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Diffusion coefficients of oxygen, hydrogen peroxide and glucose in a hydrogel

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Abstract

For the design of a new glucose sensor, a knowledge of the diffusion of all participating compounds is needed. A rotating disc electrode covered with hydrogel layer was used to determine the effective diffusion coefficients (D_{eff}) of oxygen, hydrogen peroxide and hydroquinone in a hydrogel, which is used in the sensor. Measurements were carried out under steady-state conditions. The three compounds appeared to be slowed by the gel to the same extent. A comparison was made between the D_{eff} values of glucose and hydroquinone by simultaneous diffusion through a hydrogel membrane. In this case glucose diffusion was slowed to a larger extent than hydroquinone diffusion. The effect, however, was independent of the degree of cross-linking of the hydrogel.

Keywords: Biosensors, Diffusion coefficient, Glucose, Hydrogel, Hydrogen peroxide, Oxygen

It is important to obtain continuous information about the blood glucose concentration of diabetics and an implantable sensor is a good alternative for regularly analysing blood samples.

A number of glucose sensors have already been developed [1–8]. In most of these sensors glucose reacts with oxygen to yield hydrogen peroxide [1–5]. The reaction is catalysed by the enzyme glucose oxidase (GOD). Hydrogen peroxide is oxidized or reduced at a detection electrode, its detection current is proportional to the glucose concentration. The enzyme is immobilized in a hydrogel by chemical cross-linking with a bifunctional reagent. As blood is low of oxygen, oxygen should be electrochemically produced in the sensor itself.

The disadvantage of existing sensors is that the concentration profiles and the diffusion patterns for oxygen, hydrogen peroxide and glucose in the

enzyme-containing layer are not well defined. This can be the cause of a low detection current, as only a part of the hydrogen peroxide will reach the detection electrode.

For a proper design of a glucose sensor, measurement of the diffusion coefficients of all the participating compounds in the hydrogel seems to be essential. The diffusion coefficients of oxygen and hydrogen peroxide have been determined electrochemically, but this method is not useful for glucose. The diffusion coefficient of glucose had to be determined with a diffusion cell. To correlate the data for oxygen, hydrogen peroxide and glucose properly, an additional species, viz., hydroquinone, is used, as this compound is applicable in both the electrochemical and diffusion cell methods.

THEORY

A rotating disc electrode (RDE) covered with a hydrogel layer appears to be an accurate means

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Fig. 1 Schematic profiles for the concentration of electroactive species vs. the distance from the platinum disc surface. Hydrogel layer thickness is denoted by d_{hl} and Nernst diffusion layer by d_{dl} .

of measuring diffusion coefficients of electrochemically active compounds [9,10]. Figure 1 shows schematically the concentration profile for active species.

Under steady-state conditions, the flux J ($\text{mol m}^{-2} \text{s}^{-1}$) in both the hydrogel layer (J_{hl}) and the Nernst diffusion layer (J_{dl}) is the same:

$$J = J_{hl} = J_{dl} \quad (1)$$

From the definition for J and assuming a linear concentration profile, it follows that:

$$J_{hl} = J_{dl} \Leftrightarrow D_{hl} \frac{\Delta C_{hl}}{d_{hl}} = D_{dl} \frac{\Delta C_{dl}}{d_{dl}} \quad (2)$$

At the hydrogel layer–Nernst diffusion layer interface a jump in the concentration of the active component can take place. The partition coefficient α is defined by:

$$\alpha = C_{hl}^*/C_{dl}^* \quad (3)$$

where the asterisk refers to the interface.

