

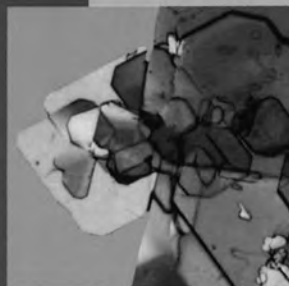
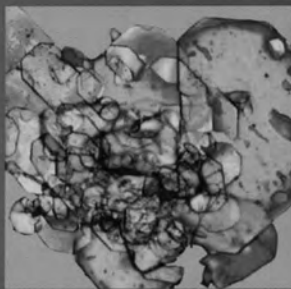
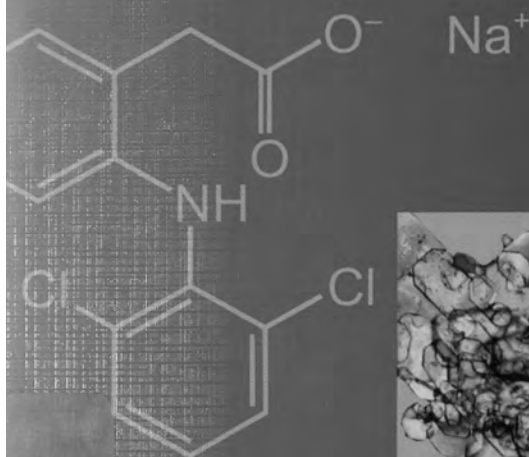



International Union
of Pure and Applied Chemistry (IUPAC)

P. Heinrich Stahl, Camille G. Wermuth (Eds.)

Handbook of Pharmaceutical Salts

Properties, Selection, and Use



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Dr. P. Heinrich Stahl
Lerchenstrasse 28
D-79104 Freiburg im Breisgau

Prof. Camille G. Wermuth
Louis Pasteur University, Strasbourg
Faculty of Pharmacy
74, route du Rhin
F-67400 Illkirch

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by P. Heinrich Stahl

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1. Usage Frequency of Acids and Bases for Forming Drug Salts

In the updated survey [1] of their earlier review [2] on salts of drug substances, *Berge*, *Bighley*, and *Monkhouse* listed the currently used salt forms of drugs based on the monographs in *The Martindale Extra Pharmacopoeia 1993*. They found 113 different anions (of which 13 are inorganic) and only 38 different cations (11 of them inorganic).

A survey in the 1995 issue of *Index Nominum* led to the following results:

| Number of drug salts with counter-ion | acidic | basic |
|--|----------------|-----------------|
| Total | 1820 | 474 |
| Percentage | 73.96% | 26.04% |
| Involved number of different | acids (anions) | cations (bases) |
| organic | 101 | 23 |
| inorganic | 7 | 14 |
| Total | 108 | 37 |

The surveys make apparent that acids by far outnumber the bases in their function as pharmaceutical salt formers. An important reason for the scarcity of available bases may be the fact that several nitrogenous bases themselves

exert biological and pharmacodynamic activities, and indeed the majority of drug substances are bases. Also most inorganic cations, within certain limits of concentration and intake, fulfill essential biological functions, and, for this reason, they can serve as relatively 'inert' counter-ions only in exceptional cases.

A more realistic picture of the present frequency of use is obtained, when current national desk-top references of drugs on national markets are consulted. As an example the German 'Rote Liste 1999' renders the following figures:

| Number of drug salts | with counter-ion | acidic | basic |
|------------------------------|------------------|----------------|-----------------|
| Total | 820 | 612 | 208 |
| Percentage | | 74.63% | 25.37% |
| Involved number of different | | acids (anions) | cations (bases) |
| | organic | 46 | 9 |
| | inorganic | 9 | 12 |
| Total | | 55 | 21 |

Interestingly, although the number of drug salts is less than half of the number listed in a cumulative drug inventory, the ratio of basic to acidic drug substances is identical. The frequency of the most relevant acids and bases is shown graphically in *Figs. 1* and *2*.

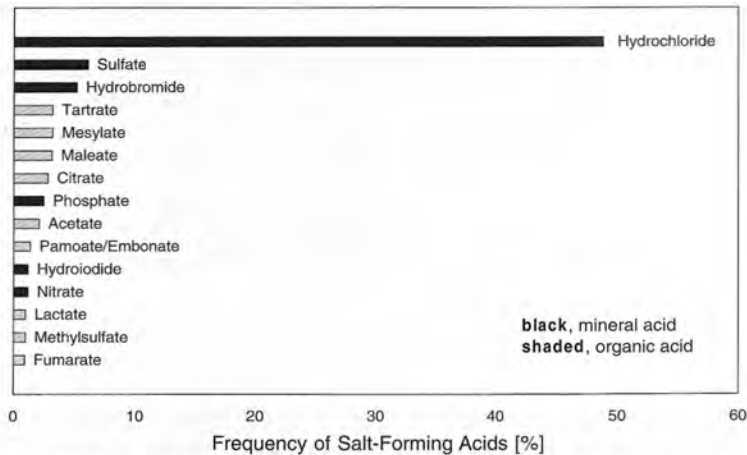


Fig. 1. Distribution of salts with the 15 most frequently occurring acids (anions)

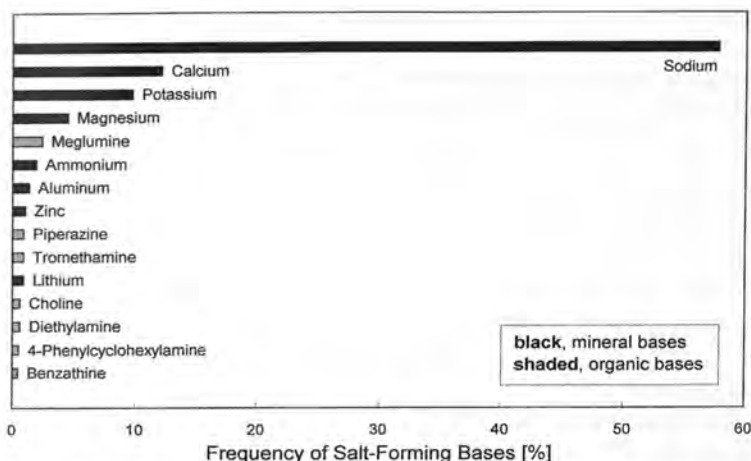


Fig. 2. Distribution of salts with the 15 most frequently occurring bases (cations)

2. Tables of Salt-Forming Acids and Bases

List of Salt Formers

The comprehensive reviews on pharmaceutical salts by *Berge, Bighley,* and *Monkhouse* [1][2] are frequently referred to when the formation of salts of a new chemical entity is considered. While these authors presented the results of a survey on the approval status of drug salts 25 years ago, the present-day situation is different. Accumulated knowledge and experience has led to a reduction of the number of acids and bases regarded as innocuous. Moreover, national health authorities reacted in different ways to certain findings in this area. Therefore, it was deemed timely to put up a revised list of useful salt-forming acids and bases.

In the following tables, an attempt has been made to group the salt-forming acids and bases into classes of *first, second,* and *third* choice. The following criteria for assignment to the respective classes were applied.

1. *First Class* salt-formers are those of unrestricted use for that purpose because they form physiologically ubiquitous ions, or because they occur as intermediate metabolites in biochemical pathways. The first group is typically and quite impressively represented by the past and present use frequency of hydrochlorides/chlorides and sodium salts. The second group comprises many acids present in food of vegetable origin, or those generated in the body's metabolic cycles.

2. *Second Class* salt-formers are considered those that are not naturally occurring, but, so far, during their profuse application have shown low toxicity and good tolerability.
3. *Third Class* salt-formers might be interesting under particular circumstances in order to achieve special effects such as ion-pair formation, or for solving particular problems. Some of them are assigned to this class because they have their own pharmacological activity. Also some of the acids and bases were used much less frequently in the past. No prohibitive adverse findings are currently known to the author except those indicated in the monographs (*cf. Chapt. 12*).

