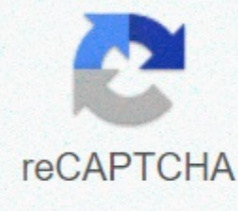




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# Base catalyzed acetal formation mechanism

Chapter 17: Aldehydes and Ketones. Nucleophilic Addition to C=O Reactions of Alcohols to give Acetals

hemi-acetal

acetal Reaction type: Nucleophilic Addition then nucleophilic substitution Summary Typical reagents : excess ROH, catalytic p-toluenesulfonic

acid (often written as TsOH) in refluxing benzene. Aldehydes and ketones react with two moles of an alcohol to give 1,1-geminal diethers more commonly known as acetals. The term "acetal" used to be restricted to systems derived from aldehydes and the term "ketal" applied to those from ketones, but chemists now use acetal to describe both. Acetals are biologically important due to their role in the chemistry of carbohydrates. Acetals are important chemically due to their role as "protecting groups" The equilibrium is shifted towards the acetal by using an excess of the alcohol and/or removing water as it forms. It is also possible to use 1,2- or 1,3-diols to form cyclic acetals, two common examples are shown below: Acetals can be readily converted back to the aldehyde or ketone by heating with aqueous acid. The mechanism for this is the reverse of that shown below for acetal formation. Study Tip: The important "piece" of an acetal is the central C which becomes the C of the carbonyl C=O. It can be recognised by looking for the C that is attached to two O atoms by single bonds. Related Reactions Formation of Hydrates Synthesis of Esters MECHANISM FOR THE ACID CATALYSED FORMATION OF ACETALS Step 1: An acid/base reaction. Since there is only a weak nucleophile we need to activate the carbonyl by protonating on O. Step 2: The nucleophilic O in the alcohol attacks the electrophilic C in the C=O, breaking the  $\pi$  bond and giving the electrons to the positive O. Step 3: An acid/base reaction. Deprotonation of the alcoholic oxonium ion neutralises the charge giving the hemiacetal. Now we need to substitute the -OH by -OEt. Step 4: An acid/base reaction. In order for the -OH to leave we need to make it into a better leaving group by protonation. Step 5: Using the electrons from the other O, the leaving group departure is facilitated. Step 6: We now have what resembles a protonated ketone (compare with step 2). The nucleophilic O of the alcohol attacks the electrophilic C and the electrons of the  $\pi$  bond move to neutralise the charge on the positive O. Step 7: An acid/base reaction. Deprotonation of the alcoholic oxonium neutralises the charge and produces the acetal product and regenerates the acid catalyst. © Dr. Ian Hunt, Department of Chemistry @misc{tibatv.19411, title={Lecture 07. Acid-Catalyzed Formation of Hydrates, Hemiacetals, & Acetals.}, author={Nowick, James}, howpublished={University of California Irvine \{UCI\}}, year={2012}, note={\{Last accessed: 05 May 2021\}}, } TY - VIDEO TI - Lecture 07. Acid-Catalyzed Formation of Hydrates, Hemiacetals, & Acetals. AU - Nowick, James PB - University of California Irvine (UCI) PY - 2012 VL - 7 DO - 10.5446/19411 UR - ER - Nowick, James: Lecture 07. Acid-Catalyzed Formation of Hydrates, Hemiacetals, & Acetals., episode 7, Chemistry 51C: Organic Chemistry (Spring 2012). Last time I left you with a problem, "what is the mechanism for the base catalyzed addition of water to a carbonyl group?" Let's go through that and see how it goes. First let's check out the electronic structure of the OH-. If we find unshared pairs we can say that the OH- is a Lewis base and a nucleophile. That would tell us that an electron pair is ready to be used to make a new bond. Then we have the question of where that bond will go. In the carbonyl group, we know that the carbon is the more positive end of the C=O dipole, so let's try to make our new bond there. This seems to be the right place to make the bond, but if we do that, the carbonyl carbon has five bonds (\*). That means ten electrons in the valence shell, so it doesn't happen. We must find a way to reduce the number of bonds to four. We can think back to the mechanism we worked out for the acid catalyzed addition of water. In that mechanism we broke the pi bond by using its electrons to make a new bond to H+. Let's look into the possibility that the C=O pi bond breaks as the C-O sigma bond forms. After all, the electrons in the pi bond are farther from the nuclei than those in a sigma bond, so they should be easier to push around. Another way to say this is that the pi bond is weaker than the sigma bond, so it takes less energy to break it. The energy required to break the pi bond comes from making the new sigma bond to the OH-. (In the acid catalyzed case, the new bond which is being formed is the bond between the carbonyl oxygen and the H+. Breaking old bonds is usually assisted by the formation of new bonds. We finish this mechanism by making the only bond which is left to do, the O-H bond. Here again, the breaking of one bond is assisted by the formation of another bond. Also, this mechanism makes a new OH- to replace the one which was used in the first step, consistent with the observation that the reaction is base catalyzed, which means that the OH- is not used up. Now let's use what we know about the acid catalyzed addition of water to make a prediction of what will happen when we mix an aldehyde with an alcohol and add a drop or two of an acid catalyst. We want to use our mechanism to predict the structure of the product. Recall the mechanism of acid-catalyzed addition of water If we follow closely the bonding changes that happen around the water oxygen, we notice that one of the hydrogens always stays attached. That bond doesn't break. That bond could just as well be a C-O bond as is the situation in an alcohol. What would happen if we just replaced water by methanol in the mechanism for acid-catalyzed hydration? Indeed, the same mechanism seems to work just fine. The OH group in methanol is a nucleophile just like the OH group in water. Another way to say this is that the functional group of water is the same as the functional group of any alcohol, an OH group. If we learn a reaction for one alcohol, it will work very much the same way for any other alcohol - often including water as the smallest possible alcohol. When we do the experiment to test our prediction, we find that yes, the product we have predicted is formed. But, we also find another product, one which hadn't been predicted. (The new product is