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Short Note

Aza-27-crown-9 Amino Acid

Andreas Späth and Burkhard König *

Institute of Organic Chemistry, University of Regensburg, D-93040 Regensburg, Germany

* Author to whom correspondence should be addressed; Fax: +49-943-941-1717;
E-Mail: Burkhard.Koenig@chemie.uni-regensburg.de.

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Abstract: A luminescent aza-27-crown-9 ether amino acid was prepared by a three-step reaction sequence. The compound signals ammonium ion binding by an increase in emission intensity.

Keywords: aza crown ether; amino acid; receptor; luminescence

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1. Introduction

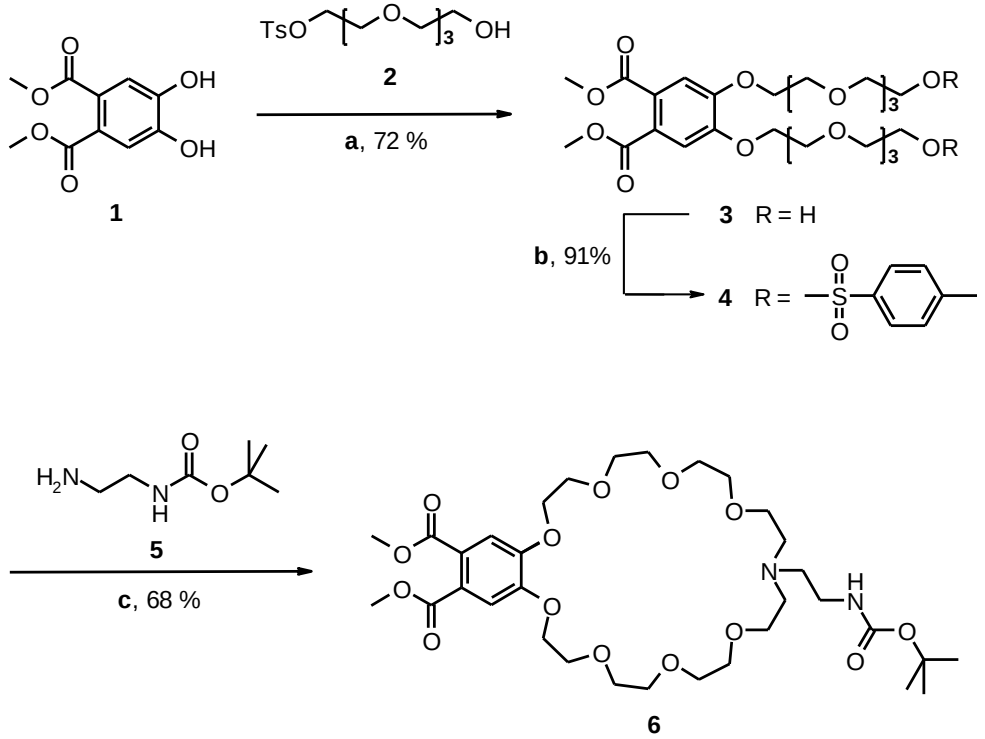
Crown ethers of appropriate size are known to be suitable hosts for a variety of ions [1–3]. We have recently developed crown ether amino acids (CEAAs, 21-crown-7) with a luminescent moiety, which bind ammonium ions and indicate the recognition event by changes in their specific emission properties. The units can be covalently linked by peptide coupling to more extended receptors showing high specificity for N-terminal lysine in peptides [4,5] or with other recognition motifs binding for example histidine peptides [6,7]. The ability of benzo-27-crown-9 ethers to bind guanidinium ions is known [8,9], was applied in extraction experiments [10] and has been proven by crystal structures [11,12]. Examples of related chemosensors were employed for detecting naturally occurring toxins [13,14].

2. Synthesis

Tetraethyleneglycol ether chains are attached to 4,5-dihydroxyphthalic acid methyl ester (**1**) by reaction with an excess of tosylate **2** at elevated temperature in DMF under basic conditions.

Subsequent tosylation and nucleophilic macrocyclisation with boc-ethylenediamine (**5**) gives the luminescent aza-27-crown-9 ether amino acid (**6**) in good overall yield of 45%.

Scheme 1. Synthesis of aza-27-crown-9 ether amino acid.



