Palladium– and Copper–Catalyzed Amination of Halogenophenyl Substituted Porphyrins for the Synthesis of Porphyrin–Azacrown Ethers Conjugates and Evaluation of Their Sensing Properties

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Dedicated to Academician of Russian Academy of Sciences Oleg. G. Sinyashin on the occasion of his 60th Birthday

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The Pd⁰- and Cu⁺-catalyzed amination of meso-(halogenophenyl)substituted porphyrins and their Zn complexes with propane-1,3-diamine and trioxadiamine was carried out to produce mono- and diaminated derivatives. Conditions for the synthesis of bis- and trismacrocyclic porphyrin-azacrown conjugates with trimethylene diamine linkers via Pd⁰-catalyzed amination reactions were established. The properties of two polymacro cyclic compounds to serve as colorimetric and fluorescent sensors for metal cations were investigated, and trismacro cyclic ligand possessing two 1-aza-18-crown-6 moieties arranged symmetrically around the porphyrin core was found to be selective for Cu²⁺ in the presence of other metals by strong emission quenching caused by copper ions.

Keywords: Macrocycles, amination, Pd catalysis, Cu catalysis, porphyrins, azacrown ethers, conjugates, chemosensor.
Amination of Substituted Porphyrins for the Synthesis of Porphyrin-Azacrown Ethers Conjugates

Introduction

Modification of porphyrins using catalytic approaches is well documented in literature.\(^1\) For example, meso-halogenophenyl substituted porphyrins are known to participate in the Pd-mediated amination reactions.\(^2\) Much more extensive catalytic transformations have been described for \textit{meso}\textendash halogenosubstituted porphyrins: amination,\(^3\) alkylation and arylxoylation,\(^4\) sulfonylation,\(^5\) and phosphorylation.\(^6\) The formation of carbon-carbon bonds via Suzuki, Sonogashira and Heck reactions are the powerful tools for various modifications of porphyrins\(^7\) and construction of di- and triporphyrin systems of various architecture.\(^8\) All these reactions were accomplished using Pd catalysis. As for copper-mediated reactions in porphyrins transformation, the majority of literature data deals with "click" reactions which give a lot of possibilities of porphyrins modifications.\(^9\) However, in other transformations copper plays a humble role; for example its application was described for the catalytic tetraarylation of \textit{meso}\textendash tetakis(4-aminophenyl) porphyrin with 4-iodoanisole.\(^10\) CuCl was employed for the synthesis of an awesome square-shaped \textit{π}-conjugated porphyrin tetramer with diacetylene linkers,\(^11\) Cu(OAc)\(_2\) was used in the synthesis of dibutadiyne-bridged porphyrin macrotricyclic dimer.\(^12\)

Recently some of us have studied the amination of mono- and bis(bromophenyl)porphyrins using diamines with secondary amino groups like propane-1,3-diamine (DMEDA) and piperazine,\(^13\) these compounds have been used for the synthesis of porphyrin dyads and triads of various architecture.\(^14\) Copper-mediated famous "click" reactions were also used in the synthesis of porphyrin trimers.\(^15\) In the present work we studied various approaches using Pd- and Cu-catalyzed amination reactions for conjugating porphyrin moiety with azacrown ethers, macrocyclic and macrorbycyclic compounds in view of the synthesis of hybrid polycyclic systems – novel polytopic ligands able to bind different metal cations.

Experimental

NMR spectra were registered using Bruker Avance 400 spectrometer, MALDI-TOF spectra were obtained with Bruker Autoflex II spectrometer using \textit{1,8,9-trihydroxynaphthacene as matrix} and PEGs as internal standards. Propane-1,3-diamine, dioxa- and trioxadiazines, azacrown ethers, 2-(isobutyryl) cyclohexanone, BINAP, DavePhos, cesium carbonate, sodium tert-butoxide, Cule were purchased from Sigma-Aldrich and used without further purification, Pd(dba), was synthesized according to the method described,\(^16\) halogenophenylsubstituted porphyrins and their Zn complexes \(\text{1, 2, 9–12}\) were synthesized according to a described procedure,\(^17\) synthesis of 3-bromobenzyl derivatives of azacrown ethers \(\text{23 and 24}\) and preparation of diamino derivatives of benzyllacron ethers \(\text{25 and 26}\) were carried out according to a known method.\(^18\) Dioxane was distilled over NaOH followed by the distillation over sodium under argon, acetone distilled was reified over Ca\(_2\)H\(_2\), DMF, dichloromethane and methanol were used freshly distilled.

