

Facile Synthesis of New Polyazamacrocycles by the Pd-Catalyzed Amination of 3,3'-Dibromobiphenyl

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Pd-Catalyzed amination of 3,3'-dibromobiphenyl using various polyamines and oxadiazines was studied. Target macrocycles were obtained in yields from moderate to good with a variety of polyamines and oxadiazines, cyclic oligomers were isolated in the majority of cases as by-products. Synthesis of the macrocycles containing two 3,3'-disubstituted biphenyls and two polyamine fragments (cyclodimers) was elaborated using intermediate di(bromobiphenyl)substituted polyamines or bis(polyamine)substituted biphenyls.

Keywords: Macrocycles, amination, catalysis, polyamines, biphenyl.

Introduction

Macrocycles containing biphenyl units attract a constant interest of researchers due to interesting coordination possibilities arising from attaching flexible and tunable polyoxa- and polyazacycles to a rigid non-planar aryl moiety. The most of reported macrocycles based on biphenyls were synthesized using non-catalytic approaches. Cyclic polyethers were formed starting from 2,2'-dihydroxybiphenyl,^[1-3] and their coordination with cations like *tert*-butylammonium was studied.^[2] Transport of Li, Na, K cations^[4,5] and of Hg(CF₃)₂^[6,7] through a liquid membrane was investigated using macrocycles of similar structure, in which one or two polyoxaethylene chains were attached to one biphenyl unit. Polyoxadiazinamacrocycles were also synthesized on the basis of 2,2'-disubstituted biphenyl and their complexation of primary alkylammonium salts, including chiral ones, was studied.^[8] Polyazamacrocycles with 3, 4 and 8 nitrogen atoms were investigated as complexing agents for Cu²⁺, Zn²⁺ and [PdCl₄]²⁻ ions.^[9] More sophisticated macrocycles like peptide-biphenyl hybrid^[10] and hemispherand macrocycle^[11] with bi- and quaterphenyl moieties have been recently reported. Cyclic triamides^[12] as well as cyclic Schiff bases (trianglimines)^[13,14] comprise three 3,3'-disubstituted biphenyls, the latter can be also built on the basis of 4,4'-disubstituted biphenyls. In some cases biphenyl fragment was built using Pd-catalyzed coupling of two benzene moieties at the step of macrocyclization, as it was in the case of the compound with diazacrown, dipeptide and biphenyl fragments.^[15] It is to be mentioned that biphenyls are incorporated in some biologically active macrocycles, e.g. tricyclic glucopeptides of vancomycin group.^[16] To the moment, there are no literature data on the synthesis of biphenyl-based macrocycles which employs catalytic bond formation between aromatic and aliphatic parts of the molecule. In recent years we have accumulated experience on the application of the Buchwald-Hartwig amination^[17] in the synthesis of polyazamacrocycles starting from various

dihaloarenes^[18-21] and we investigated this approach for the construction of biphenyl-based macrocycles.

Experimental

NMR spectra were registered using Bruker Avance 400 spectrometer, MALDI-TOF spectra were obtained with Bruker Ultraflex spectrometer using 1,8,9-trihydroxyanthracene as matrix and PEGs as standards. 2-Bromonitrobenzene, oxadiazines, polyamines, 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (BINAP), 2-dimethylamino-2'-dicyclohexylphosphinobiphenyl (DavePHOS), sodium *tert*-butoxide were purchased from Aldrich and Acros and used without further purification, Pd(dba)₂ was synthesized according to the method described earlier.^[22] 3,3'-Dibromobiphenyl was synthesized in 3 steps from 2-bromonitrobenzene according to the procedure.^[23] Dioxane was distilled over NaOH followed by the distillation over sodium under argon, dichloromethane and methanol were distilled.

Typical procedure for the synthesis of macrocycles 3.

A two-neck flask equipped with a magnetic stirrer and a condenser, flushed with dry argon, was charged with 3,3'-dibromobiphenyl (**1**) (0.5 mmol, 156 mg), absolute dioxane (25 ml), Pd(dba)₂ (24 mg, 8 mol%) and BINAP (28 mg, 9 mol%). The mixture was stirred for 2 min, then appropriate polyamine **2** (0.5 mmol) and ^tBuONa (1.5 mmol) were added, and the reaction mixture was refluxed for 24 h. After cooling to the ambient temperature and filtration of the precipitate dioxane was evaporated *in vacuo* and the residue was chromatographed on silica gel using a sequence of eluents: CH₂Cl₂, CH₂Cl₂-MeOH 500:1 – 3:1, CH₂Cl₂-MeOH-aq. NH₃ 100:20:1 – 10:4:1.

11, 22, 26-Tetraazapentacyclo[25.3.1.1^{2,6}.1^{12,16}.1^{17,21}]tetratriaconta-1(31),2(34),3,5,12(33),13,15,17(32),18,20,27,29-dodecaene, 4a (n=1). Obtained from 37 mg of propane-1,3-diamine **2a**. Eluent: CH₂Cl₂-MeOH 200:1. Yield 27 mg (24%). Pale-yellow crystals, m.p. 224-225°C (decomp.) *m/z* (MALDI-TOF) found: 448.2593. C₃₀H₃₂N₄ requires 448.2627 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 1.94 (4H, quintet, ³J = 6.1 Hz), 3.37 (8H, t, ³J = 6.1 Hz), 3.91 (4H, br.s), 6.60 (4H, dd, ³J = 7.6 Hz, ⁴J = 1.8 Hz), 6.78 (4H, br.s), 6.91 (4H, d, ³J = 7.7 Hz), 7.21 (4H, t, ³J = 7.9 Hz). ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 28.6 (2C), 42.4 (4C), 111.6 (4C), 112.1 (4C), 116.5 (4C), 129.6 (4C), 142.9 (4C), 148.3 (4C).

