Chapter 1
The Domain of Bacteria and Their Volatile Metabolic Potential

Marie-Chantal Lemfack, Hubert Bahl, Birgit Piechulla, and Nancy Magnus

Abstract The ability to produce volatile compounds is widely distributed among bacteria. A comprehensive summary of volatiles reported to be emitted by different fungal and bacterial species can be found in the *mVOC database* (http://bioinformatics.charite.de/mvoc). This chapter aims to summarize different features of bacterial phyla, classes, families, and genera present in the *mVOC database* and review the different habitats where volatile producers have been isolated from. As a result, bacteria belonging to the phylum of Proteobacteria were the most studied mVOC producers. Moreover, soil, marine environments, and the human body turned out to be the main isolation sources of the microbes compiled in the *mVOC database*. Additionally, general biosynthetic routes from the primary as well as secondary metabolism are presented which ultimately can result in the production of microbial volatile metabolites.

Keywords *mVOC database* · Phylogeny · Habitat · Volatile biosynthetic routes · Primary metabolism · Secondary metabolism

1.1 Phylogeny and Diversity of Bacteria Comprised in the *mVOC Database*

Life on Earth can be categorized into three different domains: (1) Archaea, (2) Bacteria, and (3) Eukarya. In 1990, Woese et al. were the first to introduce this new taxonomic rank which was found to be superior to the rank of kingdom. According to this model, all life derived from the *last universal common ancestor* (LUCA) which therefore represents the origin of life. Whereas bacteria and Archaea are closer related to LUCA, Eukarya are thought to have evolved later in the history of the earth (Fig. 1.1).

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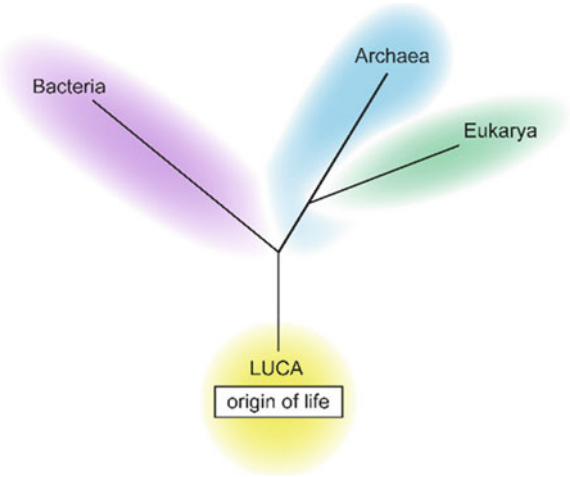

Fig. 1.1 The three domains of life. *LUCA* **l**ast **u**niversal **c**ommon **a**ncestor. Modified after Madigan et al. (2019)

Table 1.1 List of known bacterial phyla according to Parte (2018)

Phylum	Phylum
Acidobacteria	Elusimicrobia
Actinobacteria	Fibrobacteres
Aquificae	**Firmicutes**
Armatimonadetes	**Fusobacteria**
Bacteroidetes	Gemmatimonadetes
Balneolaeota	Kiritimatiellaeota
Caldiserica	Lentisphaerae
Calditrichaeota	Nitrospirae
Chlamydiae	Planktomycetes
Chlorobi	**Proteobacteria**
Chloroflexi	Rhodothermaeota
Chrysiogenetes	Spirochaetes
Coprothermobacterota	Synergistetes
Cyanobacteria	Tenericutes
Deferribacteres	Thermodesulfobacteria
Deinococcus–Thermus	Thermotogae
Dictyoglomi	Verrucomicrobia

Phyla found in *mVOC database* are indicated in bold

This chapter will only focus on the domain of bacteria. More specifically, main emphasis will be laid on phyla and genera present in the *mVOC database* (Lemfack et al. 2018). This database represents the first collection of all microbial volatile organic compounds investigated so far and comprises ca. 2000 compounds produced by roughly 1000 different microorganisms consisting of 600 bacterial and 400 fungal species (Lemfack et al. 2018). Bacterial VOC producers analyzed so far are distributed in 6 phyla (Table 1.1), 15 classes, 34 orders, 74 families, and 125 genera (Fig. 1.2). Since 10^{12} microbial species are expected to exist on Earth (Larsen et al.

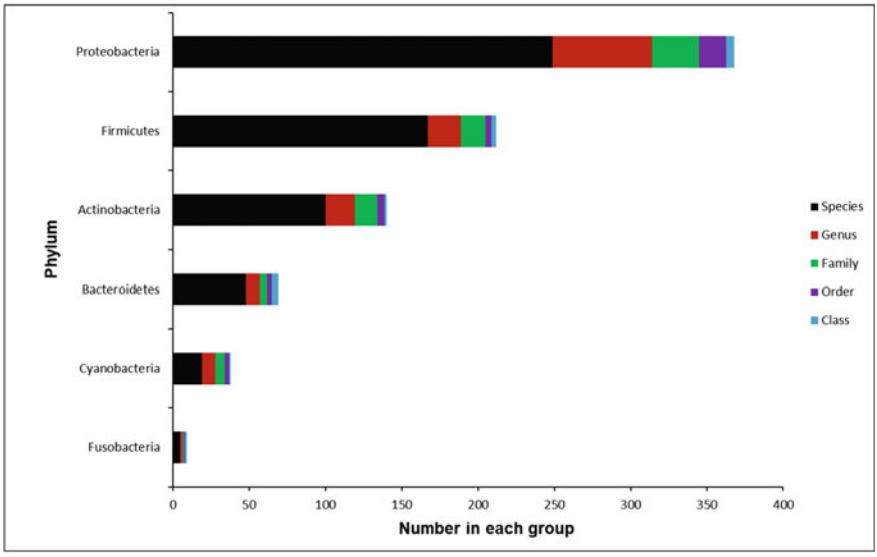

Fig. 1.2 Abundance of bacteria in *mVOC database*. The data represent the number of bacterial species, genera, families, orders, classes, and phyla compiled in *mVOC database* so far

2017; Pedrós-Alió and Manrubia 2016), the wealth of mVOCs still to be explored becomes obvious.

We will first summarize the main characteristics of bacterial phyla, classes, and genera present in the *mVOC database*, describe their distribution in nature and, furthermore, give a brief overview about the bacterial metabolism focusing on volatile end products.

The research field of bacterial phylogeny undergoes constant reconstructions which is why numbers mentioned in this chapter have to be treated with caution. According to the *List of prokaryotic names with standing in nomenclature* (LPSN, Parte 2018), the kingdom of bacteria currently comprises 34 different phyla which are listed in Table 1.1.

1.1.1 Proteobacteria

The Proteobacteria represent the largest and phenotypically most diverse division among prokaryotes (Gupta 2000). To date, more than 40 % of all validly published prokaryotic genera belong to this phylum (Kersters et al. 2006). They comprise the majority of Gram-negative bacteria and formerly have been referred to as "purple bacteria and relatives" although only a small fraction possesses purple coloration. This is why the phylum was renamed after the Greek god *Proteus* who could take on different shapes which reflects the diversity inside this phylum (Murray et al. 1990;

Stackebrandt et al. 1988). They consist of more than 200 different genera subdivided into eight classes based on 16S and 23S rRNA sequences: (1) Alphaproteobacteria, (2) Betaproteobacteria, (3) Gammaproteobacteria, (4) Deltaproteobacteria, (5) Epsilonproteobacteria, (6) Acidithiobacillia, (7) Hydrogenophilalia, and (8) Oligoflexia (Boden et al. 2017; Garrity et al. 2005; Nakai et al. 2014; Williams and Kelly 2013). Nevertheless, this classification does not reflect specific morphological or physiological traits that members of the same class have in common (Rizzatti et al. 2017). In contrast, Proteobacteria are very diverse concerning their appearance. They can form rods or cocci and curved, spiral, ring-shaped but also filamentous and sheathed cells. Most of them are motile and possess polar or peritrichous flagella. A special exception is found in the myxobacteria (Deltaproteobacteria) which possess a gliding motility (Kersters et al. 2006). The proteobacterial energy metabolism is also highly diverse including phototrophic genera (e.g., *Chromatium, Rhodospirillum*) as well as chemoorganotrophs (e.g., *Escherichia coli*) and chemolithotrophs (e.g., *Nitrobacter*) (Kersters et al. 2006).

Proteobacteria can be found ubiquitously in nature and are of high biological relevance since they include a vast number of human, animal, and plant pathogens (e.g., *Neisseria, Pseudomonas, Shigella*, *Salmonella, Yersinia, Escherichia, Helicobacter* spp.) (Bergey and Holt 2000; Collier et al. 1998; Dworkin et al. 2006; de Vos et al. 2009). Moreover, they represent one of the most abundant phyla in the gut microbiota (Rizzatti et al. 2017). Their cells mostly appear as free-living organisms with some exceptions. The most famous example is the genus *Rhizobium* which lives in symbiosis with leguminous plants. This Alphaproteobacterium is capable to reduce atmospheric nitrogen to ammonia which the host plants can readily assimilate. In turn, the plant provides the bacteria with photosynthetic products as a nutrient source. But Proteobacteria also appear as intracellular endosymbionts of protozoa and invertebrates (e.g., mussels, insects, and nematodes) (Kersters et al. 2006). Furthermore, it is anticipated that the origin of mitochondria can be traced back to the Alphaproteobacteria (Kersters et al. 2006).

When analyzing Proteobacteria present in *mVOC database* in detail, it appears that ca. 250 bacterial strains are described as VOC producers and are distributed in all five classes (Fig. 1.2). They are largely dominated by Gammaproteobacteria (150 strains) compared to Beta-(49), Alpha-(29), Delta-(29), and Epsilonproteobacteria (5) (Fig. 1.3a), while there are no data for Acidithiobacillia, Hydrogenophilalia, and Oligoflexia. Nevertheless, these last classes are composed of only few bacterial genera with validly published names. The most investigated genus concerning its VOC emission is *Pseudomonas,* accounting for one-third of all Gammaproteobacteria listed in the *mVOC database* (Fig. 1.3d) which is not surprising due to its high clinical relevance (summarized in Lyczak et al. 2000) raising the need for new, minimally invasive diagnostic tools. Other representatives of the Gammaproteobacteria which have been studied regarding their volatile emission are the genera *Serratia* and *Escherichia*, belonging to the family of *Enterobacteriaceae*. Both genera have been described to be good VOC producers (Bunge et al. 2008; Kai et al. 2010; Kai and Piechulla 2010; Umber et al. 2013; Weise et al. 2014; Yu et al. 2000; Zhu and Hill 2013) and important plant growth

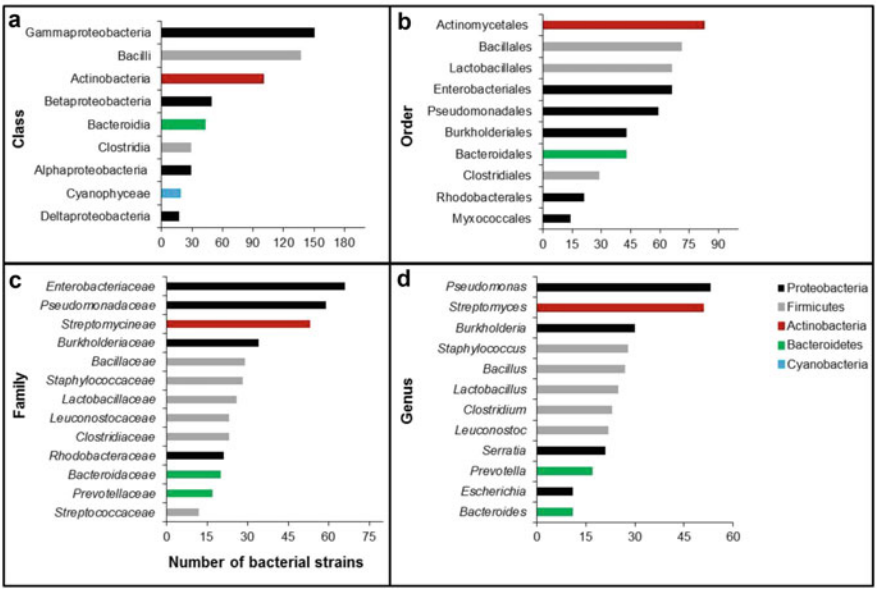

Fig. 1.3 Distribution of bacterial strains present in *mVOC database*. The data represent the number of bacterial strains (at least 10) present in each class (**a**), order (**b**), family (**c**), and genus (**d**) compiled in *mVOC database* so far. All classes, orders, families, and genera with less than 10 bacterial strains are not shown

promoting microorganisms (Devi et al. 2016; Nautiyal et al. 2010; Zaheer et al. 2016) which is why it is even more surprising to see that they are considerably less represented in the *mVOC database*. This also applies to the important plant symbiont *Rhizobium* having only one entry in the database.

