Crown ethers as sensory materials in chemical measurements: Interfaces for chemical signal transformation

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Abstract - Transformation of chemical signals into electric signals is one of the essential processes in modern chemical measurements. Compounds designed on host-guest consideration can be used as key material in developing an interface or a transducer for such signal transformation devices. The concept of chemical transducer or interface is presented with examples which use crown ether derivatives as sensory host compounds. Crown ether derivatives equipped with ion-recognition part (crown ether) and signal transformation part (chromophore) are developed for extraction photometry of mono- and di-valent metal ions. Synthetic, chiral molecular bilayer membranes which show peculiar circular dichroism are used as a transducer of ion-recognition signals which are produced by crown ether ionophores doped in the membranes. Crown ether polymer-coated electrodes give an interface which interacts with alkali metal ions and produces a change in its dielectric property, which can then be picked up as an electrical signal by impedance measurement in an alternating current circuit.

INTRODUCTION

In modern analytical chemistry, the chemical signal or chemical information carried by atoms, molecules or their assemblies is transformed eventually into electrical signal (Fig.1). The electrical signal is then recorded or is further electrically processed according to needs before recording or storing. To devise a new interface or transducer to facilitate such chemical information transformation is an important task of analytical chemists.
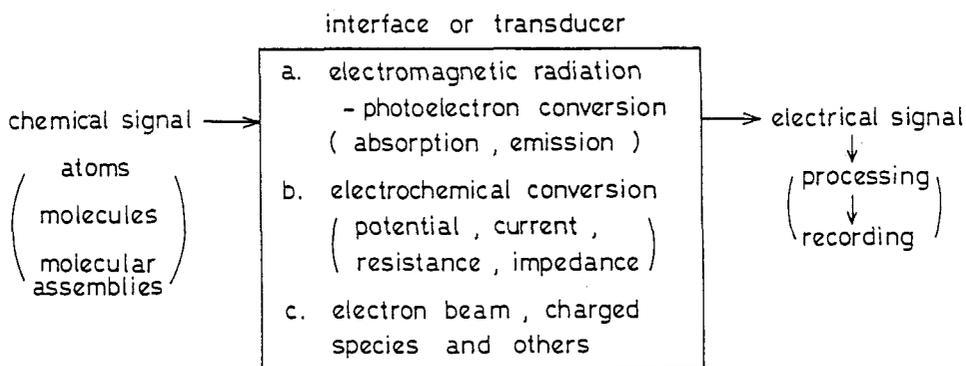
Fig. 1. Transformation of chemical signals in modern analytical chemistry

Photometry is one of the most traditional and widely-used approaches for such a purpose, where a chemical signal is first transformed into an electromagnetic radiation signal and then into an electric signal by using photoelectric detecting system. Electrochemical techniques represent another

traditional and very successful approach, which are featured by a direct chemical - electrical signal transformation mechanism at the electrode surface. Anyhow, if one focuses on the detection of molecular or ionic species, one has to develop a molecular device to carry out such a signal transformation which suits to those particular analyte species. In the present paper, some of our new attempts along this line are presented as they relate to the special features of macrocyclic polyethers.

