papers and notes on methodology

A proposed nomenclature for bile acids

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Abstract A proposal is made for a system of nomenclature of the more common unconjugated and conjugated bile acids. Acceptable trivial names for bile acids are tabulated, and guidelines are proposed for using these existing trivial names as roots to create acceptable semi-systematic names for other bile acids, as well as for new natural bile acids that will be discovered in the future. The term α-hyocholic is recommended to replace hyocholic, and β-hyocholic to replace ω-murichollic. The term murideoxycholic acid is recommended for 3α,6β-dihydroxy-5β-cholan-24-oic acid. Proposals are also made for bile acids with epimeric hydroxy groups, for unsaturated bile acids, and for bile acids with oxo- and/or hydroxy-oxo- substituents on the nucleus and/or on the side chain. For conjugated bile acids, the term "aminoacyl amidates" is recommended to replace "amidates" for bile acids conjugated in N-acyl linkage with amino acids. Nomenclature for other types of conjugates (sulfates, glucuronides, glucosides) is included as well as abbreviations. It is recommended that the historic tradition of naming a newly discovered bile acid after the species from which it was isolated be abandoned, and that in the future such a bile acid should be named using the principles contained in this paper.—**Hofmann, A. F., J. Sjövall, G. Kurz, A. Radominska, C. D. Schteingart, G.S. Tint, Z. R. Vlahcevic, and K. D. R. Setchell.** A proposed nomenclature for bile acids. *J. Lipid Res.* 1992. **33:** 599–604.

Supplementary key words conjugated bile acids • amidates • bile salts • muricholic acid • hyocholic acid

Bile acids and bile alcohols are a subclass of steroids. Steroids are defined as "compounds possessing the skeleton of cyclopentano[*a*]phenanthrene or a skeleton derived therefrom by one or more bond scissions or ring expansions or contractions. Methyl groups are usually present at C-10 and C-13. An alkyl side chain may also be present at C-17. Sterols are [a subclass of] steroids carrying a hydroxyl group at C-3 and most of the skeleton of cholestane. Additional carbon atoms may be present in the side chain." (1) Rules for numbering the atoms of the steroid ring and side chain as well as recommendations for illustrating the steroid formula are also given in reference 1. **Fig. 1** shows the structure of the cholestane skeleton and indicates the numbering system for the carbon atoms. **Fig. 2** shows the structure of a typical bile acid and indicates the stereochemistry of the ring junctures, the angular methyl groups of the nucleus, the five-carbon side chain, and the C_{21} methyl group.

Bile acids and bile alcohols are steroids whose structure is related to cholane or cholestane. Bile acids or bile alcohols may be termed cholanoids when it is convenient to have a name for this subclass of steroids.

The term bile acid is a generic term for such molecules with a carboxyl group and does not denote any state of ionization. The term "bile salt" may be used when convenient for a salt in which the anion is a conjugated bile acid, an unconjugated bile acid, or a conjugate of a bile alcohol. It may also be used as a generic term to include both conjugated bile acids and bile alcohol conjugates occurring in nature as water-soluble anions. A water-soluble zwitterionic derivative of a bile acid, such as CHAPS (3-[(3-cholamidopropyl) dimethylammonio]-1-propane sulfonate), may be termed a bile salt; such a compound may also be termed a bile acid, or bile acid derivative, or "cho-

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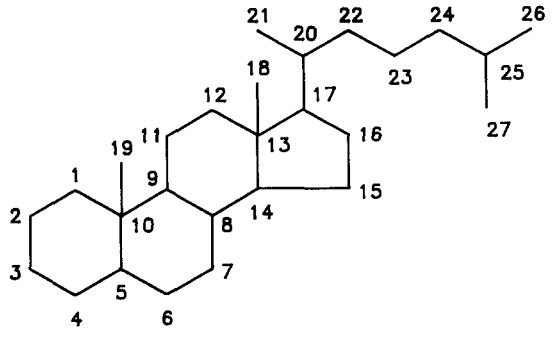

Fig. 1. Numbering system for carbon atoms of bile acid skeleton. C_{24} bile acids are termed cholanoic acids; C_{27} bile acids are termed cholestanoic acids.

lanoid." In principle, salts of cationic bile acid derivatives are also bile salts. Thus, for most mammalian and avian bile samples, the term "bile salt" usually refers to the salt of a bile acid. In other instances, this is not necessarily so.

