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New water-soluble calix[4]arene-based bipyridyl podands incorporating carboxylate groups

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Abstract—New calixarene-based bis-bipyridyl podands incorporating two sodium (4-oxo)-butanoate or four sodium carboxymethyl groups at the upper rim were synthesised and fully characterised. The (4-oxo)-butanoate derivative bearing unsubstituted bipyridyl arms was not soluble in water at neutral pH, while its 4,4′-dicarboxylate analogue was perfectly soluble, as were the carboxymethyl derivatives. The association of water solubility to the chelating behaviour of the bipyridyl subunits resulted in the ability to complex the unstable copper(I) cation in water, even in the presence of bovine serum albumin.

The translation from organic to aqueous medium of the highly interesting properties of calixarene species is currently gaining attention, as demonstrated by a rapid on-line survey on *water-soluble calixarenes* and recent review literature.[1]

The attribution of hydrophilic behaviour to calixarene platforms has been made possible by the introduction of various kinds of substituents, such as, for example, carboxylate,[2] phosphonate,[3] amine,[4] sulfonate,[5] PEG or poly-hydroxymethyl ethylene glycols[5c] groups.

In order to conduct in water some complexation experiments initially developed with lipophilic calixarene-based heterocyclic podands,[6] and to prepare future investigations in the biological field, we attempted to synthesise hydrophilic ligands able to complex the copper(I) cation, relatively unstable in this medium. Thus, giving a water-soluble character to the 1,3-bis-(2,2′-bipyridyl)-calix[4]arene podand has been made possible by means of sulfonate[7] or phosphonate[8] functions at the upper rim of the calixarene core, or by carboxylate groups directly brought by the bipyridine units.[9] These ligands displayed the expected water solubility, and a good ability to complex copper(I) in water, even in the presence of natural complexing agents. Very few other examples of water-soluble copper(I) coordination complexes have been described until now, involving a sulfonated phosphine ligand,[10] or calix[6]arene heterocyclic derivatives,[11] illustrating in part the difficulty of protecting this cation from disproportionation in water, and thus limiting investigations on its properties in aqueous media.

In order to enlarge our library of such bipyridyl podands, we developed a new approach, leading to ligand displaying carboxylate groups, at least at the upper rim of the calixarene ring. 3-Oxo-carboxypropyl and carboxymethyl groups were chosen for this purpose. With the former, two groups were preliminarily introduced in distal positions at the upper rim of the calix[4]-arene platform (Scheme 1). The di-benzoyl-di-*tert*-butyl calixarene **1**[12] was acylated with succinic anhydride and $AlCl_3$, then saponified to give the diacid **2**. The latter was carefully solubilised with aqueous NaOH to give, after dialysis and lyophilisation, the sodium salt **3**, elemental analysis and flame photometry were consistent with the presence of a third sodium ion that was associated to one of the four phenol groups. The diester **4** was then prepared by reaction of **3** with EtBr in dry DMF.

The reaction of **4** with the bromomethyl bipyridine **5**[13] was first done in $MeCN/K_2CO_3$ medium, giving in low yield two bis-bipyridyl regio-isomers in which the substitution was effective on the two *p*-*tert*-butyl phenol groups or on the two succinylated ones. They were accompanied

