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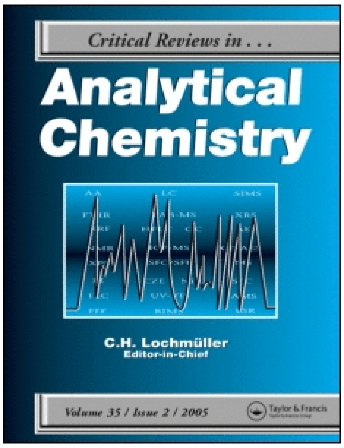

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Chemical Sensors and Biosensors Based on Prussian Blues

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ABSTRACT: This article is a review of the literature devoted to analytical sensors and biosensors based on Prussian blue and its analogues. Electrochemical and optical devices are characterized. Several sensing schemes and their practical analytical applications are reported. Trends and perspectives for development of Prussian blues-based (bio)sensors are indicated. The review contains 155 references.

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I. INTRODUCTION

Transition metal cyanide chemistry has a remarkable history that spans nearly 3 centuries, dating back to 1704 when the Berlin artist Diesbach accidentally discovered Prussian blue (PB). As a pigment PB was obtained in the reaction of the $Fe(CN)_6^{4-}$ complex anion with the Fe^{3+} cation, being the oldest coordination compound reported in the scientific literature.[1,2] Since then a lot of compounds belonging to the same family have been prepared, many of them showing unusual properties. PB has been manufactured as an important pigment for paints, lacquers, printing inks, laundry dyes, and other color-related uses due to its extraordinary intensity and durability of its color. The composition of this pigment as iron (III) hexacyanoferrate (II) has been definitely shown by spectroscopic studies.[3-5] The structure[6-8] and the nature of chemical bonding[3, 4] in PBs are now reasonably well understood. The basic structure is a three-dimensional polymeric network consisting of alternating ferric and ferrous ions on cubic lattice sites (Figure 1). In this way, iron (II) ions are surrounded octahedrically by the carbon atoms of the cyanide ions, and iron (III) ions are linked by the nitrogen ends of the cyanides, which results in a low-spin and high-spin electron configuration, respectively. The remaining charge is balanced either by potassium ions, as in so-called "soluble" PB ($KFeFe(CN)_6$),[7, 8] or by ferric ions, as in "insoluble" PB ($Fe_4(Fe(CN)_6)_3$).[6] Both compounds are highly insoluble ($K \cong 10^{-40}$) — the term "soluble" was invented by dye makers and refers to the ease with which the potassium salt can be peptized. The cubic lattice has some defects, interstitial sites, and vacancies where countercations and other molecular species can be intercalated.

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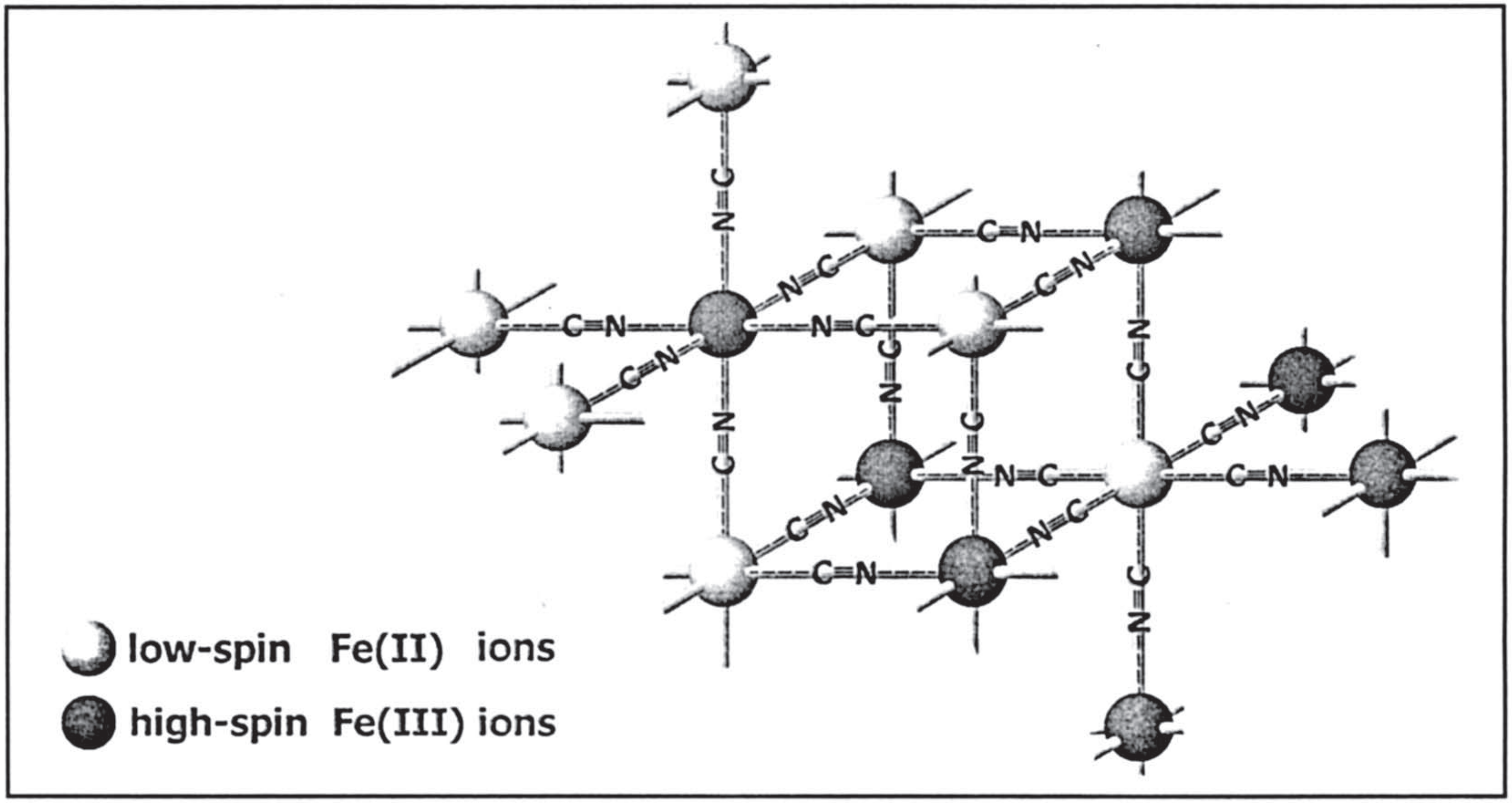

FIGURE 1. Cubic structure of PB

The open structures of PBs may accommodate large metal cations and water molecules, and they are zeolitic in nature.

Since the time of PB discovery several studies have been made on the structure and chemistry of this insoluble mixed-valence iron compound. Despite this long interest, it was not until 1978 that the first report of the electrochemistry of PB was made. Interest in ferric ferrocyanide was renewed by the development of procedures for coating it as films on electrodes by Neff.[9] Since then several fundamental investigations concerning the electrochemical and spectroelectrochemical properties of PB films have appeared,[10-15] accounted in 1986 in comprehensive review.[12] The PB electrodes have received much attention due to their chemical stability, electrochromic reactions, electro- and photocatalytic activity, easy preparation, and low cost. The PB films have been investigated intensively for use in electrochromic displays, fuel cells, solid-state rechargeable batteries, and as signal-enhancing devices due to photovoltaic and photoelectrochemical effects.

