Synthesis of Novel Tris-Crown Ether Structures

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Abstract: Six unique tris-crown ether structures were successfully synthesized from trimethylolpropane triacrylate (TMPTA) with amino- and aza-crown ethers through Michael addition. The crown ethers contained a primary amine group such as 2-aminomethyl crown ethers and 4-aminobenzo crown ethers, others contained a secondary amine group, like 1-aza crown ethers.

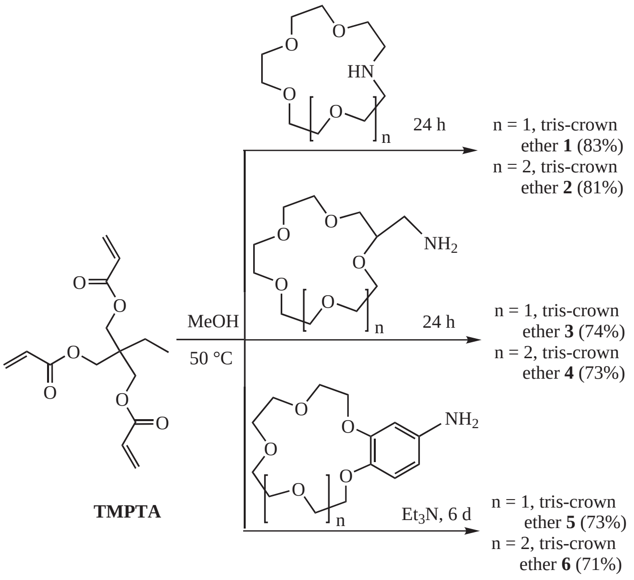
Key words: amino-crown ether, aza-crown ether, tris-crown ether, TMPTA, Michael addition

The chemistry of crown ethers and crown-like compounds has attracted a great deal of attention from various fields of science since the first crown ether was discovered by Pedersen in 1967.[1] Numerous studies on crown ethers have been reported. In recent years, special interest has been focused on the synthesis of multisite crown ether compounds. Although a large number of bis-crown ethers have been reported[2–28] along with their synthesis and their metal ion selectivity properties, only a few tris-crown ethers have been synthesized.[29–33]

Crown ethers are very effective complexing agents for alkali and alkaline earth cations, and they are commonly used in phase transfer reactions. If the size of the cation closely matches that of the crown ether cavity, complexes generally 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, a sandwich-type structure can be formed. It has been reported[25–28] 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 a particular crown ether unit. 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.[28,34–37] In this letter, we report the synthesis of novel tris-crown ether structures, which are expected to have superior properties and applications in various areas which are different to bis-crown ether compounds. The tris-crown ethers can capture not only the metal cations, which are ideal sizes for the crown rings, but also two different metal cations of different sizes at the same time.

Trimethylolpropane triacrylate (TMPTA) usually plays an important role in the polymer field. It was reported[38,39] that TMPTA can easily react with amines through Michael addition. We have succeeded[40] in using this idea to synthesize tetra-crown ethers. TMPTA has the advantage of low viscosity and high solubility in general organic solvents. In this letter, the tri-acrylate of TMPTA served as the linker in the tris-crown ethers. We think that the newly synthesized tris-crown ethers contain superior properties and applications, they can be widely applied in the host–guest, supramolecular, synthetic and medicinal chemistry fields in the future.

The synthetic approach to the six new novel structures of tris-crown ethers is shown in Scheme 1.



Scheme 1 The approaches to the new tris-crown ethers

The structures of the six new tris-crown ethers, which were synthesized through a Michael addition are outlined in Figure 1. TMPTA was synthesized from trimethylolpropane and acryloyl chloride in benzene.[41] TMPTA has three 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 TMPTA in methanol at 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 greater than 1.5:1 to give a high yield of target product. New tris-crown ethers **1** and **2** were prepared from TMPTA with 1-aza-15-crown-5 and 1-aza-18-crown-6.[42] Tris-crown ethers **3** and **4** were obtained from TMPTA with 2-aminomethyl-15-crown-5 and 2-aminomethyl-18-crown-6.[43] Tris-crown ethers **5** and **6** resulted from the