CROWN ETHER-BASED EXTRACTION PHOTOMETRIC REAGENTS

A general structure of reagent is shown in Fig. 2 for the determination of alkali metal (monovalent) and alkaline earth metal (divalent) ions (ref. 1-3). Chromophoric, proton-dissociable groups (typically phenolic groups) are introduced on the periphery of crown ether ring. In organic - aqueous, two-phase partition equilibrium, the undissociated, uncharged reagent dissolves preferentially in organic solution. On deprotonation, an anionic charge is formed on the side arm, and the reagent either stays in organic solution by extracting from aqueous solution proper metal ions which meet the structural requirement of the reagent or goes into aqueous phase when such metal ions are not available. The metal extraction and the spectral change due to deprotonation in organic solution are thus linked, and the chemical information in aqueous solution (the nature of metal ions present and their concentration) is transformed into spectral information in organic solution. This process is exactly the same as in traditional photometic reagents. However, the strategy of molecular construction is more sophisticated and conceptually more refined in Fig. 2 according to the concept of molecular signal transformation.
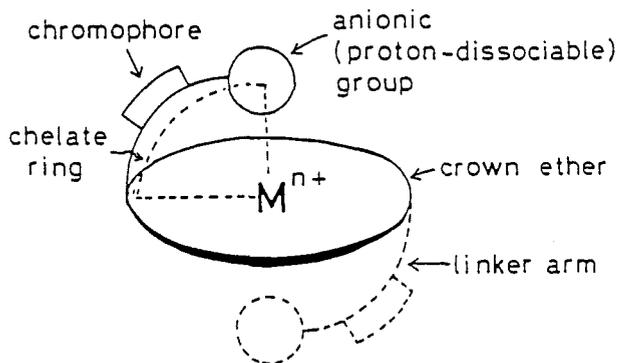
Fig. 2. Molecular construction of crown ether-based extraction photometric reagent for alkali and alkaline earth metal ions. The number of dissociable protons meets the valence number of metal ions.

In traditional extraction photometric reagents, represented typically by such azophenol derivatives as 1-(2-pyridylazo)-2-naphthol (PAN), the molecular functions which recognize metal ion and transform the recognition signal to spectral signal are carried by a single, integrated structure of pyridylazophenol. In Fig. 2 on the other hand, an ion-recognizing part (crown ether) and a signal transforming part (chromophoric anionic group) are conceptually and physically separated by a connector part which links the foregoing two structural parts together. Compounds 1 and 2 show typical examples of such molecules. In practice, the ion-recognizing part and the signal transformation part do not work independently. Particularly, since the reagent molecule is interacting with a charged analyte (positively-charged metal ion), the nature of chromophoric anion and the way of its introduction into the reagent (the nature of linker arm) sometimes causes a profound influence on the metal-recognition process of the crown ether part of the reagent molecule.

PAN   1   2
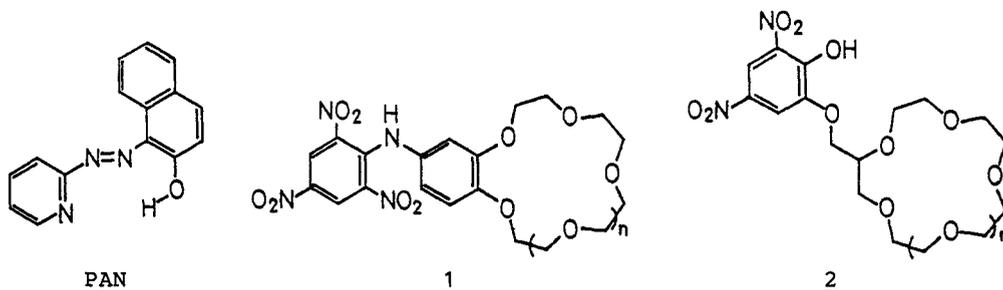
The metal extraction equilibria are described by equations 1 and 2 for monovalent and divalent metal ions, respectively, where HL and H_2L stand for proton-dissociable reagents (ligands) and subscripts a and o denote species in aqueous and organic solutions, respectively. The metal extraction ability of a particular reagent is assessed by the magnitude of extraction constants K_{ex}, and the metal extraction selectivity between metals M and M' is conveniently discussed in terms of the ratio of extraction constants, K_{ex} (M)/K_{ex} (M').

$$(HL)_o + (H^+)_a \rightleftharpoons (HL)_o + (H^+)_a \quad : \quad K_{ex} = \frac{[(ML)_o][(H^+)a]}{[(HL)_o][(M^+)_a]} \quad (1)$$

