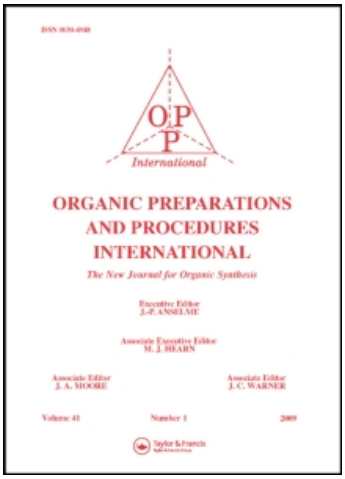

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SYNTHESIS AND ESI-MS STUDY OF NEW N-FUNCTIONALIZED MACROCYCLIC POLYAMINE AND AZACROWN ETHER DERIVATIVES

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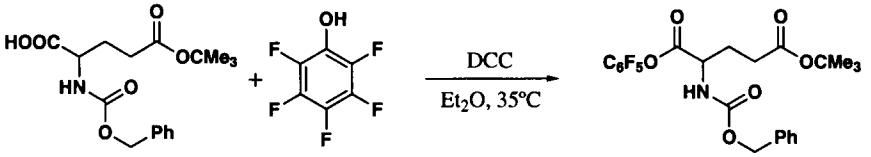
A continuing interest in macrocyclic ligands with *N*-donor atoms is a result of their versatility.[1] The possibility of using synthetic macrocycles as models for biologically important ligands has initiated a broad spectrum of research activities, including the preparation of new ring systems with pendant arms. They are characterized by formation of stable metal complexes that are useful in medicine,[2] as models for carrier molecules, in metal recovery, as metal catalysts, as agents for cleavage of phosphate esters, as MRI contrast agents, for radioactive diagnosis and treatment and as anti-HIV agents. Another area of interest considers such systems as components of devices for a cation sensor and switch.[3] The properties of any ligand studied depend strongly on modifications of the pendant arm as they provide both modification of complexing abilities and new features strictly connected with a substituent type. Thus, the presence of naphthalene linked to the macrocyclic ligand for example could give rise to a fluoroionophore formation.[4] One of the important elements of lariat ethers is their flexibility, property that may be used to advantage. Nitrogen is widely used as the attachment atom because it provides higher overall mobility of side-arms compared to those attached to carbon. Such *N*-pivot lariat ethers are based on azacrown ethers with O and N-donor atoms and aza-macrocycles with *N*-donors in the macrocyclic moiety.[5]

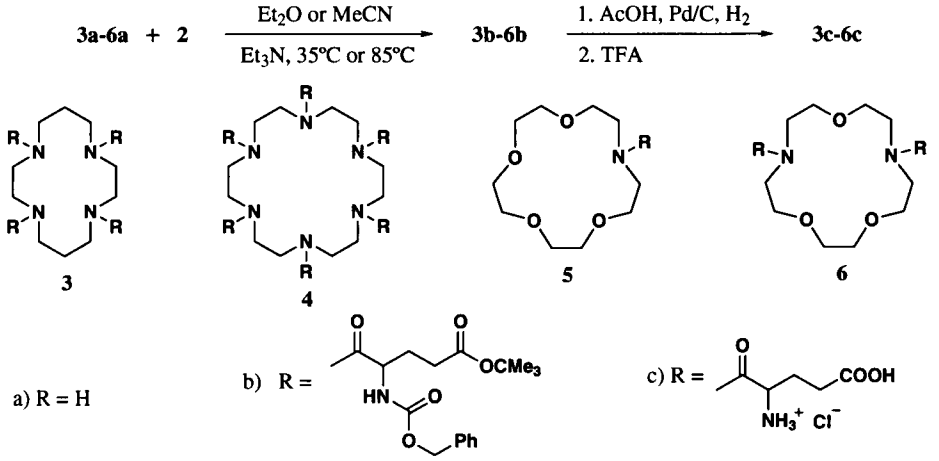
Recently we have focused on different derivatives of cyclic polyamines,[6,7] such as 1,4,8,11-tetraazacyclotetradecane (cyclam) and 1,4,7,10,13,16-hexaazacyclooctadecane (hexacyclen) and successfully obtained a collection of systems with aliphatic and aromatic pendant arms, which were a subject of dynamic and complexing ability studies. Encouraged by our previous results, we decided to prepare new *N*-functionalized macrocyclic polyamines and extend our research on azacrown ethers. This paper reports the synthesis of four novel derivatives **3c-6c** with different number of pendant primary amino groups (1 to 6). The complexation behaviour of selected systems was characterized by ESI MS.

