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Benzo Condensed Crown Ethers Containing 1,8-Naphthyridine or 4-Pyridone Units – Synthesis and Complex Formation with Organic Guest Molecules

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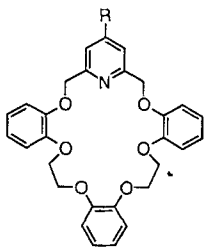
Abstract. New crown compounds **3–5** comprising beside o-phenylene groups 1,8-naphthyridine or 4-pyridone groups as characteristic building units are synthesized. They form numerous stoichiometric crystalline complexes with uncharged organic molecules including alcohols, nitro compounds and other dipolar-aprotic solvents, as well as cyclic ethers and aromatic hydrocarbons. Properties of complex formation and host-guest stoichiometries are discussed making a comparison with parent host analogues.

1 Introduction

Crown compounds involving heteroaromatic condensations – in particular pyridino condensations – proved efficient complexants for cations [1]. If additional benzo nuclei are condensed (cf. **1** and **2**) ligand property is altered. As a rule, complexation of cations decreases [2] due to the lower donor capacity of benzo compared to aliphatic bonded hetero atoms and in consequence of conformational hindrance.

On the other hand, on displacement of ethylene units in pyridino crowns by aromatic rings complexation of uncharged organic molecules is promoted [3]. But this depends also on the position of the condensations at the macroring as well as on the nature of the aromatic nuclei used [4]. Although respective parameters have been determined by a systematic study of pyridino crowns [5], the influence of the heteroaromatic building block on the complex formation with uncharged organic guests has only scarcely been worked out [6]. For obvious reasons [7], replacement of a pyridine ring by a 1,8-naphthyridine unit comprising two suitably positioned nitrogen atoms will specifically alter or perhaps improve host capacity of the crown compound to molecular guests. Moreover, specific substitution of the pyridine nucleus by electronically activating groups should increase donor ability (basicity) of the nitrogen atom thus enhancing hydrogen bonded complex formation with CH-acidic organic guests [3].

Therefore we took an interest in the macrocycles **3** – **5**. Compared to the parent compounds **1** and **2**, both being efficient crystalline hosts [5], in **3** – **5** the pyridine rings are replaced by naphthyridine or 4-hydroxy substituted pyridine units. In the latter case, tautomerism



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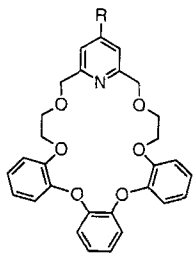
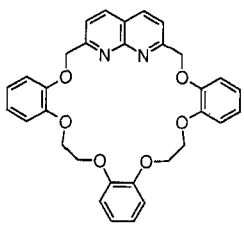
6: R = OCH_2Ph



2: R = H
7: R = OCH_2Ph



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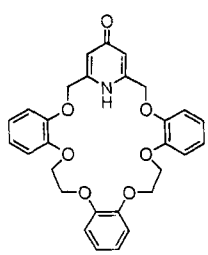

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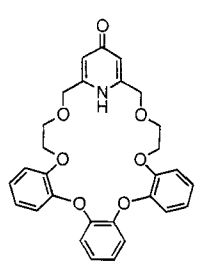

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(4-hydroxypyridine ⇌ 4-pyridone) [8] is possible having consequences on the complex formation.

We report the syntheses of the macrocycles **3 – 5** and discuss the host properties of **3 – 5** on crystalline complex formation with uncharged organic molecules.

2 Synthesis

The macrocycle **3** was synthesized by ring formation reaction between **8** and **10b** with Cs_2CO_3 in DMF [9] but without using high-dilution technique [10], in order to avoid long reaction times and not to run the risk of decomposition of **10b**. Nevertheless **3** was formed in 43 % yield.

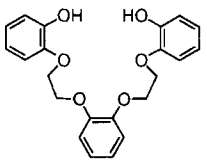
According to a literature procedure [11], the key compound **10b** should by available from **10a** via the corresponding dialdehyde. However, since we were unable to reproduce oxidation of **10a** with SeO_2, direct chlorination of **10a** with trichloroisocyanuric acid (TCC) was put to the test. The reagent proved favourable in the side-chain chlorination of nitrogen-containing heterocycles [12], as found in the present case. More strictly speaking, **10a** reacted with 1.2-fold excess of TCC (this ratio was found the optimun on screening tests) to give **10b** in 33 % yield.