Porphyrin 5. A two-necked flask flushed with dry argon, equipped with a magnetic stirrer and reflux condenser was charged with porphyrin \(\text{1 (0.11 mmol, 83 mg), trioxadime 4 (0.33 mmol, 73 mg), Pd(dba) (5 mg, 8 mol %), BINAP (6 mg, 9 mol %), absolute dioxane (2 ml) and BuO\(_2\)Na (0.2 mmol, 20 mg). The reaction mixture was refluxed for 24 hrs, cooled to ambient temperature, diluted with CH\(_2\)Cl\(_2\) (5 ml), the residue was filtered off, washed with CH\(_2\)Cl\(_2\) (5 ml), combined organic fractions were evaporated in vacuo, and chromatographed on silica gel using a gradient of eluents: CH\(_2\)Cl\(_2\) – CH\(_2\)Cl\(_2\)/MeOH 3:1 – CH\(_2\)Cl\(_2\)/MeOH/NH\(_3\)aq 100:20:1–10:14:1. The target compound was eluted with CH\(_2\)Cl\(_2\)/MeOH/NH\(_3\)aq 100:20:3. Yield: 16 mg (16 %), deep-red solid. Mass spectrum (MALDI TOF) \(m/z: 890.4753 \text{[M]+}\). \(\text{C}_{26}\text{H}_{38}\text{N}_{8}\text{O}_3\) \(\text{Zn}.\) \(\text{H NMR (CDCl}_3, 298 \text{K}) \delta: 0.98 (6H, t, J=7.3 Hz), 1.55 (4H, sextet, J=7.4 Hz), 1.75 (4H, quintet, J=7.3 Hz), 1.90 (2H, br.s), 1.99 (2H, quintet, J=5.6 Hz), 2.27 (4H, quartet, J=7.5 Hz), 2.52 (6H, s), 3.02 (2H, br.s), 3.39 (2H, br.s), 3.47–3.60 (8H, m), 3.56 (6H, s), 3.62 (2H, br.s), 3.68 (2H, t, J=5.4 Hz), 3.96 (4H, t, J=7.3 Hz), 7.04 (2H, d, J=8.2 Hz), 7.72 (2H, d, J=8.2 Hz), 9.81 (1H, s), 9.96 (2H, s), NH protons were not assigned."

Porphyrin 6. A two-necked flask flushed with dry argon, equipped with a magnetic stirrer and reflux condenser was charged with porphyrin \(\text{2 (0.15 mmol, 120 mg), propane-1,3-diamine (3) (0.45 mmol, 33 mg), Cu (3 mg, 10 mol %), 2-(isobutyryl) cyclohexanone (6 mg, 20 mol %), DMF (1 ml) and Cs\(_2\)CO\(_3\) (0.225 mmol, 75 mg). The reaction mixture was stirred at 110 °C for 24 hrs, cooled to ambient temperature, diluted with CH\(_2\)Cl\(_2\) (5 ml), the residue was filtered off, washed with CH\(_2\)Cl\(_2\) (5 ml), combined organic fractions were evaporated in vacuo to produce compound \(\text{6}.\) Yield: 55 mg (50 %), deep-red solid. Mass spectrum (MALDI TOF) \(m/z: 744.3803 \text{[M]+}\). \(\text{H NMR (CDCl}_3, 298 \text{K}) \delta: 0.98 (6H, t, J=7.3 Hz), 1.55 (4H, br.s), 1.71 (4H, br.s), 2.03 (2H, br.s), 2.30 (4H, br.s), 2.45 (6H, br.s), 2.57 (2H, br.s), 3.48–3.58 (14H, br.m), 6.34 (1H, br.s), 6.70 (1H, br.s), 7.20 (1H, br.s), 7.35 (H, br.s), NH protons were not assigned."

