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Wittig Reaction on Calixarene Upper Rim. Access to Conjugated Bipyridyl and Pyridyl Podands.

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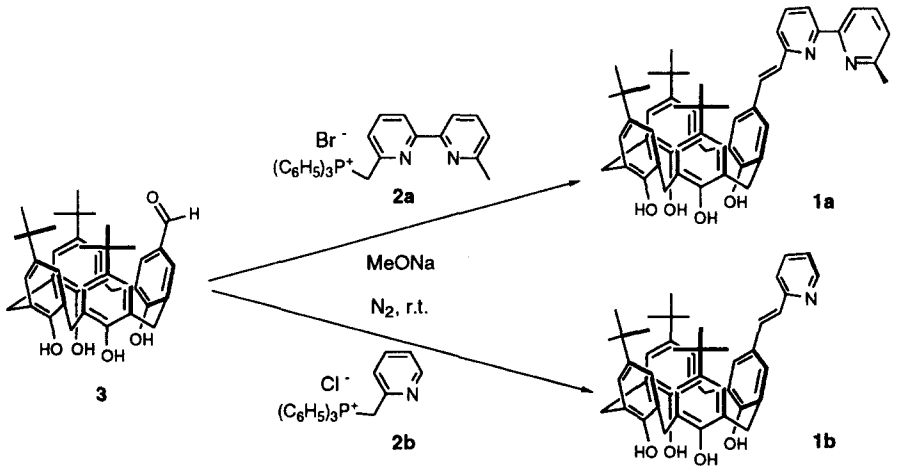
Abstract: Monoformyl-tris-(*p*-Bu^t)calix[4]arene was synthesised and reacted in smooth conditions with phosphonium salts of 6-bromomethyl-6'-methyl-2,2'-bipyridine and 2-chloromethyl-pyridine, affording the corresponding conjugated mono-armed macrocycles.

Calixarenes have been recently employed as carriers and spatial organizers of heterocyclic chelating agents, in order to access to tailor made ligands. Beer[1], Grigg[2], Ziessel[3] and our team[4] prepared pre-organized calixarene-bipyridyl hybrids in the form of podands or barrelands, in which the heterocyclic subunits are grafted at the lower rim as ether junctions *via* their 5- or 6- positions. At the upper rim, Beer *et al.* [5] introduced bipyridyl subunits *via* amide bounds. The attachement of a pyridine moiety *via* an ethylenic linkage using a Grignard-like reaction-dehydration process performed on a OH-protected formylcalix[4]arene has been recently described by Shinkai *et al.*[6],. Intramolecular unsaturated linkage has been also introduced *via* a McMurry reaction.[7] Nevertheless, these syntheses do not allow to take advantage of the presence of free phenolic OH groups, which should lead to interesting pH-driven conjugative resonance effects. For this reason, we attempted directly the Wittig reaction on the unprotected calixarene, according to the original work of Wittig[8] adapted for phenols by Friedrich *et al.*[9]

We based our synthetic programm on the new *tris*(*p*-*tert*-butyl)calix[4]arene **4**[10] which was directly

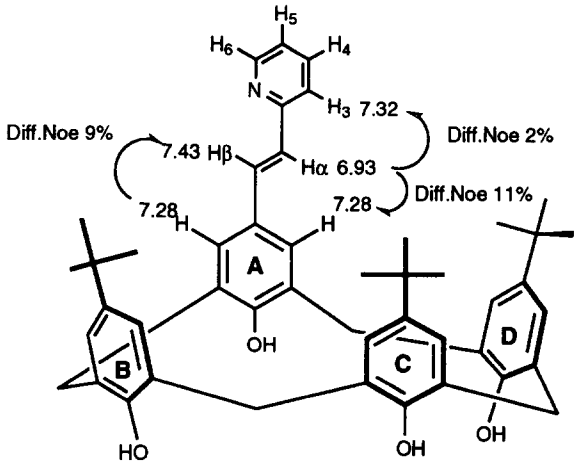


formylated according to Arduini *et al.*[11], affording the conic mono-formyl calix[4]arene **3**[12] in 57% yield. The

