Bio-Physical Chemistry
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Lecture - 12
Hydrophobic Effect

The topic today as we just left right last class was we were talking about the Hydrophobic Effect and that is what we are going to discuss today. I am not sure that we will be covering it in one lecture; I will at least need another lecture on hydrophobic effect right.

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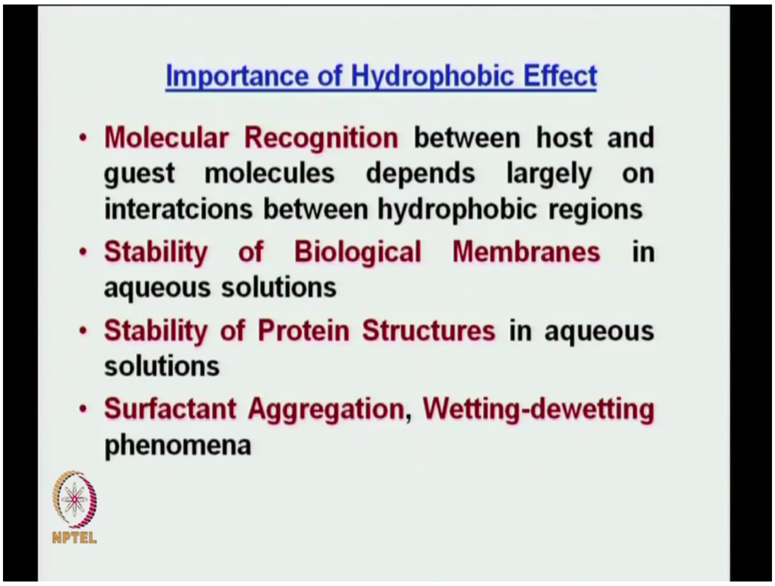

Importance of Hydrophobic Effect

- **Molecular Recognition** between host and guest molecules depends largely on interatcions between hydrophobic regions
- **Stability of Biological Membranes** in aqueous solutions
- **Stability of Protein Structures** in aqueous solutions
- **Surfactant Aggregation**, **Wetting-dewetting** phenomena

So, you know what do you mean by hydrophobic effect and why is hydrophobic effect so important? So, you can see there kind of you know four major points or four major areas where hydrophobic effect actually makes its presence felt. One is molecular recognition between host and guest molecules. So, a large extent of the non-covalent interactions that are involved in such host guest systems has to deal with hydrophobic effect right.

Because, if there are hydrophobic patches you know hydrophobic regions of these two things then these can enforce this host guest relationship. So, second one is the stability of biological membranes, we know we have membranes. And these membranes are stable and that stabilization comes because of hydrophobic effect. Next is the topic of this course which is proteins, you know proteins are made up of hydrophobic and hydrophobic parts too.

And, when you have these tertiary and co-ordinary structures a lot has to deal with hydrophobic effect which ensures that the protein is stable in aqueous solution. And last, but not the least you have heard of surfactants right, micelle formation, micellization; waiting, dewaiting phenomena you might not of heard about it. But, all these have to do with the concept of hydrophobic effect ok.

So, this is kind of few broad areas where hydrophobic effect is important and that is why someone really should try to understand what hydrophobic effect is from the very first principles.

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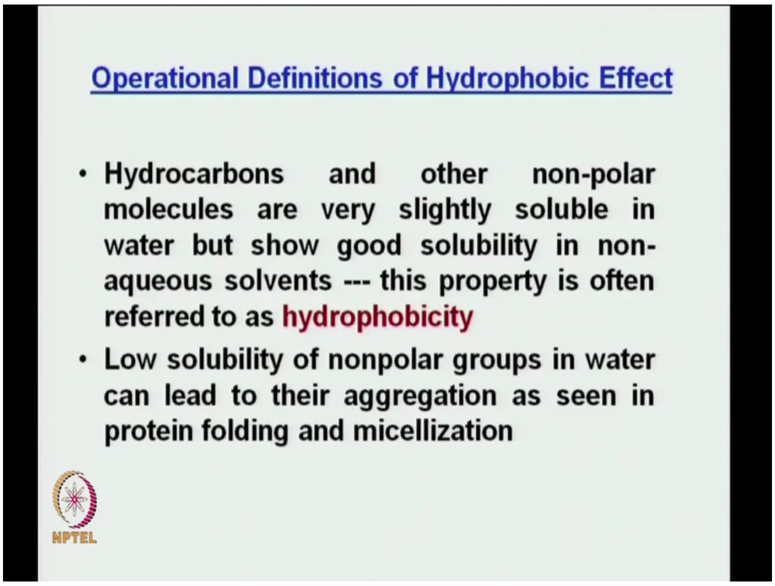

Operational Definitions of Hydrophobic Effect

- Hydrocarbons and other non-polar molecules are very slightly soluble in water but show good solubility in non-aqueous solvents --- this property is often referred to as **hydrophobicity**
- Low solubility of nonpolar groups in water can lead to their aggregation as seen in protein folding and micellization

So, let us look at some operational definitions, you know how do we define hydrophobic effect. See for us it is very simple right when we talk about hydrophobic effect for example, why when we put oil in water what happens right; that is an example or classic example of hydrophobic effect. Oil does not like water; water does not like oil right.

And, essentially that is why the solubility of oil like compounds. So, hydrocarbons in water is very low and that is you know what we have learnt to deal with that is what hydrophobicity is all about. And, the moment we you know the moment we think about it, what you really start also thinking about is that the interactions between your non-polar molecule or say oil or hydrocarbon and water are not favorable. And, that is why it is better that the oil molecules they associate among themselves, the water molecules they move a part because of this hydrophobic effect.

But is that really true? Do we really need to redefine our thought process with regards to hydrophobic effect? Let us see how we do that. So, this two operation definition, I kind of mentioned right now. One is that hydrocarbons and other non-polar molecules are very slightly soluble in water, but they show good solubility right in non-aqueous solvents. This properties often referred to as hydrophobicity, this is just feed what we just discussed.

Then the second one is the same thing. The low solubility of non polar groups in water can lead to the aggregation as seen in protein folding and micellization. So, micellization we know when micelles form these things come together. And, these are micelles then they have their polar head groups which point out and the hydrophobic effect which point inside.

Student: Inside.

And you can also have micelles in the inverted form that is reverse micelles, where if a bulk is an organic solvent then your hydrophobic tales would be pointing.

Student: (Refer Time: 05:08).

Outside and your polar head groups would be pointing inside. So, these are reverse micelles, but anyway hydrophobic effect is dominated in both the cases.

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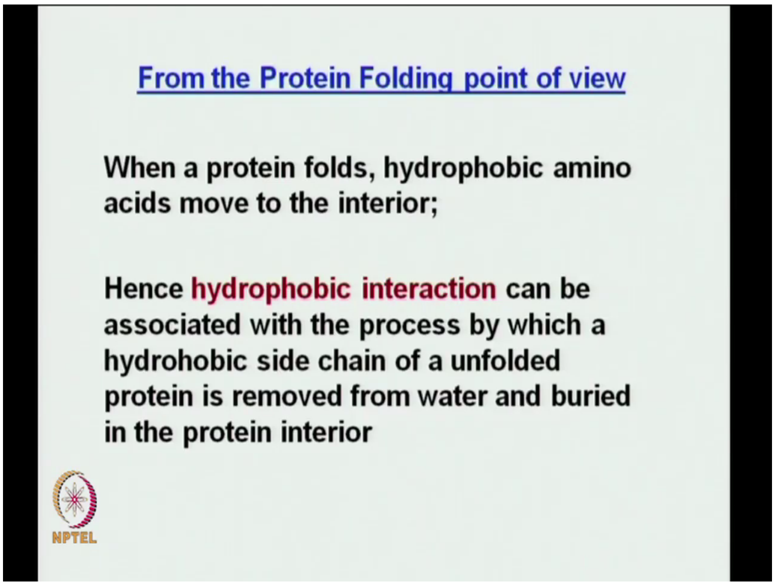

From the Protein Folding point of view

When a protein folds, hydrophobic amino acids move to the interior;

Hence hydrophobic interaction can be associated with the process by which a hydrohobic side chain of a unfolded protein is removed from water and buried in the protein interior

So, how do we relate it to proteins? When a protein folds; obviously, this we have discussed also, the hydrophobic amino acids will have to move to the interior because simply speaking hydrophobic amino acids do not like water. Hence, as has been said here hydrophobic interaction can be associated with the process by which a hydrophobic side chain of a unfolded protein is removed from water and buried in the protein interior; you know that essentially what you are doing right.

When a protein is said this side it is mostly linear though with you know some shades of structure depending upon the protein sequence or the type of protein that we have discussed before. But, there are would be many hydrophobic amino acids which would not be in the form of a structure; they would not like water. So, essentially when you go from the folded to the unfolded form what you do is, if you would be doing it you just take that hydrophobic amino acid side chain.

Take it out from water and put it inside the protein core because that protein core is shielded from the bulk solvent or water molecules. You know that essentially what you are doing right. And, this is the connection between hydrophobic effect as you know or as defined or as we think and protein folding.

