

A new bile acid-derived lariat-ether: Design, synthesis and cation binding properties[†]

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Abstract. A new *chola lariat ether* (**1**, a 21-crown-6) was constructed from readily available precursors. The association constant of compound **1** with alkali metal picrates was measured using Cram's extraction protocol. Evidence is presented for the involvement of the 3-methoxy group for the complexation. Energy minimised structures show that the A-ring gets slightly distorted upon metal ion binding.

Keywords. Crown ether; chola crown; bile acid; metal ion binding.

1. Introduction

Crown ethers are a class of synthetic cyclic polyethers with structural resemblance to naturally occurring ion transporters like valinomycin and nonactin.¹ During the past three decades a large number of reports on crown ethers have accumulated in the literature because of their potential application in phase transfer catalysis,² ion transport,³ chromatography,⁴ chromogenic reagents,⁵ as metal ion sensors,⁶ membrane mimics⁷ and in chiral recognition,⁸ to mention a few. *Lariat ethers*⁹ belong to a special class of crown ethers with covalently linked side arm(s), which enhance the binding ability of the crown ethers towards metal ions. The unusual facially amphiphilic structure of bile acids has extensively been utilised in our laboratory to design and synthesise a number of crown ethers and their binding properties with alkali metal ions have been reported.¹⁰ In this paper, we report the design and synthesis of a new chola lariat ether **1** utilizing the curved backbone of cholic acid and differential reactivity of the well-separated 3a, 7a and 12a hydroxyl groups. Structural and binding studies with alkali metal ions are also reported.

2. Results and discussion

2.1 Design

In our earlier work, compound **2** (chart 1) having a pendant 1-pyrenyl group at C-12 showed (slightly) more selective binding towards K⁺ and Rb⁺ but did not show enhanced binding as we had anticipated, possibly due to the perpendicular positioning of the pyrene moiety with respect to the mean crown plane as indicated by the geometry minimised structure of compound **2** (figure 1a)^{10b,c}. We envisioned that a C-3 hydroxyl protected 7,12-crown might show enhanced binding towards alkali metal ions. Structure opti-

[†]Dedicated to Professor C N R Rao on his 70th birthday

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minimisation¹¹ of compound **1** without (HF/3-21G* and DFT/B3LYP/6-31G*) and with K⁺ (HF/3-21G*) showed that the 3-methoxy group is located at the centre of the crown plane (figure 1b). The following structural changes were observed between minimised structures of compound **1** alone, and with K⁺ ion: (1) in the presence of K⁺ the 3-methoxy oxygen and four crown oxygen atoms coordinate with K⁺ (<3 Å distance), and (2) the A-ring of steroid backbone bends towards the crown ring presumably to maximize the interaction between the 3-OMe and the bound K⁺. The calculated energies are shown in table 1. The computed structures of (**1** + K⁺) are shown in three different views in figure 2.

2.2 Synthesis

Compound **3** was synthesized from cholic acid as reported earlier.^{10b} This was selectively methylated at the 3 α OH using NaH/MeI under phase transfer conditions to furnish compound **4** (extension of the reaction time beyond 45 min resulted in the formation of di- and tri-methylated products). The treatment of compound **4** with NaH/pentaethylene-

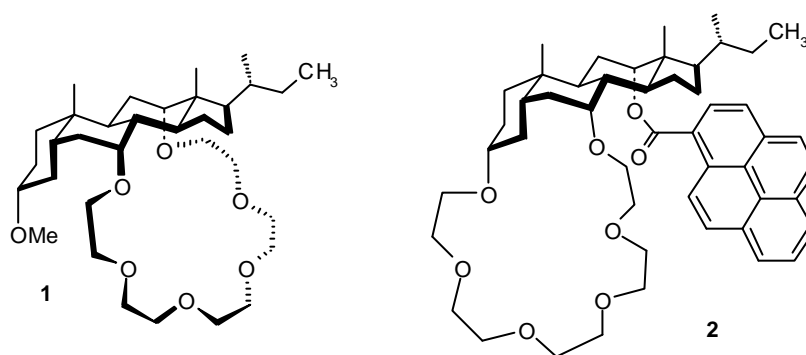


Chart 1.