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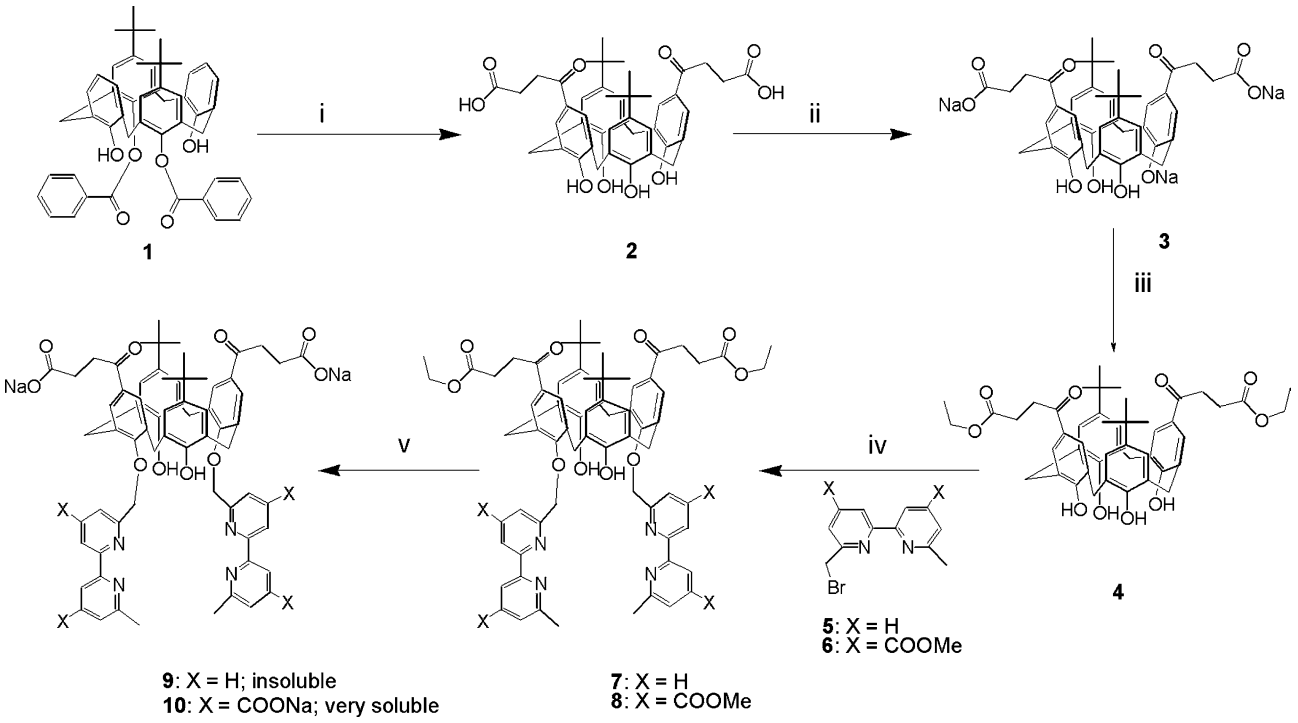


Scheme 1. Reagents and conditions: (i) (a) $AlCl_3$, succinic anhydride, CH_2Cl_2, 50 °C; (b) NaOH, EtOH/H_2O, reflux; HCl pH 3.5, 79%; (ii) NaOH 0.1 M, 84%. (iii) EtBr, DMF, 40 °C, 80%. (iv) $BrCH_2bpy(X)_2$, K_2CO_3, Me_2CO, 60–70 °C; X = H: **7**: 22%, X = COOMe: **8**: 28%. (v) (a) NaOH, EtOH/H_2O, reflux; X = H: HCl pH 8.9, **9**, 71%; X = COONa: HCl pH 2, then NaOH pH 7.4, **10**, 72%.

