Organic Acids without a Carboxylic Acid Functional Group

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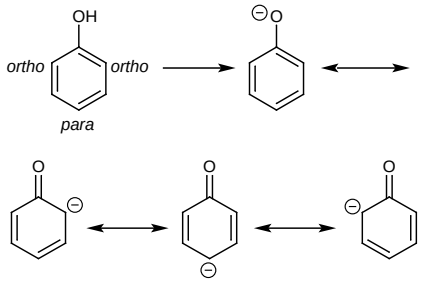
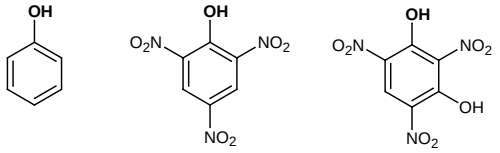
"Acid" is derived from the Latin *acidus*, to be sour; often any compound (organic or inorganic, with or without the carboxyl group) that provided a sour taste to its discoverer was termed an acid. However, modern IUPAC rules associate this organic nomenclature specifically with carboxylic acids. It could be misconstrued that all organic "acids" must contain a carboxyl group, but certain acidic organic compounds do not formally contain this functionality. Their names can belie their structures. In this article, instead of surveying all acids that are not carboxylic acids, we will concentrate on those common organic compounds that provide a simple name yet lack an easily discernible acidic proton. We have divided the review into three parts, into which most of these compounds can be distributed: phenolic-type acids, vinylogous carboxylic acids, and carbon acids.

Group I: Phenolic-Type Acids

The acidity of phenols is greater than that of normal alcohols; for example, unsubstituted phenol (pK_a = 9.89) is more acidic than the saturated alcohol, cyclohexanol (pK_a = 17) (*1*). In phenolic-type acids, the OH group is attached to an sp^2 hybridized carbon, which by induction withdraws more electron density away from the proton (ground state destabilization) than the sp^3 carbon does in cyclohexanol. Moreover, the phenolate anion can be delocalized by resonance to the ortho and para positions (product stabilization), which is lacking in the aliphatic analog (*2*). As the substitution pattern on the aromatic ring changes, the acidity of the OH group on the phenol changes. For example, nitro groups placed in the ortho and para positions are strongly electron-withdrawing and three of these groups have a large effect on the acidity (see Scheme I and structures below) (*3*). Some heterocyclic compounds with phenolic-type structures also show high acidity.

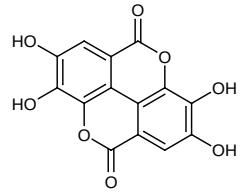


Scheme I. Resonance structures of deprotonated phenol.

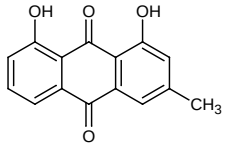


Carbolic Acid pK_a = 9.89 | Picric Acid pK_a = 0.38 | Styphnic Acid $pK_a \approx 0$

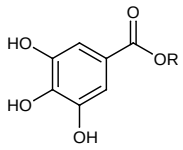
Many hydroxybenzene compounds (phenols) were isolated long before their actual structure was determined and so were named on the basis of their acidity. The "carbolic acid" that Lister used for the sterilization of operating theaters was an aqueous solution of phenol. Picric acid (Greek *pikros* [bitter]) and styphnic acid (Greek *styphnos* [contracting, astringent]) were also obviously named after their properties, not their structure. Note that many natural products listed as acids (e.g., ellagic acid from gallnuts, chrysophanic acid from rhubarb, tannic acid from oak, and usnic acid from lichen) are actually phenols (*4*).