The terms "primary bile acid" and "secondary bile acid" refer to the steroid moiety of bile acids only; they do not refer to the state of conjugation. The term "primary bile acid" refers to only the natural bile acids biosynthesized from cholesterol in the liver. The term "secondary bile acid" refers to bile acids formed by bacterial modification of primary bile acids, usually by dehydroxylation. The term "tertiary bile acid" has been used for new bile acids formed by hepatic biotransformation of secondary bile acids; this term should be abandoned. Since 7-dehydroxylation and 3 and 7 dehydrogenation or epimerization can at least in principle be mediated by hepatic as well as bacterial enzymes, the terms "primary bile acids" and "secondary bile acids" are best used as little as possible. However, they may be useful to categorize the common natural bile acids shown in Table 1. The term "secondary" may also be useful to describe a bile acid clearly known to have been formed by the action of bacterial enzymes.

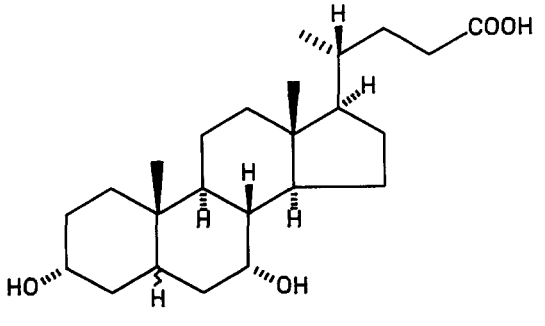

Fig. 2. Structural formula of chenodeoxycholic acid showing position and orientation of the 3α- and 7α- hydroxy groups. The stereochemistry of the A/B ring juncture is shown by a wavy line to indicate that a bile acid is either 5β (A/B ring juncture is *cis*) or 5α (A/B ring juncture is *trans*). In semi-systematic bile acid nomenclature, 5α bile acids are termed *allo* bile acids. The figure also shows the stereochemistry of the B/C and C/D ring junctures, as well as that of the side chain with its C_{21} methyl group.

Subclass names to distinguish the length of the side chain

The natural configuration of the side chain is 17β. Bile acids with 24 carbon atoms in the skeleton will be termed cholanoic acids (or cholanoates) and are designated C_{24} bile acids. Bile acids with 27 carbon atoms will be termed cholestanoic acids (cholestanoates) and are designated C_{27} bile acids. The term "coprostanoic acid" should not be used.

Each of these two major classes of bile acids can be modified by nor (for one less carbon atom in the side chain) or dinor (for two less carbon atoms in the side chain). The C_{28} and C_{29} bile acids can be termed homo- and dihomocholestanoic acids, or alternatively, by the position number and methyl or ethyl (or higher alkyl substituents). The C_{21} bile acids will be termed pregnanoic acids. The C_{20} (bile) acid will be termed norpregnanoic acid (21-norpregnanoic). This term refers to the skeleton with the 17β oriented carboxylic acid.

To indicate the number of carbon atoms in the skeleton, a subscript, and not a number followed by a hyphen, should be used, for example, a C_{24} bile acid. To refer to the position of a carbon atom, a number is used (usually followed by α or β) followed by a hyphen.

It is hoped to prepare a similar consensus statement for nomenclature of C_{27} and other "primitive" bile acids.

Bile alcohols denote molecules with a cholestane (C_{27}) or cholane (C_{24}) skeleton, as well as homologues; bile alcohols must contain at least one primary or secondary hydroxyl group and may not contain a carboxyl group.

