Porphyrin–Containing Polymacrocycles: Synthesis and Evaluation as Fluorescent Detectors of Metal Cations

Alexei A. Yakushev, a Alexei D. Averin, a,b@ Olga A. Maloshitskaya, b Oskar I. Koifman, c Sergei A. Syrbu, d and Irina P. Beletskaya a,b

a A.N. Frumkin Institute of Physical Chemistry and Electrochemistry RAS, 119991 Moscow, Russia
b Lomonosov Moscow State University, Department of Chemistry, 119991 Moscow, Russia
c Ivanovo State University of Chemistry and Technology, 153000 Ivanovo, Russia
d G.A. Krestov Institute of Solution Chemistry RAS, 153045 Ivanovo, Russia
@ Corresponding author E-mail: alexaveron@yandex.ru

Using Pd(0)-catalyzed amination reaction of zinc 5,15-bis(4-bromophenyl)porphyrinate with diazatrimacrocyclo – derivative of 3,3’-disubstituted biphenyl – a series of polymacrocyclic compounds was obtained. The investigation of their fluorescence in the presence of 18 metal cations revealed that two of them can act as molecular probes for Cu(II), Al(III) and Cr(III) by the fluorescence quenching. Tri- and tetramacrocyclic compounds of another structure were synthesized by the Pd(0)-catalyzed arylation of cryptands comprising central diazacrown ether moieties using zinc 5-(4-bromophenyl)porphyrinate. One of these compounds was characterized as a fluorescent chemosensor for Cu(II).

Keywords: Porphyrins, diazacrown ethers, polymacrocycles, Pd catalysis, amination, fluorescence, detection.

Porфирины – содержащие полимакроциклы: синтез и оценка в качестве флуоресцентных детекторов катионов металлов

А. А. Якушев, А. Д. Аверин, О. А. Малошицкая, О. И. Койфман, С. А. Сырбу, И. П. Белецкая

Порфирины, диазакраун-эфиры, полимакроциклы, Pd каталит, аминация, флуоресценция, детектирование.

С использованием Pd(0)-катализируемой реакции аминирования цинкового комплекса 5,15-бис(4-бромфенил)порофирин с диазатриоксамакроциклом – производным 3,3’-дизамещенного бифенила – получена серия полимакроциклических соединений. Исследование их флуоресценции в присутствии катионов 18 металлов показало, что два из них могут выступать в качестве молекулярных проб на катионы Cu(II), Al(III) и Cr(III) за счет тушения флуоресценции. Три- и тетрамакроциклические соединения другого строения синтезированы Pd(0)-катализируемым ампирированием криптандов, содержащих центральный фрагмент диазакраун-эфира с использованием цинкового комплекса 5-(4-бромфенил)порофирин. Одно из этих соединений охарактеризовано как флуоресцентный хемосенсор на катионы Cu(II).

Ключевые слова: Порфирины, диазакраун-эфиры, полимакроциклы, Pd катализ, аминирование, флуоресценция, детектирование.
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Introduction

Catalytic approaches to polymericacyclic compounds based on porphyrins are well documented. The vast majority of such molecules are porphyrin dyads, triads and parent compounds, while the conjugates with other nitrogen-containing macrocycles are still enough rare. The synthesis of directly meso-meso-linked porphyrins without any spacer can be achieved via Ni(II)-catalyzed oxidative coupling of meso-bromoporphyrins[3] or using Suzuki coupling[2,3]. The chemistry of porphyrin oligomers built using various aromatic, heteroaromatic or other unsaturated linkers is much more explored as they can bring additional structural and physicochemical properties to a molecule. For this purpose Suzuki,[4-6] Stille,[7,8] Heck,[9] and Sonogashira[10,11] couplings were successfully applied. Triazolyl linker can be easily introduced in the porphyrin dyads and triads by epy so-called click reactions,[12-14] and the application of Buchwald-Hartwig amination reactions was reported for the synthesis of bisporphyrin compounds in which two macroheterocycles were linked with a simple NH fragment.[15] While porphyrins possess by a similar approach in which diamines or diazacrown ether moieties served as linkers.[16,17] While porphyrins possess extremely interesting photophysical properties together with their unique binding of metal cations, they have not yet become a widespread platform for creating colorimetric or fluorometric chemosensors. The examples are still scarce, to mention the porphyrin-terpyridine conjugate which can detect Cd(II) with moderate selectivity,[18] tetrafluorometer in acetonitrile (UHPLC grade).

