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Molecular Recognition Based on Membrane Potential Changes Induced by Host–Guest Complexation with Inorganic and Organic Guests

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Abstract. Guest-induced changes in membrane potentials are one of the representative modes of electrochemical signal transduction by molecular recognition at the interface of an organic membrane and an aqueous solution. Recent approaches based on synthetic hosts capable of effecting membrane potential changes by host–guest complexation with inorganic and organic guests are described. Although the studies in this area have mainly been aimed at inorganic cations as the target guests, recent approaches for recognition of inorganic anions and further organic guests are also documented. Highly selective changes in membrane potentials can be achieved for inorganic cations by sophisticated design of crown ethers and related compounds. Hosts with complementary charge(s) or multiple hydrogen bonding sites are effective for the recognition of inorganic anions and also of the polar moieties of organic ions. On the other hand, the recognition of nonpolar moieties of organic guests can be achieved by inclusion into well-defined cavities of host molecules. Quaternary onium and protonated amine salts are recently found to be capable of effecting membrane potential changes by complexation with neutral phenolic guests.

Key words: host–guest complexation, membrane interface, signal transduction, membrane potential change, inorganic ion, organic ion, neutral molecule.

1. Introduction – Molecular Recognition Based on Membrane Potential Changes

Biological molecular recognition involving signal transduction, occurring either in a homogeneous solution or at a membrane/aqueous solution interface, frequently plays a significant role in such functions as cellular signaling, neurotransmission, hormone function, protein transport, genetic regulation, etc. The development of new molecules with a function of molecular recognition involving signal transduction is a challenging problem from the fundamental aspects of designing and synthesizing molecules with tailored functions as well as their application to new types of materials or reagents including those for analytical use [1, 2]. Of the various modes of signal transduction by synthetic hosts, the one based on optical changes has so far been most extensively studied (for leading reviews, see [3–7]). The sophisticated functions of most such chromogenic hosts have been attained

in a solution bulk (bulk of a homogeneous solution or of an organic/aqueous two phase system).

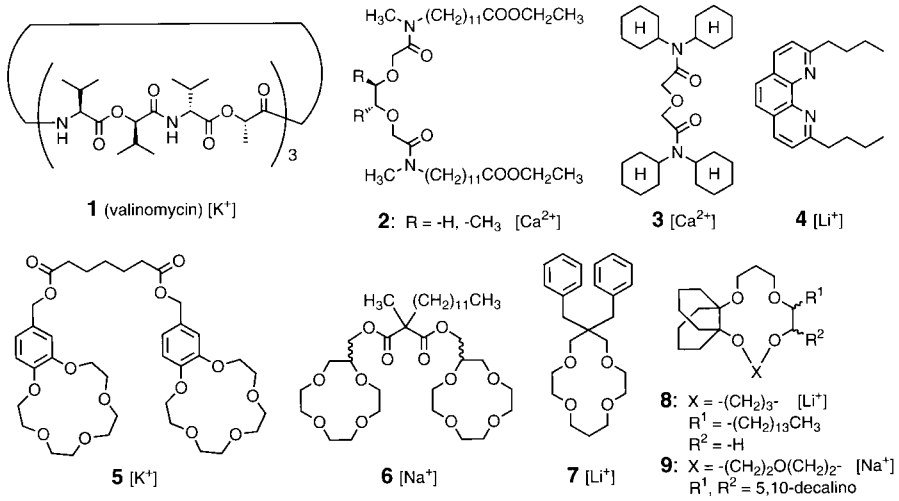
Guest-induced changes in membrane potential and permeability are another important mode of signal transduction related closely to biomembrane functions. These electrochemical signal transductions are based on molecular recognition occurring at membrane/aqueous solution interfaces, which frequently involve chemical processes that are quite different from those occurring in a solution bulk. Of the two representative modes of electrochemical signal transduction, this review article describes recent studies on molecular recognition involving membrane *potential* changes induced by host-guest complexation with inorganic and organic guests.