The concentration of the electroactive species at the electrode surface will be virtually zero, as a sufficiently high overpotential is applied. In this case, from Eqns 2 and 3 the following expression is derived:

$$D_{hl} \frac{\alpha C_{dl}^*}{d_{hl}} = D_{dl} \frac{C_b - C_{dl}^*}{d_{dl}} \quad (4)$$

where C_b is the bulk concentration (mol m^{-3}). From Eqn 4, it follows that:

$$C_{dl}^* = \frac{D_{dl} \frac{C_b}{d_{dl}}}{\frac{\alpha D_{hl}}{d_{hl}} + \frac{D_{dl}}{d_{dl}}} \quad (5)$$

As $J = D_{hl} \alpha C_{dl}^*/d_{hl}$ and using Eqn 4, it is found that:

$$J = \frac{\frac{\alpha D_{hl}}{d_{hl}} \frac{D_{dl}}{d_{dl}} C_b}{\frac{\alpha D_{hl}}{d_{hl}} + \frac{D_{dl}}{d_{dl}}} \quad (6)$$

The permeabilities P_{hl} and P_{dl} are defined by:

$$P_{hl} = \alpha D_{hl}/d_{hl} = D_{\text{eff}}/d_{hl} \quad (7)$$

and

$$P_{dl} = D_{dl}/d_{dl} \quad (8)$$

where D_{eff} is the effective diffusion coefficient ($\text{m}^2 \text{s}^{-1}$).

Combining Eqns 6, 7 and 8 and using

$$I_{\text{lim}} = nFA_e J \quad (9)$$

where I_{lim} is the limiting current (A), n the number of electrons involved in the electrode reaction, F the faraday, i.e., the charge on one mole of electrons (C), and A_e the electrode area (m^2), the following equation can be derived:

$$\frac{1}{I_{\text{lim}}} = \frac{1}{nFA_e C_b P_{hl}} + \frac{1}{nFA_e C_b P_{dl}} \quad (10)$$

The limiting current depends on two serial diffusion resistances. The total diffusion resistance ($1/k$) is defined by:

$$\frac{1}{k} = \frac{1}{k_{hl}} + \frac{1}{k_{dl}} = \frac{1}{P_{hl}} + \frac{1}{P_{dl}} \quad (11)$$

where k is the total mass transfer coefficient (m s^{-1}). The first term ($1/k_{hl}$) is independent of the rotation speed. The second term ($1/k_{dl}$), however, is proportional to the reciprocal of the square root of the angular rotation rate (ω) of the RDE as P_{dl} is inversely proportional to d_{dl} . From

the theory of mass transfer to an RDE [11], it is known that

$$d_{dl} = 1.61 (D_{dl}/\nu_{dl})^{1/3} (\nu_{dl}/\omega)^{1/2} \quad (12)$$

and so

$$P_{dl} = \frac{D_{dl}}{1.61 (D_{dl}/\nu_{dl})^{1/3} (\nu_{dl}/\omega)^{1/2}} \quad (13)$$

Hence, if the reverse of the limiting current is plotted against the reverse of the square root of the angular rotation rate, a linear plot is obtained, the slope of which and the intercept give information about the permeability of the solution (Levich slope [11]) and the permeability of the hydrogel layer, respectively

In this way, effective diffusion coefficients of oxygen and hydrogen peroxide can be determined electrochemically. However, glucose is electrochemically inactive and its diffusion coefficient has to be determined by the diffusion cell method. A comparison between the effective diffusion coefficients of hydroquinone (electrochemically determined) and glucose can be made by simultaneous diffusion through a membrane made of the same hydrogel material as used for the RDE experiments, which is strengthened by a filter-paper on each side of the membrane. The concentration profile is shown in Fig. 2. In this

method two stirred solutions, A and B, where $C_A \gg C_B$, were separated.

For relatively short times the total flux J through the various layers is constant

$$J = k \Delta C \quad (14)$$

where $\Delta C = C_A - C_B \approx C_A$ and k is, similarly to Eqn. 11, the total mass transfer coefficient (m s^{-1}).

Again, the diffusion resistance is built up of several terms

$$\begin{aligned} \frac{1}{k} &= \frac{1}{k_m} + \frac{2}{k_{dl}} + \frac{2}{k_f} \\ &= \frac{d_m}{D_{eff}} + \frac{2d_{dl}}{D_{dl}} + \frac{2d_f}{D_f} \end{aligned} \quad (15)$$

where the subscripts m, dl and f refer to the membrane, the Nernst diffusion layer and the filter-paper, respectively. Combining Eqns. 14 and 15 gives

$$J = \frac{\Delta C}{\left(\frac{2d_{dl}}{D_{dl}} + \frac{2d_f}{D_f} + \frac{d_m}{D_{eff}} \right)} \quad (16)$$

