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An Approach to Channel Type Molecular Structures. 1. Synthesis of *Bouquet*-Shaped Molecules Based on an [18]-O_6 Polyether Macrocycle#

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Abstract. An approach to a transmembrane cation channel is described. It is based on the grafting of oxygen bearing side-chains on a macrocyclic polyether unit that constitutes the organizing core. The resulting species has a structure of overall *bouquet* shape. The synthesis of such a molecule $\mathscr{B}^{O}_{M}$, **14a** is described, together with that of its analogue bearing polymethylene side-chains $\mathscr{B}^{C}_{M}$, **14b**. The physicochemical properties of these molecules indicate that they possess the features expected on the basis of their structure.

Key words. Polyether macrocycle, molecular channel, molecular bundle.

1. Introduction

Communication between two regions of space separated by an impermeable barrier (e.g. a membrane) is a crucial event in the transfer of information and of signal generation in molecular and supramolecular systems. Such communication may be established and controlled via specialized structures capable of handling selectively ionic and molecular substrates. Ion transport through biological membranes is an essential phenomenon in living cells, for processes as different as energy metabolism, transmission of nerve impulses, visual transduction, etc. (1, 2a). Its study forms a basic area of supramolecular chemistry [3], involving the design of artificial transport processes and effectors [2, 3]. Two types of transport mechanisms can be distinguished: shuttle (or free carrier) and channel processes [1, 2].

In the first case, an ion binds to a free carrier species on one side of the membrane forming a complex which diffuses through the bilayer; the ion is released on one of the two faces of the membrane depending on the different gradients present in the system, making the carrier available for a new cycle. The shuttle approach, involving comparatively small and simple carrier molecules has been extensively investigated in the last twenty years [1, 2, 4, 5]. Numerous examples have been described involving both natural (e.g. valinomycin [4], monensin A [5], etc.) and artificial (crown ethers [6], cryptands [2b]) carrier molecules.

In the second mechanism, an ion crosses the membrane directly through a specialized transmembrane structure, such as that provided by gramicidin A [7] or alamethicin [8]. Much less work has been done on the design of artificial channel

This paper is dedicated to the memory of the late Dr C. J. Pedersen.
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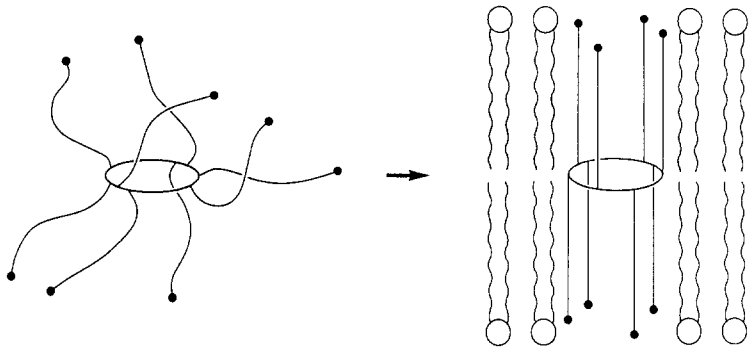


Fig. 1. The *Bouquet* approach: the functional structure might be attained by favorable organisation in a bilayer membrane of a molecule composed of flexible chains grafted on a circular core.

type species. However, several approaches have been explored [9], ranging from highly specialized structures in a well-defined conformation in the membrane to the creation of a defect in the organized bilayer and going through the generation of tubular mesophase [10a] or the face to face connection of several macrocyclic units [10b] as suggested by a solid state model [10c].

We report here an approach to the design of artificial ion channels based on the grafting of a bundle of amphiphilic chains on a central ring [11]. In appropriate anisotropic conditions (lipidic membrane of artificial vesicles for instance), these molecules might organize in a pseudo-cylindrical *structure* which may evoke the shape of a *bouquet* (or a sheaf) (Figure 1). *Functionally*, such a species represents a **ch**annel based on an organized **bundle** of chains, and may be described as a *chundle* [11]. This paper describes the synthesis and some physical properties of two molecules of *bouquet* structure *𝔅* based on a tetrasubstituted macrocyclic polyether core [12] derived from Pedersen's 18-crown-6 parent compound [6a]. Ion binding studies, incorporation into bilayer membranes and ion-transport experiments will be reported elsewhere.

2. Experimental

2.1. GENERAL PROCEDURES

Microanalyses were performed by the 'Service Central d'Analyses du CNRS' (Vernaison) or by the 'Service de Microanalyses de l'Université P. et M. Curie' (Paris). Melting points were recorded on a Perkin-Elmer DSC 2 Differential Scanning Calorimeter. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on an AM 200 SY Bruker spectrometer at room temperature unless otherwise indicated. Chemical shifts are given in ppm with protonated solvent as internal reference (^{1}H-NMR: $CHCl_3$ in $CDCl_3$ 7.26 ppm, CHD_2OD in CD_3OD 3.30 ppm, HOD in D_2O 4.70 ppm; ^{13}C-NMR: $^{13}CDCl_3$ in $CDCl_3$ 76.9 ppm, $^{13}CD_3OD$ in CD_3OD 49.0 ppm). Mass spectra (FAB positive) were performed by the 'Service de Spectrométrie de Masse du CNRS' (Vernaison). IR spectra and rotatory powers were respectively recorded on a Perkin-Elmer 297 spectrometer (film on KBr) and on a

Perkin-Elmer 241 polarimeter. Column chromatography was performed on silica gel 60 (0.040–0.063 mm) Merck. Fluorescent silica plates (analytical or preparative) Merck or Macherey-Nagel, or type E alumina Merck were used for thin layer chromatography. Analytical plates were revealed by UV (254 nm), iodine (I_2) or sulfuric acid solution (5%). Anhydrous solvents (SDS), stored on molecular sieves (3–4 Å) were used as received, except methylene chloride which was distilled from calcium hydride before use. All the catalytic hydrogenations were performed at a pressure of one bar.

Due to the physical state (waxes), satisfactory analyses were not obtained for the final products **13a**, **13b**, **14a** and **16a**. IR and ^{1}H-NMR spectroscopy respectively showed the presence of water and of residual solvent.

2.2. SYNTHETIC PROCEDURES

2.2.1. *Ethyl* 11-*Hydroxy*-3,6,9-*trioxaundecanoate* **1**

Ethyl diazoacetate (15 mL; 0.14 mol) was slowly added at room temperature to a stirred solution of triethyleneglycol (130 g; 0.87 mol) and trifluoride boron etherate (3 drops) in dry CH_2Cl_2 (200 ml). Abundant nitrogen formation occurred immediately. After stirring at r.t. for 7 h, the organic solution was washed (water, 100 mL; saturated NaCl, 2 × 50 ml), dried (Na_2SO_4), evaporated to dryness and distilled (bp: 145°C; 1–1.5 mm Hg) to give **1** as a colourless liquid (23.7 g; 70%). ^{1}H-NMR ($CDCl_3$): 4.22 (*q*, 7Hz, CH_2CH_3); 4.16 (*s*, OCH_2CO); 3.70 (*m*, 6 OCH_2); 2.43 (*s*, OH); 1.29 (*t*, 7Hz, CH_3). ^{13}C-NMR ($CDCl_3$): 169.8 (CO); 72.0 (CH_2CH_2OH); 70.2, 70.0, 69.7 (OCH_2); 68.0 (OCH_2CO); 61.0 (CH_2CH_2OH); 60.1 (CH_2CH_3); 13.6 (CH_3). TLC: SiO_2; CH_2Cl_2/MeOH (9/1); $R_f = 0.55$ (I_2). IR (cm^{-1}): 3360 (OH); 1760 (CO). *Anal. calc.* for $C_{10}H_{20}O_6$ (236) C 50.8; H 8.5; *found* C 51.5; H 8.75.

2.2.2. *Ethyl* 11-*Tosyloxy*-3,6,9-*trioxaundecanoate* **2**

Tosyl chloride (14.5 g; 77 mmol) was slowly added into a solution of **1** (15 g; 64 mmol) in pyridine (75 mL) cooled to 0°C. After one night at 4°C, the organic solution was poured onto crushed ice (100 g), then extracted with ether (150 mL). The organic phase was washed (3 M HCl, 500 mL; saturated NaCl, 50 mL), dried (Na_2SO_4) and evaporated to dryness yielding **2** as a light-yellow liquid used without further purification (22.3 g; 90%). ^{1}H-NMR ($CDCl_3$): 7.79 (*d*, 8Hz, 2H arom); 7.34 (*d*, 8Hz, 2H arom); 4.21 (*q*, 7Hz, CH_2CH_3); 4.16 (*m*, CH_2OTs); 4.13 (*s*, OCH_2CO); 3.72–3.59 (*m*, 5 OCH_2); 2.45 (*s*, CH_3 arom); 1.28 (*t*, 7Hz, CH_2CH_3). ^{13}C-NMR ($CDCl_3$): 169.9 (CO); 144.4, 132.9, 129.4, 127.5 (arom); 70.5, 70.3, 70.2, 68.9 (OCH_2); 68.3 (OCH_2CO); 60.3 (CH_2CH_3); 21.2 (CH_3 arom); 13.8 (CH_3). TLC: SiO_2; CH_2Cl_2/MeOH (95/5); $R_f = 0.63$ (UV, I_2). IR (cm^{-1}): 1760 (CO). *Anal. calc.* for $C_{17}H_{26}O_8S$ (390) C 52.3; H 6.7; *found* C 52.0; H 6.8.

