

Acids, bases, pH/pKa calculations and the Henderson Hasselbalch equation

Introductory questions:

1. What is the difference between an organic compound that is described as an acid (proton donor) and a compound described as capable of hydrogen bonding?
2. The alkaloid natural product, cocaine is a “nitrogenous base” typically isolated as the hydrochloride salt.
 - a. What is a nitrogenous base?
 - b. What is a hydrochloride salt?
 - c. What benefits if any would result from forming an alternate salt (e.g., HBr, HI, benzoate, maleate, succinate) with cocaine?
3. Three common classifications of organic compounds are polar non-protic, polar protic and non polar.
 - a. Which class is more likely to penetrate skin? Why?
 - b. Which class is more likely to dissolve in saliva? Why?
 - c. What is DMSO and which class does it belong?
 - d. One compound class that is not included is non-polar protic. Can a molecule with these properties exist?
 - e. How do these “chemical” properties relate to lipophilic/hydrophobic or lipophobic/hydrophilic?
4. Almost all modern drugs are “organic,” that is, they contain one or more carbon atoms. Name some inorganic drugs that pharmacists MUST be knowledgeable of.
5. What percentage of drugs currently prescribed are likely to be in use in 5 yrs, 10 yrs, 25 yrs from now? How will an understanding of basic molecular properties enable you to withstand this change?

Acids & bases

Keywords:

acid *base* *buffer* *pH* *pKa* *ionization* *equilibria*
Henderson-Hasselbalch equation *'salt'*

Objective(s):

- Restore understanding of fundamental acid-base ionization equilibria.
- Relate acidity and basicity of organic compounds to that of water.
- Conduct and gain confidence in ionization calculations.
- Gain a basic understanding of the physiologic importance/implication of drug ionization – specifically in relation to absorption, transport, and excretion.

Definitions and descriptions:

Hydrogen ions (H⁺): Hydrogen ions (H⁺), or protons, do not have electrons, but can bond to nitrogen or oxygen containing molecules because nitrogen and oxygen have “non-bonding” pairs of electrons. Hydrogen ions cannot bond to carbon since carbon does not have “non-bonding” electrons.

Acids: According to the Bronsted-Lowry theory of acids and bases, an acid is a substance capable of donating a proton, or hydrogen ion (H⁺) to a base.

Bases: A base is a substance that is capable of accepting a proton from an acid.

pH: A method of expressing the hydrogen ion concentration [H⁺], or more correctly, hydronium ion [H₃O⁺] concentration in solution. pH is equal to the negative log of the *molar* hydrogen ion concentration.

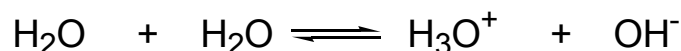
$$\text{pH} = -\log[\text{H}^+]$$

pOH: A method of expressing hydroxyl ion (OH⁻) concentration in solution. pOH is equal to the negative log of the *molar* hydroxyl ion concentration.

$$\text{pOH} = -\log[\text{OH}^-]$$

IONIZATION OF WATER

K_W and pK_W: Water ionizes (dissociates) slightly to yield hydronium and hydroxyl ions:



The dissociation constant for water is K_W:

$$K_W = [\text{H}_3\text{O}^+] \times [\text{OH}^-] . 1.0 \times 10^{-14}$$

pK_w is equal to the negative log of the dissociation constant of water:

$$pK_w = -\log K_w = pH + pOH = 14$$

So, how do pH and pOH correlate? Some pH examples:

$[H^+]$	pH	$[OH^-]$	pOH	K_w	pK_w
10^{-1}	1	10^{-13}	13	10^{-14}	14
10^{-5}	5	10^{-9}	9	10^{-14}	14
10^{-7}	7	10^{-7}	7	10^{-14}	14
10^{-10}	10	10^{-4}	4	10^{-14}	14
10^{-14}	14	1	0	10^{-14}	14
1	0	10^{-14}	14	10^{-14}	14

Note: At $[H^+] = 10^{-7}$, $[OH^-] = 10^{-7}$ and therefore $[H^+] = [OH^-]$ and $pH = pOH$. This is neutral pH ($pH = 7$).