Macrocyclic **4** and **5** were synthesized as follows: in the first step ring formation between **8** [6] or **9** [5] and **11d** to yield **6** and **7** in 55 and 57 %, respectively; followed by hydrogenolytic deblocking of the benzylic ether protective groups which gave **4** and **5** in 73 or 74 %. The ring closure reactions for making **6** and **7** were performed under high-dilution conditions [10]. In case of **6**, Cs_2CO_3 in dry DMF [9] was used as the base/solvent-system; for preparation of **7**, NaH in dry THF [5] was used.

The dichloride **11d** was obtained from diol **11c** with thionyl chloride; the latter compound was prepared from chelidamic acid following a literature procedure [13]. To prevent cleavage of the benzylic ether protective group on reaction of **11c** with thionyl chloride, pyridine was added to the reaction mixture.

An alternative route using the THP-blocked ditosylate **11e** [14] instead of **11d** as ring closure component failed because of purification problems with **11e.**

The structures proposed for the macrocyclic compounds are consistent with data obtained from spectra and combustion analyses. A bond at 1640 cm^{-1} in the ir for **4** and **5** is indicative of the pyridone carbonyl functions [14]. Macrocycles **4** and **5** also have peaks at about δ 6.3 indicative of the two ring protons in a pyridone ring [14], while benzylic ether derivatives **6** and **7** exhibit the protons in the usual aromatic range. Thus macrocycles **4** and **5** are protonionizable crowns [15] similar to previously reported cases [14].



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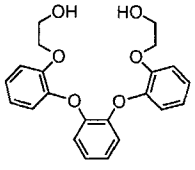

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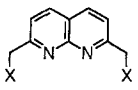
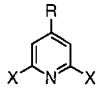


10 **a**: X = H
b: X = Cl



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	R	X
a	Cl	COOMe
b	OCH_2Ph	$COOCH_2Ph$
c	OCH_2Ph	CH_2OH
d	OCH_2Ph	CH_2Cl
e	OTHP	CH_2OTos

3 Complex Formation

A variety of solvents differing in molecular size, shape, and polarity, such as alcohols, nitro compounds, aromatic compounds and heterocycles (cf. Table 1) were used to investigate the solid-state complexation properties of potential host compounds **3 – 5**. The results are shown in Table 1.

While 4-pyridone subunit macrocycles **4** and **5** yield crystalline complexes with a rather high number of sol-

Table 1 Crystalline complexes of hosts **4** and **5** with uncharged organic guests [a]

Guest compound	Host compound	
	4	**5**
Methanol	–	1:1 [b]
Ethanol	2:1	1:1
1-Propanol	–	1:1
2-Propanol	2:1	1:1
1-Butanol	–	1:1
Nitromethane	1:1	1:2
Nitroethane	2:3	1:1
DMF	2:3	c)
DMSO	2:3	c)
THF	1:1	1:1
Dioxane	1:1	1:1
Benzonitrile	2:3	c)
Nitrobenzene	2:3	c)
Benzene	–	1:1
Toluene	–	1:1

[a] Macrocycle **3** yields only a 1:2 (host:guest) complex with nitromethane. – [b] Stoichiometric ratio host:guest. – [c] Non-stoichiometric.

vents, the naphthyridine subunit macroring **3** only forms one single complex which is the 1:2 complex with nitromethane. Without the presence of nitromethane **3** does not crystallize but forms a viscous oil. One may speculate on a possible reason for this particular behaviour of nitromethane. Perhaps it is the acidity property being highest for nitromethane (pK_s 10) [16] in the given series of solvent compounds.

Although formation of crystalline complexes of **4** and **5**, at a cursory glance, are similar, there are some distinct differences both in the range of solvent guests and in the complex stoichiometric ratios. For instance, host compound **5** is superior to **4** in the complex formation with alcohols and aromatic hydrocarbons, but **4** more readily than **5** yields crystalline complexes with DMF, DMSO, benzonitrile and nitrobenzene.

