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Poly(Xylylviologen) Electron Transfer Mediators in Amperometric Glucose Sensors

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Water-soluble poly(*o*-xylylviologen dibromide) and poly(*p*-xylylviologen dibromide) are shown to efficiently mediate electron transfer from reduced glucose oxidase to a conventional carbon paste electrode. Because of their low oxidation potentials, glucose sensors based on glucose oxidase and these mediators can be operated in a potential range where oxidation of interfering species such as ascorbic acid and uric acid does not occur. The corresponding monomeric materials, benzylviologen bromide and dibenzylviologen dibromide cannot serve as electron transfer mediators as their formal potentials are more negative than that of the flavin redox centers in glucose oxidase.

INTRODUCTION

Amperometric glucose sensors based on glucose oxidase and non-physiological redox mediators use the following mechanism to shuttle electrons between the reduced flavin adenine dinucleotide center of the enzyme ($FADH_2$) and the electrode:

$$\text{glucose} + \text{GO(FAD)} \rightarrow \text{gluconolactone} + \text{GO(FADH}_2\text{)}$$

$$\text{GO(FADH}_2\text{)} + 2\text{M}_{ox} \rightarrow \text{GO(FAD)} + 2\text{M}_{red} + 2\text{H}^+$$

$$2\text{M}_{red} \rightarrow 2\text{M}_{ox} + 2\text{e}^- \text{ (at the electrode).}$$

In this scheme, GO(FAD) represents the oxidized form of glucose oxidase and $GO(FADH_2)$ refers to the reduced form. The mediating species M_{ox}/M_{red} is assumed to be a one-electron couple. Sensors based on derivatives of the ferrocene/ferricinium redox couple,[1-3] on quinone species[4-6] and on electrodes consisting of organic conducting salts such as TTF-TCNQ (tetrathiafulvalene-tetracyanoquinodimethane)[7-10] have recently been reported.

Because of the fairly high oxidation potential of these mediators (e.g. +100 to +400 mV vs. the saturated calomel electrode, or SCE), however, these sensors must be operated at potentials where several common interferents in biological fluids, such as ascorbic acid and uric acid, are directly oxidized at the electrode.[11,12] This additional contribution to the response current may make it difficult to obtain accurate quantification of the glucose concentration in a sample. In order to minimize this interference, several research groups have modified the surface of the glucose sensors with anionic polymer coatings,[13,14] which can partially exclude the negatively charged ascorbate and urate ions from the electrode surface. The present paper describes a more effective method of avoiding interference due to these easily oxidizable species, which involves the use of poly(xylylviologen) (viologen = 4,4′-bipyridyl) electron transfer mediators. Because these mediators have very low oxidation potentials, the glucose sensors can be operated at a potential where oxidation of ascorbic acid and uric acid does not occur.

EXPERIMENTAL

Reagents. Glucose oxidase (EC 1.1.3.4, type VII, 129 units/mg) was obtained from Sigma (St. Louis, MO). Graphite powder (product no. 50870) and paraffin oil (product no. 76235) were obtained from Fluka (Ronkonkoma, NY). The α,α′-dibromoxylenes (ortho and para) and the 4,4′-dipyridyl were obtained from Aldrich (Milwaukee, WI). Glucose (Sigma, cat. no. G-5250) solutions were prepared by dissolving appropriate amounts in 0.1M phosphate/0.1M KCl buffer (pH 7.0); the glucose was allowed to reach mutarotational equilibrium before use (ca. 24 h). All other chemicals were reagent grade and were used as received.

Polymer synthesis. Poly(*o*-xylylviologen dibromide) and poly(*p*-xylylviologen dibromide) were prepared according to a literature procedure,[15] in which 7.8g (0.05 mole) of 4,4′-dipyridyl and 14.5g (0.055 mole) of the appropriate α,α′-dibromoxylene were reacted in acetonitrile. The solutions were refluxed for 24h under nitrogen atmosphere. The resulting yellow precipitate was recovered by filtration and dried at 60°C under vacuum. The polymers were characterized by IR and NMR spectroscopies.

Monomer synthesis. Benzylviologen chloride was prepared by reacting equimolar amounts of 4,4′-dipyridyl and benzyl chloride in acetonitrile; the solution was refluxed for 40 h under nitrogen atmosphere. The resulting precipitate was removed by filtration and dried under vacuum at 60°C. N,N′-dibenzylviologen dichloride was prepared by reacting a 1:2 molar ratio of 4,4′-dipyridyl and benzyl chloride in acetonitrile. As above, the solution was refluxed for 40h under nitrogen. The precipitate was removed by filtration and dried at 60°C under vacuum. The monomers were also characterized by IR and NMR measurements.