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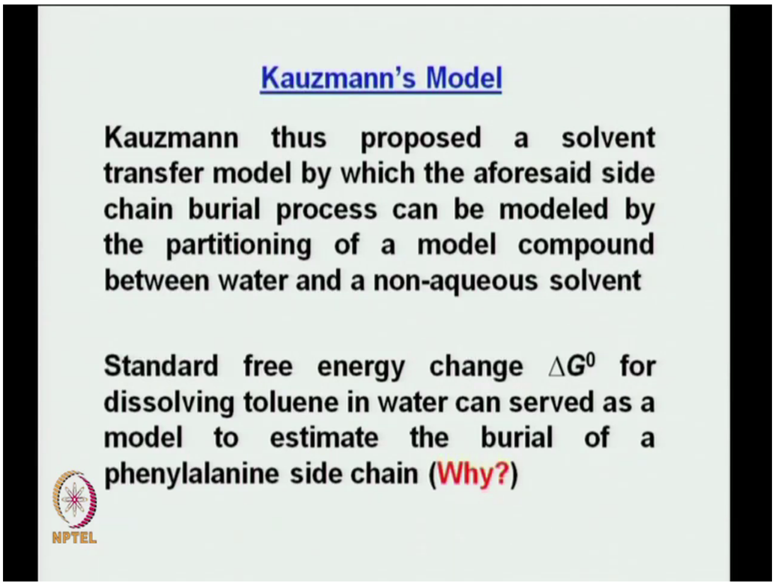

Kauzmann's Model

Kauzmann thus proposed a solvent transfer model by which the aforesaid side chain burial process can be modeled by the partitioning of a model compound between water and a non-aqueous solvent

Standard free energy change ΔG^0 for dissolving toluene in water can served as a model to estimate the burial of a phenylalanine side chain (Why?)

Now, Walter Kauzmann as I was telling you briefly yesterday, he came up with the brilliant idea. What he said was, he proposed a solvent transformer. What do you mean by that? That means, a solvent transfer model by which the aforesaid chain burial process, burial process means where you have burying the hydrophobic amino acids side chain when your protein is folding into the protein core. This can be modeled by the partitioning of a model compound between water and a non-aqueous solvent.

The same thing; that means, we have different R groups, different hydrophobic R groups. So, with relate with you know with relation to that R whatever R is if you would; if you would be able to take a compound which closely resembles that R, that hydrophobic moiety. And, what you will just look as at is the partitioning between an organic phase and the water phase, because that is essentially what you are doing, you are looking at the related solubilitys.

So, he defined something know as a standard free energy change. This is called standard energy of transfer, but let us stick to this right now. The standard free energy chain delta G 0 right for dissolving toluene in water can serve, there is a mistake it should be serve can serve as a model to estimate the burial of a phenylalanine side chain.

Now, you have to reason out why I can take toluene as model for the phenylalanine side chain yeah, now it can be taken. And, if I would look at the thermodynamics of this transfer or partitioning of toluene in water and another organic solvent.

I would get an idea of the energetic that would be involved if I would take a phenylalanine side chain in water and put it in an organic solvent. In this case the organic solvent being what? The protein core because the protein core essential is hydrophobic right, polarity is very low. So, that is why it is called the solvent transfer model; that means, you try to model the energetic involved in protein folding in real life by taking very simple model of compounds, that is essentially the idea.

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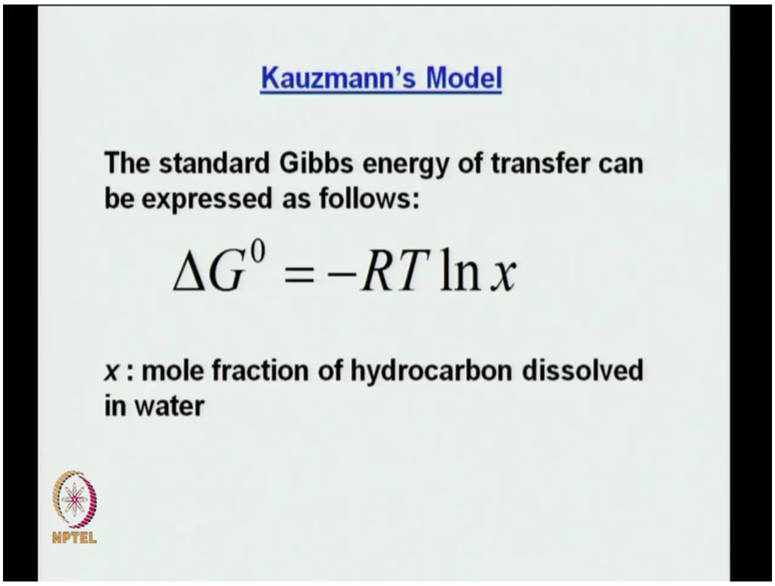

Kauzmann's Model

The standard Gibbs energy of transfer can be expressed as follows:

$$\Delta G^0 = -RT \ln x$$

x : mole fraction of hydrocarbon dissolved in water

Now so, as I was talking about solubility the standard Gibbs energy of transfer right transfer can be expressed as follows. The delta G 0 is equal to minus RT ln x, x being the.

Student: Mole fraction.

Mole fraction of hydrocarbon dissolved in water you know. So, bottom line it is very simple.

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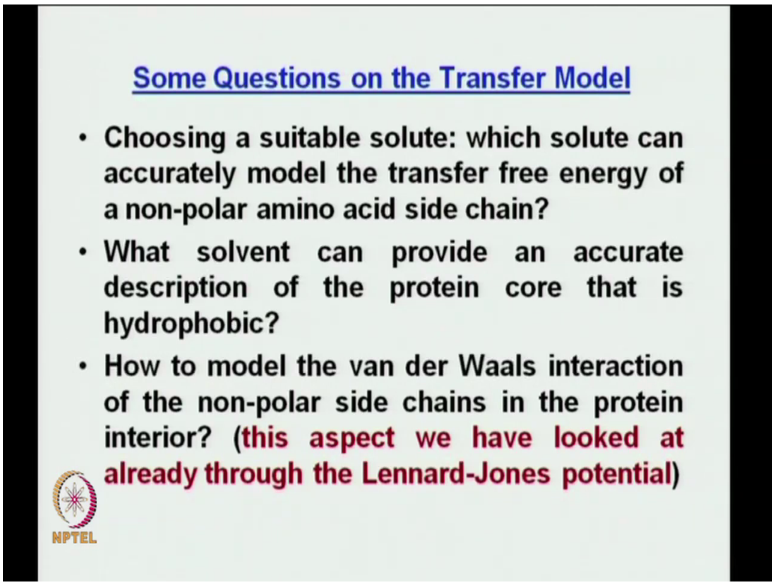

Some Questions on the Transfer Model

- Choosing a suitable solute: which solute can accurately model the transfer free energy of a non-polar amino acid side chain?
- What solvent can provide an accurate description of the protein core that is hydrophobic?
- How to model the van der Waals interaction of the non-polar side chains in the protein interior? (this aspect we have looked at already through the Lennard-Jones potential)

Now, let us consider some questions in, you know the moment you think about this transfer model and the moment you think about trying to take a model compound which will serve as an ideal model for any hydrophobic amino as a side chain. The first question that comes to your mind is or will come to your mind is how do I choose a suitable solid? Right, because I have to chose some someone which is say structurally almost identical or if not identical very similar to that hydrophobic amino as a side chain. Otherwise if that is not the case then the energetic involved will not match, we cannot compare.

So, that is the first question that comes which solid can accurately model the transfer free energy of a non-polar amino acid side chain? That is first question. Now, normally that again because we are talking about a transfer model; that means, from water to a non aqueous solvent or non-aqueous solvent to water whichever you would try to look at it which solvent would be best suited to model what? The interior of the protein because we know that the interior of the protein is non-polar, but then would there be any particular solvent which can best suit our needs for trying to model the protein interior?

That is the second question and you see these are very logical questions, if you think about. A person trying to understand from the hydrophobic point of view how a protein folds right and the third is the moment you have taken this and put it in a hydrophobic interior or the moment you have taken a non-polar chain and put in water what are the different interactions involved? Essentially Van der Waals interactions involved and this is something we have talked at you know talked about at some length; specially in the last class where we said that typically your dispersion forces are modeled with the use of the Lennard Jones potential right.

So, the last point is how to model the Van der Waals interaction of the non-polar side chains in the protein interior. And, this aspect we have looked at already through the Lennard Jones potential we know that.

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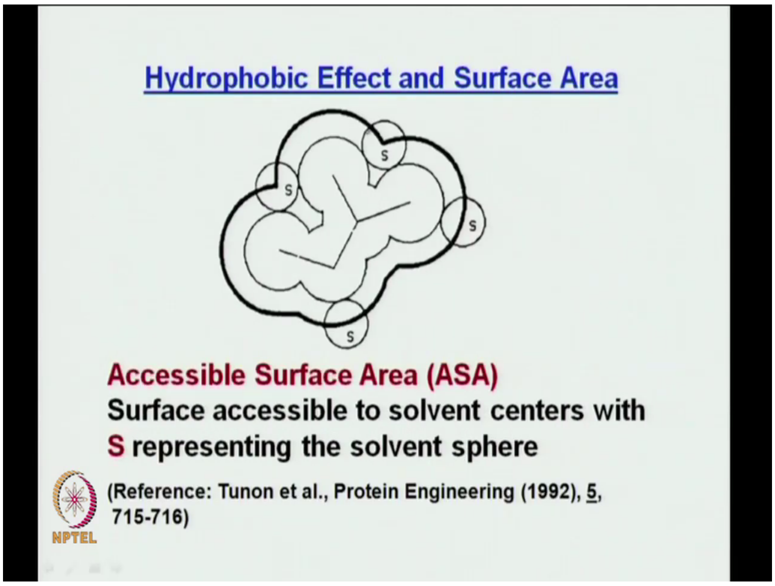

Hydrophobic Effect and Surface Area

Accessible Surface Area (ASA)
Surface accessible to solvent centers with S representing the solvent sphere

(Reference: Tunon et al., Protein Engineering (1992), 5, 715-716)

Now, let us go one step forward, is there any relation between hydrophobic effect and surface area? Now there are two ways of looking at it. So, what you can see is in the middle if you if you look at this in the middle is your hydrophobic molecule ok. These spheres which are resembled by S or which are represent by S essentially your solvents sphere.