The reader is also referred to *Chapt. 5, Sect. 3.3.3*, for further comments on the classification, also to the remarks on individual acids and bases in the monographs of *Chapt. 12*.

It is recommended to search for the latest safety records in the *RTECS* inventory and in literature at the time when a *Class 3* acid or base would be considered for salt formation with an NCE.

GRAS and ADI

While there is a chance to change unfavorable drug properties to the better by selecting less commonly used salt formers, there may be limitations with respect to the acceptability. Some substances may be considered unobjectionable because they are used profusely in food processing. This is indicated by an *ADI* (= *Acceptable Daily Intake*) assigned to them (WHO); in the USA, the *FDA* grants the *GRAS* (= '*Generally Regarded As Safe*') status to food additives and processing aids [3][4].

The *ADI* for man, expressed on a body weight basis, is the amount of a food additive that can be taken daily in the diet, even over a lifetime, without risk.

An *ADI* is assigned by the *Joint FAO/WHO Expert Committee on Food Additives* only to those substances for which the available data include either the results of adequate short-term and long-term toxicological investigations, or satisfactory information on the biochemistry and metabolic fate of the compound, or both.

An *ADI* without an explicit indication of the upper limit of intake ('*ADI* not specified') may be assigned to substances of *very low toxicity*, especially those that are food constituents or that may be considered as foods or normal metabolites in man.

While the *ADI* is limiting for the use of additives in food, it has no legal significance for the use in drug preparations. Nevertheless, this value serves as a reference mark for pharmaceutical applications.

Abbreviations in Tables 1–8: A: indicates an acidic pK_a ; B: indicates a basic pK_a ; M_r : relative molar mass; *ADI*: accepted daily intake (WHO); n.s.: *ADI* not specified; *GRAS*: +: ‘generally regarded as safe’, #: some of the salts are *GRAS*. Values given in italics were estimated with *PALLAS pKalc 3.2* (*CompuDrug Chemistry Inc.*).

Table 1. Acids: Alphabetical Order

| Class | Acid | M_r | pK_{a1} | | pK_{a2} | | pK_{a3} | | ADI up to [mg/kg] | GRAS Status |
|-------|----------------------------------|---------|-----------|---|-----------|---|-----------|---|-------------------|-------------|
| 1 | Acetic acid | 60.05 | 4.756 | A | | | | | n.s. | + |
| 3 | Acetic acid, 2,2-dichloro- | 128.95 | 1.35 | A | | | | | | |
| 1 | Adipic acid | 146.14 | 4.44 | A | 5.44 | A | | | 5 | + |
| 2 | Alginic acid | 240 000 | 2.4 | A | | | | | n.s. | + |
| 1 | L-Ascorbic acid | 176.13 | 4.17 | A | 11.57 | A | | | | + |
| 1 | L-Aspartic acid | 133.11 | 1.88 | A | 3.65 | A | 9.60 | B | | |
| 2 | Benzenesulfonic acid | 158.18 | 0.7 | A | | | | | | |
| 2 | Benzoic acid | 122.12 | 4.19 | A | | | | | | + |
| 3 | Benzoic acid, 4-acetamido- | 179.18 | 4.3 | A | | | | | | |
| 2 | (+)-Camphoric acid | 200.24 | 4.716 | A | 5.83 | A | | | | |
| 3 | (+)-Camphor-10-sulfonic acid | 232.29 | 2.17 | A | | | | | | |
| 1 | Capric acid (decanoic acid) | 172.27 | 4.9 | A | | | | | n.s. | |
| 3 | Caproic acid (hexanoic acid) | 116.16 | 4.8 | A | | | | | | |
| 2 | Caprylic acid (octanoic acid) | 144.22 | 4.91 | A | | | | | n.s. | + |
| 1 | Carbonic acid | 44.01 | 6.46 | A | 10.3 | A | | | n.s. | + |
| 3 | Cinnamic acid | 148.16 | 4.404 | A | | | | | | |
| 1 | Citric acid | 192.13 | 3.128 | A | 4.761 | A | 6.396 | A | n.s. | + |
| 2 | Cyclamic acid | 179.24 | -2.01 | A | | | | | | |
| | Decanoic acid (see capric acid) | | | | | | | | | |
| 2 | Dodecylsulfuric acid | 266.40 | -0.09 | A | | | | | | |
| 2 | Ethane-1,2-disulfonic acid | 190.20 | -2.1 | A | -1.5 | A | | | | |
| 2 | Ethanesulfonic acid | 110.13 | 2.05 | A | | | | | | |
| 2 | Ethanesulfonic acid, 2-hydroxy- | 126.13 | 1.66 | A | | | | | | |
| 3 | Formic acid | 46.02 | 3.75 | A | | | | | | |
| 1 | Fumaric acid | 116.08 | 3.03 | A | 4.38 | A | | | 6 | |
| 1 | Galactaric acid | 210.14 | 3.08 | A | 3.63 | A | | | | |
| 2 | Gentisic acid | 154.12 | 2.93 | A | | | | | | |
| 1 | D-Glucoheptonic acid | 226.18 | 3.3 | A | | | | | | |
| 1 | D-Gluconic acid | 196.16 | 3.76 | A | | | | | 50 | # |
| 1 | D-Glucuronic acid | 194.14 | 3.18 | A | | | | | | |
| 1 | Glutamic acid | 147.13 | 2.19 | A | 4.25 | A | 9.67 | B | | + |
| 1 | Glutaric acid | 132.12 | 4.34 | A | 5.27 | A | | | | |
| 2 | Glutaric acid, 2-oxo- | 146.10 | 2.7 | A | 4.5 | A | | | | |
| 1 | Glycerophosphoric acid | 172.08 | 1.47 | A | 6.19 | A | | | | |
| 1 | Glycolic acid | 76.05 | 3.28 | A | | | | | | |
| | Hexanoic acid (see caproic acid) | | | | | | | | | |
| 1 | Hippuric acid | 179.17 | 3.55 | A | | | | | | |

Table 1 (cont.)

| Class | Acid | M_r | pK_{a1} | pK_{a2} | pK_{a3} | ADI up to [mg/kg] | GRAS Status |
|-------|--|--------|-----------|-----------|-----------|-------------------|-------------|
| 3 | Hydrobromic acid | 80.92 | < -6 | A | | | |
| 1 | Hydrochloric acid | 36.46 | -6 | A | | n.s. | + |
| 2 | Isobutyric acid | 88.11 | 4.86 | A | | | |
| 1 | DL-Lactic acid | 90.08 | 3.86 | A | | | + |
| 2 | Lactobionic acid | 358.30 | 3.2 | A | | | |
| 1 | Lauric acid | 200.32 | 4.9 | A | | n.s. | |
| 1 | Maleic acid | 116.08 | 1.92 | A | 6.23 | A | |
| 1 | (-)-L-Malic acid | 134.09 | 3.459 | A | 5.097 | A | n.s. |
| 2 | Malonic acid | 104.06 | 2.826 | A | 5.696 | A | |
| 3 | DL-Mandelic acid | 152.15 | 3.372 | A | | | |
| 2 | Methanesulfonic acid | 96.10 | -1.2 | A | | | |
| | Mucic acid (see galactaric acid) | | | | | | |
| 2 | Naphthalene-1,5-disulfonic acid | 332.26 | -3.37 | A | -2.64 | A | |
| 2 | Naphthalene-2-sulfonic acid | 208.24 | 0.17 | A | | | |
| 2 | 2-Naphthoic acid, 1-hydroxy- | 188.17 | 2.7 | A | 13.5 | A | |
| 2 | Nicotinic acid | 123.11 | 4.85 | A | 2.07 | B | + |
| 3 | Nitric Acid | 63.02 | -1.32 | A | | | |
| | Octanoic acid (see caprylic acid) | | | | | | |
| 2 | Oleic acid | 282.45 | ca. 4 | A | | | |
| 2 | Orotic acid | 156.10 | 5.85 | A | 8.95 | A | |
| 2 | Oxalic acid | 90.04 | 1.271 | A | 4.266 | A | |
| 1 | Palmitic acid | 256.42 | 4.9 | A | | | n.s. |
| 2 | Pamoic acid (embonic acid) | 388.38 | 2.51 | A | 3.1 | A | |
| 1 | Phosphoric acid | 98.00 | 1.96 | A | 7.12 | A | 12.32 |
| 2 | Propionic acid | 74.08 | 4.87 | A | | | n.s. |
| 2 | (-)-L-Pyroglutamic acid | 129.11 | 3.32 | A | | | |
| 3 | Salicylic acid | 138.12 | 2.97 | A | 13.82 | A | |
| 3 | Salicylic acid, 4-amino- | 153.14 | 3.25 | A | 10 | A | 3.5 |
| 1 | Sebacic acid | 202.25 | 4.59 | A | 5.59 | A | |
| 1 | Stearic acid | 284.49 | 4.9 | A | | | n.s. |
| 1 | Succinic acid | 118.09 | 4.207 | A | 5.635 | A | n.s. |
| 1 | Sulfuric acid | 98.08 | -3 | A | 1.92 | A | n.s. |
| 1 | (+)-L-Tartaric acid | 150.09 | 3.02 | A | 4.36 | A | |
| 1 | Thiocyanic acid | 59.09 | -1.33 | A | | | |
| 2 | p-Toluenesulfonic acid | 172.21 | -1.34 | A | | | |
| 3 | Undecylenic acid (undec-10-enoic acid) | 184.27 | 4.9 | A | | | |

