

The synthesis, Na⁺ binding properties of new coumarin-crown ethers

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Abstract *o*-Dihydroxy-3-(methylphenyl)-chromenones (coumarins; **3a–3c**) were synthesized from trimethoxybenzaldehydes through a reaction with the corresponding methylphenyl-acrylonitrile in pyridine·HCl and then H₃O⁺. Dihydroxycoumarins reacted with the ditosylate or dichloride derivatives of tri- or tetraethyleneglycols in the presence of CH₃CN/Na₂CO₃ and macrocyclic ethers with a coumarin moiety were obtained. The chromatographically purified new coumarin-crown ethers (**5a–5f**) were identified by IR, ¹H NMR, and Mass spectrometry. The binding constants of Na⁺ with the coumarin-crown ethers were determined in an 80 % dioxane/water binary solvent system at 25 °C from conductance measurements.

Keywords Coumarin-crown ethers · Synthesis · Complexation · Conductometry

Introduction

Since the discovery of crown ethers by Pedersen [1], their affinities for alkali and alkaline-earth cations have been established [2–4]. They are commonly used to bind cations, catalyse phase transfer reactions and transport ions across lipophilic membranes [5]. The complexation selectivity of crown ethers has often been explained in terms of the size-fit concept that the crown ether forms a more stable complex with the cation which is more suitable in size for the crown ether cavity. From many investigations of crown ether and cation interactions it was determined that crown

ethers can form variable complexes with cations that are too large to fit into the macrocyclic cavity [4, 6–10]. These kind of macrocycle-cation interactions have also been studied in different substituted crown ethers by several methods [11–21].

Crown ethers have a very wide range of industrial as well as biological applications. On the other hand, coumarins (2*H*-chromen-2-ones, 2*H*-1-benzopyran-2-ones) are among the best known oxygen heterocyclics with a δ-lactone ring and comprise a very large class of compounds found throughout the plant kingdom [22]. The bio-activity of coumarin involving compounds and its complexes appears to be based on the coumarin nucleus [23–25]. The biological importance of both crown ether and coumarins it is worthwhile to combine these two functional molecules into a single compound via synthetic methodology which maybe a potential candidate molecule for biologically important host–guest interactions.

In this study, a new type of 6,7-dihydroxy-3-(methylphenyl)-2*H*-chromenone crown ether compounds, 14-(2-methylphenyl)-2,3,5,6,8,9-hexahydro-13*H*-[1,4,7,10]tetraoxacyclododecino[2,3-*g*]chromen-13-one (**5a**), 17-(2-methylphenyl)-2,3,5,6,8,9,11,12-octahydro-16*H*-[1,4,7,10,13]pentaoxacyclopentadecino[2,3-*g*]chromen-16-one (**5b**), 14-(3-methyl phenyl)-2,3,5,6,8,9-hexahydro-13*H*-[1,4,7,10]tetraoxacyclododecino[2,3-*g*]chromen-13-one (**5c**), 17-(3-methylphenyl)-2,3,5,6,8,9,11,12-octahydro-16*H*-[1,4,7,10,13]pentaoxacyclopentadecino [2,3-*g*]chromen-16-one (**5d**), 14-(4-methylphenyl)-2,3,5,6,8,9-hexahydro-13*H*-[1,4,7,10]tetraoxacyclododecino[2,3-*g*]chromen-13-one (**5e**), and 17-(4-methylphenyl)-2,3,5,6,8,9,11,12-octahydro-16*H*-[1,4,7,10,13]pentaoxacyclo pentadecino[2,3-*g*]chromen-16-one (**5f**) were synthesized and characterized. Complexation abilities of these compounds with Na⁺ metal cation were examined with conductometric method.

