

# Synthesis of spiro-linked macrocyclic crown formazans and a bis(crown formazan)

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## Abstract

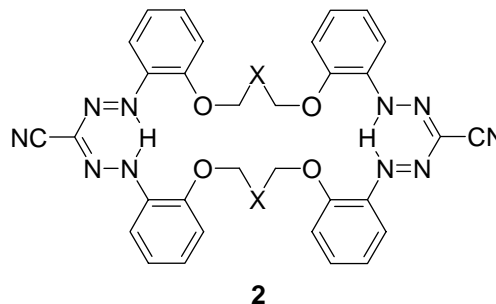
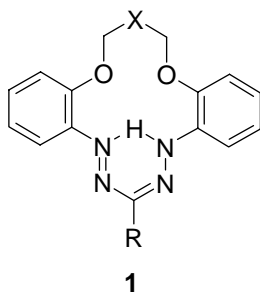
The spiro-linked crown formazans **7a,b** and bis(crown formazan) **11** were synthesized by diazotization of tetrakis(amine) hydrochlorides **6**, and **10**, respectively, followed by coupling with malonic acid or cyanoacetic acid in pyridine.

**Keywords:** Alkylation, diazotization, coupling, macrocyclic formazan

## Introduction

The chemistry and applications of acyclic formazans as well as monocyclic crown-formazans have received much attention and are the subject of several reviews.<sup>1</sup> Many macrocyclic formazans have been synthesized, and their applications in selective metal extraction<sup>2</sup> and determination<sup>3</sup> have been studied. Such applications depend mainly on the cavity size of the macrocyclic crown formazans as well as on the substituents on the macrocycle. Recently, interest has been directed toward the synthesis of multi-site crown compounds. These multi-site molecular receptors are capable of binding two or more guest metal cations.<sup>4</sup>

Previously, we have reported the synthesis of macrocyclic formazans **1** by coupling of the appropriate bis-diazonium salt with active methylene compounds under high dilution conditions; we have studied their behavior in the spectrophotometric determination of lithium and as carriers in cesium ion selective electrodes.<sup>1c,5a-f</sup>

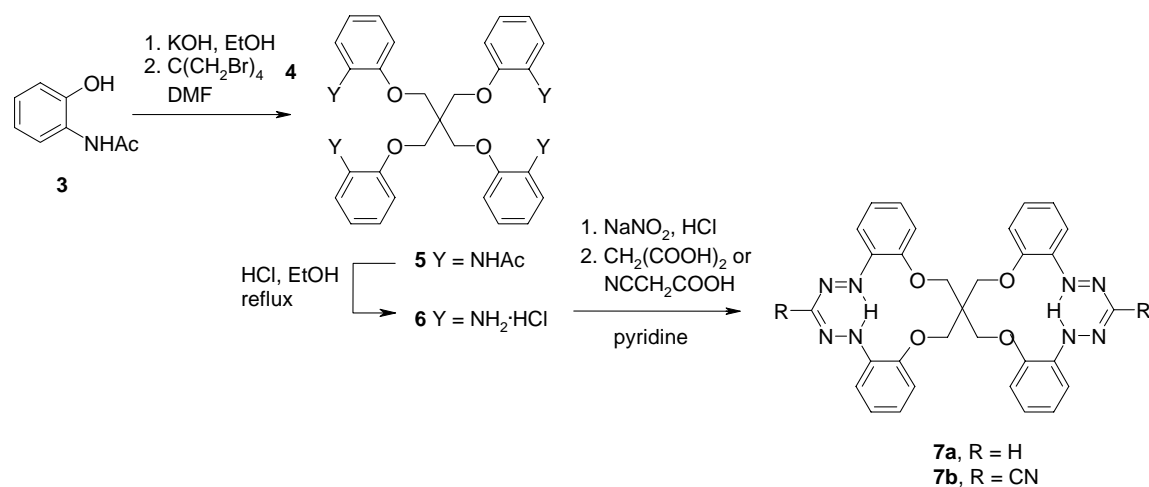


In order to improve the cation binding abilities of macrocycles **1**, Katritzky et al.<sup>1b</sup> have reported the synthesis of lariat crown-formazan **1** (X = CHO(C=O)CH<sub>2</sub>NMe<sub>2</sub>, R = Ph) containing a strong donor group as a supporting ligand at the end of the side arm. Moreover, Abbas<sup>5f</sup> reported the synthesis of crown formazans **2** with two formazyl moieties.

