**Medicinal Chemistry**
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**Quantitative Structure Activity Relationship (QSAR) Part-3**

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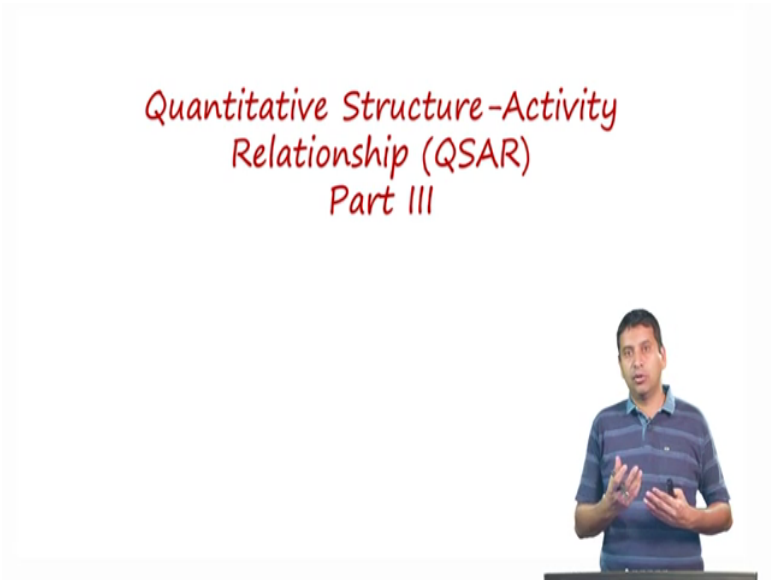


So in today's lecture we are going to continue to look at Quantitative Structure Activity Relationship and in the previous couple of lectures we have looked at how to used hydrophobicity that is a log P as a measure of how well the molecule behaves and then we have also looked at electronic effects, so we derived the Hammett equation and looked at how electronic effects can have a role and so you know log P is very important because it helps as understand whether the molecule is permeable or not and electronic effects are somewhat useful but in most terms it is not that critical however we will considered it in our analysis.

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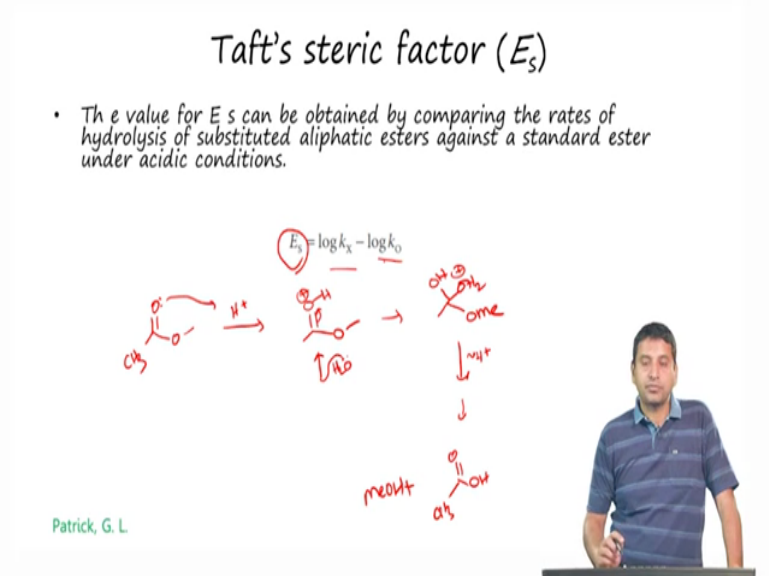


Today we are going to look at Steric is, so steric is (())(01:05) very difficult to define , this is because the size of the molecule is not very easy to understand based on simple methods. So one way in which we can assign a size is to use this Taft is Steric is factor. So here the reaction that is looked at is basically hydrolysis of esters under acidic conditions. So the mechanism of hydrolysis is at it is get protonated and then you have water attacking and then this opens up the ring to give you OH, OH and be OH 2 plus of course OMe let us say and then this trans was a proton followed by loss of Methanol to give you the Carboxylic acid, ok.

So let us say we start with the Acetate here and you end up with acidic acid and Methanol, ok. So this is the reaction that we are considering, so similarly if you go back and look at the Hammett reaction we looked at ester hydrolysis as one of the you know one of the things that we wanted to considered with respect to the equilibrium between Benzoic acid and Benzoate. So here what we looked at is we look at the hydrolysis of substituted aliphatic esters against the standard ester under acidic conditions.

So the substituent is X and the standard rate is k 0, so you do a set of experiments first derived the rate constant for the unsubstituted ester and then you put in a substituent and then you do a set of reactions experiments to find out the rate constant for the substituted molecule then you subtract the two of them the logarithm of two of them and then you arrive at E s.

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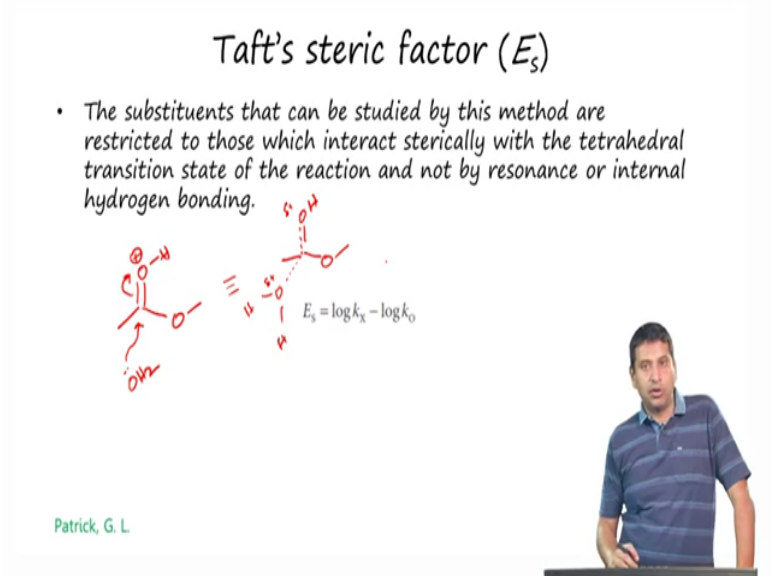


Now the substituents that can be studied by these method are restricted to those which interacts sterically with the tetrahedral transition state, so here if you see in the acid catalyzed reaction you will have an ester here and water is going to attack here and kick this out plate, so the transition state for this will involve a weak bond between the water and the carbonyl and there is going to be delta plus and so on because there is going to be some positive charge that is going to accumulate here is already delta plus over here and so this is going to be the transition state of this molecule.

So if your Steric is centered is going to interact with this tetrahedral transition state then you will see an effect, ok. So this is not by resonance or by internal hydrogen bonding, so we are going to use the substituents which do not interact by resonance or by internal hydrogen bonding.