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Experimental

General

Chemicals were from Fluka, Aldrich or Merck and were used without further purification. Initial compounds **3a–3c** were prepared as reported by our previously described method [26]. IR spectra were obtained using the KBr disc method on a Perkin Elmer BX-II spectrometer. High resolution EI mass spectra were determined by an Agilent 1100 LC/MSD, ^1H NMR spectra recorded by a Bruker-Spectrospin AvanceDPX-400 Ultra-Shield: 400 MHz and TMS was the internal standard. All melting points reported are uncorrected. Macrocycles **5a–5f** have been synthesized in our laboratories. NaCl was recrystallized three times from conductivity water and then heated to below its decomposition temperature at reduced pressure.

The conductometric study of coumarin-crown ethers with NaCl salt

All solutions were prepared in a dry box and transferred into the dry conductivity cell. All conductances were measured at 25 ± 0.05 °C. The measuring equipment consisted of a glass vessel (type Ingold) with an external jacket connected to a thermostatted water-bath (25 ± 0.05 °C) and a conductivity cell (Cole Parmer 19050-66 Model) with a conductometer (SUNTEX SC-170 Model).

The cell constant was determined to be 0.769 cm^{-1} at 25 °C by measuring the conductivity of aqueous potassium chloride solutions of different concentrations [27]. A value of molar conductivity of the pure metal ion solution (Λ_{MA}) was obtained at the appropriate electrolyte concentration before any addition of ligand was made.

General procedure for the synthesis of 3-(methylphenyl)-coumarin-crown ethers (**5a–5f**)

The typical procedure for the cyclisation reaction leading to macrocycle ethers (**5a–5f**) is as follows. A mixture of an equimolar amount of *o*-dihydroxycoumarins **3a–3c**, polyethylene glycol ditosylate or polyethylene glycol dichloride and two equimolar amount of alkali metal carbonate was dissolved in 60 mL of CH_3CN in a 250 mL reaction flask. The mixture was heated for 35–40 h at 80–85 °C. The solvent was evaporated in vacuo. Dilute HCl was added to the residue and the mixture was extracted with CHCl_3 (4×30 mL). The combined organic extracts were washed with water, dried over MgSO_4 and evaporated in vacuo. Chromatography of the crude products (silica gel 60, Merck) with chloroform gave pure coumarin-crown ethers (**5a–5f**).

14-(2-Methylphenyl)-2,3,5,6,8,9-hexahydro-13H-[1,4,7,10]tetraoxacyclododecino[2,3-g]chromen-13-one (**5a**)

Compound **3a** (1.12 mmol), Na_2CO_3 (2.24 mmol), **4a** (1.12 mmol) in CH_3CN (60 mL) reacted as described above to afford **5a**. Yield: 25.5 %. mp: 198–200 °C. IR (KBr): 2931 (C–H), 1727 (C=O), 1611–1568 (C=C), 1509–1363 (C–H), 1296–1169 (C–O) cm^{-1} ; ^1H NMR: (CDCl_3), δ (ppm): 2.35 (s, 3H), 3.82 (t, 4H), 3.87 (t, 2H), 3.97 (t, 2H), 4.26 (m, 4H), 6.95 (s, 1H), 7.13 (s, 1H), 7.28 (m, 4H), 7.55 (s, 1H); LC–MS (m/z): 383.3 ($\text{M} + 1^+$), 341 ($\text{M}^+ - \text{OCH}_2\text{CH}_2$), 268.9 (coumarin **3a**).

17-(2-Methylphenyl)-2,3,5,6,8,9,11,12-octahydro-16H-[1,4,7,10,13]pentaoxacyclopentadecino[2,3-g]chromen-16-one (**5b**)

A mixture of compound **3a** (1.12 mmol), Na_2CO_3 (2.24 mmol), and **4b** (1.12 mmol) and CH_3CN (60 mL) was stirred and heated and then worked up as described above to give **5b**. Yield: 6.03 %. mp: 163–165 °C. IR (KBr): 2866 (C–H), 1702 (C=O), 1615–1576 (C=C), 1507–1395 (C–H), 1276–1138 (C–O) cm^{-1} ; ^1H NMR: (CDCl_3), δ (ppm): 2.30 (s, 3H), 3.78 (t, 4H), 3.94 (t, 4H), 4.10 (t, 4H), 4.24 (t, 4H), 6.91 (s, 1H), 7.15 (s, 1H), 7.45 (m, 4H), 7.72 (s, 1H); LC–MS (m/z): 427.2 ($\text{M} + 1^+$), 428.1 ($\text{M} + 2^+$), 339.1 ($\text{M}^+ - 2\text{OCH}_2\text{CH}_2$), 269.0 (coumarin **3a**).

