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Synthesis and Alkali Metal Cation Complexation of *N*-Aryl [3.2.2] Cryptands

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Abstract. Two novel three-nitrogen cryptands with *N*-aryl substituents are prepared by cyclization of 1,10-diaza-18-crown-6 with mixed anhydrides of 6-arylaza-3,9-dioxadecanedioic acid followed by borane reduction of the resultant bicyclic diamides. For the alkali metal cations, the *N*-phenyl [3.2.2] cryptand exhibits strongest complexation for Rb^+ in picrate extractions.

Key words: Cryptand, alkali metal cation complexation, picrate extraction.

1. Introduction

Since the introduction of cryptands by Lehn and coworkers [1], the synthesis and cation complexation behavior of these macropolycyclic ligands have been objects of intense research interest in many laboratories [2, 3]. Most common are the bicyclic cryptands with two bridgehead nitrogens and with only oxygen heteroatoms in the bridging arms. The cation complexing properties of such [2]-cryptands is influenced by the replacement of one or more of the oxygen atoms with nitrogen or sulfur [3]. Although replacement of oxygens by —N(H)— and —N(Me)— units has been described, [2]-cryptands with two bridgehead nitrogens and a —N(aryl)— replacement unit for one oxygen atom are unknown. Such a —N(aryl)— unit could serve as a site for the type of functionalization that has been performed with *N*-phenyl monoaza-18-crown-6 [4]. We now report the synthesis of two *N*-aryl [3.2.2] cryptands and the alkali metal cation complexing abilities of one of them.

2. Experimental

2.1. PREPARATION OF DIESTERS **1a** AND **1b**

The appropriate *N*-aryl diethanolamine (0.105 mol) was dissolved in 500 ml of hot *t*-BuOH and 58.8 g (0.53 mol) of *t*-BuOK was added. The mixture was refluxed for 1 h and 19.88 g (0.21 mol) of chloroacetic acid in 150 ml of *t*-BuOH was added dropwise during 1 h. After refluxing for 48 h and solvent removal by distillation under reduced pressure, 200 ml of 3N HCl was added and the mixture was evaporated in vacuo. The residue was suspended in 200 ml of EtOH, filtered, and 400 ml of benzene was added to the filtrate. The solution was refluxed for 24 h with water removal by anhydrous sodium sulfate in a Soxhlet extractor. After filtration and evaporation in

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vacuo, the residue was dissolved in dichloromethane and washed with 1M sodium bicarbonate and then water. After drying over magnesium sulfate and evaporation in vacuo, the residue was distilled under vacuum.

1a: Yield 49%, bp 197–198 °C/0.13 torr. ^{1}H-NMR ($CDCl_3$): $\delta = 1.13$ (*t*, 6H), 3.59 (*s*, 8H), 3.9–4.5 (*m*, 8H), 6.5–7.4 (*m*, 5H). IR (neat): $cm^{-1} = 1753$ (C=0), 1138 C—0). Anal. Calcd: C, 61.17; H, 7.70. Found: C, 61.53; H, 7.85%.

2a: Yield 25%, bp 207–210 °C/0.40 torr. ^{1}H-NMR ($CDCl_3$): $\delta = 1.27$ (*t*, 6H), 2.25 (*s*, 3H), 3.68 (*br s*, 8H), 3.9–4.5 (*m*, 8H), 6.89 (*ABq*, 4H). IR (neat): $cm^{-1} = 1755$ (C=0), 1140 (C—0). Anal. Calcd: C, 62.10; H, 7.96. Found: C, 62.17; H, 8.12%.

2.2. PREPARATION OF DIACIDS **2a** and **2b**

The appropriate diethyl ester (22 mmol) was dissolved in 40 ml of 6N HCl and 10 ml of water and refluxed for 4 h. Evaporation in vacuo and addition of benzene (200 ml) followed by refluxing and water removal with a Dean-Stark trap gave a suspension which was filtered and dried under vacuum to produce the hygroscopic hydrochloride salt.

2a: Yield 100%, mp 157–158 °C. ^{1}H-NMR (DMSO-d_6): $\delta = 3.26$ (*br s*, 12H), 7.0–8.0 (*m*, 5H), 10.9–11.7 (*br s*, 3H). IR (KBr): $cm^{-1} = 3182$ (COOH), 2606 (R_3NH), 1753 (C=0), 1140 (C—0). Anal. Calcd: C, 50.38; H. 6.04. Found: C, 50.15; H, 6.08%.

2b: Yield 98%, glassy, low-melting solid. ^{1}H-NMR (DMSO-d_6): $\delta = 2.32$ (*s*, 3H), 3.2–4.6 (*m*, 12H), 7.40 (*ABq*, 4H), 8.84 (*br s*, 3H). IR (neat): $cm^{-1} = 3700$–2340 ($COOH + R_3NH^+$), 1737 (C=0), 1138 (C—0). Anal. Calcd: C, 51.80; H, 6.38. Found: C, 52.04; H, 6.67%.

