Determination of Reaction Mechanisms and Reactive Intermediates

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By

Lokanatha Rai Kuriya Madavu

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CONTENTS

Foreword viii

Preface x

Acknowledgements xii

List of Abbreviations xiii

Chapter 1 1
Acid and Bases
  1.1 Acid base concept
    1.1.1 Arrhenius concept
    1.1.2 Bronsted and Lowry concept
    1.1.3 The Lewis-acid base system
  1.2 Factors affecting relative strength of acids and bases
    1.2.1. Resonance effect
    1.2.2 Inductive effect
    1.2.3 Hydrogen bonding effect
    1.2.4 Effect due to the orbital nature of electron pair
    1.2.5 Steric effect
    1.2.6. Effect of bond length
    1.2.7 Effect of bond strength
    1.2.8 The oxidation state of the central atom
    1.2.9 Solvent effect

Chapter 2 23
Determination of Reaction Mechanism
  2.1 Introduction
  2.2 Chemical bond cleavage
  2.3 Classification of organic reactions
  2.4 Elucidation of mechanism of organic reaction

- 2.4.1 Kinetic Data
- 2.4.2 Reaction rate theory
- 2.4.3 Energy profile diagram for a reaction
- 2.4.4 Thermodynamic data
- 2.4.5 Linear free energy relationship
- 2.4.6 Influence of solvents
- 2.4.7 Effect of salt on reaction rate or kinetic salt effect
- 2.4.8 Isotopic effect on reaction rate
- 2.4.9 Steric effects

2.5 Kinetic interpretation of reaction mechanism
2.6 Entropy of activation and mechanism
2.7 Chemical evidence for reaction mechanism
- 2.7.1 Isolation of products
- 2.7.2 Isotopic labeling
- 2.7.3 Testing possible intermediates
- 2.7.4 Trapping of intermediates
- 2.7.5 Crossover experiments

2.8 Stereochemical studies

Chapter 3 171
Reaction Intermediates
- 3.1 Intoduction
- 3.2 Carbocations
- 3.3 Carbanions
- 3.4 Free radicals
- 3.5 Carbenes
- 3.6 Nitrenes
- 3.7 Benzynes
- 3.8 Ylides
- 3.9. Enamines
- 3.10 Nitrile oxides
- 3.11 Nitrile imines
- 3.12 Nitrosoolefins
- 3.13 Azoalkenes

Chapter 4 306
Probable NET Questions
Answers

References 352

FOREWORD

It is with immense pleasure and honor I am writing this foreword to a book written by Prof. K. M. Lokanatha Rai, Former Professor and Chairman, Department of Chemistry, University of Mysore. K. M. Lokanatha Rai is an outstanding example of a teacher cum researcher. He has written a number of book chapters and review articles which has been published by reputed international publishers. Recently he has published a book titled “Carbonyl Compounds, Chemistry and Synthetic Approach”.

In the plethora of practical sciences, organic chemistry has a relatively young history, having emerged as a well-defined discipline less than two centuries ago. Its growth has been phenomenal, and it has given birth to numerous subdivisions, organic reactions, mechanisms, and knowledge of intermediates are basic concepts in the steady of organic chemistry. The book entitled “Determination of Reaction Mechanisms and Reactive Intermediates” has been presented in four chapters and each chapter has been further divided into a number of sub-sections. The first chapter gives the concept of acid-base. In the second chapter, the concept of mechanism and methods for its identification are presented while, in the third chapter, the variety of reaction intermediates are discussed, using a good number of examples. Prof. Rai has included a large number of probable NET questions in the fourth chapter.

The present-day student needs besides a good teacher, a good book that supports the teaching, especially when a new ethos is sought to be created. It is this genuine requirement that induced the author to write this book.

This book contains the strong imprint of the author’s wide-ranging experience in teaching and research in chemistry for more than four decades. The essence of knowledge is that you have it and you share it with others.

The author has responded to this dictum in his characteristic style and presentation and he proceeds to illuminate the minds of students as well as young teachers who wish to gain proficiency in this area of chemistry.

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PREFACE

I have taught M.Sc. students for the last 39 years. During these years I have observed that actually students lack basic knowledge about organic chemistry. Basic concepts are missing in the newly published textbooks. For instance, the mechanism for most of the reactions is missing in one book. In order to know the exact mechanism, one has to refer many books or even the original papers. This is difficult for the students and even for the teachers since the respective journals are missing in the same university. All my students want me to write the book in details regarding determination of mechanism and reactive intermediates. It is this difficulty of the students that led to me to undertake this concise and systematic work on the determination of reaction mechanisms and reactive intermediates in the light of the modern structural theories.