2.2.3. *Ethyl* 11-*Azido*-3,6,9-*tiroxaundecanoate* **3**

A solution of **2** (25.8 g; 66 mmol) and NaN_3 (9.0 g; 138 mmol) in dry DMF (100 mL) was heated at 60°C for 20 h. The solvent was removed under vacuum and

the residue was taken up in CH_2Cl_2 (125 mL), washed (water, 50 mL), dried (Na_2SO_4) and evaporated to dryness to yield **3** as a light-yellow liquid used without further purification (16.8 g; 97%). ^{1}H-NMR ($CDCl_3$): 4.22 (*q*, 7Hz, CH_2CH_3); 4.15 (*s*, OCH_2CO); 3.8–3.6 (*m*, 5 OCH_2), 3.39 (*t*, 5 Hz, CH_2N_3); 1.29 (*t*, 7Hz, CH_3). ^{13}C-NMR ($CDCl_3$): 169.9 (CO); 70.2, 70.2, 69.6 (OCH_2); 68.2 (OCH_2CO); 60.3 (CH_2CH_3); 50.2 (CH_2N_3); 13.8 (CH_3). TLC: SiO_2; CH_2Cl_2/MeOH (9/1); $R_f = 0.82$ (I_2). IR (cm^{-1}): 2120 (N_3); 1760 (CO). MS; $(M + H)^+ = 262$.

2.2.4. *Ethyl* 11-*Amino*-3,6,9-*trioxaundecanoate* **4a**

3 (5.20 g; 20 mmol) was catalytically hydrogenated on Pd/C 10% (700 mg) in dry CH_2Cl_2(100 mL) at r.t. for 6 h. After filtration of the catalyst and evaporation of the solvent, the amine **4a** was isolated as a liquid (4.59 g; 98%). ^{1}H-NMR ($CDCl_3$): 4.21 (*q*, 7Hz, CH_2CH_3); 4.15 (*s*, OCH_2CO); 3.8–3.6 (*m*, 5 OCH_2); 3.52 (*t*, 5 Hz, CH_2NH_2); 1.9 (broad *s*; NH_2); 1.29 (*t*, 7 Hz, CH_3). ^{13}C-NMR ($CDCl_3$): 170.0 (CO); 70.5, 70.3, 69.9, 69.6 (OCH_2); 68.3 (OCH_2CO); 60.4 (CH_2CH_3); 50.4 (CH_2NH_2); 13.8 (CH_3). TLC: SiO_2; CH_2Cl_2/MeOH (9/1); $R_f = 0.1$–0.3 (I_2). IR (cm^{-1}): 3400 (broad; NH_2); 1760 (CO). MS: $(M + H)^+ = 236$.

2.2.5. *N-Benzyloxycarbonyl-N-butylglycine* **5**

Benzylchloroformate (1.71 g; 10 mmol) and 4 M NaOH solution (2.5 mL; 10 mmol) were simultaneously and separately added dropwise at 0°C over a period of 30 min to a mixture of butylglycine (1.67 g; 10 mmol) and 2 M NaOH solution (10 mL; 20 mmol). After further stirring at 0°C for 20 min, unreacted products were extracted with ether (10 mL). The aqueous phase was acidified up to pH = 1 with 1 M HCl and then extracted twice with ether (50 mL; 25 mL). The combined organic phases were washed (saturated NaCl; 20 mL), dried (Na_2SO_4) and evaporated to dryness to yield **5** as a viscous colourless liquid (1.95 g; 74%). The proton NMR spectrum shows the presence of two amide rotamers. ^{1}H-NMR ($CDCl_3$): 7.35–7.30 (*m*, 5H arom); 5.17 and 5.13 (2*s*, OCH_2); 4.06 and 4.01 (2*s*, NCH_2CO); 3.34 (2*t*, CH_2N); 1.50 (2*tt*, CH_2CH_2N); 1.30 (2*tq*; CH_2CH_3); 0.92 and 0.89 (2*t*, CH_3). ^{13}C-NMR ($CDCl_3$): 174.2 (CO); 136.4, 128.3, 128.1, 127.9, (arom); 67.5 (OCH_2); 48.5 (several peaks; CH_2N and NCH_2CO); 30.2 (several peaks; CH_2CH_2N); 19.8 (CH_2CH_3); 13.6 (CH_3). TLC: SiO_2; CH_2Cl_2/MeOH (95/5); $R_f = 0.40$ (UV, I_2).

2.2.6. *Preparation of* **6a** and **6b**

DCC was slowly added to a mixture of **5**, **4** (either the free base or its chlorhydrate), DMAP and dry CH_2Cl_2 at 0°C. After stirring at r.t. overnight, the suspension was filtered and the residual solid washed with CH_2Cl_2 (20 mL). The combined organic phases were evaporated, taken up in Et_2O (250 mL) and filtered. The filtrate was washed (1 M HCl, 2 × 50 mL; saturated NaCl, 50 mL), dried (Na_2SO_4) and evaporated to dryness. **6a** and **6b** were purified by column chromatography (SiO_2; 100–150 g; gradient of acetone in CH_2Cl_2).

6a. From **5** (4.46 g; 17 mmol); **4a** (4.00 g; 17 mmol); DMAP (2.20 g; 18 mmol); CH_2Cl_2 (60 ml); DCC (3.70 g; 18 mmol). Yield: 2.91 g (36%). NMR 2 conformers: ^1H ($CDCl_3$): 7.36 (*m*, 5H arom); 6.59 and 6.40 (broad *s*, 0.55 and 0.45 NH); 5.14 (*s*, OCH_2Ph); 4.20 (*q*, 7 Hz, OCH_2CH_3); 4.13 (*s*, OCH_2CO); 3.91 (*s*, NCH_2CO); 3.8–3.4 (*m*, CH_2N and 5 OCH_2); 3.32 (*t*, 8Hz, $CH_2CH_2CH_2N$); 1.52 (*tt*; $J_1 \approx J_2 = 8$ Hz; $CH_2CH_2CH_2N$); 1.27 (*t*; 7 Hz; OCH_2CH_3); 1.24 (*m*; $CH_2CH_2CH_2N$); 0.92 (*t*; CH_3). ^{13}C ($CDCl_3$): 170.1 (COO); 169.0 (CON); 156 (broad, OCON), 136.3, 128.3, 127.8, 127.6 (arom); 70.7, 70.3, 70.1, 69.5, 68.5, 65.6 (OCH_2CO and 5 OCH_2); 67.3 (OCH_2Ph); 60.6 (OCH_2CH_3); 51.1 (NCH_2CO); 48.3 ($CH_2CH_2CH_2N$); 39.0 (OCH_2CH_2N); 33.8 ($CH_2CH_2CH_2N$); 29.9 (CH_2CH_3); 14.0 (OCH_2CH_3); 13.6 (CH_3). TLC: SiO_2; CH_2Cl_2/Acetone (6/4); $R_f = 0.70$ (UV, I_2). IR (cm^{-1}): 3340 (NH); 1755 (COO); 1710 (OCON); 1675 (CON). *Anal. calc.* for $C_{24}H_{38}N_2O_8$ (482) C 59.75 H 7.9 N 5.8; *found*: C 59.0 H 8.1 N 6.0. MS: $(M+H)^+ = 483$.

6b. From **5** (4.67 g; 18 mmol); **4b** chlorhydrate (4.68 g; 18 mmol); DMAP (4.40 g; 36 mmol); CH_2Cl_2 (100 ml); DCC (4.12 g; 20 mmol). Yield: 6.35 g (74%). NMR 2 conformers: ^1H ($CDCl_3$): 7.28 (*m*, 5H arom); 6.33 and 6.01 (broad *s*, 0.55 and 0.45 NH); 5.09 (*s*, OCH_2Ph); 4.06 (*q*, 7 Hz, OCH_2); 3.83 (*s*, NCH_2CO); 3.27 (*t*, 7 Hz, CH_2N); 3.14 (*dt*, $J_1 \approx J_2 = 6$ Hz, CH_2N); 2.23 (*t*, 7Hz, CH_2CO); 1.6–1.1 (*m*, 10 CH_2 and OCH_2CH_3); 0.85 (*t*; 7 Hz; CH_3). ^{13}C ($CDCl_3$): 173.4 (COO); 168.9 (CON); 136.1, 128.1, 127.8, 127.6 (arom); 67.3 (OCH_2Ph); 59.8 (OCH_2); 51.4 (NCH_2CO); 48.3 (CH_2N); 39.1 (CH_2N); 34.1 (CH_2COO); 29.2–28.8 (several peaks), 26.6, 24.7, 19.6 (CH_2); 14.0 (OCH_2CH_3); 13.5 (CH_3). TLC: SiO_2; CH_2Cl_2/MeOH (95/5); $R_f = 0.73$ (UV, I_2, H_2SO_4). *Anal. calc.* for $C_{27}H_{44}N_2O_5$ (476) C 68.1 H 9.2; *found*; C 67.9 H 9.4.

