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Synthesis of lysine derivatives containing aza-crown ethers and a chromophore unit

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Abstract—The synthesis of a lysine-like chromo-ionophore and its derivatives, useful in peptide chemistry, is described. The influence of the peptide framework on the anthraquinone properties is examined with spectroscopic and electrochemical methods.

Since Pedersen's discovery of the ability of crown ethers to complex alkali metal ions, the development of ion-selective electrodes and molecular devices has become a major area of research in the field of molecular recognition.[1] Crown ethers, cyclams and cyclenes are used in analytical chemistry and radiomedicine (as metal carriers). Moreover, naturally occurring macrocycles such as valinomycine play an important role in potassium and sodium uptake in mitochondria. From the practical perspective, insertion of crown ethers into biologically active molecules could provide new tools for labelling biomolecules and for probing their structure, function and interactions with other relevant species present in the cell.[2,3]

The insertion of strong coordination centres into amino acids and peptides enables the construction of supramolecules, which may play a crucial role in molecular recognition studies. The synthesis of peptide frameworks suitable for the preparation of ion-selective molecular receptors is of particular interest. This objective can be reached by coupling the peptide with a crown ether, in which the cavity diameter can be easily changed to fit the metal ion, and a chromophore that can signal metal ion–cavity interactions. Usually, additional functional groups induce conformational changes within modified amino acids and peptides, thereby influencing their biological and chemical properties. Thus, the insertion of new coordination centres into the molecule of choice, which is necessary for constructing a new molecular device possessing a particular function, poses a real challenge from the preparative point of view.[4]

We decided to synthesise a macrocyclic system containing an ionophore able to form strong and selective ion complexes. 1,10-Anthraquinone was used as the signalling part of the supramolecule. In our previous paper we showed that a molecule consisting of a crown ether and anthraquinone is very sensitive towards alkali and alkaline earth metal ions.[5] Here the anthraquinone moiety acts as both chromophore and redox active switcher. We have now synthesised a new class of supramolecules based on aza-crown ethers and amino acids which possesses both optical and electrochemical activity.

The synthesis of lysine-containing aza-crown ethers is outlined in Scheme 1. Commercially available diaza-crown ether-12 **1** and 1-fluoroanthraquinone[6] were heated in toluene at 35 °C for 48 h with Cs_2CO_3 to yield **2** in 62% yield.[7] When the temperature was maintained at 35 °C (and no higher) for a 24 h, only one product was obtained. At temperatures above 35 °C the yield of mono-substituted diaza-crown ethers fell and that of the disubstituted products increased. A change in solvent polarity, as suggested by other studies,[8] led to a dramatic increase in the number of side products.

The aminoanthraquinone aza-crown ethers were reacted with *t*-butyl chloroacetate to form compound **3** in high yield.[9] Compound **3** can be used without additional

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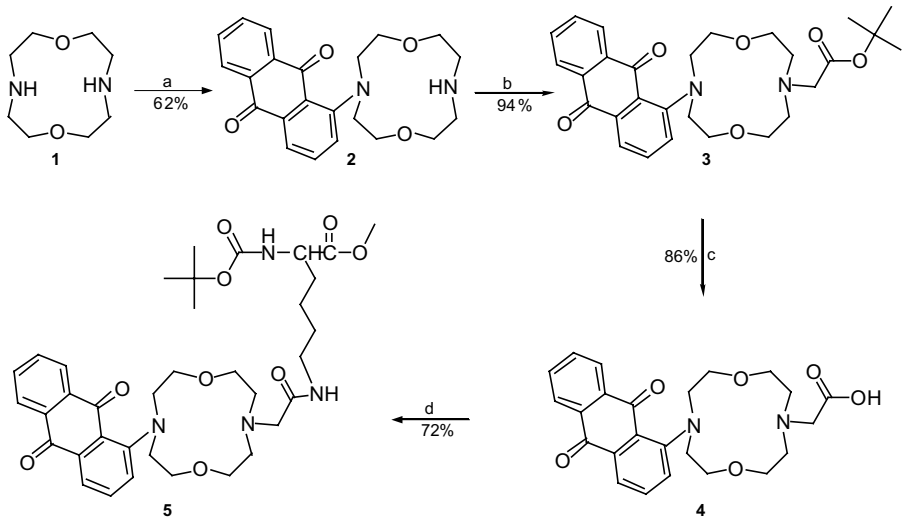

