

Welcome to an NMR tutorial on less common phenomena, or, if you prefer, weird stuff. So this is a collection of standalone topics which will not come with a great deal of detailed background, but are just here so that you're aware of them if you happen to come across them in your work. So the first of these phenomena that I'd like to address is something called the heavy atom effect. And this is where heavier elements modulate the chemicals shift attached to the nuclei. Now some elements of this remain an area of theoretical research. It's pretty complicated, but what is usually relevant for us, is that when you have one of the heavier halogens. such as a bromine or especially an iodine attached to an atom, usually a carbon, then you should expect a big upfield shift. And this is especially true if it is attached to an sp<sup>2</sup> Centre. Should mention, there is an analogous effect on protons. It's smaller and orientation dependent, its just usually less visible and relevant. And I'm not going to go into any detail on that. Now. If we look at some ethane analogues where we've start with ethane at the top And then we have successively placed one hydrogen and four different halogens Then look at the carbon shift of the attached carbon in the red box. Here. In Fluorethane, we have a huge shift in the attached carbon. This is really not surprising, after all, fluorine is the most electronegative of the elements. And we do also have a smaller shift in the other carbon signal. And now if we move on to chlorine, chlorine is a lot less electronegative than fluorine, but still considerably more electronegative than the proton in ethane. And this results in a signal that's at about 40 ppm.

We then go on further. Bromine again is less electronegative than chlorine, but more so hydrogen. And so we drop some ten ppm, to 30. Now for iodine, we'd expect this trend to continue. Again, iodine is less electronegative than bromine, but more than hydrogen. So we'd maybe expect to peak around here. However, as a result of the heavy atom effect, we see this peak attached to iodine all the way down here at around about 0. we now look at halobenzenes. These are sp<sup>2</sup>. So these are, we expect to see a stronger effect. Again, we can see a single peak for benzene at about 130. will just highlight the ipso attached carbon. And again, for fluorobenzene we're seeing the ipso carbon is Heavily influenced by the attached fluorine all the way down to 160 ppm. And again, the effect of chlorine is relatively smaller, but it's still more electronegative than the hydrogen which would otherwise be attached. And so you see it downfield shifted. By the time you get to a bromine, however, we should see the same trend as previously, so the shift should be smaller than it is in a chlorobenzene example, relative to benzene, But it should still be down. However, what we see is now forgive my terrible drawing, upfield of the benzene signal. And if we then take this example, further to the iodine, now the difference is much bigger. And the heavy atom effect shifted our carbon all the way down to around about 95 ppm, just on the edge of what we normally consider the aromatic region. And this is quite distinctive. You can tell what carbon on the ring system that signal corresponds to. And you can combine this 2D methods like HMBC and use it as a starting point for structural assignments. So now I want to talk about the effects of pi system overlaps. So here are a couple of simulations, benzene rings, and in these, the ring current in the outside is in alignment with the magnetic field, but on the inside it is in the opposite orientation. Now, we know the systems effect protons and indeed the carbons in the ring, which are deshielded usually. And this is by the ring current, aligned with magnetic field. These systems can actually affect other protons that are close enough in space. And because their exact relationship is more variable than that of the protons and carbon attached The nature of this is orientation dependent. Take you back to an example that we had in an earlier tutorial that I promised to explain. So the curious feature was that these protons are all the way up at 9.5-9.6 ppm, which is an unusually high shift for a pair of aromatic protons. And although it's much less obvious from the shift, the signal is actually also an anomalous and they're caused by the same phenomenon. So they come from this molecule. Perhaps the shift is less surprising when you see this its a cationic, double nitrated, heterocycle So you would expect the shifts to be fairly downfield.

What I want to draw your attention to, however, is that you would expect the most electron poor positions to be the ortho to the nitro group. Here. In fact, those signals are Here.