2.2.7. *Preparation of Ethyl* 11-(*N-butylglycylamino*)-3,6,9-*trioxaundecanoate* **7a** *and Ethyl* 11-(*N-butylglycyl amino*)-*undecanoate* **7b**

Hydrogenolysis of **6a** or **6b** on Pd/C 10% in CH_2Cl_2 at r.t. for 2 h gave **7a** and **7b** respectively. The catalyst was filtered off to give a solution which, after evaporation to dryness, yielded a colourless viscous liquid.

7a. 6a (543 mg; 1.2 mmol); Pd/C 10% (200 mg); CH_2Cl_2 (25 mL). Yield: 355 mg (92%). ^1H-NMR ($CDCl_3$): 7.64 (broad *s*, NH); 4.21 (*q*, 7 Hz, OCH_2CH_3); 4.14 (*s*, OCH_2CO); 3.8–3.4 (*m*, 5 OCH_2 and NCH_2); 3.32 (*s*, NCH_2CO); 2.80 (broad *s*, 1H); 2.63 (*t*, 7 Hz, $CH_2CH_2CH_2N$); 1.6–1.3 (*m*, $CH_2CH_2CH_2N$); 1.28 (*t*, 7 Hz, OCH_2CH_3); 0.91 (*t*, 7 Hz, CH_3). ^{13}C-NMR ($CDCl_3$): 170.3 (COO); 170.0 (CON); 70.6, 70.3, 70.2, 70.0, 69.5, 68.4 (OCH_2); 60.4 (OCH_2CH_3); 51.6 (NCH_2CO); 49.2 ($CH_2CH_2CH_2N$); 38.6 (CH_2N); 31.1 ($CH_2CH_2CH_2N$); 19.9 (CH_2CH_3; 13.9 (OCH_2CH_3); 13.5 (CH_3). TLC: Al_2O_3; CH_2Cl_2/MeOH (95/5); $R_f = 0.8$ (I_2).

7b. same as **7a** on a 13 mmol scale. Yield: 94%. ^1H-NMR ($CDCl_3$): 7.57 (*t*, 6 Hz, NH); 4.37 (broad *s*, NH); 3.93 (*q*, 7 Hz, OCH_2); 3.23 (*s*, NCH_2CO); 3.06 (*dt*, $J_1 = 6$ Hz and $J_2 = 7$ Hz, CH_2N); 2.52 (*t*, 7 Hz, $CH_2CH_2CH_2N$); 2.23 (*t*, 7Hz, CH_2CO); 1.5–1.0 (*m*, 10 CH_2); 1.07 (*t*, 7 Hz, OCH_2CH_3); 0.74 (*t*, 7 Hz, CH_3). ^{13}C-NMR ($CDCl_3$): 173.1 (COO); 169.4 (CON); 59.5 (OCH_2); 51.1 (NCH_2CO); 48.9 ($CH_2CH_2CH_2N$); 38.6 (CH_2N); 33.8 (CH_2CO); 30.6, 29.0, 28.9, 28.8, 28.7, 28.6, 26.4, 24.4, 19.7 (CH_2); 13.7 (OCH_2CH_3); 13.3 (CH_3). TLC: SiO_2; CH_2Cl_2/acetone (1/1); $R_f = 0.60$ (I_2).

2.2.8. *Preparation of* **9a** *and* **9b**

5-Nitro-1,3-benzenedicarbonyl chloride **8** was freshly prepared from the corresponding diacid by refluxing in excess thionyl chloride containing one drop of DMF for 2 h. After cooling to r.t. and evaporation of the solvent, the residue was taken up in benzene and evaporated twice, dissolved in dry CH_2Cl_2 and cooled to 0°C. To this solution, a solution of the appropriate amine in CH_2Cl_2 and TEA (freshly distilled; excess) was added dropwise at 0°C. The mixture was allowed to cool and was stirred at r.t. overnight. The organic solution was washed (1 M HCl; saturated NaCl), dried (Na_2SO_4) and evaporated to dryness. The purification of **9a** and **9b** was achieved by column chromatography (SiO_2; gradient of acetone in CH_2Cl_2).

9a. 5-Nitro-1,3-benzenedicarboxylic acid (500 mg; 2.4 mmol); $SOCl_2$ (3 ml); **7a** (1.81 g; 5.2 mmol); CH_2Cl_2 (25 mL); TEA (1 ml); 1 M HCl (20 mL); NaCl (10 mL); SiO_2 (100 g). Viscous liquid. Yield: 1.72 g (80%). ^{1}H-NMR ($C_2D_2Cl_4$; 375 K): 8.33 (*s*, 2H arom); 7.88 (*s*, 1H arom); 6.42 (broad *s*, 2NH); 4.22 (*q*, 7 Hz, 2 OCH_2CH_3); 4.11 (*s*, 2 OCH_2CO); 4.04 (broad *s*, 2 NCH_2CO); 3.8–3.55 (*m*, 10 OCH_2); 3.46 (*t*, 6Hz, 2 $CH_2CH_2CH_2N$); 3.42 (broad *t*, 2 NCH_2); 1.62 (*tt*, $J_1 \approx J_2 = 6$ Hz, 2 $CH_2CH_2CH_2N$); 1.4–1.2 (*m*, 2 CH_2CH_3); 1.30 (*t*, 7 Hz, 2 OCH_2CH_3); 0.90 (*t*, 7 Hz, 2 CH_3). ^{13}C ($CDCl_3$): 170.2 (COO); 168.6 (CON); 137.2, 114.1 (arom); 70.7, 70.4, 69.9, 69.5, 68.5 (OCH_2); 60.7 (OCH_2CH_3); 50 ($CH_2CH_2CH_2N$); 39.1 (CH_2N); 30 ($CH_2CH_2CH_2N$); 19.7 (CH_2CH_3); 14.0 (OCH_2CH_3); 13.5 (CH_3). TLC: SiO_2; CH_2Cl_2/MeOH (9/1); $R_f = 0.62$ (UV and I_2). *Anal. calc.* for $C_{40}H_{65}N_5O_{16}$ (871) C 55.1 H 7.5 N 8.0; *found*: C 54.4 H 7.7 N 8.1. MS: $(M+H)^+ = 873$; $(M+Na)^+ = 895$.

9b. Same preparation as for **9a** on a 16 mmol scale. Solid. Yield: 59%. ^{1}H-NMR ($CDCl_3$): 8.3–8.1 (*m*, 2H arom); 7.85–7.6 (*m*, 1H arom); 7.05–6.75 (*m*, 2NH); 3.94 (*q*, 7 Hz, 2 OCH_2CH_3); 3.9 and 3.7 (2 broad *s*, 2 NCH_2CO); 3.45–2.95 (*m*, 4 CH_2N); 2.12 (*t*, 7Hz, 2 CH_2CO); 1.55–0.9 (*m*, 20 CH_2); 1.08 (*t*, 7 Hz, 2 OCH_2CH_3); 0.9–0.6 (*m*, 2 CH_3). ^{13}C-NMR ($CDCl_3$): 173.3 (COO); 168.5, 167.4 (CON); 147.4, 137.7, 130.9, 122.3 (arom); 59.6 (OCH_2CH_3); 53.1, 51.7, 50.3, 49.1 (broad peaks; NCH_2CO and NCH_2); 39.3 (NCH_2); 33.9 (CH_2CO); 29.95, 29.1, 29.0, 28.9, 28.7, 28.6, 26.8, 24.8, 21.8, 19.4 (CH_2); 13.75 (OCH_2CH_3); 13.5, 13.1 (CH_3). M.P. 35.3°C and 87.4°C. TLC: SiO_2; CH_2Cl_2/acetone (8/2); $R_f = 0.80$ (UV, I_2). IR (cm^{-1}): 3280, 3100 (NH); 1740 (CO). *Anal. calc.* for $C_{46}H_{77}N_5O_{10}$ (859) C 64.3 H 9.0 N 8.15; *found*: C 64.4 H 9.05 N 8.2. MS: $(M+H)^+ = 861$.