Questions:

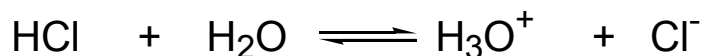
- For a 0.000001 M solution of hydroiodic acid (HI) what are:
 - the H^+ concentration
 - the pH
 - the OH^- concentration
 - pOH
 - As a successful pharmacist, you chlorinate your hottub on a regular basis and find the $pH = 5$. What is the concentration of H^+ and molarity of HCl?
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ACID-BASE EQUILIBRIA AND IONIZATION OF ELECTROLYTES

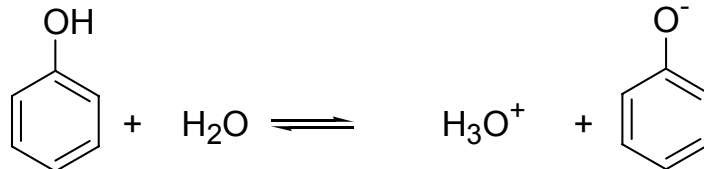
Acid-Base Reactions: Acid-base reactions are equilibrium reactions. That means that there is a forward reaction and a reverse reaction. At equilibrium, the forward and reverse reaction rates are the same, and the relative concentrations of reactants and products and remain constant.

Strong and weak acids:

Strong acid - HCl is considered a strong acid because it has a strong tendency to ionize resulting in a large $[H_3O^+]$ and the reverse reaction occurs only to a small amount. This further indicates that Cl^- is very weak as a conjugate base and not likely to accept a proton. What this means is that Cl^- is 'stable' just the way it is. This is an attribute of many strong acids – the conjugate base is stable while bearing a negative charge. This means the conjugate base happily accepts the extra electron. Strong acids are completely ionized at all pH values (pH independent ionization).

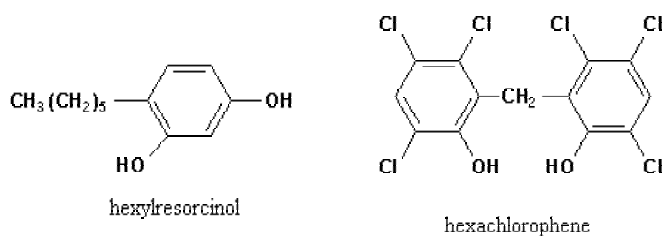


Weak Acid – Phenol is a good example of a weak acid. In comparison to HCl, phenol has a weaker tendency to ionize and the conjugate base, phenoxide ion, is moderately strong. As a result, the equilibrium shifts further to the left and the acid (protonated) form of phenol predominates.



Question: When substituents are added to the aromatic ring (e.g., methyl, nitro, etc.), what effect on the ionization might they have?

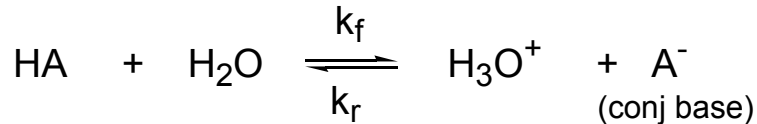
One example of how the phenol structure has been altered to achieve the desired pharmacologic property is the anti-bacterials:



Fun fact: Phenol causes some of the most serious and damaging chemical burns to the skin. In the laboratory phenol is used to lyse cells!

Anti-bacterial activity was increased by increasing the waxy chain to enhance membrane infiltration. Hexylresorcinol and hexachlorophene are used in hospital sterilization methods.

In general for a weak acid:



Note that the product (A⁻) is designated as the conjugate base. The conjugate base is also known as the salt of the acid when combined with a counterion such as Na⁺ to give Na⁺A⁻.

An equilibrium constant (K) can be defined that is equal to the forward rate constant (k_f) divided by the reverse rate constant (k_r). It is also equal to the product concentrations divided by the reactant concentrations:

$$K = \frac{k_f}{k_r} = \frac{[\text{A}^-][\text{H}_3\text{O}^+]}{[\text{HA}][\text{H}_2\text{O}]}$$

since water is constant @ 55 M

$$K_a = 55M = \frac{[\text{A}^-][\text{H}_3\text{O}^+]}{[\text{HA}]}$$

K_a is a measure of (weak) acid strength as expressed by the concentration of ionized molecules divided by the concentration of unionized molecules.