1.1.2 Firmicutes

The Firmicutes represent the second largest phylum in the *mVOC database*. Ca. 170 bacterial strains have been investigated concerning their volatile emission, so far.

Firmicutes mostly consist of low G/C-containing (<50 %), Gram-positive bacteria with rigid or semi-rigid cell walls containing peptidoglycan (Gibbons and Murray 1978). Nevertheless, this phylum also contains single Gram-negative members, e.g., *Veillonellaceae* and *Syntrophomonadaceae*. But just like the Proteobacteria, Firmicutes are phenotypically very diverse reflected by high fluctuations in the composition of this phylum (Seong et al. 2018). Diversity is displayed in terms of (1) cell appearance (spherical, straight, curved, helical rods or filaments, flagellated or not, spore-forming as well as non-sporulating forms), (2) metabolism (chemoorganotrophic or anoxygenic photoheterotrophs), and (3) way of life

(aerobic, facultative or strict anaerobes, meso-, thermo- and halophiles, growth at neutral pH but also some alkali- and acidophiles) (de Vos et al. 2009). Bacteria belonging to the Firmicutes mainly divide by binary fission and are highly abundant in soil and aquatic environments (Baik et al. 2008; Schleifer 2009). They play a central role in the decomposition of organic matter which is why they are also often part of the normal intestinal flora of mammals (Lee et al. 2009). Nevertheless, they can also lead to the development of severe diseases in humans and animals as well as in plants (Nguyen and Götz 2016).

This large phylum is separated into three different classes: (1) "Bacilli," (2) "Clostridia," and (3) Erysipelotrichia (de Vos et al. 2009). Originally, the class of Mollicutes was also included, but due to low support using alternative markers and unique phenotypic properties, it was removed from the Firmicutes later on to form a phylum on its own (Ludwig and Schleifer 2005). According to the *mVOC database*, the class of "Bacilli" is the most investigated among Firmicutes (137 bacterial strains). "Bacilli" contain only Gram-positive members and can be divided into two orders, Bacillales and Lactobacillales. The most important genera of the Bacillales are *Staphylococcus* and *Bacillus* which are also the most investigated Firmicutes concerning their VOC emission with 28 and 27 bacterial strains, respectively.

Bacillus spp. are aerobic or facultative anaerobic, motile, endospore-forming bacteria. They can form rod-shaped, straight, or slightly curved cells and are highly heterogenous concerning their physiology, ecology, and genetics (Logan and de Vos 2009; Slepecky and Hemphill 2006). *Bacillus* is a very well investigated organism which has been known to mankind for long time, since its life cycle was first described already in 1872 by Cohn.

According to Lory (2014), the genus *Staphylococcus* currently contains 54 species. *Staphylococcus* spp. are widely distributed and are frequently found in association with human and animal hosts. Their appearance resembles grape-like clusters resulting from perpendicular division planes during cell division of single cocci (Lory 2014). They are facultative anaerobes which prefer to use respiratory pathways for energy generation rather than fermentation (Lory 2014). A prominent representative of the *Staphylococcus* genus is *Staphylococcus aureus* which can cause major infections in humans reaching from abscesses and food poisoning to endocarditis, toxic shock syndrome, and pneumonia (Gordon and Lowy 2008; Kravitz et al. 2005). Especially the methicillin-resistant *S. aureus* (MRSA) poses big challenges to medical research, due to increased fitness of the pathogen, improved evasion mechanisms of the hosts' immune system, and unique toxin production (Gordon and Lowy 2008).

From the order Lactobacillales, 25 *Lactobacillus* and 22 *Leuconostoc* species have been investigated for VOC emission (Fig. 1.3d). Both genera are Gram-positive, catalase negative, belong to the lactic acid bacteria, and thus are chemoorganotrophs (Schleifer and Ludwig 1995). They grow anaerobically but can also thrive well under microaerophilic conditions and prefer slightly acidic growth conditions (pH 5.5–6.5) (Schleifer and Ludwig 1995). Whereas the genus *Lactobacillus* contains at least 13 motile species (Neville et al. 2012; Puertas et al.

2014), *Leuconostocaceae* were characterized as non-motile and are often found in nutrient-rich environments, e.g., green vegetation, roots, and food (Nieminen et al. 2014).

The second major class of Firmicutes found in the *mVOC database* is the "Clostridia." In total, only 29 bacterial strains of this class have been investigated regarding their volatile emission so far. The data further indicate that the *Clostridiaceae* and more specifically the genus *Clostridium* account for 23 of the aforementioned 29 "Clostridia"-entries in *mVOC*. Members of the *Clostridiaceae* contain more than 30 genera that can be found ubiquitously in nature which is not surprising since they can form endospores protecting them from different kinds of stresses. They are Gram-positive, rod-shaped cells that live anaerobically and contain meso-diaminopimelic acid in their peptidoglycan which is used as a diagnostic marker (Stackebrandt 2014).

As already mentioned above, several Firmicutes are known pathogens and it appears in general that only a very low number of pathogenic bacteria were analyzed for mVOC production. Genera like *Streptococcus,* responsible for oral malodor, are almost not represented (Fig. 1.3d).

1.1.3 Actinobacteria

The Actinobacteria are one of the largest taxonomic units among the major lineages in the domain of bacteria composed of Gram-positive bacteria with high G/C content and typical filamentous morphology (Barka et al. 2015; Dhakal et al. 2017; Ludwig et al. 2012a). They contain mostly free-living organisms which can be found in terrestrial as well as in aquatic and marine ecosystems (Macagnan et al. 2006). In soil, *Streptomyces* spp. are predominantly found, whereas *Salinispora* spp. are a prominent example for Actinobacteria living in aquatic environments. Moreover, bacteria of this phylum also live in close symbiosis to plants, like *Frankia* spp., or can also have pathogenic effects on plants as well as animals (e.g., *Corynebacterium*, *Mycobacterium,* and *Nocardia* spp.) (Barka et al. 2015; Macagnan et al. 2006). Actinobacteria, more specifically members of the genus *Bifidobacterium*, also affect us humans, since they are among the first bacteria to colonize our intestinal tract and are believed to exert positive health effects although the molecular mechanisms are still not understood (Cronin et al. 2011; O'Callaghan and van Sinderen 2016). Most Actinobacteria live aerobically under mesophilic conditions (optimal temperature between 25 and 30 °C) at a pH ranging from 6 to 9 with an optimum at neutral pH values (Barka et al. 2015).

Phylogenetically, this phylum is divided into six classes: (1) Actinobacteria, (2) Acidimicrobiia, (3) Coriobacteriia, (4) Nitriliruptoria, (5) Rubrobacteria, and (6) Thermoleophilia. The class of Actinobacteria comprises 16 orders including Actinopolysporales, Actinomycetales, Bifidobacteriales, Catenulisporales, Corynebacteriales, Frankiales, Glycomycetales, Jiangellales, Kineosporiales, Micrococcales, Micromonosporales, Propionibacteriales, Pseudonocardiales,

Streptomycetales, Streptosporangiales, and Incertae sedis (Ludwig et al. 2012b). Due to its large size, it is not surprising that members of this phylum are highly diverse in terms of morphology, physiology, and metabolic capabilities. Concerning morphology, most Actinobacteria form substrate mycelia in liquid and solid cultures which during growth on solid medium can transform into aerial mycelia to produce asexual exospores (Flärdh and Buttner 2009; van Dissel et al. 2014). Nevertheless, cell shapes can range from coccoid (*Micrococcus*), rod-coccoid (*Arthrobacter* spp.), and fragmented (*Nocardia*) to permanent and highly differentiated, branched mycelia (*Streptomyces, Frankia*) (Atlas 1997). Often, Actinobacteria are discriminated according to their mycelium color since most strains are capable to produce melanoid pigments which can improve survival and competitiveness of the producers. Additionally, the appearance and structure of exospores can be used to differentiate actinobacterial species (Barka et al. 2015). The most common soil-dwelling genera found are the saprophytic *Streptomyces*, already accounting for 70%, *Nocardia* and *Micromonospora* (Yokota 1997) which play important roles in the decomposition of organic matter, e.g., cellulose and chitin. As a result, they are crucial for the carbon fluxes in nature (Tarkka and Hampp 2008). Moreover, *Streptomyces* species are used extensively for the discovery of new bioactive secondary metabolites and produce 70–80% of all substances applied in pharmacy or agrochemistry, e.g., antibiotics like actinomycin or streptomycin (Bérdy 2005; Hopwood 2007; Manteca et al. 2008). Secondary metabolite production is most efficient during morphological differentiation of the cells, i.e., during transition from vegetative to aerial growth (Bibb 2005; Granozzi et al. 1990). So far, more than 500 species have been described in the genus *Streptomyces* (Tarkka and Hampp 2008) of which only 51 were also investigated regarding their volatile emission. Summarizing everything, although Actinobacteria are ubiquitous and a rich source of natural products, they are less investigated concerning volatile emission compared to other phyla or classes with *Streptomyces* being the most investigated genus, while other genera like *Corynebacterium* or *Actinomyces* are significantly less represented in the data compiled so far (Figs. 1.2 and 1.3).

1.1.4 Bacteroidetes

The phylum of Bacteroidetes is composed of Gram-negative, rod-shaped, chemoorganotrophic bacteria which form no spores and are mostly non-motile or possess a gliding motility (Hahnke et al. 2016; McBride and Zhu 2013; Paster et al. 1994; Woese 1987). It includes ca. 7000 species (Thomas et al. 2011) which are, according to the Bergey's Manual of Systematic Bacteriology, distributed into four different classes: (1) Bacteroidia, (2) Cytophagia, (3) Flavobacteriia, and (4) Sphingobacteriia (Krieg et al. 2011a). Bacteroidetes are widespread in nature and can be found in soil, decaying plant material, freshwater, marine environments, algae, and dairy products (Bernardet and Nakagawa 2006; Reichenbach 2006). Nevertheless, different classes of Bacteroidetes are also distributed differentially.