$$(H_2L)_o + (M^{2+})_a \rightleftharpoons (ML)_o + 2(H^+)_a \quad : \quad K_{ex} = \frac{[(ML)_o][(H^+)_a]^2}{[(H_2L)_o][(M^{2+})_a]} \quad (2)$$
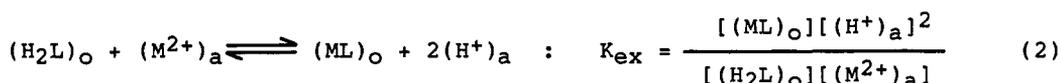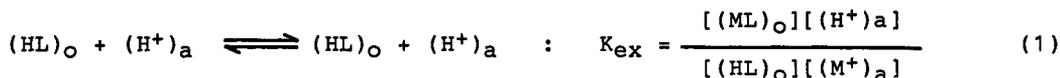
The following factors are important in determining the metal extraction selectivity: a. structure and length of linker arm (size of chelate ring formed by anionic side arm and crown ether-bound metal), b. nature of anionic group (basicity, degree of anionic charge delocalization), and c. nature of crown ether macrocycle (size, heteroatoms). Among these, the size consideration of crown ether gives the most simple and easy-to-use criterion for increasing selectivity to particular metal ions; a size-fitness between metal ion and crown ether always makes a positive contribution to the stabilization of the resultant complex, thus leading to an enhanced metal extraction ability. For example, in compound $\underline{2}$, K^+/Na^+ selectivity (K_{ex} (K^+)/K_{ex} (Na^+)) is 0.29 for $\underline{2}$ (n=1) and 6.3 for $\underline{2}$ (n=2) in the extraction from aqueous into 1,2-dichloroethane solution at 25 °C.

The influence of basicity (proton affinity) of anionic group is summarized as follows : the more basic is the anionic group in L^- or L^{2-} (the higher is the pK_a value of the conjugate acid), the greater the affinity of the ligand L^- or L^{2-} toward ions of high surface charge density. For example, consider reagent $\underline{2}$ (n=2) which contains a structural unit of 2,4-dinitrophenol. The pK_a of this compound is 3.3 in water-dioxane (9 : 1, v/v) at 25 °C. Substitution of this dinitrophenol unit by 4-(4-nitrophenylazo)phenol unit gives reagent $\underline{3}$
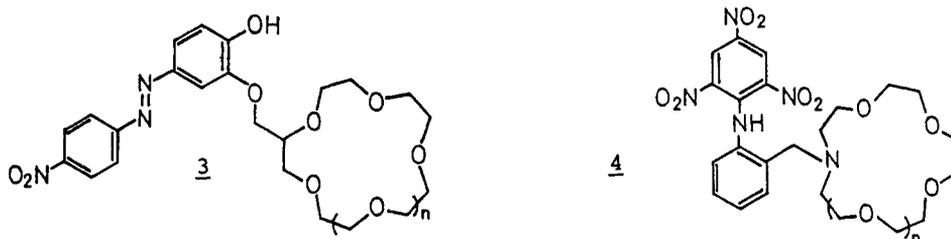
(n=2), which possesses essentially the same molecular construction as $\underline{2}$ (n=2) but has a lower proton dissociation constant (pK_a=7.5). The K^+/Li^+ selectivity is 330 for $\underline{2}$ (n=2) and 50 for $\underline{3}$ (n=2), indicating that the relative affinity of phenolate anion toward Li^+ increased 66 times on increasing the proton affinity of the phenolate by $10^{7.5-3.3}$ = 1600 times.

The linker arms which allow the formation of 5- or 6-membered chelate are suited for the extraction of small metal ions such as Li^+ in alkali metal and Ca^{2+} in alkaline earth metal ions. Reagent $\underline{2}$ formally provides 8-membered chelate complex, while the complex from reagent $\underline{1}$ can not take chelate structure but is compelled to take intramolecular ion-pair structure. A bulky, well charge-delocalized picrylamino anion prefers to form ion-pair rather than chelate (coordination) complexes even under conditions where the anionic group can physically make, as in reagent $\underline{4}$, a contact with the crown ether-bound metal ion. Ion-pair complex formation is favored by large metal ions, and reagent $\underline{4}$ is not effective for extracting Li^+ irrespective of the size of crown ether contained.