The total amount of glucose or hydroquinone transported from compartment A to compartment B can now be written as

$$C_B V = J A_m t \quad (17)$$

Fig. 2 Concentration profiles through a hydrogel membrane (d_m) with a filter-paper (d_f) on each side, placed between two compartments, A and B. Nernst diffusion layers are denoted by d_{dl} .

and so the rate of increase of the concentration in solution B is

$$\frac{dC_B}{dt} = \frac{JA_m}{V} = \frac{1}{\left(\frac{2d_{dl}}{D_{dl}} + \frac{2d_f}{D_f} + \frac{d_m}{D_{eff}}\right)} \Delta C \frac{A_m}{V} \quad (18)$$

By comparing the slope of the plots of C_B vs time, the ratio of the effective diffusion coefficients of hydroquinone and glucose in the membrane can be determined. However, first the diffusion resistance of the Nernst diffusion layers and the two filter-papers for both hydroquinone and glucose have to be checked and inserted in Eqn. 18.

In this diffusion cell method, imperfections of the gel do not matter as the two compounds diffuse simultaneously through the same membrane. The thickness and area of the membrane are also of no importance.

EXPERIMENTAL

Reagents

The hydrogel used for these experiments was made of poly(vinyl alcohol) (PVA) from Denka Poval (B24) and cross-linked with glutaraldehyde (25%, w/w, aqueous solution, Merck) and photo-sensitive DTS-18 (polyazonium salt from PCAS, Longumeau, France).

$\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ and $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$, used for the buffer solution were purchased from Merck. Hydrogen peroxide (30%, w/w, aqueous solution) was obtained from Chempro Pack, hydroquinone from Merck and D-glucose from Janssen Chimica.

Glucose detection was performed with a Sigma glucose kit (No. 635), based on the reaction of glucose with *o*-toluidine, which yields a blue-green complex. All solutions were prepared with demineralized, distilled water.

Instrumentation

For the RDE experiments a Wenking POS 73 potentiostat was used, equipped with a digital multimeter (Fluke 8600 A) and a Motomatic E-550-M stirring motor. Recording was carried out with an *x,y* recorder (Philips 8120). A circulating

water-bath (Colara NB-32981) was used for temperature control of the one-compartment cell.

Diffusion cell experiments were performed with a magnetic stirrer in both compartments, which were thermostatically controlled with a Colara NB-32981 circulating water-bath. For the determination of the glucose concentration an LKB Biochrom Ultrospec II Type 4050 spectrophotometer was used for detecting the glucose-*o*-toluidine complex at 635 nm. The same spectrophotometer was used to determine the hydroquinone concentration at 290 nm.

A Talysurf 4 roughness meter from Rank Precision Instruments was used to measure the thickness of the gel layers.

Preparation of gel layers

A 10-g amount of PVA was slowly added to 90 cm^3 of demineralized water and stirred. The solution was heated for 15 h at 80°C until all the PVA had dissolved and a homogeneous solution was obtained. The solution was cooled to room temperature. Just before the spinning procedure, 0.20 g (0.2%, w/w) of DTS-18 and 0.16 or 0.40 g of 25% (w/w) aqueous glutaraldehyde were added. With a pipette an aliquot of the resulting solution was placed on the required surface (electrode surface or glass plate). After spinning for 5 s at 1000 rpm and for 25 s at 3000 rpm, the gel layer was dried for 30 min at 40°C. The spinning and drying procedure was repeated until enough layers had been spun on the surface. Thereafter the gel layer was irradiated with UV radiation at room temperature for 90 s. The gel layer was developed in demineralized water for 2 min and unreacted reactants were washed away. Finally, the gel layer was dried for at least 1 h at 60°C.

The thickness of the gel layer on both platinum electrodes and glass plates (control measurement) was measured with a roughness meter, connected with a thermograph. The thickness of a swollen gel layer (after contact with an aqueous solution) could also be measured with this technique.

