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REVIEW

Enzymatic oligomerization and polymerization of arylamines: state of the art and perspectives

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Abstract The literature concerning the oxidative oligomerization and polymerization of various arylamines, e.g., aniline, substituted anilines, aminonaphthalene and its derivatives, catalyzed by oxidoreductases, such as laccases and peroxidases, in aqueous, organic, and mixed aqueous organic monophasic or biphasic media, is reviewed. An overview of template-free as well as template-assisted enzymatic syntheses of oligomers and polymers of arylamines is given. Special attention is paid to mechanistic aspects of these biocatalytic processes. Because of the nontoxicity of oxidoreductases and their high catalytic efficiency, as well as high selectivity of enzymatic oligomerizations/polymerizations under mild conditions—using mainly water as a solvent and often resulting in minimal byproduct formation—enzymatic oligomerizations and polymerizations of arylamines are environmentally friendly and significantly contribute to a "green" chemistry of conducting and redox-active oligomers and polymers. Current and potential future applications of enzymatic polymerization processes and enzymatically synthesized oligo/polyarylamines are discussed.

Keywords Arylamine · Enzyme · Oxidoreductase · Oxidation · Oligomer · Polymer

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Abbreviations

3-HAA	3-Hydroxyanthranilic acid
Ag	Silver
AOT	Sodium bis-(2-ethylhexyl)sulfosuccinate
$ArNH_2$	Arylamine
ARP	*Arthromyces ramosus* peroxidase
Au	Gold
CiP	*Coprinus cinereus* peroxidase
CNTs	Carbon nanotubes
CPO	Chloroperoxidase
CSA	Camphorsulfonic acid
CTAB	Cetyltrimethylammonium bromide
DAP	2,3-Diaminophenazine
DBSA	Dodecylbenzenesulfonic acid
DMF	*N,N*-dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPV	Differential pulse voltammetry
ELISA	Enzyme-linked immunosorbent assay
EtOH	Ethanol
FePOs	Iron phosphates
FrGO	Flower-like reduced graphene oxide
GOx	Glucose oxidase
HEPES	*N*-2-hydroxyethylpiperazine-*N*-2-ethane sulfonic acid
HIgG	Human immunoglobulin
H-Mn_2O_3	Mn_2O_3 nanoparticle-assembled hierarchical hollow spheres
H_2O_2	Hydrogen peroxide
HPI	Recombinant catalase-peroxidase
HRP	Horseradish peroxidase
i-PrOH	Isopropanol
LOD	Limit of detection
MeOH	Methanol

NPs	Nanoparticles
m-PDA	*m*-Phenylenediamine, 1,3-phenylenediamine
MWCNT(s)	Multiwalled carbon nanotube(s)
MWCNTs-COOH	Carboxylic acid-functionalized multiwalled carbon nanotubes
o-PDA	*o*-Phenylenediamine, 1,2-phenylenediamine
PAA	Poly(acrylic acid)
PADPA	*p*-Aminodiphenylamine, *N*-phenyl-*p*-phenylenediamine
PANI	Polyaniline
PDADMAC	Poly(diallyldimethylammonium chloride)
PNA	Peptide nucleic acid
p-PDA	*p*-Phenylenediamine, 1,4-phenylenediamine
PTMSPA	Poly(*N*-[3-(trimethoxy silyl)propyl]aniline
PTP	Palm tree peroxidase
p-TSA	*p*-Toluenesulfonic acid
PWE	Paper working electrode
QDs	Quantum dots
rGO	Reduced graphene oxide
RNA	Ribonucleic acid
SBP	Soybean peroxidase
SDBS	Sodium dodecylbenzenesulfonate
SDS	Sodium dodecyl sulfate
SPCE	Screen-printed carbon electrode
SPS	Sulfonated polystyrene, poly (sodium 4-styrenesulfonate)
SWCNTs	Single-wall carbon nanotubes
THF	Tetrahydrofuran
TvL	*Trametes versicolor* laccase

Introduction

In this review, we present and list oxidative coupling reactions of different types of arylamines ($ArNH_2$) catalyzed by oxidoreductase enzymes to form products of oligomeric or polymeric nature. In particular, work conducted in this field in the last 10 years is summarized. Arylamines consist of one or more benzene or other aromatic rings (carbocyclic or heterocyclic) with at least one amino group (primary, secondary, or tertiary) directly attached to the aromatic ring. Aniline (*I*, Fig. 1) represents the simplest arylamine. More complex arylamines are formed by adding one or more functional groups to aniline to create a wide array of substituted anilines, or by substituting aromatic hydrocarbons, such as naphthalene, with an amino group and one or more additional functional groups. Thus, the group comprising arylamines is very large. The molecular structures of the arylamines discussed in this review are shown in Figs. 1, 2, 3, 4.

The following structures can be formed upon the oxidation of arylamines, either as one single product or as a mixture of different products: branched or linear oligoarylamines (N–N, N–C, or C–C coupled) such as dimers, cyclic diarylamines (e.g., phenazines), trimers and tetramers, and branched or linear polyarylamines (Ding et al. 2010; Feng et al. 2013; Kříž et al. 2011; Stejskal et al. 2010; Stejskal and Trchová 2012; Ćirić-Marjanović 2013b; Janošević et al. 2013; Planes et al. 2010; Zhao et al. 2013). Furthermore, the formation of oxygen-containing products (arylhydroxylamine, nitrosoarene, nitroarene, azoxyarene, amino-phenols, benzoquinones, and oligomers containing such structures) is also possible (Ćirić-Marjanović 2013b; Kříž et al. 2011; Surwade et al. 2009; Zhou et al. 2015). The main product as well as the product distribution after the reaction is completed are very dependent on the reaction conditions: this includes such characteristics like the type of oxidant, the concentration of the oxidant, the concentration of the arylamine, the ratio between the oxidant and the arylamine, the solvent type, the presence of co-solvent, the ratio between the solvent and the co-solvent, and the presence and concentration of reaction-controlling templates (Ćirić-Marjanović 2013b; Rakić et al. 2015; Walde and Guo 2011). The latter point can crucially influence the course of the reaction, as will be shown later in this review. This is because the oxidation of arylamines is quite a complex process, which leads to the formation of a highly reactive arylamine radical as the first intermediate in many cases. The formation of other reactive species, e.g., arylnitrenium cations, is also possible (Marjanović et al. 2011; Ćirić-Marjanović 2013b). Templates can suppress certain unwanted reaction pathways of the formed radicals and/or other reactive species, leading to the formation of the desired product in high yield, e.g., the formation of conducting polyaniline (PANI) emeraldine salt in the case of the template-assisted enzymatic oxidation of aniline (Samuelson et al. 1998). Therefore, during the course of this review, we will show that depending on the conditions used by the investigators, the enzymatic oxidation of one type of arylamine molecule can either result in its oligomer or polymer. Often, however, a detailed and convincing analysis of the chemical structure of the obtained product(s) is missing. This is due to the fact that the products, particularly if they are polymeric (e.g., PANI), have a low solubility in many organic solvents. Nevertheless, we hope that this review is useful as an overview of the state of the art in this area of research, in particular for those who wish to enter the field. Furthermore, we hope to provide enough background in order for the reader to understand the current challenges, both with respect to a basic understanding of the reaction mechanisms and potential applications.

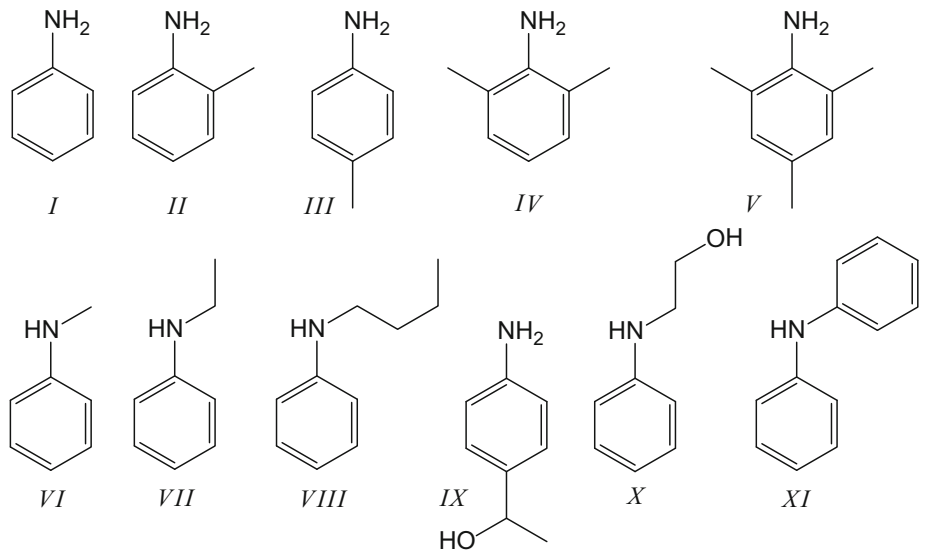

Fig. 1 Aniline (*I*); *C*-alkyl-substituted anilines: 2-methylaniline (*o*-toluidine, *II*), 4-methylaniline (*p*-toluidine, *III*), 2,6-dimethylaniline (2,6-xylidine, *IV*), 2,4,6-trimethylaniline (mesidine, *V*); *N*-alkyl-substituted anilines: *N*-methylaniline (*VI*), *N*-ethylaniline (*VII*), *N*-butylaniline (*VIII*); *N*-hydroxyalkyl-substituted anilines: 4-(1-hydroxyethyl)aniline (4-aminophenyl-methylcarbinol, *IX*), *N*-(2-hydroxyethyl)aniline (*N*-phenylethanolamine, *X*); *N*-aryl-substituted anilines: *N*-phenylaniline (diphenylamine, *XI*)

Taking into account the well-known fact that metals, especially transition metal cations, can efficiently catalyze the oxidative oligomerization and polymerization of arylamines such as aniline with hydrogen peroxide (H_2O_2) or O_2 (Della Pina et al. 2011), it is not surprising that a lot of effort has been made during the past several decades in the field of the oxidative coupling of arylamines with H_2O_2 or O_2 catalyzed by oxidoreductase metalloenzymes (Bouldin et al. 2010; Cruz-Silva et al. 2011; Gross et al. 2001; Hollmann and Arends 2012; Kadokawa and Kobayashi 2010; Kobayashi 1999; Kobayashi et al. 1995, 2001; Kobayashi and Makino 2009; Ochoteco and Mecerreyes 2010; Otrokhov et al. 2013; Shoda et al. 2016; Walde and Guo 2011; Xu et al. 2006). Such enzymes contain one or more transition metal cations in their active center. The first reference to the enzymatic oxidation of aniline can be traced back to the nineteenth century, when Bourquelot (1896) dissolved aniline in dilute acetic acid, added an infusion of *Russula delica* mushroom (champignons), and obtained a magenta-like substance upon passing an air current through the liquid. It seems that tyrosinase was the enzyme used in this case. About 40 years later, the formation of several oligomers of aniline upon its oxidation with H_2O_2 in the presence of peroxidase from horseradish (HRP) or turnips in dilute aqueous acetic acid at pH 4.5 was reported by Mann and Saunders (1935). The first reports on the enzymatic oxidation of substituted anilines appeared in the first half of twentieth century, e.g., the oxidative dimerization of *o*-phenylenediamine (*o*-PDA) (Chodat 1925) and mesidine (2,4,6-trimethylaniline) (Chapman and Saunders 1941) by peroxidase/H_2O_2, the oxidative oligomerization of *p*-toluidine (Saunders and Mann 1940) by peroxidase/H_2O_2, and the oxidative degradation of *p*-aminobenzoic acid and *o*-aminobenzoic acid (anthranilic acid) by specifically adapted enzymes of a soil bacillus/O_2 (Mirick 1943). Since then, a lot of research work was devoted to various types of enzymatic oxidations of substituted anilines including both the N/C-oxidation and coupling reactions. Corbett et al. (1978, 1979, 1980), for example, reported *N*-oxidation and ring halogenation of 4-chloroaniline using chloroperoxidase (CPO), H_2O_2, and KCl or KBr. Co-oligomerization of arylamines with phenols attracted some attention in the 1980s and 1990s, e.g., cross-linkage between halogen- or alkyl-substituted anilines and phenolic humus constituents was reported by Bollag et al. (1983), while enzymatic coupling of chloroanilines with syringic acid, vanillic acid and protocatechuic acid was reported by Tatsumi et al. (1994). Pioneering publications in the field of kinetic and/or mechanistic studies of the enzymatic oxidation of substituted anilines in the presence of various oxidoreductases were published from the 1970s to the 1990s by Claiborne and Fridovich (1979a, b), Josephy et al. (1982, 1983), Fischer et al. (1986), Doerge and Corbett (1991), Xu (1996), and Regelsberger et al. (1999).

The first successful enzymatic synthesis of a PANI-like product in its conducting green emeraldine salt form was achieved by Mann and Saunders (1935) via the oxidative polymerization of the aniline dimer 4-aminodiphenylamine (PADPA) or phenylhydroxylamine with HRP/H_2O_2 in an acetic acid/water mixture. However, it is not sure whether the product obtained was of polymeric and conducting

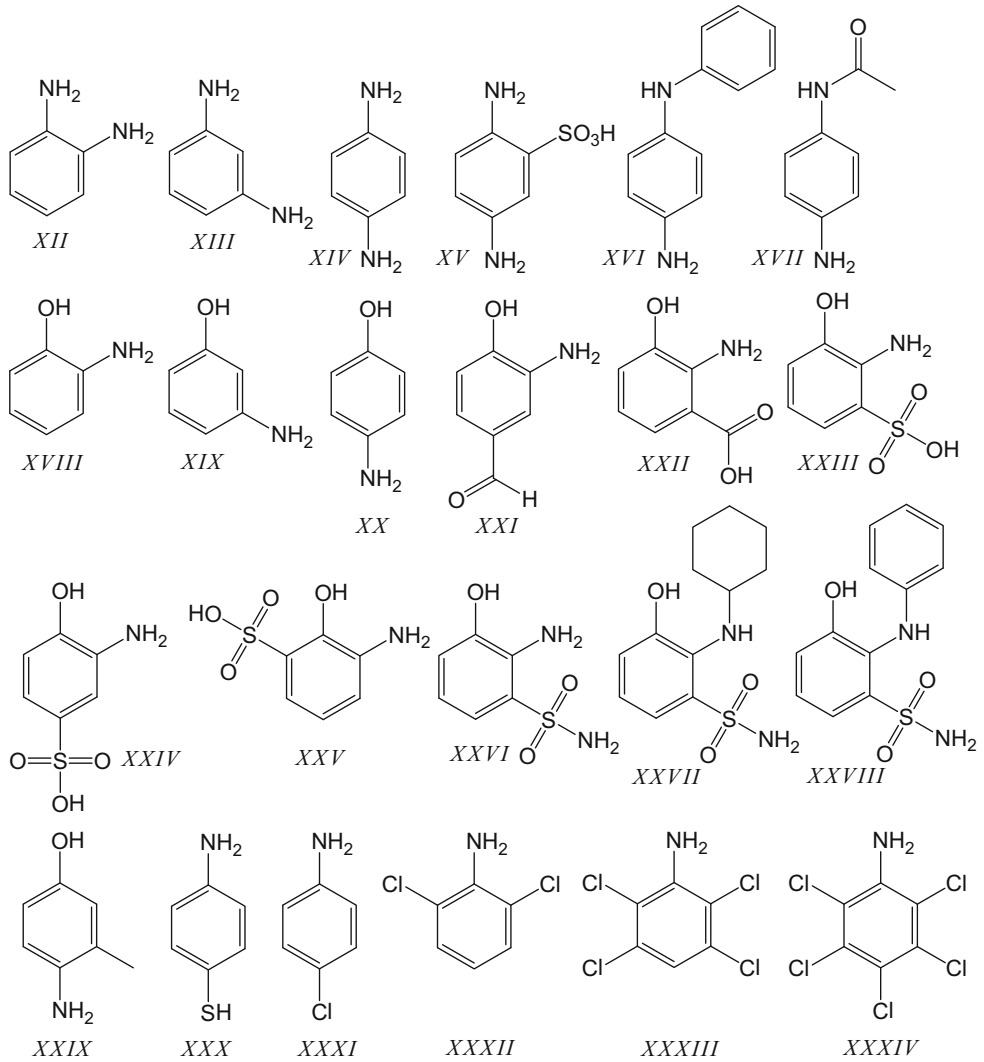

Fig. 2 Phenylenediamines: benzene-1,2-diamine (1,2-phenylenediamine, *o*-phenylenediamine, *o*-PDA, *XII*), benzene-1,3-diamine (1,3-phenylenediamine, *m*-phenylenediamine, *m*-PDA, *XIII*), benzene-1,4-diamine (1,4-phenylenediamine, *p*-phenylenediamine, *p*-PDA, *XIV*), 2,5-diaminobenzenesulfonic acid (1,4-phenylenediamine-2-sulfonic acid, *XV*), 4-*N*-phenylbenzene-1,4-diamine (*N*-phenyl-1,4-phenylenediamine, *p*-aminodiphenylamine, PADPA, *XVI*), 4-*N*-acetylbenzene-1,4-diamine (*N*-acetyl-1,4-phenylenediamine, *XVII*); aminophenols and aminothiophenols: 2-aminophenol (*o*-aminophenol, *XVIII*), 3-aminophenol (*m*-aminophenol, *XIX*), 4-aminophenol (*p*-aminophenol, *XX*), 3-amino-4-hydroxybenzaldehyde (*XXI*), 2-amino-3-hydroxybenzoic acid (3-hydroxyanthranilic acid, 3-HAA, *XXII*), 2-amino-3-hydroxybenzenesulfonic acid (3-hydroxyorthanilic acid, *XXIII*), 3-amino-4-hydroxybenzenesulfonic acid (*XXIV*), 3-amino-2-hydroxybenzenesulfonic acid (2-hydroxymetanilic acid, *XXV*), 2-amino-3-hydroxybenzenesulfonamide (*XXVI*), *N*-cyclohexyl-2-amino-3-hydroxybenzenesulfonamide (*XXVII*), *N*-phenyl-2-amino-3-hydroxy-benzenesulfonamide (*XXVIII*), 4-amino-3-methylphenol (4-amino-*m*-cresol, *XXIX*), 4-aminothiophenol (*p*-aminothiophenol, *XXX*); Cl-substituted anilines: 4-chloroaniline (*p*-chloroaniline, *XXXI*), 2,6-dichloroaniline (*XXXII*), 2,3,5,6-tetrachloroaniline (*XXXIII*), pentachloroaniline (*XXXIV*)

nature. Five decades later, Dordick et al. (1987) reported, within the frame of their study mainly focused on polymerizations of various phenols catalyzed by HRP, the enzymatic oligomerization of aniline in 85% aqueous dioxane, leading to a nonconducting oligomeric product with an average molecular weight of 1700 Da (19-mer of aniline). During this pioneer phase in the investigation of enzymatic polymerization of aniline and other arylamines, electroactive PANI films were also synthesized on a glass surface with a copper-containing oxidoreductase, bilirubin oxidase (Aizawa et al. 1990). Oxidoreductase-catalyzed polymerizations of aniline and its derivatives in organic solvent/water mixtures were thoroughly studied in the early 1990s (e.g., Akkara et al. 1991, 1994a; Kobayashi et al. 1992; Aranda et al. 1995; Arias-Marín et al. 1996). Poly(aniline-*co*-4-hexadecylaniline) was synthesized by HRP-catalyzed copolymerization of aniline with 4-hexadecylaniline, conducted at an air–water interface

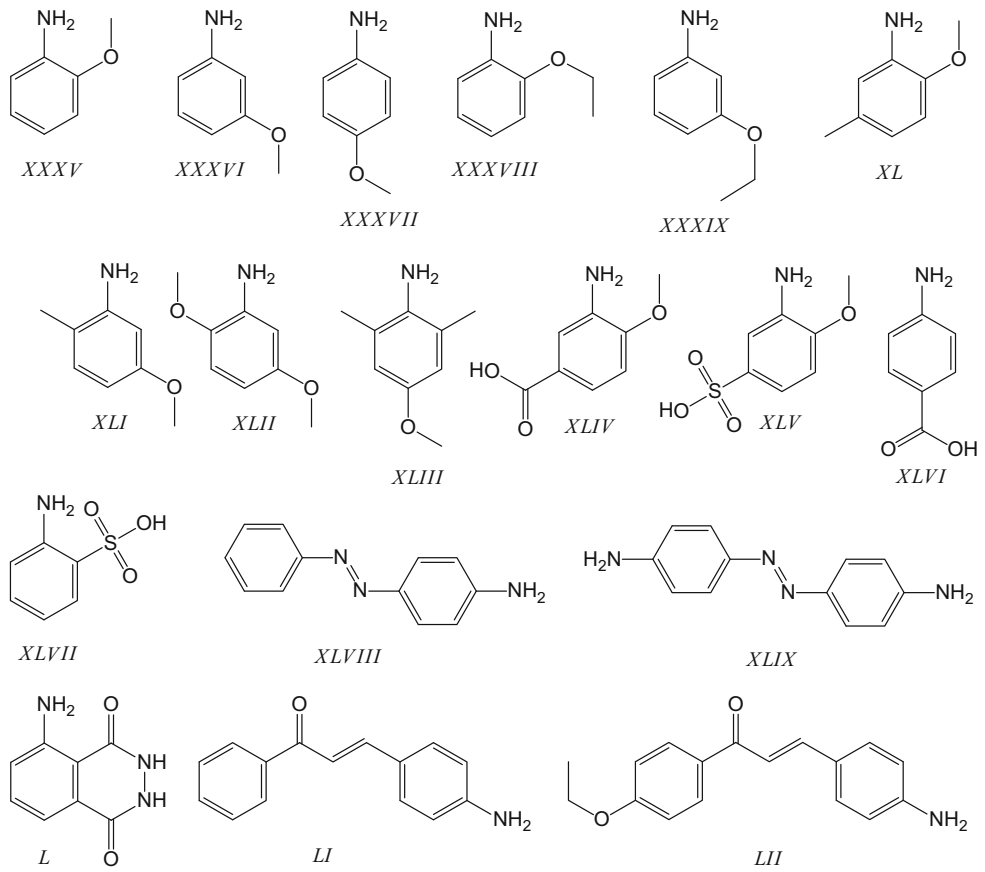

Fig. 3 Alkoxyanilines: 2-methoxyaniline (*o*-anisidine, *XXXV*), 3-methoxyaniline (*m*-anisidine, *XXXVI*), 4-methoxyaniline (*p*-anisidine, *XXXVII*), 2-ethoxyaniline (*o*-phenetidine, *XXXVIII*), 3-ethoxyaniline (*m*-phenetidine, *XXXIX*), 2-methoxy-5-methylaniline (5-methyl-*o*-anisidine, *p*-cresidine, *XL*), 5-methoxy-2-methylaniline (6-methyl-*m*-anisidine, 4-methoxy-*o*-toluidine, *XLI*), 2,5-dimethoxyaniline (*XLII*), 4-methoxy-2,6-dimethylaniline (2,6-dimethyl-*p*-anisidine, *XLIII*); aminobenzoic and aminobenzenesulfonic acids: 3-amino-4-methoxybenzoic acid (*XLIV*); 3-amino-4-methoxybenzenesulfonic acid (*XLV*), 4-aminobenzoic acid (*p*-aminobenzoic acid, *XLVI*), 2-aminobenzenesulfonic acid (*o*-aminobenzenesulfonic acid, orthanilic acid, *XLVII*); phenylazo-substituted anilines: 4-phenyldiazenylaniline (4-phenylazoaniline, aniline yellow, *XLVIII*), 4-[(4-aminophenyl)diazenyl]aniline (4,4′-diaminoazobenzene, 4,4′-azodianiline, *XLIX*); other substituted anilines: 5-amino-2,3-dihydrophthalazine-1,4-dione (luminol, *L*); 3-(4-aminophenyl)-1-phenyl-2-propen-1-one (*LI*), 3-(4-aminophenyl)-1-(4-ethoxyphenyl)-2-propen-1-one (*LII*)

(Langmuir trough) (Akkara et al. 1994b; Bruno et al. 1995a, b) or in reverse micelles (Akkara et al. 1994b; Bruno et al. 1995a, b). Alva et al. (1996, 1997) accomplished an HRP-catalyzed synthesis of water soluble poly(substituted anilines) such as poly(*p*-aminobenzoic acid) and poly(2,5-diaminobenzenesulfonate). Finally, during the late 1990s, in the quest for efficient enzymatic synthesis of conducting polymers, Samuelson et al. (1998) reported that HRP, with H_2O_2 as oxidant, could successfully be applied as a catalyst in the polymerization of aniline to obtain PANI in its conducting emeraldine salt form in an aqueous solution at pH 4.3 containing poly(-sodium 4-styrenesulfonate) (sulfonated polystyrene, SPS) as a template. The idea of using polymeric acid templates is based on previous studies on the chemical synthesis of PANI with SPS (Liu et al. 1992; Sun et al. 1997) in an attempt to mimic deoxyribonucleic acid (DNA) replication. After this breakthrough discovery by Samuelson et al. (1998), the fast development of enzymatic synthesis of conducting and semiconducting polyarylamines began. The reaction conditions employed for these enzymatic syntheses are significantly milder (slightly acidic instead of highly acidic reaction media, the use of oxidants with lower oxidation potential, etc.) than those employed in ordinary chemical and electrochemical synthesis.

