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Azacrown ethers modified with germanium-containing side-chains as heteroditopic hosts

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The cation capture/transport ability of diazacrowns, one with side chains containing germanium (5a), another with side chains not containing germanium (7), and 4,13-diaza-18-crown-6 (8), was found to decrease in the order 5a > 7 > 8. Titration experiment and ^{73}Ge NMR failed to give an unequivocal rationalization of the results. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: cation transport; heteroditopic host; azacrown ether; H-tube test; ^{73}Ge NMR; organogermanium compounds

INTRODUCTION

Heteroditopic hosts, which can simultaneously capture/transport cations and anions, have attracted considerable attention in the field of host–guest chemistry. Gielen and coworkers[1,2] reported an interesting heteroditopic host where a silicon atom acts as the anion-capturing site.

For the last few years we have attempted to prepare novel heteroditopic hosts, in which the germanium-containing moiety will act as an anion capture/transport site.[3–5]

We failed, however, to observe any cation capture/transport ability in these calixarenes. On the other hand, we found that a series of azacrown ethers **1**–**4** and diazacrown ethers **5** and **6** (Fig. 1), which are modified with a germanium-containing side chain, exhibited appreciable cation capture/transport ability,[6] as indicated by preliminary testing with an H-tube.[7]

The observations are summarized as follows: (1) When alkali metal chlorides were used, the cation transport capability of our azacrown ethers is comparable to those observed with azacrown ethers. Thus, **3** transports Na$^+$, and **4** transports K$^+$. (2) When alkali metal nitrates were used, **4a** transports K$^+$. (3) When the transport of K$^+$ by **4a** was measured with different counteranions, the largest amount of transport was observed when the iodide was used.

This preliminary study was, however, insufficient to estimate the role of germanium in the cation transport without a comparative study of the corresponding carbon analogs.

In this paper we describe the synthesis, structure and cation transport ability of bis(4,4-dimethylpentanoate) of *N*,*N*′-bis{2-(2-hydroxyethoxy)ethyl}-4,13-diaza- 18-crown-6 (**7**), and compare the results with those for the germanium analog **5a**, bis(3-trimethylgermylpropionate) of *N*,*N*′-bis{2-(2-hydroxyethoxy)ethyl}-4,13-diaza-18-crown-6, to assess the effect of germanium in **5a** to estimate the effect of the side chains, the parent compound, 4,13-diaza-18-crown-6 (**8**) (Fig. 2).

RESULTS AND DISCUSSION

Synthesis and characterization

The synthesis of **5a** was reported previously.[6] The synthesis of **7** was performed as shown in Scheme 1. Thus, *N*,*N*′-bis(2-hydroxyethyl)-4,13-diaza-18-crown-6 (**9**) was reacted with 4,4-dimethyl-1-pentanoic acid (**10**) in the presence of dicyclohexylcarbodiimide (DCC).

The structure of **7** was confirmed by elemental analysis, NMR spectroscopy and electrospray ionization mass spectrometry (ESI-MS).

NMR spectra of 5a and 7

In a previous communication[6] we reported ^{1}H and ^{13}C NMR spectra of **5a** and other aza- and diaza-crown ethers and their germanium derivatives. The previous assignment was, however, not complete. In this paper the full assignment of the ^{1}H and ^{13}C NMR spectra of **5a** and **7** is given.

In the ^{1}H NMR spectra of **5a** and **7**, the differentiation of Hα and H3 was based on the intensity. Differentiation of H2 and H8 was based on the splitting pattern. Thus, H2 showed a triplet and H8 gave a singlet because of

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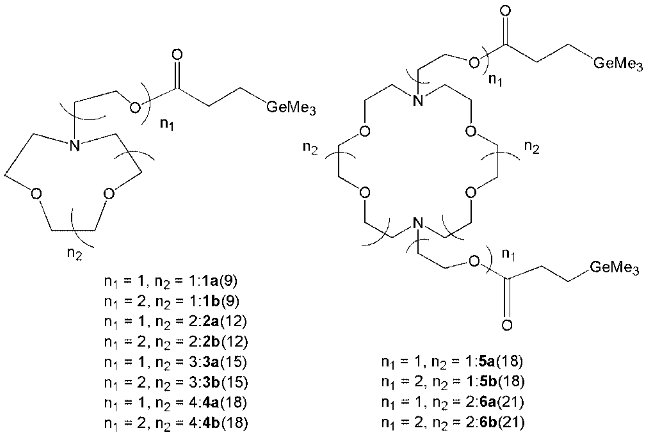


Figure 1. Azacrown ethers **1**–**4** and diazacrown ethers **5** and **6** modified with a germanium-containing side chain. Values in parentheses are the ring size.

