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Phthalocyanines and Related Compounds: XLII.[1] Synthesis of Phenyl-Substituted Tetraazachlorins and Tetraazabacteriochlorins

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Abstract — New oxidation-resistant hexaphenyl-substituted tetramethyltetraazachlorin, its nickel complex, and tetraphenyl-substituted octamethyltetraazabacteriochlorin and octamethyltetraazaisobacteriochlorin nickel complexes were synthesized for the first time by mixed condensation of diphenylmaleonitrile with tetramethylsuccinonitrile in the presence of lithium dimethylaminoethoxide or nickel chloride. The products were characterized by electronic absorption, ^{1}H NMR, and mass spectra. Mixed condensation of diphenylsuccinonitrile with phthalonitrile in the presence of nickel chloride was found to give nickel complexes of phenyl-substituted benzo-fused tetraazaporphyrins rather than their hydrogenated derivatives.
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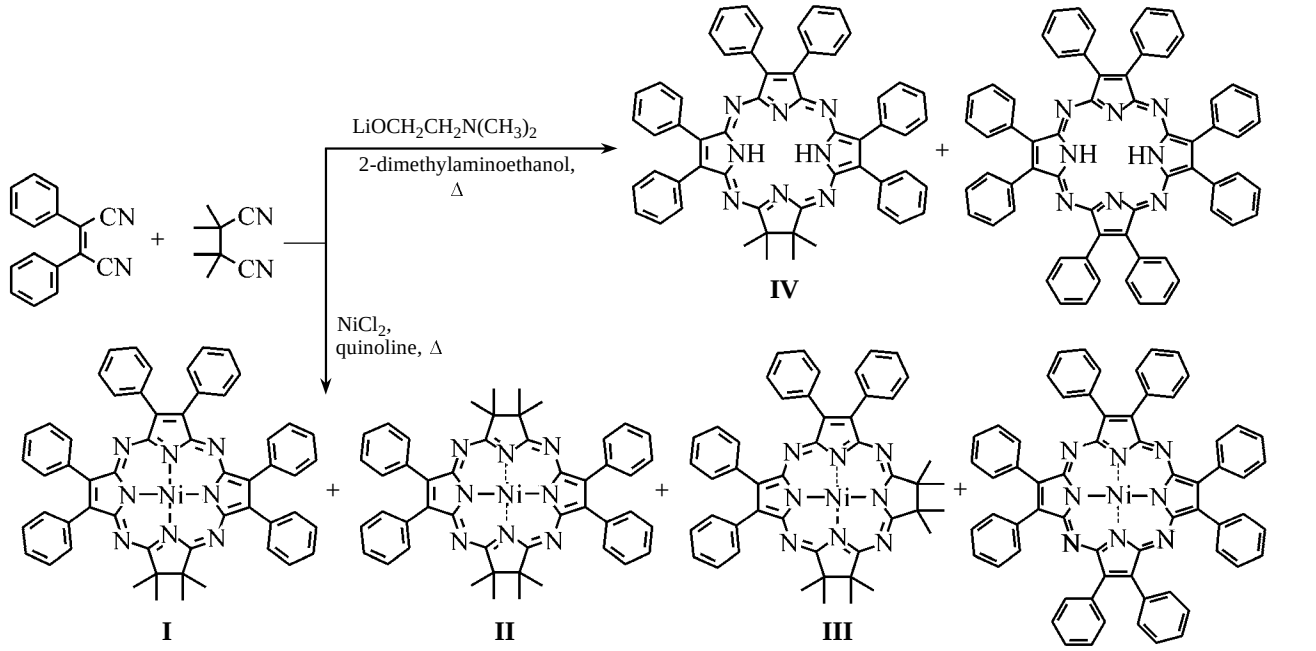
Tetraazachlorins, tetraazabacteriochlorins, and tetraazaisobacteriochlorins are derivatives of 5,10,15,20-tetraazaporphyrin hydrogenated at one or two quasi-isolated double bonds in the neighboring or opposite pyrrole fragments of the macroring. These compounds attract a considerable interest from both theoretical and practical viewpoints as a new class of so-called "functional" dyes, i.e. dyes for nontraditional applications, in particular as second-generation photosensitizers for photodynamic therapy of cancer due to their strong absorption in the "therapic window" (red and near IR region spectral region). Unlike their analogs of the porphyrin series, chlorins, bacteriochlorins, and isobacteriochlorins whose synthesis and properties were the subjects of numerous studies, the title compounds remained so far almost not studied, and no data on their synthesis were available. As a result of our studies performed in the recent years, we have developed methods for synthesis of partially hydrogenated tetraazaporphyrin derivatives. One of these methods is based on [4+2]-[2, 3] and 1,3-cycloaddition [4] at the quasiisolated double bonds in a tetraazaporphyrin molecule, by analogy with the synthesis of partially hydrogenated porphyrins [5]. An alternative method implies mixed condensation of phthalogens with different degrees of saturation. We were the first to use in these syntheses tetramethylsuccinonitrile which is a vicinal aliphatic 1,2-dinitrile with the cyano groups attached to quaternary carbon atoms. By mixed condensation of aromatic *ortho*-dicarboxylic acid derivatives (dinitriles, anhydrides, and imides) with tetramethylsuccinonitrile in the presence of metal salts or lithium alkoxides were obtained previously unknown linearly fused 2,3-naphthotetraazachlorins, -tetraazabacteriochlorins, and -tetraazaisobacteriochlorins, as well as angularly fused 1,2-naphtho isomers [6–9]. Studies on photophysical properties of the newly synthesized compounds [10–13] showed that they may be interesting from the viewpoint of practical applications.