Now, think about this we refer to something if you kind of recall there is something known as hard sphere potential right. So, here what you are saying is that solvents can be modelized hard spheres right, I can that is just an approximation. But, the most important point is if you look at the solid line, if you look at the solid line what does it say? What it says is that the center of this solvent molecular or any such solvent molecule will not be able to go beyond the solid line. That means, whatever area is out here, whatever area is out here is the one which at the most will be accessible based on the hydrophobic molecule which I have in the center; anything beyond that will not be accessible or vice versa.

If this is my hydrophobic molecule which is in the center then this is the area which it makes accessible to the solvent molecules which are or which it is immersed in; is that clear? So, that is why this term is very important accessible surface area; that means, accessible means the ones or the surface area that can be actually accessed by the solvent molecules as shown by this schematic. So, as it says S is representing the solvent sphere and I have taken it for the reference.

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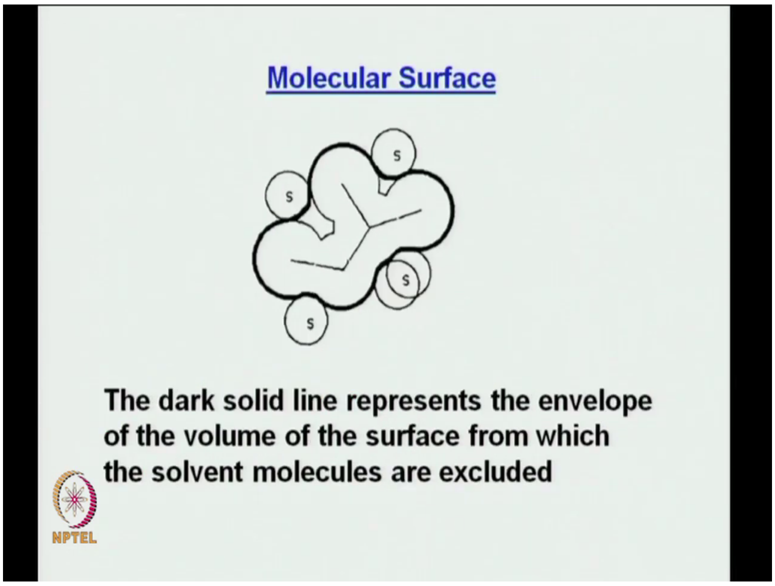

Molecular Surface

The dark solid line represents the envelope of the volume of the surface from which the solvent molecules are excluded

The other way of looking at is see here we are just we do the line through the center, here this is referred to as a molecular surface. That means, what we do is we take it right along the surface of the molecule, we do not take it through the centers of the solvent molecules right.

And, hence it is referred to as a molecular surface, but the idea essentially is the same. You are looking at the accessibility of the solvent molecule to the respective hydrophobic molecule which you have put inside the solvent right.

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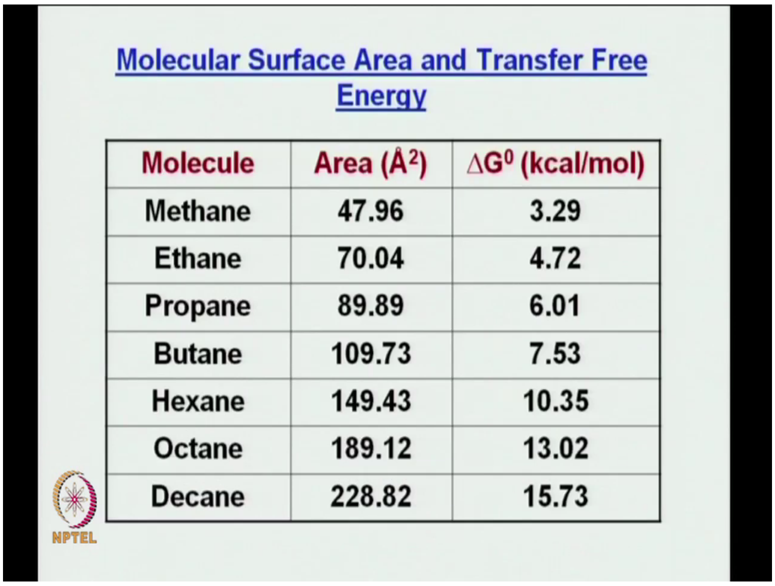

Molecular Surface Area and Transfer Free Energy

Molecule	Area ($Å^2$)	ΔG^0 (kcal/mol)
Methane	47.96	3.29
Ethane	70.04	4.72
Propane	89.89	6.01
Butane	109.73	7.53
Hexane	149.43	10.35
Octane	189.12	13.02
Decane	228.82	15.73

Let us look at some relations or a tabular in the tabular form. So, what happens? Remember delta G 0 is your transfer free energy right. We looking at a host of alkane molecules right and then in the second column what you are given is your accessible surface area that is what you are been provided with. Now, see this is no brainer as we go from methane to decane of which the chain length is increasing right. Now, is the chain length is increasing then accessible surface area has to.

Student: Increase.

Go up. So, that is exactly what is happening right, I have intentional omitted some other alkanes in between you know just so that it fit here. But, I guess it you know drives on the point and you look at del G 0, remember del G 0 is a transfer free energy. And obviously, the more is a surface area right the more will be the transfer free energy simple.

Because, there will be more interaction either favor or unfavor does not matter what it is, but there will be more surface area; that means, more solvent molecules can come close to the hydrophobic molecule; that means, there is more accessible surface area. So, if you would plot it. So, suppose you are given this and you would plot delta G 0 on the y axis versus accessible service area.

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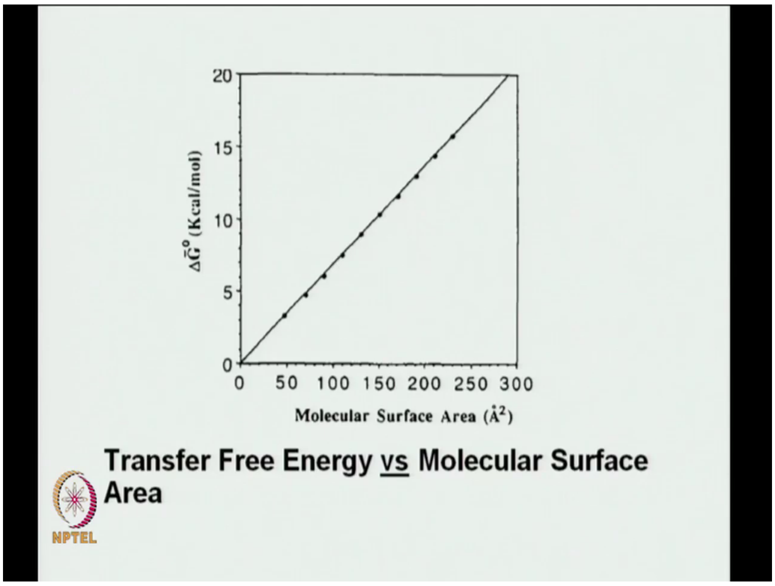

Transfer Free Energy vs Molecular Surface Area

What would you get? And you know is a very good result what you get is your transfer free energy essentially is almost a linear function of accessible surface area. Now what is it mean?

Its tells you a very simple thing, the transfer free energy is what a parameter which is giving you an idea about how hydrophobic that corresponding molecule is.

And, one immediate and one immediate effect or one immediate connection you can make is that the higher the accessible service area, the more will be delta G 0; that means, the most would be the hydrophobic effect being felt in the system. So, based on this what we can write is now based on this, what we can write is now I will use the sheet.

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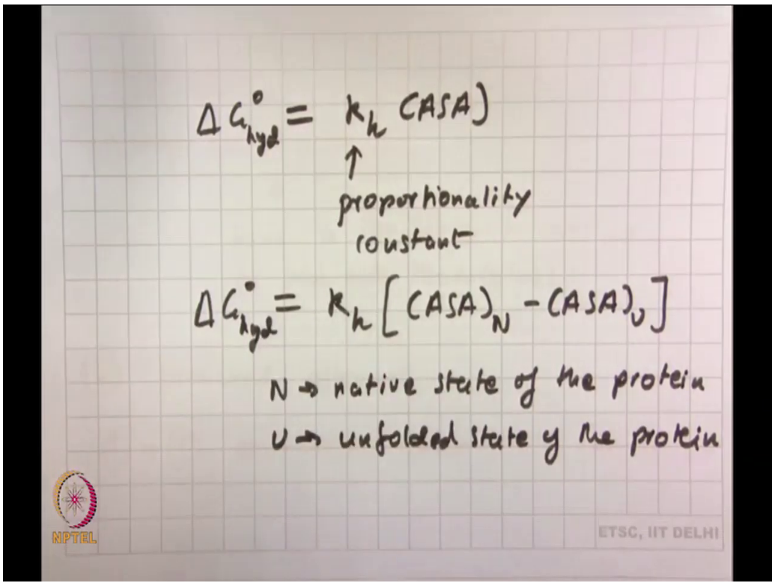

$$\Delta G^{\circ}_{hyd} = k_h (ASA)$$

$$\uparrow$$

proportionality constant

$$\Delta G^{\circ}_{hyd} = k_h \left[(ASA)_N - (ASA)_U \right]$$

N → native state of the protein

U → unfolded state of the protein

ETSC, IIT DELHI

We can write delta G 0, this is my transfer energy right delta G 0 is equal to k h, k h times say the; your accessible surface area; k h times accessible surface area. You know that is that is what you saw right, because the plot was actually passing to the origin, there was no intercept. So, I can easily write this. So, this is a certain proportionality constant you know let us not worry about the details too much.