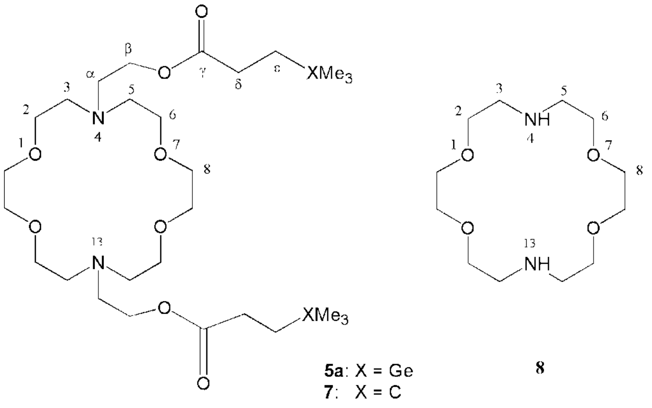
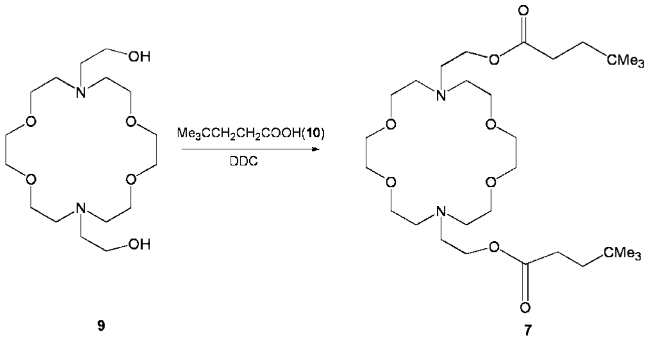


Figure 2. Numbering of azacrown ether.

symmetry. The assignment of the other protons is more or less straightforward.

With regard to the ^{13}C NMR spectra, the situation is much the same with Cα and C3. Assignment was possible based on the intensity. The differentiation of C2 and C8 is achieved with the aid of HMQC, which showed correlations between H2–C2 and H8–C8. The results are summarized in Table 1.



Scheme 1. Synthesis of **7**.

Comparison of cation transport ability

The cation transport ability of **5a** and **7** was measured using the H-tube method and the results were compared with that of **8**. The concentration of ions in the receiver phase was determined by atomic absorption spectroscopy. The results are summarized in Table 2.

From these results, it is clear that: (1) Both **5a** and **7** effectively transport Na^+ (when the counteranion is either Cl^- or NO_3^-) and K^+ (when the counteranion is NO_3^-). Thus, these are 'normal', since the other 18-membered crown ethers usually transport both Na^+ and K^+. (2) In all experiments the germylated compound **5a** transports more cations than the carbon analog **7** (**5a** > **7**). (3) The cation transport ability of **8** is inferior to both **5a** and **7** (**5a** > **7** > **8**).

Titration experiment

It has been established that the host–guest binding can be monitored by observing the change of chemical shifts of host molecules caused by addition of the guest salt in an appropriate solvent.[8,9]

Since both **5a** and **7** effectively transported Na^+, we measured their ^1H NMR spectra with Na^+ at various concentrations. Figure 3 shows the plot of the change of ^1H

Table 1. ^1H and ^{13}C chemical shifts* of **5a** and **7**[a]

Position	5a	7
2(6)	3.57 (t; J(H2–H3 = 5.5 Hz) (69.38)	3.60 (t; J(H2–H3 = 5.7 Hz) (70.03)
3(5)	2.92 (t; J(H2–H3 = 5.5 Hz) (53.86)	2.85 (t; J(H2–H3) = 5.7 Hz) (54.40)
8(18)	3.59 (s) (70.00)	3.61 (s) (70.71)
α	2.80 (t; J(Hα–Hβ = 6.0 Hz) (53.15)	2.81 (t; J(Hα–Hβ = 6.1 Hz) (53.76)
β	4.10 (t; J(Hα–Hβ = 6.0 Hz) (61.96)	4.13 (t; J(Hα–Hβ) = 6.1 Hz) (62.49)
γ	–(174.15)	–(174.36)
δ	2.33 (t; J(Hδ–Hε) = 8.5 Hz) (29.24)	2.27 (t; J(Hδ–Hε) = 8.5 Hz) (38.56)
ε	0.98 (t; J(Hδ–Hε) = 8.5 Hz) (10.84)	1.54 (t; J(Hδ–Hε) = 8.45 Hz) (30.39)
X	–(–)	–(30.03)
$(CH_3)_3$	0.13 (s) (–3.31)	0.89 (s) (29.00)

[a] Both ^1H and ^{13}C chemical shifts (in $CDCl_3$) are in δ (ppm) relative to the internal standard, tetramethylsilane (TMS). A value in parentheses is ^{13}C data and (–) indicates there is no relevant nucleus.

