Chapter 1
Microbial Degradation of Pyridine and Pyridine Derivatives

Nidhi Gupta, Edward J. O'Loughlin, and Gerald K. Sims

Abstract Pyridine derivatives belong to an important class of aromatic compounds that occur largely as a result of human activities, although they are not necessarily xenobiotic compounds. Pyridines can also be derivatized to form a wide variety of xenobiotic compounds ranging from drugs to pesticides. Analogs to phenolic compounds, pyridines exhibit properties that differ in some respects to homocyclic compounds, and this may have profound effects on their biodegradation. The presence of the ring nitrogen defines the reactivity of pyridine derivatives. After 60 years of research into biodegradation of pyridine derivatives, some themes have emerged; however, new discoveries continue to change our understanding of how pyridines are degraded in the environment. This chapter brings together the current state of knowledge on the biodegradation of pyridines.

Keywords Pyridine · Alkylpyridines · Photodegradation · Hydroxypyridines

1.1 Introduction

Simple pyridine derivatives enter the environment through natural and anthropogenic routes, and some pose documented health risks. Biodegradation of these compounds has been evaluated for more than 60 years, and these studies have revealed a number of common themes. There is, however, a considerably smaller body of literature dealing with biodegradation of pyridines than for hydrocarbons. An effort was made herein to be thorough in representing the state of knowledge regarding the

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biodegradation of pyridines. When we last reviewed this topic in 1989 (Sims GK, O' Loughlin EJ: Crit Rev Environ Control 19:309-340, 1989), there were considerable knowledge gaps in degradative mechanisms, little information on anaerobic biodegradation, and almost no evidence for any of the genes encoding degradation pathways; however, there have been a number of advances in each of these areas in the past decade.

The pyridine ring occurs in biological systems. It was originally discovered by Thomas Anderson (1851) in bone oil (Anderson 1851). Thus, both synthesis and degradative pathways exist in nature. Unsubstituted pyridine is seldom found in living organisms but has been isolated from rayless goldenrod (Buehrer et al. 1939). While pyridine and alkylpyridines generally are not present at high concentrations in living organisms, pyridine derivatives occur ubiquitously as pyridoxine (vitamin B_6) and vitamin B_3 (primarily in the form of niacin [nicotinic acid or pyridine-3-carboxylic acid] and nicotinamide [3-pyridinecarboxamide]) which is used in the synthesis of nicotinamide adenine dinucleotide (NAD^+) and nicotinamide adenine dinucleotide phosphate ($NADP^+$) and less commonly as plant alkaloids (nicotine, trigonelline, arecoline, actinidine, anabasine, anatabine, ricinine, gentianine, and trigonelline). Trigonelline is also found in the urinary waste of mammals, as it is formed by methylation during niacin metabolism. Pyridine-2,6-dicarboxylic acid (dipicolinic acid) is a major component of bacterial endospores (Slieman and Nicholson 2001). Pyridine and alkyl pyridines are flavor components of beer (Harding et al. 1977) and a variety of foods (Suyama and Adachi 1980). They are formed during cooking of meats, likely due to the reaction of alkanals with amino acids (Hui 2012). Maga (1981) listed dozens of foods in which pyridines are important organoleptic compounds (including artichoke, asparagus, barley, beans, cheeses, cocoa, coffee, eggs, peanuts, pecans, rice, rum, and whiskey). In many cases, alkylpyridines found in foods are actually formed during the cooking process. Thermal decomposition of some amino acids produces pyridines, such as alpha-alanine, which produces 2-methyl-5-ethylpyridine (Lien and Nawar 1974) and cysteine, which releases pyridine, 2-methylpyridine, and 3-methylpyridine (Kato et al. 1973). Pyridines are found in the asphaltene fractions of crude oil and, as noted below, are formed during heating of fossil fuels in gasification and extraction processes. Marine crude oils generally contain lower concentrations of pyridines than terrestrial crude, owing to solubility

More commonly, pyridines are of anthropogenic origin. They are high production volume solvents and traded internationally. The current global market is estimated to be more than $500,000,000 and increasing. Pyridines have a broad range of industrial uses, such as solvents and reactants in organic synthesis, and pyridine is added to ethanol to discourage recreational consumption. The quaternary amine detergent, cetylpyridinium bromide, is a common antiseptic in consumer products like toothpastes and mouthwash. Pyridine-based conductive polymers (Yang et al. 2014) offer promise as energy storage nanoparticles. Pyridinium compounds can be used for desulfurization of fuel oils (Verdía et al. 2011) and as a stabilizing donor ligand for olefin metathesis (Occhipinti et al. 2017). Pyridine moieties are found in a number of drugs, such as isoniazid and sulfapyridine (antibiotics), altinicline

(experimental drug for Parkinson's disease), flupirtine (non-opioid analgesic), lansoprazole (anti-ulcerative), and pantoprazole (treatment of gastroesophageal reflux disease). Other drugs include nikethamide (a respiratory stimulant), eucaine (local anesthetic), demerol (analgesic), and antihistamines, chlorpheniramine maleate and pyrilamine maleate. Pyridine rings are found in herbicides across a spectrum of modes of action, such as the photosystem I inhibitors diquat and paraquat; the acetolactate synthase (ALS)-inhibitors imazamox, imazapyr, and nicosulfuron; the synthetic auxins aminopyralid, clopyralid, fluroxypyr, picloram, and triclopyr; and the aquatic herbicide fluridone, which inhibits carotenoid synthesis. They are found in insecticides, including the organophosphate chlorpyrifos, the feeding inhibitor chlorantraniliprole, and the neonicotinoid insecticide imidacloprid. Other pesticides, such as the nitrification inhibitor nitrapyrin; the fungicide boscalid, which inhibits spore germination; and the avicide starlicide, are based on pyridine chemistry. Pyridine-based pesticides are widely used and in 2013 represented approximately 10% of the global pesticide market with total sales of $5 billion, of which chlorantraniliprole, imidacloprid, and paraquat accounted for $1240, $1070, and $905 million, respectively (Guan et al. 2016).

Over the past 30 years, the US Environmental Protection Agency (EPA) Toxics Release Inventory (TRI) reported annual releases of pyridine to the environment of roughly 250,000 kg, about 90% of which was released to soil and the remainder to air and water. Of the more than 1700 current and closed sites on the EPA National Priorities List (Superfund Program), 4 have been found to be primarily contaminated with pyridine, although not all sites were tested for it. Coal tar distillation was once a common source of pyridine derivatives (most are now prepared synthetically), thus they are often found near legacy sites (Pereira et al. 1983, 1987). Pyridine; 2-, 3-, and 4-methylpyridine; as well as other more complex alkylpyridines are common contaminants associated with fossil fuels and gasification sites (Stuermer et al. 1982). Zamfirescu and Grathwohl (2001) observed that contaminant plumes associated with a legacy gasification site changed in composition along the flowpath and that N-heterocycles tended to become enriched with distance from the source. Diesel fuels derived from either fossil fuels (Hughey et al. 2001) or biodiesel (Lin et al. 2007) often contain pyridine derivatives. A part of the asphaltene component of crude oil, pyridines and other N-heterocycles contribute to fouling of catalysts used to refine petroleum, which has led to development of catalytic techniques to convert pyridines to hydrocarbons (Duan and Savage 2011). As unconventional on-land oil and gas production has increased, so has the wastewater volume, growing from 5.7 to 138 × 10^9 m^3 between 1998 and 2010 (Gregory et al. 2011). In some cases, such as a site in Rundle, Australia, the base fraction of the process water from oil shales may be limited entirely to N-heterocyclic compounds (Dobson et al. 1985). Using 2D gas chromatography, Dijkmans et al. (2015) showed that oil shales contain pyridine derivatives, indicating the compounds may naturally be present in the shales. Alkyl pyridines are reported to be used in hydraulic fracturing fluids and have been detected in flowback or produced water from unconventional oil production (Hayes and Severin 2012). Alkyl pyridines were also detected in products of

hydrothermal liquefaction of the biofuel alga, *Nannochloropsis salina* (Sudasinghe et al. 2014).