This review deals with the analytical aspects of this intensively expanding field of research. A significant development of PB-based analytical sensors and especially biosensors has been observed during the last 10 years. Corresponding articles have been discussed in this article. PB can serve as a prototype for a number of polynuclear transition metal hexacyanometallates that form an important class of insoluble mixed-valence compounds. Practical uses of these PB analogues in analytical sensing and biosensing schemes are also reported in this review.

II. BASIC SPECTROELECTROCHEMISTRY OF PB FILMS

PB films in both “soluble” and “insoluble” forms are chemically stable. They are electroactive. A typical cyclic voltammetric response of PB films consists of two sets of peaks (Figure 2, top). The peaks are explained in terms of two reversible redox reactions of PB: reduction to Prussian White (PW, called Everitt’s salt) and oxidation to Prussian Yellow (PY) via mixed-valence form of Prussian Green (PG, also called Berlin Green). The response at negative potential (around +0.2V vs. Ag/AgCl) results from the reduction/oxidation of a high-spin system $Fe^{3+/2+}$, while the other couple at positive potentials (around +1.0V vs. Ag/AgCl)) correspond to redox reaction of low spin $Fe(CN)_6^{3-/4-}$. The reduction and oxidation reactions for “soluble” form of PB are formulated as follows:[10]

$$KFe^{III}Fe^{II}(CN)_6 + e^- + K^+ \rightarrow K_2Fe^{II}Fe^{II}(CN)_6 \tag{1}$$

$$KFe^{III}Fe^{II}(CN)_6 \rightarrow Fe^{III}Fe^{III}(CN)_6 + e^- + K^+ \tag{2}$$

Similar redox reactions have been proposed for “insoluble” form of PB:[11]

$$Fe^{III}_4[Fe^{II}(CN)_6]_3 + 4e^- + 4K^+ \rightarrow K_4Fe^{II}_4[Fe^{II}(CN)_6]_3 \tag{3}$$

$$Fe^{III}_4[Fe^{II}(CN)_6]_3 + 3X^- \rightarrow Fe^{III}_4\,[Fe^{III}(CN)_6]_3X_3 + 3e^- \tag{4}$$

The reduction procedures have been reported to lead to the incorporation of cations into the film irrespective of whether the “soluble” (1) or “insoluble” (3) PB forms are involved. The oxidation of low-spin system involves the loss of cations for the “soluble” form (2), or the incorporation of electrolyte anions for “insoluble” form (4). Oxidation and reduction reactions of the iron centers can proceed through the solid compounds as the zeolitic structure of the films allows a flux of cations to pass through the channels and holes of the solids. These ions provide the necessity of charge compensation. During the PB oxidation/reduction process cations with smaller hydrated radii freely penetrate the film, while other with larger radii can block the redox processes.[10-13]

Electrochemical processes in which PB are involved result in substantial changes of optical properties of the films.[10-12, 14] The films of iron hexacyanoferrate exhibit four-color electrochromocity, depending on its redox state. A deep blue color is connected with an intense intervalence charge-transfer absorption band of

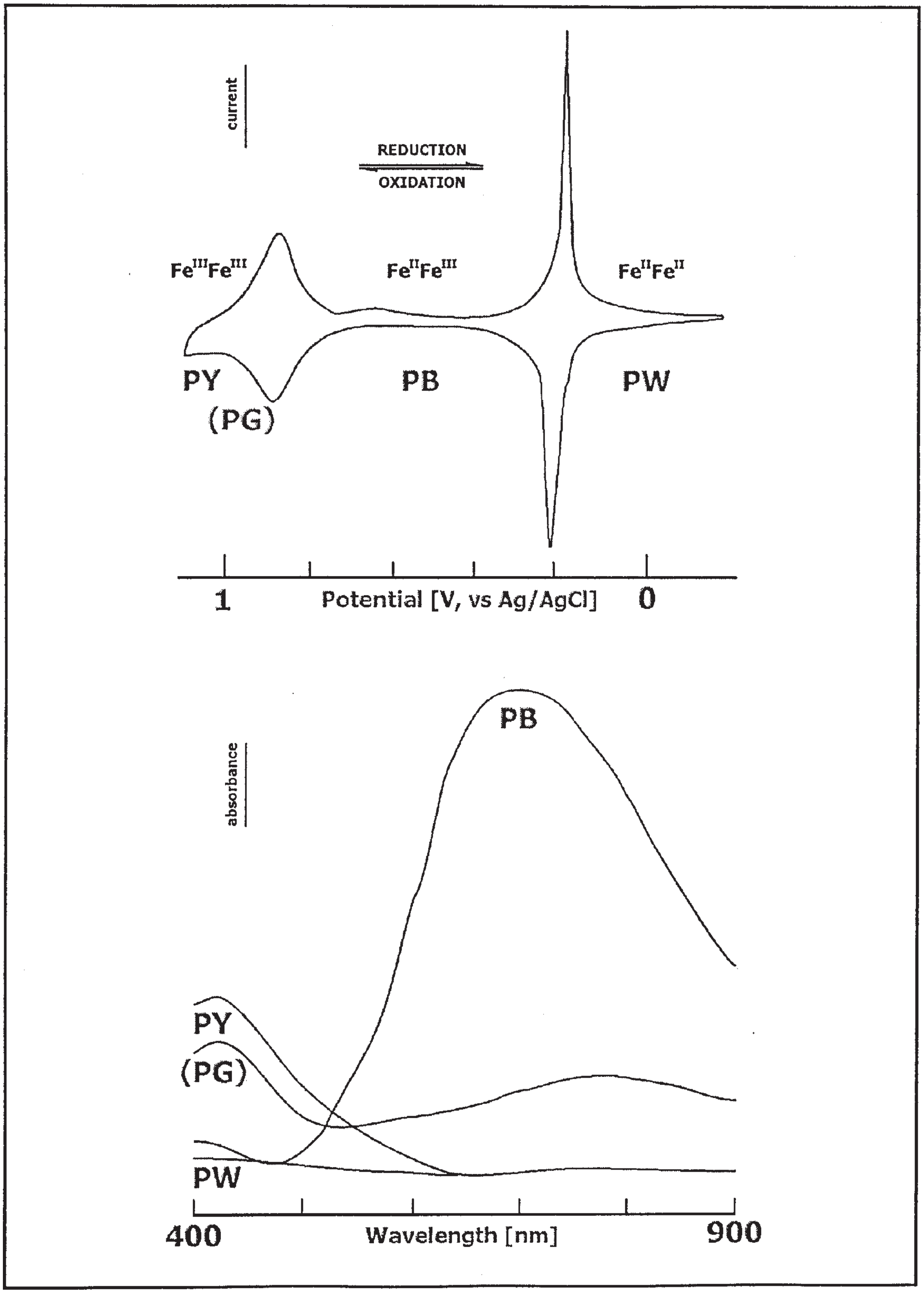

FIGURE 2. Spectroelectrochemical characteristics of PB films. (Data from Ref. 12. With Permission of American Chemical Society.)

the compound near 700 nm due to a transition from the ground state to an excited state on which an electron is transferred from $Fe^{III}Fe^{II}$ state to $Fe^{II}Fe^{III}$ state. A second absorption band near 420 nm appears in the VIS spectrum of PG. In PY (fully oxidized form of PB), which is visually yellow-brown, the absorption at 700 nm did not persist. Its spectrum showed only a band at 420 nm. The spectrum of transparent PW film did not show any distinct bands in the visible range. Typical absoption spectra of the redox forms of iron hexacyanoferrate film are shown in Figure 2 (bottom).