In the first chapter I discussed briefly the basic concepts of acids and bases including the effect of inductive effect, resonance effect, hydrogen bonding, steric effect, solvent effect etc. on the strength of acids or bases. The second chapter discusses how difficult to propose a suitable mechanism for any reaction. For instance, by studying the rate law, stoichiometry and isotopic effect, calculating the thermodynamic parameters one can predict the correct mechanism for a given reaction. Sometimes this won't help. In such cases we have to use non-kinetic methods like the identification of intermediates, trapping of intermediates, isolation of products, isotopic labeling and cross over experiments to prove the mechanism. All these are included in this chapter. This chapter also includes the derivation of the Hammett equation, showing how the substitution constant and reaction constants can be calculated.

The last chapter discusses how the structure, geometry, isolation and reactions of different intermediates (viz., carbocations, carbanions, free radicals, carbene, nitrene, benzyne, dipolar species like nitrile oxide, nitrile imines and dienophiles like α-nitrosoolefin and α-iminoolefins) with suitable examples. At the end of each chapter, I have included a few important questions. Finally, I included a few NET type questions related to this book so that students can understand its importance.

ACKNOWLEDGEMENTS

I am indebted to the University of Mysore for extending co-operation for writing this book. I wish to thank my research scholars Dr. P. T. Soumya, Smt. Sumana Y. Kotian, Smt Pavithra V Rai and Dr. Narayana N. Kudva for reading the entire manuscript and making helpful suggestions. I thank Dr. Balakrishna Kalluaaya, Professor of Organic Chemistry, Mangalore University, Mangalore for providing me the forward letter for this book. I also thank my family members for their patience and encouragement. I sincerely thank all my ex-colleagues for encouraging me. I express my sincere gratitude to the Cambridge Scholars Publishing team for publishing this book in a very short time.

LIST OF ABBREVIATIONS

AIBN	Azoisobuteronitrile
CAT	Chloramine-T
DIBAL-H	Diisobutyl aluminium hydride
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DNA	Deoxy ribonucleic acid
EPR	Electron paramagnetic resonance
ESR	Electron spin resonance
HMPA	Hexamethyl phosphoramide
HMPT	Hexamethyl phosphoric triamide
HOMO	Highest occupied molecular orbital
IR	Infra red
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
NMR	Nuclear magnetic resonance
ROS	Reactive oxygen species
THF	Tetrahydrofuran
UV	Ultraviolet

CHAPTER 1

ACID AND BASES

1.1 Acid-base concepts

1.1.1 Arrhenius concept

There are three major classifications of substances known as acids or bases. The Arrhenius definition states that an acid produces H^+ in solution and a base produces ^-OH. This theory was developed by Svante Arrhenius in 1883. When dissolved in an aqueous solution, certain ions were released into the solution (Equation 1.1). An Arrhenius acid is a compound that increases the concentration of **H^+ ions** that are present when added to water. These **H^+** ions form the hydronium ion (H_3O^+) when they combine with water molecules.

$$HCl_{(g)} + H_2O \longrightarrow H^+_{(Aq)} + Cl^-_{(Aq)} \quad \text{(Equation 1.1)}$$

An Arrhenius base is a compound that increases the concentration of ^-OH ions that are present when added to water. In this reaction, sodium hydroxide (NaOH) dissociates into sodium (Na^+) and hydroxide (^-OH) ions when dissolved in water, thereby releasing ^-OH ions into the solution (Equation 1.2). The dissociation is represented by the following equation

$$NaOH_{(s)}+H_2O \longrightarrow Na^+_{(Aq)} + HO^-_{(Aq)} \text{ (Equation 1.2)}$$

This theory successfully describes how acids and bases react with each other to make water and salts. However, it does not explain why some substances that do not contain hydroxide ions (e.g., ammonia,) can make basic solutions in water. For instance, when ammonia reacts with water; it produces ammonium ions and hydroxide ions (Equation 1.3).

$$NH_{3(g)} + H_2O \rightleftharpoons NH_4{}^+{}_{(Aq)} + HO^-{}_{(Aq)} \text{ (Equation 1.3)}$$

1.1.2 Bronsted and Lowry concept

Later, two more sophisticated and general theories were proposed. These are the Brønsted-Lowry and the Lewis definitions of acids and bases.