Oxidoreductase-catalyzed oligomerizations and polymerizations of arylamines have briefly been reviewed in the past in the frame of reviews devoted to the oligomerizations and polymerizations catalyzed by various enzymes, including hydrolases, transferases, lipases, and oxidoreductases (Kobayashi et al. 1995, 2001, Kobayashi 1999; Kobayashi and Makino 2009; Gross et al. 2001; Kadokawa and Kobayashi 2010; Walde and Guo 2011; Hollmann and Arends 2012; Shoda et al. 2016). Ochoteco

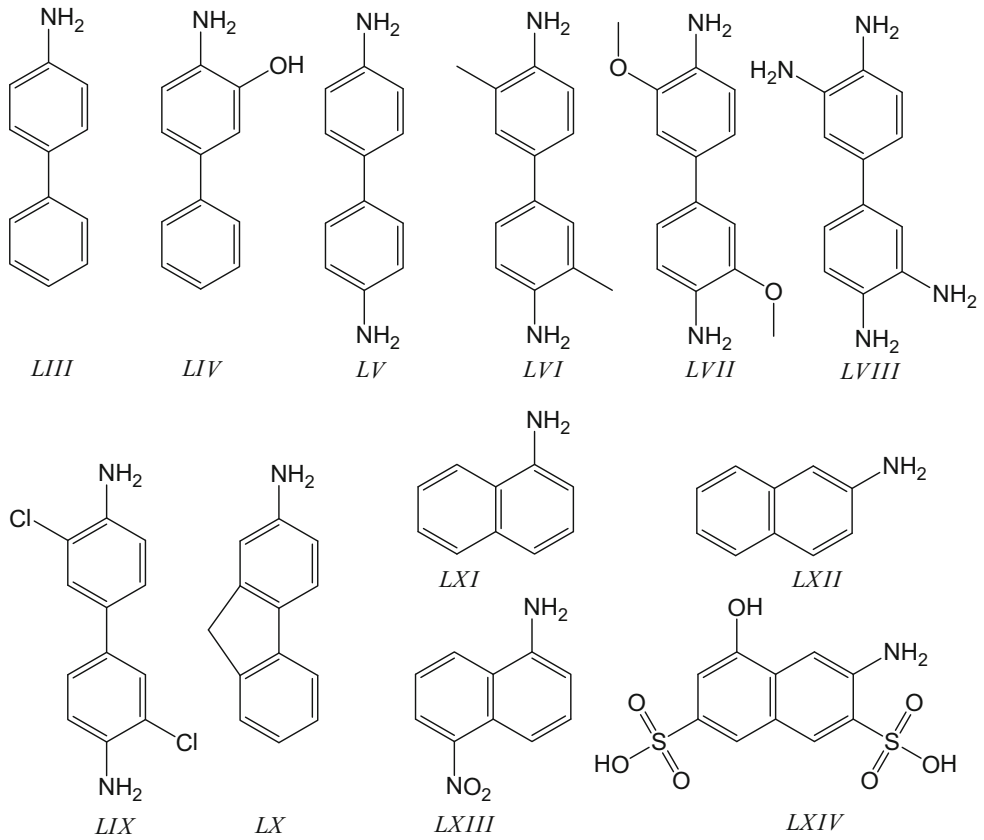

Fig. 4 Aminobyphenyls and aminofluorenes: 4-phenylaniline (4-aminobiphenyl, *LIII*), 3-phenyl-2-aminophenol (3-hydroxy-4-aminobiphenyl, *LIV*), 4-(4-aminophenyl)aniline (4,4′-diaminobiphenyl, benzidine, *LV*), 4-(4-amino-3-methylphenyl)-2-methylaniline (3,3′-dimethylbenzidine, *o*-tolidine, *LVI*), 4-(4-amino-3-methoxyphenyl)-2-methoxyaniline (3,3′-dimethoxybenzidine, *o*-dianisidine, *LVII*), 4-(3,4-diaminophenyl)benzene-1,2-diamine (3,3′-diaminobenzidine, *LVIII*), 4-(4-amino-3-chlorophenyl)-2-chloroaniline (3,3′-dichlorobenzidine, *LIX*); 9*H*-fluoren-2-amine (2-aminofluorene, *LX*); aminonaphthalenes: naphthalen-1-amine (1-aminonaphthalene, *LXI*), naphthalen-2-amine (2-aminonaphthalene, *LXII*), 5-nitronaphthalen-1-amine (5-nitro-1-aminonaphthalene, *LXIII*), 2-amino-8-hydroxy-6-sulfonaphthalene-3-sulfonic acid (2-amino-8-naphthol-3,6-disulfonic acid, *LXIV*)

and Mecerreyes (2010), Bouldin et al. (2010), Cruz-Silva et al. (2011), and Otrokhov et al. (2013) have reviewed some aspects of oxidoreductase-catalyzed oligomerizations and polymerizations of arylamines in their reviews devoted to oxidoreductase-catalyzed synthesis of conducting polymers. The most detailed review about oxidoreductase-catalyzed oligomerizations and polymerizations of arylamines was written a decade ago by Xu et al. (2006). The present review focuses on modern aspects of oxidative oligomerization and/or polymerization of arylamines catalyzed by oxidoreductases in aqueous, organic, and mixed aqueous organic monophasic or biphasic media, with a special attention to the research done in the 2010s. Template-free and template-assisted enzymatic syntheses of oligomers and polymers of arylamines, as well as mechanistic aspects of these biocatalytic processes, are comprehensively reviewed. The applicability of enzymatically synthesized oligomers and polymers of arylamines and their composites is discussed.

Oxidoreductases used as biocatalysts in the oxidative coupling of arylamines

The most frequently used oxidoreductase in the enzymatic coupling of arylamines is isolated from the roots of horseradish (*Armoracia rusticana*) and belongs to the class III family of secretory plant peroxidases (Veitch 2004). Similar to all other heme peroxidases, HRP has an iron(III) protoporphyrin IX (heme B, protoheme IX) prosthetic group (*LXV,* Fig. 5) located at the active site (Veitch 2004). The most abundant isoenzyme of HRP is HRP C (Veitch 2004). The catalytic mechanism of HRP C for the oxidation of arylamines and all other substrates is via the so-called "peroxidase cycle" (Veitch 2004) (Fig. 6). The two-electron oxidation of the native Fe(III) center with H_2O_2 leads to the formation of compound I (*LXIX*, Fig. 6), which is a high oxidation state intermediate with an Fe(IV) oxoferryl center and a porphyrin-based π-cation radical. In the succeeding second step, compound I oxidizes $ArNH_2$

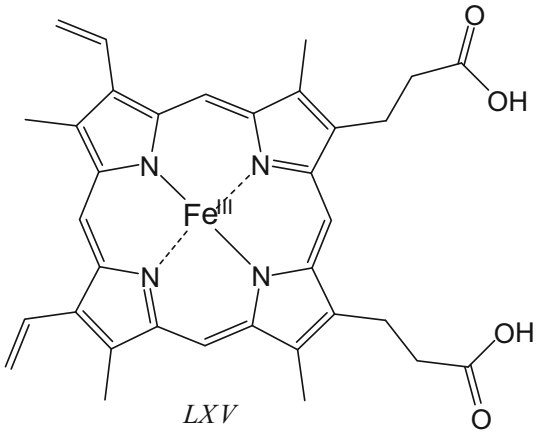

Fig. 5 Structure of iron(III) protoporphyrin IX (heme B, protoheme IX) prosthetic group (*LXV*)

(*LXVI*, Fig. 6) to yield the intermediate compound II (an Fe(IV) oxoferryl species, *LXVIII*, Fig. 6) which—in a third step—oxidizes another substrate $ArNH_2$ to yield the native Fe(III) enzyme once more, thereby completing the reaction cycle. Overall, in one peroxidase cycle, two $ArNH_2$ molecules are oxidized to two radical species (ArNH·, *LXVII*, Fig. 6), while one H_2O_2 molecule is consumed and two molecules of water form as by-products in the first and third steps. Thus, the stoichiometric equation for the peroxidase cycle for arylamines is $2ArNH_2 + H_2O_2 \rightarrow 2ArNH\cdot + 2H_2O$.

Various peroxidases other than HRP, such as fungal (chloroperoxidase, *Arthromyces ramosus, Coprinus cinereus*, and *Pleurotus sajor caju* peroxidase), plant (soybean, palm tree, and turnip peroxidase), microperoxidase, and recombinant catalase-peroxidases (HPI from *Escherichia coli*), can also be used for the enzymatic oxidation and coupling of arylamines.

Other frequently used types of oxidoreductases for the enzymatic oxidative couplings of arylamines are laccases which are found in a variety of trees and fungi. They are multicopper oxidases that catalyze the reduction of molecular oxygen to water, bypassing H_2O_2 formation (Morozova et al. 2007). They contain four copper ions, both Cu^{+} and Cu^{2+}, of three types (Fig. 7). Three copper ions comprise the catalytic site that reduces O_2 to H_2O, whereas the fourth copper ion, a Cu^{2+} cation, carries out

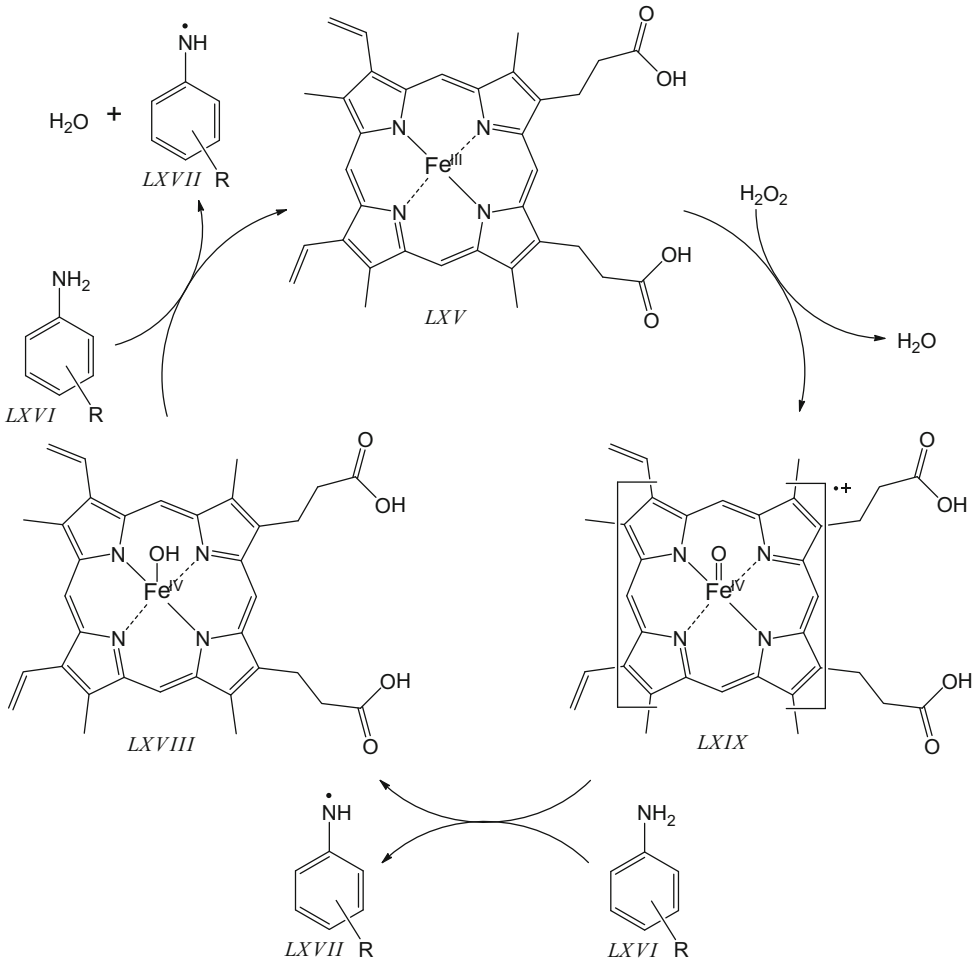

Fig. 6 Peroxidase cycle for aniline (*LXVI*, R=H) and substituted anilines (*LXVI*). Heme B (*LXV*), substituted aniline radical (*LXVII*), compound II (*LXVIII*), compound I (*LXIX*)

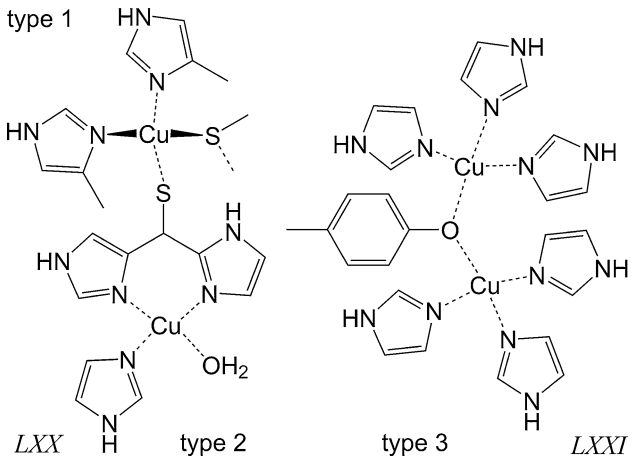

Fig. 7 Structures of active sites of laccase (*LXX* and *LXXI*) containing four copper ions of three types. Adapted with permission from Kobayashi and Makino (2009). Copyright 2009 American Chemical Society

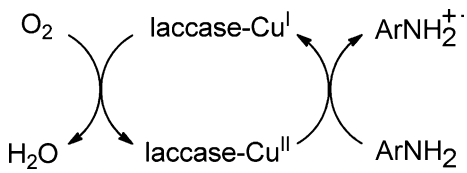

Fig. 8 Laccase cycle for arylamines

the one-electron oxidations of arylamines (Figs. 7, 8). Fungal (*Trametes versicolor*, *Trametes hirsuta*, *Trametes villosa, Rhizoctonia praticola*, *Myceliophthora thermophila*) as well as bacterial (CotA-laccase from *Bacillus subtilus*) laccases were employed in the enzymatic syntheses of oligomers and polymers of arylamines. Since the laccase-catalyzed oxidation of aniline, similar to all other enzymatic oxidations of arylamines, is hampered by the low oxidizability (high oxidation potential) of aniline in acidic media, Santiago et al. (2016) recently successfully combined a computational approach with experimental validation to rationally design a laccase mutant for improved aniline oxidation (2-fold k_{cat} increase). It seems that enzyme engineering is a promising route to improved enzymatic oxidation of arylamines.

There is also the possibility of using a cascade reaction to oxidize arylamines using the enzyme glucose oxidase (GOx), as reported by Kausaite et al. (2009). First, in the presence of glucose and dissolved O_2, GOx generates H_2O_2 (reaction 1) and D-glucono-δ-lactone. The arylamine is then oxidized with H_2O_2, either non-enzymatically or enzymatically with, e.g., HRP (reaction 2).

$$\text{Glucose} + O_2 \rightarrow \text{D-glucono-}\delta\text{-lactone} + H_2O_2, \quad (1)$$

$$2ArNH_2 + H_2O_2 \rightarrow 2ArNH\cdot + 2H_2O. \quad (2)$$

Finally, it is important to note that ceruloplasmin as a ferroxidase enzyme (associated with the oxidation of Fe^{2+} into Fe^{3+}) and DNAzyme as an artificial enzyme (made by complexation of DNA oligonucleotides with hemin; Gao et al. 2015) were also utilized in the oxidoreductase-catalyzed oligomerization (Eggert et al. 1995) and polymerization of arylamines (e.g., Shen et al. 2014), respectively.

Natural heme-containing and synthetic biomimetic catalysts

Besides heme-containing enzymes, other heme-containing proteins have successfully been utilized as catalysts in the oxidative polymerization of aniline with H_2O_2. It is of particular notice that proteins which do not normally oxidize a substrate can, under the right conditions, catalyze the oxidation of arylamines. However, in order for this to be successful, a template is required. For example, aniline was successfully polymerized using bovine hemoglobin, the heme-containing oxygen-transport protein, in the presence of various templates, such as SPS (Hu et al. 2005c), lignosulfonate (Hu et al. 2008), and micelles from sodium dodecyl sulfate (SDS) (Hu et al. 2005a, b, 2006). The electrical and electrochemical characteristics of PANI synthesized with enzyme-mimics strongly depend on the surfactants used in the formation of micelles (Hu et al. 2006). Consequently, the final product can be tuned by the type(s) and concentration of surfactant, as well as by the initial H_2O_2:aniline molar ratio. It has been shown that micelles formed by anionic surfactants based on strong acids, such as SDS, are suitable templates for the biomimetic enzymatic synthesis of conducting PANI. The results of Hu et al. (2006) also showed that the higher stability of hemoglobin in comparison with HRP was advantageous for conducting the synthesis of conductive PANI in a relatively wide pH range, with optimal pH of 2.0. The hemoglobin-catalyzed polymerization of aniline at pH $\geq$5.0 resulted in branched, insulating PANI. Another efficient reaction system with hemoglobin and H_2O_2, with sodium dodecylbenzenesulfonate (SDBS) reverse microemulsions as reaction medium, was developed by Chen et al. (2014) for the synthesis of conducting (0.90 S cm^{-1}) nanoscaled, furcate shaped PANI with excellent thermal stability and high degree of crystallinity. The reaction was controlled by tuning the water content (the water/dodecylbenzenesulfonate molar ratio) in the reverse microemulsions. Also, chiral conducting PANI nanospheres with a high degree of crystallinity were recently obtained by the oxidation of aniline with H_2O_2 in the presence of bovine hemoglobin as a chiral inducer at pH 2.0, using the dodecylbenzenesulfonic acid (DBSA) micelle-assisted (Guo et al. 2014) or

DBSA/CTAB micelle-assisted polymerization route (Guo et al. 2015). Methemoglobin was used by Li et al. (2005) to catalyze the oxidative dimerization of *o*-PDA with H_2O_2 to 2,3-diaminophenazine (DAP). The heme protein cytochrome *c* has also been used as a catalyst for arylamine oxidation and coupling, e.g., Nagasawa et al. (1959) revealed that oxidative dimerization of *o*-aminophenol and 3-hydroxy-4-aminobiphenyl by cytochrome *c*/H_2O_2 yields the corresponding phenoxazinones as major products, whereas the oxidative dimerization of 2-amino-1-fluorenol led to the indophenol-like product. Zhu et al. (1998) have suggested that the product of *o*-PDA oxidation by cytochrome *c*/H_2O_2 in water is the trimer 1,2,5,6-tetraamino-9,10-(1′,2′-di-aminobenzo)-phenanthrene, while Ono et al. (2001) and Oshima et al. (2007) used cytochrome *c* as a catalyst for the oxidative polymerization of *o*-PDA in organic solvent/water mixtures at pH 7.0–8.0.

Even synthetic, heme-containing molecules, so-called biomimetic catalysts, can oxidize and polymerize arylamines. Since hematin is water soluble only at very high pH and thus is not an effective catalyst for PANI synthesis in acidic media, appropriately chemically modified hematin was used as a catalyst in PANI synthesis. For example, poly(ethylene glycol)-coupled hematin (Nagarajan et al. 2001b; Roy et al. 2002; Sahoo et al. 2004), multilayered hematin/poly(dimethyl diallylammonium chloride) films in the presence of SPS (Ku et al. 2003), magnetite-supported hematin (Curvetto et al. 2006; Saidman et al. 2006), halloysite nanotubes-supported hematin (Tierrablanca et al. 2010), and hematin tethered with methoxypolyethylene glycol amine chains (Nagarajan et al. 2009) were utilized as biomimetic catalysts for PANI synthesis. Similar to the already mentioned excellent control over electrical conductivity, crystallinity, redox/electrochemical activity, and thermal stability of PANIs synthesized using heme-containing proteins (hemoglobin, etc.) as catalysts, fine tuning of the various properties of PANI was also achieved in the case of the hematin-catalyzed oxidative polymerization of aniline, mainly by the proper choice of the template (polyanion, etc.) and its concentration. Thus, Roy et al. (2002) showed that the presence of lignosulfonate as a polyanionic template in the poly(ethylene glycol)-coupled hematin/aniline/H_2O_2 reaction system yields PANI with desirable properties such as good electrical conductivity, redox/electrochemical activity, solubility/processability, thermal stability, biodegradability, and anticorrosion ability. 5,10,15,20-Tetrakis-(meso-hydroxyphenyl)-porphyrin (Hu et al. 2008), iron(III) tetrasulfonated tetraphenyl-porphyrin (Nabid et al. 2006b), tetrapyridylporphyrin complexes of iron (III), manganese (III) and cobalt (III) (Nabid et al. 2009b), transition metal (iron, cobalt or manganese) tetrasulfonated phthalocyanine (Nabid et al. 2007b), and iron (II) tetrasulfophthalocyanine (Hu et al. 2008, 2009) were also used as biomimetic catalysts for the oxidative polymerization of aniline with H_2O_2. The intrinsic peroxidase-like activity of Fe_3O_4-NPs (Datta and Schuster 2008, 2007a) inspired Yang et al. (2009) to perform SPS-templated Fe_3O_4-NPs-catalyzed oxidative polymerization of aniline with H_2O_2 at pH 2.5, leading to the formation of PANI/Fe_3O_4-NPs composites. Synthesis of water-dispersible PANI by oxidative polymerization of aniline with H_2O_2, in the presence of iron phosphates (FePOs) as peroxidase mimic catalyst and polystyrene sulfonate as a template, was recently presented by Li et al. (2015). In comparison with HRP, the FePOs showed apparent superior catalytic properties and the reactions with FePOs were carried out at a higher level of acidity (pH 1.5–2.6).