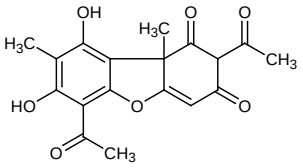
Ellagic Acid



Chrysophanic Acid

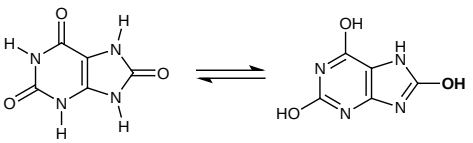


Tannic Acid Subunit

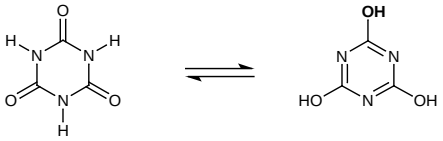


Usnic Acid

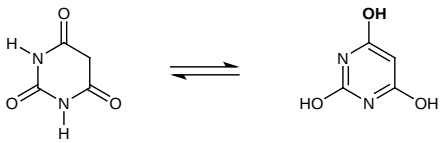
The cyclic ureides are derivatives of urea (H_2NCONH_2), one of the building blocks of nature. Interestingly, whereas urea is neutral (or slightly basic, since it forms salts with strong acids), the derivatives shown here are strongly acidic. Part of the acidity can be attributed to the production of tautomeric forms in solution. The tautomerization between the oxo form and the hydroxy form greatly affects the intramolecular H-bonding and the acidity of the proton. Also, it can be seen from the hydroxy structures that they form 6-membered rings analogous to phenol, with a hydroxy group attached to an aromatic ring. This tautomer is expected to be deprotonated.



Uric Acid pK_{a_1} = 5.4



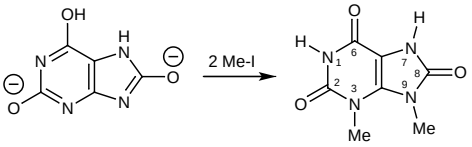
Isocyanuric Acid pK_{a_1} = 6.88



Barbituric Acid pK_{a_1} = 4.01

Isolated from human urine independently by Scheele and Bergman in 1776, uric acid (also known as lithic acid) is the oldest known of these ureides (*5*). It is ubiquitous in nature. Aside from being present in some seeds and plant parts, all carnivorous mammals have a few percent in their urine, blood, and muscle (and too high a concentration in humans leads to precipitation of the sodium salt as kidney stones or gouty deposits in certain joints). Large amounts of the ammonium salt are found in the excrement of birds, scaly reptiles (especially snakes), and some insects (e.g., caterpillars).

Several structures were initially suggested for this compound. The correct tricarbonyl structure (purine-2,6,8(1H, 3H,9H)-trione) was predicted by Medicus in 1875 and confirmed by Emil Fischer in 1883. Fischer also discovered that uric acid formed both a monosodium and a disodium salt (but not a trianion), which he predicted was due to the deprotonation of the trienol tautomer at the C2 and C6 hydroxy groups. Contrary evidence was provided when the dianion was methylated and found to provide the N3, N9 dimethyl compound, indicating that it is the C2–O and C8–O that are deprotonated (Scheme II). Of all the protons in the trienol structure, the hydroxy group on C8 (with the imine toward N9) is considered to be the most acidic (*6*).

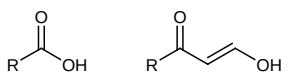


Scheme II. Methylation of the dianion of uric acid.

(Iso)cyanuric acid exists as an interconverting mixture of several possible tautomers, including the tricarbonyl (triazine-2,4,6(1H,3H,5H)-trione, also known as isocyanuric acid) and trienol (2,4,6-trihydroxy-1,3,5-triazine, or cyanuric acid) (*7*). The predominant tautomeric form in the solid state and in solution is isocyanuric acid; in basic solution the enol form is more stable. Undoubtedly, its acidity is due to removal of a proton from the hydroxy group in the enolic (cyanuric) form.

The rich history and the naming of barbituric acid has been reviewed (*8*). Both in the solid state and in aprotic solutions, the trioxo form (2,4,6-(1H,3H,5H)-pyrimidinetrione) is the only structure detected (*9*). In basic solution, the acidic proton is not removed from the central carbon but rather from the oxygen of the hydroxy tautomer (unlike Meldrum's acid, see below). It is believed that deprotonation of the enolic proton is favored owing to the greater resonance delocalization of the resulting anion.

