Pergamon

Tetrahedron Letters 42 (2001) 4799–4802

TETRAHEDRON LETTERS

Novel synthetic receptors based on *para*-amino-pyridine ligands coupled to *p-tert*-butylcalix[4]arene via amino-acid spacers

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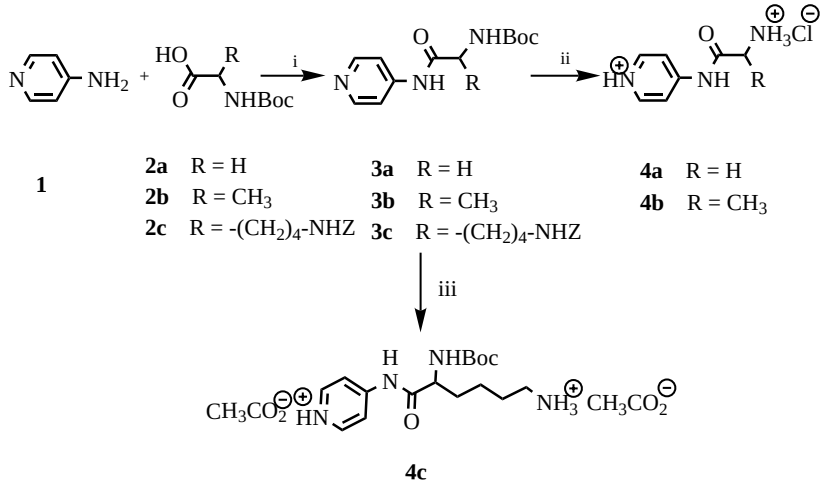
Received 2 April 2001; accepted 29 April 2001

Abstract—The synthesis of a series novel receptors based on *p-tert*-butylcalix[4]arene tetra-substituted at the lower rim by pyridinyl derivatives of the amino acids, glycine, alanine and lysine is described.

The relative rigidity of various supramolecular systems makes them interesting candidates for the introduction of spatially differentiated coordinating systems, i.e. as di- or polytopic molecular receptors.[1] There has recently been increasing interest in the use of the calix[4]arene skeleton for the development of this type of multiple coordination-centre molecule.[2] The synthetic strategy behind such development involves coupling, generally at the lower face of a calix[4]arene, a group capable of coordinating either a metal, for example the porphyrin units used by Shinkaï,[3] or for anions, the use of pyridinium units by Beer.[4] Examples of ditopic complexation including the selective complexation of sodium phosphates,[5] chloride or bromide[6] and caesium chloride[7] were developed by Reinhoudt. The choice of the spacer unit between the calix[4]arene and the complexation site is a key factor in controlling both the size of the complexation centre and the selectivity in ditopic complexation. Similarly substitution along the spacer chain will influence the preorganisation at the complexation centre.

In this paper we report the synthesis of a series of pyridinium groups attached to calix[4]arene via amino-acid derived spacer arms. By using glycine (Gly) and alanine (Ala) we have been capable of varying the stereochemistry along the spacer and introducing chirality at this point. The use of *N*-ε-lysine (Lys) based



Scheme 1. Synthesis of pyridinium derivatives: (i) DCC, HOBT, DIEA, DMF; (ii) HClg; (iii) H_2, Pd/C, MeOH, CH_3COOH.

Keywords: calix[4]arene; pyridiniums chloride and acetate; amino acids; synthesis.

