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Acidty of carboxylic Acid

pK_a's of some typical carboxylic acids are listed in the following table. When we compare these values with those of comparable alcohols, such as ethanol (pK_a = 16) and 2-methyl-2-propanol (pK_a = 19), it is clear that carboxylic acids are stronger acids by over ten powers of ten! Furthermore, electronegative substituents near the carboxyl group act to increase the acidity.

Compound	pK_a		Compound	pK_a
HCO_2H	3.75		$CH_3CH_2CH_2CO_2H$	4.82
CH_3CO_2H	4.74		$ClCH_2CH_2CH_2CO_2H$	4.53
FCH_2CO_2H	2.65		$CH_3CHClCH_2CO_2H$	4.05
$ClCH_2CO_2H$	2.85		$CH_3CH_2CHClCO_2H$	2.89
$BrCH_2CO_2H$	2.90		$C_6H_5CO_2H$	4.20
ICH_2CO_2H	3.10		$p\text{-}O_2NC_6H_4CO_2H$	3.45
Cl_3CCO_2H	0.77		$p\text{-}CH_3OC_6H_4CO_2H$	4.45

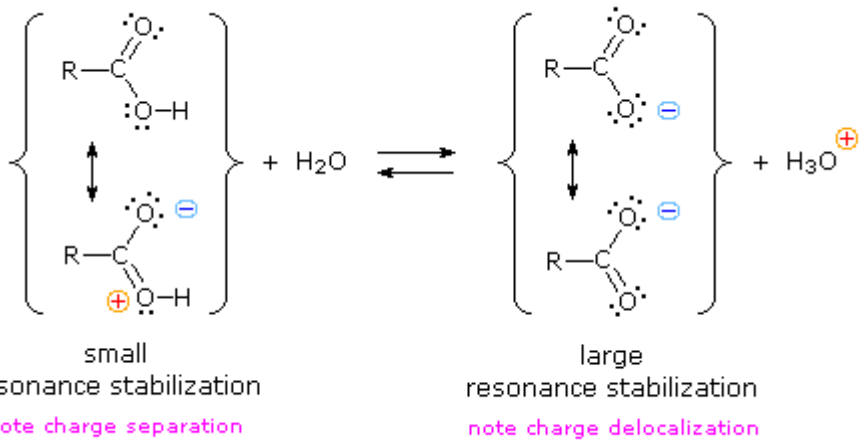
Why should the presence of a carbonyl group adjacent to a hydroxyl group have such a profound effect on the acidity of the hydroxyl proton? To answer this question we must return to the nature of acid-base equilibria and the definition of pK_a , illustrated by the general equations given below.

$$H\text{–}A + H_2O \rightleftharpoons H_3O^{\oplus} + A:^{\ominus} \qquad K_{eq} = \frac{[H_3O^{\oplus}]\,[A:^{\ominus}]}{[HA]\,[H_2O]}$$

$$K_a = \frac{[H_3O^{\oplus}]\,[A:^{\ominus}]}{[HA]} \qquad pK_a = -\log K_a = \log\left(\frac{1}{K_a}\right)$$

An equilibrium favors the thermodynamically more stable side, and that the magnitude of the equilibrium constant reflects the energy difference between the components of each side. In an acid base equilibrium the equilibrium always favors the weaker acid and base (these are the more stable components). Water is the standard base used for pK_a measurements; consequently, anything that stabilizes the conjugate base ($A:^{(-)}$) of an acid will necessarily make that acid (H–A) stronger and shift the equilibrium to the right. Both the carboxyl group and the carboxylate anion are stabilized by resonance, but the stabilization of the anion is

much greater than that of the neutral function, as shown in the following diagram. In the carboxylate anion the two contributing structures have equal weight in the hybrid, and the C–O bonds are of equal length (between a double and a single bond). This stabilization leads to a markedly increased acidity,



