Journal of Inclusion Phenomena **6** (1988), 41–47.

Synthesis and Complexing Abilities of Novel Benzocryptands

EDDY CHAPOTEAU, BRONISLAW P. CZECH*, ANAND KUMAR,
and ALEJANDRO POSE
Technicon Instruments Corporation, Tarrytown, NY 10591, U.S.A.

(Received: 17 March 1987)

Abstract. Two novel benzocryptands based on hydroquinone and 2-methoxyhydroquinone and a cylindrical tricyclic cryptand based on the former have been synthesized. Complexing abilities of the benzocryptands for Na^+, K^+ and Rb^+ and of the tricyclic cryptand for diammonium cations are determined and compared with those reported for structurally-related compounds.

Key words: Cryptands, benzocryptands, alkali metal cation complexation, diammonium cation complexation.

1. Introduction

A variety of cryptands with aromatic subunits have been synthesized and their cation binding studied [1]. Tricyclic cryptands with cylindrical topology have also attracted considerable interest as potential diatopic receptors for substrates with two ammonium groups [2]. Some literature data indicate that π-electrons may participate in complexation of para-phenylene crown compounds with alkali metal and ammonium cations [3–5]. Such conclusions were drawn on the basis of differences observed between the ^{1}H-NMR spectra of free ligands and their complexes. In this paper, we report the synthesis of two new benzocryptands **1** and **2** which incorporate para-substituted benzene subunits and a novel cylindrical cryptand **3** as well as cation complexation results for these multidentate ligands.

2. Experimental

2.1. PREPARATION OF DIACID CHLORIDE **5**

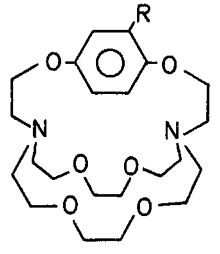
Commercially-available diacid **4** (10 mmol) was suspended in 15 mL of $CHCl_3$ and thionyl chloride (3 mL) was added dropwise. The mixture was refluxed until no solid remained (12–20 h). The solution was filtered and the solvent was removed in vacuo to give the crude diacid chloride **5** which was used without further purification. Yield 84%, pale yellow solid. ^{1}H-NMR ($CDCl_3$): $\delta = 4.90$ (s, 4H), 6.90 (s, 4H). IR (deposit): $= 1790$ cm^{-1} (C=O).

2.2. PREPARATION OF DIESTER **6**

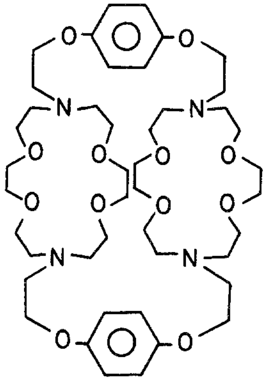
To a mixture of methyl bromoacetate (17.1 g, 112.0 mmol) and anhydrous potassium

---

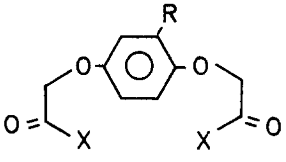
[*] Author for correspondence.



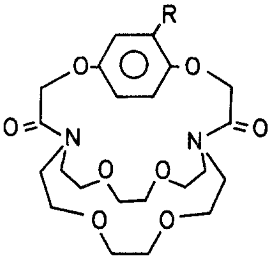
	R
1	H
2	OCH_3



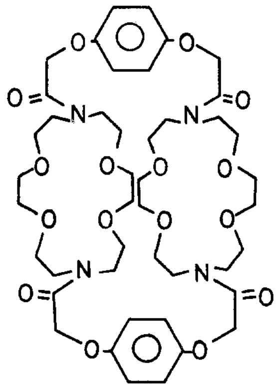
3



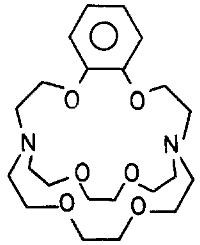
	R	X
4	H	OH
5	H	Cl
6	OCH_3	OCH_3
7	OCH_3	OH
8	OCH_3	Cl