We report here on the first synthesis of spiro-linked crown formazans **7a,b** and that of bis(crown formazan) **11**, which are expected to be analytically useful on account of their ability to bind more than one metal ion.

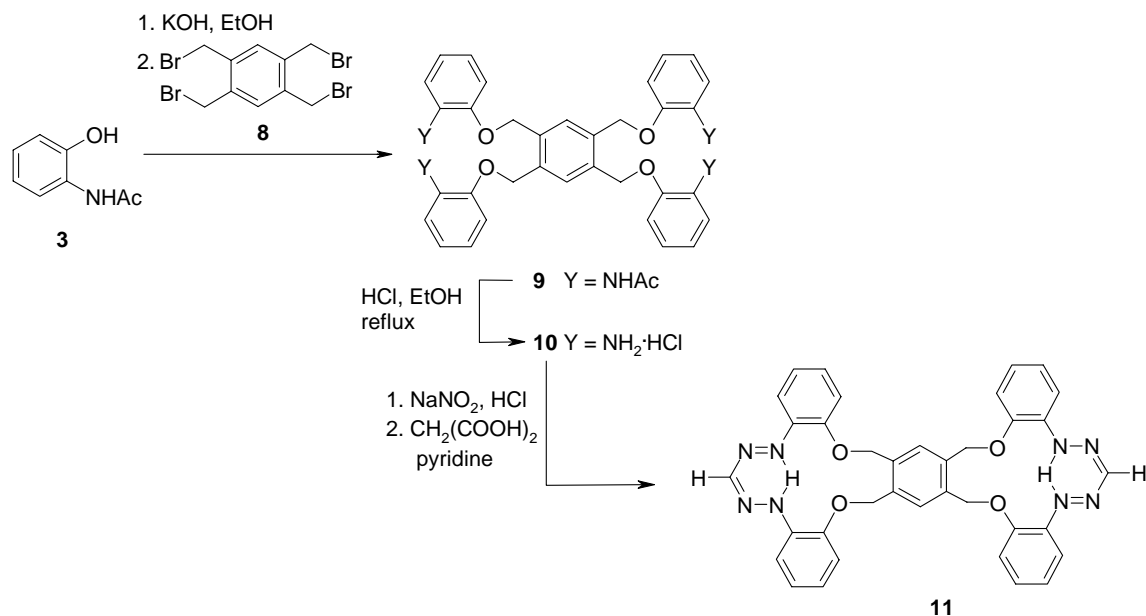
## Results and Discussion

For the synthesis of compounds **7a,b**, first the tetrakis(acetamido) derivative **5** was prepared by the reaction of the potassium salt of *o*-acetamidophenol (**3**) with pentaerythrityl tetrabromide (**4**) in boiling DMF (Scheme 1). Compound **5** was hydrolyzed with an ethanolic solution of hydrochloric acid to give the tetrakis(amine) hydrochloride **6**. Diazotization of **6** with sodium nitrite in hydrochloric acid followed by coupling with malonic acid or cyanoacetic acid in pyridine yielded the corresponding macrocyclic formazans **7a,b** as deep red crystals (16% and 18%).