In the present work we made an attempt to synthesize new partially hydrogenated tetraazaporphyrin derivatives by mixed condensation of diphenylmaleonitrile with tetramethylsuccinonitrile. The reaction of equimolar amounts of these compounds in boiling quinoline in the presence of nickel(II) chloride and a catalytic amount of ammonium molybdate gave hexaphenyltetramethyltetraazachlorin nickel complex **I** in 12.3% yield; in addition, (octaphenyltetraazaporphyrinato)nickel(II) was formed. Molecule **I** contains two quaternary carbon atoms attached to methyl groups which deviate from the macroring plane; therefore, compound **I** is readily soluble in common organic solvents, and it can readily be separated from (octaphenyltetraazaporphyrinato)nickel(II) by extraction

[1] For communication XLI, see [1].

with chloroform, followed by chromatographic purification on silica gel. It should be noted that the reaction mixture also contained small amounts of tetraphenyloctamethyltetraazabacteriochlorin **II** and tetraphenyloctamethyltetraazaisobacteriochlorin **III** nickel complexes which were detected by spectral methods. When the molar ratio of the initial nitriles was raised to 1 : 3, the yields of the latter increased to 4.1 and 3.9%, respectively, while the yield of chlorin **I** reached 32.2%. As in the condensation of tetramethylsuccinonitrile with phthalonitrile described previously [8], further raising the tetramethylsuccinonitrile-to-diphenylmaleonitrile molar ratio variation of the reaction time or temperature did not increase the yield of compounds **II** and **III**. The presence of geminal methyl groups in the macroring of the obtained compounds improves their solubility in common organic solvents and hampers their oxidation to the corresponding tetraazaporphyrin derivatives; therefore, they can be separated and purified by chromatography on silica gel. Metal-free hexaphenyltetramethyltetraazachlorin (**IV**) was formed in 3.8% yield in the reaction of diphenylmaleonitrile with tetramethylsuccinonitrile at a molar ratio of 2 : 3 in boiling dimethylaminoethanol in the presence of lithium dimethylaminoethoxide (reaction time 4 h).