Question: *Alcohol are organic ‘analogs of water meaning they share the identical functional group (OH) but vary in one component, the “switch” of an H for a Me, Et, etc. Explain the increasing trend in pK_a values (table at right) for the alcohols and the “unusual” drop in pK_a for phenol relative to the other alcohols.*

<i>R-OH</i>	<i>pK_a</i>
H-OH (water)	15.8
MeOH (methanol)	16.4
Et-OH (ethanol)	16.8
iPr-OH (isopropanol)	17.2
t-Bu-OH (tert-butanol)	18
Ph-OH	10

Trends to consider based on the K_a equation:

As acid strength increases (8):

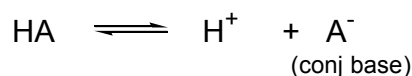
- K_a increases
- [A⁻] increases
- [H₃O⁺] increases
- [HA] decreases

A helpful utility is pK_a, which relates the strength of weak acids on logarithmic scale. It provides a means to compare the acidity of a class of compounds or across classes of compounds in whole numbers. Because the scale is log-based, comparisons are typically based on ten-fold increments, which is fine for most comparisons.

$$pK_a = -\log(K_a)$$

As the acid strength increases, so does the K_a. However, the pK_a decreases as the acid strength increases.

For weak acids, the ionization in water is:



Which can be expressed as:

$$K_a = \frac{[A^-][H^+]}{[HA]}$$

With no other ions in solution, the concentration of H⁺ and A⁻ should be equal and, therefore:

$$K_a = \frac{[H^+][H^+]}{[HA]} = \frac{[H^+]^2}{[HA]} \quad \text{and} \quad [H^+]^2 = K_a[HA]$$

$$[H^+] = \sqrt{K_a[HA]}$$

Rearrange and substitute to:

$$[H^+] = \sqrt{K_a C}$$

This equation in bold is useful for calculating the pH of a weak acid in water when you know the molar concentration and the pK_a of the weak acid or drug (usually found in tables).

if you take the -log of each side:

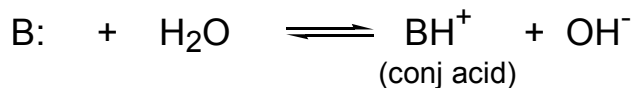
$$-\log[H^+] = 1/2 (-\log K_a - \log C) \quad \text{or}$$

$$pH = 1/2 (-\log K_a - \log C)$$

$$pH = 1/2(pK_a) - 1/2(\log C)$$

Question: Calculate the pH of a 0.1 M solution of a drug at 25 °C. The pK_a of the acid is 4.76 at 25 °C.

Weak Bases. Weak bases react with water to take up hydrogen atoms to form a conjugate acid resulting in hydroxyl ions that turn the solution alkaline (basic).



Note that the product (BH⁺) is designated as the conjugate acid. The conjugate acid is also known as the salt of the base when combined with a counterion such as Cl⁻ to give BH⁺Cl⁻.

One example of a weak base is ammonia (NH₃), which reacts with water to form ammonium hydroxide (NH₄OH or NH₄⁺ / OH⁻). Ammonia has a weak tendency to ionize and the conjugate acid is strong: the equilibrium favors the left side of the equation.

The basicity constant is defined as K_b (expressed similarly to the K_a) and is a measure of base strength. When base strength is increased the equilibrium is moved to the right. K_b is mostly unused and has been replaced by K_a.

K_a and pK_a are generally used for both acids and bases because pK_a uses the same scale and goes in the same direction as pH. For bases, K_a and pK_a indicate the strength of the conjugate acid, BH⁺.

K_a and K_b are related: $K_a \times K_b = K_w = 1.0 \times 10^{-14}$

pK_a and pK_b are also related: $pK_a + pK_b = pK_w = 14$

So, if the K_a and pK_a terms are used, as base strength increases:

K_a decreases
pK_a increases

Examples of pKa

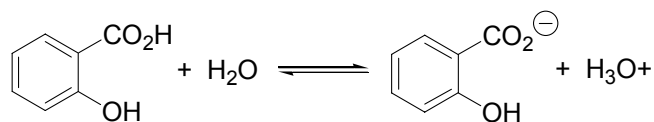
Acids and bases:

Acetic acid: $K_a = 1.75 \times 10^{-5}$; $pK_a = 4.76$



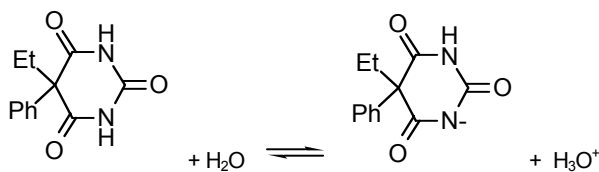
Salicylic acid:

$K_a = 1.06 \times 10^{-3}$; $pK_a = 2.97$



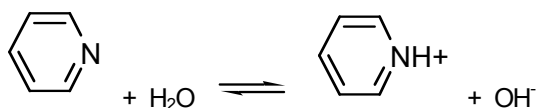
salicylic acid

Phenobarbital: $K_a = 3.9 \times 10^{-8}$, $pK_a = 7.41$



Question: Amines rarely give up a proton and behave like an acid. Why does the proton on phenobarbital serve as an acid?

Pyridine: $K_a = 7.1 \times 10^{-6}$, $pK_a = 5.15$ (the pyridinium or protonated form is the acid).



Some pKa's of interest.....

Compound	pKa	Compound	pKa
sulfuric acid	-9	RNH ₃ ⁺ (protonated primary amines)	10 to 11
hydrochloric acid	-7	HCO ₃ ⁻	10.3
nitric acid	-1.4	RSH (sulfides)	10 to 11
RCOOH (carboxylic acids)	4 to 5	water	15.7
H ₂ CO ₃	6.3	ROH (alcohols)	15 to 18
NH ₄ ⁺	9.2	RC(O)NH ₂ (amides)	17 to 18
phenol	8.5 to 11	alkanes	48-50

Weak acids and bases are weak electrolytes meaning that they are only ionized to a small extent (less than 1%) in solution. Weak acids have K_a values which are << 1 and positive pK_a values. Acetic acid, phenobarbital, and pyridine are examples of weak acids and bases. Most *drugs* are weak acids or bases.

Henderson-Hasselbalch Equation - Utility

The Henderson-Hasselbalch equation can be used to determine pH, pK_a and/or the relative amounts of acid and base in a solution. It can be used for both weak acids and weak bases and primarily for the following:

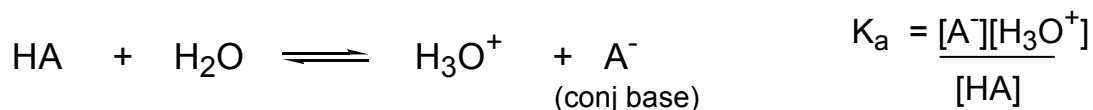
calculating the ratio of base to acid when the pK_a and pH of the solution are known. [This information can be used to prepare buffer solutions].

calculating the pH of a solution if the ratio of base to acid and the pK_a are known.

calculating the pK_a if the ratio of base to acid and pH of the solution are known.

One of the more important features of the HH equation in Pharmacy is the ability to predict the proportions of ionized and unionized forms of a drug at a given pH. Since pH varies in vivo depending on the system/location and a one (1) pKa unit difference results in a ten-fold change in the ionization (log scale), small changes in the local environment can have a dramatic effect on uptake, distribution, net effect, metabolism, and excretion. Also important to consider is that the ionized form of a drug, for example, may not bind the receptor or target whereas the neutral form of the drug does. Careful use of the HH equation, therefore, may permit better prediction of the physiologic effect.

From the equilibrium and K_a equation:



the following equation can be derived:

$$\frac{K_a}{[\text{H}_3\text{O}^+]} = \frac{[\text{A}^-]}{[\text{HA}]}$$

which in log form is converted to:

$$\log \left[\frac{K_a}{[\text{H}_3\text{O}^+]} \right] = \log \left[\frac{[\text{A}^-]}{[\text{HA}]} \right]$$

or

$$\log K_a - \log[\text{H}_3\text{O}^+] = \log \left[\frac{[\text{A}^-]}{[\text{HA}]} \right]$$

$$\log[\text{H}_3\text{O}^+] = -\log K_a + \log \left[\frac{[\text{A}^-]}{[\text{HA}]} \right]$$

or

$$\text{pH} = \text{p}K_a + \log \left[\frac{[\text{A}^-]}{[\text{HA}]} \right]$$

finally, in descriptive terms,

$$\text{pH} = \text{p}K_a + \log \left[\frac{[\text{conj base}]}{[\text{acid}]} \right]$$

Key points:

One important thing to keep in mind is that the weak acid is the proton donor. That means the “form” or “structure” of the acid may vary as a carboxylic acid, alcohol, sulfide or even amine hydrochloride, for example.