Procedures

For all electrochemical experiments a polished platinum electrode was used as the working elec-

trode ($A_e = 0.50 \times 10^{-4} \text{ m}^2$) Further, a platinum counter electrode with a surface area of $5 \times 10^{-4} \text{ m}^2 \text{ s}^{-1}$ and a saturated calomel reference electrode (SCE) with a Luggin capillary were placed in the one-compartment cell A circulating water-bath was used to keep the temperature constant As supporting electrolyte 0.1 M sodium phosphate buffer (pH 6.7) was used with a kinematic viscosity of $0.9 \times 10^{-6} \text{ m}^2 \text{ s}^{-1}$ at 25°C and $0.7 \times 10^{-6} \text{ m}^2 \text{ s}^{-1}$ at 37°C [12]

For oxygen measurements the buffer solution was saturated with oxygen (1 atm) for at least 30 min This yields an oxygen concentration of 1.1 mol m^{-3} at 25°C and 0.9 mol m^{-3} at 37°C [13] A voltammogram was recorded from +600 to –650 mV (vs SCE) at a rotation speed varying from 1 to 49 s^{-1} (Pt electrode experiment) or from 0.5 to 16 s^{-1} (Pt-PVA electrode experiment)

For hydrogen peroxide measurements ($7\text{--}8 \text{ mol m}^{-3}$) the buffer solution was saturated with argon before adding hydrogen peroxide and voltammograms were scanned from +300 to –650 mV (vs SCE) The rotation speed for both the Pt electrode and Pt-PVA electrode experiments varied between 1 and 9 s^{-1}

Hydroquinone studies (2 mol m^{-3}) were performed with an argon-saturated buffer solution with hydroquinone added before saturation Anodization from –550 to +1200 mV (vs SCE) was conducted at various rotation rates (Pt electrode $1\text{--}36 \text{ s}^{-1}$, Pt-PVA electrode $0.5\text{--}9 \text{ s}^{-1}$)

For all three compounds the electrode was rotated at high speed ($> 50 \text{ s}^{-1}$ for a Pt electrode and $> 16 \text{ s}^{-1}$ for a Pt-PVA electrode) for about 20 s before a new scan was made The scan rate varied between 25 and 50 mV s^{-1} for Pt electrode experiments and between 2 and 10 mV s^{-1} for Pt-PVA electrode experiments

With a diffusion cell containing two compartments, the ratio of the effective diffusion coefficients of glucose and hydroquinone was determined Compartment A of the cell contained 160 cm^3 of 0.1 M sodium phosphate buffer with 1.00 kmol m^{-3} glucose and $0.100 \text{ kmol m}^{-3}$ hydroquinone Initially compartment B contained only 160 cm^3 of phosphate buffer Between the two compartments a cross-linked PVA membrane (3.46 cm^2) was placed with a filter-paper

(Rotband, Schleicher and Schull) on each side for solidity purposes Thereafter both compartments were simultaneously filled with the solution The concentration increase in compartment B was followed for 5 h, with UV spectrophotometry for hydroquinone and with a glucose kit [14] and visible spectrophotometry for glucose Although only samples from compartment B were analysed, an equal amount of sample was taken from compartment A to keep the solution levels in both compartments equal and to prevent forced diffusion through the membrane and destruction of the membrane

The influence of the two filter-papers and the Nernst diffusion layers was checked by conducting a comparative experiment with only the two filter-papers placed between the two compartments

The temperature was maintained at 25°C with a circulating water-bath for all diffusion cell experiments and both compartments were stirred magnetically

RESULTS AND DISCUSSION

Properties of the gel layer on an RDE

Several PVA gel layers with different degrees of cross-linking were used to investigate the diffusion behaviour oxygen, hydrogen peroxide and hydroquinone

In Table 1 properties of gels A–D are given, such as thickness, percentage of glutardialdehyde added and swelling factor after saturation with buffer solution All gels were made on different days Although gel solutions A, B and C were

TABLE 1

Properties of the various hydrogels used for diffusion measurements

Gel	No of layers	Glutardialdehyde added (g)	d_{hl} (dry) (μm)	Swelling factor
A	4	0.16	13.5	2.3
B	2	0.16	8.0	2.3
C	4	0.16	26.0	2.3
D	4	0.40	13.0	2.1

made with the same procedure, the thickness of one spun layer, varied substantially

If the same gel solution (i.e., gel A) was spun on several surfaces (platinum discs or glass plates), it was found that the spinning and cross-linking procedure provided layers of reproducible thickness and degree of cross-linking. This means that the difference in the behaviour of the gel layers is due to the gel solution preparation.