2.3. PREPARATION OF CRYPTAND DIAMIDES **4a** AND **4b**

Finely powdered **2a** or **2b** (7.62 mmol) was suspended in 15 ml of dichloromethane and diluted to 50 ml with toluene. Triethylamine (2.40 g, 24 mmol) was added and the mixture was stirred for 15–20 min until only a light white solid was present in suspension. The mixture was cooled to 0–5 °C and isobutyl chloroformate (2.10 g, 15.4 mmol) diluted in 10 ml of cold toluene was added dropwise. The mixture was stirred at 0–5 °C for 30 min and filtered. The filtrate was diluted to 70 ml with cold toluene to make Solution A. Solution B was prepared by dissolving 2.00 g (7.60 mmol) of 1,10-diaza-18-crown-6 in 10 ml of toluene and diluting to 70 ml with toluene. Solutions A and B were placed in water-jacketed addition funnels maintained at 0–5 °C and were added simultaneously over 8 h to 300 ml of vigorously-stirred toluene at 0–5 °C under nitrogen. The solution was stirred overnight at room temperature and evaporated in vacuo. The residue was purified by chromatography on alumina with dichloromethane-chloroform (3:1) as eluent.

4a: Yield 36%, mp 118–119 °C. ^{1}H-NMR ($CDCl_3$): $\delta = 2.6$–4.5 (*m*, 36H), 6.5–7.4 (*m*, 5H). IR (neat): $cm^{-1} = 1647$ (C=0), 1116 (C—0). MS: 523.5 (M^+). Anal. Calcd: C, 59.64; H, 7.89. Found: C, 59.42; H, 7.69%.

4b: Yield 32%, mp 129–130 °C. ^{1}H-NMR ($CDCl_3$): $\delta = 2.20$ (*s*, 3H), 2.6–4.6 (*m*, 36H), 6.82 (*ABq*, 4H). IR (neat): $cm^{-1} = 1651$ (C=0), 1116 (C—0). Anal. Calcd: C, 60.31; H, 8.06. Found: C, 60.21; H, 8.06%.

2.4. PREPARATION OF CRYPTANDS **5a** and **5b**

To a solution of the cryptand diamide (2.31 mmol) in THF (20 ml) was added borane-dimethyl sulfide (1.0 ml, 10 mmol) in 19 ml of THF and the solution was refluxed for 9 h. After slow addition of water (5 ml), the suspension was evaporated in vacuo. The residue was refluxed in 25 ml of 3.6N HCl for 12 h. The solution was cooled, made strongly basic with ammonium hydroxide, and evaporated in vacuo. The solid was washed with MeOH (2×25 ml) and the washings were filtered. Diethyl ether was added to the methanolic solution and the mixture was filtered. The filtrate was evaporated in vacuo and the residue was purified by chromatography on alumina with chloroform-dichloromethane (2:1) as eluent.

5a: Yield 74%, light yellow oil. ^{1}H-NMR ($CDCl_3$): $\delta = 2.83$ (*t*, 12H), 3.4–4.0 (*m*, 28H), 6.5–7.5 (*m*, 5H). IR (neat): $cm^{-1} = 1126$ (C—0). ^{1}H-NMR ($CDCl_3$): $\delta = 2.83$ (*t*, 12H), 3.4–4.0 (*m*, 28H), 6.5–7.5 (*m*, 5H). MS: 495.5 (M^+). Anal. Calcd: C, 60.91; H, 9.24. Found: C, 60.93; H, 9.05%.

5b: Yield 74%, colorless oil. ^{1}H-NMR ($CDCl_3$): $\delta = 2.22$ (*s*, 3H), 2.73 (*t*, 12H), 3.62 (*m*, 28H), 6.77 (*ABq*, 4H). IR (neat): $cm^{-1} = 1122$ (C—0). Anal. Calcd: C, 63.62; H, 9.30. Found: C, 63.84; H, 9.10%.

2.5. PICRATE EXTRACTIONS

Picrate extractions into chloroform were performed by the reported technique [5]. Extraction constants (K_{ex}) and association constants (K_a) were calculated by the literature methods [6, 7].