Now, how can I relate it to uploading which is folding? So, what I can say is for a protein I can write delta G 0 is equal to k h, again the proportionality constant. Now, I can write this, let me write it k h times accessible surface area of the native state minus accessible surface area of the unfolded state right. So, N stands for native state of the protein and U; obviously, is the unfolded state of the protein; you know k being a proportionality constant.

You know that depends upon other factors, but let us not worry about those specifics. But, you know think about this we started with this hydrophobic effect, we looked at its relation with accessible surface area. And, then there is an immediate connection because you know when you are going to open up protein up or when you going to fold a protein there would be a change in accessible surface area right to the solvent molecules. And, that would be direct relation to your transfer free energy right direct relation.

Now, the question is if I look at this initial equation delta G 0 equal to k h times the accessible surface area; do you think it will always hold? That is the question right. What do you think? Any ideas? What is what was very special what was very special about the molecules we had considered the accessible surface area of? What did we consider? We considered methane, ethane, propane, butane right up to decane.

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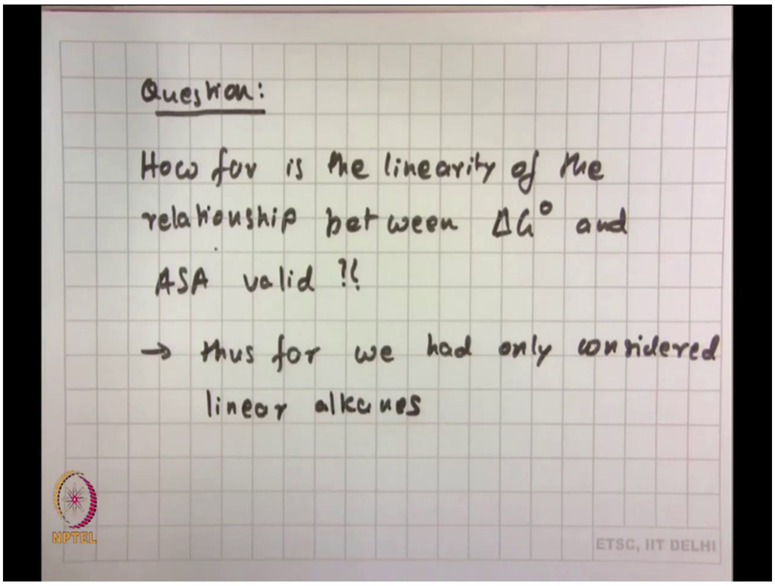

Question:

How far is the linearity of the relationship between ΔG^{0} and ASA valid ?!

→ thus far we had only considered linear alkanes

Right. So, all those were linear chain alkanes right. So now, the question is now the question is how far how far is the linearity of the relationship linearity of the relationship between the transfer free energy delta G 0 and accessible surface area valid? That is the question we trying to answer. To make the point thus for we had only considered linear alkanes, we had only considered linear alkanes.

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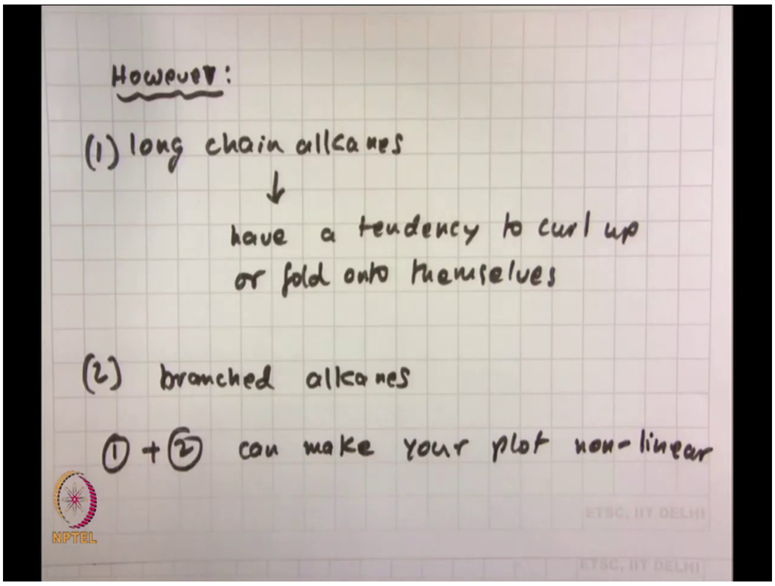

However:

(1) long chain alkanes

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have a tendency to curl up or fold onto themselves

(2) branched alkanes

① + ② can make your plot non-linear

However, think about this if we go to very long chain alkanes, if we go to very long chain alkanes what happens is these alkanes have a tendency to curl up or fold onto themselves. And, the reason is very straightforward. If the alkane chain is very long, the accessible surface area will be huge, but the alkane chain would not be liking to interact with water molecules right.

But, because the alkane chain is very long instead what it can do is, it can try to bring other parts of its chain closer to itself. And, the moment it does there can be a certain sort of collapse in the structure and that collapse will give rise to this curling or folding in some sense. Because, it has to minimize the so called unfavorable interactions with the water molecules that is essentially what it has do and the; so this is one.

And, the other one is and the other one is what if you have branched alkanes, what if we have branched alkanes? If you have branched alkanes then you know depending upon the branching your accessible surface area will vary right. And, then there is no necessity, there is no necessity that your delta G, your delta G should exactly track as your accessible surface area that is maintain the linear relationship.

So; that means, 1 and 2 together 1 and 2 together so, 1 plus 2 either or together can make your plot non-linear; can make your plot non-linear. And, just to be specific a little bit what I showed you in the previous sheet in one of the previous sheets, I can refer to this as delta h G 0 hydration and same here. Because essentially, we are looking at the interactions of this non-polar hydro carbon with water molecules and hence hydration.

So, what we already have is one measure of hydrophobicity which is your accessible surface area, now keep that in mind.

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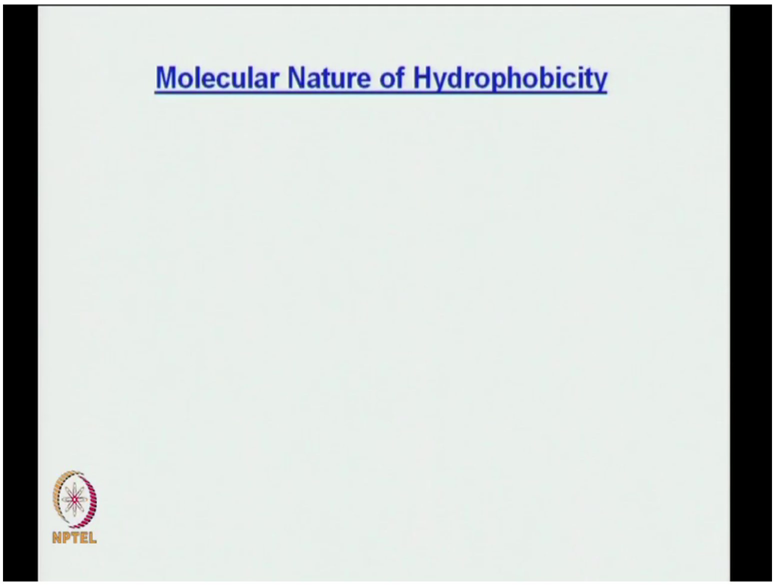

Molecular Nature of Hydrophobicity

What about the molecular nature of hydrophobicity?

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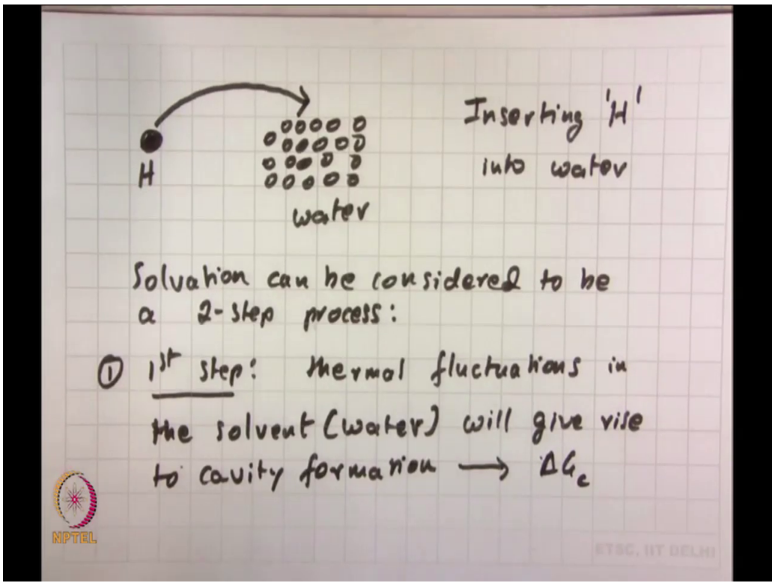

Inserting 'H' into water

Solvation can be considered to be a 2-step process:

① 1^{st} step: thermal fluctuations in the solvent (water) will give rise to cavity formation ⟶ ΔG_c

For example, if you would try to module a solvation process; that means, you take a molecule. So, we are looking at the molecular nature of hydrophobicity now. So, for example, you have a hydrophobic molecule right. So, this is the hydrophobic molecule right, this is the hydrophobic molecule H right. When you have a hydrophobic molecule H and suppose you have a series of water molecules out here, these all your open circles; so, this is water.

And, what you have to do is you have to take this and put it inside ; again what you essentially doing is you are inserting you are inserting H which is a hydrophobic molecule into water. Now, think about the process very carefully. What do you think is going to happen? See the first see its very logical right, I am taking a hydrophobe; I am taking hydrophobic molecule H.