Porphyrin 7. A two-necked flask flushed with dry argon, equipped with a magnetic stirrer and reflux condenser was charged with porphyrin \(\text{2 (0.15 mmol, 120 mg), trioxadime 4 (0.33 mmol, 66 mg), Cu (3 mg, 10 mol %), 2-(isobutyryl)cyclohexanone (6 mg, 20 mol %), DMF (1 ml) and Cs\(_2\)CO\(_3\) (0.225 mmol, 75 mg). The reaction mixture was stirred at 110 °C for 24 hrs, cooled to ambient temperature, diluted with CH\(_2\)Cl\(_2\) (5 ml), the residue was filtered off, washed with CH\(_2\)Cl\(_2\) (5 ml), combined organic fractions were evaporated in vacuo and chromatographed on silica gel using a gradient of eluents: CH\(_2\)Cl\(_2\) – CH\(_2\)Cl\(_2\)/MeOH 3:1. The target compound was eluted with CH\(_2\)Cl\(_2\)/MeOH/NH\(_3\)aq 100:20:3. Yield: 14 mg (10 %), deep-red solid. Mass spectrum (MALDI TOF) \(m/z: 980.4865 \text{[M]+}\). \(\text{C}_{34}\text{H}_{48}\text{N}_{8}\text{O}_3\) \(\text{Zn}.\) \(\text{H NMR (CDCl}_3, 298 \text{K}) \delta: 0.98 (6H, t, J=7.3 Hz), 1.55 (4H, sextet, J=7.1 Hz), 1.67–1.78 (6H, m), 1.95 (2H, br.s), 1.98 (4H, quintet, J=5.9 Hz), 2.28 (4H, br.s), 1.72 (2H, d, J=8.2 Hz), 2.72 (2H, d, J=8.2 Hz), 9.81 (1H, s), 9.96 (2H, s), NH protons were not assigned."

Ключевые слова: Макроциклы, аминирование, Pd катализ, Cu катализ, порфирины, азакраун-эфиры, конъюгаты, хемосенсоры на ионы металлов.

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(6H, s), 2.91 (2H, brs), 3.17 (2H, brs), 3.23 (2H, brs), 3.96–4.04 (4H, m), 6.99 (1H, d, J = 7.7 Hz), 7.32 (1H, s), 7.38 (1H, brd, \( J_{\text{br}} = 6.6 \) Hz), 7.47 (1H, t, \( J = 7.6 \) Hz), 9.87 (1H, s), 10.00 (2H, s), NH protons were not assigned.

**Porphyrin 13.** A two-necked flask flushed with dry argon, equipped with a magnetic stirrer and reflux condenser was charged with porphyrin 9 (0.1 mmol, 96 mg), propane-1,3-diamine (30 mmol, 22 mg), \( \text{Pd(dba)}_2 \) (2.5 mg, 4 mol %), \( \text{BuONa} \) (0.15 mmol, 15 mg). The reaction mixture was refluxed for 24 hrs, cooled to ambient temperature, diluted with \( \text{CH}_2\text{Cl}_2 \) (5 ml), the residue was filtered off, washed with \( \text{CH}_2\text{Cl}_2 \) (5 ml), combined organic fractions were evaporated in vacuo, and chromatographed on silica gel using a gradient of eluents: \( \text{CH}_2\text{Cl}_2 – \text{CH}_2\text{Cl}_2/\text{MeOH} : 1:1 \) – \( \text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3 \text{aq} 100:20:1\)–10:1. The target compound was eluted with \( \text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3 \text{aq} 100:20:3. Yield: 46 mg (49 %), deep-red solid. Mass spectrum (MALDI TOF) \( m/z \): 942.7058 [M]+. \( ^1\text{H} \text{NMR (CDCl}_3, 298 \text{ K}) \): \( \delta \) ppm: 2.30–2.35 (2H, brs), 1.00 (12H, t, \( J = 7.3 \) Hz), 1.57 (8H, sextet, \( J = 7.7 \) Hz), 1.77 (8H, quintet, \( J = 7.3 \) Hz), 1.88 (4H, quartet, \( J = 6.4 \) Hz), 2.25 (8H, quartet, \( J = 5.8 \) Hz), 2.65 (12H, s), 2.93 (4H, t, \( J = 6.4 \) Hz), 3.37 (4H, t, \( J = 6.3 \) Hz), 4.03 (8H, t, \( J = 5.8 \) Hz), 6.92 (4H, d, \( J_{\text{br}} = 8.1 \) Hz), 7.80 (4H, d, \( J = 8.1 \) Hz), 10.26 (2H, s), six NH protons were not assigned. \( ^{13}\text{C} \text{NMR (CDCl}_3, 298 \text{ K}) \): \( \delta \) ppm: 14.2 (4C), 14.9 (4C), 22.8 (4C), 32.5 (8C), 33.7 (4C), 40.2 (2C), 42.4 (2C), 96.6 (2C), 111.9 (4C), 118.4 (2C), 131.1 (2C), 133.5 (4C), 136.5 (4C), 141.3 (4C), 142.8 (4C), 145.9 (4C), 148.5 (2C).