Enzymatic oligomerization and polymerization mechanisms

The first detailed mechanistic study regarding the enzymatic oligomerization or polymerization of arylamines indicated the formation of at least three distinct species after the oxidation of *o*-dianisidine by HRP/H_2O_2 at pH 3.7 and 4 °C (Claiborne and Fridovich 1979a, b). The enzymatic oxidation of *o*-dianisidine at low concentrations yielded the free *o*-dianisidine quinonediimine, while at higher concentrations the first product was an intermolecular complex (charge-transfer complex) consisting of *o*-dianisidine and its quinonediimine. It was revealed that at near-neutral pH, the *o*-dianisidine quinonediimine undergoes irreversible self-coupling, yielding a product which has a bisazobiphenyl structure. Since continuous-flow EPR studies of *o*-dianisidine oxidation with HRP/H_2O_2 did not indicate the formation of free *o*-dianisidine semiquinone radicals in the steady state, Claiborne and Fridovich (1979a) concluded that the HRP-catalyzed oxidation of *o*-dianisidine occurs via a fast two-electron transfer. Data presented by Claiborne and Fridovich (1979a, b) also led to the conclusion that the HRP-dianisidine radical complex was intermediary formed during the early stages of the oxidation of *o*-dianisidine by HRP/H_2O_2, followed by the removal of the second electron from the bound *o*-dianisidine radical, which was found to be facilitated by binding of nitrogen-containing nucleophiles.

The mechanism of the HRP–H_2O_2 polymerization of aniline in the presence of bis-(2-ethylhexyl)sulfosuccinate (AOT, *LXXII*, Fig. 9) as vesicle-forming surfactant and dopant was recently investigated by Junker et al. (2012), on the basis of UV/VIS/NIR and EPR measurements, by tracking changes in aniline and H_2O_2 concentrations and HRP activity during the polymerization reaction. The green PANI emeraldine salt was obtained with 90-95% aniline conversion at pH 4.3 and room temperature within 24 h. The

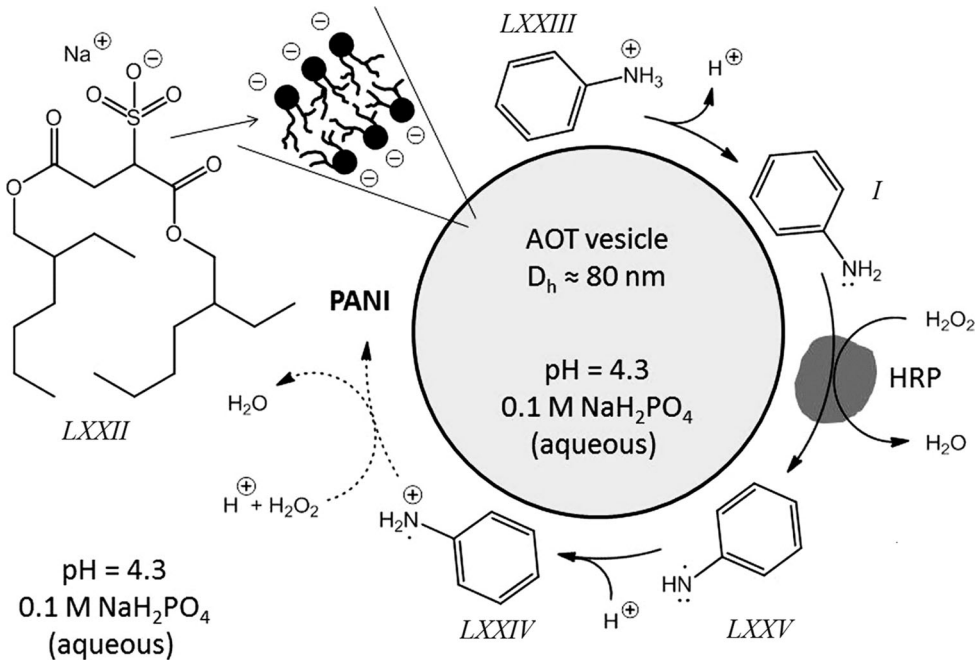

Fig. 9 Schematic illustration of the "radical cation mechanism" of HRP-catalyzed PANI chain formation on the AOT vesicle surface: Aniline (*I*), AOT (*LXXII*), anilinium cation (*LXXIII*), aniline cation radical (*LXXIV*), aniline radical (*LXXV*). For a cryo-transmission electron micrograph and a schematic representation of a vesicle, see Fig. 15 Adapted with permission from Junker et al. (2012). Copyright 2012 Royal Society of Chemistry

data led to the conclusion that PANI is formed on the AOT vesicle surface via the "radical cation mechanism", i.e., the reaction of aniline radical cations with the growing PANI chain (Fig. 9). Three kinetically distinct phases of PANI formation were observed. First, PANI emeraldine salt in bipolaron state is formed in the first 5–10 min, followed by the transformation of the bipolarons into polarons in the second and third slower phases (1–2 days). Based on a ^{2}H magic-angle spinning NMR spectroscopy analysis of the polymerizations of different types of partially deuterated aniline monomers, it was demonstrated that *para*-coupling of the aniline units dominates over *ortho*-coupling. Kinetic studies of PANI synthesis catalyzed by soybean peroxidase (SBP) in water or water/organic solvent mixtures indicated that the enzymatic polymerization of aniline does not have an induction period or autoacceleration, which is characteristic for the simple chemical polymerization of aniline (Cruz-Silva et al. 2005). Similarly, Shumakovich et al. (2014) pointed out that the growth of PANI chain during the chemical oxidative polymerization of aniline occurs via the formation of oligomeric/polymeric pernigraniline intermediates which are later reduced by unreacted aniline molecules to the PANI emeraldine salt in the final polymerization phase. In contrast, oligoaniline and PANI chains in the emeraldine oxidation state are immediately formed in the laccase-catalyzed polymerization of aniline (Junker et al. 2014a), i.e., the enzymatic polymerization of aniline proceeds without an induction period (initial accumulation of oligomeric pernigraniline intermediates).

A comparative study performed by Xu (1996) with several fungal laccases for the oxidation of various substituted anilines indicated that the first electron transfer from substituted aniline to laccase occurred via the "outer-sphere" mechanism. The steric effect of small *o*-substituents (e.g., methyl, methoxy, etc.) was found to be unimportant in comparison with the electronic factor.

It can be concluded that significant progress was made with respect to the mechanisms of enzymatic arylamine polymerization. However, the structural characterization of oligoarylamines (dimers, trimers, tetramers, etc.) formed during the early stages of the enzymatic oxidative polymerization of aniline and other arylamines is still missing. There is also a lack of quantum–chemical insights into the mechanisms of enzymatic arylamine polymerizations.

Enzymatic oligomerization of arylamines

Similar to other oligomers (Jenkins et al. 1996), arylamine oligomers (oligoarylamines) can be defined as molecules which comprise several arylamine units, most frequently 2 (dimer)–10 (decamer) monomers, and which have properties that change significantly when one or a few monomer units are removed. For example, the oxidizability of unprotonated, reduced N–C4 coupled leucoemeraldine-like oligoanilines significantly increases with increasing chain length. This has a crucial impact on the mechanism of the oxidative polymerization of aniline (Ćirić-Marjanović et al. 2006). In contrast, polyarylamines usually consist of hundreds or thousands of arylamine monomers. Therefore, their properties remain virtually the same if one or a few monomers are removed. In general, the solubility of oligoarylamines is

significantly higher than that of the corresponding polyarylamines, and it rapidly decreases with increasing chain length (Ćirić-Marjanović et al. 2008). The properties of oligoarylamines not only depend on the number of monomers but also on the coupling type (N–N, N–C, or C–C) between monomers, as well as on their oxidation state and degree of protonation. For example, half-oxidized N–C4 coupled emeraldine-like oligoanilines (Wang et al. 2010) become conducting upon protonation (doping with acids) at pH $\leq$5.5, while fully oxidized N–C4 coupled pernigraniline-like oligoanilines become powerful oxidants upon protonation at pH $\leq$2 (Ćirić-Marjanović et al. 2006, 2008). Branching, which leads to an increased number of end groups (e.g., primary amino groups) and intramolecular cyclization reactions (formation of aromatic heterocycles, e.g., phenazine), also have a significant impact on the physico-chemical properties of oligoarylamines.

After the discovery of oligoarylamines in the nineteenth century, and during the major part of the twentieth century, interest in oligoarylamines was based almost exclusively on their applicability as dyes and pigments (aniline black, mauveine, etc.). The formation of resinous polymeric products was considered as an unwanted process which should be prevented or minimized, and frequently the formed polymeric precipitates were separated from the reaction mixture by filtration and discarded as useless without any characterization. The discovery of conducting polyarylamines in the second half of the twentieth century dramatically changed the focus of scientists interested in arylamine oxidation. The scientific popularity of oligoarylamines decreased drastically. From a scientific point of view, only N–C4 coupled emeraldine-like oligoanilines (tetramers, octamers, etc.) were considered interesting because they can be used as model compounds for the corresponding conducting polyarylamines. In this period, the formation of nonconducting oligoarylamines upon the oxidation of arylamines was considered as an unwanted process in numerous research works, and frequently the formed soluble oligoarylamine products were separated from the precipitates of conducting/semiconducting polyarylamines by filtration and were not characterized. Separation of oligoarylamines, which were adsorbed on precipitates of polyarylamines and/or coprecipitated with polyarylamines, was achieved by washing the precipitates with organic solvents which dissolve the oligomers. Consequently, complete information on the full range of products obtained by the oxidation (both enzymatic and nonenzymatic) of arylamines is missing in the majority of the published studies up to the present date. It is also important to note that attempts to synthesize various conducting polyarylamines were unsuccessful in many cases and unintentionally led to the formation of nonconducting oligoarylamines.

Currently, there is a growing interest in oligoarylamines because of their promising applicability in corrosion inhibition, production of nitrogen-containing carbons, antimicrobial materials, etc. (Ćirić-Marjanović 2013b). The linear N-C4 coupled oligoanilines (e.g., aniline tetramers) are especially interesting because these oligomers combine the electrical properties of PANI (the acid–base doping–dedoping chemistry) with the characteristic properties (monodispersity and self-assembly to various nanostructures) of molecular semiconductors (Wang et al. 2010). The environmentally friendly enzymatic oligomerization of arylamines contributes to "green" oligoarylamine chemistry.

Enzymatic dimerization of arylamines

In the 1920s, Chodat proposed DAP (*LXXVI*, Fig. 10) as a major dimeric product of the oxidation of *o*-PDA with peroxidase/H_2O_2 (Chodat 1925), Fig. 10. This finding was open to discussion during the following several decades until Tarcha et al. (1987) obtained indisputable NMR and mass spectroscopic evidence which indicated that the major product of the oxidation of *o*-PDA by H_2O_2 or HRP/H_2O_2 is DAP. Liquid chromatography combined with UV/Vis, IR, 2-D NMR, and MS has also led to the unambiguous detection of DAP as a major reaction product of the HRP-catalyzed oxidation of *o*-PDA with H_2O_2, whereas 2,2′-diaminoazobenzene, which was suggested by other researchers (e.g., Gallati and Brodbeck 1982) to be the major reaction product, was not detected (Hempen et al. 2005). Because of this reaction, *o*-PDA became one of the most effective substrates for spectrophotometric HRP-mediated enzyme-linked immunosorbent assay (ELISA test) that uses antibodies and color change to identify a substance (Wolters et al. 1976; Bovaird et al. 1982; Mekler and Bystryak 1992). In addition, *o*-PDA is frequently used as a substrate to determine the activity of HRP (Mekler and Bystryak 1992; Fornera and Walde 2010). Enthalpy change and mechanism of oxidation of *o*-PDA by HRP/H_2O_2 to DAP were investigated by Liu et al. (2006) using calorimetry. The oxidation of *o*-PDA by laccase also leads to the formation of DAP, which was detected by immobilizing laccase via microencapsulation in a microreactor which was coupled offline to capillary electrophoresis (Roman-Gusetu et al. 2009). Recently, Zhou et al. (2011) synthesized DAP in high yield (63%) from *o*-PDA using fungal laccase as a biocatalyst. Methemoglobin-catalyzed oxidation of *o*-PDA with H_2O_2 to DAP was reported by Li et al. (2005). In a quite similar oxidative dimerization process as the formation of DAP from *o*-PDA, Niu and Jiao (2000) reported the formation of 2,7-diaminophenazine via the oxidation of *m*-phenylenediamine (*m*-PDA) by HRP/H_2O_2.

It was reported that the oxidation of *p*-toluidine by HRP/H_2O_2 leads to the dimeric products 4,4′-

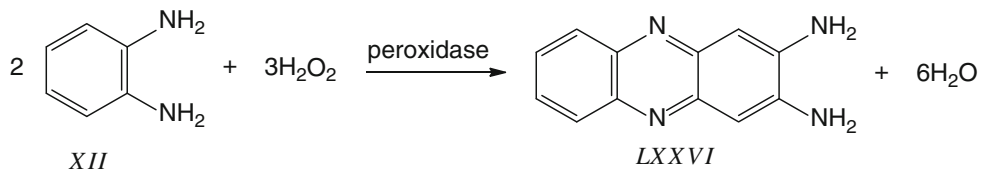

Fig. 10 Formation of 2,3-diaminophenazine (DAP, *LXXVI*) by the peroxidase-catalyzed oxidation of *o*-phenylenediamine (*o*-PDA, *XII*) with H_2O_2

dimethyldiphenylamine and 4,4′-dimethylazobenzene, besides some other oligomeric products (Saunders and Mann 1940). Chapman and Saunders (1941) showed that mesidine (2,4,6-trimethylaniline) is oxidatively dimerized by HRP/H_2O_2 at pH 4–5 to a purple crystalline compound which was determined to be 2,6-dimethylbenzoquinone-4(2′,4′,6′-trimethyl)-anil. Saunders and Watson (1950) isolated and identified 3,5-dimethylbenzoquinone-1-(4′-methoxy-2′,6′-dimethyl)anil as a product of the oxidative dimerization of 4-methoxy-2,6-dimethylaniline with HRP/H_2O_2. 4,4′-Dichloroazobenzene was detected as the dimeric product of the oxidation of 4-chloroaniline by HRP/H_2O_2 (Daniels and Saunders 1953). In the most extensive study up to the present date regarding enzymatic oxidative dimerization of aniline and its derivatives, Bordeleau and Bartha (1972) exposed forty-three substituted anilines to fungal enzymes and the reaction products were analyzed by spectrometric and gas chromatographic methods. It was observed that the susceptibility to enzymatic transformation increased with an increased electron density at the amino group, and electron-donating substituents increased the yields of longer polymers and decreased the yields of dimeric azobenzenes. Anilines substituted by electron-*accepting* groups in both *ortho* positions did not undergo enzymatic transformations (Bordeleau and Bartha 1972). It was observed by van Duijn (1955) that blue crystals which were formed upon adding a milk-peroxidase concentrate to a mixture containing benzidine, H_2O_2, and NH_4Cl, have a minimum formula of the benzidine dimer $C_{24}H_{24}N_4$-$Cl{\cdot}2H_2O$. However, this blue colored product does not represent the true benzidine dimer, but is a charge-transfer complex of benzidine with benzidine diimine. The principal organic-extractable dimer formed by the oxidation of benzidine with both prostaglandin synthase/H_2O_2 and HRP/H_2O_2 at pH 7.0 was isolated by chromatography and identified as the azo-dimer derivative of benzidine (Josephy et al. 1983). It was revealed by Claiborne and Fridovich (1979a) that the oxidation of *o*-dianisidine by HRP/H_2O_2 at near-neutral pH leads to the irreversible self-coupling of *o*-dianisidine, yielding a dimeric product with bisazobiphenyl structure. The oxidative dimerization of 2,5-diamino-benzenesulfonic acid by laccase/O_2 at pH 5.0, leading to the formation of 2,7-diaminophenazine-1,6-disulfonic acid, was performed by Shaw and Freeman (2004). Saunders and Wodak (1966) reported the formation of the dimer dibenzo[a,h]phenazine upon the oxidation of 2-naphthylamine by peroxidase/H_2O_2 in an aqueous solution of acetic acid at pH 4.5. It has recently been reported by Longoria et al. (2008) that CPO-mediated oxidation of 2,3,5,6-tetrachloroaniline with H_2O_2 in isopropanol/water mixture at pH 3.0 leads to the formation of three dimers: octachloro-4-aminodiphenylamine, nonachloro-4-aminodiphenylamine, and decahloroazobenzene, besides the formation of polymeric material. Spectroscopic measurements combined with Density Functional Theory calculations were used by Martorana et al. (2011) in order to get insight into the oxidative N–N coupling of 4-methylaminobenzoic acid by laccase/O_2, leading to the dimeric azo dye.

The monomer *o*-aminophenol can easily be transformed to its dimer 2-amino-3*H*-phenoxazin-3-one via enzymatic oxidation followed by oxidative cyclization, e.g., using HRP (Puiu et al. 2008). Fungal laccases as green catalysts for the synthesis of various colored products, including phenoxazinone-based dyes, have recently been reviewed by Polak and Jarosz-Wilkolazka (2012). To protect mammalian cells from oxidative damage, multicopper oxidases (e.g., ceruloplasmin) are involved in the oxidation of 3-HAA, a carboxylic acid derivative of *o*-aminophenol, into a natural phenoxazinone derivative, cinnabarinic acid pigment (2-amino-3-phenoxazinone-1,9-carboxylic acid, *LXXVII*, Fig. 11) (Eggert et al. 1995). Such phenoxazinone derivatives have also been synthesized in vitro by laccases (Eggert et al. 1995; Osiadacz et al. 1999; d'Acunzo et al. 2004) (Fig. 11). For example, 3-HAA was oxidatively dimerized by laccase/O_2 to cinnabarinic acid in mixtures of water with organic solvents such as dioxane, isopropanol, ethylene glycol, and acetonitrile (d'Acunzo et al. 2004), while *Trametes versicolor* laccase (TvL) immobilized in polyacrylamide gel was utilized for the oxidative transformation of 4-methyl-3-hydroxyanthranilic acid to actinocin (2-amino-4,6-dimethyl-3-phenoxazinone-1,9-carboxylic acid) in water and acetonitrile/water mixture (Osiadacz et al. 1999). The ceruloplasmin-catalyzed oxidative coupling of 3-HAA to cinnabarinic acid was also demonstrated in vitro by Eggert et al. (1995).

Low water solubility is the main drawback regarding the potential applicability of cinnabarinic acid (e.g., modulation of immune responses in autoimmune disorders, molecular

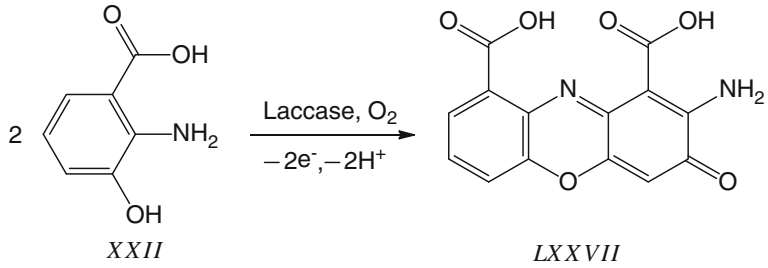

Fig. 11 Laccase-catalyzed oxidation–dimerization reaction of 3-HAA (*XXII*) to cinnabarinic acid (*LXXVII*)

probe, etc.). Therefore, the oxidation of 3-hydroxyorthanilic acid, a sulfonated analog of 3-HAA (SO_3H group instead of COOH), was performed using laccase/O_2 as a biocatalyst/oxidant system, leading to the 2-amino-3-oxo-3*H*-phenoxazin-1,9-disulfonic acid as the sulfonate analog of cinnabarinic acid (Bruyneel et al. 2008). Similarly, numerous sulfonamide derivatives of 3-hydroxyorthanilic acid (e.g., 2-amino-3-hydroxybenzenesulfonamide, *N*-phenyl-2-amino-3-hydroxybenzenesulfonamide, and *N*-cyclohexyl-2-amino-3-hydroxybenzenesulfonamide) (Bruyneel et al. 2009), as well as 3-amino-2-hydroxybenzenesulfonic acid (2-hydroxymetanilic acid) (Bruyneel et al. 2009) and 3-amino-4-hydroxybenzenesulfonic acid (Forte et al. 2010; Polak and Jarosz-Wilkolazka 2010), have also been transformed to corresponding phenoxazinones via laccase-catalyzed oxidative dimerization. Laccase-catalyzed synthesis was shown to be more efficient than the oxidation of *o*-aminophenols with silver oxide (Bruyneel et al. 2009). It is interesting to note that the oxidative dimerization of 3-HAA to cinnabarinic acid was proposed by Cantarella et al. (2003) as a reliable reaction for spectrophotometric determination of laccase activity in mixed solvents. Suzuki et al. (2006) reported the oxidative dimerization of *o*-aminophenol and its derivative 3-amino-4-hydroxy-benzaldehyde by *o*-aminophenol oxidase GriF to corresponding phenoxazinones. The presence of *N*-acetylcysteine in the in vitro oxidation of 3-amino-4-hydroxy-benzaldehyde by GriF led to the formation of grixazone A, a yellow pigment produced under phosphate depletion by *Streptomyces griseus*.

The oxidation of a mixture of 4-amino antipyrine and a *N,N*-disubstituted aniline derivative with HRP/H_2O_2, leading to a dimeric 4-amino antipyrine-*co*–*N,N*-disubstituted aniline cationic electroactive quinone–iminium dye, was utilized in the indirect electrochemical detection of HRP (Degrand et al. 2001).

Oxidoreductase-catalyzed formation of trimers and other low-molecular-weight oligoarylamines

The complexity of the molecular structure of arylamine trimers, tetramers, and other low-molecular-weight oligomers increases exponentially with increasing chain length. This is due to the different possible coupling types (N–N, N–C, C–C) between the monomers. Furthermore, for a given oligomer chain, different types of oxidation states, degree of branching, and intramolecular cyclizations are possible. Therefore, the studies devoted to enzymatic trimerizations, tetramerizations, etc. of arylamines only focus on a few major products (frequently not exceeding 30–50% yield), while the myriad of the other low-molecular-weight oligoarylamines has never been isolated and characterized. It should be noted that the formation of polyarylamines is always accompanied with the formation of low-molecular-weight oligoarylamines as by-products. Similar to polyarylamines, low-molecular-weight oligoarylamines can be conducting or nonconducting, depending on their molecular structure. The conductivity of oligoarylamines increases with increasing number of protonated emeraldine-like units in the molecular structure, whereas the presence of all other structural units leads to a decreased conductivity. It is noteworthy that in many cases the electrical conductivity of enzymatically synthesized oligoarylamines was not investigated.

