Tetrahedron Letters 49 (2008) 4765–4767

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis and characterisation of the 3-amino-derivative of γ-cyclodextrin, showing receptor ability and metal ion coordination properties

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ARTICLE INFO

Article history:
Received 30 April 2008
Revised 20 May 2008
Accepted 20 May 2008
Available online 24 May 2008

Keywords:
γ-Cyclodextrin
Copper(II)
Stability constants
Anthraquinone

ABSTRACT

The 3-hydroxy group of one glucopyranosinic ring of γ-cyclodextrin was selectively substituted with an amino moiety to obtain a new compound able to complex copper(II). Indeed, the new ligand, an altro-γ-CD, forms stable complexes with Cu(II), as the analogous 3-amino derivative β-CD previously exploited for the chiral separation of some amino acids by ligand exchange mechanism in capillary electrophoresis. Furthermore, the ligand forms a stable inclusion complex with anthraquinone-2-sulfonate.

Cyclodextrins are commonly used in separation sciences[1] because of their ability to interact with a high number of species in aqueous solutions and for their intrinsic chirality.[2] Functionalized cyclodextrins, by coupling the specific interactions due to the substituting moiety to the intrinsic inclusion properties of native cyclodextrins, are more efficient in their recognition processes.[3] In our laboratory, the synthesis of pure derivatives of β-cyclodextrin, mainly by substitution with amino moieties,[4] which, as expected, show strong coordinating properties towards metal ions has been particularly developed. It was observed that these binary complexes between the metal ion and the cyclodextrin derivative show three recognition sites towards potential ligands, namely the cyclodextrin cavity, the substituting moiety and the coordinated metal ion. The availability of this kind of cyclodextrin derivatives as pure (single isomer) compound has proved helpful to be also in separation science, and, by exploiting their ability to give rise to metal ion complexes, in ligand exchange chromatography (LEC)[4a] and in ligand exchange capillary electrophoresis (LECE).[5] Recently, the 3-amino substituted β-cyclodextrin was synthesised and some enantiomeric pairs of α-amino acids were separated by LECE.[6] In order to investigate the influence that the cavity size exerts on the ability to give rise to metal complexes, as well as to inclusion complexes, here we report a study on the analogous derivative of the γ-cyclodextrin, the 3-deoxy-3-amino-2(*S*),3(*R*)-γ-cyclodextrin (compound **5**, Scheme 1). The pure derivatives of γ-cyclodextrin reported in literature are few,[7] and even fewer those substituted on the wider (secondary) rim.[8] The coordinating ability towards proton and copper(II) ion were studied by pH-metric potentiometry, while its ability to give rise to inclusion complexes was tested using as a guest the anthraquinone-2-sulfonate (AQS) by UV–vis titrations.

To synthesize **5**, a mixture of **1** and **2** was first refluxed to obtain **3**,[9] that was purified by reverse phase chromatography. An aqueous solution of **3** and Na_2CO_3 was stirred for 3 h at room temperature to obtain the intermediate **4**. Finally, NH_3 was added and the mixture was stirred under nitrogen at room temperature for 48 h to obtain compound **5**, which was purified by column chromatography on CM-Sephadex (yield: 90%).[10] The ^{1}H NMR (COSY, TOCSY and T-ROESY) data of **5** show the unequivalency of a glucopyranosinic ring following the substitution reaction. Furthermore, the coupling constants values concerning the substituted ring indicate that the altrose residue is in a $^1C_4 \leftrightarrows {}^0S_2 \leftrightarrows {}^4C_1$ conformational equilibrium[11,12] that seems to be shifted towards the $^0S_2$ conformation, as described for other γ-cyclodextrin derivatives.[8a]

The complexes of **5** with proton and copper(II) were investigated by potentiometric titrations. Potentiometric measurements were carried out at 25 °C and at an ionic strength of 0.1 mol dm^{-3} (KNO_3) in aqueous solution, using a home-made experimental apparatus previously described.[4a] The electrodes couples were calibrated on the pH = $-\log[H^+]$ scale.[4a] Usually solutions (2 ml) containing different amounts of **5** and HNO_3 or $Cu(NO_3)_2$ were titrated with standard KOH. The γ-cyclodextrin derivative concentrations ranged from 2.0×10^{-3} to 5.0×10^{-3} mol dm^{-3}. Metal to ligand

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doi:10.1016/j.tetlet.2008.05.093

ratios ranging from 1:1 to 1:1.5 were employed. The stability constants were evaluated using the program SUPERQUAD,[13] that minimizes the error-square sum of the differences between measured and calculated electrode potentials.

Log β values for proton and copper(II) complexation of **5** are reported in Table 1 together with the corresponding values of the analogous β-derivative[6] (hereafter named **6**) for comparison purpose. Log K values for the protonation of both cyclodextrins virtually coincide with that of glucosamine,[14] a simple amino derivative of glucose. It is noteworthy that protonation of both mono and oligosaccharides NH_2 group takes place at pH values lower than those for the protonation of an amino group. This clearly indicates that, in all cases, the molecules are stabilized by hydrogen bond formation in their unprotonated form.