7,10,13,24,27,30-Hexaazapentacyclo[29.3.1.1^{2,6}.1^{4,18}.1^{19,23}]octatriaconta-1(35),2(38),3,5,14(37),15,17,19(36),20,22,31,33-dodecaene, **4b** (n=1). Obtained from 52 mg of triamine **2b**. Eluent: CH₂Cl₂-MeOH/NH₃-aq 100:20:1. Yield 29 mg (23%). Pale-yellow glassy solid. Contains admixtures of cyclotrimer **4b** (n=2) and cyclotetramer **4b** (n=3). *m/z* (MALDI-TOF) 507.39 (**4b** (n=1) [(M+H)⁺]), 760.44 (**4b** (n=2) [(M+H)⁺]), 1012.72 (**4b** (n=3) [M⁺]). ¹H NMR (CDCl₃, 297 K) δ_H ppm: 2.85 (8H, br.s), 3.12–3.30 (8H, m), 6.50–6.58 (4H, m), 6.82–6.94 (8H, m), 7.11–7.21 (4H, m), NH protons were not assigned. ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 43.0 (4C), 48.0 (4C), 111.7 (4C), 111.8 (4C), 116.4 (4C), 129.4 (4C), 142.3 (4C), 148.4 (4C).

7,11,15-Triazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene, **3c**. Obtained from 66 mg of triamine **2c**. Eluent: CH₂Cl₂-MeOH 3:1. Yield 35 mg (25%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 281.1930. C₁₈H₂₃N₃ requires 281.1892 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 1.82 (4H, quintet, ³J = 6.7 Hz), 2.71 (4H, t, ³J = 6.0 Hz), 3.37 (4H, t, ³J = 7.3 Hz), 4.06 (2H, br.s), 6.54 (2H, dd, ³J = 8.0 Hz, ⁴J = 0.8 Hz), 7.03 (2H, d, ³J = 7.5 Hz), 7.17 (2H, t, ³J = 7.8 Hz), 7.29 (2H, br.s), NH proton of the dialkylamino group was not assigned. ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 29.7 (2C), 41.3 (2C), 47.0 (2C), 109.6 (2C), 114.0 (2C), 114.8 (2C), 129.3 (2C), 142.1 (2C), 147.9 (2C).

7,11,15,26,30,34-Hexaazapentacyclo[33.3.1.1^{2,6}.1^{6,20}.1^{21,25}]dotetraconta-1(39),2(42),3,5,16(41),17,19,21(40),22,24,35,37-dodecaene, **4c** (n=1). Obtained as by-product in the synthesis of macrocycle **3c**. Eluent: CH₂Cl₂-MeOH-NH₃-aq 100:20:1. Yield 30 mg (21%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 562.3701. C₃₆H₄₆N₆ requires 562.3784 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 1.80 (8H, quintet, ³J = 6.7 Hz), 2.68 (8H, t, ³J = 5.9 Hz), 3.29 (8H, t, ³J = 5.1 Hz), 3.90 (4H, br.s), 6.53 (4H, d, ³J = 8.0), 7.02 (4H, d, ³J = 7.4 Hz), 7.16 (4H, t, ³J = 7.7 Hz), 7.17 (4H, br.s), NH proton of the dialkylamino group was not assigned. ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 28.4 (4C), 41.1 (4C), 48.0 (4C), 109.8 (4C), 114.0 (4C), 114.8 (4C), 129.3 (4C), 142.3 (4C), 147.7 (4C).

7,10,13,16-Tetraazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene, **3d**. Obtained from 73 mg of tetraamine **2d**. Eluent: CH₂Cl₂-MeOH-NH₃-aq 100:20:3. Yield 23 mg (16%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 296.1959. C₁₈H₂₄N₄ requires 296.2001 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 2.82 (4H, s), 2.87 (4H, t, ³J = 6.6 Hz), 3.29 (4H, t, ³J = 6.6 Hz), 6.54 (2H, dd, ³J = 8.0 Hz, ⁴J = 2.0 Hz), 7.02 (2H, d, ³J = 7.7 Hz), 7.06 (2H, br.s), 7.16 (2H, t, ³J = 7.7 Hz), NH protons were not assigned. ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 44.27 (2C), 48.5 (2C), 49.3 (2C), 108.9 (2C), 114.2 (2C), 115.7 (2C), 129.3 (2C), 142.2 (2C), 148.9(2C).

7,10,13,16,27,30,33,36-Octaazapentacyclo[35.3.1.1^{2,6}.1^{7,21}.1^{22,26}]tetraetraconta-1(41),2(44),3,5,17(43),18,20,22(42),23,25,37,39-dodecaene, **4d** (n=1). Obtained as by-product in the synthesis of macrocycle **3d**. Eluent: CH₂Cl₂-MeOH-NH₃-aq 100:25:5. Yield 27 mg (18%). Pale-yellow glassy solid. Contains admixture of cyclotrimer **4d** (n=2). *m/z* (MALDI-TOF) 592.33 (**4d** (n=2) [M⁺]), 888.38 (**4d** (n=2) [M⁺]). ¹H NMR (CDCl₃, 297 K) δ_H ppm: 2.74 (8H, s), 2.85 (8H, t, ³J = 5.8 Hz), 3.21 (8H, t, ³J = 5.2 Hz), 6.56 (4H, dd, ³J = 7.8 Hz, ⁴J = 1.9 Hz), 6.80 (4H, s), 6.89 (4H, d, ³J = 7.2 Hz), 7.15 (4H, t, ³J = 7.8 Hz), NH protons were not assigned. ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 43.5 (4C), 48.4 (4C), 48.8 (4C), 111.7 (4C), 111.8 (4C), 116.6 (4C), 129.5 (4C), 142.8 (4C), 148.6 (4C).

