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Multiring Macrocycles Bearing Diaza-18-crown-6 Units: Preparation and Characterization by Electrospray Mass Spectrometry

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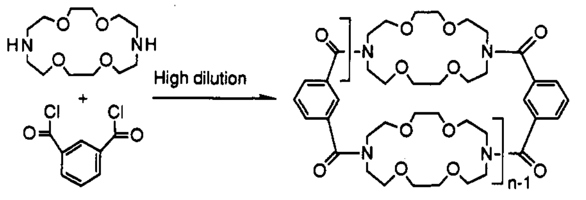
Two new macropolycycles with large cavities, **2** and **3**, were isolated in addition to known cryptand amide **1** following the high-dilution reaction of isophthaloyl dichloride and 1,10-diaza-18-crown-6 in toluene. Electrospray ionization mass spectrometry (ESI-MS) was applied for analysis and characterization of the reaction mixture of **1**, **2**, **3**, and higher derivatives and the corresponding pure products as monocharged 1:1 complexes with sodium ion. Macrotricyclic amide **2** was reduced with borane to give cryptand **6**. Structures of all mentioned compounds were supported by ^{1}H NMR, and **6** was also confirmed by X-ray crystallography.

Macrocycles containing several identical crown ether blocks connected by bridging groups represent an important class of host molecules with large cavities.[1] In particular, macropolycycles with two diaza-crown ethers, "cylindrical cryptands", are promising optical sensors easily adaptable for specific guests.[2] Macropolycyclic amides containing two or three crown ether rings feature both cavity size and water solubility similar to that of cyclodextrins and may serve as enzyme mimics.[3] Macropolycyclic ligands may be obtained by different synthetic strategies,[4] although many are both multistep and low-yielding. The most attractive approach to these compounds involves direct one-pot macrocyclization, which require normally either template ion or high-dilution conditions.

Application of high-dilution synthesis[5] to the reaction of a diaza-crown ether and an acid dichloride should lead predominantly to the 1:1 cyclocondensation product as well as higher oligomers. The major problem in characterization of these macropolycycles is their essentially identical characteristics including elemental analysis and NMR and IR spectra. The only reliable spectral method to identify them is mass spectrometry, but there is a problem detecting higher representatives as they often do not show a molecular ion.[6]

The recently developed technique of electrospray ionization mass spectrometry (ESI-MS) has been already successfully applied to accurate determination of the molecular weight of large biomolecules,[7] enzymes,[8] noncovalent receptor–ligand complexes,[9] and some natural products.[10] A recent report on multiring interlocked metal complexes[11] also demonstrated the advantages of electrospray ionization over FAB.

In this paper, we report a suitable preparation and ESI characterization of macropolycycles derived from high-dilution reaction of 1,10-diaza-18-crown-6 and isophthaloyl dichloride (eq 1). ESI-MS analysis provided an excellent insight into the composition of the product mixture. The ESI-MS of the reaction mixture is presented in Figure 1. For the macropolycycles **1**–**5** ionization is achieved by complexation with added Na$^+$. If each crown ring in the cryptand amides accommodates one metal ion, all compounds would display the identical m/z value ($m/z = 415$). However, when there was a limiting amount of sodium ions, only monocharged 1:1 complexes were observed in the ESI-MS. Earlier, only cryptand amide **1** had been isolated and documented in a similar reaction.[12]



(1)

n=1, **1**
n=2, **2**
n=3, **3**
n=4, **4**
n=5, **5**

Separation of **1** was achieved by crystallization of the reaction mixture from acetone. Column chromatography of the residue afforded **2** and **3**. ESI-MS spectra of isolated

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(1) For up-to-date reviews, see: (a) Cram, D. J. *Science* **1992**, *356*, 29–36. (b) Seel, C.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1992**, *32*, 528–549.

(2) (a) Fages, F.; Desvergne, J.-P.; Bouas-Laurent, H.; Lehn, J.-M.; Konopelski, J. P.; Marsau, P.; Barrans, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 655–658. (b) Bouas-Laurent, H.; Desvergne, J.-P.; Fages, F.; Marsau, P. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J.; Durr, H., Eds.; VCH: Weinheim, Germany, 1991; pp 265–286.

(3) Vögtle, F.; Puff, H.; Friedrichs, E.; Müller, W. M. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 431.

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(6) See, for example: (a) Constantin, E.; Kotzyba-Hibert, F.; Lehn, J.-M.; Saigo, N.; Selva, A.; Traldi, P. *Org. Mass Spectrom.* **1983**, *18*, 84–85. (b) Akabori, S.; Kumagai, T.; Habata, Y.; Sato, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1497–1505.