small
resonance stabilization
note charge separation

large
resonance stabilization
note charge delocalization

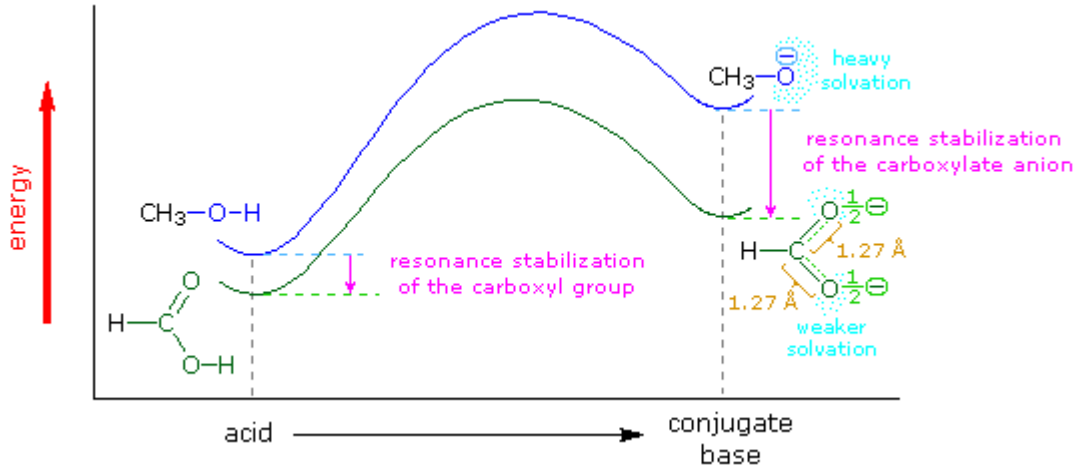
Vinylagous Acids

Compounds in which an enolic hydroxyl group is conjugated with a carbonyl group also show enhanced acidity.

The resonance effect described here is undoubtedly the major contributor to the exceptional acidity of carboxylic acids. However, inductive effects also play a role. For example, alcohols have pK_a's of 16 or greater but their acidity is increased by electron withdrawing substituents on the alkyl group..Water is less acidic than hydrogen peroxide because hydrogen is less electronegative than oxygen, and the covalent bond joining these atoms is polarized in the manner shown. Alcohols are slightly less acidic than water, due to the poor electronegativity of carbon, but chloral hydrate, $Cl_3CCH(OH)_2$, and 2,2,2,-trifluoroethanol are significantly more acidic than water, due to inductive electron withdrawal by the electronegative halogens (and the second oxygen in chloral hydrate). In the case of carboxylic acids, if the electrophilic character of the carbonyl carbon is decreased the acidity of the carboxylic acid will also decrease. Similarly, an increase in its electrophilicity will increase the acidity of the acid. Acetic acid is ten times weaker an acid than formic acid (first two entries in the second row), confirming the electron donating character of an alkyl group relative to hydrogen. Electronegative substituents increase acidity by inductive electron withdrawal. As expect the higher the electronegativity of the substituent the greater the increase in acidity (F > Cl > Br > I), and the closer the substituent is to the carboxyl group the greater is its effect Substituents also influence the acidity of benzoic acid derivatives, but resonance effects compete with inductive effects. The methoxy group is electron donating and the nitro group is electron withdrawing .

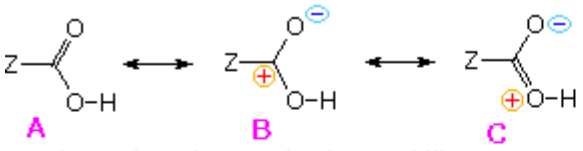
Substituent Effects on the Acidity of Carboxylic Acids