You can rearrange the equation to solve a number of calculations, but the real issue is to keep “trends” and ratios at the forefront. For example, rearrange the equation to get an understanding of the acid to base ratio as follows:

$$pH - pK_a = \log \left[\frac{[\text{conj base}]}{[\text{acid}]} \right]$$

In this instance, the difference between the pH and the pKa (typically defined for the drug in question) can tell you how much of one form the drug is in (ionized or unionized). Important: this difference is logarithmic!

pH - pKa	$\frac{[\text{base}]}{[\text{acid}]}$	% acid	% conj. base	% unionized	% ionized
4	10,000/1	0.01	99.99	0.01	99.99
3	1000/1	0.1	99.9	0.1	99.9
2	100/1	1	99	1	99
1	10/1	9	91	9	91
0	1/1	50	50	50	50
-1	1/10	91	9	91	9
-2	1/100	99	1	99	1
-3	1/1000	99.9	0.1	99.9	0.1
-4	1/10,000	99.99	0.01	99.99	0.01

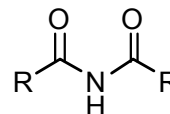
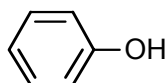
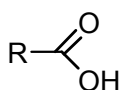
Notethat when the pKa = pH, there will be an equal amount of ionized and ionized (because the log of zero = 1).

Using the table above, one could get a “sense” for the amount of acid and base forms. So, if a drug contained a carboxylic acid group that had a pKa of 4.2, one could determine that the drug was deprotonated at physiologic pH (approx. 6.8-7.5). That is, the carboxylic acid group lost its proton to form the ionized carboxylate. However, in the stomach, at pH 1, the drug would remain in the protonated, acid form.

Question: Which form of a carboxylic acid (carboxylic acid or carboxylate anion) is more likely to traverse cell membranes?

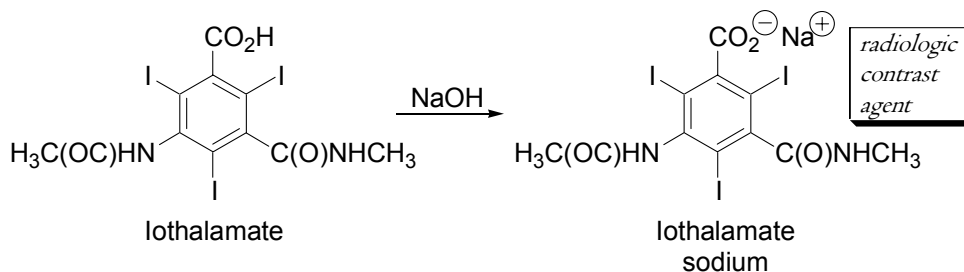
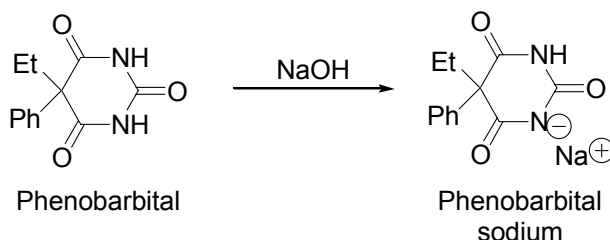
Salts of Weak Acids

In chemistry classes we learn that metals like sodium, potassium and calcium are common counterions for salts of drugs that are weak acids. Salts of weak acids have the general form $R-M^+$ where R is a carboxylic acid, phenol, imide or other ionizable group.



Question: why is lithium not used as a countercation for drugs that are weak acids in salt formation?

Example of drug salt formation:



In the case of the radiologic (x-ray) contrast agent, iothalamate, the formation of the sodium salt adds significant water solubility, which allows the contrast agent to distribute evenly throughout extracellular space. There is no significant penetration into intracellular matrices and moreover, the contrast agent is cleared rapidly from the body ($t_{1/2} = 2$ h).

