

4.24 Acyl Transfer Reactions - 1

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- Lecture 24 recap.
 1. Carboxylic acid derivatives.
 - Substances of the form in Figure 4.2, where $X \neq H, R$.
 2. Synthesis of RCO_2H .
 - Carboxylic acids (Figure 4.3): $pK_a \approx 5$.
 - Oxidation of (primary) alcohols and aldehydes (Figure 4.6).
 - Carboxylation of Grignard reagents (Figure 4.7).
 - Hydrolysis of nitriles (Figure 4.8).
 3. Acyl transfer reaction.
 - Reactivity decreases from acid chlorides > acid anhydrides > esters > amides > carboxylates.
 - Remember that carboxylates are anions.
 - See Table 4.1 and Figure 4.20.
- Before we begin in earnest, let's build a bit more off of this idea of reactivity differences in carboxylic acid derivatives.

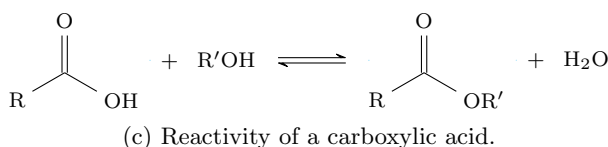
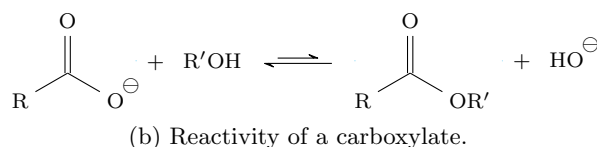
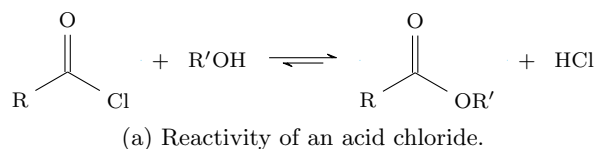


Figure 4.21: Reactivity of carboxylic acid derivatives toward esterification.

- Measures of reactivity tell us if a given acyl transfer reactions will be thermodynamically favorable, thermodynamically unfavorable, or thermoneutral.
 - Like any thermodynamically favorable reaction, thermodynamically favorable acyl transfer reactions are characterized by high energy reactants becoming low energy products and vice versa for a thermodynamically unfavorable reaction.
 - In a thermoneutral reaction ($K_{eq} \approx 1$), the reactants and products have similar energies.
- Examples.
 - Figure 4.21a: Very favorable because acid chlorides are much more reactive than esters.
 - Figure 4.21b: Very unfavorable because carboxylates are much more stable.
 - Figure 4.21c: Thermoneutral because carboxylic acids and esters have similar reactivity.
- Today: Types of acyl transfer reactions.

- Lecture outline.
 3. Acyl transfer reactions.
 - a. Background.
 - b. Reactions of acid chlorides.
 - c. Reactions of esters.
 - i. Hydrolysis.
 - ii. Transesterification.
 - iii. Amide formation.
 - d. Reactions of carboxylic acids.
 - i. Fischer esterification.
 - ii. Basic esterification (not possible).
 - iii. Formation of acid chlorides.
 - e. Reactions of amides.
 - i. Acid-catalyzed hydrolysis.
 - ii. Base-catalyzed hydrolysis.
- We begin by resuming Subtopic 3.a: Background.
- The mechanism of an acyl transfer reaction.

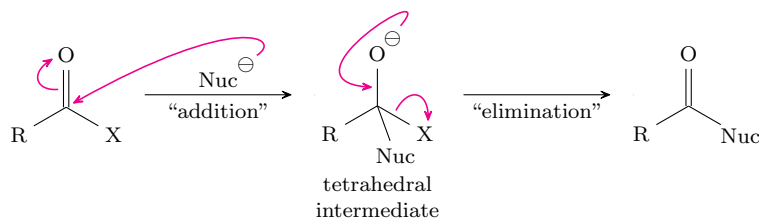


Figure 4.22: Mechanism of a (neutral) acyl transfer reaction.

- Almost always addition-elimination, not direct displacement.^[5]
- First step: Addition.
 - The nucleophile adds in to the electrophilic site.
 - This gives us a **tetrahedral intermediate**, so named because of its tetrahedral carbon.
- Second step: Elimination.
 - The best leaving group leaves.
 - There can be equilibria between which group leaves, but we won't consider those details right now.
- We now move onto subtopic 3.b: Reactions of acid chlorides.