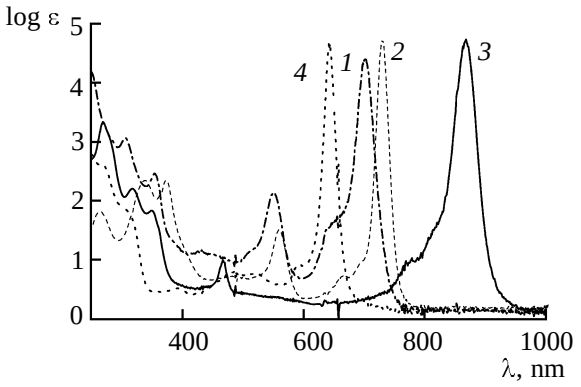


The structure of the isolated compounds was determined on the basis of their elemental compositions and ^{1}H NMR and mass spectra. The ^{1}H NMR spectrum of chlorin **I** contained a singlet in the aliphatic region at δ 1.79 ppm from the methyl protons, and in the aromatic region we observed two multiplets at δ 7.25–7.59 (*p*-H, *m*-H) and 8.0–8.06 ppm (*o*-H) from the phenyl groups. The signal intensity ratio was 2 : 3 : 2, which is consistent with the structure of chlorin **I**. The two other nickel complexes were assigned the structure with two saturated C–C bonds in the neighboring (isobacteriochlorin **III**) or opposite (bacteriochlorin **II**) pyrrole rings on the basis of their electronic absorption spectra and ^{1}H NMR data. The aliphatic region of the ^{1}H NMR spectrum of bacteriochlorin **II** contained one signal at δ 1.59 ppm from methyl protons, while isobacteriochlorin **III** displayed two signals at δ 1.47 and 1.50 ppm, indicating magnetic nonequivalence of the corresponding methyl groups in molecule **III**. The aromatic regions of the ^{1}H NMR spectra of both compounds showed no appreciable differences. Bacteriochlorin **II** displayed two multiplets at δ 7.25–7.55 (*p*-H, *m*-H) and 8.01–8.05 ppm (*o*-H), and in the spectrum of compound **III** we observed two multiplets at δ 7.25–7.46 (*p*-H, *m*-H) and 7.77–7.81 ppm (*o*-H). The signal intensity ratios were 6 : 3 : 2 for the three signals of bacteriochlorin **II** and 3 : 3 : 3 : 2 for the four signals of isobacteriochlorin **III**; these data are very consistent with the assumed structures.

The electronic absorption spectra of compounds

I–**IV** in organic solvents were examined in the range from 250 to 1000 nm. As expected, all these compounds are characterized by strong absorption in the red and near IR regions (see figure). Metal-free chlorin **IV** displayed a strong long-wave *Q* band which was split into two components with different intensities: Q_1, λ_{max} 727 nm; Q_2, λ_{max} 557 nm. Thus hydrogenation of the β-carbon atoms in one pyrrole fragment of the octaphenyltetraazaporphyrin molecule (λ_{max} 666, 600 nm [14]) leads to a red shift of the long-wave Q_1 band (by 60 nm) and blue shift of the Q_2 band (by 45 nm). The *Q* band in the spectra of nickel complexes **I** and **II** is also split into two components (unlike metal complexes of octaphenyltetraazaporphyrin) due to reduction of the molecular symmetry from D_{4h} to C_{2v} and D_{2h} as a result of hydrogenation of one or two opposite pyrrole fragments, respectively. The Q_1 band has its maximum at λ 701 nm for complex **I** and at λ 866 nm for complex **II**. Less intense Q_2 band is located at λ 550 and 467 nm, respectively, and its intensity decreases in going from tetraazachlorin **I** to tetraazabacteriochlorin **II**. The Q_1/Q_2 intensity ratio is 1.7 for compound **I** and 4.8 for bacteriochlorin **II**. The magnitude of Q_1/Q_2 splitting for bacteriochlorin **II** is 9866 cm^{-1}, which is twice as large as the corresponding parameter for chlorin **I** (4763 cm^{-1}). In the electronic absorption spectrum of isobacteriochlorin **III** which (like chlorin **I** has a C_{2v} symmetry) we observed no splitting of the *Q* band (λ_{max} 642 nm). An analogous spectral pattern was typical of other tetraazaisobacteriochlorin derivatives which were studied previously [3, 8, 9] (the results of quantum-chemical calculations, magnetic circular dichroism spectra, and band resolution procedure revealed a low-intense Q_2 band for these derivatives). In the short-wave region of the electronic absorption spectra of compounds **I**–**IV**, a *B* band with a lower intensity was present; this band is related to the Soret band in the series of porphyrin, and its position and intensity did not change to an appreciable extent in going from tetraazaporphyrin to tetraazachlorin and tetraazabacteriochlorin.