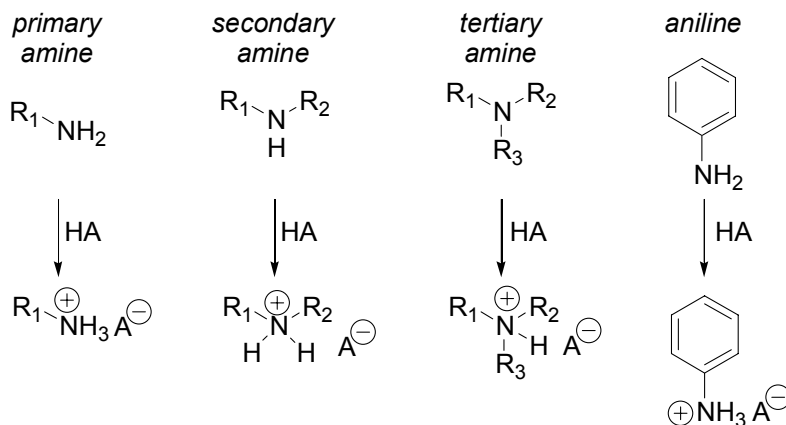
Fun fact: There are five radiologic x-ray densities: air, fat, fluid, bone and metallic, all of which show up differently on "film." And, as many know, many organs and tissues do not show up well on traditional x-ray, e.g., liver, spleen, kidneys, intestines, bladder, and abdominal muscles (all have similar density and 'shadow' each other). Certain compounds increase the radiographic contrast b/c they have x-ray absorption characteristics that afford a 'bone-like' or metal-like' density. Compounds that fall into this class are iodinated aromatic compounds (bone-like density) and barium salts (metal like density). Talk about high doses! Contrast agents are administered as 100 mL of a 60% solution. Osmotoxicity!

Examples of other drugs that are salts of weak acids and their counterions:

1. Warfarin sodium Na^+
2. Penicillin G potassium K^+
3. Fenopropfen calcium Ca^{+2}

Salts of Weak Bases

Most of the weak bases of interest to pharmacists are the amines and anilines. Both classes are capable of being protonated by an acid to form an amine or aniline salt. The acid used to do the protonation contains a conjugate anion that forms the anion after the amine has been protonated.

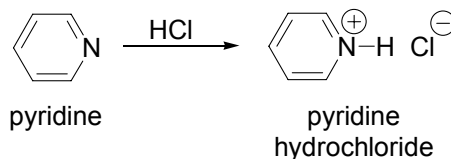


where R_1 , R_2 and R_3 are various alkyl/aryl groups and A is the conjugate base, e.g., Cl^- , Br^- , etc.

Amines have a pKa ranging from 9-11 and anilines have a pKa 4 to 5.

Question: Why are the pKa values so different for amines and anilines?

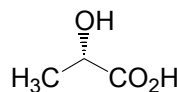
Another example of a base is the aromatic heterocycle pyridine. Its structure appears in many drugs and it readily forms salts with mineral and weak acids.



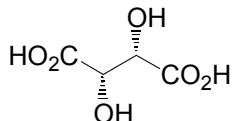
Examples of drugs that are salts of weak bases and their counterions:

Meperidine hydrochloride	Cl^-
Dextromethorphan hydrobromide	Br^-
Atropine sulfate	SO_4^{2-}
Codeine phosphate	PO_4^{3-}
Biperiden lactate	$CH_3CHOHCOO^-$
Ergotamine tartrate	$-OOCCHOHCHOHCOO^-$
Chlorpheniramine maleate	$-OOCCH=CHCOO^-$
Benztrapine mesylate	$CH_3SO_3^-$

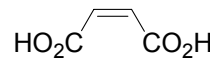
Lets examine the “organic” salts a little closer.



lactic acid



tartaric acid



maleic acid

from \$10-100/kg

These carboxylic acids serve as proton donors to weakly basic amines. Amines comprise one of the largest classes of organic molecules used as pharmaceutically important drugs. The amine and one of these acids (for example) combine to form an amine salt, which improves its water solubility. Some other important considerations in the use of these acids include: (a) low cost, (b) high chemical purity, (c) high stereochemical purity, and (d) potential to serve as ‘dual’ or as a twofold proton donor (e.g., tartaric acid and maleic acid).

Maleic acid is the *cis* isomer – the *trans* isomer is called succinic acid (succinate). You are likely to see all of these acids in advertisements for pharmaceuticals.