Switch-functionalized systems in biomimetic chemistry

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Abstract – A variety of switch-functionalized crown ethers have been
synthesized. They change their chemical and physical properties in
response to the stimuli from the outside world such as light, redox,
heat, etc. These novel crown ethers act as ion carriers in membrane
transport systems. The rate of ion transport can be thus controlled
by an on-off-type switch.

INTRODUCTION

Coupled reactions, i.e., reactions that mutually affect their chemical and physical
properties, play a fundamental role in biological processes. In biological systems, such
interactions are regarded as allosteric when binding at one site induces conformational
changes which alter the receptivity of a remote site. In vision, for instance, a
stimulus from the outside world would be beautifully transduced in the order, light→
isomerization of retinal→ conformational change in rhodopsin. To design fundamental
systems of such coupled reactions, one has to combine within a molecule an antenna
molecule to capture a stimulus with a functional group to mediate a subsequent event.
The stimuli can be pH change, redox potential, electrochemical energy, light, heat, etc.

A crown ether family has the ability to associate with charged and uncharged species and
its conformation is easily changeable because of the flexible nature of the macrocyclic
polyether. The purpose of our investigation has been to control these association
phenomena of crown ethers by the stimuli from the outside world (ref. 1). In other
words, one may expect that if the conformation of the crown ether ring is changed by the
on-off-type switch, both the ion-binding ability and the ion-selectivity would be largely
affected. When one can attach an efficient switch-function to a crown ether family, it
would act as a new class of crown ethers having the responsive functionality similar to
that of some natural ionophores.

The oldest example is a class of pH-responsive crown ethers which change their ion-
binding ability in response to medium pH: that is, the crown ethers having the
dissociative functional group serve as pH-responsive crown ethers (ref. 1). It is known,
for example, that carboxylate-capped crown ethers and azacrown ethers reduce or lose
their ion-binding ability in acidic pH media. In this article we describe new methods to
control the ion-binding ability of crown ethers, which lead to the regulation of membrane
transport phenomena by an on-off-type switch.

PHOTORESPONSIVE CROWN ETHERS

Photoresponsive systems are ubiquitously seen in nature, and light is frequently used as
a trigger to cause the subsequent life processes. In these systems, the physiological
events are frequently linked with photoinduced structural changes of photoantennas.
Thus, when mimicking the fundamental functions of the photoresponsive systems, chemical
substances which exhibit photoinduced structural changes become the potential candidates
for the photoantennas. In the artificial systems, the photochemical reactions such as
(E)-(Z) isomerism of azobenzene, dimerization of anthracene, spiropyran-merocyanine
interconversion, etc. have been employed as practical photoantennas.

(1) is an early example of photoresponsive crown ethers which has a photofunctional
azobenzene cap on an N_2O_4 crown ring (ref. 2–4). (E)-(1) having the (E)-azobenzene cap
favorably binds Na^+ while (Z)-(1) produced by UV light irradiation binds K^+ more
strongly. The result suggests that the ring size of the N_2O_4 crown is apparently
expanded by photoinduced (E)-to-(Z) isomerization (ref. 2). (E)-(2) in which the azo-
benzene cap is replaced by a 2,2'-azopyridine cap strongly binds Cu^{2+} (ref. 3). The
affinity with Cu^{2+} disappears in photoisomerized (Z)-(2). The photocontrol of ion-
binding to transition metal is effected more elegantly by using (3) and (4), since the
N_2S_4 crown ring shows the extensive affinity with these heavy metal cations (ref. 4).

