Appendix

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Contents

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	1346	474
Percentage		73.96%	26.04%
Involved number of different		acids (anions)	cations (bases)
	organic	101	23
	inorganic	7	14
Total		108	37

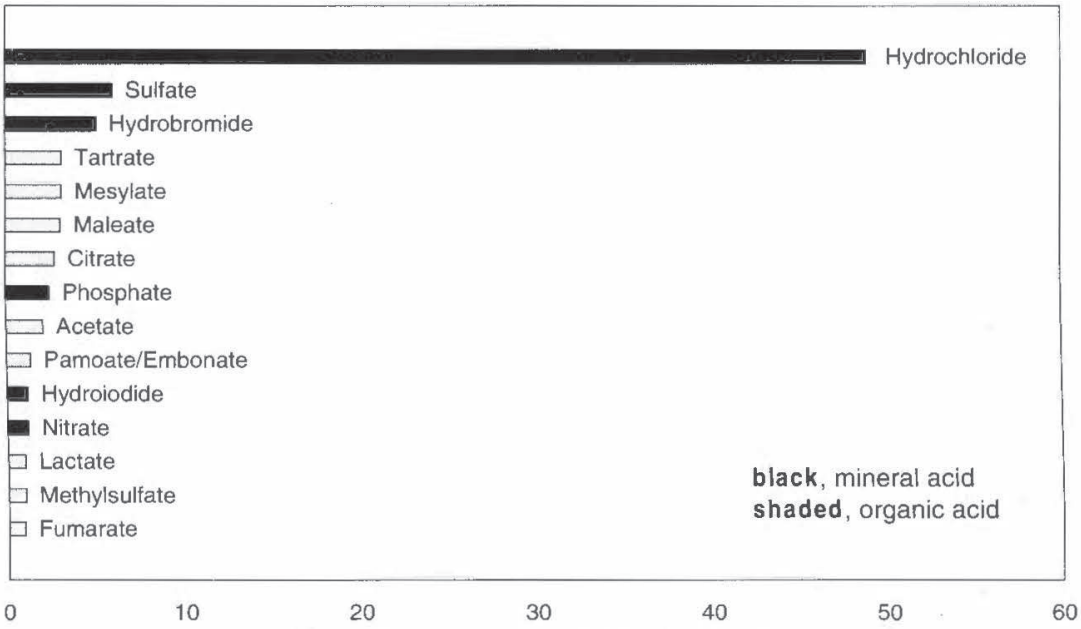
The surveys make apparent that acids by far outnumber the bases in their

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*.



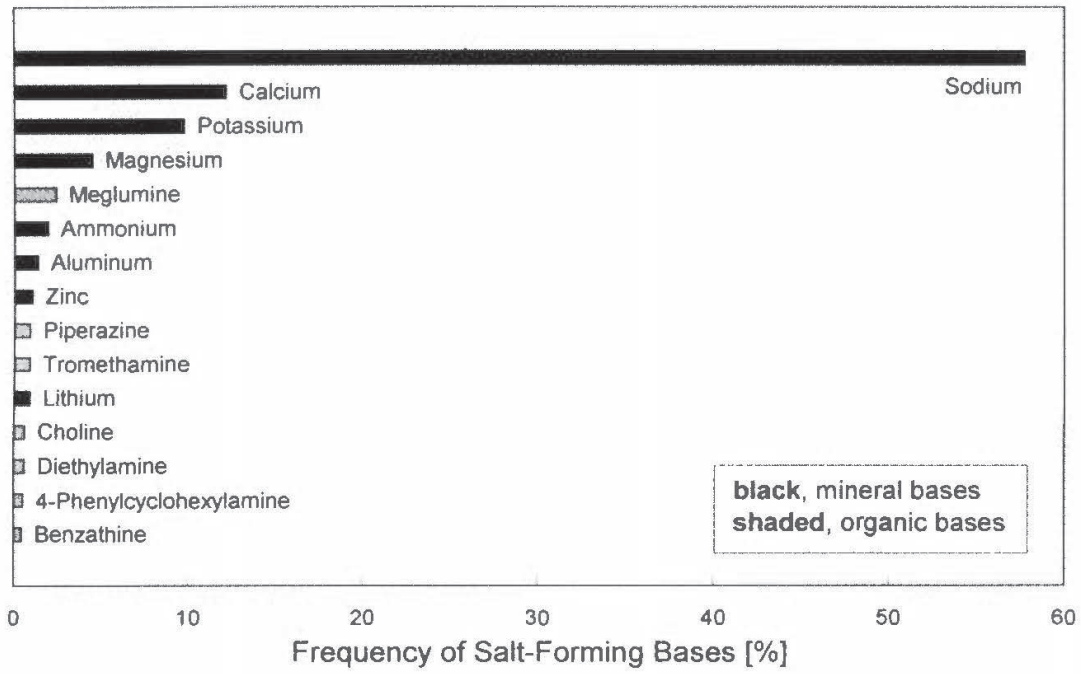


Fig. 2. *Distribution of salts with the 15 most frequently occurring bases* (cations)

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 an 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

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* (=*A*cceptable *D*aily *I*ntake) assigned to them (WHO); in the USA, the *FDA* grants the *GRAS* (='*G*enerally *R*egarded *A*s *S*afe') 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

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.*).

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