III. PB-BASED ELECTROCHEMICAL SENSORS FOR ELECTROACTIVE ANALYTES

PB films in many cases do act as three-dimensional electrocatalysts. It is well known that many zeolites used as catalysts have specific channel diameters for a particular reaction. Zeolitic nature (Figure 1) of PB and all its redox forms with channel diameters of about 0.32 μm are extremely important for diffusion of small molecules through the crystal. Without such channels PB would not be expected to act as a catalyst.

The first report on electrocatalytic properties of PB film by Itaya and co-workers[15] has been devoted to reduction and oxidation of hydrogen peroxide by PW and PG forms, respectively. The authors also reported electrocatalytic reduction of molecular oxygen; however, others did not confirm these results. Hydrogen peroxide reduction takes place inside the PW in which both H_2O_2 molecules and the products are able to diffuse rapidly. The correspondence between the electrode potential for hydrogen peroxide reduction and that of PB strongly suggests that the high spin iron ions have catalytic activity. Hydrogen peroxide is completely reduced to water before diffusion out of the crystal:

$$H_2O_2 + 2e^- + 2H^+ \rightarrow 2H_2O \qquad (5)$$

The electrochemical studies prove that the divalent iron ions are really a catalyst for reduction of hydrogen peroxide (5), not for decomposition such as the disproportionation of H_2O_2 to O_2. PB-modified electrodes also have catalytic activity for oxidation of hydrogen peroxide:

$$H_2O_2 \rightarrow O_2 + 2e^- + 2H^+ \qquad (6)$$

The catalyzed oxidation of H_2O_2 commences at potential where the low-spin iron ions are oxidized. This correspondence in the potential strongly supports the view that the trivalent low-spin iron ions act as catalyst for the oxidation of hydrogen peroxide. Finally, it was found that two kinds of electron transfer channels in the Prussian blue due to redox reactions of the high-spin $Fe^{3+/2+}$ ions and the low-spin $Fe(CN)_6^{3-/4-}$ ions work as catalysts for the reduction and oxidation of hydrogen peroxide, respectively. Reported rate constant for H_2O_2 oxidation (4×10^2 M^{-1} s^{-1}) was in order smaller than that for its reduction ($2\text{-}6 \times 10^3$ M^{-1} s^{-1}).[15]

PB-based amperometric sensors for the determination of hydrogen peroxide are very attractive tools in electroanalytical chemistry. Recently, Pt,[16] glassy carbon,[17-19] and TiO_2[20] electrodes with electrodeposited PB films were reported for H_2O_2 determination. The carbon paste electrodes with mechanically incorporated PB particles are also analytically useful,[21] but they exhibit smaller sensitivity. All these sensors can work in both catodic and anodic manner; however, determinations based on electroreduction of hydrogen peroxide are much more useful from the practical point of view. In the case of electrooxidation of H_2O_2, a sufficiently high sensitivity can be obtained at high operating potential, where many other substances usually present in real samples can also discharge electrochemically at the electrodes. All biological liquids contain a variety of electrochemically ease oxidizable reductants, for example, ascorbate, urate, bilirubin, acetaminophen, catecholoamines, and some thiol-compounds, which are oxidized at similar potential and dramatically affect the sensor selectivity, producing large parasitic anodic current and this makes quantitative determination of hydrogen peroxide impossible. On the other hand, the electrocatalytic cathodic acitivity of PB-modified electrodes towards hydrogen peroxide is nearly as high as the activity of Pt electrode, whereas it is insensitive to O_2 reduction, contrary to noble metals that are not suitable for selective reduction of H_2O_2 in the presence of oxygen. Beside this, many low-molecular-mass substances are known to be specifically adsorbed on metallic electrodes and significantly affect their electrochemical activity. Finally, the use of expensive materials increased the cost of sensors. Catalytic efficiency of PB is comparable to that of biological catalysts. The kinetics of hydrogen peroxide reduction on PB-modified electrodes was investigated using a wall-jet cell with continuous flow.[17] It was found that the bimolecular rate constant for reduction of H_2O_2 is 3×10^3 M^{-1} s^{-1}. The activity of natural enzyme peroxidase is of similar order of magnitude as the reported electrocatalytic activity of PB. Due to the characteristics of the high catalytic activity and selectivity the PB-based electrocatalyst is denoted as “artificial peroxidase”.[17] PB-based electrodes are useful for the frequent determination of hydrogen peroxide in the regime of flow-injection analysis (FIA).[19] All referred here H_2O_2 sensors based on PB films[16-20] have found wider applicability in the development of amperometric biosensors reported in this review.

There are a few reports in the literature on the application of PB electrodes in the cathodic manner for detection of electroactive species other then hydrogen peroxide. PB electrodes are useful for reduction of perborate (peroxoborate, $Na_2B_2(O)_2(OH)_4$). The determination range from 1 to 100 ppm H_2O_2 as perborate has been found.[22] PB films are effective for the electrocatalysis of the persulfate/sulfate redox system.[23] This has been exploited in the voltammetric determination of persulfate anions in commercial hair bleaching products using PB-modified platinum disc electrode.[24] Glassy carbon electrode subsequently coated with polypyrrole and PB layers was found to be useful for detection of cytochrome C.[25] The sensor was applied in a FIA system for the protein determination over micromolar range of concentration. Other low molecular electroactive and electroinactive proteins gave no specific analytical signal. Electrodes modified with PB may be used also for electrocatalytic reduction of some transition metal complexes in their oxidized state,[26] carbon oxide,[27, 28] and carbon dioxide,[29, 30] however, analytical applications of such processes have been not reported.

PB-based electrodes can also act as electrocatalysts for the oxidation of a large group of analytes; however, this implies low selectivity of such sensors and necessity of sample pretreatment or separation procedures before detection. PB electrodes allow determination of hydrazine.[31-34] The electrooxidation process occurs at potential where simultanously the oxidation of PB to PG starts.[31] Electrocatalytic reaction occurs inside the zeolitic lattice of PB (PB acts as three-dimensional catalyst). One-electron charge transfer process has been found to be rate limiting. The final product of the oxidation is gaseous nitrogen. Hydrazine compounds with large overpotential oxidized at carbon electrodes are not suitable analytes for these methods. Well-working hydrazine sensors were prepared by mechanically transferring microparticles of PB onto the surface of paraffin impregnated graphite electrode,[32] using sol-gel technology[33] or by electrodeposition of PB on glassy carbon electrode and coating it with protective Nafion membrane.[34] The latter sensor has been used successfully in flow-injection analysis system. The analytical response was linear for injected amounts of hydrazine sulfate from 32 μg to 0.6 ng (detection limit).[34] Liquid chromatography with electrocatalytic detection by PB electrodes is useful for determination of some mercaptocompounds[35, 36] and catecholoamines.[37] In the case of flow-through amperometric determination of selected cat-echoloamines (dopamine, epinephrine, norepinephrine) and dihydroxyphenylacetic acid, a linear response range over three orders of magnitude and detection limits at 10 pg were observed. Glassy carbon electrodes with adsorbed PB and coated with desorption-protecting Nafion layer were useful for the determination of cysteine, glutathione, and acetylcysteine with detection limits on ppm level. For amperometric detection of thiols also are useful PB electrodes fabricated in sol-gel technology.[39] PB films after oxidation to the PG form are able to rapid electroxidation of thiosulfate.[39] The $S_2O_3^{2-}$ ions are converted to $S_4O_6^{4-}$ ions that can be further slowly electrooxidized to sulfate ions. PB film can be also used for electrooxidiation of absorbic acid.[40, 41] PB-modified electrode has been used as an amperometric detector in flow injection analysis of vitamin C.[42]