Potentiometric analysis shows that several copper(II) complex species form in the pH range investigated (5.0–8.5), namely [CuL], $[Cu(L)_2]$, $[Cu(L)_2H_{-1}]$, $[Cu(L)_2H_{-2}]$ and $[Cu(L)_2H_{-3}]$. The last two species are the predominant ones at neutral and basic pH values, respectively (Fig. 1). Data in Table 1 reveal that the species formed by **5** are more stable than the analogous species formed by **6**. This clearly indicates that the larger cavity size and the resulting larger conformational mobility allow **5** to better fit the coordination requirements of copper(II) ion. Furthermore, data in Table 1 show that both cyclodextrins have a strong tendency to form species with a metal to ligand ratio of 1:2. This can be better appreciated by calculating the stepwise K_2 constant, concerning the following equilibrium:

$$[Cu(L)]^{2+} + L \leftrightarrows [Cu(L)_2]^{2+}$$

Contrary to the usual trend, $\log K_2$ value (4.25) is greater than $\log K_1$, thus indicating an extra-stabilization contribution due to the intramolecular interaction of the two cyclodextrin molecules in $[Cu(L)_2]$ species. Finally, even though the two cyclodextrins have the same coordinating group and thus the same set of coordinating atoms, that is, the NH_2 group and the oxygen atom of the hydroxy group in position 2, **6** forms the $[Cu(L)H_{-1}]$ species, whereas **5** does not. This behaviour should be ascribed to the strong tendency of **5** to form species containing two ligand molecules, even stronger than in **6**. It is the stronger competition by these species that prevents the formation of $[Cu(L)H_{-1}]$ species.

The complexation of **5** with AQS was studied by UV–vis titrations. The spectrophotometric measurements were carried out at 25 °C in 0.003 mol dm^{-3} acetate buffer (pH 4.8), using a diode-array Agilent 8543 spectrophotometer. Usually a 3.0×10^{-3}–5.0×10^{-3} mol dm^{-3} solution of **5** was added to a solution of the guest (1.5×10^{-5}–2.0×10^{-5} mol dm^{-3}) and 60–90 points were recorded for each independent titration runs. A multiwavelength and multivariate treatment of spectral data was performed by means of two different software programs: SPECFIT[15] and HYPERQUAD.[16] A titrations curve for **5**-AQS is shown in Figure 2.

The free guest shows two absorption bands at 256 and at 330 nm. The addition of **5** gives rise to a decreased absorbance intensity, but does not cause a shift in the λ_{max} values, as reported for similar systems.[17] The multiwavelength and multivariate treatment of data indicate the presence of a 1:1 species only for the system. The complex formation was also studied by investigating the effect of **5** on the fluorescence quenching of AQS. The fluorescence spectra were recorded by a Fluorolog3 Horiba Jobin Yvon spectrofluorimeter in the same experimental conditions employed for the UV–vis titrations. The AQS fluorescence intensity was measured at the maximum emission wavelength of 576 nm after excitation of solutions at 411 nm. An increase in the host concentration results in the decreased AQS fluorescence intensity at 576 nm, thus confirming the formation of the inclusion complex. The log β value reported in Table 1 show that **5** forms a quite stable complex with AQS, more stable than the analogous complex that underivatized γ-cyclodextrin forms with the same aromatic compound.[18] Evidently, the amino residue that is protonated at pH 4.8, serves as an anchoring point for the negatively charged sulfonate group of AQS, thus leading to a more stable inclusion complex.

The selective substitution of the 3-hydroxy group of one glucopyranosinic ring of γ-cyclodextrin with an amino moiety allowed us to obtain a compound able to coordinate copper(II) and to form a fairly stable complex with AQS. The capability of **5** to coordinate copper(II) and to quite strongly include an aromatic compound inside its cavity makes it and its copper complexes good candidates

Table 1
Log β values[a] for the complex formation of **5** and **6** with proton and copper(II) in water and for the complex formation of **5** with AQS in acetate buffer at 25 °C

Reaction	Log β (**5**)[b]	Log β (**6**)[c]
$L + H^+ \leftrightarrows [H(L)]^+$	7.76(5)	7.63
$Cu^{2+} + L \leftrightarrows Cu(L)]^{2+}$	3.95(5)	3.50
$Cu^{2+} + 2\ L \leftrightarrows Cu(L)_2]^{2+}$	8.20(5)	7.50
$Cu^{2+} + L \leftrightarrows Cu(L)H_{-1}]^+ + H^+$		−2.72
$Cu^{2+} + 2\ L \leftrightarrows Cu(L)_2H_{-1}]^+ + H^+$	2.49(1)	2.00
$Cu^{2+} + 2\ L \leftrightarrows Cu(L)_2H_{-2}] + 2H^+$	−3.82(2)	−4.99
$Cu^{2+} + 2\ L \leftrightarrows Cu(L)_2H_{-3}]^- + 3H^+$	−11.85(5)	
AQS + L ⇆ AQSL	3.7(1)	

[a] 2σ in parentheses.
[b] This work.
[c] Ref. 6.