2.2.9. *Preparation of* **10a** *and* **10b**

The nitro derivatives **9a** and **9b** were hydrogenated on Pd/C 10% in dry CH_2Cl at r.t. for 6 h. After filtration of the catalyst, the organic solution was evaporated to dryness to yield viscous colourless liquids.

10a. 9a (1.25 g; 1.4 mmol); Pd/C 10% (200 mg); CH_2Cl_2 (50 ml). Yield: 1.12 g (91%). ^{1}H-NMR ($CDCl_3$): 7.5–6.5 (*m*, 3 H arom and 2 NH); 4.16 (*q*, 7 Hz, 2 OCH_2CH_3); 4.1–2.6 (*m*, 12 OCH_2 and 6 CH_2N); 1.6–1.0 (*m*, 4 CH_2); 1.24 (*t*, 7 Hz, 2 OCH_2CH_3); 1.0–0.7 (*m*, 2 CH_3). ^{13}C-NMR ($CDCl_3$): 172.0 (CON); 170.8 (COO); 169.0 (CON); 147.8, 137.4, 113.8 (arom); 71.0, 70.5, 69.8, 68.7 (OCH_2); 61.3 (OCH_2CH_3); 52.5, 50.8, 49.3, 46.6, 39.5 (CH_2N); 30.7, 29.3 ($CH_2CH_2CH_2N$);

20.5, 20.0 (CH_2CH_3); 14.5 (OCH_2CH_3); 14.0 (2; CH_3). TLC: SiO_2; CH_2Cl_2/MeOH (9/1); $R_f = 0.46$ (UV, I_2). MS: $(M + H)^+ = 843$.

10b. Same preparation as for **10a** on a 0.45 mmol scale. Yield: 93%. ^{1}H-NMR ($CDCl_3$): 7.3 and 6.85–6.6 (*m*, 3 H arom and 2 NH); 4.10 (*q*, 7 Hz, 2 OCH_2CH_3); 4.2–3.8 (*m*, 2 NCH_2CO); 3.6–3.1 (*m*, 4 CH_2N); 2.29 (*t*, 6 Hz, 2 CH_2CO); 1.7–1.1 (*m*, 20 CH_2); 1.24 (*t*, 7 Hz, 2 OCH_2CH_3); 1.1–0.75 (*m*, 2 CH_3). TLC: SiO_2; CH_2Cl_2/acetone (6/4); $R_f = 0.29$ (UV, I_2). MS: $(M + H)^+ = 831$.

2.2.10. *Preparation of* **13a** $\mathcal{B}_M^O$ *COOEt and* **13b** $\mathcal{B}_M^C$ *COOEt*

A mixture of [18]-O_6 tetracarboxylic acid **11** [12] (75 mg; 0.17 mmol; Merck), phosphorus pentachloride (150 mg, large excess), in freshly distilled CH_2Cl_2 (5 ml) was stirred at r.t. overnight. A further amount of phosphorus pentachloride (145 mg) was added and the mixture stirred for 1 h. After solvent evaporation, the residue was taken up twice in anhydrous benzene and the solution was evaporated under vacuum at 40°C to give the tetraacyl chloride **12** [12]. A solution of that chloride and **10a** or **10b** (1 mmol) in anhydrous dimethylacetamide (7 mL) was cooled to 0°C. 4-Dimethylaminopyridine (423 mg; large excess) was slowly added and the mixture was stirred at r.t. for 24 h. After evaporation of the solvent under 1 mm-vacuum, the residue was taken up in CH_2Cl_2 (50 mL). The organic solution was washed (1 M HCl, 25 mL; saturated NaCl, 25 mL), dried (Na_2SO_4). After evaporation under vacuum and careful column chromatography (SiO_2; 120 g; gradient of MeOH in CH_2Cl_2) a colourless glassy wax was obtained.

13a. Yield: 87%. ^{1}H-NMR ($C_2D_2Cl_4$; 394 K): 10.1 (broad *s*, NH); 8.0 (broad *s*, 2 H arom); 7.3 (broad *s*, 1 H arom); 6.6 (broad *s*, 2 NH); 4.6 (broad *s*, CH); 4.24 (*q*, 7 Hz, 2 OCH_2CH_3); 4.13 (*s*, 2 OCH_2CO); 4.03 (broad *s*, 2 NCH_2CO); 4.0 and 3.8–3.3 (*m*, 10 OCH_2 and 4 CH_2N); 1.60 (*tt*, 2 $CH_2CH_2CH_2N$); 1.3 (*m*, 2 CH_2CH_3); 1.32 (*t*, 7 Hz, 2 OCH_2CH_3); 0.89 (*t*, 7 Hz, 2 CH_3). ^{13}C-NMR: ($C_2D_2Cl_4$; 383 K): 171.1 (CON); 170.4 (COO); 168.8 (CON); 138.3, 137.6, 121.8, 121.0 (arom); 81.5 (CH); 69.2 (OCH_2 crown); 71.4, 70.9, 70.8, 70.6, 69.1 (OCH_2); 60.9 (OCH_2CH_3); 51.2 (NCH_2CO); 49.4 ($CH_2CH_2CH_2N$); 39.9 (CH_2N); 30.4 ($CH_2CH_2CH_2N$); 20.2 (CH_2CH_3); 14.4 (OCH_2CH_3); 13.7 (CH_3). TLC: SiO_2; CH_2Cl_2/MeOH (9/1); $R_f = 0.45$; grafted C18 SiO_2 (Whatman LKC18F); MeOH/H_2O (95/5); $R_f = 0.28$ (UV and I_2). MS for $(M + Na)^+$: maximum calculated peak: 3759; maximum experimental peak: 3759.8; peaks distribution shape in agreement with calculated data. $[\alpha]_{589}^{25} = +15°$; $[\alpha]_{578}^{25} = +17°$; $[\alpha_{546}^{25} = +19°$ ($c = 1.06$; EtOH 95%).

13b. Yield: 71%. ^{1}H-NMR ($C_2D_2Cl_4$; 375 K): 10.05 (broad *s*, NH); 7.95 (broad *s*, 2 H arom); 7.25 (broad *s*, 1 H arom); 6.5 (broad *s*, 2 NH); 4.6 (broad *s*, CH); 4.10 (*q*, 7 Hz, 2 OCH_2CH_3); 4.0 (m, 2 OCH_2 and 6 CH_2N); 2.29 (*t*, 6 Hz, 2 CH_2CO); 1.7–1.2 (*m*, 20 CH_2); 1.24 (*t*, 7 Hz, 2 OCH_2CH_3); 0.87 (*t*, 2 CH_3). ^{13}C-NMR: ($C_2D_2Cl_4$; 375K): 174.2 (COO); 171.1, 168.8, 168.4 (CON); 138.2, 137.3, 121.8, 120.8 (arom); 81.3 (CH); 71.5, 68.9 (OCH_2 crown); 60.2 (OCH_2CH_3); 51.4 (NCH_2CO); 49.3 ($CH_2CH_2CH_2N$); 40.1 (CH_2N); 34.7, 30.3, 29.85, 29.7, 29.6, 29.5, 29.4, 27.2, 25.2, 20.2 (CH_2); 14.5 (OCH_2CH_3); 13.8 (CH_3). TLC: SiO_2; CH_2Cl_2/MeOH (9/1); $R_f = 0.65$ (UV and I_2). MS for $(M + Na)^+$: maximum calculated peak: 3711; maximum experimental peak: 3711.4; peaks

distribution shape in agreement with calculated data. $[\alpha]_{589}^{25} = +12°$; $[\alpha]_{578}^{25} = +13°$; $[\alpha]_{546}^{25} = +15°$ ($c = 1.71$; EtOH 95%).

2.2.11. *Preparation of* **14a** $\mathscr{B}_M^O$ *COONa and* **14b** $\mathscr{B}_M^C$ *COONa*

A mixture of **13a** or **13b** (32 mg; 9 μmol), 1 M aqueous NaOH (170 μL; 170 μmol) and distilled MeOH (5 mL) was stirred at r.t. for 2–4 h (the course of the reaction was followed by the disappearance of the COOEt signal in the ^{1}H-NMR spectra; the reaction was quicker with **13a** than with **13b**). Solid CO_2 was then added, the solution was evaporated to dryness and the solid residue was taken up in absolute EtOH. The suspension was weakly bath-sonicated for one minute and filtered on millipore. The resulting solution was evaporated to dryness to yield **14a** and **14b** as glassy waxes, which were used without further purification. They were stored as MeOH or EtOH solutions at 4°C.

