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The synthesis of unique structures of tetra-crown ethers through Michael addition

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Abstract—Unique structures of tetra-crown ethers were successfully synthesized by the reaction of tetramethylolmethane tetraacrylate (TMMT) reacted with crown ethers containing primary amine functional group such as 2-aminomethyl crown ethers and 4-aminobenzo crown ethers; containing secondary amine group like 1-aza crown ethers through Michael reaction. The newly synthesized tetra-crown ethers were characterized by ^{1}H NMR, ^{13}C NMR, FAB mass spectrum, elemental analyses, IR, respectively.

1. Introduction

Crown ethers have drawn a great deal of attention from various field of sciences since their synthesis and chemistry were first reported.[1] In recent years, special interest has been directed toward the synthesis of multi-site crown ethers and some tetra-crown ethers have been successfully synthesized.[2–8] For most of the tetra-crown ether compounds synthesized so far, it is noted that their well-ordered structures were constructed by self-assembly. Those crown ethers were bridged by tetrapyrrol derivatives of phthalocyanine or porphyrin.

Crown ethers have proven to be excellent extraction reagents for capturing alkali and alkaline earth cations and they are commonly used in phase-transfer reactions. Moncrown ethers have preferred sizes of metal ions, depending on the ring size of the macrocycle. It had been reported[9–12] that the 'bis-crown effect' occurs when two crown ether rings in one molecule bind a cation in a sandwich-type structure, and it enables the molecules to bind a cation that is larger than the ideal size for particular crown ether unit. The construction of multi-site molecular receptor molecules capable of binding more guest metal cations is one current area of interest in this field. In order to obtain novel structure of ionophores, which can be widely used as metal extraction reagents, phase-transfer catalyst, etc. We attempt to the synthesis of new tetra-crown ethers, which were expected to have superior properties and proper application in various areas.

Michael addition is a quite simple and useful method in the organic synthesis, and were used[13,14] successfully by reacting acrylate with active amines. Therefore, we want to use this idea to synthesize the new structures.

It would be a useful attempt to link the crown ethers with multi-acrylate and get the fascinating structures of tetra-crown ethers. The amino-crown ethers and 1-aza crown ethers contain the primary and the secondary amine group, respectively. In this letter, we describe the synthetic method to novel structures of tetra-crown ethers using tetramethylolmethane tetraacrylate (TMMT) as a linker. The structures of the newly synthesized tetra-crown ethers are outlined in Figure 1. As described,[9–12] we think the newly synthesized tetra-crown ethers can bind metal cations, which are larger than the ideal size for the particular crown rings to form a di-sandwich-type structures.

2. Results and discussion

The syntheses of six new tetra-crown ethers are shown in Scheme 1. TMMT has four active double bonds at the end of each branch chain. The primary and the secondary amine functional groups of 2-aminomethyl crown ethers, 4-aminobenzo crown ethers, and 1-aza crown ethers reacted with TMMT in methanol solution at

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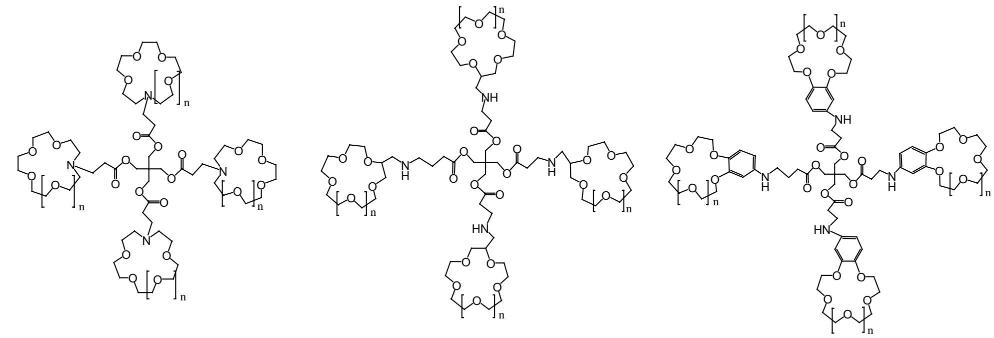
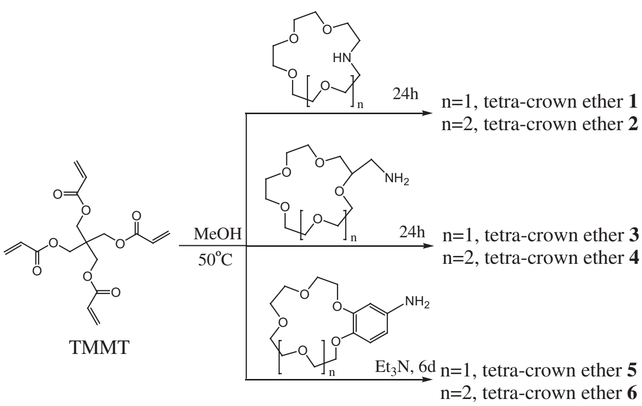