With reference to the stoichiometric ratios, host **5** nearly uniformly yields 1:1 host:guest complexes (with the exception of nitromethane as guest solvent), whereas **4** shows stoichiometric ratios in its host-guest complexes ranging between 2:1 and 2:3, with 2:3 being most and 2:1 or 1:1 being less frequently observed. Remarkably, **4** and **5** exhibit varying ratios if the same guest molecule is involved. This is an important observation since both host molecules provide the same ring size (21-membered), but the only modification is a changed position of the phenylenes in the macroring which however should alter the ring conformation [5].

Compared to the parent macrocycles **1** and **2** [5], macrocycle **3** is less efficient allowing only the isolation of a crystalline complex with nitromethane. On the other hand, a high level of specifity is demonstrated with **3**. By way of contrast, macrocycle **4** though having a proton donor (4-pyridone) instead of a proton acceptor (pyridine) group is similar to **1** while **5** is found superior to **2**.

Whether the discussed differences in complex formation refer to conformational or binding site properties, or to both, proportionately, including effects of host cavity or interstitial crystal void is a problem for crystal structure determination. Unfortunately, all complexes of the present host compounds failed to afford suitable X-ray-quality crystals. Nevertheless, some general indication for future host design based on N-containing benzo condensed crowns is deducible showing clearly that 4-pyridone is an efficient building block for the generation of macrocyclic hosts both for cations [14] and uncharged organic molecules.

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Experimental

Melting points were obtained on a Kofler apparatus (Reichert, Wien). The ^{1}H-NMR spectra were taken on a Varian EM-360 (60 MHz) spectrometer in $CDCl_3$; δ values in ppm, Me_4Si as internal reference. Mass spectra were recorded on a A. E. I. MS-50 mass spectrometer. Elemental analyses were carried out by the Micoranalytical Laboratory of the Institut für Organische Chemie und Biochemie, Bonn. For column chromatography Al_2O_3 (grade II-III; Woelm, Germany) and silica gel (0.063-0.1 nm; Merck, Germany) were used. A 10 % Pd/C catalyst of type E10N (Degussa) was used in catalytic hydrogenations. All solvents were of reagent quality or purified by standard methods.

Starting Compounds

Diphenol **8** [6], diol **9** [5], 2,7-dimethyl-1,8-naphthyridine (**10a**) [17], diester **11a** [18] were synthesized according to literature procedures.

Synthesis of Host Compound 3

2,7-Bis(chloromethyl)-1,8-naphthyridine (**10b**)

To **10a** (1.5 g, 15.8 mmol) in refluxing $CHCl_3$ (40 ml) was added over a period of 3 h trichloroisocyanuric acid (3.0 g, 12.8 mmol). Refluxing was continued for one additional h. After cooling, the solution was treated with H_2O (70 ml). The organic layer was separated, washed with diluted sodium hydroxide solution (40 ml) and with water. After drying (Na_2SO_4), the solvent was removed, and the residue chromatographed on SiO_2 (eluent CH_2Cl_2/ethyl acetate, 6:1).

Colourless crystals, m.p. 156–158 °C(from petroleum ether 60–95 °C), yield 33 %. ^{1}H-NMR ($CDCl_3$): δ = 4.88 (s, 4 H), 7.63–7.82 (s, 2 H), 8.18–8.32 (s, 2 H).

$C_{10}H_8N_2Cl_2$	Calcd. C 52.87	H 3.55	N 12.33
(227.0)	Found C 52.67	H 3.33	N 12.20

MS Calcd. 226.9746 Found 226.0053 (M^+-1)

1,4,11,14,21,34 Hexaoxa [4] (1,2) benzeno [4] (1,2) benzeno [2] (2,7) 1,8-naphthyridino [2] (1,2) benzenophane (**3**)

Diphenol **8** (3.82 g, 10 mmol) and cesium carbonate (3.25 g, 10 mmol) in dry DMF (70 ml) were stirred for 1 h at 70 °C. Then **10b** (2.27 g, 10 mmol) was added and the mixture was allowed to react for 4 h. The solvent was removed under reduced pressure and the residue partitioned between water (160 ml) and chloroform (40 ml). The organic layer was washed with H_2O (100 ml), dried (Na_2SO_4), and evaporated to obtain the crude product. Purification by column chromatography (Al_2O_3, eluent $CHCl_3$).