14a. ^{1}H-NMR (D_2O; 373K; ethanol as the internal reference; CH_3 signal; 1.14 ppm): 7.73 (*s*, 2 H arom); 7.28 (*s*, 1 H arom); 4.65 (*s*, CH); 4.08 (*s*, 2 NCH_2CO); 3.9–3.5 (*m*, 2 OCH_2 crown); 3.7 – 3.5 (*m*, 10 OCH_2); 3.5–3.2 (2*t*, 4 CH_2N); 1.49 (*m*, 2 CH_2); 1.12 (*m*, 2 CH_2CH_3); 0.74 (*t*, 7Hz, 2 CH_3). ^{13}C-NMR (D_2O; 373K; internal reference ethanol: CH_3 signal: 17.8 ppm): 177.8 (COO); 172.6, 170.6 (CON); 137.8, 121.3 (arom); 71.2; 70.4; 70.3; 69.65 (OCH_2); 50.2 (large; NCH_2): 39.9 (CH_2N); 30.1 (CH_2); 19.9 (CH_2CH_3); 13.5 (CH_3).

14b. ^{1}H-NMR (CD_3OD): 8.1–7.8 (*m*, 2 H arom); 7.4–7.2 (*m*, 1 H arom); 6.75 (broad *s*, 2 NH); 4.65 (broad *s*, CH); 4.3–3.0 (*m*, 2 OCH_2 and 6 CH_2N); 2.30 (*t*, 7 Hz, 2 CH_2CO); 1.8–1.3 (*m*, 20 CH_2); 1.0 and 0.8 (2 broad *t*, 2 CH_3). ^{13}C-NMR (CD_3OD): 176.0 (COO); 172.85, 170.2 (2; CON); 140, 138.4, 121.7 (arom); 81.85 (CH); 71.7, 69.8 (OCH_2); 53.1, 51.7, 40.6 (CH_2N); 34.8, 31.4, 30.4, 28.1, 26.0, 21.2, 20.9 (CH_2); 14.2 (CH_3).

2.2.12. *Preparation of the Model Compounds* **15a, 15b, 16a** *and* **16b**

15a. 5-Nitro-1,3-benzenedicarbonyl chloride was reacted with diethylamine under the same conditions as for the preparation of **9a** and **9b** to yield 5-nitro-*N*,*N*′-diethyl-1,3-benzenedicarboxamide (93%). This compound was catalytically hydrogenated as described for **10a** and **10b** to give 5-amino-*N*,*N*′-diethyl-1,3-benzenedicarboxamide (71%) which was then condensed with cyclohexylcarbonyl chloride as described for **13a** and **13b** to give **15a** (76%). ^{1}H-NMR ($CDCl_3$): 9.19 (*s*, NH); 7.64 (*s*, 2H arom); 6.95 (*s*, 1H arom); 3.46 (*m*, 2 NCH_2); 3.21 (*m*, 2 NCH_2); 2.22 (*m*, CH); 1.9–1.0 (*m*, 5 CH_2 and 4 CH_3). ^{13}C-NMR ($CDCl_3$): 175.1, 170.1 (CON); 139.2, 137.5, 116.7, 116.3 (arom); 45.8 (CH); 43.3 and 42.7 (NCH_2); 29.3 and 25.5 (CH_2); 13.9 and 12.8 (CH_3). *Anal. calc.* for $C_{23}H_{235}N_3O_3$ (401) C 68.8 H 8.7 N 10.5; *found*: C 68.0 H 8.6 N 10.3.

15b was prepared by esterification of 5-aminoisophthalic acid in acidic ethanol followed by condensation of the resulting diethylester with cyclohexylcarbonyl chloride as described for **13a** and **13b** (90%). ^{1}H-NMR ($CDCl_3$): 8.42 (*s*, NH); 8.40 (*s*, 2 H arom); 7.36 (*s*, 1 H arom); 4.40 (*q*, 7 Hz, 2 OCH_2); 2.27 (*m*, CH); 2.0–1.2 (*m*, 5 CH_2); 1.41 (*t*, 7 Hz, 2 CH_3). M. P. 162°C. *Anal. calc.* for $C_{19}H_{25}NO_5$ (347) C 65.7 H 7.2; *found*: C 65.6 H 7.3.

16a was prepared by reaction of 5-amino-*N*,*N'*-diethyl-1,3-benzenedicarboxamide with the tetracarbonyl chloride **12** as described for **13a** and **13b** (50%). ^{1}H-NMR ($CDCl_3$): 10.5 (broad *s*, NH); 7.86 (broad *s*, 2H arom); 7.05 (broad *s*, 1H arom); 4.59 (broad *s*, CH); 4.0–3.0 (*m*, 2 OCH_2 and 4 NCH_2); 1.4–0.8 (*m*, 4 CH_3). ^{13}C-NMR ($CDCl_3$): 169.4, 167.8 (CON); 137.7, 119.6, 116.6 (arom); 79.8 (CH); 70.1 and 67.9 (OCH_2); 43.1 and 39.1 (NCH_2); 13.9 and 12.5 (CH_3).

16b was prepared by reaction of diethyl 5- aminoisophthalic diester with the tetracarbonyl chloride **12** as described for **13a** and **13b** (35%; not optimized). ^{1}H-NMR ($CDCl_3$): 9.25 (*s*, NH); 8.30 (*s*, 2 H arom); 8.23 (*s*, 1 H arom); 4.66 (*s*, CH); 4.33 (*q*, 7 Hz, 2 OCH_2CH_3); 4.2–3.6 (*m*, 2 OCH_2); 1.38 (*t*, 7 Hz, 2 CH_3). ^{13}C-NMR ($CDCl_3$): 168.2, 165.1 (CO); 137.5, 131.0, 125.8, 124.1 (arom); 80.9 (CH); 69.8, 69.3 (OCH_2); 61.2 (OCH_2CH_3); 13.7 (CH_3). *Anal. calc.* for $C_{64}H_{76}N_4O_{26}$ (1316) C 58.3 H 5.8; *found*: C 57.5 H 5.9.

2.3. SPECTROSCOPIC MEASUREMENTS

Solvents were of spectroscopic grade. 1-pentanol and 1-octanol were distilled twice on activated charcoal before use. Solutions were prepared from a stock solution in CH_2Cl_2 or $CHCl_3$. Aliquots of mother solution were put in volumetric flasks. After complete evaporation of the volatile solvent, the appropriate solvent was added.

UV spectra were recorded on a Perkin-Elmer 554 spectrometer. Fluorescence spectra were measured with an AMINCO SPF 500 spectrometer coupled to a Kontron PSI 80 computer for data acquisition and were corrected for the residual solvent fluorescence. Slit widths were 4 nm (excitation) and 8 nm (emission). In all cases, absorbance at the excitation wavelength was less than 0.1. CD spectra were recorded on a Mark V Jobin-Yvon spectrometer and corrected for solvent residual absorption. In all cases, absorbance was less than 1.4.

3. Results

3.1. DESIGN OF THE MOLECULAR BOUQUETS $\mathscr{B}_M$

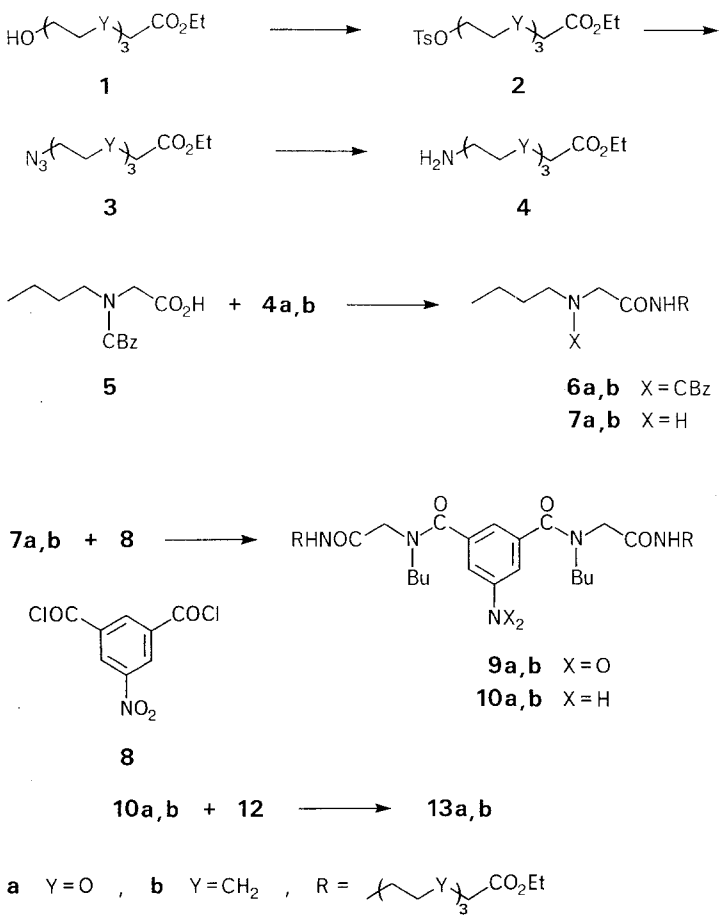
The design of the *bouquet* molecules was inspired at least in part by the geometrical and structural features of the natural peptides gramicidin A [7] and alamethicin [8]. Included in natural or artificial bilayers, they display their activity under the form of a cylinder with a length of about 30 Å and a diameter of a few Å (3–7 Å). Moreover, they present two gradients of increasing hydrophobicity: (i) from the interior to the exterior and, (ii) from the top to the middle of the cylinder. In addition to these essential structural criteria, a UV absorbing chromophore was introduced in the core of the *bouquet* molecules, in order to provide a spectroscopic label facilitating the interpretation of the eventual ionic conduction results. It may allow us to probe their incorporation and to study their possible orientations and conformations in bilayer membranes, so as to be able to draw structure-property relationships.