**Porphyrin 15.** A two-necked flask flushed with dry argon, equipped with a magnetic stirrer and reflux condenser was charged with porphyrin 11 (0.05 mmol, 48 mg), trioxadiazine 4 (0.2 mmol, 44 mg), \( \text{Pd(dbcat)} \) (4.5 mg, 16 mol %), \( \text{DavePhos} \) (3.5 mg, 18 mol %), \( \text{BuONa} \) (0.15 mmol, 15 mg). The reaction mixture was refluxed for 24 hrs, cooled to ambient temperature, diluted with \( \text{CH}_2\text{Cl}_2 \) (5 ml), the residue was filtered off, washed with \( \text{CH}_2\text{Cl}_2 \) (5 ml), combined organic fractions were evaporated in vacuo, and chromatographed on silica gel using a gradient of eluents: \( \text{CH}_2\text{Cl}_2 – \text{CH}_2\text{Cl}_2/\text{MeOH} : 1:1 \) – \( \text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3 \text{aq} 100:20:1\)–10:1. The target compound was eluted with \( \text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3 \text{aq} 100:20:3. Yield: 46 mg (49 %), deep-red solid. Mass spectrum (MALDI TOF) \( m/z \): 1236.91 [M]+. \( ^1\text{H} \text{NMR (CDCl}_3, 298 \text{ K}) \): \( \delta \) ppm: -2.45 (2H, br.s), 0.95 (12H, t, \( J = 7.1 \) Hz), 1.31 (4H, quartet, \( J = 5.8 \) Hz), 1.53 (8H, sextet, \( J = 7.2 \) Hz), 1.72 (8H, quintet, \( J = 7.2 \) Hz), 1.96 (4H, quartet, \( J = 6.2 \) Hz), 2.19 (8H, quintet, \( J = 7.2 \) Hz), 2.66 (12H, s), 2.88 (4H, t, \( J = 6.2 \) Hz), 3.03 (4H, t, \( J = 6.3 \) Hz), 3.16 (4H, t, \( J = 4.9 \) Hz), 3.33 (4H, t, \( J = 4.6 \) Hz), 3.37 (4H, t, \( J = 6.3 \) Hz), 3.41–3.67 (12H, m), 3.98 (8H, t, \( J = 7.0 \) Hz), 7.02 (2H, d, \( J = 7.7 \) Hz), 7.27 (2H, s), 7.39 (2H, brd, \( J_{\text{br}} = 6.7 \) Hz), 7.50 (2H, brt, \( J_{\text{br}} = 6.8 \) Hz), 10.21 (2H, s), six NH protons were not assigned.