1.2 Chemical Properties

The six-membered pyridine ring is planar (the average bond angle is 120°), with aromatic character and a high resonance energy (23 kcal/mol), and its chemistry is defined by the nitrogen heteroatom at position one (Fig. 1.1). Pyridine and methylpyridines are hygroscopic and miscible with water as well as a number of organic solvents. The UV absorption spectrum of pyridine varies with substitutions and pH. Molar absorptivity is generally greater in the protonated form, and there is a general tendency for a shift to longer wavelengths with most common substitutions and protonation of the ring N.

The electronegative nitrogen heteroatom results in electron-deficient ring carbon atoms, especially at positions 2, 4, and 6. The heteroatom is thus electron rich. This alters reactivity of the pyridine ring relative to benzene. For example, pyridine ring carbons resist oxidation, which is borne out in its stability in strongly oxidizing dichromate reagents, such as pyridinium dichromate and pyridinium chlorochromate, used to oxidize alcohols to carbonyls. Unlike pyrrole, the third sp2 orbital of the pyridine heteroatom has only one pair of electrons, making pyridine a stronger base than pyrrole due to the availability of the nitrogen heteroatom to share electrons with acids. Compared to aliphatic amines, pyridine is a weak base ($pK_a = 5.17$ versus 10.56 for 4-aminobutyrate) (Dean 1987); pyridine derivatives with electron-withdrawing substituents are even weaker bases than pyridine itself (e.g., $pK_a = 0.72$, 1.01, and 1.25 for 2-chloropyridine, pyridine-2 carboxylic acid, and 2-hydroxypyridine, respectively); conversely electron-donating substituents make pyridine derivatives more basic (e.g., $pK_a = 5.96$, 6.71, and 7.43 for 2-methylpyridine, 2-aminopyridine, and 2,4,6-trimethylpyridine, respectively). Moreover, the basicity of the substituted pyridine is dependent on the position of the substituent on the ring, as illustrated by the hydroxypyridine series 2-hydroxypyridine ($pK_a = 1.25$), 3-hydroxypyridine ($pK_a = 4.80$), and 4-hydroxypyridine ($pK_a = 3.23$).

In either electrophilic or nucleophilic substitution reactions, pyridine behaves similarly to benzene substituted with electron-withdrawing groups. Thus it resists

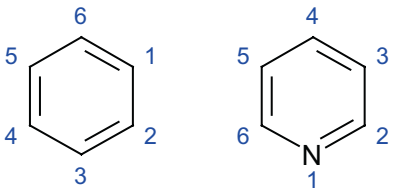

Fig. 1.1 Comparison of the structures for benzene (left) and pyridine (right). The presence of the N heteroatom causes significant changes in chemical properties relative to benzene

electrophilic reactions such as halogenation, nitration, and sulfonation, especially at positions ortho or para to the nitrogen due to the resulting positively charged nitrogen atom. Pyridine is also relatively resistant to addition reactions.

Hydroxyl groups activate pyridine to electrophilic attack, especially ortho and para to the hydroxyls (which exist predominantly as the ketone tautomer). To probe the potential reactivity toward oxygenation reactions, Houghton and Cain (1972) challenged pyridine and monosubstituted hydroxypyridines in the Udenfriend system (Udenfriend et al. 1954), which consists of Fe(II), EDTA, ascorbic acid, and molecular oxygen, which has been used to mimic biological oxidations, such as monooxygenase reactions. Pyridine was nonreactive in the Udenfriend system and in fact has subsequently been used as a solvent to conduct Udenfriend system investigations (Barton and Delanghe 1998). These findings, along with the extreme stability of pyridine toward oxidation, such as in dichromate (Holloway et al. 1951; Westheimer and Chang 1959), Kjeldahl oxidation (Dakin and Dudley 1914), or Gif reactions (Barton and Delanghe 1998), would suggest a reductive mechanism that would be more favorable for biodegradation than oxygenase attack. Houghton and Cain (1972) found that the Udenfriend system produced 2,3- and 2,5-diols from 2-hydroxypyridine, while 3- hydroxypyridine produced 2,3-, 3,4-, and 3,5- diols, and 4-hydroxypyridine produced 3,4-dihydroxypyridine and pyridine N-oxide. These results would suggest ring carbons in hydroxypyridines (or the corresponding ketone tautomer) that would be more favorable substrates for monooxygenase attack than those in pyridine and that pyridine should preferentially be attacked at the nucleophilic N heteroatom. These generalizations are consistent with early investigations into the biodegradation of pyridine and simple pyridine derivatives, in which the only oxygen-containing metabolite detected from pyridine was pyridine-N-oxide, while hydroxypyridines and alkylpyridines produced intermediates hydroxylated in the expected positions. It was generally assumed that unsubstituted pyridine could be reduced to form a dihydro- or tetrahydro-pyridine product that would be susceptible to hydroxylation by the enzymatic addition of water.

Substituted pyridines, particularly those containing hydroxyl and carboxyl groups, form complexes with a broad range of transition metals. 3-Hydroxypyridine forms complexes with Cu(II), Ni(II), Co(II), Cd(II), and Cr(III) (Koval'chukova et al. 2002). Colored complexes resulting from the reaction of dihydroxypyridines with $FeCl_2$ have been used for the identification of these compounds in culture media (Houghton and Cain 1972). Pyridine carboxylic acids including pyridine-2-carboxylic acid (picolinic acid), nicotinic acid, and pyridine-2,6-dicarboxylic acid complex metals including V(IV), Cr(III), Mn(II), Fe(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), and Ag(II)(Allan et al. 1979; Chakov et al. 1999; Chang and Foy 1982; Kleinstein and Webb 1971; Sakurai et al. 1995; Yuen et al. 1983) and several pyridine carboxylic acid complexes of Cu(II), Cr(III),V(IV), and V(V) have been investigated as therapeutic agents for the treatment of diabetes (Crans et al. 2000; Nakai et al. 2004, 2005; Preuss et al. 2008; Thompson and Orvig 2001; Willsky et al. 2011). In addition, pyridine-2,6-dicarboxylic acid is an effective extractant for the recovery of Cd(II) and Pb(II) from soils (Hong and Chen 1996; Macauley and Hong 1995). The herbicide picloram (4-amino-3,5,6-trichloro-2-pyridinecarboxylic

acid) complexes Fe(II), Fe(III), Ni(II), and Cu(II) (Michaud and Hoggard 1988; Yuen et al. 1983). Pyridine-metal complexes have found use in analytical chemistry, perhaps most notably the use of 2,2′-bipyridine and the bipyridine derivative 1,10-phenanthroline as reagents in colorimetric assays for Fe(II) (Cagle and Smith 1947; Fortune and Mellon 1938).

1.3 Abiotic Factors in the Fate of Pyridines

Photodegradation: The UV absorption maximum of pyridine is 256 nm in neutral to acidic aqueous solutions and decreases to 249 nm in the vapor phase (Errami et al. 2016). The compound is susceptible to photochemical degradation in the vapor phase (Errami et al. 2016) or in aqueous solution (Elsayed 2014), whereas sonochemical degradation proceeds only very slowly (Elsayed 2014). Abiotic degradation rates increase somewhat in the presence of H_2O_2 (Elsayed 2014). While photochemical degradation appears to be only moderately effective for wastewater treatment, degradation in the atmosphere generally occurs in less than 2 days and is likely the primary fate of atmospheric pyridine (Errami et al. 2016). Several pyridine-based pesticides are also susceptible to photochemical degradation, including the nitrapyrin (2-chloro-6-(trichloromethyl)pyridine) hydrolysis product, 6-chloropyridine-2-carboxylic acid (Redemann and Youngson 1968), paraquat (Slade 1965), diquat (Slade and Smith 1967), fluroxypyr (Hu et al. 2014), imazamox (Quivet et al. 2006), fluridone (MacDonald et al. 1996), chlorpyrifos (Wu et al. 2006), picloram (Gear et al. 1982), imazapyr (Pizarro et al. 2005), and imidacloprid (Cacho et al. 1999).