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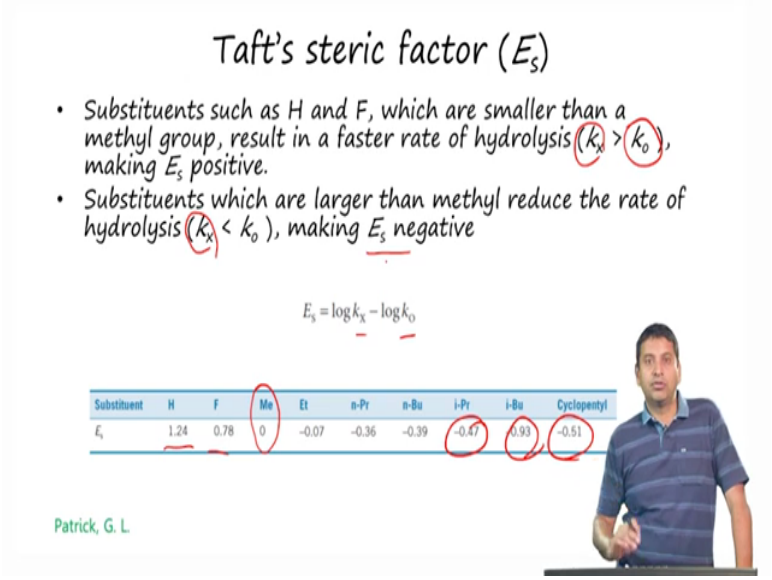


So based on this we can construct a table as shown here because we start with the Methyl ester, we are assigning this value of 0 because k x E will be equal to k 0 and so log of that will give you a value of 0. Now Hydrogen and Fluorine which are smaller than a Methyl group result in a faster rate of hydrolysis, so therefore the k x will be greater than k 0 ad and therefore you get positive values for the Steric factor, ok.

Similarly when you have a larger groups such as Ethyl or in n-Propyl and so on, the rate of hydrolysis of k x would be slower than the rate of hydrolysis of the corresponding Methyl ester. So therefore E s would be negative, so if E s is positive then the size of the substituent can be considered to be small and if E s is negative then the size of substituent can be considered too large.

So here is an example of Isobutyl, Isopropyl all of these are much larger than a Methyl group Cyclopentyl, so therefore these are going to have large negative values.

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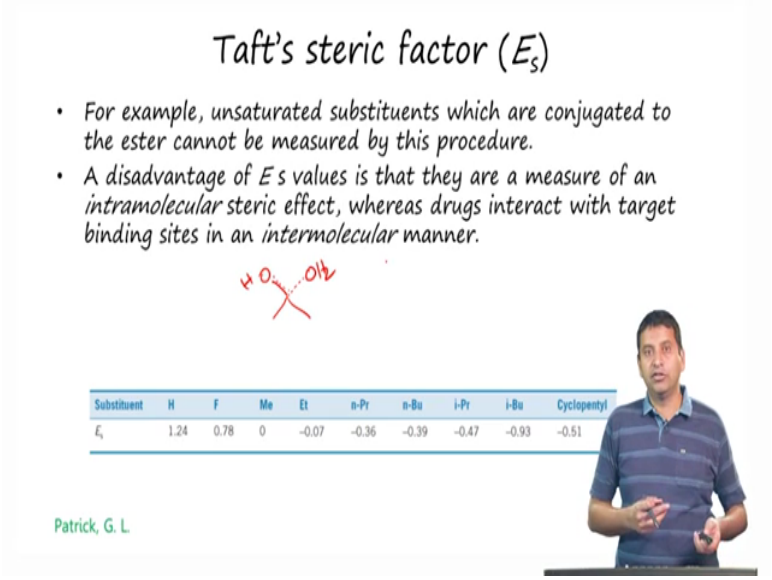


For example unsaturated substituents which are conjugated to the ester cannot be measured by this procedure because we have assumed that there is going to be no conjugation involved in this process. A disadvantage of the Taft is steric value is that there a measure of intramolecular steric effect, ok. So what we are trying to measure is the effect on the transition state leading to the formation of this you know this is a transition state that we are looking at rather than unintermolecular reaction which is what we typically used for looking at binding, right.

So this is more of intramolecular steric effect and it is a fairly good measure but it can be disadvantages in certain situations.

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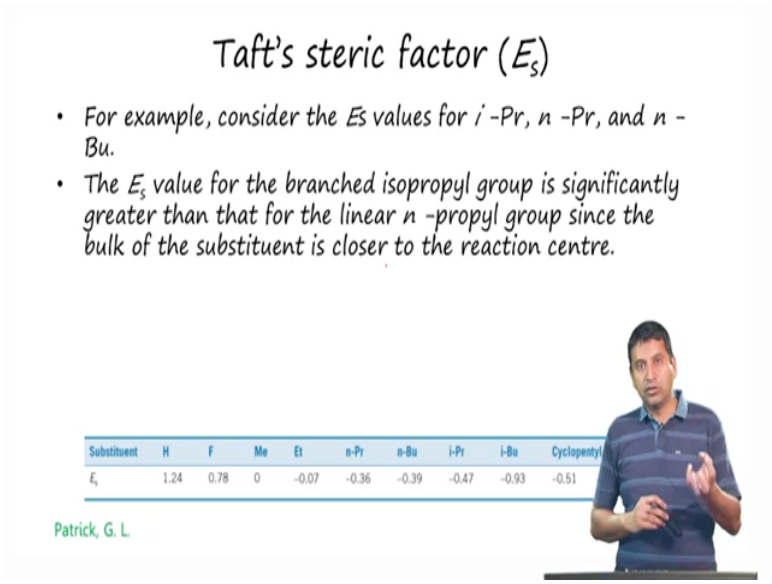

So for example if you considered the values of Isopropyl, n-Propyl and n-Butyl the Taft is steric factor for branched Isopropyl group is significantly greater than that for a linear n-Propyl group since the bulk of the substituent is closer to the reaction centre.

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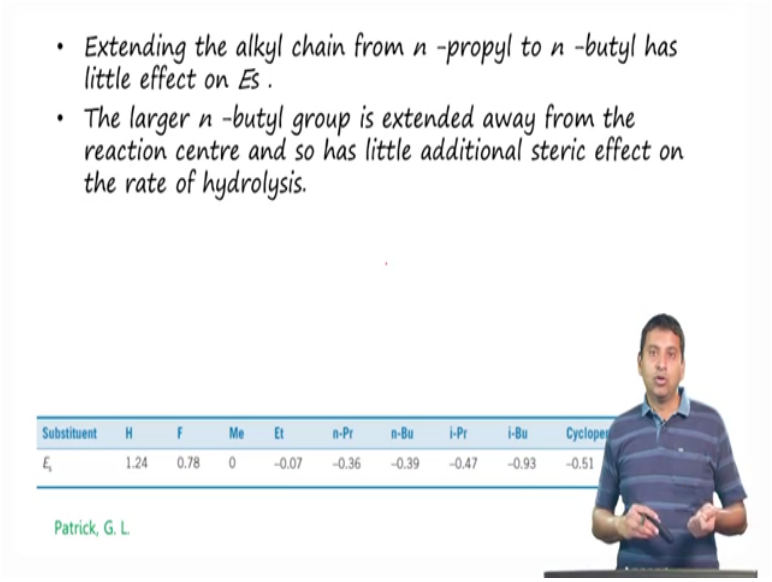


Extending the alkyl chain from n-Propyl to n-Butyl has little effect on E s, so the larger n-Butyl group is extended away from the reaction centre and so has little additional steric effect on the rate of hydrolysis.