7,10,14,17-Tetraazatricyclo[16.3.1.1^{2,6}]tricoso-1(22),2(23),3,5,18,20-hexaene, **3e**. Obtained from 80 mg of tetraamine **2e**. Eluent: CH₂Cl₂-MeOH-NH₃-aq 100:20:2. Yield 41 mg (26%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 310.2190. C₁₉H₂₆N₄ requires 310.2157 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 1.67 (2H, quintet, ³J = 6.4 Hz), 2.80 (4H, t, ³J = 6.4 Hz), 2.83 (4H, t, ³J = 6.9 Hz), 3.36 (4H, t, ³J = 6.9 Hz), 4.10 (2H, br.s), 6.57 (2H, dd, ³J = 8.0 Hz, ⁴J = 1.4 Hz), 6.96–7.00 (4H, m),

7.17 (2H, t, ³J = 7.7 Hz), NH protons of the dialkylamino groups were not assigned. ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 29.5 (1C), 44.3 (2C), 48.0 (2C), 49.2 (2C), 110.1 (2C), 114.2 (2C), 116.1 (2C), 129.3 (2C), 142.7 (2C), 148.7 (2C).

7,10,14,17,28,31,35,38-Octaazapentacyclo[37.3.1.1^{2,6}.1^{8,22}.1^{23,27}]hexatetraconta-1(43),2(46),3,5,18(45),19,21,23(44),24,26,39,41-dodecaene, **4e** (n=1). Obtained as by-product in the synthesis of macrocycle **3e**. Eluent: CH₂Cl₂-MeOH-NH₃-aq 100:20:3. Yield 12 mg (8%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 620.4307. C₃₈H₅₂N₈ requires 620.4314 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 1.69 (4H, quintet, ³J = 5.6 Hz), 2.77 (8H, t, ³J = 4.6 Hz), 2.83 (8H, t, ³J = 6.4 Hz), 3.24 (8H, br.s), 6.57 (4H, d, ³J = 7.8 Hz), 6.72 (4H, br.s), 6.85 (4H, d, ³J = 7.6 Hz), 7.14 (4H, t, ³J = 7.7 Hz), NH protons were not assigned. ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 28.9–29.7 (m, 2C), 42.6–43.0 (m, 4C), 47.8–49.3 (m, 8C), 111.2–111.8 (m, 8C), 116.3+116.4 (4C), 129.5 (4C), 142.6 (4C), 148.4+148.5 (4C).

7,11,14,18-Tetraazatricyclo[17.3.1.1^{2,6}]tetracoso-1(23),2(24),3,5,19,21-hexaene, **3f**. Obtained from 87 mg of tetraamine **2f**. Eluent: CH₂Cl₂-MeOH 3:1 - CH₂Cl₂-MeOH-NH₃-aq 100:20:2. Yield 71 mg (44%). Pale-yellow crystals, m.p. 115–116°C. *m/z* (MALDI-TOF) found: 324.2264. C₂₀H₂₈N₄ requires 324.2314 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 1.92 (4H, quintet, ³J = 6.6 Hz), 2.82 (4H, t, ³J = 6.0 Hz), 2.88 (4H, s), 3.32 (4H, t, ³J = 7.2 Hz), 3.72 (2H, br.s), 6.53 (2H, d, ³J = 7.6 Hz), 6.93 (2H, s), 6.94 (2H, d, ³J = 7.8 Hz), 7.15 (2H, t, ³J = 7.7 Hz), NH protons of the dialkylamino groups were not assigned. ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 28.1 (2C), 42.4 (2C), 47.5 (4C), 110.9 (2C), 113.3 (2C), 115.7 (2C), 129.5 (2C), 142.5 (2C), 148.3 (2C).

7,11,14,18,29,33,36,40-Octaazapentacyclo[39.3.1.1^{2,6}.1^{9,23}.1^{24,28}]octatetraconta-1(45),2(48),3,5,19(47),20,22,24(46),25,27,41,43-dodecaene, **4f** (n=1). Obtained as by-product in the synthesis of macrocycle **3f**. Eluent: CH₂Cl₂-MeOH-NH₃-aq 100:20:3. Yield 41 mg (25%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 648.4612. C₄₀H₅₆N₈ requires 648.4628 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 1.73 (8H, quintet, ³J = 6.3 Hz), 2.71 (8H, t, ³J = 6.3 Hz), 2.72 (8H, s), 3.15 (8H, t, ³J = 6.3 Hz), 6.53 (4H, dd, ³J = 7.8 Hz, ³J = 1.7 Hz), 6.76 (4H, t, ⁴J = 1.7 Hz), 6.87 (4H, d, ³J = 7.5 Hz), 7.17 (4H, t, ³J = 7.7 Hz), NH protons of the dialkylamino groups were not assigned. ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 29.1 (4C), 42.9 (4C), 48.1 (4C), 48.9 (4C), 111.3 (4C), 111.9 (4C), 116.2 (4C), 129.3 (4C), 142.9 (4C), 148.8 (4C).

7,11,15,19-Tetraazatricyclo[18.3.1.1^{2,6}]pentacoso-1(24),2(25),3,5,20,22-hexaene, **3g**. Obtained from 94 mg of tetraamine **2g**. Eluent: CH₂Cl₂-MeOH-NH₃-aq 100:20:1. Yield 69 mg (41%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 338.2410. C₂₁H₃₀N₄ requires 338.2470 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 1.70 (2H, quintet, ³J = 6.2 Hz), 1.83 (4H, quintet, ³J = 6.6 Hz), 2.74 (8H, t, ³J = 6.4 Hz), 3.22 (4H, t, ³J = 6.9 Hz), 6.53 (2H, d, ³J = 8.0 Hz), 6.85 (2H, br.s), 6.94 (2H, d, ³J = 7.6 Hz), 7.19 (2H, t, ³J = 7.8 Hz), NH protons were not assigned. ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 28.5 (2C), 29.8 (1C), 43.1 (2C), 48.4 (2C), 48.5 (2C), 110.7 (2C), 112.2 (2C), 115.4 (2C), 129.2 (2C), 142.5 (2C), 148.6 (2C).