Viscous oil, 43 %yield; recrystallization from $NeMO_2$ gave dark brown needles of the 1:2 (host:guest) inclusion compound with $MeNO_2$.

^{1}H-NMR ($CDCl_3$): δ = 3.86–4.18 (m, 8 H), 5.38 (s, 4 H), 6.64–7.20 (m, 12 H), 7.68–8.03 (m, 4 H).

$C_{32}H_{28}N_2O_6$	Calcd. C 71.63	H 5.25	N 5.22
(536.2)	Found C 71.35	H 5.18	N 5.03

MS 536 (M^+)

Synthesis of Host Compounds 4 and 5

Dibenzyl 4-(benzyloxy)pyridine-2,6-dicarboxylate (**11b**)

Dimethyl 4-chloro-pyridine-2,6-dicarboxylate (**11b**) (16.80 g, 73 mmol) was slowly added to a preformed solution of benzyl alcohol (108 g, 1 mol) and sodium (1.68 g, 73 mmol). The mixture was stirred at 100 °C for 4 h. The solution was cooled, neutralized with diluted acetic acid and extracted with $CHCl_3$. Evaporation of the solvent under reduced pressure gave a viscous oil which crystallized from MeOH.

Colourless crystals, m.p. 84–85 °C(Lit. [13] 85–85.5 °C), yield 38 %.

4-(Benzyloxy)-2,6-bis(hydroxymethyl)pyridine (**11c**)

A stirred suspension of **11b** (12.35 g, 27.25 mmol) in 100 ml anhydrous EtOH (100 ml) was cooled to 0 °C. Sodium borohydride (5.11 g, 135 mmol) was added in a way to keep the temperature below 5 °C. The mixture was stirred for 1 h at 0 °C, then for 2 h at room temperature, and then refluxed for 14 h. The solvent was removed under reduced pressure, acetone (100 ml) was added and refluxing was continued for 1 h. After evaporation of the solvent, a solution of potassium carbonate (30 g in 80 ml of H_2O) was added, and the mixture was refluxed for additonal 2 h. Then NaCl (10 g) was added and the cooled mixture was extracted with $CHCl_3$. The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure; purification by chromatography on SiO_2 (eluent $CHCl_3$/MeOH; 5:1).

Colourless crystals, m.p. 101–102 °C(from petroleum ether 60–95 °C), yield 78 %.

^{1}H-NMR ($CDCl_3$): δ = 3.62 (s, 2 H), 4.70 (s, 4 H), 5.18 (s, 4 H), 4.80 (s, 2 H), 7.40 (s, 5 H).

$C_{14}H_{15}NO_3$	Calcd. C 68.54	H 6.16	N 5.71
(245.1)	Found C 68.32	H 6.20	N 5.92

MS Calcd. 245.1048 Found 245.1057 (M^+).

4-Benzyloxy-2,6-bis(chloromethyl)pyridine (**11b**)

Diol **11c** (3.35 g, 14 mmol) was dissolved in benzene (70 ml). Pyridine (2.22 g, 29.6 mmol) was added and the solution was cooled to 0 °C. Thionyl chloride (3.52 g, 29.6 mmol) was added and the mixture was refluxed for 3 h. After cooling, the mixture was washed with aqueous sodium bicarbonate and with H_2O. The aqueous layer was extracted with toluene and the solvents were removed under reduced pressure; recrystallization of the solid residue from heptane.

Colourless crystals, m.p. 95–97.5 °C, yield 65 %.

^{1}H-NMR ($CDCl_3$): δ = 4.50 (s, 4 H), 5.03 (s, 2H), 6.83 (s, 2H), 2.23 (s, 5 H);

$C_{14}H_{13}NOCl_2$	Calcd. C 59.57	H 4.65	N 4.97
(281.0)	Found C 59.68	H 4.68	N 5.24

MS Calcd. 282.0054 Found 281.0374 (M^+-1)

25-Benzyloxy-1,4,11,14,21,30-hexaoxa [4] (1,2) benzeno [4] (1,2) benzeno [2] (2,6) pyridino [2] (1,2) benzenophane (**6**)

Diphenol **8** (3.82 g, 10 mmol) and dihalide **11d** (2.82 g, 10 mmol) in separate 250-ml portions of dry DMF were simultaneously added over a period of 10 h to a vigorously stirred suspension of Cs_2CO_3 (3.26 g, 10 mmol) in 700 ml of dry DMF at 60–80 °C. Stirring was continued for 4 h at the same temperature. Working up as described for **3**; column chromatography (Al_2O_3, eluent CH_2Cl_2).

