Organic Chemistry-2

Semester-2, CBCS

Course: CEMA CC-2-3-TH

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Recommended texts:

The Concept of Acidity and Basicity in Organic Chemistry

Effect of structure on acid and base strength of organic molecules:

C) Resonance Effect: To judge the relative basicity of two given bases, we follow the same principle of charge/lone pair delocalisation. Greater the delocalisation of the lone pair of electrons, lower is the tendency for the base to capture proton, and lower is the basicity.

Recall that a convenient way to express basicity quantitatively is to quote the pKa of the corresponding conjugate acid. The weaker the base, stronger is the conjugate acid. Thus, greater the electron pair is delocalised, weaker is the base, stronger is the conjugate acid and smaller is the pKa.

Let us consider the basicity of the following aromatic amines:

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<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>NH₂</td>
<td>NH₂</td>
<td>NH₂</td>
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<tr>
<td></td>
<td>NO₂</td>
<td>NO₂</td>
</tr>
<tr>
<td>pKₐH</td>
<td>4.58</td>
<td>2.50</td>
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<tr>
<td>1.02</td>
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conjugate acid becomes progressively stronger basicity of the amines decreases

To explain this, we have to consider the availability of the lone pair on nitrogen in each case:

\[ \text{NH}_2 \]

For aniline, the lone pair of electrons on nitrogen is involved in resonance with the benzene ring.

\[ \text{NH}_2 \]

For \( p \)-nitroaniline, the lone pair of electron on nitrogen is involved in resonance with benzene nucleus and the -I effect of nitro group aids in dispersion of electron density over "N". In addition, here the amino group is in resonance with the nitro group that shows -R effect. The canonical forms are:

\[ \begin{align*}
\text{NH}_2 & \quad \longleftrightarrow \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\end{align*} \]

This electron withdrawal through resonance further contributes to decrease the electron density over nitrogen, leading to the lowest basicity.

So, on moving from left to right in the given series, the tendency to accept proton gradually decreases and thus we have the above order of basicity.
The Concept of Acidity and Basicity in Organic Chemistry

Effect of structure on acid and base strength of organic molecules:

C] Resonance Effect: For nitroanilines, extra base-weakening effect is observed when the nitro group is in ortho position.

The o-nitro group is evidently in conjugation with the amino group, just as it is in case of p-nitroaniline. The extra base-weakening effect is, however, due in part to the short distance over which the EW inductive effect of -NO₂ group is operating and also due to direct steric interaction and intramolecular H-bonding with -NH₂ as shown:

This alignment is believed to introduce quasi-aromaticity for which the lone pair on "N" is much less available as it becomes a part of the "aromatic" sextet.

Let us consider the relative basicity of aniline and cyclohexylamine:

\[
\begin{align*}
\text{NH}_2 & \quad \text{NH}_2 \\
pK_{\text{aH}} & = 10.68 \quad 4.58
\end{align*}
\]

The data suggests that the conjugate acid of aniline is a stronger acid than the conjugate acid of cyclohexylamine, implying that aniline is less basic than cyclohexylamine.

The explanation is fairly simple. The lone pair of electrons over nitrogen in aniline is involved in resonance with benzene nucleus and so it is less available to proton. No such resonance interaction exists for cyclohexylamine and it is thus the stronger base of the two.

Also consider the -l effect of the benzene ring that acts upon the nitrogen lone pair in aniline and reduces the basicity, while, for cyclohexylamine, the cyclohexyl ring exerts a +l effect that enhances basicity.
The Concept of Acidity and Basicity in Organic Chemistry

Effect of structure on acid and base strength of organic molecules:

C] Resonance Effect:

Revisiting the relative basicity of aniline and cyclohexylamine:

\[
pK_{aH} = 10.68 \quad 4.58
\]

Relative basicity order can be explained by delocalization of lone pair on N in case of aniline due to the \(-R\) and \(-I\) effect of the adjacent phenyl ring (seen previously).