latter was then reacted with NaOMe and 6-methylene-(6'-methyl-2,2'-bipyridine)-yl triphenyl phosphonium bromide **2a**[13] to give, after column chromatography (Al_2O_3, CH_2Cl_2:MeOH, then SiO_2, CH_2Cl_2) 28 % of the E- and traces of the Z- isomers of **1a**[14]. Both the mixed and the pure isomers were rather unstable in solution, giving pink polar products. The rather poor yield of 28% may perhaps be due to this unstability.

^{1}H-NMR spectrum of **1a** resulted in a perfect superposition of patterns of bipyridyl and calixarenyl moieties. The spectrum exhibited notably in the aromatic region two well resolved doublets (J = 16 Hz) at 7.55 ppm and 7.02 ppm which were attributed to the ethylenic protons of the *trans* isomer. ^{13}C-NMR suggested, according to the literature[15], that the calixarene was in the cone conformation. Due to the rather complicated aromatic pattern observed for **1a**, the relative orientation of the bipyridine subunit with respect to adjacent phenol groups was difficult to study by NOESY experiments.

Therefore, the model compound **1b**, bearing a pyridyl moiety, was prepared by reacting **3** with 2-picolyl triphenyl phosphonium chloride **2b**[16]. Compound **1b** was fully characterized by NMR studies (HMBC, HSQC) which revealed for the ethylenic protons two well resolved doublets (J= 16 Hz) at 6.93 ppm (H_α) and 7.43 ppm (H_β), and for the substituted phenol a singlet at 7.28 ppm. For the latter, NOE Difference experiments gave values of 9% and 11% after irradiation at 7.43 and 6.93 ppm respectively, indicating a planar system. These experiments revealed that the pyridyl ring was oriented as represented in scheme 1. The same type of behaviour may be expected for **1a**.



Scheme 1: Noe Difference analysis of *trans* stilbene-like substructure A in **1b**.

The presence of a bipyridyl group at the upper rim of calixarene in **1a** may allow to connect, as previously reported for a parent compound[4a], two ligand units *via* a metallic center. Upon reaction of **1a** with $Cu(CH_3CN)_4PF_6$ in $CHCl_3$, a stable red complex was obtained displaying the expected modifications in the ^{1}H-NMR study. The signal corresponding to the bipyridyl CH_3 group was shifted upfield ($\Delta\delta$ = 0.38 ppm) and the heterocyclic signals were tightened and downfield shifted. Dealing with the ethylenic doublets, a new system at 6.97 ppm and at 6.68 ppm (J = 16 Hz), corresponding to an upfield shift of 0.58 and 0.34 ppm with respect to the free ligand, was observed. Furthermore, some of the benzenic protons were also shifted upfield. The expected [L_2M] stœchiometry was confirmed by electrospray mass analysis (m/z = 1637.7; [**1a**/Cu(I)/**1a**]$^+$). Attempts to isolate the pure complex from reaction mixture failed, affording unidentified decomposition products.

In summary, the Wittig reaction has been carried out on an unprotected calixarene aldehyde platforme with introduction at the upper rim of heterocyclic substituent. The properties of the pH-sensitive sites at both ends of the stilbene-like substructures in **1a** and **1b** are under current investigation, as well as the binding ability of **1a** towards transition metal cations.