The Ca^{2+}/Ba^{2+} extraction selectivity (water-1,2-dichloroethane) of diprotonic dyes derived from diazacrown ethers is shown in Fig. 3. This gives some idea how individual structural units mentioned above cooperate to determine the final metal extraction behavior. It is emphasized that Ca^{2+}/Ba^{2+} selectivity can be changed over the range of 4×10^7 by simply changing , while keeping the structure of diaza-18-crown-6 the same, the nature of anionic group and
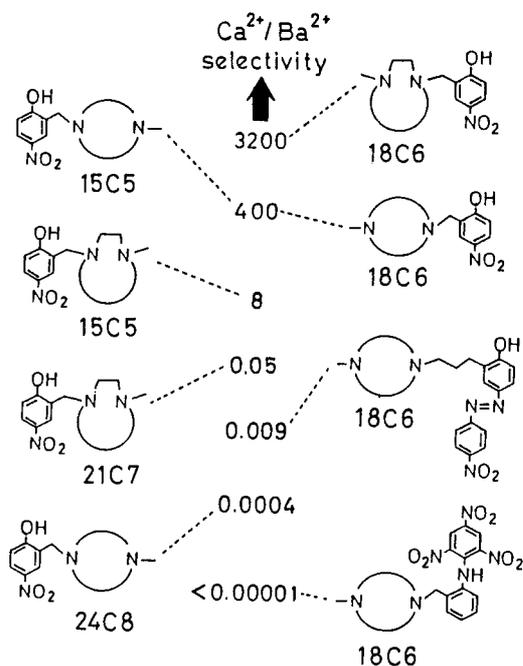
Fig. 3. Ca^{2+}/Ba^{2+} metal extraction selectivity of diprotonic diazacrown ether reagents. The large values indicate a contribution of substantial chelate character for the extracted complex. Small values indicate a contribution of substantial ion-pair character.

linker arm. This observation itself is interesting, but from the concept of "functional parts" for ion-recognition and signal transformation, the crown ether part in these diaza-18-crown-6 reagents is not performing any major function in the expected role of ion-recognition. On the other hand, the signal transformation part and connector part (or mediating part) are playing a vital role both in ion-recognition and signal transformation. In spite of this discrepancy between the concept and the behavior of actual molecules, we believe that the considerations presented here can serve as directions in developing a next generation of organic analytical reagents based on host-guest chemistry.

CIRCULAR DICHROISM (CD) RESPONSE OF CROWN ETHER-DOPED SYNTHETIC LIPID BILAYERS TO ALKALI METAL IONS

One of the important functions of biological cell membrane is molecular recognition and its signal transformation across the membrane. Recent years, a substantial progress has been made on synthetic lipid bilayer membranes which possess physicochemical properties fundamentally similar to those of biological membranes in nature. It would thus be of particular interest to develop a chemical sensing device which is based on some essential properties of molecular bilayer membranes.

Some synthetic double-chain amphiphiles such as 5 and 6, which contain a chiral center and a chromophoric group (ref. 4), show marked enhancement of CD in molecular bilayer dispersion in water. This is induced by a strong exciton
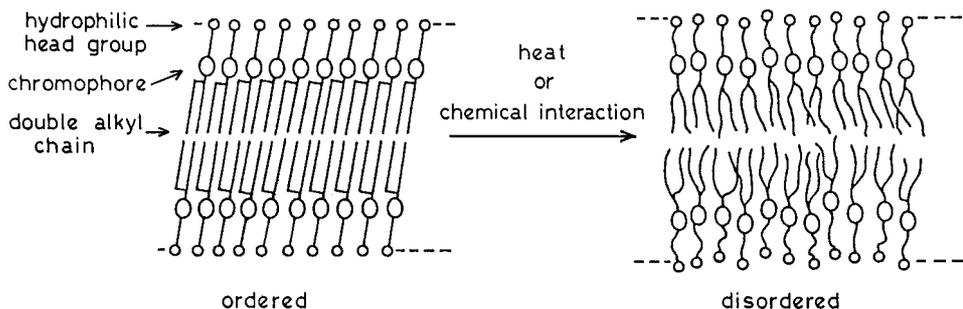
Fig. 4 Change in association structure of amphiphilic molecular bilayer membranes. The process is typically represented by thermal phase transition between gel and liquid crystal states of the membranes. Hydrophilic groups are anionic in amphiphile 5 (phosphate) and cationic in amphiphile 6 (quaternary ammonium). Chromophores are phthaloyl groups in both 5 and 6.