The acid base concept was introduced by Bronsted and Lowry system, and it involves a hydrogen ion transfer or a proton exchange approach. Thus, substances which tend to give up protons are called acids and those which tend to accept a proton are called bases. For instance (Equation 1.4),

$$NH_{3(aq)} + HCl_{(aq)} \rightleftharpoons NH_4{}^+{}_{(Aq} + Cl^-{}_{(Aq)} \text{ (Equation 1.4)}$$

Here, hydrochloric acid (HCl) "donates" a proton (H^+) to ammonia (NH_3) which "accepts" it, forming a positively charged ammonium ion ($^+NH_4{}^+$) and a negatively charged chloride ion (Cl^-). Therefore, HCl is a Brønsted-Lowry acid (donates a proton) while the ammonia is a Brønsted-Lowry base (accepts a proton). Also, Cl^- is called the conjugate base of the acid HCl and $NH_4{}^+$ is called the conjugate acid of the base NH_3.

When a Brønsted acid dissociates, it increases the concentration of hydrogen ions in the solution, $[H^+]$; conversely, Brønsted bases dissociate by taking a proton from the solvent (water) to generate $[^-OH]$.

When the acidic medium in question is a dilute aqueous solution, the H_0 is approximately equal to the pH value, which is a negative logarithm of the concentration of aqueous H^+ in solution. The pH of a simple solution of an acid in water is determined by both K_a and the acid concentration. For weak acid solutions, it depends on the degree of dissociation, which may be determined by an equilibrium calculation.

The strength of an acid i.e., the acidity is measured by the extent to which it can lose proton in a solvent medium acts as a base (Equation 1.5). Water is the most common solvent used for this purpose. Other non-aqueous solvents can also be used if required.

$$HA + \text{Solvent} \rightleftharpoons \text{Solvent.}\overset{+}{H} + A^- \text{ (Equation 1.5)}$$

Here HA is the acid and A^- is its conjugate base. Now the equilibrium constant (Equation 1.6),

$$K_a = \frac{[\text{Solvent.H}^+]\,[A^-]}{[\text{HA}]} \qquad \text{(Equation 1.6)}$$

where K_a is called the dissociation constant or ionization constant and is the measure of its acidity. The higher the value of K_a, the greater is the acidity; thus in the aqueous medium, K_a value of benzoic acid is 6.1×10^{-5} and that of acetic acid is the 1.75×10^{-5}; hence acetic acid is weaker than benzoic acid. Although the dissociation constant of an acid expresses the acidity, it is inconvenient to express it as words because of its exceedingly small numerical value. To avoid this acidity is expressed as the negative logarithm of K_a with respect to the base ten i.e., $-\text{Log}_{10}K_a$ and this is called pK_a.

Thus in water medium at 25°C, K_a of acetic acid is 1.75×10^{-5}. Therefore pK_a.= $-\text{Log}_{10}\,[1.75 \times 10^{-5}]$ or 4.70 and for benzoic acid is 4.20. Thus the smaller the value of pK_a, the stronger the acid is and vice versa. In fact, if two acids differ in their pK_a values by one unit, the acidity of one acid will be ten times that of the other acid. Therefore, benzoic acid is $[4.76\text{-}4.20] \times 10$ or 5.6 times stronger than acetic acid (Table 1.1).

Basicity, i.e. the strength of a base is measured by the extent to which it can gain proton in a solvent medium acts as an acid (Equation 1.7). Thus the base-solvent equilibrium may be represented as:

$$\text{B} + \text{HA(Solvent)} \rightleftharpoons \text{HB}^+ + \text{A}^- \text{ (Equation 1.7)}$$

Table 1.1: pKa values of acids (From S. K. Gosh, Advanced general organic chemistry, 2007, p229).

Acid	pK_a
Formic acid	3.75
Acetic acid	4.75
Propanoic acid	4.87
Trimethyl acetic acid	5.03

Trichloroacetic acid	0.64
Hexanoic acid	4.88
Heptanoic acid	4.86
2-Chlorobutanoic acid	2.86
3- Chlorobutanoic acid	4.0
4-Chlorobutanoic acid	4.5
Butanoic acid	4.5
Trifluroacetic acid	0.23
Benzoic acid	4.21
p-Hydroxybenzoic acid	4.58
p-Toluic acid	4.33
m-Toluic acid	4.24
Monochloroacetic acid	2.86
Dichloroacetic acid	1.25
Bromooacetic acid	2.9
Iodoacetic acid	3.16
α- chloropropanoic acid	2.80
β- chloropropanoic acid	4.08
Nitroacetic acid	1.68
Hydroxyacetic acid	3.83
Isobutyric acid	4.86
n-Valeric acid	4.86
Isovaleric acid	4.78
Octanoic acid	4.90
Perchloric acid ($HClO_4$)	-8
Chloric acid ($HClO_3$)	-1
Chlorous acid (HOCl=O)	2
Hypochlorus acid (HOCl)	7.53
Hydrochloric acid	-7
H_2SO_4	-9
Ammonium ($^+NH_4$)	9.24
Methylammonium	10.62

