

1. Categorize the following acids/bases pairs as Arrhenius, Brønsted–Lowry and/or Lewis pairs. [☆]
 - HCl bubbled in water: **Arrhenius, Brønsted–Lowry and Lewis.**
 - BF₃ in a diethyl ether solution: **Lewis.**
 - Boric acid (B(OH)₃) dissolved in water: **Arrhenius, Brønsted–Lowry and Lewis.**
 - Fe(III) center coordinating acetylacetonate ligands **Lewis.**
2. Qualitatively predict the position of the following equilibria. [☆]

The species that will be predominantly found are highlighted in bold:



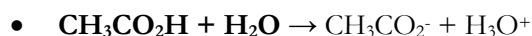
HCl is a strong acid (pK_a < 0), which can quantitatively protonate amines.



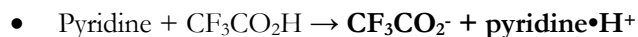
Tertiary amines are more basic than secondary ones, thanks to the electron-donating effect of alkyl substituents.



The pK_a of HBr is -9 (in water), while the first pK_a value for sulfuric acid is -3.0.



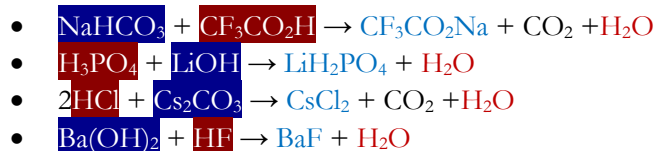
Acetic acid is a weak acid (pK_a approx. 5), therefore it is found mostly non-dissociated in water.



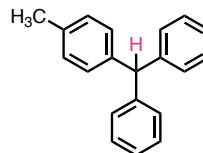
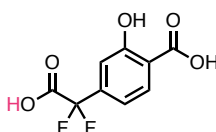
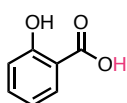
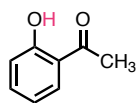
Trifluoroacetic acid is a strong acid, and pyridine can act as base and undergo quantitative protonation.

3. Indicate the acid and base reactants and define their conjugate base and acid. [☆]

Acids are highlighted in red, bases in blue; their corresponding conjugates with colored text:

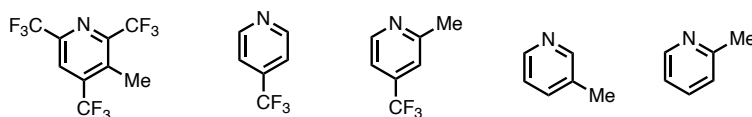


4. Indicate the proton with the lowest pK_a in the following molecules. [☆☆]

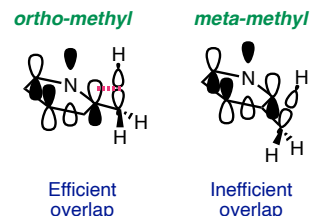


The first molecule contains a phenol moiety, that has pK_a of approximately 10. The α-carbonyl position is substantially less acidic. In the case of the second molecule, the carbonyl acid portion is the most acidic, followed by the phenolic moiety. In the third case, between the two carbonylic acid fragments, the α,α-difluorophenyl part is increasingly acidic due to inductive effects. The fourth molecule features two benzylic positions: the one adjacent to three aryl groups (trityl) is the most acidic, mainly due to stabilizing resonance effects on the ensuing carbanion.

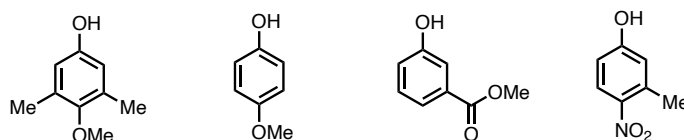
5. Order the following molecules according to increased basicity. [☆☆]



In all molecules, the pyridine lone pair is the center of basic reactivity. Inductive and mesomeric effects influence the availability of the lone pair, and thus its basicity. Trifluoromethyl groups exert a strong inductive electron-withdrawing effect, which reduces the basicity. On the other hand, methyl groups increase the heterocycle basicity *via* inductive effect. *Ortho* substitution exerts a bigger influence over *meta* substitution, which we can assess in terms of hyperconjugative molecular orbitals (interaction between the pyridine fragment LUMO and the σ_{C-H} orbital).