coupling between the adjacent chromophores which take a unique ordered configuration at temperatures below phase transition of the bilayer assembly. The CD intensity reduces when this ordered configuration is destroyed by perturbation from heat (i.e., by gel - liquid crystal transition) or by chemical interaction of the assembly with solutes in solution (Fig. 4).

The first experiment reminiscent of possible sensory application came from the work by one of us and his collaborators (ref. 5). The CD intensity of the anionic amphiphile 5 in aqueous dispersion decreases drastically on addition of polyvalent metal ions such as Ca^{2+}, Ba^{2+} and La^{3+}. Monovalent (alkali) metal ions cause no influence. This effect of metal ions is just the result of ion association or complex formation between the negatively-charged amphiphile and metal cation, which leads to disintegration of an ordered molecular configuration in the bilayer assembly. There are not much differences among polyvalent metal ions in their behavior in depressing CD intensity ; obviously the anionic membranes recognize only a charge type (monovalent or polyvalent) of the metal but not individual metal ions. To do the latter, one has to employ cationic membranes which in nature do not interact with or rather reject cations but are expected to accept cations if appropriate cation ionophores are used in a combined manner.
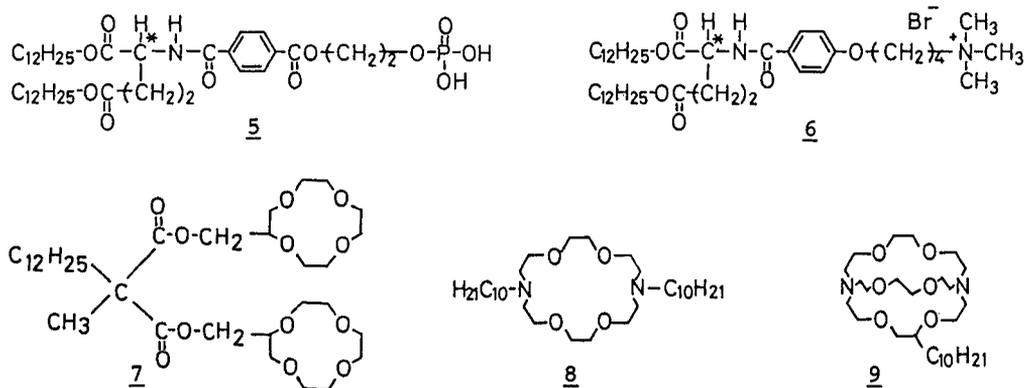
Amphiphile 6 (1 x 10^{-4} M) and Na^+-selective ionophore 7 were mixed and dispersed in water containing 0.1 M NMe_4Cl. In the absence of Na^+, CD spectra shows a strong negative peak at 260nm, the intensity of which, however, sharply diminishes on addition of 10^{-5}-10^{-4} M Na^+ (Fig. 5) (ref. 6). Other alkali metal ions caused virtually no effect (Fig. 6). The Na^+/K^+ selectivity
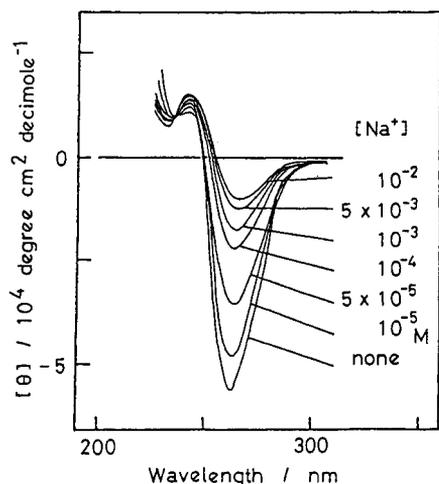
Fig. 5 CD spectra of mixed bilayer membranes composed of 6 and 7 (ionophore-doped membranes), and the response to Na^+ at 20 °C. The phase transition temperature of the mixed membrane is 28 °C, which does not change on addition of Na^+ as well as on addition of other alkali metal ions.
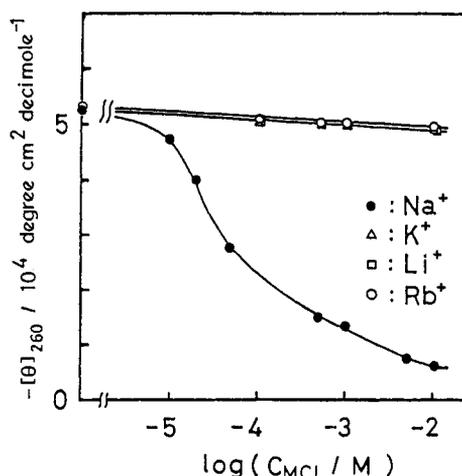
Fig. 6 CD spectral response to alkali metal ions. 20 °C, 0.1 M NMe_4Cl. Decrease in spectral intensity of the mixed membranes (6+7) is plotted against metal concentration at the spectral peak wavelength.