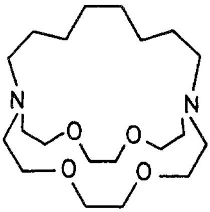
	R
9	H
10	OCH_3



11



12



13

carbonate (17.0 g) in acetone (250 mL) was added a solution of 2-methoxyhydroquinone (5.6 g, 40.0 mmol) in 50 mL of acetone. The mixture was refluxed with stirring for 20 h under nitrogen. The inorganic material was filtered and the solvent and unreacted methyl bromoacetate were removed *in vacuo*. The residue was purified by column chromatography on silica gel with dichloromethane–methanol (3 : 1) as eluent to give a crude product which was recrystallized from methanol to afford 4.7 g (41%) of **6** as a white solid with mp 69–70.5 °C. ^{1}H-NMR($CDCl_3$): $\delta = 3.80$ (s, 6H), 3.85 (s, 3H), 4.60 (s, 2H), 4.63 (s, 2H), 6.2–7.0 (m, 3H). IR (mull): 1720 cm^{-1} (C═O). Anal Calcd: C, 54.93; H, 5.67. Found: C, 55.17; H, 5.63.

2.3. PREPARATION OF DIACID 7

Diester **6** (4.00 g, 14.1 mmol) was suspended in 250 mL of water and 0.5 g of Amberlyst-IR-120(H^+) was added. The mixture was refluxed overnight, filtered, and the filtrate was concentrated to a small volume. The white precipitate was filtered and dried to give 3.50 g (97%) of **7**. Mp 181–182.5 °C. ^{1}H-NMR(DMSO-d_6): $\delta = 3.80$ (s, 3H), 4.60 (s, 2H), 4.63 (s, 2H), 6.3–7.0 (m, 3H). IR (mull): 3200–2400 cm^{-1} (COOH), 1720 (C═O). Anal Calcd (half hydrate): C, 49.81; H, 4.94. Found: C, 49.76; H, 4.69.

2.4. PREPARATION OF DIACID CHLORIDE 8

With the method given above for the synthesis of **5**, diacid **7** was converted into **8**. Yield 100%, pale yellow oil. ^{1}H-NMR($CDCl_3$): $\delta = 3.81$ (s, 3H), 4.92 (s, 4H), 6.15–7.05 (m, 3H). IR (neat): 1795 cm^{-1} (C═O).

2.5. PREPARATION OF CRYPTAND DIAMIDES 9 AND 11

Solution A was prepared by dissolving diacid chloride **5** (2.26 g, 8.60 mmol) in 120 mL of toluene. Triethylamine (3 mL) and 1,10-diaza-18-crown-6 (2.25 g, 8.60 mmol) were dissolved in 115 mL of toluene to make solution B. Solutions A and B were added simultaneously over 7 h to 280 mL of vigourly stirred toluene at 0 °C. The reaction mixture was stirred overnight at room temperature, filtered and evaporated *in vacuo*. Cryptand amides **9** and **11** were separated from the residue by flash chromatography on silica gel with dichloromethane-methanol (20 : 1) as eluent. Cryptand diamide **9**: Yield 17%, white solid, mp 243–244 °C. ^{1}H-NMR($CDCl_3$): $\delta = 2.45$–4.40 (m, 24H), 4.75 (ABq, $J = 15$ Hz, 4H), 7.02 (s, 4H). IR (deposit): 1695 cm^{-1} (C═O), 1105 (C—O). MS: 452.1 (M^+). Anal Calcd: C, 58.40; H, 7.13. Found: C, 58.43; H, 6.94. Cryptand diamide **11**: Yield 29%, white solid, mp 205–207 °C. ^{1}H-NMR($CDCl_3$): $\delta = 3.6$ (br s, 48H), 4.8(br s, 8H), 6.85 (s, 8H). IR (deposit): 1660 cm^{-1} (C═O), 1110 (C—O). Anal Calcd: C, 58.40; H, 7.13. Found: C, 58.05; H, 7.09.