(1) X=O, Y=CH (3) X=S, Y=CH
(2) X=O, Y=N   (4) X=S, Y=N   (E)-(5)   (E)-(6)   (Z)-(6)
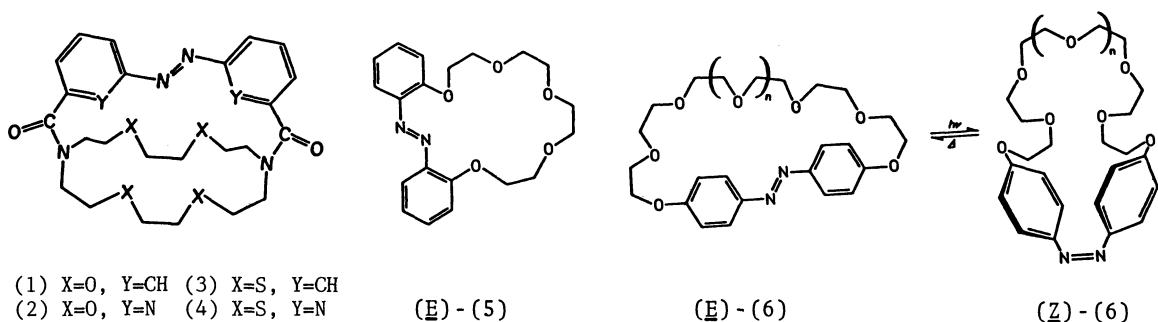
In order to design a photoresponsive crown ether exhibiting a large change in the ion-binding ability, one should search for a large photoinduced geometrical change which does not accompany any steric hindrance. However, these two requirements seem quite opposing. Crown ethers containing a photoresponsive chromophore as a ring member could satisfy these two opposing requirements. Shiga et al. (ref. 5) synthesized an azobenzenophane (5). (E)-(5) exhibits the affinity with alkali metal ions such as Na$^+$ and K$^+$ as "regular" crown ethers do. Photoisomerized (Z)-(5) completely lacks the affinity with these metal ions, but both the photo- and thermal isomerization is extremely slow and partially irreversible. This is probably due to large steric crowding expected for the transition state. In contrast, the photoisomerization of (6) occurs reversibly, indicating that there exists no steric hindrance at the transition state (ref. 6). (E)-(6) totally lacks the affinity for metal ions while (Z)-(6) can bind alkali metal ions, the selectivity for which is governed by the length of the polyoxyethylene chain.

Similar phane-type photoresponsive crown ethers have been designed by using the photodimerization of arthracene (ref. 7-9). More recently, we synthesized a crown ether (7) which has an intraannular azobenzene substituent (ref. 10). (E)-(7) shows no affinity with Na$^+$ because of steric hindrance of the intraannular substituent. When the substituent is "removed" by photoinduced (E)-to-(Z) isomerization, (Z)-(7) strongly interacts with Na$^+$ (log K = 4.8). The spectroscopoic studies established that one of the two azo nitrogens contributes to the binding of Na$^+$ ion.

It has been established that the alkali metal ion exactly fitting the cavity of the crown ether forms a 1:1 complex, whereas the alkali metal ion which has the ion radius larger than the cavity forms a 1:2 sandwich-type complex. We synthesized a series of azobis(benzocrown ether)s called "butterfly crown ethers" such as (8)(n=1-3) (ref. 11,12). In (E)-(8) each crown ring acts independently. On the other hand, the (Z)-isomers can associate with alkali metal ions with large ion radii more efficiently than the (E)-isomers. This is due to the formation of intramolecular 1:2 metal/crown sandwich-type complexes. The formation of this type of complexes is supported by the retardation of thermal (Z)-to-(E) isomerization in the presence of these large alkali metal ions. This may be regarded as the "lock-in" effect of the bridging metals.