2. Membrane Potential Changes by Inorganic Guests

The design and synthesis of hosts for molecular recognition based on membrane potential changes (potentiometric responses) have so far been aimed mainly at inorganic cations in conjunction with liquid membrane type ion-selective electrodes (ISEs), which are used extensively for clinical and other analyses [8]. Liquid membranes containing hosts are generally supported by a poly(vinyl chloride) (PVC) polymer matrix. Many successful applications of neutral hosts such as acyclic ligands, crown ethers, and more recently calixarene derivatives have been made for sensing of alkali and alkaline earth metal cations [9–14]. The general principle of these cation-selective ISEs is guest-induced charge separation of the complexed cationic hosts (lipophilic) and their counteranions (hydrophilic) across a membrane/aqueous solution interface. This process leads to a guest-selective increase in the membrane potential. In order to attain charge separation, the cationic complexes must be retained on the membrane side of the interface with sufficient inhibition of contact with water or the counteranions.

Natural ionophores such as valinomycin (**1**), which are capable of forming a completely inclusion-type, highly lipophilic complex with the target guest cation, satisfy such a requirement and hence have been conveniently used as sensory elements for cation-selective liquid membrane ISEs since the late 1960's [8]. With respect to synthetic hosts, the following molecular design has been employed to effectively attain charge separation: (1) Inclusion of the target metal cation by several molecules of acyclic ligand [9] (e.g., **2**, **3**, Simon et al. [15, 16]; **4**, Hiratani et al. [17]). (2) Formation of an intramolecular sandwich-type complex by a bis(crown ether) with crown rings slightly smaller than the target metal cation [10] (e.g., **5**, **6**, Shono et al. [18, 19]). (3) Inhibition of the formation of an intermolecular 2 : 1 sandwich-type complex by introducing bulky substituent(s) to a crown ring that fits the target metal cation [10] (e.g., **7**, Shono et al. [20]).

Recent developments of crown ether derivatives for inorganic cations include 14-crown-4 (**8**) and 16-crown-5 (**9**) derivatives with bulky substituents on the crown rings (selectivity of guest-induced membrane potential change: $Li^+/Na^+ > 1000$ (**8**), $Na^+/K^+ = 1000$ (**9**); Suzuki et al. [21, 22]), 16-crown-5 derivative **10** with



Structures 1–9.

a suitable donor arm ($Na^+/Li^+ > 5000$; Bartsch et al. [23]), as well as Ca^{2+}- and Mg^{2+}-selective diazacrown ethers with a suitable donor arm and a bulky substituent (**11** and **12**, respectively; Suzuki et al. [24]). A high Na^+/K^+ selectivity was also attained by a simpler host (**13**; $Na^+/K^+ > 1200$; Parker et al. [25]). Ester and ether derivatives of calixarenes are also excellent sensory elements for metal cations [13, 14]. Typically, per-*O*-acetic acid esters of calix[4]- and calix[6]arenes (**14** and **15**, respectively) exhibit selectivities for Na^+ and Cs^+ ions, respectively [26–28]. The selectivity for Na^+ ion was improved by the *tert*-octyl derivative of calix[4]arene (**16**; $Na^+/K^+ > 1200$; Shinkai et al. [29, 30]) as well as by a calixcrown with a crown moiety that is slightly smaller than Na^+ ion (**17**; $Na^+/K^+ > 10^5$; Shinkai et al. [31]; see also [22, 32, 33]). The reported potentiometric selectivity coefficients ($K^{pot}_{A,B}$) are listed in Table I for some selected hosts incorporated in PVC liquid membranes. Potentiometric responses of several cation-selective hosts (e.g., **1**, **6**) were also investigated in planar bilayer lipid membranes with and without added anionic sites [34, 35]. Photocontrol of membrane potentials has been attained by azocrown ethers incorporated in PVC liquid membranes (**18**, **19**, Osa et al. [36–38]; **20a,b**, Umezawa et al. [39, 40]). Based on such a property, azobis(benzocrown ether)s **20a,b**, which are lipophilic derivatives of **20c** [41], were used as molecular probes for phase boundary potentials [39, 40].

In contrast to synthetic hosts for inorganic cations, there is still only a limited number of hosts that can selectively achieve membrane potential changes by complexation with target inorganic *anions*. Liquid membranes containing several types of hosts have been shown to exhibit potentiometric selectivities that differ significantly from those of classical anion exchangers (e.g., **21**), which are governed by the lipophilicity of anions (Hofmeister series: $ClO_4^- > SCN^- > I^- >$ salicylate$^- > NO_3^- > Br^- > Cl^- > HCO_3^- > CH_3CO_2^- > SO_4^{2-} > HPO_4^{2-}$ [8]).