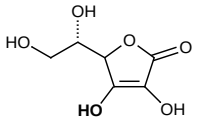
Group II: Vinylogous Carboxylic Acids



Carboxylic Acid | Vinylogous Carboxylic Acid

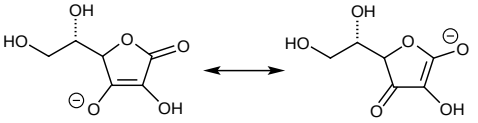
A common theme among some acidic compounds can be viewed through the "vinylogous" principle (*10*). The juxtaposition of a hydroxy group in conjugation with a carbonyl can be thought of as a "vinylogous carboxylic acid"—the proton behaves as if it were attached to a carboxylic acid rather than an alcohol. The acidic proton is on an oxygen connected to an electronegative sp^2 hybridized carbon, increasing its acidity relative to that of a simple alcohol. Recent calculations (*11, 12*) indicate that the acidity of these systems increases as the number of vinyl groups separating the hydroxy and the carbonyl groups increases. The calculated increase in acidity can be thought to arise from the dispersal of the negative charge between the two oxygens in the anion.

A 6-carbon carbohydrate derivative, originally christened hexuronic acid due to its acidity, was found to be identical to vitamin C and so was renamed ascorbic acid (*13*). It was isolated from the adrenal cortex of oxen and is found in tangy foods such as citrus fruits, hip berries, and tea leaves, which prevent scurvy (Latin *a scorbutus* [without scurvy]).



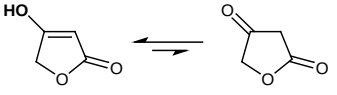
Ascorbic Acid
pK_{a_1} = 4.10

Amazingly, the enol form of 3-oxo-L-gulofuranolactone (to provide a more descriptive name) is a stronger acid than acetic acid (pK_a = 4.75). Note that the structure could be drawn in at least 3 other tautomeric forms, but X-ray crystal analysis (*14*) and solution NMR work (*15*) confirm that the structure shown is the predominant (most stable) isomer. This interesting compound and the basis for its acidity have been highlighted previously (*16*). Once deprotonated, the negative charge can be spread out over the molecule by resonance (Scheme III).



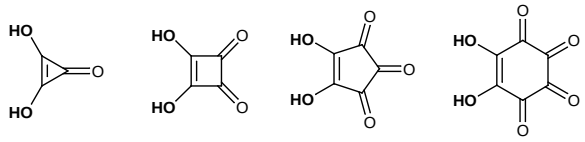
Scheme III. Resonance structures of deprotonated ascorbic acid.

Named for the 4 carbons it contains and its strong acidity, tetronic acid was another misassigned structure (*17*). Although 5-membered ring lactones are not especially prone to disassociation, the presence of a second oxygen at C3 greatly influences the acidity. The enolized form is most prevalent in the solid state (*18*), so the pK_a is probably a measure of the O–H acidity at C3. Its enolic structure is reminiscent of ascorbic acid (see above) and it shares the same enhanced acidity.



Tetronic Acid
pK_a = 3.76

The oxocarbons are a series of acidic compounds with the general formula $C_nH_2O_n$, which also fall into this second group (*19*). The brightly colored dianionic salts of croconic acid (Greek *krokos* [yellow]) (*20*) and rhodizonic acid (Greek *rhodizein* [rose-red]) (*21*) have been known for more than a century as unusual compounds. Squaric acid was not prepared until 1959 (*22*) and deltic acid was prepared in 1975 (*23*).



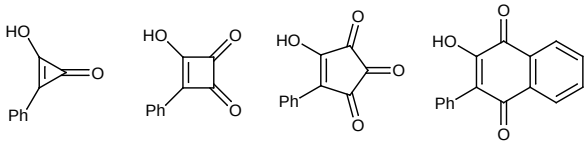
Deltic Acid
pK_{a_1} = 2.57
pK_{a_2} = 6.03

Squaric Acid
pK_{a_1} = 0.54
pK_{a_2} = 3.48

Croconic Acid
pK_{a_1} = 0.80
pK_{a_2} = 2.24

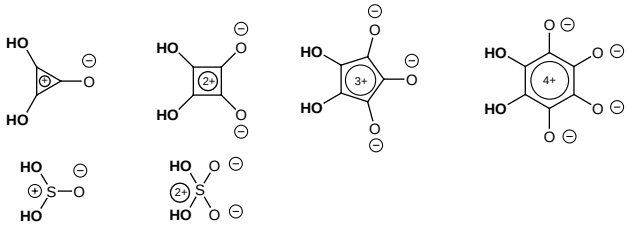
Rhodizonic Acid
$pK_{a_1} \approx 1$
$pK_{a_2} \approx 4.2$

