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Synthesis and characterization of novel ionophores of double-armed penta-crown ethers

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Abstract—Unique structures of novel ionophores of double-armed penta-crown ethers were successfully synthesized. Diaza 18-crown-6 was designed as the parent crown ring. The penta-crown ethers were prepared by the reaction of trimethylolpropane triacrylate (TMPTA) with diaza 18-crown-6 and further with 1-aza crown ethers through the Michael reaction. The newly synthesized penta-crown ethers were characterized by ^{1}H NMR, ^{13}C NMR, FAB mass spectrum, IR and elemental analyses, respectively.

1. Introduction

First introduced by Pedersen in 1967,[1] crown ethers have attracted significant attention from various fields of science. A wide variety of crown ethers have been synthesized and reported. During the last two decades, considerable research interest has been devoted to the design of multisite crown ethers. The construction of multisite molecular receptor molecules capable of binding two or more guest metal cations is one current area of interest in this field.[2–5]

Crown ether moieties are well-known for their ability to form strong complexes with alkali metal, alkaline metal and organic cations. Their affinity for a given cation depends on many factors, including the relative sizes of the cation and the macrocyclic cavity. If the cation closely matches the crown ether cavity, complexes usually form in a 1:1 ratio. When the cation size exceeds that of the crown cavity, the cation can only partially fit and, as a result, can be accommodated by two crowns.[6–10]

It has been reported[11–15] that the 'bis-crown effect' occurs when two crown ether rings in one molecule bind to a cation in a sandwich-type structure, it enables the molecules to bind to a cation that is larger than the ideal size for a particular crown ether unit. If the crowns are in close proximity, or the molecule is flexible enough, the crowns can act in concert to bind a cation. It has long been established that the formation of sandwich complexes is strongly favoured when the crowns are linked by a spacer. In this case, the selectivity towards large cations is increased.[8,10,16] The 'bis-crown effect' can be applied in synthetic method and medical chemistry when constructing new organic and inorganic molecular receptors.

Azacrown ethers have been acting as important building blocks in host–guest and supramolecular chemistry fields. Armed crown ethers are characterized by a parent crown ring such as 1-aza crown ethers and diaza crown ethers. We reported[17] the synthesis of unique structures of tetra-crown ethers. In this letter, we report the design, synthesis and characterization of a novel type of double-armed penta-crown ethers. The structures of the newly synthesized penta-crown ethers are outlined in Figure 1. To our knowledge, there have been no reports of compounds containing five crown ether rings. The binding ability of the penta-crown ethers with alkali metal cations was examined. Depending on the results, we found that the newly synthesized ionophores of penta-crown ethers own complex ability with various sizes of alkali metal cations such as Na$^+$, K$^+$ and Cs$^+$. The newly synthesized macrocyclic ionophores lead to original applications for the preparation of new types of host–guest

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Keywords: Diaza-crown ether; 1-Aza crown ether; Penta-crown ether; TMPTA.

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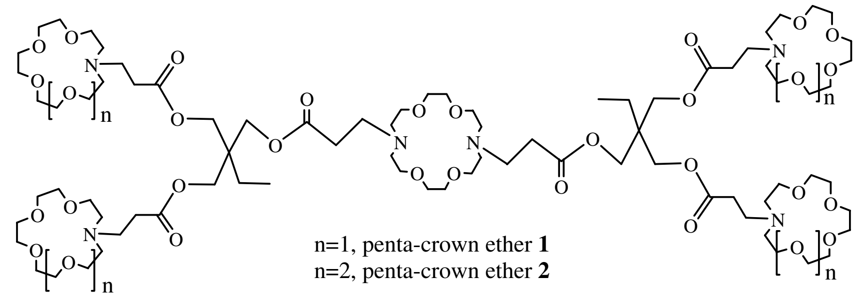


Figure 1. The new structure of penta-crown ethers.