Conditions: (a) DMF, K_2CO_3, 90 ℃, overnight; (b) THF, H_2O, KOH, TsCl, 0 ℃ to RT, 3 h; (c) MeCN, H_2O, K_2CO_3, KI, reflux, over night.

3. Experimental

Compound **1** [15–17], **2** [18] and **5** [19] were prepared following literature known procedures. The complete analytics for the intermediates **3** and **4** can be found in the supporting information.

Dimethyl 13-(2-(tert-butoxycarbonylamino)ethyl)-3,5,6,8,9,11,12,13,14,15,17,18,20,21,23,24-hexadecahydro-2H-benzo[k][1,4,7,10,13,16,19,22,25]octaoxaazacycloheptacosine-27,28-dicarboxylate (**6**)

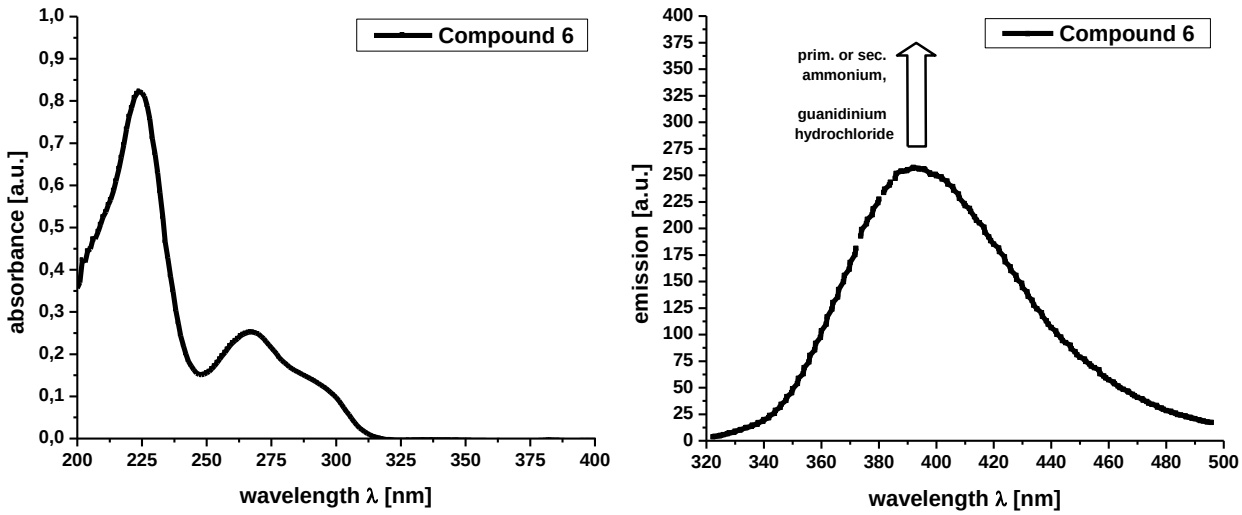
(**a**) To a mixture of 0.68 g dimethyl-4,5-dihydroxyphthalate (**1**) (3 mmol) and 1.38 g K_2CO_3 (10 mmol) in DMF (5 mL), 3.5 g tetraethyleneglykole monotosylate (**2**) (10 mmol) in DMF (5 mL) were added and stirred under nitrogen at 60 ℃ overnight. After cooling to room temperature, the mixture was poured into 30 mL of ice-cold saturated NH_4Cl solution. The resulting mixture was extracted four times with 10 mL of DCM. The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. Traces of DMF were removed with the aid of a high-vacuum pump. The residue was purified by flash chromatography on silica gel (Et_2O/EtOH 1:1, R_f = 0.16) to afford compound **3** as a yellow sticky oil (1.25 g, 2.16 mmol, 72% for step **a**).

(**b**) The product from the previous step (**3**) (1.16 g, 2.0 mmol) and 1.14 g of 4-toluenesulfonyl chloride (6.0 mmol) were dissolved in 20 mL of THF. A cold solution of potassium hydroxide (0.73 g, 13.0 mmol) in 3 mL of water was added dropwise at 0 ℃ over a period of 1 h. The mixture was stirred for 2 h at room temperature and poured into 60 mL of a vigorously stirring mixture of water and diethylether (1:3; v/v). The aqueous phase was extracted three times with 30 mL of diethylether. The combined organic phases were washed once with 30 mL of saturated aqueous NH_4Cl solution, then with 30 mL of water and dried over $MgSO_4$. The solvent was evaporated to yield **4** as a pale yellow, sticky oil (1.62 g, 1.83 mmol, 91% for step **b**).