Careful measurement of the first acidity constant of the oxoacids in water (*24*) and in the gas phase (*25*) and the pK_a of the following analogs shows that the major component in the first deprotonation reaction is an unusual ΔS that is less negative than that of most carboxylic acids (*26*). Hence, most of the acidity can be ascribed to entropic action (solvation in water) of the monoanion. The acidity of croconic and rhodizonic acid is further complicated by equilibrium with several hydrated forms of the carbonyl groups in water (*27*).



pK_a = 2.01 pK_a = – 0.22 pK_a = 1.64 pK_a = 4.35

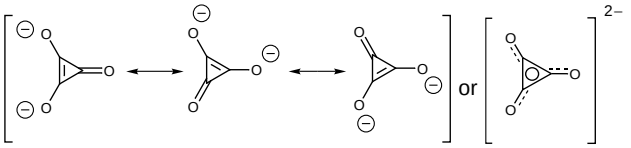
Squaric acid (2,3-dihydroxy-3-cyclobutene-1,2-dione) is perhaps the best known and studied member of the oxocarbon acids because of its unique properties (*28*). The exceptionally strong acidity, which has been described as "as acidic as sulfuric acid", of 4-membered ring enols such as squaric acid can be ascribed to dipole–dipole interactions (*29*). In squaric acid (compared to the larger oxoacids) the second deprotonation is inhibited by the charge repulsion in the dianion. Another perspective for the basis of acidity of squaric acid is to look at the alternate resonance structures for the neutral acids (*30*). For the oxocarbons, the contribution of the charge-separated resonance form decreases as the ring size increases. However, analogous to the inorganic oxoacids such as sulfurous and sulfuric acid, as the (formal) positive charge density increases on the central atom the acidity increases. Thus, in each series where the charge density on the central core contributes to the greatest degree we find the most acidic molecules, squaric acid and sulfuric acid.



Sulfurous Acid
pK_{a_1} = 1.89
pK_{a_2} = 7.21

Sulfuric Acid
pK_{a_1} = – 3.0
pK_{a_2} = 1.92

It is difficult to extend the vinylogous analogy after the first deprotonation yet these compounds also have very low pK_{a_2}. The possible involvement of aromatic stability of the dianions was recognized before they all were characterized (*31, 32*). On formation of the dianion, the negative charge can be delocalized over all carbons (illustrated in Scheme IV for deltic acid). The equivalent resonance structures can be represented as an aromatic structure: a planar, symmetric cyclic molecule with two π-electrons ($4n + 2$, where $n = 0$) distributed among the p-orbitals on every carbon.

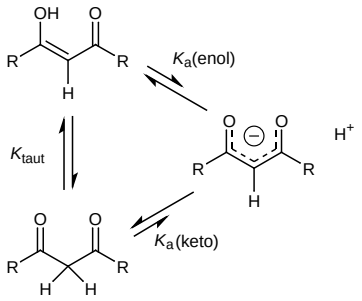


Scheme IV. Resonance structures and aromaticity of deltic acid.

The aromaticity of all the oxocarbons is suspect for several reasons (*33*). Although the controversy over aromaticity is not over, deltic acid and its anions are generally considered aromatic owing to the cyclopropenium system they contain.

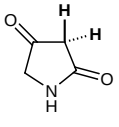
Group III: Carbon-Based Acids

The protons on the central carbon of 1,3-dicarbonyl compounds are expected to be (slightly) acidic owing to the delocalization of the negative charge of the conjugate base into both carbonyls, leading to stabilization of the anion. But the apparent acidity of β-dicarbonyls is complicated by the tautomerization between the keto and the enol forms (Scheme V). Great strides have been made in measuring the acidity of protons attached to the carbon separate from that of the enol (*34*). In general, oxygen acids (such as the vinylogous carboxylic acids above) are stronger than carbon acids; however, there are a few examples where the protons on carbon show surprisingly strong acidity.



Scheme V. Thermodynamic relationships between keto and enol tautomers.