7,11,15,19,30,34,38,42-Octaazapentacyclo[41.3.1.1^{2,6}.1^{20,24}.1^{25,29}]pentaconta-1(47),2(50),3,5,20(49),21,23,25(48),26,28,43,45-dodecaene, **4g** (n=1). Obtained as by-product in the synthesis of macrocycle **3g**. Eluent: CH₂Cl₂-MeOH-NH₃-aq 100:4:1. Yield 32 mg (19%). Contains admixtures of cyclotrimer **4g** (n=2) and cyclotetramer **4g** (n=3). Pale-yellow glassy solid. *m/z* (MALDI-TOF) 676.48 (**4g** (n=1) [M⁺]), 1014.57 (**4g** (n=2) [M⁺]), 1362.40 (**4g** (n=3) [M⁺]). ¹H NMR (CDCl₃, 297 K) δ_H ppm: 1.72 (12H, br.s), 2.67 (16H, br.s), 3.11 (8H, br.s), 6.51 (4H, d, ³J = 5.4 Hz), 6.76 (4H, br.s), 6.86 (4H, d, ³J = 6.9 Hz), 7.15 (4H, t, ³J = 6.5 Hz), NH protons were not assigned. ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 28.8 (4C), 29.1 (2C), 42.7 (4C), 48.0–48.6 (8C, m), 111.3–111.7 (8C, m), 116.0 (4C), 129.3 (4C), 142.7 (4C), 148.7 (4C).

7,10,13,16,19-Pentaazatricyclo[18.3.1.1^{2,6}]pentacosal(24),2(25),3,5,20,22-hexaene, **3h**. Obtained from 94 mg of pentaamine **2h**. Eluent: CH₂Cl₂-MeOH-NH₃-aq 100:20:3. Yield 32 mg (19%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 339.2373. C₂₀H₂₉N₅ requires 339.2423 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 2.74 (4H, t, ³J = 4.7 Hz), 2.83 (4H, t, ³J = 4.8 Hz), 2.90 (4H, t, ³J = 6.1 Hz), 3.34 (4H, t, ³J = 6.1 Hz), 6.60 (2H, d, ³J = 7.3 Hz), 6.98 (2H, s), 6.99 (2H, d, ³J = 6.7 Hz), 7.22 (2H, t, ³J = 8.0 Hz), NH protons were not assigned. ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 43.7 (2C), 48.6 (2C), 49.1 (2C), 49.5 (2C), 111.6 (2C), 112.8 (2C), 116.2 (2C), 129.5 (2C), 142.6 (2C), 148.8 (2C).

7,10,13,16,19,30,33,36,39,42-Decaazapentacyclo[41.3.1.1^{2,6}.1^{20,24}.1^{25,29}]pentaconta-1(47),2(50),3,5,20(49),21,23,25(48),26,28,43,45-dodecaene, **4h** (n=1). Obtained as by-product in the synthesis of macrocycle **3g**. Eluent: CH₂Cl₂-MeOH-NH₃-aq 100:25:5. Yield 5 mg (3%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 678.58. C₄₀H₅₈N₁₀ requires 678.48 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 2.73 (16H, br.s), 2.86 (8H, br.s), 3.22 (8H, br.s), 6.59 (4H, d, ³J = 7.7 Hz), 6.82 (4H, br.s), 6.90 (4H, d, ³J = 6.7 Hz), 7.20 (4H, t, ³J = 7.7 Hz), NH protons were not assigned. ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 43.5 (4C), 48.6 (4C), 49.0 (4C), 49.2 (4C), 111.9 (8C), 116.5 (4C), 129.5 (4C), 142.8 (4C), 148.7 (4C).

10,13-Dioxa-7,16-diazatricyclo[15.3.1.1^{2,6}]docosal(21),2(22),3,5,17,19-hexaene, **3i**. Obtained from 74 mg of dioxadamine **2i** in the presence of Pd(dba)₂ (46 mg, 16 mol%) and BINAP (56 mg, 18 mol%). Eluent: CH₂Cl₂-MeOH 100:1. Yield 60 mg (40%). Pale-yellow crystals, m.p. 211-212°C. *m/z* (MALDI-TOF) found: 298.1681. C₁₈H₂₂N₂O₂ requires 298.1706 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 3.49 (4H, t, ³J = 5.5 Hz), 3.70 (4H, s), 3.71 (4H, t, ³J = 5.6 Hz), 4.09 (2H, br.s), 6.59 (2H, ddd, ³J = 8.0 Hz, ⁴J = 1.5 Hz, ⁴J = 0.8 Hz), 7.06 (2H, d, ³J = 7.7 Hz), 7.19 (2H, t, ³J = 7.7 Hz), 7.39 (2H, t, ⁴J = 1.9 Hz). ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 45.2 (2C), 70.9 (2C), 72.6 (2C), 110.9 (2C), 114.2 (2C), 116.3 (2C), 128.9 (2C), 142.7 (2C), 148.9 (2C).