Accordingly, strains of the class Cytophagia were found only in marine habitats or soil, whereas Flavobacteriia colonize more diverse ecosystems, like soil, sediment, freshwater, brackish water, or seawater including some pathogenic species for humans, mammals, and fish (Bernardet 2015; Krieg et al. 2011b). Just like the Actinobacteria, environmental Bacteroidetes are thought to play a role in the decomposition of complex organic matter, e.g., of polysaccharides and proteins (Bowman 2006; Church 2008; Fernández-Gómez et al. 2013; Kirchman 2002). Even more importantly, Bacteroidetes are found in the gastrointestinal (GI) tract of animals as well as humans. Here, they can account for up to 50% of the microbial gut flora which makes them the dominating phylum together with the Firmicutes (Eckburg et al. 2005; Ley et al. 2008; Smith et al. 2006; Thomas et al. 2011). Moreover, recent studies indicated that the ratio between Firmicutes and Bacteroidetes in the gut microbiota raised with increasing *body mass index* (BMI) suggesting a role of Bacteroidetes in obesity (Barlow et al. 2015; Koliada et al. 2017; Sweeney and Morton 2013).

In terms of volatile emission, Bacteroidetes are rather unexplored so far. Only 48 entries (<10%) can be found in the *mVOC database* (Fig. 1.2), most of which belong to the class of Bacteroidia (43 bacterial strains) with the main genera being *Bacteroides* (20 strains) and *Prevotella* (17 strains) (Fig. 1.3a, d). Both, *Bacteroides* spp. and *Prevotella* spp. contain solely anaerobic bacteria, in contrast to the other three Bacteroidetes classes which comprise only aerobic or facultative anaerobic species. Species of the genus *Bacteroides* are generally considered as friendly commensals, although the term mutualism is much more fitting since both partners are benefitting from each other (Bäckhed et al. 2005). Moreover, this genus alone accounts for ca. 25% of the total human gut microbiota (Wexler 2007). *Bacteroides* spp. become a part of the human microbiome already very early in life and can be passed from mother to child during vaginal birth making a crucial role for the human body apparent (Reid 2004). Specifically, it has been shown that *Bacteroides* spp. produce volatile fatty acids which can be reabsorbed from the host through the large intestine and, in turn, be used as an energy source (Hooper et al. 2002). Nevertheless, when *Bacteroides* escape their native niche, for example, through rupture of the GI tract or surgical interventions, they can cause severe pathologies outside the gut, like formation of abscesses or bacteremia (summarized in Wexler 2007). The genus *Prevotella* basically fulfils equal functions in the human host. The only difference is that *Prevotella* spp. are associated with a plant-rich diet as well as with chronic inflammatory conditions which is why gut microbial communities contain either *Bacteroides* or *Prevotella*, but not both at the same time (Brook 1998, 2004; Ley 2016; Nagy 2010).

1.1.5 Cyanobacteria

Cyanobacteria are thought to have emerged ca. 3 Ga which was when the transition to oxygenic conditions through the evolution of photosynthesis took place

(Schirrmeister et al. 2011). They belong to the most diverse and widely distributed Prokaryotes and can be found in freshwater, marine, terrestrial, planktonic, and benthic habitats as well as in extreme environments, i.e., frozen lakes, hot springs, or salt works (Walter et al. 2017; Whitton 1992). Cyanobacteria are usually Gram-negative but appear much larger than most bacteria ranging from 1 μm for unicellular forms to more than 30 μm for filamentous forms (Singh and Montgomery 2011). In general, species of this phylum are oxygenic phototrophs which makes them independent from specific carbon sources like other bacteria. Nevertheless, also species growing heterotrophically on organic compounds have been reported (Halm et al. 2012; Walter et al. 2017). Furthermore, some secondary metabolites produced by cyanobacteria are potentially toxic and can lead to harmful effects on health during algal blooms (Percival and Williams 2014). Morphologically Cyanobacteria are very diverse. They exist either as unicellular or filamentous forms whereby also the unicells can be bound together by mucilaginous secretions resulting in complex formations (Broady and Merican 2012; Singh and Montgomery 2011). These complexes can also become very large which form mats, crusts, or gelatinous masses on rocks, sediments, soil, and vegetation getting visible with the naked eye (Broady and Merican 2012). Moreover, single cells can differentiate into specialized compartments like heterocysts or akinetes. Heterocysts are rounder, thick-walled cells that are capable to fix atmospheric nitrogen and produce ammonia which can further be used for amino acid biosynthesis making it an available N-source for the surrounding vegetative cells and thus promote growth during nitrogen starvation (Kumar et al. 2010; Meeks and Elhai 2002). Akinetes represent thick-walled resting spores which secure survival of the population under worst conditions (Walter et al. 2017). Moreover, some cyanobacterial species can produce gas vacuoles which allow them to float in aquatic environments or exhibit a gliding motility (Hoiczyk 2000; Lyra et al. 2005; Percival and Williams 2014).

In total, the phylum Cyanobacteria includes ca. 150 genera containing about 2000 species (Percival and Williams 2014). They can be divided into five different orders: (1) Chroococcales, (2) Pleurocapsales, (3) Oscillatoriales, (4) Nostocales, and (5) Stigonematales (Waterbury 2006). In *mVOC* only a total of 17 validated cyanobacterial strains have been investigated for their volatile emission profiles. Most of them belong to the orders Nostocales (8 strains) and Oscillatoriales (8 strains) and one representative of the Chroococcales. Nostocales include filamentous cyanobacteria that are capable to differentiate into the aforementioned heterocysts and akinetes which makes them truly multicellular organisms since differentiation is irreversible and functional specialization takes place (Komárek and Johansen 2015; Waterbury 2006). They divide by binary fission in one plane at right angles to the long axis of the trichomes (Waterbury 2006). Species belonging to the order of Nostocales listed in *mVOC* are of the genera *Anabaena* (1), *Calothrix* (3), *Rivularia* (2), and *Tolypothrix* (2). Oscillatoriales also contain filamentous cyanobacteria which are, in contrast to Nostocales, not differentiated and divide by binary fission in a single plane. Genera found in *mVOC* are *Lyngbya* (1), *Phormidium* (1), *Plectonema* (3), and *Oscillatoria* (3). As already mentioned, there is only one representative of the order Chroococcales to be found in *mVOC*

database, *Spirulina platensis*. Generally, Chroococcales entail only unicellular cyanobacteria that reproduce by binary fission or budding occurring in one to three planes at right angles to one another or in irregular planes. Cell shapes range from single cocci and rods to cell aggregates held together by sheath material, amorphous slime, or capsular material (Waterbury 2006).

1.1.6 Fusobacteria

The Fusobacteria are a rather unexplored bacterial phylum. They consist of Gram-negative, anaerobic, non-sporulating, non-motile bacilli with tapered rod-shaped cells (Brennan and Garrett 2019). Naturally, Fusobacteria species can be found as free-living organisms in marine environments (*Ilyobacter* spp.) but also in the human oral cavity (*Fusobacterium* spp.), intestinal and urogenital tracts (*Leptotrichia* and *Sneathia* spp.) and in the intestines of fishes and whales (*Cetobacterium* spp.) (Brennan and Garrett 2019). Interestingly, single Fusobacteria can harbor unique metabolic capabilities, e.g., *Psychrilyobacter atlanticus* which was shown to break down nitramine explosives (Zhao et al. 2009). Members of this phylum are differentiated in two families: (1) *Leptotrichiaceae* and (2) *Fusobacteriaceae*. In *mVOC* only five representatives of the latter are found including three strains of the species *Fusobacterium nucleatum* besides one *F. necrophorum* and *F. simiae* species each.

Fusobacterium spp. are generally found in the mouth and other mucosal sites inside humans or animals. Their presence in healthy tissues suggest that they are natural constituents of the microbiota (Brennan and Garrett 2019). Especially the genus *F. nucleatum* caught scientific interest. It is most abundant in the oral cavity and was shown to play a central role in biofilms that contribute to periodontal health and disease. It mediates biofilm formation by serving as a bridge organism between primary (e.g., *Streptococcus* spp.) and secondary colonizers (e.g., *Porphyromonas gingivalis*) (Brennan and Garrett 2019; Kolenbrander et al. 2010). Nevertheless, *F. nucleatum* is also considered as an opportunistic pathogen since it was found to play a role during periodontitis by shaping host responses and increasing its infectivity by other pathogens (Binder Gallimidi et al. 2015). Furthermore, this species was also implicated to be involved in other diseases such as appendicitis (Swidsinski et al. 2011), brain abscesses (Han et al. 2003), osteomyelitis (Gregory et al. 2015), pericarditis (Truant et al. 1983), and chorioamnionitis (Altshuler and Hyde 1988) although the definite role of *F. nucleatum* in these cases remains unclear. Still, this species is known to promote inflammatory responses by binding/invading diverse cell types in the human body strengthening the notion of *F. nucleatum* as an opportunistic pathogen (Han et al. 2000; Ikegami et al. 2009; Strauss et al. 2011).

1.2 Natural Habitat of Bacteria in *mVOC Database*

Among the 600 bacterial strains registered in *mVOC database* so far, the isolation sites of ca. 500 of them were compiled, while there were no data existing in the literature for the 100 other strains. It turned out that most of the bacteria present in the database were isolated from the rhizosphere (17%), soil (15%), aquatic environment (15%), clinical samples (15%), humans (13.5%), food products (10%), animals (5%), plants (5%), plant waste (3%), and fungi (1.5%) (Fig. 1.4). Although the volatile profiles of microbes are independent of their isolation site, the number of bacteria isolated from animals and investigated for VOC emission remains very low. Likewise, only the volatile profiles of plant-associated bacteria like *Pseudomonas*, *Bacillus,* and *Burkholderia* are commonly studied (Piechulla et al. 2017). Most of these microorganisms are isolated from the rhizosphere/soil, while the upper parts of the plants as well as animal-associated bacteria (e.g., insects) still represent an important unexplored potential.

Altogether, these analyses of the *mVOC database* reveal that among the huge number of bacterial species existing on Earth (10^{12}; Larsen et al. 2017; Pedrós-Alió and Manrubia 2016) only a very small proportion, i.e., 0.00000006%, can presently be found in the database. Furthermore, it became obvious that from 26 known bacterial phyla (most of them listed in Fig. 1.1) only six have been investigated concerning their volatile emission, so far. Therefore, the plethora of bacteria which remain to be investigated represents a huge potential in the discovery of further information regarding their ecological role(s).

