
IMPACT OF REACTIVITY AND FUNCTION OF CARBOXYLIC ACID AND ITS IMPORTANCE IN MEDICINES: A STUDY

Anjali Singh¹, Dr. V K Singh²

Department of Chemistry

^{1,2}Shri Venkateshwara University, Gajraula (Uttar Pradesh)

Abstract

The carboxylic acid compounds still may find important applications that cannot be fully covered in this research. We starting from food to medicine, from the human body to earth and environment, the production, destruction, absorption, or release of these compounds show a strong impact on all the processes/reactions that take place. As a final conclusion, this subject is an endless one, and the classes of compounds that contain the carboxyl functional group, along with all their derivatives, are inseparable from everything that life means on this earth. Carboxylic acids or organic acids are the compounds containing in the molecule the carboxyl functional group attached to the hydrocarbon radical. Different combinations of extracting and diluent with different compositions are used in the extraction of acids. Various models are developed and used to estimate the equilibrium parameters, stoichiometry of reactive extraction, and kinetic parameters. A theoretical study is also performed to predict the effect of diluent on the extraction equilibria of carboxylic acids.

1. OVERVIEW

The carboxylic acids widely used in the field of food and beverages as an acidulant, in pharmaceutical and chemical industries are important chemicals. Industrial production of carboxylic acids is carried out using the petrochemical feedstock. These acids are also produced by biotechnology based processes (fermentation processes), which uses renewable resources. The growing importance of biological production, expressed with new routes and increasing production rates, asks for adapted downstream processing for product separation. To make the fermentation route economically viable, it is necessary to develop novel fermentation processes that use highly efficient separation techniques. Separation of mono-carboxylic acids, such as formic-, acetic- and propionic acid from the aqueous waste stream is also important and essential from the industrial and environmental viewpoint.

Among various available alternatives (liquid extraction, ultrafiltration, reverse osmosis, electro-dialysis, direct distillation, liquid surfactant membrane extraction, anion exchange, precipitation, and adsorption etc.) for simultaneous removal of the product, extraction is often the most suitable



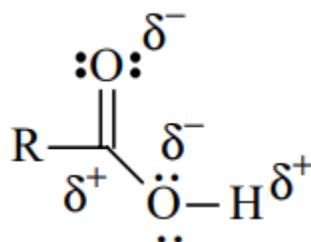
one. Reactive extraction with a chemical (solute and extractant reaction) phenomenon is developed to intensify the separation by solvent extraction. Organophosphorus-based and long-chain aliphatic amine-based extractants are useful for the separation of carboxylic acids from dilute aqueous solution. Generally, these extractants are dissolved in a diluent. It controls the viscosity and density of the solvent phase.

However, the chemical structure of diluent may also have various effects on the formation of acid-amine complexes. The literature related to the fermentation processes for the production of carboxylic acids and the reactive extraction for recovery of the carboxylic acids (lactic acid, citric acid, tartaric acid, acetic acid, and propionic acid, etc.) from fermentation broth and aqueous waste stream is extensively reviewed. These studies focus on various aspects such as solvent (extractant and diluent) selection, effects of temperature, pH, aqueous and organic phase compositions on extraction, in-situ product recovery, and chemical interactions involved in the complexation of acid with the extractant, kinetics of extraction, etc.

The use of active diluent (modifier) with inactive diluent in the extractants is limited. These reactive extraction data can also be utilized in the design of the extraction process for the separation of formic acid, acetic acid, propionic acid, and butyric acid from the aqueous waste industrial stream. The quantification of diluent effect by LSER model and a model based on μ & E T parameters is limited to a few carboxylic acids with the specific extractant. An evolutionary-based optimization routine [differential evolution (DE)] to estimate the equilibrium parameters is not explored. There are a lot of scopes to generate the reactive extraction data with less toxic or non-toxic amine/diluent systems for the intensification of propionic- and nicotinic acid production via fermentation route[1-6].

