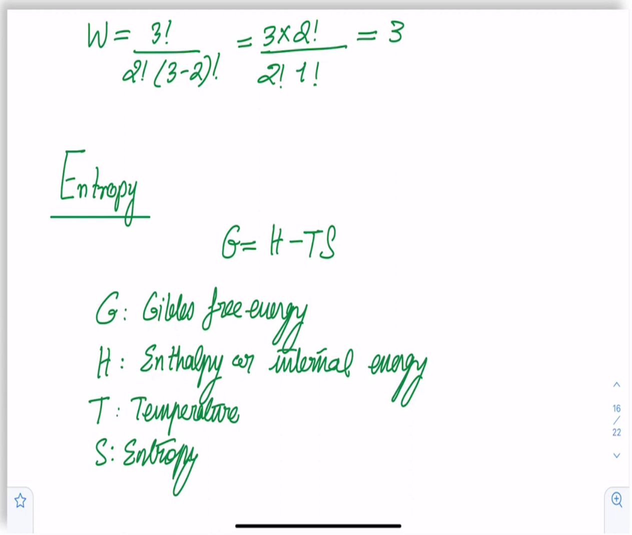
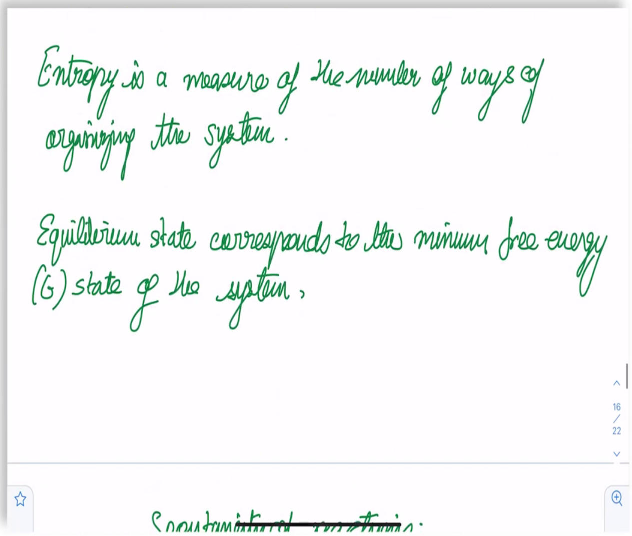


$$W = \frac{3!}{2!\,(3-2)!} = \frac{3 \times 2!}{2!\,1!} = 3$$

Entropy

$$G = H - TS$$

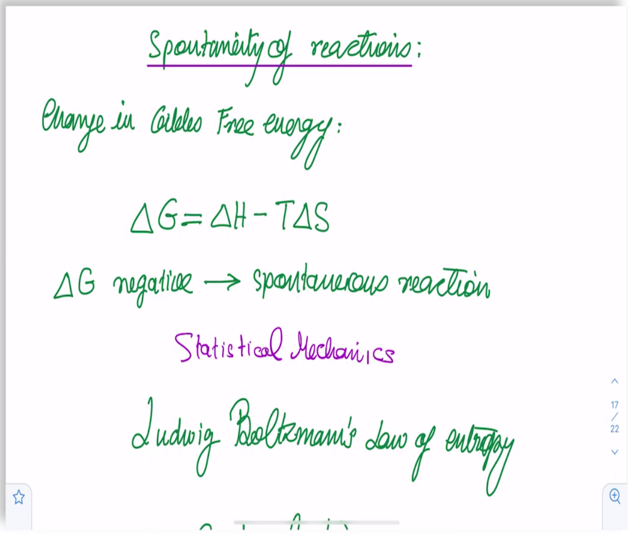
G : Gibbs free energy
H : Enthalpy or internal energy
T : Temperature
S : Entropy



Entropy is a measure of the number of ways of organizing the system.

Equilibrium state corresponds to the minimum free energy (G) state of the system.

Spontaneity:



Spontaneity of reactions:

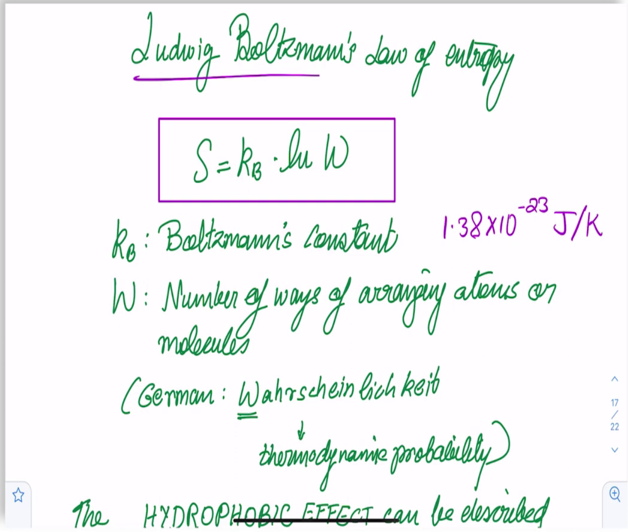
Change in Gibbs Free energy:

$$\Delta G = \Delta H - T\Delta S$$

ΔG negative → spontaneous reaction

Statistical Mechanics

Ludwig Boltzmann's law of entropy



Ludwig Boltzmann's law of entropy

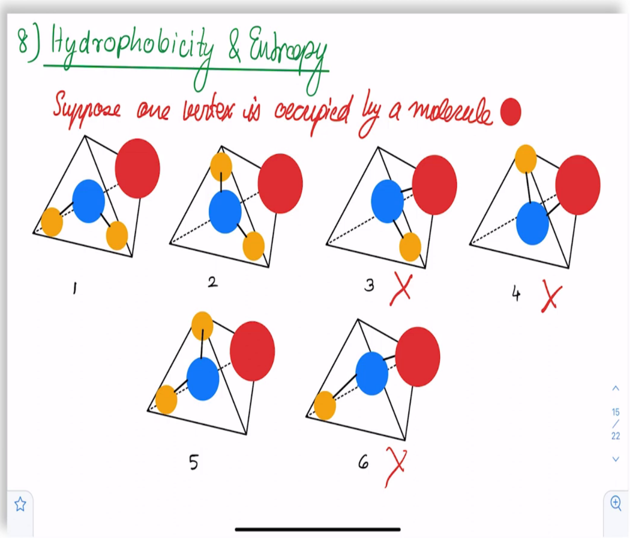
$$\boxed{S = k_B \cdot \ln W}$$

k_B : Boltzmann's constant 1.38×10^{-23} J/K

W : Number of ways of arranging atoms or molecules

(German : Wahrscheinlichkeit
↓
thermodynamic probability)

The HYDROPHOBIC EFFECT can be described



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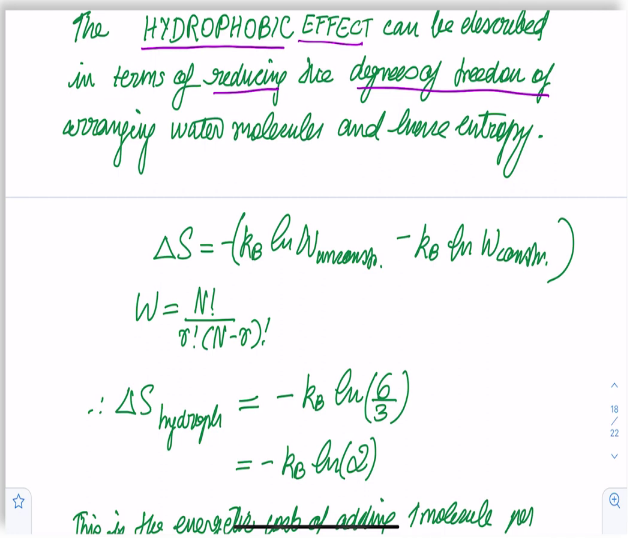
Suppose one vertex is occupied by a molecule ●



The **HYDROPHOBIC EFFECT** can be described in terms of reducing the degrees of freedom of arranging water molecules and hence entropy.

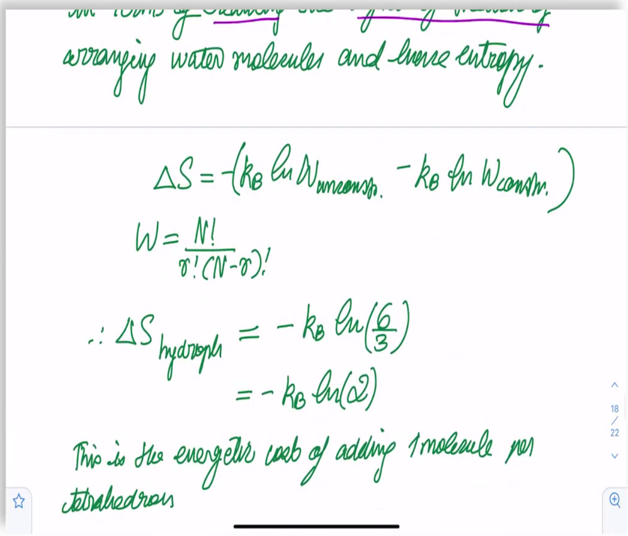
$$\Delta S = -\left(k_B \ln W_{\text{unconstr.}} - k_B \ln W_{\text{constr.}}\right)$$