IV. PB-BASED ELECTROCHEMICAL SENSORS FOR ELECTROINACTIVE ANALYTES

The cubic unit cell (Figure 1) dimensions of approximately 1.02 μm are similar for all redox forms of PB. Because of the similarities in the structures of PB, PW, and PY, partially reduced or oxidized PB film can be treated as solid solution. In that event for reactions 1 and 2 Nernstian equations are written, respectively:

$$E = E^0 + \frac{RT}{F} \ln \frac{PB \times K}{PW} \tag{7}$$

$$E = E^0 + \frac{RT}{F} \ln \frac{PY \times K}{PB} \tag{8}$$

where PB, PW, and PY denote activities of respective redox forms of PB and K refers to the activity of the potassium ion in the solution phase adjacent to the film. The midpeak potential, for both the oxidation and reduction reaction, is a function of potassium cation activity. The prediction that the voltammetric mid-peak potential would decrease with decreasing potassium ion concentration for reactions 1 and 2 is well confirmed experimentally, and the behavior is remarkably Nernstian with a slope 59 mV per decade for both reactions.[10-13] The investigation of membrane potentials of PB films on electrodes shows that zeolitic PW, PB, and PY films have ion-exchange properties, and that the variations of electrode potentials measured potentiometrically at fixed ratio of oxidized and reduced film matrix are due entirely to the changes of the Donnan potential.[43] These properties allow the application of PB electrodes as potentiometric[44-46] and voltammetric[47-49] sensors for electroinactive cations. The electrodes are ion selective in the sense that certain alkaline cations can freely migrate into and out of the PB film, whereas others are excluded. PB channel radius of 0.16 μm will accommodate K^+, Rb^+, Cs^+, and NH_4^+ hydrated ions whose radii are 0.125, 0.128, 0.119, and 0.125 μm, respectively. Cations with hydrated radii much greater than the channel radius of PB (e.g., Li^+, Na^+, H^+, and all of the group II cations) should not be able to enter the rather rigid lattice of the material. Potentiometric all-solid-state ion-selective electrodes for potassium ions are based on thin films of PB[44,45] and on heterogenous PB membranes prepared with PVC, silicone, polystyrene or exopy resin.[44] Only recently PB-modified polentiometric device based on electrolyte metal oxide semiconductor field effect transistor (E-MOSFET) was reported.[46] For voltammetric measurements composite electrodes made of PB, graphite, and paraffin have been developed.[47] The working range of both potentiometric and voltammetric sensors is from 10^{-5} to 1 *M*. However, due to low selectivity the sensors could be used in analytical practice only in limited cases of real samples where interfering cations are absent. To increase selectivity of the voltammetric detection scheme, the flux of cations in the sensing film can be simultaneously detected gravimetrically. Such types of measurements are possible with PB-coated quartz-crystal microbalance (QCM) electrodes.[48,49]

Scholz and co-workers have developed more specific sensing schemes for voltammetric detection of thallium[50] and ammonium[51] ions based on the fact that incorporation of these ions into the film can be made partially irreversible, owing to small lattice constractions and expansions accompanying the electrochemical conversion of PB.[52] The working principle of the Tl-sensor is that thallium ions are pumped into PB during alternating oxidation-reduction cycles. Two Tl^+ ions enter the holes in the PB lattice to form thallium PW ($Tl_2Fe^{II}Fe^{II}(CN)_6$), but only one Tl^+ leaves the PW lattice during its reoxidation forming $TlFe^{III}Fe^{II}(CN)_6$. The further oxidation of PB to PY is prevented by the inability of Tl^+ to diffuse through the PB matrix, as these ions are too large. They stick in the holes of the PB because the oxidation of $Tl_2Fe^{II}Fe^{II}(CN)_6$ to $TlFe^{III}Fe^{II}(CN)_6$ that is accomplished by contraction of the host lattice. The peculiarity of the sensing scheme is that the Tl^+ ions are situated in the holes of the PB matrix. After such preconcentration procedure of thallium in PB phase, the voltammetric determination follows. The thallium ions are reduced to metallic form, which is subsequently oxidized to give anodic stripping signal. This sensor system allows both very selective loading of PB with traces of thallium and their determination down to a concentration 2 × 10^{-8} *M*. Similar size-specific inhibition process of the low-spin iron voltammetric system of PB is caused by ammonium ions. The hydrated ammonium ion also has such a size that although it is able to diffuse in the crystal of PW, it cannot move in the PB lattice. In consequence, further oxidation to PY is prevented because the charge neutrality cannot be achieved. This disappearance of the low-spin system of PB has been used for the detection of ammonium ions. The voltammetric ammonium ion-selective electrode has been applied in flow-through system in conjunction with the Kjedahl method for organic nitrogen determination.

PB film deposited across interdigitated array electrodes is useful in gas sensing.[53] One side of the interdigitated array is the working electrode, with the other connected up to the auxiliary and reference electrodes. The current was found to flow when the difference of potentials became large enough to disproportionate the PB, that is, simultaneous PB → PW reduction and PB → PY oxidation occurring at opposing film/electrode interfaces. Resident mobile ions within PB must migrate from one side of the film to another, in the absence of external electrolyte, for the reasons of maintaining electroneutrality during this solid-state voltammetry. Internal cation mobility depends on the nature of the bathing gas. The detected gases such as water vapor, methanol, and dichloroethane do not act as redox species but help to solvate the internal counterionic species and lead to an increase in their mobility within the film, causing changes in the recorded voltammograms. Thick films of PB produced in Sol-gel technology have been investigated as humidity sensors also by impedance spectroscopy.[54]

At much more negative potential than for H_2O_2 electroreduction, the amperometric determination of glucose could be achieved at PB electrode (without enzyme).[55] The reverse-phase liquid chromatography PB-based electrochemical system for glucose sensing gave a linear response from 2 × 10^{-7} to 2 × 10^{-4} *M* and a detection limit of 1 pmol. The system has been used for the determination of glucose in real, clinical samples of urine. The mechanism of the detection is unclear. Under experimental conditions glucose is electroinactive (amperometric detection of reducing sugars is possible by electrooxidation in strongly alkaline media). It is suggested that the detector response is governed by the complexation reaction between the analyte and iron (II) and iron (III) ions present in the partially reduced PB molecules sustained on electrode. Glucose-iron (II) complex has higher electroactivity causing larger response in cathodic region.[55]

V. PB-BASED ELECTROCHEMICAL BIOSENSORS

Amperometric enzyme electrodes based on oxidases form a large group of biosensors. Most of them are based on the electrochemical detection of hydrogen peroxide, which is formed in the course of the enzyme-catalyzed oxidation of analyte by dissolved molecular oxygen. PB-based H_2O_2 sensors reported here seem to be very promising for the construction of such first-generation biosensors. The development of amperometric biosensors based on PB-modified electrodes was first announced by Karyakin and co-workers.[56] Since then various PB/oxidase-based biosensors have been widely reported in the literature.[57-74]

As it was shown in Section III of this review, PB-modified electrodes can detect hydrogen peroxide by both the electrocatalytic oxidation and reduction. The biosensors, the same as PB-based H_2O_2-subsensors, can work both in cathodic and anodic manner. Both sensing schemes possible for amperometric glucose biosensing with glucose oxidase (GOx, EC 1.1.3.4) are depicted in Figure 3. The anodic measurements are strongly influenced by many reducible species present in real samples. Sensitive and selective detection of enzymatically generated hydrogen peroxide is possible (also in the presence of dissolved oxygen) in the case of cathodic scheme of (bio)sensing.