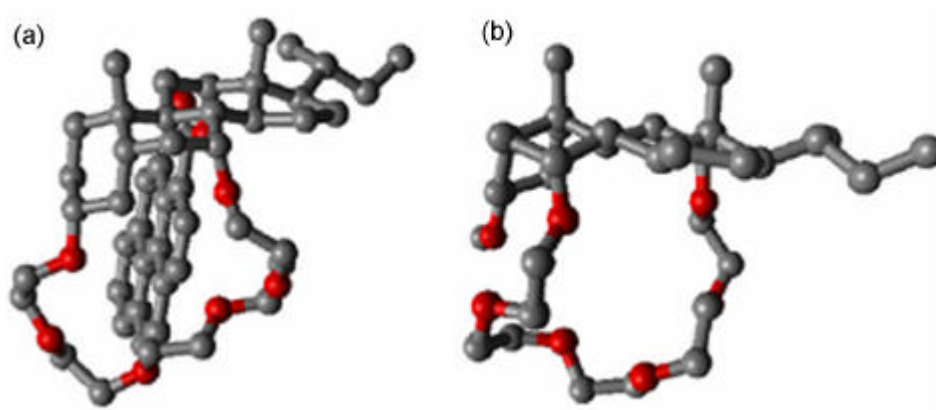
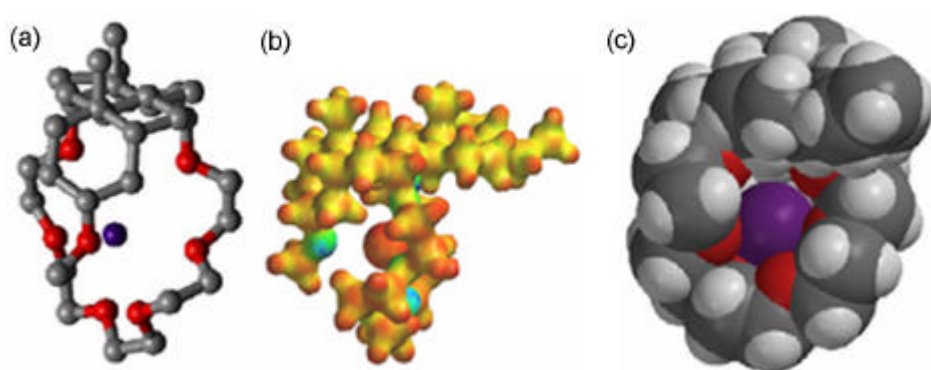


Figure 1. Minimised (gas-phase) structures of compounds (a) **2** and (b) **1**. The hydrogen atoms have been omitted for clarity.

Table 1. Total energy of the chola crown ethers without and with potassium ion calculated using SPARTAN (HF/3-21G*).

Compounds	Total energy (au)
1	-1836.2357 ^a
1 + K ⁺	-2432.4186
2	-2516.7552
2 + K ⁺	-3112.9272