$$W = \frac{N!}{r!(N-r)!}$$

$$\therefore \Delta S_{\text{hydroph}} = -k_B \ln\left(\frac{6}{3}\right)$$

$$= -k_B \ln(2)$$

This is the energetic cost of adding 1 molecule per



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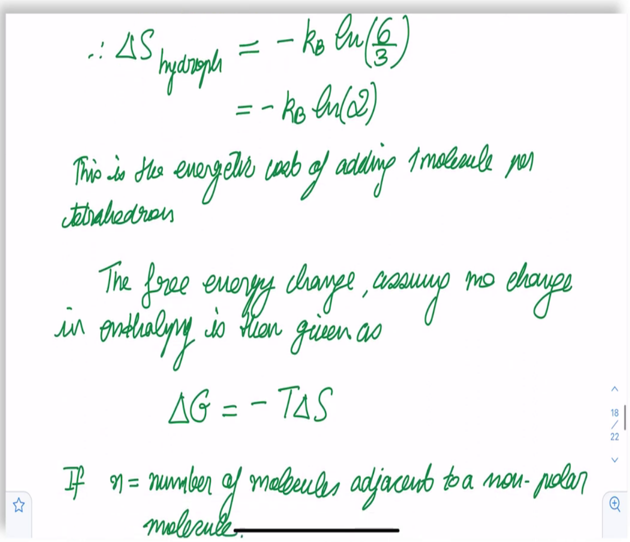
tetrahedron



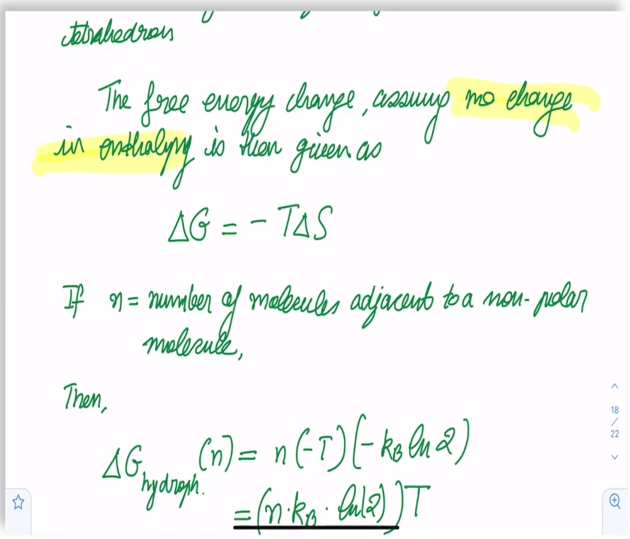
$$\therefore \Delta S_{hydroph} = -k_B \ln\left(\frac{6}{3}\right)$$
$$= -k_B \ln(2)$$

This is the energetic cost of adding 1 molecule per tetrahedron

The free energy change, assuming no change in enthalpy is then given as

$$\Delta G = -T\Delta S$$

If n = number of molecules adjacent to a non-polar molecule.



tetrahedron

The free energy change, assuming no change in enthalpy is then given as

$$\Delta G = -T\Delta S$$

If n = number of molecules adjacent to a non-polar molecule,

Then,

$$\Delta G_{hydroph.}(n) = n(-T)(-k_B \ln 2)$$
$$= \underline{(n \cdot k_B \cdot \ln(2))T}$$

Entropy on the other hand, so, this was all statistics, statistics and combinatorics. Entropy on the other hand, comes to us from thermodynamics its population it is a property of a system from thermodynamics, and it also has a linkage to statistical mechanics which we will get to in a minute.

In the thermodynamic description Gibbs free energy G is equal to the difference between the internal energy or enthalpy and the temperature multiplied by entropy the product of temperature and entropy. On the other hand, entropy is a measure in itself of the number of ways of organizing the system, we also say that the equilibrium state of any system corresponds to the minimum free energy G of the system that is either S is very high or H is very low.

The idea that S is very high is part of your second law of thermodynamics. In such a system, then the spontaneity of a reaction is determined by the change in Gibbs free energy. And again, that gives us,

$$\Delta G = \Delta H - T \Delta S,$$

ΔG is negative indicates a spontaneous reaction. This was a as far as the thermodynamics goes.