10,13,30,33-Tetraoxa-7,16,27,36-tetraazapentacyclo[35.3.1.1^{2,6}.1^{17,21}.1^{22,26}]tetratetraconta-1(41),2(44),3,5,17(43),18,20,22(42),23,25,37,39-dodecaene, **4i** (n=1). Obtained as by-product in the synthesis of macrocycle **3i**. Eluent: CH₂Cl₂-MeOH 75:1. Yield 22 mg (15%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 596.3409. C₃₆H₄₄N₄O₄ requires 596.3362 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 3.34 (8H, t, ³J = 4.7 Hz), 3.68 (8H, s), 3.73 (8H, t, ³J = 4.8 Hz), 4.23 (4H, br.s), 6.60 (4H, d, ³J = 7.7 Hz), 6.79 (4H, br.s), 6.91 (4H, d, ³J = 7.1 Hz), 7.18 (4H, t, ³J = 7.5 Hz). ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 43.7 (4C), 69.6 (4C), 70.3 (4C), 111.8 (4C), 112.5 (4C), 116.8 (4C), 129.5 (4C), 142.9 (4C), 148.5 (4C).

10,13,30,33,50,53-Hexaoxa-7,16,27,36,47,56-hexaazaheptacyclo[55.3.1.1^{2,6}.1^{17,21}.1^{22,26}.1^{37,41}.1^{42,46}]hexahexaconta-1(61),2(66),3,5,17(65),18,20,22(64),23,25,37(63),38,40,42(62),43,45,57,59-octadecaene, **4i** (n=2). Obtained as by-product in the synthesis of macrocycle **3i**. Eluent: CH₂Cl₂-MeOH 20:1. Yield 24 mg (16%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 894.56. C₃₄H₆₆N₆O₆ requires 894.50 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 3.36 (12H, br.s), 3.67 (12H, s), 3.72 (12H, br.s), 4.06 (6H, br.s), 6.62 (6H, d, ³J = 7.5 Hz), 6.84 (6H, br.s), 6.94 (6H, d, ³J = 6.8 Hz), 7.22 (6H, t, ³J = 7.4 Hz). ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 43.6 (6C), 69.7 (6C), 70.3 (6C), 112.0 (6C), 112.1 (6C), 116.8 (6C), 129.5 (6C), 142.9 (6C), 148.5 (6C).

11,16-Dioxa-7,20-diazatricyclo[19.3.1.1^{2,6}]hexacosal(25),2(26),3,5,21,23-hexaene, **3j**. Obtained from 102 mg of dioxadamine **2j**. Eluent: CH₂Cl₂-MeOH 100:1. Yield 78 mg (44%). Pale-yellow crystals, m.p. 111-112°C. *m/z* (MALDI-TOF) found: 354.2279. C₂₂H₃₀N₂O₂ requires 354.2307 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 1.76 (4H, quintet, ³J = 2.8 Hz), 1.90 (4H, quintet, ³J = 5.8 Hz), 3.36 (4H, t, ³J = 6.5 Hz), 3.47 (4H, br.s), 3.61 (4H, t,

³J = 5.3 Hz), 6.57 (2H, ddd, ³J = 8.0 Hz, ⁴J = 2.2 Hz, ⁴J = 0.7 Hz), 6.99 (2H, t, ⁴J = 2.1 Hz), 7.01 (2H, d, ³J = 7.7 Hz), 7.24 (2H, t, ³J = 7.8 Hz). ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 27.2 (2C), 29.3 (2C), 43.2 (2C), 70.3 (2C), 71.2 (2C), 111.5 (4C), 115.8 (2C), 129.3 (2C), 142.2 (2C), 149.1 (2C).

11,16,35,40-Tetraoxa-7,20,31,44-tetraazapentacyclo[43.3.1.1^{2,6}.1^{21,25}.1^{26,30}]dopentaconta-1(49),2(52),3,5,21(51),22,24,26(50),27,29,45,47-dodecaene, **4j** (n=1). Obtained as by-product in the synthesis of macrocycle **3j**. Eluent: CH₂Cl₂-MeOH 75:1. Yield 20 mg (12%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 708.42. C₄₄H₆₀N₄O₄ requires 708.46 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 1.66 (8H, quintet, ³J = 2.1 Hz), 1.85 (8H, quintet, ³J = 6.1 Hz), 3.23 (8H, t, ³J = 6.4 Hz), 3.43 (8H, quintet, ³J = 2.1 Hz), 3.52 (8H, t, ³J = 5.7 Hz), 4.13 (4H, br.s), 6.54 (4H, dd, ³J = 7.9 Hz, ⁴J = 1.5 Hz), 6.77 (4H, t, ⁴J = 1.8 Hz), 6.87 (4H, d, ³J = 7.6 Hz), 7.18 (4H, t, ³J = 7.8 Hz). ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 26.6 (4C), 29.3 (4C), 42.2 (4C), 69.5 (4C), 70.8 (4C), 111.4 (4C), 111.7 (4C), 116.3 (4C), 129.3 (4C), 143.0 (4C), 148.8 (4C).

11,14,17-Trioxa-7,21-diazatricyclo[20.3.1.1^{2,6}]heptacosal(26),2(27),3,5,22,24-hexaene, **3k**. Obtained from 110 mg of trioxadamine **2k**. Eluent CH₂Cl₂-MeOH 100:1. Yield 71 mg (38%). Pale-yellow crystals, m.p. 74-75°C. *m/z* (MALDI-TOF) found: 370.2240. C₂₂H₃₀N₂O₃ requires 370.2256 [M⁺]. δ_H (CDCl₃, 297 K) 1.91 (4H, quintet, ³J = 5.9 Hz), 3.35 (4H, t, ³J = 6.5 Hz), 3.60-3.66 (8H, m), 3.73-3.77 (4H, m), 4.26 (2H, br.s), 6.57 (2H, d, ³J = 7.9 Hz), 6.94 (2H, br.s), 6.97 (2H, d, ³J = 7.7 Hz), 7.21 (2H, t, ³J = 7.8 Hz). ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 29.3 (2C), 42.5 (2C), 70.1 (2C), 70.7 (2C), 71.0 (2C), 111.1 (2C), 111.9 (2C), 115.9 (2C), 129.2 (2C), 142.5 (2C), 149.0 (2C).

