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Poly(binaphthyl-20-crown-6) as receptor based molecular selective potentiometric electrodes for catecholamines and other 1,2-dihydroxybenzene derivatives

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Abstract: A novel type of poly(crown ether) electrode that is capable of selectively determining some 1,2-dihydroxybenzenes has been developed. A lipophilic macrocyclic crown ether, binaphthyl-20-crown-6, is electrochemically deposited on a platinum disc electrode. The film obtained is used as a sensory element for a potentiometric electrode for the determination of some neurotransmitters, namely, catecholamines. The new electrode is also capable of discriminating the steric shapes of 1,2-dihydroxybenzene moieties. The response of the new electrode is based on the principle of 'host–guest' chemistry. The potentiometric response is dependent on the pH of the solution and the nature of the buffer medium. The new sensor electrode has a useful analytical range of $1{\cdot}5 \times 10^{-8}$ M–2×10^{-5} M with a linear dynamic range between about 1×10^{-7} M–5×10^{-4} M with a 'super-Nernstian' slope of 110–130 mV/decade. The detection limit in phosphate buffer (0·1 M, pH 9·4) is *ca.* 3×10^{-8} M for catecholamine. The sensor electrode is virtually insensitive towards interference from most inorganic ions and circumvents the interference from ascorbic acid, which is often found using amperometric methods in biological samples. A partial response mechanism of the present electrode is discussed, supported by results of electron dispersive analysis by x-rays (EDAX).

Keywords: Potentiometric molecule selective electrode, binaphthyl-20-crown-6, electropolymerization, catecholamine, receptor

INTRODUCTION

Many synthetic macrocyclic host compounds have been developed as a promising class of potential-sensitive elements for ion selective electrodes because of their chemical recognition function as well as their high chemical stability. The diversity in structure design possibilities of these macrocyclic compounds expands the scope of their application. A series of crown ether derivatives for metal cation selective electrodes has been reported (Brown *et al.*, 1990; Moriarty *et al.*, 1993; Kamata *et al.*, 1991; Zhongmin *et al.*, 1989; Schefer *et al.*, 1986; Lindner *et al.*, 1984; Cosofret *et al.*, 1992; Stevens *et al.*, 1991; Johnson *et al.*, 1989). However, few compounds have been designed as anion carriers and also as neutral organic molecules employing the concept of host–guest chemistry (Simon, *et al.*, 1966; Ammann, 1986; Schulthess *et al.*, 1985). The development of direct potentiometric sensors for neutral molecules has been a major problem due to the lack of surface interaction with a charged species. A fundamental problem remains as how to form a complex between host and neutral guest and subsequently generate a charge separation at the interface between the electrode surface and the supporting electrolyte. One successful report of such a neutral compound response was obtained by Kimura *et al.* (1983). They indicated that 18-azacrown-6 (which is triprotonated) forms stable 1:1 complexes with catechol and its biological derivatives, with loss of H^+ in neutral pH solutions. Umezawa *et al.* (1988) developed a potentiometric adenosine triphosphate polyanion sensor using a macrocyclic polyamine as a sensory element.

In the late sixties, the analytical potential for liquid–membrane electrodes was first developed. Since then, these ion-selective sensors have incorporated neutral ligands specific to cations. The antibiotics valinomycin and the macrotetrolides were found to be excellent neutral complexing agents K^+ and NH_4^+ (Simon *et al.*, 1966). The macrocyclic crown ethers function as cation carriers. The ion selectivities were mainly governed by the geometric dimension of the crown cavity. Some synthetic crown compounds were also found to complex with ammonium and alkylammonium salts suitable for liquid–membrane electrodes (Pederson, 1967; Frensdorff, 1971). On the basis of these findings, D.J. Cram *et al.* (1974) synthesized the binaphthyl-20-crown-6, which was found to complex with both potassium and alkylammonium ions. The first organic amine molecular selective electrode using benzo-18-crown-6 as a host in a PVC membrane for the potentiometric determination of amphetamine was investigated by Hassan *et al.* (1989). Binaphthyl-20-crown-6 has also been used to construct a potentiometric drug electrode for micinlex (Liu *et al.*, 1990). Micinlex is a drug commonly used for heart disease. A serotonin molecular selective electrode based on this crown ether in PVC also has been investigated (Wang *et al.*, 1994).

In the present study, a new potentiometric electrode was constructed by means of electrochemical polymerization of the binaphthyl-20-crown-6 on a platinum electrode for the determination of catecholamines, known as important neurotransmitters. The synthesized polybinaphthyl-20-crown-6 was employed as the sensing material of the electrode and the Pt electrodes served as the support matrix basic sensing element. A partial model of the potentiometric response mechanism of this electrode is discussed.