(E)-(7)   (Z)-(7)   (E)-(8)   (Z)-(8)·M$^+$ complex
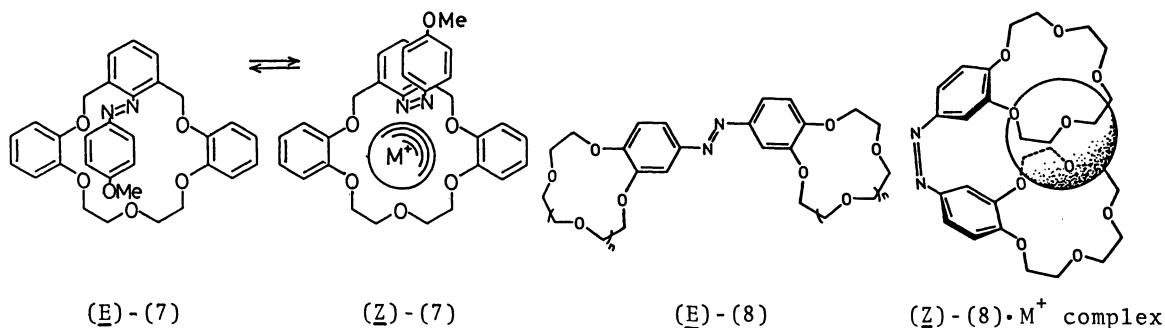
The concept described above is readily applicable to the design of photoresponsive crown ethers with the ionic caps. (9) is designed so that the phenolate anion can be placed on the top of the crown ring upon photoisomerization to (Z)-(9) (ref. 13). The nitro group and the n-butyl group are appended to lower the pK$_a$ of the phenol group and to enhance the lipophilicity, respectively. The two-phase solvent extraction with (9) indicates that (Z)-(9) efficiently extracts K$^+$, Rb$^+$, and Ca$^+$. (10) is named photoresponsive "tail-biting" crown ether. (10) has been synthesized so that intramolecular biting of the ammonium tail group to the crown can only occur upon photoisomerization to the (Z)-form (ref. 14,15). (E)-(10) can bind K$^+$ selectively as does the "regular" benzo-18-crown-6, but the metal affinity is markedly reduced by UV-light irradiation. The marked difference is rationalized in terms of competitive binding of K$^+$ with the intramolecular ammonium tail to the crown ring.

(Z)-(9)   (E)-(10)   (Z)-(10)
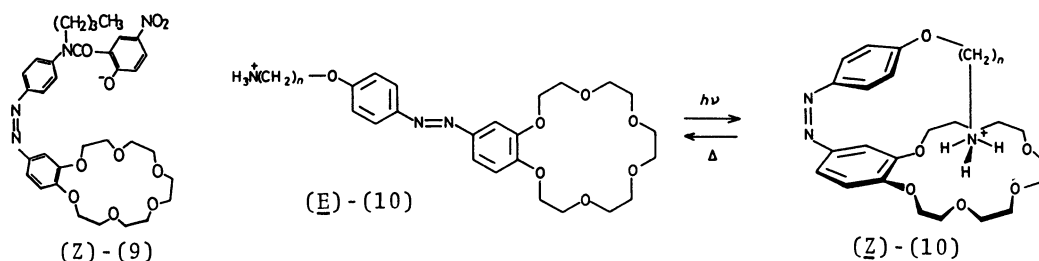
PHOTOCONTROL OF MEMBRANE TRANSPORT

Some polyether antibiotics (e.g., monensin and nigericin) feature the interconversion between the cyclic and noncyclic form in the membrane phase, a feature which is believed to lead to the high functionality of these antibiotics as ion carriers. Thus, the method of the reversible interconversion of crown functionalities attained by photoresponsive crown ethers may be fruitfully applied to the control of membrane transport phenomena. In K^+ transport with (8:n=2) across a liquid membrane, we found that the rate is accelerated by irradiating the ion-binding side of the liquid membrane phase by UV light (ref. 11,16). The photoinduced rate enhancement can be represented schematically as in Fig. 1. (9) and (10) serve as ion carrier for active transport of K^+ from the basic IN aqueous phase to the acidic OUT aqueous phase (ref. 13-15). The rate of the active transport is effectively speeded up by UV light irradiation. The possible transport mechanisms are illustrated in Figs. 2 and 3.
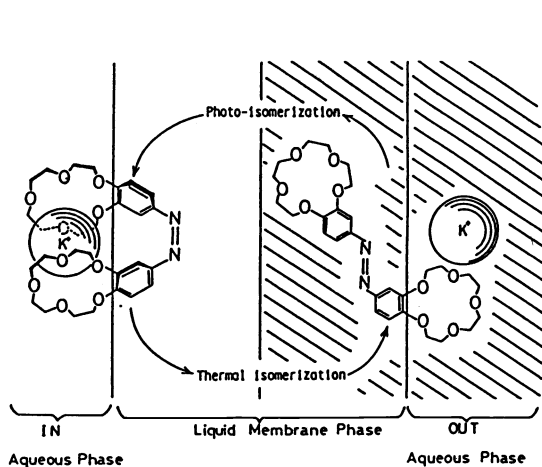