You can see those are doublets of doublets. Now in reality, these signals, which are the ones in the back of the ring system are significantly downfield, despite not being in the more activated position with regard to the nitro group. So this is despite being in the meta position where they're not conjugated with the nitro group. So what's the explanation for this? Well, is caused by pi system overlap. Each of these protons is experiencing some of the adjacent pi system from the rest of this ring system. And that is was reinforcing the shielding effect of the aromatic system. And they're pushed down to these very high chemical shifts. And I said this proton is also anomalous, and I think that's more obvious when you look at the structure. Again, this one is ortho, it is conjugated directly to our nitro group. And you wouldn't necessarily expect it's electronics to be terribly different. This proton here, which is also a narrow doublets of doublets, we can see it's all the way here. But in fact, it a full, almost a full one ppm, downfield of this signal. What's making that difference? Well, this is also a pi system overlap. And what's happening here is that this ring is, this attach string here, is differently orientated and they can see this better when you look at the model. So if we look first for the two downfield protons, I mentioned, here the two Greens, you can see they are rigid and held in position and they're being affected by the larger pi system in the ring. If we look by contrast, at this proton here, we can see that a is actually orientated to interact with the centre of this pi system due to this being perpendicular to the main ring plane. And this therefore has a shielding effect and actually pushes the signal quite significantly upfield. Okay. Sometimes things which are far away do couple to one another. We've given you as an approximation that you are, for hydrogens, looking at 2 and 3 bond relationships really. Now, you're already familiar with the idea that there are exceptions to that rule. Aromatics, you usually see meta couplings if present. Sometimes we even see para coupling. Those are 4 and 5 bond couplings respectively. And this has to do with how good the overlap between the bonds in-between are, to allow those two spins to influence one another. And so you tend to observe longer range couplings in bridged systems that have good overlap. And in particular that are specific geometries that accommodate this, and the most important is the W coupling. And you can see a meta coupling as being an example of this in fact.

We have four bonds And we have a W shape. And it's a rigid system. And this holds all of these bonds in the correct orientation for the orbital overlap, which allows these two spins to influence one another. Now, the same overlap can be seen in allylic systems. And the different U-shaped overlap is sometimes seen in homoallylic systems. This is less common than a W shaped coupling, but it's still sometimes observed. And even without a conjugated system, if your ring geometry is rigid enough, as in the case of this bicyclic system here, you can see the W shape geometry. And actually you can see a reasonably sizable coupling between these two protons. So to give you a personal example, This is a thiazoline, which I've made many times. And you would not expect the red and green protons to couple, for the red proton you'd expect what would be a doublet of doublets, and may appear as a triplet depending on the sizes of the Couplings. However, if you build a model of this, you can see that your ring system is actually very rigid, You have this short double bond here. Actually this holds the geometry between the proton, which is locked in its position and the methyl group which can spin around this axis only quite firmly together. And if we go over here, we can actually see, see if you tilt the protons, its less obvious the shape of the ring, But it's a little bit clearer perhaps if you find the bonded sulfur here that we have a W shaped coupling, and in fact the signal that you observe here looks a lot like a triplet of quartets So those are not something you'll see in every molecule, but seeing some kind of slightly longer range proton-proton coupling, four bonds occasionally five, is not that rare. It is something you will come across. Something that's quite a lot

rarer, I just wanted to raise briefly is the idea of through space coupling. And I know this makes no sense according to everything you've previously been told about needing bonding interactions in order to transmit the interaction between nuclear spins. Even so it, it does occasionally happen, usually at happens with heteroatoms, in the examples I'm aware of involve fluorine. So here it is a classic literature example. And these two ring systems are held at a slight angle to one another. That means the system is rigid and hydrogen and the fluorine are in relatively close contact. And this means that you can actually get coupling these two atoms through space. If it was mediated by bonding, this would be a seven bond interaction. But it isn't - you'd be able to see it from the carbon coupling. And I also have a personal example where I think I observed this. Again. You can see that it's related to some of my other previous work. And here it is possible to see a splitting for interaction of the fluorine with this hydrogen and this carbon, but not for this carbon here. So I just wants to take a moment to show you a real life example of this longer range coupling. So here is compound I mentioned.