EXPERIMENTAL

Reagents

The lipophilic macrocyclic crown ether, binaphthyl-20-crown-6, was synthesized in our laboratories (Wang *et al.*, 1994) and verified with IR and

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^{1}H NMR. L-dopa, L-dopamine, L-epinephrine and DL-norepinephrine, 3-(3,4-dihydroxyphenyl)-2-methyl-L-alanine(methyl-L-dopa), 3,4-dihydroxybenzylamine hydrobromide (DHBA), 3,4 dihydroxyphenyl acetic acid (DHPAA), norephedrine, 3-(2,4-dihydroxyphenyl) propionic acid (DPPA), tyramine, *p*-cresol, *p*-nitrophenol, serotonin, and tryptamine were purchased from Fluka Chemical Company and used as received. Tetrabutylammonium tetrafluoroborate (TBATFB), resorcinol, L-phenylalanine, and *o*-phenyldiamine were purchased from Aldrich Chemical Company. Catechol was purchased from Fisher Scientific Company. Hydroquinone, *p*-aminophenol, phenol, and ascorbic acid were purchased from Sigma Chemical Company. A list of names and formulas of all compounds used in the present work is given in Fig. 1. The acetonitrile was dried by double distillation over calcium hydride and stored in tightly sealed containers. The phosphate buffer stock solution (pH 9·4, 1 M) was prepared with potassium dihydrogen phosphate and the pH was adjusted by the addition of KOH. The standard solutions of L-dopa, L-dopamine, L-epinephrine and D, L-norepinephrine were prepared with 0·01 M HCl and stored in brown glass bottles. All chemicals used in the present study were of reagent grade. Deionized water of 17·8 MΩ resistance was used throughout.

Polycrown ether electrode preparation

A stationary platinum disc electrode with a 1·6 mm diameter (MF-2012, Bioanalytical Systems Inc., USA), was used as the basic transducer element matrix. This electrode was polished with 600-grid emery paper to a mirror surface and then ultrasonicated. Finally, the electrode was washed with High Performance Liquid Chromatographic (HPLC) grade acetone and dried in air for about 15 min before the electropolymerization.

The polymerization of binaphthyl-20-crown-6 on the platinum electrode was carried out in a three-electorde single compartment cell containing 20 mM of the crown ether derivative and 200 mM tetrabutylammonium tetrafluoroborate as the supporting electrolyte in freshly distilled acetonitrile. The above mentioned stationary platinum electrode was used as the working electrode, a platinum wire coil as the auxiliary electrode, and an Ag/AgCl electrode (MF-2063, BAS, USA), as the reference electrode. The electrochemical polymerization was performed with a PAR 175 Potentionstat/Galvonostat (EG&G), (Princeton Applied Research, USA), with an applied potential of +3·2 V *vs* Ag/AgCl electrode for 5 min. Visible dark films on the electrode were observed. Surface coverage of the polymer film was not successful at lower potentials than +3·2 V (*vs* Ag/AgCl). At potentials above +3·2 V gas evolution was observed and the polymer film did not adhere. The polymerized electrode was then rinsed with acetone, air dried, and immersed in a three-electrode single compartment cell containing monomer-free acetonitrile solution of TBATFB for about 25 min at an applied potential of +0·5 V *vs* Ag/AgCl electrode. This polymerized electrode was then rinsed with water and dried in air for 20 min before use.

Potential measurements

Potential measurements were made with an Orion Model 601A Ionanalyzer using a BAS Ag/AgCl as the reference electrode filled with 3 M KCl. The electrode potential was measured in 25 mL of 0·1 M phosphate buffer solution (pH 9·4) while stirring at 22°C and recorded using a chart recorder. The polymerized electrodes were conditioned in stirred water until a steady potential value was obtained before use. After use, the electrode was stored in air. Under these conditions, individual electrodes had a reproducibility of potential measurement of ±3%, no measurable drift over 8 h and a response rise time of less than 10 s.

RESULTS AND DISCUSSION

The pH dependence of poly(crown ether) electrode response

Figure 2 shows the pH dependence of the observed potential for the poly(crown ether) electrode in 0·1 M potassium phosphate buffer in the presence of 2×10^{-6} M dopamine or epinephrine (pH 6–12). As depicted in Fig. 2, this poly(crown) ether electrode response is highly pH dependent. The pH response of the electrode is linear with a Nernstian slope of 56–59 mV/decade in the pH range of 6–8·5 (see Fig. 2). At pH values greater than 10·5, the potential response rapidly decreased. In this pH