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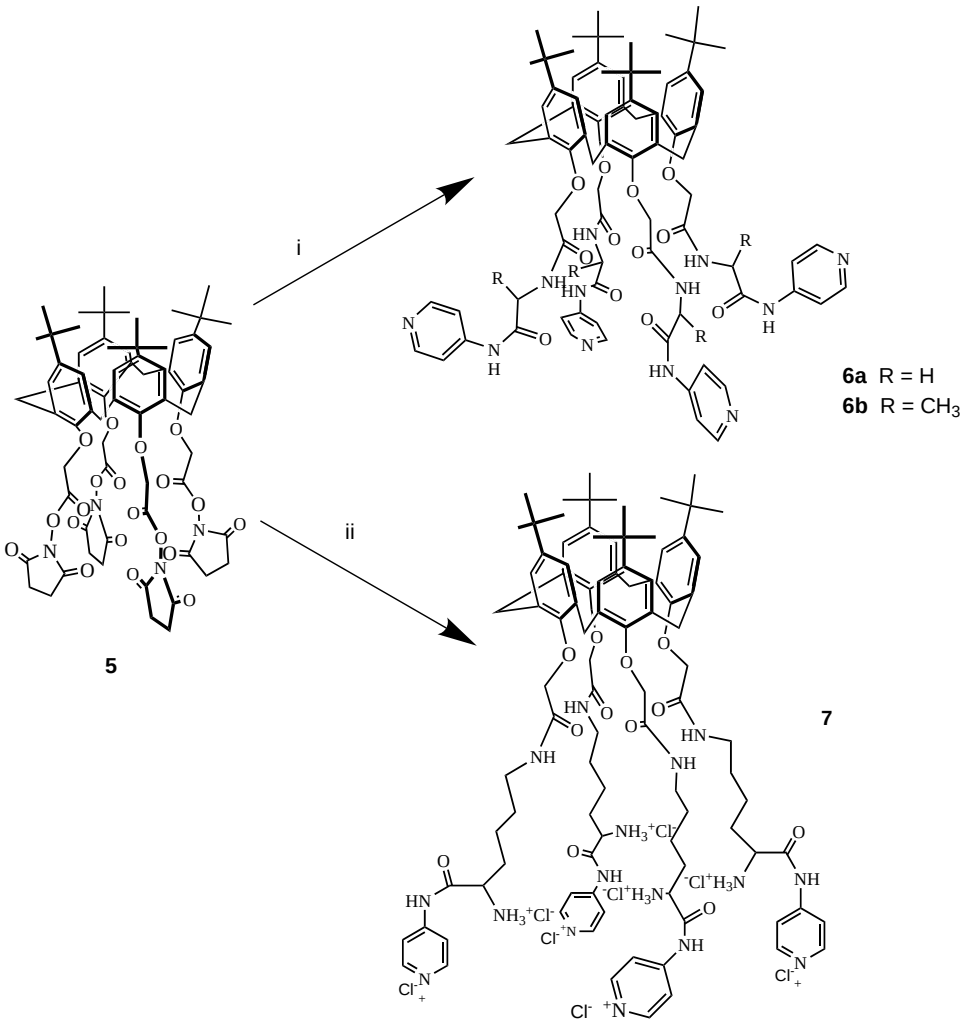
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00849-8

systems allows variation in the length of the spacer as compared to the other two systems. The pyridine derivatives **4a**, **4b** and **4c** were synthesised from the 4-aminopyridine **1** in two steps (Scheme 1). 4-Aminopyridine **1** (18 mmol) was condensed with the *N*-protected amino-acid derivatives *t*-butyloxycarbonyl-glycine (Boc-Gly-OH) **2a**, *t*-butyloxycarbonyl-alanine (Boc-Ala-OH) **2b** and *t*-butyloxycarbonyl-lysine-*N*-ε-benzyloxycarbonyl (Boc-Lys(Z)-OH) **2c** (15 mmol) in dry DMF (250 mL) in the presence of 1,3-dicyclohexylcarbodiimide (DCC, 18 mmol), hydroxy-benzotriazole (HOBT, 18 mmol) and diisopropylethylamine (DIEA, 21 mmol) for 3 h at 0°C followed by 2 h at 20°C. After elimination of dicyclohexylurea (DCU), the solvent was eliminated and the crude product purified by crystallisation from acetone for **3a**[8] (44% yield) and toluene for **3b**[8] (43% yield). Purification by chromatography on silica gel ($CHCl_3$: acetone 6:4) gave **3c** in 77% yield.[8] The derivatives **4a** (95% yield) and **4b** (97% yield)[9] were obtained after complete deprotection by gaseous HCl in CH_2Cl_2. The benzyloxycarbonyl group (Z) was removed from **3c** by hydrogenolysis in MeOH:CH_3COOH (1 M aqueous) 20:3 in the presence of the Pd/C 10% to yield **4c** (91% yield).[9]