Table I. Reported selectivities of guest-induced changes in membrane potential for PVC liquid membranes incorporated with hosts for alkali metal cations.[a]

Host	Membrane solvent[b]	Li^+	Na^+	K^+	Rb^+	Cs^+	Ref.
1	NPOE		2×10^{-4}	1	1.4	3×10^{-1}	[e]
4	NPOE	1	7.9×10^{-4}	5.0×10^{-4}			[17]
5	NPOE		3×10^{-4}	1	2×10^{-1}	1×10^{-2}	[18]
6	NPOE	1×10^{-3}	1	9×10^{-3}	4×10^{-3}	1×10^{-2}	[19]
7	NPOE	1	4.4×10^{-3}	5.5×10^{-3}			[20]
8	BBPA	1	1.0×10^{-3}	2.5×10^{-4}	2.5×10^{-4}	3.2×10^{-4}	[21]
9	TEHP	1.0×10^{-3}	1	1.0×10^{-3}	2.5×10^{-4}	1.0×10^{-4}	[22]
10	NPOE	1.9×10^{-4}	1	3.24×10^{-2}	6.9×10^{-3}	2.5×10^{-3}	[23]
13	NPOE	7.9×10^{-1}	1	7.9×10^{-4}			[25]
14[c]	FPNPE	1.0×10^{-3}	1	3.8×10^{-3}	7.9×10^{-4}	3.2×10^{-4}	[27]
15[d]	DOS	$<1 \times 10^{-4}$	$<1 \times 10^{-4}$	4.0×10^{-2}	2.5×10^{-1}	1	[63]
16	FPNPE	2.5×10^{-5}	1	7.9×10^{-4}	7.9×10^{-6}	1.6×10^{-6}	[29]
17	NPOE	1.6×10^{-3}	1	1.0×10^{-5}	1.6×10^{-5}	1.0×10^{-5}	[31]

[a] Potentiometric selectivities are represented by selectivity coefficients ($K^{pot}_{A,B}$).

[b] Membrane solvents. NPOE: 2-nitrophenyl octyl ether; BBPA: bis(1-butylpentyl) adipate; TEHP: tris(2-ethylhexyl) phosphate; FPNPE: 2-fluorophenyl 2-nitrophenyl ether; DOS: bis(2-ethylhexyl) decanedioate ("dioctyl sebacate").

[c] R^1 = —$(CH_2)_9CH_3$, R^2 = —$C(CH_3)_3$.

[d] R^1 = —$(CH_2)_9CH_3$, R^2 = —H.

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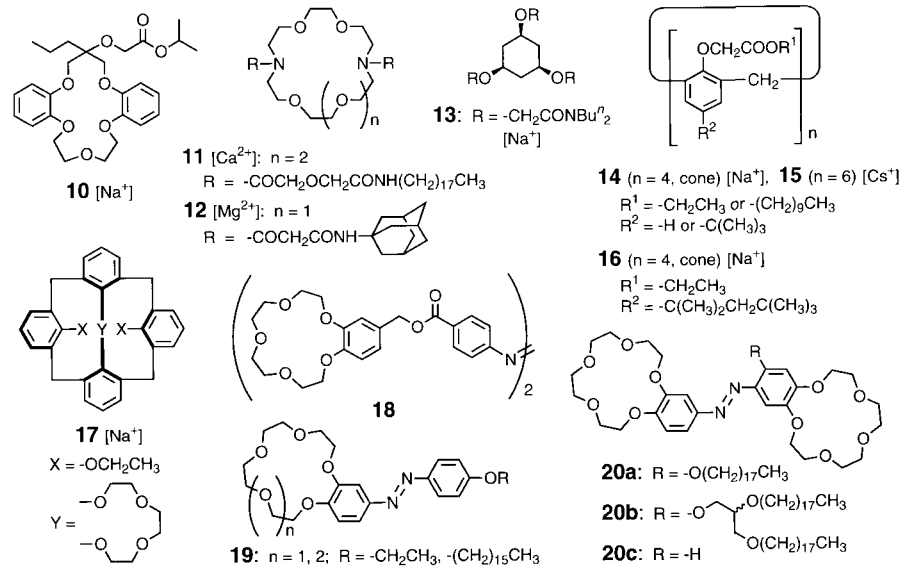