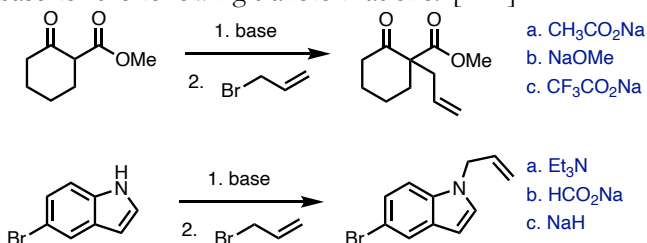


6. Order the following phenols according to increased acidity. [☆☆]



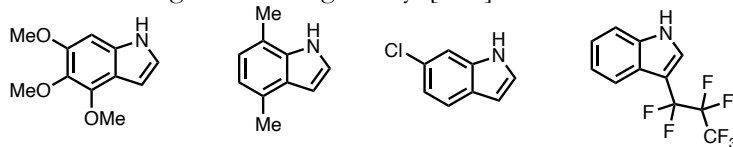
An increased number of electron-donating groups (methyls, methoxys) reduces the relative acidity of the phenol moiety. *Para*-positioned nitro groups exert the most intense electron-withdrawing effect, thus increasing the acidity of the phenol. Esters are electron-withdrawing, but their effect is mitigated when occupying the *meta*-position.

7. What is the most suitable base for the following transformations? [☆☆]



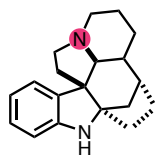
In the first case, the 1,3-dicarbonyl compound is increasingly acidic, due to the highly mesomeric stabilizing effect on the ensuing carbanion. Therefore, sodium methylate (pK_a approx. 16) represents a suitable base (b), while both trifluoroacetate and acetate are not strong enough to promote its quantitative and rapid deprotonation. In the second case, sodium hydride (c) is the only strong enough base to promote the quantitative deprotonation of indoles.

8. Order the following indoles according to increasing acidity. [☆☆]

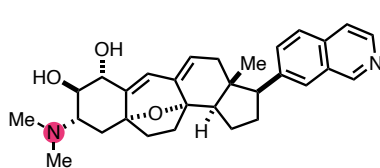


Analogously to previous exercises, electron-withdrawing groups increase the acidity of the corresponding system, while electron-donating ones reduce its acidity. Methoxy groups are stronger donors than methyls, thus causing the highest acidity reduction. Among electron-withdrawing groups, perfluorinated substituents exert a strong inductive effect than simple halides, and thus have the biggest impact on acidity.

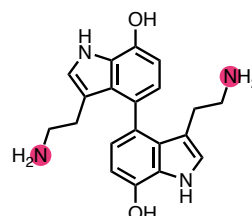
9. Indicate the most basic atom for each of the following natural products. [☆☆]



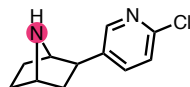
Aspidofractinine



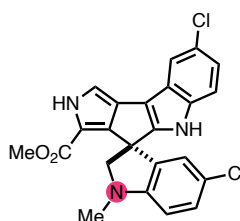
Cortistatine A



Dendridine A



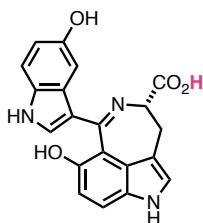
Epibatidine



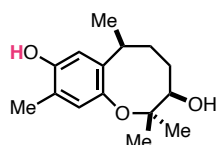
Spiroindimicin B

In the case of aspidofractinine, the tertiary aliphatic amine is more basic than the secondary aniline moiety, due to the absence of electron-withdrawing effect from the phenyl moiety and increased donation from the additional substituent. In the case of cortistatine A, the aliphatic tertiary amine is more basic than the isoquinoline fragment. For symmetric dendridine A, the primary aliphatic amine group is substantially more basic than the indole fragment. The same applies for epibatidine, where the secondary bicyclic aliphatic amine is substantially more basic than the chloropyridine moiety. For spiroindimicin B, both indole and pyrrole cores are less basic than the tertiary aniline fragment. In general, observation regarding the presence of either aliphatic or aromatic N-containing species, as well as the extent and identity of their substitution, define their increased or decreased basic character.