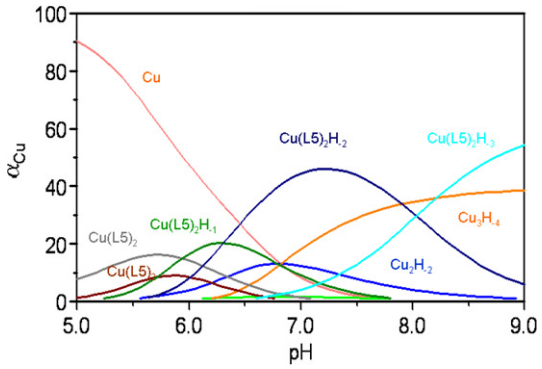


Figure 1. Species distribution diagram for Cu-**5**. $[Cu^{2+}] = 0.005$ mol dm^{-3}; Cu^{2+}:**5** = 1.2.

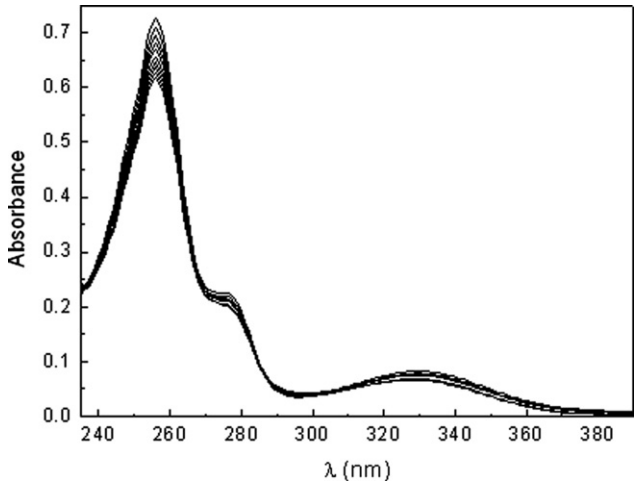
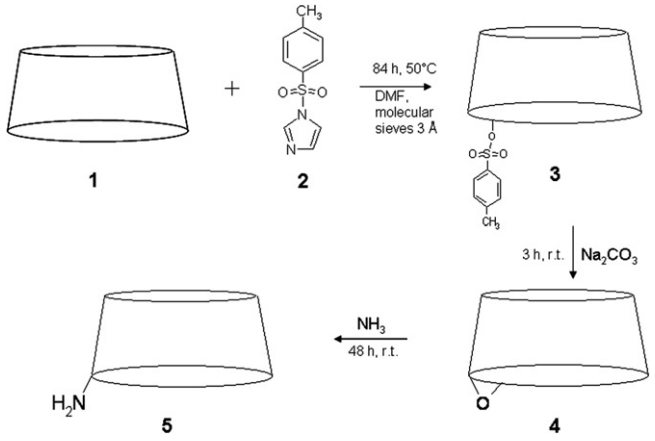


Figure 2. UV–vis selected titration curves for the AQS-**5** system in acetic buffer 10 out of 100.



Scheme 1.

as chiral selectors in LECE. The larger rim size and the different complex species formed in solution probably could give rise to different performances from **6**.

Acknowledgements

Dr. Angela Mammana is kindly acknowledged for spectrofluorimetric measurements. Università di Catania (Fondo di Ricerca di Ateneo 2006) is also acknowledged for partial financial support.

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10. ^{1}H NMR (D_2O, 500 MHz) ppm: 2.90 (dd, 1H, H-3A, $J_{3,4}$ = 4.0 Hz; $J_{3,2}$ = 8.4 Hz), 3.45–3.54 (m, 14H, H-2, H-4), 3.59 (m, H, H-2A, $J_{1,2}$ = 5.9 Hz; $J_{2,3}$ = 8.4 Hz), 3.73–3.93 (m, 29H, H-3, H-6, H-5), 4.1 (m, 1H, 5A), 4.71 (d, 1H, H-1A, $J_{1,2}$ = 5.9 Hz), 4.87 (d, 1H, H-1H, $J_{1,2}$ = 3.9 Hz), 4.94 (m, 2H), 4.97 (d, 1H, H-1, $J_{1,2}$ = 3.8 Hz), 4.99 (d,1H, H-1, $J_{1,2}$ 4.0 Hz), 5.05 (d, 1H, H-1, $J_{1,2}$ = 4.0 Hz). Anal. Calcd for $C_{48}H_{81}O_{39}N$: C, 44.48; H, 6.30; O, 48.14; N, 1.08. Found: C, 44.02; H, 6.56; O, 47.90; N, 1.28. This compound was also characterized by ESI-MS (m/z 1296 $(M+1)^+$), UV–vis measurements (λ_{max} (H_2O)/nm 222; ε/dm^3 mol^{-1} cm^{-1} 27053) and thermogravimetric analysis.
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