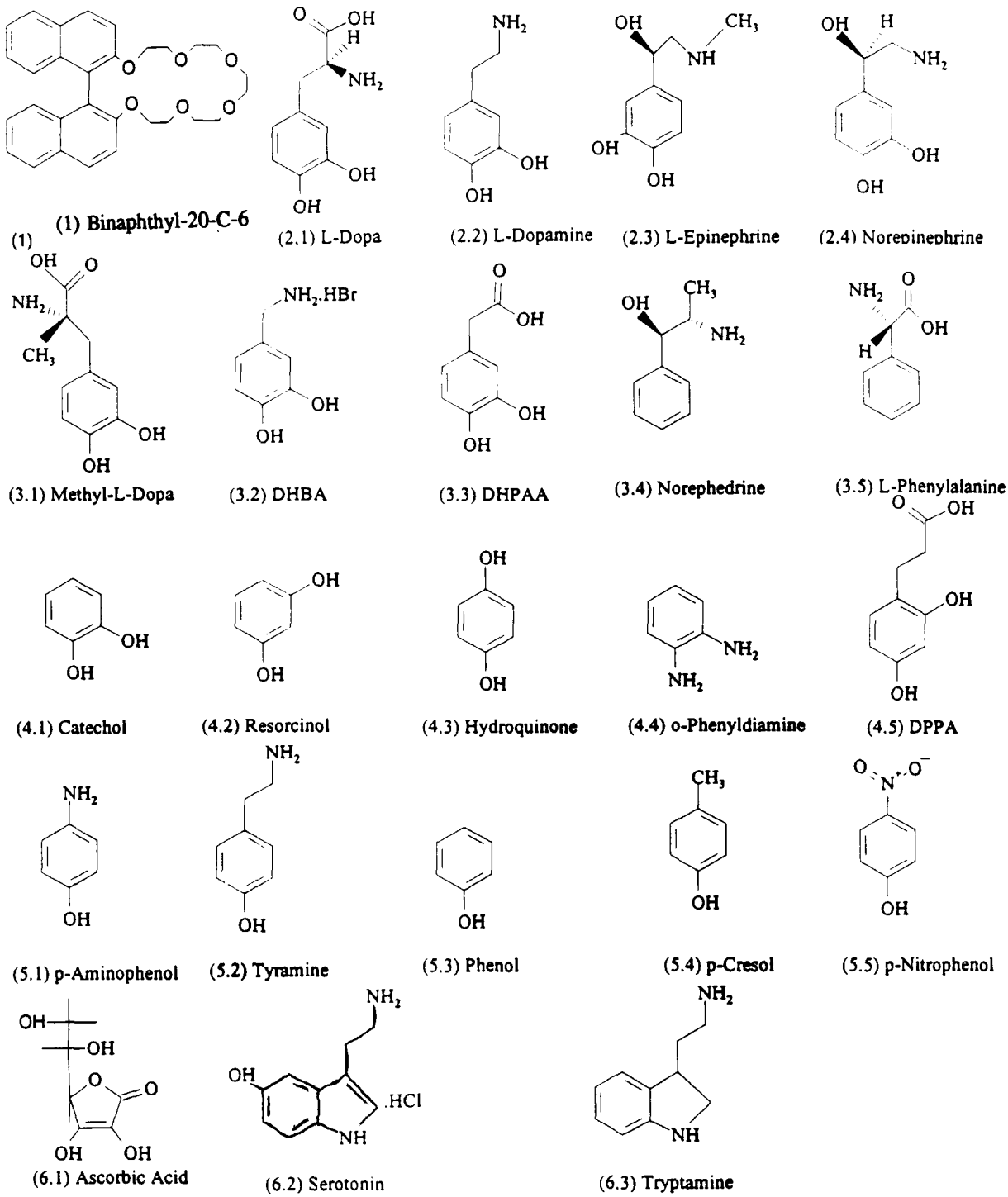


Fig. 1. The organic compounds used in the present study.

region the two hydroxy groups are neutralized (*Handbook of Chemistry and Physics, 1990*). The graph levels off between pH 8·5 and 10 compared to other pH ranges where response diminishes. This is the pH region where only one hydroxy group of the catechol moiety is protonated. In the present case, potassium ions, which exist at the high concentrations in the buffer solution, occupy the cyclic ring of crown ether as the electrode was preconditioned in the potassium

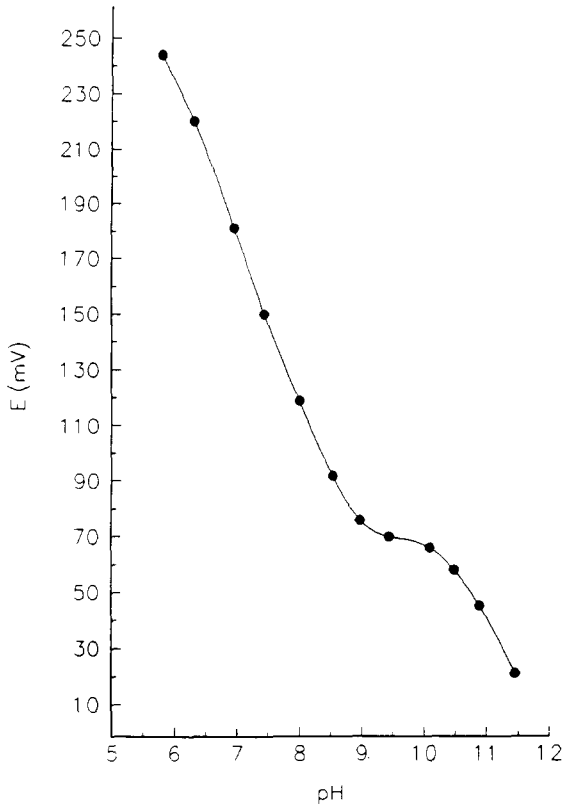


Fig. 2. The pH dependence of potentiometric response of poly-(binaphthyl-20-crown-6) electrodes. 0·1 M K-phosphate buffer; 10^{-6} M dopamine and/or epinephrine.

solution. At pH values between 8·5 and 10, the monoprotonated catechol moiety (dopamine) probably interacts with the crown ether as discussed later. At lower pH values (less than 8·5) amino groups will be protonated and would be expected to interact with crown ethers, resulting in a normal Nernstian pH response behavior. However, this is not the cause of the potential–pH response in this range as catechol and DHPAA behave identically. For pH values greater than 10·5, hydroxy groups of catecholamines will be totally deprotonated resulting in a dramatic shift of the electrode response in the negative direction as the pH increases. In the present study, phosphate buffer solutions of pH 9·4 were chosen and used throughout the evaluation of the electrode response. It was only in this pH range that this particular buffer gave a 'super-Nernstian' response for catechol, as discussed below.