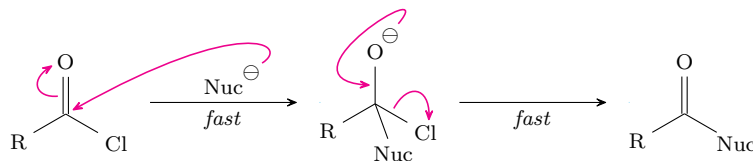


Figure 4.23: Mechanism of an acyl transfer reaction with an acid chloride.

⁵Think about the molecular orbital reasons for why! Nucleophile donation into the C=O π^* -orbital (at the Bürgi-Dunitz angle) *forces* the C=O π -bond to break as the new C–Nuc σ -bond is formed, with the former C=O π -electrons migrating to become a lone pair on the more electronegative atom (oxygen).

- The addition step is fast in this case because the acid chloride is the least resonance stabilized of the carboxylic acid derivatives we've considered.
 - This is because the chlorine atom is a really bad π -donor; there is a large energy mismatch between the n_{Cl} and $\pi_{\text{C=O}}^*$ MOs.
- The elimination step is also fast because Cl^- is a great leaving group.
 - We know that Cl^- is a great leaving group because $\text{p}K_{\text{a}}(\text{HCl}) = -7$ (see Table 4.1), meaning that the conjugate base (Cl^-) is weak.
 - When the conjugate base is weaker, it's a better leaving group.
- Thus, overall, acid chlorides are very reactive and no catalyst is needed for their acyl transfer reactions.
- Aside: Like acid chlorides, acid anhydrides are very reactive and also don't need a catalyst to participate in an acyl transfer reaction.
- Example acyl transfer reaction of an acid chloride: Forming an ester.

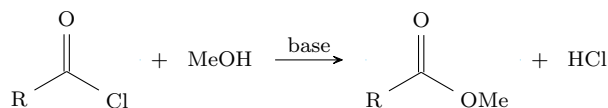


Figure 4.24: Acyl transfer: Acid chloride to ester.

- This is a very vigorous reaction: Lots of bubbling, flask gets really hot, releases a white cloud of caustic gas (HCl).
- As such, you usually add a base to solution.
 - The base is not necessary for the reaction to work, but rather for us to be alive.
 - Indeed, the base neutralizes the acid as it's formed, making a salt: $\text{B} + \text{HCl} \longrightarrow \text{HB}^+ \text{Cl}^-$.
- Typical bases: Et_3N or pyridine.
- Example acyl transfer reaction of an acid chloride: Forming an amide.

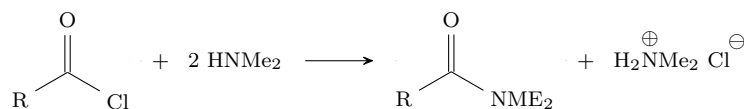


Figure 4.25: Acyl transfer: Acid chloride to amide.

- This reaction forms an amide.
 - Recall from Figure 4.20 that amides are very stable.
- We do not need an additional base this time because the amine already acts as one!
 - Indeed, a *second* equivalent of the amine forms a salt at the end of the reaction, again preventing us from dying.
- Do we need two equivalents of HNMe_2 ?
 - If you have a valuable amine, maybe add in Et_3N as a second base because it will do basically the same thing.
- We now move onto Subtopic 3.c: Reactions of esters.
 - Three ester reactions to consider: **Hydrolysis**, **transesterification**, and **amide formation**.

- We now discuss Subtopic 3.c.i: Hydrolysis of esters.
- Let's first consider the energetics of the overall reaction.

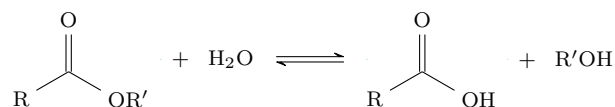


Figure 4.26: Acyl transfer: Ester hydrolysis.