Stereochemistry at the A/B ring junction

The common C_{24} bile acids (with a 5β hydrogen; A/B ring junction in *cis* configuration) are considered normal; and in trivial nomenclature, the stereochemistry of the A/B ring junction will not be indicated. The bile acids with a 5α hydrogen will be termed "allo" bile acids. For C_{27} bile acids, the term cholestanoic acid should be preceded by 5α- or 5β- (with a hyphen) since the name coprostanoic is no longer recommended. A hyphen should not be used between prefixes or between the prefix and the stem. (Such prefixes include hydroxy, epi, iso, oxo, nor, dinor, homo, dihomo, allo, and deoxy.)

For structural formulas, the 18 and 19 methyl groups may be represented by a bold line, as recommended by IUPAC. The configuration of the hydrogen at C-5 should always be shown, with the letter H included in the figure.

If trivial or semi-systematic names are used for bile acids in manuscripts, the systematic name should be given in a footnote or under Materials and Methods. A less desirable alternative is to cite this article.

Trivial names for natural bile acids with only nuclear hydroxyl group substituents

Common, natural polyhydroxy bile acids. Names of the common bile acids that are considered to be "grandfathered" and to be used as building blocks for other trivial names are given in **Table 1**. They have been widely and consistently used. The general structure of those names is usually the identifying prefix followed by cholic acid. The term "cholic" thus has two meanings—one for the specific compound (3α,7α, 12α-trihydroxy-5β-cholan-24-oic acid) and one that means the cholanoic acid skeleton where the pattern of hydroxyl substituents is indicated by the prefix urso, muri, hyo, etc. These in turn refer to the species from which the bile acid was originally isolated.

Some other natural bile acids. **Table 2** contains recommended semi-systematic nomenclature for some other natural bile acids. Bile acids 1–4 occur in only trace proportions in bile or feces of common mammals. Bile acid 5 is a major biliary bile acid in the Australian opossum *(Trichosurus vulpecula)*. The trivial names that have been used in the recent literature are also included. These names can be defended and may be convenient for conversational purposes. Nonetheless, they are not to be used in publications. Alternative acceptable trivial names are also given. (See also the section dealing with epimeric hydroxy groups.)

Secondary bile acids formed by bacterial dehydroxylation. The most common bacterial dehydroxylation that is likely is 7-dehydroxylation. The prefix "deoxy" means loss of the 7-hydroxyl group. If there is dehydroxylation at another position, the number of the position will be indicated where the hydroxyl group is missing, e.g., 3-deoxycholic acid for 7α,12α-dihydroxy-5β-cholan-24-oic acid.

Monohydroxy bile acids (nuclear hydroxy group). For monohydroxy bile acids (with the single exception of lithocholic acid, which is "grandfathered"), no new trivial names will be proposed; rather, cholanoic acid will be used as a building block to give, for example, 7α-hydroxycholanoic acid.

Tetra- or pentahydroxy bile acids (nuclear substituents only). For tetrahydroxy or pentahydroxy bile acids (with the additional hydroxyl groups being in the nucleus), the position and configuration of the additional hydroxyl will be stated, e.g., 6α-hydroxycholic acid. Whenever possible, cholic acid will be used as the building block, but in some instances, it will be necessary to use chenodeoxycholic acid, deoxycholic acid, or lithocholic acid, or even other names listed in Table 1. As an example, the name 6α-hydroxycholic acid is preferable to 12α-hydroxyhyocholic acid). The principle should be to choose a building block if possible from the first five names given in Table 1 (cholic, deoxycholic, chenodeoxycholic, ursodeoxycholic, and lithocholic) and to choose the bile acid with the highest number of hydroxyls as the building block. The aim is to develop the simplest possible name. Some examples are given in Table 2. (The practice