11,14,17,36,39,42-Hexaoxa-7,21,32,46-tetraazapentacyclo[45.3.1.1^{2,6}.1^{22,26}.1^{27,31}]tetrapentaconta-1(51),2(54),3,5,22(53),23,25,27(52),28,30,47,49-dodecaene, **4k** (n=1). Obtained as by-product in the synthesis of macrocycle **3k**. Eluent: CH₂Cl₂-MeOH 50:1. Yield 22 mg (12%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 740.4473. C₄₄H₆₀N₄O₆ requires 740.4512 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 1.84 (8H, quintet, ³J = 6.0 Hz), 3.23 (8H, t, ³J = 6.4 Hz), 3.55 (8H, t, ³J = 5.8 Hz), 3.55-3.60 (8H, m), 3.63-3.67 (8H, m), 4.18 (4H, br.s), 6.54 (4H, dd, ³J = 7.7 Hz, ⁴J = 1.9 Hz), 6.73 (4H, br.s), 6.85 (4H, d, ³J = 7.4 Hz), 7.17 (4H, t, ³J = 8.0 Hz). ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 29.0 (4C), 41.7 (4C), 69.7 (4C), 70.2 (4C), 70.6 (4C), 111.3 (4C), 111.8 (4C), 116.1 (4C), 129.3 (4C), 143.0 (4C), 148.8 (4C).

Synthesis of *N,N'*-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(5'-bromobiphenyl-3-amine), **5i**, is analogous to the procedure described for the preparation of macrocycles **3**, from 3,3'-dibromobiphenyl (**1**) (1.5 mmol, 468 mg) and dioxadamine **2i** (0.5 mmol, 74 mg), in absolute dioxane (5 ml), in the presence of Pd(dba)₂ (12 mg, 4 mol%), Xanthphos (13 mg, 5 mol%) and ^tBuONa (1.5 mmol). Reflux time: 8 h. Eluent: CH₂Cl₂-MeOH 200:1. Yield 82 mg (27%). Pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 608.0713. C₃₀H₃₀Br₂N₂O₂ requires 608.0674 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 3.36 (4H, t, ³J = 5.2 Hz), 3.68 (4H, s), 3.74 (4H, t, ³J = 5.2 Hz), 4.20 (2H, br.s), 6.63 (2H, dd, ³J = 8.1 Hz, ⁴J = 1.4 Hz), 6.77 (2H, t, ⁴J = 1.4 Hz), 6.88 (2H, d, ³J = 7.7 Hz), 7.22 (2H, t, ³J = 7.9 Hz), 7.25 (2H, d, ³J = 7.8 Hz), 7.42-7.47 (4H, m), 7.69 (2H, t, ⁴J = 1.6 Hz). ¹³C NMR (CDCl₃, 297 K) δ_C ppm: 43.5 (2C), 69.6 (2C), 70.2 (2C), 111.6 (2C), 112.6 (2C), 116.6 (2C), 122.7 (2C), 125.7 (2C), 129.7 (2C), 129.9 (2C), 130.0 (2C), 130.1 (2C), 140.8 (2C), 143.8 (2C), 148.6 (2C).

Synthesis of *N²,N³*-bis(2-(2-(2-aminoethoxy)ethoxy)ethyl)biphenyl-3,3'-diamine, **6i**, is analogous to the procedure described for the preparation of compound **5i**, from 3,3'-dibromobiphenyl **1** (0.5 mmol, 156 mg) and dioxadamine **2i** (2 mmol, 296 mg), in absolute dioxane (5 ml), in the presence of Pd(dba)₂ (12 mg, 4 mol%), BINAP (14 mg, 4.5 mol%) and ^tBuONa (1.5 mmol). Reflux time: 8 h. *m/z* (MALDI-TOF) found: 446.42. C₂₄H₃₈N₄O₄ requires 446.29 [M⁺]. ¹H NMR (CDCl₃, 297 K) δ_H ppm: 2.83 (4H, t, ³J =

5.3 Hz), 3.32 (4H, t, $^3J = 5.3$ Hz), 3.49 (4H, t, $^3J = 5.2$ Hz), 3.60-3.66 (8H, m), 3.71 (4H, t, $^3J = 5.2$ Hz), 6.59 (2H, ddd, $^3J = 8.1$ Hz, $^4J = 2.4$ Hz, $^4J = 0.7$ Hz), 6.80 (2H, t, $^4J = 2.1$ Hz), 6.89 (2H, d, $^3J = 7.6$ Hz), 7.19 (2H, t, $^3J = 7.8$ Hz), NH protons were not assigned. ^{13}C NMR (CDCl_3 , 297 K) δ_c ppm: 41.5 (2C), 43.4 (2C), 69.6 (2C), 70.2 (4C), 73.4 (2C), 112.0 (4C), 116.7 (2C), 129.3 (2C), 142.8 (2C), 148.4 (2C).

Synthesis of cyclodimer **4i** ($n=1$) from compound **5i** is analogous to the procedure described for the preparation of macrocycles **3**, from compound **5i** (0.135 mmol, 82 mg) and dioxadiazine **2i** (0.135 mmol, 20 mg), in absolute dioxane (7 ml), in the presence of $\text{Pd}(\text{dba})_2$ (6.5 mg, 8 mol%), BINAP (7.5 mg, 9 mol%) and $t\text{BuONa}$ (0.4 mmol, 39 mg). Reflux time: 24 h. Eluent; CH_2Cl_2 -MeOH 20:1. Yield 33 mg (27%).