Transport: Pyridines are mobile in the environment. Volatilization is a major path for loss of pyridine and alkylpyridines from soil and aquatic environments (Sims and Sommers 1985, 1986). The vapor pressure at 25 °C is approximately 0.15 MPa for pyridine (Weast et al. 1989) and 0.03 MPa for methylpyridines (Chirico et al. 1999). Pyridine derivatives occur in tobacco smoke (Schmeltz and Hoffmann 1977) and are detected in indoor environments in which smoking occurs (Jenkins et al. 2000). Pyridines are emitted into the atmosphere from shale wastewater (Hawthorne et al. 1985). Pyridine and all three methylpyridine isomers are completely miscible with water, and, as a result, pyridines occur in groundwater near coal gasification sites (Leenheer and Stuber 1981), wastewater from unconventional on-land oil and gas production (Brown et al. 2015; Dobson et al. 1985; Leenheer et al. 1982; Riley et al. 1981), and in aquifers beneath major pyridine spills (Fuller 2015; Ronen et al. 1996). Pyridine pesticides including chlorantraniliprole (Vela et al. 2017), imazapyr (Porfiri et al. 2015), picloram (Pang et al. 2000), fluroxypyr, and clopyralid (Ulen et al. 2014) have been shown to leach through soil, and picloram (Lym and Messersmith 1988) and boscalid (Reilly et al. 2012) have been detected in groundwater.

Sorption: Pyridines absorb to a broad range of geologically/environmentally relevant materials including clay minerals (Baker and Luh 1971; Laird and Fleming

1999; O'Loughlin et al. 2000; Sabah and Celik 2002; Zachara et al. 1990), zeolites (Rawajfih et al. 2010), metal oxides (Vasudevan et al. 2001), organic matter (Ahmed et al. 2014; Graber and Borisover 1998), and whole soils (Bi et al. 2006, 2007; Zhu et al. 2003). Moreover, sorption of pyridines by agricultural and geological waste materials can be an effective treatment for wastewaters contaminated with pyridines (Ahmed et al. 2014; Lataye et al. 2008a, b; Mohan et al. 2005; Zhu et al. 1988). The sorption of pyridines to soils can occur by specific and nonspecific interactions with both organic matter and mineral components. As discussed previously, the nitrogen heteroatom of pyridine is a base with pK_a values ranging from −0.4 to 9.1 depending on the substituents and their position on the ring (Dean 1987). As such, the sorption of pyridines to soils is typically dominated by cation exchange processes at pH values where the protonated form is the dominant species (i.e., below the pK_a) (Baker and Luh 1971; Bi et al. 2007; Laird and Fleming 1999; Zachara et al. 1987, 1990; Zhu et al. 2003); however, surface acidity can lead to predominance of the protonated form 1 to 1.5 pH units above the pK_a of a given pyridine (Laird and Fleming 1999). At pH values far in excess of the pK_a, as well as for pyridines with nonionizable nitrogen heteroatoms (e.g., hydroxypyridines) or with highly nonpolar substituents, sorption is primarily by means of surface complexation or van der Waals interactions (Bi et al. 2006; Laird and Fleming 1999; Sabah and Celik 2002; Vasudevan et al. 2001). Sorption of pyridines to soils and sediments has significant impacts on their environmental behavior including mobility, reduction in bioavailability (e.g., reduced toxicity and biodegradation), and increase in persistence (Bi et al. 2006; Johnson et al. 1995; Gebremariam et al. 2012; Leenheer and Stuber 1981; Loux et al. 1989; O'Loughlin et al. 2000; Starr and Cunningham 1975; Stougaard et al. 1990).

1.4 Biological Factors in the Environmental Fate of Pyridines

Biodegradability: Though often described as refractory, pyridine and alkyl pyridine derivatives are often highly biodegradable; however, as with homocyclic compounds, the nature and position of ring substituents have profound effects on biodegradation rates. Pyridine has a relatively short biodegradation half-life of 7 days or less in aqueous media. Alkylpyridines, pyridine carboxylic acids, and hydroxypyridines degrade somewhat more slowly, with half-lives ranging from 7 to 24 days. Among the most recalcitrant of the simple pyridines are halopyridines and aminopyridines (Naik et al. 1972; Sims and Sommers 1985, 1986).

Degradation in natural and engineered environments: Pyridines can be removed from wastewater using biodegradation. Phenol-fed aerobic granules have been used as supports for microbial removal of pyridine from pharmaceutical wastewater (Adav et al. 2007). Wastewater from a coke processing plant was treated with a microbial bioreactor to remove organic contaminants, including pyridine (Li et al. 2003). Pyridine biodegradation has been coupled to energy production in microbial fuel cells (Zhang et al. 2009).

A large body of literature is available on the environmental behavior of many pyridine pesticides. Biodegradation of picloram, chlorpyrifos, triclopyr, and fluroxypyr in the environment usually involves initial hydroxylation (Lee et al. 1986; Lehmann et al. 1990; Leoni et al. 1981; Meikle et al. 1974). The trichloromethyl moiety of the nitrification inhibitor, nitrapyrin, is converted to 6-chloropyridine-2-carboxylic acid in soils (Wolt 2000). The organophosphate insecticide, chlorpyrifos, exhibited faster degradation in mineral than organic soil, possibly owing to enhanced sorption (Chapman and Harris 1980). In the field, a pyridinol metabolite was shown to persist for months after chlorpyrifos was degraded (Leoni et al. 1981). Numerous authors have demonstrated biodegradation of chlorpyrifos by diverse genera of bacteria and fungi (Chishti et al. 2013). Fluridone appears to be persistent in soils, especially under flooded conditions (Marquis et al. 1982), and often remains detectable in oxic soils a year after application (Banks et al. 1979; Schroeder and Banks 1986); prior exposure enhanced degradation rates, suggesting microbial involvement (Banks et al. 1979). Degradation of imazethapyr, which also appears to be mediated by microorganisms in soils, is limited by bioavailability due to soil sorption (Loux et al. 1989). Though highly persistent, the avicide, 4-aminopyridine was sufficiently sorbed to soils to exhibit limited leaching (Starr and Cunningham 1975).

1.5 Aerobic Biodegradation of Pyridine

Early work on the microbial metabolism of the pyridine ring was motivated primarily by a need to better understand metabolism of nicotine (3-[(2S)-1-methyl-2-pyrrolidinyl]-pyridine), nicotinic acid, nicotinamide, and the coenzymes NAD and NADP. Interest in pyridines as environmental contaminants increased after a surge in the development of synfuel plants following passage of the US Energy Security Act in 1980. The Energy Security Act included the US Synthetic Fuels Corporation Act, which called for a drastic increase in synfuel production to reduce dependence on oil imports. Early research on the environmental impacts of synfuel plants identified contamination of water with pyridine and alkylpyridines as a major risk factor. This discovery spurred research on the environmental fate of pyridine and alkylpyridines throughout the 1980s. Also in the 1980, a major spill (227,000 L) of mixed pyridines resulted in significant groundwater contamination in Indianapolis, IN, which further promoted research on the fate of these compounds.

The degradation of pyridines has been reported under both oxic and anoxic conditions (Fetzner 1998; Kaiser et al. 1996; Li et al. 2001; Rhee et al. 1997) by pure or mixed cultures (Lodha et al. 2008) across a range of phylogenetically diverse microorganisms including *Nocardia* sp. (Watson and Cain 1975), *Bacillus* sp. (Watson and Cain 1975), *Paracoccus* spp. (Bai et al. 2008; Lin et al. 2010; Qiao and Wang 2010; Wang et al. 2018), *Pseudomonas* spp. (Mohan et al. 2003; Padoley et al. 2009), *Rhodococcus* spp. (Do et al. 1999; Yoon et al. 2000a), *Arthrobacter* spp. (Kolenbrander et al. 1976; Kolenbrander and Weinberger 1977; Zefirov et al. 1994), *Shewanella* sp. (Mathur and Majumder 2008), *Alcaligenes* sp. (Ronen et al. 1994),

Shinella sp. (Bai et al. 2009), *Gordonia* sp. (Yoon et al. 2000b), *Pimelobacter* sp. (Lee et al. 1994), and *Achromobacter* sp. (Deng et al. 2011), among others. The biodegradation of pyridine is reported to occur via two different mechanisms: ring reduction or ring hydroxylation followed by ring fission. Resistance of the pyridine ring to oxidation (as discussed above), as well as the frequent detection of reduced metabolites, supports the existence of a reductive mechanism. On the other hand, the identification of pyridine ring fission products containing oxygen is evidence for pathways involving hydroxylation. However, the question of biological oxidation of the unsubstituted ring remained a question for many years.