In all cited papers[56-73] GOx has been investigated as a model enzyme. There are, in principle, no limits to use other oxidases for the preparation of PB-based amperometric biosensors. Utilization of alcohol oxidase (EC 1.1.3.13), D-amino acid oxidase (EC 1.1.3.3), glutamate oxidase (EC 1.4.3.11), and choline oxidase (EC 1.1.3.17) and lactate oxidase (EC 1.1.3.2) allows the development of PB-based enzyme electrodes for the detection of ethanol,[58] D-alanine,[65] glutamate,[59,60] and choline,[73] and lactice acid,[74] respectively, as the enzymes catalyzed hydrogen-peroxide-producing reactions:

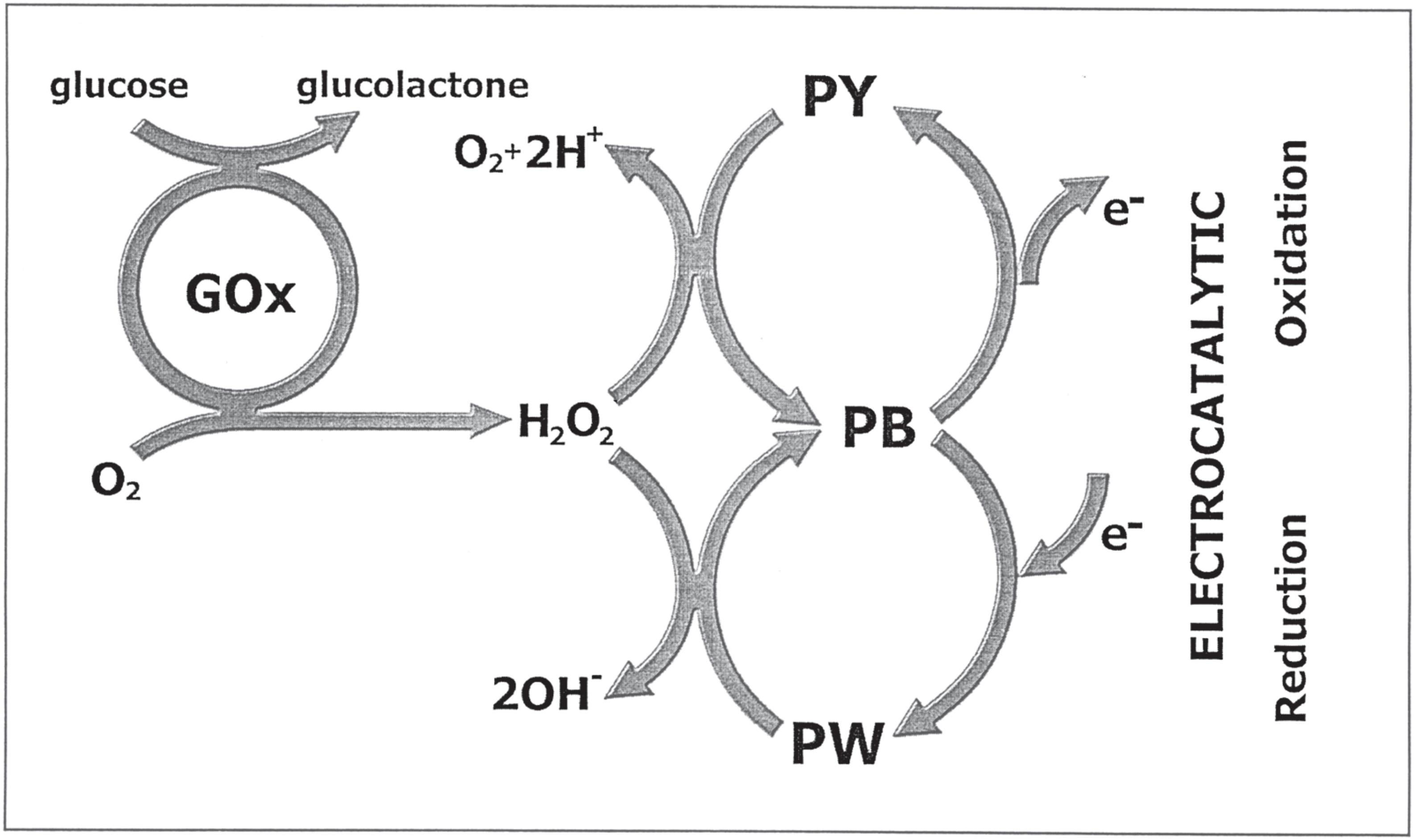

FIGURE 3. Schemes of glucose biosensing with Gox-modified PB electrodes.

$$\text{R-CH}_2\text{OH} + \text{O}_2 \xrightarrow{\text{EC1.1.3.13}} \text{R-CHO} + \text{H}_2\text{O}_2 \tag{9}$$

$$\text{R-CH(NH}_2\text{)-COOH} + \text{O}_2 + \text{H}_2\text{O} \xrightarrow{\text{EC 1.1.3.3}} \text{R-CO-COOH} + \text{NH}_3 + \text{H}_2\text{O}_2 \tag{10}$$

$$\text{L-glutamate} + \text{O}_2 + \text{H}_2\text{O} \xrightarrow{\text{EC 1.4.3.11}} \alpha\text{-ketoglutarate} + \text{NH}_3 + \text{H}_2\text{O}_2 \tag{11}$$

$$\text{Choline} + \text{O}_2 + \text{H}_2\text{O} \xrightarrow{\text{EC 1.1.3.17}} \text{betaine} + \text{H}_2\text{O}_2 \tag{12}$$

$$\text{CH}_3\text{-CHOH COOH} + \text{O}_2 \xrightarrow{\text{EC 1.1.3.2}} \text{CH}_3\text{-CO-COOH} + \text{H}_2\text{O}_2 \tag{13}$$

For the construction of the biosensors various glassy carbon,[56-62,74] carbon,[63,64] graphite,[65-67] platinum,[68-70] and titanium dioxide[71] electrodes coated with electrochemically deposited PB films were applied. For such purposes graphite pastes mixed with PB powder are also used.[72,73] The pastes are useful for screen printing fabrication of the sub-sensors.[73] Also, different enzyme immobilization methods have been investigated, including adsorption,[56,57,74] crosslinking with albumins using glutaral as bifunctional linking agent,[63,71] entrapment in Nafion,[58-62,72,74] poly(vinyl alcohol) grafting vinylpyridine self-gelatinizable copolymer,[66] screen-printable inks[73] and electrochemically deposited organic polymers.[68-70] The original method of immobilization is based on enzyme incorporation into structure of PB film during its electrochemical growth process.[64,65] This method, specific for the PB-based sensors, offers the advantages of producing amperometric biosensors, including electrochemical, one-step preparation procedure, and the control of the film thickness and enzyme loading. The coverage of biosensors with additional membranes further improves their stability, avoiding both mechanical destruction of PB and escape of enzyme molecules from biocatalytic layer. Moreover, the membranes are useful as antiinterference layers improving the selectivity of the biosensors. These additional membranes are made of Nafion,[56-65] polyuretane,[63] or electrodeposited polymers, such as polyphe-nylenediamine,[63,64] polypyrrole[69] and polyaniline.[70] Some PB-based amperometric enzyme electrodes have been used successfully for the determination of glucose in human serum samples from healthy persons and diabetic patients.[66,71] PB-based biosensors for potential biomedical *in vivo* measurements can be fabricated in micro-scale.[63] Also, a glucose nanosensor based on PB modified carbon-fiber cone nanoelectrode and an integrated reference electrode has been reported.[64] PB-based biosensors having high sensitivity and stability are also useful in systems for FIA.[58-61]