Experim ental

NMR spectra were registered using Bruker Avance 400 spectrometer, MALDI-TOF spectra were obtained with Bruker Autoflex II spectrometer using 1,8,9-trihydroxyanthracene as matrix and PEGs as internal standards. UV-Vis spectra were recorded with Agilent Cary 60 spectrophotometer in MeCN, spectra of fluorescence were obtained with Hitachi 2700 spectrofluorometer in acetonitrile (UHPLC grade). Rac-BINAP and DavePhos ligands, sodium tert-butoxide, were purchased from Sigma-Aldrich Co and used without further purification, Pd(dba)2 was synthesized according to the method described.[20] Macrocycles 3 was obtained according to the described method,[20] macrobicycles 12-14 were synthesized according to a published procedure,[20] zinc porphyrinates 4, 15 and 18 were obtained by method described in ret.[26] Column chromatography was carried out using silica gel 40–63 μm (Fluka). Acetonitrile of UHPLC grade was used without additional purification, dioxane was successively distilled over NaOH and sodium. Dichloromethane was distilled over CaH2, methanol was used freshly distilled.

Method for the synthesis of polymacrocycles 5, 8, 16, 17, 19. A two-neck flask equipped with a magnetic stirrer and reflux condenser, flushed with dry argon, was charged with corresponding amounts of Pd(dba)2, DavePhos, zinc porphyrinates 4 or 18, macrocyclic compound 3 or cryptands 12-14, absolute dioxane and sodium tert-butoxide. The reaction mixture was stirred under reflux for 24h, cooled down to ambient temperature, the residue was filtered off, washed with CH2Cl2 (3 ml), the combined organic fractions were evaporated in vacuo and the residue was chromatographed on silica gel using a sequence of eluents: CH2Cl2, CH2Cl2–MeOH 500:1 – 3:1.

Trisporphyrin compound 5. Obtained from zinc porphyrinate 4 (0.1 mmol, 102 mg), macrocycle 3 (0.2 mmol, 74 mg) in the presence of Pd(dba)2, (16 mol %, 9 mg), DavePhos, (18 mol %, 7 mg), BuONa (0.3 mmol, 29 mg) in 2 ml dioxane. Eluent: CH2Cl2–MeOH 100:1. Yield 14 mg (9 %), dark-red crystalline powder. M.p. 195–200 °C. m/z (MALDI-TOF) found: 1596.0969. C50H43N3O4Zn requires 1596.9395 [M]+. UV-Vis (CH3CN) λmax (nm) of: 416 (5.29). H NMR (CD3CN, 298 K) δ ppm: 1.00 t (12H, J = 7.3 Hz), 1.54–1.61 (12H), 1.78 quintet (8H, J = 7.4 Hz), 2.17–2.26 m (12H), 2.63 s (12H), 3.24 brzt (4H, J1 = 4.7 Hz), 3.31 (2H, J = 3.3–3.63 m (16H), 3.67 brt (4H, J1 = 4.9 Hz), 4.00 brs (8H), 4.21 t (4H, J = 6.1 Hz), 5.70 brs (2H), 6.12 brs (2H), 6.90 d (2H, J = 7.2 Hz), 7.00 (2H, J = 7.1 Hz), 7.16 d (2H, J = 7.3 Hz), 7.28 d (2H, J = 8.5 Hz), 7.36–7.43 m (8H), 7.87 d (4H, J = 7.6 Hz), 10.14 s (2H) (NH protons were not assigned). 13C NMR (CD3CN, 298 K) δ ppm: 14.2 (4C), 15.4 (4C), 22.9 (4C), 26.9 (4C), 27.8 (2C), 32.7 (4C), 33.2 (4C), 42.9 (2C), 49.1 (2C), 68.5 (2C), 70.5 (8H), 4.21 t (4H, J = 6.1 Hz), 5.70 brs (2H), 6.12 brs (2H), 6.90 d (2H, J = 7.2 Hz), 7.00 (2H, J = 7.1 Hz), 7.16 d (2H, J = 7.3 Hz), 7.28 d (2H, J = 8.5 Hz), 7.36–7.43 m (8H), 7.87 d (4H, J = 7.6 Hz), 10.14 s (2H) (NH protons were not assigned). 15C NMR (CD3CN, 298 K) δ ppm: 135–140 (C).
**Results and Discussion**