In order to introduce the *N*-(2-amino-4-carboxybutanoyl) group into cyclic polyamines (**3a** and **4a**) and azacrown ethers (**5a** and **6a**), the reactive carboxylic group of Z-L-glutamic acid 5-*tert*-butyl ester (**1**) was protected as the pentafluorophenyl ester (**2**) as shown in *Scheme 1*.



1 **Scheme 1** 2

Compound **2** was reacted with the macrocyclic substrates (**3a-6a**) in the presence of triethylamine (Et_3N) to provide the intermediate products (**3b-6b**) respectively. Final conversion to stable final products (**3c-6c**) was then carried out in two-stage process (*Scheme 2*). The new *N*-functionalized derivatives (**3c-6c**) were characterized by ^1H NMR spectroscopy and ESI mass spectrometry. All compounds were obtained in high yields (85-95%).



Scheme 2

The complexes of compounds **5c** and **6c** with alkali metal ions were prepared by addition of a solution of **5c** or **6c** to the perchlorate salts of lithium, sodium, potassium, rubidium and cesium in methanol or acetonitrile in a 1:1 ratio. ESI mass spectrometric m/z data obtained showed a general tendency of 1:1 complex formation with all alkali metal cations. However, the strongest MS signals come from complexes of smaller cations such as lithium and sodium, whose height in each case is comparable with the molecular ion ($M+H^+$) peak. The signals of potassium complex are one-half the intensity of molecular peaks and the lowest intensity peaks are observed for rubidium and caesium systems. Increased cone voltage causes further fragmentation of the system studied. The main fragmentation paths are: a) water molecule elimination; b) the bonding splitting -$COCH(NH_2)$ in the substituent R and -$C(NH_2)CH_2CH_2COOH$ separation; c) pendant arm R separation. We did not observe complex formation between any cation and molecules **3c** and **4c** applying ESI MS technique. It is the result of poor donor properties of

amide nitrogen atoms. Moreover, molecules **5c** and **6c** are characterized by the presence of oxygen atoms in macrocyclic parts, which prefer binding of alkali metal cations.[5,8] These two aspects lead to different behavior of totally *N*-substituted systems studied.

In summary, we have developed an efficient synthesis process of *N*-substituted macrocycles, using a variety of cyclic polyamines and one type of aminoacid like pendant arm.

EXPERIMENTAL SECTION

Nuclear magnetic resonance (NMR) spectra were recorded in DMSO-d_6 using a Varian Gemini 300 MHz spectrometer. All spectra were locked to deuterium resonance of solvent. The error in ppm values was 0.01. All ^{1}H NMR measurements were carried out at the operating frequency 300.075 MHz; flip angle, pw = 45°; spectral width, sw = 4500 Hz; acquisition time, at = 3.0 s; relaxation delay, d_1 = 1.0 s; T = 293.0 K and TMS as the internal standard. No window function or zero filling was used. Digital resolution was 0.2 Hz/point. Mass spectra (MS) were recorded on ZQ Waters/Micromass Mass Spectrometer (Manchester, UK) with quadrupole analyser with the following parameters used: source potential ESI on capillaries - 3 kV; voltage on focal plate - 0.5 V; voltage on extractor - 4V; the cone voltage (cv) - 30 V, source temperature - 120°C; evaporation temperature - 300°C; nitrogen was used as a spraying and drying gas with rate of flow - 80 and 300 l h^{-1}. We also recorded spectra at different cone voltages (cv = 30V, 50V, 70V, 90V) to determine the influence of increasing energy on the stoichiometry of the complexes. ESI mass spectra of positive ions of cyclic amines and their spectra in metal salts methanol & acetonitryle solutions were registered in MCA mode (Multi Channel Acquisition) in m/z = 100 - 1000 interval. The typical spectrum obtained is the average of 10 scans with 0.6 s interval of time. The solutions studied were introduced to the ionization source (with the flow rate 40 µl min^{-1}) through Harvard's pump.