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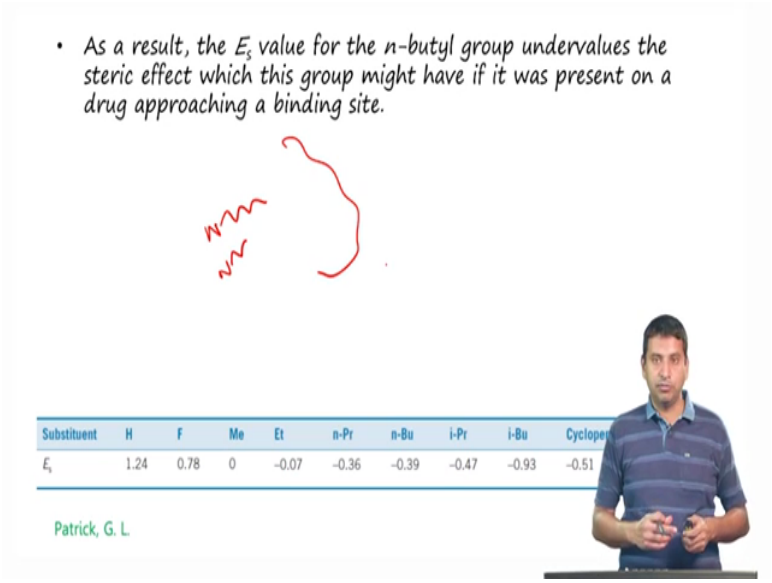


As a result the Taft is Steric value E s for the n-Butyl group under values the steric effect which this group might have if it was present on a drug approaching a binding site. So if you

have for example n-Butyl approaching a binding site versus n-Propyl you would expect that the n-Butyl would be definitely having a higher steric influence.

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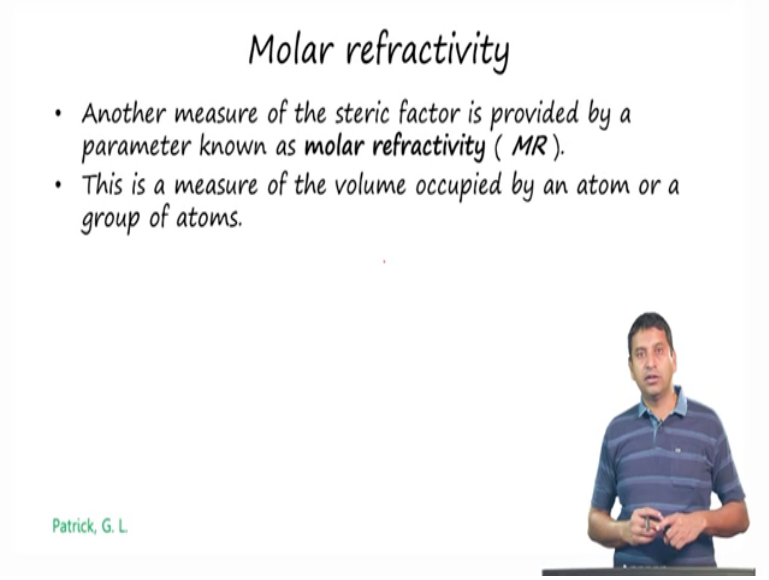


The next parameter that we would like to define for our QSAR analysis is molar refractivity, so this is also a measure of steric factor and it gives us a value of the measure of the volume occupied by an atom or a group of atoms.

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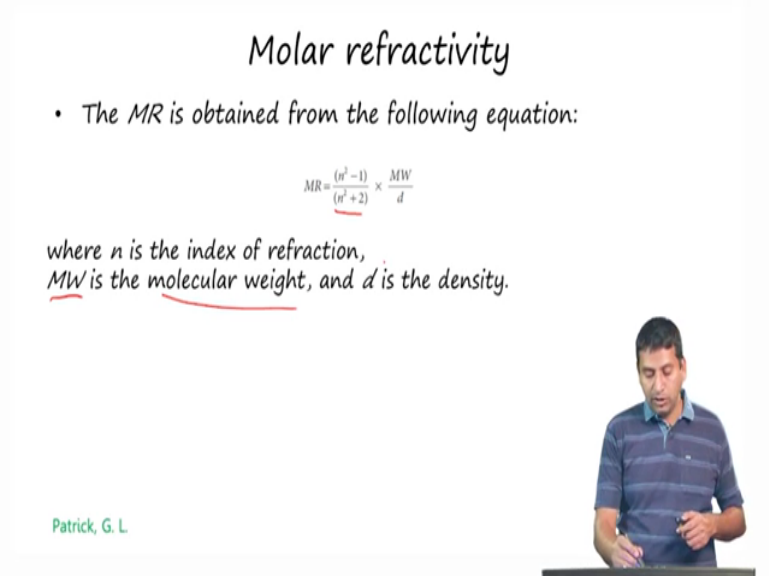


So the equation that we follow is the following here we have n square minus 1 divided by n square plus 2 times MW divided by d, here MW is the molecular weight of the compound and d is the density, ok.

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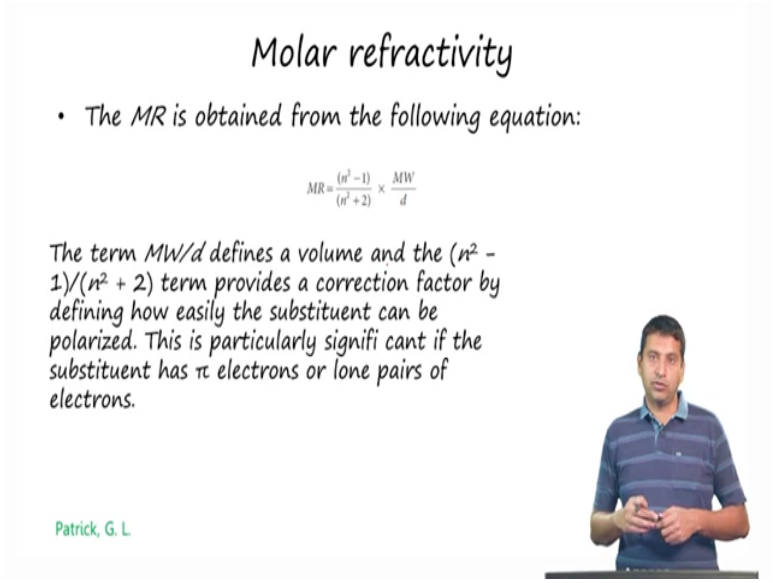


So the term MW by d defines a volume, ok and the n square minus 1 divided by n square (pul) plus 2 provides a correction factor by defining how easily the substituent can be polarized. So this is particularly significant if the substituent has pi electrons or lone pairs of electrons.

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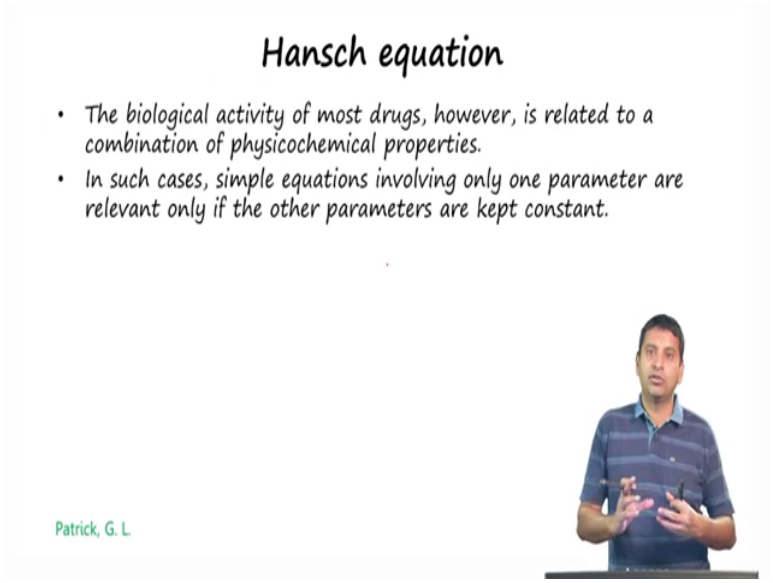


So we have now defined several parameters that is we have looked at log P, we have looked at electronic effects using Hammett, we have looked at steric effects using task parameters and the molar refractivity. Now we want to start putting these terms to use in a quantitative manner. We have already looked at previously that you can use a single parameter and very rare and find out whether it has any effect on the inhibitory potency or binding potency but

the biological activity of most drugs is related to the combination of these physicochemical properties.