I am trying to put it in water because, I am I have to look at the corresponding energetics right. Now, if I have to try to take this H and put it water, the first thing I have to do is I have to be able to make a cavity because I have to place that hydrophobic molecule in water. That means, I have to find a cavity where the hydrophobic molecule go and move the water molecules out from there. Hence, this insertion or this solvation can be considered to be a two step model.

So; that means, I can write this insertion or solvation can be considered to be a two step process. What is the first step? The first step so, in the first step what happens is thermal fluctuations, thermal fluctuations in the solvent which in this case is water will give rise to cavity formation; will give rise to cavity formation will give rise to cavity formation ok. And, let this process be reflected by the thermodynamic parameter say delta G c right.

There is the first step. Now what do you think will the logical second step be? You have already produced the cavity; see how is the cavity in produce because you know your thermal fluctuations, because the thermal fluctuations the molecules are fluctuating. And, instantaneous it is like instantaneous dipole, it instantaneously give rise to cavities. Once it gives cavity, if you have the hydrophobe that you stick that hydrophobe or hydrophobic molecule into the cavity which is H the hydrophobic molecule.

What is the second step? If the hydrophobic molecule has to stay in the cavity, it has to start interacting with the surrounding solvent molecules right which in the case is water. So, the second step can be thought about like this.

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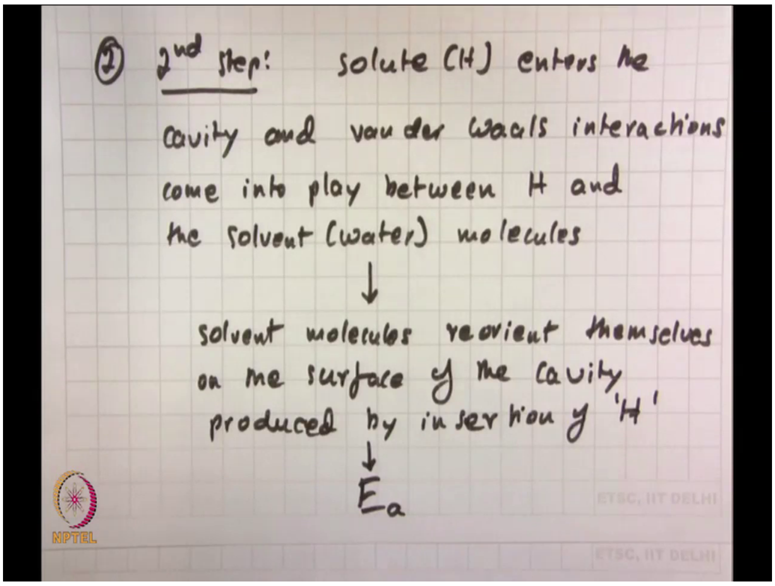

② 2nd step: solute (H) enters the cavity and van der Waals interactions come into play between H and the solvent (water) molecules

↓

solvent molecules reorient themselves on the surface of the cavity produced by insertion of 'H'

↓

E_a

So, this is your second step. The solute which is the hydrophobic solute which is H enters the cavity, the solute H enters the cavity and Van der Waals interaction interactions come into play; come into play between H and the solvent molecules; between H and the solvent molecules. So, essentially here what happens is solvent molecules reorient themselves, reorient themselves on the surface of the cavity produced by insertion of H which is the hydrophobic molecule.

And, what we say is this energetics, this Van der Waals interaction we refer to as E a ; the Van der Waals interactions we refer to as E a. So, I have two components, what are the two components? One is delta G c which is energetics involved in cavity formation and the second is your Van der Waals interactions, because after it is there it starts interacting with the surrounding solvent molecules.

See if you think about it you know the way people devised models of trying to look at hydrophobicity or hydrophobic effect, see this is a very logical way of looking at it right. And, it is nothing unique, it is nothing out of the blue; its just that you have to be able to think like this to you have to be able to design your problem like this. It is not hard right; have this are two very logical ways of looking at it at a solvation.

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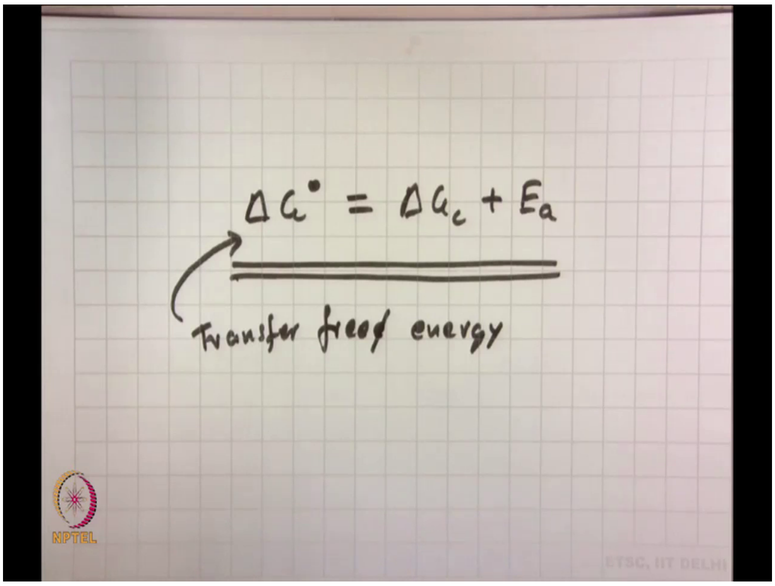

$$\Delta G^{\circ} = \Delta G_c + E_a$$

Transfer freed energy

So, what we can do now is we can combine these two processes and say that there my delta G 0 which is my transfer is a combination of delta G c and E a. Remember this one is a transfer free energy, this is the transfer free energy that is what we looked at before.

So, whether this transfer is favorable or not favorable is dictated by two terms delta G c and E a. Now, remember if you think about what we know with regards to hydrophobic effect, this E a is the one we think is the main culprit right. Because, your interaction between hydrophobic molecule and water based on just regular solutions right, regular hydrophobes all in water is E a should be the culprit right.

The E a is the one because your interactions are not favorable at all and that is the one which would actually make delta G positive, that is the transfer unfair not favorable right; that is simply what we want to think like. And, we know that is what I do not know about you, but at least that is what I having thinking about it. The way I have been thinking about it ok, but is that true? Let us look at a table.

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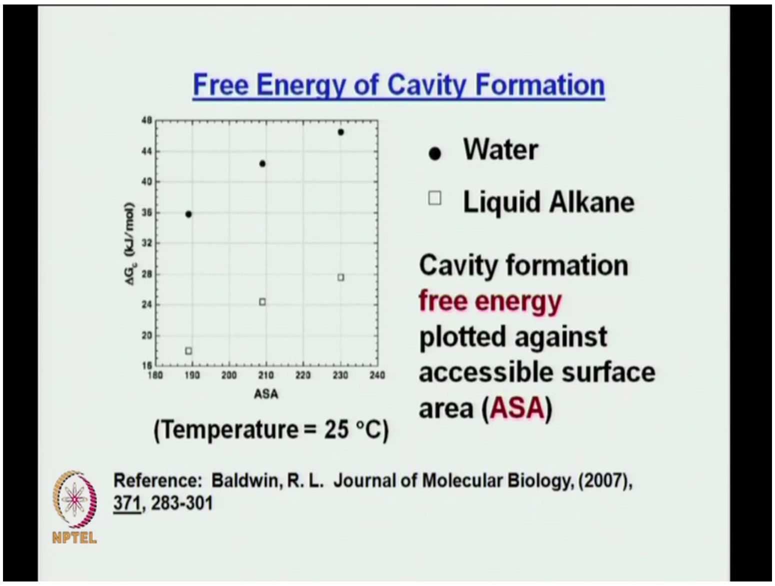

Free Energy of Cavity Formation

- ● Water
- ☐ Liquid Alkane

Cavity formation **free energy** plotted against accessible surface area (**ASA**)

(Temperature = 25 °C)

Reference: Baldwin, R. L. Journal of Molecular Biology, (2007), 371, 283-301

But before the table let us look at this figure. This figure is referred to as the free energy of cavity formation. Now what does it mean? If you look at the figure I have plotted this delta G c, remember what I say delta G c is the free energy with relationship with cavity formation.

And what do I have on the x axis? Accessible surface area, this is something we know by now right, what accessible surface area means.

Now, this solid circles or the field circles are for certain organic molecules in water and the open squares are for the same organic molecules in a liquid alkane ok. I am not telling you what the molecules are, I am you tell you what those are in the next slide right; where I actually give you the table. But, look at this what is very surprising may be of we are not thought about it before may be this what this would encourages us to think like this. You look at the cavity formation free energy, where is it more? Is it more in alkanes or is it more in water?

Student: (Refer Time: 33:29).

It is always it is more in water right ok. Now, this is something we never thought about ; that means, I am trying to produce a cavity in water and I am explaining so much more energy than I can do it, do in alkanes. But, see I am not even talking about interactions now, I am not even talking about interactions. I am just talking about trying to separate the solvent molecules so, that I can bring the hydrophobic molecules inside or molecule inside rather, if you get one molecule ok. And, because this is plotted against accessible surface area you can understand, so as we are going from left to right or from low surface accessible surface area to higher accessible surface area. It means I am essentially increasing the chain length of my organic molecule or hydrophobic molecule.