Substrates **1, 3a-6a**, pentafluorophenol, DCC and the perchlorates: $LiClO_4$, $NaClO_4$, $KClO_4$, $RbClO_4$ and $CsClO_4$ were commercial products of Aldrich or Fluka, and were used without any purification. Solvents were purified by standard procedures.

Preparation of Compound 2.- In a round bottom flask equipped with a reflux condenser, *Z*-l-glutamic acid 5-*tert*-butyl ester **1** (1.35 g, 4 mmol), pentafluorophenol (755 mg, 4.1 mmol) and *N,N'*-dicyclohexylcarbodiimide (846 mg, 4.1 mmol) were dissolved in diethyl ether (100 mL) and heated at reflux for 2 hrs. The mixture was then cooled to room temperature and the precipitated dicyclohexylurea was removed by filtration. Evaporation of the filtrate *in vacuo* gave **2** as a yellow oil (1.80 g, 90% based on **1**), which was used without further purification in the next step.

1,4,8,11-tetrakis-(2-Amino-4-carboxybutanoyl)-1,4,8,11-tetraazacyclotetradecane Tetrahydrochloride. Representative Procedure.- A solution of **2** (2.0 g, 4 mmol), 1,4,8,11-tetraazacyclotetradecane (cyclam) **3a** (200 mg, 1 mmol) and Et_3N (505 mg, 5 mmol) in diethyl ether (100 mL) was heated under reflux for 4 days. The ethereal phase was washed with 0.1 M HCl and then with 0.1 M Na_2CO_3. The organic phase was dried ($MgSO_4$) and evaporated to give intermediate product **3b** (1.40 g, 95%). Glacial acetic acid (2 mL) and Pd/C (10%) (0.5 g) were added to a solution of N-substituted cyclam derivative **3b** (1.48 g, 1 mmol) in dry methanol (100 mL), and

then the solution was hydrogenated under atmospheric pressure by bubbling hydrogen through mixture until evolution of CO_2 was complete (about 5 h). The catalyst was filtered off and washed with hot methanol (20 mL). The combined methanol solutions were evaporated under vacuum. The obtained product was dissolved in trifluoracetic acid (TFA) (10 mL) and the solution was left for 24 hrs. Then TFA was evaporated and the residue was dissolved in 2M HCl (10 mL). The solvent was evaporated and the residue was purified by crystallisation from methanol. Filtration gave 690 mg (80%) of flesh-colored crystals of **3c**, mp ~315°C (dec.).

^{1}H NMR: δ 12.1 (bs, 1H); 8.5 (bs, 3H); 4.4 (bt, 1H); 3.2-3.6 (bm, 4H); 2.4 (bs, 2H); 2.0 (bs, 2H); 1.7 (bs, 2H). ESI MS: 717 $(1+H)^+$, 699 $(1-H_2O+H)^+$, 588 $(1-R+H)^+$, 570 $(1-R-H_2O+H)^+$, 459 $(1-2R+H)^+$, 441 $(1-2R-H_2O+H)^+$.

Anal. Calcd for $C_{30}H_{56}Cl_4N_8O_{12}$: C 41.77; H 6.54; N 12.99. Found: C 41.61; H 6.28; N 12.85.