So here simple equations using only one parameter are not very useful, ok.

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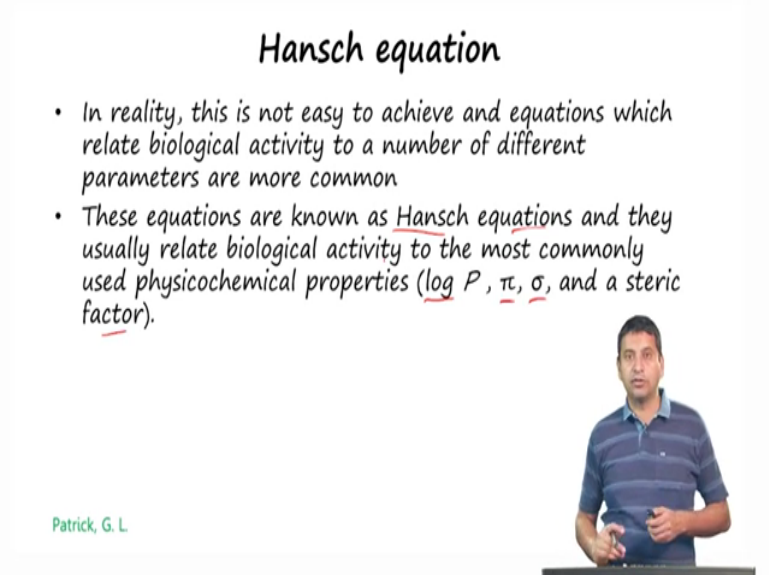


So therefore we would want to start incorporating a these (para) think parameters in the equation that we want to construct. So these equations are known as Hansch equation, ok and they usually relate to biological activity or to the most commonly used physicochemical properties that is log P, pi, sigma and a steric factor ok.

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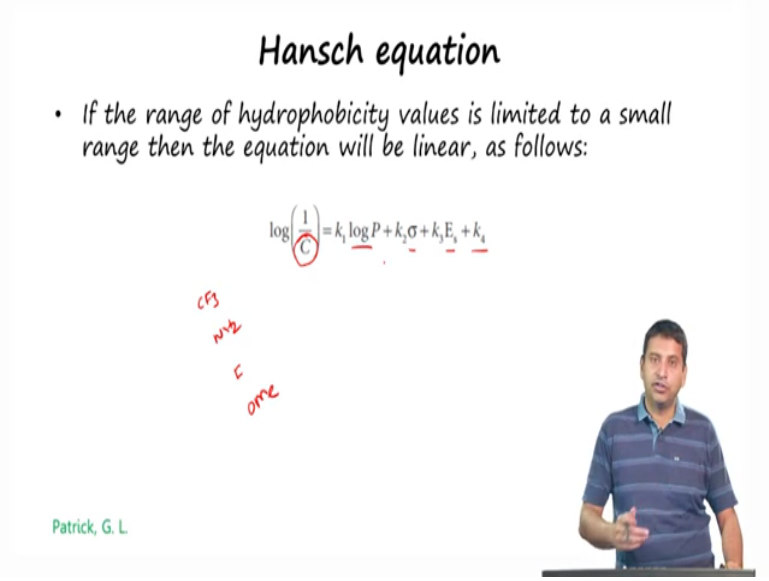

So here is an example of the Hansch equation, so what you would do is you take the log of 1 by concentration and then we have various log p, sigma is, Taft is Steric parameter and perhaps other constants, ok. So what you do is you fit these, so you use a fitting curves which can be done computationally and you fit the log of 1 by C, so let us say you have a molecule which has a substituent CF 3 or you have a substituent NH2 or you have a substituent Fluorine OMe and so on, each of these will give you 1 IC50 or EC50 or something like that, so we used that value here and each of these have a log P, sigma E s, now using these we start fitting it, so at some point when we start fitting this you might get a linear relationship.

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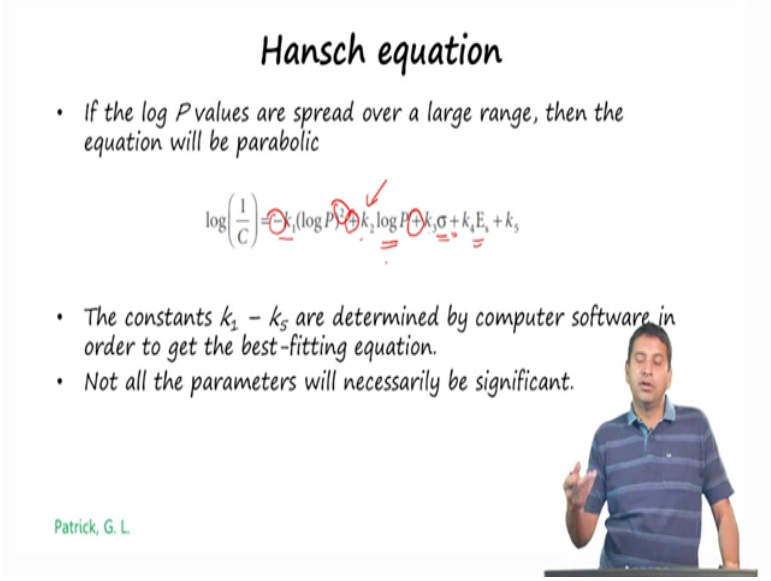


So for example here is one of the equations that you get by adopting the best fit and so here k 1 has a that is log P has a negative term and a square term, so square term means that the effect of that is going to be more significant when you change the hydrophobicity, ok. Here you have a plus term and log P also involved here, ok so you can have two different constraints k 1 and k 2 which can be incorporated into the same Hansch equation, you also have sigma and there is a plus involved here and lastly you have a steric factor where you also have a positive effect.

So therefore if you get an equation like this and this gives you a linearity and we have already looked at how to asses linearity based on r square and significant standard deviation. Now using this best-fitting equation you can now predict what would be the change that we want to make, so based on these constants k 1, k 2, k 3, k 4, and k 5 we can now figure out which parameter is more important.

So in this equation for example k 2 maybe significantly larger compare to k 3 and it may be smaller than k 4, so based on these we can now sort of start constructing, start understanding how the activity depends on the various parameters that we have defined.