Fig. 1. Light-driven K^+ transport mediated by a photoresponsive crown ether (8:n=2)
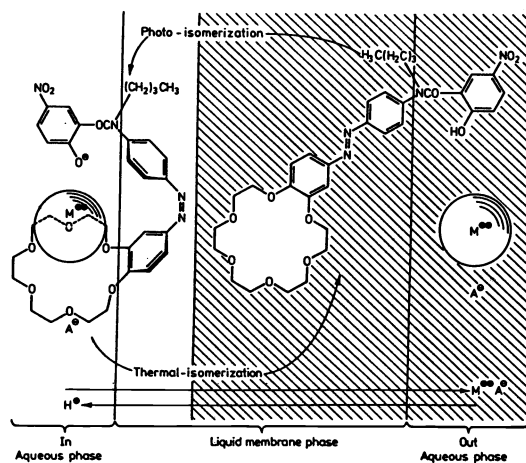

Fig. 2. Light-driven M^{2+} transport mediated by (9). M^{2+} is transported from the basic IN aqueous phase to the acidic OUT aqueous phase across a liquid membrane.
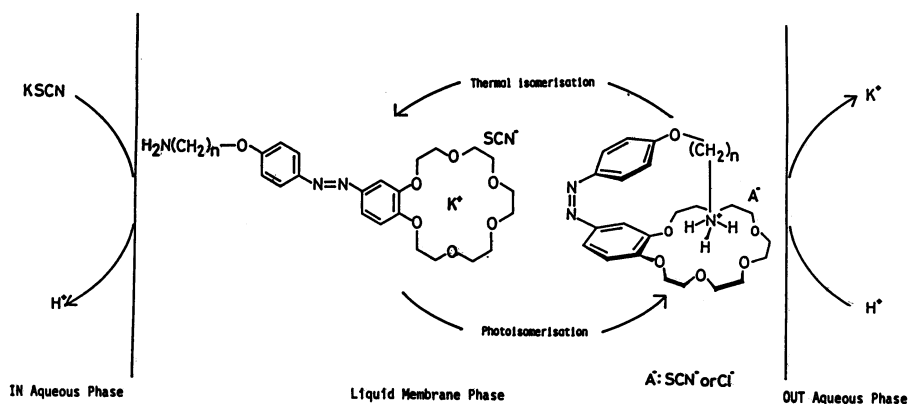

Fig. 3. Light-driven active transport of K^+ mediated by (10). K^+ is transported from the basic IN aqueous phase to the acidic OUT aqeous phase across a liquid membrane.

(8:n=2) immobilized in polymer/liquid crystal composite membranes also exhibits (E)-(Z) isomerism in response to photoirradiation (ref. 17). The liquid crystal phase in the membrane is fluid above the phase transition temperature, so that (8:n=2) acts as an ion carrier across the composite membrane. We found that the K^+ ion permeation is significantly facilitated by photoirradiation (ref. 17). This is in strong relation to an altered affinity of (Z)-(8:n=2) for K^+ ion.

