Ion-selective Electrodes Sensitive to Some Organic Compounds Used as Drugs

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Drug ion-selective electrodes with a liquid membrane have been developed which are sensitive to methacholine, neostigmine, *N*-1-methyl nicotinamide, diphenhydramine, vitamin B_1, vitamin B_6, *p*-aminosalicylic acid (PAS), and salicylic acid. Crystal violet or ferroin-compound cations and dipicrylamine or tetraphenylborate anions were used as the ion-exchange sites in the liquid membrane. Each liquid membrane was prepared by using the solvent-extraction method and exhibited an appropriate Nernstian response to the respective ion down to 10^{-4} or to 10^{-5} M. The electrode performances, including the selectivity coefficients, are summarized in Table 1.

In a previous paper vitamin-sensitive electrodes based on the solvent extraction of the protonated vitamin cation have been reported on.[1] Among other drugs, we found many ionic and water-soluble organic compounds. For example, methacholine chloride, neostigmine bromide, and *N*-1-methyl nicotinamide chloride are water-soluble salts of quarternary ammonium or pyridinum cations. Diphenhydramine, vitamin B_1, and B_6 are present as protonated cations in an acidic aqueous solution from pH 3 to 5. From the acid-dissociation constants of *p*-aminosalicylic acid and salicylic acid, it can easily be understood that they are present as singly-charged anions in the pH range from 6 to 11. These organic ions can be extracted with the ionic extractant into an organic solvent such as 1,2-dichloroethane or nitrobenzene; the resulting organic solution is useful as a "liquid membrane" for the corresponding ion-selective electrode.

This paper will describe the performance of the electrodes sensitive to some organic compounds used as drugs.

Experimental

Chemicals and Liquid-membrane Solutions. The crystal violet (CV) and the dipicrylamine (Hexyl) were obtained from the Kishida Kagaku Co. The sodium tetraphenylborate (TPB), *o*-phenanthroline (Phen), and bathophenanthroline (Bphen) were obtained from the Dojindo Co., Ltd. The objective drugs were obtained from the Kishida Kagaku Co. or the Tokyo Kasei Co.

The liquid membranes of the electrodes were prepared by using the ion-association extraction method.[1]

As the extractant of a drug cation, sodium tetraphenylborate or dipicrylamine was used, whereas the crystal violet cation or the ferroin compound (the iron chelate of *o*-phenanthroline or bathophenanthroline) was used as the extractant of the drug anion. Nitrobenzene (NB) or 1,2-dichloroethane (DCE) was used as the membrane solvent; the concentration of the liquid membrane was 1×10^{-4} M.

Evaluation of the Electrode Performance. Either a U-shaped glass tube or an Orion liquid-membrane barrel was used for the drug ion-sensitive electrode.

The selectivity and sensitivity of the drug ion-selective electrode were estimated by measuring the electromotive force of the following concentration cell:

+SCE/Reference solution (′)/Organic liquid membrane/Sample solution (″)/SCE−

The reference solution and sample solution were separated by means of the liquid membrane in the lower part of a U-shaped glass tube. The details of the cell assembly have been described in earlier papers.[2]

An Orion liquid-membrane barrel equipped with a Milliporefilter solvinert membrane (Pore size 0.25 micron) was used for the dynamic response and potentiometric titration studies. The outer chamber of the barrel was filled with the "liquid membrane." The internal reference chamber was filled with a corresponding drug-ion solution.

The measurements of the membrane potential were made by means of a Takeda Riken electrometer, TR-8651. The dynamic response of the electrode was recorded with a National Pen Recorder (Model VP-653A).

Results and Discussion

Response of the Electrode. The electrode potential in the presence of an interfering ion is empirically given by:

$$E = \text{Constant} + (2.303RT/nF)\log(A_i'' + K_j(A_j'')^{n/z}) \quad (1)$$

where n and z are the charges of the i and j-ions respectively and where K_j is the selectivity coefficient of the j-ion for the i-ion-sensitive electrode. As the reference solution we used a 1×10^{-3} M solution of the objective drug ion. The A_i'' and A_j'' activities in Equation (1) were approximated by the use of the molar concentration, because the dilute solution was used. The selectivity coefficient was determined by using the separate-solution method.[3] The observed electrode performance is summarized in Table 1. Methacholine and neostigmine electrodes are most sensitive, having useful response ranges up to 1×10^{-6} M. This suggests that methacholine and neostigmine cations are well extractable into the organic solvent, because the electrode of the higher extractable ion is usually more sensitive.[4]

The sequence of selectivity coefficients is consistent with the order of the extractability of the ion into the

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3) G. J. Moody and J. D. R. Thomas, "Selective Ion Sensitive Electrode," Merrow Pub. Co. Ltd., Watford, Herfordshire, England (1971), p. 12.