In their study of the enzymatic oxidative oligomerization of aniline, Mann and Saunders (1935) reported that the enzymatic oxidation of aniline by HRP/H_2O_2 or peroxidase from turnips/H_2O_2 in dilute aqueous acetic acid at pH 4.5 predominantly leads to the formation of oligoaniline products which they proposed to be 2,5-dianilino-*p*-benzoquinoneimineanil, 2-amino-8-anil-*N*-phenyldiphenazine (pseudomauveine), induline, and "ungreenable" aniline black. Purification of recombinant catalase-peroxidase (HPI) from *Escherichia coli* and its application in the enzymatic oligomerization of aniline were recently reported by Di Gennaro et al. (2014). Size-exclusion and MALDI-TOF analysis of the products led the authors to conclude that predominantly, two different oligomers are formed, the tetramer and the decamer. The oxidation of aniline was also performed using HRP/H_2O_2 under the same reaction conditions as above (phosphate buffer, pH 7) (Di Gennaro et al. 2014), leading to the formation of the aniline dimer and decamer. A laccase from *Trametes villosa*, in the presence of poly(ethylene glycol) of various average molar masses, was shown to be an efficient catalyst in the oxidative coupling of aniline to the corresponding low-molecular-weight soluble brown-colored oligomers

(Steevensz et al. 2012). The enzymatic syntheses of low-molecular-weight oligoanilines in the conducting emeraldine salt state form were reported by Datta and Schuster (2008), Datta et al. (2006) and Shumakovich et al. (2014). Datta and Schuster (2008), Datta et al. (2006) synthesized a series of aniline oligomers from aniline monomers covalently linked to duplex DNA. It was observed that the treatment of DNA oligomers containing 4–6 aniline monomers with HRP/H_2O_2 led to the formation of oligoanilines which have PANI emeraldine salt-like structure (Datta and Schuster 2008; Datta et al. 2006). A method for the enzymatic synthesis of low-molecular-weight oligoanilines (up to heptamers) in the emeraldine oxidation state, by the oxidation of aniline with laccase from the fungus *Trametes hirsuta* and atmospheric O_2 in the presence of SDBS, was recently developed by Shumakovich et al. (2014). This synthetic method is based on the fact that, in contrast to chemical polymerization, the laccase-catalyzed polymerization of aniline can be stopped at the stage when oligoanilines are in the emeraldine oxidation state.

The trimer 4-amino-2,5-toluquinonebis-*p*-tolylimine and tetramer 4-*p*-toluidino-2,5-toluquinonebis-*p*-tolylimine were recorded by Saunders and Mann (1940) as the major products of the oxidative oligomerization of *p*-toluidine by HRP/H_2O_2. The enzymatic oxidative coupling of *o*-, *m*-, and *p*-toluidine to the corresponding low-molecular-weight soluble orange-brown to purple-brown colored oligomers was achieved using laccase from *Trametes villosa* in the presence of poly(ethylene glycol) (Steevensz et al. 2012). The oxidative oligomerization of *p*-anisidine by H_2O_2 catalyzed by peroxidase was examined by Daniels and Saunders (1951). It was found that major products are the *p*-anisidine tetramer, 2-amino-5-(*p*-anisidino)benzoquinone-di-*p*-methoxyphenylimine, and the pentamer, tetra-methoxyazophenine. Daniels and Saunders (1953) also revealed that the major oligomeric products of the oxidation of 4-chloroaniline by HRP/H_2O_2 are the tetramer, 2-amino-5-(4-chloroanilino)benzoquinone-di-4-chloroanil, and the pentamer, tetra-4-chloroazophenine, besides the dimer 4,4′-dichloroazobenzene. Holland and Saunders (1968) also examined the oxidative oligomerization of 4-chloroaniline by HRP/H_2O_2, and their study confirmed that the oxidation of 4-chloroaniline by peroxidase/H_2O_2 prevalently leads to the tetramer, 2-amino-5-(4-chloroanilino)benzoquinone-di-4-chloroanil. It was observed that the oxidative oligomerization of various halogen-, alkyl-, and alkoxy-substituted anilines with TvL laccase/O_2 proceeds smoothly, whereas the laccase of *Rhizoctonia praticola* was able to oligomerize only *p*-methoxyaniline (Hoff et al. 1985). The product of *p*-phenylenediamine (*p*-PDA) oxidized with HRP/H_2O_2 in Britton–Robinson (B–R) buffer at various acidities (pH 3.0–7.0) was found to be the trimer, 2,5-diamino-*N*,*N*′-di-(4-aminophenyl)-2,5-cyclohexadiene-1,4-diimine (Bandrowski's base) (Jiao et al. 2000). The oxidation of primary aromatic amines with *p*-electron-donor substituents, e.g., 4-aminophenol, *p*-PDA, PADPA, and *N*-acetyl-1,4-phenylenediamine, using two different laccases, CotA-laccase from *Bacillus subtilus* and TvL (Sousa et al. 2013) (Fig. 12), has led to the formation of orange-red to purple trimeric products. The product of *p*-PDA oxidation was shown to be Bandrowski's base (Sousa et al. 2013), a *p*-PDA trimer.

Ryabov et al. (1999) found that colored water-soluble oligomers, which do not inactivate enzymes, are formed upon the oxidation of *p*-ferrocenylaniline with HRP/H_2O_2 and laccase/O_2. 4-Aminobiphenyl monomers covalently linked to the nucleobases of duplex DNA were oxidized with HRP/H_2O_2, thus leading to the formation of oligo(4-aminobiphenyl)s covalently linked to DNA (Datta and Schuster 2008; Schuster 2008). The formation of the trimer of 2-aminonaphthalene, 5-(2-naphthylamino-)-dibenzo[a,h]phenazine, was observed upon its oxidation with peroxidase and H_2O_2 (Saunders and Wodak 1966). The formation of co-trimeric products upon the oxidation of the

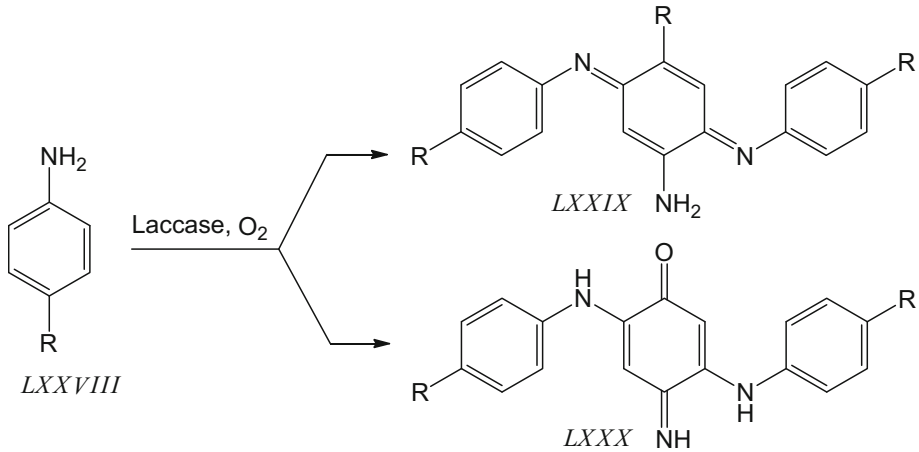

Fig. 12 Laccase-catalyzed oxidation–trimerization reaction of 4-aminophenol (*LXXVIII*, R=OH), *p*-PDA (*LXXVIII*, R=NH_2), PADPA (*LXXVIII*, R=NH-phenyl), and *N*-acetyl-1,4-phenylenediamine (*LXXVIII*, R=$NHCOCH_3$) to corresponding Bandrowski's base-like trimers (*LXXIX*, R=NH_2, NH-phenyl, $NHCOCH_3$; and *LXXX*, R=OH). Adapted with permission from Sousa et al. (2013). Copyright 2013 Wiley

mixture of 2-(*N*-phenylamino)-5-aminobenzenesulfonic acid and 5-amino-2-naphthalenesulfonic acid with laccase/O_2 was reported by Shaw and Freeman (2004).

As can be seen from the presented results of numerous research works devoted to the enzymatic synthesis of arylamine trimers and other low-molecular-weight oligoarylamines, there are only a few reports on the enzymatic syntheses of low-molecular-weight oligoanilines in the conducting emeraldine salt state form (Datta et al. 2006, 2008; Shumakovich et al. 2014), whereas other oligoarylamines have not yet been synthesized in a conducting form.

Enzymatic polymerization of arylamines

Enzymatic polymerizations of arylamines, similar to corresponding ordinary chemical polymerizations, can be performed with and without templates (template-assisted and template-free polymerization, respectively). Templates are dispersed additives which have a positive and desired effect on the polymerization of arylamines by *inter alia* controlling the chemical structure and the morphology of the synthesized polyarylamine (Walde and Guo 2011). Templates can be classified as being either hard or soft. Hard templates are insoluble organic or inorganic solid materials with a specific structure and morphology, for example CNTs or zeolites. Soft templates are soluble or dispersible polymers and supramolecular aggregates or self-assemblies of soluble amphiphilic or surfactant molecules (e.g., micelles and vesicles). Templates interact directly with the reacting arylamine monomers and the growing polyarylamine chains, or they can spatially confine the reaction (Walde and Guo 2011; Küchler et al. 2016).

Template-free enzymatic syntheses of PANI

Although the importance of templates for obtaining the emeraldine salt form of PANI from aniline with oxidative enzymes has been shown convincingly (Liu et al. 1999b; Junker et al. 2012), there are reports on apparent template-free enzymatic synthesis of PANI in the emeraldine salt form. The importance of templates was shown using SDBS micelles vs. non-aggregating sodium benzenesulfonate (Liu et al. 1999b), or AOT vesicles vs. non-aggregating sodium di-*n*-butylsulfosuccinate (Junker et al. 2012). The non-aggregating sulfonates did not yield a PANI product in the emeraldine salt form although in both cases, the sulfonate concentration was kept constant. Whether in some reports of the template-free PANI synthesis, there was no aggregation of sulfonates, which were present in the reaction mixture, remains to be seen. Nevertheless, template-free PANI synthesis is possible, but it may yield a PANI which is less defined and with an unclear protonation or oxidation state.

Template-free enzymatic syntheses of PANI were performed in pure water as well as in water-organic solvent mixtures containing miscible (*N,N*-dimethylformamide (DMF), dioxane, tetrahydrofuran (THF)) or immiscible organic solvents (CH_2Cl_2, CCl_4, toluene) (Table 1). Besides HRP, which was most frequently used in the template-free PANI preparation (Table 1), SBP at 1 °C (Cruz-Silva et al. 2005), recombinant *Coprinus cinereus* peroxidase (CiP) (Kim et al. 2005), *Trametes hirsuta* laccase (Vasil'eva et al. 2007), and GOx (Kausaite et al. 2009) have also been used. Without templates, the extent of *ortho*-coupling is significant (Lim and Yoo 2000; Sahoo et al. 2002). It was found that the structure of PANI, obtained by the oxidative polymerization of aniline with HRP/H_2O_2 in a buffered water/organic solvent mixture, significantly depended on the pH of the buffer and the organic solvent type (Lim and Yoo 2000). PANI consisting prevalently of *ortho*-coupled units was formed at higher pH or in the presence of an organic solvent with a high dielectric constant or log *P* value (Lim and Yoo 2000). In contrast, recent NMR measurements demonstrated that *para*-coupling still dominated in the case of the oxidative polymerization of aniline with HRP/H_2O_2 at pH 4.3, independently of whether or not templates were present (Junker et al. 2012).

PANI films were synthesized enzymatically on macroscopic and not dispersed interfaces. This can be seen as an intermediate between conventional template-assisted and template-free polymerization. Thus, PANI films on various substrates have been synthesized using immobilized oxidoreductases. Electroactive PANI films were synthesized by the enzymatic polymerization of aniline on the surface of a bilirubin oxidase-adsorbed glass slide, a plastic plate, or a Pt electrode which were in contact with a phosphate buffer solution (pH 7.0) containing aniline (Aizawa et al. 1990). Synthesis of PANI films using HRP covalently immobilized on plasma-treated polyethylene surfaces in aqueous solution was reported by Alvarez et al. (2003). Also, enzymatically synthesized PANI films were obtained by the SBP-catalyzed oxidative polymerization of aniline with H_2O_2 in the presence of *p*-toluenesulfonic acid (*p*-TSA) at pH 3, followed by solution casting (Cruz-Silva et al. 2004). Layer-by-layer self-assembly of PANI synthesized by the enzymatic method of Akkara et al. (1991) was employed by Espinosa-González et al. (2003) for the production of alternate PANI/poly(phenyl-ethynylene) films. Vasil'eva et al. (2007) reported the laccase-catalyzed formation of chiral conducting PANI films on glass microscope slides by dipping the slides into the reaction vessel containing an aqueous solution of aniline, (+)- or

Table 1 Reaction conditions (enzyme/oxidant, solvent, acid/buffer, and pH) applied for the enzymatic template-free oxidative polymerization of aniline

Enzyme/oxidant	Solvent	Acid/buffer	pH	References
HRP/H_2O_2	DMF, dioxane, THF, CH_2Cl_2, and toluene mixtures with water	HEPES	7.5	Akkara et al. (1994a)
HRP/H_2O_2	Dioxane/water	Acetate	5.0	Akkara et al. (1991)
		Phosphate	7.0	
		HEPES	7.5	
HRP/H_2O_2/Cu(II), Ni(II), or Fe(III)	Water	HEPES	7.5	Cui et al. (2002)
HRP/H_2O_2 or SBP/H_2O_2	Water or dioxane/water	*p*-TSA	3.0 or 5.0	Cruz-Silva et al. (2005)
CiP/H_2O_2	CCl_4/water	CSA	pH <2.0 in water	Kim et al. (2005)
Laccase/O_2	Water	(+)-CSA	2.8	Vasil'eva et al. (2007)
		(−)-CSA		
GOx/O_2 in situ formed H_2O_2	Water	Acetate	4.0–7.0	Kausaite et al. (2009)
		Phosphate		

HEPES *N*-2-hydroxyethylpiperazine-*N*-2-ethane sulfonic acid, *p-TSA* *p*-toluenesulfonic acid, *CSA* camphorsulfonic acid

(−)-camphorsulfonic acid (CSA), and laccase at pH 2.8 under air saturated conditions. The formation of electroactive PANI films on indium-tin oxide and gold-coated quartz-crystal electrodes by the enzymatic oxidative polymerization of aniline at low oxidation potential has recently been studied by open circuit potential and quartz-crystal microbalance measurements (Carrillo et al. 2012). Zhang et al. (2013) recently reported the hemoglobin/GOx-catalyzed synthesis of electroactive PANI films on polystyrene nanospheres deposited on a glassy carbon electrode surface.

Template-assisted enzymatic syntheses of PANI

It was revealed by Liu et al. (1999b) that soft polymeric templates provide a quite different local environment (i.e., reaction conditions such as pH and charge density) than that of the bulk solution. They can be said to act as nanoreactors, which anchor, align, and control the reaction of the aniline monomers. Thus, they have a crucial impact on the obtained form of PANI (linear or branched, conducting or insulating). PANI has frequently been synthesized by the HRP-catalyzed oxidation of aniline in slightly acidic aqueous solution at pH 4.0–5.0 (most efficiently at pH 4.3) in the presence of various soft polymeric templates such as synthetic and natural neutral polymers (e.g., poly(ethylene glycol) (Liu et al. 1999b), poly(ethylene oxide) (Takamuku et al. 2003), poly(vinyl alcohol) (Takamuku et al. 2003), poly(vinyl pyrrolidone) (Takamuku et al. 2003), denaturated bovine serum albumin complexed with SDS (Gu et al. 2009), polymeric acids and their salts as polyanionic templates (e.g., poly(sodium acrylate) (Liu et al. 1999b), SPS (Samuelson et al. 1998; Liu et al. 1999a, b, c; Wang et al. 1999; Takamuku et al. 2003; Kimura and Kumar 2004; Sahoo et al. 2004) (Fig. 13), poly(sodium vinylsulfonate) (Shen et al. 2005), poly(maleic acid co-olefin) sodium salt (Liu et al. 1999b), poly(vinylphosphonic acid) (Nagarajan et al. 2000; Sahoo et al. 2001, 2002, 2004), poly(vinylbenzylthymine-*co*-vinylphenylsulfonate) (Trakhtenberg et al. 2005), ribonucleic acid (RNA) (Liu et al. 1999b), DNA (Nagarajan et al. 2001a, b; Samuelson et al. 2001; Ma et al. 2004; Nickels et al. 2004; Gao et al. 2007b; Zeifman et al. 2012), and synthetic oligonucleotides (Nagarajan et al. 2001b), and polycationic templates (e.g., poly(diallyldimethylammonium chloride) (PDADMAC); Liu et al. 1999b). Strong acid polyelectrolytes and their salts (e.g., SPS) were proven to be the most favorable soft polyanionic templates which provide a local environment with considerably higher acidity than that of the bulk solution because strongly acidic polyelectrolytes electrostatically attract hydrogen ions (Liu et al. 1999b). Strongly acidic polyelectrolytes serve to both protonate and align the aniline monomers through electrostatic and hydrophobic interactions to promote the desired N–C4 coupling (Liu et al. 1999b). Since a low pH environment is necessary for the linear chain growth of conducting PANI emeraldine salt, it follows that polycations and neutral polymers, as well as weak polymeric acids (weak acid polyelectrolytes) and their salts, do not provide a sufficiently acidic environment for the formation of conducting PANI. Consequently, branched low-molecular-weight PANIs were obtained in the presence of neutral and polycationic templates, as well as in the presence of weak polymeric acids and their salts, whereas conducting linear high-molecular-weight PANI was formed in the presence of strong polymeric acids and their salts (Liu et al. 1999b). Jin et al. (2001) reported a method for the synthesis of a water-dispersible PANI using H_2O_2

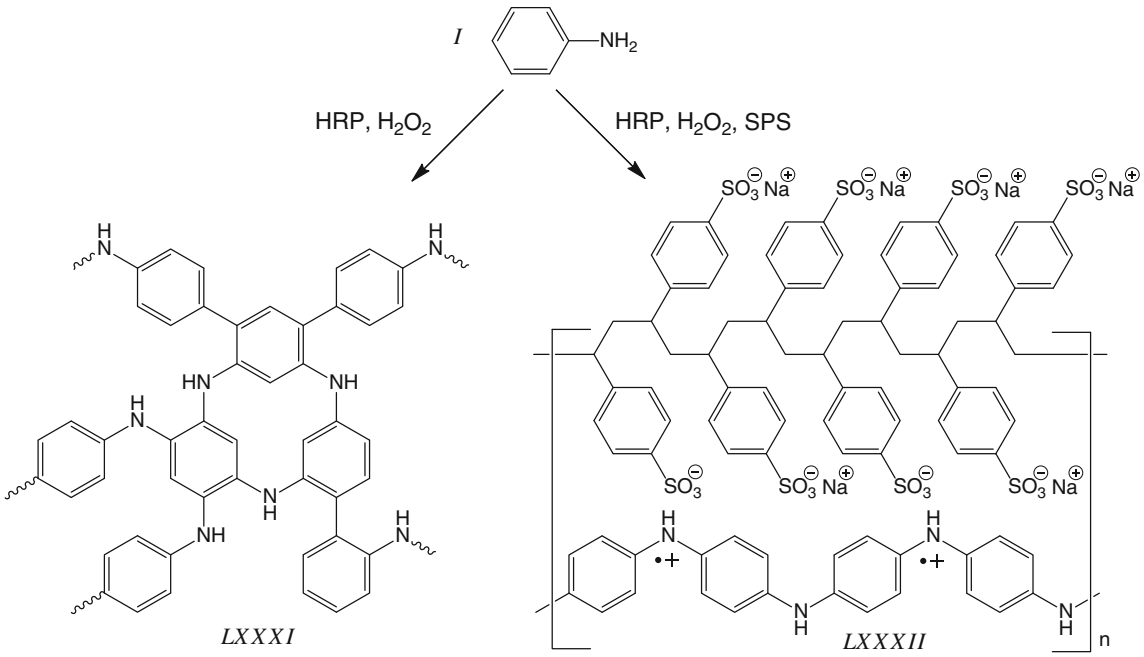

Fig. 13 Classic oxidative polymerization of aniline (*I*) with HRP/H_2O_2, resulting in a branched nonconducting PANI (*LXXXI*), vs polymerization of aniline with HRP/H_2O_2 in the presence of SPS at pH 4 resulting in the conducting PANI emeraldine salt (*LXXXII*)

and HRP immobilized on linear polysaccharide chitosan by a simple glutaraldehyde bridge method. A poly(acrylic acid) guided enzymatic approach was developed by Thiyagarajan et al. (2003a, b) and Cholli et al. (2005) to synthesize optically active conducting PANI with HRP/H_2O_2 in the presence of (+)- and (−)-10-CSA as a dopant and chiral inductor. Sfez et al. (2006) reported the enzymatic formation of a PANI monolayer on modified hydroxyl-terminated surfaces with a three-step method which includes: (a) chemical modification of hydroxyl-terminated surfaces using 3-aminopropyltrimethoxysilane as a coupling agent which contains a positively charged amine end group, (b) electrostatic deposition of polyanionic SPS template followed by electrostatic adhesion of protonated aniline molecules, and (c) enzymatic oxidative polymerization of the aniline monolayer with HRP/H_2O_2. An HRP-catalyzed oxidative polymerization of aniline in the presence of a photo-cross-linkable thymine-based polymer with phenylsulfonate groups as template, which allows for an aqueous, environmentally benign photopatterning of conductive PANI, was presented by Trakhtenberg et al. (2005).

Besides the extensive use of HRP as a biocatalyst, other oxidoreductases have also been used in the enzymatic polymeric acid/polyanion-assisted synthesis of PANI. Palm tree peroxidase (PTP) was utilized as a biocatalyst in the oxidative polymerization of aniline with H_2O_2 in the presence of SPS (Sakharov et al. 2003, 2004) at pH 3.5 and poly(2-acrylamido-2-methyl-1-propanesulfonic acid) at pH 2.8 (Caramyshev et al. 2005; Mazhugo et al. 2005). Laccase-catalyzed synthesis of PANI with polymers as templates was also reported, e.g., in the presence of SPS (Karamyshev et al. 2003), poly(2-acrylamido-2-methyl-1-propanesulfonic acid) (Vasil'eva et al. 2009; Shumakovich et al. 2010; Simagina et al. 2010), and lignosulfonate (Zhang et al. 2016b) at pH 3.5. *P. sajor caju* derived enzymes/H_2O_2 systems produced dispersed PANI in the presence of SPS (Curvetto et al. 2006). Longoria et al. (2010) reported the oxidative polymerization of aniline by CPO/H_2O_2 in an isopropanol/water mixture at pH 3.0 in the presence of SPS. Conducting PANI/DNA complexes were recently synthesized by microperoxidase-catalyzed oxidative polymerization of aniline in the presence of DNA (Zeifman et al. 2012). The synthesis of PANI in an acidic aqueous medium in a pH ranging from 2.0 to 5.0 via DNAzyme-catalyzed oxidative polymerization of aniline with H_2O_2 in the presence of poly(acrylic acid) as a template was recently described by Shen et al. (2014). The utilization of DNAzyme, which consists of single-stranded DNA and hemin, is more cost-effective than the use of HRP as the catalyst in the polymerization of aniline, and DNAzyme showed a higher tolerance towards high acidity of the reaction medium and high concentrations of H_2O_2. Wang et al. (2013) recently assembled DNA strands containing the sequence of DNAzyme with two complementary DNA strands, and in some cases with spacer DNA, into DNA nanostructures with various morphologies (Y, etc.). These DNA structures were used as templates in the synthesis of conducting PANI emeraldine salt nanostructures with controlled morphology via the DNAzyme-

catalyzed aniline polymerization with H_2O_2 (Fig. 14). It was found that PANI grew from the DNAzyme sites and then coated the DNA template to form 1-dimensional PANI nanostructures. Wang et al. (2014b) also demonstrated the fabrication of 2-dimensional PANI nanostructures via the arrangement of DNAzyme arrays on 2-dimensional triangular DNA origami templates, thus enabling site-selective enzymatic synthesis of PANI at specific regions on the DNAzyme sites. A DNAzyme hydrogel matrix for the oxidative polymerization of aniline with H_2O_2 was recently obtained by incorporating hemin into stimuli-responsive G-quadruplex-crosslinked hydrogel, which was assembled from a guanine-rich nucleic acid-tethered acrylamide/*N*-isopropylacrylamide copolymer chains in the presence of K^+ ions (Lu et al. 2015). The PANI emeraldine salt/DNAzyme hydrogel hybrid, formed upon doping with HCl, exhibited an electrical conductivity of 9×10^{-4} (cm $\Omega)^{-1}$.