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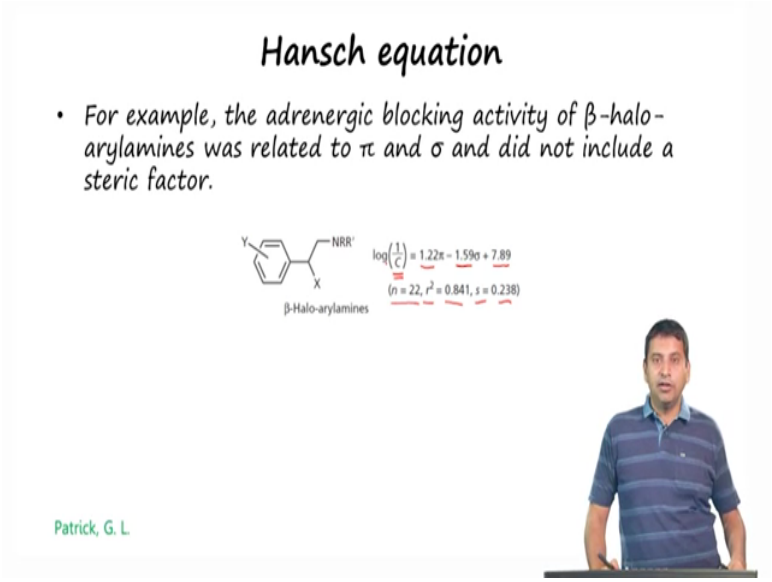


So here is an example, so if you take this Adrenergic blocking activity of beta-halo-arylamines and then you found out that when you fit this in a Hansch equation log of 1 by C equals 1 point 22 times pi minus 1 point 59 times sigma plus 7 point 89, so here in order to understand how significant this is we need to know how many compounds were made and the value is 22 which is quite large and the r square is point 841 which is pretty good because we sort of figure out that anything more than point 8 is considered pretty good and the standard deviation is point 238 which is also in the acceptable range. So therefore you can now look at this set of data and start making some conclusion from this.

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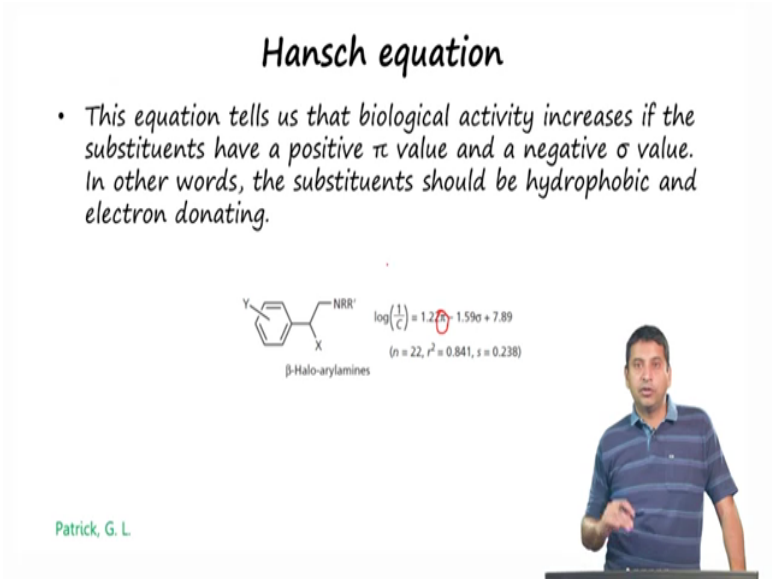


So this equation tells us that the biological activity increases if the substituents have a positive pi value, ok and a negative sigma value in other words the substituent should be hydrophobic and electron donating.

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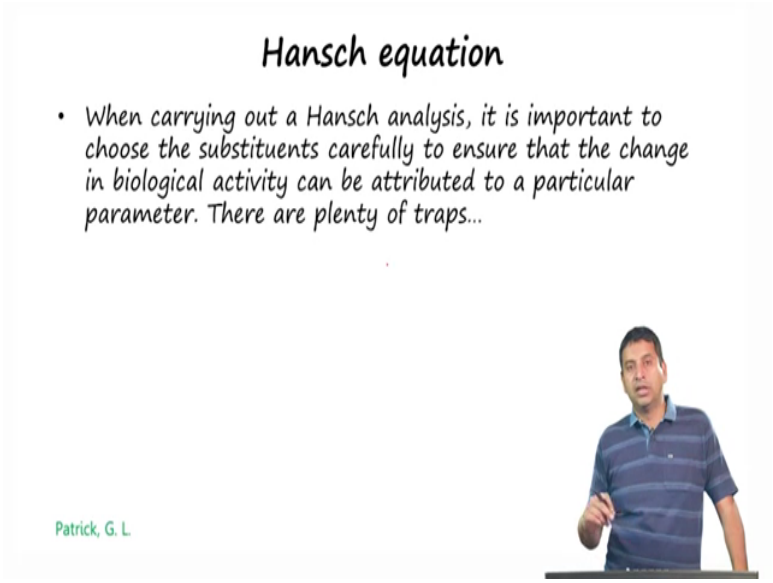


So when carrying out a Hansch analysis it is important to choose the substituent carefully to ensure that the change in biological activity can be attributed to a particular parameter. Of course there are plenty of traps that we need to be aware of.

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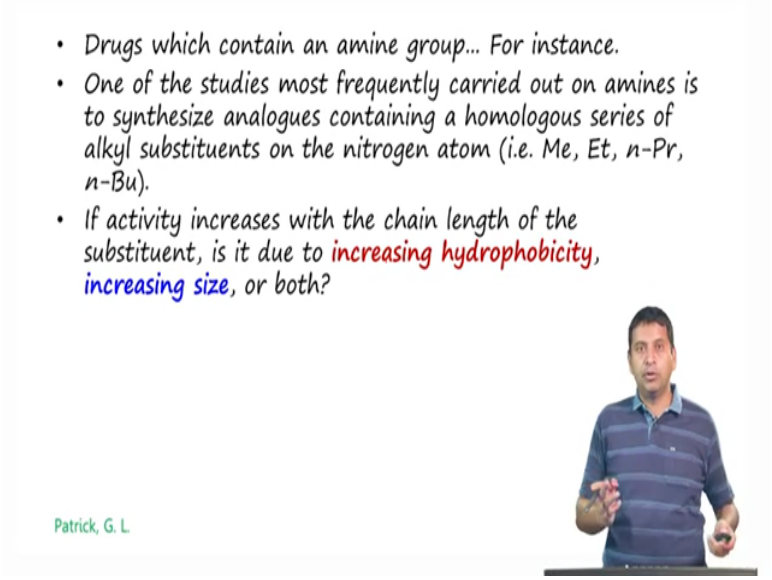


So drugs which have an Amine group for example, so one of the studies more frequently carried out an Amines is to synthesize analogues containing a homologous series of Alkyl substituents, so for example you have Methyl Ethyl, n-Propyl, n-Butyl and so on, but if the activity increases with chain length of the substituent is it due to increasing hydrophobicity or it is due to increasing size or both.

So these are something that we need to keep in mind when we are interpreting data from the Hansch equation.