Dimethylammonium	10.77
Trimethylammonium	9.8
Phenylammonium	4.60
Hydrobromic acid	-8.8
Hydriodic acid	-9.5
Hydrofluoric acid (HF)	3.2
Nitric acid	-1.6

The ionization constant or equilibrium constant of the base, B is (Equation 1.8)

$$K_b = \frac{[HB^+]\,[A^-]}{[B]} \qquad \text{(Equation 1.8)}$$

As the K_b increases, the basicity increases. Thus K_b of pyridine is 2.3×10^{-9} and that of ammonia is 1.8×10^{-5}; this means ammonia is stronger base than pyridine. For the same reason as with K_a, the basicity is expressed by pK_b; naturally the greater the numerical value of pK_b, the weaker is the base and vice versa. Thus, pK_b value of CH_3NH_2 and $(CH_3)_2NH$ are 3.36 and 3.23 respectively. Therefore, dimethylamine is a stronger base than methylamine; the former base is $(3.36\text{-}3.23) \times 10$ or 1.3 times stronger than the latter base in the aqueous medium.

The relationship between the equilibrium constant and a standard free energy change can be safely be used in the case of dissociation of acids. The relation is

$$\Delta G^* = -RT\ln K_a \quad \text{(Equation 1.9)}$$

Where ΔG^* is the standard free energy change, K_a, the equilibrium constant (i.e., the dissociation constant of the acid at 298K (T).

$$
\begin{aligned}
\Delta G^* &= -8.314 \times 298 \times 2.303 \times \log Ka \;\; \text{J mol}^{-1} \\
&= -5.706 \times \log Ka \;\; \text{kJ mol}^{-1} \\
&= 5.706 \times \; pKa \;\text{kJ mol}^{-1} \quad [\because \; -\log Ka = pKa] \\
\therefore \quad pKa &= \frac{\Delta G^*}{5.706 \text{ kJ mol}^{-1}}
\end{aligned}
$$

The unit of ΔG* is kJ mol^{-1}, so both the denominator and the nominator have the same unit; pK_a has therefore no unit.

For instance, ΔG* of ionization of benzoic acid is 24 KJ mol^{-1}. On substitution in the above equation, pK_a value for benzoic acid is 4.21. Again, we know that ΔG* = ΔH* -TΔS*. Making use of these equations one can calculate the various thermodynamic parameters (Table 1.2).

Table 1.2: ΔG*(in $KJmol^{-1}$), ΔH* (in $KJmol^{-1}$), ΔS* (in KJ $deg^{-1}mol^{-1}$) values of organic acids (From S. K. Gosh, Advanced general organic chemistry, 2007, p229).

Acid	ΔG*	ΔH*	ΔS*
Formic acid	+21.5	-0.17	-0.073
Acetic acid	+27.14	-0.46	-0.092
Propionic acid	+27.8	-0.96	-0.096
Trimethylacetic acid	+28.8	-3.02	-0.107
Trichloroacetic acid	+3.64	+6.14	+0.008
Benzoic acid	+24	+0.37	-0.08
p-Toluic acid	+24.70	+1.25	-0.079
m-Toluic acid	+24.10	+0.29	-0.080
p-Bromobenzoic	+22.8	0.46	-0.075
p-Chlorobenzoic	+22.7	0.83	-0.073
m-Chlorobenzoic	+21.8	0.84	-0.073
p-Cayanobenzoic	+20.3	0.12	-0.068

Acidity and basicity depend on the solvents. For instance, alcohol in the presence of a strong base behaves as an acid and in presence of an acid it behaves as a base.

$$EtOH + B: \longrightarrow BH^+ + EtO^-$$

$$EtOH + HCl \longrightarrow Et\overset{+}{O}H_2 + Cl^-$$

The ions on the right which remain after proton departs from each of the acids are called the conjugate base of the respective acids.

$$CH_3COOH \longrightarrow CH_3COO^- + H^+$$

Although the Bronsted definition of an acid is very similar to the classical definition, it includes a number of molecules or ions that classically might not have been regarded as acids.