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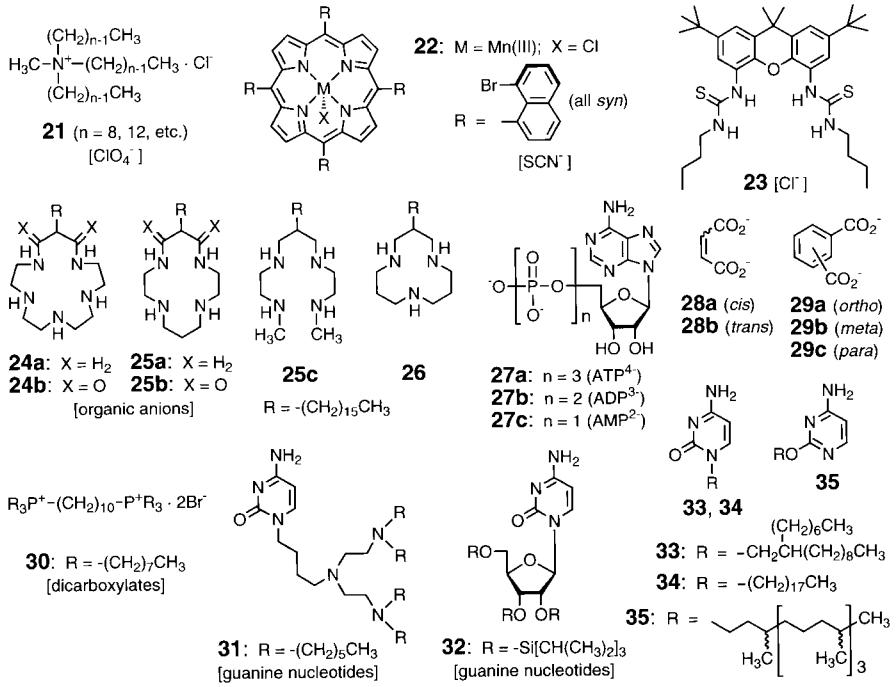
Porphyrin derivative **22** with bulky substituents on the same side showed a selectivity to a small linear anion (SCN^-) (Meyerhoff et al. [42]). Host **23** with multiple hydrogen bond donors showed a good selectivity to Cl^- against Br^- and HCO_3^- ions (Umezawa et al. [43]). Saturated macrocyclic polyamine **24a** also showed a non-Hofmeister selectivity for inorganic anions [44]. It is interesting that the corresponding dioxo-type macrocyclic polyamines (**24b**, **25b**) displayed potentiometric discrimination of anionic metal cyano complexes with planar and octahedral structures (e.g., $[Ni(CN)_4]^{2-}$, $[Pt(CN)_4]^{2-}$ vs $[Fe(CN)_6]^{3-}$, $[Fe(CN)_6]^{4-}$; Umezawa et al. [45]).

3. Membrane Potential Changes by Organic Guests

Similar to the situation for the synthetic hosts for inorganic anions, there is still only a limited number of hosts that are capable of discriminating structural differences of *organic* guests at membrane/aqueous solution interfaces. Whereas the difficulties for the design of host molecules for inorganic anions arise from the limited availability of suitable structural units, the problem with regard to organic guests lies with their structural complexity compared to inorganic guests. To establish the basic principles for potentiometric discrimination of organic guests, we have been focusing our efforts on the design and synthesis of hosts that are capable of discriminating organic guests at membrane/aqueous solution interfaces according to the differences in both polar and nonpolar structures of the guests [46–48].