TABLE 1. Recommended semi-systematic names for common natural bile acids

Bile Acid	Hydroxyl Substituents	Abbreviation When Present as Side Chain Conjugate	Abbreviation for Acid with Underivatized Carboxyl Group
Cholic	3α,7α,12α	C-	CA
Deoxycholic	3α,12α	DC-	DCA
Chenodeoxycholic	3α,7α	CDC-	CDCA
Ursodeoxycholic	3α,7β	UDC-	UDCA
Lithocholic	3α	LC-	LCA
Muricholic acids (two epimers)			
α-Muricholic	3α,6β,7α	αMC-	αMCA
β-Muricholic	3α,6β,7β	βMC-	βMCA
Murideoxycholic[a]	3α,6β	MDC-	MDCA
Hyocholic acids (two epimers)			
α-Hyocholic	3α,6α,7α	αHC-	αHCA
β-Hyocholic[b]	3α,6α,7β	βHC-	βHCA
Hyodeoxycholic	3α,6α	HDC-	HDCA

[a]The term "murocholic" has also been used in the French literature for this bile acid (3).

[b]This bile acid has generally been referred to as ω-muricholic. This document is the first time that the new name, β-hyocholic acid, is proposed. In this new proposal, for both hyocholic and muricholic epimers, the prefix α or β denotes the orientation of the 7-hydroxy group. One of the authors (KDRS) objects to the name, believing we should continue to use ω-muricholic acid.

TABLE 2. Recommended semi-systematic nomenclature for some uncommon bile acids

No.	Substituents	Recommended Name	Alternative Acceptable Name	Name Proposed in Literature but No Longer Acceptable	Reference
1	3α,7β,12α	7-epicholic acid	7β-hydroxydeoxycholic acid	ursocholic acid	4,5
2	3α,7α,12β	12-epicholic acid	12β-hydroxychenodeoxycholic acid	lagocholic acid	6
3	3α,12β	12-epideoxycholic acid	12β-hydroxylithocholic acid	lagodeoxycholic acid	6
4	3α,5β,7α		5β-hydroxychenodeoxycholic acid	cricetocholic acid	7
5	1α,3α,7α		1α-hydroxychenodeoxycholic acid	vulpecholic acid	8

here is the same as is proposed for hydroxy-oxo-bile acids; see below.)

"Iso" or 3β-hydroxy bile acids. For 3β-hydroxy bile acids, the prefix "iso" is usually used, for example, isolithocholic acid. A hyphen should not be used.

Natural bile acids with epimeric hydroxyl groups. For bile acids with epimeric hydroxyl groups (other than 3β hydroxy epimers) for which there is no accepted trivial name, the prefix "epi" will be used preceded by a number (and a hyphen), indicating the position at which the epimeric hydroxyl group is present; a hyphen should not be used to separate "epi" from the root. In general, it is expected that such "epi" bile acids will be β-hydroxy epimers other than at the C-3 position. The term "epi" will be used as little as possible, and the compound in question always defined by systematic nomenclature. Although the prefix "epi" should be used as little as possible, its use can be justified if it greatly shortens the trivial name of a bile acid. That is why 12-epicholic is preferable to 12β-hydroxychenodeoxycholic acid. Use of the prefix "epi" is discussed in the IUPAC recommendations (1). When it is necessary to use both "epi" and "iso" in the same name, epi should precede iso; and both should precede allo.

Unsaturated bile acids. For unsaturation, the location of the double bond will be indicated, only if it is not one more carbon atom than the first, e.g., 5-cholenoic and 5,8-choladienoic [or 5,8(14)-choladienoic acid] and 22-cholenoic acid. Thus, when only one number is given, the double bond is between the indicated carbon atom and the carbon atom having the next higher number. When the stereochemistry at C-5 must be indicated, this is done at the beginning of the name; and the position of unsaturation is given after the stem, e.g., 5β-chol-22-enoic acid. (The widely used name 3β-hydroxy-Δ^5-cholenic acid will now become 3β-hydroxy-5-cholenoic acid.) (For conversational purposes only, the number of the double bond may be preceded by the word "delta" since this alerts the listener that a double bond is present in the molecule.)

Oxo and hydroxy-oxo bile acids

Oxo bile acids. For oxo bile acids, the term "oxo" will be used, giving the location and number of the oxo substituents, followed by cholanoic acid. [For the reason why oxo should be used instead of keto, see the IUPAC recommendations (1).] For example, 3,7,12-trioxocholanoic acid should be used instead of dehydrocholic acid.