The carboxylic acids are a large and structurally diverse class of compounds. Since most are at least partially soluble in water and have pK_a's in the 2 to 5 region, the influence of functional substituents and structural features on aqueous acidity have been studied extensively. Formic acid, HCO_2H, is the simplest member of this class, and will serve as a useful reference point, pK_a=3.75. Although the greater acidity of formic acid compared with methanol has been attributed to resonance stabilization of the formate anion, the different solvation demands of the respective conjugate anions result in an entropy difference that also favors the formate base. Both factors are depicted in the following illustration.. Resonance delocalization of the negative charge in the formate anion produces a large enthalpic stabilization shown by the magenta arrow. In water solution both methanol and formic acid are incorporated into the dynamic hydrogen bonded structure of liquid water. On ionization, each of these solutes produces a hydrated proton (hydronium ion) and a negatively charged conjugate base. The hydronium ion is common to both cases and can be ignored. The negative charge in the methoxide anion is concentrated on a single oxygen atom and demands strong solvation by water molecules, indicated by the aqua-colored dots. This solvation forces significant structural organization on many water molecules at the cost of decreased entropy. The formate anion also carries a single negative charge, but it is distributed over two oxygen atoms, so the charge density at either site is halved, compared with methoxide. This lower charge density demands much less solvation by water, resulting in a smaller entropy cost.

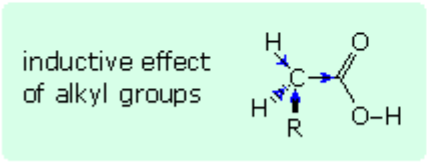


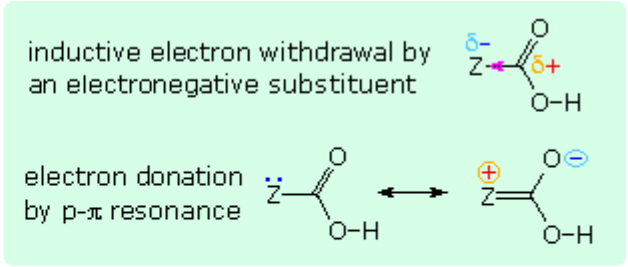
The importance of solvation and the accompanying entropy changes to any discussion of acidity may be seen by comparing the pK_a's of methanol and formic acid in water and DMSO, a solvent that poorly solvates anions. In water the pK_a of methanol is 15.5, nearly 12 powers of ten less acidic than formic acid (3.75). In DMSO the pK_a's of methanol and formic acid are roughly 29 and 13 respectively, representing a very large decrease in Brønsted acid strength for both compounds (more than ten powers of ten). Furthermore, the difference in acid strength between methanol and formic acid in DMSO is magnified about ten thousand times, even though the enthalpic resonance stabilization presumably remains constant. A more extensive discussion of solvent effects on acidity was presented earlier. When comparing the acidities of different acids, care must be taken to use pK_a's measured in the same solvent. In this discussion all the pK_a's were taken in or extrapolated to water at 25 ºC. Measurements in mixed aqueous solvents, using water-soluble organic co-solvents such as ethanol, acetonitrile, dioxane, DMSO and acetone, generally give significantly larger pK_a's.

In all other carboxylic acids an organic substituent replaces the hydrogen of formic acid, and it is instructive to analyze the change in acid strength caused by this change. To begin with, we must recognize that the carbonyl moiety of the carboxyl group is electrophilic and withdraws electrons from substituents. The deactivating nature of the carboxyl group on electrophilic substitution of benzoic acid is one example of this property. Resonance structures, such as A, B & C in the following diagram, are often drawn to describe this electrophilic character. The inductive effect of substituent Z in this diagram may enhance or diminish this character, depending on its overall electronegativity. Inductive electron withdrawal will increase the electrophilic character and the acidity of the carboxyl group, as shown in the green shaded box on the right. Resonance electron donation, either by p-π or π-π interaction, would act to stabilize the carboxylic acid, reducing its electrophilicity and acidity. These two effects often act in opposition, and in the case of carbonic acid (H_2CO_3) electron donation overcomes inductive withdrawal, resulting in a pK_a^1=6.63.