And now, we come to a set of a simple definition which took many years to accept from statistical mechanics which is, in some sense the statistical postulate of entropy. And in its most straightforward form, coined by Ludwig Boltzmann, the pioneer of statistical mechanics. So, like I was saying, the Boltzmann's entropy law states that,

$$S = K_B lnW$$

where K_B is nothing but the Boltzmann's constant in SI units, it is 1.38×10^{-23} Joules per Kelvin. And W is the number of ways of arranging atoms or molecules, it always begs the question why W, what is the meaning of W? it does not seem to make sense, it is not a probability right. But W is a historical term in honor of Boltzmann who was himself a German speaker from Austria. He is married in the Vienna cemetery. W stands for Wahrscheinlichkeit, which is nothing but probability with the colloquial meaning of thermodynamic probability.

So, you remember, we talk we began this segment with hydrophobicity. And we are going to sort of ask, how hydrophobic effects can be put in terms of thermodynamics, and in this particular case, we spoke about the degrees of freedom, you remember that we said there are certain permitted positions for water and an apolar molecule placed in the matrix will result in restricting the freedom of water molecules to be placed.

And so, we are going to describe the hydrophobic effect in terms of reducing the degrees of freedom of arranging water molecules and therefore, giving rise to hydrophobic effects through entropy. So, in the sense, we will frame this as the change in entropy ΔS is the difference, negative difference between the unconstrained situation minus the constraint situation, constraint being with the hydrophobic elements in them the molecules in the lattice, W by definition, is N! divided by r!, and still in the denominator (N-r)! .

This is how we are described upon combinational other. ΔS hydrophobic then becomes - K_B x ln(6/3), 6 being the edges, and 3 being the constraint edges.

$$\Delta S_{\text{hydrophobic}} = -\, K_B \ln(6/3)$$

So, let us look over here. So, there are edges 1 let me mark them 1 2 3 which are permitted. And these are the constraint edges, and the original number of edges were 6.

So, the energetic cost of adding a molecule per tetrahedron can be thought of in terms of the free energy change in enthalpy, which is ΔG, and so we just simply write Δ G is equal to minus, in terms of changing internal Gibbs free energy, we assumed that there is no change in enthalpy. No change in enthalpy.

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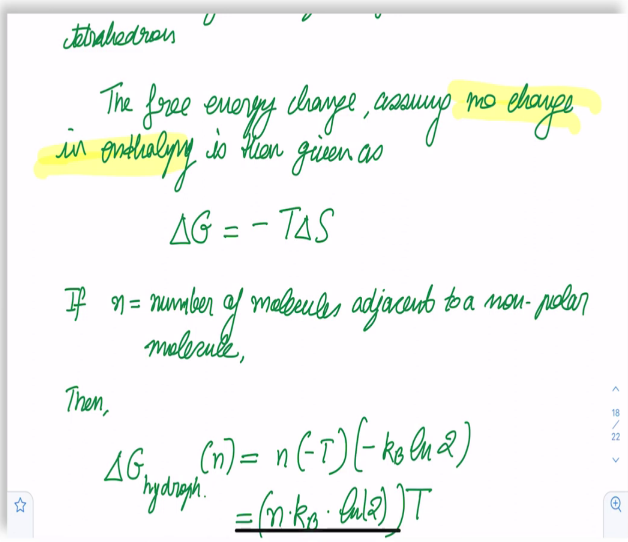


tetrahedron

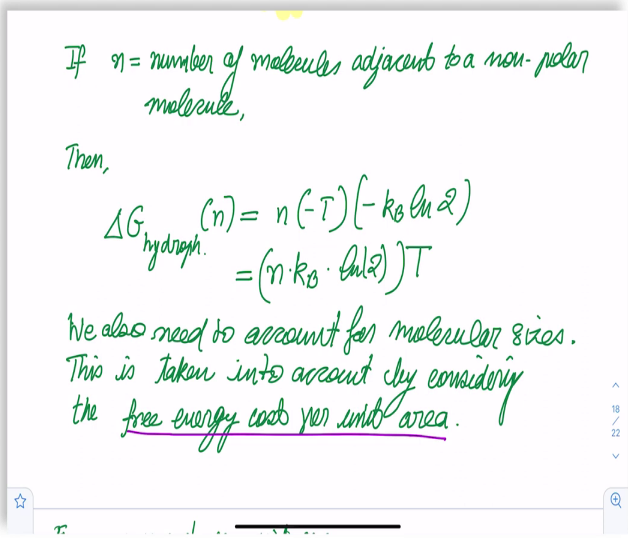
The free energy change, assuming no change in enthalpy is then given as

$$\Delta G = -T\Delta S$$

If n = number of molecules adjacent to a non-polar molecule,

Then,

$$\Delta G_{hydroph.}(n) = n(-T)(-k_B \ln 2) = (n \cdot k_B \cdot \ln(2))T$$



If n = number of molecules adjacent to a non-polar molecule,

Then,

$$\Delta G_{hydroph.}(n) = n(-T)(-k_B \ln 2) = (n \cdot k_B \cdot \ln(2))T$$

We also need to account for molecular sizes. This is taken into account by considering the free energy cost per unit area.