**Porphyrin 19.** was obtained as the second product in the synthesis of porphyrin 15. Eluent \( \text{CH}_2\text{Cl}_2/\text{MeOH} : 3:1 \). Yield: 7 mg (12 %), deep-red solid. Mass spectrum (MALDI TOF) \( m/z \): 1096.6558 [M]+. \( ^{13}\text{C} \text{NMR (CDCl}_3, 298 \text{ K}) \): \( \delta \) ppm: 14.4 (4C), 14.9 (4C), 22.8 (4C), 32.5 (4C), 33.7 (4C), 40.2 (2C), 42.4 (2C), 96.6 (2C), 111.9 (4C), 118.4 (2C), 131.1 (2C), 133.5 (4C), 136.5 (4C), 141.3 (4C), 142.8 (4C), 145.9 (4C), 148.5 (2C).
worked up in a similar manner as described for compound 28. The
target compound was eluted with CH₂Cl₂/MeOH/NH₃aq 100:35:6–
10:4:1: Yield: 28 mg (15 %), deep-red solid. UV-Vis (CH₂CN) λ nm
(ige): 417 (4.80), 546 (3.45), 578 (3.17). Mass spectrum (MALDI
TOF) m/z: 1707.03 [M⁺]: C₈₁H₆₅N₃O₁₆Zn. 'H NMR (CDCl₃, 298
K) δ ppm: 0.96 (12H, t, J = 7.3 Hz), 1.53 (8H, sextet, J = 7.0 Hz),
1.73 (8H, quintet, J = 6.8 Hz), 2.01 (4H, br.s), 2.18 (8H, quintet,
J = 6.4 Hz), 2.56 (12H, s), 2.70 (8H, br.s), 3.21 (4H, br.s), 3.35–
3.68 (48H, m), 3.94 (8H, t, J = 7.1 Hz), 4.64 (2H, d, J = 5.4 Hz),
6.63 (4H, d, J = 7.0 Hz), 6.93 (4H, d, J = 7.8 Hz), 7.10 (2H,
t = 7.8 Hz), 7.77 (4H, d, J = 7.8 Hz). 10.10 (2H, s), four NH
protons were not assigned. 14.2 (4C), 15.5 (4C), 22.8 (4C), 26.7
(9 mg, 16 mol %), BINAP (11 mg, 18 mol %), absolute dioxane (1 ml) and BuONa (0.3 mmol, 29 mg). The reaction mixture was refluxed for 24 hrs and then worked up in a similar manner as described for compound 28. The target compound was eluted with CH₂Cl₂/MeOH/NH₃aq 100:20:3: Yield:
32 mg (20 %), deep-red solid. Mass spectrum (MALDI TOF) m/z:
1557.04 [M⁺]: C₈₁H₆₅N₃O₁₆. 'H NMR (CDCl₃, 298 K) δ ppm: 0.95
(2H, br.s), 0.95 (12H, t, J = 7.2 Hz), 1.51 (8H, sextet, J = 7.3 Hz),
1.91 (8H, quintet, J = 7.4 Hz), 2.11 (4H, d, J = 7.8 Hz), 2.19
(8H, quintet, J = 7.1 Hz), 2.61 (12H, s), 2.84 (8H, br.s), 3.42 (4H,
t = 6.3 Hz), 3.53 (4H, t, J = 6.1 Hz), 3.64 (36H, br.s), 3.98 (8H,
t = 7.0 Hz), 6.60 (2H, d, J = 7.6 Hz), 6.69 (2H, d, J = 7.1 Hz),
6.86 (2H, br.s), 6.98 (4H, d, J = 8.1 Hz), 7.17 (2H, t, J = 7.7 Hz),
7.79 (4H, d, J = 8.1 Hz), 10.20 (2H, s), four NH protons were not
assigned. 14N NMR (CDCl₃, 298 K) δ ppm: 14.2 (4C), 14.9 (4C),
22.8 (4C), 26.7 (4C), 29.5 (2C), 32.5 (4C), 33.0 (4C), 42.2 (2C),
42.4 (2C), 54.4 (4C), 60.7 (2C), 69.9 (4C), 70.2 (4C), 70.5 (4C),
70.9 (4C), 96.6 (2C), 111.1 (2C), 112.0 (4C), 113.7 (2C), 118.1 (4C),
122.5 (2C), 129.1 (2C), 133.5 (4C), 136.5 (4C), 141.3 (4C), 142.8
(4C), 145.8 (2C), 148.3 (2C), 148.4 (2C), four quaternary carbon
atoms were not assigned.

Conjugate 30. A two-necked flask flushed with dry argon, equipped with a magnetic stirrer and reflux condenser was charged with porphin 9 (0.1 mmol, 96 mg), azacrown derivative 26 (0.2 mmol, 76 mg), Pd(dba)₂ (9 mg, 16 mol %), BINAP (11 mg, 18 mol %), absolute dioxane (1 ml) and BuONa (0.3 mmol, 29 mg). The reaction mixture was refluxed for 24 hrs and then worked up in a similar manner as described for compound 28. The target compound was eluted with CH₂Cl₂/MeOH/NH₃aq 100:20:3: Yield:
32 mg (20 %), deep-red solid. Mass spectrum (MALDI TOF) m/z:
1557.04 [M⁺]: C₈₁H₆₅N₃O₁₆. 'H NMR (CDCl₃, 298 K) δ ppm: 0.95
(2H, br.s), 0.95 (12H, t, J = 7.2 Hz), 1.51 (8H, sextet, J = 7.3 Hz),
1.91 (8H, quintet, J = 7.4 Hz), 2.11 (4H, d, J = 7.8 Hz), 2.19
(8H, quintet, J = 7.1 Hz), 2.61 (12H, s), 2.84 (8H, br.s), 3.42 (4H,
t = 6.3 Hz), 3.53 (4H, t, J = 6.1 Hz), 3.64 (36H, br.s), 3.98 (8H,
t = 7.0 Hz), 6.60 (2H, d, J = 7.6 Hz), 6.69 (2H, d, J = 7.1 Hz),
6.86 (2H, br.s), 6.98 (4H, d, J = 8.1 Hz), 7.17 (2H, t, J = 7.7 Hz),
7.79 (4H, d, J = 8.1 Hz), 10.20 (2H, s), four NH protons were not
assigned. 14N NMR (CDCl₃, 298 K) δ ppm: 14.2 (4C), 14.9 (4C),
22.8 (4C), 26.7 (4C), 29.5 (2C), 32.5 (4C), 33.0 (4C), 42.2 (2C),
42.4 (2C), 54.4 (4C), 60.7 (2C), 69.9 (4C), 70.2 (4C), 70.5 (4C),
70.9 (4C), 96.6 (2C), 111.1 (2C), 112.0 (4C), 113.7 (2C), 118.1 (4C),
122.5 (2C), 129.1 (2C), 133.5 (4C), 136.5 (4C), 141.3 (4C), 142.8
(4C), 145.8 (2C), 148.3 (2C), 148.4 (2C), four quaternary carbon
atoms were not assigned.