We also made an attempt to synthesize partially hydrogenated tetraazaporphyrin derivatives having phenyl substituents at the sp^3-carbon atoms. As shown previously [15, 16], the reaction of pyrrolidine-2,5-diimine with isoindole-1,3-diimine or 4-*tert*-butylisoindole-1,3-diimine leads to the formation of benzofused tetraazaporphyrins. We performed mixed condensation of diphenylsuccinonitrile as a saturated component with phthalonitrile. However, the reaction between these compounds taken at a ratio of 1:1 to 2:1 in the presence of $NiCl_2$ and a catalytic amount of ammonium molybdate (boiling quinoline, 1 h,



Electronic absorption spectra of compounds (*1*) **I**, (*2*) **IV**, (*3*) **II**, and (*4*) **III** in chloroform.

argon atmosphere) gave a mixture of phenyl-substituted benzo-fused tetraazaporphyrin nickel complexes instead of the expected hydrogenated derivatives. Unfortunately, we failed to separate the products by column chromatography because of their poor solubility in common organic solvents. A small amount of that mixture was separated by thin-layer chromatography on Silufol UV-254 plates (toluene–chloroform, 2:1). We thus isolated four fractions; on the basis of the mass and electronic absorption spectra and taking into account published data for phenyl-substituted benzofused tetraazaporphyrin palladium complexes [17], these fractions were identified as nickel complexes of hexaphenylbenzotetraazaporphyrin (λ_{max} 655, 613 nm), tetraphenyldibenzotetraazaporphyrin with oppositely arranged benzene rings (λ_{max} 693, 592 nm), its isomer with neighboring benzene rings (λ_{max} 638 nm), and diphenyltribenzotetraazaporphyrin (λ_{max} 673, 630 nm). In the electronic absorption spectrum of the reaction mixture we observed an absorption band with its maximum at λ 727 nm, which is likely to belong to intermediately formed diphenyltribenzotetraazachlorin; however, no such band was detected after chromatographic separation. We can conclude that benzo-fused derivatives of tetraazachlorin and tetraazabacteriochlorin are less stable to oxidation than unsubstituted tetraazachlorin [18] and dibenzobarrelenosubstituted analogs [2]; the reasons are extension of the macroring π system due to fusion of benzene rings and the presence of hydrogen atoms at the sp^3-carbon atoms (unlike oxidation-resistant exhaustively methylated analogs) [6–8].

EXPERIMENTAL

The electronic absorption spectra were measured on a Hewlett–Packard 8453 spectrophotometer using 10-mm rectangular quartz cells; solutions with a

concentration of about ~10^{-5} M were examined. The ^{1}H NMR spectra were recorded on a Bruker WM-250 instrument (250.13 MHz) from solutions in $CDCl_3$. The mass spectra were obtained on a Finnigan-LCQ/Electrospray spectrometer.

2,3-Diphenylmaleonitrile [14], 2,3-diphenylsuccinonitrile [19], and tetramethylsuccinonitrile [20] were synthesized by known methods.

(2,2,3,3-Tetramethyl-7,8,12,13,17,18-hexaphenyltetraazachlorinato)nickel(II) (I), (2,2,3,3,12,12,13,13-octamethyl-7,8,17,18-tetraphenyltetraazabacteriochlorinato)nickel(II) (II), and 2,2,3,3,7,7,8,8-octamethyl-12,13,17,18-tetraphenyltetraazaisobacteriochlorinato)nickel(II) (III). *a*. Nitrile molar ratio 1 : 1. A mixture of 0.490 g of tetramethylsuccinonitrile, 0.820 g of diphenylmaleonitrile, 0.470 g of anhydrous $NiCl_2$, and 0.003 g of ammonium molybdate in 5 ml of quinoline was heated for 3 h at the boiling point under stirring. The mixture was cooled and diluted with 50% aqueous acetone, and the precipitate was filtered off, washed with 50% aqueous acetone and water and dried in air. The product was thoroughly ground and extracted with chloroform, and the extract was subjected to chromatography on silica gel using hexane–chloroform (1 : 1) as eluent. A lilac fraction (R_f 0.35, Silufol UV-254, hexane–chloroform, 1 : 1) was collected; removal of the solvent gave 0.129 g (12.3%) of compound **I**. Electronic absorption spectrum ($CHCl_3$), λ_{max}, nm ($\log\varepsilon$): 701 (4.80), 645 sh (4.28), 550 (4.44), 355 (4.48), 306 (4.59). ^{1}H NMR spectrum, δ, ppm: 1.70 s (12H, Me), 7.25–7.59 m (18H, *p*-H, *m*-H), 8.01–8.06 m (12H, *o*-H). Found, %: C 76.76, 76.57; H 5.11, 5.33; N 12.67, 12.55. $C_{56}H_{42}N_8Ni$. Calculated, %: C 75.94; H 4.78; N 12.65.