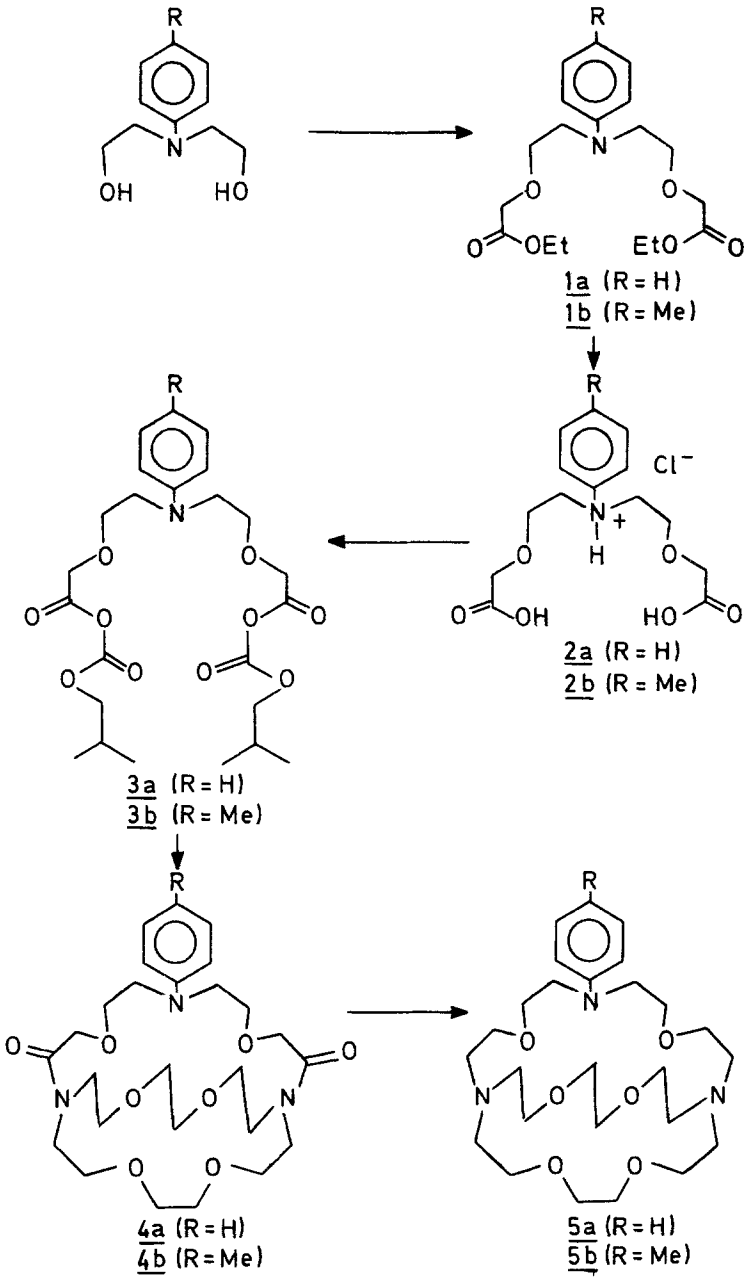
3. Results and Discussion

3.1. SYNTHESIS OF *N*-ARYL [3.2.2] CRYPTANDS

The synthetic route to *N*-aryl [3.2.2] cryptands **5a** and **5b** is shown in the Scheme. Starting from the *N*-aryl diethanolamine, reaction with two equivalents of chloroacetic and *t*-BuOK in *t*-BuOH followed by conversion of the diacid to the diester for purification gave **1a** and **1b** in yields of 49 and 25%, respectively. Subsequent acid-catalyzed hydrolysis produced the dicarboxylic acid amine hydrochlorides **2a** and **2b** quantitatively. Attempts to form the diacid chloride of **2a** resulted in an unreactive deep blue-colored substance of unknown identity. Ring closure was effected by adaptation of a method from peptide synthesis [8]. Mixed anhydrides **3a** and **3b** formed by reaction with two equivalents of isobutyl chloroformate in the presence of triethylamine were cyclized with 1,10-diaza-18-crown-6 in toluene to produce the corresponding cryptand diamides **4a** and **4b** in 36 and 32% yields, respectively. Reduction with borane-dimethyl sulfide in THF provided 74% yields of **5a** and **5b**.

3.2. ALKALI METAL CATION COMPLEXATION

The alkali metal cation complexing ability of cryptand **5a** was assessed by the picrate extraction method with deuteriochloroform as the organic solvent [5]. Calculated extraction constants (K_{ex}) and association constants (K_a) are presented in



Scheme 1.

Table I. The data reveal that cryptand **5a** exhibits strongest complexation for Rb^+ in agreement with complexation studies conducted with [3.2.2] cryptand itself [6].

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Table I. Alkali metal picrate extraction into deuteriochloroform by cryptand **5a**.

M^+	log K_{ex}	log K_a	$-\Delta G$(kcal/mole)
Li^+	3.10	5.96	8.10
Na^+	3.95	6.70	9.10
K^+	5.19	7.79	10.58
Rb^+	5.87	8.20	11.15
Cs^+	5.83	8.10	11.00

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