Calix[4]arene derivatives **6a**, **6b** (87 and 40% yield, respectively) and **7**[10] were synthesised by condensation at 25°C of the tetra-succinimidoyl activated ester **5**[11] with the pyridinium derivatives **4a**, **4b** or **4c** in CH_2Cl_2 in the presence of DIEA (Scheme 2). The desired compound **7**, for the lysine system, was obtained by deprotection of the *N*-α-Boc protecting group by means of gaseous HCl/CH_2Cl_2 treatment. The dichloride salt **7** is obtained in 73% yield. Electrospray mass spectrometry (positive mode) clearly demonstrates that **6a**, **6b** and **7** are tetrasubstituted derivatives (*m*/*z* 1414 [**6a**+H]$^+$, 1492 [**6b**+Na]$^+$ and 1699 [**7**+H]$^+$ and that under-substituted derivatives are absent. The presence of mono, di and tri-charged species for each compound is to be noted.

^{1}H NMR shows the highly symmetrical nature of **6a** and **7**. The cone conformation[12] is confirmed by the presence of an AB ($J = 13.4$ Hz) system characteristic of methylene bridges ($ArCH_2Ar$) and by the position of the carbon atoms of the methylene bridges in the ^{13}C NMR: 31.52, 29.97 and 31.76 ppm for **6a**, **6b** and **7**, respectively. The presence of a stereogenic carbon near



Scheme 2. Synthesis of calixarenic ligand. (i) **4a** or **4b**, DIEA, CH_2Cl_2, 25°C, 5 days; (ii) 1. **4c**, DIEA, CH_2Cl_2, 25°C, 5 days; 2. HCl_g, CH_2Cl_2, 25°C, 2 hours.

the calixarene rim leads to structural modifications for **6b**, which are shown by an expanded AB system of the methylene diastereotopic protons (3.95–4.65 ppm) and by shielding at 6.54 ppm of the amide proton doublet (8.54 and 8.26 ppm for **6a** and **7**). There would therefore seem to be no hydrogen bonds for **6b** at the level of the crown constituted by the four NHCO, as has been observed in other works.[13] This non-existence of hydrogen bonding leads to the unshielding of the CHα (5.21 ppm) compared to the CHα of **6a** (4.03 ppm) and of **7** (4.33 ppm). The aromatic calixarene protons of **6b** are also disturbed and are differentiated in the form of two singlets at 7.11 and 7.14 ppm each of intensity 4, whereas one singlet alone of intensity 8 is observed for **6a** (6.88 ppm) and for **7** (6.79 ppm). All these elements indicate a distortion of the calixarene cavity induced by the pro-helical structure due to the stereogenic carbons of **6b**. A similar result has been observed in previous work.[11] However, for **7** the stereogenic carbon is too distant from the calix[4]arene cavity to give rise to this effect.

Transition metal complexation studies where the geometry of the coordination sphere at the metal centre is of square–planar type are in progress. The grafting four 4-amino-pyridine ligands on a calix[4]arene skeleton via amino-acid spacers leads to novel ditopic receptors and presents a potential route to porous organic structures.

Acknowledgements

We are grateful MENRT for financial support. The authors wish to thank Mrs. Nicole Marshall for correcting the manuscript.