Table 2. Cation transport experiments[a]

	5a	7	8
LiCl	0.00	−0.96	0.00
NaCl	8.38	3.94	2.40
KCl	−0.13	0.40	−0.40
RbCl	−0.60	−1.20	−0.58
$NaNO_3$	10.82	2.59	—
KNO_3	8.70	2.47	—
$RbNO_3$	—	−3.93	—

[a] The figures show the change of concentration of cations in the receiver phase (10^{-3} mol l^{-1}).

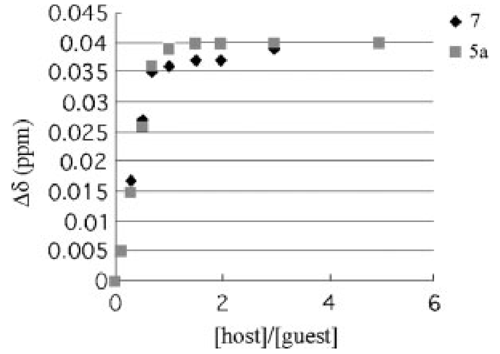


Figure 3. The plot of the change of ^1H chemical shifts of **5a** and **7** versus the amount of $NaNO_3$ added (in $CDCl_3$).

chemical shifts of H1 of **5a** and **7** in $CDCl_3$ versus the amount of $NaNO_3$ added. The plot, which showed the saturation of the chemical shift at a 1 : 1 ratio, confirmed the 1 : 1 complexation between $NaNO_3$ and the two hosts.

Since 1 : 1 complexation between **5a** (and **7**) and $NaNO_3$ was confirmed, we determined the ^1H NMR spectra of **5a** in $CDCl_3$ in the presence of $NaNO_3$ and KNO_3 in 1 : 1 ratio, which are given in Fig. 4.

Changes of ^1H chemical shifts were observed for H2, H3, H8 and Hα. This is not surprising, since these protons are more or less close to the cation trapped in the crown ring.

On the other hand, shifts observed for Hδ and Hε are very small, which would exclude the possibility that the side chain will bend over to the ring and interact with the trapped cation. The fact that the shift is larger for methyl protons bonded to germanium would then be due to the interaction with the anion.

It occurred to us that the interactions between divalent cations and **5a** would be interesting, since these may show a somewhat different mode of interaction using the side chains. With this in mind, we determined ^1H NMR spectra of **5a** in the presence of Mg^{2+} and alkaline earth metal ions in 1 : 1 molar ratio. The spectra are shown in Figure 5.

Except for Hδ and Hε, which are at the end of the side chains, all other protons show large shifts or substantial collapse of the shape. This may indicate that the interaction between **5a** and divalent cations is strong, involving not only the crown ring but also the side chains, and that the structure of the complex is rather labile compared with the NMR time scale.