REDOX-SWITCHED CROWN ETHERS

The thiol group is useful to give a redox-type switch-function to a crown ether family, because the redox reaction between dithiol and disulfide occurs reversibly under the mild reaction conditions. In 1970, Schwyzer (ref. 18) suggested a feasibility to use cyclic polypeptides having a cysteine residue as carriers for redox-driven ion transport, but the actual experimental data are not reported.

We have synthesized four different types of redox-switched crown ethers (11)-(14) (ref. 19-23). The affinity of $(11:X=none)_{ox}$ for alkali metal cations is almost equal to monobenzo-15-crown-5, indicating each crown ring in $(11:X=none)_{ox}$ acts independently (ref. 19). On the other hand, $(11:X=CH_2)_{ox}$ has an affinity for large alkali metal cations greater than $(11:X=CH_2)_{red}$ because of the co-operative action of the two crown rings to form intramolecular 1:2 cation/crown complexes. The difference is accounted for by a difference in the conformational freedom. (12) corresponds to a redox-switched podand (ref. 20). Furthermore, the interconversion between crown and cryptand is achieved in (13) (ref. 21). For Na^+ $(13)_{red}$ and $(13)_{ox}$ show a similar ion affinity, but $(13)_{ox}$ binds K^+, Rb^+, and Cs^+ more efficiently than $(13)_{red}$ because of the coordination of the cap oxygens to the complexed metal cations. The difference was rationalized by assuming such that K^+ (Rb^+ and Cs^+ also) "perches on" the crown ring whereas Na^+ "nests in" it.