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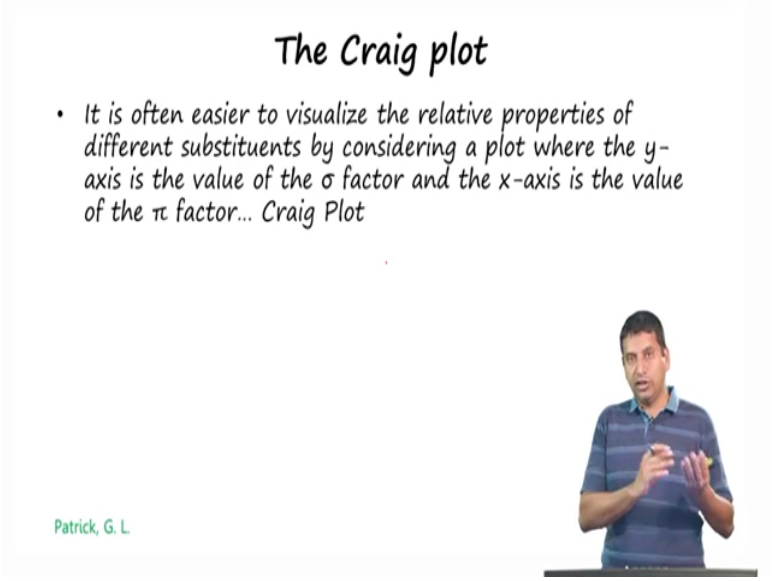

Another way to analyze this data is to use what is known as Craig Plot, here it is often easy for us to visualize the relative properties of different substituents by considering a plot where the y axis is the value of sigma and the x axis is the value of pi this is defined as the Craig Plot.

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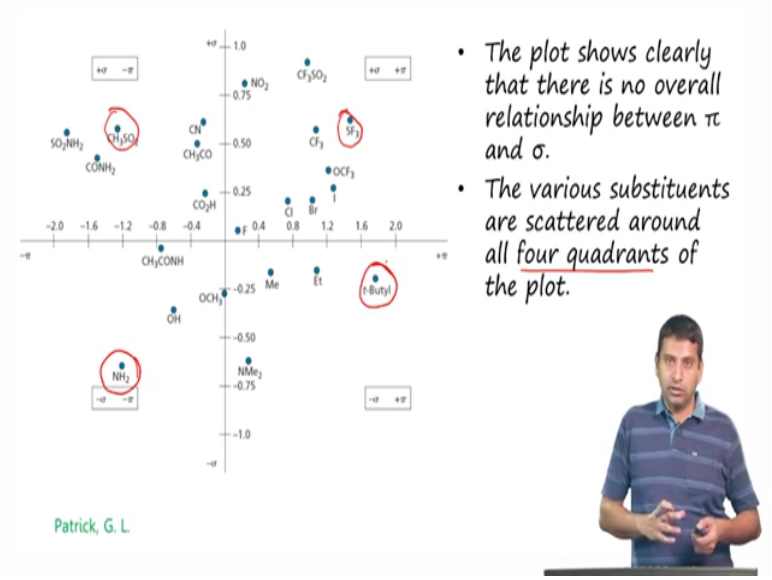


So here is an example of a Craig Plot, so this plot clearly shows that there is no overall relationship between the two values which is pi and sigma, so here for example you have this substituent which has a positive sigma as well as positive pi and here you have a substituent between which has a negative sigma and a negative pi and here you have a substituents which have positive sigma but negative pi and here you have a substituent which has negative sigma but positive pi, so these are the four quadrants that we are going to deal with, ok.

So here what we have done in this process is we have tried to look at both these parameters and tried to plot them suggests that we have an understanding as to what the effect of changing one functional group would be on the activity of the molecule. So when we want to look at how to make new analogues then perhaps we could think about using similar molecules in this quadrant.

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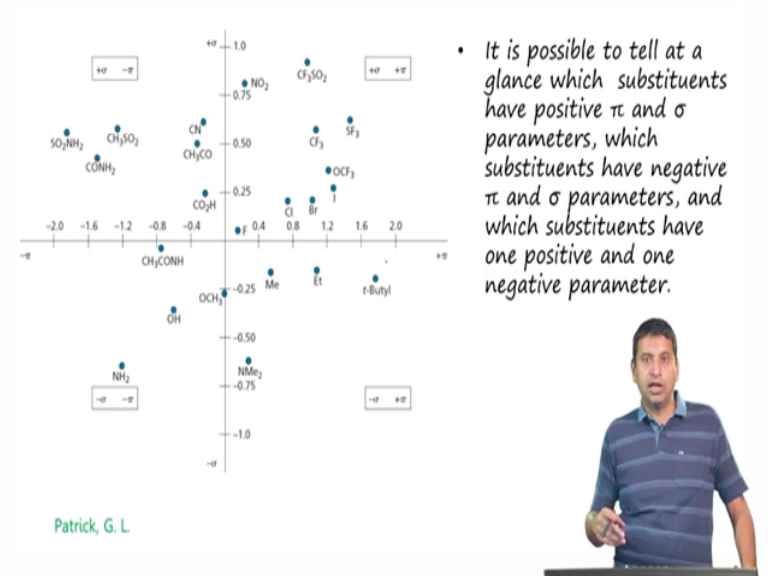


So it is possible to tell at a glance which substituents have positive pi and sigma parameters and which substituents have negative pi and sigma parameters which we have just looked at, ok.

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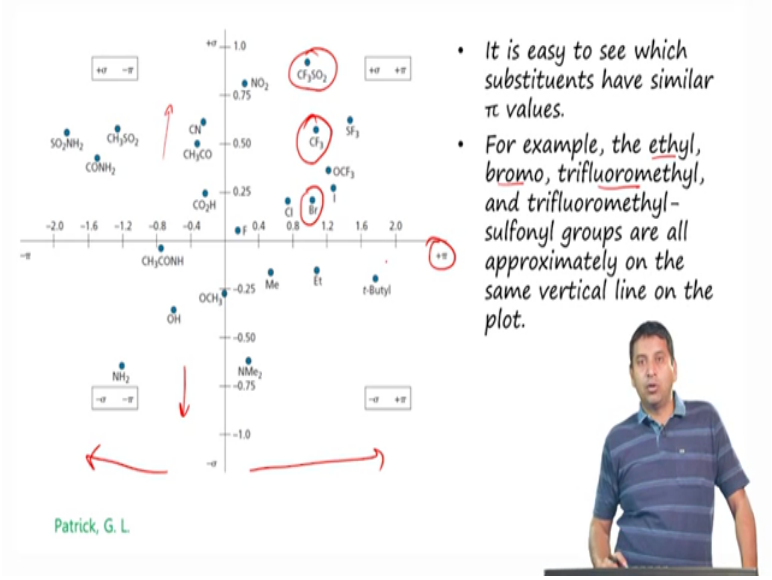


It is also easy to see which have a to see substituents which have similar pi values, ok so all of these which are have a positive pi value or located on the right hand side of this curve of this line whereas all the ones which have negative pi value or located on the left. Similarly if you have a positive sigma you go in the positive y direction and a negative sigma goes in the negative y direction.

So for example Ethyl, Bromo, Trifluoromethyl and Trifluoromethyl Sulfonyl groups are all approximately on the same vertical line of the plot, so Ethyl, Bromo, Trifluoromethyl, so Trifluoromethyl, Bromo, Trifluoromethyl Sulfonyl and they are all in the same quadrate, ok.