n=1, tetra crown ether **1**
n=2, tetra crown ether **2**

n=1, tetra crown ether **3**
n=2, tetra crown ether **4**

n=1, tetra crown ether **5**
n=2, tetra crown ether **6**

Figure 1. The new structures of tetra-crown ethers.



Scheme 1.

50 °C. Since the primary amine group has two hydrogen atoms, the reagent mole ratio of the primary amine group to the double bond should be higher than 1.5:1 to get a high yield of the target product. New tetra-crown ethers **1** and **2** were prepared through Michael addition from the TMMT with 1-aza-15-crown-5 and 1-aza-18-crown-6. Tetra-crown ethers **3** and **4** were obtained by the TMMT with 2-aminomethyl-15-crown-5 and 2-aminomethy-18-crown-6. Tetra-crown ethers **5** and **6** were prepared from the TMMT with 4-aminobenzo-15-crown-5 and 4-aminobenzo-18-crown-6.

All the reactions took place under a mild condition, the functional groups reacted directly, and the yields were all higher than 65%. In our initial work, we found that the reaction of the 4-aminobenzo crown ethers that reacted with the acrylate double bonds could not be performed easily under the same condition. The reactions proceeded while some triethylamine was added as catalyst and continued for six days to give the corresponding pure product of tetra-crown ethers **5** and **6** with good yields of about 65%. We think that the electron-rich benzene ring contained in the 4-aminobenzo crown ethers reduces the activity of the amine group.

In the ^{1}H NMR spectra, the proton signals of the new tetra-crown ethers were observed at the expected chemical shift. For example, in the tetra-crown ether **1**, the ethereal protons of the crown ether group appeared as multiplets at δ 3.48–3.75 ppm. The 1-aza-crown ether ring –CH_2–N–CH_2 protons were observed as triplets at δ 2.73–2.77 ppm. The newly formed –CH_2–N proton which connects the TMMT with aza crown ether nitrogen atom, were at δ 2.86–2.90 ppm (triplets). At the δ 5.8–6.5 ppm range, the double bond proton signals were not found, which indicates that the Michael addition is completed. The ^{1}H NMR spectra of the other tetra-crown ethers were similar to **1**.

The chemical shift signals of benzene ring protons of the tetra-crown ether **5** and **6** were at δ 6.13–6.27 ppm and δ 6.72–6.79 ppm, respectively. The N–H proton signals of tetra-crown **3**–**6** were not found as, respectively, peaks in ^{1}H NMR spectra, we think they were mixed in the strong intensity peaks of ethereal protons.

In the ^{13}C NMR spectra, we observed the removal of the double bond carbon signals, which had been located around δ 128 and 131 ppm. The chemical shift of C=O carbon moved from δ 165 to 173 ppm. The chemical shifts of crown ether carbon were seen around δ 70 ppm. The chemical shifts of all other carbon atoms of the tetra-crown ethers were as expected.

All the new tetra-crown ethers were checked by mass spectrometry. The mass spectroscopy data further supported the structures of the new tetra-crown ethers. In the FAB mass spectrum of the tetra-crown ether **5**, we observed a molecular ion peak at *m/z* 1485.3 $[M+H]^+$ (calcd for $C_{73}H_{104}N_4O_{28}$: M, 1484.7). In addition, the base peak was *m/z* 1202.4, which corresponds to a fragmentary product formed by removing one 4-aminobenzo-15-crown-5 ion. An intense peak at *m/z* 635.6 was the fragment of three 4-aminobenzo-15-crown-5 ions be broken away. An intense peak at *m/z* 864.6 was the fragment of removing two 4-aminobenzo-15-crown-5 ions away. Other ion peaks are indicated in Figure 2. The mass spectra of other tetra-crown ethers, molecular ion peaks were evident and all correct as we had expected. Tetra-crown ether **1**, found MS(FAB): *m/z* 1229.5 $[M+H]^+$ (calcd for $C_{57}H_{104}N_4O_{24}$: M, 1228.7). Tetra-crown ether **2**, found: *m/z* 1407.0 $[M+H]^+$ (calcd for $C_{65}H_{120}N_4O_{28}$, M, 1405.7). Tetra-crown ether **3**, found: *m/z* 1349.2 $[M+H]^+$ (calcd for

