Supramolecular complexes of bambusuril with dialkyl phosphates

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Synthesis

Sodium dipropargyl phosphate (**2a**) and sodium bis(but-3-ynyl) phosphate (**2b**) were prepared from the corresponding alcohols and phosphoryl chloride in a two-step synthesis (*Scheme S1*).

Scheme S1: Preparation of dialkyl phosphates **2a** and **2b** bearing terminal alkyne groups.

Tripropargyl Phosphate (**5a**)

Compound **5a** was prepared according to a literature procedure.^[2] Propargyl alcohol (6.8 g, 121 mmol), triethyl amine (TEA, 33 mL), and 4-dimethylaminopyridine (DMAP, 50 mg) were dissolved in CH_2Cl_2 (100 mL) and the solution was cooled down to 0 °C in an ice/water bath. Phosphoryl chloride (6.6 g, 43 mmol) was added dropwise within 15 min. The resulting solution was stirred for further 60 min at 0 °C, then for 4 h at r.t. Water (100 mL) was added resulting in the formation of two phases. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried over anhydrous MgSO_4 and concentrated *in vacuo*. Pure tripropargyl phosphate **5a** was obtained as a yellowish oil after purification by silica gel column chromatography using hexane–ethyl acetate (7:3 to 1:1 v/v) as the mobile phase. Yield: 3.7 g (17 mmol, 43 %).

^1H NMR (500 MHz, CDCl_3): 2.60 (t, $J = 2.4$ Hz, 3H, C^3H); 4.71 (dd, $J_1 = 10.1$ Hz, $J_2 = 2.4$ Hz, 6H, C^1H_2).

^{13}C NMR (125 MHz, CDCl_3): 55.7 (d, $J = 2.6$ Hz, C^1H_2); 76.6 (C^3H); 77.2 (C^2).

Sodium Dipropargyl Phosphate (**2a**)

Compound **2a** was prepared according to a literature procedure.^[2] Compound **5a** (3.6 g, 17 mmol) and sodium hydroxide (0.67 g, 17 mmol) were dissolved in MeCN (28 mL) and water (7 mL). The resulting solution was heated at 80 °C for 3 h. The reaction mixture was concentrated *in vacuo* and residual water was removed by azeotropic evaporation with acetonitrile. The crude yellow oil was purified by silica gel column chromatography using CH₂Cl₂–MeOH (9:1 to 7:3 v/v) as the mobile phase. Pure sodium dipropargyl phosphate was obtained as a hygroscopic yellowish solid after drying under high vacuum. Yield: 2.9 g (15 mmol, 87 %).

¹H NMR (500 MHz, MeOD): 2.82 (t, $J = 2.5$ Hz, 3H, C³H); 4.50 (dd, $J_1 = 8.1$ Hz, $J_2 = 2.5$ Hz, 6H, C¹H₂).

¹³C NMR (125 MHz, MeOD): 54.2 (d, $J = 4.5$ Hz, C¹H₂); 75.3 (C³H); 80.7 (d, $J = 9.6$ Hz, C²).

³¹P NMR (121 MHz, MeOD): 0.92.

Tribut-3-yn-1-yl Phosphate (**5b**)

But-3-yn-1-ol (8.3 g, 118 mmol), TEA (31 mL), and DMAP (51 mg) were dissolved in CH₂Cl₂ (100 mL) and the solution was cooled down to -15 °C in an ice/ethanol bath. Phosphoryl chloride (6.4 g, 42 mmol) was added dropwise within 20 min. The resulting solution was stirred for further 60 min with constant cooling, then for 4 h at r.t. Water (100 mL) was added resulting in the formation of two phases. The organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (3×50 mL). The combined organic extracts were dried over anhydrous MgSO₄ and concentrated *in vacuo*. Pure compound **5b** was obtained as a yellowish oil after purification by silica gel column chromatography using hexane–ethyl acetate (7:3 to 1:1 v/v) as the mobile phase. Yield: 6.1 g (24 mmol, 56 %).