It was found by Liu et al. (1999b) that micelles consisting of anionic surfactant molecules based on strong sulfonic acids, which allow aniline monomers to intercalate between the headgroups of the micelles, also provide a favorable local soft template environment for the formation of conducting PANI. The local environment created by the micelles of strong acid-based anionic surfactant molecules (electrical double layers with increased local concentration of H^+, accompanied with hydrophobic pockets with which the aniline monomers may associate) is quite similar to that of the already mentioned polyanionic salts of strong polymeric acids. The conducting emeraldine salt form of PANI was not obtained if the concentration of the surfactant was lower than the critical micellar concentration or if the distance between the headgroups in the micellar system was too large (Liu et al. 1999b). Micelles from SDBS (Liu et al. 1999b, 2002; Samuelson et al. 2001; Sahoo et al. 2004) and their mixtures with polyoxyethylene(10) isooctylphenyl ether (Liu et al. 1999b) and ionic liquids (1-butyl-3-methylimidazolium trifluoromethansulfonate (Gu and Tsai 2012) or 1-butyl-3-methylimidazolium hexafluoride (Rumbau et al. 2006), as well as micelles formed from sodium dodecyl diphenyloxide disulphonate (Rumbau et al. 2007) and AOT (Zou et al. 2013, 2014), have been used as soft templates in HRP-catalyzed polymerizations of aniline, leading to conducting PANI. In the case of AOT, the claim that *micelles* and not vesicles served as template seems to be in disagreement with the work on AOT *vesicles* (see below, Fig. 15), although the type of aggregate that forms in dilute aqueous solution depends on the salt content (Guo et al. 2011). The presence of micelles formed from CTAB or polyoxyethylene(10) isooctylphenyl ether

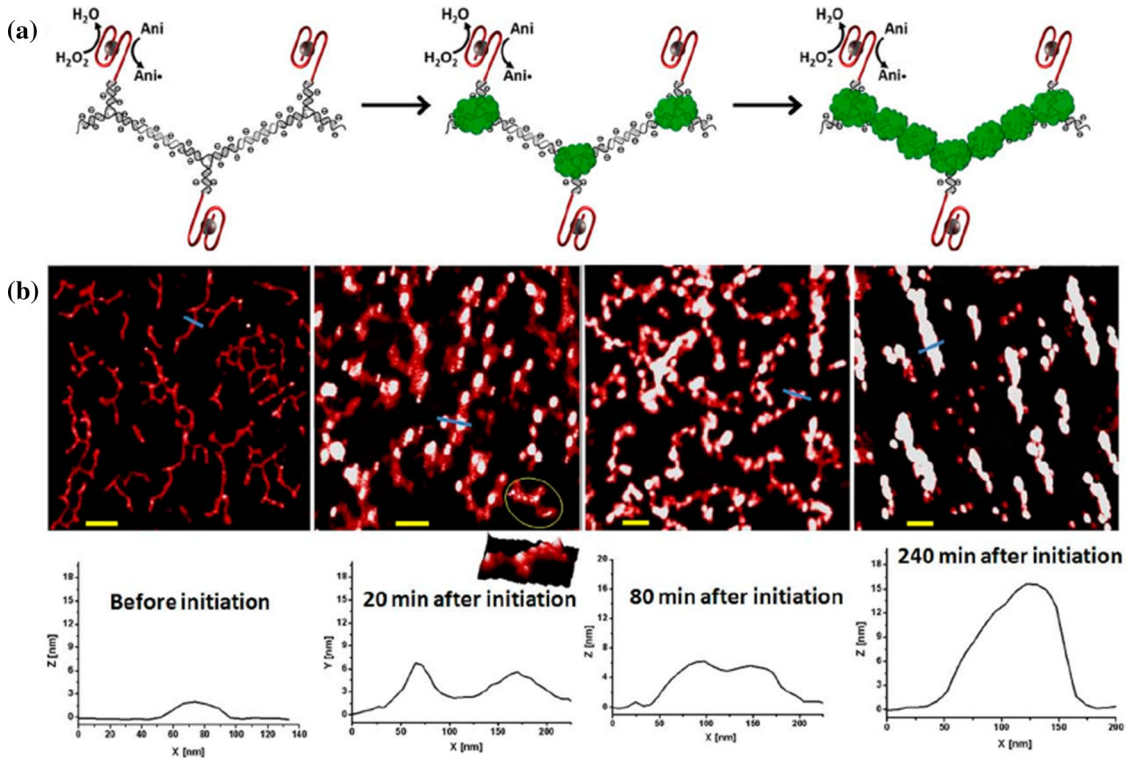

Fig. 14 Regioselective PANI growth guided by the DNA nanostructures containing DNAzyme: **a** scheme of the PANI formation on DNA templates; **b** atomic force microscopy images before initiation, and 20–240 min after initiation of the PANI growth. The height of the corresponding cross section is shown on the *bottom panels*. Reprinted with permission from Wang et al. (2013). Copyright 2013 American Chemical Society

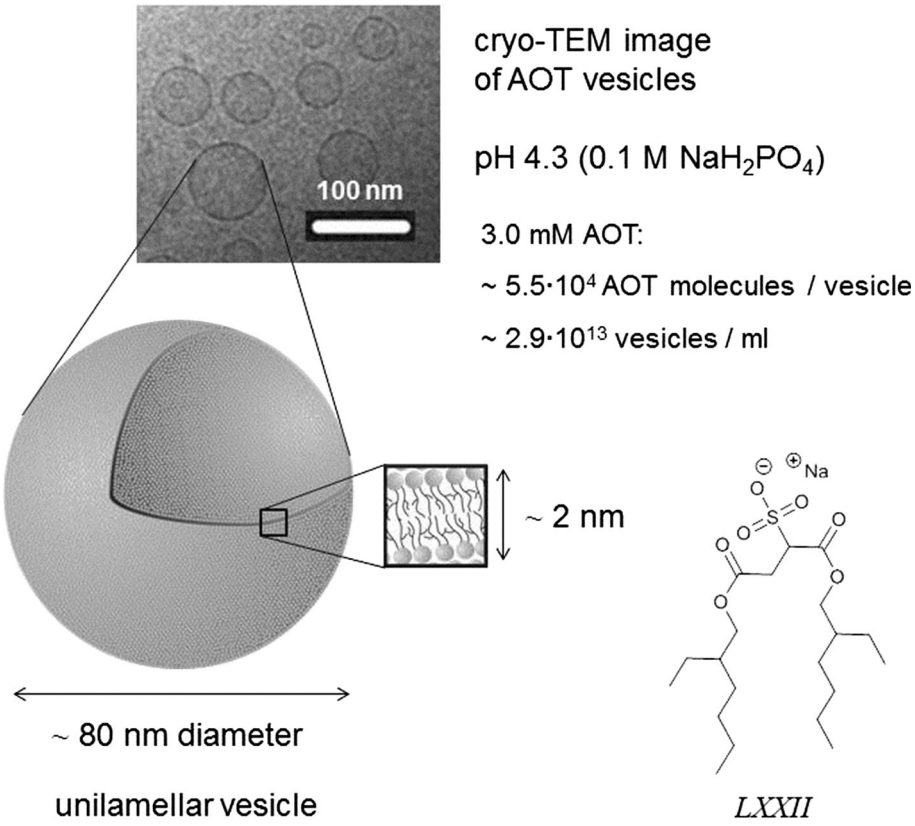

Fig. 15 Cryo-transmission electron micrograph of an AOT (*LXXII*) vesicle suspension (*top*) and schematic represenation of one unilamellar vesicle formed in aqueous solution at pH = 4.3 (0.1 M NaH_2PO_4). For the conditions given, see Junker et al. (2013). Electron micrograph taken by T. Ishikawa, PSI, Villigen, Switzerland

in the HRP-catalyzed oxidation of aniline with H_2O_2 did not lead to the formation of the conducting emeraldine salt form of PANI but to branched low-molecular-weight PANI (Liu et al. 2002). It was recently claimed that chiral, conducting, and water-dispersible PANI was prepared by the HRP/H_2O_2-triggered polymerization of aniline in AOT micellar solution without any other chiral inducer but HRP itself (Zou et al. 2013). Micelles from dodecylbenzenesulfonate in the presence as well as the absence of optically active CSA were also used as templates for the formation of chiral conducting PANI with PTP/H_2O_2 at pH 3.5 (Caramyshev et al. 2007). The SDBS micelle-assisted laccase-catalyzed oxidative polymerization of aniline with O_2 at pH 3.5–4.0, leading to stable dispersions of PANI, was reported by Streltsov et al. (2008, 2009) and Zhang et al. (2014b). This method was further improved by Shumakovich et al. (2012) by the addition of tetrapotassium octacyanomolybdate(IV) as a redox mediator to accelerate the polymerization. Also, Zhang et al. (2014a) recently found that ionic liquid tetramethylammonium trifluoromethanesulfonate improves the SDBS micelle-assisted laccase-catalyzed synthesis of water-dispersible conducting PANI. Furthermore, it has been demonstrated that β-cyclodextrin improves the linearity, and consequently conductivity, of PANI synthesized by the laccase-catalyzed aniline polymerization in AOT micellar solution (Zou et al. 2014).

Vesicles from SDBS and decanoic acid (1:1 mol ratio) or from SDS and decanol (1:1 mol ratio) were also found to be useful as soft templates for the HRP-catalyzed synthesis of conducting PANI, whereas the presence of vesicles from 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine did not lead to the formation of conducting PANI (Guo et al. 2009a, b). Unilamellar vesicles with a diameter of ≈70–80 nm from AOT (Fig. 15) were recently applied as templates for the oxidative polymerization of aniline with HRP/H_2O_2 at pH 4.3, leading to a stable dispersion containing conducting PANI-coated vesicles (Guo et al. 2011; Junker 2013). The HRP is thought to bind to the AOT vesicle surface, thus leading to preferential initiation of aniline polymerization on the vesicle surface. It was revealed that HRP is more stable in the presence of AOT vesicles than in the presence of the SDBS/decanoic acid vesicles used previously by Guo et al. (2009a, b), which were already shown to be better than SDBS micelles with regard to HRP stability (Guo et al. 2009a, b). It is also important to mention that at temperatures below 10 °C the AOT vesicles are stable, whereas SDBS/decanoic acid vesicles precipitate. It was noted that in the case of the oxidative polymerization of aniline with HRP/H_2O_2, vesicles are different from

polyanions and micelles since vesicles in principle allow for the preparation of hollow PANI capsules (Guo et al. 2011). HRP was replaced with SBP because SBP is more stable towards inactivation by H_2O_2; however, this replacement was not advantageous (Junker et al. 2013). This is due to the fact that the oxidation of aniline with SBP/H_2O_2 was much slower than the corresponding oxidation of aniline with HRP/H_2O_2, and SBP became completely inactivated in the presence of AOT vesicles before all the aniline molecules were oxidized, thus leading to low yields of PANI and the formation of over-oxidized products due to excess, unconsumed H_2O_2 (Junker et al. 2013). As an alternative to the peroxidase-catalyzed polymerization, enzymatic polymerization of aniline with TvL and O_2 at pH 3.5, again with AOT vesicles as templates, was recently conducted (Junker et al. 2014a). The kinetics of this polymerization reaction and the characteristics of the synthesized PANI were significantly different in comparison with the corresponding aniline polymerization with HRP/H_2O_2. Under comparable optimal conditions, the reaction with TvL/O_2 was found to be much slower than with HRP/H_2O_2, i.e., $\approx$27 days vs. 1 day reaction time to reach equilibrium with >90% yield at 25 °C. Although *para*-coupling of aniline monomers occurred prevalently in both cases, it was found that overoxidized products were predominantly obtained by the oxidative polymerization of aniline with TvL/O_2. Similar to previous findings regarding enzyme inactivation in HRP/H_2O_2/AOT/aniline and SBP/H_2O_2/AOT/aniline reaction systems, TvL was inactivated during the polymerization in the TvL/O_2/AOT/aniline reaction system. The paramagnetic properties of the PANI samples obtained by HRP- or TvL-catalyzed polymerization of aniline in the presence of AOT vesicles could be related to their conductivities (Rakvin et al. 2014). Significantly lower conductivities of the isolated, solid products in comparison with the conductivity of chemically synthesized PANI emeraldine salt were attributed to decreased interchain spin interactions, which were indicated by a splitting of the EPR triplet spectrum at low temperatures 5–10 K (Rakvin et al. 2014). The increased effective distance between the PANI chains in the case of enzymatically synthesized PANI, in comparison with PANI interchain distance characteristic for chemically synthesized PANI emeraldine salt, is most probably due to the presence of AOT which was not completely removed during the PANI isolation and purification.

Although soft template polyanion/micelles/vesicles-assisted polymerization of PANI has many advantages (Walde and Guo 2011), there are still limitations which need to be addressed (Kim et al. 2007a). The conductivities of PANI complexes with polyanionic template molecules and/or supramolecular aggregates/self-assemblies of soluble amphiphilic/surfactant molecules (micelles, vesicles) are relatively low compared with inorganic/organic acid-doped PANI. Despite the fact that PANI shows increased water dispersibility due to the polyanionic/micellar/vesicular template, the wettability of the PANI/soft template solution/dispersion is not good because of the pronounced hydrophobicity of the substrate (Kim et al. 2007a). If a PANI complex is dried on a substrate, the complex cannot be redissolved or resuspended, which is disadvantageous regarding the recyclability of the materials (Kim et al. 2007a). Finally, it is worthwhile to note that the removal of the soft template by ion exchange is a time-consuming and difficult process. Consequently, PANI complexed with soft templates (polyanions, micelles, vesicles) cannot easily be modified/functionalized for certain applications (Kim et al. 2007a).

Hard dispersed templates have rarely been employed in the enzymatic syntheses of PANI. The effect of various inorganic hard templates such as controlled pore glass, mordenite, zeolite Y, zeolite MCM-41, Wollastonite, silica gel, fuming silica and short glass fibers type E, on the molecular structure of PANI, synthesized by the HRP or SBP-catalyzed oxidation of aniline with H_2O_2 in the presence of *p*-TSA, was studied by Flores-Loyola et al. (2007). It was revealed that the composition of the inorganic substrates has a considerable influence on the degree of electron delocalization in PANI, e.g., substrates containing alkaline ions (Na^+, Ca^{2+}) promoted the formation of branched, non-conducting PANI, whereas the pore size and the enzyme type had no observable influence. Carboxylic acid-functionalized multiwalled carbon nanotubes (MWCNTs-COOH), with covalently attached HRP and GOx, were also used as a hard template for the deposition of electroactive PANI under ambient conditions (Sheng and Zheng 2009).

Enzymatic synthesis of PANI colloids

Based on what has been elaborated during the last years, anionic polyelectrolytes serve three critical functions: (a) they seem to preferentially align the aniline monomers and promote their N-C4 coupling as required for obtaining the emeraldine salt form of PANI, (b) they provide counterions for PANI doping, and (c) they maintain water dispersibility and, consequently, increase the processability of PANI. Therefore, the polyanionic template-assisted enzymatic polymerization of aniline, leading to stable dispersions of doped PANI, is certainly advantageous regarding PANI processability (Liu et al. 1999a, b, c; Sakharov et al. 2003, 2004; Curvetto et al. 2006); however, isolating undoped PANI is impeded because the polycationic PANI emeraldine chain is strongly bound to the polyanionic template. Therefore, numerous reports have appeared in the past on the enzymatic synthesis of colloidal PANI, based on the fact that steric colloidal stabilizers (commonly non-ionic polymers) adsorbed on the PANI particles can simply

be eliminated by multiple centrifugation–redispersion cycles. In addition, the use of low-molecular-weight dopant acids instead of polymeric acids also allows for easy undoping–redoping of synthesized PANI emeraldine salt. Cruz-Silva et al. (2006) reported the HRP/H_2O_2 oxidative polymerization of aniline to PANI colloidal particles in the presence of hydrochloric acid, *p*-TSA, and CSA as doping acids, and poly(vinyl alcohol) as a steric stabilizer. The synthesis of PANI colloids was also successfully achieved by the oxidative polymerization of aniline with HRP/H_2O_2 in the presence of *p*-TSA and poly(*N*-isopropylacrylamide) (Cruz-Silva et al. 2007a), or with SBP/H_2O_2 in the presence of *p*-TSA and chitosan as a biopolymeric template/steric stabilizer (Cruz-Silva et al. 2007a, b). Photosensitive PANI colloids were prepared by enzymatic polymerization using HRP/H_2O_2 as catalyst/oxidant, *p*-TSA as dopant acid, and the photo- and temperature-responsive poly(*N*,*N*-dimethylacrylamide-*co*–*N*-4-phenylazo-phenylacrylamide) as a steric stabilizer (Güizado-Rodríguez et al. 2010).

Enzymatic copolymerization of aniline with other arylamines

The synthesis of aniline copolymers, especially with other arylamines, by careful tuning of the initial molar ratio of aniline to the other monomers is an efficient approach that may significantly improve the relatively poor processability of PANI. Copolymerization is also a convenient route to functionalized PANI with versatile applicability. The enzymatic syntheses of aniline copolymers with other arylamines have only occasionally been explored (Akkara et al. 1994b; Bruno et al. 1995a, b; Huh et al. 2007; Nabid et al. 2010), while the enzymatic copolymerization of aniline with heterocyclic compounds was scarcely reported (Chen and Schuster 2013).

The HRP-catalyzed copolymerizations of aniline with 4-hexadecylaniline at an air–water interface (Langmuir trough), or in the presence of reverse micelle templates, accomplished by Akkara et al. (1994b) and Bruno et al. (1995a, b), were the first reports regarding enzymatic synthesis of aniline copolymers with other arylamines.

The self-doped copolymer poly(aniline-*co*-3-aminobenzeneboronic acid) with various molar ratios of aniline to 3-aminobenzeneboronic acid was synthesized by oxidative enzymatic polymerization using HRP/H_2O_2 and a polyanionic template (SPS) at pH 4.5 (Huh et al. 2007). A green emeraldine salt form of poly(aniline-*co*-3-aminobenzeneboronic acid) was obtained in the case of an aniline boronic acid to aniline ratio of 1:2. The 3-aminobenzeneboronic acid behaved as a dopant at low concentrations, whereas at higher concentrations it worked as a bulky pendant group which decreased the PANI conductivity, thus allowing for a modulation of the electrical properties of the copolymer. Nabid et al. (2010) have recently reported the enzymatic synthesis of water-dispersible aniline/*o*-anisidine copolymer at various initial aniline/*o*-anisidine molar ratios, using HRP as a catalyst, H_2O_2 as an oxidant, and SPS as a polyanionic template. Due to the much higher oxidizability of *o*-anisidine in comparison with aniline, the molecular structure and physico-chemical properties of the aniline/*o*-anisidine copolymer were found to be dominated by the *o*-anisidine units.

Enzymatic polymerization of substituted anilines and other arylamines

The first successful polymerizations of substituted anilines were reported in the first half of the twentieth century, e.g., Mann and Saunders (1935) observed that a green precipitate of PANI-like emeraldine salt was obtained upon the dissolution of the aniline dimer PADPA or phenylhydroxylamine in an aqueous solution of acetic acid followed by the addition of H_2O_2 and HRP. After this discovery, numerous substituted anilines were enzymatically polymerized, e.g., alkyl-, aryl-, and arylalkyl-substituted anilines (Tables 2, 3), phenylenediamines (Table 4), halogen-

Table 2 Reaction conditions (enzyme/oxidant, solvent, acid/buffer, pH, and template) applied in enzymatic polymerization of alkyl-substituted anilines

Alkylaniline	Enzyme/oxidant	Solvent	Acid/buffer	pH	Template	References
2-Methylaniline	HRP/H_2O_2	Water	Phosphate	4.3	SPS	Nabid and Entezami (2003a)
	HRP/H_2O_2	Water	Phosphate CSA	4.3	PAA	Nabid et al. (2006a)
2,6-Dimethylaniline	CPO/H_2O_2	i-PrOH/water	Acetate	3.0	–	Longoria et al. (2010)
2-Ethylaniline	HRP/H_2O_2	Water	Phosphate	4.0–10.0	SPS	Nabid and Entezami (2003b)
N-Methylaniline	HRP/H_2O_2	Water	Phosphate	3.0	SPS	Nabid and Entezami (2005)
N-Ethylaniline	HRP/H_2O_2	Water	Phosphate	3.0	SPS	Nabid and Entezami (2005)
N-Butylaniline	HRP/H_2O_2	Water	Phosphate	3.0	SPS	Nabid and Entezami (2005)

CPO chloroperoxidase, *CSA* camphor sulfonic acid, *i-PrOH* isopropanol, *PAA* poly(acrylic acid), *SPS* poly(sodium 4-styrenesulfonate)

Table 3 Reaction conditions (enzyme/oxidant, solvent, buffer, and pH) applied in enzymatic polymerization of aryl-substituted anilines and arylalkyl-substituted anilines

Arylaniline or arylalkylaniline	Enzyme/oxidant	Solvent	Buffer	pH	References
4-Aminobiphenyl	HRP/H_2O_2	Water	Acetate	7.0	Klibanov and Morris (1981)
Benzidine	HRP/H_2O_2	Water	Acetate	5.5	Klibanov and Morris (1981)
	HRP/H_2O_2	EtOH/water	Phosphate	7.0	Josephy et al. (1983)
			Arachidonic acid		
	HRP/H_2O_2	Dioxane/water	Acetate	5.0	Akkara et al. (1991)
			Phosphate	7.0	
			HEPES	7.5	
	HRP/H_2O_2	Dioxane/water	HEPES	7.5	Aranda et al. (1995)
o-Tolidine	HRP/H_2O_2	Water	Acetate	5.5	Klibanov and Morris (1981)
o-Dianisidine	HRP/H_2O_2	Water	Acetate	5.5	Klibanov and Morris (1981)
3,3′-Diaminobenzidine	HRP/H_2O_2	Water	Acetate	5.5	Klibanov and Morris (1981)
3,3′-Dichlorobenzidine	HRP/H_2O_2	Water	Acetate	5.5	Klibanov and Morris (1981)
2-Aminofluorene	HRP/H_2O_2	Dioxane/water	Phosphate	7.0	Bilici et al. (2010)
Diphenylamine	ARP/H_2O_2	Water	Phosphate	6.0–7.4	Biswas et al. (2007)
	Laccase/O_2	Water	Phosphate	7.0	Saha et al. (2008)