(**c**) Compound **4** (1.11 g, 1.25 mmol) was dissolved in acetonitrile (20 mL), containing 0.2 mL of water. The mono-boc-protected ethylene diamine **5** (205 mg, 1.25 mmol), KI (310 mg, 1.8 mmol) and K_2CO_3 (1.67 g, 12.5 mmol) were added successively. The mixture was refluxed overnight and filtered over celite after cooling. The filter cake was washed with acetonitrile and dichloromethane. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (ethyl acetate / ethanol 3:1) to give the product **6** as a clear, yellow oil (R_f = 0.1) in an overall yield of 45% (610 mg, 0.85 mmol, 68% for step **c**).

MF: $C_{34}H_{57}N_2O_{14}$; **FW:** 717.84 g/mol; **UV** (MeOH): λ (ε) = 269 (8900), 225 (29600); **IR** (KBr): ν [cm^{-1}] = 3360 (w), 2920 (m), 2946 (m), 2870 (m), 1714 (s), 1598 (m), 1516 (m), 1436 (m), 1351 (m), 1285 (s), 1251 (m), 1182 (s), 1122 (s), 1062 (m), 978 (m), 946 (m), 882 (w), 782 (m), 659 (w); **MS** (ESI-MS, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): e/z (%) = 703.4 (100, MH^+); - **HRMS** (PI-LSIMS FAB, MeOH/Glycerine): calc. for $C_{33}H_{55}N_2O_{14}^+$ [MH^+]: 703.3653, found: 736.3659; **EA** ($C_{34}H_{57}N_2O_{14}$ * 2 H_2O): calc. C 53.6, H 7.9, N 3.8, found. C 53.3, H 7.8, N 3.7.; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 1.42 (s, 9 H), 2.74 (m, 2 H), 2.83 (m, 4 H), 3.20 (m, 2 H), 3.51–3.78 (m, 20 H), 3.80–3.96 (m, 4 H), 3.86 (s, 6 H), 4.20 (m, 4 H), 5.61 (bs, 1 H), 7.18 (s, 2 H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ [ppm] = 28.5 (+, 3 C), 29.7 (-, 1 C), 38.9 (-, 1 C), 52.6 (+, 2 C), 54.3 (-, 2 C), 68.8 (-, 2 C), 69.2 (-, 2 C), 69.5 (-, 2 C), 70.5 (-, 2 C), 70.7 (-, 2 C), 70.7 (-, 2 C), 71.1 (-, 2 C), 78.9 (C_{quat}, 1 C), 113.7 (+, 2 C), 125.4 (C_{quat}, 2 C), 150.5 (C_{quat}, 2 C), 156.2 (C_{quat}, 1 C), 167.8 (C_{quat}, 2 C).

Figure 1. Absorption and emission spectra of compound **6** (c = 2.8 × 10^{-5} mol/L) in methanol solution.