Determination of diffusion coefficients

Plots of I_{lim}^{-1} versus $\omega^{-1/2}$ gave straight lines, as expected, for measurements with both the Pt electrodes and Pt-PVA electrodes (Figs 3 and 4).

Table 2 shows the diffusion coefficients in the buffer solution and the effective diffusion coefficients in the gel layer for various gels and at two temperatures (25 and 37°C). The ratio $D_{\text{eff}}/D_{\text{dl}}$ is also given.

For oxygen, hydrogen peroxide and hydroquinone the $D_{\text{eff}}/D_{\text{dl}}$ ratios are virtually identical and depend on the properties of the gel and temperature. This means that the ratio of the effective diffusion coefficients for the three compounds in the hydrogel layer is almost identical with this ratio in the buffer solution.

Simultaneous diffusion of glucose and hydroquinone through two filter-papers shows a linear increase of C_B/C_A for both species (Fig. 5). C_B was divided by C_A ($\approx \Delta C$) to correct for the different starting concentrations. The slopes of the lines of glucose and hydroquinone have a

Fig. 3 Rotating disc electrode data with a Pt electrode ($T = 25^\circ\text{C}$) for (Δ) H_2O_2 , (+) O_2 and ($\circ$) hydroquinone.

ratio of 0.81. Washburn [12] gave a diffusion coefficient of $0.52 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ for glucose in pure water at 15°C and of $0.66 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ for hydroquinone. The ratio of the diffusion coefficients under these conditions is 0.79, which makes it acceptable to consider the two filter-papers as a stagnant layer of buffer solution with a diffusion coefficient equal to that in the Nernst diffusion layer. The diffusion resistance of the Nernst diffusion layer and the filter-paper (Eqn. 15) can

TABLE 2

Diffusion coefficients in the buffer solution and effective diffusion coefficients in the various gels for O_2 , H_2O_2 and hydroquinone (HQ) at two temperatures

T (°C)		Buffer			Gel A		Gel B		Gel C		Gel D	
		D_{dl} (10^{-9} $\text{m}^2 \text{ s}^{-1}$)	D_{eff} (10^{-9} $\text{m}^2 \text{ s}^{-1}$)	$D_{\text{eff}}/D_{\text{dl}}$	D_{eff} (10^{-9} $\text{m}^2 \text{ s}^{-1}$)	$D_{\text{eff}}/D_{\text{dl}}$	D_{eff} (10^{-9} $\text{m}^2 \text{ s}^{-1}$)	$D_{\text{eff}}/D_{\text{dl}}$	D_{eff} (10^{-9} $\text{m}^2 \text{ s}^{-1}$)	$D_{\text{eff}}/D_{\text{dl}}$	D_{eff} (10^{-9} $\text{m}^2 \text{ s}^{-1}$)	$D_{\text{eff}}/D_{\text{dl}}$
25	O_2	1.93	0.40	0.21	0.68	0.35	0.55	0.28	0.36	0.19	0.19	0.19
	H_2O_2	1.43	0.31	0.21	0.50	0.35	0.40	0.28	0.27	0.19	0.19	0.19
	HQ	0.89	0.20	0.22	0.31	0.35	0.25	0.28	0.18	0.20	0.20	0.20
37	O_2	2.46	0.60	0.25	0.99	0.40	0.82	0.33	0.54	0.22	0.22	0.22
	H_2O_2	1.83	0.45	0.25	0.73	0.40	0.58	0.31	0.37	0.22	0.22	0.22
	HQ	1.17	0.27 ^a	0.23 ^a	0.43 ^a	0.37 ^a	—	—	—	—	—	—