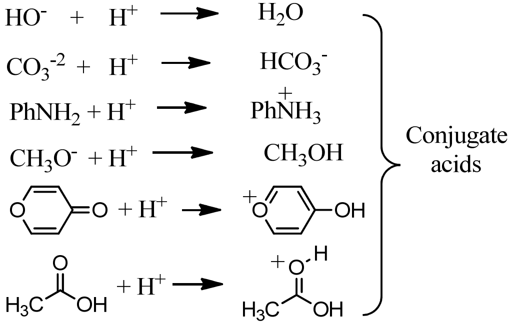
$$CH_3NO_2 \longrightarrow {}^-CH_2NO_2 + H^+$$

$$(CH_3)_3\overset{+}{N}H \longrightarrow (CH_3)_3N + H^+$$

$$Al(H_2O)_6^{+3} \longrightarrow Al(H_2O)_5^{+2}OH + H^+$$

Note that these reactions are not spontaneous. Here the H^+ is pulled off by a base. The reaction above is actually half a reaction.

Bronsted bases, species that will take a proton, are generally negative ions or neutral molecules.



$$HO^- + H^+ \longrightarrow H_2O$$

$$CO_3^{-2} + H^+ \longrightarrow HCO_3^-$$

$$PhNH_2 + H^+ \longrightarrow Ph\overset{+}{N}H_3$$

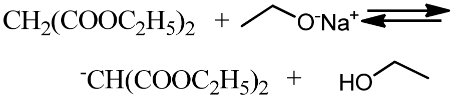
$$CH_3O^- + H^+ \longrightarrow CH_3OH$$

Conjugate acids

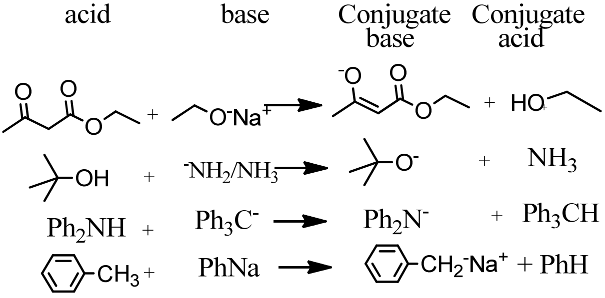
A strong acid is the one which completely ionizes in a solution whereas; a weak acid only partially ionizes. Strong acids are corrosive in nature and cause severe burns when they come in contact with skin. But the weak acids are only mildly corrosive and are even present in our food and body. Hydrochloric acid and sulphuric acid are examples of strong acids. Ethanoic acid, citric acid (present in citrus fruits) and acetic acid (present in vinegar) are a few examples of weak acids.

Very weak acids:

Among organic compounds there are a number of very weak acids, which even in the basic solvent ammonia are not measurably ionized. These may be persuaded to part with H^+ ions, only by the stronger negatively charged bases. The most common of such bases is of course the ^-OH ion, but this is too weak a base to convert many of the very weak organic acids to their own conjugate base. For such a purpose, even a strong base (i.e., conjugate bases of acid weaker than base) are needed. For instance, ethyl malonate (a very weak acid) is converted into its conjugate base (the ethyl malonate carbanion) by the addition of sodium ethoxide (strong base) in an ether solution, the conjugate base of the weak acid (ethanol) (Equation 1.10).



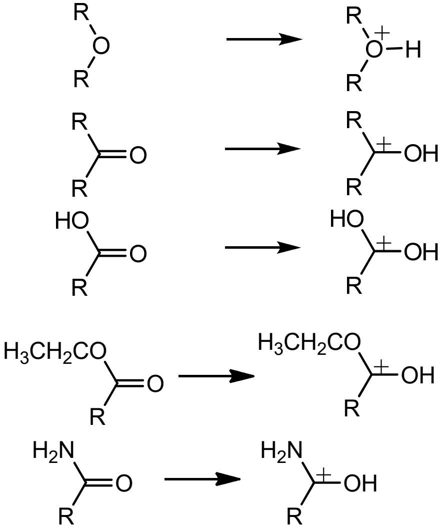
(Equation 1.10)



It should be noted that many compounds therefore behave as acids or bases in selected solvents whereas in water they behave as neutral compound.