Effect of changing the nature of the buffer solution on electrode response

The effects of changing the nature of the buffer solutions with the same concentration and pH on the potentiometric response of the poly(crown ether) electrode are shown in Figs 3(a) and 3(b). The following observations can be concluded from the Fig. 3(a): (i) the poorest detection limit for the determination of dopamine was observed in borate buffer, (ii) the determination of dopamine in phosphate or tris buffers, on the other hand, had the lowest detection limits, (iii) relatively wide linear dynamic ranges and relatively high Nernstian slopes were observed for the potentiometric responses in glycine and phosphate buffers. In borate and tris buffer, the electrodes had a Nernstian slope closer to 56–59 mV/decade within the linear range. The 'super-Nernstian' slope of 110–130 mV/decade was observed in the case where phosphate buffer and glycine were used.

The effect of changing the concentration of phosphate buffer on the response behavior of the poly(crown ether) electrode is illustrated in Fig. 3(b). The detection limit of the electrode towards dopamine shifts to higher values as the concentration of the phosphate increases. At buffer concentrations above 0·2 M, the calibration curve showed the poorest value for the detection limit but a better upper detection limit. Concentrations of the buffer between 0·1 and 0·2 M were the most suitable for optimum electrode response. It was found that this electrode response did not change over weeks of continuous use. Similar responses were obtained as for platinum that was simply emersed in a poly(crown ether) solution. However, the response decreased by about 20% after 1 h. This, plus the fact that no visible film was observed, indicates that the crown in this case is probably an adsorbed layer formed at the Pt surface.

The calibration characteristics of the electrode

A typical calibration curve of the polycrown ether electrode for catecholamine is shown in Fig. 4. The general characteristics of the calibration curves of dopamine, epinephrine, and norepinephrine are similar. The calibration curve of dopa has better linearity than that of catecholamine. The polycrown ether electrode has a linear response range of 1×10^{-7} M to 5×10^{-4} M and