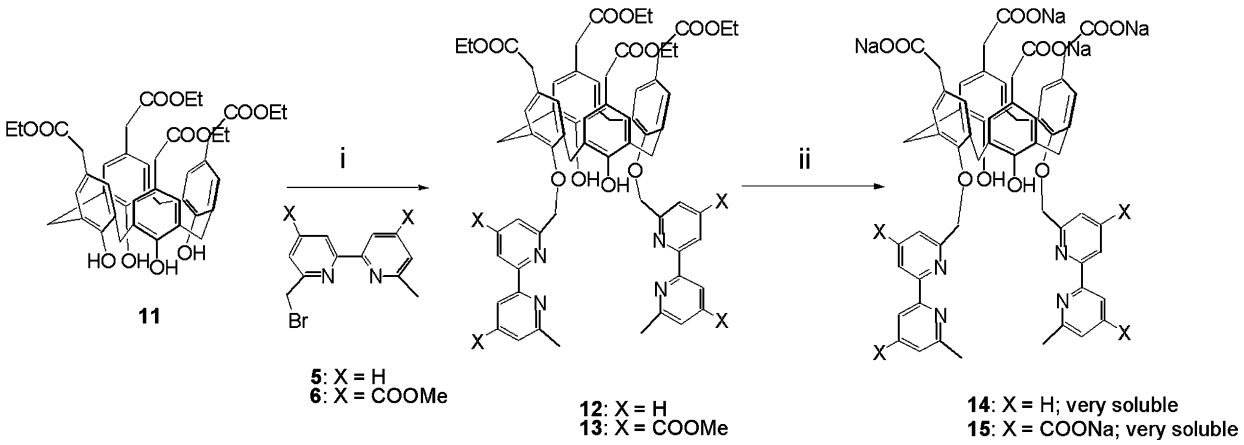
by poly-substituted analogues. All attempts to separate them in pure form were unsuccessful. Replacing MeCN by Me_2CO afforded as main product the podand displaying, as assessed by 2D NMR analyses (^1H, ^{13}C-HMBC), the two bipyridines tethered to the succinylated phenols (**7**, 22%). Only traces of the regio-isomer were found and easily removed by chromatography. Saponification of the two succinic esters of **7** afforded the di-sodium salt **9**, which remained, a contrario to our previsions, insoluble in water. At pH 11, **9** can be solubilised, but precipitates again with natural carbonation that occurs on contact with air. Attempts to connect this behaviour with the amphoteric character of **9** are under investigation.

In order to by-pass this unexpected solubility problem, the bipyridyl unit **5** was replaced by its 4,4′-di-carbomethoxy analogue **6**.[9b] The hexa-ester **8** was isolated with a yield of 28%. Saponification, followed by acidification to pH 2 afforded the insoluble hexa-acid derivative; a pH-controlled solubilisation of the latter with 0.1 M NaOH, followed by dialysis and lyophilisation, gave the expected water-soluble hexa-sodium salt **10**.

Attempts to synthesise the tetra-succinoyl analogue of **2** resulted in unsolvable mixtures of derivatives/conformers. This led us to introduce the expected water solubility through carboxymethyl groups displayed at the upper rim of the calixarene, according to the procedures of Gutsche and coll.[4,14] The bipyridine arms were attached in distal positions at the lower rim of the tetra-ethylester **11**, by reaction with the bromo-derivatives **5** or **6** in the MeCN/K_2CO_3 medium (Scheme 2). As for compound **10**, basic hydrolysis of the ester functions, followed by acidification, afforded the corresponding insoluble tetra- and octa-acid derivatives. Solubilisation with 0.1 M NaOH, followed by dialysis and lyophilisation, gave the pure tetra- and octa-sodium salts **14** and **15**.

All compounds were fully characterised and gave satisfactory NMR, electrospray mass spectrometry and elemental analyses.[15] In each case, the calixarene subunit is in the cone conformation, as assessed by Ar–CH_2–Ar ^{13}C NMR resonance signals observed around 31–32 ppm.[16] Complementing elemental analyses, the evaluation of the sodium content by flame spectrometry was consistent with the proposed formulas for **10**, **14** and **15**; due to its insolubility in water, **9** was not analysed in this way. Compound **10** was thus found to be associated to 1NaCl and $10H_2O$, **14** to 2NaCl and $5H_2O$ and **15** to 16NaCl and $7H_2O$. All attempts to diminish the high amount of NaCl in **15** have been unsuccessful until now, even with long dialysis processes.