2.6. PREPARATION OF CRYPTAND DIAMIDE 10

With the procedure given for the synthesis of **9**, diacid chloride **8** and 1,10-diaza-18-crown-6 were cyclized to form cryptand diamide **10**: Yield 32%, white solid, mp 224–226 °C. ^{1}H-NMR($CDCl_3$): $\delta = 2.45$–5.35 (m, 31H), 6.6–7.2 (m, 3H). IR (deposit): 1650 cm^{-1} (C═O), 1110 cm^{-1} (C—O). MS: 482.1 (M^+). Anal Calcd: C, 57.25; H, 7.10. Found: C, 57.32; H, 7.21.

2.7. PREPARATION OF CRYPTANDS 1–3

To a suspension of the cryptand diamide (2.00 mmol) in 70 mL of tetrahydrofuran was added borane-dimethyl sulfide (3.3 mL, 33 mmol) and the mixture was refluxed overnight. Water (15 mL) was added and the suspension was evaporated *in vacuo*. Tetrahydrofuran (50 mL) and 6N hydrochloric acid (100 mL) were added to the residue and the mixture was stirred overnight at room temperature. (A double amount of borane-dimethyl sulfide was used in the case of **11** and hydrolysis of the borane-adduct was achieved by stirring for three days with 9N hydrochloric acid at room temperature). The mixture was evaporated to dryness in vacuo and the residue was treated with 5% aqueous lithium hydroxide and repeatedly extracted with methylene chloride (3 × 50 mL). The combined extracts were dried over potassium carbonate and evaporated to give a crude product which was purified by column chromatography on alumina with chloroform-methanol (20 : 1) as eluent.

1: Yield 67%, white crystals, mp 106–107 °C. ^{1}H-NMR($CDCl_3$): $\delta = 2.4$–2.8 (m, 12H), 3.3–3.8 (m, 16H), 4.20 (t, 4H), 7.10 (s, 4H). ^{13}C-NMR($CDCl_3$): $\delta = 56.9$, 57.6, 69.1, 70.7, 116.7. IR (deposit): 1115 cm^{-1} (C—O). MS: 424.2 (M^+). UV λ_{max} 243.9 ($\varepsilon = 3322$); 295.6 ($\varepsilon = 2666$). Anal Calcd: C, 62.24; H, 8.55. Found: C, 62.45; H, 8.77.

2: Yield 88%, white crystals, mp 92–93 °C. ^{1}H-NMR($CDCl_3$): $\delta = 2.4$–2.9 (m, 12H), 3.35–4.0 (m, 19H), 4.15–4.5 (m, 4H), 6.50 (d, 1H), 7.0–7.65 (m, 2H). IR (deposit): 1120 cm^{-1} (C—O). MS: 454.1 (M^+). Anal Calcd: C, 60.77; H, 8.42. Found: C, 60.79; H, 8.59.

3: Yield 80%, white solid, mp 99–101 °C. ^{1}H-NMR($CDCl_3/CD_3OD$, 9/1): $\delta =$ 2.7–3.05 (m, 24H), 3.45–3.75 (m, 32H), 4.00 (s, 8H), 6.81 (s, 8H). IR (deposit): 1110–1130 cm^{-1} (C—O). Anal Calcd: C, 62.24; H, 8.55. Found: C, 61.90; H, 8.53.

2.8. PREPARATION OF CRYPTATE 1 · KSCN

Cryptand **1** (80.5 mg, 0.19 mmol) and potassium thiocyanate (18.4 mg, 0.19 mmol) were dissolved in 4 mL of acetone and the solution was refluxed for 20 min. A few drops of diethyl ether were added and the solution was left overnight at room temperature to produce the crystalline complex. **1** · KSCN: Yield 85%. Transparent crystals, mp 217–219 °C. ^{1}H-NMR($CDCl_3$): $\delta = 2.3$–3.0 (m, 12H), 3.65 (br s, 16H), 4.25 (t, 4H), 6.91 (s, 4H). ^{13}C-NMR($CDCl_3$): $\delta = 56.7$, 58.0, 66.7, 67.7, 70.2, 116.4. UV λ_{max} 243.9 ($\varepsilon = 4491$); 298.8 ($\varepsilon = 2430$). Anal Calcd: C, 52.95; H, 6.95. Found: C, 53.11; H, 6.75.