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3.1. DISCRIMINATION OF POLAR STRUCTURES OF ORGANIC IONS

Discrimination of *polar* structures of organic ions by selective changes in membrane potentials can be achieved on the basis of electrostatic interaction and/or hydrogen bonding with the polar moieties of guests. Such a mode of structure discrimination has been attained by several types of hosts incorporated in PVC liquid membranes. Long alkyl chain derivatives of macrocyclic polyamines (**24a**, **25a**, **26**), capable of bearing a strong polycationic property by multiple protonation, showed potentiometric discrimination of multiply charged organic anions such as adenine nucleotides and dicarboxylate isomers (Umezawa et al. [44, 49, 50]). Potentiometric discrimination of these organic anions was shown to be based on the amount (response magnitude: ATP^{4-} (**27a**) $\gg$ ADP^{3-} (**27b**) $\gg$ AMP^{2-} (**27c**); [44, 50]) or the proximity (*cis* (**28a**) > *trans* (**28b**); *ortho* (**29a**) > *meta* (**29b**) > *para* (**29c**); [49, 50]) of negative charges within the anionic guests (the structures are shown in the scheme). The essential role of concentrated positive charges arising from multiple protonation within a confined cyclic system was clearly shown by comparison of the potentiometric behaviors of cyclic hosts (**24a**, **25a**, **26**) and an acyclic reference (**25c**) [50, 51]. In particular, the N_5 host (**24a**) showed a linear response to ATP^{4-} (**27a**) from a concentration as low as 10^{-7} M [44]. As another example of a host capable of potentiometrically discriminating

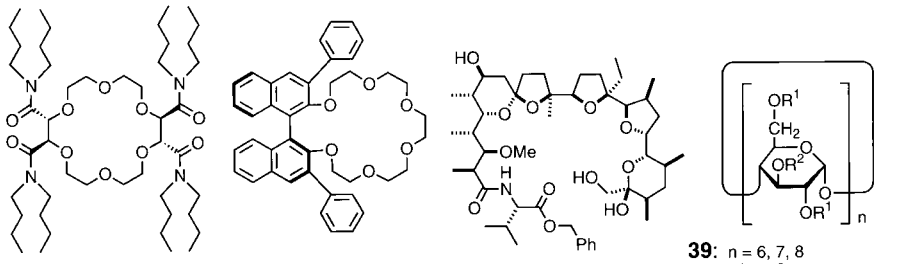
organic anions on the basis of charge-charge interactions, diphosphonium host **30** exhibited a selectivity to the para isomer of dianion **29c** (Ohki et al. [52]).

Concerning the recognition of polar moieties of guests, multiple hydrogen bonding such as complementary base pairing is another important and more sophisticated principle because it involves directed, multipoint interactions. This mode of potentiometric discrimination was achieved by liquid membranes containing a host with a ditopic receptor function (**31**, Umezawa et al. [53]) or a mixture of hosts for electrostatic binding and complementary base pairing (**25a,b** + **32**; **21** (*n* = 12) + **33**, **34** or **35**; Umezawa et al. [54, 55]), which were shown to be capable of potentiometrically discriminating nucleotides bearing guanine and adenine bases with a selectivity to the former. Potentiometric discrimination of carboxylate guests by hydrogen bonding and charge-charge interactions with protonated guanidinium hosts were also reported (Bachas et al. [56, 57]). As a related work concerning electrochemical signal transduction with a hydrogen bonding acceptor, selective detection of guanidinium cation by chemically modified field effect transistors (CHEMFETs) with PVC liquid membranes incorporated with calix[4]- and calix[6]arene derivatives was reported (Reinhoudt et al. [58]).

3.2. Discrimination of nonpolar structures of organic ions

Considering the ubiquitous existence of nonpolar moieties in the structures of organic guests, discrimination according to the differences in *nonpolar* structures will be equally important as discrimination according to the differences in polar structures. Although inclusion into well-defined hydrophobic cavities of hosts such as cyclodextrins and cyclophanes affords a general principle for the former mode of structure discrimination in aqueous systems, there exists a difficulty in achieving such a mode of discrimination in organic membrane systems because of competitive inclusion of organic guests and membrane components. Due to such an intrinsic difficulty, discrimination of nonpolar moieties of organic guests by membrane potential changes has so far been achieved mainly on the basis of simple lipophilicity or chirality of guests [9–11, 47]. Potentiometric discrimination of the chirality of protonated amines and amino acid esters has been achieved by PVC liquid membranes incorporated with chiral crown ethers (e.g., **36**, Simon et al. [59]; **37**, Shinbo et al. [60]) as well as with derivatives of natural ionophore (e.g., **38**, Tsukube et al. [61]) and cyclodextrin (e.g., **39** (*n* = 6), Parker et al. [62]).