Hydroxy-oxo bile acids (oxo derivatives of natural bile acids). For oxo derivatives of the natural bile acids, the compound will be considered to be derived from the parent compound by addition of the oxo group. Thus, the term oxo will be used without hyphenation linked to the natural bile acid that would result from removal of the oxo substituent. Some examples are 12-oxochenodeoxycholic acid and 12-oxoursodeoxycholic acid. Trivial names for 3-oxo bile acids are not recommended, but the term dehydro may be used, as is done for steroid hormones, for example, 3-dehydrocholic acid (7α,12α-dihydroxy-3-oxo-5β-cholan-24-oic acid). Also, 3-oxocholanoic acid (and analogous names) may be used for bile acids possessing only one oxo substituent.

Unnatural bile acids

For unnatural bile acids, that is, bile acids that do not occur in nature, possess only nuclear hydroxyl groups, and are prepared synthetically, e.g., 3β,6β,7β-trihydroxy-5β-cholan-24-oic acid, no trivial names will be proposed. This includes 7α,12α-dihydroxy-5β-cholan-24-oic acid which may be termed 3-deoxycholic acid, as noted above.

Obviously, one exception will be compounds that have pharmaceutical usage, in which case nomenclature will be proposed by regulatory bodies. The cases of chenodiol and ursodiol are examples.

Natural bile acids with hydroxyl and oxo substituents on the side chain (in addition to nuclear hydroxyl groups)

Trivial bile acid names are recommended when simple modification of the accepted trivial names appears convenient. For example, side chain substituents such as hydroxy or oxo can be denoted by the carbon number of the substituent and by its configuration, *R* or *S*. As an example, today phocaecholic acid (3α,7α, 23*(R)* hydroxy) should be termed "23*(R)*-hydroxy-

chenodeoxycholic acid." Also, haemulcholic acid should be termed 22(*R*)-hydroxychenodeoxycholic acid.

Conjugated bile acids

Initial considerations. The desideratum is convenient trivial nomenclature as well as convenient abbreviations.

Functional groups on naturally occurring bile acids and bile alcohols are normally limited to hydroxy groups on the steroid nucleus and side chain; bile acids have hydroxy groups on the nucleus, may or may not have hydroxy groups on the side chain, but also have a carboxy group on the side chain. The term "conjugated bile acid" means a bile acid conjugated to a group that gives additional hydrophilicity or charge to the molecule. Thus, a bile acid acetate is not a conjugated bile acid. When the term conjugated bile acid is used, the nature of the conjugating moiety must be stated. In this context, taurine may be termed an amino acid.

Molecules used for conjugation are: glycine, taurine (and other amino acids); sulfuric acid (for which the term "sulfate" may be used); glucuronic acid (for which the term "glucuronate" may be used); glucose and other uncharged sugars; coenzyme A. Other conjugating molecules are known and new ones will be discovered.

The classes of bile acids will be named as follows: Sulfates, Glucuronides, Glucosides, *N*-acetylglucosaminides, xylosides, etc., and Aminoacyl amidates (replaces amidates).

A bile acid conjugated only with sulfate (or glucuronate) may be classified as a "non-amidated" bile acid conjugate.

Recommendations. Nomenclature for conjugators. For trivial names, the following combining forms will be used:

Molecule	Trivial combining form
taurine	taurine
glycine	glycine
sulfuric acid (sulfate)	sulfo-, sulfate
Coenzyme A	CoA
glucuronic acid (glucuronate)	glucuronyl,[2] glucuronide
glucose	glucosyl, glucoside
N-acetylglucosamine	*N*-acetylglucosaminyl-, *N*-acetylglucosaminide

Note that the trivial names cholyltaurine and chenodeoxycholyltaurine for bile acid aminoacyl amidates are preferred to taurocholate or taurochenodeoxycholate. The reasons for this recommendation have been discussed elsewhere (9).