¹H NMR (300 MHz, CDCl₃): 2.02 (t, $J = 2.7$ Hz, 3H, C⁴H); 2.60 (td, $J_1 = 6.9$ Hz, $J_2 = 2.7$ Hz, 6H, C²H₂); 4.16 (dt, $J_1 = 8.1$ Hz, $J_2 = 6.9$ Hz, 6H, C¹H₂).

^{13}C NMR (125 MHz, CDCl_3): 20.8 (d, $J = 7.3$ Hz, C^1H_2); 65.6 (d, $J = 5.8$ Hz, C^2H_2); 70.6 (C^4H); 79.4 (C^3).

^{31}P NMR (121 MHz, CDCl_3): -1.45.

IR (ATR): 1260.1 (P=O); 3292.2 (C–H).

HRMS: calculated M_r for $[\text{C}_{12}\text{H}_{15}\text{O}_4\text{P} + \text{Na}]^+ - 277.0600$, found – 277.0599.

Sodium Dibut-3-yn-1-yl Phosphate (2b)

Compound **5b** (5.9 g, 23 mmol) and sodium hydroxide (0.94 g, 23 mmol) were dissolved in acetonitrile (40 mL) and water (10 mL). The resulting solution was heated at 80 °C for 3 h. The reaction mixture was concentrated *in vacuo* and residual water was removed by azeotropic evaporation with acetonitrile. The crude yellow oil was purified by silica gel column chromatography using CH_2Cl_2 –MeOH (9:1 to 7:3 v/v) as the mobile phase. Pure compound **2b** was obtained as a hygroscopic yellowish solid after drying under high vacuum. Yield: 4.1 g (18 mmol, 79 %).

^1H NMR (300 MHz, MeOD): 2.24 (t, $J = 2.7$ Hz, 2H, C^4H); 2.51 (td, $J_1 = 7.1$ Hz, $J_2 = 2.7$ Hz, 4H, C^2H_2); 3.94 (dt, $J_1 = J_2 = 7.1$ Hz, 4H, C^1H_2).

^{13}C NMR (125 MHz, MeOD): 21.6 (d, $J = 7.9$ Hz, C^1H_2); 64.8 (d, $J = 5.6$ Hz, C^2H_2); 70.7 (C^4H); 81.6 (C^3).

^{31}P NMR (121 MHz, MeOD): -1.00.

IR (ATR): 1239.0 (P=O); 3292.1 (C–H).

HRMS: calculated M_r for $[\text{C}_8\text{H}_{10}\text{O}_4\text{PNa} - \text{Na}]^- - 201.0322$, found – 201.0320.

Azide **3a** is commercially available. Azide **3b** was prepared from dimethyl 5-aminoisophthalate (**6**, *Scheme S2a*). Azide **3c** was prepared in two steps from trityl bromide (**7**, *Scheme S2b*).

Scheme S2: Preparation of organic azides **3b** and **3c**. Tr = trityl (triphenylmethyl).

Dimethyl 5-Azidoisophthalate (3b)

Compound **3b** was prepared by modifying a literature procedure.^[3] A suspension of dimethyl 5-aminoisophthalate (**6**, 2.0 g, 9.6 mmol) in 10 % aq. HCl (40 mL) was cooled to $0\text{ }^\circ\text{C}$ under an argon atmosphere. A solution of NaNO_2 (0.79 g, 11 mmol) in water (10 mL) was added dropwise over 10 min at constant cooling and the resulting solution was stirred at $0\text{ }^\circ\text{C}$ for further 30 min. Subsequently, a solution of NaN_3 (0.75 g, 11 mmol) in water (10 mL) was added dropwise over 5 min at constant cooling resulting in evolution of N_2 and the formation of a white precipitate. The reaction mixture was stirred at $0\text{ }^\circ\text{C}$ for further 30 min and then at r.t. overnight. The product was extracted with Et_2O (150 mL + $3 \times 50\text{ mL}$), dried over anhydrous MgSO_4 and concentrated *in vacuo* to give compound **3b** as a white solid. Yield: 2.2 g (9.4 mmol, 98 %).