$(11)_{red}$ $(11)_{ox}$

$(12)_{red}$ $(12)_{ox}$

$(13)_{red}$ $(13)_{ox}$ $(14)_{ox}$ $(14)_{red}$
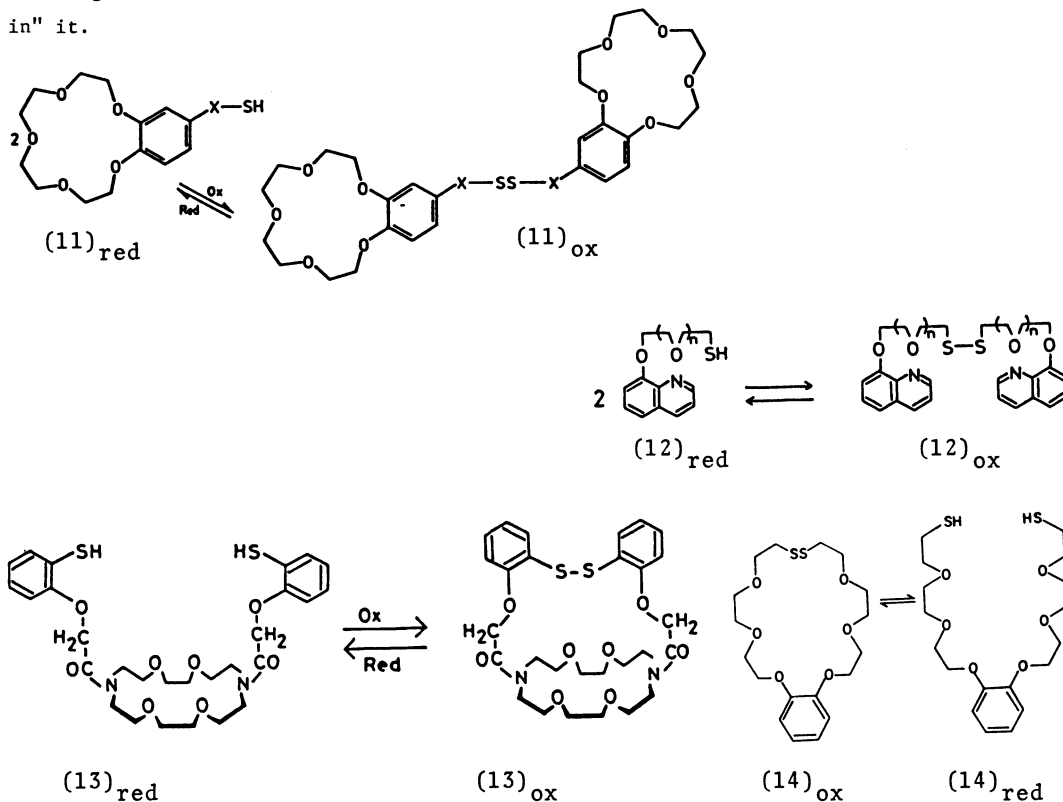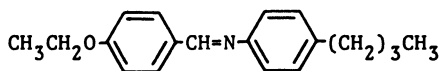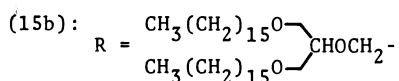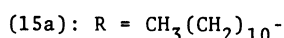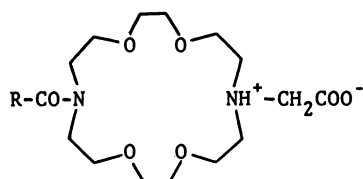
A more direct example for redox-switched crown ethers is (14) which has a dithiol group at α,ω-positions and a disulfide bond in the ring (ref. 22, 23). In (14) the direct change in the cavity shape is attained by reversible bond formation and bond scission leading to cyclic-acyclic interconversion. Raban et al. (ref. 24) also synthesized an analogue of (14). We found that the oxidation process $((14)_{red} \rightarrow (14)_{ox})$ is remarkably subject to the metal template effect: that is, the oxidation of $(14)_{red}$ in the presence of the template gives the polymeric products in 66% yield, whereas the main products in the presence of Cs^+ are $(14)_{ox}$ (70%) and cyclic dimer (28%). The results of solvent extraction and evaluation of the association constants established that (i) the association constant for $(14)_{ox}$ is smaller than monobenzo-21-crown-7 but show the selectivity for Cs^+ and (ii) importantly, $(14)_{red}$ scarcely binds alkali metal cations.