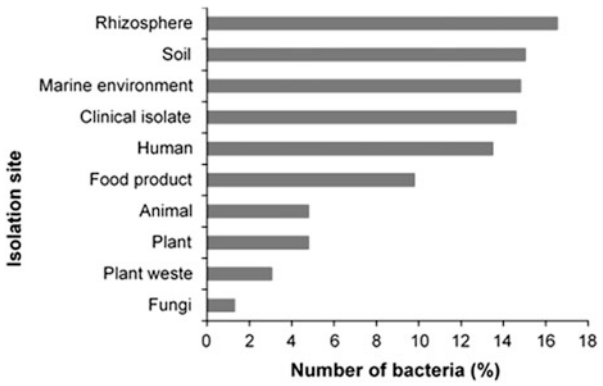

Fig. 1.4 Isolation site of bacteria described in *mVOC database*. All isolation sites with less than 1% of bacteria are not represented

1.3 Bacterial Volatiles Derived from the Primary Metabolism

The emission of volatiles by bacteria is known for decades. These volatiles are mainly generated during the catabolic activity of these microorganisms. In general, these substances are considered either as primary or as secondary metabolites, depending on whether they are produced during the exponential growth phase or during the transition to or in the stationary growth phase, respectively. The vast majority of volatiles is certainly formed during secondary metabolism. Despite their limited number, also primary metabolism volatiles such as CO_2 should not be neglected, e.g., when the interaction between organisms is determined (Piechulla 2017). In the following section, the formation of volatiles by bacteria during primary metabolism is described.

The diversity of bacteria is primarily not marked by a large variability in morphology but by a vast number of different metabolic, especially catabolic, pathways. Bacteria can make a living by generation of energy (ATP) for biosynthetic activity using either light (phototrophy) or the oxidation of chemical compounds (chemotrophy) as energy source. Besides organic material (chemoorganotrophy), a number of inorganic molecules can serve as electron donors for energy generation (chemolithotrophy). The carbon source of bacteria is either organic material or CO_2. In Table 1.2, the different types of chemotrophic metabolism and the main volatile products are depicted.

In general, during primary metabolism the ultimate ambition of the bacteria is to generate as much energy (ATP) for growth as possible. In addition, the amount of energy gained during chemotrophic metabolism (oxidation of the substrate) depends on the electron acceptor available or utilizable by a specific bacterium. Some bacteria are very flexible with this respect. Enteric bacteria such as *E. coli* are a good example for this. They can oxidize glucose, e.g., completely to the inorganic volatile CO_2 in the presence of oxygen. If no oxygen but nitrate is on hand, it carries out anaerobic respiration and reduces nitrate to NH_3, which also is released into the atmosphere. If no external electron acceptor is present, *E. coli* switches to fermentation and transfers the electrons to internal acceptors, which finally leads to the excretion of acetate, ethanol, and formate which are altogether organic volatiles (Fig. 1.5). Thus, with respect to the production of volatiles by bacteria the incomplete oxidation of an organic substrate is of special interest, since a greater variety of volatiles might be generated compared to the main volatile CO_2 as end product of complete oxidation. In addition to the main alternative electron acceptors nitrate and sulfate listed in Table 1.2, several other compounds can serve as electron sink during growth of certain bacteria, e.g., dimethyl sulfoxide (DMSO) is reduced to dimethyl sulfide and trimethyl amine-*N*-oxide (TMAO) to trimethyl amine (Fuchs et al. 2007; Madigan et al. 2017). A special metabolic type is the incomplete oxidation of the substrate despite the fact that oxygen is present. Here, a complete oxidation is not possible, since either, an enzyme of the tricarboxylic acid cycle is missing (acidic acid bacteria) or is repressed (bacilli) (Gottschalk 1986). Examples of an incomplete

Table 1.2 Major volatiles produced by bacteria during primary metabolism

Metabolic type	Electron donor	Electron acceptor	Inorganic volatiles	Organic volatiles	Example
Chemoorganotrophy					
Aerobic respiration	Carbohydrate	O_2	CO_2	–	*Pseudomonas aeruginosa*
	Protein, amino acids[a]	O_2	CO_2, NH_3, H_2S	Methanethiol dimethyl disulfide	*Micrococcus luteus*
Incomplete oxidation	Carbohydrate	O_2	CO_2	Acetoin, 2,3-butandiol, acetic acid, pyruvate	*Bacillus subtilis*
Anaerobic respiration[b]					
Nitrate respiration	Carbohydrate	NO_3^-	CO_2, NO, N_2O, N_2, NH_3		*Pseudomonas stutzeri*
Sulfate respiration	Lactic acid	SO_4^{2-}	H_2S	Acetic acid	*Desulfovibrio vulgaris*
Sulfur respiration	Acetic acid	S^0	CO_2, H_2S		*Desulfobacter curvatus*
Fermentation	Carbohydrate	Internal metabolite	H_2, CO_2	Alcohols, ketones, fatty acids[c]	*Clostridium acetobutylicum*
Chemolithotrophy					
Anaerobic respiration[b] nitrate respiration	H_2S	NO_3^-	NO, N_2O, N_2, NH		*Thiobacillus denitrificans*
Sulfate/sulfur respiration	H_2	SO_4^{2-}, S^0	H_2S		*Desulfobacterium autotrophicum*
Carbonate respiration	H_2, CO	CO_2		Acetic acid, ethanol CH_4[d]	*Clostridium aceticum*

[a]The volatiles listed here are likely be produced also in other metabolic types as long as proteins or amino acids are present in the medium as carbon or nitrogen source
[b]The list of electron acceptors for anaerobic respiration shown in this table is not complete, see text
[c]For an overview on bacterial fermentation products see Fig. 1.5
[d]CH_4 is not produced by bacteria but by methanogenic archaea

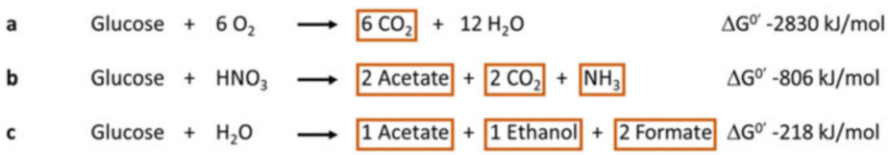

Fig. 1.5 Volatile production of facultative aerobic bacteria according to the electron acceptor used. (**a**) aerobic respiration (O_2 as electron acceptor); (**b**) anaerobic respiration (nitrate as electron acceptor); (**c**) fermentation (internal electron acceptor). Volatiles are highlighted by a red box

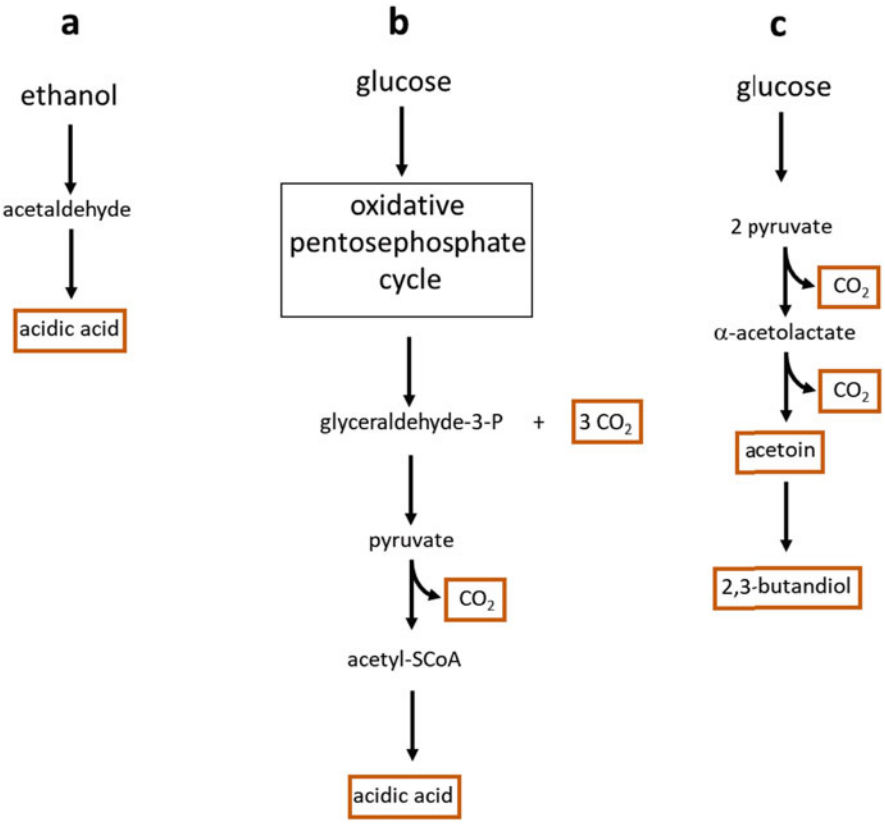

Fig. 1.6 Volatile production caused by incomplete oxidation of the substrate in the presence of oxygen. (**a**) incomplete oxidation of ethanol by acidic acid bacteria; (**b**) incomplete oxidation of glucose by acidic acid bacteria; (**c**) incomplete oxidation of glucose by *Bacillus subtilis*. Volatiles are highlighted by a red box

oxidation of glucose and ethanol and the formation of corresponding volatiles are shown in Fig. 1.6. Bacterial fermentation processes lead to the emission of a number of organic volatiles (alcohols, fatty acids, ketones) in addition to the gases CO_2 and H_2. Figure 1.7 demonstrates in more detail the diversity of volatiles produced from glucose by different fermentative bacteria. Especially clostridia carrying out butyric acid or an acetone–butanol fermentation can emit a rich bouquet of volatiles.

In summary, which volatiles (and other products) bacteria produce as primary metabolites depends on the substrate they grow on and on the growth conditions.

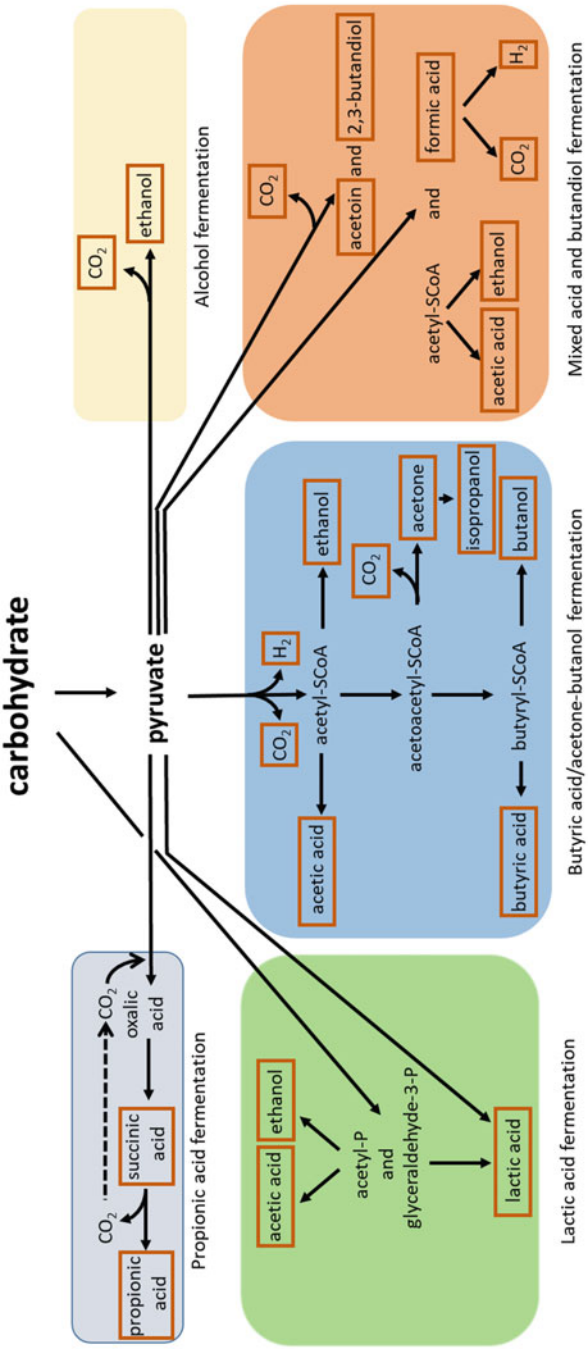

Fig. 1.7 Volatile production during fermentation. Volatiles are highlighted by a red box

1.4 Bacterial Volatiles Derived from the Secondary Metabolism

Many organisms produce metabolites which are not essential for the central processes of growth and development (= primary metabolism). These compounds are referred to as secondary or specialized metabolites, or natural products. They are often unique to individual species or groups of species and mediate interactions with other organisms (defense and attraction arsenal). Typical secondary metabolite classes found in plants are terpenes, cyanogenic glycosides glucosinolates, phenylpropanoids, alkaloids, fatty acid derivatives, S- and N-containing compounds. Chemical convergence of some biosynthetic pathways between plants and insects was documented recently (Beran et al. 2019), while chemical convergences between the microbial and plant and/or animal kingdoms are less well studied, despite the fact that microorganisms release a wealth of secondary metabolites.