When the conjugator is linked to a hydroxy group on the steroid moiety or side chain, it will precede the name of the bile acid, and the number of the carbon atom where it is located will be given, for example, 3-sulfolithocholic acid.

When the conjugator is linked to the carboxyl group on the side chain, it will follow the name of the bile acid. If there is more than one carboxyl group on the side chain, the number of the carbon atom will be noted. The distinction between 3-ethereal and 24-ester glucuronides should be implicit in the fundamental considerations of the molecule; however, they can be stated in the text if necessary. Some examples of the conjugated bile acids: cholylglycine, 3-(β-D-glucuronyl)-7-sulfocholyltaurine or 3-(β-D-glucuronido)-7-sulfocholyltaurine, 3-(β-D-glucosyl)-chenodeoxycholylglycine, deoxycholyl-CoA, and 1-sulfo-1α-hydroxychenodeoxycholylglycine.

Abbreviations. Lower case abbreviations will be used for conjugators (with the exception of CoA). For amino acids, the abbreviations approved by IUPAC will be used: taurine, Tau; glycine, Gly; glucuronic acid (glucuronide), GlcA; glucose, Glc; N-acetylglucosamine, GlcNAc; xylose, Xyl; and sulfuric acid (sulfate), Sul.

For the bile acids, one-, two-, or three-letter abbreviations in upper case letters will be used, as specified earlier in this document and following the recommendations of the previous meeting on bile acid nomenclature (2).

Abbreviations: 3-GlcA-CDC-GlcA; 3-Sul-C-Gly. For unconjugated bile acids, the capital letter A may be added to the letter abbreviation of the bile acid to indicate that the carboxyl group is underivatized. Example: 3-Sul-CA (see Table 1). (Hyphens are not to be used for simple conjugated bile acids, e.g., cholylglycine; however, they are to be used in the three-letter abbreviations.)

Final comment

These proposals are made not only for the purpose of initiating dialogue but also for the purpose of promoting consistency in the published literature. We may hope to be as fortunate as Berzelius, who proposed the one- and two-letter abbreviations that are used today for the elements (as a replacement for alchemical symbols) (*Journal de Physique.* **73:** 253–286, 1811). The Royal Society for England appointed a committee which met for 5 years but could not come up with a better system!

This document was drafted in 1990 by Alan F. Hofmann and Jan Sjövall and was revised at a meeting of the above group

[2]Some committee members prefer glucuronosyl- or glucuronido- as the prefix and glucuronate as the suffix.

on October 9, 1990, in Freiburg, Germany, supported by the Falk Foundation, e.V., Freiburg, Germany. This document was also reviewed by the following individuals: G.A.D. Haslewood (Shoreham-by-Sea), F.C. Chang (Claremont), T. Iida (Koriyama), P.T. Clayton (London), H. Takikawa (Tokyo), S. Barnes (Birmingham), M. Parquet, M. Riottot, and C. Lutton (Orsay), T. Hoshita (Hiroshima), K. Uchida (Osaka), T. Nambara (Sendai), K. Wikvall (Uppsala), and E.H. Mosbach (New York). It received additional minor modifications by Alan F. Hofmann and Jan Sjövall based on the suggestions of anonymous reviewers and Claudio D. Schteingart in late 1991. This document may be considered to supplement those parts of the 1989 recommendations of the IUPAC-IUB Joint Commission on Biochemical Nomenclature that pertain to bile acids (1), and it is hoped that there are no conflicts with those recommendations. However, these proposals have not been approved by that body, although they have been reviewed by G.P. Moss, London, UK, who is a member of the IUPAC-IUB Joint Commission on Biochemical Nomenclature, and who informed the Commission of its publication. It will be cited in future publications of the Commission. Previous brief recommendations on bile acid nomenclature were made in 1975 (2), and the present document should supersede the recommendations made therein. The IUPAC 1989 recommendation (1) contains a bibliography of previous recommendations for steroid nomenclature. We acknowledge the editorial assistance of Vicky Huebner and Agneta Sjövall.

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