Further extension of redox-switched crown ethers is now being attempted by using quinones, azo- and nitro-groups, and ferrocenes as redox-switches (ref. 25-29). Thus, these redox-switched crown ethers are applicable to carriers in redox-driven ion transport. For example, ion transport mediated by (14) is illustrated as in Fig. 4 (ref. 23).

THERMOCONTROL OF ION PERMEATION

Biological membranes are composed of various kinds of phospholipids, cholesterols, and proteins and the fundamental functions such as permeation and selectivity are frequently associated with the gel-liquid crystal phase transition. In order to apply this phenomenon to practical systems without losing their membrane-mimetic functions, one can use liquid crystalline compounds instead of natural phospholipids.

R-CO-N   NH$^+$-CH$_2$COO$^-$

(15a): R = CH$_3$(CH$_2$)$_{10}$-

(15b):
R = CH$_3$(CH$_2$)$_{15}$O
      CH$_3$(CH$_2$)$_{15}$O⟩CHOCH$_2$-

Fig. 4. Control of the ion transport rate by a redox switch.

CH$_3$CH$_2$O-⟨⟩-CH=N-⟨⟩-(CH$_2$)$_3$CH$_3$

EBBA

Ternary composite membranes composed of polycarbonate (PC)/ liquid crystal (N-(4-ethoxy-benzylidene)-4'-butylaniline: EBBA)/ amphiphilic crown ethers (15) were prepared (ref. 30). The DSC study established that (15a) is homogeneously dispersed while (15b) forms phase-separated aggregates in the polymer/ liquid crystal composite membrane. As shown in Fig. 5, permeation of K$^+$ ion through the PC/EBBA/(15a) membrane was observed below and above T$_{KN}$ (crystal-nematic liquid crystal phase transition temperature of EBBA), and the Arrhenius plot consisted ot two straight lines intersecting each other at T$_{KN}$. In contrast, K$^+$ permeation through the PC/EBBA/(15b) membrane was completely suppressed below T$_{KN}$ and increased with increasing transport temperature above T$_{KN}$. The finding indicates that ion permeation below T$_{KN}$ is largely governed by the dispersion state of the carriers. Similarly, crown ethers covalently-linked to a fluorocarbon chain forms phase-separated aggregates in the composite membrane phase (ref. 31). Thus, ion (K$^+$ and Cs$^+$) permeation through a ternary composite membrane composed of PC/EBBA/fluorocarbon-containing crown ether was "completely" controlled by a temperature on-off switch (ref. 31). These are the novel examples for "complete" thermocontrol of ion permeation through the polymer composite membranes.
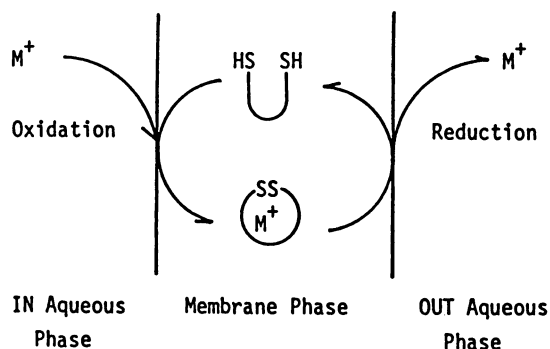

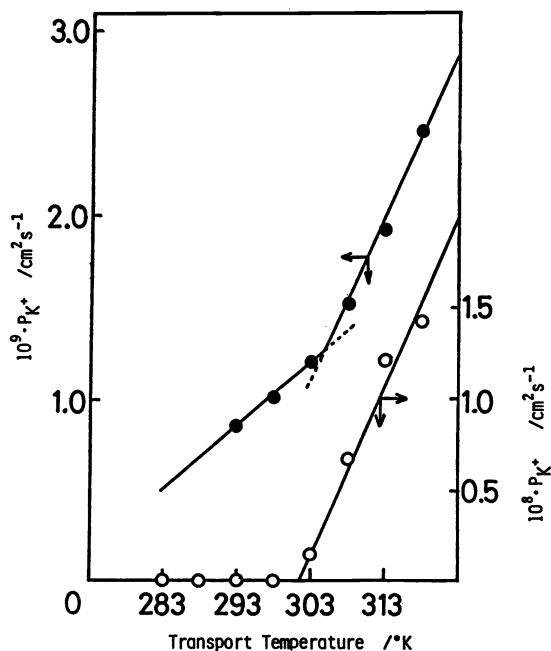**Fig. 5.** Plots of P$_{K^+}$ (permeability coefficient for K$^+$) vs. transport temperature. (●) PC/EBBA/(15a), (○) PC/EBBA/(15b). IN aqueous phase, pH 10.0, [KSCN] = 0.30 M; OUT aqueous phase, pH 7.0.

CONCLUSIONS

Since the unexpected discovery of dibenzo-24-crown-8 by Pedersen in 1967, the chemistry of crown ethers has rapidly expanded as a new field. In the initial stage of the crown ether chemistry the synthesis of crown compounds and the determination of association constants were the main subjects of the investigation, while the functional facet of crown ethers has been left as an escaped attention for a long time. "To let the crown ethers work" is the basic idea for us to develop functionalized "switched-on" crown ethers. The novel switched-on functions described in this article were attained because they combine within a molecule both a functional group (crown ether) and an antenna sensitive to the stimuli from the outside world.

In order to further elaborate the switched-on systems, the experimental efforts should be directed toward (i) the response speed, (ii) the high reversibility, and (iii) the control method with clean energy sources. As further possibilities, the new functional groups such as cyclodextrin, micelles, membranes, polypeptides, etc. may be used. We believe that further elaborations of this concept lead to eventual development of a new series of useful "switched-on" systems.

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