Different biosensing scheme for PB film deposited on quartz-crystal microbalance (QCM) electrode suggested by Komplin and Pietro[75] is illustrated in Figure 4. The surface of rubidium PB ($\text{RbFe}^{\text{III}}\text{Fe}^{\text{II}}(\text{CN})_6$) film deposited on QCM is functionalized with nicotinamide adenine dinucleotide (NAD^+). The immobilized coenzyme retains its activity as a redox transfer agent toward enzyme-catalyzed reaction. Electron transfer to PB film requires the uptake of a rubidium ion from solution to maintain charge neutrality of the film. Electrochemical signal and mass change is detected by QCM electrode. Replacing potassium with heavier rubidium ions enhances sensitivity of the gravimetric detection. Biocatalytic reduction of the NAD^+, by the way of an enzymatic reaction, transfers electrons to the PB film with concomitant uptake of solution cations, and regeneration of surface-bound NAD^+, as evidenced by gravimetric and electrochemical measurements. The prototype of such hybrid biosensor transducer in connection with glucose-6-phosphate dehydrogenase (G-6-PDH, EC 1.1.1.49) can be used for the detection of glucose-6-phosphate. The enzyme substrate causes the mass increase measured with QCM, according to the scheme shown in Figure 4. The reduction of PB film by glucose-6-phosphate is also confirmed by loss of blue color and by a drop in open-circuit potential. Redox coenzyme functionalized PB films seem to be useful for biosensing with various NADH-dependent enzymes.

Amperometric PB-electrode modified with acetylcholinesterase (EC 3.1.1.7) is sensitive to acetylthiocholine. The enzyme catalyses hydrolysis of the substrate:

$$\text{CH}_3\text{COSCH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3 + \text{H}_2\text{O} \xrightarrow{\text{EC 3.1.1.7}} \text{CH}_3\text{COOH} + \text{HS-CH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3 \tag{14}$$

The formed thiocholine is electrocatalytically oxidized to dithiocholine. The enzyme electrode has been used as a disposable electrochemical

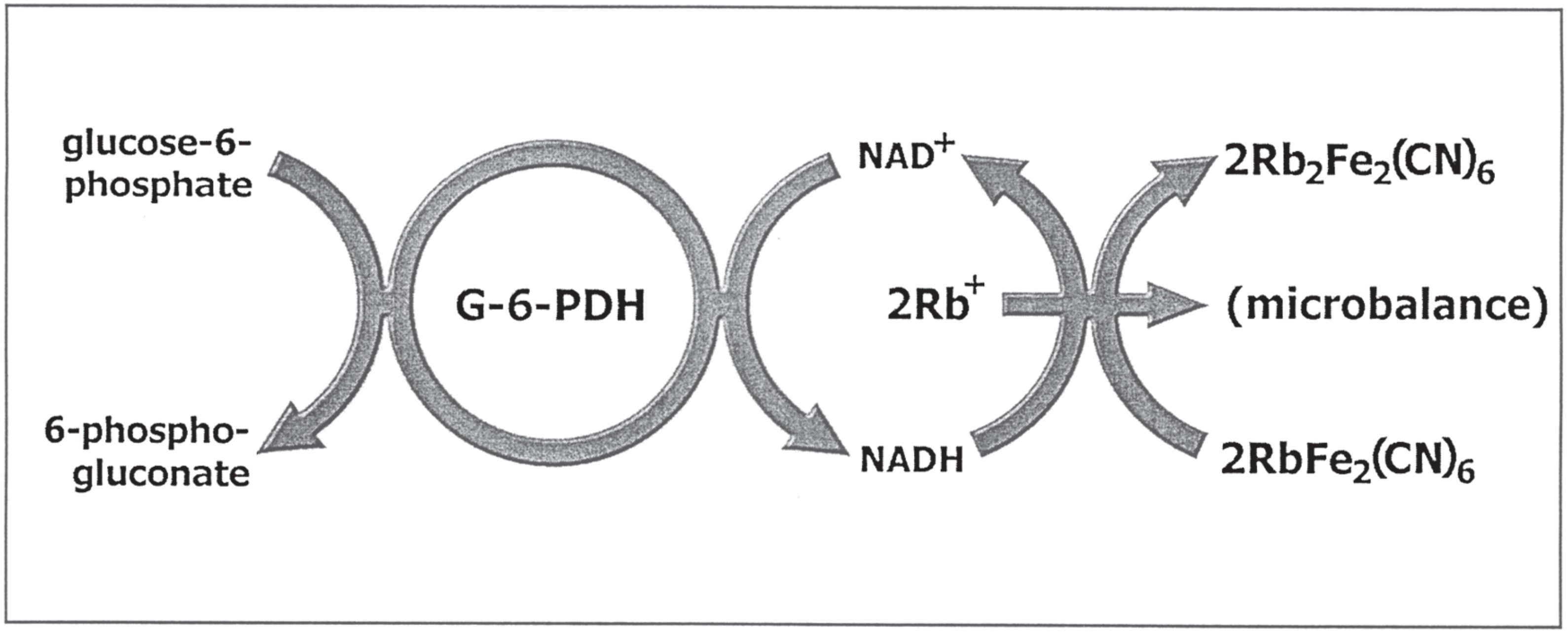

FIGURE 4. Redox coenzyme functionalized PB film acting as a mass-transducer of the biocatalytic biosensor.

probe for some pesticides (diazinon, fenthion, and dichlorvos), as these organophosphate compounds selectively inhibited the enzyme causing decrease of sensitivity of the biosensor. This amperometric assay allows the determination of the pesticides in submicromolar concentration ranges.[76]

VI. PB-BASED OPTICAL SENSORS AND BIOSENSORS

PB film has a deep blue color and its spectrum (Figure 2) is compatible with near-infrared light emitted by low-cost diode lasers and light-emitting diodes. Taking into account the unique chemistry of this compound substantial changes in its optical properties are to be expected as a result of various processes of chemical recognition in which PB can be involved. This implies that PB films can play a role of a receptor part of optical sensors for variety of analytes. Koncki and Wolfbeis[77] first indicated the potential applications of thin films of PB for optical chemical sensors. Exploiting both the redox and protolytic properties of such films for optosensing purposes was suggested. A dedicated, nonelectrochemical method for the deposition of robust and crack-free composite films of PB was developed,[78,79] as for optical uses nonconducting materials such as plastics and glasses are predominantly applied.

The optical detection of some reductants and oxidants is possible to exploit redox properties of the PB/PW film system (see Figure 2). PB films are easily discolorated by selected reductants according to Reactions 1 and 3. In the detection system PB film plays a double role: first as an immobilized reagent (oxidant), and second as an optical sensing element. The film has been utilized in disposable cuvettes for detection of ascorbic acid[80] and some mercaptocompounds.[81] The optical tests with the integrated sensing layer made of PB have been applied for quantitative analysis of simple and complex pharmaceuticals. The detection of reductants using PB film is a stoichiometric, kinetic process: an analyte reacts with the reagent phase and converts it into a colorless product (PW film). The amount of PB decreases over time and no steady-state signal is reached. The analytical signal (change of the film absorbance) is related to the integrated amount of analyte that has contacted with PB phase, rather than to the analyte concentration. Until renewing of the reagent phase is impossible, sensor based on stoichiometric reaction is useful only as single-use device. However, it was shown that utilization of the PB/PW-based reaction-detection scheme in FIA format enables both optical detection and chemical regeneration of the sensor layer.[79] In other words, the developed FIA system allows application of the nonindicating, stoichiometric scheme of analyte recognition for reversible and multiple optical sensing. The flow-through sensor based on PB/PW system film is sensitive to strong reductants, but also enables indirect optical detection of electroinactive alkaline cations involved in the process of PB reduction.[79] Moreover, *in situ* generated PW film can be used for the optical detection of various oxidants, including H_2O_2. The reported PB/PW sensor is useful for the determination of vitamin C, cysteine, and hydrogen peroxide in pharmaceutical products.[82] Optical sensing schemes based on PG/PB or PY/PB redox systems have not been investigated until now.