Synthesis of cyclodimer **4i** ($n=1$) from compound **6i** is analogous to the procedure described for the preparation of macrocycles **3**, from the mixture of compound **6i** (*ca* 0.25 mmol) with dioxadiazine **2i** (*ca* 0.5 mmol) and 3,3'-dibromobiphenyl (**1**) (0.75 mmol, 234 mg), in absolute dioxane (12 ml), in the presence of $\text{Pd}(\text{dba})_2$ (36 mg, 8 mol%), BINAP (42 mg, 9 mol%) and $t\text{BuONa}$ (2.25 mmol, 216 mg). Reflux time: 24 h. Eluent; CH_2Cl_2 -MeOH 20:1. Yield 98 mg (44%).

Results and Discussion

The reactions of equimolar amounts of 3,3'-dibromobiphenyl **1** with a variety of di- and polyamines **2a-k** (Figure 1) were run in enough dilute dioxane solutions ($c = 0.02$ M) using $\text{Pd}(\text{dba})_2/\text{BINAP}$ (8/9 mol%) catalytic system^[24] which was found to be almost universal for the synthesis of polyazamacrocycles, the products were isolated by column chromatography on silica gel. The results are given in Table 1.

As expected, propane-1,3-diamine **2a** was too short to give a desired mono-cycle **3**, and it produced

cyclodimer **4a** ($n=1$) in 24% yield as well as a mixture of higher mass oligomers **4a** ($n=2-7$) (37%) (Table 1, entry 1). Diethylenetriamine **2b** (7 atoms in the chain) also gave only cyclooligomers **4b** ($n=1-5$) (entry 2), but beginning from triamine **2c** (9 atoms) target macrocycles **6** were formed successfully in yields from moderate to good (entries 3-13). The best yields (44%, entries 6, 11) were achieved with tetraamine **2f** and dioxadiazine **2j**, also enough high yields for the macrocyclization reaction (*ca* 40%) were afforded by tetraamine **2g** and trioxadiazine **2k** (entries 7, 12). We increased the yield of the macrocycle **3k** to 45% by the application of 2-dicyclohexylphosphino-2'-dimethylamino-biphenyl (DavePHOS) ligand instead of BINAP (entry 13), however, this approach did not work in the case of dioxadiazine **2i**, but the use of 16% mol catalyst gave corresponding macrocycle **3i** in 40% yield (entry 10). In many cases cyclodimers **4** ($n=1$) were isolated from oligomeric mixtures in 8-25% yields, and in the reactions with dioxadiazine **2i** even cyclotrimer **4i** ($n=2$) was obtained separately in 16% yield. It is to be mentioned that 40% yields of polyazamacrocycles are among the highest ever achieved by the Pd-catalyzed amination of dihaloarenes, *e.g.* they notably surpass those obtained recently with 2,7-dibromonaphthalene.^[25] Mono-cycles **3** contain from 15 (**3c**) to 21 atoms (**3k**) in the cycle, cyclodimers **4** possess from 22 (**4a**, $n=1$) to 42 atoms (**4k**, $n=1$), while cyclotrimer **4i** ($n=2$) has a cavity formed by 48 atoms.

Cyclodimers which possess two biphenyl units and two polyamine chains and thus have a larger cavity size are of interest for the coordination studies with big cations and anions and organic molecules. We elaborated two approaches to such compounds. According to the first route, we synthesized *N,N'*-di(bromobiphenyl) substituted dioxadiazine **5i** which was