An alternative approach, however, may be taken to rationalise the relative basicity of aniline and cyclohexylamine.

Aniline is stabilized through resonance with the participation of the lone pair of electrons on nitrogen. But no such stabilization is possible for the conjugate acid of aniline.

So the resonance stabilization involving the N lone pair is lost on protonation.

Protonation tendency is therefore low.

Protonation of cyclohexylamine does not include any such loss of resonance (there is no resonance to start with!) - so protonation tendency is high.

Cyclohexylamine is a stronger base than aniline (as seen in the \(pK_a\) values of the respective conjugate acids).

Note that this is again a resonance-based argument, but, instead of focussing on the availability of lone pair towards an incoming proton, this points to the loss of resonance stabilisation entailed with protonation of aniline.

Obviously, such base-weakening effect is expected to be more pronounced when further phenyl groups are introduced on the nitrogen atom. Thus, diphenylamine is a very weak base and triphenylamine is not basic at all.

\[
pK_{aH} = 0.8 \quad -5
\]
The Concept of Acidity and Basicity in Organic Chemistry

Effect of structure on acid and base strength of organic molecules:

C] Resonance Effect: From the above study we can infer that introduction of electron-donating substituents in the benzene nucleus of aniline will enhance its basicity.

Thus alkyl substituted anilines are expected to be more basic than aniline. We have the following data:

As per our expectation, the m- and the p-methylaniline (also known as toluidines) are more basic than aniline.

The electron-donating \(+I\) effect of the methyl group enhances the basicity for the m-isomer.

In addition to the \(+I\) effect, for the p-isomer, the methyl group can exert electron-donating hyperconjugative effect that further enhances the basicity.

In other words, the conjugate acid for the p-isomer the conjugate acid is more stabilized in comparison to that of the m-isomer as methyl group from p-position can exert the electron-donating hyperconjugative effect more effectively.

However, the o-isomer shows an anomalous result and, contrary to our expectation, is actually less basic compared to aniline.

The reason behind such anomaly is not absolutely known.

This result may be due to cumulative effects arising out from steric effect, solvation effect and other associated factors.

This type of atypical behaviour is often referred to as "Ortho Effect".
The Concept of Acidity and Basicity in Organic Chemistry

Effect of structure on acid and base strength of organic molecules:

C] Resonance Effect: Let us consider the basicity trends of aminophenols and anisidines.

Both the -OH and -OCH₃ groups both have unshared pair of electrons and can exert the +R effect from α- and ρ-positions to intensify the electron density over the ring and consequently increase the basicity of these molecules.

In other words, these groups, when placed at the α- or ρ-positions w.r.t. the NH₂, are better able to stabilise the conjugate acid via electron donation.

The +R effect cannot operate when these groups are placed at the ρ-position and consequently, the ρ-isomer is expected to be a stronger base than m-isomers.

This is actually the case.

It is important to note that the ρ-isomers are found to be weaker bases than aniline itself, due to electron-withdrawing, base-weakening -I effect of oxygen.

The -I effect of the OMe and OH group also operates when they are placed ρ- w.r.t. the ammonium, but +R effect of those groups is more powerful at those positions, so we neglect the -I effect for these isomers.

Again, the effect of the ortho-substituent remains somewhat anomalous, most probably due to direct interaction of the substituent with the -NH₂ group by steric and polar effects.

- I effect destabilises the conjugate acid, proton release tendency relatively higher than the conjugate acid of aniline

(R = Me or H)

- I effect destabilises the conjugate acid; however, +R effect stabilises the conjugate acid to a much greater extent, so the -I effect is ignored. Also note that inductive effect decreases with increasing distance, so it should be much weaker at the para position.
The Concept of Acidity and Basicity in Organic Chemistry

Effect of structure on acid and base strength of organic molecules:

C) Resonance Effect: Let us compare the basicity of an amidine (carrying the \(-\text{C(\text{NH})NH}_2\) moiety) with that of a common amine:

The amidine is thus a stronger base than the amine.