PB films enable fast, selective, and reversible optical evaluation of pH in physiological range.[45,78] In contrast to sensors based on redox or/and ion-exchange processes of PB, the protolytic properties of the material are exploited in this case. Optical pH sensitivity of PB films is associated with pH-dependent equilibria between fully isocyano hexacoordinated and partially hydrated high-spin Fe(III) ions in the film. The reversibility of the sensing system depends on complex protolytic processes. In acidic solutions (pH<3) protolysis of PB is negligible. With increasing pH, reversible hydrolysis of PB is observed according to

$$\begin{aligned} &Fe_4[Fe(CN)_6]_3 + 3H_2O \\ &\rightarrow Fe(OH)_3 + 3FeFe(CN)_6^- + 3H^+ \end{aligned} \tag{15}$$

This protolytic process is fully reversible, because it is not associated with destruction of the zeolitic lattice of the PB film. In other words, optical measurements of pH in range up to 8 are connected with the indicating process. The range of concentrations detected by PB depends on the equilibrium for reaction of the indicator with the analyte. For higher pH, the recognition process becomes stoichiometric and therefore irreversible. In more alkaline solutions (pH>8) further and irreversible decomposition of PB takes place:

$$FeFe(CN)_6^- + 3OH^- \rightarrow Fe(OH)_3 + Fe(CN)_6^{4-} \quad (16)$$

This process is irreversible due to destruction of zeolitic structure of PB and escape of hexacyanoferrate (II) ions out of the film. The formed film is yellow and consists of hydrated ferric oxide. Regeneration of the film to PB form is impossible.

PB films have found application as optical transducers in biosensing schemes based on hydrolases and oxidases.[83] Specially prepared PB films doped with organic functionalized polymers were developed as "ready to use" supports for covalent immobilization of enzymes.[84] Carboxylic or amine groups present on the surface of the composite films allow direct covalent binding of biomolecules to the subsensor PB membrane forming an extremely thin, monomolecular enzyme layer. The biofilms are fully transparent and do not disturb optical measurements. PB films biomodified with urease (EC 3.5.1.5), acetylcholinesterase (EC 3.1.1.7), and peptidases (α-chymotrypsin – EC 3.4.21.1 and trypsin – EC 3.4.21.4) can be used for detection of substrates of respective biocatalyzed reactions accompanied by changes of pH:

$$(H_2N)_2CO + 3H_2O \xrightarrow{\text{EC 3.5.1.5}} 2NH_4^+ + HCO_3^- + OH^- \quad (17)$$

$$\text{acetylcholine} + H_2O \xrightarrow{\text{EC 3.1.1.7}} CH_3COO^- + H^+ + \text{choline} \quad (18)$$

$$\text{R-COHN-R}' + H_2O \xrightarrow{\text{EC 3.4.21.}} \text{R-COO}^- + H^+ + \text{R}'\text{-NH}_2 \quad (19)$$

The films are useful as receptor elements of pH-based enzyme biooptodes enabling the determination of urea, acetylcholine, some peptides, and esters in millimolar range of concentration.[84] Flowthrough cell detector based on a urease-modified PB film has been used for the determination of urea in samples of urine and extracts from pharmaceutical ointments.[83] This urea biosensor has also been applied in flow-injection bioanalytical system dedicated to the monitoring of real clinical processes of hemodialysis.[85]

Hydrogen peroxide-sensitive PW film with covalently immobilized GOx molecules enables the spectrophotometric detection of glucose[83,86] utilizing a similar biosensing scheme as in first-generation amperometric PB-based biosensors (see the previous section). The flowthrough optical biosensor has been applied for the determination of glucose in various real biomedical (urine and serum), pharmaceutical (infusion fluids), and food (milk, honey, nutrients, juices, soft drinks, and wines) samples.[86]

VII. SENSORS AND BIOSENSORS BASED ON ANALOGUES OF PB

PB is the prototype of a number of polynuclear transition metal hexacyanometallates, which form an important class of insoluble mixed-valence compounds. They have general formula $M^A_a[M^B(CN)_b]_c$ where M^A and M^B are transition metals with different formal oxidation numbers. They may contain ions other then the metals and various amounts of water. They have different PB mechanical, electrochemical, and spectroelectrochemical properties. Chemistry and modern perspectives of transient metal cyanide compounds have been widely reported by Dunbar and Heintz.[87] Cox et al.[88] reviewed electrodes modified with various insoluble cyanometallates including cyanorutenates, cyanomolybdates, etc. intensively investigated in the 1980s. In this section the sensors that have found practical analytical application are reviewed. Nearly all sensing schemes reported in this article for PB-based sensors can be adopted for electrodes modified with other metal hexacyanoferrates (MHCF).

Electrodes modified with copper.[16,21,89] nickel,[21,90] cobalt,[21,91] and chromium[92] and manganese[93] hexacyanoferrates were investigated as H_2O_2 sensors. CuHCF-based sensor has been used in FIA system for amperometric detection of H_2O_2.[89] MnHCF-modified aluminium electrode has been applied for H_2O_2 determinatin in seawater samples.[93] Comparing with PB electrodes MHCF sensors have a similar or lower ability to catalytic electroreduction of hydrogen peroxide, but they are more stable over a wide range of pH, especially in neutral solutions. This is an important advantage, taking into account that the reduction of H_2O_2 leads to the formation of an alkaline product (Eq. 5).

The use of MCHFs circumvents stability problems inherent to PB in alkaline solutions, and hence permits the operation at physiological pHs well tolerated by enzymes. This is the main reason for the development of oxidase-biosensors based on MCHFs rather than on PB. Amperometric glucose biosensors based on glucose oxidase were prepared using CuHCF,[61,94-96] NiHCF,[97,98] CoHCF,[99,100] CrHCF[101] electrodes. The enzyme was immobilized by protein cross-linking,[97-99] entrapment in electrodeposited film of MHCF,[100,101] in Nafion[61] or in carbon paste containing MHCF.[94-96] The modified carbon paste is useful in screen-printing technology, enabling fast and large-scale production of thick-film disposable glucose biosensors.[95] NiCHF-based glucose biosensor has been applied in FIA of human blood samples from diabetic patients.[98] Principles of action for all reported MHCF/GOx biosensors are well illustrated in Figure 3. An enzyme biosensor for oxalate working in similar biosensing scheme has been developed by cross-linking of oxalate oxidase (EC 1.2.3.4) at the surface of CrHCF-modified graphite electrode. The enzyme catalyzes the oxidation of oxalate to carbon dioxide and hydrogen peroxide. CrHCF electrode enables the measuring of a current, resulting in the electrocatalytic reduction of H_2O_2 proportional to oxalate concentration. The biosensor has been used for the determination of oxalate in different real food samples[102] as well as in human urine.[102,103] Oxalates have been also determined in real food samples and in samples of different brands of beer using a similarly prepared biosensor based on mixed ruthenium-nickel-iron hexacyanoferrate.[104]