Very Weak Bases:

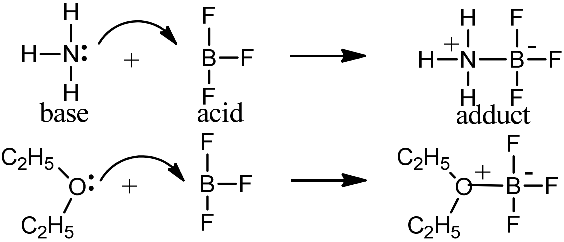
On the other side of the coin, we find a very large number of organic compounds having very weak basicities. Among these are ethers, carboxylic acids, amides, ketones, nitro compounds and even some aromatic hydrocarbons. Although certain of such compounds are appreciably soluble in water, addition of strong acid to the dilute aqueous solution result almost exclusively in the formation of H_3O^+, the conjugate acid of H_2O.



$$Ph_3COH \longrightarrow Ph_3C^+ + H_3O^+ + 2HSO_4^-$$

1.1.3 The Lewis-acid base system (Electron-pair Transfer)

A Lewis acid is a chemical species that contains an empty orbital which is capable of accepting an electron pair from a Lewis base to form a Lewis adduct. A Lewis base, then, is any species that has a filled orbital containing an electron pair which is not involved in bonding but may form a dative bond with a Lewis acid to form a Lewis adduct. For example, NH_3 is a Lewis base, because it can donate its lone pair of electrons. Trimethylborane (Me_3B) is a Lewis acid as it is capable of accepting a lone pair. In a Lewis adduct, the Lewis acid and base share an electron pair furnished by the Lewis base, forming a dative bond. In the context of a specific chemical reaction between NH_3 and Me_3B, the lone pair from NH_3 will form a dative bond with the empty orbital of Me_3B to form an adduct $NH_3 \bullet BMe_3$. The terminology refers to the contributions of Gilbert N. Lewis.



System with unshared pair electron should function as base (ROH, ROR, RNH_2, RCOR, RSH etc.) while systems that are positively charged or electron deficient are called as Lewis acid (AlX_3, PX_3, PX_5, $SnCl_4$, ZnO etc.).

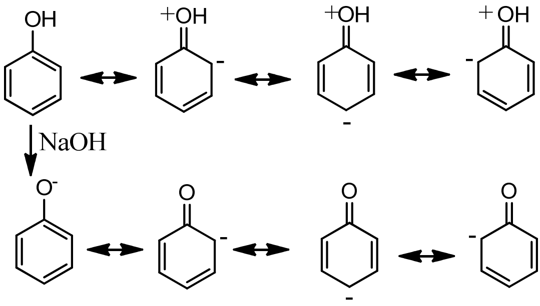
1.2 Factors affecting relative strength of acids and bases

Relative stabilities of species can be assessed by considering the following structural effects: resonance effect, inductive effect, hydrogen bonding effect, effect due to the orbital nature of electron pair, steric effect, solvation effect, bond length and electronegativity of the bonded atom.

1.2.1 Resonance effect

Resonance effects involving aromatic structures can have a dramatic influence on acidity and basicity. The stability of a species is determined by the number and nature of contributing structures in a resonance hybrid of the species. The more the number of contributing structures in a resonance hybrid of a natural or negatively charged species, the more is the acidity of the hybrid and the greater is the delocalization of electrons. The greater the delocalization, the lower is the probability of donating electron pair. Therefore, as the resonance stabilization, i.e., delocalization increases, basicity decreases and hence relatively acidity increases.

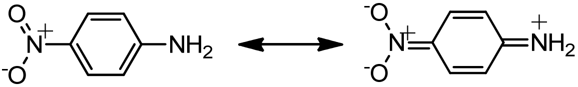
For example, the difference in acidity between phenol (pK_a = 10) and cyclohexanol (pK_a = 16). Looking at the conjugate base of phenol, we see that the negative charge can be delocalized by resonance to three different carbons on the aromatic ring (Scheme 1.1).



Scheme 1.1

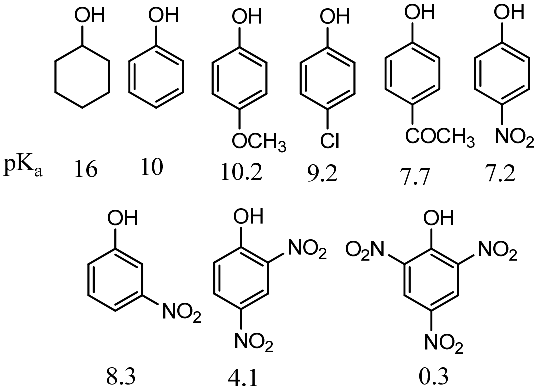
Although these are all minor resonance contributors (negative charge is placed on a carbon rather than the more electronegative oxygen), they nonetheless have a significant effect on the acidity of the phenolic proton.

For the same reason, aniline is more basic than p-nitroaniline; N atoms of $–NH_2$ are electron donor in these compounds. In other words, we can say p-nitroaniline is a stronger acid than aniline because of resonance involving $–NH_2$ and $–NO_2$ groups.