- Esters are not great electrophiles, and water is not a great nucleophile.
 - Thus, the general addition-elimination mechanism (Figure 4.22) will proceed very slowly here.
- Additionally, the reaction is thermoneutral overall ($K_{\text{eq}} \approx 1$), so we'll get a 50 : 50 mixture of reactants and products under many experimental setups.
- So how do we get the reaction to proceed? Two ways:
 - Use an acid to make the ester a better electrophile.
 - Use a base to make water a better nucleophile.
- Acid-catalyzed mechanism.

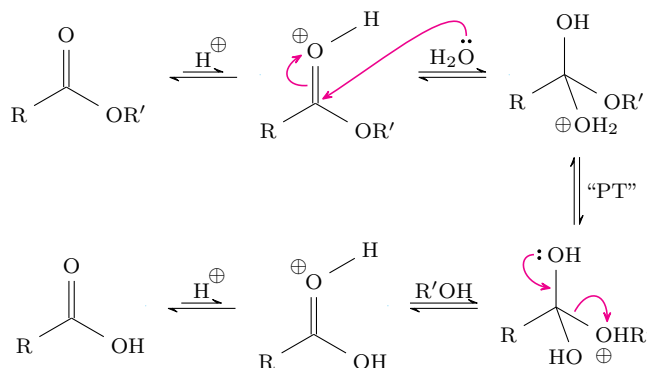


Figure 4.27: Ester hydrolysis mechanism (acid-catalyzed).

- First step: We get a small quantity of protonated, activated ester that is a much better electrophile.
- Second step: Now that we have a much better electrophile, water can add in.
- Third step: Proton transfer (PT), likely intermolecular and possibly stepwise.
- Fourth step: Elimination.
- Fifth step: Deprotonation.
- Observe that we have only drawn positively charged intermediates.
 - If we're in acidic solution, we should not draw any anionic intermediates!
 - This is because anions will immediately be protonated, stopping the reaction there.
- Since acid adds in at the beginning and leaves at the end, this mechanism is *catalytic* in acid.
- Basic mechanism.

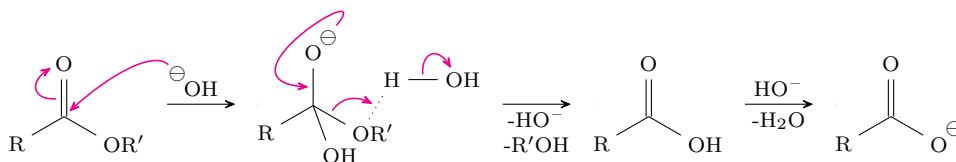


Figure 4.28: Ester hydrolysis mechanism (basic).

- This is much more similar to the general mechanism (Figure 4.22): The starting material undergoes addition by hydroxide, followed by subsequent elimination.^[6]
 - However, a final deprotonation step will make the *carboxylate* the major product, not the carboxylic acid.
 - If we want the carboxylic acid, we can recover that with a water workup.
- Problem: RO^- is a bad leaving group (see Table 4.1).
 - Solution: In aqueous media, RO^- will be a slightly better leaving group due to hydrogen bonding with water.
 - This spreads out and stabilizes its negative charge, and also provides a nearby proton donor.
- Since carboxylates are the most stable carboxylic acid derivative we've considered (see Figure 4.20), this *is* a thermodynamically favorable pathway.
- Observe that analogously to Figure 4.27, we have only drawn *negatively* charged intermediates.
 - This is again because cations should not be formed in basic solution.
- Since one equivalent of base is used in this mechanism, it is *not* catalytic in base.
 - We may think of this pathway as *base-accelerated* if we prefer.
- We now discuss Subtopic 3.c.ii: Transesterification.
- Let's first consider the energetics of the overall reaction.

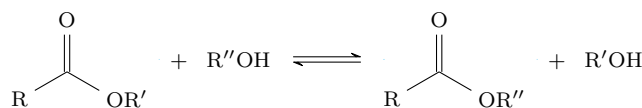


Figure 4.29: Acyl transfer: Transesterification.

- This reaction involves taking one ester and going to another ester.
- Usually, $K_{\text{eq}} \approx 1$ and the reaction is not very fast, so we use catalysis again.
- Acid-catalyzed mechanism.