Scheme 1. Reagents: (a) 1-fluoroanthraquinone, Cs_2CO_3, toluene, 35 °C; (b) *t*-butyl chloroacetate, Na_2CO_3, acetonitrile, reflux; (c) trifluoroacetic acid, rt; (d) Boc-Lys-OMe, HOBt, TEA, dichloromethane, rt.

purification for the next step of the synthesis. The *t*-butyl group was removed using CF_3COOH to yield **4**.[10] The crude product was purified by ion-exchange chromatography (Sepharose Q, OH-form) and then by flash chromatography on silica gel. Compound **4** was then reacted with Boc-Lys-OH forming **5** in 72% yield.[11]

The anthraquinone derivatives, synthesised according to the procedures described above, exhibited the expected spectroscopic characteristics.[12] The UV–vis absorption of 1-aminoanthraquinones derivatives is of a π–π* nature and is due to electron intramolecular transfer (EIT) from the substituted amino group to the anthraquinone nucleus. The position, as well as the extinction coefficients, of maxima in the long-wavelength region of the UV–vis spectra of the anthraquinone derivatives **2**–**5** in acetonitrile, DMSO and MeOH:H_2O (1:1) solutions are shown in Table 1.

The introduction of lysine into the anthraquinone aza-crown ether system does not change the position of the absorption band, but does decrease its intensity from $\varepsilon = 4570$ for **2** to $\varepsilon = 3430$ for **5** (in acetonitrile). For all the compounds analysed, a change in solvent to the more polar DMSO, caused a bathochromic shift of the long-wavelength absorption band to 510–518 nm and increased its intensity by 5–10%.

All electrochemical measurements were carried out in acetonitrile solution on a glassy carbon electrode. The cyclic voltammograms (CV) of **2**, **3**, and **5** exhibited two principal successive one-electron reduction steps.[13] The reversibility of the first electron transfer in all the compounds investigated is demonstrated in Figure 1. The second reduction process is practically irreversible and leads to the formation of dianions Q^{2-}, which appear to be unstable in solution:

$$Q + e^- \leftrightarrows Q^{\cdot -}$$

$$Q^{\cdot -} + e^- \leftrightarrows Q^{2-}$$

In the anodic part of the cyclic voltammograms, there was one additional oxidation wave with respective maxima at −0.739 V, −0.755 V and −0.739 V for **2**, **3** and **5** (Fig. 1). However, the mechanism of this oxidation process is unclear.[14]

A quite different behaviour was found for species **4**. Only one reduction wave with a reduction peak at maximum (E_{pc}) at −0.80 V was visible in the cyclic voltammogram, whereas the anodic wave appeared at −0.25 V ($E_{pa} = -0.25$ V). The double height of the reduction pick at −0.80 V in comparison with other compounds suggests that the reduction is a two-electron process.

$$Q + 2e \leftrightarrows Q^{2-}$$

In the next step, the electrochemically generated dianion Q^{2-} reacts with a proton to form a carboxylic group, which reoxidises at a more positive potential

Table 1. The absorption maxima λ (nm) and their molar extinction coefficients ε [M^{-1}, cm^{-1}] for the anthraquinone derivatives **2**–**5** in acetonitrile, DMSO and H_2O/MeOH (1:1) solution

	CH_3CN		DMSO		H_2O/MeOH	
Compound	λ (nm)	ε (dm^3/molcm)	λ (nm)	ε (dm^3/molcm)	λ (nm)	ε (dm^3/molcm)
2	502	4570	512	4280	511	3570
3	510	4620	518	4920	518	s[a]
4	502	3620	514	3450	515	3370
5	503	3430	512	3650	513	3380

[a] Very slightly soluble.

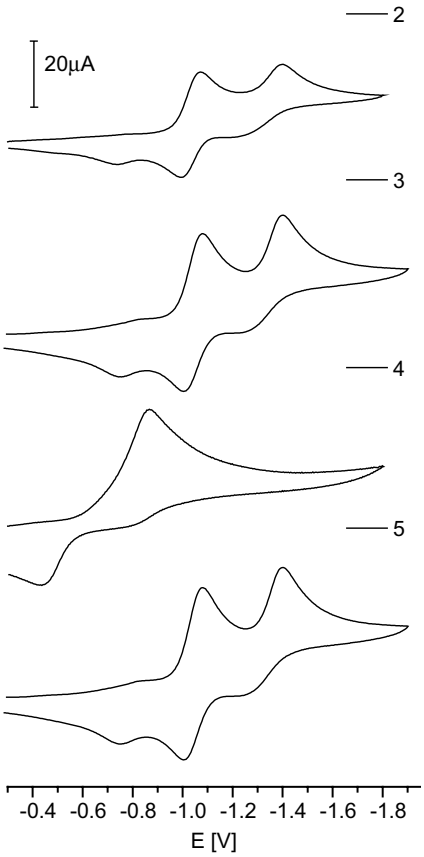

Figure 1. Cyclic voltammetry of the compounds **2**, **3**, **4** and **5** on a glassy carbon electrode in acetonitrile solution. 0.1 M TEAP, SCE, scan rate 0/1 V/s.