Glucose sensor construction. The modified carbon paste for the sensors was made by thoroughly mixing 50mg of graphite powder with a measured amount of the viologen polymer; in the present work, the molar amount of the viologen moiety was the same for all electrodes (36μmole of viologen per gram of graphite powder). 5mg of glucose oxidase (129 units/mg) and 10μl of paraffin oil were then added, and the resulting mixture was blended into a paste. The paste was packed into a 1.0ml plastic syringe which had previously been partially filled with unmodified carbon paste, leaving approximately a 2mm deep well at the base of the syringe. The resulting surface area of the electrode was 0.025cm^2. Electrical contact was achieved by inserting a silver wire into the top of the carbon paste.

Electrochemical methods. Cyclic voltammetry and constant potential measurements were performed using a Princeton Applied Research Potentiostat (Model 173) and a Universal Programmer (Model 175). All experiments were carried out in a conventional electrochemical cell containing pH 7.0 phosphate buffer with 0.1M KCl at 23(±2)°C. For the constant potential glucose measurements, the solutions were deaerated by bubbling N_2 through the solution for at least 10min; a gentle flow of N_2 was also used to facilitate stirring. In addition to the modified carbon paste working electrode, a saturated calomel reference electrode (SCE) and a platinum wire auxiliary electrode were employed. In the constant potential experiments, the background current was allowed to decay to a constant value before samples of a stock glucose solution were added to the buffer solution. A constant background current was attained approximately 10min after application of the potential.

RESULTS AND DISCUSSION

Cyclic voltammetry. Most monomeric viologens are not suitable as electron transfer mediators in glucose oxidase-based sensors because their formal potentials are more negative than that of FAD. For example, as shown in the voltammetric results in Figure 1, N,N′-dibenzylviologen has a more negative formal potential (E^0, taken as the midpoint between the oxidation and reduction peaks) than flavin mononucleotide (the E^0 for FAD is nearly the same as that for flavin mononucleotide[16]), and thus is incapable of reoxidizing the reduced flavin. Upon polymerization, however, the formal potential of the dibenzylviologen is raised to a value[17] which is more positive than that of the flavin moiety; this is apparent from the voltammogram for poly(*o*-xylylviologen) shown in Figure 1. A summary

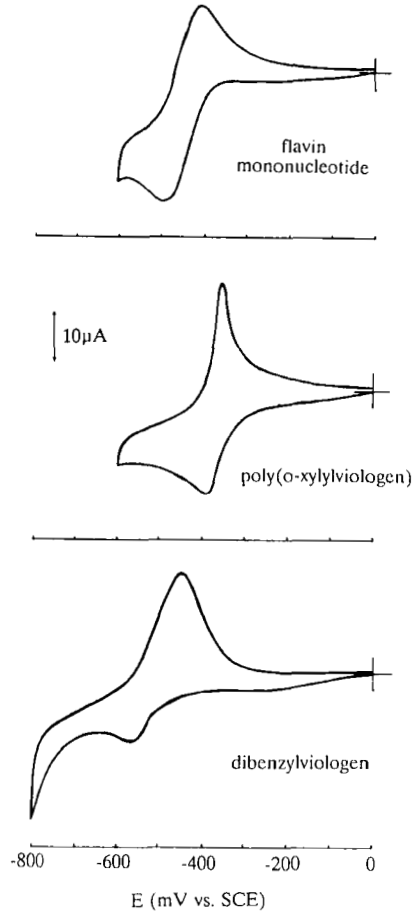

FIGURE 1 Cyclic voltammograms for flavin mononucleotide (10mM), poly(*o*-xylylviologen) (2.0mM concentration of viologen subunit), and dibenzylviologen monomer (1.1mM) at a Pt wire working electrode in pH 7.0 phosphate buffer (with 0.1M KCl) solution (scan rate: 20mV/s).

of the E^0 values for the benzyl-substituted monomers and polymers, obtained from cyclic voltammetry, is shown in Figure 2. It is clear from these results that the poly(xylylviologens) are capable of reoxidizing the reduced flavin species.

Glucose sensor measurements. Figure 3 shows glucose calibration curves for carbon paste electrodes containing glucose oxidase and the poly(xylylviologen) electron transfer mediators at an applied potential of −100mV (vs. SCE). These sensors display a good response to glucose over a clinically relevant concentration range, and are capable of working at more negative potentials; preliminary studies indicate that glucose calibration curves for an applied potential of −200mV are very similar to those shown in Figure 3. At this lower potential, we have found