Results and Discussion
In the course of our investigation we proposed several approaches to create a combination of the porphin moiety with azacrown ethers. The first route employed the diamine or oxadiamine linker between these two macrocycles, and for this purpose first the amination reactions of meso-
(halogenophenyl)porphyrins 1 and 2 with propane-1,3-diamine (3) and trioxadiamine 4 were studied. Amination of meso(4-bromophenyl)porphyrin 1 taken as its Zn complex was conducted using a standard Pd-catalyzed procedure in the presence of Pd(dba)₂/BINAP system (dba=dibenzylideneacetone, BINAP=2,2′-bis(diphenylphosphino)-1,1′-
binaphthylene). The reaction was carried out using 3 equiv. of the trioxadiamine 4 in boiling dioxane with BuONa as a base and provided 16 % yield of the target derivative 5 (Scheme 1). It should be noted that the same reaction with free porphin was unsuccessful and did not provide the desired coupling product. It is of undoubtful interest that the Cu-catalyzed amination of 3-iodophenyl substituted Zn porphyrinate 2 with excess of propane-1,3-diamine (3) was substantially more successful as it provided ca 50 % yield of the amination product 6. 2-iso-Butyryl)cyclohexanone li-
gand (L) was used in the reaction run in DMF at 110 °C. The amination of the same prophyrrinate 2 with trioxadiamine 4 carried out under similar conditions was less efficient and compound 7 was isolated in 10 % yield (Scheme 1). Having obtained such encouraging results, we have explored the possibility to synthesize a bisporphin compound with trioxadiamine linker between two porphin moieties and reacted 2 equiv. of 2 with trioxadiamine 4 under the catalysis by Cu/L/DMF at 140 °C. However, in this case we have managed to isolate the target compound 8 in trace amounts and it could not be purified from various admixtures. It was detected by MALDI-TOF mass spectrometry (m/z=1560.60 [M⁺]). This result demonstrates, as enough general rule, that N,N'-diarylation of diamines and oxadiamines is often

Scheme 1.
problematic under Cu\(^{+}\) catalysis\(^{34,35}\), what is unlikely for Pd\(^{0}\)-catalyzed diarylation\(^{36,37}\).

Contrary to the amination of 4-bromophenylporphyrin (1), the Pd\(^{0}\)-catalyzed reaction of the free di-meso-(4-bromophenyl)porphyrin (9) with excess of propane-1,3-diamine was quite successful and provided 49% yield of the diamination product 13 (Scheme 2). The attempt to use Cu\(^{+}\) catalysis by reacting zinc di-meso-(4-bromophenyl)porphyrinate 10 with the same amine was unsuccessful as it has given the target diamination product 14 and the product of monoamination 18 only in small amounts in the reaction mixture and they could not be separated from the starting porphyrin 10 by the column chromatography. Compounds 14 and 18 were detected by MALDI-TOF spectra (m/z = 1005.64 and 1011.44 [M+H]\(^{+}\), resp.). Free porphyrin 11 with 3-bromophenyl substituent have reacted with excess of trioxadiamine 4 under Pd\(^{0}\) catalysis conditions and have given the corresponding diamination product 15 in 15% after column chromatography. Also the monoamination product 19 was isolated in 12% yield. A similar reaction with dioctadiamine 12 provided bis(diamino) derivative 16 in a better 30% yield due to easier chromatographic isolation of a less polar compound. The yield of the product of monoamination 20 was 18%. These reactions were conducted in the presence of another ligand DavePhos (2-dimethylamino-2'-dicyclohexylphosphino)biphenyl which promotes diamination of dihalogenoaryl derivatives (m-bromophenyl porphyrin derivative is less active in the catalytic amination than p-bromophenyl derivative). The reaction of Zn porphyrinate 12 with two 4-bromophenyl substituents in the porphyrin core catalyzed by Cu\(^{+}\) proceeded with 18% yield in the reaction mixture.