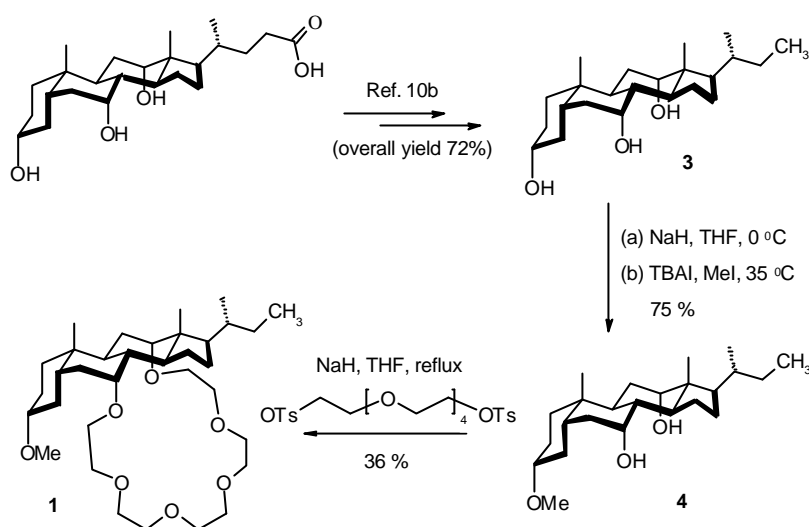
^aDFT/6-31G* calculation gave a value of -1858.2421 au

**Figure 2.** Minimised structures of **1** with K⁺: (a) view perpendicular to the crown ether plane from the A-ring side (without H-atoms), (b) the potential surface viewed along the plane of the crown ether, (c) view of the space filling model perpendicular to the crown ether plane from the D-ring side.

glycol ditosylate under high dilution-reflux conditions afforded compound **1** (chola-21-crown-6) in 34% yield (scheme 1).

2.3 Binding properties

Association constants were measured in CHCl₃ using Cram's extraction protocol¹² using metal picrates. The binding constants are presented in table 2. Compound **1** showed enhanced binding towards alkali metal ions with slightly higher selectivity for K⁺, Rb⁺ and Cs⁺. The binding constants decreased in the order Rb⁺ > Cs⁺ > K⁺ > Na⁺ > Li⁺. The higher binding constants observed for crown ether **1** compared to compound **2** is presumably due to the additional stabilisation provided by the pendant 3-*a*-methoxy group. In order to verify the coordination of the 3-methoxy group with the metal ion, a CDCl₃ solution of crown ether **1** (8.7 mM) was equilibrated with an equal volume of a D₂O solution of K⁺ picrate (17.2 mM). ¹H NMR of the D₂O layer did not show peaks corresponding to the crown ether, whereas the CDCl₃ layer showed 32% complex formation (by NMR integration). In the complex, the 3-*b* hydrogen peak shifted downfield by 0.02 ppm, which may result from the distortion of the A-ring. A (smaller) downfield shift of the 3-methoxy group (0.005 ppm) is also consistent with the interaction suggested by our model.



Scheme 1.

Table 2. Association constants of alkali metal ions with **1** in CHCl_3 at 25°C by Cram's method.

Chola crown	Binding constant ($\log K_a$)				
	Li^+	Na^+	K^+	Rb^+	Cs^+
1	5.10	5.85	6.20	6.33	6.28
2	4.17	4.56	5.68	5.54	4.83

3. Experimental

Melting points were recorded in open capillaries and are uncorrected. ^1H NMR spectra were recorded on a JEOL Lambda-300 spectrometer. Unless otherwise stated ^1H NMR were recorded in CDCl_3 using TMS as the internal standard. LRMS spectra were recorded in JEOL LMS_DX 303 with JEOL JMA-DA mass data system, MALDI-TOF MS were recorded on a Kompack Seq model (Kratos Analytical, UK) fitted with a nitrogen laser, HRMS spectra was recorded in Q-TOF micro. Infrared spectra were recorded on a Jasco FT-IR-410 spectrometer. All reactions were conducted under dry nitrogen and stirred magnetically. Reaction temperatures refer to external or bath temperatures. Thin layer chromatography was performed using precoated plates (silica gel 60F-254) purchased from Sigma. These plates were stained either with iodine vapour or with Liebermann–Buccharadt reagent. Purification of the products were usually done using gravity columns. All solvents were purified and distilled before use. Toluene, benzene and tetrahydrofuran were distilled from sodium/benzophenone ketyl.