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8. Selected spectra data for **3a**: mp 153°C, ^{1}H NMR (DMSO-d_6 300 MHz): δ (ppm) 1.39 (s, 9H, Boc), 3.75 (d, 2H, CH_2), 7.12 (t, 1H, NHBoc), 7.55 (d, 2H, Hpy), 8.42 (d, 2H, Hpy), 10.33 (s, 1H, NHCO); ES–MS (m/z): 252.5 for $[M+H]^+$. **3b**: mp 169°C, ^{1}H NMR (DMSO-d_6 300 MHz): δ (ppm) 1.25 (d, 3H, CH_3), 1.37 (s, 9H, Boc), 4.09 (t, 1H, Hα), 7.20 (d, 1H, NHBoc), 7.57 (d, 2H, Hpy), 8.42 (d, 2H, Hpy), 10.33 (s, 1H, NHCO); ES–MS (m/z): 266 for $[M+H]^+$. **3c**: mp 63°C; ^{1}H NMR ($CDCl_3$ 300 MHz): δ (ppm) 1.45 (s, 9H, Boc), 1.55–1.96 (m, 6H, CH_2), 3.21 (q, $J=6.6$ Hz, 2H, $CH_2\beta$), 4.19 (m, 1H, Hα), 4.95 (t, $J=6.3$ Hz, 1H, NH(Z)), 5.10 (s, 2H, $CH_2\Phi$), 5.34 (d, $J=7.7$ Hz, 1H, NHBoc), 7.35–7.36 (m, 5H, H-Ar), 7.44 (d, $J=6.2$ Hz, 2H, Hpy), 8.44 (d, $J=6.2$ Hz, 2H, Hpy), 9.05 (s, 1H, NH-C=O); ES–MS (m/z): 457 for $[M+H]^+$.
9. Selected spectra data for **4a**: ^{1}H NMR (DMSO-d_6+D_2O 300 MHz): δ (ppm) 3.92 (s, 2H, CH_2), 8.03 (d, $J=7.35$, 2H, Hpy), 8.64 (d, $J=7.35$, 2H, Hpy). **4b**: (D_2O 300 MHz): δ (ppm) 1.66 (d, $J=7.35$ Hz, 3H, CH_3), 4.35 (q, $J=7.35$ Hz, 1H, CHα), 8.15 (d, $J=7.35$ Hz, 2H, Hpy), 8.63 (d, $J=7.35$ Hz, 2H, Hpy). **4c**: (DMSO-d_6, 300 MHz): δ (ppm) 1.27 (m, 2H, CH_2), 1.37 (s, 9H, Boc), 1.54–1.65 (m, 4H, CH_2), 1.87 (s, 6H, CH_3COO^-), 2.75 (m, 2H, CH_2), 4.06 (m, 1H, Hα), 7.18 (d, $J=7.5$ Hz, 1H, NHβ), 7.61 (d, $J=5.9$ Hz, 2H, Hpy), 8.41 (d, $J=6.2$ Hz, 2H, Hpy), 10.75 (s, 1H, NHpy); ES–MS(+) (m/z): 323 for $[M-2CH_3COOH+H]^+$.
10. Selected spectra data for **6a**: mp 235°C, IR (KBr) 1677 (CO(NH)), 3334 (NH); UV (CH_2Cl_2): λ 242 nm ($\varepsilon=900000$);^{1}H NMR (DMSO-d_6 300 MHz): δ (ppm) 1.06 (s, 36H, ^{t}Bu), 3.25–4.57 (AB, $J_{AB}=11.86$ Hz, 8H, Ar-CH_2-Ar), 4.03 (d, $J=4.41$ Hz, 8H, $CH_2\alpha$), 4.61 (s, 8H, OCH_2), 6.88 (s, 8H, H-Ar), 7.48 (d, $J=5.14$ Hz, 8H, Hpy), 8.34 (d, $J=3.68$ Hz, 8H, Hpy), 8.55 (t broad, 4H, NH), 10.38 (s, 4H, NHpy); ^{13}C NMR: δ (ppm) 31.52, (Ar-CH_2-Ar), 31.96 (Me, ^{t}Bu), 34.46 (C, ^{t}Bu), 43.62 (Cα), 74.78 (OCH_2), 114.05 (H-C_{py}), 126.30 (3, 5-Ar), 133.65, 145.64, 146.22, 154.11 (1,2,4,6-Ar, 4-Py), 151.09 (H-C_{py}), 169.65, 170.67 (CONH); ES–MS (+) (m/z): 1414 for $[M+H]^+$, 1436 for $[M+Na]^+$. Anal. calcd for $C_{80}H_{92}O_{12}N_{12}$+Na^++$4H_2O$: C, 63.67; H, 6.68; N, 11.14; O, 16.97. Found C, 63.83; H, 6.70; N, 10.80.