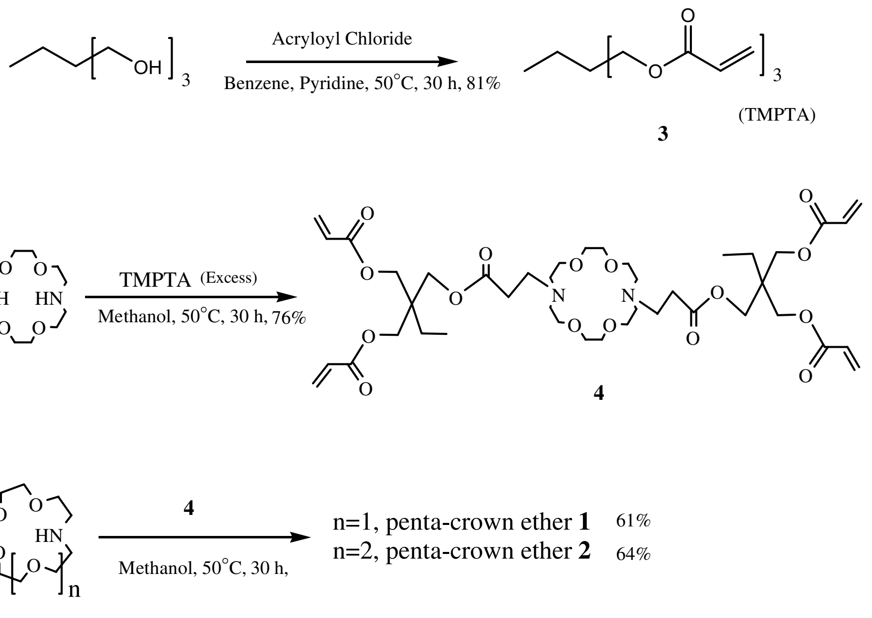
complexes. The properties can be applied in various areas, such as synthetic and medical chemistry, host–guest and supramolecular chemistry.

2. Results and discussion

The synthetic approach of new penta-crown ethers is shown in Scheme 1. Trimethylolpropane triacrylate (TMPTA) was synthesized from trimethylolpropane and acryloyl chloride in benzene. TMPTA usually plays an important role in the field. TMPTA has the advantage of having low viscosity and high solubility in general organic solvents. TMPTA contains three branch chains, and each branch chain has enough length and all are very flexible. In this letter, the diaza 18-crown-6 was designed to serve as the parent crown ether ring, and the TMPTA acted as the linker. The reactions of the secondary amine groups in the diaza crown ether ring with the active double bond of TMPTA were accomplished easily under mild conditions. Because TMPTA has three double bonds at the end of each branch chain, and diaza 18-crown-6 has two active secondary amine groups, in order to avoid polymerization and to obtain a high yield of compound **4**, we used more excess TMPTA to react with diaza 18-crown-6. Penta-crown ethers **1** and **2** were prepared from compound **4** with 1-aza 15-crown-5 and 1-aza 18-crown-6 with a yield of about 60%.

All the compounds **1**–**4** were characterized by ^{1}H and ^{13}C NMR spectra, FAB MS, IR and elemental analyses (C, H and N). In the ^{1}H NMR spectra, the proton signals of the new compounds could be observed at expected chemical shifts. For example, in the penta-crown ether **1**, the ethereal protons of the crown ether groups appeared as multiplets at δ 3.48–3.74 ppm. The aza-crown ether –CH_2–N proton chemical shift were at δ 2.73–2.77 ppm (triplets). The –OCO–CH_2–CH_2–N proton which connected the TMPTA with aza crown ether nitrogen atom appeared at δ 2.85–2.90 ppm (triplets). The double bond proton signals, which were located at the δ 5.8–6.4 ppm region, were not found indicating that the Michael addition was accomplished. The case of penta-crown ether **2** is similar to that of **1**.

The ^{13}C NMR spectra revealed the removal of the double bond carbon signals which were around δ 128 ppm



Scheme 1.