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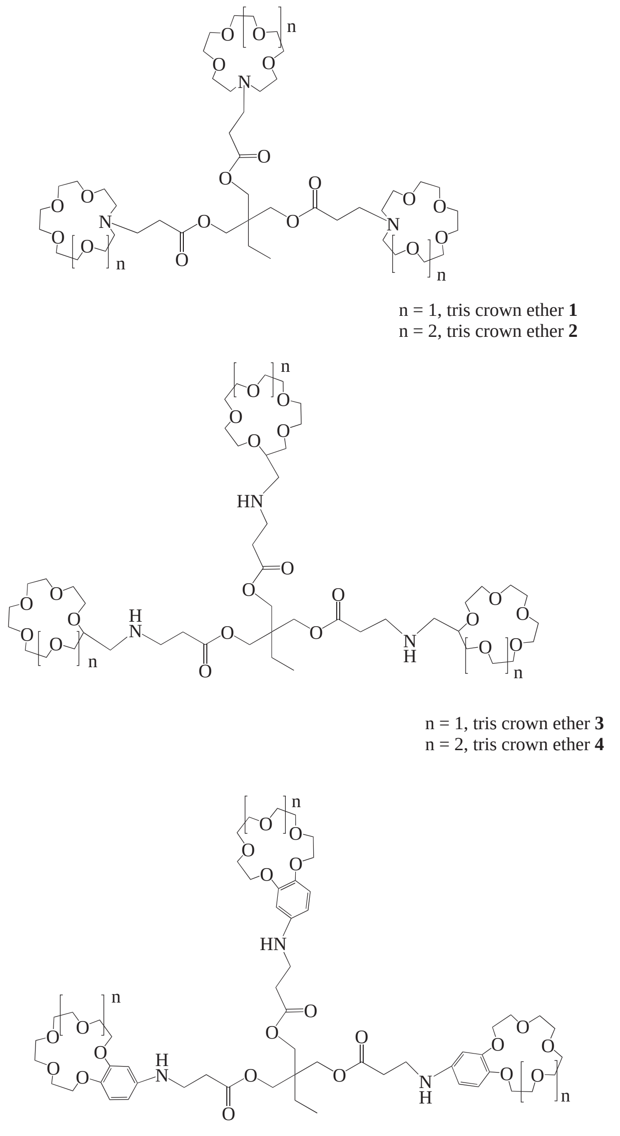
reaction of TMPTA with 4-aminobenzo-15-crown-5 and 4-amino-benzo-18-crown-6.[44] All the reactions took place under mild conditions. The functional groups reacted directly, and in only one step and the yields were all higher than 70%. In our initial work, we found that the 4-aminobenzo crown ethers reacted with the acrylate double bonds, and thus it could not be performed easily under the same conditions used above. The reactions proceeded as soon as triethylamine was added, as catalyst, and the reaction was continued for six days to give the corresponding pure tris-crown ethers **5** and **6** with excellent yields of about 70%. We think that the electron-rich benzene ring contained in the 4-aminobenzo crown ethers reduced the activity of the amine group.

In the ^{1}H NMR spectra, resonances of the new tris-crown ethers were observed at the expected shifts. For example, in the tris-crown ether **1**, the ethereal protons of the crown ether groups appeared as multiplets at 3.48–3.75 ppm. The 1-aza-crown ether CH_2NCH_2 proton chemical shift occurred at 2.75 ppm (triplets). The signals corresponding to the six protons in $OCOCH_2CH_2N$ which connected the TMPTA core with the aza-crown ether nitrogen atom appeared at 2.88 ppm (triplets). In the 5.8–6.5 ppm range, the double bond proton signals were not found, indicating that the Michael addition had occurred. All new tris-crown ethers were similar to **1**. The chemical shift signals of the benzene ring protons of tris-crown ether **5** and **6** appeared at 6.13–6.27 ppm and 6.77–6.79 ppm. The NH proton signals of tris-crown ethers **3**–**6** were not found, presumably due to rapid exchange with the solvent protons.



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

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

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

Figure 1 The structures of new tris-crown ethers

The ^{13}C NMR spectra revealed that the removal of the double bond carbon signals which were located around 128 ppm and 131 ppm. The C=O carbon chemical shift moved from 165 ppm to 173 ppm. The crown ether carbon chemical shifts were seen around 69–70 ppm. All the other chemical shifts of the tris-crown ethers occurred as expected.

All the newly synthesized tris-crown ethers were analyzed by mass spectrometry. The IR spectra revealed the crown ether COC group absorption peaks at 1100–1130 cm^{-1} as expected.

We have developed a new efficient approach to synthesize tris-crown ethers. The synthesis and characterization of six new tris-crown ethers was described. The structures are novel, the reaction conditions are gentle, and the yield is high. The reactions can take place directly without protection-deprotection. The tris-crown ethers show promise to potentially carry different metal cations. We plan to further investigate their ability as phase-transfer catalysts and ionophores.