We assume therefore, that ΔG can be written as $-T\Delta S$ because ΔH is 0.

$$\Delta G = -T\Delta S$$

If the number of molecules adjacent to non-polar molecules is n, then we can say ΔG hydrophobic for any molecules is n into minus T. Remember this came from above here into minus K_B ln 2 that came from here, which means that the ΔG hydrophobic is equal to n into K_B into ln 2 times T, we also need to account for molecular sizes, and this is taken into account by considering the free energy cost per unit area.

$$\Delta G_{hydrophobic}(n) = n \times (-T) \times (-k_B \ln 2) = (n\, k_B \ln(2))T$$

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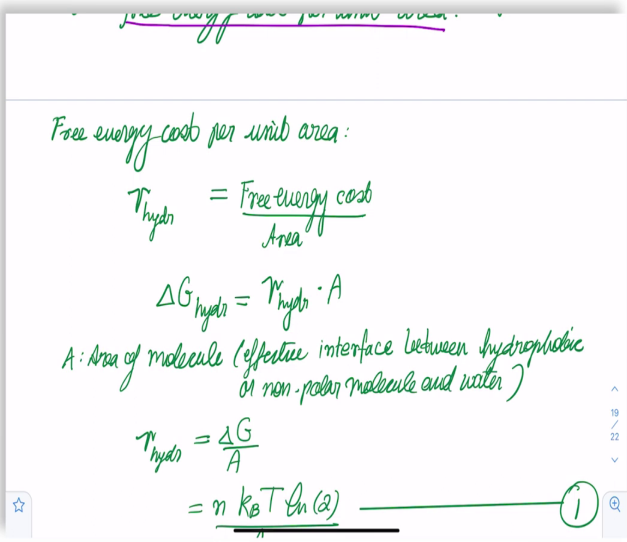


Free energy cost per unit area:

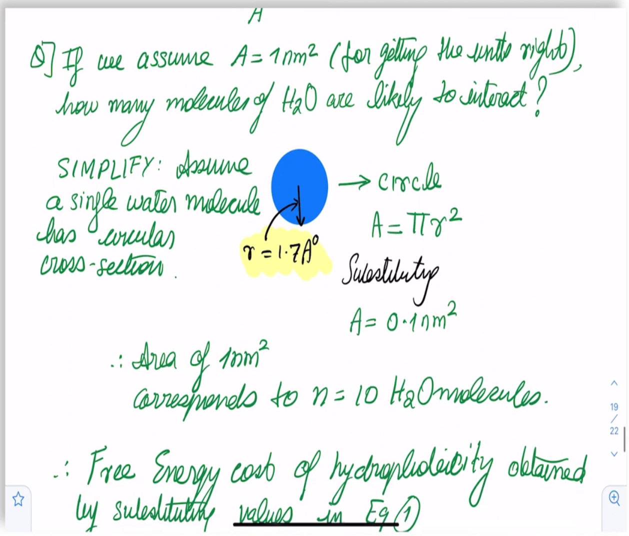
$$\gamma_{hydr} = \frac{\text{Free energy cost}}{\text{Area}}$$

$$\Delta G_{hydr} = \gamma_{hydr} \cdot A$$

A : Area of molecule (effective interface between hydrophobic or non-polar molecule and water)

$$\gamma_{hydr} = \frac{\Delta G}{A}$$

$$= \frac{n\, k_B T \ln(2)}{A} \text{ ——— } ①$$



Q] If we assume $A = 1\,nm^2$ (for getting the units right), how many molecules of H_2O are likely to interact?

SIMPLIFY: Assume a single water molecule has circular cross-section.