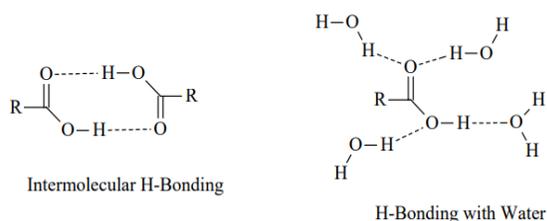
2. CARBOXYLIC ACID SOLUBILITY AND HYDROGEN BONDING

The carboxylic acid moiety is considered to be a highly polar organic functional group. This polarity results from the presence of a strongly polarized carbonyl (C=O) group and hydroxyl (O-H) group. Recall that oxygen is a relatively electronegative atom and when covalently bound to carbon and particularly hydrogen, a strong permanent dipole is created. In the case of carboxylic acids, the O-H group is even more strongly polarized than the O-H group of alcohols due to the presence of the adjacent carbonyl moiety. These structural features not only enhance dipole strength, but also are responsible for the acidity of these compounds as discussed later in this tutorial.

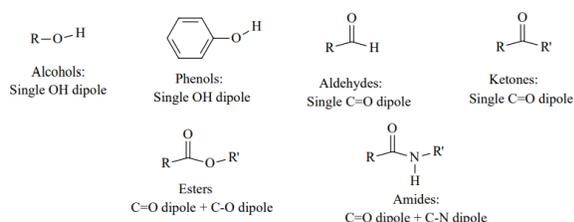


The dipolar nature of acids

The dipoles present in carboxylic acids allow these compounds to participate in energetically favorable hydrogen bonding (H-bonding) interactions with like molecules and water, functioning as both a H-bond donor and acceptor as shown below:



The total energy of H-bonding interactions for carboxylic acids is greater than that observed for other organic compounds containing OH and/or C=O dipoles such as amines, alcohols, phenols, aldehydes, ketones, esters, amides and isosteric compounds. Carboxylic acids have a greater number of dipoles and stronger dipoles than these other organic compounds, and thus can form more and stronger H-bonds with other substances capable of H-bonding interactions. The dipolar nature of these other organic functional groups is discussed in more detail in the appropriate Tutorials:



The energy associated with the dipoles present in carboxylic acids is directly reflected by physicochemical properties such as boiling points and water solubility. As indicated in the table below, carboxylic acids have relatively high boiling points. This is due to the high degree of relatively high energy intermolecular H-bonding interactions between acid molecules as shown in an earlier figure above.

RCOOH R =	Boiling Point (°C)	Water Solubility (g/100 mL)	Ethanol Solubility (g/100 mL)
H	101		
CH ₃ -	118		
CH ₃ CH ₂ -	141		
CH ₃ CH ₂ CH ₂ -	164		
CH ₃ CH ₂ CH ₂ CH ₂ -	187	3.7	Soluble
CH ₃ CH ₂ CH ₂ CH ₂ CH ₂ -	205	1.0	Soluble
C ₆ H ₅ -	250	0.34	Soluble
CH ₃ (CH ₂) ₈ -		0.015	Soluble
CH ₃ (CH ₂) ₁₀ -		Insoluble	100
CH ₃ (CH ₂) ₁₂ -		Insoluble	Soluble
CH ₃ (CH ₂) ₁₆ -		Insoluble	5.0

Table 1: Boiling Points and Solubility's of Carboxylic Acids

As a result of the high degree of intermolecular association between acids, these compounds have significantly higher boiling points than corresponding non-polar hydrocarbons of the alkane, alkene, alkyne and aromatic classes. They also have higher boiling points than other compounds with weaker or fewer dipoles such as amines, alcohols, phenols, aldehydes, ketones, esters, amides and isosteric compounds of corresponding hydrocarbon structure (similar number of carbon atoms).