6b: mp 240°C, IR (KBr) 1675.8 (CO(NH)), 3331.6 (NH); UV (CH_2Cl_2): λ 242 nm ($\varepsilon=900000$);^{1}H NMR (DMSO-d_6 300 MHz): δ (ppm) 1.15 (s, 36H, ^{t}Bu), 1.18 (d, $J=6.88$ Hz, 12H, CH_3), 3.33–4.37 (AB, $J_{AB}=11.86$ Hz, 8H, Ar-CH_2-Ar), 3.95–4.65 (AB, $J_{AB}=13.39$ Hz, 8H, OCH_2), 5.21 (m, $J=6.51$ Hz, 4H, CH_α), 6.54 (d, $J=5.74$ Hz, 4H, NH-Cα), 7.11 (s, 4H, H-Ar), 7.14 (s, 4H, H-Ar), 7.88 (dd, $J_1=4.97$ Hz, $J_2=1.53$ Hz, 8H, H-Py), 8.49 (dd, $J_1=4.98$ Hz, $J_2=1.53$ Hz, 8H, H-Py), 10.34 (s, 1H, NH-Py); ^{13}C NMR 20.60 (CH_3-Cα), 29.97 (Ar-CH_2-Ar), 31.67 (Me, ^{t}Bu), 34.55 (C, ^{t}Bu), 50.57 (Cα), 74.81 (OCH_2), 113.7 (H-C_{py}), 125.90, 126.27 (3, 5-Ar), 134.58, 135.15, 145.83, 148.41, 150.27 ((1,2,4,6-Ar, 4-Py), 151.53 (H-C_{py}), 168.83, 172.96 (CONH); ES–MS (+) $[M+Na]^+$ 1492. Anal. calcd for $C_{84}H_{100}O_{12}N_{12}$+$H_2O$+$Na^+$: C, 66.76; H, 6.81; N, 11.13; O, 13.77. Found: C, 66.69; H, 6.98; N, 11.19.
7: mp 239°C, IR (KBr) 1678 (CO(NH)), 3330 (NH); UV (CH_2Cl_2) λ 242 ($\varepsilon=880000$); ^{1}H NMR (DMSO-d_6 500 MHz): δ (ppm) 1.03 (s, 36H, ^{t}Bu), 1.44 (s brd, 16H, $CH_2\gamma$+$CH_2\delta$), 1.97 (s brd, 8H, $CH_2\beta$), 3.11 (s brd, 8H, $CH_2\varepsilon$), 3.18–4.48 (AB, $J_{AB}=13.6$ Hz, 8H, $ArCH_2Ar$), 4.33 (s brd, 4H, CHα), 4.42 (s, 8H, OCH_2), 6.79 (s, 8H, HAr), 8.26 (d, $J=6.6$ Hz, 8H, Hpy), 8.41 (s brd, 4H, $NHCH_2\varepsilon$), 8.73 (s brd, 12H, NH_3^+), 8.79 (d, $J=6.3$, 8H, Hpy), 12.87 (s large, 4H, NH); ^{13}C NMR 22.50, 29.47,

31.20 ($CH_2\beta,\gamma,\delta$), 31.76 ($ArCH_2Ar$), 31.96 (Me), 34.38 (C^{t}Bu), 38.98 ($CH_2\varepsilon$), 54.18 ($CH\alpha$), 74.76 (OCH_2), 115.67, 143.68 (2,3,5,6-py), 126.11 (3,5-Ar), 133.59, 145.20, 152.94, 153.82 (1,2,4,6-Ar+4-py), 169.75, 171.12 (CONH); ES–MS (+) $[M+H]^+$ 1699. Anal. calcd for $C_{96}H_{136}O_{12}N_{16}Cl_8+6H_2O+2Na^+$: C, 53.73; H, 6.96; N, 10.45. Found C, 53.85; H, 7.04; N, 10.4.

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