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(41) **TMPTA**: 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 added dropwise to the flask over 3 h, then the reaction was stirred below 50 °C. After 30 h the solution was washed with aqueous K_2CO_3 (2 N, 20 mL), water (3 × 20 mL), active carbon was added, and the mixture was dried over magnesium sulfate for 12 h. After filtration, the solvent was evaporated and filtered again through a pad of silica to give a colorless oil (24.1 g, isolated yield 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.5 Hz, 3 H), 1.53–1.61 (q, 2 H), 4.18 (s, 6 H), 5.83–5.88 (d, *J* = 10.5 Hz, 3 H), 6.07–6.17 (dd, *J* = 10.8 Hz, 6.6 Hz, 3 H), 6.38–6.44 (d, *J* = 17.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.87, 131.33, 128.27, 64.10, 40.88, 23.19, 7.41; MS(GC): *m*/*z* = 296 $[M]^+$. Anal. calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.68; H, 6.81.

(42) **Tris-crown ether 1**: TMPTA (30 mg, 0.1 mmol) and 1-aza-15-crown-5 (88 mg, 0.4 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 (EtOAc), affording tris-crown ether **1** as a yellow oil (79 mg, isolated yield 82.8%). IR (NaCl): 2921.6, 2878.3, 1957.4, 1730.8, 1581.4, 1458.9, 1393.3, 1355.7, 1297.9, 1252.5, 1196.6, 1119.5, 1062.6, 989.3, 940.1, 852.4, 829.2, 778.1 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.5 Hz, 3 H), 1.22–1.27 (q, 2 H), 2.49 (t, *J* = 7.2 Hz, 6 H), 2.75 (t, *J* = 6.0 Hz, 12 H), 2.88 (t, *J* = 7.5 Hz, 6 H), 3.48–3.75 (m, 54 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.16, 70.96, 70.38, 70.16, 69.92, 66.58, 54.47, 51.98, 42.75, 32.49, 23.09, 7.50; MS (EI): *m*/*z* = 954.5 $[M]^+$; MS (FAB): *m*/*z* = 955.4 $[M + H]^+$; Anal. calcd for $C_{45}H_{83}N_3O_{18}$: C, 56.65; H, 8.77; N, 4.40. Found: C, 56.38; H, 8.81; N 4.32.

Tris-crown ether 2: TMPTA (30 mg 0.1 mmol) and 1-aza-18-crown-6 (105 mg 0.4 mmol) were dissolved in MeOH (5 mL), the reaction was carried out as above, to afford a yellow oil (88 mg, isolated yield 81.0%). IR (NaCl): 2877.3, 2500.3, 1968.9, 1730.8, 1644.0, 1577.5, 1459.9, 1352.8, 1289.2, 1249.7, 1110.8, 988.3, 951.7, 835.0, 777.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.5 Hz, 3 H), 1.22–1.27 (q, 2 H), 2.48 (t, *J* = 7.2 Hz, 6 H), 2.77 (t, *J* = 6.0 Hz, 12 H), 2.88 (t, *J* = 7.2 Hz, 6 H), 3.46–3.70 (m, 66 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.19, 70.83, 70.72, 70.70, 70.49, 70.45, 70.36, 70.25, 70.17, 70.03, 69.80, 65.55, 53.85, 51.56, 42.80, 32.43, 22.89, 7.53; MS(FAB): *m*/*z* = 1087.4 $[M + H]^+$. Anal. calcd for $C_{51}H_{95}N_3O_{21}$: C, 56.39; H, 8.81; N, 3.87. Found: C, 56.12; H, 8.90; N, 3.78.

(43) **Tris-crown ether 3**: TMPTA (30 mg, 0.1 mmol) and 2-aminomethyl-15-crown-5 (125 mg, 0.5 mmol) were dissolved in MeOH (5 mL), the reaction was carried out as above, to afford tris-crown ether **3** as a slight yellow oil (77 mg, isolated yield 73.8%). IR (NaCl): 2926.5, 2880.2, 1731.8, 1644.0, 1596.8, 1460.8, 1382.1, 1354.8, 1250.6, 1194.7, 1117.6, 1061.6, 989.3, 947.8, 871.7, 844.7, 778.1 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.8 Hz, 3 H), 1.22–1.27 (q, 2 H), 2.51 (t, *J* = 6.6 Hz, 6 H), 2.70 (d, *J* = 6.0 Hz, 6 H), 2.88 (t, *J* = 6.6 Hz, 6 H), 3.58–3.78 (m, 66 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.05, 70.90, 70.64, 70.53, 70.45, 66.49, 51.57, 50.21, 42.75, 32.56, 23.04, 7.48; MS (FAB): *m*/*z* = 1044.5 $[M + H]^+$. Anal. calcd for $C_{48}H_{89}N_3O_{21}$: C, 55.21; H, 8.59; N, 4.02. Found: C, 54.94; H, 8.62; N, 3.95.