Ring reduction: Nocardia sp. Z1 was the first microbe reported to utilize pyridine as a sole carbon, nitrogen, and energy source (Houghton and Cain 1972). No hydroxyl-substituted metabolites were identified during pyridine degradation, suggesting the involvement of a reductive mechanism. *Brevibacterium* sp., *Corynebacterium* sp., *Bacillus* sp. 4, and *Streptomyces* sp. HJ02 were subsequently reported to degrade pyridine by ring reduction (Shukla 1973; Shukla and Kaul 1974; Watson and Cain 1975; Li et al. 2009). Based on radiolabeling studies and the use of mutant strains to examine pyridine metabolism by *Bacillus* sp. 4 and *Nocardia* sp. Z1, two different fission pathways were proposed (Watson and Cain 1975) resulting in the accumulation of either glutaric acid semialdehyde or succinic acid semialdehyde, respectively (Fig. 1.2). Different products have been shown to accumulate depending upon the bonds involved in ring fission. Cleavage between C-2 and C-3 resulted in the formation of succinic acid, whereas cleavage between C-1 and C-2 resulted in the formation of glutaric acid (Fig. 1.2). *Micrococcus luteus* was

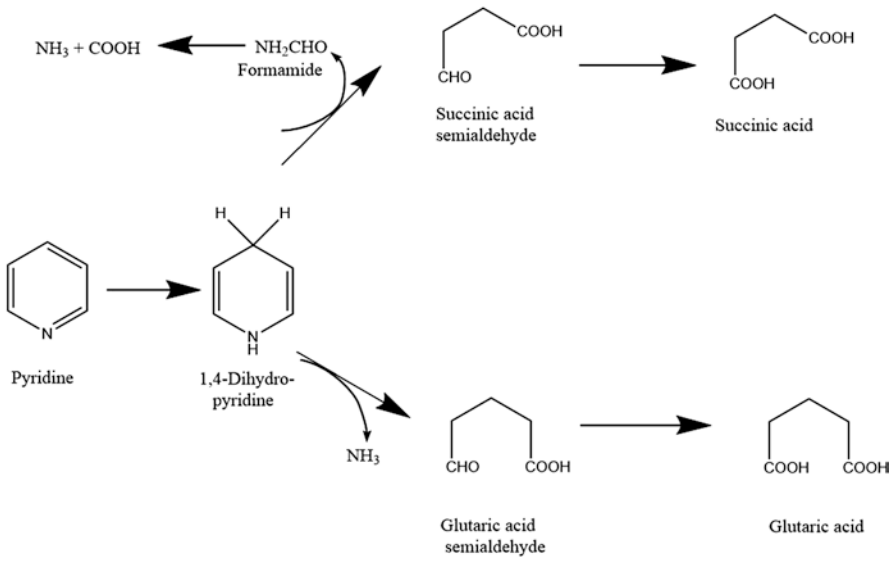

Fig. 1.2 Proposed mechanism for degradation of pyridine via hydration in *Bacillus* sp. and *Nocardia* sp. (Kaiser et al. 1996)

also reported to utilize pyridine via the pathway leading to succinate (Sims et al. 1986) as proposed by Watson and Cain (1975) for *Bacillus* sp. 4. However it was observed that in addition to pyridine degradation products, pyridine metabolism by *M. luteus* also resulted in the accumulation of riboflavin (Sims and O'Loughlin 1992). Although riboflavin was not an intermediate product of pyridine degradation, it was produced only during growth on pyridine, suggesting that pyridine may have played a role in regulating riboflavin production. Riboflavin overproduction has also been reported in hydrocarbon degradation (Sabry et al. 1989) and degradation of 2-methylpyridine (O'Loughlin et al. 1999; Shukla 1974).

The primary evidence for ring reduction prior to cleavage has been the liberation of reduced fission products. The inability to detect the initial dihydropyridine intermediates is not surprising, given their tendency to auto-oxidize to their pyridine analogs very quickly, sometimes in as little as 2 h (Baranda et al. 2006). In addition, tetrahydropyridines can be oxidized to their pyridine analogs by oxygenases (such as monoamine oxidase or MAO) without concomitant incorporation of oxygen into the product (Przedborski et al. 2001). Alternatively, the inability to detect cyclic intermediates may be explained by their absence, as it has recently been demonstrated that it is possible to open a pyridine ring without hydroxylation through direct fission of the C5-C6 bond (Perchat et al. 2018), although this has only been shown for N-methylnicotinate. However, some of the missing steps in a reductive mechanism have finally been demonstrated. Wang et al. (2018) have identified several reduced cyclic compounds produced during pyridine metabolism by *Paracoccus* sp. NJUST30, unequivocally demonstrating that the ring was initially reduced before it was hydroxylated. The hydroxylation step would only require a simple hydration of a double bond. That work, which will be discussed further below, revealed a simple "work around" to biologically produce hydroxylated metabolites from pyridine without the need to overcome pyridine's resistance to oxidation. Oxygenase activity was not evaluated by Wang et al. (2018), thus it is not clear whether simple hydration of a double bond or perhaps oxygenase activity was involved in hydroxylation. Alternatively, the absence of oxygenase activity may account for the authors' success in isolating the reduced cyclic metabolites, which otherwise may have converted to pyridine analogs, as has been shown with dihydropyridines (Baranda et al. 2006).

The *Paracoccus* sp. isolated from a sequencing batch reactor by Wang et al. (2018) was able to degrade pyridine at relatively high concentrations (500 mgL^{-1}) within roughly 1 week. Numerous metabolites were isolated that provide insight into possible variations of a reductive pathway for pyridine degradation, leading the authors to propose three possible arrangements of the metabolites detected, each beginning with a hydroxylated dihydropyridine derivative. Once aromaticity was lost due to reduction, the ring would have been susceptible to a wide variety of common catabolic reactions. Other metabolites reported in Wang et al. (2018) were consistent with alternating dehydrogenation and hydration steps, ubiquitous in hydrocarbon degradation. Fully reduced piperidin-2-ol was observed, as was succinate semialdehyde, the latter of which has been reported in other studies in which C2-C3 ring cleavage occurred. A reduced form of glutamate (4-formylamino-

butyric acid) was reported as well. Glutamate is converted to succinate via succinate semialdehyde in the gamma-aminobutyrate (GABA) shunt in bacteria. Processing pyridine metabolites by recruitment of such ubiquitous pathways likely reduces the number of novel mechanisms required for the organism to degrade pyridine.

Ring hydroxylation: The resistance of pyridine to hydroxylation is predicted by its chemistry, and early studies of pyridine biodegradation did not show evidence of formation of hydroxypyridine intermediates (Shukla and Kaul 1974, 1975, 1986; Sims et al. 1986; Watson and Cain 1975). However, since our 1989 review, the degradation of pyridine via ring hydroxylation has been reported for *Rhodococcus opacus* (VKM Ac-1333D) (Zefirov et al. 1994), *Arthrobacter crystallopoietes* (VKM Ac-1334D) (Zefirov et al. 1994), and *Arthrobacter* sp. KM-4 (Khasaeva et al. 2011). Zefirov et al. (1994) was the first to propose the degradation of pyridine via hydroxylation by *R. opacus* and *A. crystallopoietes*. Hydroxylation products 2-hydroxypyridine and 2,6-dihydroxypyridine were detected in the media containing pyridine with *R. opacus*, whereas 3-hydroxypyridine, 2,3-dihydroxypyridine, and 2,3,6-trihydroxypyridine were identified with *A. crystallopoietes* (Fig. 1.3). Catabolism of pyridine was proposed by hydroxylation at positions 2, 3, and 6 followed by C_2-C_3 bond cleavage resulting in the formation of N-formamide followed by 2,5-pyrroldione. This metabolite is finally reduced to succinate semialdehyde. A similar pathway involving initial hydroxylation to 2-hydroxypyridine, followed by hydroxylation to 2,3-dihydroxypyridine and ultimately leading to succinate semialdehyde, was proposed for pyridine metabolism by *Arthrobacter* sp. KM-4 (Khasaeva et al. 2011).