→ circle

$A = \pi r^2$

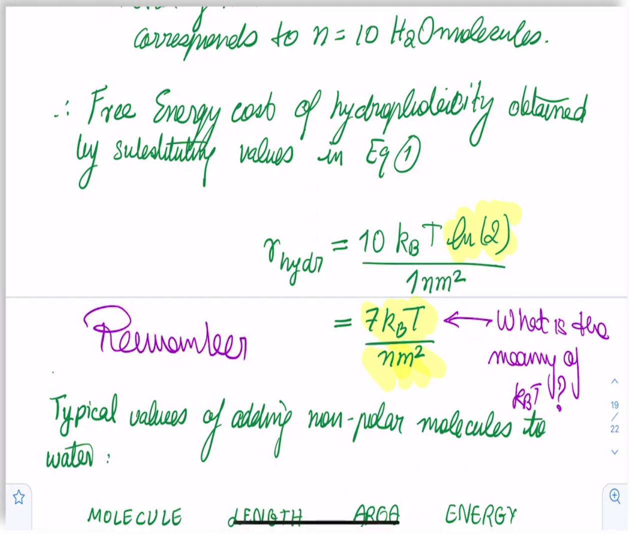
$r = 1.7\,Å$

Substituting

$A = 0.1\,nm^2$

∴ Area of $1\,nm^2$ corresponds to $n = 10$ H_2O molecules.

∴ Free Energy cost of hydrophobicity obtained by substituting values in Eq ①



corresponds to $n = 10$ H_2O molecules.

∴ Free Energy cost of hydrophobicity obtained by substituting values in Eq ①

$$\gamma_{hydr} = \frac{10\,k_BT\,\ln(2)}{1\,nm^2}$$

Remember

$$= \frac{7k_BT}{nm^2}$$

← What is the meaning of k_BT ??

Typical values of adding non-polar molecules to water :

MOLECULE	LENGTH	AREA	ENERGY

The free energy cost per unit area is indeed, free energy cost divided by area, which means delta G hydrophobic is equal to the energy cost per unit area multiplied by the area of the molecule. It is kind of a simple arithmetic. So, the area of the molecule is the effective interface between hydrophobic or non-polar molecule and water.

And this is effectively saying that the area encountered by a water molecule or coated by a water molecule in the presence of a hydrophobic molecule, that is what A indicates. Therefore, we can write ΔG in its full form as n K_BT ln 2 which we saw here. And K_BT we combine into one term and divide by area.

$$\Delta G = nK_BT\ln(2)/(A) \quad (1)$$

And this is very exciting, because now we can do some sums, we can do some arithmetic to get an idea of how much this energetic cost of adding a molecule into water is actually. In order to do that, we want to make some simplifications. We asked we assume that area is 1 nanometer square A is equal to 1 nanometer square.

And we then ask how many water molecules are likely to interact for a 1 nanometer square area of interface, effective interface area, that is what we call A. So, a simplified, I assume a single water molecule has a circular cross section it is not unreasonable if it is if assume a whole molecule to be a sphere, we know it is a molecule from tetrahedron to stick 2 hydrogen sticking out of a single oxygen. But we can also assume that it is one big sphere with a radius of gyration. So, and many of you are familiar with radii of gyration.

So, if we a simplify it in this fashion, then the radius of a water molecule is 1.7 angstroms. It is a circle with πr^2, substituting r in the πr^2 equation, we get A is equal to 0.1 nm^2, which means that if one molecule is 0.1 nm^2, how many molecules fit into 1 nm^2, it is evident it is 10.

So, 10 water molecules correspond to 1 nm^2 cross sectional area. So, now the free energy hydrophobicity can be arranged and inferred from substitution in equation 1, because we now know n which is 10, A which is 1 nm^2, and K_BT is a constant. And so, we end up with a term which is and we can solve ln(2) and many of you probably know this.

This gives us 7 K_BT per nm^2, this is the $\gamma_{hydrophobic}$ energy of adding into water per unit area, depending on the size of the molecule, however, this is what it indicates per nm^2, depending on how many fold of per nm^2, the area is, or in nanometer, what the area of interaction of a molecule, you will have higher or lower values, then $7K_BT$, this is a separate topic, which I want to spend a little bit of time about, which is what is the meaning of K_BT?

We will encounter it again and again. And this will be something that I hope you will find has some almost universal relevance for cellular biophysics. It is one of those kinds of numbers that I really want you to remember.