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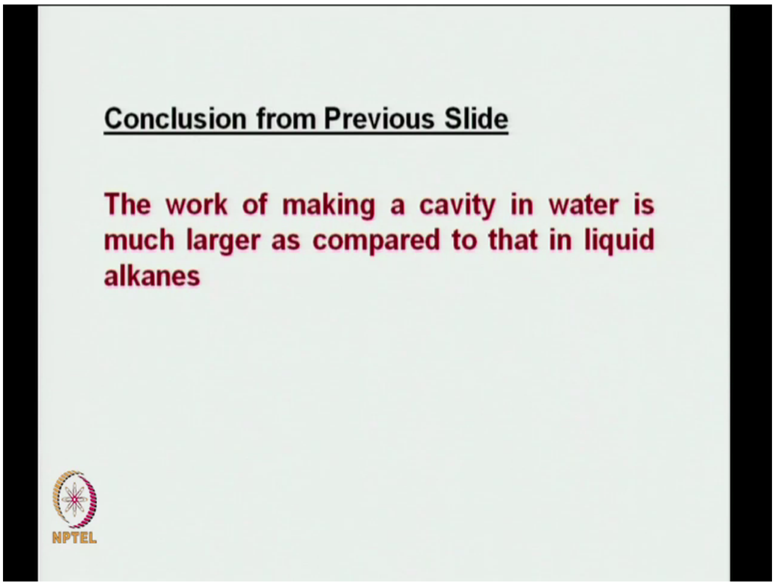

Conclusion from Previous Slide

The work of making a cavity in water is much larger as compared to that in liquid alkanes

So, the main conclusion is of the previous slide or the figure, the work of making a cavity in water is much larger as compared to that in liquid alkanes, that we know by now. Now, let us look at the table.

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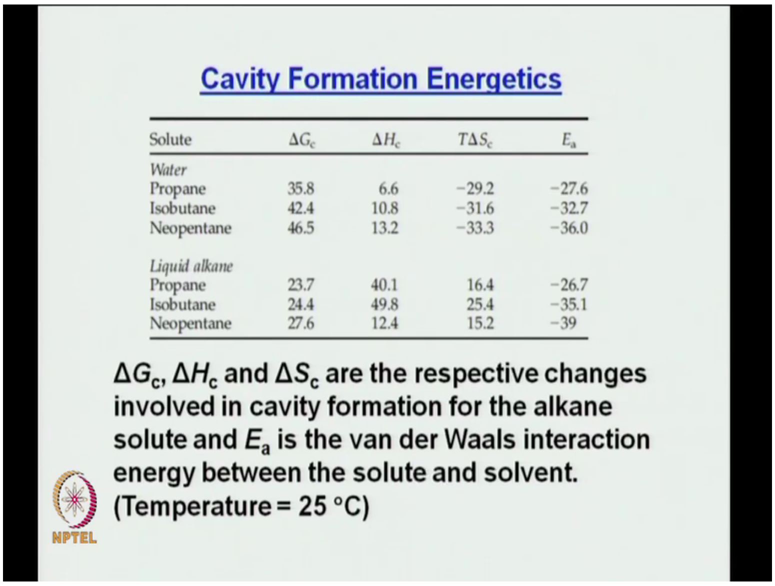

Cavity Formation Energetics

Solute	ΔG_c	ΔH_c	$T\Delta S_c$	E_a
Water				
Propane	35.8	6.6	−29.2	−27.6
Isobutane	42.4	10.8	−31.6	−32.7
Neopentane	46.5	13.2	−33.3	−36.0
Liquid alkane				
Propane	23.7	40.1	16.4	−26.7
Isobutane	24.4	49.8	25.4	−35.1
Neopentane	27.6	12.4	15.2	−39

ΔG_c, ΔH_c and ΔS_c are the respective changes involved in cavity formation for the alkane solute and E_a is the van der Waals interaction energy between the solute and solvent. (Temperature = 25 °C)

So, what was the solute? You look at the solute, the solute respectively was first propane then isobutane then neopentane right. So, this was the solute, this was the solute which you dissolved in water. Then you took the same solutes and you dissolve it in the corresponding alkane, see you know propane you take propane and you dissolve it in propane, you take propane and you dissolve it in water. Similarly, you take isobutane you dissolve it in isobutane, you take isobutane then you dissolve it in water.

And you compare them energetics, that is what you are doing; the same for neopentane. So, look at this delta G c right, the moment you go to water you are typically from propane to neopentane the delta G c is increasing. Now, this is expected based on surface area, accessible surface area and that is what we saw in that figure. Now, table is I mean the picture is based on this or the figure. If you go to liquid alkane now you know the same thing happens. But, here what you can see is delta G c is immediately lower than that in case of water.

But, still it is positive because you are having to insert it inside the solvent and your having to do work; that means, you are spending energy. So, it is positive. Now, let us not worry about the enthalpy of the cavity. You look at the you look at the entropy, you look at the entropy ok; do not know what the entropy right now. What is that biggest difference you think? When I take.

Student: (Refer Time: 36:13).

Propane right, when I take propane I put in water and if I take the same molecule and I put it in the corresponding liquid alkane. You can see that delta S in all cases for liquid alkane is positive and that corresponds to a negative delta G right; because its minus t delta S. But, for all cases in water the delta S is what? Negative or t delta S is negative, that is what you are plotting essentially. Which will correspond to what? Positive free energy right because this will give a positive contribution to a Gibbs thermal equation.

But, see again we have not talked about energetics, this is just a entropy formation with relation to what? The cavity ok. Now, look at the last column, isn't it surprising? What is your last column? Your last column is essentially a Van der Waals interactions, the interactions we have so far thought to be absolutely unfavorable between what? Between your hydrophobic molecule and your solvent molecules which is water in this case.

But do you see much of a difference? Essentially the E a if you go to water and you go to liquid alkane, they are negative in both the cases and they are almost of similar magnitude. So, we might have to redefine or recalibrate our thoughts with respect to hydrophobicity. It is not your E a, it is not your unfavorable interaction, it is something else. It is coming from your delta G c, where the major culprit is what? Entropy because you look at enthalpy, enthalpy in both the cases is positive.

Can you look at the you look at delta H c, in both the cases your enthalpy is positive right. So, there is no distinction. What happens is a the what is the actual determinant is your entropy, that is the one which makes the free energy of cavity formation in water so high. It is not your E a, please again it is not your E a, it is not Van der Waals interactions ; is it clear? Ok. So, all these were done at you know 25 degrees Celsius, you have to do at fixed degree temperature; obviously.

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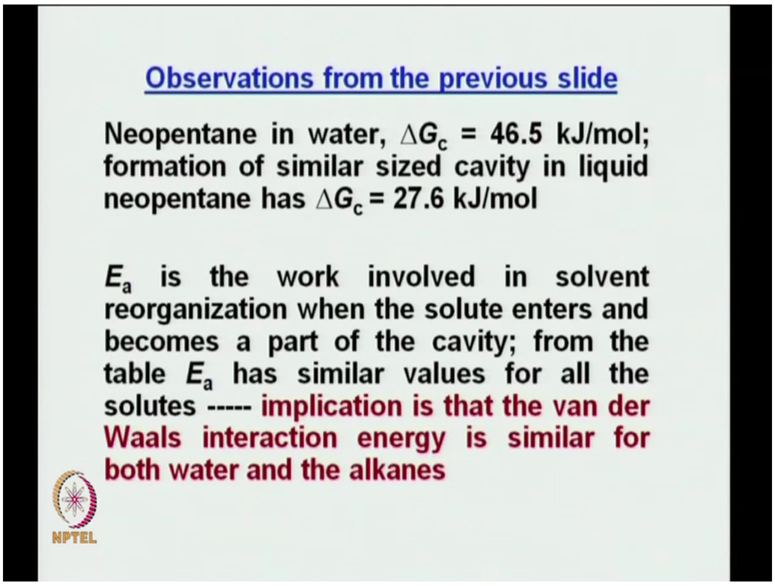

Observations from the previous slide

Neopentane in water, ΔG_c = 46.5 kJ/mol; formation of similar sized cavity in liquid neopentane has ΔG_c = 27.6 kJ/mol

E_a is the work involved in solvent reorganization when the solute enters and becomes a part of the cavity; from the table E_a has similar values for all the solutes ----- implication is that the van der Waals interaction energy is similar for both water and the alkanes

So, just to you know kind of look the look at the observations again from the previous slide. If we take neopentane the delta G c is 45 46.5 kilo Joules per mol and if you would. So, neopentane in water and if you take the neopentane same neopentane and put it a liquid neopentane, what would del G c be? 27.6 kilo Joules per mol right and we have defined E a, E a is the work involved in solvent reorganization when the solid enters and becomes the part of the cavity, that is how we have defined E a to be.

Now, from the table E a has similar values for all the solutes that is what we also just discussed. So, what is implication? The implication is again we were discussing that the Van der Waals interaction energy is similar for both water and the alkanes. This is do not you think it is surprising its, do not you think it is surprising with respect to what we have been thinking all these days, with regards to hydrophobicity? Or, maybe you have been thinking of cavity; I do not know, but you know I think it is a different way of looking at.

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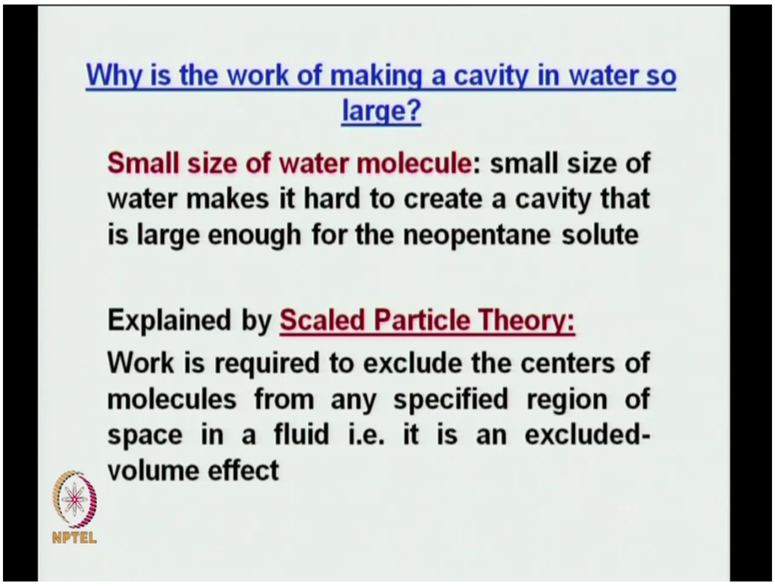

Why is the work of making a cavity in water so large?