the carbonyl group is electrophilic





Saturated aliphatic acids are generally ten times weaker than formic acid, which may seem surprising since carbon has a higher Pauling electronegativity than hydrogen (2.55 versus 2.20). However, we must recognize that a carbon atom is larger and more polarizable than hydrogen, allowing it to shift electrons toward the more electronegative carbonyl carbon of the carboxyl group. Also, hydrogen and alkyl substituents on the α-carbon assist in this inductive electron shift, as shown in the green box on the left. This analysis is supported by the activating influence of alkyl substituents in electrophilic aromatic substitution, the Markovnikov rule, and the greater reactivity of aldehydes with nucleophiles compared with equivalent methyl ketones.

The four carboxylic acids in the first row of the following table illustrate the electron donating quality of alkyl groups. As the number of carbon atoms in the group increases from one to five, the inductive electron donation also increases. The compounds in the next three rows of the table demonstrate that electronegative substituents on an alkyl group can shift its inductive effect from donating to withdrawing (relative to hydrogen). Thus, all the haloacetic acids are more acidic than formic acid, with fluoroacetic acid being the most acidic. Additional halogen substituents have an additive influence, and moving the substituent from the α to a β-carbon reduces its influence on the acidity. Note that a hydroxyl substituent has a much weaker effect than any of the halogens, despite the higher electronegativity of oxygen (3.44 compared with 3.16 for chlorine).

pK_a Values for Some Aliphatic Carboxylic Acids (25 ºC in H_2O)

Compound	**pK_a**	**Compound**	**pK_a**	**Compound**	**pK_a**	**Compound**	**pK_a**
CH_3CO_2H	4.76	$CH_3CH_2CO_2H$	4.87	$CH_3(CH_2)_2CO_2H$	4.91	$(CH_3)_3CCO_2H$	5.05

FCH_2CO_2H	2.59	$ClCH_2CO_2H$	2.85	$BrCH_2CO_2H$	2.89	ICH_2CO_2H	3.13
$NCCH_2CO_2H$	2.50	$HOCH_2CO_2H$	3.82	Cl_2CHCO_2H	1.25	Cl_3CCO_2H	0.77
$NCCH_2CH_2CO_2H$	3.98	$ClCH_2CH_2CO_2H$	3.95	$BrCH_2CH_2CO_2H$	4.00	$ICH_2CH_2CO_2H$	4.06

Conjugation and Hybridization

The aliphatic acids discussed above do not provide any insight into p-π or π-π conjugation effects, since the sp^3-hybridized α-carbon insulates the carboxyl group from such interactions. Conjugation may be studied by using α,β-unsaturated and aromatic carboxylic acids. The two parent compounds of these classes, acrylic acid (CH_2=$CHCO_2H$) and benzoic acid ($C_6H_5CO_2H$), are both slightly stronger than acetic acid and have similar pK_a's of 4.26 and 4.20 respectively. Since their influence is probably a combination of inductive and resonance effects, it would be helpful to evaluate one of these alone. The following four compounds represent acetic acid derivatives in which a methyl hydrogen has been replaced with a methyl group, a vinyl group, a phenyl group and a chlorine atom respectively. In each compound a methylene group insulates the substituent from the carboxyl group, prohibiting conjugative interactions. As noted above, the methyl substituent is weakly electron donating and the chlorine exerts a strong electron withdrawing influence. Comparatively, the vinyl and phenyl groups have an electron withdrawing inductive effect roughly 25% that of chlorine. From this we may conclude that resonance electron donation to the carboxyl function in acrylic acid and benzoic acid substantially dilutes the inductive effect of the sp^2 substituent groups.