14-(3-Methylphenyl)-2,3,5,6,8,9-hexahydro-13H-[1,4,7,10]tetraoxacyclododecino[2,3-g]chromen-13-one (**5c**)

A mixture of compound **3b** (1.49 mmol), Na_2CO_3 (2.98 mmol) and **4a** (1.49 mmol) and CH_3CN (60 mL) was treated as described above to give **5c**. Yield: 16 %. mp: 92 °C. IR (KBr): 2923–2853 (C–H), 1704 (C=O), 1627–1567 (C=C), 1508–1357 (C–H), 1295–1127 (C–O) cm^{-1} ; ^1H NMR: (CDCl_3), δ (ppm): 2.40 (s, 3H), 3.75 (t, 4H), 3.90 (t, 4H), 4.20 (t, 4H), 6.80 (s, 1H), 7.10 (s, 1H), 7.30 (s, 1H), 7.55 (m, 3H), 7.70 (s, 1H); LC–MS (m/z): 383.1 ($\text{M} + 1^+$), 295.1 ($\text{M}^+ - 2\text{OCH}_2\text{CH}_2$), 269.1 (coumarin **3b**).

17-(3-Methylphenyl)-2,3,5,6,8,9,11,12-octahydro-16H-[1,4,7,10,13]pentaoxacyclopentadecino[2,3-g]chromen-16-one (**5d**)

Compound **3b** (1.49 mmol), Na_2CO_3 (2.98 mmol) and **4b** (1.49 mmol) in CH_3CN (60 mL) reacted as described to give **5d**. Yield: 6.3 %. Oily product. IR (KBr): 2920 (C–H), 1719 (C=O), 1600 (C=C), 1459 (C–H), 1291–1104 (C–O)

cm^{-1} ; $^1\text{H NMR}$: (CDCl_3), δ (ppm): 2.25 (s, 3H), 3.50 (m, 8H), 3.85 (t, 4H), 4.10 (t, 4H), 6.75 (s, 1H), 6.90 (s, 1H), 7.15 (m, 3H), 7.40 (s, 1H), 7.60 (s, 1H); LC-MS (m/z): 427.2 ($\text{M} + 1^+$), 428.1 ($\text{M} + 2^+$), 339.2 ($\text{M}^+ - 2\text{OCH}_2\text{CH}_2$), 295.0 ($\text{M}^+ - 3\text{OCH}_2\text{CH}_2$), 267.1 (coumarin **3b**).

14-(4-Methylphenyl)-2,3,5,6,8,9-hexahydro-13H-[1,4,7,10]tetraoxacyclododecino[2,3-g]chromen-13-one (5e)

A mixture of compound **3c** (1.49 mmol), Na_2CO_3 (2.98 mmol) and **4a** (1.49 mmol) and CH_3CN (60 mL) was stirred and heated and then worked up as described above to give **5e**. Yield: 6 %. mp: 238–240 °C. IR (KBr): 2925–2868 (C–H), 1706 (C=O), 1616–1573 (C=C), 1506–1350 (C–H), 1282–1100 (C–O) cm^{-1} ; $^1\text{H NMR}$: (CDCl_3), δ (ppm): 2.40 (s, 3H), 3.68 (t, 4H), 3.87 (t, 4H), 3.96 (t, 2H), 4.16 (t, 2H), 6.92 (s, 1H), 7.15 (s, 1H), 7.45 (d, 2H), 7.60 (d, 2H), 7.70 (s, 1H); LC-MS (m/z): 384.6 ($\text{M} + 2^+$), 293.2 ($\text{M}^+ - 2\text{OCH}_2\text{CH}_2$), 270.7 (coumarin **3c**).