Table 2. Acids: Sorted by Increasing pK_a Value

| Class | Acid | M_r | pK_{a1} | pK_{a2} | pK_{a3} | ADI up to [mg/kg] | GRAS Status |
|-------|---|---------|------------|-----------|-----------|-------------------|-------------|
| | Decanoic acid (see <i>capric acid</i>) | | | | | | |
| | Hexanoic acid (see <i>caproic acid</i>) | | | | | | |
| | Mucic acid (see <i>galactaric acid</i>) | | | | | | |
| | Octanoic acid (see <i>caprylic acid</i>) | | | | | | |
| 3 | Hydrobromic acid | 80.92 | < -6 | A | | | |
| 1 | Hydrochloric acid | 36.46 | -6 | A | | n.s. | + |
| 2 | Naphthalene-1,5-disulfonic acid | 332.26 | -3.37 | A | -2.64 | A | |
| 1 | Sulfuric acid | 98.08 | -3 | A | 1.92 | A | n.s. |
| 2 | Ethane-1,2-disulfonic acid | 190.20 | -2.1 | A | -1.5 | A | |
| 2 | Cyclamic acid | 179.24 | -2.01 | A | | | |
| 2 | <i>p</i> -Toluenesulfonic acid | 172.21 | -1.34 | A | | | |
| 1 | Thiocyanic acid | 59.09 | -1.33 | A | | | |
| 3 | Nitric Acid | 63.02 | -1.32 | A | | | |
| 2 | Methanesulfonic acid | 96.10 | -1.2 | A | | | |
| 2 | Dodecylsulfuric acid | 266.40 | -0.09 | A | | | |
| 2 | Naphthalene-2-sulfonic acid | 208.24 | 0.17 | A | | | |
| 2 | Benzenesulfonic acid | 158.18 | 0.7 | A | | | |
| 2 | Oxalic acid | 90.04 | 1.271 | A | 4.266 | A | |
| 3 | Acetic acid, 2,2-dichloro- | 128.95 | 1.35 | A | | | |
| 1 | Glycerophosphoric acid | 172.08 | 1.47 | A | 6.19 | A | |
| 2 | Ethanesulfonic acid, 2-hydroxy- | 126.13 | 1.66 | A | | | |
| 1 | L-Aspartic acid | 133.11 | 1.88 | A | 3.65 | A | 9.60 |
| 1 | Maleic acid | 116.08 | 1.92 | A | 6.23 | A | |
| 1 | Phosphoric acid | 98.00 | 1.96 | A | 7.12 | A | 12.32 |
| 2 | Ethanesulfonic acid | 110.13 | 2.05 | A | | | |
| 3 | (+)-Camphor-10-sulfonic acid | 232.29 | 2.17 | A | | | |
| 1 | Glutamic acid | 147.13 | 2.19 | A | 4.25 | A | 9.67 |
| 2 | Alginic acid | 240 000 | ≥ 2.4 | A | | | n.s. |
| 2 | Pamoic acid (embonic acid) | 388.38 | 2.51 | A | 3.1 | A | |
| 2 | Glutaric acid, 2-oxo- | 146.10 | 2.7 | A | 4.5 | A | |
| 2 | 2-Naphthoic acid, 1-hydroxy- | 188.17 | 2.7 | A | 13.5 | A | |
| 2 | Malonic acid | 104.06 | 2.826 | A | 5.696 | A | |
| 2 | Gentisic acid | 154.12 | 2.93 | A | | | |
| 3 | Salicylic acid | 138.12 | 2.97 | A | 13.82 | A | |
| 1 | (+)-L-Tartaric acid | 150.09 | 3.02 | A | 4.36 | A | |
| 1 | Fumaric acid | 116.08 | 3.03 | A | 4.38 | A | 6 |

Table 2 (cont.)

| Class | Acid | M_r | pK_{a1} | pK_{a2} | pK_{a3} | ADI up to [mg/kg] | GRAS Status |
|-------|--|--------|-----------|-----------|-----------|-------------------|-------------|
| 1 | Galactaric acid | 210.14 | 3.08 | A | 3.63 | | |
| 1 | Citric acid | 192.13 | 3.128 | A | 4.761 | A | 6.396 |
| 1 | D-Gluconic acid | 194.14 | 3.18 | A | | | n.s. |
| 2 | Lactobionic acid | 358.30 | 3.2 | A | | | |
| 3 | Salicylic acid, 4-amino- | 153.14 | 3.25 | A | 10 | A | 3.5 |
| 1 | Glycolic acid | 76.05 | 3.28 | A | | | |
| 1 | D-Glucoheptonic acid | 226.18 | 3.3 | A | | | |
| 2 | (-)-L-Pyroglutamic acid | 129.11 | 3.32 | A | | | |
| 3 | DL-Mandelic acid | 152.15 | 3.372 | A | | | |
| 1 | (-)-L-Malic acid | 134.09 | 3.459 | A | 5.097 | A | n.s. |
| 1 | Hippuric acid | 179.17 | 3.55 | A | | | |
| 3 | Formic acid | 46.02 | 3.75 | A | | | |
| 1 | D-Gluconic acid | 196.16 | 3.76 | A | | | 50 |
| 1 | DL-Lactic acid | 90.08 | 3.86 | A | | | |
| 2 | Oleic acid | 282.45 | ca. 4 | A | | | |
| 1 | L-Ascorbic acid | 176.13 | 4.17 | A | 11.57 | A | |
| 2 | Benzoic acid | 122.12 | 4.19 | A | | | |
| 1 | Succinic acid | 118.09 | 4.207 | A | 5.635 | A | n.s. |
| 3 | Benzoic acid, 4-acetamido- | 179.18 | 4.3 | A | | | |
| 1 | Glutaric acid | 132.12 | 4.34 | A | 5.27 | A | |
| 3 | Cinnamic acid | 148.16 | 4.404 | A | | | |
| 1 | Adipic acid | 146.14 | 4.44 | A | 5.44 | A | |
| 1 | Sebacic acid | 202.25 | 4.59 | A | 5.59 | A | |
| 2 | (+)-Camphoric acid | 200.24 | 4.716 | A | 5.83 | A | |
| 1 | Acetic acid | 60.05 | 4.756 | A | | | n.s. |
| 3 | Caproic acid (hexanoic acid) | 116.16 | 4.8 | A | | | |
| 2 | Nicotinic acid | 123.11 | 4.85 | A | 2.07 | B | |
| 2 | Isobutyric acid | 88.11 | 4.86 | A | | | |
| 2 | Propionic acid | 74.08 | 4.87 | A | | | n.s. |
| 1 | Capric acid (decanoic acid) | 172.27 | 4.9 | A | | | n.s. |
| 1 | Lauric acid | 200.32 | 4.9 | A | | | n.s. |
| 1 | Palmitic acid | 256.42 | 4.9 | A | | | n.s. |
| 1 | Stearic acid | 284.49 | 4.9 | A | | | n.s. |
| 3 | Undecylenic acid (undec-10-enoic acid) | 184.27 | 4.9 | A | | | |
| 2 | Caprylic acid (octanoic acid) | 144.22 | 4.91 | A | | | n.s. |
| 2 | Orotic acid | 156.10 | 5.85 | A | 8.95 | A | |
| 1 | Carbonic acid | 44.01 | 6.46 | A | 10.3 | A | n.s. |