We have synthesised two series of molecules exhibiting these required characteristics. The first $\mathscr{B}_M$ is built up on an [18]-O_6 macrocyclic crown ether core and is the

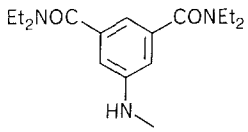
object of the present paper. The second $\mathscr{B}_{CD}$ is elaborated from a β-cyclodextrin derivative and will be described elsewhere. In view of comparative studies, two analogs were synthesised in each series: (i) the first, denoted $\mathscr{B}^{O}$, bears polyoxyethylenic chains and contains the oxygen sites necessary for the binding of cations along the channel in a functional ionophore, (ii) the second, denoted $\mathscr{B}^{c}$, is the alkyl analogue, which should display a similar structural behaviour but much weaker interactions with ions. Further criteria such as synthetic accessibility, chemical and structural characterization, means of visualization, postulated interactions with ions, geometric features in isotropic and anisotropic media, led finally to the two molecules $\mathscr{B}^{O}_{M}$ and $\mathscr{B}^{c}_{M}$ (**14a** and **14b**; Scheme 3) as first approaches to the *bouquet* type structures and to potential *chundle* type ion transport functions.

3.2. SYNTHESIS OF THE $\mathscr{B}_{M}$ MOLECULES

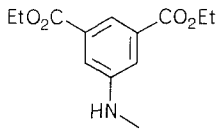
The linear aminoester chain **4a** was obtained in four steps starting from triethyleneglycol (Schemes 1 and 2). The condensation of ethyl diazoacetate in the



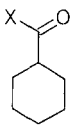
Scheme 1



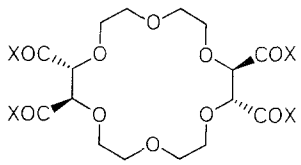
a



b



15a X = a
15b X = b



11 X = OH
12 X = Cl
16a X = a
16b X = b

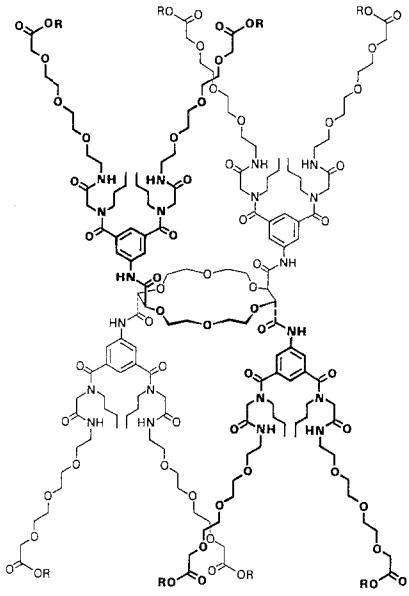
Scheme 2

presence of BF_3 etherate [13] gave the hydroxyester **1** in 70% yield. **1** was then transformed into the aminoester **4a** via the tosylate **2** (TsCl, Pyr, 4°C) and the azide **3** (NaN_3, DMF, 60°C) which was hydrogenated to the amine **4a** (H_2, Pd/C 10%, CH_2Cl_2, RT). **4b** was obtained from the commercial aminoacid by esterification in acidified absolute ethanol [14]. The aminoesters **4a** and **4b** were coupled with carbobenzyloxybutylglycine **5** (obtained from *n*-butylglycine [15] and benzylchloroformate in the usual way [15]) using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) to give **6a** and **6b**. Removal of the protecting groups by hydrogenolysis and condensation of the amines **7a** and **7b** with 5-nitro-1,3-benzenedicarbonyl chloride **8** yielded **9a** and **9b** (TEA, CH_2Cl_2, RT). After catalytic hydrogenation of the nitro group, the anilines **10a** and **10b** were grafted on the (+)-tartrocrown tetracarbonyl tetrachloride **12** [12] to give **13a** ($\mathscr{B}^{\circ}_{M}$ COOEt) and **13b** ($\mathscr{B}^{c}_{B}$ COOEt), respectively. The final saponification of the terminal ester groups to **14a** ($\mathscr{B}^{\circ}_{m}$ COONa) and **14b** ($\mathscr{B}^{c}_{M}$ COONa) was achieved by sodium hydroxide in methanol at room temperature. Polarimetric measurements were used to ensure that no epimerization had occured during saponification.

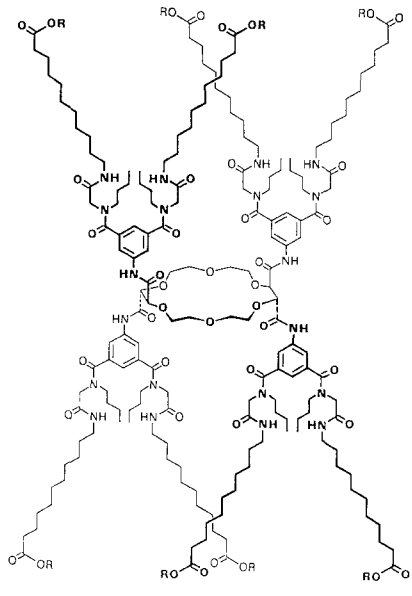
3.3. PROPERTIES OF THE *BOUQUET* MOLECULES $\mathscr{B}_M$

The properties of the $\mathscr{B}_M$ *bouquets* in solution were investigated mainly in order to prepare the further steps of this work i.e. membrane incorporation and ion transport studies.

The first features examined are related to the molecular geometry of the $\mathscr{B}_M$ species and its modification according to the medium. The aromatic chromophores were used as visualisation and potential conformational probes of the *bouquets*. UV spectra are affected by solvent effects, aggregation phenomena and conformational perturbation. In order to analyse eventual changes of UV spectra in membrane



13a R = Et
14a R = Na



13b R = Et
14b R = Na

Scheme 3

medium relative to solvent, spectra were collected in several solvents displaying a wide range of liquid state characteristics: refraction index (from MeOH to DMSO), lipophilicity (from light alcohols, MeOH or EtOH, to higher homologs such as pentanol or octanol).

The second type of properties to be studied will deal with the interaction of the $\mathscr{B}_M$ *bouquets* with cations in an isotropic solvent. In view of their potential ionophore properties, it is necessary to investigate their possible associations with cations, though the molecular geometry may not be the same in an isotropic and in a membrane medium. Using the esters, **13a** and **13b**, or the model compounds **16a** and **16b**, allows the study of the interactions of cations mainly with both the core and the chains or the core alone of the *bouquets*. These results will be reported elsewhere.

3.3.1. *Spectroscopic Properties*

Electronic spectroscopy studies were performed on **13a**, **13b**, **14a** and **14b**. For comparison purposes, reference compounds containing the basic chromophore, **15a** and **15b**, as well as models devoid of chains, **16a** and **16b**, were also examined (Scheme 2) (Tables I and II). Figure 2 shows typical UV absorption and fluorescence emission spectra of these molecules. The UV spectra display a maximum with a strong molecular extinction coefficient ($\lambda_M = 210-225$ nm) and a shoulder ($\lambda_s = 240-245$ nm). When excited at λ_s, these molecules fluoresce weakly at about 360 nm. **13a**, **13b**, **14a**, **14b**, **16a** and **16b** being chiral and bearing strongly absorbing

Table I. UV absorption characteristics of **13a**, **13b**, **14a**, **14b**, **15a**, **15b**, **16a** and **16b** in several solvents

Solvent	n_D^{25} [a]	Compound	λ_M(nm)	ε_M	λ_s(nm)	ε_s
Methanol	1.326	**13a**	212	160 000	242	105 000
		13b	212	85 000	240	105 000
		15a	214	37 000	244	26 000
		15b	223	48 000	254	17 000
		16a	214	110 000	240	76 000
		16b	220	120 000	260	40 000
Ethanol 95%	1.359	**14a**	216	130 000		
		14b	210[c]	130 000		
		16b	220	120 000	260	35 000
n-Pentanol	1.408	**13a**	212	111 000	242	80 000
		13b	220	400 000		
		15a	215	29 000	240	25 000
		15b	225	41 000	256	12 500
		16a	216	91 000	240	67 000
		16b	222	100 000	260	35 000
n-Octanol	1.427	**13a**	220	330 000		
		13b	216	138 000	240	92 000
		15a	217	25 000	240	19 000
		15b	225	33 000	256	8 900
		16a	216	93 000	240	69 000
		16b	223	100 000	260	26 000
Chloroform	1.444	**16b**			260	29 000
DMSO	1.479[b]	**16b**			260	18 000

[a] Refraction index at 25°C.
[b] At 20°C
[c] Not a maximum.