The ring hydroxylation steps in pyridine degradation pathways have been proposed based on the hydroxylated intermediates detected, but the enzymes involved

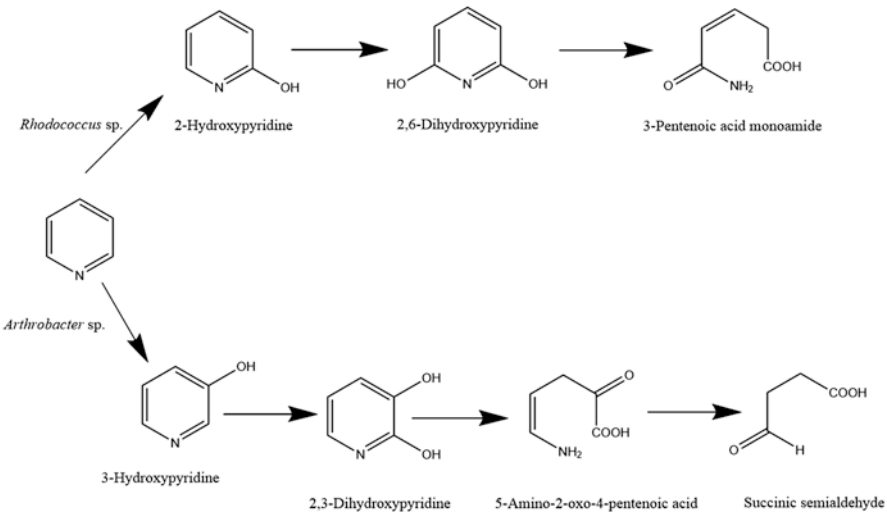

Fig. 1.3 Proposed pathways for the degradation of pyridine via hydroxylation by *R. opacus* and *A. crystallopoietes*. (After Zefirov et al. 1994)

in catalysis have not been identified as yet; however, the involvement of phenol hydroxylase has been suggested. A *Rhodococcus* sp. with the ability to utilize pyridine as the sole carbon and nitrogen source with an increased ability to utilize pyridine in the presence of phenol was isolated by Sun et al. (2011). In addition to pyridine and phenol, it also has the ability to reduce chromium (VI) simultaneously. It was reported that the phenol hydroxylase gene was induced in the presence of pyridine as a nitrogen source and the addition of pyridine with phenol induced increased expression of phenol hydroxylase. Owing to the structural similarity of phenol with pyridine, increased expression of the hydroxylase gene, and the identification of hydroxylated pyridine intermediates, it was proposed that phenol hydroxylase catalyzes the hydroxylation of pyridine leading to metabolites similar to those reported by Zefirov et al. (1994) for pyridine degradation by *R. opacus*. However, the hydroxylation of pyridine by *Diaphorobacter* sp. J5-51, *Acinetobacter* sp. SJ-15, *Acinetobacter* sp. SJ-16, *Acidovorax* sp. J5-66, and *Corynebacterium* sp. JOR-20 resulted in the accumulation of 1-hydroxypyridinium, and no growth was observed (Sun et al. 2014), suggesting that this reaction is a metabolic dead end. Indeed, heterologous expression of the phenol hydroxylase gene in a non-pyridine-degrading *Pseudomonas* sp. CO-44 resulted in the detection of metabolites observed during pyridine metabolism in *Diaphorobacter* sp. J5-51, but the metabolite accumulated was not utilized further.

Pyridine degraders may possess multiple mechanisms to produce a given metabolite within a single organism. Two initial monooxygenase reactions were described to compete for reductant during pyridine degradation via an oxidative mechanism. The first monooxygenase, which formed 2-hydroxypyridine, was observed to preferentially utilize available reductant. Competition continued even after 2-hydroxypyridine concentration exceeded that of pyridine (Yang et al. 2018). Ring hydroxylation and interactions between oxygenases and pyridine rings should be a rewarding areas for future research, as such interactions have recently been shown capable of producing unexpected results. For example, oxidation of tetrahydropyridines (Przedborski et al. 2001) as well as direct cleavage of a pyridine ring in the alkaloid trigonelline (Perchat et al. 2018) by oxygenases without the incorporation of a hydroxyl group has now been demonstrated.

1.6 Aerobic Biodegradation of Hydroxypyridines/Pyridones

As discussed above, hydroxypyridines have been identified as intermediates in the degradation of pyridine by several bacteria (Khasaeva et al. 2011; Zefirov et al. 1994). However, many microorganisms not known to degrade pyridine have been shown to degrade monohydroxypyridines (or their corresponding pyridone tautomer) including members of the genera *Achromobacter* (Cain et al. 1974), *Agrobacterium* (Watson et al. 1974a), *Arthrobacter* (O'Loughlin et al. 1999; Kolenbrander et al. 1976; Gasparaviciute et al. 2006), *Bacillus* (Sharma et al. 1984), *Burkholderia* (Stankeviciute et al. 2016), *Pseudomonas* (Zefirov et al. 1993), and

others. Most proposed 2-hydroxypyridine degradation pathways begin with hydroxylation to 2,5-dihydroxypyridine, followed by maleamic acid, maleic acid, and fumaric acid formation (i.e., the maleamate pathway) as reported for *Achromobacter* sp. G2 (Cain et al. 1974), *Bacillus brevis* (Sharma et al. 1984), *Burkholderia* sp. MAK1 (Stankeviciute et al. 2016), and *Nocardia* sp. (in which case 2,3,6-trihydroxypyridine is a purported intermediate between 2,5,-dihydroxypyridine and maleamic acid) (Shukla and Kaul 1986) (Fig. 1.4). Stankevičiūtė et al. (2016) reported the presence of an inducible 2-hydroxypyridine 5-monooxygenase enzyme in *Burkholderia* sp. MAK1 responsible for converting 2-hydroxypyridine to 2,5-dihydroxypyridine. This monooxygenase is a soluble di-iron monooxygenase encoded by a five-gene cluster (*hpdA, hpdB, hpdC, hpdD, hpdE*) (Petkevicius et al. 2018). 2,5-Dihydroxypyridine is converted by *Burkholderia* sp. MAK1 to N-formylmaleamic acid which is further degraded to fumaric acid via the maleamate pathway (Petkevicius et al. 2018) (Fig. 1.4), analogous to the degradation of 2,5-dihydroxypyridine by *Pseudomonas putida* KT2440, *P. putida* S16, and *Ochrobactrum* sp. SJY1 (Jiménez et al. 2008; Tang et al. 2012; Yu et al. 2015).

