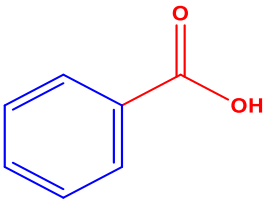
Benzoic acid is aromatic carboxylic acid having no substitution, with the following structural formula:



It had been used as preservative in cosmetics, food and pharmaceuticals because it has antimicrobial activity. *Sodium benzoate is often preferred over benzoic acid as preservative because of its greater water solubility.*

ROLE OF BENZOIC ACID IN ORGANIC PHARMACEUTICAL CHEMISTRY

A. BINDING ROLE OF CARBOXYLIC ACID GROUP IN DRUG DESIGN

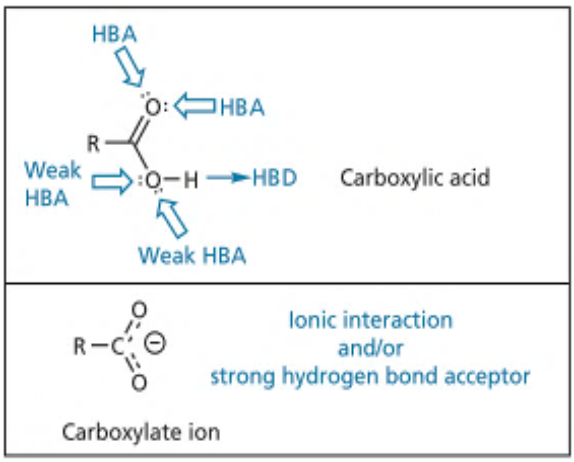
The carboxylic acid group is reasonably common in drugs:

1. *It can act as hydrogen bond acceptor or as a hydrogen bond donor*.
2. *It may exist as the carboxylate ion*. ***This allows for***

a. *The possibility of an ionic interaction*

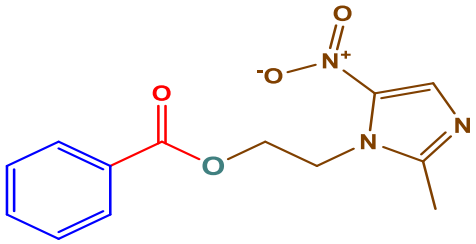
b. *Strong hydrogen bond where the carboxylate ion acts as the hydrogen bond acceptor*

c. *The carboxylate ion is also a good ligand for metal ion cofactors present in several enzymes, for example zinc metalloproteinases*



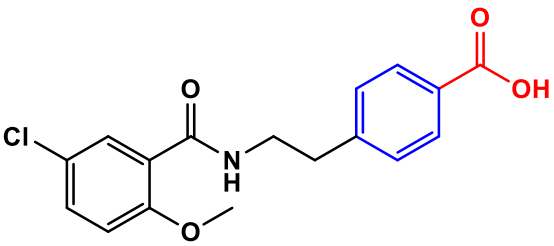
B. DRUG EXAMPLES

Metronidazole benzoate: *which is prodrug of metronidazole synthesized to mask the taste of metronidazole.*

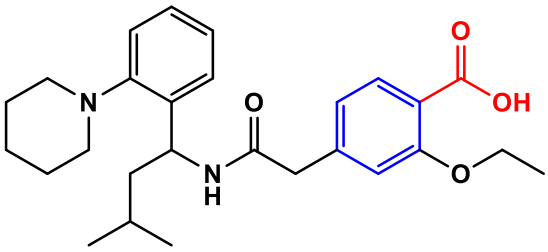


1. *How to be synthesized? (Mechanism).*
2. *Which type of prodrug is considered?*

Meglitinides*: *can be considered as benzoic acid derivatives



Meglitinide



Repaglinide

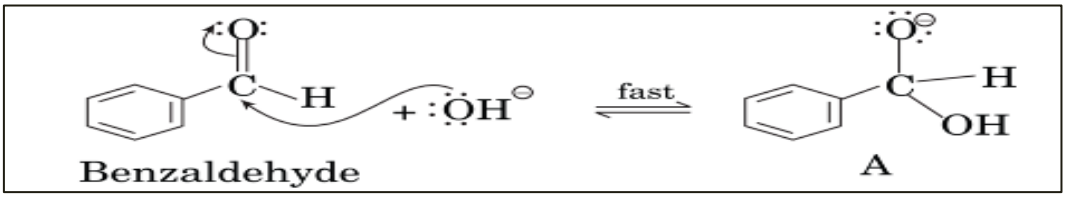
SYNTHESIS OF BENZOIC ACID

Of course there are many methods for synthesis of benzoic acid, but we like to talk about ***Cannizzaro Reaction*** as method for benzoic acid synthesis.