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12. *General*: M.p., uncorrected. IR in KBr pellets, 1/ν in cm^{-1} (attribution). UV in CH_2Cl_2, ν in nm, (ε $mol.l^{-1}.cm^{-1}$). ^1H and ^{13}C-NMR in $CDCl_3$ + TMS, Bruker AC200 or AM300, chemical shifts in ppm, J in hertz. Mass spectrometry: electrospray technique, positive or negative modes. Elemental analyses performed at Ecole de Chimie, Montpellier.
    3. Calixarene **4** (0.5g, 0.84 mmol) was dissolved in cold $CHCl_3$ (50 ml, -10°C) then $SnCl_4$ (1 ml, 8.4 mmol) was slowly added, followed by dichloromethyl-methylether (1.15 ml, 12.65 mmol). The pink mixture was stirred at r.t. during 1 h, then H_2O (50 ml) was added.The organic phase was collected, dried on Na_2SO_4 then evaporated to dryness. The residue was dissolved in MeOH (20 ml), mixed with Al_2O_3 and allowed to stand at r.t. overnight. Evaporation of the solvent, followed by column chromatography (SiO_2, CH_2Cl_2) afforded pure **3**. White powder. (0.3 g; 57%). M.p. > 320°C (dec). IR: 1690 (strong, conjugated C=O stretch). UV: 279.8 (13000). ^1H-NMR (200 MHz): 1.19(s, 9 H, Bu^t); 1.22(s, 18H, Bu^t); 3.54-4.23(br AB, 8H, bridge CH_2); 7.06(s, 2H, Ar); 7.10, 7.13(AB, J_{AB} 2, 4H, Ar); 7.64(s, 4H, Ar), 9.77(s, 1H, CHO); 10.35(br s, 4H, OH). ^{13}C-NMR (50.32 MHz): 31.49, 31.58(Me, Bu^t); 32.25, 32.52(bridge CH_2); 34.11, 34.24(C, Bu^t); 125.91, 126.02, 126.59, 131.25(C(H), aromatic); 126.55, 127.49, 128.34, 129.45, 131.15, 144.87, 145.20, 146.34, 146.40, 155.40(C_o, p, i, aromatic); 190.75(CHO). Elemental analysis. Found: C 75.96, H 8.13, N 12.48. Calc. for $C_{41}H_{48}O_5$, 0.5 CH_2Cl_2 (663.30): C 76.36, H 7.54, O 12.93. ES.MS: pos. mode: m/z 643.4($[M + Na]^+$); neg. mode: m/z 619.4($[M - H^+]^-$).
13. **2a.** A solution of 6-bromomethyl-6'-methyl-2,2'-bipyridine (0.2 g, 0.76 mmol) and triphenyl-phosphine (0.2 g, 0.76 mmol) in benzene (30 ml) was refluxed under N_2 during 24 h. After cooling to r.t., the resulting white precipitate was filtered off, washed with Et_2O (3x50 ml) then dried *in vacuo*. White powder. (0.38 g; 95%). M.p.: 275-276°C. IR: 2780 (weak, CH stretch, CH_2-P); 1575 (strong, C=N stretch); 1440, 1110, 1000 (strong, R_4P^+). UV: 305 (s, 10800), 294 (15035), 277 (s, 11900), 270 (s, 9700). ^1H NMR(200 MHz): 2.57(s, 3H, Me, bpy); 5.71(d, $J_{H\text{-}P}$ 14, 2H, CH_2-P); 7.02(d, J 8, 1H, bpy); 7.10(d, J 8, 1H, bpy); 7.41(t, J 8, 1H, bpy); 7.56-7.88(m, 15 H, aromatic and bpy); 7.95(d, J 8, 1H, bpy); 8.27(d, J 8, 1H, bpy). ^{13}C NMR (50.32 MHz): 24.49(Me, bpy), 32.67(d, $J_{C\text{-}P}$ 52, CH_2-P); 117.50(C(H), bpy); 118.86(d, $J_{C(i)\text{-}P}$ 87, C(*i*) of Ar); 120.11(d, $J_{C(4)\text{-}P}$ 2, C(4), bpy); 123.45(C(H), bpy); 126.78(d, $J_{C(5)\text{-}P}$ 8, C(5), bpy); 129.95(d, $J_{C(o)\text{-}P}$ 13, C(o), Ar); 134.11(d, $J_{C(m)\text{-}P}$ 10, C(m), Ar); 134.58(d, $J_{C(p)\text{-}P}$ 3, C(p), Ar); 136.59, 138.30(C(H), bpy); 148.99(d, $J_{C(6)\text{-}P}$ 9, C(6), bpy); 154.28, 157.97(C(2') and C(6'), bpy); 155.49(d, $J_{C(2)\text{-}P}$ 2, C(2), bpy). Elemental analysis. Found: C 71.38, H

5.07, N 4.91. Calc. for : $C_{30}H_{26}N_2PBr$, C_6H_6(603.54): C 71.64, H 5.34, N 4.64. ES-MS: pos. mode; m/z 445.3 [M - Br^-]$^+$; m/z 969.3, 971.3 [2 M - Br^-]$^+$.