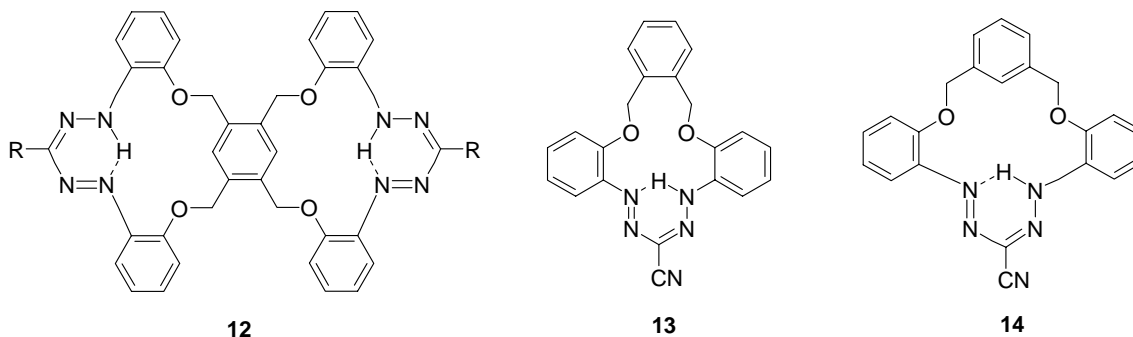
### Scheme 1

Substitution of tetrakis(bromomethyl)benzene (**8**) with four equivalents of the potassium salt of *o*-acetamidophenol (**3**) in refluxing DMF gave the corresponding tetrakis(acetamidophenoxy)methyl)benzene **9** as colorless crystals (92%; Scheme 2). Treatment of the latter with an ethanolic solution of hydrochloric acid gave the tetrakis(amine) hydrochloride **10** (88%). Diazotization of **10** with sodium nitrite in hydrochloric acid followed by coupling with malonic acid in pyridine and subsequent purification gave **11** as deep red crystals (15%). No traces of the isomeric bis(crown formazan) **12** has been obtained from the coupling reaction.



## Scheme 2

The structure of compound **11** was confirmed by comparison with related crown formazans **2**<sup>5f</sup>, **13**<sup>5c</sup>, **14**<sup>4b</sup>.



Comparison of the positions of the NH signals in the <sup>1</sup>H NMR spectra of the proposed structure **11** with those of crown formazans **13** and **14** as well as macrocyclic bis(formazans) **2** led to the assumption of the formation of **11** rather than **12**. Compounds **11** and **13** exhibit sharp NH signals in the downfield region at  $\delta$  15.70 and 15.43, respectively, indicative of an intramolecular hydrogen bond.<sup>6</sup>

On the other hand, the NH signal of the macrocyclic formazan **14** was found at  $\delta$  11.94, for **2** at  $\delta$  10.73–13.25. These upfield shifts of the NH signal indicates a weakening of the intramolecular hydrogen bond, which can be attributed to the increased size of the macrocycles **2** and **14** compared with that of **13**. The absence of a characteristic NH signal in the region  $\delta$  10–13 of the product molecule supports the supposed structure **11**.

Structures of **7a,b**, **11** were confirmed by IR, NMR and MS and elemental analyses. The symmetry of the novel compounds is manifested by a singlet characteristic of the four equivalent OCH<sub>2</sub> groups in the <sup>1</sup>H NMR spectrum.

## Experimental Section

**General Procedures.** IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer. NMR spectra were measured with a Varian Mercury 300 (<sup>1</sup>H: 300 MHz, <sup>13</sup>C: 75 MHz). Mass spectra were recorded on GC MS-QP1000 EX (70 eV) or MS 5988 (15 eV). Elemental analyses were carried out at the Microanalytical Centre, Cairo University.

Pentaerythrityl tetrabromide and tetrakis(bromomethyl)benzene were used as purchased from Aldrich.

**Tetrakis(2-aminophenoxy)methylmethane tetrahydrochloride (6).** *o*-Actamidophenol (**3**) (3.02 g, 20 mmol) was dissolved in hot ethanolic KOH, prepared by dissolving KOH (1.12 g, 20 mmol) in absolute ethanol (20 mL). The solvent was then removed in vacuo; the residual material was dissolved in DMF (15 mL), and pentaerythrityl tetrabromide (**4**) (1.94 g, 5 mmol) was added. The reaction mixture was refluxed for 15 min, and KBr precipitated. KBr was filtered off, and the solvent was removed in vacuo. The residue, tetrakis(2-acetamidophenoxy)methylmethane (**5**) without further purification was used for the next step.