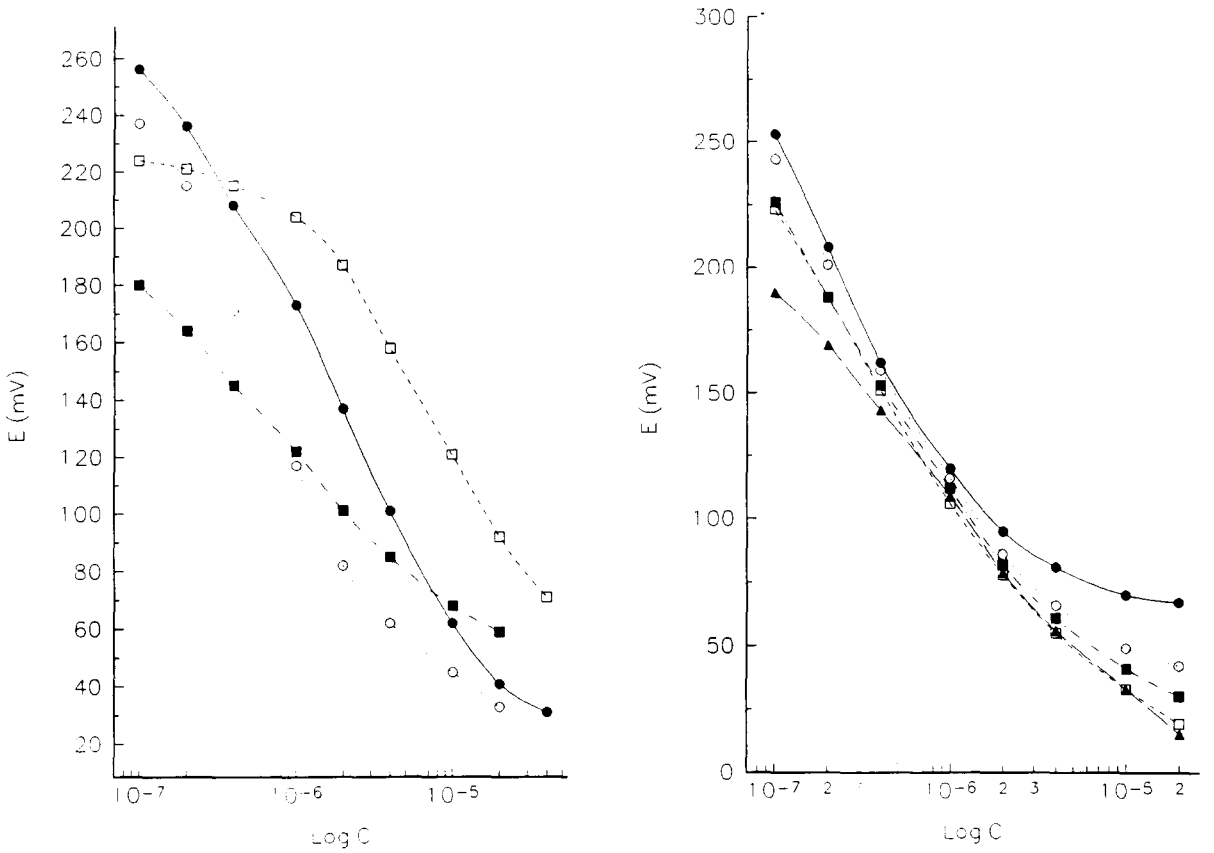


Fig. 3. Effects of buffer solution on electrode response to dopamine. (a) ●, Phosphate; ■, Tris; ○, Glycerine; □, Borate. (b) Influence of concentration of phosphate buffer on electrode response. ●, 0·02 M; ■, 0·1 M; ▲, 0·5 M; ○, 0·05 M; □, 0·2 M. All of the buffer solution at concentration of 0·1 M; pH 9·4, K^+ 0·01 M. E(mV) vs Log (dopamine).

a super-Nernstian response slope of 110–130 mV/decade with a detection limit of 3×10^{-8} M for the catecholamines. The usable analytical dynamic range of the various calibration curves was about $1{\cdot}5 \times 10^{-8}$ M–2×10^{-5} M.

Response to inorganic anions

It was known that binaphthyl-20-crown-6 could complex with potassium ions due to the size matching of the potassium ion (1·33 Å) and the crown cavity (1·35 Å) (Umezawa *et al.*, 1988). In the present case, high concentrations of potassium (up to 0·1 M) were used to make the phosphate buffer solution. However, all interferences that might be caused by the interaction of potassium (control cation) and other inorganic cations are negligible compared to the dopamine response as shown in Fig. 5. The anions tested (Cl^-, F^-, Br^-, NO_3^-, NO_2^-, HCO_3^-, Ac^-, $B_4O_4^{2-}$, ClO_4^-, SCN^-, SO_4^{2-}, $S_2O_3^{2-}$ and I^-) showed relatively poor response as indicated by the shaded area of Fig. 5.

Response to other similar organic derivatives and catecholamines

All alkyl derivatives of catecholamines and similar compounds listed in Fig. 1 were tested for their response behavior and the results are shown in Figs 6(a) and (b). Figure 6(a) indicates that the electrode responded to methyl-L-dopa, 3,4-dihydroxybenzylamine (which have amino groups), and 3,4-dihydroxyphenyl acetic acid (without an amino group), and did not respond to norephedrine and L-phenylalanine. The compounds to which the electrode responded have a common factor in their chemical structure; that is, the presence of a 3,4-dihydroxyphenyl moiety. Moreoever, the presence or absence of the amino

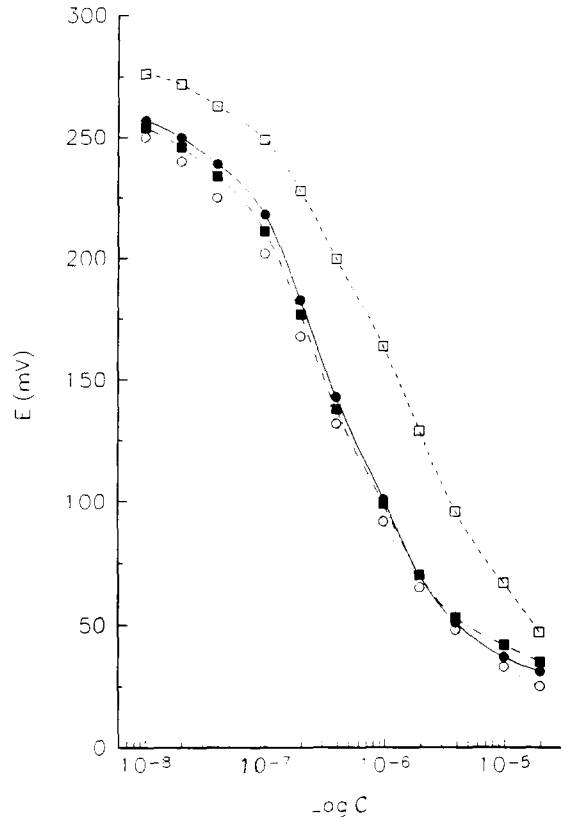


Fig. 4. Calibration curves of polycrown ether electrode for catecholamines. ●, Dopamine; ■, Norepinephrine; ○, Epinephrine; □, L-dopa.