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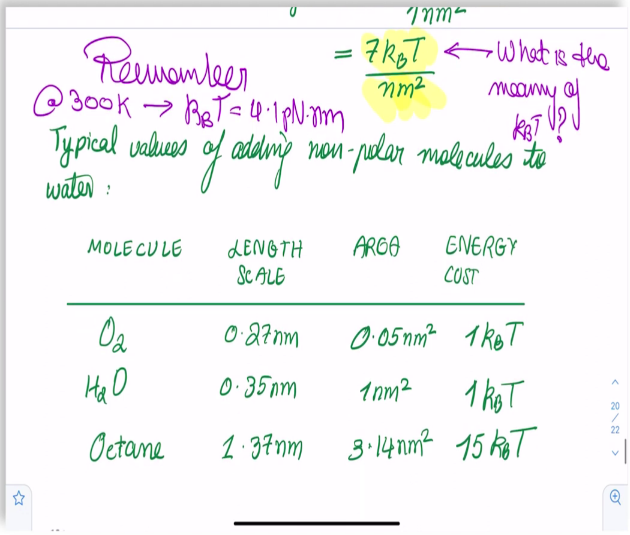


$1\,\mathrm{nm}^2$

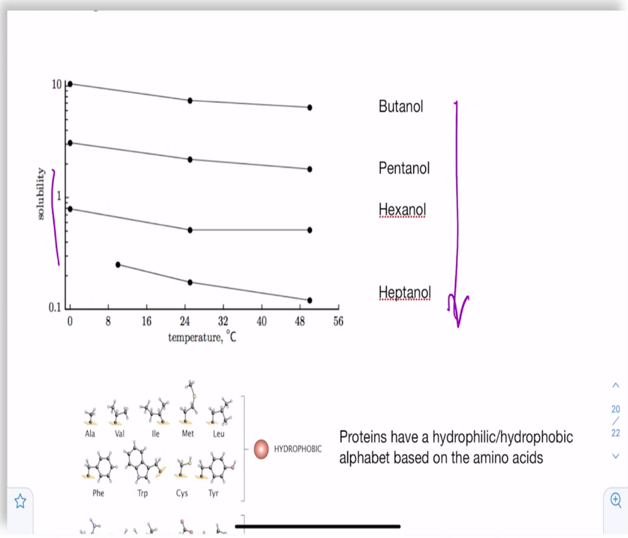
Remember

$$= \frac{7 k_B T}{\mathrm{nm}^2} \longleftarrow \text{What is the meaning of } k_B T \text{ ?}$$

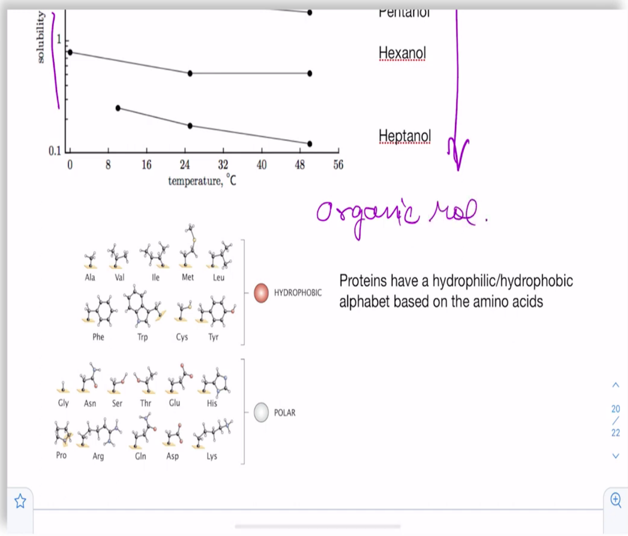
@ 300K → $k_B T = 4.1\,\mathrm{pN \cdot nm}$

Typical values of adding non-polar molecules to water :

MOLECULE	LENGTH SCALE	AREA	ENERGY COST
O_2	$0.27\,\mathrm{nm}$	$0.05\,\mathrm{nm}^2$	$1 k_B T$
H_2O	$0.35\,\mathrm{nm}$	$1\,\mathrm{nm}^2$	$1 k_B T$
Octane	$1.37\,\mathrm{nm}$	$3.14\,\mathrm{nm}^2$	$15 k_B T$

