Fundamentals and Applications of Supramolecular Chemistry
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Lecture 07

W2L7_Understanding of sigma and pai-hole directed interactions

Hello everybody, so now we are going to discuss further on the next set of interactions which are extremely important, and which have essentially been developed in the past one and a half decades.

So now we are going to look at experimental and computational ways in which we can have an understanding of sigma and pi-hole directed intermolecular interactions.

So, this is the topic which we would like to discuss that is what is the origin of sigma-hole and pi-hole directed interactions and what is the sigma hole, what is a pi hole, how is it generated in a molecular system, and how the sigma holes and pi holes which are intrinsically electron deficient in nature, interact with electron rich species.

So, before we go into the definition of a halogen bond and the origin of the sigma hole. Let us first try to understand the origin of sigma hole. So, to start with let us consider a chlorine atom.

Chlorine has got 1s2, 2s2, 2p6, 3s2, 3px2, 3py2, 3pz1. This is the electronic configuration of chlorine. So intrinsically there is a one electron deficiency in the chlorine atom.

So now when the chlorine atom participates in covalent bond formation with the odd electron, which is in the pz orbital, and we know that the pz orbital overlaps with another pz orbital to form the covalent bond.

So, originally one chlorine atom had one electron, the other chlorine atom had one electron, these two participate in covalent bond formation. And during the process of covalent bond formation, the electron density from the pz orbital is now pulled towards the center of the chlorine-chlorine bond.

So, when the chlorine-chlorine bond formation takes place, these two electrons which form the bond are now pulled away from the pz orbital towards the center of the Cl-Cl bond and to start with it is one electron deficient and in the process of covalent bond

formation because of the electron density being pulled into the inter nuclear region that is where the bond formation takes place.

Along the bond axis there is now a region of electron deficiency, there is now a region of electron deficiency. So, along the bond axis you will see there is a region on the chlorine atom which is electron deficient.

Because now the covalent bond formation has taken place, and it has got the octet configuration the three lone pairs corresponding to each chlorine atom, we have the three lone pairs also. They are now redistributed such that we have now got an anisotropic electron density distribution around the halogen atom.

So, we know that each atom has octet configuration, there are three lone pairs of electrons. The lone pairs of electrons are now present in a region which is perpendicular to the C-Cl bond axis. So, see this is the C-Cl bond axis and the electrons corresponding to the lone pairs are present perpendicular to this axis.

This leads to anisotropic electron density distribution, and this electron deficient region which is now generated because of the pull of this 3pz electron which participates in covalent bond formation is what is termed as the sigma hole.

So, the origin of the sigma hole is the anisotropic electron density distribution on account of the covalent bond formation wherein the $3pz^1$ electrons are now redistributed such that the sigma hole is formed along the bond axis or the inter nuclear axis and the lone pair density corresponding to the $3px^2$, $3py^2$ and $3s^2$ orbitals are present perpendicular to the bond axis.

So, because of this reason we now have got an atom which is deformed. We have a deformation in the atom such that we have the sigma hole here and this is the electron rich region. So, this is along the bond axis, this is perpendicular to the bond axis, this is the lone pair density.

The sigma hole and the lone pair density they are essentially perpendicular to each other and now the atom is also polarized. The electron density distribution more resembles an ellipsoid. So, this is the origin of the sigma hole.

So, keeping this thing in mind we can now define what is a halogen bond because in this case we are considering halogens particularly the heavier halogens, Cl_2, Br_2 and I_2. It has been observed that there is a sigma hole which is formed and if you were to actually compute or calculate the electrostatic potential it will be having a positive value.

Whereas if you look at the region perpendicular to the bond axis, then it will have a

negative electrostatic potential. So, this electrostatic potential which we will look at further is a very fundamental quantity which is related to the electron density distribution of atoms and molecules.

So, when you have a R-X molecule where R is a methyl ethyl propyl. Then, we will see that around the halogen there is an anisotropic electron density distribution and because this is electron deficient the sigma hole it can now interact with a Y-Z molecule, which is where the Y atom is electron rich. For example, the Y atoms can have lone pairs.

So, the interaction of the sigma hole containing a halogen atom, this is referred to as a halogen bond donor, and Y is called the halogen bond acceptor. So definitely there is electrostatic interaction to start with because this is deficient, and this is electron rich, and this constitutes the halogen bond which is driven by the sigma hole.

Now this definition of halogen bond is as follows, where they say there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom which I have defined in any molecular entity, and a nucleophilic region in another specimen, either of the same or a different molecular entity you can have.

You can have X interacting with another X. At that moment, the lone pair of X will interact with the sigma hole of X, or you can have another molecular entity Y-Z, where the sigma hole interacts with the lone pair of electrons.