Table 1. Changes of ^{1}H NMR chemical shifts of penta-crown ethers with various metal salts

	$\Delta\delta$ of H^a	$\Delta\delta$ of H^b	$\Delta\delta$ of CH_2–N–CH_2	$\Delta\delta$ of crown H
1 + Na^+	0.099	0.030	0.076	0.102
1 + K^+	0.103	0.050	0.076	0.078
1 + Cs^+	0.073	0.063	0.051	0.071
2 + K^+	0.088	0.032	0.060	0.077
2 + Cs^+	0.080	0.033	0.065	0.062

H^a and H^b are protons of O–CO–CH^a_2–CH^b_2–N in penta-crown ether.

and δ 131 ppm region. The C=O carbon chemical shift moved from δ 165 ppm to δ 173 ppm. The crown ether carbon chemical shifts appeared around δ 69–70 ppm ranges. All the other carbon atoms' chemical shifts of the penta-crown ethers were as expected.

All the newly synthesized penta-crown ethers and intermediates were checked by mass spectrometry. The results of mass spectroscopy further supported the structures of the new penta-crown ethers. In the FAB mass spectrum of the penta-crown ether **2**, we observed a molecular ion peak at *m*/*z* 1908.6 $[M+H]^+$ (calcd for $C_{90}H_{166}N_6O_{36}$, M, 1907.1). In addition, the base peak is *m*/*z* 855.6, which corresponds to a decomposition product formed by the removal of four 1-aza 18-crown-6 ions. In the FAB MS spectrum of penta-crown ether **1**, we found the molecular ion peak at *m*/*z* 1732.5 $[M+H]^+$ (calcd for $C_{82}H_{150}N_6O_{32}$, 1731.0).

In the IR spectrum, the crown ether C–O–C group adsorption peaks were observed around the 1100–1120 cm^{-1} region. In the elemental analyses, all the values of the C, H and N of the new penta-crown ethers were within acceptable ranges.

The binding interactions of the new penta-crown ethers with the alkali metal cations were examined with ^{1}H NMR spectroscopy and absorption investigation on UV spectra.

In the ^{1}H NMR (300 MHz, acetone-d_6) analysis, sodium picrate, potassium picrate and cesium picrate were dissolved in acetone-d_6 to make a 1×10^{-2} M solution, respectively. The newly synthesized penta-crown ethers were dissolved in acetone-d_6 to make 1×10^{-3} M solutions. The gradual chemical downfield shift was observed when alkali metal picrate salt was added to the penta-crown solution. The stoichiometry of the complexation between the penta-crown and the alkali cation was confirmed to be 1:5. For example, with the addition of sodium picrate to penta-crown ether **1** solution, the chemical shift of H^a (O–CO–CH^a_2–CH^b_2–N) downfield shifted from δ 2.422 ppm (chemical shift δ was relative to acetone-d_6 2.050 ppm) to δ 2.521 ppm (triplet), $\Delta\delta = 0.099$ ppm. The chemical shift of H^b downfield shifted from δ 2.794 ppm to 2.824 ppm (triplet), $\Delta\delta = 0.030$ ppm. The chemical shift of aza-crown unit CH_2–N–CH_2– protons shifted from δ 2.681 ppm to δ 2.757 ppm, $\Delta\delta = 0.076$ ppm, the shape of the peaks became more complex. The crown ether ring proton multiple peaks became more broader, and the chemical shift changed from δ 3.497–3.614 ppm to δ 3.480–3.699 ppm, and the peak intensity decreased. These chemical shift changes were due to the interaction of crown rings with the metal cation.

The case of penta-crown **1** and **2** interacting with K^+, Cs^+ was similar to that of the above. The changes of ^{1}H NMR chemical shifts $\Delta\delta$ of H^a, H^b, aza-crown unit CH_2–N–CH_2– and the changed crown ring proton peak width are summarized in Table 1.