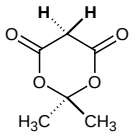
Tetramic acid (the amide derivative of tetronic acid) was synthesized and characterized more recently than the lactone and was found to exist mainly as the dioxo tautomer (*35*). As a carbon acid rather than a oxoacid, tetramic acid is expected (and confirmed by the comparison of pK_a's) to be a weaker acid than tetronic acid (*36*). Nevertheless, it is acidic enough to protonate sodium bicarbonate in aqueous solution to form bubbles of carbon dioxide, a common chemical test for carboxylic acids.



Tetramic Acid
pK_a = 6.4

Meldrum's acid is perhaps one of the most complex compounds for such a deceptively simple structure. Originally

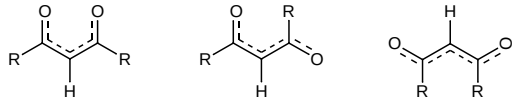
isolated from the condensation between malonic acid and acetone (*37*), it was classified as a carboxylic acid because of its strong acidity. Not until 40 years later was its true structure identified (2,2-dimethyl-1,3-dioxane-4,6-dione) and the acidic proton was astonishingly assigned to the central carbon (*38*). It took almost another 40 years to determine the most stable conformation (boat) (*39*) and to remove any doubt that the enol tautomer was a very minor component in solution (*40*).



Meldrum's Acid
pK_a = 4.85

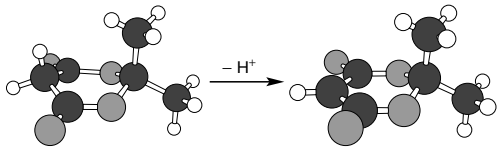
Why this compound is so acidic has been a mystery until recently. Consider the model compound dimedone (5,5-dimethyl-1,3-cyclohexanedione) compared to Meldrum's acid and the acyclic analogs of both (Table 1) (*41*).[1] It is expected that the protons on the α-carbon of ketones are more acidic that those of esters because electron donation by the ester oxygen into the carbonyl (ester resonance) diminishes the electronegativity of the carbonyl and hence lowers the ground-state energy of the ester with respect to the ketone. On comparing Meldrum's acid to dimedone, we see this trend is reversed; that is, the ester protons are more acidic than the ketone protons. Furthermore, all 1,3-diketones (or 1,3-diesters) should have approximately the same pK_a, in the absence of any obvious steric or electronic influence. Unexpectedly, the mere incorporation of the 1,3-dicarbonyl in a 6-membered ring lowers the pK_a significantly.

Part of the acidity difference between acyclic and cyclic 1,3-dicarbonyls can be explained by stabilization of the enolate in the cyclic form. There are three possible conformations of the delocalized anion; all are planar and are expected to have good overlap for the π system (*42*). They differ in energy stabilization because of the dipole–dipole interactions. In the absence of steric interactions, the U-shaped enolate has the greatest Coulombic repulsion, followed by the sickle-shaped, and the W shape should be the most stabilized. For acyclic dicarbonyls, all conformations are accessible (the relative population would depend on R), whereas the 6-membered cyclic compounds must form only the W-shaped enolate. Most or all of the difference between the cyclic and the acyclic diketones (~3.1 kcal/mol) can be attributed to this enolate stabilization.



U-Shaped Sickle-Shaped W-Shaped

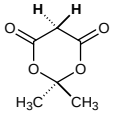
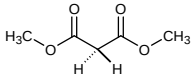
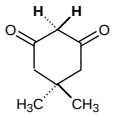
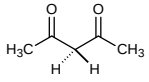
There is a difference of 8.55 pK_a units (11.7 kcal/mol) between the acyclic diester (dimethyl malonate) and Meldrum's acid. We have seen how the conformation of the enolate carbonyls in cyclic diketones can account for approximately 3.1 kcal/mol; this energy difference still leaves approximately 8.6 kcal/mol unresolved in the diester case. One possible explanation for this anomaly is that Meldrum's acid is destabilized in its initial state because of 1,4-steric interactions in the boat conformation (which are relieved in the half-chair enolate) (Scheme VI), which would increase the energy difference between the protonated and deprotonated forms (*43*). However, this suggestion was dismissed because dimedone adopts a half-chair conformation in its initial state and, if steric compression were present in Meldrum's acid, it is remarkable that the enol tautomer content is so low. The geometry of the ester groups in these molecules provides a clue to the source of the energy difference and hence the variance of pK_a.