Substitution of the hydroxyl hydrogen atom is even easier with phenols, which are roughly a million times more acidic than equivalent alcohols. This phenolic acidity is further enhanced by electron-withdrawing substituents ortho and para to the hydroxyl group, as displayed in the following diagram. It is noteworthy that the influence of a nitro substituent is over ten times stronger in the para position than it is in meta position, despite the fact that the latter position is closer to the hydroxyl group. Furthermore, additional nitro groups have an additive influence if they are positioned in ortho or para locations. The trinitro compound shown at the lower right is a very strong acid called picric acid.

Table 1.3 pKa values of substituted phenols



Why is phenol a much stronger acid than cyclohexanol? The resonance stabilization in these two cases is very different. An important principle of resonance is that charge separation diminishes the importance of canonical contributors to the resonance hybrid and reduces the overall stabilization. The contributing structures to the phenol hybrid all suffer charge separation, resulting in very modest stabilization of this compound. On the other hand, the phenolate anion is already charged, and the canonical contributors act to disperse the charge, resulting in a substantial stabilization of this species. The conjugate bases of simple alcohols are not stabilized by charge delocalization, so the acidity of these compounds are similar to that of water. Supporting evidence that the phenolate negative charge is delocalized on the ortho and para carbons of the benzene ring comes from the influence of electron-withdrawing substituents at those sites.

p-Nitrophenol is a stronger acid than m-nitrophenol. The conjugate base of p-nitrophenol is p-nitrophenoxide ion and that of m-nitrophenol is m-nitrophenoxide ion. The former conjugate base stabilizes because of resonance interaction but the latter does not. The more stable the conjugate base, stronger the acid.

1.2.2 Inductive effect

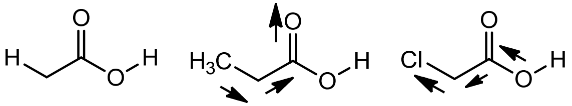
If the electronegative atom is then joined to a chain of atoms, usually carbon, the positive charge is related to the other atoms in the chain. This is the electron-withdrawing inductive effect, also known as the ***-I* effect**. However, some groups, such as the alkyl group, are less electron-withdrawing than hydrogen and are therefore considered as electron-releasing. This is electron-releasing character and is indicated by the ***+I* effect**. In short, alkyl groups tend to give electrons, leading to an induction effect.

The inductive effect also plays a vital role in deciding the acidity and basicity of a molecule. Groups having +*I* effect attached to a molecule increases the overall electron density on the molecule and the molecule is able to donate electrons, making it basic. Similarly, groups having -*I* effect attached to a molecule experience a decrease in the overall electron density on the molecule, making it electron deficient which results in its acidity. As the number of -*I* groups attached to a molecule increases, its acidity increases; as the number of +*I* groups on a molecule increases, its basicity increases.

The strength of a carboxylic acid depends on the extent of its ionization: the more ionized it is, the stronger it is. As an acid becomes stronger, the numerical value of its pKa drops. In acids, the electron-releasing inductive effect of the alkyl group increases the electron density on oxygen and thus hinders the breaking of the O-H bond, which consequently reduces the ionization. In the alkyl substituted anion the increased electron availability on oxygen would serve to promote its recombination with protons, as compared with the methanoate anion, methanoic acid system. Due to its greater ionization, formic acid (pK_a=3.74) is stronger than acetic acid (pK_a = 4.76).

The relative effect of the different halogens in the expected order, fluorine being the most electronegative and producing a hundred fold increase in the strength of fluroethanoic acid as compared with ethanoic acid itself. Monochloroacetic acid (pK_a=2.86), though, is stronger than formic acid, due to the electron-withdrawing effect of chlorine promoting ionization. The effect is very much greater than that produced, in the opposite direction, by the introduction of an alkyl group, and the introduction of further halogens still produces large increase in acid strength; trichloroethanoic acid is thus a very strong acid.

Table 1.4 pK_a values of halogen substituted acetic acids

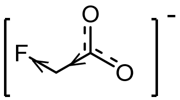


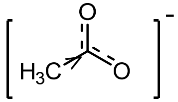
pK_a	4.75	4.88	2.86

CH_3COOH	ICH_2COOH	$BrCH_2COOH$	$ClCH_2COOH$
pK_a 4.75	3.12	2.90	2.86

FCH_2COOH	$Cl_2CHCOOH$	Cl_3CCOOH
2.66	1.80	0.65

Here again it is important that K_a (and hence pKa) is related to ΔG^* for the ionization, and that ΔG^* includes both ΔH^* and ΔS^* terms. In this series of halogen substituted ethanoic acids ΔH^* is found to differ little from one compound to another, the observed change in ΔG^* along the series being largely due to variation in ΔS^*. This arises from the substituent halogen atom effecting delocalization of the negative charge over the whole of the anion.