$CH_3CH_2CO_2H$	4.87	CH_2=$CHCH_2CO_2H$	4.34	$C_6H_5CH_2CO_2H$	4.30	$ClCH_2CO_2H$	2.85

The increased electronegativity of sp^2 and sp hybridized carbon compared with sp^3 carbon was noted earlier. This increase is particularly dramatic for triply bonded substituents, as seen in the acidity of 2-propynoic acid, $HC{\equiv}CCO_2H$, and 3-butynoic acid, $HC{\equiv}CCH_2CO_2H$, having respective pK_a's of 1.90 and 3.30. Conjugative electron donation in 2-propynoic acid is very small, compared with acrylic acid, reflecting the poor electron donating character of the triple bond.

Another aspect of conjugation concerns the ability of a double bond, triple bond or aromatic ring to transmit the influence of a remote substituent to the carboxyl group. The compounds in the following table provide information bearing on this issue. The top row consists of β-substituted acrylic acid derivatives. Methyl and phenyl substituents exert a weakening effect; whereas chlorine strengthens the acid. Comparing these relationships with similar substituent effects in equivalent saturated acids (previous table) leads to some interesting differences.

- A β-chlorine substituent exerts the same acidity strengthening effect regardless of unsaturation in the connecting chain.
- A β-methyl group decreases the acidity of the unsaturated acid ten fold over that of the saturated analog.
- A β-phenyl group increases the acidity of the saturated acid, but decreases that of the unsaturated acid by roughly the same degree.

These observations may be interpreted in several ways. First, the inductive electron

withdrawal by chlorine through a C–C sigma-bond is about the same as through a pi-bond. Second, The inductive electron donation by a methyl group occurs to a significant degree by hyperconjugation or conjugated hyperconjugation. Finally, the curious inversion of the phenyl influence may be attributed to an exclusive inductive electron withdrawal down the saturated connecting group, overpowered by a conjugative donation through the unsaturated chain.

Substituent Effects in Some Unsaturated or Aromatic Carboxylic Acids (25 ºC in H_2O)

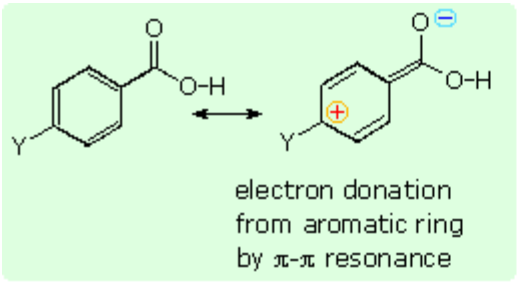
Compound	**pK_a**	**Compound**	**pK_a**	**Compound**	**pK_a**	**Compound**	**pK_a**
t-$CH_3CH=CHCO_2H$	4.74	$(CH_3)_2C=CHCO_2H$	5.12	$ClCH=CHCO_2H$	3.32	t-$C_6H_5CH=CHCO_2H$	4.50
p-$CH_3C_6H_4CO_2H$	4.36	p-$ClC_6H_4CO_2H$	3.98	p-$CH_3OC_6H_4CO_2H$	4.48	p-$O_2NC_6H_4CO_2H$	3.42
m-$CH_3C_6H_4CO_2H$	4.27	m-$ClC_6H_4CO_2H$	3.82	m-$CH_3OC_6H_4CO_2H$	4.10	m-$O_2NC_6H_4CO_2H$	3.47