^1H NMR (300 MHz, CDCl_3): 3.95 (s, 6H, CH_3); 7.85 (d, $J = 1.4\text{ Hz}$, 2H, C^2H); 8.42 (d, $J = 1.4\text{ Hz}$, 1H, C^4H).

^{13}C NMR (125 MHz, CDCl_3): 52.7 (CH_3); 124.2 (C^2H); 127.0 (C^4H); 132.5 (C^3); 141.4 (C^1); 165.5 ($\text{C}=\text{O}$).

2-Trityloxyethanol (**8**)

Compound **8** was prepared by modifying a literature procedure.^[4] A solution of trityl bromide (**7**, 2.54 g, 7.73 mmol), ethylene glycol (4.3 mL, 77 mmol), pyridine (1.25 mL) and 4-dimethylaminopyridine (DMAP, 55 mg, 0.49 mmol) in DMF (25 mL) was stirred at r.t. for 22 h with TLC monitoring (petroleum ether–ethyl acetate 9:1). The solution was diluted with water (75 mL) and extracted with Et₂O (4×50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous MgSO₄ and concentrated *in vacuo* to provide a crude solid which was recrystallized from a mixture of MeCN (7 mL) and water (4 mL). Further purification was achieved by silica gel column chromatography using hexane–ethyl acetate (9:1 to 4:1 v/v) as the mobile phase. Pure alcohol **8** was obtained as a white crystalline solid. Yield: 1.68 g (5.52 mmol, 70 %).

Melting point: 104.6 – 105.1 °C (ref.^[5] 103.8 – 104.4 °C).

¹H NMR (300 MHz, CDCl₃): 1.91 (t, *J* = 6.1 Hz, 1H, OH); 3.27 (t, *J* = 4.8 Hz, 2H, COCH₂); (dt, *J*₁ = 6.1 Hz, *J*₂ = 4.8 Hz, 2H, CH₂OH); 7.21 – 7.34 (m, 9H, Ph); 7.42 – 7.47 (m, 6H, Ph).

¹³C NMR (125 MHz, CDCl₃): 62.5; 65.0; 86.8; 127.2; 128.0; 128.8; 144.1.

2-Trityloxyethyl Azide (**3c**)

A solution of alcohol **8** (0.50 g, 1.6 mmol), diphenyl phosphoryl azide (DPPA, 0.425 mL, 2.0 mmol), NaN₃ (0.53 g, 8.0 mmol) and DBU (0.30 mL, 2.0 mmol) in dry DMF (5 mL) was heated under argon at 90 °C for 4 h. The resulting solution was diluted with water (25 mL) and extracted with Et₂O (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous MgSO₄ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography using pentane–Et₂O (50:1 v/v) as the mobile phase. Pure azide **3c** was obtained as a white crystalline solid. Yield: 0.45 g (1.4 mmol, 83 %).

Melting point: 117.8 – 118.0 °C.

¹H NMR (300 MHz, CDCl₃): 3.34 (m, 4H, CH₂CH₂); 7.23 – 7.37 (m, 9H, Ph); 7.46 – 7.51 (m, 6H, Ph).

^{13}C NMR (75 MHz, CDCl_3): 51.6, 62.9 (CH_2CH_2); 87.3 (Ph_3C); 127.3, 128.0, 128.8, 143.9 (Ph).

IR (ATR): 2104.7 (N_3).

HRMS: calculated M_r for $[\text{C}_{19}\text{H}_{15}]^+$ – 243.1168, found – 243.1168. Only the trityl cation was observed by ESI MS.