called an hemiacetal.) Since the hemiacetal seems to be about halfway to the acetal, we'll explore converting the hemiacetal into the acetal. If we look closely at the differences between these two products, we see that to do this, we need to replace the OH group of the hemiacetal with the OCH3 group of the acetal. (We can rule out the seemingly simpler alternative of replacing the H with the CH3 because isotopic labelling experiments show that the O-CH3 bond is not broken and the bond between the central carbon and the OH oxygen is broken.) This reaction is also acid catalyzed, so we may begin by making a bond between H+ and the OH oxygen, using the Lewis base electrons of the oxygen (electron pairs are often symbolized by bars). In the next step the bond between the central carbon and the oxygen we have just broken is broken. This produces water and leaves the central carbon atom with only three bonds and a vacancy in its valence shell. A formal charge calculation tells us that this atom is also positively charged, but it is the electron pair vacancy which is more important. The central atom is consequently an electrophile, open to making a bond with a nucleophile. The nucleophile is the oxygen of another molecule of methanol, whose unshared electron pair becomes the new carbon oxygen bond. It remains to break the bond between the hydrogen and the positively charged oxygen which produces the acetal and replaces the H+ to regenerate the catalyst. Just to have the whole process in one place, here's the full mechanism from the aldehyde through the hemiacetal to the acetal: There are a couple of general ideas we can extract from what we did in working out this mechanism. Charge and Reactivity: Let's contrast two positively charged molecules we found in this mechanism, one with three bonds to oxygen and one with three bonds to carbon. Both molecules are positively charged, and formal charge calculations tell us where that charge is. But there is an important difference in their structures and that difference makes an important difference in their reactions. The positively charged cation (we call it a carbocation) with three bonds has only six electrons in its valence shell. It is an electrophile. It makes a fourth bond using electrons from a nucleophile (the methanol oxygen atom here). The positively charged oxygen (we call it an oxonium ion) has three bonds and an unshared pair. It has a complete octet in its valence shell. It needs no more electrons so it makes no more bonds. It is not an electrophile. Its reaction is to break a bond, keeping the electrons, by dropping off an H+. This distinction is important. The charge alone does not tell us what to expect. It does provide a means of determining whether a positively charged atom has a vacancy or not. From that we can decide whether a such an atom is an electrophile -- ready to accept electrons to make a bond -- or not. ROH as Nucleophile: Notice that whenever we used an alcohol (general formula, ROH) as a nucleophile, the order of the steps was: Reaction of the unshared pair on oxygen to form a new covalent bond. The oxygen gets a positive charge. Then an H+ is lost from the positively charged oxygen (oxonium ion). Students often wonder why we don't reverse the order so that the H+ comes off first to make RO-, which would then act as the nucleophile. This does not happen because the reaction is occurring in an acidic solution. A strong base like RO- (about as basic as OH-) would be immediately consumed by reaction with the acid and would not survive. The alcohol (weaker base, about as basic as water) is the solvent, so there are many alcohol molecules surrounding the carbocation. This makes its reaction with an alcohol rather than RO- (called an alkoxide ion) very likely. Intermediates: The aldehyde, the methanol, the hemiacetal, and the acetal are all stable molecules. They can be isolated and studied over a period of time. All the other molecules in this mechanism are much less stable. They have relatively high energies and thus short lifetimes. When they are formed, they react quickly. The main clue to this in their structures is that they have unusual bonding patterns such as three bonds to carbon (with a positive charge) instead of four, or three bonds to oxygen instead of two. Such molecules are called reactive intermediates; reactive because their unusual bonding pattern suggest that a change in bonding will happen, and intermediates because they appear between the reactants and the products. To finish up, let's return to one of our carbocation intermediates. Recall that we began thinking about acid catalyzed reactions of aldehydes by using a C-O pi bond to supply the electrons to make a new bond with H+. There is an alternative. We could also think about using one of the unshared electron pairs on the oxygen atom. Let's compare the two molecules we obtain in this way. Notice first that the "connectivity" of these two structures is identical. That is, each atom is connected to exactly the same atoms in one structure as it is in the other. Then, notice that the only difference is in the location of an electron pair. On the left, an electron pair is shown as unshared on the oxygen. On the right, that pair is shown as making a pi bond. When two (or more) structures differ only in the location of electrons, without changing which atoms are bonded to which other atoms, those structures are different ways of describing a single molecule. The symbols differ, but there is only one molecule being described. The notation for this is to connect the two structures by a double headed arrow, which does not imply equilibrium. (We can use the curved arrow symbol to keep track of the formal electron motions.) This situation is called resonance. When resonance is involved the real structure (called a resonance hybrid) is more stable than any of the formal (called contributing) structures we might draw. This is called resonance stabilization. Often, I will only draw one structure and expect that you will recognize that resonance is involved and know what other structures might be included in describing the resonance hybrid. The structure presented will be the one which most directly connects to the reaction being described. We will use resonance many more times during the semester, so there will be many opportunities to clarify your understanding. Contributors Kirk McMichael (Washington State University)

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