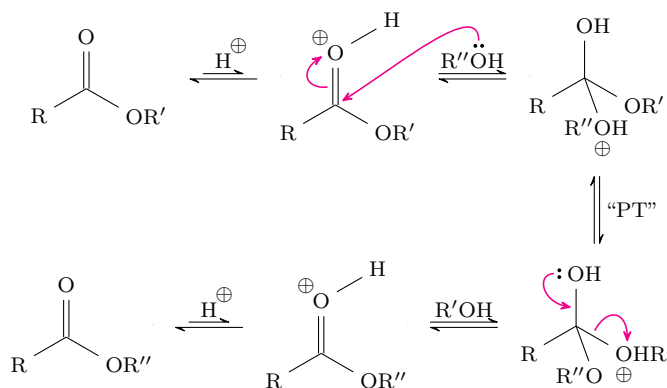


Figure 4.30: Transesterification mechanism (acid-catalyzed).

- Mostly the same as Figure 4.27.
- Proton transfer is thermoneutral, so we'll get a mixture of the final product and the pre-PT intermediate.

⁶A good way of introducing hydroxide base is with NaOH.

- Two methods to drive the acid-catalyzed mechanism in the forward direction.

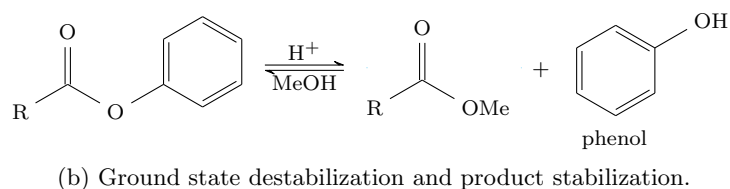
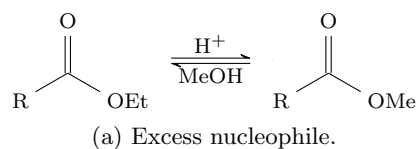


Figure 4.31: Driving the transesterification equilibrium.

- Use R''OH as the solvent.
 - Example: If we want to change an ethyl ester into a methyl ester, use methanol (MeOH) as the solvent instead of just as the nucleophile (Figure 4.31a).
- Destabilize the reactants and stabilize the products.
 - Example: Use a phenyl ester (Figure 4.31b).
 - The phenyl ester is more electrophilic than, for example, a methyl ester. This is because the n_{O} lone pair can now donate into the aromatic ring as well, lowering its electron density near the carbonyl carbon.
 - Additionally, phenol is a very stable byproduct (again, due to resonance delocalization of its lone pair).
 - Phenol was the horrible smell of paste used in nursery schools.
- Base-accelerated conditions.

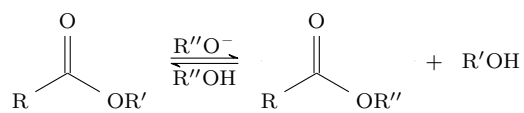


Figure 4.32: Transesterification (basic).

- The mechanism is analogous to Figure 4.28.^[7]
- We now discuss Subtopic 3.c.iii: Amide formation from esters.

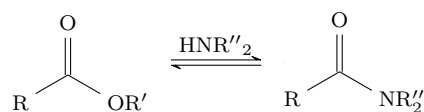


Figure 4.33: Acyl transfer: Ester to amide.

- The mechanism is also analogous to Figure 4.28, and we don't need base because HNR_2 is one!
- This reaction is driven forward by the greater resonance stabilization of amides relative to esters (see Figure 4.20).

⁷A good way of introducing alkoxide base is with NaOR.

- We now move onto Subtopic 3.d: Reactions of carboxylic acids.
- We'll begin with Subtopic 3.d.i: The Fischer esterification.

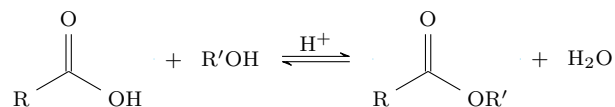


Figure 4.34: Fischer esterification.

- Combine a carboxylic acid and an alcohol under acidic conditions.
- Again, $K_{\text{eq}} \approx 1$.
- However, we can drive the reaction forward by removal of water (either by distillation or drying agents).
- We now discuss Subtopic 3.d.ii: Why basic esterification isn't possible.
- Under basic conditions, the first thing that happens will be an acid-base reaction between the carboxylic acid and whatever base we've added to solution.

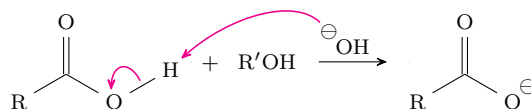


Figure 4.35: Side reaction under “basic esterification” conditions.