Table II. Fluorescence emission characteristics of **13a**, **15b** and **16b** in different solvents

Solvent	Compound	$\lambda_{excitation}$ (nm)	$\lambda_{emission}$ (nm)
Methanol	**13a**	270	364
	15b	260	361
	16b	260	356
n-Pentanol	**13a**	270	362
	15b	260	358
	16b	260	355
n-Octanol	**13a**	270	360
	15b	260	357
	16b	260	351

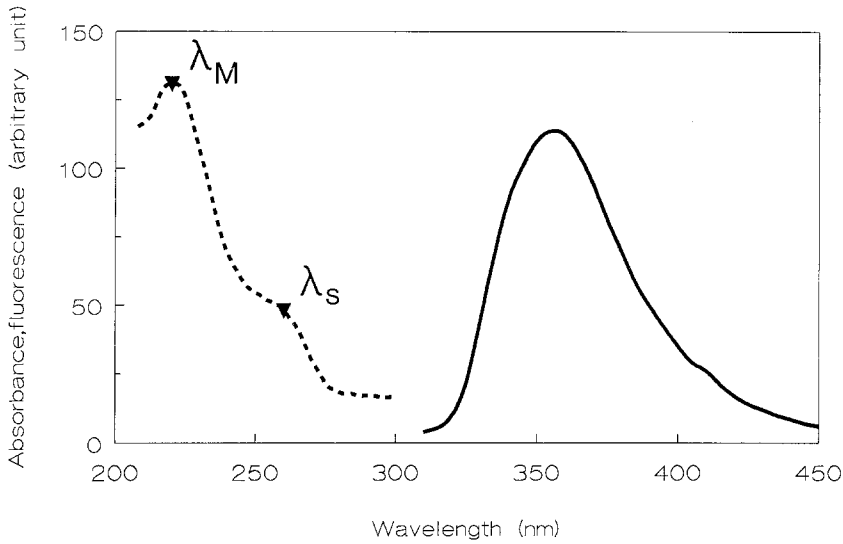


Fig. 2. UV absorption (- - -) and fluorescence emission (——) spectra (excitation at 260 nm) of **16b** in MeOH. λ_M and λ_s indicate the wavelengths mentioned in the text.

chromophores, some circular dichroism spectra were also recorded. They display an intramolecular excitonic coupling. The circular dichroism spectra show a negative $\Delta\varepsilon$ wave at long wavelength. Figure 3 presents a typical spectrum and Table III summarizes the results.

3.3.2. *^{1}H-NMR and ^{13}C-NMR Investigations*

The 200 MHz proton NMR spectrum of **13a** shows broad peaks at room temperature and is not informative. It is much better resolved at 394 K as shown in Figure 4.

The 50.3 MHz ^{13}C-NMR spectrum of **13a** at 298 K (Figure 5, bottom) displays broadened peaks as well as a doubling of the signals of the CH_2 carbons in α and β positions to N of the tertiary amide functions (in the 30 and 50 ppm regions). On heating to 383 K (Figure 5, top) sharp resonances are obtained and the doubled signals coalesce into narrow singlets.

Measurements of ^{13}C-NMR relaxation times are of general use to assess the degree of local and overall molecular mobility [17]. Because of the complexity of the ^{13}C-NMR spectra of **13a** and **13b** at room temperature, the longitudinal relaxation times T_1 of all the macrocycle-carbon atoms were determined on **16b** (Table IV). When corrected for the number of hydrogen atoms carried by each carbon atom, all the positions on the ring display the same mobility behavior. For **13a** it was possible to determine the ^{13}C relaxation times at room temperature for the carbon atoms of the side chains. They increase from the aromatic carbons ($NT_1 \approx 0.19$ s) towards the end of the chain: $NT_1 \approx 0.3$–0.6 s (CH_2 polyoxy), 1.8 s (CH_2 ester), 6 s (CH_3 ester) (N = number of hydrogens on the carbon atom). A similar behaviour was found for **13b**.

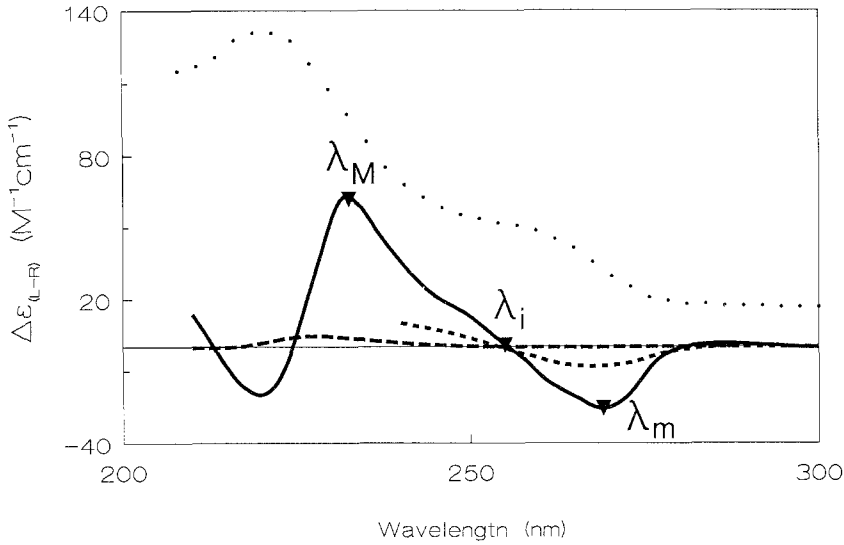


Fig. 3. Circular dichroism spectra in MeOH (——), *n*-pentanol (- - -), *n*-octanol (– – –) and UV absorption spectrum of **16b** in MeOH (. . . .). λ_M, λ_i and λ_m indicate the wavelengths mentioned in the text.

Table III. Cicular dichroism characteristics of **13a**, **13b**, **14a** and **16b** in different solvents

Solvent	Compound	λ_M(nm)	λ_i(nm)	λ_m(nm)
Methanol	**13a**	246	267	273
	13b	249	268	291
	14a	253	270	278
	16b	232	256	269
n-Pentanol	**13a**	—	266	272
	13b	—	273	288
	14a	—	245	264
	16b	—	254	267
n-Octanol	**13b**	249	—	—
	13b	246	276	290
	14a	—	252	267
	16b	228	253	—

Table IV. ^{13}C-NMR longitudinal relaxation times T_1 of the carbon atoms of the macrocycle in **16b**

Carbon	δ (ppm)	T_1(s)	Standard deviation	NT_1(s)
CH	80.1	0.11	0.03	0.11
CH_2	70.3	0.06	0.06	0.12
CH_2	68.0	0.065	0.03	0.13

100 mg of **16b** in 0.5 mL of $CDCl_3$ at r.t. (without degassing). δ = ^{13}C chemical shifts; N = number of hydrogens bound to the carbon atom.

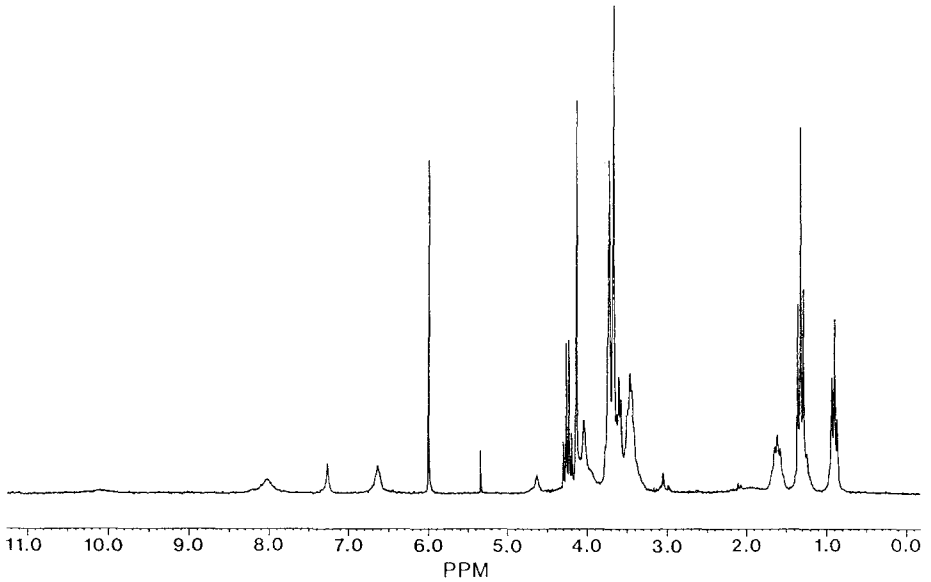


Fig. 4. 200 MHz proton NMR spectrum of the *bouquet* molecule **13a** at 394 K in $C_2D_2Cl_4$ (solvent signal at 6.0 p.p.m.); see experimental section for peak assignment.