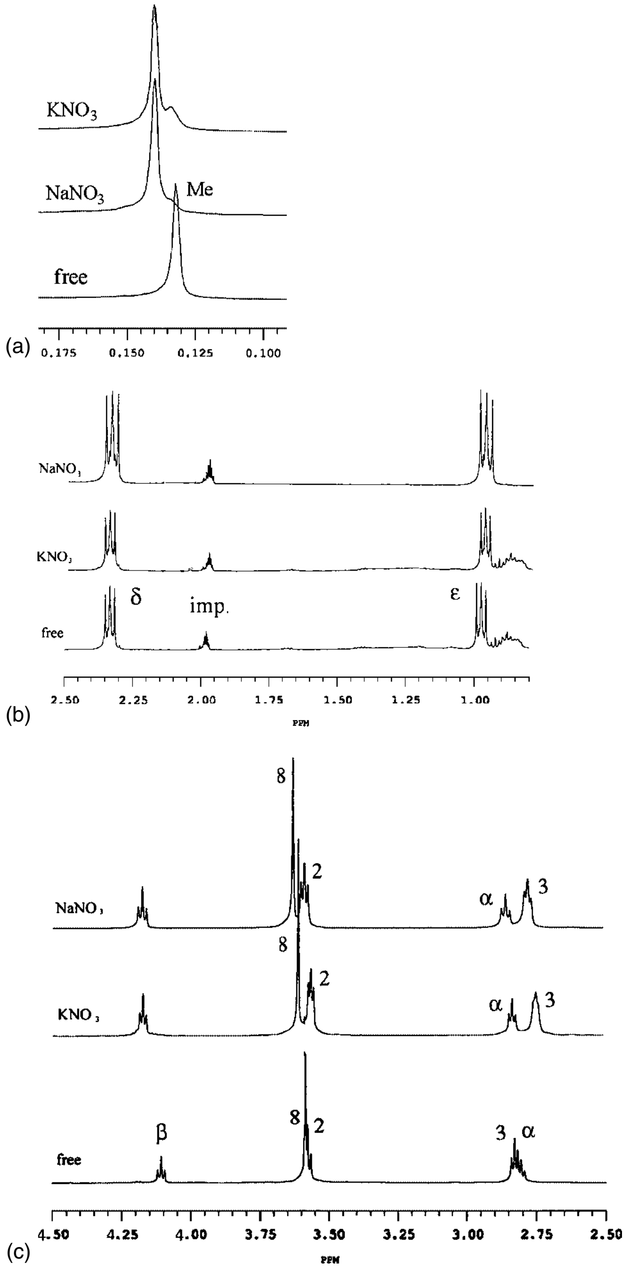


Figure 4. ^1H NMR spectra of **5a**; free, with KNO_3 and with $NaNO_3$ in 1 : 1 ratio in $CDCl_3$: (a) Me; (b) high field part; (c) low field part.

The stronger interaction of alkaline earth metal ions is in line with the general trend expected from the hard and soft acids and bases (HSAB) rule.[10,11]

Role of germanium: ^{73}Ge NMR spectra

If the germanium atom of **5a** in fact captures the counteranion, there is expected to be some effect on the chemical shifts of the side chain moiety containing germanium.

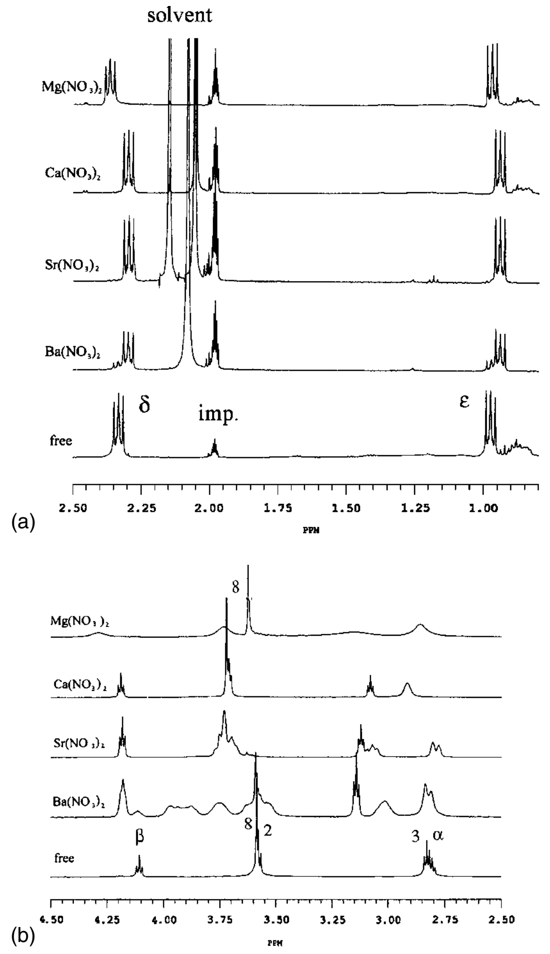


Figure 5. ^{1}H NMR spectra of **5a** with magnesium and various alkaline earth metal nitrates in 1 : 1 ratio in $CDCl_3$: (a) high field part; (b) low field part.

A direct way to monitor the germanium–anion interaction is by ^{73}Ge NMR spectra. Recently, it has been shown that hypercoordinate organogermanium compounds exhibit much broader signals (when signals are observable), and this broadening can be used as a criterion for hypercoordination. A substantial upfield shift is often accompanied with the broadening.[12–14]

With this in mind, we determined ^{73}Ge NMR spectra of **5a** and in the presence of $NaNO_3$, $Ca(NO_3)_2$ or $Ba(NO_3)_2$ and the chemical shift and line width were compared with those determined without metal nitrates. The results are summarized in Table 3.

It seems that the change of both chemical shift and line width is within the experimental error, indicating that the distance between the anion and germanium is too large, or that the interaction between germanium moiety and NO_3^- is very weak, if any.