To explain this, we may consider the stabilities of the bases with that of corresponding conjugate acids.

The conjugate acid from ethylamine is

\[
\text{Me}^+\text{NH}_3
\]

which may be stabilized by the +1 effect of ethyl group and through solvation.

Now we have to draw the conjugate acid from ethanamidine. This poses a selectivity problem, as there are two nitrogen atoms that can be protonated. Out of these two possible sites, only one gets preferentially protonated.

This regioselectivity is easily explained by considering the stability of the respective conjugate acids:

This is not completely new to you, recall that you did decide on the preferential site of protonation for 1,3-butadiene when reacting with HBr in this way.

(HW: Noting the preferred site of protonation of amidine, think carefully where protonation would take place, if you try to protonate a carboxylic acid by, say, concentrated sulphuric acid. Of course, the carboxylic acid is acting as a base in this case.)

Now that we have identified correctly the conjugate acid from ethanamidine, let us look at the factors that contribute to stabilise it.

The conjugate acid derives stabilisation from -

i) +1 effect of the methyl group and

ii) through resonance, as outlined above. We redraw the canonical forms once again:

The resonance stabilization is particularly effective as the canonical forms are equivalent.

Just as with phenols and carboxylic acids, one may argue that ethanamidine itself is resonance stabilized, and the canonical forms are:

But this entails separation of charge and consequently, the resonance stabilization is less effective.

So the thermodynamic stabilization of the conjugate acid of ethanamidine is greater than that of ethylamine. Thus ethanamidine has a higher tendency to accept proton in comparison to ethylamine. So we have the above order of basicity.
The Concept of Acidity and Basicity in Organic Chemistry

Effect of structure on acid and base strength of organic molecules:

C] Resonance Effect: The exceptionally high basic nature of guanidine, 

\[
pK_{aH} \text{ (guanidine)} = 13.6
\]

is due to the large stabilization of the conjugate acid guanidinium ion gathered through resonance. The canonical forms are:

The three equivalent canonicls imply high degree of resonance stabilisation resulting in the unusually high acidity.

The resonance in guanidine is associated with charge separation, so it is much less effective.

We also understand why guanidine is more basic than amidine, just by counting the number of equivalent canonicls of the respective conjugate acids. It is three for guanidine and two from amidines like acetamidine. So the basicity of guanidine is higher.

Compared to the highly basic ethanamidine and guanidine, urea, that bears some structural similarity with the previous two, shows a remarkably low basicity:

This apparently anomalous result becomes clear if we consider the resonance stabilisation of the base itself and the corresponding conjugate acid:

resonance in urea:

resonance in conjugate acid of urea:

Make sure you understand why protonation of urea takes place on the more electronegative oxygen and not on either of the two nitrogen atoms.
The Concept of Acidity and Basicity in Organic Chemistry

Effect of structure on acid and base strength of organic molecules:

C) Resonance Effect:

The basicity of guanidine and amidine and the lack of basicity of urea can be explained by considering the following points:

\[
\begin{align*}
\text{guanidine} & : & \text{NH} & \text{N} & \text{H}_2 & \\
\text{pK}_a \text{H} & : & 13.6 & & & \\
\text{ethanamide} & : & \text{NH} & \text{Me} & \text{N} & \text{H}_2 & \\
\text{pK}_a \text{H} & : & 12.4 & & & \\
\text{urea} & : & \text{O} & \text{N} & \text{N} & \text{H}_2 & \\
\text{pK}_a \text{H} & : & 0.10 & & & \\
\end{align*}
\]

i) The difference between guanidine or amidine and urea is the heteroatom that is protonated - nitrogen for both guanidine and amidine, and oxygen for urea. Oxygen is more electronegative and reluctant to give up its electrons while nitrogen can do that comparatively easily. Thus guanidine and amidine is more basic than urea.