Table 3. Acids: Sorted by Increasing Molecular Weight

| Class | Acid | M_r | pK_{a1} | | pK_{a2} | pK_{a3} | ADI up to [mg/kg] | GRAS Status |
|-------|---|--------|-----------|---|-----------|-----------|-------------------|-------------|
| | Decanoic acid (see <i>capric acid</i>) | | | | | | | |
| | Hexanoic acid (see <i>caproic acid</i>) | | | | | | | |
| | Mucic acid (see <i>galactaric acid</i>) | | | | | | | |
| | Octanoic acid (see <i>caprylic acid</i>) | | | | | | | |
| 1 | Hydrochloric acid | 36.46 | -6 | A | | | n.s. | + |
| 1 | Carbonic acid | 44.01 | 6.46 | A | 10.3 | A | n.s. | + |
| 3 | Formic acid | 46.02 | 3.75 | A | | | | |
| 1 | Thiocyanic acid | 59.09 | -1.33 | A | | | | |
| 1 | Acetic acid | 60.05 | 4.756 | A | | | n.s. | + |
| 3 | Nitric Acid | 63.02 | -1.32 | A | | | | |
| 2 | Propionic acid | 74.08 | 4.87 | A | | | n.s. | + |
| 1 | Glycolic acid | 76.05 | 3.28 | A | | | | |
| 3 | Hydrobromic acid | 80.92 | <-6 | A | | | | |
| 2 | Isobutyric acid | 88.11 | 4.86 | A | | | | |
| 2 | Oxalic acid | 90.04 | 1.271 | A | 4.266 | A | | |
| 1 | DL-Lactic acid | 90.08 | 3.86 | A | | | | + |
| 2 | Methanesulfonic acid | 96.10 | -1.2 | A | | | | |
| 1 | Phosphoric acid | 98.00 | 1.96 | A | 7.12 | A | 12.32 | A |
| 1 | Sulfuric acid | 98.08 | -3 | A | 1.92 | A | n.s. | + |
| 2 | Malonic acid | 104.06 | 2.826 | A | 5.696 | A | | |
| 2 | Ethanesulfonic acid | 110.13 | 2.05 | A | | | | |
| 1 | Fumaric acid | 116.08 | 3.03 | A | 4.38 | A | 6 | |
| 1 | Maleic acid | 116.08 | 1.92 | A | 6.23 | A | | |
| 3 | Caproic acid (hexanoic acid) | 116.16 | 4.8 | A | | | | |
| 1 | Succinic acid | 118.09 | 4.207 | A | 5.635 | A | n.s. | + |
| 2 | Benzoic acid | 122.12 | 4.19 | A | | | | + |
| 2 | Nicotinic acid | 123.11 | 4.85 | A | 2.07 | B | | + |
| 2 | Ethanesulfonic acid, 2-hydroxy- | 126.13 | 1.66 | A | | | | |
| 3 | Acetic acid, 2,2-dichloro- | 128.95 | 1.35 | A | | | | |
| 2 | (-)-L-Pyroglutamic acid | 129.11 | 3.32 | A | | | | |
| 1 | Glutaric acid | 132.12 | 4.34 | A | 5.27 | A | | |
| 1 | L-Aspartic acid | 133.11 | 1.88 | A | 3.65 | A | 9.60 | B |
| 1 | (-)-L-Malic acid | 134.09 | 3.459 | A | 5.097 | A | n.s. | + |
| 1 | Salicylic acid | 138.12 | 2.97 | A | 13.82 | A | | |
| 2 | Caprylic acid (octanoic acid) | 144.22 | 4.91 | A | | | n.s. | + |
| 2 | Glutaric acid, 2-oxo- | 146.10 | 2.7 | A | 4.5 | A | | |
| 1 | Adipic acid | 146.14 | 4.44 | A | 5.44 | A | 5 | + |

Table 3 (cont.)

| Class | Acid | M_r | pK_{a1} | pK_{a2} | pK_{a3} | ADI up to [mg/kg] | GRAS Status |
|-------|--|---------|-----------|-----------|-----------|-------------------|-------------|
| 1 | Glutamic acid | 147.13 | 2.19 | A 4.25 | A 9.67 | B | + |
| 3 | Cinnamic acid | 148.16 | 4.404 | A | | | |
| 1 | (+)-L-Tartaric acid | 150.09 | 3.02 | A 4.36 | A | | + |
| 3 | DL-Mandelic acid | 152.15 | 3.372 | A | | | |
| 3 | Salicylic acid, 4-amino- | 153.14 | 3.25 | A 10 | A 3.5 | B | |
| 2 | Gentisic acid | 154.12 | 2.93 | A | | | |
| 2 | Orotic acid | 156.10 | 5.85 | A 8.95 | A | | |
| 2 | Benzenesulfonic acid | 158.18 | 0.7 | A | | | |
| 1 | Glycerophosphoric acid | 172.08 | 1.47 | A 6.19 | A | | |
| 2 | <i>p</i> -Toluenesulfonic acid | 172.21 | -1.34 | A | | | |
| 1 | Capric acid (decanoic acid) | 172.27 | 4.9 | A | | n.s. | |
| 1 | L-Ascorbic acid | 176.13 | 4.17 | A 11.57 | A | | + |
| 1 | Hippuric acid | 179.17 | 3.55 | A | | | |
| 3 | Benzoic acid, 4-acetamido- | 179.18 | 4.3 | A | | | |
| 2 | Cyclamic acid | 179.24 | -2.01 | A | | | |
| 3 | Undecylenic acid (undec-10-enoic acid) | 184.27 | 4.9 | A | | | |
| 2 | 2-Naphthoic acid, 1-hydroxy- | 188.17 | 2.7 | A 13.5 | A | | |
| 2 | Ethane-1,2-disulfonic acid | 190.20 | -2.1 | A -1.5 | A | | |
| 1 | Citric acid | 192.13 | 3.128 | A 4.761 | A 6.396 | A | n.s. |
| 1 | D-Glucuronic acid | 194.14 | 3.18 | A | | | |
| 1 | D-Gluconic acid | 196.16 | 3.76 | A | | 50 | # |
| 2 | (+)-Camphoric acid | 200.24 | 4.716 | A 5.83 | A | | |
| 1 | Lauric acid | 200.32 | 4.9 | A | | n.s. | |
| 1 | Sebacic acid | 202.25 | 4.59 | A 5.59 | A | | |
| 2 | Naphthalene-2-sulfonic acid | 208.24 | 0.17 | A | | | |
| 1 | Galactaric acid | 210.14 | 3.08 | A 3.63 | A | | |
| 1 | D-Glucoheptonic acid | 226.18 | 3.3 | A | | | |
| 3 | (+)-Camphor-10-sulfonic acid | 232.29 | 2.17 | A | | | |
| 1 | Palmitic acid | 256.42 | 4.9 | A | | n.s. | |
| 2 | Dodecylsulfuric acid | 266.40 | -0.09 | A | | | |
| 2 | Oleic acid | 282.45 | ca. 4 | A | | | |
| 1 | Stearic acid | 284.49 | 4.9 | A | | n.s. | + |
| 2 | Naphthalene-1,5-disulfonic acid | 332.26 | -3.37 | A -2.64 | A | | |
| 2 | Lactobionic acid | 358.30 | 3.2 | A | | | |
| 2 | Pamoic acid (embonic acid) | 388.38 | 2.51 | A 3.1 | A | | |
| 2 | Alginate acid | 240 000 | ≥ 2.4 | A | | n.s. | + |