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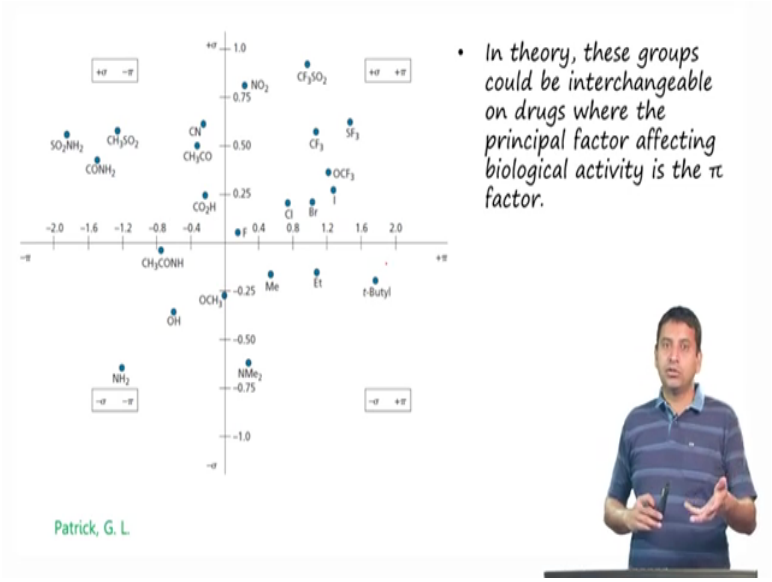


So in theory these groups could be interchangeable on a drug, ok where the principle factor affecting the biological activity is the pi factor. So if we obtain Hansch equation which gives a very large k value to pi then we could use one of these substituents perhaps interchangeably, ok.

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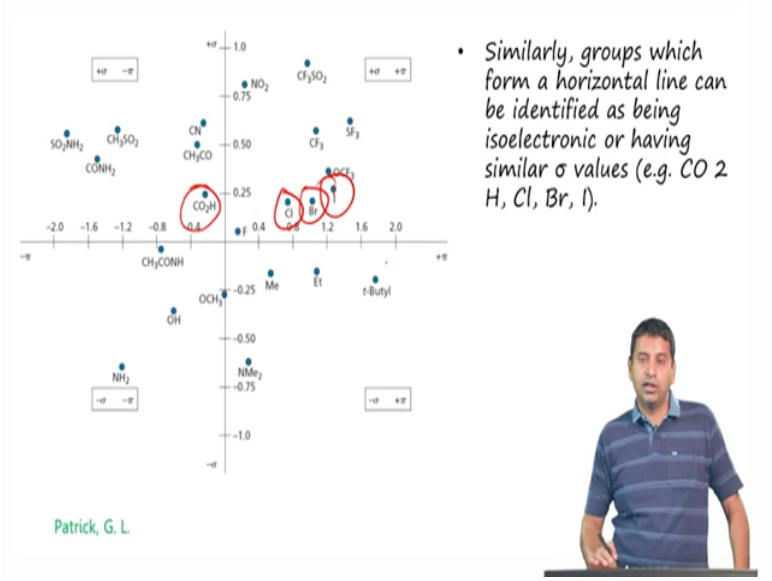

Similarly groups which form a horizontal line can be identical as being isoelectronic or having a similar sigma values. So for example CO 2, H, Cl and Br, so here Cl, Br and here CO, H all of these have similar and I they all have similar sigma values, ok. So you can think about these are being perhaps interchangeably if sigma value is important in determining the activity.

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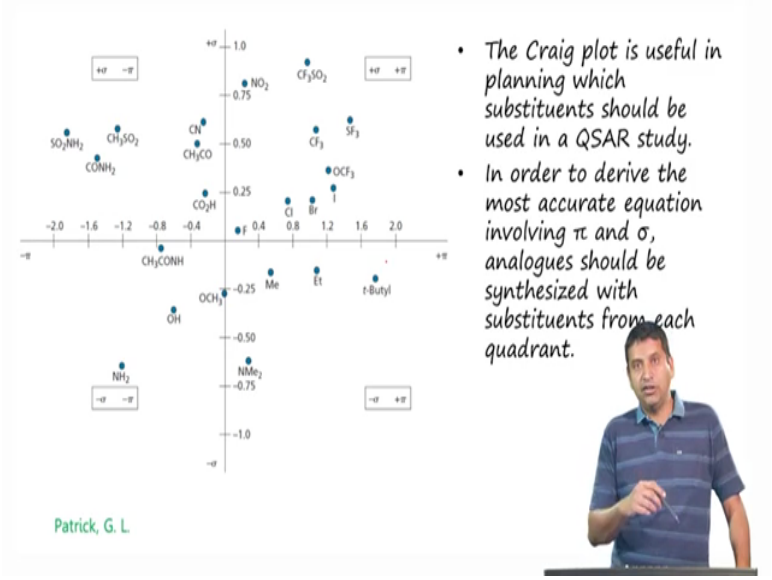


So the Craig Plot is useful in planning which substituents should be used in a QSAR study. In order to derive the most accurate equation involving pi and sigma analogues should be synthesized where you have substituents of each quadrant. So in order for you to make a good interpretation of the Hansch equation or a QSAR study we need to have substituents in each of these quadrants.

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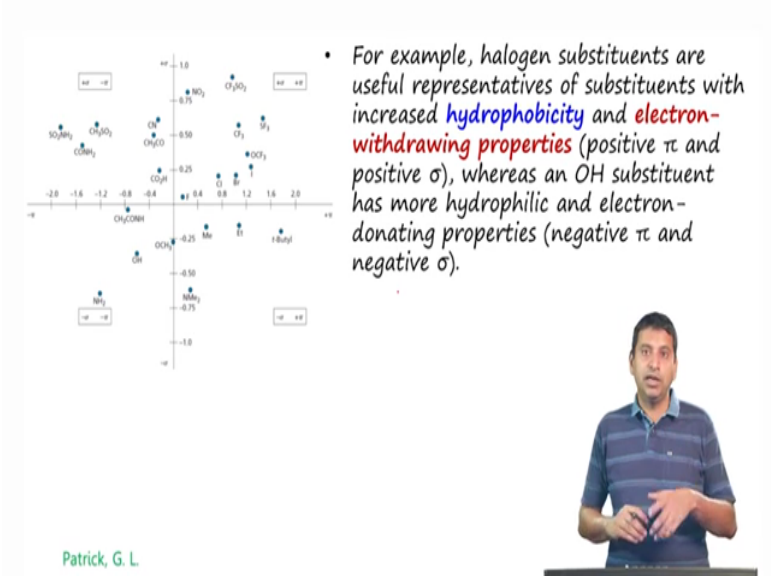


For example Halogen substituents are useful representatives of substituents with increase hydrophobicity as well as electron withdrawing properties, so they have both of positive pi as well as a sigma whereas Hydroxide substituents is more hydrophilic but it has electron donating properties, so it has negative pi and a negative sigma.

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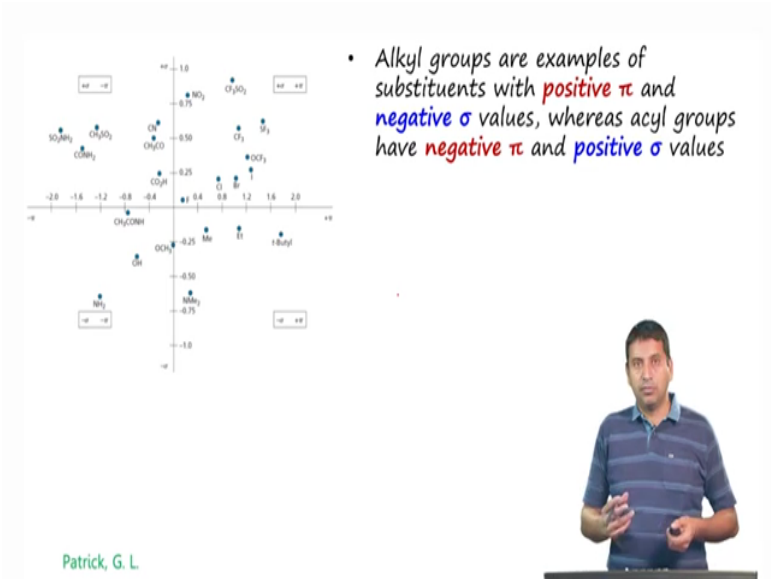


Alkyl groups have positive pi and negative sigma values whereas Acyl groups have negative pi and positive sigma values, so all of these are going to become important when we are designing the QSAR study.