One of the reasons why the expected upfield shift/line broadening was not observed is excessive solvation of the ion, which will inhibit the approach of the anion to germanium.

Table 3. ^{73}Ge NMR spectral data of **5a**

	δ_{Ge} (ppm)	Half width (Hz)
5a	23.8	50
5a + $NaNO_3$	24.1	60
5a + $Ca(NO_3)_2$	23.1	61
5a + $Ba(NO_3)_2$	24.0	62

CONCLUSIONS

The cation capture/transport ability of diazacrown ethers with side chains containing germanium (**5a**) and with side chains not containing germanium (**7**) was determined. A diazacrown without side chains (**8**) was also compared. The amount of cation transport decreases in the order **5a** > **7** > **8**. Several experiments were performed to rationalize the observed order. None of the experiments gave conclusive evidence for the observation.

EXPERIMENTAL

General

All manipulations were performed under an inert atmosphere of nitrogen or argon. Dry, oxygen-free solvents were employed throughout. Diethyl ether was distilled from sodium before use. Tetrahydrofuran and CH_3CN were dried by lithium aluminum hydride (LAH) and molecular sieve respectively.

^{1}H NMR spectra were determined on a JEOL ECP-500 spectrometer operating at 500 MHz, and the chemical shifts were reported in δ (ppm) with respect to TMS. ^{13}C NMR spectra were determined on the same spectrometer operating at 125 MHz and the chemical shifts were reported in δ (ppm) with respect to TMS. The ^{73}Ge NMR spectra were recorded with JEOL ECP 300 spectrometer operating at 10.48 MHz, equipped with a probe modified for this purpose. The design of the probe is essentially the same as one for observation of ^{107}Ag. Pulse width: 45°; pre-delay: 1 s; delay: 0.25 s; number of accumulation: 28 000–40 000. The chemical shifts were reported in δ (ppm) with respect to external Me_4Ge. ESI mass spectra were recorded with a PerSeptive Biosystems DE MALDI-TOF mass spectrometer, Voyager Elite XL. Atomic absorption spectra were determined with the aid of a Hitachi 12–8100 polarized Zeeman atomic absorption spectrometer. Elemental analysis was carried out by the Microanalytical Laboratory, Department of Chemistry, The Graduate School of Science, The University of Tokyo.

Synthesis and characterization of 5a and 7

The synthesis of *N*,*N*′-bis(2-hydroxyethyl)-4,13-diaza-18-crown-6 (**9**) has been described previously.[6] 4,4-Dimethyl-1-pentanoic acid (**10**) was prepared by the method reported in the literature.[15]

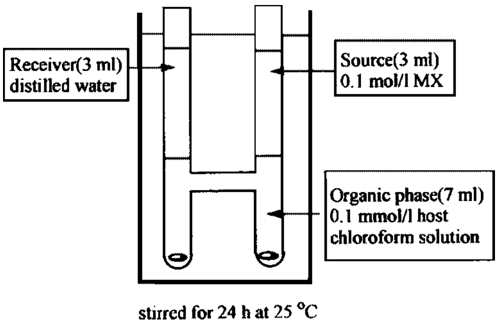


Figure 6. H-tube test of cation transport ability.

A solution of **9** (0.37 g, 1.06 mmol), **10** (0.30 g, 2.30 mmol) and **4**-dimethylaminopyridine (0.28 g, 2.30 mmol) in $CHCl_3$ (10 ml) was cooled to 0 °C and DCC (0.43 g, 2.10 mmol) was added. The resulting mixture was stirred for 24 h, filtered filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using 1 : 1 benzene–ethyl acetate as the eluate, followed by separation by octadecylsilyl (ODS) column to give a colorless oil of **7** (0.10 g, 16.4%). The oil was crystallized from Et_2O, m.p. 41.5–42.5 °C. Anal. Found: C, 62.51; H, 9.99; N, 4.64. Calc. for $C_{30}H_{58}O_8N_2$: C, 62.69; H, 10.17; N, 4.87%. ESI-MS mu (observed molecular ion peak) is 597.40926, which is only different from the calculated mu (597.40908 for $^{12}C_{30}{}^{1}H_{58}{}^{14}N_2{}^{23}Na^{16}O_6$ ($[M + Na]^+$) by 0.18 mmu.

Cation transport experiment

The apparatus used and the experimental conditions is given in Fig. 6. Thus, in the source phase an aqueous solution of an appropriate salt MX (0.1 mol l^{-1}), and in the organic phase, the $CDCl_3$ solution of the host are placed. After stirring gently for 24 h, the concentration of the cation in the receiving phase was determined by atomic absorption spectroscopy.

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