(−0.412 V). Moreover, the reduction pattern of compound **4** is different from that observed for **2** in acidic solution.

The spectroscopic data shows that the aminoanthraquinone derivative **2** is not protonated in acetonitrile solution in the presence of weak carboxylic acids. However, for all the compounds investigated in acetonitrile, the molar absorption coefficient at 510 nm decreases as a result of the sub-molecular concentration of strong acids like CF_3COOH. In neutral solution, the absorption coefficient of compound **4** exhibited a very small decrease in the wavelength range, as compared to other anthraquinone derivatives (see Table 1). These facts suggest that the anthraquinone site is not protonated in **4** in spite of the presence of the carboxylic group. Intramolecular proton transfer probably takes place during the reduction of **4**, since a single-step, two-electron reduction is recorded rather than the two successive one-electron reduction steps observed with **2** and **3**. The electrochemical investigations support the hypothesis that the reduction potential in acidic solution for all the compounds investigated appears at much higher positive potentials than those observed for **3**.[15] Our studies indicate that the peptide framework present in the lysine derivatives containing an azamacrocycle and anthraquinone has a significant impact on the coordination properties and reaction/oxidation potentials of the macrocycles under investigation.

Acknowledgments

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References and notes

1. For an overview, see: Gockel, G. W. In *Comprehensive Supramolecular Chemistry*; Pergamon, 1996; Vol. 1.
2. Lankiewicz, L.; Malicka, J.; Wiczk, W. *Acta Biochim. Pol.* **1997**, *44*, 477–490.
3. De Sousa, E. S.; Hirata, I. Y.; Juliano, L.; Ito, A. S. *Biochem. Biophys. Acta* **2000**, *1474*, 251–261.
4. Voyer, N.; Lamothe, J. *Tetrahedron* **1995**, *51*, 9241–9284.
5. Ossowski, T.; Kira, J.; Rogowska, D.; Warmke, H.; Młodzianowski, J. *J. Chem. Soc. Dalton Trans.* **2000**, 689–696.
6. Valkanas, G.; Hopff, H. *J. Org. Chem.* **1962**, *27*, 3680–3682.
7. Compound **2**. A mixture of 1,7-dioxa-4,10-diaza-cyclododecane (2 g, 11.5 mmol), 1-fluoroanthraquinone (2.84 g, 12.6 mmol), caesium carbonate (7.47 g, 23 mmol) and toluene (12 mL) was placed in a round-bottomed flask and maintained at 35 °C for 48 h. After cooling to room temperature the reaction mixture was filtered and the precipitate rinsed with methylene chloride (60 mL). Next, the red organic layer was washed with 1 M tetrabutylammonium hydroxide (50 mL), water (50 mL) and dried over anhydrous magnesium sulphate. The solid was purified using flash column chromatography on silica gel (eluting with CH_2Cl_2/MeOH, 5/1) to afford 2.7 g of **2** as a red solid (62%); mp: 96 °C. ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 2.89 (4H, s), 3.51–3.63 (12H, m), 7.65 (1H, t, J = 8 Hz), 7.71–7.79 (2H, m), 7.96–7.99 (2H, m), 7.22 (2H, q, J = 7.2 Hz; ^{13}C-NMR (100 MHz, $CDCl_3$), δ (ppm): 50.22, 57.12, 69.26, 71.86, 116.52, 119.36, 124.05, 129.88, 131.92, 139.46, 141.35, 187.02. FAB-MS, (*m*/*z*): 381.1 $[M + H]^+$, (MW = 380.1). Elemental analysis calculated for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36%; found: C, 69.22; H, 6.45; N, 7.42%.
8. Echegoyen, L.; Lawson, R. C.; Lopez, C. *J. Org. Chem.* **1994**, *59*, 3814–3820.
9. Compound **3**. A mixture of **2** (1.5 g, 4 mmol), sodium carbonate (0.85 g, 8 mmol), *t*-butyl chloroacetate (0.63 mL, 4.4 mmol) and acetonitrile (7 mL) was refluxed for 24 h. After cooling to room temperature, the mixture was filtered and the residue washed with methylene chloride (40 mL). The organic layer was washed with water (40 mL), dried over anhydrous magnesium sulphate and the solvent was evaporated to yield 1.86 g (94%) of the desired compound as a red solid; mp: 82 °C. ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.45 (9H, s), 2.87 (4H, t, J = 4.6 Hz), 3.31 (2H, s), 3.43 (4H, t, J = 4.6 Hz), 3.67 (8H, t, J = 6.6 Hz), 7.55 (1H, t, J = 8 Hz), 7.68–7.84 (4H, m) 8.21 (2H, t, J = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$), δ (ppm): 28.61, 54.74, 55.86, 58.33, 69.60, 70.68, 82.31, 120.38, 127.77, 129.97, 134.55, 135.53, 137.12, 153.05, 173.00, 183.55; FAB-MS, (*m*/*z*): 495.2 $[M+H]^+$, (MW = 494.5). Elemental analysis calculated for $C_{28}H_{34}N_2O_6$: C, 68.00; H, 6.93; N, 5.66%; found: C, 67.95; H, 6.88; N, 5.69%.
10. Compound **4**. Trifluoroacetic acid (15 mL) was added to 1.2 g of **3** (2.4 mmol) and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated to dryness and the residue dissolved in water and purified using ion-exchange chromatography (Sepharose Q OH^- form, eluting with 0.01 M ammonium acetate). Water was