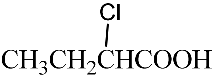




The introduction of halogen atom further away from the carboxyl group than the adjacent α-position has much less influence. Its inductive effect quickly dies away down a saturated chain, with the result that the negative charge becomes progressively less spread, i.e., more concentrated in the carboxylate anion. The acid thus increasingly resembles the corresponding simple aliphatic acid itself as the following pK_a values show:

Table 1.5

pK$_a$ vlaues of chlorinated butanoic acid derivatives

$CH_3CH_2CH_2COOH$	$ClCH_2CH_2CH_2COOH$
pK$_a$ 4.82	4.52
 $CH_3\overset{Cl}{C}HCH_2COOH$	 $CH_3CH_2\overset{Cl}{C}HCOOH$
4.06	2.84

Other electron withdrawing groups like R_3N^+, CN, NO_2, SO_2R, and COOR increase the strength of simple aliphatic acids. The unshared electrons on the oxygen atoms of the last two groups are not able to exert a mesomeric effect in the opposite direction to their inductive effect, owing to the intervening saturate carbon atoms. All this is seen in the pK$_a$ values.

Table 1.6 pK$_a$ values of substituted acetic acid

O_2NCH_2COOH	$EtOOCCH_2COOH$	$Me_3\overset{+}{N}CH_2COOH$
pK$_a$ 1.68	3.35	1.83
$NCCH_2COOH$	$MeOCH_2COOH$	$HOCH_2COOH$
2.47	3.53	3.81

In benzoic acid, the carbon atoms which are present in the ring are sp^2 hybridized. As a result, benzoic acid (pK$_a$=4.20) is a stronger acid than cyclohexane carboxylic acid (pK$_a$=4.87). Also, in aromatic carboxylic acids, electron-withdrawing groups substituted at the *ortho* and *para* positions can enhance the acid strength. Since the carboxyl group is itself an electron-withdrawing group, dicarboxylic acids are, in general, stronger than their monocarboxylic analogues. The inductive effect will also help in polarization of a bond making certain carbon atom or other atom positions. This has important applications in chemistry.

The introduction of alkyl groups into the benzene ring has very little effect on the strength of benzoic acid. The presence of groups such as OH, OMe, halogens having an electron withdrawing effect, but an electro-donating mesomeric effect may cause the p-substituted benzoic acids to be weaker than the benzoic acid itself.

As the carboxylic group itself has an electron-withdrawing inductive effect, the presence of a second group in an acid might be expected to make it stronger as shown by the following pK_a value [HCOOH, 3.17; HOOCCOOH, 1.23; CH_3COOH, 3.17; $HOOCCH_2COOH$, 2.83; CH_3CH_2COOH, 4.83; $HOOCCH_2CH_2COOH$, 4.19; C_6H_5COOH, 4.17; $HOOCC_6H_4COOH$ (o- 2.98, m- 3.46 & p- 3.51) etc.].

1.2.3 Hydrogen bonding effect

Hydrogen bonding is a very strong and polar bond which is very stable; this would reduce the tendency to give H^+ ion so it would probably increase the basicity. If the hydrogen bonding is strong then the acid is unable to release enough H^+ ions on disassociation and therefore is a weak acid for example in the H-bonding of HF the bonding is in zigzag manner and the H ion is locked or strongly attracted by two highly electronegative F so it does not give much H^+ ions and therefore is weak acid. The lower the H bonding, lower will be the force of attraction, so consider the example of H-Cl. If the attraction is less, more H^+ ions will be released which will increase the acidic strength thus basicity will decrease.

In some isomeric carboxylic acids, the carboxylate anion in one of them is stabilized through hydrogen bonding, thus making it a stronger acid. The pK_a values of the isomeric carboxylic are shown below:

2-Hydroxybenzoic acid ($pK_a = 2.98$); 3-Hydroxybenzoic acid ($pK_a = 4.08$); 4-Hydroxybenzoic acid ($pK_a = 4.58$).

Only the anion from the ortho-isomer is stabilized through hydrogen bonding thus responsible for greater acidity of the acid. This stabilization is not present in the other isomers due to unfavourable geometry. The effect is even more enhanced if OH groups are present in both ortho positions as in 2, 6-dihydroxybenzoic acid ($pK_a = 2.98$). A similar case in point is the two isomeric dicarboxylic acids: maleic acid, the *cis* isomer (cis-butenoic acid) while fumaric acid, its *trans* isomer.