**Scheme 2.**

![Scheme 2](image_url)

**Figure 1.** Unsuccessful attempts of porphyrin – azacrown ethers conjugation.
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by Cul/L/DMF was inefficient and led to the products of monoamination 21 and 22 (in the latter compound the resting C-Br bond was reduced) obtained as an inseparable mixture in ca 7 % yield \( (m/z=1078.49 \text{ and } 1156.39 \text{ [M]}^+, \text{ resp.}) \), while the target diamination product 18 was isolated in trace amounts and detected using MALDI-TOF mass-spectrometry \( (m/z=1296.79 \text{ [M]}^+) \).

In order to obtain conjugates of azacrown ethers with porphyrins we first tried the Pd\(^0\)-catalyzed coupling of mono- and diaminosubstituted porphyrins 6 and 13 with 3-bromobenzyl substituted azacrown ethers 23 and 24 (Figure 1). However, in all attempts we did not observe the formation of the amination products even in the reaction mixtures and noted the reduction of the C-Br bond in azacrown derivatives. Thus this way of constructing conjugates was abandoned.

Another approach for constructing azacrown-porphyrin conjugates was more successful (Scheme 3). At first amino derivatives of N-benzyl substituted crown ethers 25 and 26 were synthesized by the Pd\(^0\)-catalyzed amination of 3-bromobenzyl substituted precursors according to a previously described procedure.\(^{[33]}\) Then compounds 25 and 26 were introduced in the second catalytic amination reactions with Zn 3-bromophenylporphyrinate 27 and with di-meso-(4-bromophenyl)porphyrins 9 and 10 (free base and Zn complex, resp.). All reactions were enough successful and provided biscmacrocycles 28 or trismacrocycle 29, 30 in comparable 15–20 % yields (Scheme 3). Again it was shown that monophenyl substituted porphyrin could react normally only as its Zn complex 1 while diphenyl derivative provided similar yields of the diamination products both as free base 9 and in the form of the Zn complex 10.

Compounds 28–30 can be viewed as di- or tritopic ligands interesting for the synthesis of heterodi- or heterotrinuclear complexes. In these polymacrocycles the trimethylene diamine linker between porphyrin and azacrown moieties could have been replaced for a longer trioxadiamine fragment which contains several donor atoms. This could have led to the synthesis of pentatopic ligands, unfortunately, all our attempts to change trimethyleneamine linker for trioxadiamine failed. Trioxadiamine derivatives of either meso-phenylporphyrin or N-benzyl azacrown ether would not participate in the Pd\(^0\)-catalyzed coupling reactions similar to those shown in Figure 1 and Scheme 3. They led only to partial reduction of C-Br bonds and formation of complex mixtures of unidentified compounds indicating severe limitations of the process.

The UV-Vis spectrum of conjugate 28 contains a strong Soret band \( (\lambda=409 \text{ nm, } \lg e=5.55) \) and two less intensive Q bands \( (\lambda=539 \text{ nm and } 574 \text{ nm, } \lg e=4.32 \text{ and } 4.13, \text{ respectively}) \). The comparison with the starting zinc porphyrinate 1 shows insignificant bathochromic shifts of all bands by 2–3 nm and a notable increase of the intensity of Q bands.

The fluorescence spectrum of compound 28 possesses two bands of almost equal intensities at 589 and 641 nm. The UV-Vis spectrum of conjugate 29 contains a strong Soret band \( (\lambda=417 \text{ nm, } \lg e=4.80) \) and two less intensive Q bands \( (\lambda=546 \text{ and } 578 \text{ nm, } \lg e=3.45 \text{ and } 3.17, \text{ respectively}) \). The comparison with the starting zinc porphyrinate 10 shows small bathochromic shifts of all bands by 3–6 nm and a small increase of the intensity of the Soret band and one Q band.

The fluorescence spectrum of compound 29 possesses two bands at 594 and 648 nm, the first being more intensive. It is worth noting that the absorption of monophenyl substituted porphyrin 28 in the visible range is substantially stronger than that of di-meso-phenyl substituted porphyrin 29.