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Table 1. Performance of the drug ion-sensitive electrodes

Electrode	Solvent	Exchange site	Slope, −mV/log C[a]	Useful range	Selectivity coefficient, K_j
Methacholine	NB	Hexyl	−59	10^{-1}—10^{-6} M (pH 4—10)	V.B_1 0.0017, TEA[b] 28, $K^+ < 10^{-4}$ Benzethonium 19, Neostigmine 5
Neostigmine	NB	TPB, Hexyl	−60	10^{-1}—10^{-5} M (pH 4—10)	TEA 0.61, Methacholine 0.16, N-1-methyl nicotinamide 0.004
	DCE	TPB	−60	10^{-1}—10^{-6} M (pH 4—10)	TEA 1.4, Methacholine 0.13, N-1-methyl nicotinamide 0.005
N-1-methyl-nicotinamide	NB	Hexyl	−60	10^{-1}—10^{-5} M (pH 4—10)	Na^+ 1×10^{-4}, K^+ 4.2×10^{-3}, NH_4^+ 1.3×10^{-3}, TEA 2.4×10^{2}, Methacholine 42.7
Diphen-hydramine	NB	Hexyl	−59	10^{-1}—10^{-5} M (pH 3—5)	Na^+ 1.9×10^{-5}, $K^+ < 10^{-4}$; $NH_4^+ < 10^{-4}$, TEA 0.04, Methacholine 0.02, Neostigmine 0.05
Vitamin B_1	DCE	TPB	−30	10^{-1}—10^{-5} M (pH 3—5)	$Na^+ < 10^{-4}$, $K^+ < 10^{-4}$, NH_4^+ 1×10^{-4}, V.B_6 70
Vitamin B_6	NB	Hexyl	−57	10^{-1}—10^{-5} M (pH 3—5)	$Na^+ < 10^{-4}$, $K^+ < 2.5\times10^{-2}$, NH_4^+ 8×10^{-3}, V.B_1 1×10^{-1}
p-Amino-salicylic acid (PAS)	NB	CV $Fe(Bphen)_3$	60	10^{-1}—10^{-5} M (pH 6—10)	Salicylic acid 30, Benzoic acid 9×10^{-2}, *p*-Aminobenzoic acid 8×10^{-2}, Phthalic acid 1×10^{-1}, Isophthalic acid 2×10^{-4}, Terephthalic acid 1×10^{-3}, Br^- 0.53, NO_3^- 3.7, Cl^- 0.012
	DCE	CV	60	10^{-1}—10^{-5} M (pH 6—10)	Br^- 1.05, NO_3^- 6.6
Salicylic acid	NB	CV, $Fe(phen)_3$ $Fe(Bphen)_3$	60	10^{-1}—10^{-5} M (pH 6—10)	$Cl^- < 10^{-4}$, I^- 1.03, *p*-Aminobenzoic acid $< 10^{-4}$

a) C denotes the molar concentration of drug ion. b) TEA denotes tetraethylammonium ion.

organic solvent.[5] Among the coexisting competitive ions, the easily extractable ion produces a large interference. Salicylic acid interferes remarkably with the performance of the *p*-aminosalicylic acid-sensitive electrode. This reflects a decreased extractability of *p*-aminosalicylic acid resulting from its hydrophilic amino group.

According to Eisenman's theoretical prediction of the liquid membrane potential,[6] the selectivity of the electrode depends entirely on the membrane solvent rather than on the particular exchange-site species in the limiting case of the complete dissociation in a liquid membrane. The ion-pair complex in the nitrobenzene membrane may be completely dissociated, because nitrobenzene has a relatively high dielectric constant and because the concentration of the ion pair is sufficiently dilute.[4]

As can be seen in the cases of the neostigmine-, *p*-aminosalicylic acid-, and salicylic acid-sensitive electrodes in Table 1, no difference in either the selectivity or the sensitivity was found among different exchange sites when nitrobenzene was used as the membrane solvent. The 1,2-dichloroethane membrane gives a selectivity quite different from that of the nitrobenzene membrane. Hence, the observed selectivity coefficients qualitatively support Eisenman's expectation.

Dynamic Response and Potentiometric Titration. The dynamic response was evaluated on the methacholine ion-sensitive electrode by exposing the electrode to a rapid change of methacholine-ion concentration from 10^{-5} to 10^{-3} M. The solution was agitated with a magnetic stirrer.

The electrode potential changed rapidly, and the resulting constant potential was obtained within one second, although the response time depends on the efficiency of the solution mixing. Such a rapid response is, in practice, sufficiently useful for performing the potentiometric titration. The methacholine ion-selective electrode was used in the potentiometric titration of methacholine chloride by using the sodium tetraphenylborate solution as a titrant. The end point of the potentiometric titration agreed well with that of the argentimetric titration of the chloride ion. As has been mentioned above, the several drug ion-selective electrodes have comparatively good analytical responses from the view points of sensitivity and selectivity.

These drug ion-selective electrodes, therefore, could be used in the analyses of mixed pharmaceutical preparations.

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