Small size of water molecule: small size of water makes it hard to create a cavity that is large enough for the neopentane solute

Explained by **Scaled Particle Theory:**

Work is required to exclude the centers of molecules from any specified region of space in a fluid i.e. it is an excluded-volume effect

So, the next question is see, I am not worried about E a anymore why? Because they were very similar; so, the only thing I need to worry about is delta G c. So, then the next question that comes to your mind is why is the work of making a cavity in water so large? What do you have to spend so much more energy in trying to make a cavity in water as corresponding to an alkane? Right. The first one is the first reason is the small size of the water molecule. Now what will happen if you have a small size?

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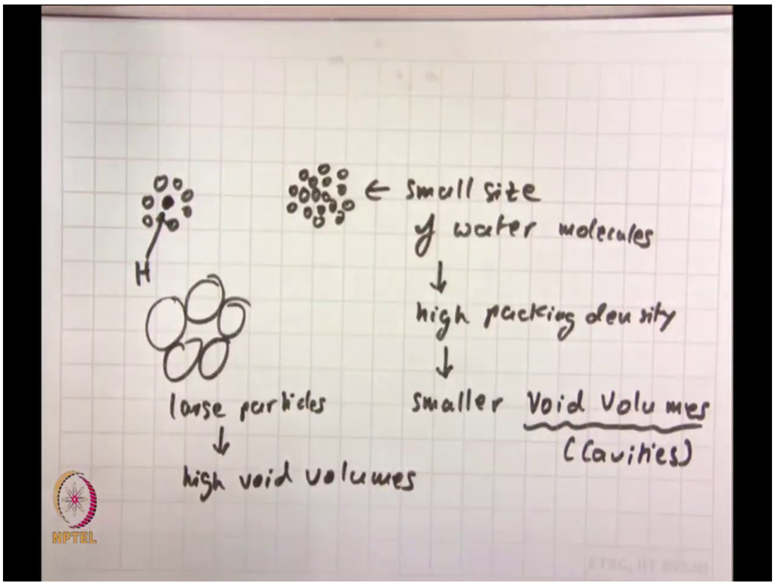

If you happen if you have if you happened have a small size and if you can just try to give you a schematic. If the size is very small suppose these are water molecules, if the size is very small; this is the small size of water molecules. If the size is very small what would it lead to? It would lead to high packing density, isn't it? It would lead to high packing density, there is smaller that is smaller void volumes which is essentially your cavities.

So, this one is clear to you; if the size is small they would pack a lot more densely. And, hence because the packing density is very high, the number of gaps or void spaces would be very low. So, definitely to take a hydrophobic molecule and put it inside, you have to make you have to you know put in more work, put in more energy in creating a cavity as opposed to large spherical particles. So, if we have large particles like this, if would if your particles would be large they would come close, but they would leave many huge voids ok.

So, large particles if the large particles we can write high void volumes ok. So, it is the small size of the water. So, you know this can be explained by a theory known as scaled particle theory; we will not worry about it. But, what scale particle theory essentially says is work is required to exclude the centers of molecules from any specified region of space in a fluid, that is it is an excluded volume effect. What it means is suppose you have a hydrophobic molecule here and you have water molecules here right, you have water molecules here and this is your H.

So, this was your initial this; so, this was your initial and you put you took the hydrophobic molecule and inside the water. You have to create a cavity. Now, when the cavity was not therefore, the hydrophobic molecule what did we have? You essentially had water molecules are there. So, for example: if you are sitting there or if you are standing there and if I if I go and try to occupy your place or your space, I will not be to because that, volume is excluded to me.

The only way I can do it is if I push you out of there, the same thing has to be done by the hydrophobic molecule. Initially, when there was no hydrophobic molecule all the water molecules were covering all space of your container or whatever. Now, the moment you try to put in the hydrophobic molecule, you have to move water molecules out. That means, the water molecule was excluding some volume and you have to make sure that it is moved out; so, that you can place the hydrogen molecule in.

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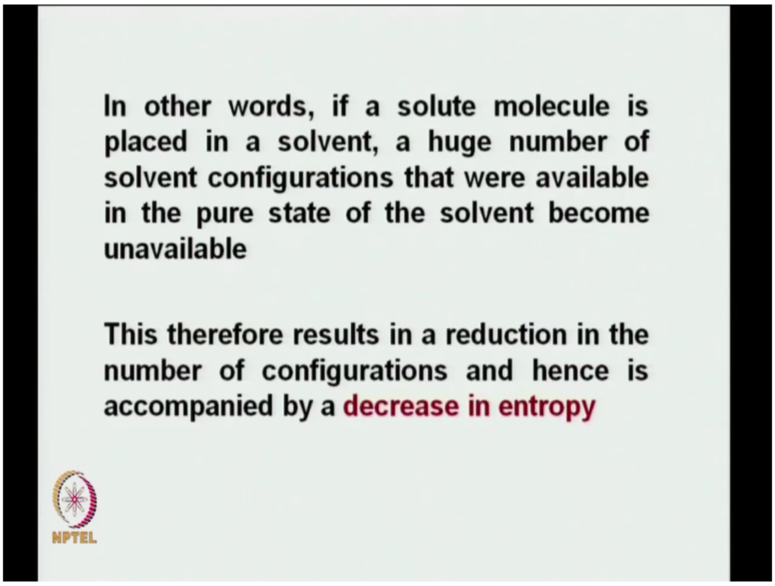

In other words, if a solute molecule is placed in a solvent, a huge number of solvent configurations that were available in the pure state of the solvent become unavailable

This therefore results in a reduction in the number of configurations and hence is accompanied by a decrease in entropy

So, what we can say is in other words if a solute molecule is placed in a solvent a huge number of solvent configurations that were available in the pure state on the solvent become unavailable. Now, is this clear? See for water we know you have extensive of hydrogen bonding, extensive ordering right. Now, the moment you put in a hydrophobic molecule do not worry of hydrogen bonds now, what happens is in that space is not available to the water molecules right.

So, immediately what would happen is because that is that is excluded volume to the water molecules; the volume excluded by the hydrophobic molecule it cannot occupy that place; that means, it cannot occupy, it cannot have certain orientations. The moment it cannot have certain orientations, what are you doing? It actually decreasing the number of microstates as you have done in statistical thermodynamics. Essentially what you are doing? You are decreasing the entropy; you are essentially decreasing the entropy.

And, remember what was delta S in the table? t delta S was negative which corresponds to this right, the entropy been negative. So, this therefore, results in a reduction in the number of configurations and hence is accompanied by decrease in entropy. So now, you can imagine that this hydrophobic effect, what we know by name might essentially be an entropic effect rather than your E a rather than your Van der Waals interactions. Now, what is the other way of looking at it? So, this is one, the small size of the solute.

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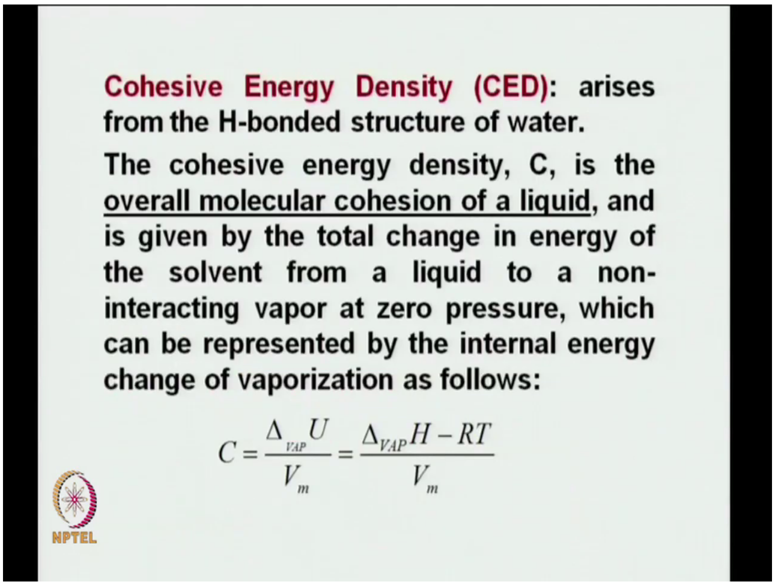

Cohesive Energy Density (CED): arises from the H-bonded structure of water.

The cohesive energy density, C, is the overall molecular cohesion of a liquid, and is given by the total change in energy of the solvent from a liquid to a non-interacting vapor at zero pressure, which can be represented by the internal energy change of vaporization as follows:

$$C = \frac{\Delta_{VAP} U}{V_m} = \frac{\Delta_{VAP} H - RT}{V_m}$$

The other one is something known as cohesive energy density. Now, what do you mean by that? See water has a very high cohesive density, energy density; what do you mean is see water has extensive hydrogen bonds. They like each other so; that means, the cohesion force;

that means, these water molecules; so, stay together, the ability is very high. So, cohesion means cohesive forces right, this like to stay together.

So, the Cohesive Energy Density which is the CED is the overall molecular cohesion of a liquid. It is given by the total change in energy of the solvent from a liquid to a non-interacting vapor at zero pressure. What do I mean zero pressure? Why is zero pressure so important? Can someone tell me why zero pressure so important? See I am taking this and moving the solvent from the liquid to a non-interacting vapor, its ideal gas.