here are the two relevant signals. So this is the proton and you can see in this case it has identical couplings to these two. And that is the two 9.3 hertz couplings here. And then it further couples to this methyl group. And that gives rise to a quartet You can see quite clearly and it as a J value of 1.7. And this is mirrored if you then go look at the methyl signal in a doublet, that has a J of 1.7. So this is an example of a long range coupling. I just want to finish off with some brief mention of quadrupolar coupling. So we have so far assumed that only spin 1/2 nuclei are ever relevant. And basically I want you to keep assuming this for the most part. Thankfully, for medicinal chemists, this is almost always true. And the reason for this is a lot of the isotopes we have to deal with are spin 1/2, inactive or not visible under common NMR settings. So oxygen and the major sulfur isotope, are inactive, hydrogen, fluorine, phosphorous, silicon the less abundant carbon-13 are all spin half. The likes of the halogens are quadrupolar, but you don't see them. There are however, a few cases where quadrupolar nuclei, do matter. And a major one, possibly the major one, is boron 11. It's about 80% of boron and actually boron 10 is also NMR active. But these will be smaller there's less and you're less likely see them. Now being spin 3/2 means instead of plus a half, minus a half, you have plus three over two, plus one over two, minus one over two, and minus three over two lines. And this gives you a 1:1:1:1 quartet. As it happens, this is taken from a boron hydrogen example. But your carbon coupling will be relevant to a lot more often. Actually, a typical example of what you'd see is this phenyl boronic acid we use quite a lot of boronic acids for Suzuki couplings. And actually the effect between splitting signal four ways and broadening it is to make it much smaller. And since carbon 13 is low abundance and signal to noise is not usually that good anyway, in practice, you generally won't see the carbon to which your boron nucleus is attached. And here's just an example of that, where the red is the simulated spectra of the phenyl boronic acid. And the black is a real spectra. And you can see that there is a carbon signal missing, and this is the one that would be attached to the boron. Okay. So the last example, nitrogen 14, which is very high abundance, and obviously nitrogen is a nucleus we use lot, is actually spin one. However, it is not normally visible. Normally we can't see any couplings from it. However, in the case of ammonium salts is occasionally possible to see this interaction. between hydrogen and nitrogen, being spin one plus 1, 0 minus one, will give you a 1:1:1 triplet. So this is just something to watch for with ammonium salts. And if you're not prepared for it, it will look very strange indeed. So I just thought I'd pointed out. incidentally, if this signal looks familiar, this is also the origin of that 1:1:1 triplet to one triplet in your chloroform solvent peak, which is from deuterium, which is also spin one. Ok.

Ok. So coming to the end of this, I just wanted to take a moment to talk about what the procedure is when you see something odd in your NMR. And this is relevant for the various weird things i am pointing out to you today. But it's also relevant to rotamers and second-order effects we've talked about in other tutorials. If you

don't understand something that's happening in your NMR and you suspect something unusual is going on I would suggest the first thing to do is just to try running it in a different solvent. see if what you're observing changes and if you can make any sense of those changes. However, if that doesn't clarify the issue, then I would suggest first, get your compound absolutely pure and get good data on it. You should bounce what you're seeing off experienced colleagues, You should always check your data against other analytical techniques. What do you see on TLC? What's the LCMS trace and mass look like, can your IR spectra tell you anything? Does the MS or even the high resolution MS. Agreeed with you having the correct compound? So look for consistency there with your expected structure or indeed the structure that you're postulating for your unexpected NMR. I think it's important to define exactly what you think is happening. And of course use the literature, compare it to related structures, if necessary, even do some measurements from calculation. There is a reasonable amount of quite powerful NMR prediction software out there. And once you have a good idea of what you think is happening, try and work out how to test it. What can you do to your NMR experiment? That will tell you if you are correct. I just want to caution about how not to use this information, because it's very tempting when you have lots of bits and pieces of information like this to use it to produce kind of vague explanations for things that don't make sense in your NMR data. And I just want to caution you that these are unusual phenomenon, some previously observed things like second-order events, and rotamers are more common. But even so, the most common explanation for an NMR spectra that looks impure, is a sample that is in fact impure. So you need to be careful in explaining away problems with your spectra. So I hope that was useful to you and let me know if you have any questions or want further information.