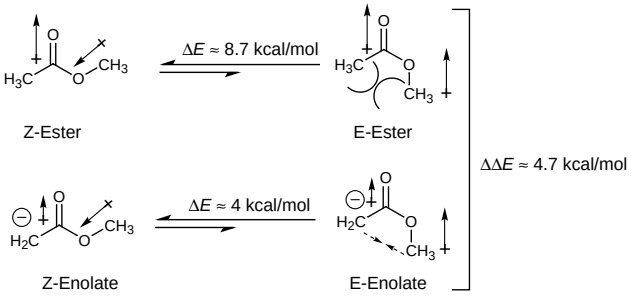
Scheme VI. Models of Meldrum's acid in protonated and deprotonated forms.[2]

Theoretical calculations were then applied to solve this enigma (*44*, *45*). With the model compound methyl acetate, the relative energy levels and atomic charge distribution of E and Z esters and enolates were calculated at high ab initio levels of theory. In the neutral molecules, the Z-ester conformation is calculated to be favored by about 8.7 kcal/mol owing to a combination of steric repulsion and electrostatic (dipole–dipole) repulsion in the E conformation (Scheme VII) (*46*). However, on formation of the enolate the dipole from the polarization of the carbonyl is reduced, which reduces the dipole–dipole interactions. Furthermore, there could be a small attractive stabilization in the E enolate between the negatively charged α-carbon and the partial positive charge at the methoxy carbon. If the energy difference (4.7 kcal/mol) derived from all these factors for the model esters is doubled for the diesters, the acidity range can be explained: dimethyl malonate prefers the bis-Z ester and enolate conformation, whereas Meldrum's acid has both its ester groups pinned into the E conformation. These examples illustrate one of the few cases in which attenuation of pK_a can be directly related to

Table 1. pK_a Values and Energy Differences of Meldrum's Acid and Analogs

Molecule		pK_a in DMSO	ΔΔ*E*/ (kcal/mol)
Name	Structure		
Meldrum's acid		7.32	
			+11.7
Dimethyl malonate		15.87	
Dimedone		11.2	
			+3.1
2,4-Pentanedione		13.3	

differences in molecular geometry.



Scheme VII. Energy differences between Z and E esters and enolates

Since the above calculations only apply to gas-phase molecules, further studies were done to model the effect of solvents and solvation on the relative stability of E and Z esters (*47*, *48*). The E ester is preferentially solvated by a polar solvent, owing to its larger dipole. The E enolate is also expected to be more stabilized by solvation, but to a lesser extent than the neutral ester. Overall, there is a difference of about 1 kcal/mol between the acidity in the gas phase and in polar solvents, dropping the calculated energy difference $\Delta\Delta E$ to slightly less than 4 kcal/mol for each ester grouping.

Closing Notes

There are, of course, many other examples not included in this discussion. Most textbooks include at least some of these compounds, but rarely is the "non-IUPAC" name explained. In the absence of a structure, organic nomenclature can produce misconceptions without the proper historical and chemical background. By collecting these examples into one compilation we hope to provide a useful reference for the identification and explanation of these organic acids.

Notes

1. The pK_a values were compared in DMSO to remove any solvent stabilization effects that might be operating on the anion or cation in aqueous solution. pK_a values in DMSO have a good correlation with gas-phase acidities.

2. The structures were modeled using *CHEM3D*, version 4.0; CambridgeSoft Corp., Cambridge, MA, 1997.

Literature Cited

1. All pK_a values are for aqueous solution at room temperature (unless otherwise specified) and can be found in the *CRC Handbook of Chemistry and Physics*, 77th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL, 1997. The most acidic proton in each structure is highlighted in bold text.
2. There is some controversy over explanations of why acetic acid is more acidic than ethanol or phenol more acidic than cyclohexanol. For example, see Siggel, M. R.; Thomas, T. D. *J. Am. Chem. Soc.* 1986, *108*, 4360. Hibert, P. C.; Byrman, C. P. *J. Am. Chem. Soc.* 1995, *177*, 9875. Wiberg, K. B.; Ochterski, J.; Streitwieser, A. *J. Am. Chem. Soc.* 1996, *188*, 8291. The "classical" arguments will be illustrated as well as other theoretical models, where appropriate.
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