One prominent ecological role of specialized compounds released by bacteria is to structure the microbial community and populations living in the same habitat. Many of these compounds are well-known antibiotics that are produced to inhibit the growth of different (microbial) species and are therefore often used in human health care. Most secondary metabolites have unusual structures and their biosyntheses are catalyzed by enzymes that are normally clustered on the chromosome and infrequently on plasmids (e.g., cyt P450 enzymes, glucosyltransferases). Despite the huge variety of chemical structures, the sequence of reactions by which they are made can be grouped into three polymerization reactions:

1. Condensation of acetate-malonate units (polyketide biosynthesis).
2. Condensation of amino acids to oligopeptides (non-ribosomal peptide biosynthesis).
3. Condensation of carbohydrate units (often amino sugars).

The polyketide biosynthetic pathway among prokaryotes is prominent in actinomycetes, but some polyketide compounds are also produced by myxobacteria, cyanobacteria, *Bacillus* sp., and pseudomonads. Polyketides produced by microorganisms show an extraordinary diversity (Helfrich et al. 2014; Jenke-Kodama and Dittmann 2009), despite its core biosynthesis based on repeated cycles of decarboxylative Claisen-like condensations of simple acyl-CoA building blocks which resemble fatty acid biosynthesis. A multienzyme complex (type II fatty acid biosynthesis) is present in bacteria and plants, while type I single multifunctional FAS are present in invertebrates. Polyketides are typically synthesized by type II PKS. Acetate and malonate or alternatively propionate and methylmalonate form chains in which the keto groups and methylene groups alternate. When methylmalonate is used instead of malonate, the chain becomes branched with methyl groups. The biosynthesis starts with acetyl CoA and malonyl CoA, both bound to the synthase as thioesters (Fig. 1.8a). Acetate (= initiator) binds to the condensing enzyme domain and malonate binds to acyl carrier protein (ACP). Acetate is condensed with the methylene carbon of malonate, while at the same

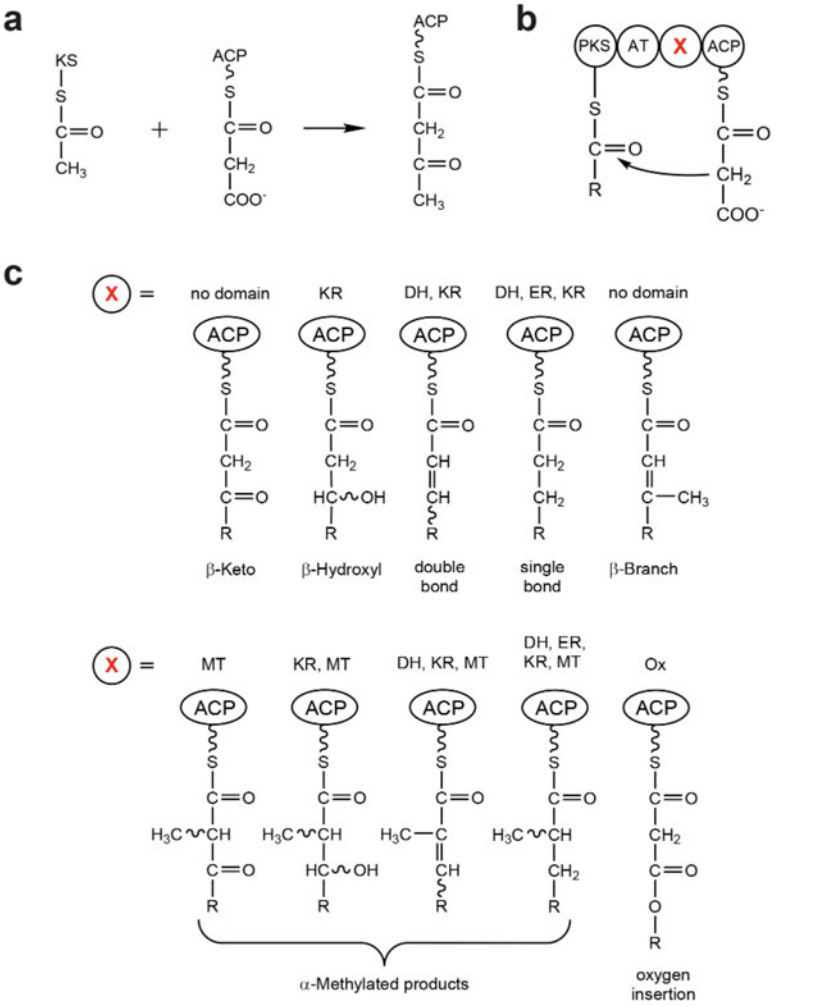

Fig. 1.8 Polyketide biosynthesis (PKS). (**a**) First condensation step of the classical fatty acid biosynthesis. (**b**) A single round of elongation in a type I *cis*-acyltransferase (AT) PKS module. Examples of modifications and derivatizations are introduced via various domains (red X). In *trans*-AT PKS, the AT and ER domains are usually missing. (**c**) Modification reactions, *DH* dehydratase, *ER* enoyl reductase, *KR* ketoreductase, *MT* methyltransferase, *Ox*: oxygenase. Modified based on Nguyen et al. (2008) and Meoded et al. (2018)

time the carboxyl group of malonate eliminates carbon dioxide resulting in an acetoacetate bound to ACP. In fatty acid biosynthesis three reactions reduce the keto group of acetoacetate to a methylene group. These steps are partially or totally omitted during secondary metabolite biosynthesis. Consequently, the chain can bear keto or hydroxyl groups or double bonds are formed adjacent to methylene groups.

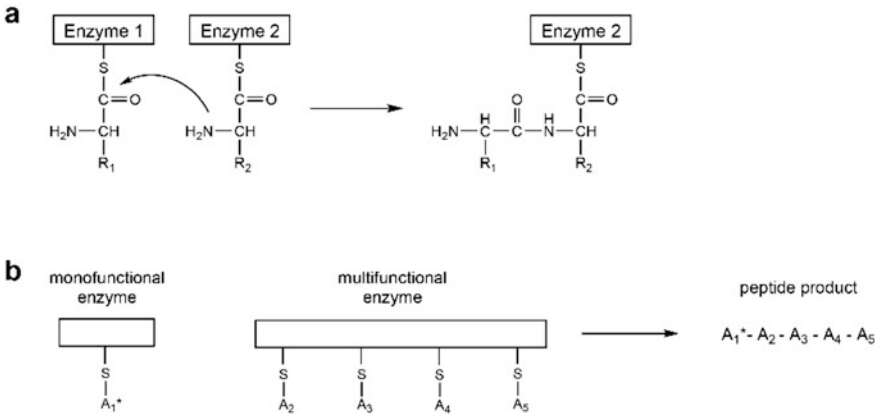

Fig. 1.9 Non-ribosomal peptide synthesis (NRPS). (**a**) Amino acids are linked via thioesters to mono- or multifunctional enzymes. (**b**) Amino group and carboxyl group of amino acid 2 and 1, respectively, form peptide bonds until the peptide is released by a thioesterase from the enzyme. The mono- as well as multifunctional enzymes may encompass domains which modify the amino acids, e.g., isomerization from L- to D isomer (*)

The extended chain is then transferred to the condensing enzyme and another malonate-ACP is used for chain elongation.

The complexity and diversification of polyketides is large and depends on (1) the selection of building blocks, (2) the facultative enzymatic modifications, and (3) additional activity of a variety of auxiliary enzymes during or after chain elongation (e.g., dehydratase, enoylreductase, ketoreductase, methyltransferase, oxygenase, Fig. 1.8c, Meoded et al. 2018; Nguyen et al. 2008). Depending on the nature of the enzymes involved as well as altered initiator and extender molecules, the chain can be converted by the aldol reaction into aromatic rings and either linear molecules or macrocyclic rings are formed, subsequently many different structures are produced, e.g., erythromycin, tetracycline, rifamycin, and monensin A. Polyketide synthases (PKS) also encompass different types regarding their enzyme architecture (non-modular, mono-modular, multi-modular) and mode of operations (iterative, non-iterative, *cis*- and *trans*-AT). They can also form hybrid enzymes containing components of different PKS classes and/or non-ribosomal peptide synthetases (NRPS) (Helfrich et al. 2014). Very recently, several putative Diels-Alderases (cycloaddition) have been characterized in PKS/NRPS pathways which act in tailoring events (summarized in Scott and Piel 2019).

The vast majority of peptide antibiotics are synthesized by the thiotemplate mechanism (*non-ribosomal protein biosynthesis*). This process starts with the activation of the amino acids as adenylates, followed by the condensation of the carboxyl group of the amino acid to thiol groups of the non-ribosomal peptide synthases (NRPSs) to form thioesters and stepwise polymerization. The polymerization initiates with the formation of a peptide bond between the carboxyl group of the first amino acid and the amino group of the second amino acid (Fig. 1.9a). These

condensation reactions are repeated until the chain is completed. A thioesterase releases the peptide. The NRPSs that catalyze this process can comprise up to four multifunctional enzymes, containing domains which catalyze the activation of an amino acid, its esterification to the thiol group of a pantetheine moiety and the formation of the peptide bond. The enzymes may also encompass domains that catalyze isomerization from L- to D-isomers or methylation of the nitrogen of a newly formed amide, resulting in, e.g., gramicidin biosynthesis (Fig. 1.9). This principle of this process resembles that of polyketide biosynthesis.

Antibiotics often contain sugar residues. The biosynthesis of oligosaccharides is identical with the polysaccharide biosynthesis of bacterial cell walls, they are formed by the assembly of monomers, activated as nucleoside diphosphates at the anomeric carbon. Unusual oligosaccharides, often present in antibiotics, either are first assembled and then modified, or sugars are first modified and then stepwise condensed to the precursor.