To the solution of **5** in absolute ethanol (20 mL) was added concentrated hydrochloric acid (16 mL). The reaction mixture was then heated under reflux for 2 h. After the solvent was removed in vacuo, the remaining solid was collected and crystallized from ethanol/HCl to give colorless crystals **6** (2 g, 62%); mp > 310 °C. IR (KBr):  $\tilde{\nu}$  3417 (NH) cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O):  $\delta$  4.79 (s, 8H, 4 OCH<sub>2</sub>), 7.15–7.57 (m, 16H, H<sub>Ar</sub>). Anal. calcd. for C<sub>29</sub>H<sub>36</sub>Cl<sub>4</sub>N<sub>4</sub>O<sub>4</sub> (646.44): C, 53.88; H, 5.61; N, 8.67. Found: C, 54.02; H, 5.85; N, 8.48.

**1,2,4,5-Tetrakis(2-acetamidophenoxy)methylbenzene (9) and 1,2,4,5-tetrakis(2-aminophenoxy)methylbenzene tetrahydrochlorides (10).** *o*-Acetamidophenol (**3**) (3.02 g, 20 mmol) was dissolved in hot ethanolic KOH, prepared by dissolving (1.12 g, 20 mmol) in absolute ethanol (20 mL). The solvent was then removed in vacuo; the residual material was dissolved in DMF (15 mL), and tetrakis(bromomethyl)benzene (**8**) (2.25 g, 5 mmol) was added. The reaction mixture was refluxed for 15 min, and KBr precipitated. KBr was filtered off, and the solvent was removed in vacuo. The remaining solid was collected and crystallized from ethanol to give colorless crystals **9** (3.36 g, 92%); mp 218–220 °C. IR (KBr):  $\tilde{\nu}$  3282 (NH), 1697 (CO) cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.96 (s, 12H, 4 CH<sub>3</sub>), 5.21 (s, 8H, 4 OCH<sub>2</sub>), 6.91–8.27 (m, 22H, H<sub>Ar</sub>, 4 NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  24.6 (CH<sub>3</sub>), 70.0 (OCH<sub>2</sub>), 113.55, 121.47, 122.91, 124.27, 128.93, 131.78, 135.76, 146.79 (C<sub>Ar</sub>), 168.60 (C=O). Anal. calcd. for C<sub>42</sub>H<sub>42</sub>N<sub>4</sub>O<sub>8</sub> (730.82): C, 69.03; H, 5.79; N, 7.67. Found: C, 68.98; H, 5.60; N, 7.79.

To a solution of **9** (3.65 g, 5 mmol,) in absolute ethanol (20 mL) was added concentrated hydrochloric acid (16 mL). The reaction mixture was then heated under reflux for 2 h. After the solvent was removed in vacuo, the remaining solid was collected and crystallized from ethanol/HCl to give colorless crystals **10** (3.11 g, 88%); mp > 360 °C. IR (KBr):  $\tilde{\nu}$  3417 (NH)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{D}_2\text{O}$ ):  $\delta$  5.55 (s, 8H, 4  $\text{OCH}_2$ ), 7.10–7.48 (m, 16H,  $\text{H}_{\text{Ar}}$ ), 7.79 (s, 2H,  $\text{H}_{\text{Ar}}$ ). Anal. calcd. for  $\text{C}_{34}\text{H}_{38}\text{Cl}_4\text{N}_4\text{O}_4$  (708.52): C, 57.64; H, 5.41; N, 7.91. Found: C, 57.33; H, 5.75; N, 8.03.

### Formazans **7a,b** and **11**. General procedure

A solution of the appropriate tetrakis(amine hydrochlorides) **6**, **10** (1 mmol) in water (5 mL) and conc. HCl (3 mL) was diazotized at  $-5$  °C with a solution of sodium nitrite (0.23 g in 5 mL water) for 0.5 h. Stirring was continued for 1 h at  $-5$  °C, and then the reaction mixture was added dropwise to a stirred solution containing malonic acid or cyanoacetic acid (2 mmol) in pyridine (150 mL),  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (0.5 g), and water (20 mL) over a period of 1 h. The reaction mixture was stored at 0 °C overnight. Upon addition of concentrated hydrochloric acid the solid precipitate formed was collected and purified by preparative TLC using silica gel (60  $\text{F}_{254}$ ) with proper eluents.