ii) The resonance in the basic species is more effective in urea, than it is in guanidine or amidine. This is because the negative charge in the charge-separated canonical resides on the more electronegative oxygen in urea, while for guanidine and for acetamidine, it is on the less electronegative nitrogen. The overall effect of this difference is that resonance in urea is more effective than it is in guanidine or acetamidine, resulting in lower basicity of urea compared to the other two.

iii) Urea can be considered as an amide derivative while guanidine and acetamidine are not. Thus the pK\text{aH} of urea is typically close to that of amides:

\[
\begin{align*}
\text{urea} & : & \text{O} & \text{N} & \text{H}_2 & \\
\text{pK}_a \text{H} & : & 0.10 & & & \\
N,N\text{-dimethylacetamide} & : & \text{Me} & \text{N} & \text{Me}_2 & \\
\text{pK}_a \text{H} & : & -0.5 & & & \\
\end{align*}
\]

This is not an explanation per se, and when we venture to explain why the amide's pK\text{aH} is so low, we will have to invoke the same arguments as outlined in points i) and ii).

However, this point does emphasize that the basicity of urea is expected to be widely different from that of guanidine and amidines as they are very different species from one another.

For comparison's sake, we have the following order of basicity,

\[
\begin{align*}
\text{urea} & \rightarrow & \text{acetamidine} & \rightarrow & \text{guanidine} \\
\text{basicity increases} & & & & \\
\end{align*}
\]
The Concept of Acidity and Basicity in Organic Chemistry

Effect of structure on acid and base strength of organic molecules:

C] Resonance Effect:

Let us consider the relative basicity of pyrimidine and acetamidine:

\[
\begin{align*}
\text{pyrimidine} & \quad \text{NH} \\
\text{acetamidine} & \quad \text{H}_3\text{C} - \text{NH}_2
\end{align*}
\]

\[\text{pK}_{\text{a,H}} = 1.3 \quad \text{12.4}
\]

basicity increases

At a first glance this result may seem surprising because the same type of N-C=N linkage is present in both these compounds, but, a closer inspection reveals that linkages are very different from one another.

In acetamidine, the N lone pair on NH\(_2\) resides on a p-orbital and it is able to come into conjugation with the adjacent C=N grouping,

In pyrimidine, the lone pairs on both nitrogens reside on sp\(^2\)-orbitals and being orthogonal to the adjacent C=N bonds, cannot participate in resonance.

The overall effect is that the conjugate acid of acetamidine is resonance-stabilised while that of pyrimidine is not.

The following diagram is instructive:

\[
\text{conjugate acid of acetamidine} \quad \text{resonance between N-Lp and C=N bond possible}
\]

\[
\text{conjugate acid of pyrimidine} \quad \text{resonance between N-Lp and C=N bond impossible}
\]

In other words,

\[
\begin{align*}
\text{resonance-stabilised} & \quad \text{resonance not possible}
\end{align*}
\]

That we are dealing with very different systems is actually evident from the start. The two N-atoms of acetamidine is non-equivalent, but the two of pyrimidine are.
The Concept of Acidity and Basicity in Organic Chemistry

Effect of structure on acid and base strength of organic molecules:

C] Resonance Effect:

What we have illustrated in the preceding example is the lack of resonance due to improper orbital alignment. A further example is the following series of compounds:

\[
\begin{align*}
N,N\text{-dimethylaniline} & \quad \text{p}K_a &= 5.20 \\
\text{benzoquinuclidine} & \quad \text{p}K_a &= 7.79 \\
\text{quinuclidine} & \quad \text{p}K_a &= 10.65
\end{align*}
\]

basicity increases

The comparison between the aromatic amine \(N,N\text{-dimethylaniline}\) and the aliphatic amine \(\text{quinuclidine}\) is pretty straightforward. The electron-withdrawing -I and -R effect of the phenyl ring work in unison to reduce the electron pair availability in the former, while the +I effect of the three alkyl chains in \(\text{quinuclidine}\) increases its affinity towards protonation.