as revealed in potential response of polyvinyl chloride membrane electrode is about 100, while the response selectivity in Fig. 6 is at least several times greater than this under optimal conditions.

It was suggested that the reduction of CD intensity is caused by change in the distribution of membrane components 6 and 7 in the bilayers ; compound 7 perturbs the ordered chromophore configuration (orientation) through its binding to Na$^+$. Thus, the chemical signal produced by ion-binding at the crown ether ionophore is transformed into CD signal by means of a chiral molecular bilayer assembly in which the ionophore is placed. It is important that the signal transformation process involves amplification of Na$^+$/K$^+$ selectivity signal, the process being presumably associated with an allosteric effect in the molecular ordering in the bilayers. Similar results were obtained by using other crown ether ionophores such as 8 and 9, which gave CD signals selective to K$^+$.

The results presented above is important from the following two points. First, they constitute the first indication that a so-called self-organizing property of molecular bilayers can be used as a transducer and an amplifier of chemical signals. Secondly, a successful combination of synthetic bilayer membranes as signal transformer and a synthetic host compound as chemical receptor suggests a possible generalization of such a system to the detection and determination of a variety of chemical species, charged or uncharged. However, some drawbacks of the system in the present style have to be also pointed out. CD measurement is rather special in ordinary laboratory. Preparation of aqueous dispersion of bilayer membranes requires some experience, especially to obtain good reproducibility.

ELECTRIC IMPEDANCE DETECTION ON A CHEMICALLY-MODIFIED ELECTRODE—NEW SENSORY PRINCIPLE

Electrochemical sensing techniques now widely used involve potentiometry and amperometry, both of which are based on an electric circuit dealing with direct current (d.c.). In these d.c. techniques, it is essential that the analytes are either ionic or electroactive (redox-active), and this places some serious limitations on the scope of analytes to be handled in conventional electrochemical sensing.

We recently reported that the phase transition between gel state and liquid crystal state of synthetic bilayer membranes (10) is readily and conveniently detected by electrical impedance measurement on a pair of electrodes coated

$$CH_3\text{-}(CH_2)_{17}\text{-}O\overset{O}{\overset{\|}{C}}\text{-}\underset{\underset{}{|}}{CH}\text{-}NH\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}\overset{+}{N}(CH_3)_3 \quad \cdot \quad$$

$$CH_3\text{-}(CH_2)_{17}\text{-}O\overset{}{\underset{O}{\overset{\|}{C}}}\text{-}(CH_2)_2$$
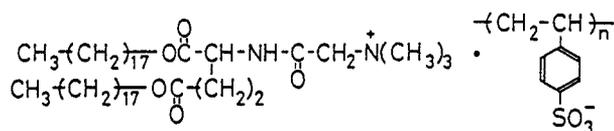
10

with the said membranes (Fig. 7) (ref. 7). A frequency dependence study(frequency response analysis) on this process suggested that the impedance change in this system reflects the change in dielectric property of the coated membranes, particularly those changes associated with the change in fluidity of the bilayer membranes and the accompanying intrusion of supporting electrolytes in the solution. This information is now generalized to derive the following new electrochemical sensing principle based on an alternating current (a.c.) impedance measurement (ref. 8).