Negative mode electrospray mass spectrometry of the hexa-sodio derivative **10** showed a succession of two groups of signals attributed to di- and tri-charged species resulting from the loss of two and three sodium ions, or more with equilibration by protonation. No groups of signals corresponding to the mono-, tetra-, penta- and hexa-anionic species were clearly detected. The tetra sodium salt **14** exhibited two groups of well defined signals; the first one was attributed to mono-charged species resulting from the loss of one to four Na^+ ions, equilibrated by the gain of one to three protons, and a second group attributed to di-charged



Scheme 2. Reagents and conditions: (i) K_2CO_3, MeCN, reflux; X = H: **12**: 57%, X = COOMe: **13**: 56%. (ii) (a) NaOH, EtOH/H_2O, reflux; (b) HCl 1 M; (c) X = H: **14**, NaOH 0.1 M, pH = 8.25, dialysis (cut-off 100 D) 78%; X = COONa: **15**, NaOH 0.1 M, pH 7.9, dialysis (cut-off 100 D) 53%.

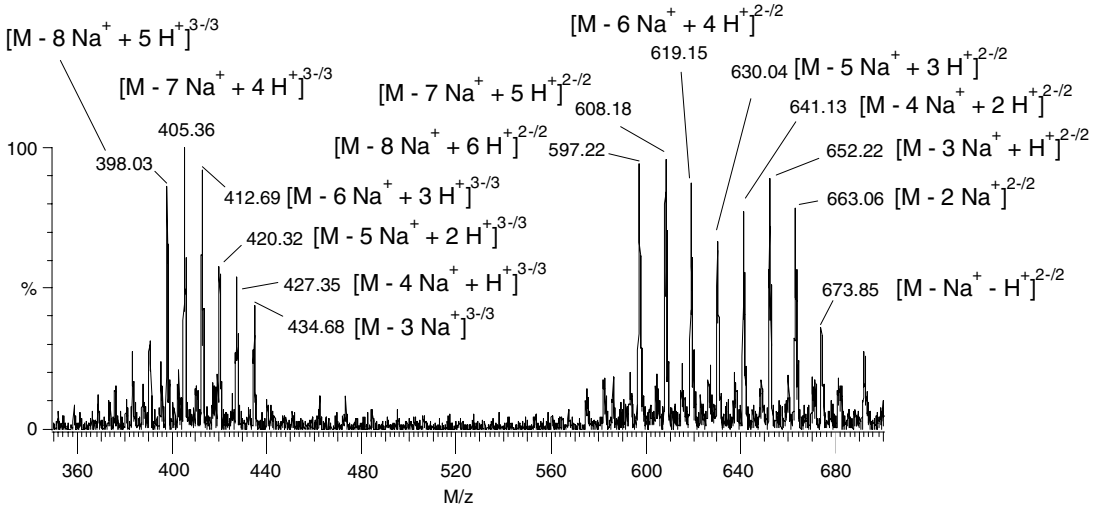


Figure 1. Negative mode ES-MS of the octa-sodium salt **15** in MeOH; di- and tricharged species area.

species. The results obtained with the octa sodium salt **15** (Fig. 1) were similar to **10**, with a group of well defined signals attributed to di-charged species resulting from the loss of one to eight sodium ions equilibrated by protonation, and a group attributed to tri-charged species issued from similar ionisation processes.

The complexing ability of **10**, **14** and **15** towards copper(I) was measured in water by UV–vis spectroscopy. The addition of $Cu(MeCN)_4PF_6$ to aqueous solution of the ligands resulted in each case in the formation of a 1:1 complex characterised by the specific metal-to-ligand charge transfer (MLCT) band at ca. 466 nm encountered in tetrahedral copper(I)/heterocycle complexes (Fig. 2). A preliminary evaluation of the behaviour of these complexes in biological media was performed by addition of 1, 5 and 10 equiv of BSA in the UV titration solution. The MLCT band that remains unchanged in these conditions, demonstrates that the copper(I) complex is stable enough in this medium, and that **10**, **14** and **15**, as for the three previous