At the first stage of our research we synthesized the macrocycle 3,3'-disubstituted biphenyl and tetradiamidoxane motifs. The synthesis was carried out according to a known procedure,[24] starting from 3,3'-dibromobiphenyl (1) and linear tetradiamidoxane 2, in the presence of a standard catalytic system Pd(dba)/BINAP (dba=dienezildieneacetone, BINAP=2,2'-bist(diethyolphosphino)-1,1’-binaphthalen). The target coupling was isolated in 40 % yield and introduced in the second catalytic reaction with zinc 5,15-di(4-bromophenyl)porphyrinate 4 (Scheme 1). This coupling was conducted using DavePhos phosphine ligand (DavePhos=2-(dicyclohexylphosphino)-2,2'-dimethylamino-phenyl) as a special experiment revealed the superiority of this donor ligand over more conventional BINAP in the arylation of the secondary amino groups with bromophenyl porphyrinates. It was also important to use Zn(II) complex as free porphyrins often failed to give desired products in similar arylation reactions. The ratio of the starting compounds 3 and 4 was taken as 2:1, as a result we obtained a series of polymacrocycles: the expected trimacrocycles 5,15-di(4-bromophenyl)porphyrinate and oligomeric tetracyclic and pentacyclic compounds and porphyrin, the product of monoamination 6, and oligomeric tetraacyclic and pentacyclic compounds 7 and 8 (Scheme 1). Compounds 6 and 7 were formed in the result of the catalytic amination and catalytic reduction of the C-Br bonds. The isolated yields of all these compounds were small and ranged from 9 to 16 %. The isolation of individual products by chromatography on silica gel was quite tedious and obviously oligomers with higher molecular masses were not obtained in individual state.

Another structural type of porphyrin-containing polymacrocycles is based on the cryptand-like derivatives of diazacycrown ethers 12-14. These compounds were obtained by a previously described method[25] in sufficient yields (24–38 %) (Scheme 2), they differ by the size of the central diazacycrown moiety as well as by the nature of the trioxadiazole linker and substitution pattern in the benzyl spacers. Cryptands 12 and 13 were introduced in the Pd(0)-catalyzed diylation reaction with zinc 5-(4-bromophenyl)porphyrinate 15 (2 equiv) using the same catalytic system.

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Pd(dba)/DavePhos as in the previous case. As the number of reaction centers decreased in these processes, the target tetramacrocyclic products of diarylation 16 and 17 were isolated in fairly better yields (23 and 20 %, respectively) (Scheme 2). It is interesting that in the case of the reaction of zinc porphyrinate 15 with the cryptand 12 BINAP was found to be also efficient for the coupling.

Next we explored the possibility to introduce an isomeric zinc 5-(3-bromophenyl)porphyrinate 18 in the similar reaction with the cryptand 14 (Scheme 3). Porphyrin derivative 18 possesses less active bromine atom compared to its isomer 15 in which bromine is situated in para-position to a strong electron-withdrawing porphyrin unit. As expected, the reaction with less reactive zinc porphyrinate 18 resulted in a lower yield of the desired bisporphyrin tetramacrocycle 19 (11 %) while the product of monoarylation, i.e. trimacrocycle 20 was obtained in 16 % yield (Scheme 3).