In the absorption investigation of the UV spectrum, the new penta-crown ethers were made into 5×10^{-4} M solutions in methanol. The sodium picrate, potassium picrate and cesium picrate were dissolved in methanol to make very low concentration solutions, respectively. The absorption maximum of the picrate anion in methanol was observed at 354 nm. Interestingly, with the addition of the penta-crown ether solution into the alkali picrate salt solutions, the absorption intensity at 354 nm increased. The increased ratio of the absorption intensity was different. In the penta-crown ether **1** case, the increased intensity ratio was $Na^+ < K^+ < Cs^+$, and $K^+ < Cs^+$ in the penta-crown **2** case. This indicates that interactions of the new penta-crown ethers with the alkali metal cations of Na^+, K^+ and Cs^+ have taken place in the methanol solution.

From the results described above, we think the newly synthesized penta-crown ethers can capture not only the metal cations of Na^+ and K^+, which is in ideal sizes for the crown rings of 15-crown-5 and 18-crown-6, respectively, but also larger size metal cations such as Cs^+. For instance, the penta-crown ethers **1** can complex Na^+, the 1-aza 15-crown-5 rings also can complex a metal cation which has a larger size than Na^+ as sandwich-type structures at both sides of the parent diaza 18-crown-6 ring to form intramolecular sandwich complexes, and produce a double-armed di-sandwich-type structure complex. The occurrence of sandwich complexes is therefore of high interest.

3. Conclusion

As described above, we have developed a new efficient approach to synthesize novel ionophores of penta-crown ethers. The synthesis and characterization of the new penta-crown ethers were described. The structures are novel, the reaction condition is gentle, and the yield is pretty high. The reactions can take place directly without protection–deprotection. The penta-crown ethers are highly promising having the ability of binding different metal cations. More detailed investigations are in progress.

4. Experimental

Elemental analyses (C, H and N) were performed using a Vario EL Elementar. The ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury 300 NMR spectrometer in $CDCl_3$. The chemical shifts were expressed in ppm (δ scale) using tetramethylsilane as an internal standard. GC–MS data were obtained from a Shimadzu GC–Mass Spectrometer GCMSD-QP5050. FAB MS data were obtained from a Jeol JMS 700 mass spectrometer. FT-IR spectra were recorded on a Mattson Instrument Genesis II spectrometer. The absorption spectrum was recorded on a Hewlett Packard UV–vis spectrophotometer UV-8453.

All the crown ethers and reagents were purchased from the Aldrich Company and used as received. The solvents were of analytical grade, purchased from DC Chemical Co. Ltd of Korea, and used without further purification.

4.1. TMPTA 3

Trimethylolpropane 13.42 g (0.1 mol) was dissolved in benzene (50 mL). Pyridine (3 mL) was added and the mixture stirred for 30 min. In an ice bath acryloyl chloride 29.90 g (0.33 mol) was dropped into the flask over 3 h, then the reaction mixture was stirred below 50 °C. After 30 h the solution was washed with aqueous K_2CO_3 (2 N, 20 mL), water (20 mL × 3), some active carbon added and dried over magnesium sulfate for 12 h. After filteration, the solvent was evaporated and filtered again through a pad of silica to give a colourless oil 24.1 g, isolated yield 81%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 0.88–0.96 (t, 3H), 1.53–1.61 (q, 2H), 4.18 (s, 6H), 5.83–5.88 (d, 3H), 6.07–6.17 (d–d, 3H), 6.38–6.44 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 165.87, 131.33, 128.27, 64.10, 40.88, 23.19, 7.41; MS(GC): *m/z* 296 $[M]^+$, calcd for $C_{15}H_{20}O_6$: M, 296.1. Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.68; H, 6.81.