14. **1a.** The phosphonium salt **2a** (0.11 g, 0.209 mmol) was dissolved in a solution of NaOMe in MeOH (10 ml; from 0.05 g (2.1 mmol) of Na). To the resulting yellow solution was added the calixarene aldehyde **3** (0.13 g, 0.21 mmol). The solution was stirred at r.t. overnight then neutralized with 1M HCl. Evaporation of the solvent afforded a glassy material which chromatographed (Al_2O_3, CH_2Cl_2 then CH_2Cl_2:MeOH 99/1) to give raw alcene free of triphenyl phosphine oxide. Further purification on SiO_2 (CH_2Cl_2) gave the pure alcene 1. White powder. (0.045 g; 28%). M.p.: 317-318°C. IR: 1625 (weak, C=C); 1590 (medium, C=N stretch); 960 (medium, C=C, trans). UV: 332 (21800), 315 (s, 20400), 288.4 (25400). ^{1}H NMR (200MHz): 1.19(s, 9H, Bu^t); 1.24(s, 18H, Bu^t); 2.64(s, 3H, Me, bpy); 3.53,4.27(br AB, 8H, bridge CH_2); 7.02(d, J_{trans} 16, 1H, ethylenic); 7.03(s, 2H, aromatic); 7.10(s, 4H, aromatic); 7.18(d, *J* 7.5, 1H, bpy); 7.31(s, 2H, aromatic); 7.35(dd, *J* 8 and 1, 1H, bpy); 7.55(d, J_{trans} 16, 1H, ethylenic); 7.73(t, *J* 8, 1H, bpy); 7.74(t, *J* 8, 1H, bpy); 8.22(dd, *J* 8 and 1, 1H, bpy); 8.30(d, *J* 8, 1H, bpy); 10.33(s, 4H, OH). ^{13}C NMR (50.32 MHz): 24.72(Me, bpy); 31.40(Me, Bu^t); 31.52(Me, Bu^t); 32.47(bridged CH_2); 34.00(C, Bu^t); 34.13(C, Bu^t); 118.29, 119.32, 121.46, 123.26, 137.04, 137.24(3-, 3'-, 4-, 4'-, 5-, 5'-, bpy); 125.82, 125.91, 126.21 and 127.98(3,5-Ar); 126.76 and 132.22(α, β, ethylenic); 127.02, 127.61, 128.11, 128.78, 131.00, 144.64, 144.70, 146.31, 146.62, 149.61(2,6-Ar, 4-Ar, 1-Ar); 155.28, 155.86, 156.15 and 157.91(2-, 2'-, 6-, 6'-bpy). Elemental analysis. Found: C 79.84, H 7.58, N 3.54, O 8.42. Calc. for $C_{53}H_{58}N_2O_4$, 0.1 $CHCl_3$ (799.0): C 79.82, H 7.32, N 3.50, O 8.00. ES.MS: neg. mode; m/z 785.4 [M(-H)]$^-$, 619.3 [M-(py)]$^-$.
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16. **2b.** 2-Picolyl chloride, HCl (0.3 g, 1.83 mmol) and triphenylphosphine (0.96 g, 3.66 mmol) were solubilised in a mixture of C_6H_6(30 ml) and MeCN(15 ml). The solution was refluxed under N_2 during 70 h, then solvent were evaporated to dryness; the residue was triturated with Et_2O to remove excess of triphenylphosphine and the resulting solid was dissolved in CH_2Cl_2 (2 ml) and MeOH (15 ml). Addition of Et_2O resulted in the precipitation of pure **2b**. Light brown solid. (0.5 g; 70%). M.p.: 273-274°C. UV: 278 (s, 4130), 268.5 (6600), 262 (6500). ^{1}H NMR (200MHz): 5.86(d, *J* 15, 2 H, CH_2-P); 7.31(t, *J* 8, 1H, py); 7.58-7.89(m, 15 H of Ar, 1 H of py); 8.00(d, *J* 8, 1H, py); 8.27(d, *J* 5, 1 H, py). ^{13}C NMR (50.32 MHz): 31.77(d, $J_{C\text{-}P}$ 50, CH_2-P); 118.28(d, $J_{C(i)\text{-}P}$ 88, C(i), Ar); 123.67(s, C(H), py); 127.80(d, $J_{C(3)\text{-}P}$ 7, C(3), py); 130.00(d, $J_{C(o)\text{-}P}$ 13, C(o), Ar); 134.20(d, $J_{C(m)\text{-}P}$ 10, C(m), Ar); 134.78(d, $J_{C(p)\text{-}P}$ 3, C(p), Ar); 139.01(s, C(H), py); 147.13(s, C(H), py); 148.99(d, $J_{C(2)\text{-}P}$ 9, C(2), py). Elemental analysis. Found: C 71.66, H 5.67, N 3.68. Calc. for $C_{24}H_{21}ClNP$, 0.75 H_2O (403.37): C 71.46, H 5.50, N 3.47. ES.MS: pos. mode; m/z 353.9[M-Cl^-]$^+$.