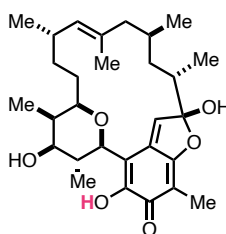
10. Indicate the most acidic atom in each of the following natural products. [☆☆]



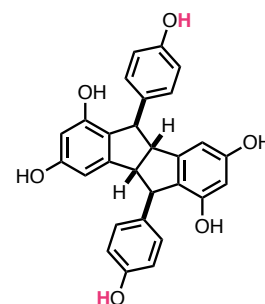
Hyrtiazepine



Hellannuol A



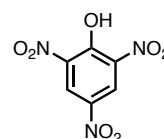
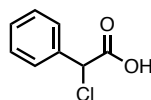
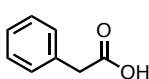
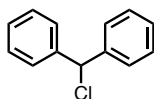
Kendomycin



Pallidol

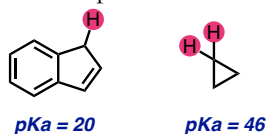
For hyrtiazepine, we consider the indole, two phenols and carboxylic acid moieties to be increasingly acidic. Carboxylic acids are comparatively more acidic than the other moieties. For hellannuol A, two alcohols, phenol, and aliphatic alcohol must be compared. The former is substantially more acidic, due to resonance stabilization of the corresponding conjugate base. For kendomycin, the enol proton is increasingly acidic due to resonance stabilization of the conjugate base and potential aromaticity of its resonance structures. For symmetric pallidol, phenol systems substituted with less-donating substituents are predicted to be more acidic than their resorcinol-based counterparts.

11. Order these molecules from the least acid to the most acidic. [☆☆]



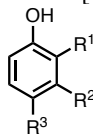
Chlorodiphenylmethane does not have heteroatom attached protons, therefore is the least acidic, followed by phenylacetic acid. Addition of chlorine at the alpha position increases its acidity due to inductive effect. Picric acid is the most acid species, as three nitro-groups exert strong EWG effect and stabilize the negative charge on the conjugate base via mesomeric effect.

12. Explain the pKa of the following molecules in comparison to other alkanes. [☆☆]



For indene, the corresponding conjugate base (indenyl anion) is aromatic ($4n+2$, $n = 2$), and therefore the high stability of the conjugate base renders the species highly acidic. In the case of cyclopropane, each C–C bond is characterized by a high π -component since ring-strain causes less-than-ideal σ -overlap (“banana bonds”). The presence of substantial π -bond component can alternatively be described the cause of carbon hybridizations that deviate from the ideal sp^3 . The increased s -character (cf. olefinic proton acidity) renders then ensuing negative charge more stabilized than sp^3 centers, and therefore enhances the stability of the conjugate base (carbanion).

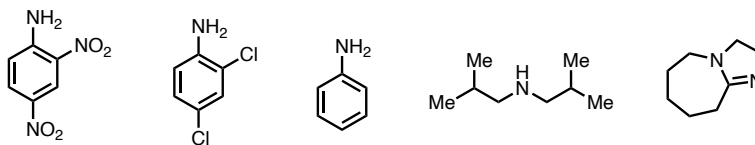
13. Describe the variation of acidity of the following phenol: [☆☆]



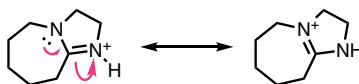
When:

- R^1 is bromo: acidity increases due to inductive electron-withdrawing effect of the substituent.
- R^2 is dimethylamino: acidity decreases, due to the electron-donating effect of the substituent. In the case of amine substituents, the inductive withdrawing effect is substantially negligible when compared to the mesomeric donating effect.
- R^1 is nitro: acidity increases due to mesomeric electron-withdrawing effect of the substituent. The corresponding conjugate base is highly stabilized by the presence of the group.
- R^3 is methoxy and R^2 is cyano: there are two competing effects. The methoxy group releases electron density, thereby reducing the acidity of the system, while the cyano group withdraws electron density from the ring.

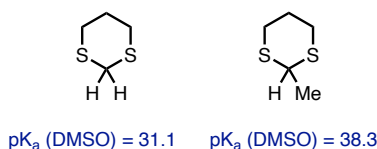
14. Order the following N-containing compounds according to increasing basicity. [☆☆]