"The electrode surface is modified in such a way that an analyte in solution selectively interacts with the electrode to induce a reversible change in the dielectric property of the modified electrode surface. It is then possible to detect, by electrical impedance measurement, the analyte which selectively interacts with the electrode surface (impedometry). The electrodes possessing such a property are most conveniently obtained by chemically modifying the surface with specifically designed, host-guest type organic materials which incorporate such functions as ion-exchange, chelate formation, inclusion, enzymic catalysis and so on."
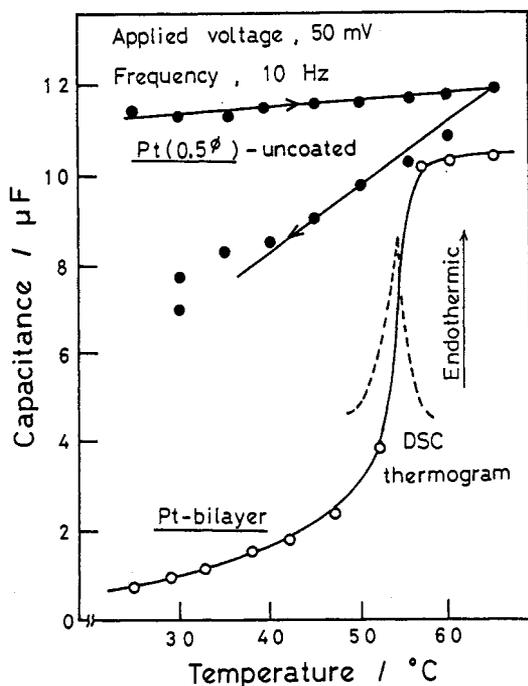
Fig. 7   Impedance response and
differential scanning thermometry
response of gel - liquid crystal
phase transition of 10. The bilayer
membranes were used as a thin film
of polyion complex 10, which was
developed on a platinum electrode
by dip-and-dry method from
chloroform solution. ● , uncoated
electrode; O , coated electrode.
Electrical measurements were made
on a pair of equivalent electrodes
dipped in aqueous solution con-
taining 0.1 M KCl. Electrical
impedances measured were arbi-
trarily simulated by a parallel
combination of a resistor and a
capacitor, and the change of
capacitance component was plotted
as a function of temperature. A
dotted line schematically shows a
thermogram measured for 10 in
aqueous suspension.

The a.c. sensing technique based on the above principle is obviously free from
limitations which are imposed to the scope of analytes in conventional
potentiometry and amperometry.   Several exploring studies have been made in
order to substantiate the proposed technique.   Electrical impedance exhibited
by a pair of i) polypyrrole-coated platinum electrodes, ii) crown ether
polymer-coated platinum electrodes, and iii) enzyme-immobilized titanium
electrodes was investigated in the presence of appropriate analytes or
substrates in solution. The components of measured impedance, i.e.,
capacitance and resistance, were found to correlate to the concentration of
the analyte which specifically interacts with the surface of the modified
electrode.   In addition, double-chain cationic amphiphiles developed on an
interdigitated-form electrode (comb electrode) responded to atmospheric
moisture and ammonium vapor, and its impedance (capacitance) response was
found to correlate to the humidity and ammonium concentration in vapor phase.
These are   convincing evidences that the idea presented here works in
electrochemical sensing of a variety of chemical species in solution as well
as in gas phase.   In the following are shown some selected examples (ref. 8).