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References and Notes

1. Gokel, G.W. *Crown Ethers and Cryptands*; Royal Society of Chemistry: Cambridge, UK, 1991.
2. Izatt, R.M.; Pawlak, K.; Bradshaw, J.S. Thermodynamic and Kinetic data for macrocycle interactions with cations and anions. *Chem. Rev.* **1991**, *91*, 1721–2085.
3. Izatt, R.M.; Bradshaw, J.S.; Nielsen, S.A.; Lamb, J.D.; Christensen, J.J. Thermodynamic and kinetic data for cation-macrocycle interaction. *Chem. Rev.* **1985**, *85*, 271–339.
4. Späth, A.; König, B. Modular synthesis of di- and tripeptides of luminescent crown ether aminocarboxylic acids. *Tetrahedron* **2009**, *65*, 690–695.
5. Mandl, C.P.; Koenig, B. Luminescent crown ether amino acids-selective binding to N-terminal lysine in peptides. *J. Org. Chem.* **2005**, *70*, 670–674.
6. Kruppa, M.; Mandl, C.; Miltschitzky, S.; König, B. A luminescent receptor with affinity for N-terminal histidine in peptides in aqueous solution. *J. Am. Chem. Soc.* **2005**, *127*, 3362–3365.
7. Stadlbauer, S.; Riechers, A.; Späth, A.; König, B. Utilizing reversible copper(II) peptide coordination in a sequence-selective luminescent receptor. *Chem. Eur. J.* **2008**, *14*, 2536–2541.
8. Kyba, E.P.; Helgeson, R.C.; Madan, K.; Gokel, G.W.; Tarnowski, T.L.; Moore, S.S.; Cram, D.J. Host-guest complexation. 1. Concept and illustration. *J. Am. Chem. Soc.* **1977**, *99*, 2564–2571.
9. Lehn, J.-M.; Vierling, P.; Hayward, R.C. Stable and selective guanidinium and imidazolium complexes of a macrocyclic receptor molecule. *J. Chem. Soc. Chem. Commun.* **1979**, 296–298.
10. Stolwijk, T.B.; Grootenhuis, P.D.J.; van der Wal, P.D.; Sudhölter, E.J.R.; Reinhoudt, D.N.; Harkema, S.; Uiterwijk, J.W.H.M.; Kruise, L. Crown ether mediated transport of guanidinium thiocyanate through a bulk liquid membrane and the correlation with the complex stability constants. *J. Org. Chem.* **1986**, *51*, 4891–4898.
11. de Boer, J.A.A.; Uiterwijk, J.W.H.M.; Geevers, J.; Harkema, S.; Reinhoudt, D.N. Macrocyclic receptor molecules for guanidinium cations. Preparation, X-ray structures, and kinetic stabilities of 1:1 complexes of guanidinium perchlorate with benzo-27-crown-9, dibenzo-27-crown-9, and dibenzo-30-crown-10. *J. Org. Chem.* **1983**, *48*, 4821–4830.
12. Van Staveren, C.J.; Hertog, H.J.; Reinhoudt, D.N.; Uiterwijk, J.W.H.M.; Kruise, L.; Harkema, S. Syntheses and crystal structures of encapsulated guanidinium complexes of 27-membered macrocyclic ligands. *J. Chem. Soc. Chem. Commun.* **1984**, 1409–1411.
13. Gawley, R.E.; Mao, H.; Haque, M.M.; Thorne, J.B.; Pharr, J.S. Visible fluorescence chemosensor for saxitoxin. *J. Org. Chem.* **2007**, *72*, 2187–2191.
14. Mao, H.; Thorne, J.B.; Pharr, J.S.; Gawley, R.E. Effect of crown ether ring size on binding and fluorescence response to saxitoxin in anthracylmethyl monoazacrown ether chemosensors. *Can. J. Chem.* **2006**, *84*, 1273–1279.
15. Murai, S.; Ryu, I. Two types of indirect cyclodimerization of biacetyl via its enol silyl ethers. *Chem. Lett.* **1977**, 1219–1222.

16. House, H.O.; Czuba, L.J.; Gall, M.; Olmstead, H.D. Chemistry of carbanions. XVIII. Preparation of trimethylsilyl enol ethers. *J. Org. Chem.* **1969**, *34*, 2324–2336.
17. Drager, A.S.; O'Brien, D.F. Novel synthesis of liquid crystalline phthalocyanines. *J. Org. Chem.* **2000**, *65*, 2257–2260.
18. Menzer, R.; Parsons, I.W.; Preece, J.A.; Stoddart, J.F.; Tolley, M.S.; White, A.J.P.; Williams, D.J. Bis[2]catenanes and a bis[2]rotaxane-model compounds for polymers with mechanically interlocked components. *Chem. Eur. J.* **1996**, *2*, 31–44.
19. James F.; Callahan, J.F.; Ashton-Shue, D.; Bryan, H.G.; Bryan, W.M.; Heckman, G.D.; Kinter, L.B.; McDonald, J.E.; Moore, M.L.; Schmidt, D.B.; Silvestri, J.S.; Stassen, F.L.; Sulat, L.; Yim, N.C.F.; Huffman, W.F. Structure-activity relationships of novel vasopressin antagonists containing C-terminal diaminoalkanes and (aminoalkyl)guanidines. *J. Med. Chem.* **1989**, *32*, 391–396.