17-(4-Methylphenyl)-2,3,5,6,8,9,11,12-octahydro-16H-[1,4,7,10,13]pentaoxacyclopentadecino[2,3-g]chromen-16-one (5f)

Compound **3c** (1.49 mmol), Na_2CO_3 (2.98 mmol) and **4b** (1.49 mmol) in CH_3CN (60 mL) reacted as described to give **5f**. Yield: 5.3 %. Oily product. IR (KBr): 2923–2852 (C–H), 1678 (C=O), 1585–1542 (C=C), 1450–1376 (C–H), 1302–1163 (C–O) cm^{-1} ; $^1\text{H NMR}$: (CDCl_3), δ (ppm): 2.32 (s, 3H), 3.61 (s, 2H), 3.70 (t, 6H), 3.88 (m, 4H), 4.11 (m, 4H), 6.75 (s, 1H), 6.85 (s, 1H), 6.95 (s, 1H), 7.40 (s, 1H), 7.50 (d, 1H), 7.65 (t, 1H), 7.85 (s, 1H); LC-MS (m/z): 427.1 ($\text{M} + 1^+$), 428.1 ($\text{M} + 2^+$), 339.1 ($\text{M}^+ - 2\text{OCH}_2\text{CH}_2$), 267.0 (coumarin **3c**).

Results and discussion

Organic synthesis

3-Aryl-6,7-dihydroxy-2H-chromenone compounds, **3a-3c**, were prepared from reaction of trimethoxybenzaldehyde and methylphenylacetonitrile in ethanol followed by treatment with pyridine.HCl and then H_3O^+ , as reported by us previously [26] and reacted with the triethyleneglycol ditosylate or tetraethyleneglycol dichloride in $\text{CH}_3\text{CN}/\text{Na}_2\text{CO}_3$ to afford 12-crown-4 and 15-crown-5-chromenones. The purified products were identified with IR, $^1\text{H NMR}$ and mass spectroscopy.

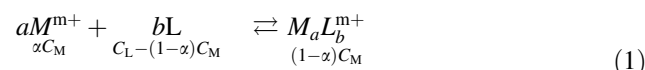
The IR spectra of **5a-5f** showed the characteristic absorption band of the carbonyl group (C=O) and benzene

ring should appear in the region 1,702–1,727 cm^{-1} and 1,542–1,627 cm^{-1} , respectively. One absorption band in the range 1,302–1,100 cm^{-1} corresponding to C–O–C ether chain. The $^1\text{H NMR}$ spectra of **5a-5f** in CDCl_3 show the expected peak resonances and peak integrals due to the protons of 3-methylphenyl-coumarin-crown ether derivatives. The $^1\text{H NMR}$ spectra of **5a-5f** showed characteristic signals for ether (–O–CH₂–CH₂–O–) protons at δ 3.50–4.20 ppm each a triplet. The peak at δ 2.30–2.40 ppm indicated the presence of –CH₃ group. In addition the chemical shifts of the aromatic protons are observed at δ 6.75–7.85 ppm. Also LC-MS spectra of **5a-5f** confirmed the formation of 3-methylphenyl-coumarin-crown ether derivatives (Scheme 1).

Complexation equilibria in 80 % dioxane/water; conductometric measurements

Various methods to calculate the stability constants from measurements of properties involving factors such as molar conductivity etc. have been described in the literature [28, 29].