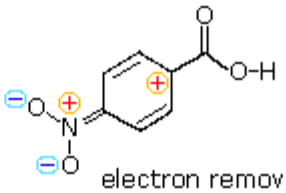
The substituted benzoic acids in the above table exhibit many of the same effects noted for the acrylic acid derivatives. It must, however, be noted that the meta and para-substituent locations in these compounds are further removed from the carboxyl group, both in distance and number of connecting bonds, than in the acrylic acid examples. This will reduce the magnitude of any inductive effects. The para-location permits conjugative interaction of the substituent with the carboxyl function; the meta location does not. For comparison purposes remember that benzoic acid itself has a pK_a = 4.2.
A para-methyl substituent appears to have double the electron donating effect of a meta-methyl group, again suggesting that conjugative hyperconjugation may be important. The meta-chlorobenzoic acid isomer is significantly more acidic than the para-isomer, largely because it is closer to the carboxyl function, and in part due to resonance electron donation by the para-chlorine. The two methoxybenzoic acids are particularly informative, inasmuch as the meta isomer has a slightly increased acidity, whereas the para-isomer is significantly weakened. Oxygen has a much larger electronegativity than carbon, but it is an excellent p-π electron donor to sp^2 carbon functions. For the meta isomer, the inductive effect is somewhat stronger than the resonance donation, but the para-isomer is able to donate an oxygen electron pair directly into the electrophilic carboxyl function. Both the meta and para-nitro substituent withdraw electrons from the benzene ring by a combination of inductive and resonance action, and the corresponding acids are greatly strengthened.

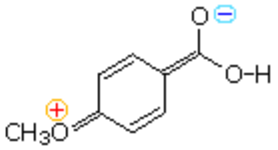
The Ortho Effect

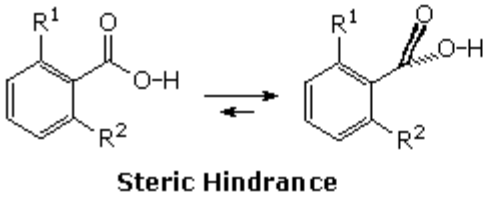
In general, ortho-substituted benzoic acids are stronger acids than their meta and para isomers, regardless of the nature of the substituent. The ortho effect is large for the nitrobenzoic acids, which show nearly a 20 fold increase in acidity, roughly an 8 fold factor for the halobenzoic acids, and a 2.5 to 3 fold increase for methyl and cyano substituents. The methoxybenzoic acids are exceptional, in that the ortho and meta isomers have nearly identical pK_a's (ca. 4.1), presumably due to the exceptional p-π electron donation from oxygen noted above.

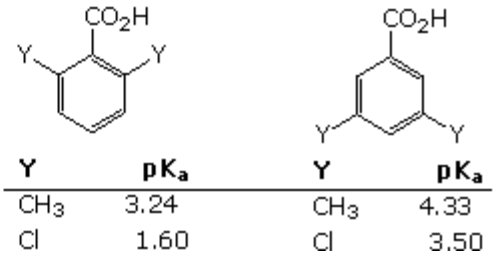
Many of the factors that influence the acidity of substituted benzoic acids are summarized in the following diagram. First, although the phenyl group is inductively electron withdrawing, it can donate electrons to a carboxyl group by π-π resonance, as shown in the green shaded box in the upper left. A substituent Y may perturb the balance of these two factors by its inductive influence or by resonance. Two resonance cases, one showing electron withdrawal by a nitro substituent and the other electron donation by a methoxy substituent, are shown to the right of the green box.











Y	pK_a	Y	pK_a
CH_3	3.24	CH_3	4.33
Cl	1.60	Cl	3.50

The increased acidity of ortho-substituted benzoic acids is attributed to steric hindrance that forces the carboxyl group to twist out of the plane of the benzene ring. The inductive character of the phenyl group does not change with such twisting, but resonance (conjugative electron donation) requires a coplanar relationship. For example, ortho-toluic acid ($R^1 = CH_3$ & $R^2 = H$) has a pK_a of 3.9 compared with 4.2 for benzoic acid itself. If the methyl is changed to a larger *tert*-butyl group the pK_a drops to 3. 53. By sandwiching the carboxyl group between two ortho substituents, it is forced to lie perpendicular to the plane of the aromatic ring, and conjugation is prohibited completely. The dimethyl and dichlorobenzoic acid isomers shown at the lower right in the diagram provide dramatic evidence of this conformational effect, with the bis-ortho (2,6-) isomers representing the exclusive action of the inductive effect.
Steric interference with conjugation may also perturb the acidity of acyclic unsaturated acids. Thus, 2,3-dimethyl-2-butenoic acid has a pK_a of 4.41, compared with the 5.12 pK_a of 3-methyl-2-butenoic acid.