^a Unreliable measurement, gel destroyed

Fig 4 Rotating disc electrode data with a Pt-PVA electrode ($T = 25^\circ\text{C}$) for (Δ) H_2O_2 , (+) O_2 and ($\circ$) hydroquinone

be considered as one resistance of a buffer solution layer

$$\frac{2}{k_{\text{dl}}} + \frac{2}{k_{\text{f}}} = \frac{1}{k_{\text{bl}}} = \frac{d_{\text{bl}}}{D_{\text{bl}}} = \frac{d_{\text{bl}}}{D_{\text{dl}}} \quad (19)$$

Fig 5 Data for a diffusion cell with two filter-papers $C_{\text{B}}/C_{\text{A}}$ plotted against time for (+) hydroquinone and (Δ) glucose $T = 25^\circ\text{C}$

Fig 6 Data for a diffusion cell with a hydrogel membrane and two filter-papers $C_{\text{B}}/C_{\text{A}}$ plotted against time for (+) hydroquinone and (Δ) glucose $T = 25^\circ\text{C}$

where the subscript bl refers to the buffer solution layer

As the diffusion coefficient of hydroquinone in 0.1 M phosphate buffer at 25°C is $0.89 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$, it can be calculated that the diffusion coefficient of glucose under the same conditions is $0.72 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$. Also, k_{bl} can be calculated for both compounds using the slopes of Fig 5, as in this case $dC_{\text{B}}/dt = k_{\text{bl}}\Delta C A_{\text{f}}/V$ with $A_{\text{f}} = A_{\text{m}} = 3.46 \times 10^{-4} \text{ m}^2$. For hydroquinone a value of $k_{\text{bl}} = 5.9 \times 10^{-7} \text{ m s}^{-1}$ was found and for glucose $k_{\text{bl}} = 4.8 \times 10^{-7} \text{ m s}^{-1}$.

A gel C membrane, together with a filter-paper on each side, was placed between the two com-

TABLE 3

Diffusion coefficients in the buffer solution and effective diffusion coefficients in two gels with different degrees of cross-linking for hydroquinone and glucose at 25°C

Compound	Buffer D_{dl} ($10^{-9} \text{ m}^2 \text{ s}^{-1}$)	Gel C		Gel D	
		D_{eff} ($10^{-9} \text{ m}^2 \text{ s}^{-1}$)	$\frac{D_{\text{eff}}}{D_{\text{dl}}}$	D_{eff} ($10^{-9} \text{ m}^2 \text{ s}^{-1}$)	$\frac{D_{\text{eff}}}{D_{\text{dl}}}$
Hydroquinone	0.89	0.25	0.28	0.18	0.20
Glucose	0.72	0.062	0.086	0.045	0.062

partments and also gave straight lines (Fig. 6). Now the slopes have a ratio of 0.63, which means that glucose is slowed by the membrane to a greater extent than hydroquinone. The ratio of 0.63 can also be seen as the ratio of the total mass transfer coefficients of hydroquinone and glucose, so

$$\frac{\left(\frac{1}{k_m} + \frac{1}{k_{bl}}\right)_{\text{hydroquinone}}}{\left(\frac{1}{k_m} + \frac{1}{k_{bl}}\right)_{\text{glucose}}} = 0.63 \quad (20)$$

Inserting the value of k_{bl} for both glucose and hydroquinone, the ratio of the effective diffusion coefficients is found to be 0.25 ($D_{\text{eff}}/D_{\text{dl}})_{\text{hydroquinone}} = 0.28$ whereas $(D_{\text{eff}}/D_{\text{dl}})_{\text{glucose}} = 0.086$ (Table 3). For a second, extra cross-linked membrane (gel D), the same ratio of the slopes of 0.63 is found (Table 3). The ratio of the effective diffusion coefficients is 0.24, and $(D_{\text{eff}}/D_{\text{dl}})_{\text{hydroquinone}} = 0.20$ whereas $(D_{\text{eff}}/D_{\text{dl}})_{\text{glucose}} = 0.062$.

The conclusion can be drawn that glucose is slowed more than hydroquinone and also than oxygen and hydrogen peroxide, because of an interaction of glucose with the gel matrix. In both gels glucose is slowed 3.2 times more than hydroquinone (0.086 vs 0.28 and 0.062 vs 0.20). A size-exclusion effect can be excluded because, although gel D is far more cross-linked than gel C, this has evidently no influence.

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