\(\text{Benzoquinuclidine}\) is, however, a different thing altogether. It is like the aromatic amine but the N-lone pair cannot take part into conjugation here as the bicyclic nature of the compound forces the orbital carrying the electron pair on N to be almost orthogonal to the \(\pi\)-system of the ring. So it is expected to be more basic than \(N,N\text{-dimethylaniline}\).

On the other hand, the strong -I effect of the \(sp^2\)-carbon of the benzene ring in \(\text{benzoquinuclidine}\) reduces the same lone pair's availability in comparison to that of \(\text{quinuclidine}\). Thus \(\text{benzoquinuclidine}\) is less basic than \(\text{quinuclidine}\).
The Concept of Acidity and Basicity in Organic Chemistry

Effect of structure on acid and base strength of organic molecules:

C) Resonance Effect: An outcome of the concept of resonance through conjugation via one or more vinyl group(s) is the "principle of vinyllogy". It is often a common pattern to consider the acidity or basicity of several compounds where there is conjugation through vinyl group.

Consider the molecule squaric acid which is a pretty strong acid in terms of organic standards with two $pK_a$ values being 1.54 and 3.48 respectively.

These $pK_a$ values suggest that these hydroxyl protons are even more acidic than protons of a typical carboxylic acid!

This exceptionally low first $pK_a$ has been attributed to:

i) dipole-dipole repulsion between the adjacent C-O dipoles in the parent acid, which is to some extent alleviated upon deprotonation,

ii) the effective dispersal of the negative charge in the conjugate base through resonance where the two canonical forms are equivalent:

It is evident that the OH group of squaric acid not just an alcoholic hydroxyl, rather, it is more like the hydroxyl group of a carboxylic acid, only difference is that here the OH is separated from the C=O by a vinyl (C=C) unit.

It is thus not surprising that the first ionisation of squaric acid is much more favoured than that of an alcohol.
The Concept of Acidity and Basicity in Organic Chemistry

Effect of structure on acid and base strength of organic molecules:

C] Resonance Effect: The principle of vinylogy can be extended in case of the second deprotonation of the squaric acid molecule as well. Note that the second pKa is exceptionally low but it is higher than the first pKa.

In fact, the second deprotonation is expected to be inhibited by the charge repulsion in the resulting dianion.

This dianion is, however, also expected to have charge dispersion due to extensive conjugation, represented by four equivalent canonicals:

Likewise, possible aromatic character and concomitant stabilization of the dianion involving a cyclobutadienyl cation ring system is also considered to be another possible factor contributing to such a low second pKa of squaric acid.

In the same token, p-hydroxybenzaldehyde and p-nitrophenol can be thought of as vinylogous acids of formic acid and nitric acid respectively.

These two substituted phenols are indeed much more acidic than phenol itself (pKₐ of phenol 9.95), but these are several orders of magnitude less acidic than the 'parent molecules', i.e. formic acid and nitric acid. This is probably because, unlike the case of squaric acid as discussed above, here the vinylogous conjugation in the anion disrupts the aromaticity of the intervening benzene ring and is consequently less effective. In the parent molecules' conjugate base, the dispersion of negative charge through resonance is markedly good, as evident from equivalent canonicals.

Another factor responsible for such disparity in acidity is undoubtedly the poorer solvation of the phenoxides in the aqueous medium compared to smaller anions formate and nitrate.
The Concept of Acidity and Basicity in Organic Chemistry

Effect of structure on acid and base strength of organic molecules:

C) Resonance Effect: As we have seen previously, resonance is one of the most vital factors that controls the acidity and basicity of many organic molecules. Lack of resonance, where it is expected, also has similar role in throwing up unexpected results.

Consider the relative acidity of the following compounds:

\[
\text{Cyclohexane-1,3-dione is an active methylene compound and when treated with a base, it undergoes regioselective deprotonation from the methylene carbon that is flanked by two carbonyl groups. The negative charge in the conjugate base is dispersed here through conjugation with the two adjacent carbonyl groups:}
\]

Thus the methylene protons flanked by two carbonyls are very acidic (\(pK_a 4.8\)) and are easily abstracted by alkali.