3.1 3-Methoxy-7 α ,12 α -dihydroxy-24-nor-cholane (**4**)

To a suspension of NaH (~50% dispersion, 558 mg, 11.6 mmol) in THF (10 ml), compound **3** (1.1 g, 3 mmol) was added under an argon atmosphere, and stirred at 0°C .

After 1 h, a reflux condenser was fitted, tetrabutylammonium iodide (160 mg, 0.43 mmol) and iodomethane (0.56 mM, 9 mmol) were added and the mixture was warmed to 35°C. After 45 min, the reaction mixture was quenched with AcOH (0.5 ml), extracted with EtOAc (25 ml), washed with water (50 ml), saturated NaHCO₃ solution (30 ml) and brine (25 ml) and dried over anhyd. Na₂SO₄. The crude product was purified by column chromatography on silica gel (2 cm × 25 cm) using 25–40% EtOAc/pet ether mixture, to mg (75%) of the product. m.p.: 144.7 °C.

IR (neat, cm⁻¹): 3454 (s), 2937 (s), 2870 (s), 1464 (m), 1374 (m), 1093 (s), 759 (s). ¹H NMR (300 MHz, CDCl₃): 3.99 (s, 1H), 3.8 (br s, 1H), 3.34 (s, 3H), 3.07–2.98 (m, 2. –1. m), 0.97 (d, J = 6.1 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H), 0.69 (s). ¹³C NMR (75 MHz, CDCl₃): 57, 72.96, 68.45, 47.13, 46.00, 41.45, 39.72, 36.87, 35.19, 35.58, 28.29, 28.42, 26.84, 26.20, 22.68, 17.12, 12.42. LRMS: 342 (–2H₂O), 253 (100%).

3.2 3-*a*-Methoxy-24-nor-chola-21-crown-6 (1)

To a refluxing suspension of NaH (~50% dispersion, 113 mg, 2.3 mmol) in dry THF (25 ml), a solution of **4** (149 mg, 0.390 mmol) and pentaerythritol ditosylate (216 mg, 0.4 mmol) in dry THF (15 ml) was added dropwise over a period of 34 h under argon. The resulting solution was refluxed for an additional 35 h. The reaction mixture was concentrated, diluted with CHCl₃ (25 ml), quenched with AcOH (0.5 ml), washed with water (20 ml) and dried over anhyd. MgSO₄. The crude product was purified by column chromatography on silica gel (3 cm × 25 cm) by eluting with 40–75% EtOAc/pet ether mixture. The title compound (15 mg, 34% based on recovered starting material) was obtained as a viscous liquid.

IR (neat, cm⁻¹): 2929 (s), 2864 (s), 1459 (m), 1372 (m), 1104 (s). ¹H NMR (300 MHz, CDCl₃): 3.85–3.63 (m), 3.47 (s, 1H), 3.33 (s, 3H), 3.25 (m, 1H), 3.00 (m, 1H), 2.20–0.95 (m, 22H), 0.91 (d, J = 7.5 Hz, 3H), 0.90 (s, 3H), 0.84 (t, J = 7.2 Hz, 3H), 0.65 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): 80.96, 80.77, 76.30, 71.42, 71.38, 70.98, 70.93, 70.86, 70.80, 70.72, 70.66, 69.16, 68.71, 55.26, 46.24, 42.39, 41.88, 39.63, 37.00, 35.26, 34.72, 28.72, 28.33, 27.89, 27.53, 26.88, 23.16, 22.91, 22.73, 17.32, 12.38, 10.61. MALDI-TOF: 603.8 (Calc. M + Na 603.42) and 619.8 (Calc. M + K 619.397). HRMS (ES-TOF): 619.3958 (Calc. M + K 619.3976).

4. Conclusions

chola lariat ether.

1 showed greater binding with alkali metal ions compared to crown-7. The enhanced binding may be due to an additional stabilization of crown-ion complex by the 3-chiral recognition properties of this molecule.

This work

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