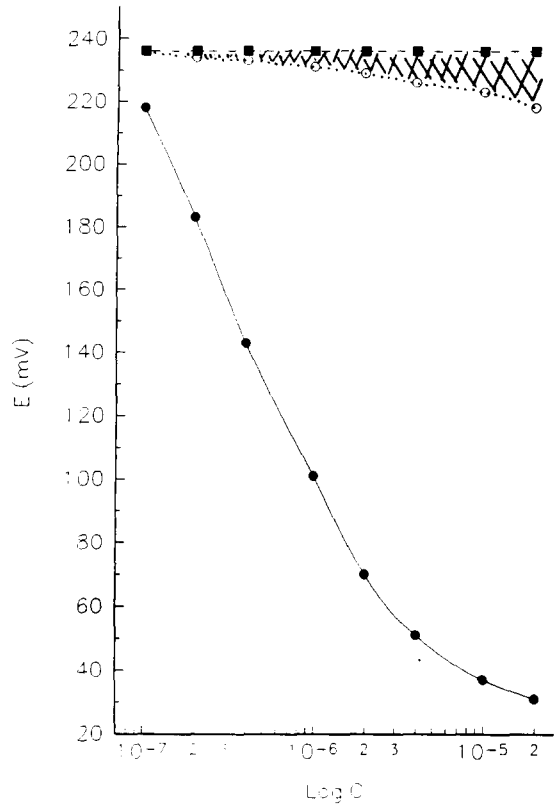


Fig. 5. The potentiometric response to inorganic anions. ●, Dopamine; ■, Chloride; ○, Iodide; curves for all anions (F^-, Br^-, NO_3^-, NO_2^-, HCO_3^-, Ac^-, $B_4O_7^{2-}$, ClO_4^-, SCN^-, SO_4^{2-}, SO_3^{2-}) below fall between chloride and iodide.

group in the compound did not significantly affect the electrode response. Therefore, it could be concluded that for this group of compounds the sensor electrode should have a selective response to the 3,4-dihydroxyphenyl derivatives of organic compounds. The aforementioned assumption was confirmed by inspecting the data of Fig. 6(b) as follows: (i) the response towards catechol was relatively superior, and therefore will be taken as a reference measure of the electrode response behavior, (ii) a relatively poorer response was observed for the determination of *o*-phenyldiamine which bears two amino groups, (iii) the interaction of the other dihydroxy derivatives is also important as can be observed for the moderate response towards hydroquinone and the poor response towards resorcinol and DPPA. Figure 6(c) shows further evidence for this explanation; the electrode responded to *p*-aminophenol, and did not respond to phenol, *p*-cresol or *p*-nitrophenol. It is, however, important to note that *p*-aminophenol is an exception to the general trend. Moreover, another important aspect about the selective nature of the mechanism of interaction of the analyte and the crown ether can be observed from the data of Fig. 6(c), as tyramine and the *p*-aminophenol possess the same functional groups, amino and hydroxy groups. However, the steric effect exerted by the relatively long chain in tyramine could possibly explain the poor response compared to that of *p*-aminophenol, or else the basicity differences of the aromatic and aliphatic amine groups in these compounds might cause the response difference.

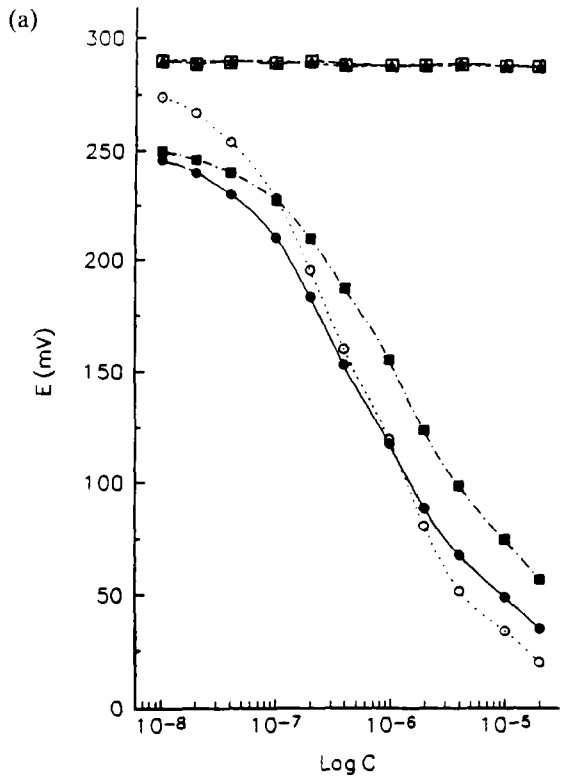
The comparison of these electrode responses to dopamine and common interferent compounds in biological media (ascorbic acid, serotonin, and tryptamine) is shown in Fig. 6(d). The electrode exhibited a negligible response to tryptamine but had a moderate response to serotonin with a sub-Nernstian slope of about 45 mV/decade. The

electrode had virtually no response to ascorbic acid, except at high concentrations. These results show that ascorbic acid below 3×10^{-5} M does not interfere with the potentiometric determination of catecholamines. This is important for the analysis of catecholamines in natural biological media which contain a relatively high concentration of ascorbic acid and represents a classical problem encountered in the amperometric determination of dopamine, etc., in biological fluids.