Not all 2-hydroxypyridine biodegradation pathways proceed through 2,5-dihydroxypyridine. Conversion of 2-hydroxypyridine to *cis*-5,6-dihydro-5,6-

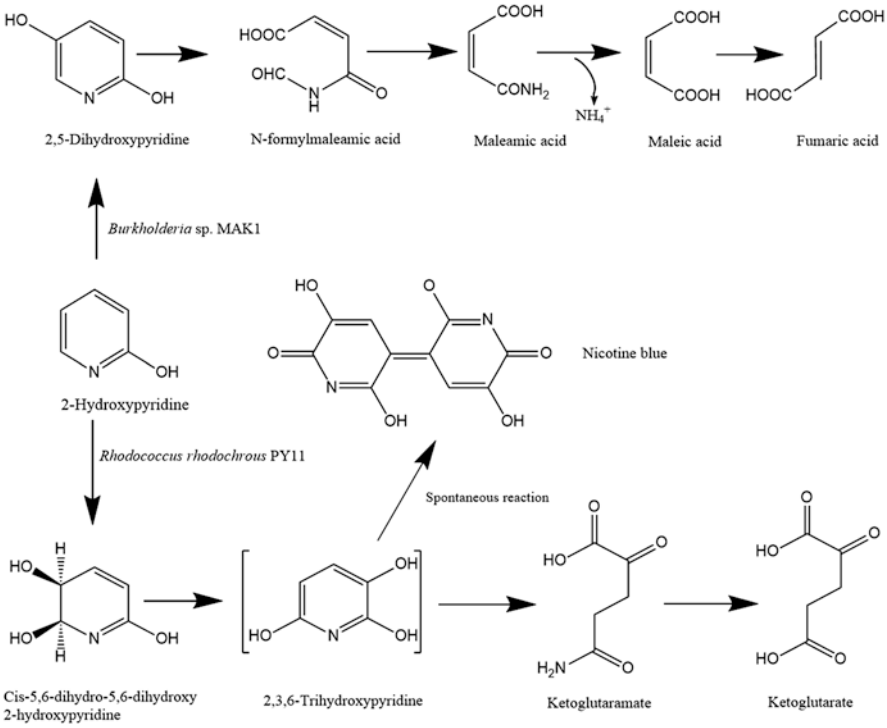

Fig. 1.4 Proposed pathway for the degradation of 2-hydroxypyridine by *Burkholderia* sp. MAK1 (Petkevicius et al. 2018) and *R. rhodochrous* PY11. (Vaitekunas et al. 2016)

dihydroxy-2-hydroxypyridine catalyzed by HpoBCDF, a four-component dioxygenase, is the first reaction of 2-hydroxypyridine degradation in *Rhodococcus rhodochrous* PY11 (Vaitekunas et al. 2016). The product of the first reaction is converted to 2,3,6-trihydroxypyridine by 2-pyridone-5,6-dihydro-cis-5,6-diol dehydrogenase (HpoE). The 2,3,6-trihydroxypyridine ring is opened by a hydrolase (HpoH) to form 2-ketoglutaramate which is subsequently transformed to α-ketoglutarate by 2-ketoglutaramate amidase (HpoI). *hpoH* encodes for the hydrolase protein catalyzing the ring opening step, and *hpoI* encodes amidase catalyzing the removal of amide group from 2-ketoglutaramate.

Although several proposed pyridine/2-hydroxypyridine pathways have included 2,3,6-trihydroxypyridine as an intermediate (Shukla and Kaul 1986; Vaitekunas et al. 2016; Zefirov et al. 1994), it is unstable under oxic conditions and has not been directly observed as an intermediate in 2-hydroxypyridine degradation; rather its formation has been inferred. The formation of a blue pigment is often reported during 2-hydroxypyridine degradation (Shukla and Kaul 1986; Vaitekunas et al. 2016), particularly among *Arthrobacter* spp. (Ensign and Rittenberg 1963; Kolenbrander et al. 1976; Kolenbrander and Weinberger 1977; O'Loughlin et al. 1999; Semenaite et al. 2003; Gasparaviciute et al. 2006; Stanislauskiene et al. 2012). The blue pigment produced during 2-hydroxypyridine degradation by *A. crystallopoietes* (Ensign and Rittenberg 1963) was identified as 4,5,4′,5′-tetrahydroxy-3,3′-diazadiphenoquinone-(2,2′)(Kuhn et al. 1965), also known as nicotine blue, and has been confirmed as the blue pigment produced during 2-hydroxypyridine degradation by *Arthrobacter pyridinolis* (Kolenbrander et al. 1976), *Arthrobacter viridescens* (Kolenbrander and Weinberger 1977), and a *Nocardia* sp. (Shukla and Kaul 1986). Since the spontaneous oxidation of 2,3,6-trihydroxypyridine in air results in the formation of nicotine blue (Holmes et al. 1972), the presence of a blue pigment during pyridine/2-hydroxypyridine degradation is often cited as evidence for the formation of 2,3,6-trihydroxypyridine (O'Loughlin et al. 1999; Semenaite et al. 2003; Shukla and Kaul 1986; Vaitekunas et al. 2016; Zefirov et al. 1994). Further support for nicotine blue serving as a proxy for 2,3,6-trihydroxypyridine formation is provided by enzymatic studies. Nicotine blue was the observed product of 2,3,6-trihydroxypyridine by 2-pyridone-5,6-dihydro-cis-5,6-diol dehydrogenase (HpoE) in the 2-hydroxypyridine degradation pathway proposed for *Rhodococcus rhodochrous* PY11 that requires 2,3,6-trihydroxypyridine as in intermediate (Vaitekunas et al. 2016). Moreover, the reaction of 2,6-dihydroxypyridine oxidase from *Arthrobacter oxydans* with 2,6-dihydroxypyridine under low oxygen conditions resulted in the transient accumulation of a product with UV-Vis spectral properties similar to 2,3,6-trihydroxypyridine, followed by accumulation of nicotine blue (Holmes et al. 1972).

Compared to 2-hydroxypyridine, the microbial degradation of 3-hydroxypyridine and 4-hydroxypyridine is less well characterized. *Rhodococcus* sp. Chr-9 can grow with 3-hydroxypyridine as a sole carbon source, but metabolite production was not investigated as the focus of the study was on pyridine degradation (Sun et al. 2011). Zefirov et al. (1993) identified 2,3-dihydroxypyridine, 3,4-dihydroxypyridine, 3-hydroxypyridine-N-oxide, and 1,2-dihyro-2,3-dihydroxypyridine and

2,3-dihydroxypyridine and 3,4-dihydroxypyridine as products of 3-hydroxypyridine transformation by *Pseudomonas fluorescens* PfE1 and *R. opacus*, respectively. Similarly, pyridine-degrading Nocardia sp. Z1 was able to convert 3-hydroxypyridine to 2,3- and 3,4-dihydroxypyridine, which were not metabolized further (Houghton and Cain 1972). *Achromobacter* spp. 7 N and 2 L were isolated by enrichment with 3-hydroxypyridine as the principal carbon source (Houghton and Cain 1972). Both strains were able to convert 3-hydroxypyridine to 2,5-dihydroxypyridine, with particularly high accumulation of this product by strain 7 N. Further study of strain 2 L determined that 2,5-dihydroxypyridine was degraded by the maleamate pathway (Fig. 1.4) (Cain et al. 1974).

Watson and Cain isolated a 4-hydroxypyridine-degrading bacterium, *Agrobacterium* sp. 35S, that transforms 4-hydroxypyridine to 3,4-dihydroxypyridine by means of 4-hydroxypyridine-3-hydrolase (Watson et al. 1974a). 3,4-Dihydroxypyridine was transformed to 3-formiminopyruvate (with 3(N-formyl)-formiminopyruvate as a purported intermediate), followed by 3-formylpyruvate and finally pyruvate and formate (Watson et al. 1974b). *Arthrobacter* sp. IN13 is able to grow on both 2- and 4-hydroxypyridine as sole carbon sources; however no intermediates for 4-hydroxypyridine degradation have been identified (Gasparaviciute et al. 2006).

1.7 Aerobic Biodegradation of Alkylpyridines

The biodegradation of alkylpyridines has been reported for a range of microorganisms including *Bacillus* sp. (Reddy et al. 2009a), *Pseudomonas* sp. (Padoley et al. 2009), *Nocardia* sp. (Padoley et al. 2009), *Gordonia* sp. (Stobdan et al. 2008), *Arthrobacter* spp. (O'Loughlin et al. 1999; Shukla 1974; Khasaeva et al. 2011), *Pseudonocardia* sp. (Lee et al. 2006), and *Saccharomyces cerevisiae* (Gulyamova et al. 2006). Alpha-substituted alkylpyridines have been the most extensively studied. An *Arthrobacter* sp. isolated by enrichment on 2-methylpyridine by Shukla (1974) was able to use both 2-methylpyridine and 2-ethylpyridine as sole carbon and nitrogen sources. No aromatic intermediates were observed during 2-methylpyridine degradation, but based on metabolite analysis and differential substrate utilization, it was proposed that 2-methylpyridine degradation was not initiated either via methyl oxidation or by hydroxylation of the pyridine ring. Several tentative 2-methylpyridine pathways were proposed, all of which converged on the formation on succinate semialdehyde. Degradation of both 2-methylpyridine and 2-ethylpyridine by a different *Arthrobacter* sp. (strain R1) was reported by O'Loughlin et al. (1999). Unlike the *Arthrobacter* sp. isolate by Shukla, R1 could also degrade 2-hydroxypyridine. Both *Arthrobacter* spp. produced riboflavin during 2-methylpyridine degradation, as did *M. luteus* during pyridine degradation (Sims and O'Loughlin 1992).