NMR Experiments

Figure S1: ^1H NMR spectra (300 MHz, CDCl_3) of Bn₁₂BU[6] (2 mM) **a)** in the absence and in the presence of **b)** 0.3 equiv., **c)** 0.6 equiv., **d)** 0.9 equiv. and **e)** 1.2 equiv. of **1a**, and **f)** ^1H NMR spectrum (300 MHz, CDCl_3) of pure **1a**.

Graph S1: Job plot of the Bn₁₂BU[6]·**4a** complex. The maximum at a molar fraction of 0.50 indicates a predominant 1:1 stoichiometry. Bn₁₂BU[6] is denoted as BU in the graph.

NMR Spectra of Compounds Reported for the First Time

Figure S2: ¹H NMR (300 MHz, MeOD) of compound **2b**.

Figure S3: ¹³C NMR (125 MHz, MeOD) of compound **2b**.

Figure S4: ¹H NMR (300 MHz, CDCl₃) of compound **3c**.

Figure S5: ¹³C NMR (75 MHz, CDCl₃) of compound **3c**.

Figure S6: ¹H NMR (300 MHz, MeOD) of compound **4a**.

Figure S7: ¹³C NMR (125 MHz, CDCl₃-MeOD 1:1) of compound **4a**.

Figure S8: ¹H NMR (300 MHz, MeOD) of compound **4b**.

Figure S9: ¹³C NMR (125 MHz, DMSO-*d*₆) of compound **4b**.

Figure S10: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) of compound **4c**.

Figure S11: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) of compound **4d**.

Figure S12: ¹H NMR (300 MHz, CDCl₃) of compound **5b**.

Figure S13: ¹³C NMR (125 MHz, CDCl₃) of compound **5b**.

Figure S14. IR (ATR) spectrum of tribut-3-yn-1-yl phosphate (**5b**).

Figure S15. IR (ATR) spectrum of sodium dibut-3-yn-1-yl phosphate (**2b**).

Figure S16. IR (ATR) spectrum of compound **4a**.

Figure S17. IR (ATR) spectrum of 2-trityloxyethyl azide (**3c**).

Figure S18. IR (ATR) spectrum of compound **4b**.

Figure S19. IR (ATR) spectrum of compound **4c**.

Figure S20. IR (ATR) spectrum of compound **4d**.

Crystallographic Data

Crystallographic data for $C_{62}H_{102}N_{28}O_{22}P_2$, $M_r = 1653.65$, crystal dimensions 0.25 x 0.20 x 0.18 mm, space group $P-1$, $a = 11.8795(13)$ Å, $b = 12.4748(10)$ Å, $c = 15.0474(9)$ Å, $\alpha = 106.989(6)^\circ$, $\beta = 93.277(5)^\circ$, $\gamma = 110.045(9)^\circ$, $V = 1954.82$ Å³, $Z = 1$, $\rho_{\text{calcd}} = 1.405$ Mg/m³, $\mu = 0.15$ mm⁻¹. X-ray intensity data were measured at 120 K on a Rigaku MicroMax-007 HF rotating anode four-circle diffractometer using Mo-K α ($\lambda = 0.71075$ Å) radiation; 22273 reflections collected, 7369 unique reflections ($R_{\text{int}} = 0.025$), data/restraints/parameters: 7369/210/658, final R indices ($I > 2\sigma(I)$) $R1 = 0.051$ and $wR2 = 0.141$, $\Delta\rho_{\text{max}}/\Delta\rho_{\text{min}}$: 0.43/-0.30 e Å⁻³. Diethyl phosphate molecule (excluding phosphorus atom) and five (non-H) atoms of macrocycle were treated as positionally disordered, with the sum of the site occupancy factors (SOF) of respective subresidues fixed to 1.0, with appropriate geometry restraints and ADP restraints applied. SOFs of oxygens O11 and O12 were also refined, with their sum restrained to 1.0. No reasonable positions of water hydrogens (on O11 or O12) were found. CCDC 1439451 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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