b. Nitrile molar ratio 1 : 3. A mixture of 0.490 g of tetramethylsuccinonitrile, 0.276 g of diphenylmaleonitrile, 0.470 g of anhydrous $NiCl_2$, and 0.003 g of ammonium molybdate in 5 ml of quinoline was heated for 3 h at the boiling point under stirring. The mixture was then treated as described above in *a*. Three fractions were collected. The first fraction (green–brown, R_f 0.51, Silufol UV-254, hexane–chloroform, 1 : 1) contained 0.018 g (4.1%) of compound **II**. The second fraction (blue, R_f 0.37, Silufol UV-254, hexane–chloroform, 1 : 1) contained 0.017 g (3.9%) of compound **III** which was isolated by repeated chromatography on silica gel using hexane–chloroform (1 : 1) as eluent. The third fraction (lilac, R_f 0.35, Silufol UV-254, hexane–chloroform, 1 : 1) contained 0.144 g (32.2%) of compound **I**.

Tetraazabacteriochlorin II. Electronic absorption spectrum ($CHCl_3$), λ_{max}, nm ($\log\varepsilon$): 866 (4.75), 811 sh (4.22), 775 sh (4.05), 467 (4.04), 350 (4.31), 317 (4.39). ^{1}H NMR spectrum, δ, ppm: 1.59 s (24H, Me), 7.25–7.55 m (12H, *p*-H, *m*-H), 8.0–8.05 m (8H, *o*-H). Found, %: C 71.99, 72.15; H 5.80, 5.79; N 14.03, 13.96. $C_{48}H_{44}N_8Ni$. Calculated, %: C 72.83; H 5.60; N 14.15.

Tetraazaisobacteriochlorin III. Electronic absorption spectrum (CHCl3), λ_{max}, nm ($\log\varepsilon$): 642 (4.92), 594 sh (4.24), 520 (4.15), 486 (4.16), 312 (4.53). ^{1}H NMR spectrum, δ, ppm: 1.47 s (12H, Me), 1.50 s (12H, Me), 7.25–7.46 m (12H, *p*-H, *m*-H), 7.77–7.81 m (8H, *o*-H). Found, %: C 73.13, 72.98; H 5.56, 5.83; N 13.25, 13.38. $C_{48}H_{44}N_8Ni$. Calculated, %: C 72.83; H 5.60; N 14.15.

2,2,3,3-Tetramethyl-7,8,12,13,17,18-hexaphenyltetraazachlorin (IV). Metallic lithium, 0.010 g, was dissolved on heating in 20 ml of 2-dimethylaminoethanol, the solution was cooled to room temperature, and a mixture of 0.820 g of diphenylmaleonitrile and 0.490 g of tetramethylsuccinonitrile was added. The mixture was slowly heated to the boiling point under stirring, and was then heated for 4 h under reflux. The mixture was cooled and diluted with 100 ml of water, and the precipitate was filtered off, washed in succession with hot water and 50% aqueous ethanol, and dried in air. The product was ground and extracted first with ethanol to remove impurities and then with chloroform. Chromatographic purification on silica gel gave 0.025 g (3.8%) of compound **IV**. Mass spectrum, *m/z*: 829.2 (M^+). Electronic absorption spectrum (CHCl3), λ_{max}, nm ($\log\varepsilon$): 727 (4.63), 691 sh (3.85), 662 sh (3.69), 557 (4.10), 488 (3.72), 371 (4.32), 336 (4.33). Found, %: C 78.45, 78.67; H 5.66, 5.40; N 12.76, 12.68. $C_{56}H_{44}N_8 \cdot H_2O$. Calculated, %: C 79.41; H 5.47; N 13.23.

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