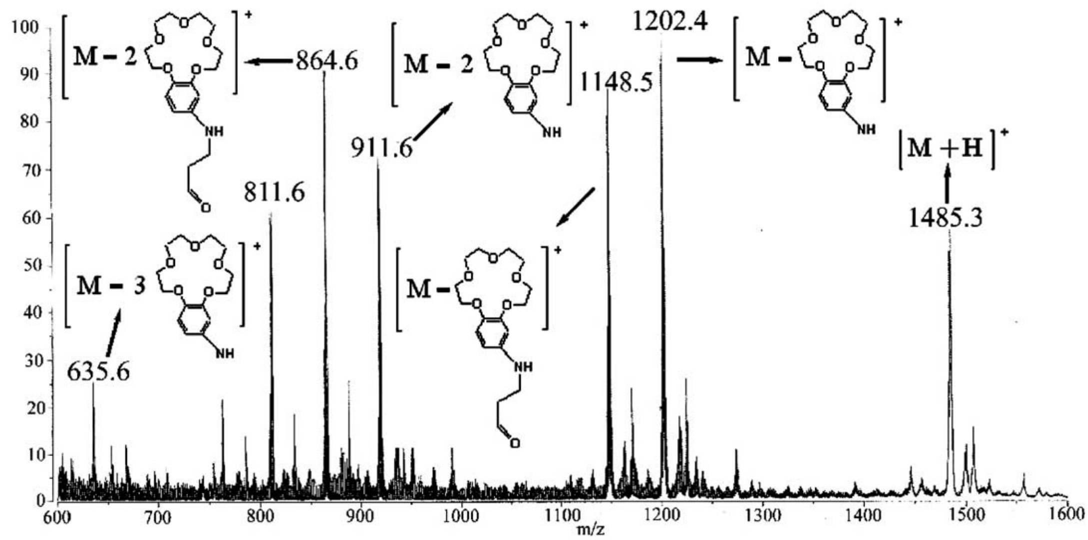


Figure 2. FAB mass spectrum of tetra-crown ether **5**.

$C_{61}H_{112}N_4O_{28}$, M, 1348.7). Tetra-crown ether **4**, found: *m/z* 1526.3 $[M+H]^+$ (calcd for $C_{69}H_{128}N_4O_{32}$, M, 1525.8). Tetra-crown ether **6**, found: *m/z* 1661.3 $[M+H]^+$ (calcd for $C_{81}H_{120}N_4O_{32}$: M, 1660.8).

In IR spectrum, the crown ether C–O–C group absorption peaks were observed around 1100–1130 cm^{-1} region with strong intensity. In the elemental analyses, we found all the C, H, N values of the six new tetra-crown ethers were within acceptable ranges.

3. Conclusion

We have developed a new efficient approach to synthesize tetra-crown ethers. The details of synthesis and characterization of six new tetra-crown ethers were described. The structures are novel, the reaction condition is gentle, and the yield is high. The reactions can take place directly without protection–deprotection. We plan to take further investigation employing a newly synthesized crown ether as an ionophore hence.

4. Experimental

Elemental analyses (C, H, N) were performed using a Vario EL Elementar. The ^1H and ^{13}C NMR spectra were obtained on a Varian Mercury 300 NMR spectrometer in $CDCl_3$, and the chemical shifts were expressed in ppm (δ scale) using tetramethylsilane as an internal standard. FAB MS data were obtained from a Jeol JMS 700 Mass Spectrometer. FT-IR spectra were recorded on a Mattson Instrument Genesis II spectrometer.

All the crown ethers and reagents were purchased from Aldrich Company and used as received. The TMMT contains some triester, we found that the purity of TMMT is around 91% based on the ^1H NMR and ^{13}C NMR analysis. The solvents were analytical grade, purchased from DC Chemical Co. Ltd. of Korea, and they were used without further purification.