In contrast to the well-known and established biosynthesis pathways for high molecular weight compounds in microorganisms/bacteria, the biosyntheses of some small molecular compounds of microorganisms, such as terpenes and pyrazines, are less well studied.

Presently, ca. 2000 VOCs released from microorganisms are known (*mVOC database*, Lemfack et al. 2018) which are categorized into fatty acid derivatives, aromatic compounds, nitrogen-containing compounds, volatiles sulfur compounds, terpenoids and others such as halogenated compounds, and metalloid compounds (summarized in Schulz and Dickschat 2007).

Schenkel et al. (2015) used the *mVOC database* to quantify and compare compound classes released from microbes and plant roots. It is interesting to note that the same compound classes are found in both headspaces, while the quantitative distribution is different in these organisms. It is presently not studied in detail whether the appearance of identical or similar compounds in both kingdoms are due to evolutionary convergence (in analogy as described by Beran et al. 2019) or due to horizontal gene transfer (Jia et al. 2019). Fatty acids and respective derivatives such as alkanes, alkenes, aldehydes, ketones, alcohols, as well as ethers and esters are most likely products of incomplete oxidations of the primary metabolism. However, typical secondary metabolites are found in the groups of terpenes, aromatic compounds, furans, and S- and N-containing compounds.

Terpene Biosynthesis Terpenoids are the most diverse class of natural products, 80,000 compounds are estimated to be biosynthesized (Christianson 2017). Monoterpene (C10) and sesquiterpene (C15) compounds are most relevant as volatile organic compounds. Terpene synthases catalyze the most complex chemical reactions in biology since the carbon atoms of the substrates undergo complicated changes in bonding and hybridization during single enzyme catalyzed cyclization reactions. The classical substrates of terpene synthases are geranyl pyrophosphate (GPP), farnesyl pyrophosphate (FPP), and geranylgeranyl pyrophosphate (GGPP) which are synthesized from C5 building blocks (isopentenyl pyrophosphate IPP and dimethylallyl pyrophosphate DMAPP). The latter derive either from the mevalonate

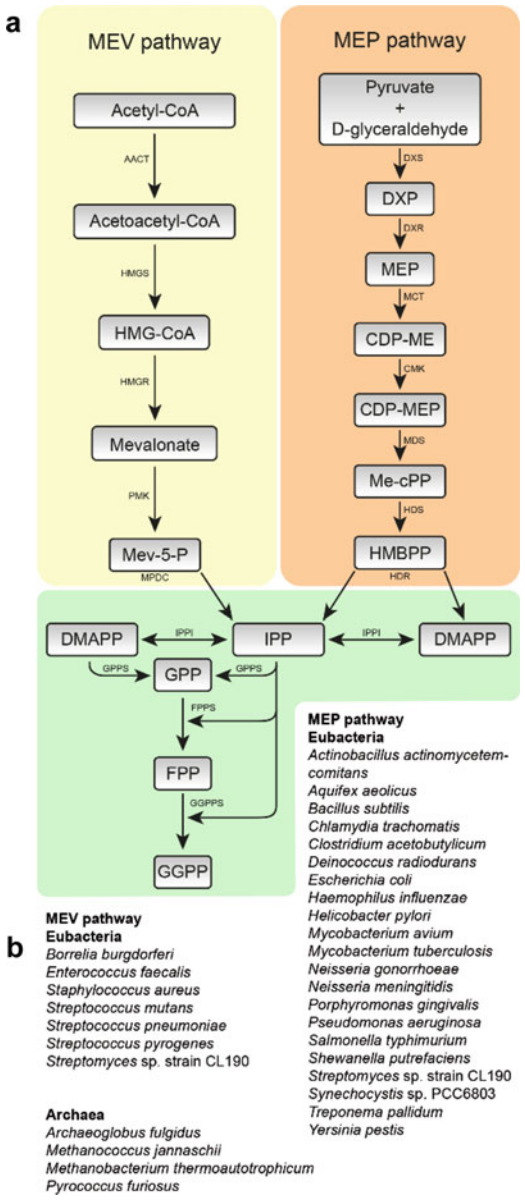

Fig. 1.10 Terpene biosynthesis. (**a**) Mevalonate and MEP pathway for IPP biosynthesis. (**b**) Examples of bacteria using one or the other pathway to produce IPP

or MEP pathway present in the different bacterial species (examples given in Fig. 1.10). Many terpene synthases are very specific and accept only one substrate (single substrate enzymes), while multisubstrate enzymes react with more than one prenyl pyrophosphate. However, the most outstanding and common feature of terpene synthases is their ability to produce multiple products from one substrate

(multiproduct enzymes). Often the products are released in defined ratios indicating that precise pathways of biosynthesis are underlying.

Beside the canonical substrates of terpene synthases GPP and FPP and their respective isomers (*E,E; Z,Z; E,Z*), NPP (neryl pyrophosphate) was described as a substrate (Jia et al. 2018; Sun et al. 2016), and it was shown that methyl-GPP was the substrate for methylisoborneol biosynthesis in *Streptomyces coelicolor* (Komatsu et al. 2008; Wang and Cane 2008). The latter opened a new route of structural diversity due to the fact that C11 compounds are also substrates for terpene synthases (Kschowak et al. 2018). Such methylation reactions also occur with IPP in *Streptomyces* species resulting in C6 substrates (Drummond et al. 2019) and FPP as shown in *Serratia plymuthica* 4Rx13 (Fig. 1.11a; von Reuss et al. 2018). The latter is particularly interesting because the FPP-methyltransferase (FPPMT) not only methylates the C15 FPP to a C16 compound but also performs a cyclisation reaction which is unique for methyltransferases. The product of the FPPMT is presodorifen pyrophosphate and expands the repertoire of non-canonical substrates of terpene synthases uniquely. So far, the methylation and cyclization reactions of IPP, GPP, and FPP (Fig. 1.11b) were only found in the bacterial metabolism.

Ca. 100 volatile monoterpenes and sesquiterpenes of bacterial origin were summarized by Schulz and Dickschat (2007). Several genome mining approaches were performed (Cane and Ikeda 2012; Yamada et al. 2012), however, up to now only 63 bacterial terpene synthases, primarily sesquiterpene synthases from *Streptomyces* species, have been isolated (Dickschat 2016). The architecture of bacterial terpene synthases is distinct compared to respective plant enzymes which typically are built of alpha, beta, and gamma domains, while respective bacterial enzymes are comprised of either single or double alpha domains or beta-gamma domains. The "alpha-only" type is most prevalent in bacteria. Furthermore, the characteristic aspartate-rich motive of plant terpene synthases (DDxxD) is slightly altered to DDxxxD in bacteria (Jia et al. 2018, 2019).

Aromatic Compounds

The basal biosynthetic pathway for aromatic secondary metabolites in plants and bacteria is the shikimate pathway whose primary products are the aromatic amino acids tyrosine, phenylalanine, and tryptophane. While the phenylpropane biosynthesis is very widespread and common in plants, the aromatic compound biosynthesis is (to date) not universally observed and well-studied in bacteria. However, compounds like 2-phenylethanol, phenol, benzyl alcohol, methyl benzoate, benzaldehyde, acetophenone, and closely related compounds were shown to be released from several bacteria (summarized by Schulz and Dickschat 2007, *mVOC database* Lemfack et al. 2018). Two alternative pathways (phenylalanine lyase pathway and phenylpyruvate–phenylacetate–phenylglycolate pathway, Figs. 1.12 and 1.13, respectively) are known to be involved in the biosynthesis of the above-mentioned compounds. However, it is difficult to distinguish these two pathways by feeding experiments with isotope labelled intermediates, and in many cases the bacteria developed individually altered enzymatic reactions supporting and expanding these general pathways. While benzaldehyde can be biosynthesized via both pathways, it

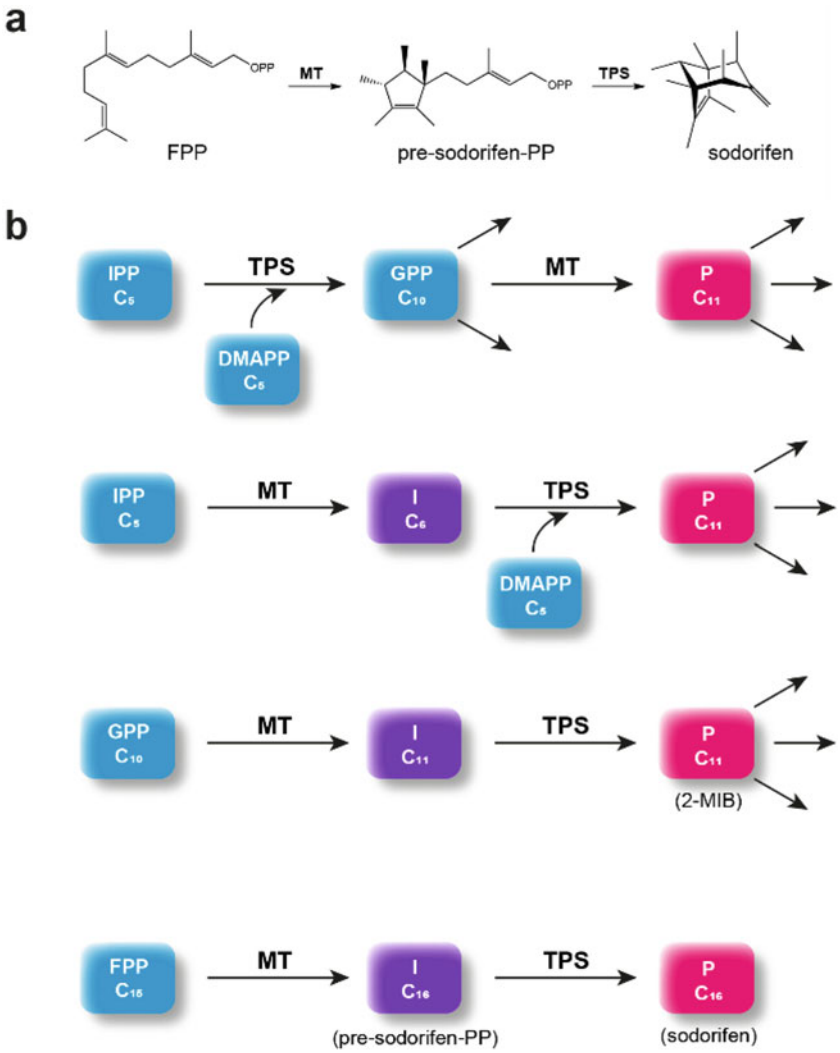

Fig. 1.11 (**a**) Biosynthesis of the extraordinary biosynthesis of sodorifen by *S. plymuthica* (after von Reuss et al. 2018). In a first step a methyltransferase methylates and forms a 5-carbon ring from the canonical substrate FPP; presodorifen is subsequently rearranged to sodorifen by a terpene synthase. (**b**) Schematic presentation of the canonical and non-canonical terpene biosynthesis to reveal methylated terpene products

seems straightforward that many bacteria synthesize β-phenylethanol via phenylacetaldehyde.