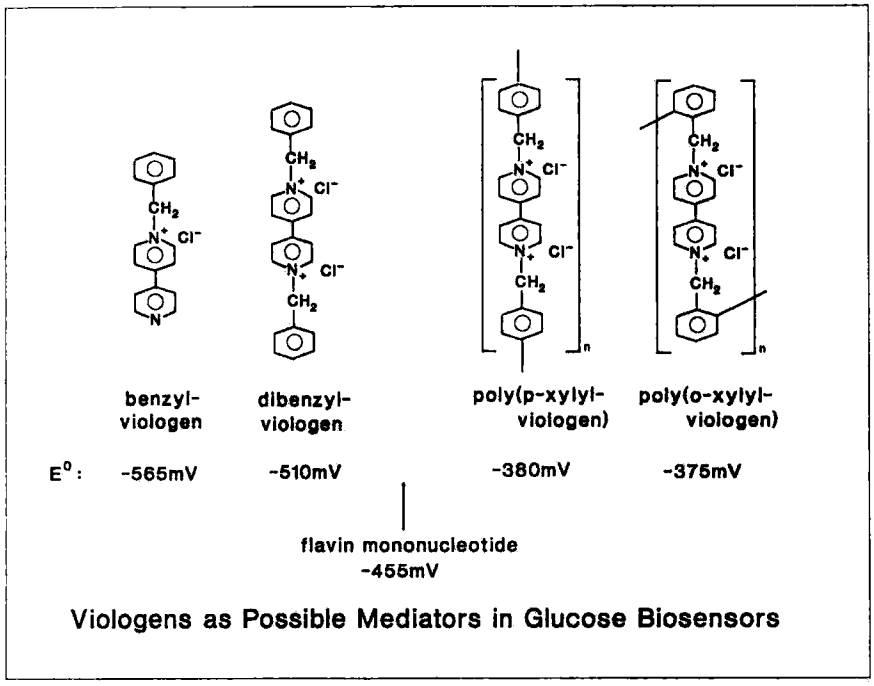

FIGURE 2 Formal potentials of benzyl-substituted monomers and polymers as determined from cyclic voltammetry (conditions as in Figure 1). For comparison, the formal potential of flavin mononucleotide is also indicated.

that common interferents such as ascorbic acid and uric acid are not oxidized at the carbon paste electrode.

Similar constant potential measurements have demonstrated that carbon paste electrodes containing glucose oxidase and benzylviologen or dibenzylviologen monomers show no response to glucose. As discussed above, this is due to the fact that these monomers cannot reoxidize the reduced flavin centers of the enzyme.

Conclusions. The water-soluble poly(xylylviologens) efficiently mediate electron transfer from reduced glucose oxidase to a conventional carbon paste electrode. Because of the low oxidation potentials of these mediators, the glucose sensors can be operated at potentials where oxidation of interfering species such as ascorbic acid and uric acid does not occur. Work is presently underway to develop insoluble viologen polymers based on the siloxane[18,19] backbone for use as electron transfer mediators in flavoenzyme-based amperometric sensors.

Acknowledgment

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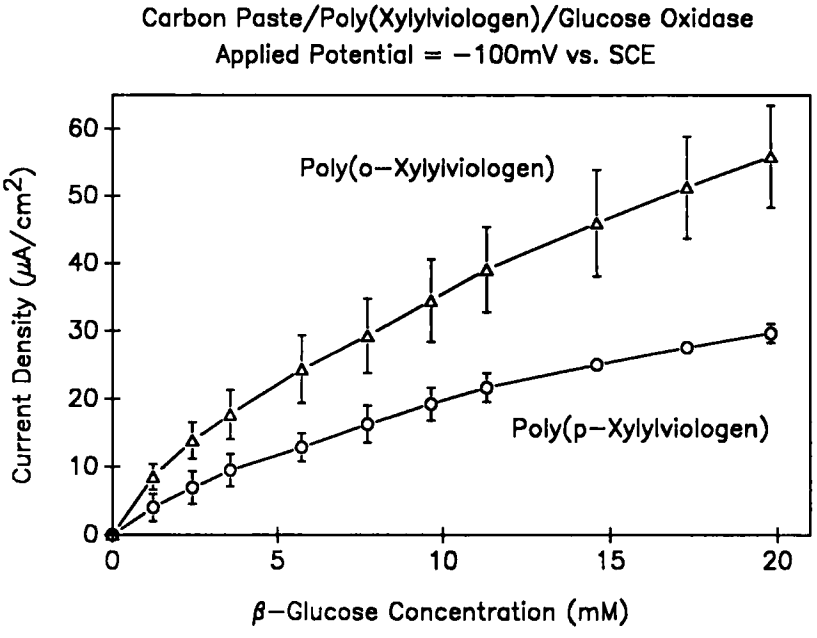

FIGURE 3 Glucose calibration curves for the poly(xylylviologen)/glucose oxidase/carbon paste electrodes at E = −100mV (vs. SCE). Each curve is the mean result for three electrodes.

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