2.9. COMPLEXATION OF ALKALI METAL CATIONS

Stability constants for association of sodium, potassium, and rubidium chlorides with cryptands **1**, **2** and **12** were determined with cation selective electrodes in methanol [6].

2.10. COMPLEXATION OF DIAMMONIUM CATIONS $H_3N^+(CH_2)_nNH_3^+$ ($n = 4 - 6$)

Complexation of diammonium picrates by **3** in deuteriochloroform-methanol-d$_4$ (9 : 1) was monitored by ^{1}H-NMR [7].

3. Results and Discussion

3.1. SYNTHESIS OF CRYPTANDS 1–3

Cyclization of diacid chloride **5** with 1,10-diaza-18-crown-6 under high dilution conditions in toluene gave both a 1 : 1 cryptand diamide adduct **9** and a 2 : 2 cryptand tetraamide compound **11** in yields of 17 and 29%, respectively. Similar reaction of diacid chloride **8** with 1,10-diaza-18-crown-6 produced a 32% yield of the 1 : 1 cryptand diamide adduct **10** and an undetermined yield of a 2 : 2 cryptand tetraamide compound which was present as a mixture of stereoisomers. Reduction of **9**, **10** and **11** with borane-dimethyl sulfide in tetrahydrofuran gave cryptands **1**, **2** and **3** in yields of 67, 80, and 80%, respectively.

3.2. COMPLEXATION STUDIES

Examination of CPK molecular models of the new benzocryptands **1** and **2** indicates that the molecules are very compact and relatively rigid. Interactions between a complexed cation and the π-electrons of the benzene ring should be more pronounced with these para-substituted benzocryptands than with an analogous ortho-substituted benzocryptand **12**.

Stability constants (log K_s) values for association of **1**, **2** and **12** with Na^+, K^+ and Rb^+ in methanol as determined by potentiometry with cation selective electrodes are compared with reported values for the alkyl cryptand **13** in Table I. Compared with *ortho*-substituted benzocryptand **12**, the new *para*-substituted benzocryptands **1** and **2** exhibit much weaker interactions with alkali metal cations. Since the two aryl alkyl ether oxygen atoms in **1** and **2** cannot participate in binding (CPK model), the lower stability constants are not surprising. Unexpectedly, benzocryptands **1** and **2** complex Na^+ and K^+ even weaker than does cryptand **13** which is devoid of coordination sites in one of the three connecting chains. This indicates that the π-electrons of the benzene subunit do not participate in the complexation.

Table I. Stability constants for associations of alkali metal cations with cryptands in methanol at 25 °C

	log K_s		
	Na^+	K^+	Rb^+
1	3.0	4.7	3.7
2	2.65	4.6	3.4
12	7.4	9.0	7.2
13[a]	3.5	5.2	3.4

[a] Data taken from Ref. [8].

To probe this conclusion further, the potassium thiocyanate complex of benzocryptand **1** was prepared and NMR and UV spectra of the complex and the free ligand were determined (Table II). Both the ^{1}H-NMR chemical shifts for the aromatic protons and the UV absorption maxima show slight shifts in going from the uncomplexed cryptand to the cryptate complex. This suggests that the π-electrons of the benzene subunit do interact to a small extent with the complexed cation.