ARP Arthromyces ramosus peroxidase, *EtOH* ethanol

Table 4 Reaction conditions (enzyme/oxidant, solvent, buffer, pH, and template) applied in enzymatic polymerizations of phenylenediamines

Phenylenediamine	Enzyme/oxidant	Solvent	Buffer	pH	Template	References
o-Phenylenediamine	HRP/H_2O_2	Dioxane/water	Phosphate		–	Kobayashi et al. (1992)
	HRP/H_2O_2	Dioxane/water	HEPES	7.1	–	Ichinohe et al. (1998a, b)
			Phosphate			
	HRP/H_2O_2	Isooctane/water	HEPES	7.1	AOT inverse micelles	Ichinohe et al. (1997, 1998a, 1998c)
	HRP/H_2O_2	Dioxane/water	Phosphate	6.0–7.0	–	Shan and Cao (2000)
	SBP/H_2O_2	Water	Acetate	4.5–5.2	–	Al-Ansari et al. (2009)
m-Phenylenediamine	HRP/H_2O_2	Dioxane/water	HEPES	7.1	–	Ichinohe et al. (1998a, b)
			Phosphate			
	HRP/H_2O_2	Isooctane/water	HEPES	7.1	AOT inverse micelles	Ichinohe et al. (1997, 1998a, c)
	HRP/H_2O_2	Dioxane/water	Acetate	5.0	–	Akkara et al. (1991)
			Phosphate	7.0		
			HEPES	7.5		
	HRP/H_2O_2	Dioxane/water	Phosphate	6.0–7.0	–	Shan and Cao (2000)
	SBP/H_2O_2	Water	Acetate	5.4	–	Al-Ansari et al. (2009)
p-Phenylenediamine	HRP/H_2O_2	Dioxane/water	HEPES	7.1	–	Ichinohe et al. (1998a, b)
			Phosphate			
	HRP/H_2O_2	Isooctane/water	HEPES	7.1	AOT inverse micelles	Ichinohe et al. (1997, 1998a, c)
	HRP/H_2O_2	Dioxane/water	Phosphate	6.0–7.0	–	Shan and Cao (2000)
	SBP/H_2O_2	Water	Acetate	5.6	–	Al-Ansari et al. (2009)
N-Phenyl-*p*-phenylenediamine (PADPA)	Laccase/O_2	Water	Phosphate	3.5	AOT vesicles	Junker et al. (2014b), Carić et al. (2015), Janošević-Ležaić et al. 2016
	Laccase/O_2	Water	Citrate	3.8	SDBS micelles	Shumakovich et al. (2011)
			Phosphate			

Table 5 Reaction conditions (enzyme/oxidant, solvent, buffer, and pH) applied in enzymatic polymerizations of halogen-substituted anilines, aminophenols, and aminothiophenols

Arylamine	Enzyme/oxidant	Solvent	Buffer	pH	References
2,6-Dichloro-aniline	CPO/H_2O_2	i-PrOH/water	Acetate	3.0	Longoria et al. (2010)
2,3,5,6-Tetrachloro-aniline	CPO/H_2O_2	i-PrOH/water	Acetate	3.0	Longoria et al. (2008, 2010)
Pentachloroaniline	CPO/H_2O_2	i-PrOH/water	Acetate	3.0	Longoria et al. (2008)
2-Aminophenol	HRP/H_2O_2	Dioxane/water	Phosphate	7.0	Shan et al. (2003)
	Laccase/O_2	Water			Pałys et al. (2010)
3-Aminophenol	HRP/H_2O_2	Dioxane/water	Phosphate	7.0	Shan et al. (2003)
4-Aminophenol	HRP/H_2O_2	Dioxane/water	Phosphate	6.0–7.0	Shan and Cao (2000), Shan et al. (2003)
4-Amino-*m*-cresol	HRP/H_2O_2	Dioxane/water	Acetate	5.0	Akkara et al. (1991)
			Phosphate	7.0	
			HEPES	7.5	
4-Aminothiophenol	HRP/H_2O_2	MeOH/water		6.0–7.0	Xu and Kaplan (2004)

i-PrOH isopropanol, *MeOH* methanol

substituted anilines, aminophenols, and aminothiophenols (Table 5), alkoxyanilines (Table 6), azoarylamines, arylaminoalcohols, arylaminoketones, aminobenzoic acids, and aminobenzenesulfonic acids (Table 7), in the presence as well as in the absence of polymeric, micellar, and vesicular templates.

It was found that the size, type, and substitution pattern of the functional groups have a substantial effect on the properties of the final poly(substituted aniline)s. Since the majority of enzymatically synthesized poly(substituted aniline)s are obtained in the form of stable aqueous dispersions in the presence of polymer/micelle/vesicle templates, data on their electrical conductivities are frequently missing. The conclusions on the presence or absence of conducting emeraldine salt-like structural units in enzymatically obtained poly(substituted aniline)s were mainly based on FTIR spectroscopy data and visible/NIR spectroscopy. These measurements indicated whether the characteristic transformation of PANI took place: from green conducting emeraldine salt-like, to blue nonconducting emeraldine base-like upon dedoping of the as-synthesized products. It was observed that in most cases, whenever the C4-position of substituted benzene ring in aniline derivatives is not occupied by the substituent, the so-called head-to-tail *para*-coupling (N–C4), leading to emeraldine salt-like structural units, is the dominant coupling type in enzymatically synthesized poly(substituted aniline)s. Comparative studies on the molecular structure and properties of enzymatically synthesized poly(substituted aniline)s have rarely been reported. Thus, regarding comparison of the properties of enzymatically prepared poly(alkyl-substituted aniline)s, Nabid and Entezami (2005) showed that the electroactivity of enzymatically synthesized poly(*N*-alkyl-substituted aniline)s complexes with SPS increased, while their solubility and thermal stability decreased, with increasing bulkiness of the alkyl substituents.

Since the work of Klibanov and Morris (1981) more than three decades ago, which was devoted to the removal of several aryl-substituted anilines and arylalkyl-substituted anilines from industrial aqueous effluents by their HRP-catalyzed oxidative polymerization with H_2O_2, enzymatic polymerization of this type of substituted anilines was occasionally investigated. The recent results of Bilici et al. (2010) on the HRP-catalyzed oxidative polymerization of 2-aminofluorene (*LX*, Fig. 16) showed that poly(2-aminofluorene) is built up of C–C coupled dimeric units containing a pyrazine ring (*LXXXIII*, Fig. 16). The obtained polymer is soluble in common polar and apolar organic solvents and has an optical band gap of 2.60 eV. It emits red light and its emission maxima are significantly affected by the solvent. It is interesting to note that there is no report regarding the enzymatic template-guided polymerization of aryl-substituted anilines and/or arylalkyl-substituted anilines to the corresponding conducting polymers.

Numerous reports regarding enzymatic polymerization of phenylenediamines and their derivatives have appeared since the early 1990s. Akkara et al. (1991) reported on the polymerization of *m*-phenylenediamine with HRP/H_2O_2 in an aqueous dioxane solution, and Kobayashi et al. (1992) claimed that the enzymatic oxidation of *o*-PDA by HRP/H_2O_2 in an aqueous dioxane leads to polymeric materials with an average molar mass of 20,000 g/mol, composed mainly of imino-2-aminophenylene units, while the simple nonenzymatic oxidation of *o*-PDA with H_2O_2 yielded oligomeric products ($M_w = 800$) (Table 4). A comparative study of the HRP-catalyzed polymerizations of *o*-, *m*-, and *p*-PDA in homogeneous dioxane/water systems was performed by Ichinohe et al. (1998a, b). It was found that the

Table 6 Reaction conditions (enzyme/oxidant, solvent, buffer, pH, and template) applied in enzymatic polymerizations of alkoxyanilines

Alkoxyaniline	Enzyme/oxidant	Solvent	Buffer	pH	Template	References
2-Methoxyaniline	HRP/H_2O_2	Water	Phosphate	4.0	SPS	Nabid et al. (2007a)
	HRP/H_2O_2	Dioxane/water	Phosphate	7.0	–	Shan et al. (2003)
	HRP/H_2O_2	Water	Phosphate	4.3	SPS	Zamiraei and Tanzadeh (2016)
3-Methoxyaniline	HRP/H_2O_2	Water	Phosphate	4.0	SPS	Nabid et al. (2007a)
	HRP/H_2O_2	Dioxane/water	Phosphate	7.0	–	Shan et al. (2003)
4-Methoxyaniline	HRP/H_2O_2	Dioxane/water	Phosphate	7.0	–	Shan et al. (2003)
2-Ethoxyaniline	HRP/H_2O_2	Water	Phosphate	4.0	SPS	Nabid et al. (2007a)
3-Ethoxyaniline	HRP/H_2O_2	Water	Phosphate	4.0	SPS	Nabid et al. (2007a)
2,5-Dimethoxyaniline	HRP/H_2O_2	Water/EtOH	Phosphate	3.0	–	Kim et al. (2007a)
	HRP/CH_3CO_3H	Water/DMF Water/DMSO Water/dioxane				
	HRP-dendron/H_2O_2	EtOH/water	Phosphate Citrate	3.0	–	Khosravi et al. (2013)
	HRP-dendron/ H_2O_2/$FeCl_3$	EtOH/water	Phosphate Citrate	3.0	–	Khosravi et al. (2013)
2-Methyl-5-methoxyaniline	HRP/H_2O_2	Water/EtOH	Phosphate	3.0	–	Kim et al. (2007a)
	HRP/CH_3CO_3H	Water/DMF Water/DMSO Water/dioxane				
2-Methoxy-5-methylaniline	HRP/H_2O_2	Water/EtOH	Phosphate	3.0	–	Kim et al. (2007a)
	HRP/CH_3CO_3H	Water/DMF Water/DMSO Water/dioxane				

DMSO dimethyl sulfoxide, *EtOH* ethanol

polymeric yield significantly depends on the dioxane/water ratio, and the highest yields of polyphenylenediamines were obtained in a 15/85 (v/v) dioxane/water mixture (Ichinohe 1998b). All phenylenediamines were also successfully polymerized by HRP/H_2O_2 in a reversed micellar system of isooctane/water/AOT (Ichinohe et al. 1997, 1998a, c). Polyphenylenediamines synthesized by both enzymatic methods, in a homogeneous dioxane/water system as well as in a heterogeneous reversed micellar isooctane/water/AOT system, showed ferromagnetic behavior (Ichinohe et al. 1997, 1998a). Poly(*o*-PDA) and poly(*p*-PDA) exhibited lower values of saturation magnetization than poly(*m*-PDA) (Ichinohe et al. 1998a).

Shumakovich et al. (2011) studied the oxidative polymerization of the aniline dimer PADPA by *Trametes hirsuta* (*Wulfen*) *Pilát* laccase and O_2 in aqueous micellar solution of SDBS. MALDI-TOF analysis showed that PADPA was oxidatively polymerized mainly to dodecamers, which form a dispersion which is stable for at least 6 months. The obtained PADPA oligomers prevalently have the molecular structure of emeraldine salt. Poly(-PADPA) was also synthesized with TvL and O_2 at pH 3.5 in an aqueous solution in the presence of AOT vesicles as templates (Junker et al. 2014b; Carić et al. 2015; Janošević-Ležaić et al. 2016) (Fig. 17). It was observed that the polymerization of PADPA is faster and more efficient (less enzyme is required) than the corresponding polymerization of aniline. The assumption that the TvL-catalyzed polymerization of PADPA is localized on the AOT vesicle surface, mainly because of the strong binding of PADPA to the surface of AOT vesicle, was supported by molecular dynamics simulations and turbidity measurements. Poly(-PADPA) showed both a structural resemblance to the polaronic form of PANI emeraldine salt, as well as some notably different spectroscopic features in comparison with PANI emeraldine salt. ESI–MS measurements indicated that the extent of formation of unwanted oxygen-containing species during the early stages of PADPA polymerization is decreased in the presence of AOT vesicles (Junker et al. 2014b). The conversion of PADPA into poly(PADPA) in the TvL/O_2/AOT reaction system was also recently monitored during the reaction by in situ Raman spectroscopy which indicated, in accordance with complementary UV/Vis/NIR and EPR measurements, that at least some of the poly(PADPA) products resemble the conductive PANI emeraldine salt form (Janošević-Ležaić et al. 2016). The Raman measurements showed that structural units different from those of "ordinary" PANI emeraldine salt are also present in poly(PADPA) (Janošević-Ležaić et al. 2016). It is important to note that PANI emeraldine salt-like poly(PADPA) products were not obtained in the PADPA/TvL/O_2 system without AOT

Table 7 Reaction conditions (enzyme/oxidant, solvent, buffer, pH, and template) applied in enzymatic polymerizations of azoarylamines, arylaminoalcohols, arylaminoketones, aminobenzoic acids, and aminobenzenesulfonic acids

Arylamine	Enzyme/oxidant	Solvent	Buffer	pH	Template	References
4-Phenylazoaniline	HRP/H_2O_2	Water	Acetate	4.0	–	Klibanov and Morris (1981)
	HRP/H_2O_2	EtOH/water	Phosphate	4.0	–	Tripathy et al. (1999)
4,4′-Diaminoazobenzene	HRP/H_2O_2	EtOH/water	Tris–HCl	6.0	–	Alva et al. (1998)
N-Phenylethanolamine	HRP/H_2O_2	Water	Phosphate	3.0	SPS	Nabid and Entezami (2005)
4-Aminophenylmethyl-carbinol	HRP/H_2O_2	Dioxane/water	HEPES	7.5	–	Arias-Marín et al. (1996)
3-(4-aminophenyl)-l-phenyl-2-propen-1-one	HRP/H_2O_2	Dioxane/water	Phosphate	7.0	–	Goretzki and Ritter (1998)
3-(4-aminophenyl)-1-(4-ethoxyphenyl)-2-propen-1-one	HRP/H_2O_2	Dioxane/water	Phosphate	7.0	–	Goretzki and Ritter (1998)
4-Aminobenzoic acid	HRP/H_2O_2	Water	Tris–HCl	6.0	–	Alva et al. (1996)
3-Amino-4-methoxy-benzoic acid	HRP/H_2O_2	Water	Phosphate	4–6	Polycationic templates	Kim et al. (2006a)
	HRP/H_2O_2	Water	Phosphate	3–6	Polycationic template PDADMAC	Kim et al. (2006b)
2-Aminobenzenesulfonic acid	HRP/H_2O_2	Water		3.5	–	Román et al. (2012)
	CPO/H_2O_2	Water		3.5	–	Román et al. (2012)
2,5-Diaminobenzene-sulfonic acid	HRP/H_2O_2	Water	Phosphate	6.0	–	Alva et al. (1997)
3-Amino-4-methoxy-benzenesulfonic acid	HRP/H_2O_2	Water		4.0	Polycationic micelles	Kim et al. (2007b)

CPO chloroperoxidase, *polycationic templates* poly(diallyldimethylammonium chloride) (PDADMAC), poly(vinylbenzyldimethylhydroxyethylammonium chloride), poly(4-vinyl-1-methylpyridinum bromide), poly(acrylamide-co-diallyldimethylammonium chloride), poly[bis(2-chloroethyl)ether-alt-1,3-bis[3-(dimethylamino)propyl]urea]; polycationic micelles made of poly(vinylbenzyldimethylhydroxyethylammonium chloride)

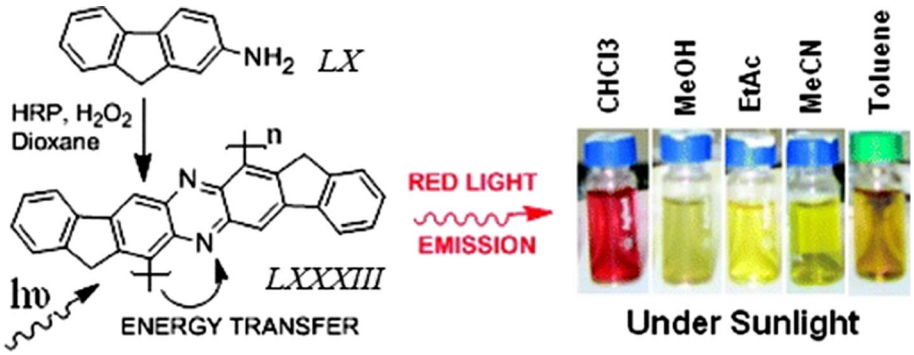

Fig. 16 Schemattic illustration of the oxidative polymerization of 2-aminofluorene (*LX*) by HRP/H_2O_2 Adapted with permission from Bilici et al. (2010). Copyright 2010 ACS

vesicles. Cyclic voltammetry measurements indicated an extended *pH* range of the redox activity of poly(PADPA) products obtained in the presence of AOT vesicles, i.e., poly(PADPA) produced in the PADPA/TvL/O_2/AOT system is redox active not only at pH 1.1 (characteristic for PANI emeraldine salt) but also at pH 6.0, unlike PANI emeraldine salt and poly(PADPA) synthesized without AOT vesicles (Janošević-Ležaić et al. 2016).

Since the 1990s, special attention has been paid to the enzymatic polymerization of halogen-substituted anilines, aminophenols, and aminothiophenols (Table 5). Recently, semiconducting polymers of chloro-substituted anilines such as 2,6-dichloroaniline, and 2,3,5,6-tetrachloroaniline, doped with (1*S*)-(+)-10-CSA, dodecylbenzenesulfonic acid, and 2-acrylamido-2-methyl-1-propanesulfonic acid, were enzymatically prepared using CPO from *Caldariomyces fumago* and H_2O_2 at pH 3.0 (Longoria et al. 2010). Comparison of the properties of polyaminophenols obtained by the HRP-catalyzed oxidative polymerization of corresponding aminophenols with H_2O_2 in water/dioxane mixture at pH 7.0 showed that the molecular weights of the obtained polymeric products are in the range

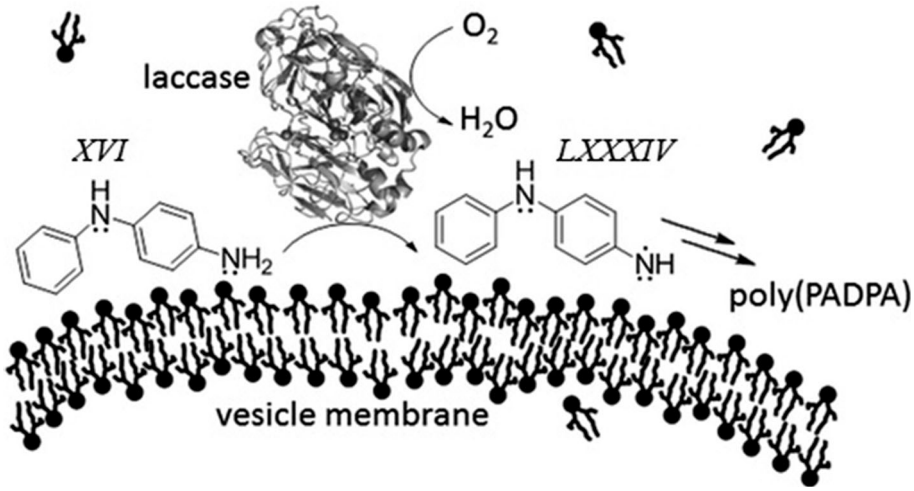

Fig. 17 Schematic illustration of the AOT vesicle-assisted laccase-catalyzed oxidative polymerization of *N*-phenyl-1,4-phenylenediamine (*p*-aminodiphenylamine—PADPA, *XVI*) via PADPA radical (*LXXXIV*) to poly(PADPA). Adapted with permission from Junker et al. (2014b). Copyright 2014 ACS

4900–17300 Da and increase in the order poly(2-aminophenol) < poly(4-aminophenol) < poly(3-aminophenol) (Shan et al. 2003). The enzymatically synthesized poly(2-aminophenol) was shown to be a linear polymer containing phenoxazine-like structural units, whereas poly(4-aminophenol) was also linear but contains 1,2,4-trisubstituted benzene rings with free hydroxyl groups (Shan et al. 2003). The combined electrochemical and enzymatic oxidation of *o*-aminophenol was studied under various conditions to evaluate the applicability of poly(*o*-aminophenol) as a laccase redox mediator (Pałys et al. 2010) and the influence of the enzyme on poly(*o*-aminophenol) electrodeposition. It was found that the presence of laccase facilitates the electrodeposition of poly(*o*-aminophenol) and influences its structure. The morphology of poly(*o*-aminophenol) precipitated from the solution containing *o*-aminophenol and laccase (round microstructures composed of nanoneedles) was found to be different from the morphologies of poly(*o*-aminophenol) synthesized chemically or electrochemically. It was concluded that laccase is a promising biocatalyst for the synthesis of conducting polymer nanostructures. Xu and Kaplan (2004) performed oxidative polymerization of 4-aminothiophenol with HRP/H_2O_2 (a) in bulk of the solution, using a methanol/water mixture as solvent; (b) on a Au surface by dipping the Au-coated slide into a methanol solution containing 4-aminothiophenol, followed by drying and immersing the slide into an HRP/H_2O_2 solution; and (c) by dipping an atomic force microscopy tip into a DMF solution containing 4-aminothiophenol, followed by drying and dip-pen nanolithography on the Au surface in the presence of HRP/H_2O_2.

HRP-catalyzed polymerization of alkoxyanilines was frequently explored during the 2000s and 2010s (Table 6). Mono-substituted methoxyanilines and ethoxyanilines were oxidatively polymerized with HRP/H_2O_2 at pH 4.0 in the presence of SPS as template (Nabid et al. 2007a). A comparison of the properties of the obtained polyalkoxyanilines showed that the pair poly(2-methoxyaniline) and poly(2-ethoxyaniline), as well as the pair poly(3-methoxyaniline) and poly(3-ethoxyaniline), have quite similar molecular structures and, consequently, quite similar optical and electrochemical properties. Kim et al. (2007a) reported that HRP-catalyzed polymerization of aniline derivatives with electron-donating substituents (e.g., alkyl and alkoxy) at the *ortho* and *meta* positions, such as 2,5-dimethoxyaniline, 2-methyl-5-methoxyaniline, and 2-methoxy-5-methylaniline, leads to the corresponding conducting electroactive polymers without a template. Enzymatic synthesis of conducting poly(2,5-dimethoxyaniline) in emeraldine salt state, using HRP with dendritic macromolecules as a catalyst, was recently studied by Khosravi et al. (2013) as a function of the reaction media. Nanostructured poly(2,5-dimethoxyaniline) was also prepared by the oxidative polymerization of 2,5-dimethoxyaniline with HRP/$FeCl_3$/H_2O_2 (Khosravi et al. 2013).