We investigated the possibilities of polymacrocyclic compounds to act as fluorescent chemosensors for metal cations. In the course of investigation UV-Vis and fluorescent spectra of the polymacrocycles 5, 6, 17 and 20 were recorded in MeCN in the presence of 1, 2, 5 equiv. (in some cases also 10, 20, 30 equiv.) of corresponding metal perchlorates: Li(I), Na(I), K(I), Mg(II), Ca(II), Ba(II), Al(III), Mn(II), Fe(II), Co(II), Ni(II), Cr(III), Cu(II), Zn(II), Cd(II), Hg(II), Ag(I), Pb(II). It was found out that the bismacrocylic compound 6 could serve as the fluorescent molecular probe for Cu(II), Al(III) and Cr(III) cations because the addition of only these metals led to full quenching of emission (Figure S1). To achieve this full quenching, one needs 2 equiv. of Al(III) (Figure S2), 5 equiv.
of Cr(III) (Figure S3) or only 1 equiv. of Cu(II). We carried out both UV-Vis and fluorescent titrations (Figures S4, S5) and calculated the stability constants of two complexes with Cr(III): for (6)∙Cr(III) complex \( \lg K = 6.20 \pm 0.10 \) and for (6)∙2Cr(III) \( \lg K = 12.25 \pm 0.07 \). In UV-Vis spectra Cr(III) and Al(III) caused insignificant decrease in the intensity of the absorption band with bathochromic shift by 12 nm while the addition of Cu(II) salt led to a disappearance of this absorption band.

Emission of the \textit{tris}macrocyle 5 with one central porphyrin and two peripheral diazatrioxamacrocycles is less susceptible to the addition of Cr(III) as only 10 equiv. led to full quenching (Figure S6). However, Cu(II) and Al(III) quench emission efficiently (Figure S7), thus this molecule can be also regarded as a molecular probe for these three cations. The effect of the metal cations on the UV-Vis spectra are quite similar to that of compound 6 (Figure S8).
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Tetramacrocyclic ligand 17 can be seen as a chemosensor for Cu(II) cations as only this metal fully quenches its emission upon addition of 10 equiv. (Figures S9, S10). Moreover, this detector is characterized by a low detection limit (0.23 µM). The stability constant of the complex (17)·Cu(II) was found to be equal $K_{\text{s}} = 5.15 \pm 0.04$ by fluorimetric titration. *Tris*macrocyclic compound 20 which includes only one porphyrin structural unit and possesses a slightly shorter trioxadiamine linker though selectively responses for Cu(II) cations, is less efficient in detecting this metal as its emission diminishes only 2.5 times after the addition of 15 equiv. of this metal (Figures S11, S12). This fact implies the necessity of fine tuning of the polymeric structures for increasing selectivity and sensitivity of the detector. In UV-Vis spectra of polymacrocycles 17 and 20 the decrease in the intensity of the absorption maxima upon addition of Cu(II) cations without notable shift was observed (Figures S13, S14).

Conclusions

To sum up, our research revealed the possibility to construct polymacrocyclic compounds incorporating porphyrin and oxazamacrocyclic structural units using Pd(0)-catalyzed amination reactions. They were tested as potential fluorimetric detectors of metal cations and the strong dependence of the emission quenching in the presence of certain cations on the type and number of macrocycles attached to porphyrin units was firmly established. Two of them (monoporphyrin-based bis- and *tris*macrocycles 5 and 6) were found to be prospective fluorescent detectors for Al(III), Cr(III) and Cu(II) while tetramacrocyclic bisporphyrin derivative 17 can serve as the fluorimetric chemosensor for Cu(II).

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