Another biosensing scheme is based on the possibility of electrocatalytic oxidation of reduced nicotinamide adenine dinucleotide at CoHCF,[105] or NiHCF[106-108] electrodes (direct NADH oxidation at metal electrodes takes place with considerable overpotentials). Such sensors can cooperate with dehydrogenases that constitute a large class of redox enzymes using the redox cofactor (NAD^+) and produce the reduced form (NADH). The NiHCF electrode is useful for detection of NADH produced by reaction of lactate with NAD^+. Such sensing system has been used as an amperometric bioassay of lactate dehydrogenase (EC 1.1.1.27) activity.[107] NiHCF electrodes coated with a cross-linked layer of alcohol dehydrogenase (EC 1.1.1.1) enable amperometric determination of alcohols[108,109] by electrochemical detection of NADH generated in enzymatic oxidation of analyte to aldehyde. Similar biosensing scheme (but with gravimetric, not amperometric transduction of analytical signal) is shown in Figure 4. An amperometric alcohol biosensor has been used for the determination of ethanol in human urine samples.[108]

Various MHCF electrodes similarly to PB-based sensors are useful for the electrocatalytic oxidation of a large spectrum of electroactive species, including mercaptocompounds,[110-113] thiosulfate,[39,114-118] sulfite,[119] ascorbate,[90,120,121] dopamine,[122] and hydrazine.[32,118,123,124] A few of the sensors have found analytical applications. The determination of cysteine, glutathione, and thiopurine with picomolar detection limits is possible using liquid chromatography with amperometric detection at InHCF electrode.[111] The method is useful for the determination of cysteine in human urine and other thiocompounds in artificial urines. Similar results were obtained using LC with CoHCF-based electrochemical detector.[112] The coupling of microdialysis sampling with the detector system has been used for the *in vivo* determination of glutathione in the brain of a freely moving rat. NiHCF-based amperometric sensors for thiosulfates have been utilized for the analysis of photographic wastes.[114,116] CuHCF-based amperometric electrode enables the determination of sulfite ions and sulfur dioxide with a detection limit below 10 ppm.[119] The same CuHCF electrode has been used for determination of vitamin C in pharmaceuticals utilizing as an analytical signal changes of both anodic peaks corresponding to Cu^+/Cu^{2+} and $Fe(CN)_6^{4-}/Fe(CN)_6^{3-}$ redox couples.[121] Mixed cobalt and copper hexacyanoferrate (CoCuHCF)-modified carbon fiber microelectrode has been developed as an all-solid-state potentiometric sensor for hydrazine with a detection limit below 10^{-6} *M* and nearly-Nernstian sensitivity.[125] CuHCF electrode incorporated in FIA system enables the amperometric detection of nitrites.[126] Fe(III) ions can be determined by LC with amperometric detection based on electroreduction at the NiHCF electrodes.[127] A nonconventional sensing scheme of Fe(III) can be realized with AgHCF-modified electrodes.[128] Silver ions are reduced to a metallic form and simultaneously liberated hexacyanoferrate ions react with determined iron ions to form PB.

After this preconcentration, the analyte is determined by characteristic analytical signals of PB in differential pulse voltammetry. The AgHCF electrodes have also been used for potentiometric and amperometric detection of silver ions.[121]

MHCF-modified electrodes can be used as potentiometric and voltammetric sensors for electroinactive cations similarly as discussed in the case of PB-based sensors (Section IV). CoHCF,[131] NiHCF,[132,133] and CuHCF[132] electrodes have been investigated as potentiometric sensors for alkaline cations. A voltammetric response to alkali metal cations (changes of mid-peak potential) has been observed for sensors based on NiHCF,[134-138] CuHCF,[138-142] InHCF,[143] ZnHCF,[144] and VHCF.[145] The detectors have poor selectivity; however, some of them in cases of noncomplex samples or in connection with separation techniques have found practical analytical applications. NiHCF electrode in FIA system has been applied for determination of potassium in syrups samples.[136] CuHCF-based sensor has been used as alkaline cations detector in ion chromatography, and promising results were obtained for urine and blood serum samples.[138,139] Similarly, an InHCF-based detector in single ion chromatography column has been applied for the determination of electroinactive monovalent cations in rain and mineral waters.[143] A cation-sensitive CuHCF electrode incorporated into the FIA system with a gas-diffusion unit enabled fast and selective determination of ammonium ions in rain and lake water samples.[142] Using a special method for the processing of the analytical signal (calibration of the anodic peak potential against the Na^+/K^+ ratio is linear in physiological range) NiHCF-based electrode has been applied successfully for the simultaneous determination of sodium and potassium ions in whole blood and blood serum samples.[137] Although selectivity toward alkali cations is not too high, NiHC electrode has been used also as a voltammetric ammonium ion-selective sub-sensor for urea biosensor development.[146] This biosensor is useful in flow injection analysis.

VIII. PRESPECTIVES FOR DEVELOPMENT OF PB-BASED ANALYTICAL DEVICES

The final goal of sensors development should be their utility for solving real analytical problems. As reported in this review, PB-based sensors and biosensors are fully useful analytical tools in various practical applications. Sensing schemes and applications reported in this article do not present all analytical possibilities offered by PB-based sensors. An increasing number of investigations dealing with such sensors indicates a continuous development of these analytical tools. Three following trends seem to be the most promising:

1. Material chemistry development leading to more stable and robust films of PB and new analogues of PB such as mixed metal hexacyanoferrates, surface modified films, composite films, ceramic materials … prepared using advanced technologies such as sol-gel, screen-printing, etc.
2. Search of new, more selective, and sensitive sensing and especially biosensing schemes.
3. The development of new schemes for the transduction of the analytical signal generated by PB-based sensing layer (receptor part). Especially promising seems to be hybrid transducer systems leading to an increase of selectivity and sensitivity of sensors. QCM electrodes enable simultaneous gravimetric and electrical measurements.[48,49,75] QCM-based signal transduction can be improved further by *in situ* IR spectroscopic measurements.[147,158] Hybrid, electrochemical, and optical measurements are possible using optically transparent electrodes. An optical signal generated by electrochemical manipulation of the electrodes can be monitored by either transmission or attenuated total reflection. The primary advantage of the spectroelectrochemistry is the cross-correlation of information attainable from simultaneous electrochemical and optical measurement. Heineman and co-workers[149-151] have demonstrated recently the concept of such an spectroelectrochemical sensing based on the multimode selectivity simultaneously achievable in a single device. Selectivity for analyte relative to interferents has been obtained by choice of chemosensitive material, electrolysis potential, and wavelength for optical monitoring. The use of a mediator to detect a nonabsorbing analyte during spectroelectrochemical modulation has been

shown also.[151] This concept can be applied for PB-based sensing and can be extend to biosensors. Only recently was the feasibility of a dual optical-electrochemical mode of analysis demonstrated using a single-pass optically transparent PB electrodes for potassium ion sensing.[152] Similar enzymatically modified electrodes were used for the spectroelectrochemical detection of glucose.[153] Ultrasensitive spectroelectrochemistry of PB is possible using an electroactive-integrated optical waveguide.[154] This single planar waveguide coated with indium-tin oxide layer is similar to 10.000-fold more sensitive to changes in absorbance occurring during electrochemical events vs. a single-pass transmission spectroelectrochemistry. Other possibilities are offered by a fiber-optic-based surface plasmon resonance (SPR) instrument working as an optical transducer of electrochemical processes in which the PB film can be involved.[155] The reported PB/PW-modified SPR probe is a natural detector of charge flow connected with these redox-sensing processes.

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