Table 4. Acids: Sorted by Class

| Acid | M_r | pK_{a1} | pK_{a2} | pK_{a3} | ADI up to [mg/kg] | GRAS Status |
|---|---------|------------|-----------|-----------|-------------------------|----------------|
| Decanoic acid (see <i>capric acid</i>) | | | | | | |
| Hexanoic acid (see <i>caproic acid</i>) | | | | | | |
| Mucic acid (see <i>galactaric acid</i>) | | | | | | |
| Octanoic acid (see <i>caprylic acid</i>) | | | | | | |
| Class 1 | | | | | | |
| Acetic acid | 60.05 | 4.756 | A | | n.s. | + |
| Adipic acid | 146.14 | 4.44 | A | 5.44 | 5 | + |
| L-Ascorbic acid | 176.13 | 4.17 | A | 11.57 | | + |
| L-Aspartic acid | 133.11 | 1.88 | A | 3.65 | 9.60 | B |
| Capric acid (decanoic acid) | 172.27 | 4.9 | A | | n.s. | |
| Carbonic acid | 44.01 | 6.46 | A | 10.3 | n.s. | + |
| Citric acid | 192.13 | 3.128 | A | 4.761 | 6.396 | A |
| Fumaric acid | 116.08 | 3.03 | A | 4.38 | 6 | |
| Galactaric acid | 210.14 | 3.08 | A | 3.63 | | |
| D-Glucoheptonic acid | 226.18 | 3.3 | A | | | |
| D-Gluconic acid | 196.16 | 3.76 | A | | 50 | # |
| D-Glucuronic acid | 194.14 | 3.18 | A | | | |
| Glutamic acid | 147.13 | 2.19 | A | 4.25 | 9.67 | B |
| Glutaric acid | 132.12 | 4.34 | A | 5.27 | | |
| Glycerophosphoric acid | 172.08 | 1.47 | A | 6.19 | | |
| Glycolic acid | 76.05 | 3.28 | A | | | |
| Hippuric acid | 179.17 | 3.55 | A | | | |
| Hydrochloric acid | 36.46 | -6 | A | | n.s. | + |
| DL-Lactic acid | 90.08 | 3.86 | A | | | + |
| Lauric acid | 200.32 | 4.9 | A | | n.s. | |
| Maleic acid | 116.08 | 1.92 | A | 6.23 | | |
| (-)-L-Malic acid | 134.09 | 3.459 | A | 5.097 | | + |
| Palmitic acid | 256.42 | 4.9 | A | | n.s. | |
| Phosphoric acid | 98.00 | 1.96 | A | 7.12 | 12.32 | A |
| Sebacic acid | 202.25 | 4.59 | A | 5.59 | | |
| Stearic acid | 284.49 | 4.9 | A | | n.s. | + |
| Succinic acid | 118.09 | 4.207 | A | 5.635 | | n.s. |
| Sulfuric acid | 98.08 | -3 | A | 1.92 | | n.s. |
| (+)-L-Tartaric acid | 150.09 | 3.02 | A | 4.36 | | + |
| Thiocyanic acid | 59.09 | -1.33 | A | | | |
| Class 2 | | | | | | |
| Alginate acid | 240 000 | ≥ 2.4 | A | | n.s. | + |
| Benzenesulfonic acid | 158.18 | 0.7 | A | | | |
| Benzoic acid | 122.12 | 4.19 | A | | | + |

Table 4 (cont.)

| Acid | M_r | pK_{a1} | pK_{a2} | pK_{a3} | ADI up to [mg/kg] | GRAS Status |
|--|--------|--------------|-----------|-----------|-------------------|-------------|
| (+)-Camphoric acid | 200.24 | 4.716 | A 5.83 | A | | |
| Caprylic acid (octanoic acid) | 144.22 | 4.91 | A | | n.s. | + |
| Cyclamic acid | 179.24 | ~ -2.01 | A | | | |
| Dodecylsulfuric acid | 266.40 | -0.09 | A | | | |
| Ethane-1,2-disulfonic acid | 190.20 | -2.1 | A -1.5 | A | | |
| Ethanesulfonic acid | 110.13 | 2.05 | A | | | |
| Ethanesulfonic acid, 2-hydroxy- | 126.13 | 1.66 | A | | | |
| Gentic acid | 154.12 | 2.93 | A | | | |
| Glutaric acid, 2-oxo- | 146.10 | 2.7 | A 4.5 | A | | |
| Isobutyric acid | 88.11 | 4.86 | A | | | |
| Lactobionic acid | 358.30 | 3.2 | A | | | |
| Malonic acid | 104.06 | 2.826 | A 5.696 | A | | |
| Methanesulfonic acid | 96.10 | -1.2 | A | | | |
| Naphthalene-1,5-disulfonic acid | 332.26 | -3.37 | A -2.64 | A | | |
| Naphthalene-2-sulfonic acid | 208.24 | 0.17 | A | | | |
| 2-Naphthoic acid, 1-hydroxy- | 188.17 | 2.7 | A 13.5 | A | | |
| Nicotinic acid | 123.11 | 4.85 | A 2.07 | B | | + |
| Oleic acid | 282.45 | ca. 4 | A | | | |
| Orotic acid | 156.10 | 5.85 | A 8.95 | A | | |
| Oxalic acid | 90.04 | 1.271 | A 4.266 | A | | |
| Pamoic acid (embonic acid) | 388.38 | 2.51 | A 3.1 | A | | |
| Propionic acid | 74.08 | 4.87 | A | | n.s. | + |
| (-)-L-Pyroglutamic acid | 129.11 | 3.32 | A | | | |
| <i>p</i> -Toluenesulfonic acid | 172.21 | -1.34 | A | | | |
| Class 3 | | | | | | |
| Acetic acid, 2,2-dichloro- | 128.95 | 1.35 | A | | | |
| Benzoic acid, 4-acetamido- | 179.18 | 4.3 | A | | | |
| (+)-Camphor-10-sulfonic acid | 232.29 | 2.17 | A | | | |
| Caproic acid (hexanoic acid) | 116.16 | 4.8 | A | | | |
| Cinnamic acid | 148.16 | 4.404 | A | | | |
| Formic acid | 46.02 | 3.75 | A | | | |
| Hydrobromic acid | 80.92 | < -6 | A | | | |
| DL-Mandelic acid | 152.15 | 3.372 | A | | | |
| Nitric Acid | 63.02 | -1.32 | A | | | |
| Salicylic acid | 138.12 | 2.97 | A 13.82 | A | | |
| Salicylic acid, 4-amino- | 153.14 | 3.25 | A 10 | A 3.5 | B | |
| Undecylenic acid (undec-10-enoic acid) | 184.27 | 4.9 | A | | | |