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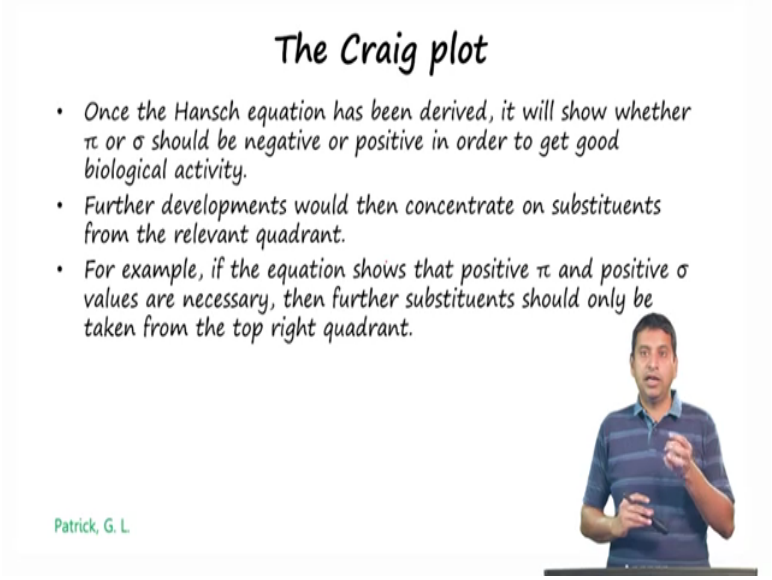


So once the Hansch equation has been derived it will show whether pi or sigma should be negative or positive in order to get good biological activity. So further developments or further synthesize can concentrate on substituents from the relevant quadrant. So for example if the equation shows that positive pi and positive sigma values are necessary then further substituents should only be taken from the top right quadrant.

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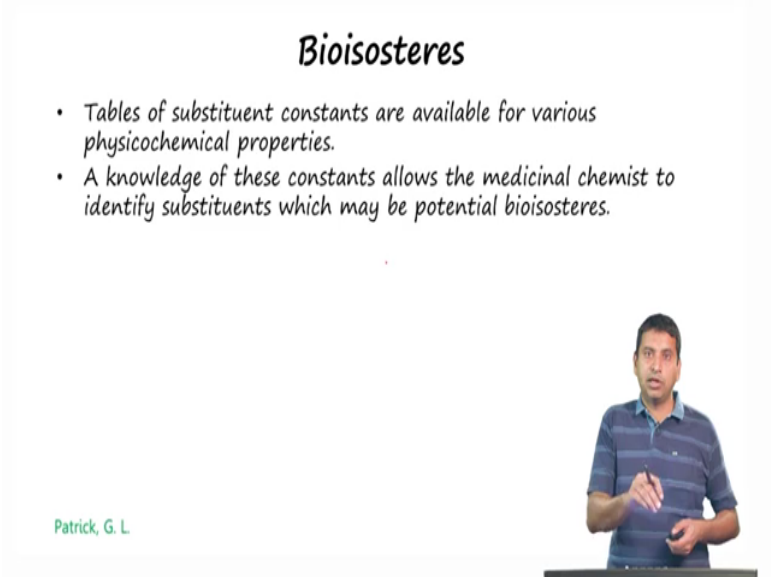


Now Bioisosteres we have already looked at previously and a table of substituents constants are available for various physicochemical properties and a knowledge of these constants allows to Medicinal Chemist to identify substituents which may be potential Bioisosteres, so

we are always looking for molecules which can retain the biological activity and by making a substituent change and these are known as Bioisosteres.

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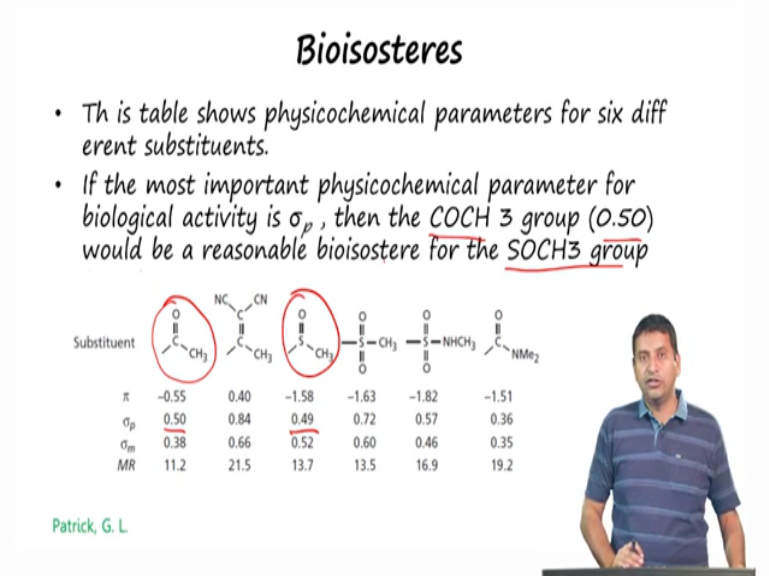


So here is a table where we have a physicochemical properties for six different substituents. If the most important physicochemical parameter is sigma p then the COCH 3 group which has a value of point 5 would be a reasonable Bioisostere for the SOCH3 group because if you see here COCH 3 group and SOCH3 group have very similar values of sigma p, ok. So again this is something that we can derive using our Hansch equation.

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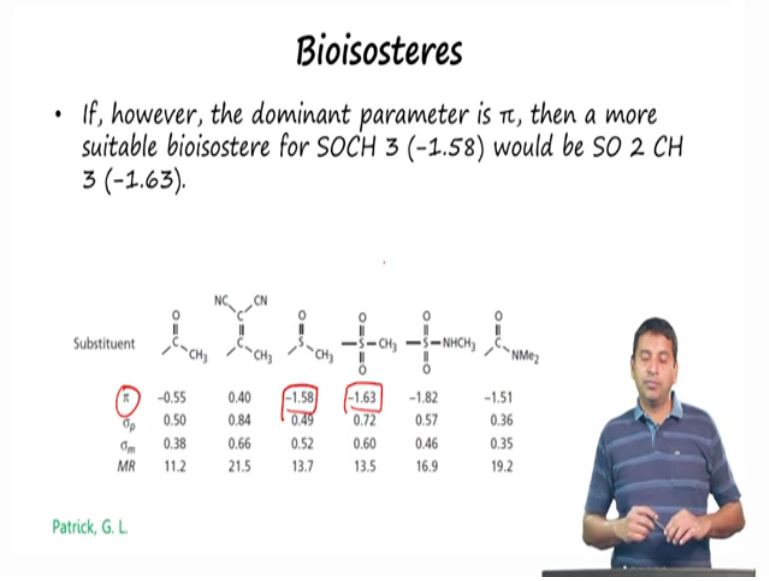

However if the dominant parameter is pi, so here is pi then a more suitable Bioisostere for SOCH 3 would be S double bond O CH 3 which is a Sulfonyl group. So using these kinds of analysis one can identify new Bioisosteres in a library of molecules.