Khasaeva et al. (2011) proposed two pathways for the degradation of 2-methylpyridine by *Arthrobacter* sp. KM-4, both of which ultimately converge

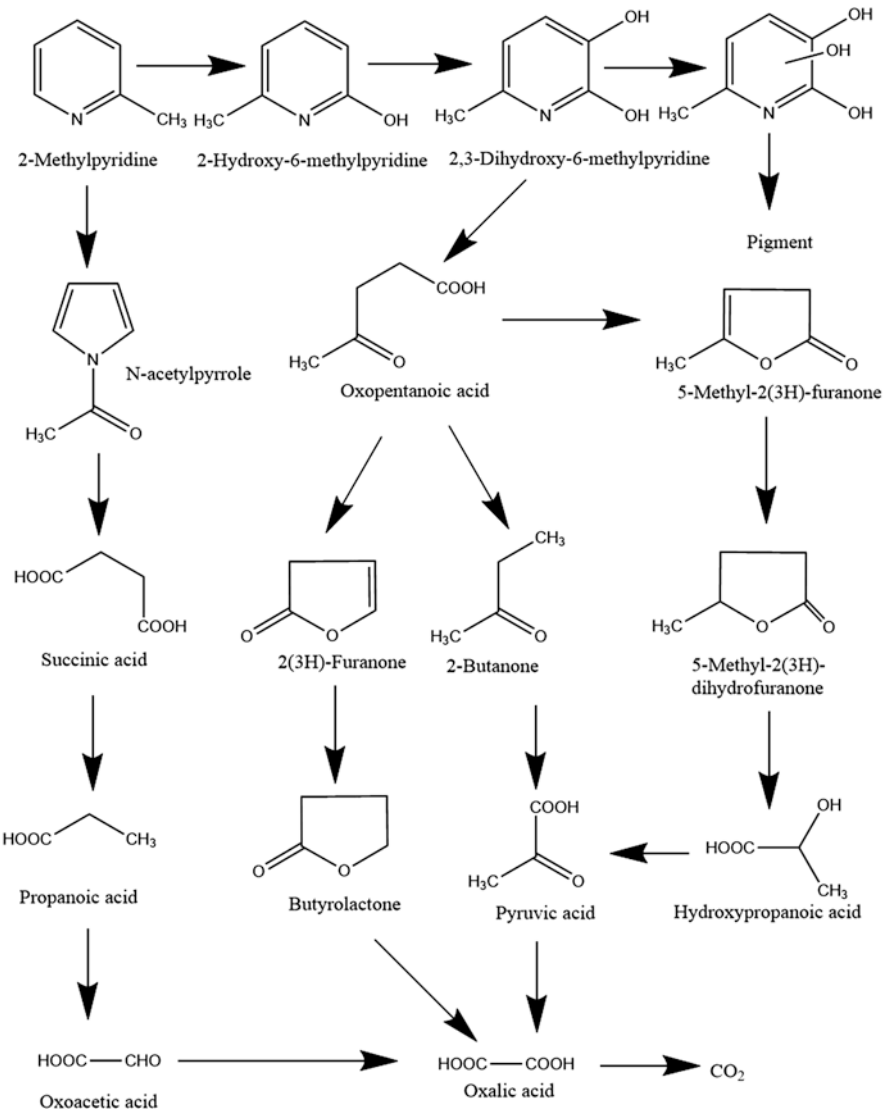

Fig. 1.5 Proposed pathway for 2-methylpyridine degradation by *Arthrobacter* sp. KM-4

with the formation of oxalic acid (Fig. 1.5). The first pathway involved formation of acetylpyrrole by means of a putative oxidative opening of the pyridine ring between C-2 and C-3 followed by cyclization to form a pyrrole ring. The second pathway involved double hydroxylation to form 2,3-dihydroxy-6-methylpyridine followed by ring cleavage between the hydroxyl groups and formation of 4-oxopentanoic acid.

2-Methylpyridine was used as the sole carbon and nitrogen source by *Bacillus cereus* GMHS (Reddy et al. 2009a). The degradation of 2-methylpyridine by *B. cereus* GMHS was initiated by hydroxylation of the methyl group resulting in 2-pyridinemethanol (Reddy et al. 2008). Reddy et al. (2009b) identified an 11 kb plasmid containing 2-methylpyridine degradation genes; elimination of the plasmid resulted in loss of 2-methylpyridine catabolism. Homology modeling and binding studies based on toluene dioxygenase from *P. putida* indicated that 2-methylpyridine was the preferred substrate after toluene, suggesting the involvement of toluene dioxygenase in 2-methylpyridine degradation by *B. cereus* GMHS (Reddy et al. 2008).

The degradation of other alkylpyridines has been less well studied than 2-methylpyridine. Although not degradation in the conventional sense, the yeast *S. cerevisiae* 913a-1 transforms 3-methylpyridine into nicotinic acid (pyridine-3-carboxylic acid) (Gulyamova et al. 2006). *Pseudomonas pseudoalcaligenes* strain KPN and a *Nocardia* sp. can use 3-methylpyridine as a sole carbon and nitrogen source (Padoley et al. 2009). Both 3-methyl- and 3-ethylpyridine can be used by *Gordonia nitida* LE31 as sole carbon and nitrogen sources (Yoon et al. 2000b). No cyclic intermediates were detected during 3-methyl- or 3-ethylpyridine degradation by LE31; however, the induction of levulinic acid degradation and the expression of levulinic aldehyde dehydrogenase activity in 3-methyl- or 3-ethylpyridine grown cells are consistent with C-2–C-3 ring cleavage (Fig. 1.6) (Lee et al. 2001). 4-Methylpyridine was used as a sole carbon and nitrogen source by *Gordonia terrae* strain IIPN1 (Stobdan et al. 2008) and *Arthrobacter* sp. strain KM-4 (Khasaeva et al. 2011). Transient accumulation of 2-hydroxy-4-methylpyridine and 2-hydroxy-4-ethylpyridine was observed during growth of *Pseudonocardia* sp. strain M43 on 4-methyl- and 4-ethylpyridine as sole carbon and nitrogen sources, respectively (Lee et al. 2006). Feng et al. (1994) reported that a mixed culture obtained from a soil enrichment was able to degrade 2-, 3-, and 4-ethylpyridine; 2-hydroxy-6-ethylpyridine and 2-hydroxy-4-ethylpyridine/4-ethyl-2-piperidinone were identified as intermediates in the degradation of 2-ethyl- and 4-ethylpyridine, respectively. Among di- and trimethylpyridines, 3,4-dimethylpyridine is degraded by *Pseudonocardia* sp. strain M43 (Lee et al. 2006); 2,6-dimethylpyridine is degraded by *P. pseudoalcaligenes* strain KPN and a *Nocardia* sp. (Padoley et al. 2009) and *Arthrobacter* sp. strain KM-4 (Khasaeva et al. 2011); and an *Arthrobacter* sp. degrades 2,4-dimethyl- and 2,4,6-trimethylpyridine (Shukla 1975).