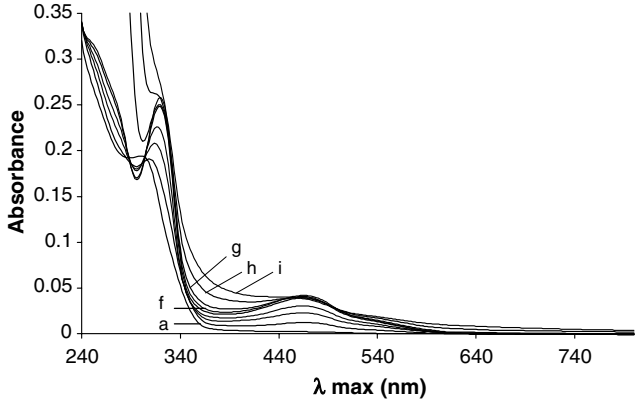


Figure 2. UV–vis titration of hexa-sodium salt **10** by $Cu(MeCN)_4PF_6$. (a)–(f) **10** 3 mL $7.56\ 10^{-6}$ M in H_2O, $+5 \times 10$ μL aliquotes of $Cu(MeCN)_4PF_6$ $4.5\ 10^{-4}$ M in MeCN; (g): (f) + 1 equiv of BSA 10^{-3} M in H_2O (22.7 μL); (h): (f) + 5 equiv of BSA 10^{-3} M in H_2O (113.5 μL); (i): (f) + 10 equiv of BSA 10^{-3} M in H_2O (227 μL).

ligands,[7–9] can play an interesting role of cation carrier for biological applications. This point is under current investigation.