When a crown compound forms a (M:L) complex with a cation, the equilibrium equation is written as



where M^{m+} , L, and α are the cation, crown compound, and fraction of free cations, respectively. Thus the equilibrium constants, K_e of complex formation, were calculated using Eqs. (2)–(13)

$$K_e = \frac{[M_a L_b^{m+}]}{[M^{m+}]^a [L]^b} \quad (2)$$

$$C_M / C_L = 1 \quad (3)$$

$$C_M = [M^{m+}] + [M_a L_b^{m+}] \quad (4)$$

$$C_L = [L] + [M_a L_b^{m+}] \quad (5)$$

$$\alpha = [M^{m+}] / C_M \quad (6)$$

$$\eta = \frac{[M_a L_b^{m+}]}{C_M} = K_e [L] / (1 + K_e [L]) \quad (7)$$

The observed conductivity, κ , is given by

$$\kappa = \kappa_{\text{MAm}} + \kappa_{\text{MaLbAm}} \quad (8)$$

The molar conductivities are

$$\Lambda_{\text{MAm}} = \kappa_{\text{MAm}} / [M^{m+}] \quad (9)$$

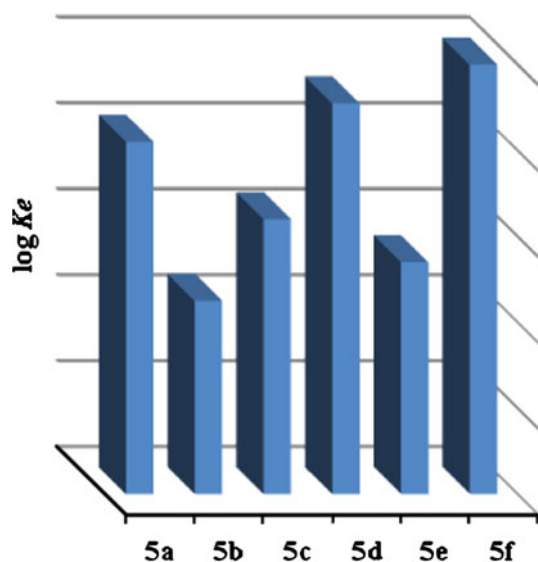
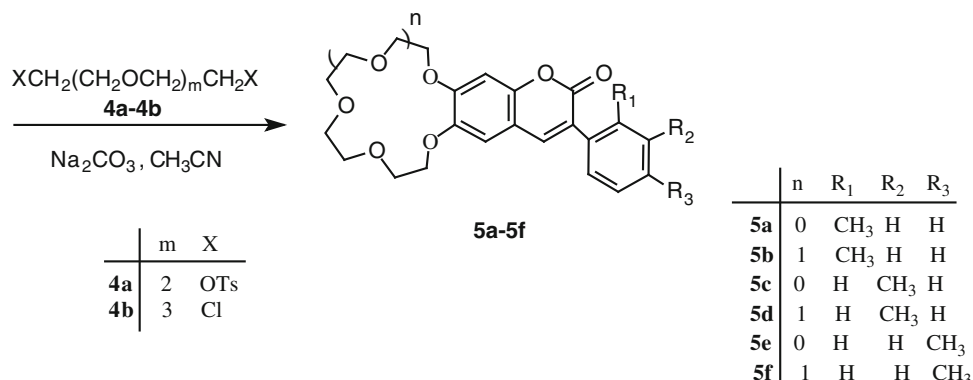
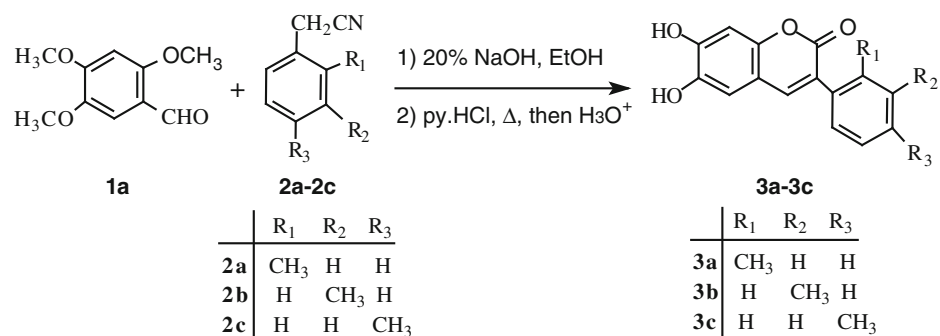
$$\Lambda_{\text{MaLbAm}} = \kappa_{\text{MaLbAm}} / [M_a L_b^{m+}] \quad (10)$$

$$\Lambda = \kappa / C_m \quad (11)$$

$$\Lambda = \alpha \Lambda_{\text{MAm}} + (1 - \alpha) \Lambda_{\text{MaLbAm}} \quad (12)$$