Colourless powder, m.p. 76–78 °C(from MeOH), yield 55 %.

^{1}H-NMR ($CDCl_3$): δ = 4.14–4.38 (m, 8 H), 4.92 (s, 2 H), 5.05 (s, 4 H), 6.62–7.42 (m, 19 H).

$C_{36}H_{33}NO_7$	Calcd. C 73.07	H 5.63	N 2.39
(591.2)	Found C 72.77	H 5.65	N 2.71

MS 591 (M^+)

8-Benzyloxy-1,4,13,16,23,30-hexaoxa [4] (2,6) pyridino [4] (1,2) benzeno [1] (1,2) benzeno [1] (1,2) benzenophane (**7**)

Diol **9** (3.82 g, 10 mmol) and dihalide **11d** (2.82 g, 10 mmol) were reacted as described for **6** using boiling THF instead of DMF and NaH (1.0 g) instead of Cs_2CO_3. The excess of NaH was quenched with MeOH. Further working up as given for **6**.

Colourless powder, m.p. 150–152 °C(from EtOH), yield 57 %.

^{1}H-NMR ($CDCl_3$): δ = 3.60–3.83 (m, 8 H), 3.99–4.23 (m, 4 H), 5.06 (s, 2 H), 6.71–7.05 (m, 12 H), 7.22 (s, 2 H), 7.32–7.43 (s, 5 H).

$C_{36}H_{33}NO_7$	Calcd. C 73.07	H 5.63	N 2.39
(591.2)	Found C 72.61	H 5.69	N 2.57

MS 591 (M^+)

1,4,11,14,21,30-Hexaoxa [4] (1,2) benzeno [4] (1,2) benzeno [2] (2,6) 4-pyridono [2] (1,2) benzenophane (**4**)

A suspension of the corresponding benzyl ether **6** (2.96 g, 5 mmol) and of 10 % Pd/C (0.6 g) in 50 ml of ethyl acetate/EtOH (8:1) was hydrogenated in a Parr apparatus at 3 atm H_2 at 25 °C for 4 h. The filtrate after evaporation solidified and was recrystallized from MeOH.

Colourless powder, m.p. 81–83 °C, yield 73 %.

^{1}H-NMR ($CDCl_3$): δ = 4.24–4.42 (m, 8 H), 4.93 (s, 4 H), 6.38 (s, 2 H), 6.82–7.01 (m, 12 H).

$C_{29}H_{27}NO_7$	Calcd. C 69.43	H 5.43	N 2.79
(501.2)	Found C 69.10	H 5.67	N 3.04

MS 501 (M^+)

1,4,13,16,23,30-Hexaoxa [4] (2,6) 4-pyridono [4] (1,2) benzeno [1] (1,2) benzeno [1] (1,2) benzenophane (**5**)

As described before starting from **7** in i-PrOH; recrystallization from MeOH.

Colourless powder, m.p. 177–179 °C, yield 74 %.

^{1}H-NMR ($CDCl_3$): δ = 3.62–3.90 (m, 4 H), 4.05–4.32 (m, 4 H), 4.42 (s, 4 H), 6.25 (s, 2 H), 6.82–7.09 (m, 12 H).

$C_{29}H_{27}NO_7$	Calcd. C 69.43	H 5.43	N 2.79
(501.2)	Found C 69.25	H 5.62	N 2.92

MS 502 (M^+)

Preparation of Crystalline Host-Guest Complexes

The corresponding host compound was dissolved under heating in a minimum amount of the respective guest solvent. After storage for 12 h at room temperature, the crystals which formed were collected by suction filtration and dried (1 h, room temperature, 15 Torr). Host:guest stoichiometry was determined by ^{1}H-NMR integration. Data for each compound are given in Table 1.

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