Mechanistic model of electrode response

With respect to the present data, some observations concerning the mechanism of the interaction can be made: (i) the pH dependence shown in Fig. 2 of the crown polymer electrode does not result from the proton exchange of the complex formed between the amino group of catecholamine and poly(crown ether) at low pH values and, (ii) a catechol-like structure with a 1,2-dihydroxy substitution is critical for good response (except for the two 1,4 difunctional species mentioned above). Before we consider a systematic response model of the poly(crown ether) electrode the negative potential response of the electrode with increased concentration of catecholamines has to be considered. A possible response model of macrocyclic poly(amine) liquid membrane electrode for catechol has been suggested (Umezawa *et al.*, 1988). This poly(amine) liquid membrane electrode had a negative potential response for catechol in the acetate buffer of pH 6·1. It was thought that two protons on the aza crown cycle of polyamine were ejected due to hydrogen bonding between the host and guest at the membrane surface. This model was suspected for two reasons. First, electrode response to catechol was in acid buffer where the amine groups are protonated. Second, the hydrogen bonds were possibly not strong enough to eject the protons bonded with other nitrogen atoms. There may be other factors that caused the negative response for catechol. In the present case, the working pH of the poly(crown ether) electrode is 9·4. The catechol 'functionality' of the guest compounds, catecholamines, should have an approximate alkali dissociation constant similar to that of catechol, *ca.* $pK_{a1} = 9{\cdot}3$ (*Handbook of Chemistry and Physics, 1990*). Thus, the catechol group loses two protons, producing the negative charge in phosphate buffer of pH 9·4. The poly(crown ether) groups on the electrode surface will take up a potassium ion and probably be 'sandwiched' between two crown moieties as proposed recently for HS^- response to the binaphthyl-20-crown-6 electrode (Ma *et al.*, 1994). Therefore, this would explain the 'super-Nernstian' slope. This assumption was not confirmed by the data obtained from electron dispersive analysis by x-rays (EDAX) of the electrode surface. A freshly prepared poly-(binaphthyl-20-crown-6) electrode exposed to a potassium–phosphate buffer solution alone, and one exposed to a buffer–catecholamine solution, were compared. Figures 7(a)–(c) show the results of the EDAX analyses. In this case, the potassium peak is high for the electrode preconditioned in the potassium buffer (0·1 M) only, as indicated in Fig. 7(a) (peak at 3·1 KeV). If the electrode is treated with the buffer solution containing 1×10^{-5} M dopamine (Fig. 7(b)) or epinephrine (Fig. 7(c)) the potassium peak intensities decrease significantly. This indicates that the mono anion of the catecholamines was interacting with the poly(crown ether) film and subsequently ejecting the K^+ ion. Furthermore, it was found that variation of the cation of the buffer (Li^+, Na^+, K^+, and Cs^+) had no effect on the electrode response. Also, the fact that the tris buffer also exhibited a similar potential response (Fig. 3) further indicates that incorporation of cations in the crown had no effect on the electrode response to catechols. The 'super-Nernstian' slope observed does suggest that each binaphthyl-20-crown-6 unit may be arranged in a parallel layer (stacked) structure and the catechol moiety is sandwiched between two adjacent crown rings. However, no direct experiment has yet been found to support this mechanism nor indicate