This definition has been proposed by a committee set up by the International Union of Pure and Applied Chemistry, IUPAC and published in this journal of Pure and Applied Chemistry in 2013 which essentially defines the halogen bond. And this is something which is similar to that, or conceptually similar, to that of a hydrogen bond, where you had a hydrogen bond donor and you have an acceptor, which actually interacts with the hydrogen atom.

Here it is the halogen X which interacts with the acceptor atom Y. So, the halogen bond donor is intrinsically electron deficient, the halogen bond acceptor is electron rich. And similar to hydrogen bonds, if you want to maximize the strength of the halogen bonding interaction, the directionality associated with the halogen bond center that is at X must be close to 180 degree, that is what is expected to be idle.

And the strength of the halogen bond is also quite high, it lies in the range of 1 to 40 kilo kcal per mole around is around 4 to 160 kilo joule per mole. And what is the proof of this concept to start with.

Already, before halogen bond and sigma hole were discovered, O. Hassel had discovered the first iodine-ammonia complex way back in 1863, where iodine interacts with the nitrogen atom of ammonia molecule.

Now to start with, this will appear to be counterintuitive because iodine also has got lone pair of electrons if you were not to have the understanding of the halogen bond and nitrogen also has a lone pair of electrons.

So why is it that two relatively electron rich species like iodine and nitrogen, they come close to each other and the separation between the iodine and the nitrogen atoms is approximately equal to the sum of the van der Waals radii of iodine plus nitrogen.

Sometimes it is slightly smaller, that means there is a contraction or a decrease in the distance between iodine and nitrogen atoms. That means there is an entity which is having electrophilic character on iodine which pulls the lone pair density of nitrogen towards itself and that is what constitutes the origin of the halogen bond which we have now discovered.

So, following the identification of the halogen bond it was primarily attributed to the sigma hole. And as we have already discussed that the electron density of the interacting atoms is redistributed depending on the electronic environment and this results in the anisotropic distribution of the electron density.

And this can lead to the development of a positive electrostatic region on the surface of the atom, which is opposite to the covalent bond, thereby known as the sigma hole. So, this origin of the sigma hole is extremely important, and this was first observed in case of halogens, the heavier halogens. In case of fluorine, it is to be kept in mind that fluorine is a highly electronegative atom. Therefore, in case of F2 species, no sigma hole was observed.

To start with because of the high electronegativity associated with fluorine. And because it has got high electronegativity and high electron density because of the small size of the atom when they approach each other there exist strong electron-electron repulsions.

So, therefore, the redistribution of the electron density really does not take place. They more retain their spherical nature, the deformation of the electron density is also less and therefore, the sigma hole does not exist in case of F2 molecule. So, the next thing is let us look at how we can compute the electrostatic potential. Let us visualize this electrostatic potential.

It is very important to see how the electrostatic potential looks like and what is the basis of the electrostatic potential. This is the expression for electrostatic potential, and you can

see that there are two contributions. The first contribution is the nuclear contribution, and the second is the electronic contribution.

$$V(r) = \sum_A \frac{Z_A}{|r_A - r|} - \int \frac{\rho(r_e)}{|r_e - r|} dr_e$$

(electronic)

(nuclear)

We can call it as V plus and we can call it as V minus but because it is associated with electrons and electrons are intrinsically negative, therefore, the first term is positive, and the second term is negative.

So, this expression gives you the electrostatic contribution and at regions where the V(r) is positive, it tells you that the nuclear contribution is greater and at regions where the V(r) is negative, it tells you that the electronic contribution that is the contribution coming from the electrons is going to be greater.

So, keeping this viewpoint in mind, now let us systematically see 4 different compounds, CF4, CF3Cl, CF3Br and CF3I. And what we have done is replaced one fluorine with a chlorine atom, then with a bromine atom and then with an iodine atom.

And we are now looking at the electrostatic potential which has been computed at this particular level of calculation. We are not interested to know the details of this, but this is for information, and this is drawn on the 0.001 atomic unit electron density isosurface where essentially the electron density has tapered to 0.

So when you plot it on this isosurface the MESP value you will see that the green region represents the electrostatically negative regions, that is the V minus, and the blue regions are actually the electrostatically positive regions.

Now the moment you add chlorine you can see when you look along the C-Cl bond axis that means you look at the face of the C-Cl bond you can see now that there is a positive electrostatic potential, and this is the representation of the sigma hole. Now you can very clearly see the sigma hole on the chlorine atom.

And when you go to bromine atom the magnitude of the sigma hole even increases because bromine is less electronegative than chlorine and chlorine is the most electronegative atom which essentially has got no sigma hole. Bromine now has got also a sigma hole and when you go to iodine again you can see that there is an increase in the intensity of the blue color.