- This will produce a carboxylate, which (recall from Figure 4.20) is a *terrible* electrophile with a *terrible* leaving group.
- As such, we *cannot* do basic esterification of carboxylic acids!
- So what do we do if we want to convert a carboxylic acid into an ester but can't use acidic conditions, perhaps because there are other functional groups in our molecule that would react with acid?
- The answer lies in Subtopic 3.d.iii: Formation of acid chlorides.

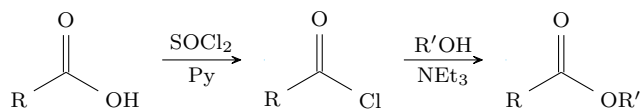


Figure 4.36: Acyl transfer: Carboxylic acid to ester.

- Essentially, we back off and run the reaction in two steps: A review reaction from 5.12 followed by Figure 4.24.
- Note that Py stands for pyridine.
- We now move onto Subtopic 3.e: Reactions of amides.
- Recall that amide-bond formation is an incredibly useful driving force in other reactions (e.g., see Figures 4.25 & 4.33).
 - As such, amides are very stable, and we might not expect them to do much.
 - Regardless, however, they hydrolyse to the carboxylic acid under acidic conditions.

- Let's first consider the energetics of the overall reaction.

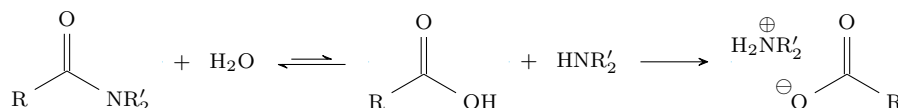


Figure 4.37: Acyl transfer: Amide hydrolysis.

- As stated above, it seems unlikely that a stable SM would become a less stable product.
 - Indeed, the first step has $K_{\text{eq}} < 1$.
- However, we get a subsequent acid-base reaction between the carboxylic acid and amine base.
 - This forms $\text{H}_2\text{NR}'_2^+ \text{RCOO}^-$ (a salt), taking the reaction to near completion.
- This process is called **linking** steps!
- Linked** (steps): A phenomena in which a disfavored reaction step is coupled to an irreversible reaction step to drive product formation.
- We now discuss Subtopic 3.e.i: Acid-catalyzed hydrolysis.

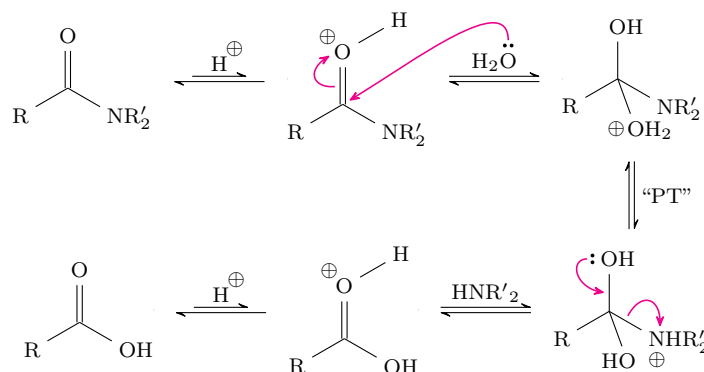


Figure 4.38: Amide hydrolysis mechanism (acid-catalyzed).

- Acid catalysis is needed because, per Figure 4.20, amides are very poor electrophiles.
 - Indeed, there is excellent $n_{\text{N}} \rightarrow \pi_{\text{C=O}}^*$ resonance.
- We protonate the carbonyl instead of the amide because the carbonyl has lone pairs not currently in resonance; if we protonate the amide nitrogen, the result no longer has resonance stabilization.
- Once we protonate/activate the carbonyl, the rest of the mechanism is analogous to Figure 4.27.
- We now discuss Subtopic 3.e.ii: Basic hydrolysis.

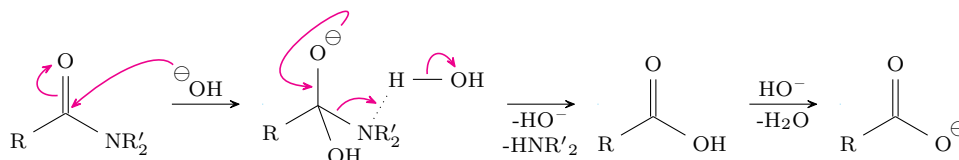


Figure 4.39: Amide hydrolysis mechanism (basic).