Fig. 6. Response to derivatives and other similar compounds. (a) Response to derivatives with and without catechol groups. ●, Methyl-L-dopa; ○, Dihydroxybenylamine; ■, Dihydroxyphenylacetic acid; □, Norephedrine; ▲, Phenylalanine. (b) Effects of hydroxy position and substitution of amino group on potentiometric response. ●, Catechol; ○, Resorcinol; ■, Hydroquinone; □, o-phenyldiamine; ▲, 3-(2,4-dihydroxyphenyl) propionic acid (DPPA). (c) Response to phenol and its p-substituted derivatives. ●, p-aminophenol; ○, Tyramine; ■, Phenol; □, p-cresol; ▲, p-nitrophenol. (d) Response to other dopamine-like derivatives. Phosphate buffer 0·1 M; pH 9·4. ●, Dopamine; ○, Ascorbic acid; ■, Serotonin; □, Tryptamine.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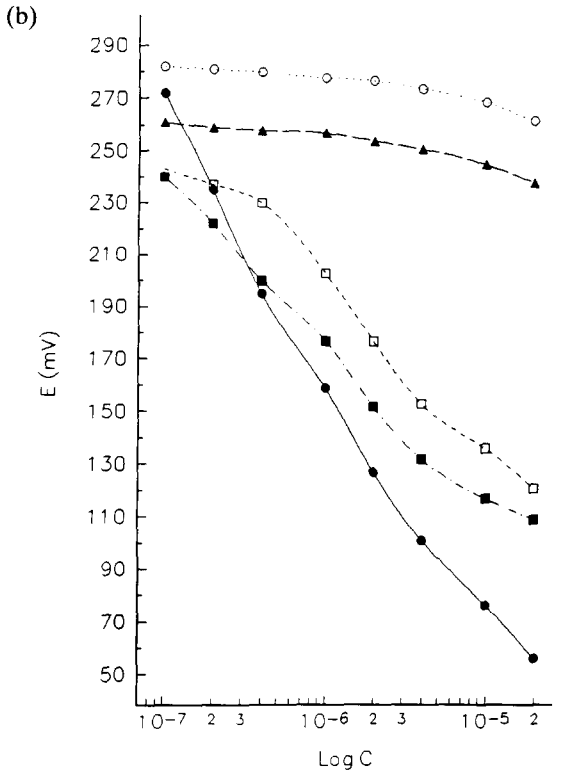
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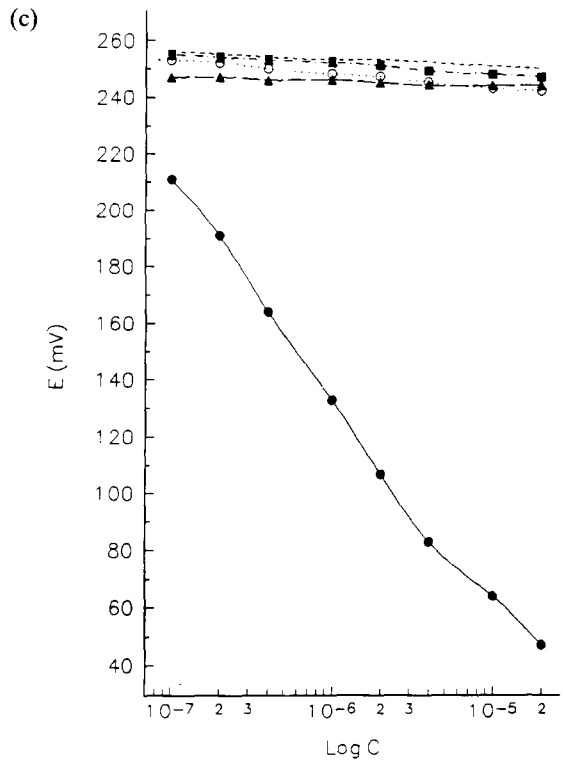
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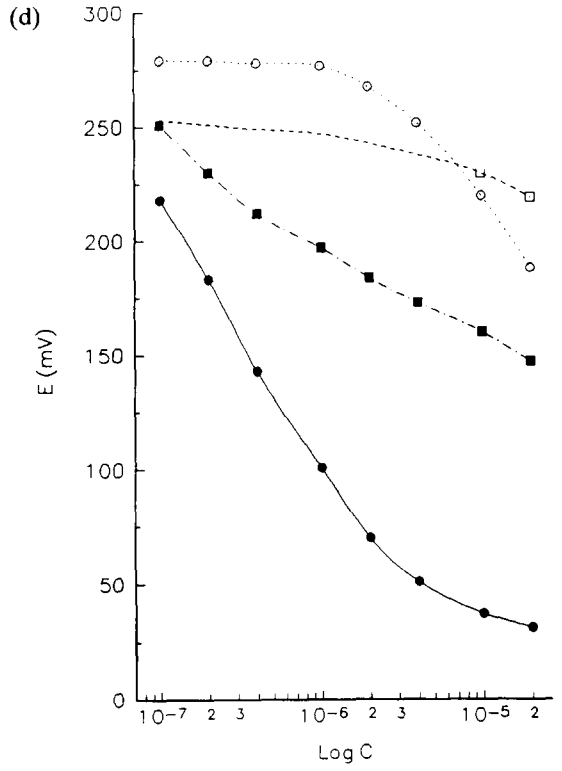
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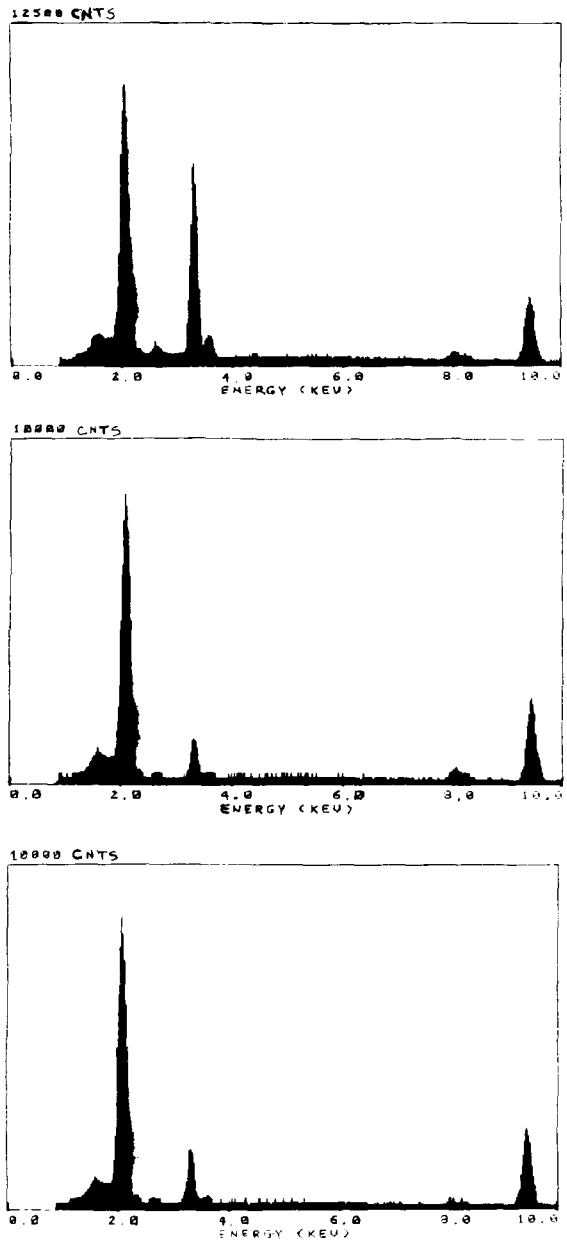

Fig. 7. EDAX analysis before and after electrode response to catechol amines. (a) 0·1 M phosphate buffer (pH 9·4). 12500 counts vs energy (KeV). (b) Buffer + 10^{-5} M dopamine. 10000 counts vs energy (KeV). (c) Buffer + 10^{-5} M epinephrine. 10000 counts vs energy (KeV).

what interaction occurs between the monoanion and the crown rings. At present, we are synthesizing a water soluble version of this crown compound in an attempt to directly observe the interaction by NMR.

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