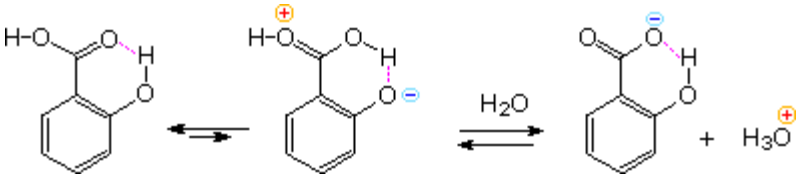
Hydrogen Bonding

The presence of a hydrogen bond donor near a carboxyl group may act to enhance its acidity, as demonstrated by the three isomeric hydroxybenzoic acids and three isomeric benzenedicarboxylic acids (phthalic acids) shown in the following table. Compared with benzoic acid, the meta and para-isomers display expected changes in acidity, due to combined inductive and resonance effects. However, the ortho isomers are both roughly 15 times more acidic, even though the hydroxyl and carboxyl substituents have opposite influences in the para-location.

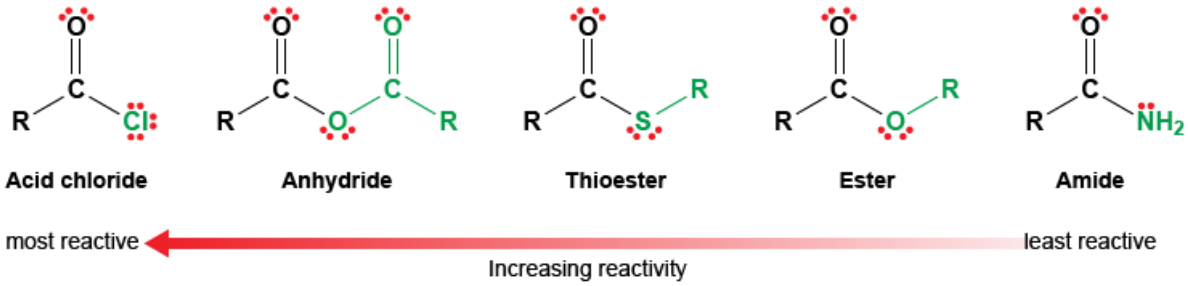
Orthorelationship	**pK_a^1**	**pK_a^2**	**meta relationship**	**pK_a^1**	**pK_a^2**	**para relationship**	**pK_a^1**	**pK_a^2**

salicylic acid	2.97	13.44	meta-hydroxybenzoic acid	4.08	9.91	para-hydroxybenzoic acid	4.58	9.40
phthalic acid	2.98	5.28	isophthalic acid	3.46	4.46	terephthalic acid	3.51	4.82

Intramolecular hydrogen bonding of an ortho OH donor to the carbonyl oxygen of the carboxyl group, acting as an acceptor, increases the positive charge on the carbonyl carbon and consequently the acidity of the carboxyl OH. This is illustrated for salicylic acid in the following diagram. Phthalic acid engages in a similar seven-membered cyclic hydrogen bond with a similar outcome. This intramolecular hydrogen bonding also explains the decreased acidity of the remaining acidic function - that is the phenolic OH in salicylic acid and the second carboxyl group in phthalic acid.



The stereoisomeric 2-butenedioic acids, maleic and fumaric acid display a similar behavior. The cis isomer, maleic acid, has pK_a^1 = 2.00 and pK_a^2 = 6.50. This contrasts with the values for the trans-isomer, fumaric acid, pK_a^1 = 3.00 and pK_a^2 = 4.50.



Reference: Libratext