1b. Same procedure than **1a**. From **2b** (0.063 g, 0.161 mmol) and **3** (0.1 g, 0.161 mmol). Light green powder. (0.045 g, 40%) M.p.: 358-357°C. IR: 1650 (weak, conjugated C=C); 1600 (medium, C=N stretch); 985 (medium, C=C, trans). UV: 329.5 (21400), 312 (s, 20280), 288.5 (16850), 280 (s, 15280). ^{1}H NMR (300MHz),: 1.18(s, 9H, Bu^t C); 1.23(s, 18H, Bu^t B and D); 3.40-3.62(br t, 4 H, bridge CH_2); 4.15-4.40(br d, 4H, bridge CH_2); 6.93(d, J_{trans} 16, Hα, ethylenic); 7.02(s, 2H, aromatic C); 7.05(hidden dd, 5-H, py); 7.08(AB, *J* 2, 4H, aromatic B and D); 7.28(s, 2H, aromatic A), 7.32(d, *J* 9, 3-H, py); 7.43(d, J_{trans} 16, Hβ, ethylenic); 7.57(br t, *J* 7, 4-H, py); 8.52(br s, 6-H, py); 10.30(s, 4H, OH). ^{13}C NMR (75.47 MHz): 31.35(Me, Bu^t); 31.48(Me, Bu^t); 32.38(bridged CH_2); 32.44(bridged CH_2); 33.96(C, Bu^t); 34.08(C, Bu^t); 121.70(5-py); 121.80(3-py); 136.53(4-py); 149.41(6-py); 155.78(2-py); 126.00(α-ethylenic); 132.34(β-ethylenic); 127.01, 128.79(2,6-Ar, A); 128.06(3,5-Ar, A); 130.71(4-Ar, A); 149.65(1-Ar, A); 125.86(3,5-Ar, C); 144.61(4-Ar, C); 146.23(1-Ar, C); 127.57, 127.93(2,6-Ar, C, B, D); 125.73, 126.18(3,5-Ar, B, D); 144.69(4-Ar, B, D); 146.58(1-Ar, B, D). Elemental analysis. Found: C 80.59, H 7.54, N 1.84. Calc. for $C_{47}H_{53}NO_4$ (695.95): C 81.11, H 7.66, N 2.01. ES.MS: pos. mode; m/z 696.1 [M+H]$^+$.

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