Since the 1980s, various azoarylamines, arylaminoalcohols, arylaminoketones, aminobenzoic acids, and aminobenzenesulfonic acids have successfully been enzymatically polymerized (Table 7). The enzymatic polymerization of aminobenzoic acids and aminobenzenesulfonic acids has led to self-doped carboxylated and sulfonated PANIs containing acid moieties in the polymer backbone (Alva et al. 1996, 1997; Kim et al. 2006a, b, 2007b; Román et al. 2012). Polyanionic templates were found to be unsuitable for the enzymatic polymerization of acid-functionalized aniline derivatives (Kim et al. 2006a). However, it was shown that the utilization of polycationic templates, via the complexation of substituted, negatively charged aniline monomers (carboxylate group), can lead to the formation of linear, conducting, self-doped carboxylated PANI (Kim et al. 2006a) under optimal conditions. Fully sulfonated semiconducting PANIs were recently enzymatically synthesized from 2-amino-benzenesulfonic acid (Román et al. 2012). It was observed that there is no

Table 8 Reaction conditions (enzyme/oxidant, solvent, buffer, and pH) applied in enzymatic polymerization of aminonaphthalenes and their derivatives

Aminonaphthalene	Enzyme/oxidant	Solvent	Buffer	pH	References
1-Aminonaphthalene	HRP/H_2O_2	Water	Acetate	5.5	Klibanov and Morris (1981)
	HRP/H_2O_2	Dioxane/water	Phosphate	7.0	Shan et al. (2003)
5-Nitro-1-aminonaphthalene	HRP/H_2O_2	Water	Acetate	4.5	Klibanov and Morris (1981)
2-Aminonaphthalene	HRP/H_2O_2	Water	Acetate	7.0	Klibanov and Morris (1981)
2-Amino-8-naphthol-3,6-disulfonic acid	ARP/H_2O_2	Water	Phosphate	6.0–7.4	Biswas et al. (2007)

difference in the UV–Vis and FTIR spectra of the sulfonated PANIs obtained using CPO, HRP, or a chemical as an oxidant. The catalytic activity (k_{cat}) was higher with CPO than with HRP, but due to a higher affinity constant (K_M) the catalytic efficiency (k_{cat}/K_M) of CPO was lower than for HRP. Significant differences in the redox (cyclovoltammetric) behavior of the products from HRP- and CPO-catalyzed reactions were found.

The oxidative polymerization of luminol (5-amino-2,3-dihydroxy-1,4-phthalazinedione) with HRP/H_2O_2 in a phosphate buffer at pH 8 in the presence of SPS was reported by Nabid et al. (2011). According to the authors, a green, water-dispersible conducting polyluminol/SPS complex was obtained, a chemiluminescent material which is highly sensitive towards Fe^{3+} ions.

Aminonaphthalenes and their derivatives have occasionally been explored as monomers in enzymatic polymerizations (Table 8), but there is only a single report on the molecular structures and properties of these polyaminonaphthalenes (Shan et al. 2003). The HRP-catalyzed polymerization of 1-aminonaphthalene yielded a polymer which had a molecular weight in the range 7000–14,700 Da, with good solubility in DMF, DMSO, THF, and acetone (Shan et al. 2003).

Enzymatic syntheses of polyarylamine composites

It was shown that the processability of polyarylamines and their utilization as absorbers of electromagnetic radiation, actuators, adsorbents, antioxidants, catalysts, corrosion inhibitors, electrodes, field emitters, membranes, sensors, and supercapacitors are significantly improved by combining them with other materials (e.g., metals, metalloids, nonmetals, metal oxides) (Ćirić-Marjanović 2013a, 2015), especially with nanostructured materials (e.g., metal NPs, CNTs, graphene) (Ćirić-Marjanović 2013a). Also, the use of polyarylamines as fillers to synergistically improve the performance and applicability of other electroactive, electrochromic, electroconducting, electrorheological, ferroelectric, fluorescent, magnetic, non-linear optic, photoluminescent, photovoltaic, redox-active, superhydrophobic, and thermoelectric materials has proven to be quite useful (Ćirić-Marjanović 2013a, 2015). It is worth noting that the enzymatic synthesis of polyarylamine composites was almost exclusively focused on PANI composites. The enzymatically synthesized composites of oligoarylamines are not yet reported.

Up to the present date, the only metallic-polyarylamine composites which have been synthesized enzymatically are with silver (Nabid et al. 2013) or gold (Komathi et al. 2013; Sharma et al. 2014). PANI/Ag nanocomposites were synthesized with HRP/H_2O_2 in the presence of SPS, using aniline covalently bound to a 2-aminothiophenol monolayer on the Ag nanoparticle surfaces (Nabid et al. 2013). Komathi et al. (2013) have recently reported the simultaneous immobilization of poly(*N*-[3-(trimethoxy silyl)propyl]aniline (PTMSPA) and HRP on Au nanorods, leading to HRP/PTMSPA/Au nanorods, based on the HRP-catalyzed polymerization of *N*-[3-(trimethoxy silyl)propyl]aniline. The fact that GOx generates H_2O_2 was exploited by Sharma et al. (2014) to form Au nanoparticle/PANI composites at room temperature. Enzymatic coupling of arylamines under mild conditions (slightly acidic reaction media, the use of relatively weak oxidants) looks very promising for the preparation of composites of polyarylamines with non-noble metals (Zn, Fe, Al, etc.). Non-noble metals degrade in highly acidic solutions in the presence of strong oxidants, which are the reaction conditions characteristic of conventional chemical oxidative polymerization of arylamines.

The majority of the efforts regarding enzymatic syntheses of composites of polyarylamines with nonmetals were devoted to PANI/CNTs composites. PANI composites with carboxylic acid-functionalized MWCNTs (MWCNTs-COOH) have been obtained by enzymatic polymerization of aniline using HRP and GOx covalently attached to MWCNTs-COOH (Sheng and Zheng 2009). The in situ HRP-catalyzed polymerization of aniline onto MWCNTs and carboxylated MWCNTs in aqueous medium at pH 4 was reported by Nabid et al. (2012), while Otrokhov et al. (2014) and Shumakovich et al. (2015) recently reported the laccase-catalyzed synthesis of MWCNTs/PANI core/shell-structured composites. The enzymatic synthesis of PANI composites with graphene and its derivates has rarely been explored. An enzymatic approach for the production of PANI complexed with reduced graphene oxide (rGO) has recently been proposed by Akin et al. (2014) (Fig. 18). GOx produced H_2O_2 from the oxidation of glucose with O_2, which

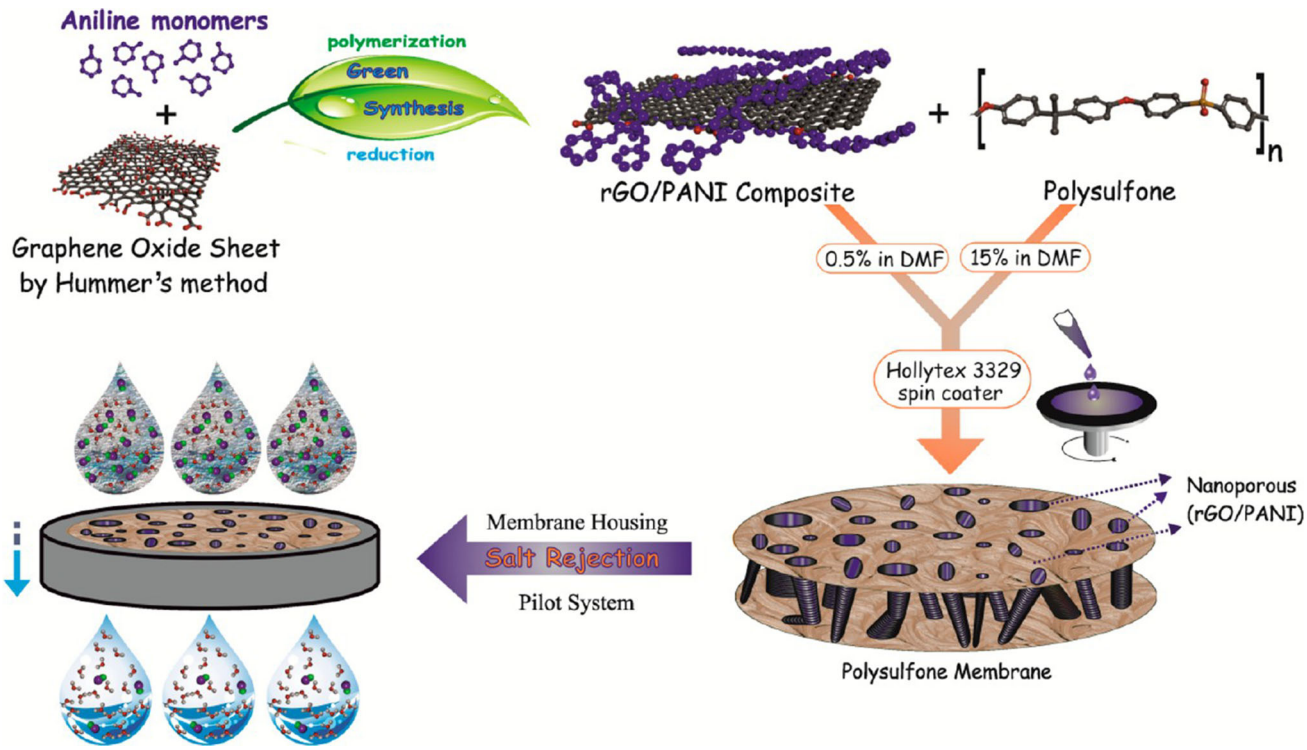

Fig. 18 Schematic illustration of the production of a PANI composite with reduced graphene oxide (rGO), followed by the dispersion of the obtained rGO/PANI composite in polysulfone. The mixed polysulfone/rGO/PANI membranes were used for salt rejection. Reprinted with permission from Akin et al. (2014). Copyright 2014 ACS

then led to the oxidation and polymerization of aniline in the presence of rGO under ambient conditions. The obtained rGO/PANI composite was dispersed in polysulfone, and the mixed membranes were then prepared using the phase inversion polymerization method.

There are a few reports about the enzymatic synthesis of PANI composites with metal oxides. An enzymatic route for the synthesis of conducting nanocomposites containing PANI and anatase TiO_2 NPs, via HRP-catalyzed, SPS-guided polymerization of aniline in the presence of TiO_2 NPs, was presented by Nabid et al. (2008). Similarly, a γ-Al_2O_3/PANI nanocomposite was synthesized by HRP-catalyzed SPS-guided polymerization of aniline in water in the presence of γ-alumina nanosheets and SDS (Nabid et al. 2009a). There are a lot of unexplored possibilities regarding the synthesis of polyarylamine composites with metal oxides, especially those sensitive to highly acidic environment, via mild enzymatic routes.

Applications

There are not yet as many publications on applications of enzymatically synthesized oligomers and polymers of arylamines as for non-enzymatically synthesized oligoarylamines or polyarylamines (Ćirić-Marjanović 2013b). In the following sections, some of the different reports on the successful application of the enzymatic reaction systems are highlighted. Both the reactions itself, and the products of the reactions, were taken advantage of. The applications are in the fields of ELISA and other immunoassays, for the detection and sensing of various analytes, and in wastewater treatment. Micro- and nanostructured enzymatically synthesized oligoanilines/PANIs were successfully used in recent years to make sensors, electrochromic devices, supercapacitors, anticorrosion coatings, membranes, and photothermal agents for cancer treatment. However, the examples we show in the following sections are from proof-of-concept publications and, thus, the devices have not been produced commercially. For this reason, no comment is made on their shelf-life, stability, longevity or price.

ELISA and other immunoassays

The first application of enzymatic oxidative coupling reactions of arylamines was the extensive use of the oxidative dimerization of *o*-PDA with HRP/H_2O_2 to DAP in the ELISA test (Wolters et al. 1976; Bovaird et al. 1982). The enzymatic coupling of arylamines has also successfully been used in electrochemical immunoassay (Jiao et al. 2000; Lai et al. 2014; Zhang et al. 2016a), which attracted

significant attention because of its simple instrumentation, low cost, and good portability. It is comparable with the conventional methods such as ELISA, radioimmunoassay and fluorescence method. One example is the application of *p*-PDA as a substrate for an HRP-mediated voltammetric enzyme immunoassay (Jiao et al. 2000). As discussed above, the reaction of *p*-PDA with HRP/H_2O_2 leads to the formation of Bandrowski's base. Thus, the detection of its voltammetric peak current allowed for the detection of HRP with a limit of detection (LOD) of 0.95 mU l^{-1} and a linear range of 1.75–750 mU l^{-1}. The combination of the HRP/H_2O_2/*p*-PDA voltammetric system with a direct antigen coating ELISA allowed for a significantly more sensitive detection of the cucumber mosaic virus (LOD 0.5 ng ml^{-1}) compared to the conventional spectrophotometric HRP/H_2O_2/*o*-PDA-based ELISA method. Two further electrochemical immunoassays where the redox activity of PANI is exploited were recently developed by Lai et al. (2014) and Zhang et al. (2016a). Conceptually, the two sensors are quite similar because they combine a modified electrode with the so-called nanoprobes. In both cases, the electrode was modified with the antibody of the analyte of interest so that after placing a solution containing the analyte onto the surface of the electrode, the analyte quantitatively bound to the electrode via an immunoreaction. The nanoprobes are nanoparticles suspended in a solution, which were modified with both HRP and the antibody to the analyte. Thus, after the analyte had bound to the electrode (and after washing), the solution containing the nanoprobe was added to the surface of the electrode, where the nanoprobe then bound to the analyte. This so-called sandwich immunoassay was then exposed to aniline and H_2O_2 for a certain amount of time so that redox-active PANI was formed on the surface. After appropriate calibration, the signals from cyclic voltammetry and differential pulse voltammetry (DPV) due to PANI were used to quantify the analyte. Lai et al. (2014) used this strategy to quantify human immunoglobin (HIgG) at the screen-printed carbon electrode (SPCE) and used Au NPs as nanoprobes (Fig. 19). Zhang et al. (2016a) used this strategy to quantify *E. coli*, using modified CNTs as nanoprobes.

Wastewater treatment

More than three decades ago, Klibanov and Morris (1981) have developed an enzymatic method for the efficient removal of carcinogenic arylamines (benzidine, 3,3′-diaminobenzidine, 3,3′-dichlorobenzidine, *o*-tolidine, *o*-dianisidine, 4-aminobiphenyl, *p*-phenylazoaniline, 1-aminonaphthalene, 2-aminonaphthalene, and 5-nitro-1-aminonaphthalene) from industrial aqueous effluents. The arylamines were polymerized with HRP/H_2O_2 and the corresponding polymers precipitated, which made them easy to remove with centrifugation or filtration. Saidman et al. (2006) presented a UV–Vis study of aniline removal via polymerization, leading to the prevalent formation of PANI in pernigraniline form, using peroxidases from different sources (*P. sajor caju* peroxidase, HRP) as well as hematin, both free and magnetite-supported. It was found that free biocatalysts were more active than supported biocatalysts. Biswas et al. (2007) showed that carcinogenic and mutagenic sulfonated arylamines, generated by anaerobic degradation of textile industry effluents containing reactive azo dyes, can be effectively removed by oxidative polymerization catalyzed by ARP. The

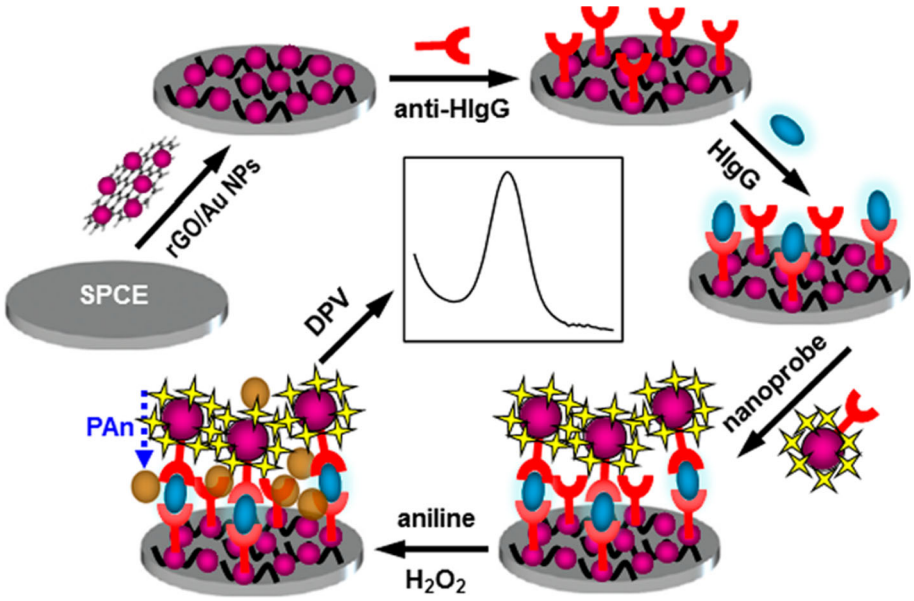

Fig. 19 The preparation of SPCE/rGO/Au-NPs/anti-HIgG/HIgG immunosensor and sandwich immunoassay based on the electrochemical DPV measurement of PANI enzymatically deposited by an HRP/anti-HIgG/Au-NP nanoprobe. Reprinted with permission from Lai et al. (2014). Copyright 2014 ACS

enzymatic polymerization of sulfonated arylamines generated soluble colored compounds, which were removed by a coagulant. A laccase from *Myceliophthora thermophila* was used to catalyze the oligomerization/polymerization of the arylamines formed upon the decolorization of several azo dyes (Franciscon et al. 2010). The resulting polymers precipitated and were easily removed with physical methods. The decolorization of the azo dyes was conducted by bacteria isolated from a textile wastewater effluent under microaerobic conditions (Franciscon et al. 2010). The potential of using enzymatic treatment to remove diphenylamine from buffered synthetic wastewater was demonstrated by Saha et al. (2008). This treatment method included the oxidative polymerization of diphenylamine by *Trametes villosa* laccase/O_2 at pH 7 in the presence of poly(ethylene glycol), followed by removal of the formed poly(diphenylamine) via adsorptive micellar flocculation using SDS and hydrated $Al_2(SO_4)_3$. Al-Ansari et al. (2009) reported the optimum pH and H_2O_2/phenylenediamine concentration ratio, as well as the minimum SBP concentration, required to achieve >95% conversion of phenylenediamines to the corresponding polymers in synthetic wastewater, which could be removed using SDS. Hemoglobin, a pseudo-peroxidase, encapsulated in a silica-based matrix by the modified "fish-in-net" approach has successfully been used by Liu et al. (2012) for the efficient catalytic removal of aniline from aqueous solution (65% aniline removal). It was found that encapsulated hemoglobin showed more stable peroxidase-like activity and substantially increased storage and pH stability than free hemoglobin.

Sensors

Sensors to detect lead cations, using electrodes modified with hybrid DNA structures as both a sensing platform and catalyst for PANI formation, have recently been reported by several research groups (Li et al. 2013; Zhang et al. 2015a; Ge et al. 2016). Li et al. (2013) developed an Au electrode modified with guanine-rich DNA as a probe. This G-rich DNA is initially in a random coil conformation. Its conformation can be changed by the presence of Pb^{2+} to form stable, so-called G4 structures. Hemin was then added to the electrode, which intercalated into these G4 structures, generating an HRP-mimicking DNAzyme. The DNAyme catalyzed the formation of PANI from added aniline and H_2O_2, and the electrochemical signal generated by PANI was measured. Through calibration, a linear correlation between the PANI signal and the Pb^{2+} concentration in a range from 1.0×10^{-9} to 1.0×10^{-6} M, with an LOD of 5.0×10^{-10} M, can be established. Similarly, Zhang et al. (2015a) also presented a Pb^{2+} assay. Pb^{2+} triggered the specific cleavage of a hybrid oligonucleic structure which was immobilized on an Au electrode. Due to this cleavage, a new hybridization reaction with two new oligonucleotide acid strands was able to take place to form longer DNA strands. Hemin was then added to this DNA structure to form a so-called hemin/G-quadruplex structure which resembles the peroxidase activity of HRP. Thus, aniline was polymerized with added H_2O_2 on the surface of the DNA. PANI was detected with electrochemical methods, and the electrochemical signal could be linearly correlated with the concentration of Pb^{2+} in a range from 5.0×10^{-11} to 5.0×10^{-8} M with an LOD of 3.2×10^{-11} M. Finally, Ge et al. (2016) also developed a Pb^{2+} probe using a combined approach. First, a paper electrode was modified with rGO and Au NPs. Then, similar to the work of Zhang et al. (2015a), a hybrid DNA was placed upon the electrode. Again, in the presence of Pb^{2+}, this DNA was selectively cleaved and a new hybridization reaction was possible with another complementary DNA strand. However, in this case, the complementary DNA strand was covalently attached to Mn_2O_3 NP-assembled hierarchical hollow spheres as a nanoprobe carrying both HRP and GOx, which catalyzed the formation of PANI in the presence of aniline and glucose (in situ generation of H_2O_2). The electrochemical signal generated from PANI was linearly correlated with the Pb^{2+} concentration in a wide range from 5.0×10^{-12} to 2.0×10^{-6} M.

A H_2O_2 biosensor with an LOD of 1.7×10^{-7} M based on the HRP-catalyzed PANI deposition on graphene/CNT/nafion/Au–Pt alloy NPs modified glassy carbon electrode was described by Sheng et al. (2011), while a H_2O_2 sensor with an LOD of 9.0×10^{-7} M based on the HRP-catalyzed PANI deposition on an HRP/aligned SWCNT-modified Au electrode was fabricated by Tang et al. (2011). A simple H_2O_2 sensor with an LOD of 2.0×10^{-7} M based on efficient fluorescence resonance energy transfer between the highly fluorescent carbon quantum dots and PANI, synthesized via oxidation of aniline adsorbed on carbon quantum dots with HRP/H_2O_2, was recently developed by Zhang et al. (2015c). An HRP/PTMSPA/Au nanorods modified electrode recently showed a quick amperometric response (<5 s) for the reduction of H_2O_2, a wide linear range from 1×10^{-5} to 1×10^{-3} M with an LOD of 6.0×10^{-8} M, and high selectivity and sensitivity (0.021 μA/μM) toward H_2O_2 (Komathi et al. 2013). In order to get insight into the role of H_2O_2 in the aggregation of α-Synuclein in Lewi bodies (abnormal aggregates of protein that develop inside nerve cells in Parkinson's disease), Xu et al. (2015) recently reported on a plasmonic assay for H_2O_2 with a designed nanoplasmonic probe, composed of Au-NP with surface-attached double-stranded DNA and HRP (Fig. 20). Detection of H_2O_2 with an LOD of 8×10^{-9} M was achieved by monitoring the plasmonic response associated with the in situ formation of

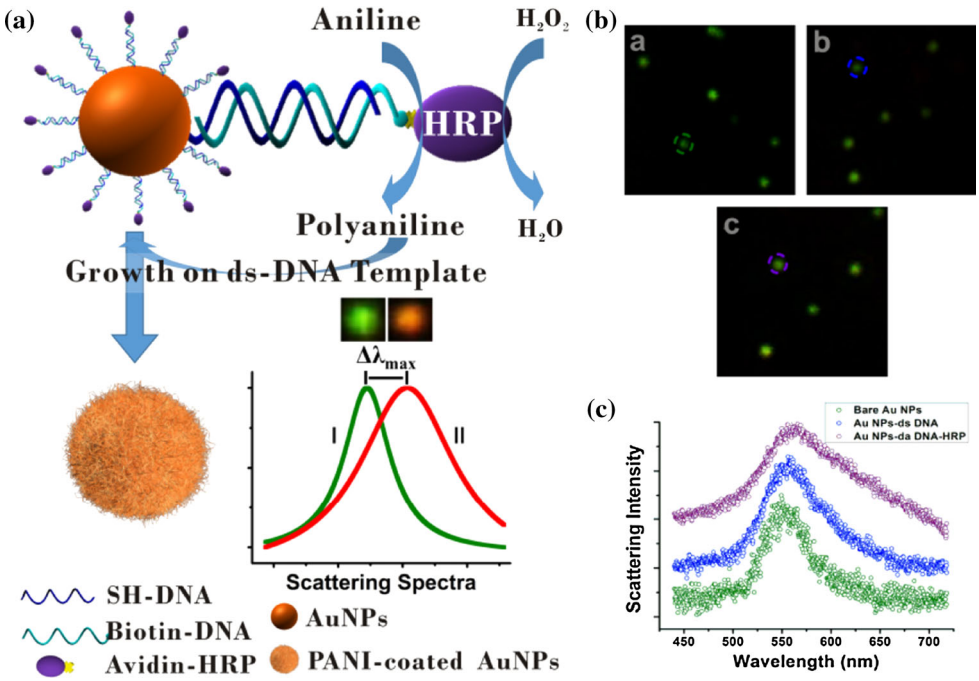

Fig. 20 **a** Schematic illustration of a H_2O_2 assay based on the HRP-catalyzed PANI deposition on an AuNPs/double-stranded-DNA/HRP nanoplasmonic probe. The polymerization of aniline with HRP/H_2O_2 on double-stranded-DNA templates leads to the color changes and plasmon band shifts. **b** Dark-field images of (a) bare Au NPs, (b) double-stranded-DNA-loaded Au NPs, and (c) double-stranded-DNA/HRP-loaded Au NPs. **c** Plasmon resonance Rayleigh scattering spectra of Au NPs during sequential modifications. Reprinted with permission from Xu et al. (2015). Copyright 2015 ACS

a layer of conducting PANI on the nanoplasmonic probe via the oxidative polymerization of aniline with HRP/H_2O_2 (Fig. 20).