**Macrocyclic formazan 7a.** Following the general procedure, **6** (0.65 g, 1 mmol) and malonic acid (0.21 g, 2 mmol) gave after purification using  $\text{CH}_2\text{Cl}_2$  as an eluent ( $R_f = 0.65$ ) deep red crystals **7a** (92 mg, 16%); mp 272–274 °C. IR (KBr):  $\tilde{\nu}$  3428 (NH)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.51 (s, 8H, 4  $\text{OCH}_2$ ), 6.92–7.85 (m, 16H,  $\text{H}_{\text{Ar}}$ ), 8.36 (s, 2H, 2 Formazyl-CH), 15.76 (s, 2H, 2 NH,  $\text{D}_2\text{O}$  exchangeable). MS:  $m/z$  (%) 576 (100,  $\text{M}^+$ ), 533 (18), 307 (11), 145 (29). Anal. calcd. for  $\text{C}_{31}\text{H}_{28}\text{N}_8\text{O}_4$  (576.62): C, 64.57; H, 4.89; N, 19.43. Found: C, 64.93; H, 4.85; N, 19.30.

**Macrocyclic formazan 7b.** Applying the general procedure, **6** (0.65 g, 1 mmol) and cyanoacetic acid (0.17 g, 2 mmol) gave after purification using  $\text{CH}_2\text{Cl}_2$  as an eluent ( $R_f = 0.48$ ) deep red crystals **7b** (112 mg, 18%); mp 236–238 °C. IR (KBr):  $\tilde{\nu}$  3383 (NH), 2229 (CN)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.44 (s, 8H, 4  $\text{OCH}_2$ ), 7.06–7.93 (m, 16H,  $\text{H}_{\text{Ar}}$ ), 16.03 (s, 2H, 2 NH,  $\text{D}_2\text{O}$  exchangeable). MS:  $m/z$  (%) 626 (35.7,  $\text{M}^+$ ), 570 (39), 507 (61), 386 (30), 120 (100). Anal. calcd. for  $\text{C}_{33}\text{H}_{26}\text{N}_{10}\text{O}_4$  (626.64): C, 63.25; H, 4.18; N, 22.35. Found: C, 63.51; H, 4.30; N, 22.20.

**Macrocyclic formazan 11.** Applying the general procedure, **10** (0.71 g, 1 mmol) and malonic acid (0.21 g, 2 mmol) gave after purification using  $\text{CH}_2\text{Cl}_2$ /petroleum ether (40–60 °C) (5:1) as eluent ( $R_f = 0.45$ ) deep red crystals **11** (95.7 mg, 15%); mp > 360 °C. IR (KBr):  $\tilde{\nu}$  3428 (NH)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  5.42 (s, 8H, 4  $\text{OCH}_2$ ), 7.01 (t,  $J = 7.5$  Hz, 4H,  $\text{H}_{\text{Ar}}$ ), 7.33 (t,  $J = 7.5$  Hz, 4H,  $\text{H}_{\text{Ar}}$ ), 7.58–7.65 (m, 8H,  $\text{H}_{\text{Ar}}$ ), 7.87 (s, 2H,  $\text{H}_{\text{Ar}}$ ), 8.25 (s, 2H, 2 Formazyl-CH), 15.43 (s, 2H, 2 NH,  $\text{D}_2\text{O}$  exchangeable). MS:  $m/z$  (%) 638 (6.3,  $\text{M}^+$ ), 530 (4), 354 (13), 183 (17), 109 (100). Anal. calcd. for  $\text{C}_{36}\text{H}_{30}\text{N}_8\text{O}_4$  (638.69): C, 67.70; H, 4.73; N, 17.54. Found: C, 67.30; H, 5.06; N, 17.40.

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