An increase in the intensity of the blue color tells that the magnitude of the positive electrostatic potential is increasing from chlorine to bromine to iodine. As you can see from the scale that the red represents in a MESP calculation or a computation it represents the most negative region, then we go to yellow, then there is an intermediate pale green and then finally blue to intense blue.

So, the spectrum tells you the magnitude of the electrostatic potential. So, we now are clearly able to see the origin of the sigma hole when you have replaced one fluorine with iodine, bromine, chlorine and fluorine. When you have replaced one halogen with fluorine in CF4.

Now, if you were to compare this with CH3F, CH3Cl, CH3Br and CH3I, then the sigma hole is practically not present. The sigma hole on chlorine, bromine and iodine is practically not present.

So, that means when you have methane, and you replace one hydrogen by fluorine, chlorine, bromine and iodine you have actually not really polarized the electron distribution sufficiently so as to have a sigma hole on the C-X bond axis.

So, what is important is to modify the electronic environment around the CH3 and that is as we discussed constitutes the origin of the sigma hole and therefore, we have now replaced the hydrogens with fluorines. Now when you replace the hydrogens with fluorines, CF3 is a highly electron withdrawing group and it withdraws lot of electron density from the C-I bond or the C-X bond.

And as a result of which more is the electron density withdrawal by the CF3 group, more is going to be the magnitude of the sigma hole. So, you are now introducing electron withdrawing groups essentially to polarize the C-CI bond.

So, when you have put these fluorine atoms, the electron density contained in the C-I bond is more polarized, more is the drift of the electron density towards the carbon, more is the magnitude of the sigma hole on the iodine atom.

So, to start with chlorine will have a sigma hole that increases in bromine and finally, in iodine the magnitude of the sigma hole is the maximum. So I hope you have been able to appreciate that putting electron withdrawing groups enhances the magnitude of the

electrostatic potential corresponding to the sigma hole on the incipient halogens.

And you can also now consider for example you can also put other electron withdrawing groups like nitro, cyano and you can actually compute the magnitude of the electrostatic potentials.

So, this can be very systematic study where you can actually determine the magnitude of the sigma hole on the parent compound and we need to do this because this sigma hole in any molecule is now going to interact with another molecule, particularly the electron density region of either the same molecule as we discussed or a different molecule to participate in non-covalent interactions.

And we can now look at some other examples as well. So, the concept of sigma hole is not only relevant to halogens, but also of relevance to the chalcogens. For example, sulfur, selenium, tellurium.

Oxygen, sulfur, selenium, tellurium is the chalcogen family. Oxygen is quite electronegative and observing a sigma hole is rare unless you actually have an oxophilic species like O plus.

In contrast, sulfur, selenium and tellurium which are relatively less electronegative can have sigma holes. So, for example, now we can see the fluoro chloro selenide, where we have this particular compound.

And now we are able to understand that the fluorine atom is a highly electronegative atom, it will pull the electron density of the SeF covalent bond towards itself.

Therefore, the sigma hole will come out in this particular direction, this is the sigma hole, it is not the lone pair, this is rather the sigma hole, and similarly the chlorine be more electronegative will pull the electrode density towards itself. So, this will be another sigma whole region.

Now, where are the lone pairs? The lone pairs are towards u that is above the plane of the board and below the plane of the board. So, now you can see very clearly that there are two sigma holes which are along the Se-F and Se-Cl bond and there are two lone pairs which are above and below the plane. So, overall, this kind of constitutes a tetrahedral kind of arrangement essentially.

So, you can see here now that this region which is opposite to the Se-Cl bond axis, and this is opposite to the Se-F. So, this is opposite to the Se-F, this is opposite to the Se-Cl bond axis, this constitutes the sigma hole, which you can see very clearly on the selenium atoms along the bond axis and the lone pairs as I told you are above and below the plane.

So, you have the tetrahedral arrangement of these two sigma holes and the two lone pairs. Along the same lines, we can now go to the pnictogens also. Pnictogens correspond to the nitrogen, phosphorus, arsenic, antimony and bismuth.

So now if you consider for example the heavier nitrogens, for example, phosphorus and you replace in case of phosphine if you replace one hydrogen atom with chlorine so you can see very clearly that there is a sigma hole on the phosphorus atom.

And the concept can also be extended to the family of atoms of carbon, silicon, germanium, tin and lead which we call as the tetrel class or the tetrel atoms where for example, in case of germanium, if you now replace, in case of germane, you replace one hydrogen with bromine, you will be able to see the sigma hole on the germanium center at the germanium atom which is opposite to the GeBr bond.

And these are the hydrogens which you will see are more towards the neutral side, but the blue region as we have seen constitutes the sigma hole. The electrostatic potential here is positive and here you can see again that the electrostatic potential is the highest for iodine provided you have got two highly electronegative fluorine atoms which polarize the carbon-iodine bond and therefore result in an extremely high magnitude of the electrostatic potential.