Pyrazines are a special class of volatile heterocyclic compounds that are often produced by many bacteria during fermentation processes (*mVOC database* Lemfack et al. 2018).

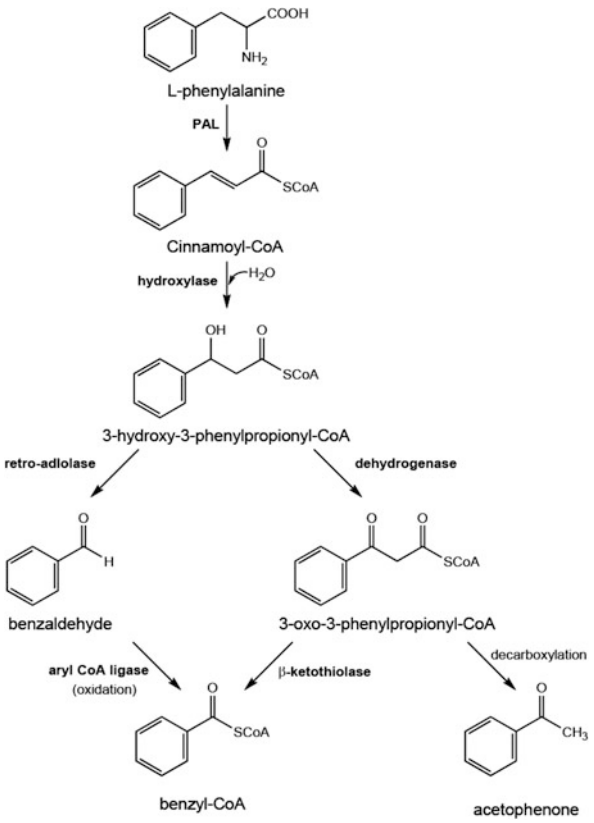

Fig. 1.12 Biosynthesis of aromatic compounds via phenylalanine lyase pathway

They exhibit strong odor properties and are therefore used as flavoring compounds from the aroma industry. Particularly widespread are pyrazines with one to four methyl or ethyl groups (simple alkylated pyrazines). Caution has to be taken because these pyrazines may also originate from cultivation media or are formed during heating or autoclaving. Pyrazines with longer side chains are less often found as bacterial volatiles. To clarify the biosynthesis of pyrazines, more research is needed. At present, one non-enzymatic pathway via amination of acyloins is postulated for the biosynthesis of simple pyrazines. This biosynthesis results in the formation of aminocarbonyl compounds. Condensation of two aminocarbonyl compounds leads to unstable dihydropyrazines (Fig. 1.14) which are easily oxidized to pyrazines. Higher alkylpyrazines require enzymatic reactions and derive from amino acids (Fig. 1.15). The methoxy methyl-group originates from *S*-adenosyl methionine.

Indole is a very prominent volatile biosynthesized by *E. coli*, other *Enterobacteriaceae* such as *Klebsiella* and *Enterobacter*, and other bacteria as well (e.g., *Loktanella*). It derives from a one-step reaction of the enzyme tryptophanase of the aromatic amino acid tryptophane (Fig. 1.16). The malodourous

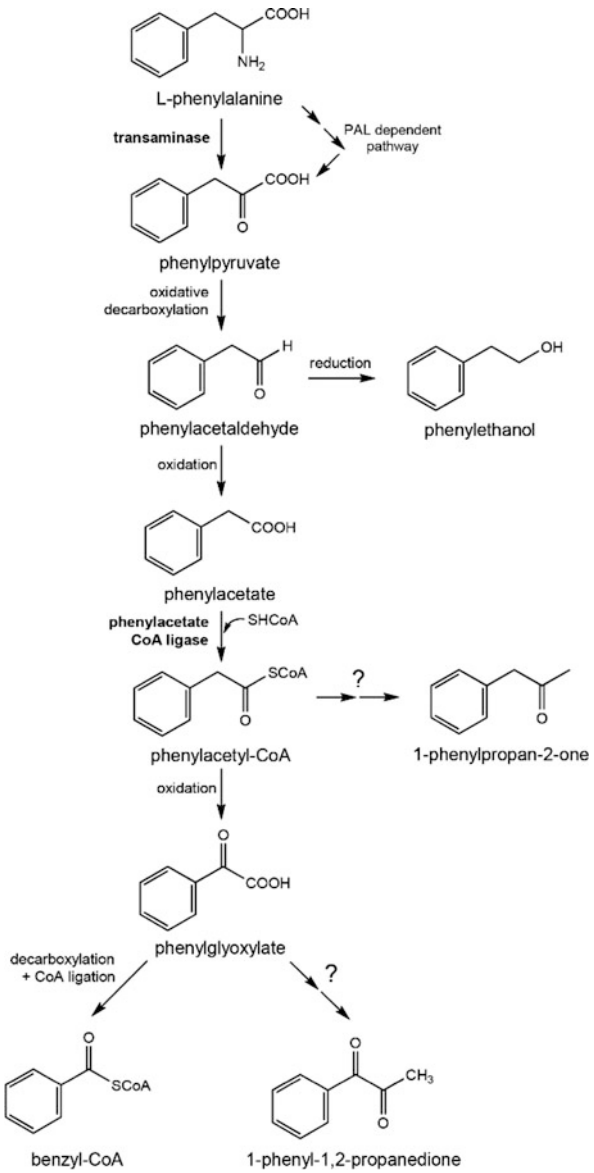

Fig. 1.13 Biosynthesis of aromatic compounds via phenylpyruvate–phenylacetate–phenylglycolate pathway

skatole also derives from tryptophane; it is released from *Calothrix* and biosynthesized via indole acetic acid (IAA) which is a well-known phytohormone.

N-Compounds

Ammonia is an inorganic, highly volatile compound and produced by many bacteria, including *Enterobacter*, *Serratia*, *Klebsiella*, *Staphylococcus*, *Micrococcus*, and *Bacillus* by degradation of amino acids, by nitrite ammonification, by

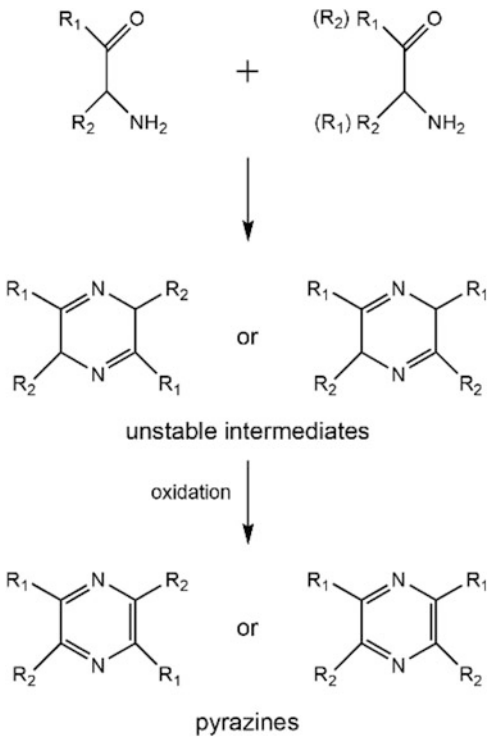

Fig. 1.14 Biosynthesis of simple pyrazines with methyl or ethyl side chains

urease-mediated hydrolytic degradation of urea, and by decarboxylation of amino acids (summarized in Piechulla et al. 2017). Biogenic amines such as trimethylamine, 2-methylpropylamine, 2-methylbutylamine, 3-methylbutylamine, cyclohexylamine, and phenylethylamine are also often found in the headspace of bacteria.

Biogenic amines can be converted by aminooxidases to respective aldehydes which furthermore can react with biogenic amines to produce imines.

S-Compounds

Dimethyl disulfide (DMDS) and dimethyl trisulfide (DMTS) are the most prominent volatile sulfur organic compounds released from bacteria (*mVOC database*, Lemfack et al. 2018). Three major pathways are known for their biosynthesis (Fig. 1.17). Marine bacteria (Alpha-, Beta-, Gamma-, Deltaproteobacteria) mainly use the dimethylsulfoniopropionate (DMSP) which is produced by algae in high amounts from L-methionine and is therefore prevalent in oceans (Fig. 1.17a). Depending on the bacterial species and its genetic repertoire, DMSP is converted to acrylate and DMS via CoA ester and acyl-CoA transferase, lytically cleaved or degraded by an unknown mechanism of DMSP lyase. Alternatively, DMSP can also be degraded on the demethylation pathway to 3-(methylmercapto) propionic acid by the DMSP demethylase and further to methanethiol and acrylate by an unknown

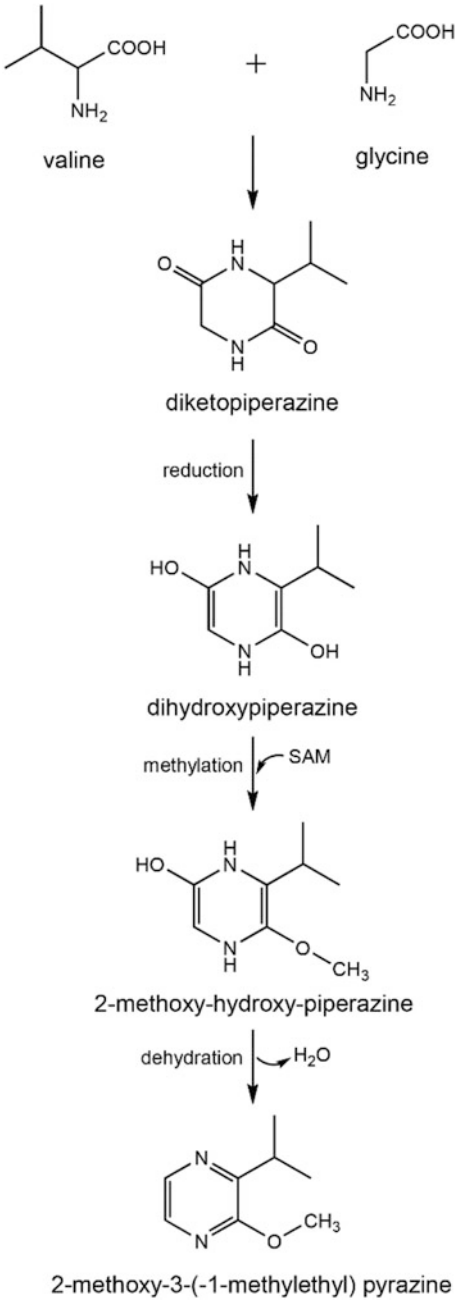

Fig. 1.15 Biosynthesis of higher alkylpyrazines

enzyme (Dickschat et al. 2010). In freshwater habitats, bacteria produce methanethiol and DMS through methylation of inorganic sulfide (Fig. 1.17b). In a