Recently, potentiometric discrimination according to the differences in the steric structures of nonpolar moieties was achieved by per-*O*-acetic acid esters of calix[6]arene (**15a**,**b**) incorporated in PVC liquid membranes (Odashima et al. [63, 64]). Potentiometric selectivity coefficients ($K^{\mathrm{pot}}_{A,B}$) for simple amines and catecholamine guests are listed in Table II. In the case of dibenzo-18-crown-6 (**40**) used as a reference host, the potentiometric selectivity reflected, as expected, the lipophilicity of the guests because strong tripodal hydrogen bonds are available for all protonated primary amine guests (Figure 1a). In contrast, the calix[6]arene hexaester (**15a**,**b**)

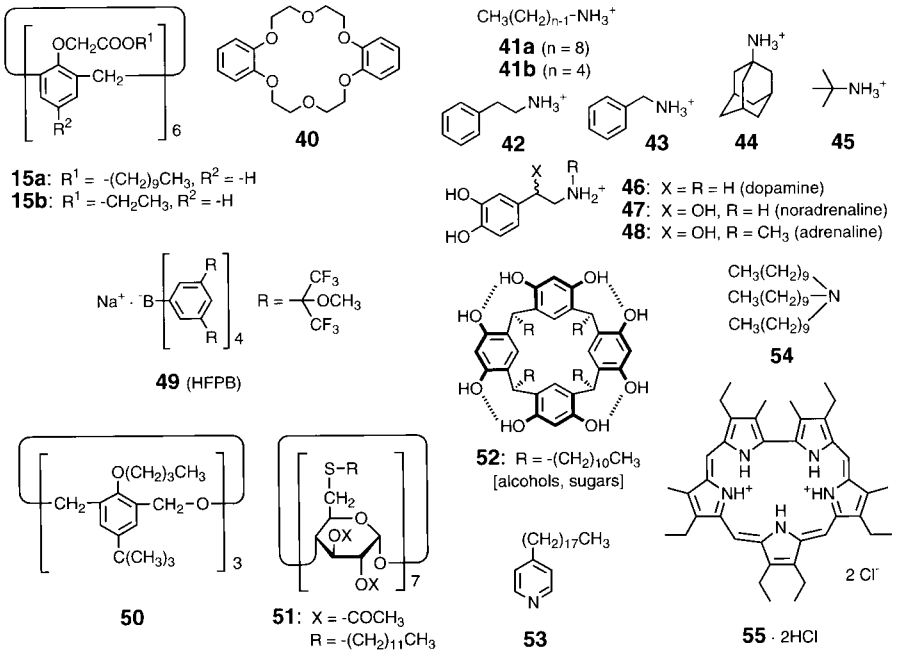


Structures 36–39.

displayed quite a different selectivity, the magnitude of response being in the order of **41** $\geq$ **42** $\gg$ **43** $\gg$ **44** $>$ **45**. Of the catecholamine neurotransmitters (**46** $\sim$ **48**), by far the strongest response was observed for dopamine (**46**), particularly by the calix[6]arene hexaesters. The potentiometric selectivities for both types of guests were unaffected by the length of the alkyl chains (**15a** (C_{10}) vs **15b** (C_2)) or the presence of the lipophilic anionic site **49** added in the membrane (Table II) [64].

In the case of calix[6]arene hexaesters (**15a**,**b**), the potentiometric selectivity is determined by the availability of tripodal hydrogen bonds, which is greatly affected by the steric hindrance between the nonpolar moiety of the guest and the inclusion cavity of the host if the formation of *inclusion* complexes is assumed (Figure 1b). For guests **41**, **42**, and **46**, the formation of strong tripodal hydrogen bonds will not be interfered with because there is no substituent around the NH_3^+ group. In contrast, the guests with a tertiary alkyl structure at the α position (**44**, **45**), as well as with a phenyl group attached directly to the α-carbon (**43**), are sterically hindered from the formation of tripodal hydrogen bonds and hence will be unfavorable for the formation of inclusion complexes. Thus, the characteristic potentiometric selectivity of the calix[6]arene hexaesters for primary amine guests can be reasonably interpreted on the basis of the structural factors relevant to the nonpolar moieties of the guests. From a practical viewpoint of measuring dopamine (**46**) in biological samples, the dopamine-selective calixarene hexaesters (**15a**,**b**) still suffer from severe interference by K^+ ion, as indicated by the $K^{pot}_{A,B}$ value ($K^{pot}_{68,K} = 5 \sim 7$; Table II). It was found [64] that the interference by K^+ ion was greatly reduced by using homooxacalix[3]arene triether **50** [65] ($K^{pot}_{68,K} = 6.5 \times 10^{-3}$, $K^{pot}_{68,K} = 6.0 \times 10^{-4}$; Table II).