Tris-crown ether 4: TMPTA (30 mg, 0.1 mmol) and 2-aminomethyl-18-crown-6 (147 mg, 0.5 mmol) were dissolved in MeOH (5 mL), operated the same as above, afforded tris-crown ether **4** as a slight yellow oil (86 mg, isolated yield 73.1%). IR (NaCl): 2922.6, 2881.1, 1730.8, 1665.2, 1592.0, 1461.8, 1384.6, 1352.8, 1285.3, 1249.7, 1187.9, 1107.9, 1060.7, 989.3, 882.3, 835.0, 777.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.8 Hz, 3 H), 1.22–1.27 (q, 2 H), 2.52 (t, *J* = 6.9 Hz, 6 H), 2.70 (d, *J* = 6.0 Hz, 6 H), 2.89 (t, *J* = 6.6 Hz, 6 H), 3.53–3.82 (m, 78 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.09, 70.95, 70.71, 70.52, 70.45, 70.31, 70.01, 69.55, 69.52, 65.76, 51.68, 50.15, 42.84, 32.57, 22.78, 7.44; MS (FAB): *m*/*z* = 1177.6 $[M + H]^+$. Anal. calcd for $C_{54}H_{101}N_3O_{24}$: C, 55.13; H, 8.65; N, 3.57. Found: C, 54.89; H, 8.57; N, 3.53.

(44) **Tris-crown ether 5**: TMPTA (30 mg, 0.1 mmol) and 4-aminobenzo-15-crown-5 (142 mg, 0.5 mmol) were dissolved in MeOH (6 mL), triethylamine(catalyst) was added and the reaction was continued for six days at 50 °C. The reaction afforded tris-crown ether **5** as a red brown oil (84 mg, isolated yield 73.3%). IR (NaCl): 3364.2, 3037.4, 2924.5, 2871.5, 1965.1, 1726.0, 1615.1, 1513.9, 1455.0, 1408.8, 1357.6, 1226.5, 1184.1, 1123.3, 1057.8, 984.5, 939.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.84$ (t, $J = 7.5$ Hz, 3 H), 1.22–1.27 (q, 2 H), 2.61 (t, $J = 6.3$ Hz, 6 H), 3.39 (t, $J = 6.6$ Hz, 6 H), 3.67–3.75 (m, 30 H), 3.86–3.91 (m, 12 H), 4.05–4.11 (m, 12 H), 6.13–6.27 (dd, ArH, 6 H), 6.77–6.79 (d, ArH, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.91$, 150.43, 143.19, 141.61, 117.48, 104.80, 101.03, 70.89, 70.80, 70.73, 70.43, 70.39, 69.92, 69.58, 69.55, 67.92, 51.76, 40.17, 33.68, 23.78, 7.44; MS (FAB): $m/z = 1146.4$ $[M + H]^+$. Anal. calcd for $C_{57}H_{83}N_3O_{21}$: C, 59.72; H, 7.30; N, 3.67. Found: C, 59.84; H, 7.41; N, 3.62.

Tris-crown ether 6: TMPTA (30 mg, 0.1 mmol) and 4-aminobenzo-18-crown-6 (163 mg, 0.5 mmol) were dissolved in MeOH (6 mL), affording tris-crown ether **6** as a deep brown oil (91 mg, isolated yield 71.2%). IR (NaCl): 3367.1, 3037.4, 2917.8, 2880.2, 1967.0, 1729.8, 1617.0, 1516.7, 1455.0, 1408.8, 1354.8, 1280.5, 1230.4, 1186.0, 1117.6, 989.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 7.5$ Hz, 3 H), 1.22–1.27 (q, 2 H), 2.60 (t, $J = 6.3$ Hz, 6 H), 3.37 (t, $J = 6.3$ Hz, 6 H), 3.62–3.76 (m, 42 H), 3.84–3.93 (m, 12 H), 4.02–4.12 (m, 12 H), 6.13–6.27 (dd, ArH, 6 H), 6.76–6.79 (d, ArH, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 172.88, 150.43, 143.22, 141.30, 117.51, 104.85, 101.20, 70.82, 70.78, 70.75, 70.71, 70.65, 70.56, 70.48, 69.93, 69.67, 69.63, 68.81, 67.91, 51.73, 40.11, 33.65, 22.57, 7.53; MS (FAB): $m/z = 1278.6$ $[M + H]^+$. Anal. calcd for $C_{63}H_{95}N_3O_{24}$: C, 59.19; H, 7.49; N, 3.29. Found: C, 59.37; H, 7.43; N, 3.22.