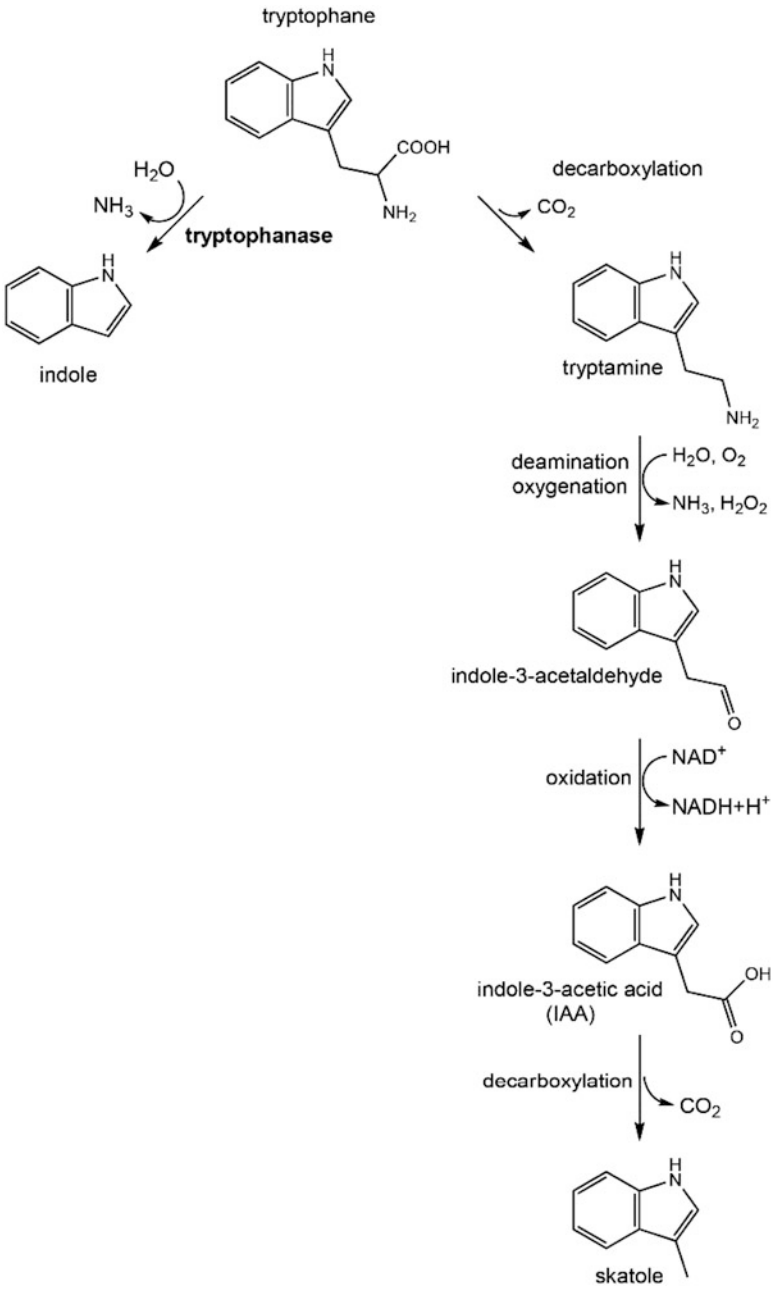

Fig. 1.16 Biosyntheses of indole and skatole derived from tryptophane

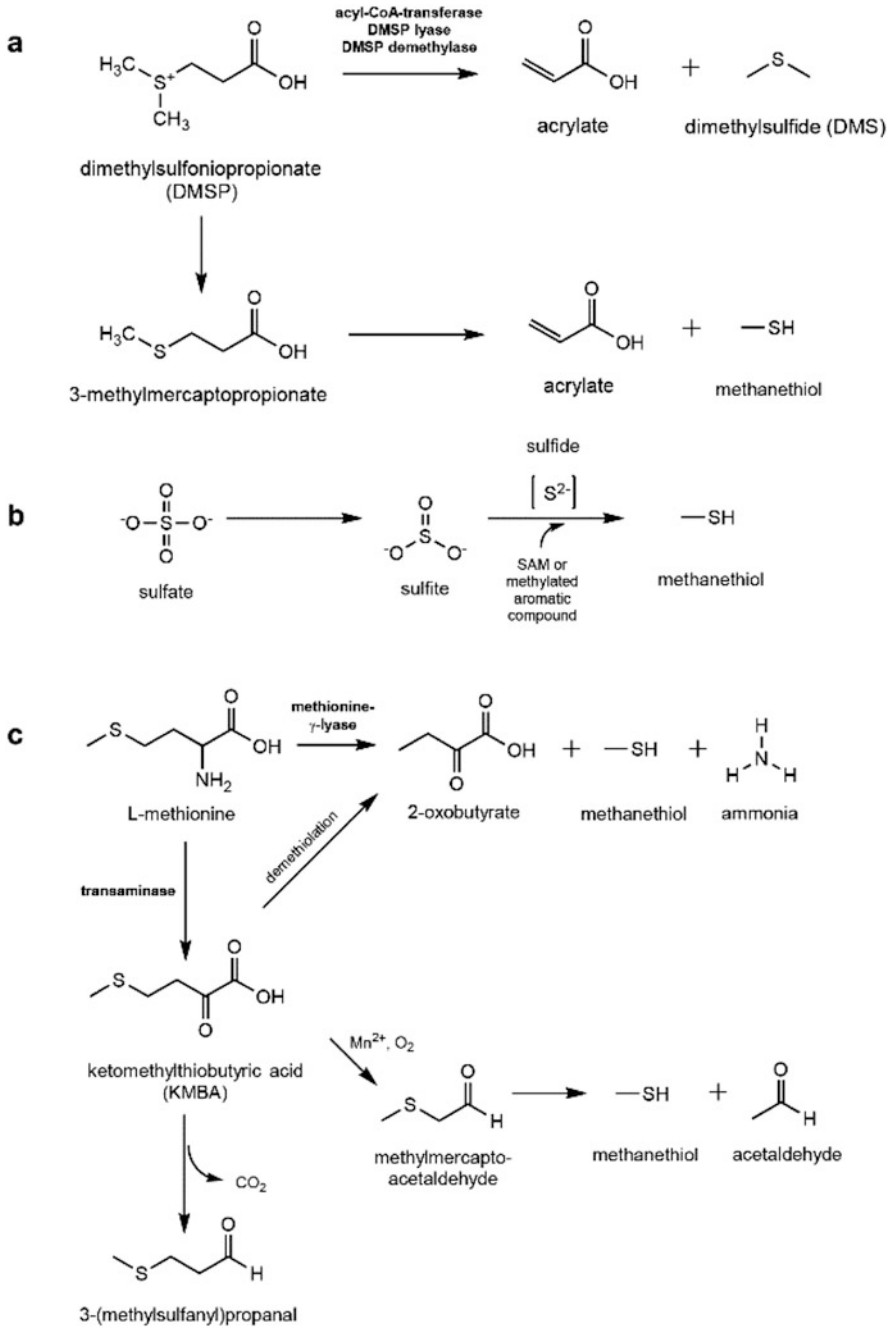

Fig. 1.17 Three biosynthetic pathways for volatile sulfur compounds in bacteria. (**a**) Dimethylsulfoniopropionate (DMSP) from bacteria of marine or estuarine habitats is converted into acrylate and dimethyl sulfide (DMS). (**b**) Bacteria in freshwater mainly produce methanethiol from sulfate. (**c**) L-Methionine is degraded by methionine lyase to ammonia, 2-oxobutyrate, and methanethiol or transaminated to ketomethylthiobutyric acid (KMBA). The latter may be converted by a proposed demethiolase to 2-oxobutyrate and methanethiol. KMBA can be chemically (Mn^{2+}, O_2) degraded to methyl mercapto acetaldehyde and subsequently converted to methanethiol and acetaldehyde, or to 3-(methylsulfanyl) propanal and several derivatives. (**d**) Methanethiol is a precursor for DMS, dimethyl disulfide (DMDS), dimethyl trisulfide (DMTS)

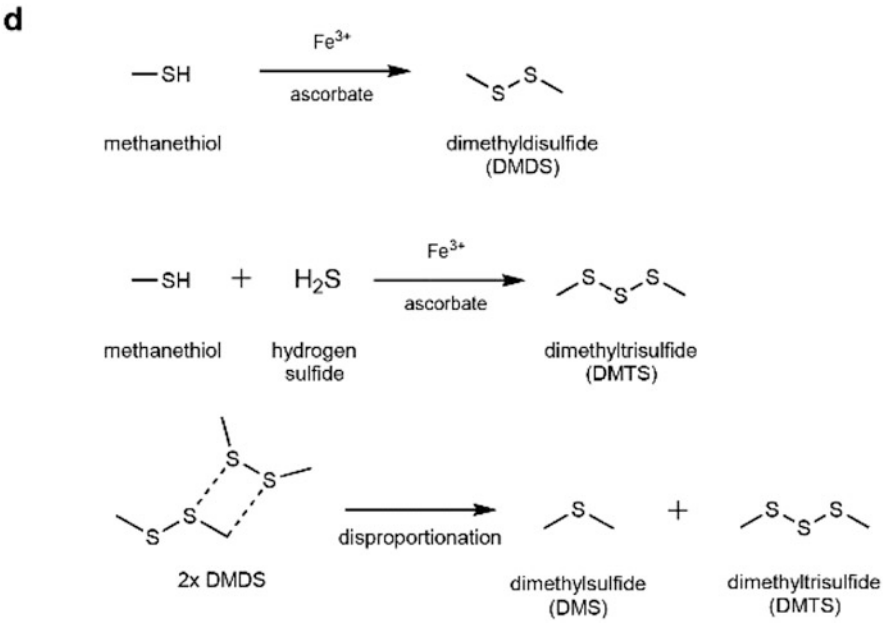

Fig. 1.17 (continued)

first step, sulfate is reduced to sulfite by sulfite reductase, which is an evolutionary old reaction/enzyme also present in archaea.

Methanethiol and DMS are then either produced by a SAM dependent methyltransferase or via methoxylated aromatic compounds (e.g. in, *Halophaga foetida, Sporobacter termitidis, Sporobacterium olearium;* and *Parasporobacetrium paucivorans*, respectively). Finally, L-methionine is the major source for volatile sulfur compounds of dairy product producing bacteria such as *Brevibacterium, Corynebacterium, Staphylococcus, Lactococcus,* and *Lactobacillus*. These bacteria produce a wide array of sulfur compounds biosynthesized via two methionine degradation pathways, (1) direct cleavage of methionine and (2) transamination to ketomethylthiobutyric acid (KMBA) and subsequent reductive demethiolation or decarboxylation (Fig. 1.17c). In the direct cleavage pathway methionine lyase produces ammonia, 2-oxobutyrate and methanethiol. The second pathway is initiated by a transaminase reaction and demethiolase to reveal 2-oxobutyrate and methanethiol, or alternatively KMBA is converted to 3-(methylsulfanyl) propanal, which is the precursor for subsequent reduction and oxidation reactions forming sulfur compound derivatives. Methanethiol can be converted by rapid autooxidation to DMDS, or by reaction with H_2S to DMTS. Alternatively, two molecules of DMDS can be transformed by disproportionation to DMS and DMTS (Fig. 1.17d).

Taken together, investigating more bacterial strains, even those from less representative phyla, classes, families, or genera, could help to discover new interesting

and bioactive natural products, especially those derived from the secondary metabolism. These could, in turn, be used for new applications since mVOCs are seen as new frontier in bioprospecting and can be applied as eco-friendly alternatives to synthetic compounds for biotechnological applications.

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