evaporated and the residue was filtered though silica gel (eluting with AcOEt/MeOH, 1/1) affording 0.92 g of **4** as a red solid (86% yield); mp: 115 °C. ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 3.16 (4H, s), 3.55 (2H, s), 3.57–3.62 (12H, m), 7.69–7.81 (4H, m), 7.94 (1H, d, J = 6.8 Hz), 8.18–8.24 (2H, m): ^{13}C-NMR (100 MHz, $CDCl_3$), δ (ppm): 54.72, 56.33, 59.61, 65.46, 70.11, 121.93, 127.50, 128.08, 132.47, 134.53, 135.60, 152.65, 174.82, 181.12; FAB-MS, (*m*/*z*): 439.4 $[M + H]^+$, (MW = 438.4); RP-HPLC: R_T = 15.88 min (100%). Elemental analysis calculated for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39%; found: C, 65.65; H, 5.87; N, 6.33%.

11. Compound **5**. Boc-Lys-OMe was added to a mixture of **4** (0.26 g, 0.6 mmol), HOBt (0.081 g, 0.6 mmol), TEA (0.246 mL, 1.8 mmol) in dichloromethane (4 mL), and the reaction mixture was stirred at room temperature for 4 h. Then 30 mL of dichloromethane was added, the organic layer was washed twice with water (40 mL) and dried over anhydrous magnesium sulphate. The solid was purified by flash column chromatography on aluminium oxide (eluting with CH_2Cl_2/MeOH 200:1) to afford 0.3 g of **5** (72% yield), mp: 58 °C. ^{1}H-NMR (400 MHz, DMSO), δ (ppm): 1.33 (9H, s), 1.38–1.78 (6H, m), 2.61 (2H, t, J = 4.2 Hz), 3.02–3.05 (2H, m), 3.31 (15H, s), 3.61 (2H, s), 3.67–3.68 (2H, m), 3.72–3.82 (1H, m), 7.64–7.72 (3H, m), 7.83–7.90 (4H, m), 8.10 (2H, t, J = 7.2 Hz); ^{13}C-NMR (100 MHz, DMSO), δ (ppm): 22.72, 28.34, 30.25, 51.49, 53.39, 58.54, 67.60, 118.18, 126.52, 133.38, 135.08, 149.15, 150.87, 160.82, 170.22; FAB-MS, (*m*/*z*): 681.7 $[M + H]^+$, (MW = 680.7); RP-HPLC: R_T = 22.60 min (100%).
12. Yoshida, Z.; Takalayasi, F. *Tetrahedron* **1968**, *24*, 933–943.
13. Lehman, M. W.; Evans, D. H. *J. Electroanal. Chem.* **2001**, *500*, 12–20.
14. Lehman, M. W.; Evans, D. H. *J. Phys. Chem. B* **2001**, *105*, 8877–8884.
15. Ossowski, T.; Zalewski, L.; Niedziałkowski. P.; Szymańska, A., unpublished data.