We have investigated the dependence of the spectral properties of the compounds 28 and 29 possessing one and two 1-aza-18-crown-6 moieties in their structures on the presence of seventeen metal cations in order to find perspective.
optical chemosensors. For this purpose we have measured UV-Vis and fluorescent spectra of these polymacrocycles in MeCN adding 0.5, 1 and 2.5 equiv. of corresponding metal perchlorates. Excitation of bismacrocycle 28 was carried out at 410 nm, that of trismacrocycle 29 – at 418 nm. As for bismacrocycle 28, no significant changes in its electronic and fluorescent spectra could be noted for the majority of metals except for CuII which led to a partial decrease of the intensity of the absorption peak at 409 nm (Figure 1S) and produced two-fold quenching of the emission intensity (Figure 2S). PbII has also caused notable quenching of fluorescence, other metals have changed it insignificantly. The maxima of absorption and emission bands did not change in all cases studied. We have investigated the dependence of the electronic and fluorescent spectra of bismacrocycle 28 on the amount of copper perchlorate added. In the UV-Vis spectra one can observe gradual weakening of the absorption maximum at 409 nm up to 10 equiv. of CuII added, its further attenuation together with bathochromic shift to 425 nm occurred in the presence of 20–30 equiv. of CuII salt (Figure 3S). Fluorescence was quenched gradually without any shift of two maxima at 589 and 641 nm, and with 30 equiv. of Cu(ClO4)2 it was almost fully quenched (Figure 4S).

The addition of 2.5 equiv. of different metal perchlorates to the solution of trismacrocycle 29 did not result in significant changes in its absorption and emission spectra (Figures 5S and 6S), except for Cu(ClO4)2 which dramatically decreased the intensity of absorption and led to a bathochromic shift of its maximum (from 417 to 432 nm, Figure 3S). The quenching of emission with CuII was almost total (Figure 6S) while PbII has decreased it only by 25 %, and the ligand was quite insensitive for other metal cations. It is interesting that the addition of 0.5 and 1 equiv. of CuII gradually decreased the absorption (Figure 2), however, it did not result in the shift of the absorption maximum both of Soret and Q bands. The addition of the second equivalent has given rise to above mentioned bathochromic shift of the Soret band and simultaneously the Q band almost totally disappeared. Also, upon the addition of 0.5 and 1 equiv. of CuII emission gradually decreased (ca 2 and 6 times, resp.), but with the second equivalent it was fully quenched (Figure 3). These facts might be explained by the formation of a non-emissive dicopper complex with trismacrocycle 29 possessing two azacrown fragments each capable of complexing with one CuII cation.

Special experiments have been undertaken to verify cross-selectivity of the ligand 29 towards CuII using NaI, KI, MgII, CaII, BaII, ZnII, PbII and HgII perchlorates which can be viewed as the most expected interfering ions. The UV-Vis and fluorescence spectra in all cases were absolutely the same as in the presence of sole copper perchlorate (weak maximum at 432 nm and no emission). We have evaluated the detection limits of CuII ions by the ligand 29 and found out that it was 1.2 mM by UV spectrophotometer and 0.23 mM by spectrofluorimeter. These figures are among the best judging by the analysis of the literature data. Indeed, there are several recently developed fluorimetric chemosensors for copper which provided detection at 1–10 mM level, [38-42] while there is only one sensor based on thiacalix[4]crown ether with two pyrene fluorophores able to detect 40 nm concentration of CuII. [43] It should be also noted that there is a plenty of colorimetric detectors of copper ions, [44-51] however, their detection limits are not as low, moreover, some of them are indeed not chemosensors but rather molecular probes as they sense also other cations like HgII or FeIII. Thus conjugate 29 can be proposed as a perspective two-channel fluorimetric and colorimetric chemosensor for CuII ions.
Conclusions

To sum up, we have showed the possibility to decorate porphyrins with diamine and oxadiamide podands via Pd⁰ and Cu¹-catalyzed amination reactions, however, the palladium catalysis proved to be more universal. Pd⁰-catalyzed amination was applied to the synthesis of bis- and trismacrocyclic conjugates of porphyrin with azacrown ethers using trimethylenediamine linkers. This target can be achieved using only one approach, i.e. combining meso-(bromophenyl) substituted porphyrins with aminobenzyl derivatives of azacrown ethers. All these compounds can be used as polytopic ligands in the synthesis of polynuclear metal complexes. The properties of two compounds, bismacrocycle 28 and trismacrocycle 29, to perform as colorimetric and fluorescent sensors for metal cations were investigated, and ligand 29 possessing two 1-aza-18-crown-6 moieties arranged symmetrically around the porphyrin core was found to be enough selective for Cu²⁺ in the presence of other metals by strong emission quenching caused by copper ions.

Acknowledgements. This work was financially supported by the RFBR grant 13-03-00813.

References


Received 07.12.2015
Accepted 16.02.2016