Table 5. Bases: Alphabetical Order

| Class | Base | M_r | pK_{a1} | pK_{a2} | pK_{a3} | ADI up to [mg/kg] | GRAS Status |
|-------|--|--------|-----------|-----------|-----------|-------------------|-------------|
| 1 | Ammonia | 17.03 | 9.27 | B | | | # |
| 1 | L-Arginine | 174.20 | 13.2 | B | 9.09 | B 2.18 A | |
| 2 | Benethamine | 197.28 | 4.46 | B | | | |
| 2 | Benzathine | 240.35 | 9.99 | B | 9.39 | B | |
| 2 | Betaine | 117.15 | 12.16 | B | | | |
| 1 | Calcium hydroxide | 74.10 | 12.6 | B | 11.57 | B | + |
| 1 | Choline | 121.18 | > 11 | B | | | # |
| 2 | Deanol | 89.14 | 8.83 | B | | | |
| 3 | Diethanolamine (2,2'-iminobis(ethanol)) | 105.14 | 9.28 | B | | | |
| 2 | Diethylamine | 73.14 | 10.93 | B | | | |
| 2 | Ethanol, 2-(diethylamino)- | 117.19 | 9.58 | B | | | |
| 3 | Ethanolamine (2-aminoethanol) | 61.08 | 9.50 | B | | | |
| 3 | Ethylenediamine | 60.10 | 7.00 | B | 10.09 | B | |
| 1 | Glucamine, <i>N</i> -methyl- | 195.22 | 8.03 | B | | | |
| 2 | Hydrabamine | 596.99 | 11.92 | B | 11.32 | B | |
| 3 | 1 <i>H</i> -Imidazole | 68.08 | 7.03 | B | | | |
| 1 | Lysine | 146.19 | 10.79 | B | 9.18 | B 2.16 A | |
| 1 | Magnesium hydroxide | 58.33 | 11.4 | B | | | + |
| 2 | Morpholine, 4-(2-hydroxyethyl)- | 131.18 | 7.39 | B | | | |
| 3 | Piperazine | 86.14 | 5.68 | B | 9.82 | B | |
| 1 | Potassium hydroxide | 56.11 | ca. 14 | B | | | + |
| 2 | Pyrrolidine, 1-(2-hydroxyethyl)- | 115.18 | 9.44 | B | | | |
| 1 | Sodium hydroxide | 40.00 | ca. 14 | B | | | + |
| 3 | Triethanolamine (2,2',2"-nitrilotris(ethanol)) | 149.19 | 7.82 | B | | | |
| 2 | Tromethamine | 121.14 | 8.02 | B | | | |
| 3 | Zinc hydroxide | 99.38 | ca. 14 | B | 9.64 | B | # |

Table 6. Bases: Sorted by Decreasing pK_a Value

| Class | Base | M_r | pK_{a1} | pK_{a2} | pK_{a3} | ADI up to [mg/kg] | GRAS Status |
|-------|---|--------|-----------|-----------|-----------|-------------------|-------------|
| 1 | Potassium hydroxide | 56.11 | ca. 14 | B | | | + |
| 1 | Sodium hydroxide | 40.00 | ca. 14 | B | | | + |
| 3 | Zinc hydroxide | 99.38 | ca. 14 | B | 9.64 | B | # |
| 1 | L-Arginine | 174.20 | 13.2 | B | 9.09 | B 2.18 A | |
| 1 | Calcium hydroxide | 74.10 | 12.6 | B | 11.57 | B | + |
| 2 | Betaine | 117.15 | 12.16 | B | | | |
| 2 | Hydrabamine | 596.99 | 11.92 | B | 11.32 | B | |
| 1 | Magnesium hydroxide | 58.33 | 11.4 | B | | | + |
| 1 | Choline | 121.18 | > 11 | B | | | # |
| 2 | Diethylamine | 73.14 | 10.93 | B | | | |
| 1 | Lysine | 146.19 | 10.79 | B | 9.18 | B 2.16 A | |
| 2 | Benzathine | 240.35 | 9.99 | B | 9.39 | B | |
| 2 | Ethanol, 2-(diethylamino)- | 117.19 | 9.58 | B | | | |
| 3 | Ethanolamine (2-aminoethanol) | 61.08 | 9.50 | B | | | |
| 2 | Pyrrolidine, 1-(2-hydroxyethyl)- | 115.18 | 9.44 | B | | | |
| 3 | Diethanolamine (2,2'-iminobis(ethanol)) | 105.14 | 9.28 | B | | | |
| 1 | Ammonia | 17.03 | 9.27 | B | | | # |
| 2 | Deanol | 89.14 | 8.83 | B | | | |
| 1 | Glucamine, N-methyl- | 195.22 | 8.03 | B | | | |
| 2 | Tromethamine | 121.14 | 8.02 | B | | | |
| 3 | Triethanolamine (2,2',2''-nitrilotris(ethanol)) | 149.19 | 7.82 | B | | | |
| 2 | Morpholine, 4-(2-hydroxyethyl)- | 131.18 | 7.39 | B | | | |
| 3 | 1 <i>H</i> -Imidazole | 68.08 | 7.03 | B | | | |
| 3 | Ethylenediamine | 60.10 | 7.00 | B | 10.09 | B | |
| 3 | Piperazine | 86.14 | 5.68 | B | 9.82 | B | |
| 2 | Benethamine | 197.28 | 4.46 | B | | | |

Table 7. Bases: Sorted by Increasing Molecular Weight

| Class | Base | M_r | pK_{a1} | pK_{a2} | pK_{a3} | ADI up to [mg/kg] | GRAS Status |
|-------|---|--------|-----------|-----------|-----------|-------------------------|----------------|
| 1 | Ammonia | 17.03 | 9.27 | B | | | # |
| 1 | Sodium hydroxide | 40.00 | ca. 14 | B | | | + |
| 1 | Potassium hydroxide | 56.11 | ca. 14 | B | | | + |
| 1 | Magnesium hydroxide | 58.33 | 11.4 | B | | | + |
| 3 | Ethylenediamine | 60.10 | 7.00 | B | 10.09 | B | |
| 3 | Ethanolamine (2-aminoethanol) | 61.08 | 9.50 | B | | | |
| 3 | 1 <i>H</i> -Imidazole | 68.08 | 7.03 | B | | | |
| 2 | Diethylamine | 73.14 | 10.93 | B | | | |
| 1 | Calcium hydroxide | 74.10 | 12.6 | B | 11.57 | B | + |
| 3 | Piperazine | 86.14 | 5.68 | B | 9.82 | B | |
| 2 | Deanol | 89.14 | 8.83 | B | | | |
| 3 | Zinc hydroxide | 99.38 | ca. 14 | B | 9.64 | B | # |
| 3 | Diethanolamine (2,2'-iminobis(ethanol)) | 105.14 | 9.28 | B | | | |
| 2 | Pyrolidine, 1-(2-hydroxyethyl)- | 115.18 | 9.44 | B | | | |
| 2 | Betaine | 117.15 | 12.16 | B | | | |
| 2 | Ethanol, 2-(diethylamino)- | 117.19 | 9.58 | B | | | |
| 2 | Tromethamine | 121.14 | 8.02 | B | | | |
| 1 | Choline | 121.18 | > 11 | B | | | # |
| 2 | Morpholine, 4-(2-hydroxyethyl)- | 131.18 | 7.39 | B | | | |
| 1 | Lysine | 146.19 | 10.79 | B | 9.18 | B 2.16 | A |
| 3 | Triethanolamine (2,2',2"-nitrilotris(ethanol)) | 149.19 | 7.82 | B | | | |
| 1 | L-Arginine | 174.20 | 13.2 | B | 9.09 | B 2.18 | A |
| 1 | Glucamine, <i>N</i> -methyl- | 195.22 | 8.03 | B | | | |
| 2 | Benethamine | 197.28 | 4.46 | B | | | |
| 2 | Benzathine | 240.35 | 9.99 | B | 9.39 | B | |
| 2 | Hydrabamine | 596.99 | 11.92 | B | 11.32 | B | |