Table II. Spectral differences between cryptand **1** and cryptate **1** · KSCN

	^{1}H-NMR [ppm][a]	^{13}C-NMR [ppm][a]	UV λ_{max} [nm] (ε)[b]
1	2.4–2.8 (m, 12), 3.3–3.8 (m, 16), 4.20 (t, 4), 7.10 (s, 4)	56.9, 57.6, 69.1, 70.7, 116.7	243.9 (3322) 295.6 (2666)
1 · KSCN	2.3–3.0 (m, 12), 3.65 (br s, 16), 4.25 (t, 4), 6.91 (s, 4)	56.7, 58.0, 66.7, 67.7, 70.2, 116.4	243.9 (4491) 298.9 (2430)

[a] In $CDCl_3$.
[b] In CH_2Cl_2.

Although both benzocryptands **1** and **2** exhibit similar binding of K^+ in methanol, a crystalline complex could only be obtained from **1**. Similarly, cryptand diamides **9** and **10** showed differing abilities to form a solid complex with a neutral guest molecule. When **9** was purified by column chromatography with dichloromethane as eluent, a solid 1 : 1 complex was formed as evidenced by ^{1}H-NMR. Extended heating under vacuum only partially removed the methylene chloride. Total decomplexation was achieved by recrystallization from benzene. In contrast, no complex of cryptand diamide **10** was obtained upon column chromatography with dichloromethane as eluent.

By ^{1}H-NMR Sutherland [9–11] and Lehn [7, 12, 13] have studied the binding of diammonium cations of the type $H_3N^+(CH_2)_nNH_3^+$ by tri- and tetracyclic macrocycles which contained aromatic subunits. It was found that the protons of the guest molecule surrounded by aromatic groups were substantially shifted upfield in the ^{1}H-NMR spectrum and the magnitude of this shift depended on how well the host and the guest molecule fit together. Examination of the CPK molecular model of **3** indicates that dications derived from penta ($n = 5$) – and hexa ($n = 6$) methylene diamine would provide the best fit. In agreement maximum upfield chemical shifts of −1.35 ppm and −1.30 ppm for $n = 5$ and $n = 6$, respectively, were found with **3**. No upfield chemical shift was observed with the tetramethylenediamine based dication.

Acknowledgements

The authors wish to thank Professor Richard A. Bartsch for helpful comments and Ms. Jill Harry for typing the manuscript.

References

1. B. Dietrich: in *Inclusion Compounds*, vol. 2 (eds. J. L. Atwood, J. E. D. Davies, and D. D. McNicol), pp. 337–405, Academic Press, New York (1984).
2. J. M. Lehn: in *Biomimetic Chemistry*, (eds. Z. I. Yoshida and N. Ise), p. 163, Kodansha, Tokyo, Elsevier, Amsterdam (1983).
3. K. Frensch and F. Vögtle: *Tetrahedron Lett.* 2573 (1977).
4. H. F. Beckford, R. M. King, and J. F. Stoddart: *Tetrahedron Lett.* 171 (1978).
5. N. Kawashima, T. Kawashima, T. Otsubo, and S. Misumi: *Tetrahedron Lett.* 5025 (1978).

6. H. K. Frensdorff: *J. Am. Chem. Soc.* **93**, 600 (1971).
7. F. Kotzyba-Hibert, J. M. Lehn, and K. Saigo: *J. Am. Chem. Soc.* **103**, 4266 (1981).
8. R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb, and J. Christensen: *Chem. Rev.* **85**, 271 (1985).
9. M. R. Johnson, I. O. Sutherland, and R. F. Newton: *J. Chem. Soc. Chem. Commun.* 309 (1979).
10. R. Mageswaran, S. Mageswaran, and I. O. Sutherland: *J. Chem. Soc., Chem. Commun.* 722 (1979).
11. N. F. Jones, A. Kumar, and I. O. Sutherland: *J. Chem. Soc., Chem. Commun.* 990 (1981).
12. J. P. Kintzinger, F. Kotzyba-Hibert, J. M. Lehn, A. Pagelot, and K. Saigo: *J. Chem. Soc., Chem. Commun.* 833 (1981).
13. A. D. Hamilton, J. M. Lehn, and J. L. Sessler: *J. Am. Chem. Soc.* **108**, 5158 (1986).