Dibenzo-18-crown-6 was electrochemically oxidized and polymerized on a
platinum wire electrode according to the described method.   Figure 8
summarizes an impedance response on a pair of such coated electrodes to alkali
and alkaline earth metal ions. After a series of measurements with a
particular metal ion, the electrodes were thoroughly washed with water or with
aqueous EDTA-2Na solution before going to the measurements with other metal
ions.   After such a washing treatment, a slight increase in capacitance values
(~0.5 μF) was observed at zero metal ion concentration.   Therefore, the
capacitance value at zero metal ion concentration (initial capacitance, C_O)
was chosen as a standard, and the difference (ΔC) between C_O and the
capacitance at a particular concentration is plotted as a function of metal
ion concentration.

In Fig. 8, the magnitude of response is the greatest with Ba^{2+}, followed by K^+
and Na^+.   Only small response is obtained with Mg^{2+} which is known not to
interact with crown ether compounds.   The effect of ionic strength caused by
the added analyte ions is negligible, which is checked by using NMe_4Cl (dotted
line).
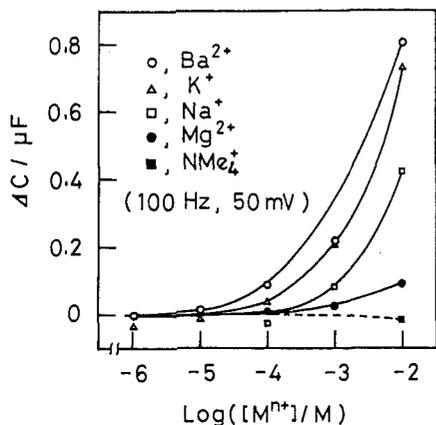
Fig. 8 Electrode response of crown
ether polymer-coated electrodes to
the concentration of metal ions in
0.1 M aqueous NMe_4Cl at 25 °C.
Capacitance values were extracted
from impedance values by assuming a
resistor-capacitor parallel equiva-
lent circuit.
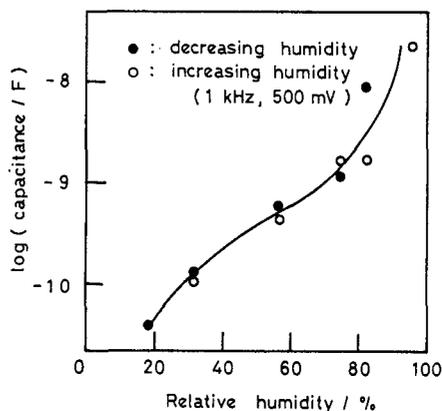
Fig. 9   Response of amphiphile
(6) - coated interdigitated - form
electrode to atmospheric moisture.
Capacitance values were extracted
by assuming a resistor-capacitor
parallel equivalent circuit. Small
hysteresis was observed whether the
moisture was increased or de-
creased. Annealing at 80 - 100 %
humidity after film development
improved hysteresis problem. Re-
sponse time are within several
minutes.

Figure 9 shows a response of amphiphile-coated electrode to moisture.   In
contrast to Fig. 8, the range of capacitance variation is quite large. It was
shown that the amount of water molecules adsorbed per mole of amphiphile 6 at
equilibrium varies continuously and reproducibly with a change in humidity in
the air under which it was equilibrated. The increased equation of
amphiphilic salt 6 leads to an increased mobility of ions (Cl^-) or ionic
portion (cationic head group) of the molecule.   This corresponds to an
decreased impedance (increased capacitance, decreased resistance) value in
electrical measurements.

A serious problem with the proposed "a.c. impedometry" in practical
applications is a difficulty in obtaining an electrode surface of good quality
and of good reproducibility. The chemical modification should be complete in a
rather strict sense; incomplete modifications or defects of surface layer give
such electrically - inhomogeneous sites as uncovered metal or metal oxide
surfaces, which seriously deteriorate the quality of electric signal generated
by the sensing surface. In addition, since metal or metal oxide surfaces are
usually strongly polarized in aqueous solution, such unmodified sites on the
electrode (or even the surface defects of the supporting electrode itself)
produce strong responses in impedance measurement which can sweep out small
signals from the intended analytes. The chemical and physical stability of the
modified layer is also an important factor. A development of surface
modification technique is a key to solve these problems.

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