1.8 Anaerobic Biodegradation of Pyridines

As with aerobic biodegradation studies, early work on anaerobic degradation of the pyridine ring focused on nicotinic acid and its analogs and metabolites. *Clostridium* sp. (Harary 1957a, b) and *Clostridium barkeri* (Stadtman et al. 1972) produce 6-hydroxynicotinate, acetate, propionate, ammonium, and CO_2 from nicotinic acid. *C. barkeri* was shown to have a nicotinic acid hydrolase that produced

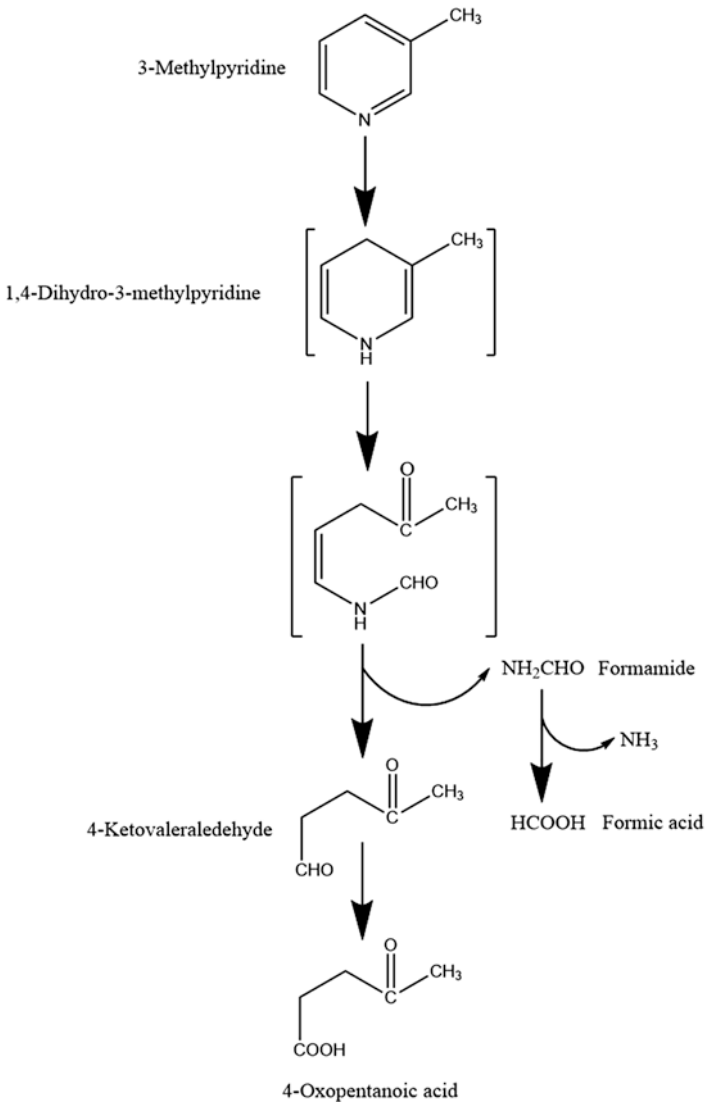

Fig. 1.6 Proposed pathway for the degradation of 3-methylpyridine by *Gordonia nitidia* LE31 (Lee et al. 2001)

6-hydroxynicotinate using oxygen derived from water. Nicotinic acid was also mineralized by *Desulfococcus niacini* under sulfate-reducing conditions (Imhoff-Stuckle and Pfennig 1983).

The occurrence of pyridine and pyridine derivatives in the subsurface near synfuel plants raised the question of the potential for their anaerobic biodegradation. Pyridine degradation has since been evaluated under fermentative, nitrate-reducing,

iron-reducing, sulfate-reducing, and methanogenic conditions, with highly variable results depending on source materials. The bulk of information available for anaerobic degradation of the unsubstituted pyridine ring has been published since 1989. In one of the earliest such studies, pyridine degraded slowly (requiring 8 months for depletion) in sulfate-reducing or methanogenic aquifer materials, whereas nicotinic acid was degraded in approximately 1 month under either redox regime (Kuhn and Suflita 1989). In that study, mono-methylpyridines exhibited variability among redox regimes as a function of the position of the methyl group. In freshwater sediments (Liu et al. 1994), pyridine degraded more rapidly under nitrate-reducing conditions (1 month) versus sulfate-reducing or methanogenic conditions (3 months). In aquifer materials from a 2-methylpyridine contaminated site, pyridine exhibited degradation under nitrate-reducing, sulfate-reducing, and methanogenic conditions (Kaiser and Bollag 1991; Kaiser and Bollag 1992; Kuhn and Suflita 1989; Bak and Widdel 1986; Ronen and Bollag 1992).

Azoarcus evansii strain pF6 degraded pyridine under both aerobic and nitrate-reducing conditions via a pathway that did not involve hydroxylated intermediates (Rhee et al. 1997). Rapid degradation of pyridine (under 60 h) was reported for acclimated sludge materials derived from coke plant wastewater (Li et al. 2001). A hydroxylated intermediate (4-methyl-2-(1H)- pyridone) was formed from 4-methylpyridine under sulfate-reducing conditions (Kaiser et al. 1993). Partial transformation of 3-hydroxypyridine and complete transformation of 2- and 4-hydroxypyridine were observed in contaminated aquifer materials incubated under sulfate-reducing conditions for 3 months (Kaiser and Bollag 1992). Pyridine was found to be persistent in an anoxic estuarine sediment for nearly a year, whereas 2- and 3-hydroxypyridines were degraded in just over 2 weeks (Kuo and Liu 1996; Liu and Kuo 1997). In this same sediment, 4-hydroxypyridine was persistent (for over 6 months). In most cases, intermediates were not detected; however it was apparent that 2,3-dihydroxypyridine was formed during dissipation of 3-hydroxypyridine. Among the dihydropyridines, 2,3-, 2,5-, and 3,4-dihydroxypyridine were dissipated over a 4-month period.

Structure-biodegradability relationships among monosubstituted pyridines in sulfate-reducing sediments showed some similarities to previous reports for aerobic environments. For example, substitution with carboxyl or hydroxyl groups favored biodegradation, whereas chlorine groups slowed biodegradation (Liu et al. 1998). The authors also observed slower degradation of methylpyridines under anoxia.

The presence of electron acceptors may be necessary for pyridine degradation under anoxia. A two-component bioreactor system (aerobic/anaerobic) was examined for potential to remove pyridine (Shen et al. 2015). Pyridine degradation was enhanced in the anaerobic system, resulting in mineralization of both pyridine carbon and nitrogen. Under anoxia, nitrogen was released as ammonium, which when recycled in the aerobic bioreactor was oxidized to nitrate. Nitrate thus formed could be used as an electron acceptor to drive pyridine degradation in the anaerobic bioreactor. Both nitrate and pyridine inhibited degradation at high concentrations. Sediment samples taken across a salt gradient in the Tsengwen River were incubated with pyridine under iron-reducing or sulfate-reducing conditions (Liu and

Kuo 1997). Supplementing with electron acceptors (amorphous $Fe(OH)_3$, MnO_2, or sulfate) promoted pyridine degradation only in the freshwater samples. A denitrifying bacterium related to *Azoarcus* (isolated from industrial wastewater) was found to degrade pyridine under either aerobic or anaerobic conditions (Rhee et al. 1997). Since the organism possessed pyridine-induced glutarate-dialdehyde dehydrogenase and isocitratase activities, it was concluded that metabolism was likely through one of the previously demonstrated reductive pathways involving cleavage between the nitrogen heteroatom and the carbon at position two. Similarly, the lack of oxygenase involvement in atrazine metabolism allows the same organism to degrade atrazine both aerobically and anaerobically (Crawford et al. 1998).

1.9 Conclusion

In the past 30 years, significant advancements have been made in understanding microbial metabolism of simple pyridine derivatives. Considerably more is known of the behavior of these compounds in anaerobic environments, including evidence for biodegradation under nitrate-reducing, iron-reducing, sulfate-reducing, and methanogenic environments. Missing metabolites in the long-known reductive pathways for pyridine metabolism have been identified, and several studies have shown susceptibility of pyridine rings to oxidative degradation. The alkaloid trigonelline has even been shown to undergo ring fission by oxygenase attack without the introduction of an oxygen atom. Slow progress has been realized in the understanding of genes involved in pyridine degradation. Despite the advancements in the science of pyridine biodegradation, the routes for introduction of pyridine contaminants into the environment remain largely unchanged. Both natural and anthropogenic routes of introduction are well-established, with the latter being responsible for most of the occurrences of simple pyridines. The resurgence of energy extraction techniques associated with heterocyclic wastes ensures interest in the fate of pyridine derivatives will continue for some time.

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