So, if you would like to see more, you can refer to this particular review article from where the understanding has been done.

So, we can see that you not only have sigma holes in halogens, but you also have sigma holes in chalcogens, in pnictogens, as well as in tetrels. So, overall, this is a very generalized concept, the sigma hole, which was actually first discovered in case of halogens, but later on extended to chalcogens, pnictogens as well as tetrels, and the key feature here is the modification of the electronic environment by the introduction of electron withdrawing groups.

So, if you were to simply consider say hydrogen selenide H2Se, then there is no sigma hole, or H2Te. But, if you modify replace the hydrogens with more electronegative atoms then the sigma hole is generated. It is present in the structure and that is what now is a key driving force when it comes to recognition.

So, when you would like to talk about these kind of atoms, particularly the heavier p block elements now we can call these are the heavier p block elements like germanium, tin, lead, selenium and tellurium or bromine and iodine they participate in both, sigma driven bonding that is sigma driven halogen bond and you will also have to keep in mind that the lone pairs are also present to interact.

But what is important to keep in mind is the orientation of the sigma hole in comparison to the lone pairs. The lone pairs have got a different orientation and the sigma holes have got a completely different orientation. So, the orientations are very very important here. So, with this in mind, we can now look at, as we have just now discussed, we can now look at other species where we have for example, the nitrogen bond here in nitrogen, phosphorus, arsenic, and antimony.

We have got a chalcogen bond and you can see here that this is the region of the sigma hole, this is the region of the sigma hole, this is the region of the sigma hole, and this interacts with an electron which species to form tetrel bond or pnictogen bond or chalcogen bond. Again, these are to start with primarily electrostatic in nature.

And the next concept which is important is in addition to the presence of a sigma hole, we also have the concept of pi holes. Sigma whole originates because of the uneven distribution of the electron density along the bond axis.

But then we have also got pi rich systems. For example, we have got benzene, and we have just discussed in the previous lecture that in case of benzene you will see the electron distribution let us see we have that for you.

So, now let us look at the electron density distribution in benzene the electrostatic distribution rather. So, in case of benzene you can see that the central region is red that means it is electrostatically negative V minus then it goes to the yellow region a neutral region green and then the hydrogens are relatively more acidic and therefore, they constitute the electrostatically positive regions.

In contrast in case of hexafluorobenzene, as I mentioned the strong electron withdrawal. Now, you can see that the central region is electrostatically positive, and the outermost regions constitute the fluorine atoms is relatively electron rich.

That means, they are more electrostatically negative because there is more electronic contribution in comparison to the nuclear contribution. So, when you have so now you can actually put different kind of groups on this benzene and modify the electrostatic potential on this benzene.

So, now if you start putting electron withdrawing groups, the electrostatic potential will start decreasing, becoming less negative, becoming 0 and eventually become positive. Now, this region is referred to as a pi rich surface. This is referred to as a pi rich surface because it is electrostatically negative, but now when it becomes depleted, electrostatically positive, then instead of it being a pi rich species it becomes a pi deficient species which we refer to as a pi hole.

So, hole always refers to a region where there is deficiency and rich refers to a region which is electron rich there are more electrons associated with that region. So, this is the origin of the pi hole and the pi rich region, and it is the mutual electrostatic complementarity between the pi hole and the pi rich region which favors stacking in case of benzene-hexafluorobenzene which is the last example we discussed in the previous lecture. So, this pi hole contribution is also very important.

And not only for benzene, even if you were to consider an isolated double bond, for example, if you consider ethylene, it has a certain electron density distribution and electrostatic potential. And if you now start putting electron withdrawing groups, for example, if you go to CF2=CF2, which is highly electron withdrawing, then it will polarize the electron density of the double bond and that will modify the electrostatic potential in the middle region where the double bond is present.

So, these are the attributes of your sigma hole and pi hole as well as pi rich interactions. And now as you can see, we can now take a case of di-iodo-tetrafluorobenzene, a more complicated case where we will see the coexistence of both sigma hole as well as pi hole in the same molecule.

So, now, this is a molecule which has a sigma hole because of the carbon-iodine bond and opposite to the C-I bond is a sigma hole, and then and perpendicular to the ring, we have the pi hole, why, because the fluorines have withdrawn electron density and you will see the negative regions corresponding to the fluorine here, electrostatically negative regions, corresponding to the fluorine.

So, this is the negative belt, and the sigma hole is the positive belt and the pi hole which is again above and below the plane of the molecule is the positive belt. So, now, in the next class we will take up more examples, we will discuss about the more examples where we have pi hole, sigma hole and how these pi holes and sigma holes interact with electron rich species.

Thank you.