Table 8. *Bases: Sorted by Class*

| Base | M_r | pK_{a1} | pK_{a2} | pK_{a3} | ADI up to [mg/kg] | GRAS Status |
|---|--------|-----------|-----------|-----------|-------------------|-------------|
| Class 1 | | | | | | |
| Ammonia | 17.03 | 9.27 | B | | | # |
| L-Arginine | 174.20 | 13.2 | B | 9.09 | B 2.18 A | |
| Calcium hydroxide | 74.10 | 12.6 | B | 11.57 | B | + |
| Choline | 121.18 | > 11 | B | | | # |
| Glucamine, <i>N</i> -methyl- | 195.22 | 8.03 | B | | | |
| Lysine | 146.19 | 10.79 | B | 9.18 | B 2.16 A | |
| Magnesium hydroxide | 58.33 | 11.4 | B | | | + |
| Potassium hydroxide | 56.11 | ca. 14 | B | | | + |
| Sodium hydroxide | 40.00 | ca. 14 | B | | | + |
| Class 2 | | | | | | |
| Benethamine | 197.28 | 4.46 | B | | | |
| Benzathine | 240.35 | 9.99 | B | 9.39 | B | |
| Betaine | 117.15 | 12.16 | B | | | |
| Deanol | 89.14 | 8.83 | B | | | |
| Diethylamine | 73.14 | 10.93 | B | | | |
| Ethanol, 2-(diethylamino)- | 117.19 | 9.58 | B | | | |
| Hydrabamine | 596.99 | 11.92 | B | 11.32 | B | |
| Morpholine, 4-(2-hydroxyethyl)- | 131.18 | 7.39 | B | | | |
| Pyrrolidine, 1-(2-hydroxyethyl)- | 115.18 | 9.44 | B | | | |
| Tromethamine | 121.14 | 8.02 | B | | | |
| Class 3 | | | | | | |
| Diethanolamine (2,2'-iminobis(ethanol)) | 105.14 | 9.28 | B | | | |
| Ethanolamine (2-aminoethanol) | 61.08 | 9.50 | B | | | |
| Ethylenediamine | 60.10 | 7.00 | B | 10.09 | B | |
| 1 <i>H</i> -Imidazole | 68.08 | 7.03 | B | | | |
| Piperazine | 86.14 | 5.68 | B | 9.82 | B | |
| Triethanolamine (2,2',2''-nitrilotris(ethanol)) | 149.19 | 7.82 | B | | | |
| Zinc hydroxide | 99.38 | ca. 14 | B | 9.64 | B | # |

3. Diagrams

3.1. Nomographs for Predicting pH Values of Aqueous Solutions of Salts

The following diagrams are designed for quickly estimating the pH of aqueous solutions of a salt, if the pK_a value of the constituting drug base is known. Prediction of pH is particularly useful in cases of intended salts of weak and very weak bases. If calculated pK_a values [5] are entered into the diagrams, the expected aqueous pH values and pH ranges of certain salts can be estimated even before a compound is synthesized.

Diagrams are provided for three of the most frequently used acids for salts of basic drug substances: hydrochloric, sulfuric, and maleic acid. The graphs have been calculated based on exact equations for pH calculation presented in [7].

As the pH of an aqueous salt solution depends not only on the nature of the constituting salt ions but also on their concentrations, the pH functions are presented for the molar concentrations 0.01 to 1.0M.

How to read pH values from the graphs is shown in *Fig. 4,a* for the sulfates of the weakly basic fungicide econazole as an example, with a calculated pK_a value of 6.4. For the hydrogen sulfate, $\text{Base}^+ \cdot \text{HSO}_4^-$, at concentrations 0.01 – 0.1M, the pH would range between 2.2 and 1.55, whereas a 0.05M solution of the neutral sulfate, $(\text{Base}^+)_2 \cdot \text{SO}_4^{2-}$, is expected to measure pH 4.3.

Fig. 3, drawn for hydrochlorides, can also be used for salts of other very strong acids with pK_a values below -1 , e.g., for methanesulfonates. The course of the pH curves of the bivalent acids demonstrates the extent of the typical pH-lowering effect of the acid salts (*Figs. 4* and *5*; hydrogen sulfates, hydrogen maleates). The very low dependence of the pH on concentration of maleates exemplifies the buffering effect of organic acids of moderate strength.

3.2. Aqueous Solutions of Lactic Acid

As described in the monograph on lactic acid in *Chapt. 12*, the composition of aqueous solutions of lactic acid depends on the concentration. *Fig. 6* shows the relationship between free and polymerized lactic acids as a function of the water content.

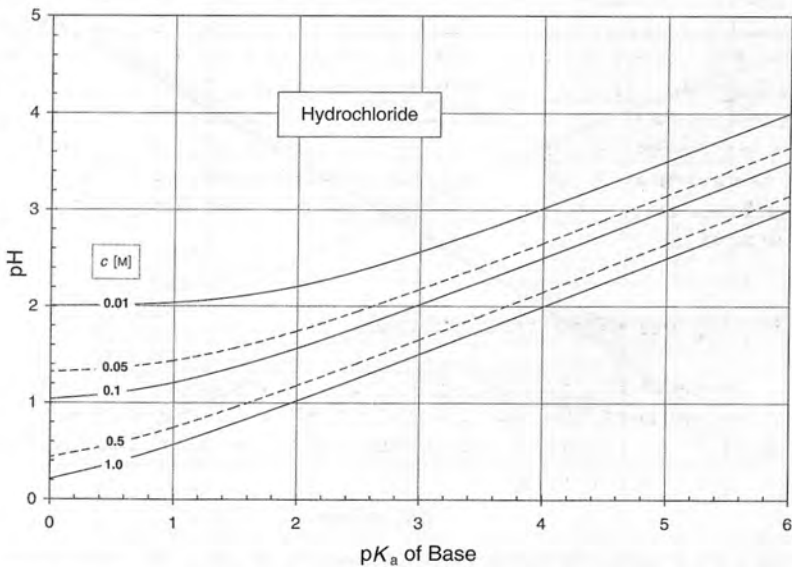
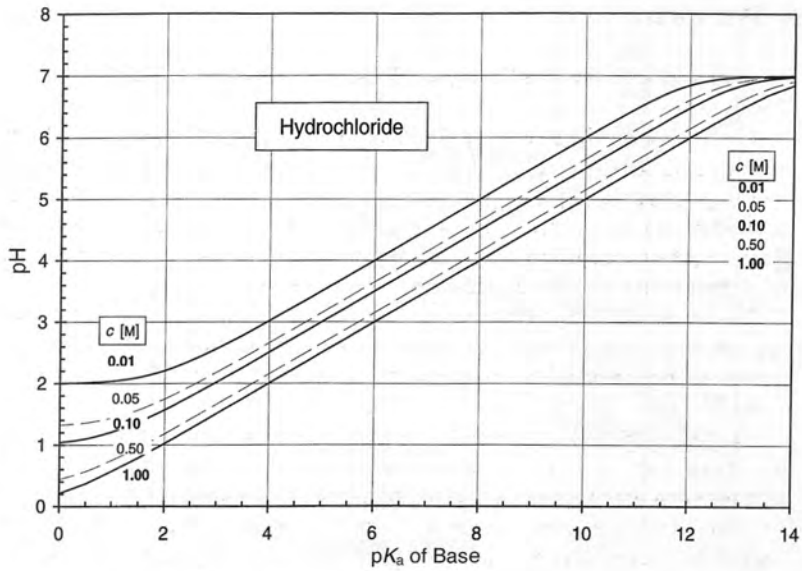


Fig. 3. pH of hydrochlorides dependent on the pK_a of the conjugate base. Top: Base pK_a range 0–14; bottom: base pK_a range 0–6.