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15. For each compound, **A** describes the unsubstituted phenol ring, **B** the substituted one. *Compound* **9**: Mp: >245 °C (dec). IR (KBr): 1676.5 (CO); 1572.6 (COO). UV–vis ($CHCl_3$/MeOH 1:1): 288 (44,038). ^{1}H NMR (400 MHz, DMSO-6*d*): 1.22 (s, 18H, CMe_3); 2.12 (t, $J = 6.7$ Hz, 4H, $COCH_2CH_2COONa$); 2.55 (s, 6H, CH_3bpy); 2.89 (t, $J = 6.5$ Hz, 4H, $COCH_2CH_2COONa$); 3.59–4.33 (AB, $J_{AB} = 12.7$ Hz, 8H, ArCH_2Ar); 5.21 (s, 4H, OCH_2bpy); 7.25 (m, 4H of Ar **A** and 2H of bpy); 7.64 (t, $J = 7.7$ Hz, 2H, bpy); 7.76 (m, 4H of Ar **B** and 4H of bpy); 8.19 (d, $J = 7.8$ Hz, 2H, bpy); 8.33 (d, $J = 7.5$ Hz, 2H, bpy). ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD locked on CD_3OD): 1.28 (s, 18H, CMe_3); 2.42 (m, 4H, $COCH_2CH_2COONa$); 2.59 (s, 6H, CH_3bpy); 2.98 (m, 4H, $COCH_2CH_2COONa$); 3.48–4.43 (AB, $J_{AB} = 13.3$ Hz, 8H, ArCH_2Ar); 5.22 (s, 4H, OCH_2bpy); 7.15 (m, 6H, H(5′)bpy and Ar*H* **A**); 7.56 (s, 4H, Ar*H* **B**); 7.58 (t, $J = 7.5$ Hz, 2H, H(4′)bpy); 7.66 (t, $J = 7.8$ Hz, 2H, H(4)bpy); 7.93 (d, $J = 7.9$ Hz, 2H, H(5)bpy); 8.05 (d, $J = 7.8$ Hz, 2H, H(3′)bpy); 8.26 (d, $J = 7.8$ Hz, 2H, H(3)bpy). ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD): 25.39 (*Me*bpy); 30.33 ($COCH_2CH_2COONa$); 31.74 (CMe_3); 32.16 (ArCH_2Ar); 34.12 ($COCH_2CH_2$-COONa and CMe_3); 78.59 (OCH_2bpy); 118.99 (C(3′)bpy); 120.83 (C(3)bpy); 121.37 (C(5)bpy); 123.92 (C(5′)bpy); 126.12 (C_m of Ar **A**); 126.62 (C_o of Ar **A**); 129.56 (C_m of Ar **B**); 133.51 (C_p of Ar **B**); 134.17 (C_o of Ar **B**); 137.55 (C(4′)bpy); 138.48 (C(4)bpy); 142.51 (C_p of Ar **A**); 151.06 (C_{ipso} of Ar **A**); 155.42 (C(6′) bpy); 155.90 (C(2)bpy); 156.25(C(6)bpy); 156.78 (C_{ipso} of Ar **B**); 158.33 (C(2′)bpy); 181.39 (COONa); 200.27 (CO). Anal. Calcd for $C_{68}H_{66}N_4O_{10}Na_2$, 2NaCl, H_2O (1278.10): C 63.90, H 5.36, N 4.38. Found: C 63.93, H 5.55, N 4.26. ES-MS (negative mode): 1172.72 $[M-2Na^+ + H^+ + K^+ + Cl^-]^-$, 1156.68 $[M-2Na^+ + H^+ + Na^+ + Cl^-]^-$, 1136.79 $[M-2Na^+ + K^+]^-$,1120.87 $[M-Na^+]^-$, 1098.8 $[M-2Na^+ + H^+]^-$, 955.00 $[M-bpy-2Na^+ + K^+ + H^+]^-$, 939.00 $[M-bpy-Na^+ + H^+]^-$, 917.00 $[M-bpy-2Na^+ + 2H^+]^-$, 949.3 $[M-2Na^+]^{2-/2}$. *Compound* **10**: Mp: >280 °C (dec). IR (KBr): 3420.7 (OH); 1711.1 (CO); 1601.0 (COO). UV–vis (H_2O): 300 (25,713). ^{1}H NMR (400 MHz, D_2O): 1.10 (s, 18H, CMe_3); 2.31 (t, $J = 6.8$ Hz, 4H, CH_2CH_2COONa); 2.60 (s, 6H, *Me*bpy); 2.92 (t, $J = 6.5$ Hz, 4H, CH_2CH_2COONa); 3.26–4.08 (AB, $J_{AB} = 13.5$ Hz, 8H, ArCH_2Ar); 5.46 (s, 4H, OCH_2bpy); 7.15 (s, 4H, Ar*H* **A**); 7.37 (s, 4H, Ar*H* **B**); 7.66 (s, 2H, H(5′)bpy); 7.99 (s, 2H, H(3′)bpy); 8.04 (s, 2H, H(5)bpy); 8.35 (s, 2H, H(3)bpy). ^{13}C NMR (100 MHz, D_2O): 23.23 (*Me*bpy); 31.05 (Me_3C); 31.32 (ArCH_2Ar); 31.71 ($COCH_2CH_2COONa$); 33.65 (CMe_3); 35.04 ($COCH_2CH_2COONa$); 78.14 (OCH_2bpy); 119.20 (C(3′)bpy); 121.65 (C(3)bpy); 123.54 (C(5)bpy); 123.75 (C(5′)bpy); 126.22 (C_m of Ar **A**); 128.19 (C_o of Ar **A**); 129.50 (C_m of Ar **B**); 134.72 (C_o of Ar **B**); 144.13 (C_p of Ar **A**); 149.51 (C_{ipso} of **A**); 155.97 (C_{ipso} of **B**); 159.57 (C(2)bpy); 172.49 (C(4)*C*OOMe); 172.92 (C(4′)*C*OOMe); 181.58 (COONa); 202.46 (CO); 133.31, 147.47, 147.65, 154.93, 156.24, 156.35 (C(2), C(4), C(4′), C(6), C(6′), C_p of Ar **B**). Anal. Calcd for $C_{72}H_{62}O_{18}N_4Na_6$, NaCl, 10 H_2O (1665.82): C 51.91, H 4.96, N 3.36. Found: C 51.76, H 4.47, N 3.24. Flame photometry: calcd for Na: 9.65%; found: 9.03%. ES-MS (positive mode): 716.13 $[M+Na^+ + H^+]^{2+/2}$, 727.04 $[M+2Na^+]^{2+/2}$, 735.00 $[M+Na^+ + K^+]^{2+/2}$; (negative mode): 681.10 $[M-2Na^+]^{2-/2}$, 670.18 $[M-3Na^+ + H^+]^{2-/2}$, 659.09 $[M-4Na^+ + 2H^+]^{2-/2}$, 648.18 $[M-5Na^+ + 3H^+]^{2-/2}$, 637.20 $[M-6Na^+ + 4H^+]^{2-/2}$, 535.25 $[M-(bpy)-Na^+ - H^+]^{2-/2}$,524.22 $[M-(bpy)-2Na^+]^{2-/2}$, 513.30 $[M-(bpy)-3Na^+ + H^+]^{2-/2}$, 502.27 $[M-(bpy)-4Na^+ + 2H^+]^{2-/2}$, 446.62 $[M-3Na^+]^{3-/3}$, 439.29 $[M-4Na^+ + H^+]^{3-/3}$, 432.03 $[M-5Na^+ + 2H^+]^{3-/3}$, 424.67 $[M-6Na^+ + 3H^+]^{3-/3}$. *Compound* **14**: Mp: >250 °C (déc). IR (KBr): 1573.0 (COO^-). UV–vis (H_2O): 288 (27,189). ^{1}H NMR (400 MHz, D_2O): 2.50 (s, 6H, CH_3bpy); 3.13 (s, 4H, CH_2COONa of **A**); 3.43 (s, 4H, CH_2COONa of **B**); 3.55–4.38 (AB, $J_{AB} = 13.1$ Hz, 8H, ArCH_2Ar); 5.10 (s,