As a result of Eq. (12), Eq. (2) can be transformed into

$$K_e = (\Lambda_{\text{MAm}} - \Lambda) / ((\Lambda - \Lambda_{\text{MaLbAm}})[L]) \quad (13)$$

Scheme 1 Synthesized compounds**Fig. 1** The $\log K_e$ values for interactions of **5a–5f** with Na^+ in 80 % dioxane/water

where

$$[\text{L}] = C_L - C_M \eta$$

$$[\text{L}] = C_L - C_M (\Lambda_{\text{MAm}} - \Lambda) / (\Lambda_{\text{MAm}} - \Lambda_{\text{MaLbAm}})$$

Notations: C_M and C_L are the total concentrations of alkali metal and crown ether, respectively; $[\text{M}^{m+}]$, $[\text{L}]$ and $[\text{M}_a\text{L}_b^{m+}]$

Table 1 The $\log K_e$ and $-\Delta G^\theta$ (kcal/mol) values for the interactions of synthesized coumarin-crown ethers with NaCl in 80 % dioxane/water at 25 °C by a conductometric study

Coumarin-crown ethers	$\log K_e$	$-\Delta G^\theta$
5a	5.42	7388.55
5b	5.05	6884.21
5c	5.24	7141.11
5d	5.51	7512.38
5e	5.14	7014.69
5f	5.60	7637.96

Correlation coefficient: 0.999

are the concentrations of uncomplexed cation, uncomplexed crown ether and complexed cation respectively; η is the experimental mole fraction of the complexed cation or the ligand [Eqs. 1–13], κ_{MAm} , κ_{MaLbAm} are the observed conductivities of the electrolyte and the crown compound–electrolyte complex, respectively; Λ_{MAm} and Λ_{MaLbAm} are the designated molar conductivities of the electrolyte and the crown compound–electrolyte complex, respectively.

In the present work, the determination of equilibrium constants, $\log K_e$ of Na^+ ion with **5a–5f** (see Fig. 1), only the monomeric and electrically neutral crown compounds have been studied. Conductometric measurements in 80 % dioxane/water at 25 °C were used for the thermodynamic interpretations of the cation-macrocyclic ether interactions.

Dioxane is miscible in all proportions not only with many organic solvents but, in spite of its comparatively low relative permittivities, also with water (as a highly polar compound). This property has allowed numerous important ion–solvent interaction and conductometric cation binding studies with macrocycles [30–33]. Hence, we have chosen the 80 % dioxane/water binary solvent system.

Conclusions

The binding affinities of the sodium ion for coumarin-crown ethers **5a–5f** in 80 % dioxane/water have been measured by conductometric methods at 25 °C. The equilibrium constants and free energies, ΔG^θ of crown compound-cation complexes in 80 % dioxane/water have been estimated from Eqs. (1)–(13) and given in Table 1. The determined $\log K_e$ values of NaCl for the coumarin-crown ether compounds in 80 % dioxane/water decreased in the order of **5f** > **5d** > **5a** > **5c** > **5e** > **5b**. This indicates that complexation occurs between the coumarin-crown ethers and the sodium metal ions, and that the coumarin-crown ether-alkali metal ion complexes are less mobile than the free Na^+ ions. In the previous study [34], it was found that 15-crown-5- Na^+ metal ion and 12-crown-4- Na^+ metal ion complexes are more mobile than free Na^+ ions in 80 % dioxane/water mixture. Our results show that mobility of coumarin substituted crown ether- Na^+ metal ion complexes decreases when compared with mobility of non-substituted crown ether- Na^+ metal ion complexes.

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