- Conundrum: Like with basic ester hydrolysis (see Figure 4.28), NR_2^- is a poor leaving group.
 - However, we can once again solve this issue with a hydrogen bond to water
- Under basic conditions, we can't form the salt in Figure 4.37, but we are still thermodynamically driven toward the more stable carboxylate (see Figure 4.20).

- Application to real-world chemistry: Wine.
- Carboxylic acids in wine.

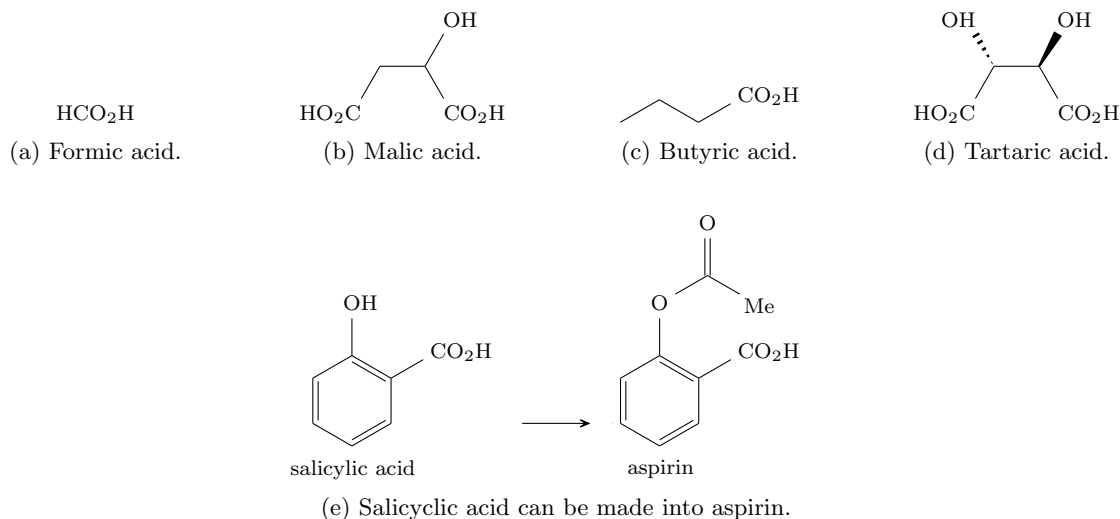


Figure 4.40: Wine contains carboxylic acids.

- Formic acid (Figure 4.40a): Used in the leather tanning industry.
- Malic acid (Figure 4.40b): An ingredient in dermatology products; a skin exfoliating agent.
- Butyric acid (Figure 4.40c): The smell in dirty gym socks.
- Salicylic acid (Figure 4.40e): No real connection to taste or smell, but it's a precursor in the synthesis of the pain medication, aspirin.
- You ever notice the crystalline material at the bottom of a wine glass?
 - It's just (2*R*,3*R*)-(+)-tartaric acid (Figure 4.40d)!
 - The potassium salt of tartaric acid (which contains the carboxylate, tartarate!) is more commonly known as cream of tartar and used in many baking recipes.
- Bonus: What does it mean to say that a bad-tasting wine is “corked?”

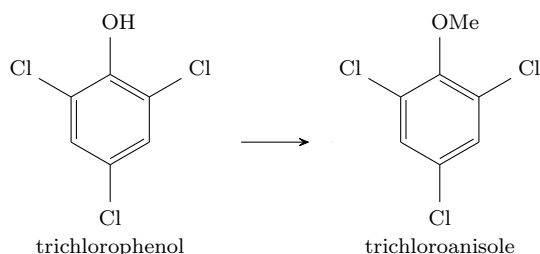


Figure 4.41: Wine can be “corked.”

- It means that the wine has too much trichloroanisole, a compound that smells and tastes bad.
- Trichloroanisole can be transferred to the wine from the cork.
 - Cork comes from a cork tree.
 - Humans spraying synthetic trichlorophenol insecticides onto trees led fungi to evolve and detoxify it by adding a methyl group.
 - Trichloroanisole is then good for the fungi, but tastes bad to us.