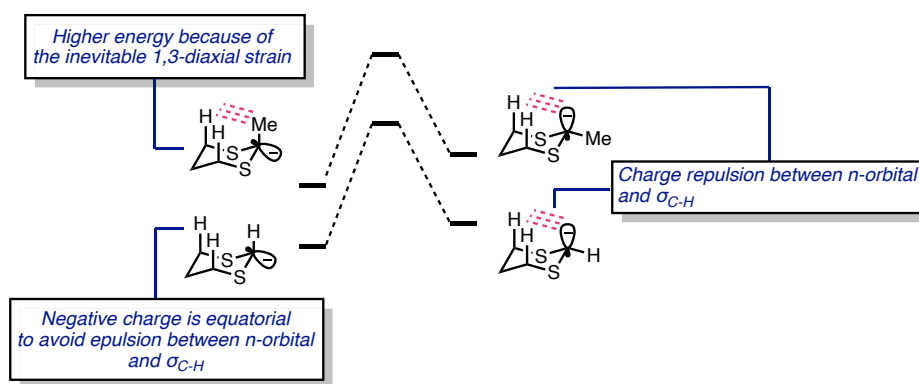
In general, aliphatic amines are more basic than anilines. Aliphatic substituents can donate electron-density *via* inductive effects, while aromatic substituents have a mesomeric withdrawing effect (one can represent it with resonance structures where the nitrogen lone pair is delocalized onto the aromatic ring). Among anilines, the presence of electron-withdrawing groups reduces their basicity, with nitro-groups exerting the most relevant effect. DBU represents a particular strong, non-nucleophilic base. Amidine species are increasingly basic due to the stabilization of the corresponding conjugate acid *via* mesomeric effect (see resonance structure below).



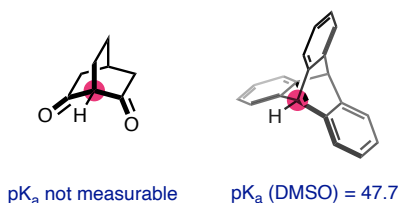
15. Hypothesize the reason of the substantial pK_a difference between the two compounds: [☆☆☆]



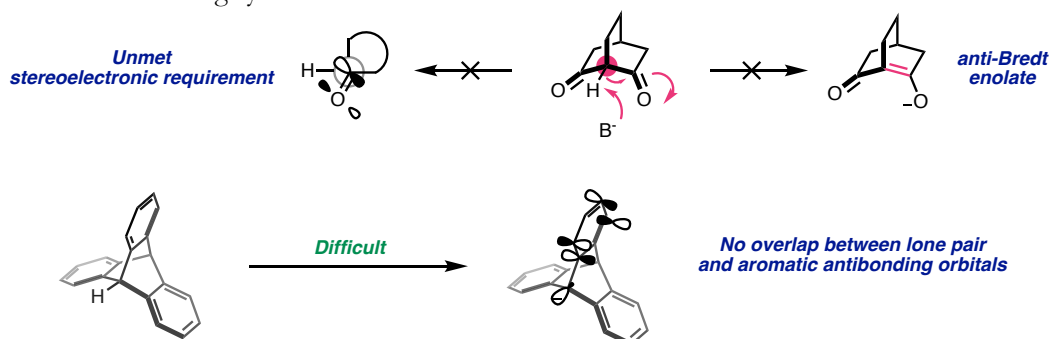
It is commonly assumed (*J. Am. Chem. Soc.* **1975**, 97, 190–191) that the dithianyl anions adopt a conformation with the negative charge adopting an equatorial conformation (reduced electron repulsion between the negative charge and the σ_{C-H} electron density). Then, if a substituent is placed on the same carbon, 1,3-diaxial strain destabilize the conjugate base, and therefore reduced the acidity of the dithiane species.



16. Explain the anomalous pK_a values: [☆☆☆]



In the case of the first molecule, the experimental pK_a value is substantially higher than a typical 1,3-dicarbonyl compound, and cannot be experimentally measured. Two explanations can account for this observation. To ensure π-delocalization to the negative charge on the carbonyl system, planarization of the carbon atom is required. Planarization creates a bridgehead alkene, which is predicted to be a high energy species according to the Bredt's rule. One can compare this situation as analogous to a *trans*-double bond across a small ring system.



Furthermore, there is an implicit stereoelectronic requirement that must be satisfied: the $\sigma_{\text{C-H}}$ bond that is being broken must be antiperiplanar to the $\pi^*_{\text{C=O}}$ system, since the two orbitals must combine to forge the new enolate π -system. Hypothetically, an α -carbonyl anion could be generated. These species cannot exist, due to the repulsion between negative charge and oxygen lone pairs.

In the case of trypticene, despite being a bridged trityl system, its acidity is surprisingly low. Once again, stereoelectronic effects explain the experimental observation. The orbital hosting the negative charge cannot engage productive overlap with any of the aromatic rings (it is on the nodal plane of each system, see figure), thus making the conjugate base substantially unstabilized. The pK_a value is comparable to a regular alkane (*e.g.* *tert*-butane).