4.1. Tetra-crown ether 1

TMMT 35 mg (0.1 mmol) and 1-aza-15-crown-5 110 mg (0.5 mmol) were dissolved in MeOH (5 mL), the reaction was stirred at 50 °C, after 24 h, the solvent was evaporated in vacuo and purified via column chromatography on silica gel (EtAc), the by product which came from the impurity of triester and the excess 1-aza-15-crown-5 were isolated, and affording 101 mg tetra-crown ether **1** as a yellow oil. Yield 82.1%. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 2.45–2.50 (t, 8H, $–OCO–CH_2–$), 2.73–2.77 (t, 16H, $–CH_2–N–CH_2$), 2.85–2.90 (t, 8H, $–OCO–CH_2–CH_2–N$), 3.50–3.75 (m, 72H, $–CH_2–O–$); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 173.12, 70.95, 70.63, 70.38, 70.14, 69.97, 64.26, 54.42, 51.98, 51.56, 32.54; IR (NaCl, cm^{-1}): 2877.3, 1943.9, 1730.8, 1649.8, 1579.4, 1455.0, 1397.2, 1355.7, 1297.9, 1251.6, 1199.5, 1118.5, 939.2, 852.4, 828.3; MS(FAB) [Found: *m/z* 1229.5 $[M+H]^+$, calcd for $C_{57}H_{104}N_4O_{24}$: M, 1228.7]; Anal. Calcd for $C_{57}H_{104}N_4O_{24}$: C, 55.68; H, 8.47; N, 4.56. Found: C, 54.83; H, 8.49; N 4.61.

4.2. Tetra-crown ether 2

TMMT 35 mg (0.1 mmol) and 1-aza-18-crown-6 132 mg (0.5 mmol) were dissolved in MeOH (5 mL), operated the same as above, to afford 116 mg tetra-crown ether **2** as a yellow oil. Yield 82.5%. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 2.46–2.51 (t, 8H, $–OCO–CH_2$), 2.74–2.78 (t, 16H, $–CH_2–N–CH_2$), 2.85–2.90 (t, 8H, $–OCO–CH_2–CH_2–N$), 3.59–3.74 (m, 88H, $–CH_2–O–$); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 173.18, 70.86, 70.76, 70.58, 70.39, 70.16, 69.85, 64.45, 53.87, 51.56, 51.06, 32.48; IR (NaCl, cm^{-1}): 2869.6, 1966.1, 1735.6, 1642.1, 1586.2, 1440.6, 1352.8, 1296.9, 1250.6, 1199.5, 1118.5, 990.3, 948.8, 837.9; MS(FAB) [Found: *m/z* 1407.0 $[M+H]^+$, calcd for $C_{65}H_{120}N_4O_{28}$. M, 1405.7]; Anal.

Calcd for $C_{65}H_{120}N_4O_{28}$: C, 55.56; H, 8.60; N, 3.99. Found: C, 55.77; H, 8.63; N, 4.04.

4.3. Tetra-crown ether 3

TMMT 35 mg (0.1 mmol) and 2-aminomethyl-15-crown-5 150 mg (0.6 mmol) were dissolved in MeOH (5 mL), operated the same as above, affording 89 mg tetra-crown ether **3** as a light yellow oil. Yield 66.0%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 2.49–2.54 (t, 8H, –OCO–CH_2), 2.69–2.71 (d, 8H, crown-CH_2–N–), 2.87–2.92 (t, 8H, –OCO–CH_2–CH_2–N), 3.43–3.89 (m, 84H, –CH_2–O–); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 173.09, 78.74, 72.68, 71.05, 70.95, 70.77, 70.68, 70.58, 70.52, 70.45, 70.42, 70.28, 69.97, 64.20, 51.50, 50.20, 45.13, 34.57; IR (NaCl, cm^{-1}): 2913.9, 2874.4, 1966.1, 1732.7, 1644.0, 1586.2, 1456.0, 1391.4, 1354.8, 1295.0, 1250.6, 1196.6, 1116.6, 985.5, 943.0, 872.6, 842.7. MS(FAB) [Found: *m/z* 1349.2 $[M+H]^+$, calcd for $C_{61}H_{112}N_4O_{28}$, M, 1348.7]; Anal. Calcd for $C_{61}H_{112}N_4O_{28}$: C, 54.29; H, 8.36; N, 4.15. Found: C, 53.58. H, 8.47. N, 4.25.