4H, OCH_2bpy); 6.91 (s, 4H, Ar*H* of **B**); 7.14 (s, 4H, Ar*H* of **A**), 7.18 (d, $J = 7.55$ Hz, 2H, H(5′)bpy); 7.53 (d, $J = 7.55$ Hz, 2H, H(5)bpy); 7.58 (t, $J = 7.8$ Hz, 2H, H(4′)bpy); 7.66 (t, $J = 7.8$ Hz, 2H, H(4)bpy); 7.72 (d, $J = 7.55$ Hz, 2H, H(3′)bpy); 7.79 (d, $J = 7.81$ Hz, 2H, H(3)bpy). ^{13}C NMR (100 MHz, D_2O): 23.44 (*Me*bpy); 30.99 (Ar*C*H_2Ar); 43.97 (*C*H_2COONa of **A**); 44.03 (*C*H_2COONA of **B**); 78.08 (O*C*H_2bpy); 120.10 (C(3′)bpy); 121.67 (C(3) bpy); 122.62 (C(5)bpy); 124.58 (C(5′)bpy); 128.05 (C_o of **A**); 129.06 (C_p of **B**); 130.06 (C_m of **A**); 130.31 (C_m of **B**); 133.59 (C_o of **A**); 135.32 (C_p of **A**) 138.44 (C(4′)bpy); 138.85 (C(4)bpy); 150.49 (C_{ipso} of **B**); 151.06 (C_{ipso} of **A**); 154.77 (C(6′)bpy); 155.75 (C(2)bpy); 155.89 (C(6)bpy); 158.50 (C(2′)bpy); 180.97 (CO of **B**); 181.78 (CO of **A**). Anal. Calcd for $C_{60}H_{48}O_{12}N_4Na_4$, $5H_2O$, 2NaCl (1315.90): C 54.76, H 4.44, N 4.24. Found: C 54.78, H 4.35, N 4.08. Flame photometry: calcd for $C_{60}H_{48}O_{12}N_4Na_4$, $5H_2O$, 2NaCl (1315.90): Na 10.4; found: 10.16. ES-MS (negative mode): 1084.67 $[M-Na^+]^-$, 1062.63 $[M-2Na^+ + H^+]^-$, 1040.70 $[M-3Na^+ + 2H^+]^-$, 1018.71 $[M-4Na^+ + 3H^+]^-$, 531.20 $[M-2Na^+]^{2-/2}$, 520.24 $[M-3Na^+ + H^+]^{2-/2}$, 509.28$[M-4Na^+ + 2H^+]^{2-/2}$. *Compound* **15**: Mp: >250 °C (déc). IR (KBr): 1602.0, 1550.8 (COO^-). UV–vis (H_2O): 292 (24,982); 304 (26,052); 365 (3207). ^{1}H NMR (400 MHz, D_2O): 2.58 (s, 6H, CH_3bpy); 3.11 (s, 4H, CH_2COOEt of **B**); 3.40 (s, 4H, CH_2COOEt of **A**); 3.40-4.19 (AB, $J_{AB} = 12.8$ Hz, 8H, ArCH_2Ar); 5.37 (s, 4H, OCH_2bpy); 6.85 (s, 4H, Ar*H* **B**); 7.08 (s, 4H, Ar*H* **A**); 7.62 (s, 2H, *H*(5′)bpy); 8.09 (s, 4H, *H*(3′) and *H*(5)bpy); 8.27 (s, 2H, *H*(3)bpy). ^{13}C NMR (100 MHz, D_2O): 23.43 (*Me*bpy); 30.99 (Ar*C*H_2Ar); 43.83 (*C*H_2COONa of **A**); 43.88 (*C*H_2COONa of **B**); 78.48 (O*C*H_2bpy); 119.25 (*C*(3′)bpy); 121.76 (*C*(3)bpy); 123.18 (*C*(5)bpy) 123.29 (*C*(5′)bpy); 128.43 (C_o of **A**); 129.19 (C_p of **A**); 129.83 (C_m of **A**); 130.20 (C_m of **B**); 133.76 (C_o of **B**); 135.11 (C_p of **B**); 147.07, 147.44 (*C*(4) and *C*(4′)bpy); 150.32 (C_{ipso} of **B**); 150.71 (C_{ipso} of **A**); 155.67 (*C*(6) or *C*(6′)bpy); 156.65 (*C*(2)bpy and *C*(6) or *C*(6′)bpy); 159.80 (*C*(2′)bpy); 172.84 (*C*OONa(4)); 173.70 (*C*OONa(4′)); 181.05 (*C*OONa of **B**); 181.93 (*C*OONa of **A**). Anal. Calcd for $C_{64}H_{44}O_{20}N_4Na_8$, $7H_2O$, 16NaCl (2433.94): C 31.58, H 2.40, N 2.30. Found: C 31.36, H 2.87, N 2.30. Flame photometry: calcd for $C_{64}H_{44}O_{20}N_4Na_8$, $7H_2O$, 16NaCl (2433.94): Na 22.7; found: Na 22.4. ES-MS (negative mode): 673.85 $[M-Na^+-H]^{2-/2}$; 663.06 $[M-2Na^+]^{2-/2}$; 652.22 $[M-3Na^+ + H^+]^{2-/2}$; 641.13 $[M-4Na^+ + 2H^+]^{2-/2}$; 630.04 $[M-5Na^+ + 3H^+]^{2-/2}$; 619.15 $[M-6Na^+ + 4H^+]^{2-/2}$; 608.18 $[M-7Na^+ + 5H^+]^{2-/2}$; 597.22 $[M-8Na^+ + 6H^+]^{2-/2}$; 434.68 $[M-3Na^+]^{3-/3}$; 427.05 $[M-4Na^+ + H^+]^{3-/3}$; 420.32 $[M-5Na^+ + 2H^+]^{3-/3}$; 412.69 $[M-6Na^+ + 3H^+]^{3-/3}$; 405.36 $[M-7Na^+ + 4H^+]^{3-/3}$; 398.03 $[M-8Na^+ + 5H^+]^{3-/3}$.

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