Potentiometric or optical discrimination of the nonpolar structures of organic ions has also been attained for protonated amines by calix[6]arene hexaester **15b** (Chan et al. [66, 67]), for aldehydes (as protonated lipophilic hydrazones generated *in situ*) by calix[4]arene tetraester **14** (R^1 = —CH_2CH_3, R^2 = —$C(CH_3)_3$) (Chan et al. [68, 69]), for onium salts by per-*O*-octylated cyclodextrins **39** (Kataky et al. [70]), and for the positional isomers of substituted benzylamine salts by β-cyclodextrin derivative **51** [71] (Odashima et al. [72]).



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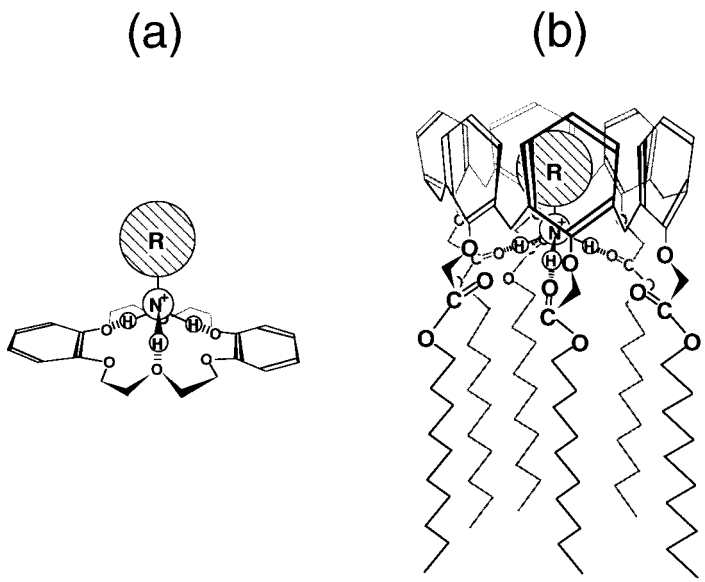

Figure 1. Schematic representations of the possible geometries of host-guest complexes. (a) Nesting complex of dibenzo-18-crown-6 (**40**) and a protonated primary amine guest. (b) Inclusion complex of calix[6]arene hexaester (**15a**) and a protonated primary amine guest. (Adapted from *Anal. Chem.*, **65**, 1074 (1993), p. 1077).

Table II. Selectivities of guest-induced changes in membrane potential for PVC liquid membranes incorporated with calix[6]arene hexaesters (**15a**,**b**), dibenzo-18-crown-6 (**40**), or homooxacalix[3]arene triether (**50**)[a].

Guest	**15a**[b] (pH 7.0)[h]	**40**[c] (pH 7.0)[h]	**15a**[d,e] (pH 5.0)[i]	**15b**[d,f] (pH 5.0)[i]	**50**[d,g] (pH 5.0)[i]
41a	2.60	20.0			
41b			2.58	3.52	0.57
42	1	1	1	1	1
43	0.29	4.77	0.15	0.15	0.45
44	<0.01	20.0	<0.01	<0.01	1.85
45	<0.01	0.35	<0.01	<0.01	0.31
46	1	1	1	1	1
47	0.20	0.94	0.10	0.096	<0.01
48	0.27	0.88	0.089	0.090	<0.01
K^+			5.24	7.02	0.0065
Na^+			0.031	0.060	0.00060