1,4,7,10,13,16-hexakis-(2-Amino-4-carboxybutanoyl)-1,4,7,10,13,16-hexaazacyclooctadecane Hexahydrochloride.- Compound **4c** was synthesized as described for compound **3c**, with the modifications specified below:

2 (3.02 g, 6 mmol), 1,4,7,10,13,16-hexaazacyclooctadecane (hexacyclen) **4a** (258 mg, 1 mmol), Et_3N (707 mg, 7 mmol) in acetonitrile. After recrystalisation from ethanol product **4c** was obtained as flesh-colored crystals (1.09 g, 87%), mp ~330°C (dec.).

^{1}H NMR: δ 12.2 (bs, 1H); 8.4 (bs, 3H); 4.4 (bt, 1H); 3.2-3.6 (bs, 2H); 2.4 (bs, 2H); 1.9 (bs, 2H). ESI MS: 1033 $(2+H)^+$, 1015 $(2-H_2O+H)^+$, 904 $(2-R+H)^+$, 646 $(2-2R+H)^+$, 517 $(2-3R+H)^+$.

Anal. Calcd for $C_{42}H_{78}Cl_6N_{12}O_{18}$: C 40.30; H 6.28; N 13.43. Found: C 40.41; H 6.11; N 13.39.

1-(2-Amino-4-carboxybutanoyl)-1-aza-15-crown-5 Hydrochloride.- The compound **5c** was synthesized as described for the compound **3c**, with the modifications specified below:

2 (500 mg, 1 mmol), 1-aza-15-crown-5 **5a** (219 mg, 1 mmol), Et_3N (121 mg, 1.2 mmol). After solvent evaporation product **5c** was obtained as flesh-colored oil (370 mg, 95%), mp 278-279°C (~300°C dec.).

^{1}H NMR: δ 12.0 (bs, 1H); 8.2 (bs, 3H); 4.4 (bt, 1H); 3.4-3.8 (m, 20H); 2.4 (m, 2H); 1.9 (m, 2H). ESI MS: 349 $(3+H)^+$, 331 $(3-H_2O+H)^+$, 248 $(3-C(NH_2)CH_2CH_2COOH+H^+)$, 220 $(3-R+H)^+$, 355 $(3+Li)^+$, 371 $(3+Na)^+$, 242 $(3-R+Na)^+$, 387 $(3+K)^+$, 258 $(3-R+K)^+$, 433 $(3+Rb)^+$, 481 $(3+Cs)^+$.

Anal. Calcd for $C_{15}H_{29}ClN_2O_7$: C 46.81; H 7.60; N 7.28. Found: C 46.78; H 7.54; N 7.25.

7,13-bis-(2-Amino-4-carboxybutanoyl)-1,4,10-trioxa-7,13-diazacyclopentadecane Dihydrochloride.- The compound **6c** was synthesized as described for the compound **3c**, with the modifications specified below:

2 (1.00 g, 2 mmol), 1,4,10-trioxa-7,13-diazacyclopentadecane **6a** (219 mg, 1 mmol), Et_3N (505 mg, 2.5 mmol). After recrystalisation from methanol product **6c** was obtained as flesh-colored crystals (480 mg, 88%), mp ~300°C (dec.).

^{1}H NMR: δ 12.4 (bs, 1H); 8.4 (bs, 3H); 4.3 (bt, 1H); 3.4-3.9 (m, 10H); 2.5 (m, 2H); 2.0 (m, 2H).

ESI MS: 477 $(4+H)^+$, 459 $(4\text{-}H_2O+H)^+$, 348 $(4\text{-}R+H)^+$, 330 $(4\text{-}R\text{-}H_2O+H)^+$, 485 $(4+Li)^+$, 501 $(4+Na)^+$, 369 $(4\text{-}R+Na)^+$, 517 $(4+K)^+$, 388 $(4\text{-}R+K)^+$, 562 $(4+Rb)^+$, 610 $(4+Cs)^+$.

Anal. Calcd for: $C_{20}H_{38}Cl_2N_4O_9$: C 43.72; H 6.97; N 10.20. Found: C 43.98; H 7.11; N 10.46.

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