When can you expect gases to behave ideally? When pressure is very low turning to zero pressure, that is what we are trying to put in ok; which can be represented by the change in internal energy or the change of vaporization as C which is your cohesive energy density is given by the change in vaporization internal energy over V m which is the molar volume of the corresponding solvent. And, you know H is equal to U plus PV, from there I can write that delta U is equal to delta vaporization H of delta is vaporization minus RT over V m.

Keeping in mind because it zero pressure PV is equal to nRT my ideal gas law is valid right. So, you can immediately understand water is one of the liquids having the highest what? Delta H vaporization, also water is one of the liquids having a very small V m. So, these things in combination make the cohesive energy density to be very high right.

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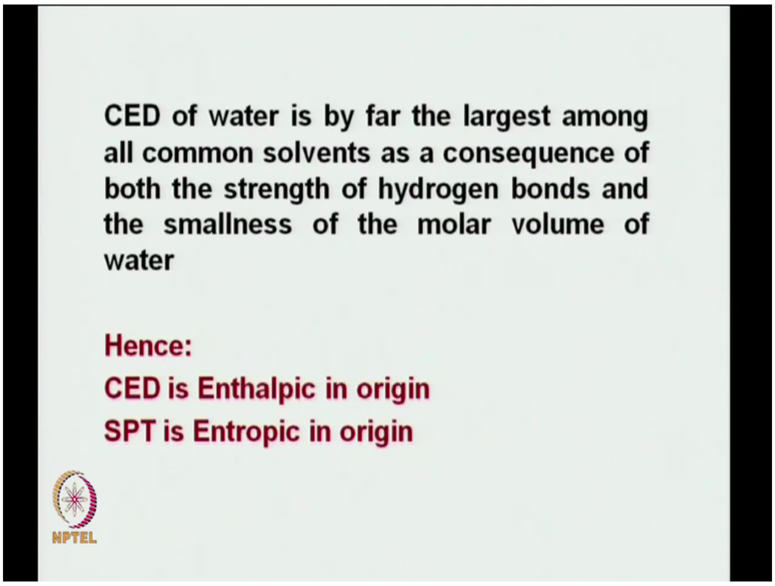

CED of water is by far the largest among all common solvents as a consequence of both the strength of hydrogen bonds and the smallness of the molar volume of water

Hence:

CED is Enthalpic in origin

SPT is Entropic in origin

So, as I said CED of water is by far the largest among all common solvents and as a consequence of both the strength of hydrogen bonds and the smallest of the molar volume of water right. That is what it is, your delta is vaporization depends upon the strength of the hydrogen bonds. The more hydrogen bonds you have, the more energy you need to break the hydrogen bonds and try to vaporize them.

So, delta vaporization is higher and also the molar volume is low; the molar volume was in the denominator. So, if it is low; obviously, then the C factor increases. So, hence you are looking at two effects now: one is the CED you can understand which is enthalpic in origin right, because you have delta H. The other one is what? This scale particle theory which is the size which is essentially what? Entropic in origin; then the obvious question is which one is more instrumental? Right.

Which one dominates or which one is more important? Ok. We look at that later.

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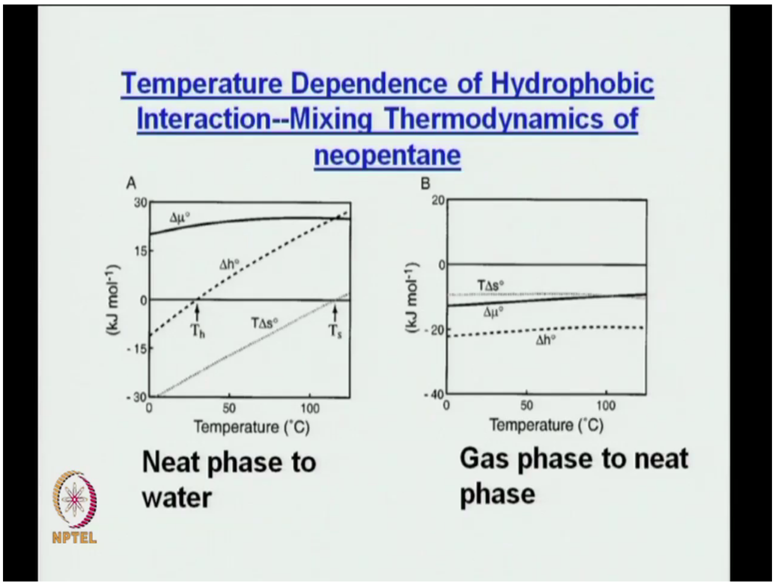

Temperature Dependence of Hydrophobic Interaction--Mixing Thermodynamics of neopentane

Neat phase to water

Gas phase to neat phase

But let us look into some thermodynamics. I will just start with this and then in the next class, I will elaborate on it more. See what you are looking at are two very interesting figures. What we are going to discuss now is temperature dependence of hydrophobic interaction ok; that means, how this varies as a function of temperature; obviously. And, here what you are looking at is the mixing thermodynamics of this organic molecule neopentane.

So, look at your left and right figures or the first figure which says a neat phase to water means you are taking neopentane in the neat phase; that means, neopentane is a neopentane, that is a neat phase, liquid phase. You take a neopentane molecule out and you put it in water and this is the corresponding thermodynamics. The right panel what does it show? It tells you that you are taking a neopentane molecule now; see does not make sense to take a neopentane molecule out of neopenatne and put back into neopentane again right. So, what it tells you is you take a neopentane molecule in the gas state, vapor state and then put it in neopentane itself that is why it says gas phase to neat phase.

That means, neopentane gas phase to neopentane liquid phase and there are other one was neopentane liquid to neopentane in water, is it clear? Now, what is delta mu 0 delta h 0 delta s 0? You know what it is, now delta mu; mu essentially is a chemical potential. Now we talking about chemical potential, remember the chemical potential essentially is an escaping (Refer Time: 50:20) gives an idea of how probable is this or you know what is the potential of this occurring. What I mean by this is solubility essentially right.

So, here I have delta u 0 or mu 0 rather and then I have the corresponding delta h 0, the enthalpy 0 reference to standard state and delta s 0 is entropy. Again let us do not worry exactly what they mean, but just look at it. Look at the left figure where we say neat phase; that means, neopentane is taken from liquid to water. How does the delta mu 0 vary?

First of all this delta mu 0 is positive right, it should be positive. Why? Because it is not favorable to take neopentane and dissolve it in water your delta G; obviously, would be positive; there no doubt about that. But, look it is not a straight line; as you increase a temperature which is temperature on your x axis you see it goes to a certain curvature; that means, it has a temperature dependence ok; good is that clear?

Now, look at these the dotted line and the well the dashed line and the dotted line. So, the dashed line is one which is delta h 0 and the dotted line is one which is T delta h 0 ok. You see these have extensive slopes, these have extensive slopes right. They are not just lines parallel to the x axis. Now, tell me what is this slope of delta h over temperature? That means, if I have d of delta h 0 over d of t what is that equal to?

Student: c p.

Very good, it is not c p; it is actually a delta c p because c p is equal to d h over d of t and d of del h over d of t would be delta c p.

Student: (Refer Time: 52:09).

What does it mean? What it means is the only way I can have a big slope is that my delta c p, that was the change in heat capacity is huge right because that is what the slope is. Same thing for T delta s, you know what is the relation between entropy and heat capacity is? You know what it is? Look at up will do it next class, but there also this d of del s over del of t would be having a c p dependence, delta c p dependence. So, the change in heat capacity is huge and that is why you have a slope for both delta h and delta s.

Now, please keep this in mind, you go to the next one; that means, the right figure. Here you can see delta mu 0 is negative, now this is expected right. If you are taking neopentane and put it in a neopentane liquid, it has to be negative because it is a favorable process, spontaneous process. Now, not only that see both T delta s 0 and delta h 0 these lines they have slopes, they have certain curvatures. But is these slope as evident as the one you see in the left figure?

Student: No.

No what does it mean? It means that the change in heat capacity in case of taking neopentane from gas phase to neopentane is very small; is very small as compared to the same change in heat capacity when you take neopentane from neat neopentane to water ok. So, heat capacity change is actually the one which to a huge extent defines your hydrophobicity right. And, this is something we will try to develop in the next class.

You know this is really unique the way you look at this is really unique and I will tell you one thing just before ending; you look at this T h and T s. See what happens at T h? What is happening at T h is your this delta h is line is crossing this 0 free energy right. So, what it means? 0 energy kilo Joule per mol I mean, what it means is at this your delta h 0 is equal to what?

Student: (Refer Time: 54:38).

0 right, because that is the 0 line. So, this, this, this line is the 0 line right, this line is 0 line; you see there is a line in the middle which is 0 line. So, when the delta h 0 crosses that line; that means, it is 0 and that occurs at a certain temperature. So, that is T h, the T h is that temperature where delta h 0 is equal to 0. Similarly, if you go over to high temperature side what happens? You can see the entropy line T delta s 0 crosses 0 at this temperature T s. So, T s is defined as that temperature, where the delta s 0 goes to 0.

So, now guys you think about this on the left side lower temperature your enthalpy is 0 right, your delta h 0 is 0 right. At the lower temperature your delta h 0 is 0. Hence, your contribution at del h is what? Essentially what? Entropic or enthalpic?

Student: Entropic.

Entropic, you move to higher temperatures what happens? Your delta s 0 becomes 0. So, your contribution of becomes essentially what?

Student: Enthalpic.

Enthalpic. So, when you look at the temperature dependence you actually do a change from parameter dependences; that means, you do a change from entropy dependence to what? You go to enthalpy dependence and that something which is extremely interesting. We will try to look at this and little more details in the next class.