(7) Fenn, J. B.; Mann, M.; Meng, C. K.; Wong, S. F.; Whitehouse, C. M. *Science* **1989**, *246*, 64–71.

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(9) Ganem, B.; Li, Y.-T.; Henion, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 6294–6296.

(10) Wilson, S. R.; Perez, J.; Wu, Y. *Nat. Prod. Lett.* **1992**, *1*, 103–108.

(11) Bitsch, F.; Dietrich-Buchecker, C. O.; Khemiss, A.-K.; Sauvage, J.-P.; Van Dorsselaer, A. *J. Am. Chem. Soc.* **1991**, *113*, 4023–4025.

(12) Buhleier, E.; Wehner, W.; Vögtle, F. *Chem. Ber.* **1979**, *112*, 546–558.

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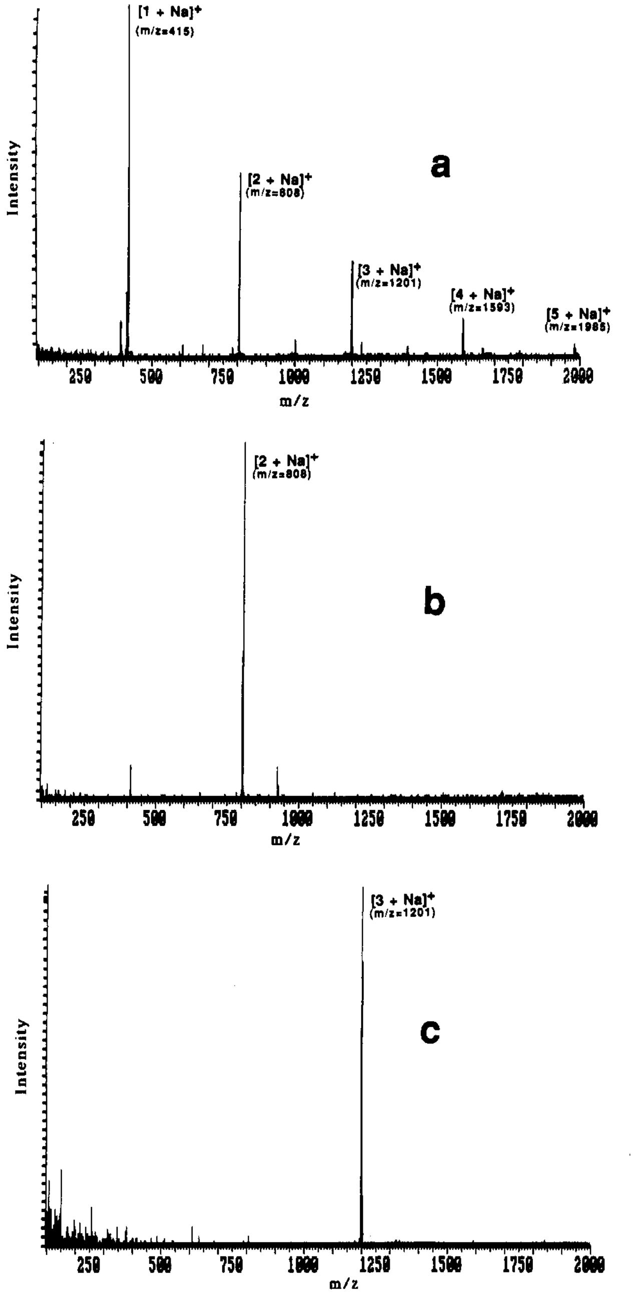
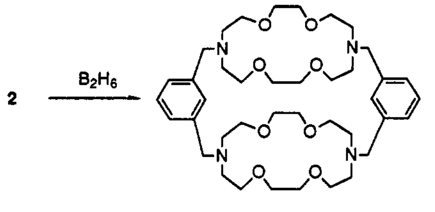


Figure 1. ESI-MS spectra: (a) a reaction mixture of macrocyclic amides formed; (b) isolated **2**; (c) isolated **3**.

2 and **3** are shown in Figure 1b,c. Reduction of **2** with borane resulted in **6** (eq 2), whose X-ray structure is



(2)

6

presented in Figure 2 (supplementary material) clearly confirming the assignments by ESI-MS.[13]

The compound **6** has recently been reported as a minor product in a cyclocondensation of α,α'-dibromo-*m*-xylene and 1,10-diaza-18-crown-6.[14]

In summary, an expedient preparation and an effective analysis of a series of macropolycyclic amides **1–3** and cylindrical cryptand **6** has been efficiently performed. The new ESI-MS technique has been shown to be invaluable for macrocycle characterization. A further study of the intriguing binding properties of **1–6** is currently in progress.