Carboxylic Acid Acidity:

The most important chemical property of carboxylic acids in terms of drug chemistry is their acidic nature. Traditionally the term "acid" is reserved for those compounds that transfer protons measurably to water. The mineral acids (HCl, HBr, HI, H₂SO₄, and H₃PO₄) are defined as "strong acids" because they undergo complete dissociation, donating a proton to water to form the hydronium ion.

3. USES OF ALDEHYDES AND KETONES

What are the smallest ketone and simplest aldehyde? The simplest aldehyde is formaldehyde, and the smallest ketone is acetone. Aldehydes and ketones, in combination with other functional groups, are widely available in nature. There are many essential uses of aldehydes and ketones, and they form an inevitable part of many industrial processes.

Aldehydes and ketones are widespread, including plants, microorganisms, animals, and humans. Compounds of plants and microorganisms containing aldehydes and ketones include cinnamaldehyde in cinnamon bark, Citra in lemongrass, vanillin in vanilla bean, carvone in spearmint and caraway, helminthosporal- a fungal toxin, and camphor in camphor trees.

Hormones of animal and human origin contain aldehydes and ketones such as muscone in musk deer, female sex hormone- progesterone, male sex hormone-testosterone, and adrenal hormone-cortisone. A famous ketone "methadone" helps in curing addiction of opiates such as heroin, opium, and morphine. In this topic, we will study the many uses of aldehydes and ketones.

Aldehydes and Ketones

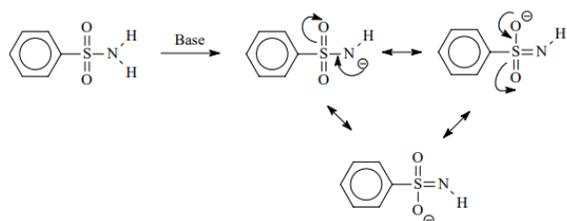
These classes of organic compounds contain a carbonyl functional group (C=O) with structures CHO for aldehydes and RC(=O)R' for ketones. Here, R and R' denotes substituents of carbon. They also refer to as the methanoyl group or formyl group. Aryl or alkyl group or its substituents fill in the remaining bonds of carbon atom in this group.

However, if the substituents in neither of the 2 remaining bonds are hydrogen, then the organic compound is a ketone. However, if one of the substituents is hydrogen then the organic compound is an aldehyde. The properties of aldehydes and ketones play a very important role in the uses of aldehydes and ketones.

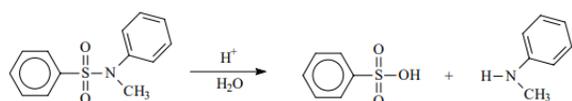
4. IMPORTANT APPLICATION IN MAKING DRUGS

There are several drug classes containing the sulfonamide group including the sulfonamideantibacterials, some diuretics, and the sulfonylurea hypoglycemics (more on these below and in the Antidiabetic Drug Tutorial). Primary sulfonamides contain two hydrogen atoms on the sulfonyl group, and secondary sulfonamides contain one hydrogen atom.

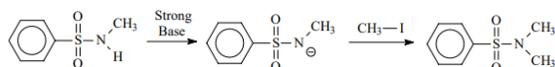
These hydrogens are relatively acidic, again because the charge formed in the conjugate base can be stabilized by resonance. Sulfonamides are less acidic than carboxylic acids, due to the formation of a negative charge on a less electronegative nitrogen atom. However, they display greater acidity than amides because the negative charge formed in the conjugate base can be stabilized over more electronegative atoms as shown by the following resonance structures:



Again it is important to realize that tertiary sulfonamides are NOT acidic because they do not contain an "ionizable" proton. Generally sulfonamides are relatively unreactive compounds. They can be hydrolyzed under relatively extreme conditions to the corresponding sulfonic acid and amine as shown below:

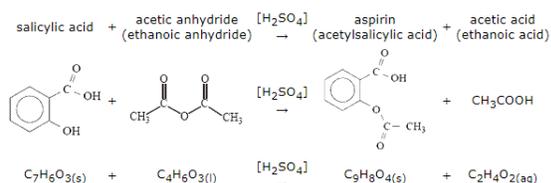


Also, although relatively unreactive as nucleophiles, similar to amides, primary and secondary sulfonamides can be converted to more nucleophilic anions upon treatment with strong bases, and these nucleophiles can participate in displacement reactions similar to ionized amides as shown below:

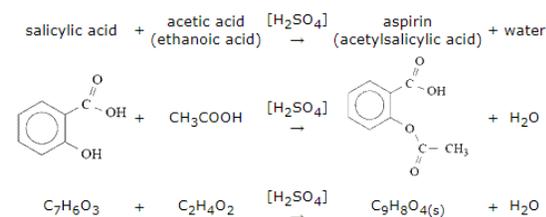


Synthesis of Aspirin (acetylsalicylic acid)

Salicylic acid will rapidly react with acetic anhydride in the presence of an acid catalyst to produce aspirin (acetylsalicylic acid) and acetic acid (ethanoic acid). Sulfuric acid or phosphoric acid are often used to catalyse the reaction.



Salicylic acid can react with acetic (ethanoic) acid in an esterification reaction, but the reaction is very slow, taking days to reach equilibrium, and the yield is low:



For this reason, the commercial preparation of aspirin relies on the faster reaction between salicylic acid and the more reactive acetic anhydride which produces a greater yield of aspirin.

Aspirin (acetylsalicylic acid)

- Aspirin is widely used as an analgesic (pain reliever) and an antipyretic (for reducing fever). It is also used to help prevent heart attacks, strokes, and blood clot formation in people at risk of developing blood clots.
- Aspirin (acetylsalicylic acid) is an aromatic compound containing both a carboxylic acid functional group and an ester functional group.
- Aspirin is a weak acid that is only slightly soluble in water.



- Aspirin can be prepared by reacting salicylic acid and acetic anhydride in the presence of an acid catalyst

5. CONCLUSION

The present study aims to accomplish the reactive phase equilibria and to obtain the data for the recovery of carboxylic acids. In the present study, extraction of acids from its aqueous solutions is performed to determine the optimum conditions for the recovery of acids from fermentation broth as well as an aqueous waste stream. The effects of various parameters on the reactive extraction are investigated with the aim of implementing the data obtained to a future industrial separation unit. Long-chain aliphatic amines and organophosphorus based derivatives dissolved in different diluents [inert, active (modifier) and a mixture of both] are used as the organic phases for the extraction of acids from aqueous solutions. Since the growth of microorganisms is inhibited by the toxicity of solvents in the fermentation units, equilibrium studies are also carried out using biocompatible system (extractant/diluent) for the reactive extraction of propionic acid and nicotinic acid.

Attempts have been made to quantify the effect of diluents on extraction efficiency (distribution coefficient) of extractant (TOA) using LSER model for the extraction of formic acid, acetic acid, propionic acid, and butyric acid. The effect of diluents on extraction efficiency (equilibrium constant) of extractant (TOPO) is quantified using a model based on dipole moment (μ) and E for the extraction of nicotinic acid. The solvation strength of complexes is estimated through the mathematical models using an optimization procedure [a population-based search algorithm called differential evolution (DE)] and graphical methods. The kinetic study is also carried out to obtain the kinetic data using TOA as an extractant for reactive extraction of propionic- and nicotinic acids.

It is important for the production of carboxylic acid from the biological origin, as used in foods and pharmaceuticals. The existing literature on carboxylic acids suggests that great strides have been made in the separation of lactic acid from aqueous solution using reactive extraction to enhance microbial production (90%) of lactic acid. Nicotinic acid and propionic acid (even though a feasible industrial bioprocess has not yet been developed) have huge potential as a building-block chemicals used in various industries. Data on reactive extraction for the recovery of nicotinic acid from aqueous solutions for intensification of microbial production are still scarce.

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