A lot of different sensors have been prepared for the detection of glucose, usually using the GOx/HRP cascade reaction (Sheng and Zheng 2009; Wang et al. 2014a; Zhang et al. 2015c; Gong et al. 2016). The voltammetric characteristics of an enzymatically synthesized PANI/MWCNTs-COOH/HRP/GOx biosensor were investigated by cyclic voltammetry in the presence of glucose (Sheng and Zheng 2009). The current response of PANI was linearly proportional to the glucose concentration in the range of 5.0×10^{-5}–1.2×10^{-2} M with a correlation coefficient of 0.994. Kausaite-Minkstimiene et al. (2010, 2011) reported an elegant enzymatic method for the preparation of a carbon rod/GOx/PANI electrode. GOx was first immobilized on the electrode. A PANI matrix was then enzymatically synthesized from aniline with H_2O_2, which was formed by the GOx-catalyzed oxidation of glucose. The formed PANI layer encapsulated GOx, leading to an electrically conductive layer from GOx to the electrode. The peculiarity of this sensor is that the activity of GOx is exploited to both synthesize the final electrode and to oxidize glucose for detection and quantification purposes. Thus, this sensor can be utilized as amperometric glucose biosensor and/or anode of a biofuel cell powered by glucose. The GOx/PANI electrode showed increased stability and an increased upper limit of glucose detection in comparison to an unmodified GOx-electrode. Gong et al. (2016) recently used a 4-aminothiophenol/Au-NP/GOx–HRP/6-mercapto-1-hexanol-11-mercaptoundecanoic acid/Au electrode to detect glucose in the range 1.65×10^{-5}–1.0×10^{-2} M, with a high sensitivity of 41.78 μA mM^{-1} cm^{-2} and good selectivity. The detection is based on the oxidative polymerization of aniline by HRP and H_2O_2, whereas H_2O_2 is formed by oxidation of glucose with GOx/O_2. The concentration of H_2O_2 increases with an increase of the glucose concentration and, consequently, an increased quantity of PANI film was formed on the electrode surface, resulting in a decrease of the peak current of $Fe(CN)_6^{3-/4-}$, thus allowing for accurate and selective glucose concentration determination. Alternatively, the electrode can also be used for direct H_2O_2 detection. A thioglycollic acid-capped CdS quantum dots (QDs)/GOx/HRP composite was recently prepared by Wang et al. (2014a) for glucose determination. The fluorescence quenching of the thioglycollic acid-capped CdS QDs, efficiently achieved by the products of the HRP-catalyzed oxidation of *o*-PDA and 3,3′-diaminobenzidine, was proportional to the glucose concentration. The glucose LODs of 1.0×10^{-7} M or 2.0×10^{-8} M were achieved in the case of the *o*-PDA or 3,3′-diaminobenzidine oxidation, respectively. The thioglycollic acid-capped CdS QDs/GOx/HRP sensor was successfully used for simple determination of glucose in human serum without any interference of fructose, sucrose and lactose (Wang et al. 2014a). Sensing of glucose down to submicromolar levels based on the quenching of the fluorescence of the carbon QDs by a thin PANI layer, formed by HRP-catalyzed oxidative polymerization of aniline on the surface of carbon QDs with H_2O_2 which was generated during the enzymatic oxidation of glucose, was recently achieved by Zhang et al. (2015c).

It has recently been found that the square wave voltammetric response of PANI, deposited on a glassy carbon electrode modified with polystyrene nanospheres via the hemoglobin/GOx-catalyzed polymerization of aniline, increased proportionally with the increase of glucose concentration in the range of 1.0×10^{-7}–1.0×10^{-5} M (Zhang et al. 2013). It was shown that UV–vis spectroscopy and potentiometric/cyclovoltammetric detection of saccharides with enzymatically synthesized poly(aniline-co-3-aminobenzeneboronic acid) was significantly more sensitive (Huh et al. 2007) in comparison to the corresponding detection of saccharides using chemically synthesized copolymer.

Development of analytical methods for sialic acid detection became interesting in recent years because sialic acid overexpression on cell surfaces is associated with many malignant diseases. Liu et al. (2015) reported a selective and sensitive method for sialic acid detection on cancer cell surfaces and electrochemical cytosensing of living cells by combining 3-aminophenylboronic acid modified carbon nanospheres (CNS-APBA) for sialic acid recognition and Au-NPs/HRP as nanoprobes for signal amplification via enzymatic polymerization of aniline (Fig. 21).

Xie et al. (2014) recently fabricated an electrochemical aptasensor for the detection of thrombin in the range of 5.0×10^{-13}–3.0×10^{-8} M with an LOD of 1.4×10^{-13} M, based on the enzymatic, in situ formation of PANI as a redox mediator by employing a peroxidase-like manganese-porphyrin/double-stranded DNA as a catalyst and template. A hybridization chain reaction was utilized for the production of double-stranded-DNA for the binding of manganese-porphyrin and PANI. The activity of telomerase was determined using telomeric hemin/G-quadruplex-DNAzyme-triggered polymerization of aniline on DNA tetrahedron structures (Liu et al. 2016).

Both RNA and DNA sensors based on the enzymatic deposition of polyarylamines were frequently reported over the past ten years. For example, amino-terminated peptide nucleic acid (PNA) capture probes were immobilized on interdigitated comb-like microelectrodes (Fan et al. 2007). This was followed by hybridization with their complementary target microRNA and the subsequent HRP-catalyzed deposition of conducting PANI nanowires. Thus, microRNA in total RNA extracted from cancer cells in the range 1.0×10^{-14}–2.0×10^{-11} M with an LOD of 5.0×10^{-15} M (Fan et al. 2007) was quantified (Fig. 22). Based on a hybridized microRNA-guided deposition of PANI, catalyzed by G-qudraplex-hemin DNAzyme, an impedimetric microRNA biosensor capable of detecting 5.0×10^{-16} M target microRNA was recently developed by Deng et al. (2014). The detection of microRNA in blood and RNA extracted from cultured cells was performed in a label-free manner in a range from 5.0×10^{-15} M to 2.0×10^{-12} M with an LOD of 2.0×10^{-15} M (Gao et al. 2013). The sensor was based on the hybridized microRNA-templated HRP-catalyzed deposition of an insulating poly(3,3′-dimethoxybenzidine) film and electrochemical impedance spectroscopic detection (Gao et al. 2013). The

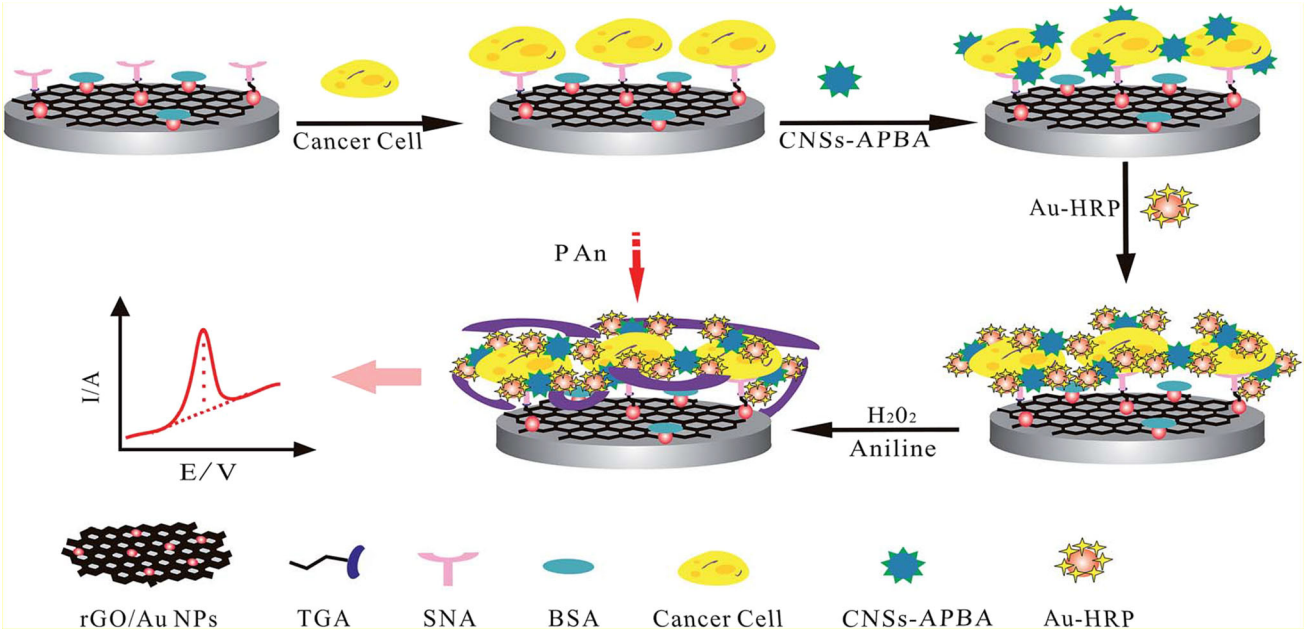

Fig. 21 Schematic illustration of the electrochemical sialic acid assay on the cell surface based on HRP-catalyzed PANI deposition. *TGA* thioglycolic acid, *SNA Sambucus nigra* agglutinin, *BSA* bovine serum albumin. Reprinted with permission from Liu et al. (2015). Copyright 2015 Royal Society of Chemistry

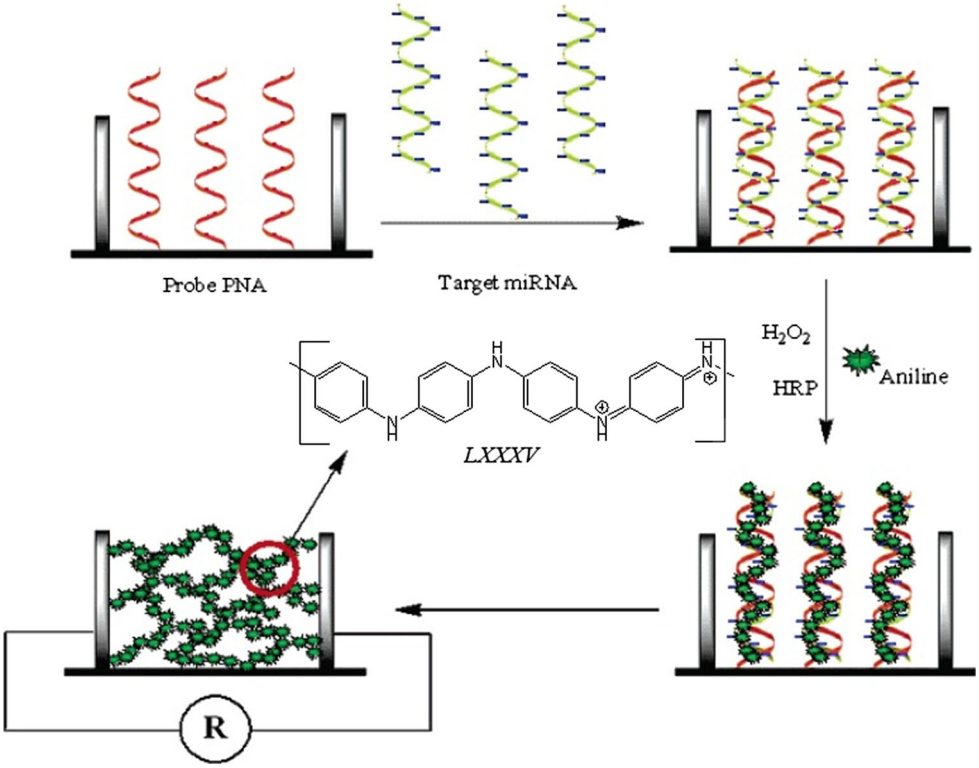

Fig. 22 Schematic illustration of the sensing mechanism of a biosensor for the electrical detection of microRNAs, fabricated via the immobilization of peptide nucleic acid (PNA) capture probes in nanogaps of a pair of interdigitated microelectrodes, followed by their hybridization with their complementary target microRNA, and the subsequent HRP-catalyzed deposition of conducting PANI (*LXXXV*) nanowires. Adapted with permission from Fan et al. (2007). Copyright 2007 ACS

detection of nucleic acids was conducted by modifying an Au electrode with PNA capture probes, onto which the target DNA binded (Gao et al. 2007b). HRP labeled with a complimentary oligonucleotide to the DNA bound to the hybrid DNA on the electrode. The immobilized HRP catalyzed the formation of PANI from aniline and H_2O_2 on the hybrid DNA, leading to an electrochemical signal proportional to the concentration of the target DNA (Gao et al. 2007b). An electrochemical "sandwich-type" DNA sensor with a linear response toward DNA in the concentration range 6.0×10^{-15} M–1.0×10^{-9} M, based on the DNAzyme-catalyzed PANI deposition by Au NP nanoprobes containing DNA complimentary to the target DNA as well as longer DNA strands complexed with hemin, was developed by Hou et al. (2014). A biosensor for the detection of syphilis DNA with an LOD of 5.0×10^{-13} M was developed by Sheng et al. (2010). It is based on DNA hybridization between an oligonucleotide-modified Au electrode and the target DNA. After binding of the target DNA to the oligonucleotide on the electrode, another complementary oligonucleotide strand, functionalized with biotin, was added and bound to the target DNA. Then, HRP functionalized with streptavidin was added, which bound very strongly to the biotin. HRP then catalyzed the formation of PANI, which was measured electrochemically. Thus, a linear relationship between the electrochemical signal from PANI and the concentration of syphilis DNA was established (Sheng et al. 2010). To improve the ability of the surface plasmon resonance spectroscopy to detect extremely small refractive index changes, which are useful in ultrasensitive DNA analysis, Su et al. (2008) reported a signal amplification via HRP-catalyzed DNA-templated PANI deposition, suitable for DNA hybridization analysis with charge neutral PNA as probes. The LOD was lowered from 5.0×10^{-9} M for conventional surface plasmon resonance detection to 1.0×10^{-13} M, which is much better than that of AuNP-based amplification using a secondary hybridization process and labeled DNA detection probes. Recently, a surface plasmon resonance-based DNA sensor with a detection limit in the femtomolar range was fabricated using graphene nanosheets, functionalized with pyrene groups and nickel-chelated nitrilotriacetic acid, as a substrate and streptavidin/HRP-catalyzed PANI deposition as mass relay (Yuan et al. 2016).

DNA methylation and methyltransferase activity, which are linked to the development of cancer, have recently been detected electrochemically in human serum samples in the range of 0.5–0.6 U ml^{-1} with an LOD of 0.12 U ml^{-1} (Zhang et al. 2015b). It is based on methylation sensitive restriction endonuclease *Hpa*II and the DNAzyme-catalyzed polymerization of aniline. PANI is formed on the double-stranded-DNA template in the presence of methylated DNA, thus producing the DPV signal. There is no PANI deposition in the presence of non-methylated DNA because the double-stranded-DNA is cleaved and digested by *Hpa*II and exonuclease III.

Miscellaneous applications

An electrochromic device composed of an enzymatically synthesized PANI/SPS complex, polyelectrolyte, lithium salt and indium tin oxide glass showed reversible color change (green/blue/purple) when a voltage of about 2.5 V was applied between two indium tin oxide glasses (Kimura and Kumar 2004). An enzyme nanolithography strategy based on the scanning of an atomic force microscope tip modified with peroxidase, in the presence of aniline (Luo et al. 2009) or 4-aminothiophenol (Xu and Kaplan 2004) and H_2O_2, was used for biocatalytic patterning of different PANI (Luo et al. 2009) and poly(4-aminothiophenol) nanostructures (Xu and Kaplan 2004). It was shown by Junker et al. (2014a) that enzymatically obtained highly stable aqueous PANI/AOT vesicle dispersions can be used as ink in a conventional thermal inkjet printer for printing on paper or on the surface modified polyimide films. Also, printed green PANI emeraldine salt patterns on paper changed color to blue emeraldine base form after exposure to ammonia gas, thus showing the expected ammonia sensing ability. The applicability of aniline oligomers, obtained by SDBS micelles-assisted laccase-catalyzed oligomerization of aniline, to protect copper against corrosion has recently been demonstrated by Shumakovich et al. (2014). The performance of enzymatically synthesized rGO/PANI/polysulfone membranes regarding salt rejection and pure water flux was studied by Akin et al. (2014) (Fig. 18). The rGO-incorporated polysulfone membrane was found to have a hydrophobic surface with enhanced macro-voids, whereas the rGO/PANI-incorporated polysulfone membrane surface was found to be partly hydrophilic due to the presence of PANI fibers in the membrane. Polysulfone membranes exhibited an improved salt rejection, mean porosity, and water flux after incorporation of rGO/PANI. Layer-by-layer films of enzymatically synthesized PANI and poly(γ-glutamic acid), synthesized by a bacterial reaction, for the construction of nanocapacitors were reported by Barrientos et al. (2007). The enzymatically synthesized PANI/MWCNT composite with a PANI content of ca. 49 wt% could be used in supercapacitors since it had high specific capacitance (440 F/g at 5 mV/s) and cycle stability during doping/dedoping, i.e., the specific capacitance of the PANI/MWCNT composite decreased by less than 7% of its maximum value after 1000 scan cycles between −0.1 and 0.7 V (Otrokhov et al. 2014). It was demonstrated by Li et al. (2015) that PANI, obtained using synthetic biomimetic catalysts, could be efficiently utilized as a photothermal agent capable of converting light into heat with a high efficiency. The temperature increased above the thermal damage threshold to destroy cancer cells. A high light-to-heat conversion efficiency of 39.6%, excellent biocompatibility and remarkable anti-tumor effect with human cervical cancer cells were observed for PANI prepared using FePOs, an HRP-mimetic catalyst (Li et al. 2015) (Fig. 23).

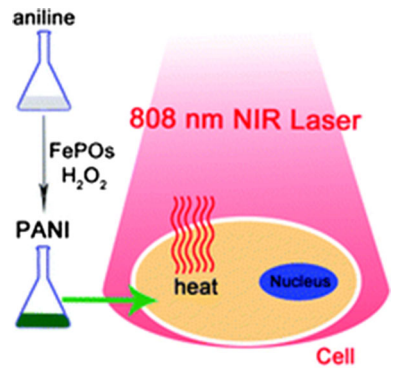

Fig. 23 Schematic illustration of anti-tumor effect with human cervical cancer cells observed for the PANI prepared using FePOs. Reprinted with permission from Li et al. (2015). Copyright 2015 RSC

Conclusions and outlook

The majority of industrially important arylamines (aniline, substituted anilines, aminonaphthalenes, etc.) were subjected to enzymatic oxidation and coupling. Often, HRP and H_2O_2 or laccases with dissolved O_2 were used, and in many cases templates (most frequently anionic polymers or micelles) were added to shift the reaction towards the desired product. This review is as a kind of inventory of the literature which has been published in the field, with a detailed compilation of published results.

There are four points which we feel are important to keep in mind. First, the oxidation of arylamines—independent of whether they occur enzymatically, chemically, or electrochemically—often leads to a *mixture of different products*, and not to one single molecule. Second, the types of products obtained from the enzymatic oxidation of an arylamine very much depend on the *details of the experimental conditions*, e.g., initial concentration of arylamine, pH, temperature, enzyme type and concentration, type and concentration of template, reaction time, etc. Third, the products obtained often have a *low solubility*, which makes their separation and chemical analysis difficult. Therefore, fourth, in many cases the *chemical structures of the products obtained are not known with certainty*; the structures given in the literature may only represent ideal or assumed structures, or parts of larger molecules, drawn on the basis of the available analytical data. Nevertheless, the product mixtures may have excellent properties for different possible applications of poly(arylamines). In this case, one may argue that a detailed knowledge of the composition and the chemical structures of the products is not of first importance; it is more the property which

counts. From a scientific point of view, however, the challenge remains in understanding which products are obtained, how they are formed (mechanism) and why they are formed, for example due to the presence of a (Luginbühl et al. 2016). With such detailed investigations and a deeper understanding, one may be able to optimize the reaction conditions for obtaining a desired product in higher yield or with less enzyme, and one may also be able to apply the concepts to other related systems.

Interestingly, there is still a large number of important carbocyclic (e.g., 2-aminodiphenylamine, sulfanilamide, benzocaine, anthranilic acid, substituted aminonaphthalenes, and aminoanthracene and its derivatives, etc.) and heterocyclic arylamines which have never been oxidatively coupled using the enzymatic route. It may be that these monomers cannot efficiently be oxidatively polymerized with the available enzymes, and that through protein engineering it will only be possible in the future.

In the case of the peroxidases, other heme-containing biomacromolecules with peroxidatic activity have been utilized as catalysts for the oxidative polymerization of aniline with H_2O_2, e.g., hemoglobin and cytochrome *c*. Future studies will show how these proteins compare with the "true" peroxidases in terms of required amounts of proteins and product characteristics. In another line of research, various synthetic biomimetic catalysts have also been used for the oxidative polymerization of aniline with H_2O_2. From a more environmental point of view, the use of enzymes (or other proteins) as biocatalysts is attractive, since the reactions can be carried out at ambient temperature in an aqueous medium. However, there is also a limitation with this if the water solubility of the monomers is very low. In this case, either only small amounts of monomer can be used, or co-solvents, which are tolerated by the enzymes, have to be added. Exactly 120 years after the first reported aniline enzymatic oxidation at the end of nineteenth century, followed by the extensive research during the middle part of twentieth century devoted to arylamine oligomerization, and pioneering work in the 1980s and 1990s devoted to the enzymatic syntheses of conducting polyaniline and other polyarylamines, the development of novel templates as well as apparent template-free enzymatic synthetic techniques in the twenty-first century opens up new perspectives in advanced applications, especially regarding fabrication of ultrasensitive biosensors based on redox-active and conducting polyaniline, other polyarylamines, and their composites. It seems that crucial breakthroughs regarding the enzymatic and enzyme-mimetic oligomerization and polymerization of aniline and other arylamines are still ahead of us.

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