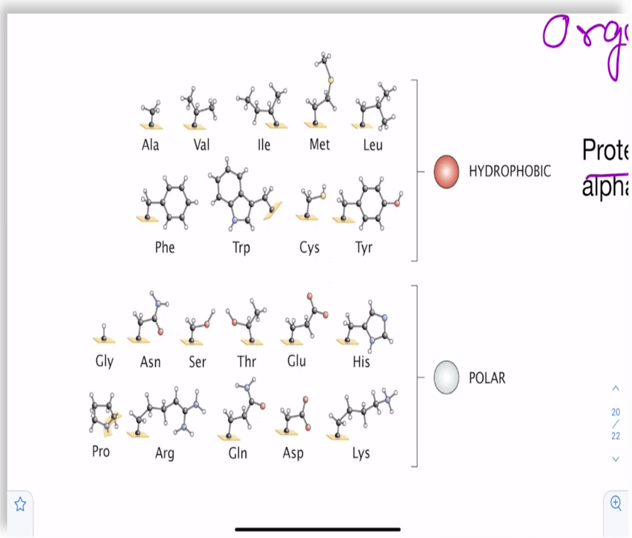


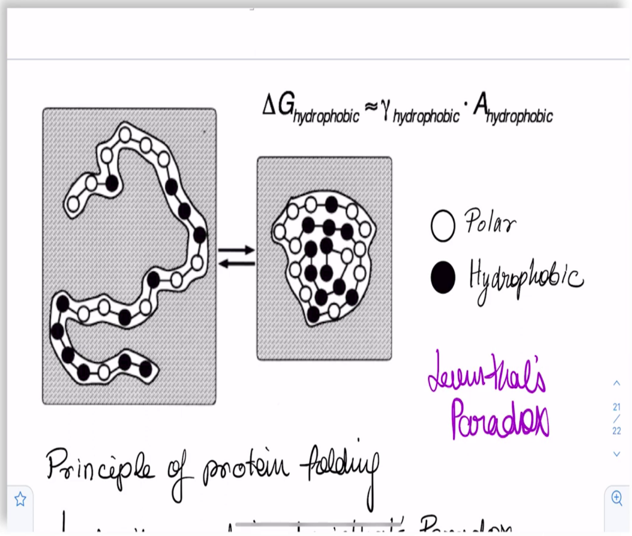
Proteins have a hydrophilic/hydrophobic alphabet based on the amino acids



Organic mol.

Proteins have a hydrophilic/hydrophobic alphabet based on the amino acids





$$\Delta G_{hydrophobic} \approx \gamma_{hydrophobic} \cdot A_{hydrophobic}$$

Principle of protein folding

For now, I am going to tell you that at 300 Kelvin, the value of K_BT is equal to 4.1 pNnm very unusual unit. Remember this and we talk about this later, the typical values of adding non-polar molecules to water are as follows. For oxygen with a length scale of 0.27 nm diameter of 0.27 nm assume a circle or sphere, the area is 0.05 nm^2 and the energy cost is 1 K_BT, remember I said could be lower?

The energy costs could be lower than 7 K_BT. And this is really interesting, because it is saying that the energy is very low of adding water. This is kind of oxygen into water and this is something that you can enrich oxygen in water you can dissolve oxygen up to a certain concentration in water. And this is what fish and is what all aquatic organisms live on. Dissolving water in water is also 1 K_BT?

Octane on the other hand, which is an carbon 8 molecule at I came gives you 1.37 nm^2, nanometer 3.14 nm^2 which means 15 K_BT. 15 times higher energy than oxygen for dissolving in water. In other words, the hydrophobic energy cost is very high, which is another way of saying that it is somewhat hydrophobic.

And as the solubility or as the length of the chain of carbon chains increases in this direction, Butanol, Pentanol, Hexanol, Heptanol and octane, as I said earlier, and these are alcohols, of course, you notice that the solubility of these goes down and down and down. This is what this solubility is telling us meaning to say that the energy cost is so high that they are less and less likely to be dissolved. Ethanol is not on this but it is somewhere on the higher side.

Now, all this is fine as far as organic molecules are concerned, what about biological molecules. The most biological molecule we can think of are proteins. And here I have put together the standard amino acid table consisting of a categorization of amino acids into hydrophobic and polar.

Hydrophobic meaning those that are apolar and therefore, unable to form the kind of hydrogen bonding network integrate with hydrogen bonding network as compared to polar and you will see that there is almost an equal distribution with slight bias towards polar molecules in terms of side chains of amino acids.

This means that we can also think of amino acids in terms of an alphabet of a hydrophobic hydrophilic. And this is not a very normal idea, because this has been proposed to be part of a principle that may govern protein folding. So, from hydrophobicity and water, statistical mechanics and entropy terms, suddenly.

We come back to protein folding, which is the most fundamental mystery under similar scale in terms of biophysics, because, as you know alpha fold and all these new machine learning algorithms, while they been successful at folding, by learning the pattern that is existing, we as humans as a brain as a principal in terms of equations still do not have fundamental principles to explain how proteins fold and this is also sometimes called the Levinthal's Paradox.

And some of you may have come across it in biology. Some of you may want to learn more about it, these are for the biochemistry textbook. I will not be dealing with it in detail because more mathematics problem, but there are fascinating combinatorial question that arise automatically and so with this, I am going to sort of end here and we will continue on the next topic of viscosity and Reynolds numbers.