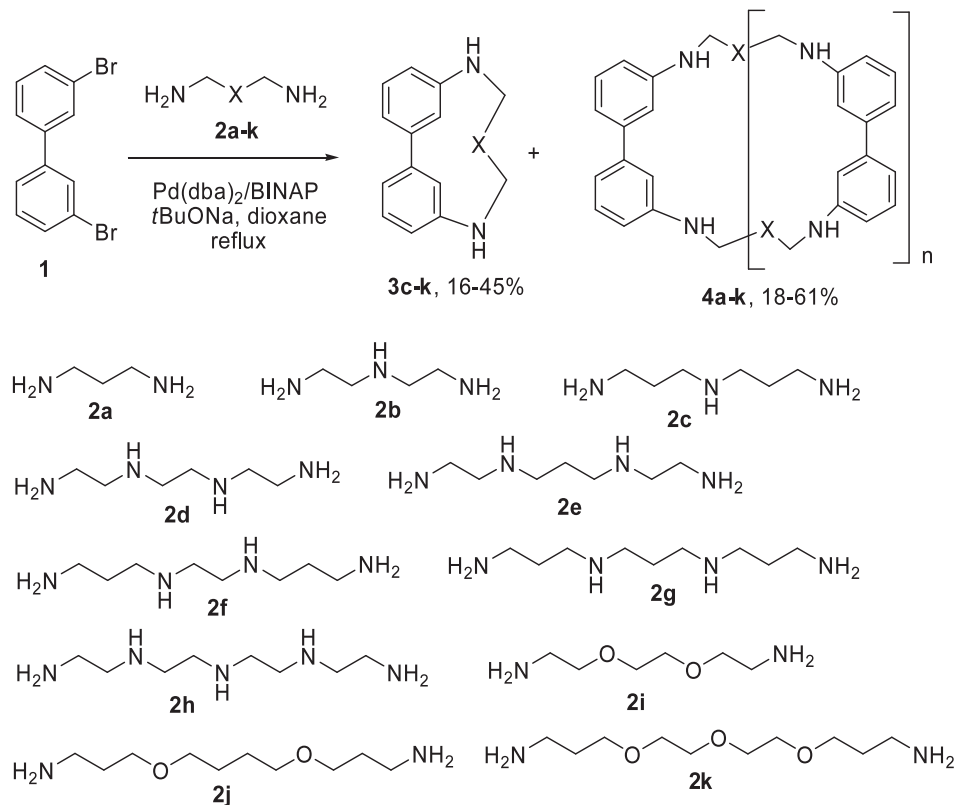
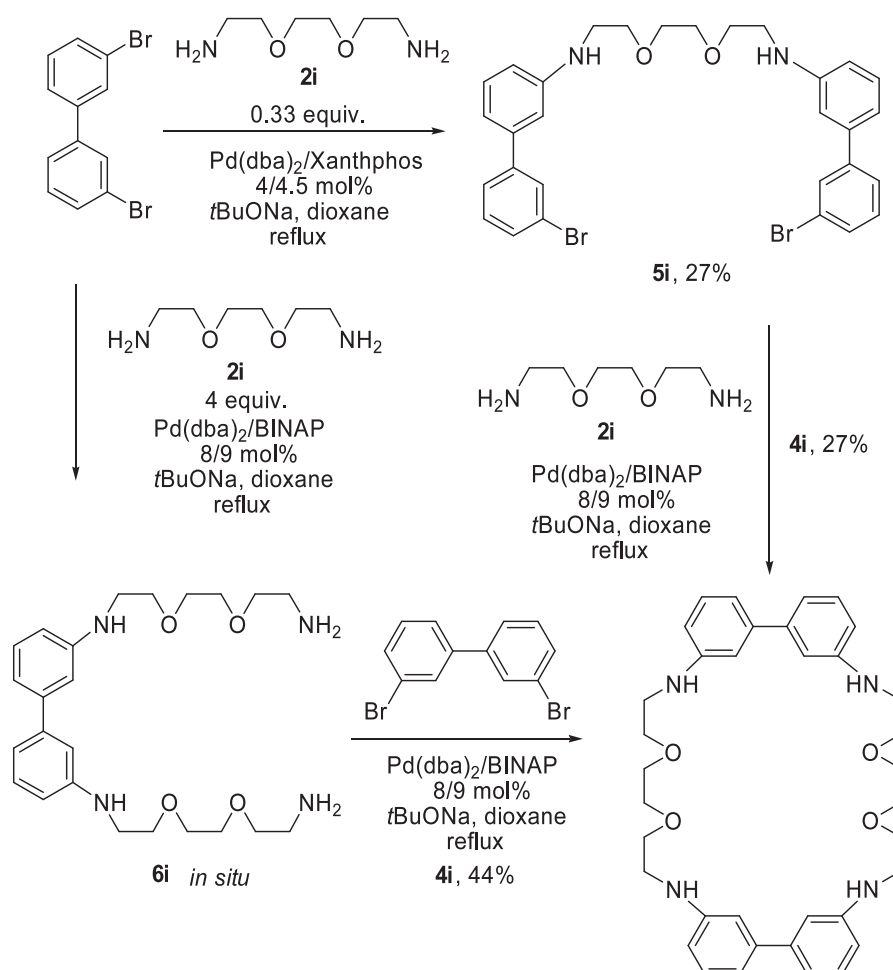


Figure 1.

Table 1. Pd-Catalyzed amination of 3,3'-dibromobiphenyl (**1**).

Entry	Amine	Pd(dba) ₂ /BINAP, mol%	Isolated yields of 3 , %	Yields of 4 , %
1	2a	8/9	3a , 0	4a (n=1), 24 4a (n=2-7), 37 (mixture)
2	2b	8/9	3b , 0	4b (n=1), 23 4b (n=2-5), 38 (mixture)
3	2c	8/9	3c , 25	4c (n=1), 21 4c (n=2-5), 23 (mixture)
4	2d	8/9	3d , 16	4d (n=1,2), 18 (mixture)
5	2e	8/9	3e , 26	4e (n=1), 8 4e (n=1-3), 27 (mixture)
6	2f	8/9	3f , 44	4f (n=1), 25 4f (n=1,2), 17 (mixture)
7	2g	8/9	3g , 41	4g (n=1-3), 19 (mixture)
8	2h	8/9	3h , 19	4h (n=1), 3 4h (n=1,2), 12 (mixture)
9	2i	8/9	3i , 19	4i (n=1), 12
10	2i	16/18	3i , 40	4i (n=1), 15 4i (n=2), 16
11	2j	8/9	3j , 44	4j (n=1), 12 4j (n=1-4), 18 (mixture)
12	2k	8/9	3k , 38	4k (n=1), 12 4k (n=1-4), 17 (mixture)
13 ^{a)}	2k	8/10	3k , 45	4k (n=1), 21 4k (n=1-3), 9 (mixture)

^{a)} DavePHOS was used instead of BINAP

**Figure 2.**

taken as an exemplary amine (Figure 2). Three equivalents of 3,3'-dibromobiphenyl **1** were employed in the presence of 4 mol% catalyst to give **5i** in 27% yield. The reaction was severely complicated by *N,N*-diarylation and diamination processes, thus the application of Xanthphos ligand instead of BINAP was helpful. The cyclization into cyclodimers with dioxadiazine **2i** was carried out under the conditions similar to those used for the macrocycles **3**. As a result, **4i** (n=1) was isolated in 27% yield. The attempts to introduce diaryl derivative **5i** *in situ* were totally unsuccessful. Alternative approach included the synthesis of bis(dioxadiazine) substituted biphenyl **6i** using 4 equivalents of dioxadiazine **2i**. The yield of this compounds in the reaction mixtures was very high according to NMR data, and **6i** was used *in situ* in the further reaction with 3,3'-dibromobiphenyl (Scheme 2). Target macrocycle **4i** (n=1) was obtained in 44% yield. This approach to cyclodimers was found to be much more efficient because it is carried out as a one-pot procedure and provides higher overall yield of the target compound.

Conclusions

To sum up, we have investigated 3,3'-dibromobiphenyl in the Pd-catalyzed amination reactions with polyamines and oxadiazines, demonstrated the possibilities to obtain polyazamacrocycles in enough high yields, elaborated two approaches to the corresponding cyclodimers and found out the advantage of the route through bis(polyamine) derivatives.

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