[a] Potentiometric selectivities are shown by selectivity coefficients ($K^{pot}_{A,B}$) determined by the matched potential method in mixed solutions (V. P. Y. Gadzekpo and G. D. Christian: *Anal. Chim. Acta* **164**, 279–282 (1984); Y. Umezawa, K. Umezawa, and H. Sato: *Pure Appl. Chem.* **67**, 507–518 (1995)). Bis(2-ethylhexyl) decanedioate ("dioctyl sebacate", DOS) was used as a membrane solvent.
[b] Membrane composition: **15a**/DOS/PVC = 5 : 68 : 27 wt% [63].
[c] Membrane composition: **40**/DOS/PVC = 2 : 66 : 32 wt% [63].
[d] Lipophilic anionic site **49** was added (host/**49** = 1 : 0.3 (molar ratio)].
[e] Membrane composition: **15a**/DOS/PVC/**49** = 5 : 68 : 27 : 1.5 wt% [64].
[f] Membrane composition: **15b**/DOS/PVC/**49** = 3 : 69 : 28 : 1.4 wt% [64].
[g] Membrane composition: **50**/DOS/PVC/**49** = 3 : 68 : 29 : 2 wt% [64].
[h] Measured in 0.1 M Tris-HCl buffer. [i] Measured in 0.1 M CH_3CO_2Li—CH_3COOH buffer.

3.3. Discrimination of neutral molecules

Although membrane potential changes are generally induced by charged species, there have been some instances in which membrane potentials are affected by neutral molecules. With respect to a synthetic host, potentiometric responses to monosaccharides and some other hydrogen-bonding guests were reported for Langmuir-Blodgett type monolayers containing host **52** (Kunitake et al. [73]). However, it is generally difficult to give an explicit explanation for potentiometric responses to uncharged species.

Based on the previous findings of Kimura et al. [74] that a macrocyclic polyamine forms stable complexes with neutral catecholic guests in aqueous solutions, we have examined potentiometric responses to various phenolic guests by

PVC liquid membranes incorporated with lipophilic macrocyclic polyamines (e.g., **24a**) [75]. A number of phenols examined induced a decrease in the membrane potential (anionic response) under the pH conditions in which the phenols exist almost exclusively as their undissociated, neutral forms. The prerequisite for the responses to phenols seemed to be the presence of a phenolic OH. Interestingly, such unexpected "potentiometric" responses to *neutral* species were observed for several types of nitrogen-containing, lipophilic compounds, including intrinsically cationic ones (lipophilic quaternary ammonium or phosphonium salts; e.g., **21**) [76] as well as those that acquire a cationic property by protonation (e.g., lipophilic aliphatic and heteroaromatic amines; e.g., **53** ∼ **55**) [77]. On the basis of the results on potentiometric responses, complexation, and extraction behaviors, a model for potentiometric responses to *neutral* phenols, which explains the anionic responses on the basis of a guest-induced decrease in the amount of charge-separated species at the membrane/aqueous solution interface, was proposed [76]. Whereas the selectivities of the potentiometric responses were found to be determined in most cases by the acidity and lipophilicity of the phenols [76, 77], sapphyrin (**55** [78]) exhibited a high selectivity to catechol against its positional isomers, possibly due to a two-point hydrogen bonding [77]. The understanding of the response mechanism for neutral phenols may afford a starting point for developing "potentiometric" sensing systems for a variety of uncharged species.

4. Concluding Remarks

The advance of host-guest chemistry and its recent evolution to supramolecular chemistry has made significant contributions to the development of a number of new host molecules capable of effecting various modes of signal transduction including electrochemical signal transduction at a membrane/aqueous solution interface. In contrast to guest-induced changes in membrane *potential* as described in this chapter, there are still only a limited number of investigations on guest-induced changes in membrane *permeability*, which is another important mode of electrochemical signal transduction. Although the design of host molecules with the latter mode of signal transduction is still in its initial stage, a number of relevant studies for controlling membrane permeability by host-guest complexation have been reported, not only for inorganic but also for *organic* guests. For organic guests, in addition to the control of membrane permeability through intermolecular voids between membrane components [79–84], the control of permeability through intramolecular channels of membrane hosts [85] has also been investigated. Understanding of the behaviors of host molecules at membrane/aqueous solution interfaces by both theoretical approach and surface sensitive observation (for examples, see [39, 76, 86]) are expected to contribute to the rational design of interfacial receptor molecules in the future.

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