Experimental Section

Electrospray mass spectra (ESI-MS) were obtained on a Vestec Model 200 ES instrument with a mass range of 2000. The samples in methanol (500 μg in 1 mL of solvent in the presence of 10^{-3} M NaOAc) were electrosprayed at 3 μL min^{-1} with needle voltage 2.0–2.4 kV, ES chamber temperature 45–60 °C, nozzle voltage 200 V, block temperature 245–250 °C, lens temperature 120 °C, repeller voltage 20 V.

Cryptand Diamides. Solutions of isophthaloyl dichloride (2.03 g, 10 mmol) in 100 mL of toluene and of 1,10-diaza-18-crown-6 (2.62 g, 10 mmol) and Et_3N (2.03 g, 25 mmol) in a mixture of toluene (60 mL) and THF (40 mL) were simultaneously added to 500 mL of vigorously stirred toluene under nitrogen over 5 h. The reaction mixture was then stirred for 1 h and filtered followed by evaporation of the solvents. ESI-MS spectrum of the mixture is presented in Figure 1.

Crystallization of the residue from acetone afforded 1.37 g (35%) of pure **1**. The mother liquor was concentrated and chromatographed on alumina with benzene–ethanol (25:1) as eluent to afford 0.785 g (20%) of **2** and 0.43 g (11%) of **3**. Crude **2**, which is appropriate for further reduction, can be also obtained by subsequent crystallization of the evaporated mother liquor from acetone–$CHCl_3$.

Cryptand amide 1: mp 223–224 °C (lit.[12] mp 224–225 °C); ^{1}H NMR ($CDCl_3$) δ 3.02 (m, 8 H), 3.49–3.67 (m, 16 H), 7.46 (t, J = 7.8 Hz, 1 H), 7.71 (d, J = 7.8 Hz, 2 H), 8.30 (s, 1 H); ESI-MS, *m/z* 415 (M + Na$^+$).

Cryptand amide 2: mp 230–231 °C; ^{1}H NMR ($CDCl_3$) δ 3.49–3.72 (m, 48 H), 7.22–7.48 (m, 8 H); ESI-MS, *m/z* 808 (M + Na$^+$). Anal. Calcd for $C_{20}H_{28}N_2O_6$: C, 61.21; H, 7.19; N, 7.14. Found: C, 61.25; H, 7.04; N, 6.99.

Cryptand amide 3: mp 93–95 °C; ^{1}H NMR ($CDCl_3$) δ 3.51–3.74 (m, 72 H), 7.24–7.50 (m, 12 H); ESI-MS, *m/z* 1201 (M + Na$^+$). Anal. Calcd for $C_{30}H_{42}N_3O_9$: C, 61.21; H, 7.19; N, 7.14. Found: C, 61.06; H, 7.07; N, 7.01.

Cryptand 6. Diamide **2** (0.785 g, 1 mmol) was dissolved in THF (50 mL), and 10 mL of 1.0 M borane solution in THF (10 mmol) was added. The mixture was refluxed for 4 h followed by addition of about 2 mL of H_2O to quench excessive boranes. Then the solvent was evaporated and the residue was refluxed for 3 h with 6 N HCl (20 mL). After removal the solvent in vacuo, a residual solid was treated with 5 mL of 5% aqueous LiOH and the solution was extracted with toluene (5 × 5 mL). The combined extracts were dried with 3-Å molecular sieves and evaporated to give a crude product, which was chromatographed on alumina with $CHCl_3$ as eluent to yield 0.517 g (71%) of **6** as a white solid: mp 113–114 °C; ^{1}H NMR ($CDCl_3$) δ 2.82 (t, J = 5.6 Hz, 16 H), 3.62–3.70 (m, 40 H), 7.15–7.20 (m, 6 H), 7.5 (s, 2 H); ESI-MS, *m/z* 752 (M + Na$^+$).

Supplementary Material Available: ^{1}H NMR and ESI-MS spectra for compounds 1–3 and 6 and a Pluto drawing of the X-ray structure of 6 (Figure 2) (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(13) The crystal structure was determined by Dr. John C. Dewan, New York University. The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(14) Krakowiak, K. E.; Bradshaw, J. S.; Dalley, N. K.; Zhu, C.; Yi, G. *J. Org. Chem.* 1992, *57*, 3166–3173. The authors reported the inaccurate ^{1}H NMR spectrum of 6 as well as erroneously cited two articles in regard to the mp of 6, where an isomer of 6 had been documented instead. Our X-ray analysis unequivocally confirms the structure of 6.