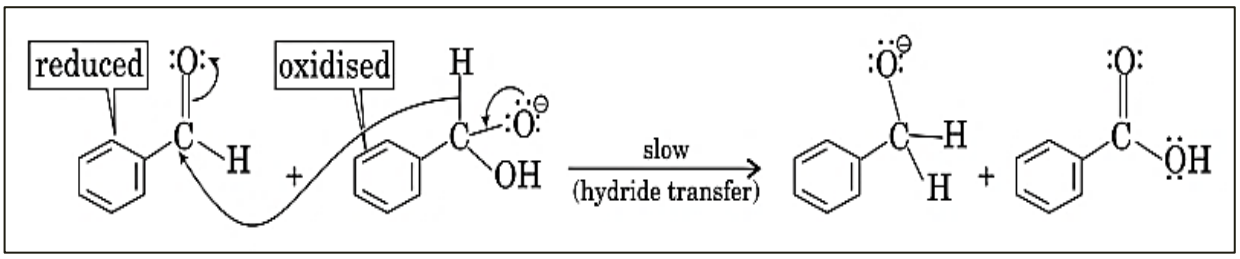
In Cannizzaro reaction two molecules of any non-enolizable aldehyde (does not contain α-hydrogen) will undergo ***self-oxidation-reduction*** **[*in which one molecule of the aldehyde gets reduced to the corresponding alcohol, while another molecule gets oxidized to the corresponding carboxylate ion*]**.

MECHANISM OF THE REACTION

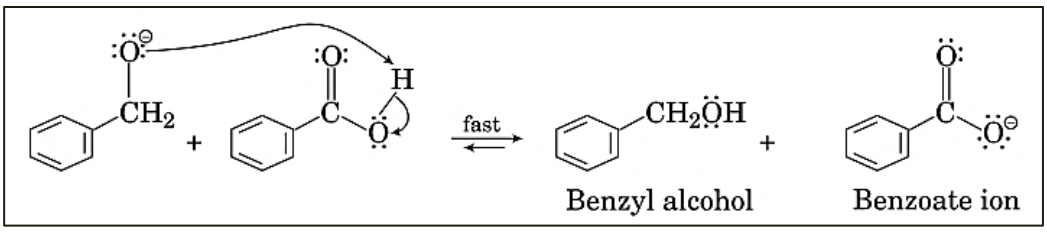
Step 1: ***Rapid reversible addition of hydroxide ion to the carbonyl carbon of benzaldehyde to yield the intermediate A*** [potential hydride donor].



Step 2: ***Slow transfer of a hydride ion from A to the electrophilic carbonyl carbon of another benzaldehyde molecule.***



Step 3: ***Rapid proton exchange between the carboxylic acid and the alkoxide ion to form the salt of the acid and a primary alcohol (a stable pair). A strong acid and a strong base reacts to produce a weak acid and a weak base.***



PROCEDURE

1. KOH **(61g)** was dissolved by **120ml** D.W in beaker and left to cool; **6ml** of this solution was placed in R.B.F.
2. While stirring; **4ml** of benzaldehyde was gradually added to the above solution.
3. The mixture was refluxed for **20 minutes**.

4. At the end of 20 minutes; the heating was switched off and the mixture was **cooled** and then **10-15ml** of water was added to dissolve the formed precipitate.
5. The solution is transferred to separatory funnel and extracted **2 times by 10ml** dichloromethane.
6. The aqueous layer was taken in beaker and acidified by conc. HCl **[dropwise added]** until white precipitate was **completely formed**.
7. The product was **filtered and dried** by drying oven.

QUESTIONS

1. How percentage of yield will be calculated???
2. What the organic layer will contain???