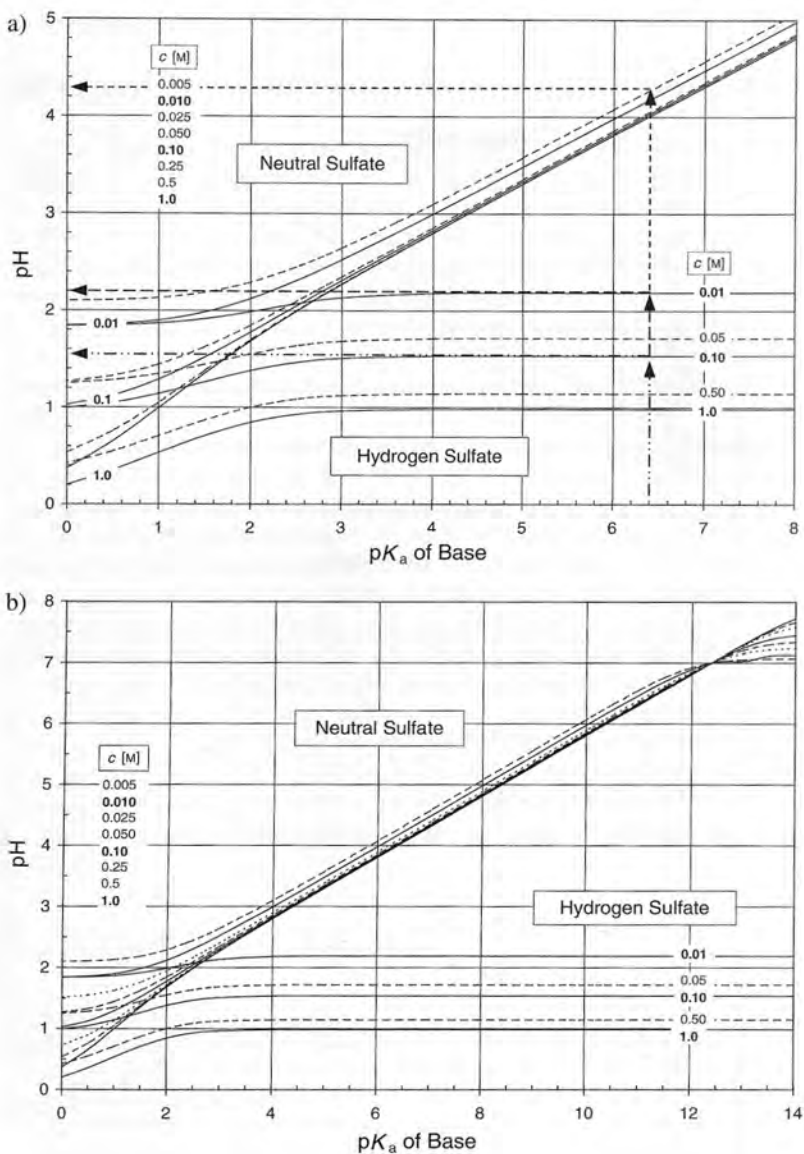


Fig. 4. pH of sulfates and hydrogensulfates dependent on the pK_a of the conjugate base. a) Example of reading pH for the acid sulfate (lines entered: $c = 0.01M$ and $0.1M$, resulting pH: 2.2 and 1.6) and for the neutral sulfate (line entered: $c = 0.05M$, resulting pH: 4.3) of a weak base, $pK_a = 6.4$ (e.g., econazole); b) base pK_a range 0–14; c) base pK_a range 0–6.

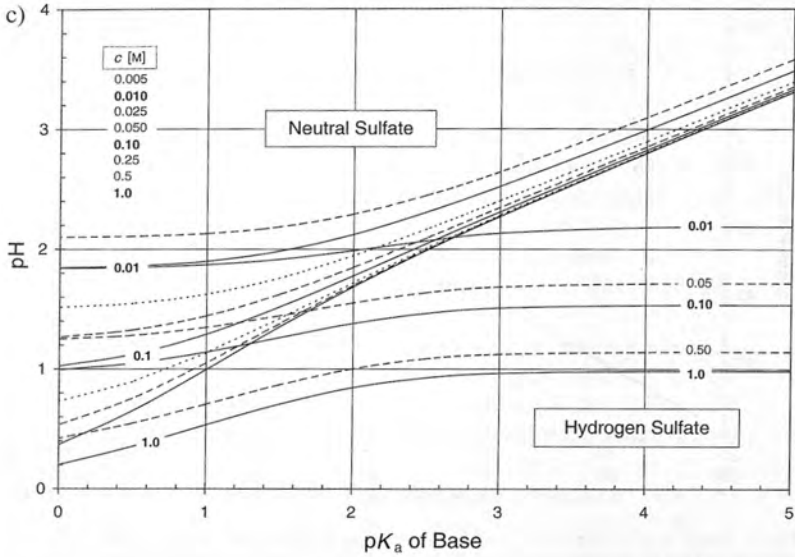


Fig. 4 (cont.)

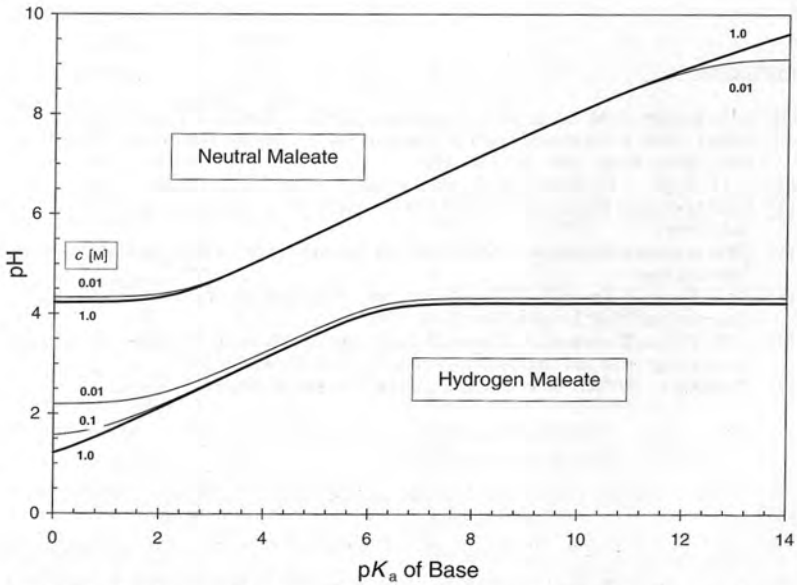


Fig. 5. pH of maleates and hydrogenmaleates dependent on the pK_a of the conjugate base

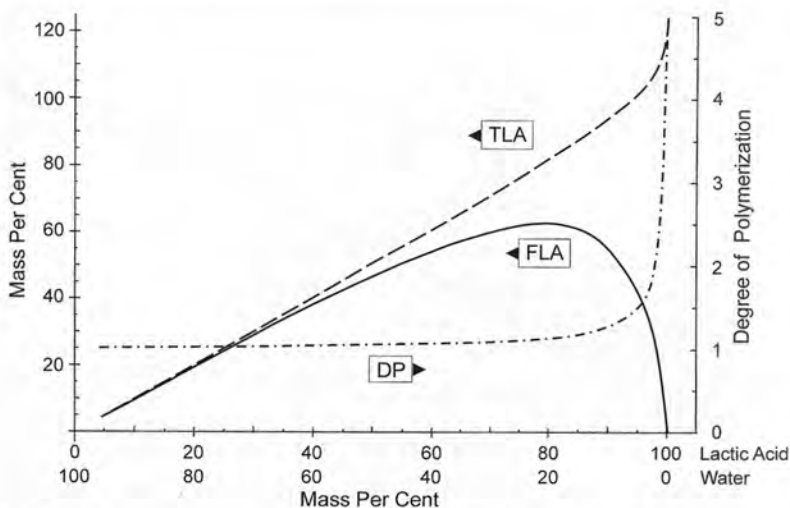


Fig. 6. Lactic acid in aqueous solution: free lactic acid (FLA) and degree of polymerization (DP) in relation to the total content of titrated acid (TLA), calculated as lactic acid as a function of the water content (drawn from values tabulated in [6])

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Subject Index

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