But in the case of

\[
\text{the conjugate base is:}
\]

Here dispersion of negative charge through conjugation with the carbonyls is not possible because of the lack of coplanarity of the p-orbitals of the carbonyl groups with the orbital containing the electron pair. Almost orthogonal orbitals, barely any overlap

Thus the bridgehead protons are not acidic at all and cannot be abstracted by alkali.

This is very similar to the case of benzoquinuclidine, where, the N-l.p. cannot come into conjugation with the adjacent benzene ring and consequently, shows a greater basicity than otherwise expected.
The Concept of Acidity and Basicity in Organic Chemistry

Effect of structure on acid and base strength of organic molecules:

C) Resonance Effect: You have just witnessed a couple of cases where resonance is hampered due to the misalignment of involved orbitals enforced by the geometrical and structural constraints of the molecules.

There may also be the classic steric inhibition of resonance.

For example, \(N,N\)-dimethylanilnine and aniline have nearly the same basicity.
But \(N,N\)-dimethyl-2,4,6-trinitroaniline is 40,000 times more basic than 2,4,6-trinitroaniline.

In order to explain this, we have to look at the availability of the N-Lp in each of these cases.

Due to the presence of the two electron-donating methyl groups on the N-atom, the \(N,N\)-dimethylaniline is slightly more basic than aniline, as evident from the pKaH data.

If we place a nitro group either ortho or para w.r.t. the amine moiety, the N-Lp., due to conjugation, will become less available for protonation, i.e. the basicity will be lowered.

Let us inspect if this type of conjugation can take place for \(N,N\)-dimethyl-2,4,6-trinitroaniline and 2,4,6-trinitroaniline:

Now in this case, conjugation between the N-Lp. and the aryl ring is absent because of the steric clash between the N-methyls and the o-nitro groups, that forces the amino group out of the plane of the aryl ring plane. This loss of conjugation is steric inhibition of resonance.

On the other hand, in this case, the conjugation is feasible as the steric interaction, because of the smaller size of hydrogen of \(\text{NH}_2\), is far less severe.

In addition, for 2,4,6-trinitroaniline, the following intramolecular H-bonding in fact helps to keep the amino group and nitro groups in the same plane as that of the aryl ring:

As a result, a quasi-aromaticity is introduced and the above type of conjugation is more pronounced.

Thus the unshared pair of electrons on the dimethylamino group is more available than that of the amino group in 2,4,6-trinitro derivative.
As a result, \(N,N\)-dimethyl-2,4,6-trinitroaniline exhibits exceptionally high basicity and is 40,000 times more basic than 2,4,6-trinitroaniline.
The Concept of Acidity and Basicity in Organic Chemistry

Effect of structure on acid and base strength of organic molecules:

C] Resonance Effect: Steric inhibition of resonance can also explain the following result:

\[
\begin{align*}
&\text{OH} & & \text{OH} \\
&\text{OH} & & \text{NO}_2 \\
&\text{Me} & & \text{Me} & & \text{Me} & & \text{NO}_2 \\
&9.98 & & 7.14 & & 10.18 & & 8.25
\end{align*}
\]

\[\Delta pK_a = 2.84 \quad \Delta pK_a = 1.93\]

In other words, introduction of a NO\textsubscript{2} at the \( p \)-position of the aryl ring enhances the acidity of phenol to a much greater extent than it does for 3,5-dimethylphenol.

In the 3,5-dimethyl-4-nitrophenol, the nitro group is forced out of plane by the adjacent methyls on C-3 and C-5, thus compromising the resonance stabilisation of the corresponding phenoxide.

No such problem exists for 4-nitrophenol, and the nitro group's acid-strengthening effect is much more prominent there.

Thus, the conjugate base from the 4-nitrophenol has a greater resonance stabilisation and lower tendency to pick up a proton than the conjugate base of the 3,5-dimethyl-4-nitrophenol, and we have the observed acidity trend.