4.4. Tetra-crown ether 4

TMMT 35 mg (0.1 mmol) and 2-aminomethyl-18-crown-6 176 mg (0.6 mmol) were dissolved in MeOH (5 mL), the same as above, obtained 103 mg tetra-crown ether **4** as a slight yellow oil. Yield 67.5%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 2.49–2.54 (t, 8H, –OCO–CH_2), 2.69–2.71 (d, 8H, crown-CH_2–N–), 2.86–2.91 (t, 8H, –OCO–CH_2–CH_2–N), 3.44–3.93 (m, 100H, –CH_2–O–); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 173.06, 78.32, 72.82, 70.85, 70.82, 70.80, 70.74, 70.70, 70.58, 70.50, 70.39, 70.11, 69.78, 69.63, 64.08, 51.56, 50.79, 45.12, 34.57; IR (NaCl, cm^{-1}): 2874.4, 1967.0, 1733.7, 1651.7, 1583.3, 1455.0, 1352.8, 1293.0, 1250.6, 1195.6, 1111.8, 989.3, 953.6, 839.8; MS(FAB) [Found: *m/z* 1526.3 $[M+H]^+$, calcd for $C_{69}H_{128}N_4O_{32}$, M, 1525.8]; Anal. Calcd for $C_{69}H_{128}N_4O_{32}$: C, 54.32; H, 8.46; N, 3.67. Found: C, 53.93; H, 8.66; N, 3.98.

4.5. Tetra-crown ether 5

TMMT 35 mg (0.1 mmol) and 4-aminobenzo-15-crown-5 170 mg (0.6 mmol) were dissolved in MeOH (8 mL), the reaction was proceeded by adding some triethylamine as catalyst and continued reaction for six days at 50 °C, after the reactions accomplished, operated as above to get 101 mg tetra-crown ether **5** as a red brown oil. Yield 68.0%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 2.59–2.63 (t, 8H, –OCO–CH_2–), 3.36–3.41 (t, 8H, –OCO–CH_2–CH_2–N), 3.58–3.75 (m, 40H), 3.86–3.91 (m, 16H), 4.05–4.11 (m, 16H). 6.13–6.27 (dd, 8H, ArH), 6.72–6.79 (d, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 172.88, 150.43, 143.22, 141.30, 117.31, 104.85, 101.20, 70.83, 70.75, 70.71, 70.68, 70.56, 70.53, 70.45, 70.38, 70.06, 69.87, 69.52, 69.50, 67.91, 51.73, 40.11, 33.65; IR (NaCl, cm^{-1}): 3362.3, 3038.3, 2918.8, 2871.5, 1966.1, 1729.8, 1614.1, 1514.8, 1456.00, 1408.8, 1357.6, 1228.4, 1186.0, 1132.0, 1058.7, 984.5, 938.2; MS(FAB) [Found: *m/z* 1485.3 $[M+H]^+$, calcd for $C_{73}H_{104}N_4O_{28}$: M, 1484.7]; Anal. Calcd for $C_{73}H_{104}N_4O_{28}$: C, 59.02; H, 7.06; N, 3.77. Found: C, 58.76; H, 7.24; N, 3.96.

4.6. Tetra-crown ether 6

TMMT 35 mg (0.1 mmol) and 4-aminobenzo-18-crown-6 196 mg (0.6 mmol) were dissolved in MeOH (8 mL), operated the same as above, affording 108 mg tetra-crown ether **6** as a deep purple oil. Yield 65.0%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 2.58–2.62 (t, 8H, –OCO–CH_2), 3.37–3.42 (t, 8H, –OCO–CH_2–CH_2–N), 3.61–3.75 (m, 56H). 3.83–3.92 (m, 16H). 4.01–4.12 (m, 16H). 6.13–6.27, dd, Ar, 8H. 6.73–6.79, d, ArH, 4H. ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ: 172.88, 150.36, 143.23, 141.49, 117.43, 104.66, 100.89, 70.82, 70.78, 70.75, 70.72, 70.69, 70.62, 70.54, 70.30, 69.93, 69.67, 67.90, 51.72, 40.11, 33.64; IR (NaCl, cm^{-1}): 3364.2, 3036.4, 2911.0, 2877.3, 1967.0, 1728.9, 1616.1, 1516.7, 1455.0, 1408.8, 1355.7, 1277.6, 1230.4, 1187.0, 1121.4, 1060.7, 988.3, 949.8. MS(FAB) [Found: *m/z* 1661.3 $[M+H]^+$, calcd for $C_{81}H_{120}N_4O_{32}$: M, 1660.8]; Anal. Calcd for $C_{81}H_{120}N_4O_{32}$: C, 58.54; H, 7.28; N, 3.37. Found: C, 57.92; H, 7.42; N, 3.69.

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