4.2. Compound 4

Diaza 18-crown-6 262 mg (1 mmol) and TMPTA 1.778 g (6 mmol) were dissolved in methanol (15 mL). The mixture was stirred at 50 °C for 30 h. The solvent was evaporated and subjected to flash chromatography on silica gel ($CHCl_3$/EtAc) to afford a colourless oil 651 mg, isolated yield 76%. ^{1}H NMR(300 MHz, $CDCl_3$, ppm) δ 0.81–0.91 (t, 6H), 1.26–1.53 (q, 4H), 2.45–2.50 (t, 4H), 2.53–2.67 (t, 8H), 2.71–2.83 (t, 4H), 3.28–3.62 (m, 16H), 4.00–4.13 (m, 6H), 5.80–5.84 (d, 4H), 6.02–6.14 (d–d, 4H), 6.33–6.40 (d, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 173.22, 165.78, 131.30, 128.08, 70.93, 70.91, 70.67, 70.65, 70.60, 69.78, 64.10, 54.39, 51.56, 40.80, 32.52, 23.67, 7.52; MS(FAB): *m/z* 855.2 $[M+H]^+$, calcd for $C_{42}H_{66}N_2O_{16}$: M, 854.4. Anal. Calcd for $C_{42}H_{66}N_2O_{16}$: C, 59.00; H, 7.78; N, 3.28. Found: C, 59.29; H, 7.72; N, 3.19.

4.3. Penta-crown ether 1

Compound **4** 86 mg (0.1 mmol) and 1-aza 15-crown-5 110 mg (0.5 mmol) was dissolved in methanol (5 mL). The mixture stirred at 50 °C for 30 h. The solvent was evaporated and was subjected to flash chromatography on silica gel (EtAc) affording a yellow oil 106 mg, isolated yield 61%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 0.82–0.87 (t, 6H), 1.24–1.27 (q, 4H), 2.46–2.51 (t, 12H), 2.73–2.77 (t, 24H), 2.85–2.90 (t, 12H), 3.48–3.74 (m, 92H), ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 173.18, 70.90, 70.87, 70.75, 70.69, 70.66, 70.62, 70.31, 70.11, 69.86, 65.98, 54.47, 51.95, 51.62, 42.81, 32.40, 23.10, 7.48; IR (NaCl, cm^{-1}): 2921.6, 2895.3, 1730.8, 1575.4, 1454.9, 1355.7, 1252.5, 1191.6, 1114.5, 1061.6, 985.3, 939.1, 851.4; MS(FAB): *m/z* 1732.5 $[M+H]^+$, calcd for $C_{82}H_{150}N_6O_{32}$: M, 1731.0. Anal. Calcd for $C_{82}H_{150}N_6O_{32}$: C, 56.86; H, 8.73; N, 4.85. Found: C, 57.09; H, 8.72; N, 4.77.

4.4. Penta-crown ether 2

Compound **4** 86 mg (0.1 mmol) and 1-aza 18-crown-6 132 mg (0.5 mmol) were dissolved in methanol (5 mL). Operating similarly to that of **1** afforded a yellow oil 122 mg, isolated yield 64%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 0.82–0.87 (t, 6H), 1.25–1.27 (q, 4H), 2.46–2.51 (t, 12H), 2.74–2.78 (t, 24H), 2.85–2.90 (t, 12H), 3.44–3.77 (m, 108H), ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 173.23, 70.95, 70.92, 70.88, 70.76, 70.71, 70.67, 70.61, 70.30, 70.09, 69.84, 65.76, 54.29, 51.96, 51.65, 42.72, 32.37, 23.14, 7.49; IR (NaCl, cm^{-1}): 2905.7, 2879.3, 1727.1, 1577.5, 1456.9, 1352.8, 1249.7, 1190.2, 1110.8, 1060.2, 982.3, 948.7, 835.0; MS(FAB): *m/z* 1908.6 $[M+H]^+$, calcd for $C_{90}H_{166}N_6O_{36}$, M, 1907.1. Anal. Calcd for $C_{90}H_{166}N_6O_{36}$: C, 56.65; H, 8.77; N, 4.40. Found: C, 56.28; H, 8.71; N, 4.29.

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