4. Discussion

4.1. SPECTROSCOPIC PROPERTIES

The UV spectra in homogeneous medium clearly show the absence of a marked solvatochromic effect in the $\mathscr{B}_M$ molecules **13a** and **13b** investigated (little or no variation of the λ_{max} in the solvents studied). Thus a modification of medium polarity does not affect their UV spectra. As a consequence, any change which might take place on membrane incorporation would have to arise from other factors such as aggregation phenomenon or conformational effects.

4.2. MOLECULAR GEOMETRY OF THE BOUQUET MOLECULES $\mathscr{B}_M$

The structural features of the *bouquet* molecule $\mathscr{B}^{\circ}_M$ **14a** correspond to those desired for *chundle* type cation transport functions. The oxygen containing chains and core should be able to bind metal ions. With the side-chains in their extended state, the molecule is long enough (about 45–50 Å) to span a bilayer membrane. The terminal carboxylate groups provide the charged sites required for anchorage at the water/membrane interfaces and transmembrane orientation. The rigid phenyl groups may be expected to hinder back-bending of the chains and the *n*-butyl groups confer lipophilicity facilitating membrane inclusion.

The relaxation times of all carbon atoms of the macrocycle in **16b** are found to be similar (Table IV). This indicates that the crown ring is rigid on this time scale, and that all positions play the same role. The local dynamical properties are not significantly perturbed by the attached substituents. Although these results do not

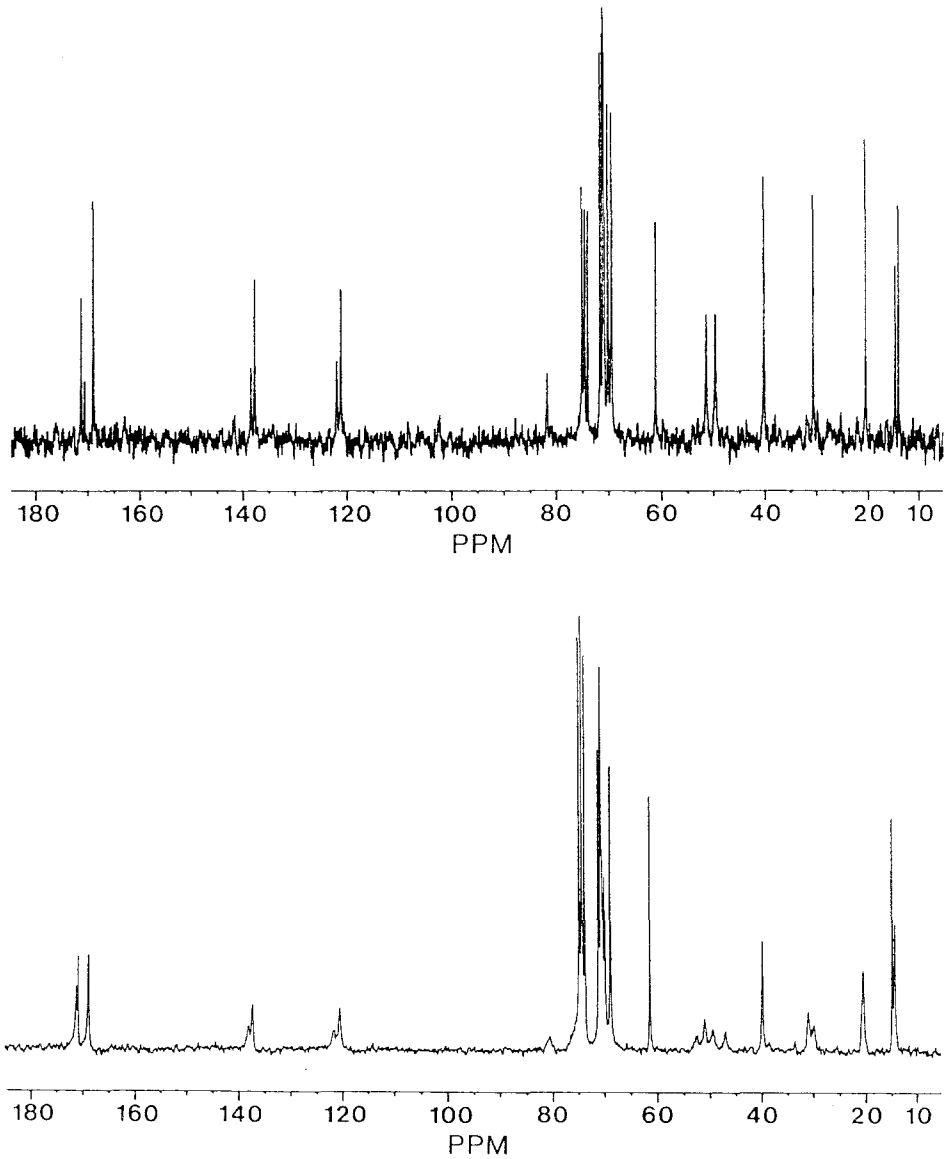


Fig. 5. 50.3 MHz carbon-13 NMR spectra of the *bouquet* molecule **13a** at 298 K (bottom) and at 383 K (top) in $C_2D_2Cl_4$ (solvent signal at 74.3 p.p.m.); see experimental section for peak assignment.

give information about the exact shape of the macrocycle, they agree with an axial symmetry, as in a circular core, but do not exclude other shapes. Indeed the parent [18]-O_6 ring displays structural flexibility, adopting different conformations [18]. It does not itself have a circular shape (D_{2d}) in the crystal [19], but takes it up in aqueous solution [20]. In the crystal structures of complexes of derivatives of the basic unit **11** the macrocycle is of circular shape, but this may well be a result of the complexation [10c, 21, 22]. The marked increase in ^{13}C relaxation

times along the side chains agrees with the expected increase in local motions due to their flexibility.

The close similarity between UV and fluorescence emission spectra for all the molecules, including the models containing the elementary chromophores **15a** and **15b**, excludes the presence of a strong interaction between the four chains of $\mathscr{B}_M$ bouquets. This, together with the ^{13}C-NMR results, suggests that the ring is not a collapsed form under these conditions.

The circular dichroism spectra are only slightly informative. The $\Delta\varepsilon$ values are linearly related to the molecular masses. The qualitative similarity of all the recorded spectra in MeOH points to the similarity of the ring-chromophore environments in **13a**, **13b**, **14a** and **16b** in this solvent. The modifications observed for **14a** support this assumption; indeed, among the different molecules studied and in these poor solvents for ions and polyoxy chains, **14a**, which is charged and bears polyoxy elements, is the most likely to display a constraint, and a conformational change.

In order to specify the orientation of the chains with respect to the macrocycle, the determination of the dihedral angle in the tartaric units was attempted, but even for **16b** a precise value of the vicinal coupling constant could not be obtained from examination of the ^{13}C satellite of the CH resonance. The observed width at half-height (4 Hz) is in agreement with the amide groups on the ring being approximately in a *trans*-diaxial conformation. This is in line with earlier NMR studies [12] as well as crystal structure determinations [23] on derivatives of the tartocrown **11** bearing CONHR amide groups, which indicated that these side chains are oriented perpendicularly to the mean plane of the macrocycle.

The ^{13}C-NMR spectral data for **13a** and their temperature dependent features (Figure 5; see above) indicate (1) that the expected two rotamers around each tertiary amide CO–N bond are present and, (2) that rotation around these bonds is slow at 298 K and fast at 383 K, on the NMR time scale, in agreement with the well-known NMR features of such functional groups. In both rotamers the chains linked to the tertiary amide nitrogens have a similar overall orientation with respect to the axis of the macrocyclic core. Structures **13** and **14** represent just one of the 27 rotameric forms (three forms for each of the four side chains with D_2 symmetry of the core macrocycle). Medium and membrane incorporation effects (Figure 1) will affect the population of each form and the orientation of the lateral polyoxy and polymethylene chains.

5. Conclusions

We have synthetised two molecules $\mathscr{B}^{o}_{M}$ and $\mathscr{B}^{c}_{M}$ in order to investigate an approach to transmembrane structures. In particular, $\mathscr{B}^{o}_{M}$ displays favorable characteristics as a potential ionic channel; its structural and geometrical properties should allow its incorporation into phospholipid bilayer membranes with preservation of the geometry of the macrocycle core (existence of a central cavity and preferential diaxial orientation of the lateral carboxy groups). Whether these features will allow the functioning of the $\mathscr{B}^{o}_{M}$ bouquet molecule as an ion channel, will depend on its ion binding properties [23] and its incorporation into bilayer membranes. Such studies will be described elsewhere.

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